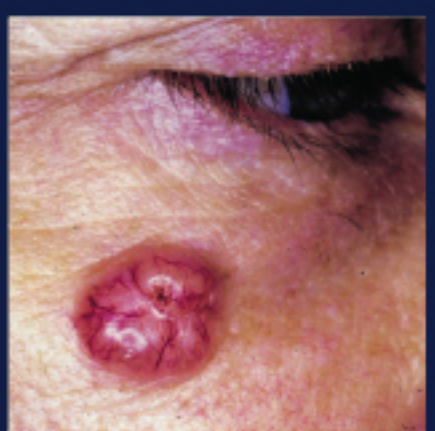
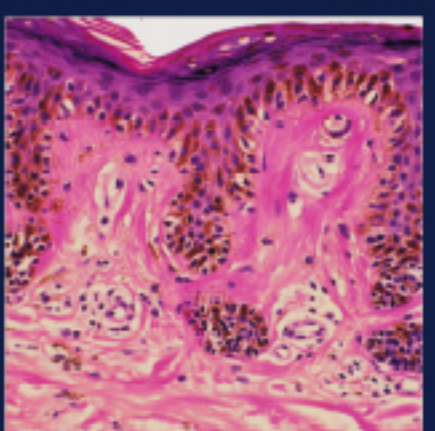
World Health Organization Classification of Tumours

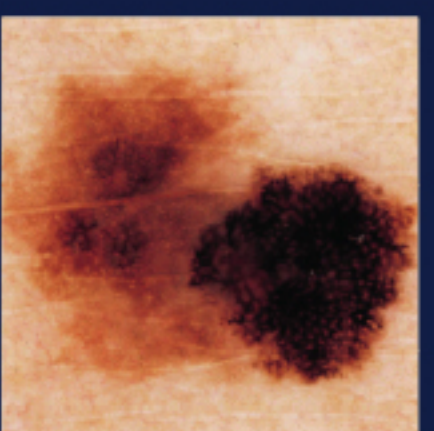
Pathology & Genetics

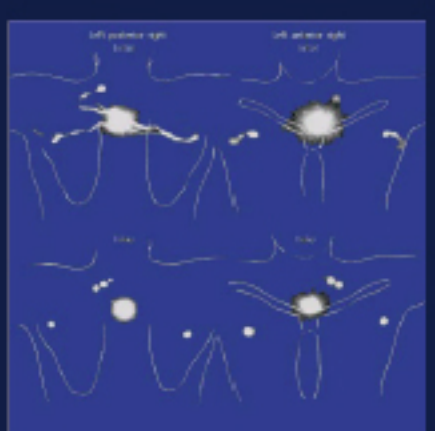
Skin Tumours

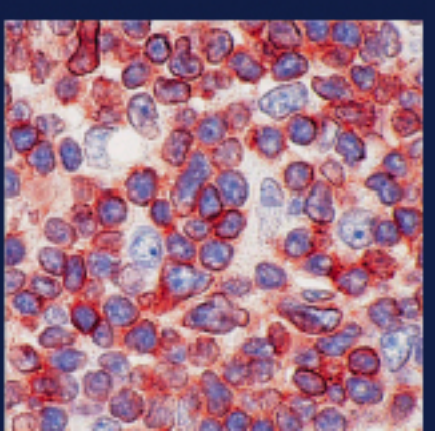
Edited by Philip E. LeBoit, Günter Burg, David Weedon, Alain Sarasin

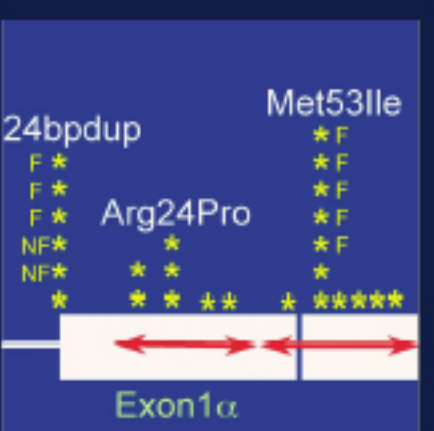












WHO Classification Skin Tumours

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Lyon, 2006

World Health Organization Classification of Tumours

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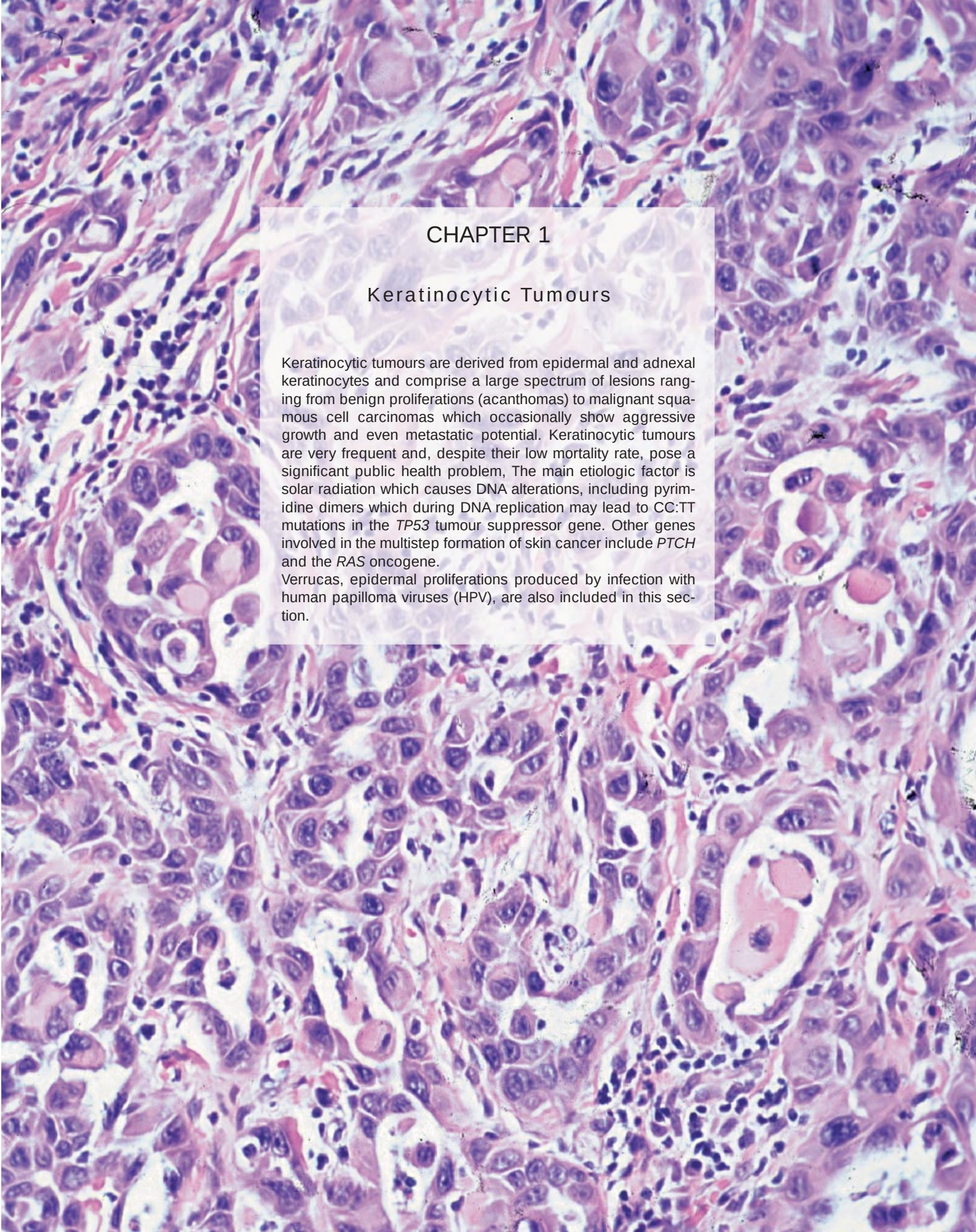

CHAPTER 1

Keratinocytic Tumours

Keratinocytic tumours are derived from epidermal and adnexal keratinocytes and comprise a large spectrum of lesions ranging from benign proliferations (acanthomas) to malignant squamous cell carcinomas which occasionally show aggressive growth and even metastatic potential. Keratinocytic tumours are very frequent and, despite their low mortality rate, pose a significant public health problem, The main etiologic factor is solar radiation which causes DNA alterations, including pyrimidine dimers which during DNA replication may lead to CC:TT mutations in the *TP53* tumour suppressor gene. Other genes involved in the multistep formation of skin cancer include *PTCH* and the *RAS* oncogene.

Verrucas, epidermal proliferations produced by infection with human papilloma viruses (HPV), are also included in this section.

WHO histological classification of keratinocytic skin tumours

Keratinocytic tumours	
Basal cell carcinoma	8090/3
Superficial basal cell carcinoma	8091/3
Nodular (solid) basal cell carcinoma	8097/3
Micronodular basal cell carcinoma	8090/3
Infiltrating basal cell carcinoma	8092/3
Fibroepithelial basal cell carcinoma	8093/3
Basal cell carcinoma with adnexal differentiation	8098/3
Basosquamous carcinoma	8094/3
Keratotic basal cell carcinoma	8090/3
Squamous cell carcinoma	8070/3
Acantholytic squamous cell carcinoma	8075/3
Spindle-cell squamous cell carcinoma	8074/3
Verrucous squamous cell carcinoma	8051/3
Pseudovascular squamous cell carcinoma	8075/3
Adenosquamous carcinoma	8560/3
Bowen disease	8081/2
Bowenoid papulosis	
Actinic keratosis	
Arsenical keratosis	
PUVA keratosis	
Verrucas	
Verruca vulgaris	
Verruca plantaris	
Verruca plana	
Acanthomas	
Epidermolytic acanthoma	
Warty dyskeratoma	
Acantholytic acanthoma	
Lentigo simplex	
Seborrhoeic keratosis	
Melanoacanthoma	
Clear cell acanthoma	
Large cell acanthoma	
Keratoacanthoma	8071/1
Lichen planus-like keratosis	

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for in situ carcinoma and /1 for borderline or uncertain behaviour.

TNM classification of skin carcinomas

TNM classification[1,2]

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but no more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N – Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

[1] {894,2219}.
[2] A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508 .

Keratinocytic tumours: Introduction

D. Weedon
R. Marks
G. F. Kao
C.A. Harwood

The keratinocytic tumours are a clinically and histopathologically diverse group of lesions derived from the proliferation of epidermal and adnexal keratinocytes. At one end of the spectrum the proliferations are benign (acanthomas) and usually of cosmetic importance only, while at the other there are malignant tumours, which uncommonly may be aggressive with metastatic potential, as seen with some squamous cell carcinomas. Included in the spectrum are the epidermal dysplasias (actinic keratosis, arsenical keratosis and PUVA keratosis) and intraepidermal carcinomas (Bowen disease and bowenoid papulosis). Ackerman and others have proposed that solar keratoses should be regarded as squamous cell carcinoma de novo and not as pre-malignancies or pre-cancers that evolve into squamous cell carcinoma {994,1443,1701}.

Epidemiology

Keratinocytic tumours are an important public health problem, despite their comparatively low mortality rate {2484}. The lifetime risk for the development of skin cancer in the USA is now 1 in 5 {1937}. It is much higher in subtropical Australia. There is an increasing incidence of squamous cell carcinoma of the skin in some countries {2462}. Keratinocytic tumours account for approximately 90% or more of all skin malignancies, of which approximately 70% are basal cell carcinomas. The latter exceed squamous cell carcinomas in frequency by a factor of approximately 5:1 although in lower latitudes the incidence of squamous cell carcinoma increases and this ratio becomes 3:1. If solar keratoses are regarded as squamous cell carcinomas (see above), then squamous cell carcinoma becomes the more common tumour {300}.

Precursor lesions

There are no known precursor lesions to basal cell carcinoma. On the other hand, there are a number of intra-epidermal proliferative disorders (dysplasias) that may be precursors of squamous cell carcinoma. These include actinic keratosis and Bowen disease (intraepidermal carcinoma/squamous cell carcinoma in-situ).

Actinic keratoses are erythematous, scaling lesions occurring on heavily sunlight exposed areas that increase in prevalence with increasing age in fair skinned people. Histologically, they demonstrate confluent keratinocytic atypia involving predominantly the keratinocytes in the basal layer of the epidermis {2475}.

It is difficult to determine the incidence of actinic keratoses as they come and go over time {788}. Longitudinal studies suggest that they are likely to be a precursor of squamous cell carcinoma, although the malignant transformation rate is small, certainly less than one in a hundred per year {1517}. Data suggest, also, that remission of these lesions will occur if sunlight exposure can be reduced. Thus the majority of lesions do not progress to squamous cell carcinoma {1516,2349}.

Bowen disease demonstrates keratinocyte atypia involving the full thickness of the epidermis. There is also involvement of the hair follicle and rarely the sweat duct. Although Bowen disease has been classified as a full thickness in-situ squamous cell carcinoma, there are no longitudinal studies published on the frequency of malignant transformation. Even if invasive squamous cell carcinoma does occur within one of these lesions, it is believed that the in-situ phase may be very prolonged, lasting many years {1203}.

Etiology

Findings regarding the genetic basis of non-melanoma skin cancer (NMSC) have confirmed that UV radiation, especially UVB (290-320 nm in the solar spectrum), contributes to the formation of squamous {1336} and basal cell carcinomas {602}. Squamous cell carcinomas (SCCs) of the skin develop through a multistep process that involves activation of proto-oncogenes and/or inactivation of tumour suppressor genes in the human skin keratinocytes. NMSCs are caused by genetic abnormalities, most often induced by UVB exposure. Actinic keratoses, which lead to SCCs, have gene mutations in K-ras {2235}. H-rasV12 and cyclin dependent kinase 4 (CDK4) produce human epidermal neoplasia. Therefore, a combination of these genetic abnormalities might be crucial to the carcinogenesis at least in a subset of SCCs {1336}.

High doses of ultraviolet light can also lead to skin cancers by inducing reactive oxygen species (ROS) that play an important role in tissue injury. Increased production of ROS and/or decreased efficiency of antioxidant defence system contribute to a number of degenerative processes including cancer {1161}. UV induces pyrimidine dimers and loss of heterozygosity (LOH). TP53 and PTCH, two tumour suppressor genes, have LOH which lead to basal cell carcinoma (BCC) {1265}. LOH in TP53 is related to elevated microsatellite instability at selected tetranucleotide repeats {587}. LOH at 9q22 loci in PTCH genes causes non-melanoma skin cancer tumours {1265}. The type of mutations for TP53 and PTCH are predominantly UV-signature transitions, C->T and CC->TT at dipyrimidine sites {1265}. SCCs have mutations of H-Ras gene and the INK4a locus whereas BCC has missense mutations leading to rasGTPase activating protein {168}. Further, mutations have been found in both TP53 tumour suppressor gene and ras in patients with xeroderma pigmentosum (XP), a disease of DNA repair deficiencies {1717}.

Common exogenous carcinogenic agents in addition to UV radiation include 1) tobacco use {2457}, 2) human papilloma viruses {1703}, 3) arsenic {2184}, 4) industrial chemicals such as vinyl chloride {1362}, polycyclic aromatic hydrocarbons {1086}, 5) MNNG (N-methyl-N'-nitro-N-nitrosoguanidine), an alkylating agent {335}, and 6) exposure to gasoline or gasoline vapours {1567}.

Clinical features
Keratinocytic tumours vary in their clinical appearance depending on the type of lesion and stage of development.

Histopathology
The histopathologic changes noted in keratinocytic proliferative lesions involve disturbance of normal surface maturation. The degree and extent of keratinocytic atypia vary in these lesions. The atypical keratinocytes show enlarged nuclei with hyperchromasia, dyskeratosis and mitoses in any layer of the epidermis. In lesions of epidermal dysplasias (AK, arsenical, and PUVA keratoses), surface keratinocytic maturation is present, i.e. a granular cell layer is usually noted.
In intraepidermal carcinomas (Bowen disease, bowenoid papulosis), there is full-thickness involvement of the epidermis by the atypical keratinocytes.

Molecular markers
A number of potentially useful molecular markers or tests have been proposed. These include the demonstration of a different pattern of basic fibroblast growth factor expression in neoplastic keratinocytes by in situ hybridization and the persistence of integrated HPV sequences in the host cell genome of HPV associated keratinocytic lesions detected by ligation mediated PCR assay. The lower level of TIG-3 mRNA expression in SCC is visualized by immunohistochemistry or by in situ mRNA hybridization. Upregulation of S100 protein subtypes in specific keratinocyte disorders is confirmed by immunohistochemistry.

Prognosis and predictive factors
Most patients with primary cutaneous non-melanoma skin cancer (NMSC) have an excellent prognosis. The overall mortality rates are generally low, on average approximately 0.1% of the incidence rates, but significantly higher for SCCs than BCCs {2483}. Invasive SCC has the potential to recur and metastasize with an overall 5-year rate of recurrence for primary tumours of 8%. With the exception of lip tumours, sqamous cell carcinomas arising in actinic keratoses have a frequency of metastatic spread of 0.5-3% {1459,1630}. For those with metastatic disease the long-term prognosis is poor; 10-year survival rates are <20% for patients with regional lymph node involvement and <10% for patients with distant metastases {50}. More than 70% of SCC recurrences and metastases develop within 2 years of treatment of the primary tumour {635}, and 95% within 5 years {1985}. The 3-year cumulative risk of non-melanoma skin cancer developing in an individual diagnosed with SCC is 35-60% and the risk of melanoma is also increased {1507}. Five-year cure rates for BCC of up to 99% are obtainable with surgical techniques {1617, 1984}, and metastasis is extremely rare, occurring in approximately 0.05% of cases {1440}. As with SCC, patients with BCC are at high risk of further primary BCCs; in patients with one lesion the 5-year risk is 27%, and in those with 10 lesions the risk is 90% {1208}, and the risk of SCC and malignant melanoma is also increased {1208,1430}.

Basal cell carcinoma

S. Kossard
E.H. Epstein, Jr.
R. Cerio
L.L. Yu
D. Weedon

Definition
A group of malignant cutaneous tumours characterised by the presence of lobules, columns, bands or cords of basaloid cells ("germinative cells").

ICD-O code 8090/3

Synonyms
Basal cell epithelioma, trichoblastic carcinoma.

Epidemiology
Basal cell carcinomas (BCC) develop predominantly in sun-damaged skin in individuals who are fair skinned and prone to sunburn {330,888,889}. Migration of such individuals particularly as children, to countries with high UV radiance is associated with increased rates of skin cancer. Although basal cell carcinomas typically occur in adults, the tumours also develop in children {1873}. Arsenic exposure {924} and ionizing radiation may also induce basal cell carcinomas.
Nodular basal cell carcinomas occur at a later age than superficial basal cell carcinomas and are more frequently on the head whereas the trunk is the most frequent site for superficial tumours {1550, 2121}.
Basal cell carcinomas are very frequent tumours particularly in light-skinned individuals living in countries at low latitudes. Incidences of 2000 per 100,000 population have been recorded in Queensland, Australia. The rate of basal cell carcinomas has increased in the older age groups. Older men have a higher incidence of basal cell carcinoma than women, but women have been found to outnumber men in younger age groups. The latter may be due to increased sun exposure in younger women in association with tanning bed use as well as smoking {293}.

Clinical features
Basal cell carcinomas typically have a pearly appearance with telangiectasia that may appear as a papule or nodule that can be eroded or ulcerated. These features may be more subtle in the superficial forms that appear as erythematous patches resembling an area of dermatitis. Pale scar-like lesions may also be a presentation of basal cell carcinoma and these slowly grow over years. Pigmented basal cell carcinomas may masquerade as melanomas but usually can be distinguished by the presence of a pearly component. Dermatoscopy is also helpful in analysing pigmented basal cell carcinoma and distinguishing these from melanocytic tumours {1587}. Erosive lesions on the lower limbs may be mistaken for slowly healing traumatic wounds. Delays in clinical diagnosis may occur for basal cell carcinomas that are localized within non-sun exposed sites {225} such as the perianal area {1312} or between the toes, young age of onset, tumours with very slow growth, or superficial erythematous patches that appear as a dermatitis or tumours complicating vaccination scars, rhinophyma or a venous ulcer. The clinical capacity to differentiate some basal cell carcinomas from squamous cell carcinoma or even melanoma may be impossible without skin biopsy. In countries with a high incidence of basal cell carcinomas it is not unusual to have individuals with multiple basal cell carcinomas, and regular review is required to deal with new skin tumours. Incomplete removal of basal cell carcinoma may result in delayed recurrences that may not be recognized for years, particularly if the tumour recurrence is deep or masked by skin grafts.

Genetics
Genetic analysis of sporadic basal cell carcinoma {2024} has been propelled by the identification of mutations in PTCH1 (chromosome 9q22.3) as the cause of the basal cell nevus syndrome (BCNS), a rare autosomal dominant disorder {110, 1146,2395}. These patients develop multiple basal cell carcinomas which may appear in childhood (see Chapter 2). PTCH1 encodes a protein that functions as an inhibitor of the hedgehog signaling pathway, and BCCs, whether sporadic or occurring in BCNS patients, all have abnormalities of this signaling pathway {110,1146,2272,2395}. In most sporadic BCCs this is due to somatically-acquired mutations in PTCH1 {802}, and in many

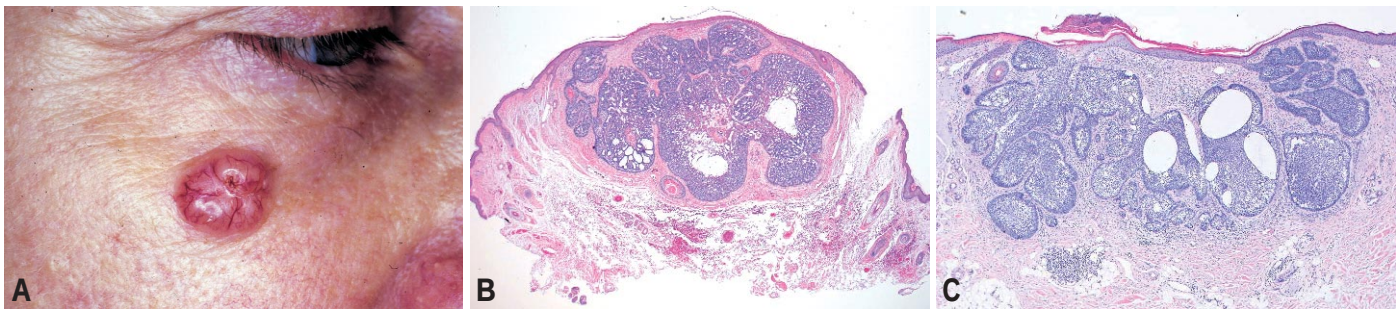

Fig. 1.1 Basal cell carcinoma, nodular type. **A** and **B** The epidermis is raised with flattening of the rete ridges overlying solid and cystic groups of atypical basaloid cells with peripheral palisading showing invasion of the deep dermis in a nodular pattern. **C** High power view of nodular basal cell carcinoma showing focal cystic change, peripheral palisading and cleft between tumour nests and stroma.

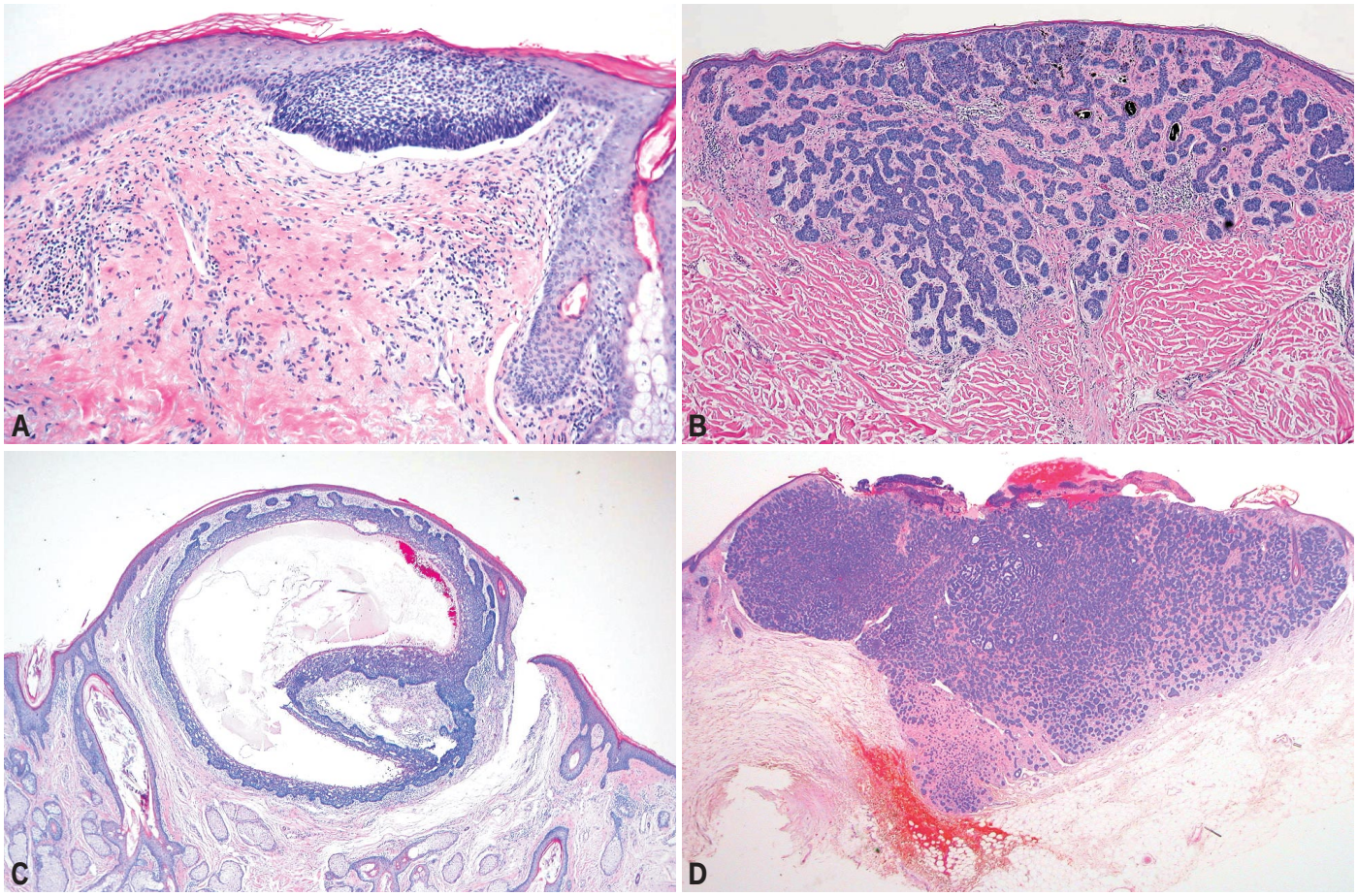

Fig. 1.2 **A** Basal cell carcinoma, superficial type. A solid group of atypical basaloid cells is present at the dermo-epidermal junction showing peripheral palisading and cleft formation between tumour nest and dermis. The dermis shows fibrosis and a patchy lymphocytic infiltrate which frequently accompany basal cell carcinoma of the superficial type. **B** Basal cell carcinoma, nodular type, pigmented. The appearances are those of typical nodular basal cell carcinoma with the additional feature of melanin pigmentation of the tumour nests. **C** Basal cell carcinoma, cystic type. There is extensive cystic change in an otherwise nodular basal cell carcinoma. The cystic space contains connective tissue type mucin. In the purely cystic variant, tumour cells may be compressed to only 1 to 2 cell layers thick. **D** Basal cell carcinoma, micronodular type. The tumour cell nests are tightly packed, with a diameter of 3 to 10 cells across with deep dermal invasion. In this example, there is also tumour-associated amyloid in the stroma.

tumours the type of PTCH1 mutations are those expected from UV-mutagenesis {108,1265}. Approximately 10% of sporadic BCCs have mutations in SMOOTHENED which encodes the protein whose function is inhibited by the PATCHED1 protein {2553}. Thus it appears that the relevant dysfunction driving BCCs is abnormal hedgehog signaling, irrespective of which gene controlling that signaling is mutated. The identification of hedgehog signaling abnormalities as crucial to BCC formation has stimulated the development of genetically-engineered mice with hedgehog signaling abnormalities {109,708, 1716,2163}. Unlike previously studied mouse carcinogenesis models, which uniformly produce tumours of the squamous cell lineage, these mice develop BCCs and either spontaneously or in response to environmental mutagens (i.e. UV or ionizing radiation) develop BCCs and adnexal basaloid tumours.

Histopathology

The multiple variants of basal cell carcinoma are connected by the common histological feature of lobules, columns, bands and cords of basaloid cells ("germinative cells") associated with scant cytoplasm and a characteristic outer palisade of cells associated with a surrounding loose fibromucinous stroma {2147,2282}. Artefactual retraction spaces between the tumour and stroma are often present. The tumour-stromal interaction is weakened by the characteristic lack of the hemidesmosomes that anchor the normal epidermis to the dermis {475}. Apoptosis is usually apparent. The release of keratin into the stroma as a result of apoptosis may lead to the formation of amyloid deposits {2067}. Mucinous cystic degeneration, focal vacuolation with lipid or ductular differentiation, and in rare cases, sebocytes or follicular differentiation with squamous eddies, trichohyaline granules and blue-grey corneocytes may be seen. Melanocytes may proliferate within some tumours and produce pigmentation by melanin production that can be stored in tumour cells or in surrounding melanophages {1365}.

Problematic lesions include tumours that merge with squamous cell carcinoma (basaloid squamous cell carcinoma) or those that share adnexal differentiation demonstrating trichilemmal or seba-

ceous areas. Some examples of morphoeic or sclerotic basal cell carcinoma may resemble desmoplastic trichoepithelioma or microcystic adnexal carcinoma particularly when a small sample is obtained for analysis. The growth pattern of the basal cell carcinoma should be included in the pathology report as well as the presence of perineural involvement and excision margins particularly if less than 1 mm. Although the majority of basal cell carcinomas can be classified into the nodular, micronodular, superficial, sclerosing/morpheic or infiltrative subtypes, it is not unusual to have a mixed pattern.

Immunoprofile

Occasionally in curette specimens, differentiation from small cell melanoma may require the use of a combination of light-weight keratin markers and S100 acidic protein to differentiate the tumours. BerEP4, a keratin marker, has been used to differentiate basal cell carcinoma from squamous cell carcinomas {2334}. CK20, a marker for Merkel cells, has been used to differentiate some forms of trichoblastoma, trichoepithelioma or fibroepitheliomas as these have scattered CK20 positive Merkel cells compared to basal cell carcinoma where they are rare or absent {13,2104}.

Prognosis and predictive factors

Basal cell carcinomas are locally invasive tumours and metastases occur in less than 1 in 10,000 tumours {1440, 1950,2443}. Morbidity is increased with deeply invasive tumours which may extend into the deep tissue to bone and follow fusion planes particularly on the face where they follow nerves through bony channels. Morbidity also increases with neglected tumours that may measure more than 10 cm in diameter and have been described as giant basal cell carcinomas {1502,2009}. Multiple recurrences with deep residual tumour on the head may be associated with particular morbidity as basal cell carcinomas can ultimately penetrate the cranium. Increased recurrences are associated with infiltrative, morphoeic and micronodular basal cell carcinomas as surgical margins may be underestimated {639, 1940}. The possibility of the BCNS should be considered in children who develop BCCs. Families can be screened for mutations of the PTCH1 gene. Low bcl-2 protein expression has been found to correlate with clinically aggressive basal cell carcinomas with infiltrative, sclerosing/morphoeic patterns as compared to superficial and nodular tumours {296,1883}.

BCC recurrences are more common in lesions on the nose and nasolabial fold, but this may be in part due to the difficulty in achieving adequate margins in these sites {638,651}. Tumours recurring after radiotherapy are usually aggressive and infiltrative {2209}. Lesions which metastasize are usually large, ulcerated, deeply infiltrating and recurrent {70}. The risk of further primary BCCs is increased by male gender, age over 60 years and truncal site {1208,1378}.

Rarely, extensive perineural invasion is seen in infiltrative primary BCCs of the face, presenting life-threatening complications of CNS extension {317,946}. Distance to the closest resection margin is an important predictor of BCC recurrence {639}.

Superficial basal cell carcinoma

ICD-O code 8091/3

Clinical features

This variant appears as erythematous patches that are often multiple and may vary from a few millimetres to over 10 cm in diameter. A fine pearly border or central superficial erosions with a history of contact bleeding may be present. Areas of regression may appear as pale patches or fibrosis. This variant makes up 10-30% of basal cell carcinomas and occurs most frequently on the trunk.

Histopathology

The histopathology consists of superficial lobules of basaloid cells which project from the epidermis or from the sides of follicles or eccrine ducts into the dermis and are surrounded by loose myxoid stroma. The lobules are usually confined

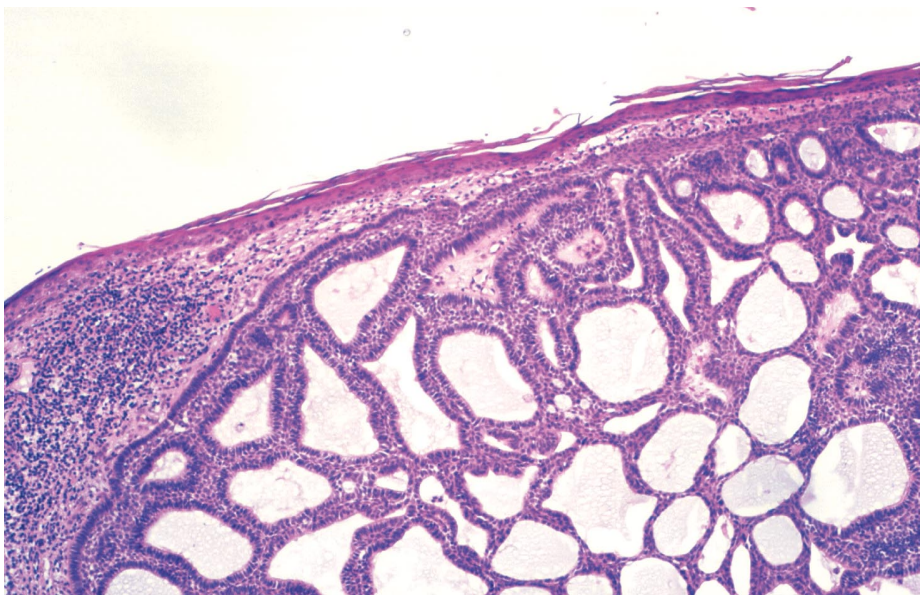

Fig. 1.3 Nodular BCC. Cribriform nodular basal cell carcinoma.

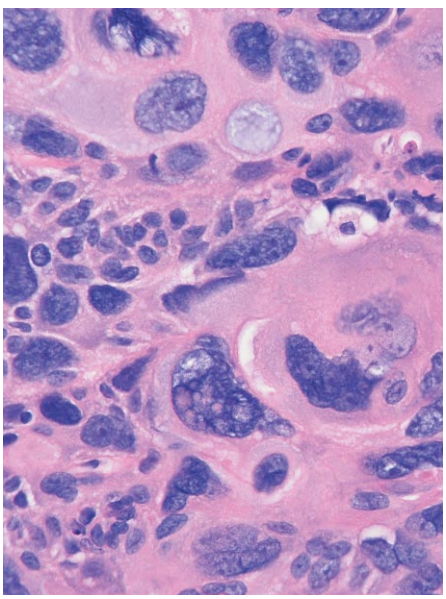

Fig. 1.4 Nodular BCC with monster giant cells.

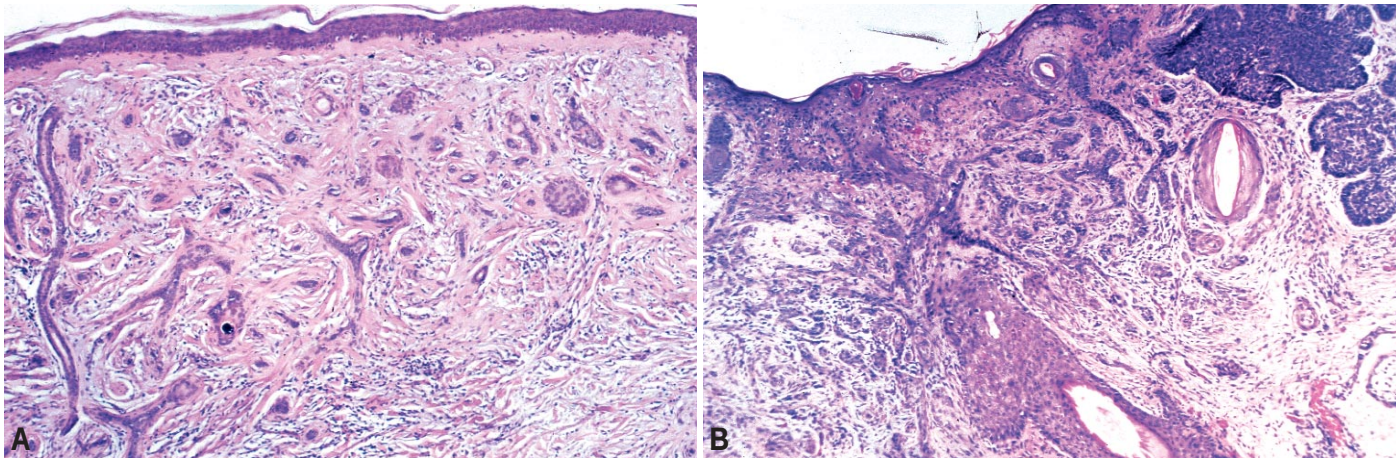

Fig. 1.5 A Infiltrative basal cell carcinoma. **B** 0172.Mixed nodular and infiltrative basal cell carcinoma.

to the papillary dermis. Some examples of superficial basal cell carcinoma appear multifocal on vertical sections but may be connected by a stroma when reconstructed by three-dimensional techniques using digital image analysis. There are, however, examples of multifocal superficial basal cell carcinoma where the lobules are separated by large distances and represent discrete tumours that are truly multifocal and may measure only a few millimetres in diameter. Mixed patterns with a nodular, micronodular or infiltrative component may be seen in some tumours.

Nodular basal cell carcinoma

ICD-O code 8097/3

Clinical features

Nodular (solid) basal cell carcinomas often appear as elevated pearly nodules associated with telangiectasia but may become ulcerated or cystic. Endophytic nodules may present as flat indurated lesions. Haemorrhagic lesions may resemble haemangiomas or melanoma when pigmented. Nodular basal cell carcinomas make up 60-80% of tumours and occur most frequently on the head.

Histopathology

Histopathology shows large lobules of basaloid cells ("germinative cells") with peripheral palisading nuclei that project into the reticular dermis or deeper. The lobules may have associated mucinous degeneration with cysts or have an adenoid (cribriform) pattern. Some nodules may have an organoid appearance with smaller basaloid lobules that are connected by loose fibromucinous stroma. The periphery of such nodules should be scanned to ensure that an outlying micronodular pattern has not developed.

Micronodular basal cell carcinoma

ICD-O code 8090/3

Clinical features

Micronodular basal cell carcinoma presents as elevated or flat infiltrative tumours. The most common site is the back.

Histopathology

This variant has small nodules that permeate the dermis {1010}. Individual nodules may appear to be separated by normal collagen. The tumour nodules may approximate the size of follicular bulbs and form subtle extensions into deep tissue. In contrast to nodular basal cell carcinoma the surgical margins of micronodular basal cell carcinoma may be underestimated. Perineural extension may be seen.

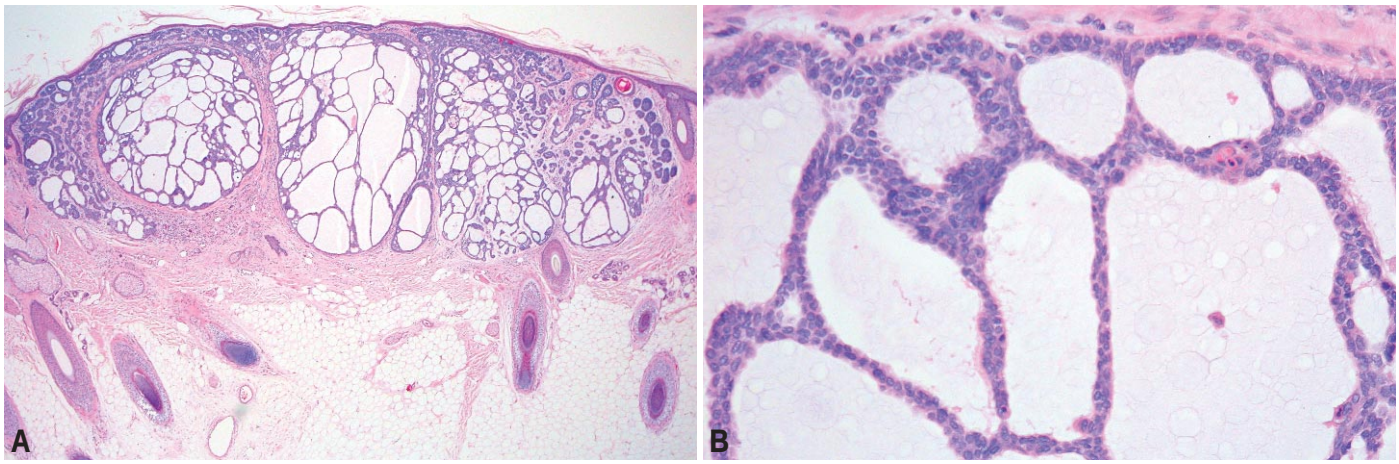

Fig. 1.6 Nodular cystic BCC **A** There are well circumscribed cystic nodules of atypical basaloid cells pushing into the deep dermis in a nodular pattern. **B** High power view of nodulocystic basal cell carcinoma showing cribriform cystic spaces filled with stromal mucin.

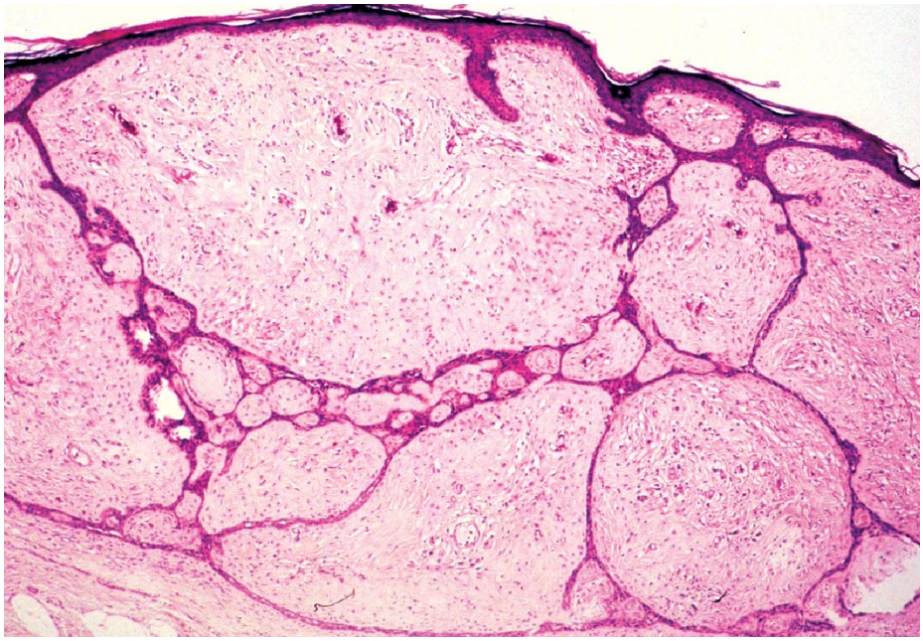

Fig. 1.7 Fibroepithelial basal cell carcinoma (fibroepithelioma of Pinkus).

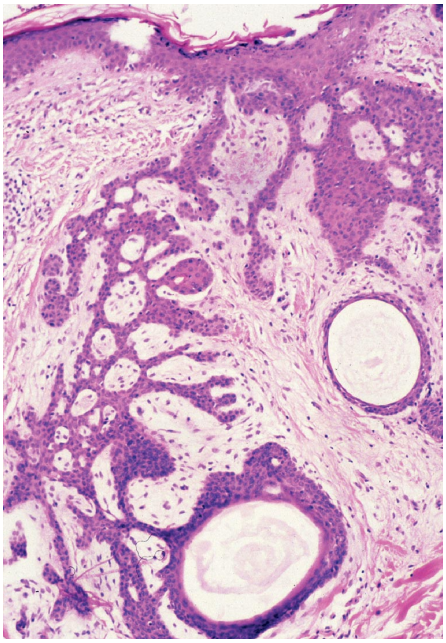

Fig. 1.8 BCC with adnexal differentiation; basaloid follicular hamartoma.

Infiltrating basal cell carcinoma

Definition
This variant of BCC is composed of thin strands, cords and columns of basaloid cells that infiltrate between the collagen bundles of the dermis and may extend into deeper tissues.

ICD-O code 8092/3

Clinical features
The infiltrative basal cell carcinoma presents as a pale, indurated poorly-defined plaque. These tumours are usually found on the upper trunk or face. Paraesthesia or loss of sensation may develop rarely as a manifestation of perineural extension, particularly in lesions on the face. This variant is important in that the margins at the time of surgery may be frequently underestimated.

Histopathology
Infiltrative patterns of basal cell carcinoma appear as strands, cords and columns of basaloid cells with scant cytoplasm. Peripheral palisading and retraction spaces are usually not seen. There is no fibrosis/sclerosis as seen in the sclerosing/morphoeic variant. The infiltrative pattern is particularly associated with perineural invasion. Low molecular-weight keratin markers are useful in highlighting subtle groups of tumour cells (that may consist of 1-2 keratinocytes on cross section), in assessing clearance of the tumour and in confirming perineural involvement.

Differential diagnosis
Due to the cord-like arrangement of this variant there is a morphological overlap with the tumour pattern seen in microcystic adnexal carcinoma (sclerosing sweat duct carcinoma), desmoplastic squamous cell carcinoma and desmoplastic trichoepithelioma.

Fibroepithelial basal cell carcinoma

Definition
This variant of BCC is characterised by a unique clinicopathological presentation and an indolent behaviour.

ICD-O code 8093/3

Synonyms
Fibroepithelioma of Pinkus, Pinkus tumour

Clinical features
These tumours usually appear as an elevated flesh coloured or erythematous nodule that may resemble a seborrhoeic keratosis or acrochordon. The lesions are most often found on the back and are rarely multiple {1834}. Prior radiotherapy may predispose to these tumours.

Histopathology
The histopathology is characterised by an arborising network of cords of basaloid cells that extend downwards from the epidermis and create a fenestrating pattern. There are strands of basaloid cells that surround fibrovascular stroma. Ductules may be present in some of the cords which may represent extension of the tumour down pre-existing eccrine ducts {2263}. The cords also are associated with small follicle-like bulbs which project into the surrounding connective tissue.

Histogenesis
Fibroepitheliomas, like BCCs, may be best classified as a form of appendageal tumour. These tumours have mutations of the PTCH1 gene. In some fibroepitheliomas transition to classical basal cell carcinomas may be seen, and this conversion may reflect a further mutation. A variant of fibroepithelioma with extramammary Paget's cells has been described in the perianal area {2461}.

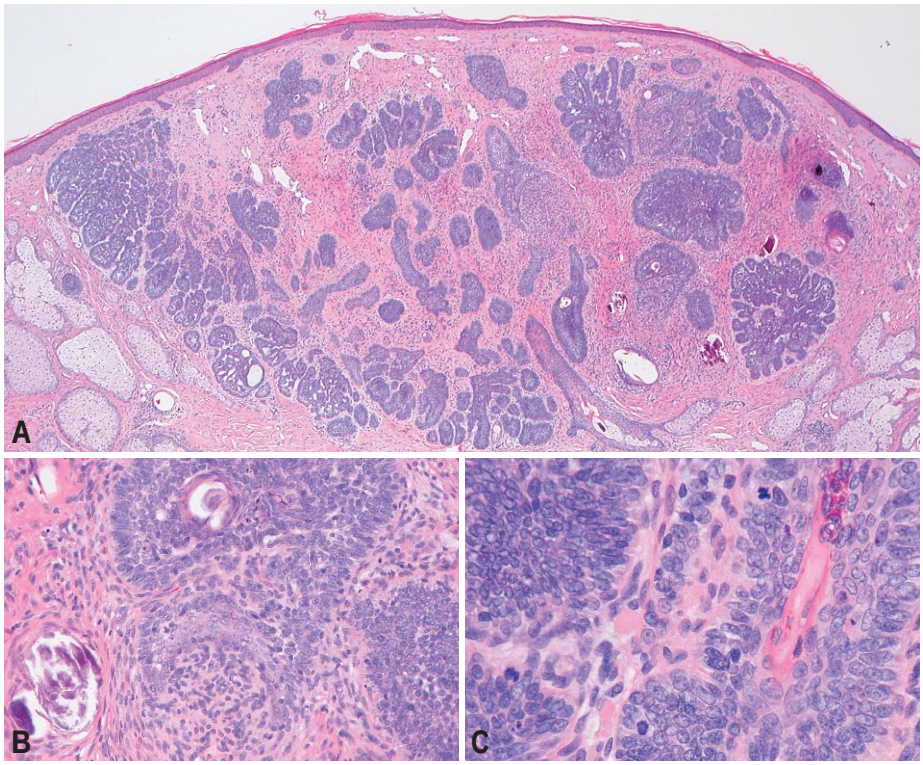

Fig. 1.9 Basal cell carcinoma, nodular type, with follicular differentiation. **A** The overall view shows a resemblance to typical nodular basal cell carcinoma, with the addition of a cellular fibrous stroma. **B** There is follicular bulbar differentiation in parts of the tumour, with formation of hair bulb accompanied by mesenchymal bodies. Focal dystrophic calcification. **C** 1603 High power view showing groups of atypical basaloid cells with peripheral palisading with trichohyaline granules and abrupt trichilemmal keratinization.

Basal cell carcinoma with adnexal differentiation

Definition
This variant is characterized histologically by adnexal differentiation in a BCC.

ICD-O code 8098/3

Clinical features
This variant has no distinguishing clinical features.

Histopathology
This variant is characterized by the presence of adnexal differentiation including basaloid buds, ductal, sebaceous and trichilemmal elements. Follicular differentiation may be prominent in more superficial BCCs. Eccrine or apocrine differentiation has also been observed in some basal cell carcinomas {997,2022}. It is important to distinguish such tumours from sweat gland carcinomas which have an increased risk for metastases. Some forms of adnexal basal cell carcinomas show overlap and may be better classified as benign adnexal tumour such as a basaloid follicular hamartoma, trichoepithelioma, trichoblastoma or trichilemmoma.

Histogenesis
The cytokeratin profile of basal cell carcinoma is essentially identical to that of trichoblastomas (immature trichoepithelioma) and developing fetal hair follicles linking all basal cell carcinomas to the pilosebaceous pathway of differentiation {2086}. It has been proposed that basal cell carcinoma be renamed trichoblastic carcinoma {1623}.

Prognosis and predictive factors
These patterns of adnexal differentiation do not appear to have any prognostic implications.

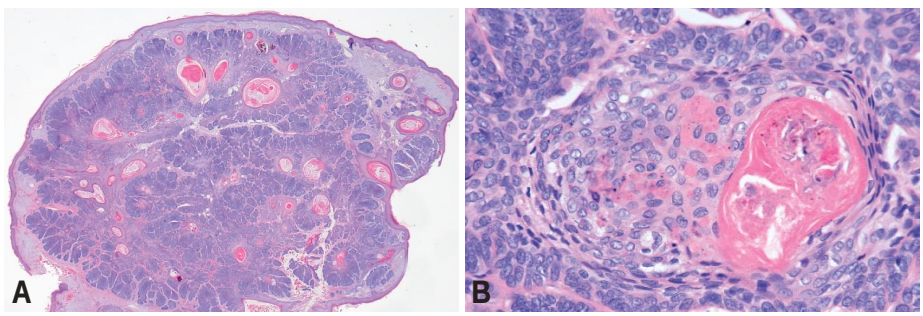

Fig. 1.10 Basal cell carcinoma, keratotic type. **A** Prominent keratin horn cysts in the center of the tumour nests. **B** Detail of trichilemmal keratinization.

Basosquamous carcinoma

Definition
Basosquamous carcinoma is a term used to describe basal cell carcinomas that are associated with squamous differentiation {285,2102}.

ICD-O code 8094/3

Synonyms
Metatypical carcinoma, basosquamous cell carcinoma

Clinical features
This variant has no distinguishing clinical features.

Histopathology
The tumour cells have more abundant cytoplasm with more marked keratinization than typical basal cell carcinomas. The nuclei have vesicular chromatin with pleomorphism and palisading may be focally lost. Some examples of this variant may merge with sebaceous carcinoma as lipid vacuoles or ducts may be focally apparent. This tumour may also have central fibrosis and a radiating peripheral rim of infiltrative cells extending into the deep dermis or subcutis.

Prognosis and predictive factors
This variant has a more aggressive behaviour and has been associated with regional or widespread metastases {1525}.

Keratotic basal cell carcinoma

Definition
This variant is characterized by the presence of prominent keratin formation (horn cysts) in the centre of tumour islands.

ICD-O code 8090/3

Clinical features
This variant characteristically appears pearly and may be studded with small keratin cysts (milia).

Histopathology
These tumours share the overall architectural features of a nodular BCC. Keratinization may be laminated and infundibular in type or hyaline and trichilemmal in type or consist of keratinised shadow cells representing pilomatricomal differentiation {66}. Dystrophic calcification is frequently present. Trichilemmal keratin may be associated with accentuated apoptosis in surrounding tumour cells and the presence of pale keratinocytes.

Differential diagnosis
This variant is distinguished from basosquamous carcinoma by the presence of numerous, superficial small keratin cysts. Basosquamous carcinoma is usually larger and less well circumscribed.

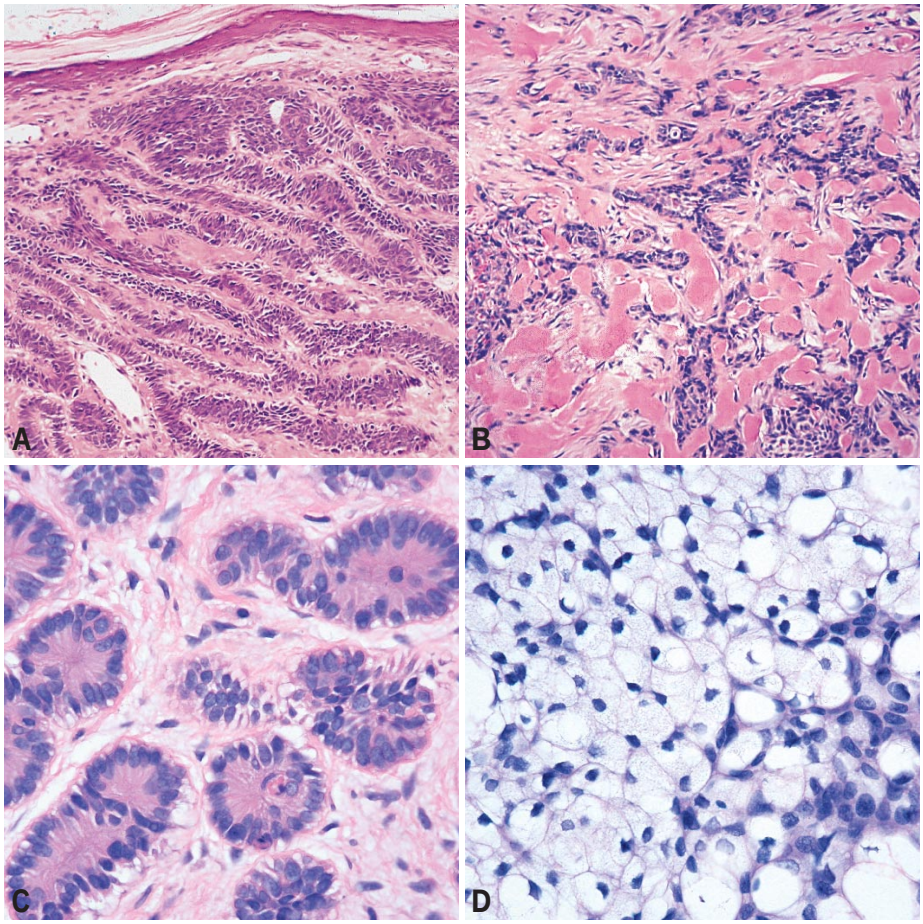

Fig. 1.11 Basal cell carcinoma (BCC). **A** Adenoid BCC. **B** Morpheiform BCC. **C** BCC with rosettes. **D** BCC with sebaceous differentiation.

Other variants

Other variants account for less than 10% of all basal cell carcinomas. Many of them do not have distinctive clinical features.

Cystic
One or more cystic spaces, of variable size, are present near the centre of the tumour nests. There is sometimes increased mucin between the cells bordering the central space {2112}.

Adenoid
There are thin strands of basaloid cells in a reticulate pattern. Stromal mucin is often present. The adenoid type may occur in association with the nodular (solid) type.

Sclerosing / morpheiform
Strands and nests of tumour cells are embedded in a dense fibrous stroma {1932}. Some authors use the term morphoeic for any BCC with a fibrous stroma, while others restrict it to those BCC's with keloidal collagen bundles in the stroma {1923}. Enhanced procollagen gene expression has been found in this variant {1657}. Furthermore, smooth muscle α-actin is often present in the stroma. This variant usually presents as an indurated, pale plaque with a slightly shiny surface and indistinct margins.

Infundibulocystic
Often confused with the keratotic type, this variant is composed of small infundibular-like structures with a central keratinous plug and a peripheral component of basaloid cells {1218}. The nests are arranged in an anastomosing pattern. Multiple lesions are sometimes present {1178}.

Pigmented
Pigmentation may occur in several of the variants including the nodular, micronodular, multifocal superficial and keratotic types. Melanocytes are scattered through the tumour nests, while melanophages are present in the stroma {1495}. This variant can be misdiagnosed clinically as malignant melanoma.

Miscellaneous
Other rare variants, subject to isolated case reports, include the clear-cell {165}, "signet-ring"-cell {1269,2503}, granular-cell {1659} and giant ("monster")-cell {680} types. Adamantanoid {1403}, neuroendocrine {817} and schwannoid {2032} variants have also been described.

Squamous cell carcinoma

D. Weedon
M.B. Morgan
C. Gross
E. Nagore
L.L. Yu

Definition
Squamous cell carcinoma is a malignant neoplasm of epidermal (and mucous membrane) keratinocytes in which the component cells show variable squamous differentation.

ICD-O code 8070/3

Epidemiology
Most cases arise on the sun-exposed skin of elderly people. They can occur on all cutaneous surfaces and mucous membranes, and in younger patients, especially those with a fair complexion who tan poorly. Its incidence in an Australian study was 166 cases per 100,000 of the population, the highest in the world {828}. It is relatively uncommon in Black people.

Etiology
Ultraviolet-B radiation is the most important etiological factor. Less important factors include radiation therapy, previous burns, arsenic, coal tar {1759}; industrial carcinogens, immunosuppresion, HPV infection, and inflammatory lesions and ulcers of long standing (see Introduction). Organ transplant recipients are particularly prone to develop these tumours. Most of the fatal cases have been reported from Australia, suggesting that sunlight, which also has a profound effect on the cutaneous immune system plays a role in the formation of these aggressive tumours {1974}. HPV infection is commonly found in these immunosupressed patients {264}.

Localization
Most SCCs arise in areas of direct exposure to the sun, such as the forehead, face, ears, scalp, neck and dorsum of the hands. The vermilion part of the lower lip is another common site.

Clinical features
Squamous cell carcinomas present as shallow ulcers, often with a keratinous crust and elevated, indurated surrounds, or as plaques or nodules. The surrounding skin usually shows changes of actinic damage.

Histopathology
Squamous cell carcinoma consists of nests, sheets and strands of squamous epithelial cells which arise from the epidermis and extend into the dermis for a variable distance. The cells have abundant eosinophilic cytoplasm and a large, often vesicular, nucleus. There are prominent intercellular bridges. There is variable central keratinization and horn pearl formation, depending on the differentiation of the tumour.
The degree of anaplasia in the tumour nests is used to grade the tumours. A rather subjective assessment is usually made using the categories of 'well,' 'moderately' and 'poorly' differentiated. Most squamous cell carcinomas arise in solar keratoses and evidence of this lesion is usually present at the periphery of the invasive tumour.
Squamous cell carcinomas occasionally infiltrate along nerve sheaths, the adventitia of blood vessels, lymphatics, fascial planes and embryological fusion plates {218}. The presence of perineural lymphocytes is a clue to the likely presence of perineural invasion in deeper sections {2289}.
There may be a mild to moderate chronic inflammatory cell infiltrate at the periphery of the tumours. This infiltrate sometimes includes eosinophils {1455}.
Rare histological variants of SCC include clear-cell {1344}, signet-ring {1557}, pigmented {451}, basaloid {573}, inflammatory, infiltrative {1395}, desmoplastic {1546} and rhabdoid {1534} types.
The cells in SCC are positive for epithelial membrane antigen and cytokeratin. The keratins are of higher molecular weight than those found in basal cell carcinoma {1672}.

Prognosis and predictive factors
The majority of squamous cell carcinomas are only locally aggressive and are cured by several different modalites {1656}. SCC developing in patients who are immunocompromised (including those infected with the human immunodeficiency virus {1704}, are usually more aggressive. Tumours with deep invasion, poor differentiation, perineural invasion and acantholytic features are more likely to recur or metastasize. Narrow surgical margins are another risk factor for recurrence {2389}.
The clinical setting in which the SCC arises also influences the risk of metastasis. Tumours arising in sun-damaged skin have the lowest risk, in the order of 0.5% or less, while for those arising in skin not exposed to the sun, the risk is 2-3%. The risk is further increased for tumours arising in Bowen disease {1203}, on the lip, vulvar, perineal and penile skin and in a Marjolin ulcer, radiation scar or thermal burn. Tumour thickness is a prognostic variable, just as it is for melanoma. SCCs less than 2 mm in thickness rarely metastasize, while those between 2 and 5 mm thick are of intermediate risk (about 5%). Tumours greater than 5 mm in thickness have a risk of metastasis of about 20% {1254}. Tumours greater than 2 cm in diameter are more likely to recur and metastasize than smaller lesions {1985}.

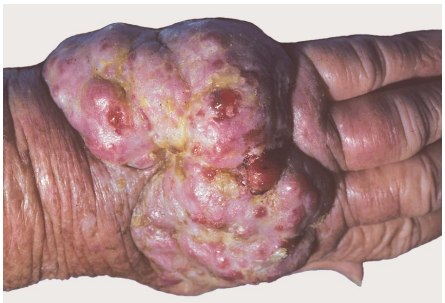

Fig. 1.12 Squamous cell carcinoma in an elderly male with delayed medical treatment. This is an unusually large neoplasm which spread to the regional lymph nodes.

Acantholytic squamous cell carcinoma

Definition
Acantholytic squamous cell carcinoma (ASCC) is a histologic variant of cutaneous squamous cell carcinoma (SCC) that is histologically defined by loosening of the intercellular bridges resulting in acantholysis. These tumours may present as intraepidermal (in-situ) or invasive SCC.

ICD-O code 8075/3

Synonyms
Adenoid squamous cell carcinoma, pseudoglandular squamous cell carcinoma

Epidemiology
The acantholytic variant accounts for 2-4% of all cutaneous SCC {1149,1687, 1819,2549}. The age range is wide but it usually affects aged individuals with a male predominance.

Etiology
As in conventional SCC, ultraviolet light constitutes the most important etiologic risk factor.

Localization
The tumour involves predominantly the skin of the head and neck region, particularly on and around the ears {1149, 1687,1819,2549}.

Clinical features
ASCC presents similarly to conventional SCC, as a slowly growing scaly and occasionally ulcerated papule/plaque on the sun-exposed skin.

Histopathology
Invasive lesions typically show a thickened, and/or ulcerated epithelium. Scanning magnification reveals a flattened thinned, normal or hyperplastic epidermis with or without asymmetric and infiltrating dermal tumour islands. At intermediate power, prominent suprabasilar or intratumoural acantholysis is seen. Zones of acantholysis are capable of producing large intra-epidermal cavities. Acantholytic areas may extend down adjacent follicular structures involving the follicular epithelium and rarely, circumscribe the follicle simulating a glandular arrangement. Acantholytic foci may also produce a pseudovascular pattern mimicking angiosarcoma (pseudovascular SCC) {139,1675,1688}. At high power typical features of squamous malignancy are identified including dyskeratosis, keratinocytic atypia, consisting of an increased nuclear-to-cytoplasmic ratio and nuclear hyperchromasia, altered maturation within the epithelium, and increased typical and atypical mitotic figures.

Immunoprofile
The lesional cells in ASCC stain for cutaneous epithelial markers that include high molecular weight keratins such as AE-2/3. Involucrin, vimentin and EMA immunostains may also be positive {1808,2011}. Low-molecular weight keratins such as AE-1, CAM 5.2 are typically negative. Various intercellular peptides have been invoked in the pathogenesis of acantholysis including the intercellular adhesion molecule syndecan, E-cadherin and the anhidrotic ectodermal dysplasia gene product {183,1635}. It has also been recently shown that decreased TP53 and PCNA expression correlated with a decrement in desmosomes seen ultrastructurally {1889}.

Differential diagnosis
The changes described above constitute an important histologic means of separating this entity from acantholytic disorders. The differential also includes true adenosquamous cell carcinoma of the skin that exhibits squamous and glandular differentiation on ultrastructural examination and histochemical staining {2482}.

Prognosis and predictive factors
The behaviour of ASCC like other SCCs is depth-dependent and may be more aggressive than conventional SCC {461, 1097,1149,1687,1819,1985}. In-situ lesions are capable of recurrence and in up to 10% of cases, may show microinvasion. The overall rate of metastases with lesions greater than 2.0 cm of invasion ranges from 5-19%.

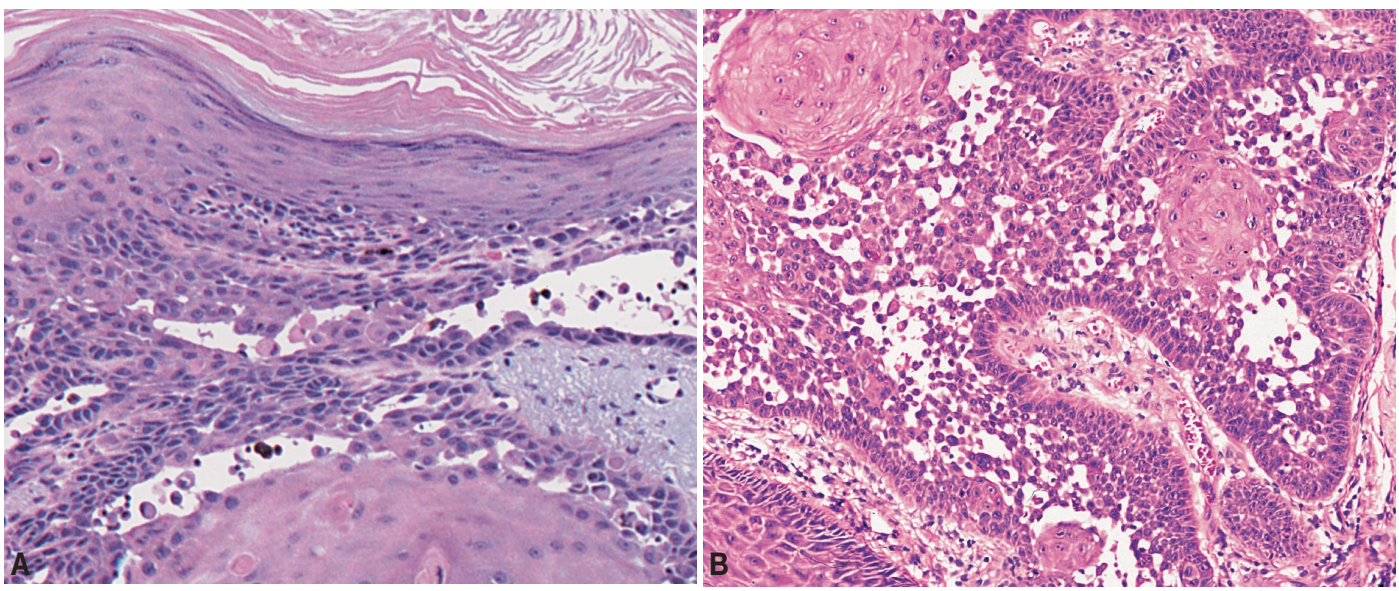

Fig. 1.13 A Acantholytic SCC, Intermediate-power photomicrograph depicting acantholysis extending down adjacent follicle epithelium. **B** Squamous cell carcinoma (acantholytic)

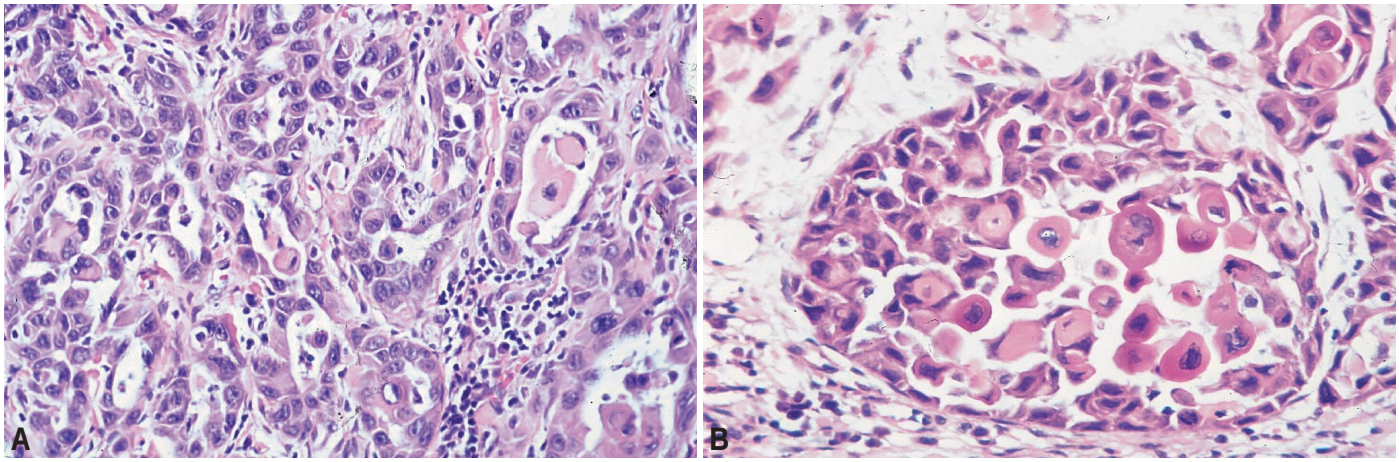

Fig. 1.14 Squamous cell carcinoma (acantholytic) **A**, **B** Note the pseudoglandular pattern and the loss of cohesion between tumour cells.

Spindle-cell squamous cell carcinoma

Definition
This is an uncommon variant of squamous cell carcinoma that exhibits a prominent spindle cell morphology.

ICD-O code 8074/3

Etiology
Lesions usually arise in sun-damaged or irradiated skin. A case has been reported in association with lichen sclerosus of the vulva {2057}. The incidence of this variant may be higher in immuosuppressed patients.

Clinical features
Spindle-cell squamous cell carcinoma presents as a plaque or nodule on the skin. It may be clinically indistinguishable from the more usual type of squamous cell carcinoma. Sometimes there is a history of rapid growth.

Histopathology
It may be composed entirely of spindle cells, or have a variable component of more conventional squamous cell carcinoma. The spindle cells have a large vesicular nucleus and scanty eosinophilic cytoplasm, often with indistinct cell borders. There is variable pleomorphism, usually with many mitoses.

Differential diagnosis
It may be difficult to separate from other cutaneous spindle cell neoplasms including spindle cell melanoma, atypical fibroxanthoma and, less often, leiomyosarcoma. Some cases can only be confirmed ultrastructurally, as all keratin markers are negative {2180}. CK5/6 is positive in two-thirds of all cases, a higher figure than obtained with AE1/3, CAM5.2 or MNF116. Some tumours may coexpress cytokeratin and vimentin, suggesting metaplastic change to a neoplasm with mesenchymal characteristics {1116}.

Prognosis and predictive factors
Spindle-cell squamous cell carcinoma is a poorly differentiated variant of squamous cell carcinoma that may be associated with an aggressive clinical course {2180}. These tumours account for slightly over one-third of cutaneous squamous cell carcinomas which metastasize {1985}. Metastases usually occur to the regional lymph nodes in the first instance.

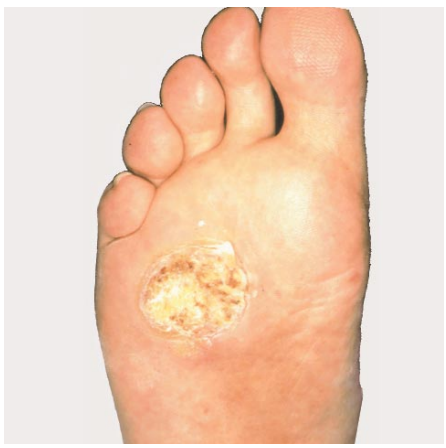

Fig. 1.15 Verrucous squamous cell carcinoma

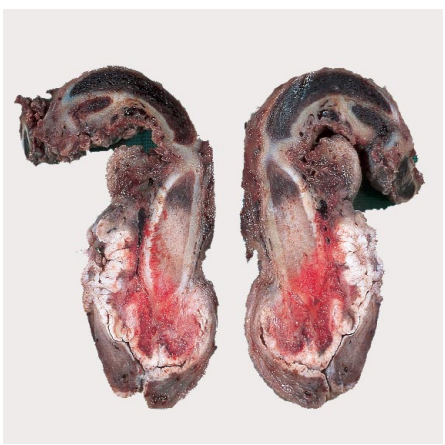

Fig. 1.16 Verrucous squamous cell carcinoma

Verrucous squamous cell carcinoma

Definition
Verrucous squamous cell carcinoma is a rare variant of well-differentiated squamous cell carcinoma with low malignant potential.

ICD-O code 8051/3

Synonyms
Oral florid papillomatosis, Ackerman's tumour {32,348}, epithelioma cuniculatum {41,2096,2108}, giant condyloma acuminatum, Buschke-Löwenstein tumour {359,1347,1947,2124,2570}, papillomatosis cutis carcinoides {218,870, 2108}.

Epidemiology
Verrucous carcinoma comprises 2-12%

of all oral carcinomas, and is found predominantly in men (age peak in 5th decade, range 34-85) {348}. Verrucous carcinoma of the extremities (epithelioma cuniculatum) most often affects men in the 6th decade {2108}. The incidence of the genital type (Buschke-Löwenstein tumour) varies between 5- and 24% of all penile cancers; the tumour tends to occur in men younger than 50 years (range 18-86) {218}.

Etiology
Leading theories of the pathogenesis include chronic irritation, inflammation and impaired immune response {2096, 2108}. Important factors for the development of oral verrucous carcinomas are poor oral hygiene with ill-fitting dentures or decaying teeth, chewing of tobacco or betel nuts, and use of snuff. In genital lesions poor hygiene and phimosis play a major role. Other theories include HPV infection (mostly HPV 6, 11) {898} and chemical carcinogens {2096,2108}.

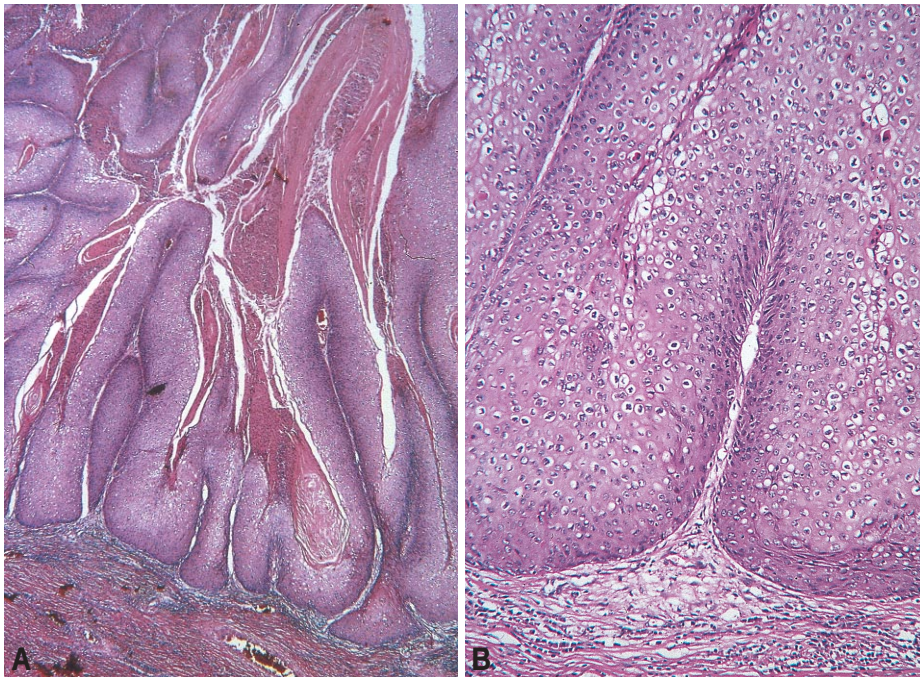

Fig. 1.17 Verrucous squamous cell carcinoma **A, B** Note the well-differentiated proliferative process and the bulbous nature of the squamous downgrowths.

Localization
Common sites include buccal and retromolar mucosa, gingiva, floor of mouth, tongue and hard palate. They also arise on the soles, rarely the palms and distal fingers, and on amputation stumps. Genital lesions occur primarily on the glans and prepuce of the penis {778, 2108,2570}. It is uncommon in the vagina and the perianal region {1347,1947, 2124}. Rare cases have been described on the scalp, face, back and extremities, sometimes associated with long-standing ulcerations or scars, especially in the pretibial area (papillomatosis cutis carcinoides) {218,870,2096,2108}.

Clinical features
These lesions show cauliflower-like appearance with exophytic and endophytic growth, and a papillomatous surface. They are pale in colour and sometimes have draining sinuses. Some are tender and painful, particularly on the sole of the foot. There is slow but relentless growth over the course of a long time {2570}.

Histopathology
In all cases a well-differentiated proliferative epithelial process is visible, the malignant nature of which may easily be overlooked, particularly if the biopsy is small and superficial. The squamous epithelium shows an asymmetric exo- and endophytic growth pattern with pushing rather than destructive or infiltrative margins. Usually, there is deep penetration below the level of the surrounding epidermis / mucosa. Tumour cells exhibit only minimal atypia and very low mitotic activity. The presence of neutrophils is an important diagnostic clue; they may form small intraepidermal abscesses. Draining sinuses containing inflammatory cells and keratin debris may also be present. No foci of the usual squamous cell carcinoma should be found {1833}.

Differential diagnosis
The separation from benign reactive processes and SCC of the more usual type can be difficult. The presence of blunted projections of squamous epithelium in the mid and/or deep dermis is suspicious for verrucous carcinoma. The squamous downgrowths are bulbous. Small collections of neutrophils may extend into the tips. Clinicopathological correlation and adequate sampling are often helpful.

Precursor lesions
Oral lesions may develop in areas of previous leukoplakia, lichen planus, lupus erythematosus or candidiasis {218}.

Prognosis and predictive factors
If the tumour is completely excised, prognosis is excellent; after inadequate excision, the recurrence rate is high and the survival decreases. In long-standing cases or after irradiation and / or chemotherapy the biologic character of the disease may change into a metastasizing squamous cell carcinoma {1216}.

Pseudovascular squamous cell carcinoma

Definition
Pseudovascular SCC is an aggressive variant of SCC with marked acantholysis resulting in angiosarcoma-like areas {139,1688}.

ICD-O code 8075/3

Synonyms
Pseudoangiosarcomatous SCC, pseudoangiomatous SCC

Epidemiology
The tumour is exceedingly rare.

Clinical features
It usually presents as a circumscribed white-grey ulcer or a nodular tan-red/pink tumour, most often located on sun-

exposed areas of middle-aged or elderly patients.

Histopathology
It is characterized by areas of anastomosing cord-like arrays of polygonal or flattened tumour cells, with internal pseudolumina that contain detached tumour cells and amorphous basophilic material {550,1675,2558}. Erythrocytes may also be seen in pseudovascular spaces. Immunohistochemical examination is essential to differentiate it from angiosarcoma. Pseudovascular SCC is positive for one or more monoclonal antibodies to cytokeratin and consistently negative for CD31 and factor VIII-related antigen.

Differential diagnosis
In classical angiosarcoma vascular markers are positive, keratin staining is negative; in epithelioid angiosarcoma in addition to vascular markers epithelial markers are frequently expressed.

Prognosis and predictive factors
The prognosis is worse than it is for other variants of SCC, with a mortality up to 50%. Large size may confer a worse prognosis {1675}.

Adenosquamous carcinoma

Definition
Adenosquamous carcinoma is a rare variant of squamous cell carcinoma arising from pluripotential cells related to acrosyringia, characterized by the formation of mucin secreting glands.

ICD-code 8560/3

Epidemiology
Most reported cases occurred on the head and neck of elderly patients, with male predominance {120,140,572, 1933,2482}. The penis can also be involved {120}.

Clinical features
It can present as an asymptomatic smooth surfaced dermal nodule or a large ulcerated deeply invasive tumour indistinguishable from squamous cell carcinoma or basal cell carcinoma.

Histopathology
The tumour consists of invasive tongues, sheets, columns and strands of atypical dyskeratotic squamous cells, merging with glandular structures with epithelial mucin secretion, which can be demonstrated by a PAS, mucicarmine or alcian blue stain at pH 2.5. The mucin is hyaluronidase resistant and sialidase sensitive. Intracytoplasmic neolumina containing targetoid mucin secretions can also be seen. The tumour cells are positive for cytokeratin and epithelial membrane antigen, whereas those cells forming glands stain with carcinoembryonic antigen. There may be connection between tumour cells and acrosyringia, as well as perineural invasion.

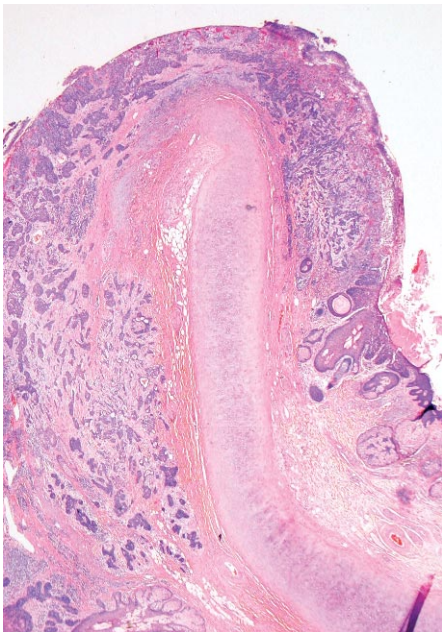

Fig. 1.18 Adenosquamous carcinoma of the ear. There are deeply invasive tongues, columns and strands of atypical dyskeratotic squamous cells abutting the cartilage.

Differential diagnosis
Adenosquamous carcinoma should be distinguished from mucoepidermoid carcinoma, which had been reported as adenosquamous carcinoma in early reports. Adenosquamous carcinoma has well formed glands with mucin secretion and no goblet cells. Mucoepidermoid carcinoma consists of polygonal squamous cells and goblet cells without glands. Signet ring squamous

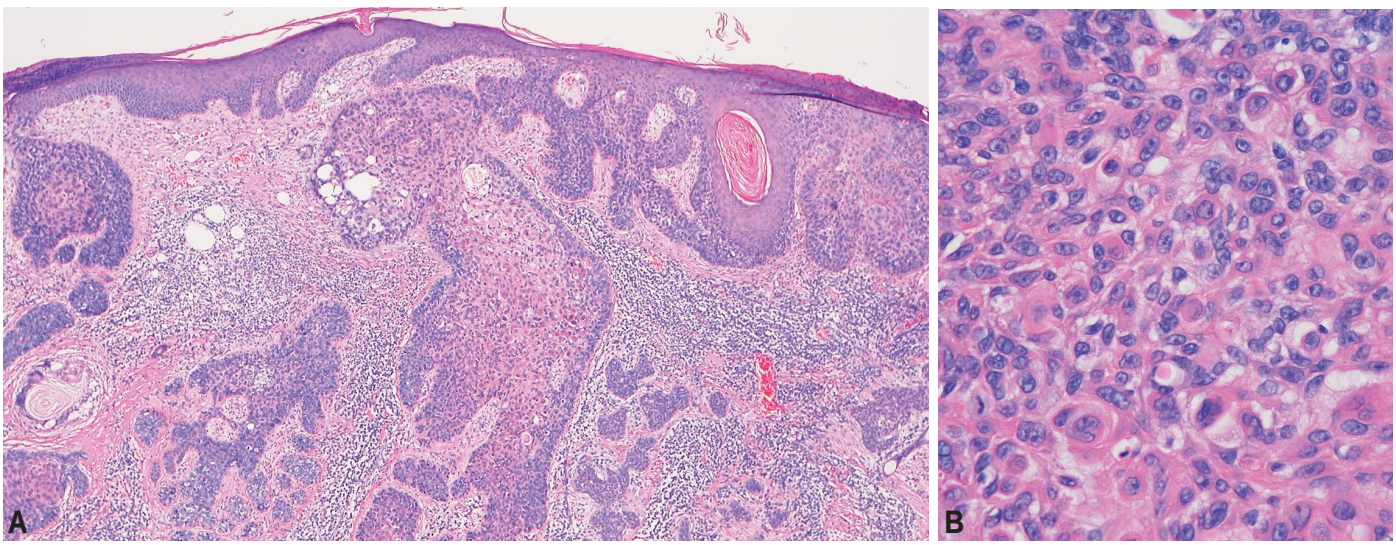

Fig. 1.19 Adenosquamous carcinoma. **A** Overt squamous differentiation in parts of the tumour. **B** Sheets of atypical dyskeratotic squamous cells from the squamous area of the tumour.

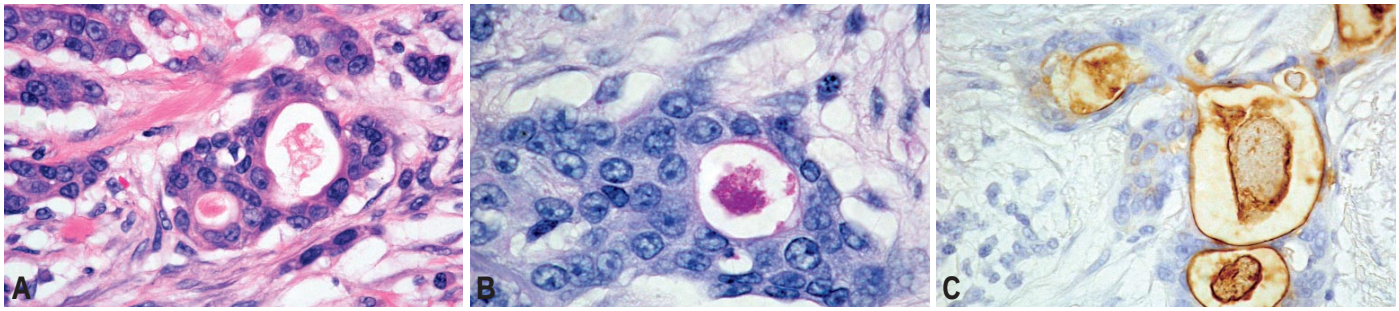

Fig. 1.20 Adenosquamous carcinoma. **A** Well formed glandular structures containing mucinous secretion in the glandular area of the tumour. **B** PAS stain. Intracytoplasmic targetoid PAS positive and diastase sensitive globules in the glandular areas of the tumour. **C** CEA immunohistochemical stain. Positive luminal staining in glandular structures.

cell carcinoma has foamy cytoplasmic mucin globules with displacement of the cell nucleus but no glands. Microcystic adnexal carcinoma (syringomatous carcinoma, sclerosing sweat duct carcinoma) shows a more ductal appearance with prominent tubular structures but no mucin secretion. Metastatic adenosquamous carcinoma from other primary sites such as the lung, salivary gland, female genital tract should also be excluded.

Prognosis and predictive factors

The tumours usually follow an aggressive course with the capacity for metastasis and local recurrence. Early superficially located tumours tend to have a better prognosis.

Bowen disease

G.F. Kao
R. Cerio
R. Salom
S. Pala

Definition
Bowen disease (BD) is a form of squamous cell carcinoma in situ. It is a distinct clinicopathologic entity of the skin and mucocutaneous junction.

ICD-O code 8081/2

Synonyms
Squamous cell carcinoma in situ (SCCIS), intraepidermal carcinoma, bowenoid dysplasia, bowenoid squamous carcinoma in situ (BSCIS), vulvar intraepithelial neoplasia (VIN III).
The terms bowenoid dysplasia and BSCIS are customarily applied to cutaneous and mucocutaneous lesions of the male and female external genitalia. BD is no longer used in gynaecological pathology. It has been replaced by the concept of vulvar intraepithelial neoplasia (VIN). The degree of epithelial atypia seen in BD corresponds to VIN, grade III (VIN III) {362,1580}.

Epidemiology
Bowen disease occurs predominantly in fair-complexioned Caucasian men, but both sexes are affected. One in five patients (20%) is a woman. The disease commonly affects patients in the 6-8th decades of life. However, the average age at onset of the disease is 48 years, and the average age at first biopsy is 55 years. Both exposed and non-exposed skin sites are equally affected. The disease uncommonly affects black skin, in which it is found more commonly on non-sun-exposed areas.

Etiology
The exact underlying cause of BD remains unclear, although multiple factors are likely to be responsible for it. Many lesions arise without an apparent cause. However, it is known that chronic sun damage disrupts normal keratinocytic maturation, causes mutation of the tumour suppressor gene protein (TP53) {375,1075}, and results in the development of keratinocytic atypia as seen in lesions of BD. The predilection for anatomic sites affected by BD on sun-exposed glabrous skin and lesions being reported more commonly in patients with a history of PUVA or UVB therapy {1410}, attest to the critical role of causal relationship between UV damage and BD. Ingestion of inorganic arsenic may play a role, as lesions of arsenical keratosis (As-K) may display identical histopathologic features to BD. A large number of cases of As-K with associated invasive carcinoma have been reported in a rural population using well water containing a high concentration of inorganic arsenic {2567,2572}. Human papillomavirus (HPV) genomes have been demonstrated by in situ hybridization in the nuclei of keratinocytes in the stratum malpighii and stratum corneum of the BD lesions. HPV types 16 and 18 have been linked to lesions of genital BD and non-condylomatous genital warts, i.e., bowenoid papulosis {1098}. HPV is less commonly associated with nongenital BD. HPV types 15 and 16 have been identified in some cases of BD of the distal extremities. Evidence of other papillomavirus types, including HPV31, 54, 58, 61, 62 and 73, have also been identified in some cases of BD. Aberrations in local and systemic immunity, trauma, chronic irritation, mutagenic factors, and tobacco exposure are other possible etiologies of BD.

Localization
Based upon a large series of 1001 biopsy-proven BD in Australia, most lesions occurred on a sun-exposed glabrous area {1315}. About one-third (33%) of the lesions occured in the head and neck areas, especially the face. Men had predominance of lesions on the scalp and ears, whereas women had a predominant involvement of the legs and cheeks. BD rarely affects the nail bed and periungual area {2070}.

Clinical features
The classic appearance of cutaneous BD is a single or multiple erythematous, rounded to irregular, lenticular, scaly, keratotic, fissured, crusty, nodular, eroded, pigmented patches or plaques. The plaques are devoid of hair, and usually appear sharply demarcated from the surrounding unaffected skin. Areas of normal-appearing skin may occur within the boundaries of larger lesions of BD. The plaques vary from 1-5 cm in overall dimensions. In intertriginous areas, BD may appear as moist patches without scale. In anogenital locations, the lesions appear polypoid or verrucoid, frequently pigmented. Erythroplasia of Queyrat (EPQ) presents as an asymptomatic,

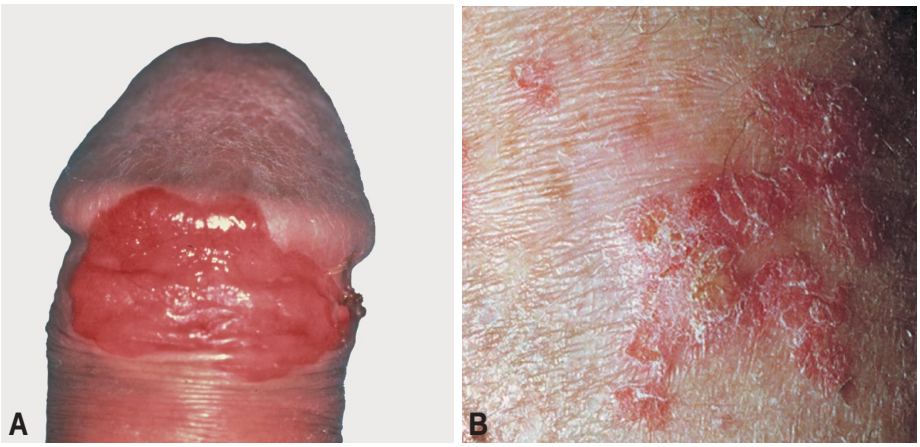

Fig. 1.21 **A** Bowen disease. Sharply circumscribed, bright red plaque of erythroplasia of Queyrat (EPQ). **B** Bowen disease. Erythematous, scaly, fissuring plaques of BD on lower leg of a middle-aged woman.

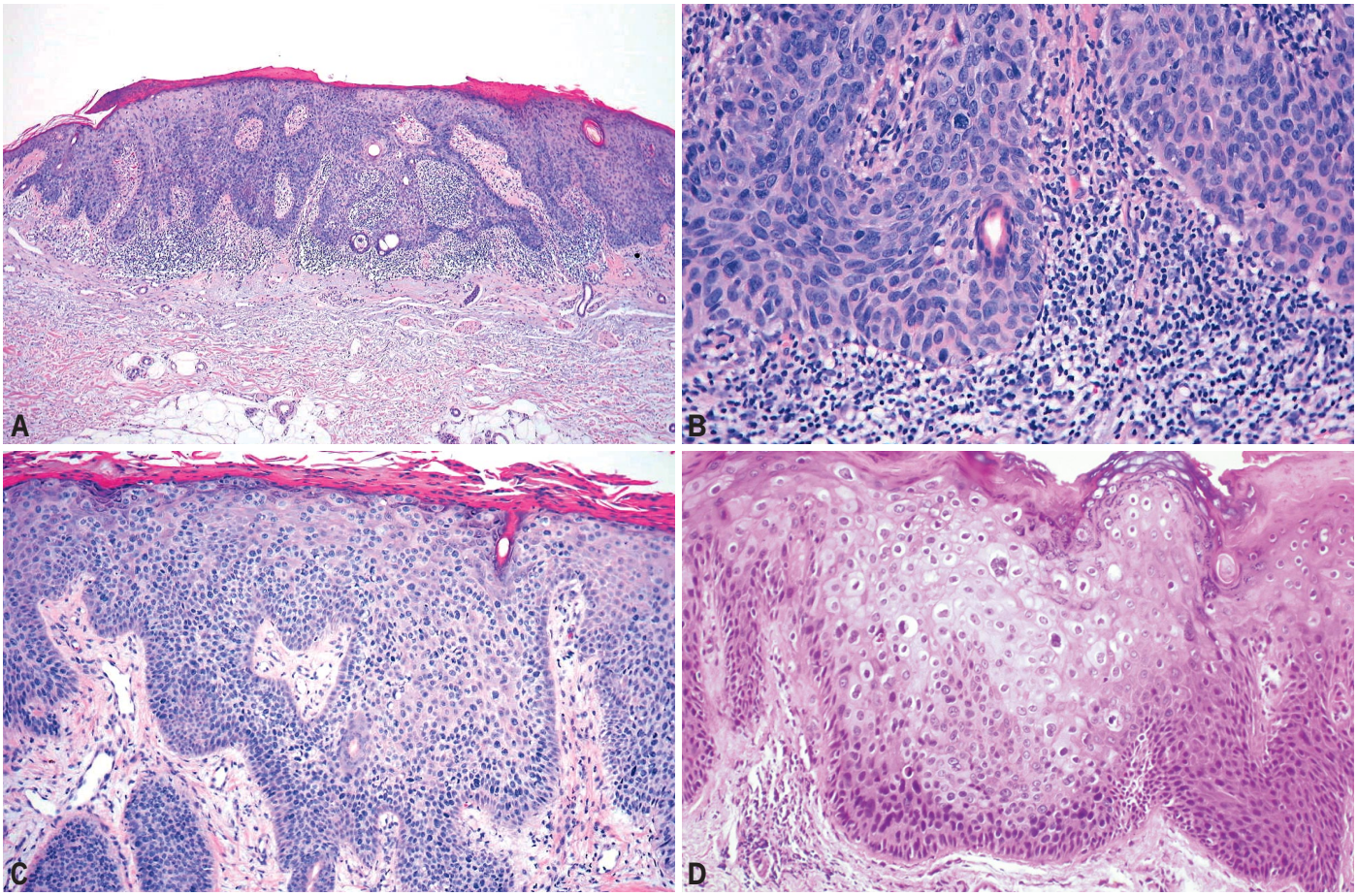

Fig. 1.22 Bowen disease (BD). **A** Low-power photomicrograph of BD. Note hyperkeratosis, full-thickness of epidermal atypia, extensive pilar epithelial involvement, and a lichenoid upper dermal mixed chronic inflammatory infiltrate. **B** Atypical keratinocytes encircle an acrosyringium. **C** Atypical squamous cells extend along acrosyringia. **D** Prominent vacuolated atypical cells, focally mimicking koilocytotic change and pagetoid appearance seen in BD.

bright red, velvety to shiny, sharply circumscribed plaque. The mucocutaneous junction of the glans penis, coronal sulcus, or undersurface of the foreskin is involved, and lesions are usually found in older, uncircumcised men.

There are two clinical variants of BD: those involving glabrous skin, and those of the anogenital area. On the glabrous skin, BD manifests as asymptomatic, slowly enlarging, scaly patches or plaques. The average duration of the lesion is 6.4 years. Plaques of BD enlarge slowly, and expand centrifugally, sometimes for decades. Anogenital BD involves the mucocutaneous junction and adjacent mucosa. If untreated, 5-8% of patients may develop invasive carcinoma. The invasive carcinomas are larger (up to 15 cm), rapidly growing tumours that occur in pre-existing scaly plaques {1203}.

The clinical entity of erythroplasia of Queyrat (EPQ) is regarded as BD of the glans penis. Such lesions have a greater potential for developing into invasive carcinoma than does BD involving glabrous skin {875}. Although evidence for the association of BD and internal malignancies is reported in earlier studies, more recent population-based cohort studies do not confirm the link {484}.

Histopathology

The typical low-power microscopic features of BD are hyperkeratosis, parakeratosis, hypo- or hypergranulosis, plaque-like acanthosis with increased cellularity, and a chronic inflammatory infiltrate in the upper corium. The epidermis exhibits loss of normal polarity and progression of normal surface keratinocytic maturation. A “windblown” appearance of crowding of atypical keratinocytes, with hyperchromatism, pale-staining to vacuolated cells, occasional multinucleated cells, individual cell keratinization (dyskeratosis), and abnormal mitoses are noted. These changes are confined by an intact dermoepidermal basement membrane. Lesions of BD from hair-bearing areas invariably demonstrate involvement of the pilar acrotrichium, infundibulum, and sebaceous gland. In some lesions, prominent vacuolated atypical cells focally mimic koilocytotic viral cytopathic change and exhibit a pagetoid appearance. The acrosyringium is occasionally involved. An inflammatory infiltrate of lymphocytes, macrophages, and plasma cells is seen in the upper dermis. Capillary ectasia is commonly noted. Prominent solar elastosis is also present in lesions on sun-exposed skin. An invasive carcinoma arising in BD shows variable histologic differentiation, with squamous, basosquamous, pilar, sebaceous {1120}, pilosebaceous, poorly-differentiated, and occasionally ductal features {1203,2016}. The atypical vacuolated keratinocytes are negative for cytoplasmic mucin; some, however, contain

glycogen. Melanin pigment may be present in the atypical cells, and in the pigmented genital lesions, melanophages are numerous. The abnormal keratinizing cells are intensely reactive with glucose-6-phosphate dehydrogenase. Ultrastructural changes of BD include decrease in tonofilament-desmosomal attachments, aggregated tonofilaments and nuclear substance, and absence of keratohyaline granules {1204}.

Differential diagnosis
Bowenoid solar keratosis differs from BD by its clinically smaller size, exclusive location on sun-exposed skin, and presence of superficial keratinocytic maturation. Bowenoid papulosis is distinguished from BD by its clinical appearance of multiple papular to coalescing lesions on the anogenital areas, and the typical microscopic salt and pepper distribution of atypical keratinocytes and mitoses in the affected cutaneous and mucocutaneous lesions, as well as frequent HPV positive koilocytotic cells {1790}. The pagetoid variant of BD is sometimes difficult to distinguish from extramammary Paget disease. In the latter, mucicarmine, Cam 5.2 and CEA positive tumour cells are present in the epidermis, individually or in small nests, forming glandular structures at the dermoepidermal junction. These features are absent in BD. The vacuolated cells in BD contain glycogen and not mucin. In malignant melanoma in situ, the basilar keratinocytes are replaced by neoplastic melanocytes. The presence of intercellular bridges and prominent dyskeratotic keratinocytes are features favouring the diagnosis of BD. Melanoma cells do not contain cytokeratins of 54 and 66 kilodaltons (kd); the reverse applies with the cells in BD.

Histogenesis
It has been suggested that BD most likely originates from germinal cells of the pilar outer root sheath and the pluripotential epidermal cells of the acrotrichium. This concept is substantiated by the findings of various types of histologic differentiation in carcinoma arising in BD {1120,1203,2016}. Using immunohistochemical localization of keratins and involucrin, the atypical cells of BD exhibit a diversity of differentiation {1093}.

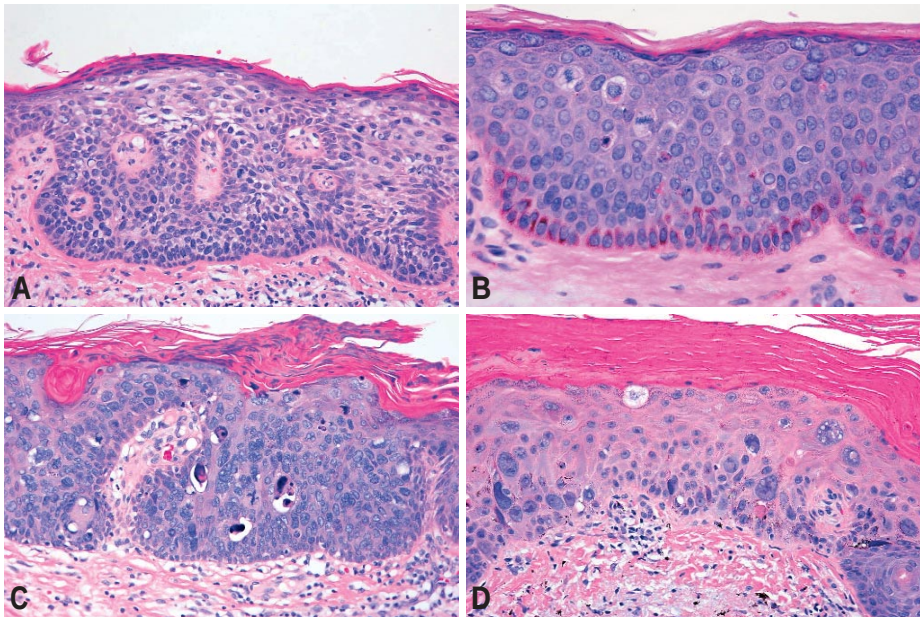

Fig. 1.23 Bowen disease. **A** Full thickness squamous cell atypia. **B** There is full thickness squamous cell atypia with apparent sparing of the basal keratinocytes and hyperpigmentation of the basal keratinocytes. **C** Full thickness squamous cell atypia with scattered bizzare keratinocytes. **D** Full thickness squamous cell atypia with marked nuclear pleomorphism.

Genetics
The atypical keratinocytes of BD contain large numbers of aneuploid cells {241}. Increased expression and mutation of TP53 observed in lesions of BD suggest that loss of normal TP53 tumour suppressor activity may be an important mechanism of oncogenesis in BD {375,1075, 1946}. Allelic deletion of one or more 9q chromosome markers has been detected in occasional lesions of BD. However, no deletion of 9p markers was seen {1866}. There have been no clonal chromosomal abnormalities by cytogenetic analysis of cell cultures from BD {1003}.

Prognosis and predictive factors
Surgical excision with complete removal may cure BD. The origin of BD from pilar outer root sheath cells at the sebaceous gland level explains in part the high recurrence rate, following treatment with superficial curettage and desiccation, topical fluorouracil, and X-ray. Invasive adnexal carcinoma may develop in untreated plaques of BD of prolonged duration following expansile growth. The metastatic rate in these uncommon tumours was 18% and fatality was observed in 10% of cases in a large case series {1203}.

Bowenoid papulosis

Definition
Bowenoid papulosis is a clinicopathological entity characterised by the presence on the genitalia of solitary or multiple verruca-like papules or plaques with histology resembling full thickness epidermal dysplasia as seen in Bowen disease.

Synonyms
Multicentric pigmented Bowen disease, multifocal indolent pigmented penile papules

Epidemiology
Bowenoid papulosis occurs mainly in young individuals and although uncommon the incidence is increasing. There is a male predominance.

Etiology
The etiopathogenesis of this condition almost certainly favours linkage to human papillomavirus infection particularly oncogenic types 16, 18, 33,35 and 39. DNA sequences have been identified by various workers {908,1737,2113}. Consequently in females there is a higher incidence of abnormal cervical/vaginal smears both in affected patients and in partners of men with penile lesions. Whilst controversies regarding the bio-

logical potential of bowenoid papulosis exist, with the possibility of invasive malignancy, in most cases the clinical course is benign and some lesions regress.

Localization
Bowenoid papulosis was first described as a condition affecting the groin {1438}. It was later defined {1305,2447} as an entity involving the genitalia or perigenital areas. Isolated cases of extragenital bowenoid papulosis have been described {902,1147}.

Clinical features
The lesions are usually asymptomatic with variable clinical presentation: multiple generally small, round fleshy papules, isolated or confluent (2.0-20 mm), with a smooth papillomatous surface, sometimes with desquamation resembling lichenoid or psoriasiform dermatoses. The colour of lesions can vary from pink to reddish-purple to brown / black.

Histopathology
The histological features demonstrate epidermal atypia ranging from partial to full thickness atypia similar to in situ squamous cell carcinoma i.e. Bowen disease. On the genitalia changes may be termed vulvar intraepithelial neoplasia (VIN) III or penile intraepithelial neoplasia (PIN) III by some pathologists {570}. There is loss of architecture. The basement membrane is intact. Mitoses are frequent, sometimes with abnormal forms often in metaphase. Dyskeratotic cells are also seen. Typical koilocytes are uncommon {908}. The stratum corneum and granular cell layer often contain small inclusion - like bodies which are deeply basophilic, rounded and surrounded by a halo.

Differential diagnosis
The basophilic bodies, together with the numerous metaphase mitoses, are the features which suggest a diagnosis of bowenoid papulosis rather than Bowen disease itself.

Histogenesis
A study based on histomorphology and DNA ploidy analysis has suggested that bowenoid papulosis is a form of low-grade squamous cell carcinoma in situ {269}. Electron microscopy has shown structures resembling viral particles {1274,1790} within the granular layer.

Somatic genetics
Many of the atypical keratinocytes of bowenoid papulosis not unlike Bowen disease, contain large numbers of aneuploid cells. Increased expression and mutation of TP53 observed in lesions suggest that loss of normal TP53 tumour suppressor activity is likely to be an important mechanism of oncogenesis in bowenoid papulosis. To date, there have been no clonal chromosomal abnormalities by cytogenetic analysis of cell cultures from bowenoid papulosis.

Prognosis and predictive factors
Bowenoid papulosis appears in many cases to remain benign {1790} and spontaneous regression has occasionally occurred; however, close follow up is essential.

Actinic keratosis

C. James
R.I. Crawford
M. Martinka
R. Marks

Definition
A common intraepidermal neoplasm of sun-damaged skin characterized by variable atypia of keratinocytes.

Synonyms
Solar keratosis

Epidemiology
Actinic keratoses (AK's) usually present in older individuals. The fair-skinned, the freckled and those who do not tan easily are at increased risk. Lesions have developed in areas of vitiligo {2023, 2564}. The rate is higher in men because of greater sun exposure {1049}. In the Australian Caucasian population, AK's are discovered in 40-60% of individuals over 40 {789,1515}, rising to 80% in the seventh decade {1049}. Patients with Rothmund-Thompson, Cockayne and Bloom syndromes and xeroderma pigmentosum are at increased risk {791}.

Etiology
Both cumulative and intermittent sunlight exposure is implicated {790}. Ultraviolet B (UVB) is the most harmful, but a supplemental effect of ultraviolet A (UVA) is demonstrated {694}. AK's are increased after PUVA therapy {11}. UVB induces DNA thymidine dimer formation, which can target TP53, with impaired apoptosis

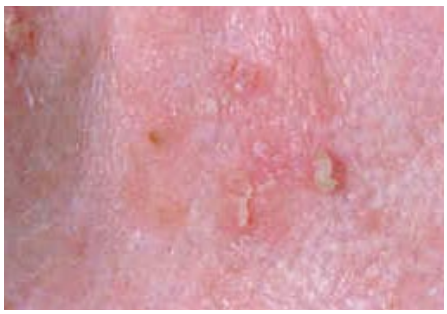

Fig. 1.24 Actinic keratosis on the face, presenting as a group of irregularly shaped small papules.

of damaged keratinocytes in cells with two TP53 mutations {1150,1396,1696, 2602}. Clonal proliferations of these cells form actinic keratoses and after further genetic damage, invasive SCC may develop. Ultraviolet light can act as an initiator and promoter of carcinogenesis {2602}. Epidermodysplasia verruciformis–associated HPV types have been discovered in AK's after renal transplantation {2354}.

Localization
Sun-exposed areas are involved: face, ears, balding scalp, dorsal hands, forearms and lateral neck {2218}.

Clinical features
Patients commonly present with multiple persistent, asymptomatic erythematous lesions. Most measure less than 1 cm and are hyperkeratotic. Atrophic lesions predominate on the face. Thickening and tenderness may indicate the development of invasive carcinoma.

Macroscopy
Most lesions are circumscribed <1cm scaly macules or slightly elevated papules or plaques, ranging from erythematous to grey-brown with adherent yellow-brown scale. Some are larger, more irregularly shaped and pigmented {1128}, whilst others, particularly on the dorsal hands and forearms, are hyperkeratotic or verrucous {244}. A keratin horn may be produced.

Histopathology
Six types of AK are described: hypertrophic, atrophic, bowenoid, acantholytic, pigmented and lichenoid {233,1446}. Most lesions reveal parakeratosis and hypogranulosis. Disordered keratinocyte maturation with cytologic atypia is present, including nuclear enlargement, hyperchromasia, pleomorphism, nucleolar prominence, mitotic activity, dyskeratosis and cytoplasmic pallor. Grading as Keratinocyte Intraepidermal Neoplasia (KIN I, II and III) in a manner similar to that used for the uterine cervix {506} has

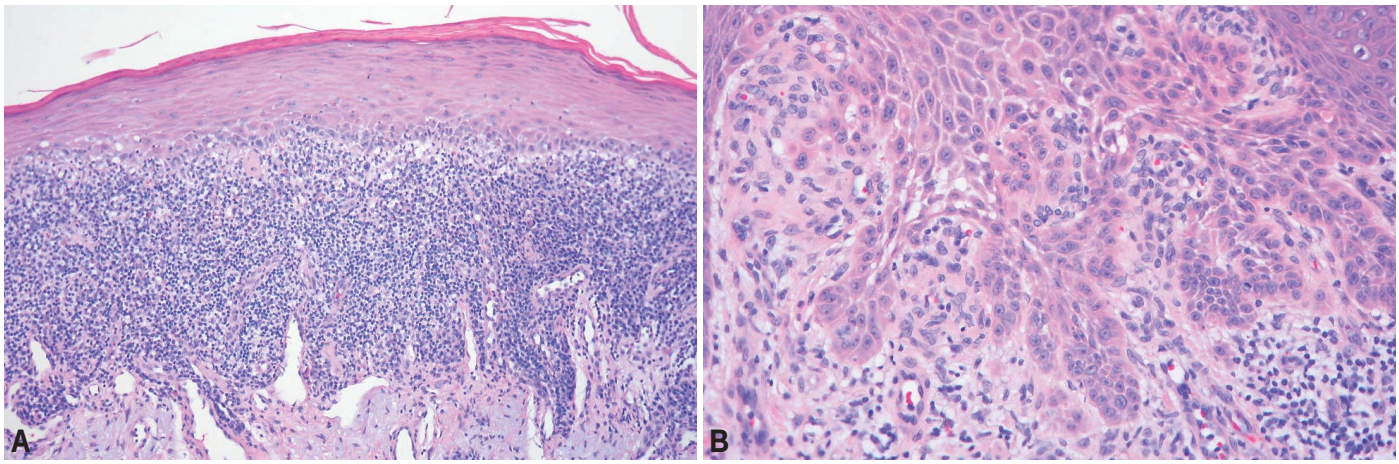

Fig. 1.25 Actinic keratosis. **A** There is focal parakeratosis, acanthosis and basal squamous atypia overlying a dense lichenoid inflammatory infiltrate. **B** Actinic keratosis. There are elongated rete ridges with squamous cell atypia and focal acantholysis.

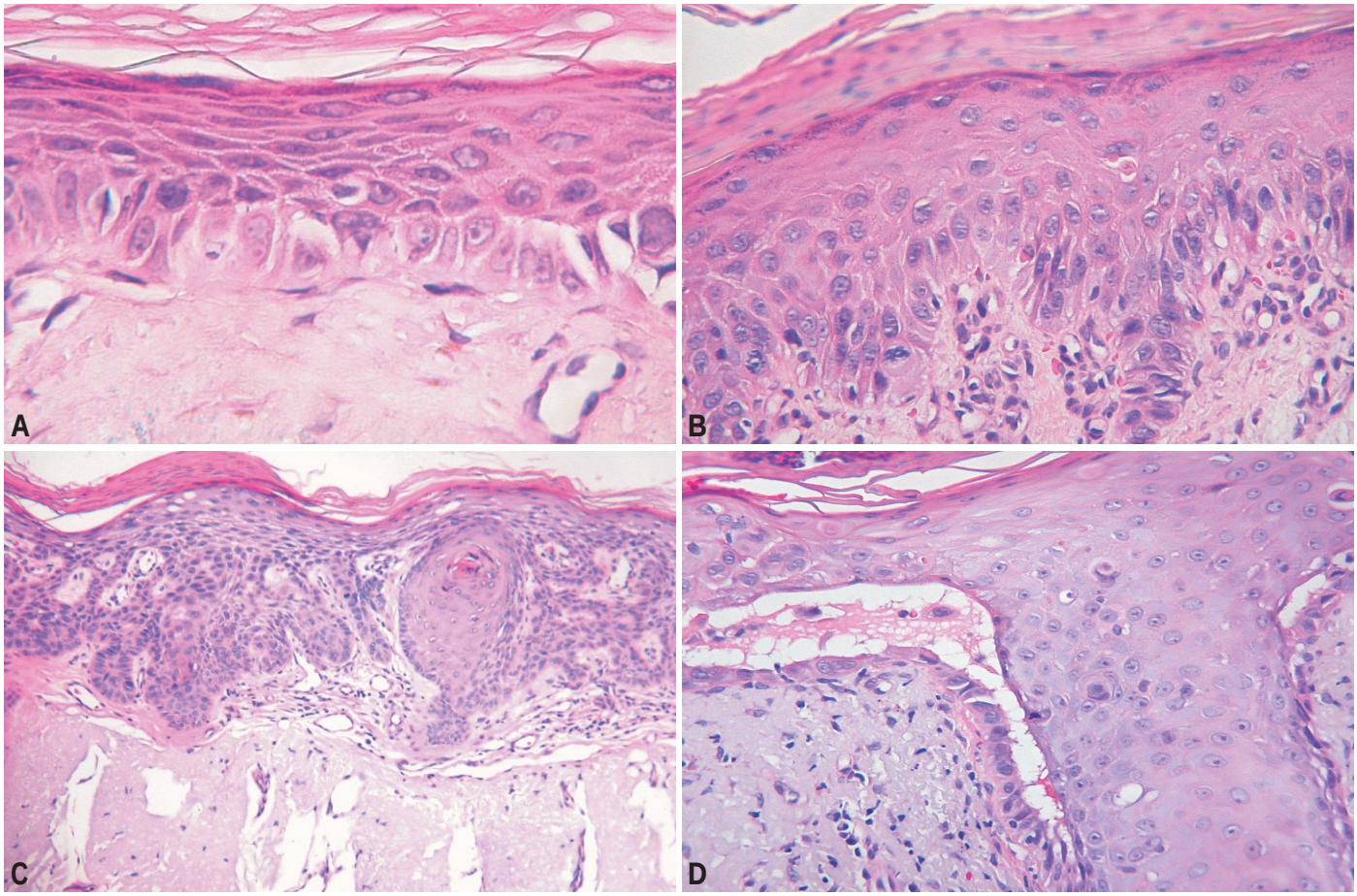

Fig.1.26 Actinic keratosis. **A** Atrophic variant with atypical basal keratinocytes and focal parakeratosis. **B** Medium power magnification shows keratinocyte atypia in the stratum malpighii with a loss of polarity, nuclear enlargement, hyperchromasia, dyskeratosis, increased mitotic activity and parakeratosis. **C** Downward prolongations and buds of atypical squamous cells does not indicate true stromal invasion. Note severe dermal solar elastosis and telangiectasia. **D** Acantholytic variant with suprabasal acantholysis, squamous atypia, dyskeratosis and superficial follicular involvement.

been proposed, however, invasive SCC commonly arises from KIN I or II.

Lesions in which impaired maturation and atypia appear to involve the full epidermal thickness have been labelled "bowenoid actinic keratoses" (BAK) {1128}. Multinucleate keratinocytes and a verrucous architecture, can be seen in AKs in the setting of immunosuppression {294,1856}.

The abnormal keratinization often involves the epidermis between spared acrotrichia and acrosyringia, which in contrast retain columns of normal keratinization. Some lesions show spread into the infundibular and isthmic segments of follicles or less commonly along eccrine ducts {1835}. Dermal changes include solar elastosis, an infiltrate of lymphocytes and plasma cells and increased vascularity. Inflammation is most frequent in lesions of the head and neck, particularly the lips.

The *hypertrophic* variant shows acanthosis, papillomatosis and conspicuous hyperkeratosis with alternating parakeratosis {244}. Elongation of rete ridges, dilated vessels and vertically oriented collagen bundles in the papillary dermis suggest superimposed lichenification.

The *atrophic* AK variant is easily misdiagnosed if the basal keratinocytic atypia in a parakeratotic epidermis devoid of rete ridges is missed. Budding of the basal epidermis and extension of atypia into adnexae are common.

The *bowenoid* variant is difficult to differentiate from Bowen disease. Whilst some claim they are identical, others emphasize the lack of full thickness atypia, less defined edge, follicular sparing and acrosyringeal involvement in BAK {1128,2476}.

The *acantholytic* variant reveals clefting, usually suprabasal, with varying acantholysis and dyskeratosis {1409}. Keratinocyte atypia aids distinction from acantholytic dermatoses. Downward extensions of the basal epidermis can induce pseudoducts, and acantholysis may spread along appendages.

The *pigmented* variant shows increased melanization of atypical keratinocytes and dermal macrophages {1128}.

The *lichenoid* variant has keratinocyte apoptosis and vacuolation, exocytotic lymphocytes and a band-like superficial dermal lymphocytic infiltrate including colloid bodies {2318}. The epidermis in early lesions is acanthotic, but more advanced regressing lesions are atrophic with pigment incontinence. Keratinocyte atypia exceeding that expected in a reactive process differentiates this lesion from benign lichenoid keratosis.

The confident identification of early SCC in an AK can be difficult {1158}. Detachment of individual irregular aggre-

gates of keratinocytes from the epidermis, keratin pearl formation and extension of atypical squamous cells into the reticular dermis are helpful {1158,2476}

Immunoprofile
Keratin and involucrin distribution is similar to normal epidermis {1093} whilst CD95 (Fas) is lost in two thirds of AK {741} and retinoid receptors are reduced {2554}. Expression of E-cadherin/catenin and TP53 increases in the progression to invasive SCC {1770,2170}.

Genetics
There is a 2-fold risk of AK in an Australian Caucasian population carrying the glutathione-S-transferase null genotype {386}, further increased by fair skin and an inability to tan.
Around 50% of AK's show TP53 mutations {1696,2602} and over-expression of cyclin D1 {2235} whilst independent activation of HRAS is identified in 16% {2235,2307}.
The majority of TP53 mutations involve single cytosine to thymine substitution {1396,1696,2307}. Progression of AK into invasive SCC may involve deletion of the 9p21 region of the p16 (CDKN2A) tumour suppressor gene {1653}.
Loss of heterozygosity (LOH) at four or more loci has been demonstrated in >50% of AK's in a UK Caucasian population {1913} and in just under 20% of lesions in a Japanese group {1350}. PCR microsatellite analysis has exposed loss on 17p(64%), 13q(52%), 17q(46%), 9p(39%), 3p(31%) and 9q(22%) {1914}. The higher rate of LOH in AK than invasive SCC could reflect the low progression rate of the former {1350}.
69% of AK were aneuploid in one image analysis DNA-cytometry study {241}. Recurrent chromosomal changes are numerical (+7,+20) and structural, involving the distal long arm of chromosome 4,1p31,3p13 and the centromeric region of chromosome 3 {1143}.

Prognosis and predictive factors
Untreated AK have been reported to develop into invasive SCC in 8-20% of patients {838}. AK's are also risk markers for basal cell carcinoma and melanoma {2023}. Individual AK's can however be stable for many years, and may regress after sun protection. One estimate has suggested a rate of malignant transformation less than 0.1% yearly {1516, 1517}. Older patients with multiple lesions followed over 10 years demonstrate a lifetime risk of progression between 6-10% {641} whilst 14% of patients with >10 AK's develop invasive SCC within 5 years {1639}. Sixty percent of invasive SCC's have been proposed to develop from AK's and, more recently, contiguous AK has been identified in 82.4-97% of SCC {1085,1517,1627}. Clinically hypertrophic lesions reveal invasive SCC in 36% {2290}.
Some classify AK as a type of SCC {791,994,1442} rather than a precursor. It cannot however be proven that AK inescapably progresses to invasive SCC. The hypothesis that AK requires further genetic aberrations before the expression of clinical malignancy, is plausible {1810}.
Immune responses and adjacent normal keratinocytes modulate the behaviour of AK {791}. Metastases from invasive carcinomas arising in AK are infrequent if the lip is excluded, occurring in 0.5-3% of such carcinomas {1459,1630}.

Arsenical keratosis

Definition
Arsenical keratosis is a precancerous lesion occurring in patients exposed (therapeutic, environmental or occupational) to arsenic {2109}. This is a clinicopathological diagnosis. Arsenic is concentrated in a variety of tissues, including skin, hair, and nails {49,421,2007, 2109}.

Epidemiology
Lesions may occur after a latent period of 2 years, but usually take 20-30 years to manifest {2568}. A study of 262 exposed individuals revealed characteristic keratoses of the palms and soles in over 40% {49}. Other skin lesions include melanosis, Bowen disease, squamous cell and basal cell carcinoma {421,2007, 2109}. Visceral cancers, particularly involving the lung, and genitourinary tract can also occur {49,421,2007,2109}. There is a high arsenic content in some drinking waters and naturopathic medicines {1823,2007,2109}.

Clinical features
Arsenical keratoses begin as yellowish verrucous papules, 4-10 mm in diameter. These typically occur on thenar eminences, lateral borders of palms, base or lateral surfaces of fingers, soles, heels and toes {49}. A combination of mela-

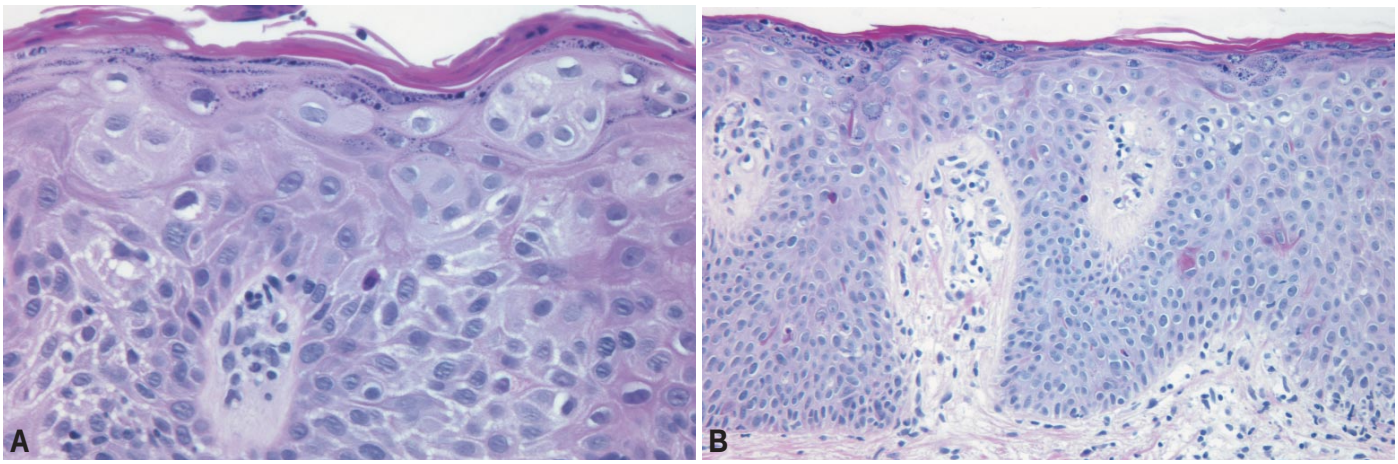

Fig. 1.27 Arsenical keratosis. **A** Arsenical keratosis with vacuolation of the keratinocytes. **B** Arsenical keratosis showing acanthotic epidermis, some vacuolation of the keratinocytes and dysplasia.

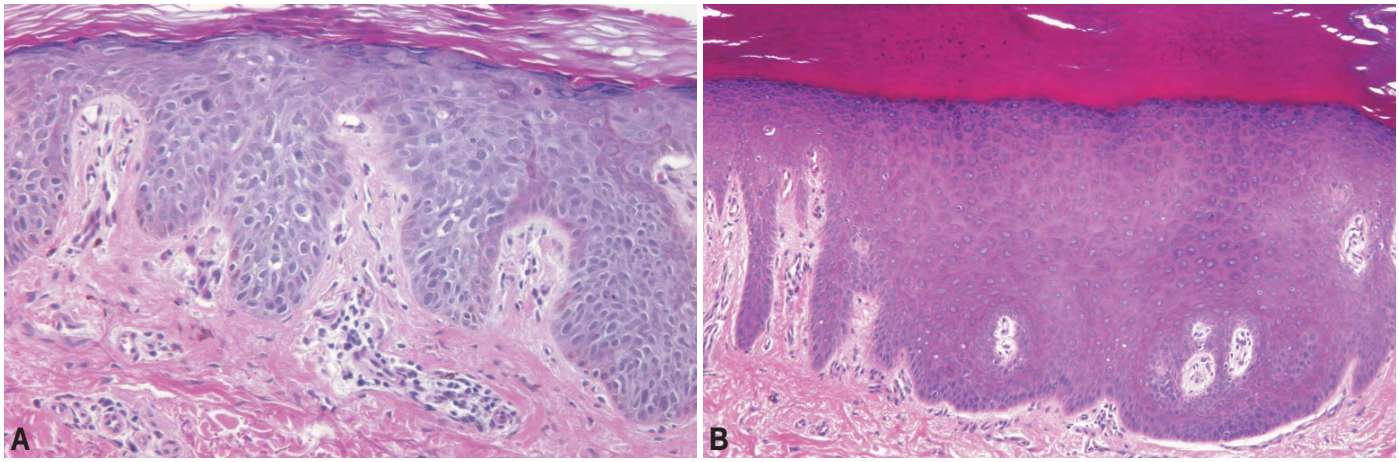

Fig. 1.28 Arsenical keratosis. **A** .Arsenical keratosis with full thickness dysplasia, resembling Bowen disease. **B** Hyperkeratotic type.

nosis and multiple keratoses in non-sun-exposed areas in adults is highly suggestive of chronic arsenic exposure {2007}.

Histopathology
A spectrum of histological appearances exists {49,421,2007,2109}. Lesions may show compact hyperkeratosis, acanthosis, papillomatosis, hypertrophic actinic keratosis-like lesions and a pattern resembling seborrhoeic keratosis {2007, 2109,2568}. Vacuolated cells in the Malpighian layer suggest arsenical keratosis, but this is not a reliable criterion. Arsenical keratoses may spare adnexae, similar to solar-related keratoses {2109}. Bowenoid arsenical keratoses may display vacuolated, dyskeratotic cells with abnormal mitoses and multinucleated giant cells {1823}. Arsenical-induced pigmentation comprises melanosis and dermal arsenic deposition {49}.

Histogenesis
The exact nature of arsenical carcinogenesis is unclear.
Arsenic and its metabolites are shown to cause chromosomal abnormalities and gene amplification {421,1823,2109}. Human papillomavirus may be a co-factor in the pathogenesis {820}.

PUVA keratosis

Definition
PUVA keratosis is a form of keratosis that arises in response to PUVA therapy.

Epidemiology
There are no detailed studies on the true frequency of actinic keratoses attributable solely to PUVA, but estimates have varied from 2-5% {11,1057}. There are long term epidemiological data indicating increased risk of squamous cell carcinoma in patients on high dose PUVA, recorded as 300 treatments or more {2265}. More recently, phototherapy using a narrow band of ultra-violet radiation in the UVB range has been used with increasing frequency, substituting for PUVA therapy in a substantial proportion of patients {2264}. There are no long-term data published as yet on the risk of actinic keratoses and squamous cell carcinoma in patients receiving narrow band UVB phototherapy.

Etiology
PUVA is a photochemotherapy using either an oral or topical psoralen product in association with long-wave ultraviolet radiation (UVA) {374}. This treatment is locally immunosuppressive, and delivers high doses of UVA to epidermal keratinocytes. PUVA is used in the treatment of patients with psoriasis and other disorders.
Patients treated with long-term PUVA therapy are at increased risk for development of actinic keratoses and squamous cell carcinoma.

Clinical features
PUVA keratoses resemble actinic keratoses. They occur on PUVA-treated skin.

Histopathology
PUVA keratoses are said to have less keratinocytic atypia than sunlight-induced actinic keratoses {2417}.

Verrucas

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Definition

Verrucas or condyloma are common, contagious, epithelial tumours caused by human papillomaviruses (HPV).

Synonyms

Verrucae vulgares (common warts); verrucae palmares (deep palmar or hand warts); verrucae plantares (deep foot warts, myrmecia); superficial plantar warts (mosaic warts); verrucae planae (plane warts, flat warts); condylomata acuminata (genital warts); condylomata plana (flat cervical condylomas, plane condylomas).

Epidemiology

HPVs are widespread in nature and the prevalence of cutaneous warts is up to 10% in children 2-12 years old, occurring with equal frequency in both sexes and regressing spontaneously in 1-2 years {1282}. HPV infection of the lower genital tract is one of the most common sexually transmitted diseases among adolescents and adults. Most benign genital warts resolve spontaneously and are usually caused by HPV types 6 and 11, which are considered low-risk types as they are rarely found in high-grade genital dysplasias and almost never in invasive cancer. However, persistent infection with high-risk types, predominantly HPV-16 and 18, represents the most important risk factor for development of anogenital malignancies and their precursors, squamous intraepithelial lesions {288}. HPV infection occurs by direct contact with individuals who harbour clinical or subclinical HPV-associated lesions, or indirectly via contaminated surfaces and objects. Autoinnoculation from the lesion to surrounding skin is frequently observed {1282,1641}. Impaired cell-mediated immunity is associated with markedly increased incidence of viral warts, for example after organ transplantation, HIV infection, chronic lymphocytic leukaemia and lymphoma {1641}.

Table 1.01
Clinical manifestations and associated HPV types

Skin lesions	Frequently detected HPV	Less frequently detected
Common, palmar, plantar, mosaic	1,2,4	26,27,29,41,57,60,63,65
Flat warts	3,10	28,29
Butcher's warts	2,7	1,3,4,10,28
Epidermodysplasia verruciformis	3,5,8,10	9,12,14,15,17,19-25,36-38, 46,47,49,50
EV-squamous cell carcinoma	5,8	14,17,20,47
Periungual SCC	16	34,35
Other SCCs	EV HPV types	Other cutaneous types
Mucosal lesions		
Condyloma acuminata	6,11	42-44,54,55,70, 2,27,57
High grade intraepithelial neoplasia (including cervical tumours, bowenoid papulosis)	16,18	31,33-35,39,40,51-59,61,62
Buschke-Lowenstein tumours	6,11	
Recurrent respiratory papillomatosis, conjunctival papillomas	6,11	
Focal epithelial hyperplasia (Heck's disease)	13,32	

Etiology

Verrucas are caused human papillomaviruses (HPV), a large family of DNA viruses which are epitheliotropic and induce benign and malignant epithelial tumours in skin and mucosa. The definition of an HPV type is based upon nucleotide sequence homology; more than 95 HPV types have been fully characterized to date, and additional partial DNA sequences have been obtained indicating the existence of at least 130 HPV genotypes {188,605,1738}.

HPV structure and lifecycle {2283, 2608,2609}: HPVs are 55 nm diameter, non-enveloped, double-stranded DNA viruses. The icosohedral capsid surrounds the viral genome which is approximately 8kb in length and is composed of the upstream regulatory region containing the origin of replication and control elements for transcription and replication, the early region containing the open reading frames for viral genes that are principally expressed early in the papillomavirus lifecycle (E1, E2, E4, E5, E6, E7), and the late region encoding the viral capsid proteins (L1, L2). Productive infection and induction of hyperproliferation are initiated when the virus enters proliferating basal epithelial cells, and this requires abrasion or other minor trauma to the epithelium. The HPV lifecycle is only completed in fully differentiated squamous epithelia since the programme of viral gene expression is intimately linked to the differentiation state of keratinocytes. HPV does not encode

the enzymes required for transcription or replication of viral DNA and therefore is entirely dependent on subverting cellular proteins for these functions. In particular, in HPV types 16 and 18, proteins E6 and E7 promote continued cell cycling of suprabasal epidermal cells by abrogation of the functions of TP53 and pRb respectively. HPV genomes are thereby amplified to high levels during vegetative viral replication for assembly into infectious virions after encapsulation by L1 and L2 proteins in the granular layer and above. Virus assembly does not lyse keratinocytes, but rather the infectious virus is shed with desquamating cornified cells, and viral release is facilitated by disruption of the keratinocyte intracellular filamentous network by viral E4 proteins.

Host immune response {2246,2608}: Persistent papillomavirus infections are common, indicating that HPVs have evolved mechanisms to evade immune surveillance. There is no viraemic phase, low levels of viral proteins are expressed in the basal cell layer, and extensive virion production only occurs in the more immunologically privileged terminally differentiated layers. However, a successful immune response is eventually generated in most cases, since two thirds of cutaneous warts regress spontaneously within 2 years and multifocal lesions often regress concomitantly. Cell mediated immune responses appear to be primarily responsible.

Localization

Warts can occur on any skin or mucosal surface. Certain HPV subtypes cause specific kinds of warts and show special affinity for particular body locations. Subtypes causing common warts are found on the hands, fingers, and palms. Periungual subtypes are often seen in nail biters. Verruca plantaris is seen on the sole of the feet. Condylomata acuminata lesions (genital HPV infection) appear on the vulva, cervix, perineum, anus, or penis. Scrotal condylomata are very rare and only seen in 1% of HIV positive males.

Table 1.02
Correlation between cytopathological changes of verrucas and causal HPV types

Clinical manifestation	HPV types[a]	Epidermal changes[b]	Cytopathic effect (location)
Verruca vulgaris			
	2	Prominent	Eccentric nucleus; condensed heterogeneous keratohyaline granules (granular)
	4	Prominent; endophytic	Large, vacuolated keratinocytes with no keratohyaline granules and small, peripherally located, 'signet ring' nuclei (granular)
	7 (Butcher's wart)	Prominent	Central, small, shrunken nuclei within proliferating rete ridges (granular)
Palmo-plantar			
	1 (Myrmecia)	Prominent, endophytic	Vacuolated cells with large, eosinophilic keratohyaline granules forming ring-like and sickle-like figures. Basophilic nuclear inclusions (spinous, granular)
	60 (Ridged wart)	Acanthosis and mild papillomatosis; endophytic	Eosinophilic, homogeneous and solitary inclusions
	65 (Pigmented plantar wart)	Prominent; endophytic	Eosinophilic, homogeneous and solitary inclusions
	63	Prominent; endophytic	Intracytoplasmic, heavily stained keratohyaline material with filamentous inclusions that encase the vacuolated nucleus
Verruca Plana	3	Subtle; no parakeratosis and basket-weave like appearance of stratum corneum	Central, pyknotic, strongly basophilic 'bird's eyes' nuclei (upper spinous and granular)
Epidermodysplasia verruciformis	5	Nests of large, clear cells; stratum corneum loose with basket-weave like appearance	Basophilic cytoplasm containing keratohyaline granules of various shapes and sizes; clear nucleoplasm (upper spinous and granular)
Condyloma acuminata	6,11	Marked acanthosis, some papillomatosis and hyperkeratosis	Less prominent vacuolisation of granular cells

[a] Most common associated HPV genotype
[b] Epidermal changes comprise papillomatosis, compact hyperkeratosis, focal parakeratosis, hypergranulosis, acanthosis.

Clinical features and correlation with viral genotyping
Cutaneous and mucosal HPV types form two distinct groups that infect skin or mucosa, although viral tropism is not absolute {605}. Clinical manifestations depend on the HPV type involved, the anatomical location and the immune status of the host {1282}.
Cutaneous infections: In general, classification of warts is based on morphology and anatomic localization and cutaneous warts have traditionally been classified as verruca vulgaris or common warts, palmoplantar warts, including superficial and deep types, verruca plana or plane warts and epidermodysplasia verruciformis (EV). Recent studies suggest that histological and clinical characteristics of warts are mainly determined by viral genotype, indicating that HPV typing may allow a more accurate classification. However, the use of highly sensitive PCR techniques for HPV detection and genotyping has highlighted the presence of a greater diversity of HPV types than was previously appreciated {975}. These individuals often harbour multiple HPV types, particularly epidermodysplasia-verruciformis (EV)-HPV types. These HPVs were previously thought to occur only in the context of the rare genodermatosis EV, characterised by infection with unusual, widespread, cutaneous warts and associated with increased risk of non-melanoma skin cancers harbouring EV-HPV types on ultraviolet radiation exposed sites {1492}. There is also mounting evidence that EV-HPV types play a cofactor role with UVR in NMSCs arising in immunosuppressed individuals {974}.
Mucosal infections: Over 25 HPV types are recognized to infect anogenital and aerodigestive mucosa {605}, and subclinical infections are more common than visible warts {1282}. Genital warts are generally caused by low-risk mucosal HPV types rather than the high-risk types associated with anogenital neoplasia {605}. Bowenoid papulosis (section 1.5.01) may clinically resemble genital warts, but histologically resembles squamous cell carcinoma in situ and contains high-risk HPV types. Giant condyloma acuminata (Buschke-Lowenstein tumour) may also resemble genital warts but is an anogenital verrucous carcinoma harbouring low -risk HPV types {2476}. Oral warts are also associated with HPV types 6 and 11 and focal epithelial hyperplasia (Heck's disease) resembling gingival, buccal and labial flat warts or condylomata usually harbours HPV 13 or 32 {2476}.

Verruca vulgaris

Definition
Verruca vulgaris is a benign, squamous papillomatous lesion caused by infection with the human papilloma virus (HPV).

Synonym
Common wart.

Epidemiology
Verruca vulgaris occurs predominantly in children and adolescents, although adults are also frequently infected. They have been found in up to 20% of school students {1262}. Clinically detectable verrucae develop from a few weeks to 18 months after inoculation {1691}.

Etiology
Common warts are preferentially associated with HPV-2, but they may also be caused by other types such as HPV-1, HPV-4 and HPV-7. In children, HPV-6 and/or HPV-11 are rarely found. Other HPV types have rarely been implicated, usually in immunosuppressed individuals {106}.

Localization
Common warts may be solitary or multiple, and they are usually found on exposed parts, particularly the fingers and on the dorsum of the hands.

Clinical features
They are hard, rough-surfaced papules that range in diameter from about 0.2:1.5-2.0 cm. New warts may sometimes form at sites of trauma (Koebner phenomenon).

Histopathology
Common warts show marked hyperkeratosis and acanthosis. There are outgrowths of epidermis presenting as slender spires in filiform warts or blunter digitate processes in other variants. Columns of parakeratosis overlie the papillomatous projections. There may be haemorrhage into these columns. Hypergranulosis is present where the cells contain coarse clumps of keratohyaline granules. Koilocytes (large vacuolated cells with small pyknotic nuclei) are present in the upper malpighian layer and the granular layer. Small amounts of keratohyalin may be present in the cytoplasm of these cells. There is often some inward turning of the elongated rete ridges at the edges of the lesion. Tricholemmal differentiation and squamous eddies may be seen in old warts. Dilated vessels are often found in the core of the papillomatous projections. A variable lymphocytic infiltrate is sometimes seen, and this may be lichenoid in presumptive regressing lesions.

Prognosis and predictive factors
Most warts are only a cosmetic problem. Rarely, Bowen disease or squamous cell carcinoma may develop in a common wart, usually in immunocompromised patients {1611}. Thrombosis of superficial vessels, haemorrhage and necrosis of the epidermis are rarely seen in regressing common warts.

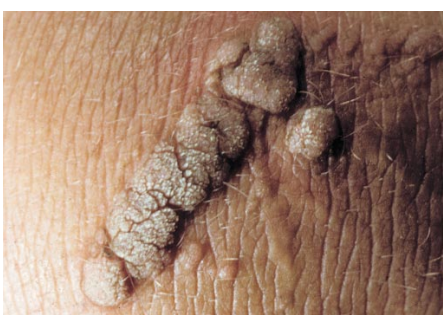

Fig. 1.29 Verruca vulgaris showing the Koebner phenomenon. Note the linear arrangement of the lesions as a consequence of scratching.

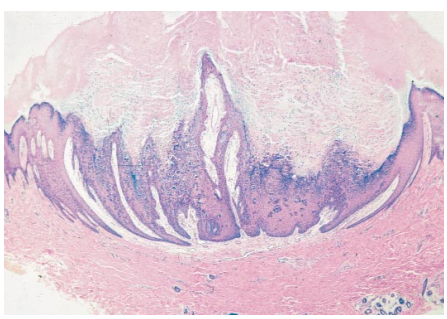

Fig. 1.30 Verruca vulgaris. There is hyperkeratosis, papillomatosis and interning of the elongated rete ridges.

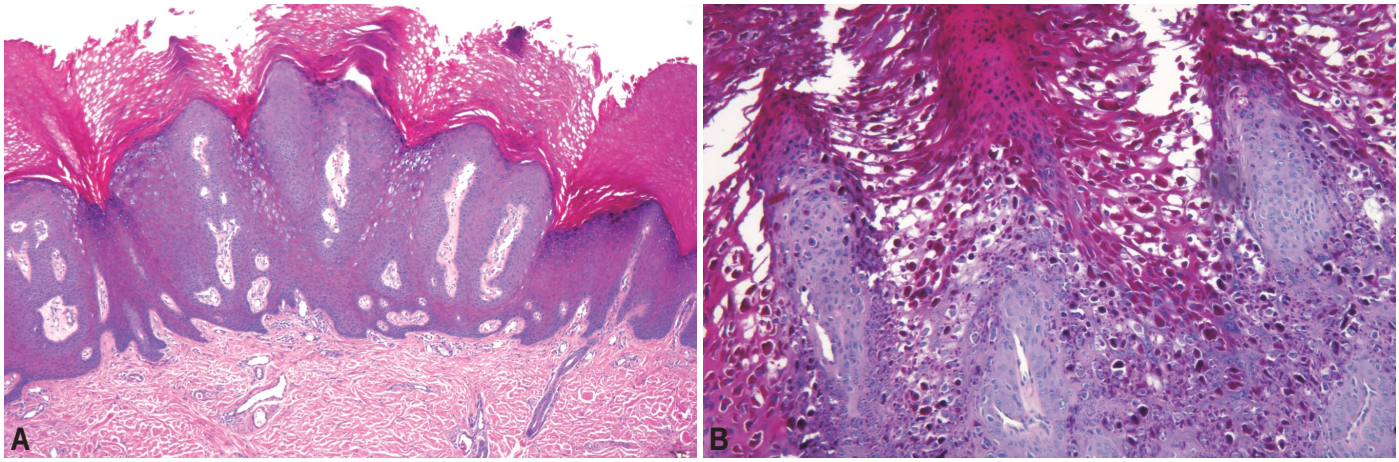

Fig. 1.31 Verruca plantaris. **A, B** Plantar wart. Note papillomatosis, acanthosis, hyperkeratosis, viral cytopathic changes.

Verruca plantaris

Definition

Verruca plantaris is a benign, human papillomavirus (HPV)-induced epithelial proliferation occurring on the sole of the foot. It is characterized by the formation of thick, hyperkeratotic lesions {505,648, 1214}.

Synonyms

Plantar wart, deep foot warts, myrmecia

Epidemiology

Plantar warts are most common in children and young adults; possibly because of immaturity of the immune system or sport-related repetitive microtrauma. They are most frequent over pressure points {505,648}. Particularly in children they may spontaneously regress within a few months, but in adults and immunocompromised patients they can persist for years. Rarely chronic lesions are associated with the development of verrucous carcinoma {594}.

Clinical features

Plantar warts are sharply defined, rounded lesions, with a rough keratotic surface, surrounded by a thickened horn. They tend to grow into the foot and are covered by black dots representing thrombosed capillaries {505,648,1214}. They do not retain the normal fingerprint lines of the feet, as calluses (corns) do. They often occur in multiples, and can be painful {1055,2390}. They are traditionally divided into the superficial warts (mosaic), which are ordinary verrucae, and deep warts (myrmecia). Several other variants have been recently described {1055,1214,1556}.

Histopathology

The mosaic–type shows acanthosis, papillomatosis, hyperkeratosis, vacuolated cells (koilocytes) in the upper Malpighian layer, vertical tiers of parakeratotic cells and clumped keratohyaline granules. Myrmecia are characterized by an endophytic proliferation of rete ridges covered by thickened keratin and prominent eosinophilic intracytoplasmic inclusions. The nuclei are retained in the stratum corneum and appear as basophilic round bodies surrounded by a clear halo {505,1055,1214}.

Regression of palmo-plantar warts is often associated with thrombosis of superficial vessels, haemorrhage and necrosis of the epidermis and a mixed inflammatory cell infiltrate.

Pathogenesis

HPV is the established cause. Correlations between the variety of wart and the HPV type are as follows:

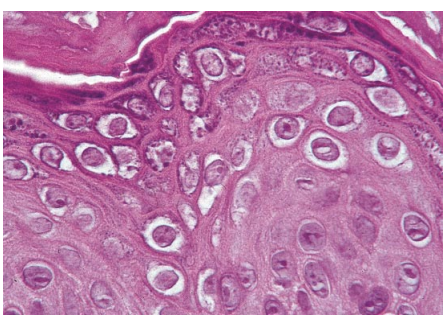

Fig. 1.34 Flat wart.

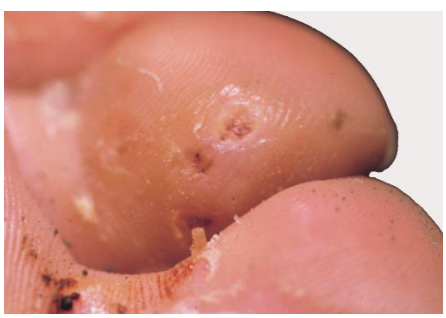

Fig. 1.32 Verruca plantaris on the volar surface of the toe. Clinically, the lesion was painful.

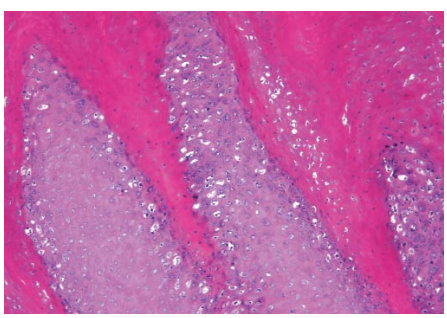

Fig. 1.33 Plantar wart (myrmecia type). Nuclei are retained in the stratum corneum as basophillic round bodies surrounded by a clear halo.

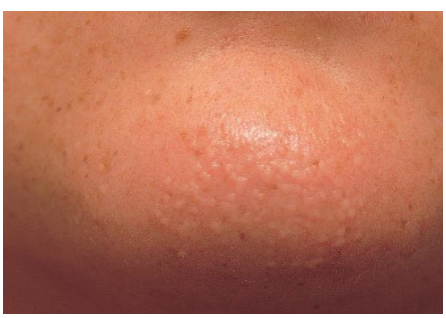

Fig. 1.35 Multiple flat warts on the chin of a young female.

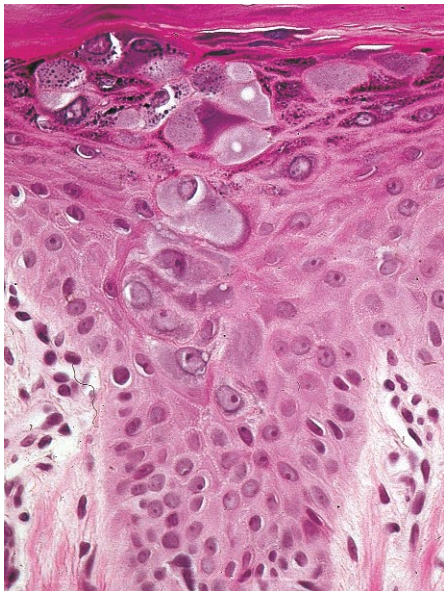

Fig. 1.36 Flat wart in a patient with epidermodysplasia.

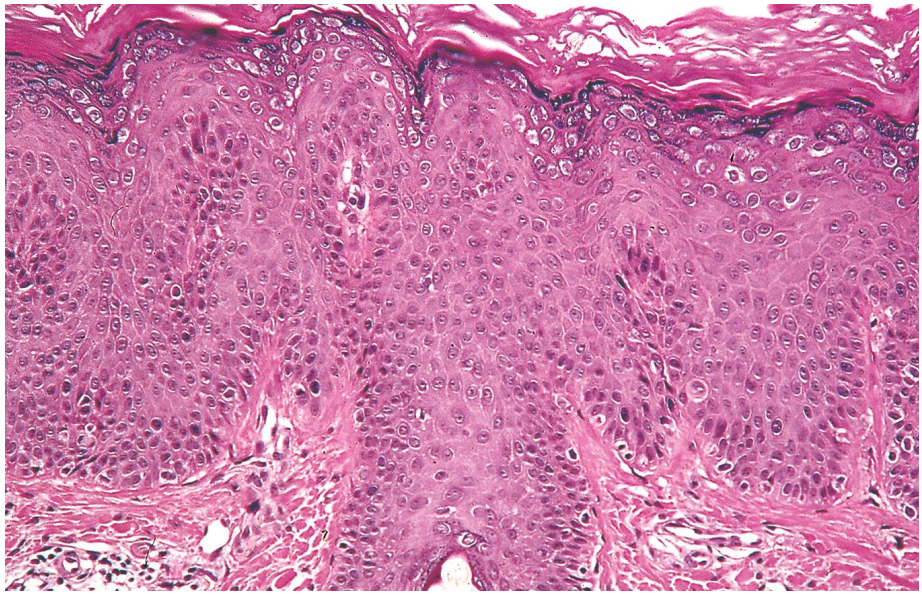

Fig. 1.37 Flat wart. There are superficial vacuolated keratinocytes with perinuclear clearing.

Deep plantar wart (myrmecia) - HPV1, HPV63 {505,2390}.
Common and mosaic wart - HPV2, HPV4 {1055}
Endophytic common wart - HPV4 {1055}
Ridged and flat warts (associated with or without cyst, respectively) - HPV60 {505, 1055,1214,2390}
Large plantar wart - HPV66 {1556}

Verruca plana

Definition
Verruca plana are benign, HPV-induced, slightly elevated, flat-topped, smooth papules.

Synonyms
Flat wart, verruca plana juvenilis.

Epidemiology
Verruca plana are relatively common. Children, adolescents and young adults are most frequently affected.

Etiology
HPV types 3 and 10 are most commonly associated with verruca plana. Minor trauma, atopic dermatitis and immunosuppression are possible predisposing factors {778,909,2262}.

Localization
Most lesions are located on the back of the hands and fingers, distal forearm, lower leg and face.

Clinical features
Flat warts generally are smaller than common warts and typically develop as small round to oval epidermal papules measuring 1-4 mm in diameter. Lesions are mostly skin-coloured with a smooth and flat surface, but may be hyperpigmented. The number ranges from one to several hundred and the distribution is asymmetric, sometimes linear (Koebner phenomenon).

Histopathology
Histology reveals a loose hyperkeratosis with basket-weave-pattern but little or no papillomatosis as in verruca vulgaris. There is plate-like epidermal hyperplasia of about twice the thickness of the surrounding normal epidermis with compressed papillae but dilatation and tortuosity of capillaries in the papillary dermis. Superficial epidermal layers show koilocytosis, vacuolated keratinocytes with perinuclear clearing around centrally located nuclei (so-called “birds-eye cells”) and hypergranulosis.
Flat wart-like lesions can be encountered in patients with epidermodysplasia verruciformis. These lesions may show typical blue-grey cytoplasm {907,909,1491}.
Regression of plane warts is accompanied by superficial lymphocytic infiltrate in the dermis with exocytosis and single epidermal cell apoptosis {2476}.

Prognosis and predictive factors
Flat warts commonly persist for several years. Due to immunologic rejection in some long-standing cases, lesions have disappeared almost from one day to the next showing some local inflammation without leaving a scar. There are no reports regarding recurrences in such cases. In other cases warts lose evidence of viral cytopathic change and persist as localized verrucous epidermal hyperplasia {909}.

Acanthomas

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R.M. Williamson
G.F. Kao
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S. Chimenti
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Definition
Acanthomas are benign tumours of epidermal keratinocytes. The proliferating keratinocytes may show normal epidermoid keratinization or a wide range of aberrant keratinization, which includes epidermolytic hyperkeratosis (epidermolytic acanthoma), dyskeratosis with acantholysis (warty dyskeratoma) or acantholysis alone (acantholytic acanthoma). Seborrhoeic keratosis, melanoacanthoma, clear cell acanthoma, large cell acanthoma and keratoacanthoma all fulfil the criteria for an acanthoma.

Epidermolytic acanthoma

Definition
A benign tumour presenting as solitary or multiple discrete lesions and demonstrating the characteristic histologic features of epidermolytic hyperkeratosis {1628, 2151}.

Epidemiology
The reported age range is 3-72 years with a slight male predominance and various racial groups affected {515}.

Etiology
The etiology remains unknown but trauma {2033}, sun exposure {2298} and PUVA {1677} have been proposed as causes of disseminated epidermolytic acanthoma.

Localiz.ation
They can occur at any skin site and may involve oral or vaginal mucosa {515, 601,1869,2151}.

Clinical and macroscopic features
Epidermolytic acanthomas are generally asymptomatic, flat or elevated keratotic papules 2-12 mm in diameter {515,601, 1291,1628,1677,1712,1869,2033,2151, 2298}. Lesions may be solitary, multiple (localized to a region), or disseminated {515}.

Histopathology
Epidermolytic acanthoma is characterised by compact hyperkeratosis, perinuclear vacuolisation of the cells of the stratum Malpighii sparing only the basal layer, indistinct reticulate cell boundaries and hypergranulosis with larger basophilic keratohyaline granules than normal and intracytoplasmic amorphous eosinophilic bodies i.e. epidermolytic hyperkeratosis {14}.

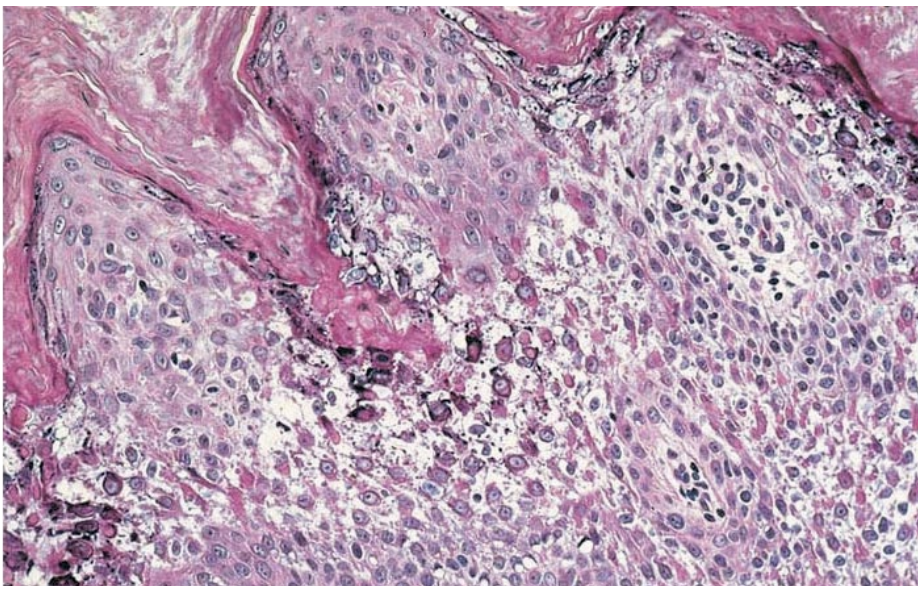


Fig. 1.38 Epidermolytic acanthoma. This lesion shows hypergranulosis and marked cytoplasmic vacuolization with clumps of eosinophilic material, sparing the basal layer.

Genetics
Based on patterns of keratin expression determined by immunohistochemical techniques, a somatic mutation involving K1 and K10 genes has been postulated {515}.
Patients with disseminated disease may also have germline mutations, with offspring at risk for congenital ichthyosiform erythroderma/generalized epidermolytic hyperkeratosis.

Warty dyskeratoma

Definition
Warty dyskeratoma is a benign papulonodular lesion characterized by an endophytic proliferation of squamous epithelium typically occurring in relation to a follicular sebaceous unit and showing prominent acantholytic dyskeratosis.

Synonyms
Isolated dyskeratosis follicularis
Follicular dyskeratoma

Epidemiology
Warty dyskeratoma occurs mostly in middle aged to elderly adults {1166}.

Etiology
There are no known etiological factors. A recent study showed no evidence of HPV in 13 cases using PCR {1166}.

Localization
The head and neck region is most commonly involved {873,1166,2306,2321}. Cases arising in oral {869} and laryngeal {1185} mucosa and in a subungual {147} location have been reported. It has been suggested that lesions arising in sites devoid of hair follicles maybe a separate entity {1166}.

Clinical features
Most lesions are solitary flesh coloured to

brown papules, nodules or cysts with an umbilicated or pore-like centre or central keratin plug {873,1166}. Most are 1-10mm in size {873}. Occasionally the lesions are multiple {121,2306}.

Histopathology
Warty dyskeratoma is a well-demarcated endophytic lesion characterized by prominent acantholytic dyskeratosis. This results in suprabasal clefting with formation of villi which protrude into a lacuna. There is typically abundant keratin present within the centre of the proliferation forming a plug {829,873,1166, 2306}. Keratin pearls are commonly seen as are small cysts lined by infundibular type epithelium {1166}. Mitotic figures are commonly identified and may exceed 5 per HPF {1166}.
Three architectural variants have been described namely cup-shaped, cystic and nodular and combinations of these may occur {1166}. There may be an epidermal collarette present and the surrounding epidermis may show papillomatosis, hypergranulosis and hyperplasia {1166}. A connection to folliculosebaceous structures is commonly demonstrable {873,1166}.
The stroma often shows a characteristic appearance with dense collagen or fibroblasts and focal intrastromal clefts. There may be an associated mixed inflammatory cell infiltrate {873,1166, 2321}.

Differential diagnosis
Comedonal Darier disease shows identical histological features and is differentiated on clinical grounds {623}.
Familial dyskeratotic comedones is a rare condition which tends to spare the scalp and face and shows less marked acantholysis and dyskeratosis than warty dyskeratoma {941}.

Histogenesis
It has been recently suggested that this lesion is a follicular adnexal neoplasm {1166}.

Acantholytic acanthoma

Definition
Acantholytic acanthoma is a rare benign epidermal tumour. The lesion displays a striking characteristic microscopic feature of acantholysis that bears resemblance to that seen in several vesiculobullous disorders {320,1566,1885,2476}.

Epidemiology
In the 31 cases reported by Brownstein {320}, the patients ranged in age from 32-87 years. The median age was 60 years; the male to female ratio was 2:1.

Etiology
Although it is known that immunosuppression increases the incidence of cutaneous neoplasms, the role of impaired immune surveillance resulting in acantholytic acanthoma is speculative {1885}.

Localization
Truncal skin, i.e., back, chest, or flank, is most commonly involved, followed by extremities, neck, groin, axilla, ear, scrotum and shoulder.

Clinical features
Acantholytic acanthoma is a solitary, keratotic, asymptomatic to occasionally pruritic papule or nodule. Multiple lesions have been recorded in a renal transplant patient {1885}.

Macroscopy
The scaly, flesh-coloured, hyperkeratotic growths range in size from 0.5-1.2 cm.

Histopathology
The tumour shows a well-defined area of papillomatous epidermal hyperplasia. There is hyperkeratosis with prominent acantholysis involving multiple levels of the epidermis. Suprabasal or subcorneal clefts with some dyskeratotic cells (corps ronds and grains) and occasional villi are noted. The upper dermis contains a variable perivascular lymphohistiocytic and occasional eosinophilic infiltrate.

Differential diagnosis
Acantholytic acanthoma must be distinguished from other acantholytic disorders and from various acanthomas. Pemphigus, Grover disease, and Hailey-Hailey disease are disorders with more extensive clinical papulovesicular eruptions.
Epidermolytic acanthoma shows epidermolytic hyperkeratosis, and no acantholysis is present. Clear cell acanthoma contains numerous pale cells, with abundant intracytoplasmic glycogen, which is absent in acantholytic acanthoma.

Lentigo simplex

Definition
Lentigo simplex is characterized by a clinically flat epidermis with microscopic acanthosis and highly localized well-circumscribed pigment on sun exposed skin.

Synonyms
Solar lentigo, actinic lentigo, “ink spot” lentigo and lichen planus like keratosis.

Epidemiology
Lentigines are common pigmented lesions most frequently seen on the sun-exposed skin of light skinned individuals.

Localization
These lesions occur essentially only on skin or mucosa and spare the palms and soles. There is relative sparing of sun-protected areas, but some lesions may occur in these sites.

Clinical features
Lentigines are well-circumscribed mainly flat (macular) localized collections of pigment. The lesions are common and are ubiquitous in light skinned individuals. Most are somewhat randomly distributed on sun-exposed skin. The presence of many lesions may raise the consideration of a syndrome, particularly when there is extensive involvement of the lips. Peutz-Jeghers syndrome is the presence of numerous lentigines associated with multiple hamartomatous gastrointestinal polyps {893}.

Macroscopy
Individual lesions may be smooth-edged, but many have an irregular outline. Most appear entirely uniform in colour and range from light tan to brown to black. While lesions may approach 1 cm in greatest dimension, nearly all clinical lesions are 1-5 mm.
In the large cell acanthoma variant, the tumours are macroscopically very deeply pigmented and may simulate malignant melanoma in situ.
Lichen planus like keratoses have a highly variable appearance and may show pink, orange, or rust coloured hues. Most are minimally raised from the skin surface and have a paving stone outline that is frequently polygonal rather than rounded {677}.

Histopathology
All lentigines demonstrate a sharply circumscribed focus of epidermal hyperplasia. The tumours are strikingly melanized, and many retain residual melanin in the overlying stratum corneum. This pigment occasionally simulates parakeratotic nuclei seen in dermatitis, a feature referred to as "pigmented parakeratosis".
While clinically macular, the typical lesion of lentigo simplex demonstrates a specific form of epidermal hyperplasia characterized by elongate rete ridges with somewhat club shaped or bulbous ends. This appearance is characteristic of other settings of epidermal hypermelanization, such as in melanocytic nevi. However, it is so typical of lentigines that in every circumstance where found, this form of epidermal hyperplasia is referred to as lentiginous epidermal hyperplasia. In most circumstances where it is seen, the underlying papillary dermis demonstrates a variable amount of eosinophilic collagen deposition (or fibrosis). This may imply that the epidermal proliferation requires a scar like response in the underlying dermis. However, inflammation is an inconstant feature in these lesions {277,1634}.
Because of the histologic similarity to the epidermis of melanocytic nevi, lentigines are defined partially by what is absent in the tumours: namely nevomelanocytic nests. The presence of even rare nests is sufficient to separate the diagnosis as lentiginous junctional nevus (or "jentigo").
Thus, to make a diagnosis of lentigo the requisite features are: localized lentiginous epidermal hyperplasia, marked epidermal hypermelanosis, and the lack of nevomelanocytic nests. In fact, despite the remarkable melanization of the tumour, increased numbers of melanocytes are not found in lentigines.
Two clinical variants are known: large cell acanthoma and lichen planus like keratosis. In large cell acanthoma, the presence of a localized proliferation of larger-than-normal keratinocytes with marked melanization is seen. These lesions are strikingly dark and are often clinically highly suspicious for malignant melanoma.
The other characteristic histologic feature of this variant is the larger than normal appearance of the keratinocytes. The reason for this feature is unknown, but may relate to the marked accumulation of melanin pigment {277,1033,1959}.
A final variant is the lichen planus like keratosis. While some authors maintain that a variety of lesions may develop into these lichenoid proliferations, most concur that a large proportion begin as lentigines. Several lines of evidence point to this origin and have been reviewed. Histologically, these lesions often suggest a solitary lesion of lichen planus as they were initially described. Most demonstrate hypergranulosis and a band like superficial infiltrate but unlike routine lichen planus they may show overlying parakeratosis or an inflammatory infiltrate which contains a mixture of inflammatory cell types with some neutrophils or eosinophils. Careful evaluation of most lesions demonstrates some residual lentigo simplex and pigment within dermal melanophages {1373}.

Differential diagnosis
The separation between seborrhoeic keratosis and lentigo is somewhat arbitrary, but most authors describe the epidermis as flat in lentigo simplex while the skin surface is clearly raised in seborrhoeic keratosis.

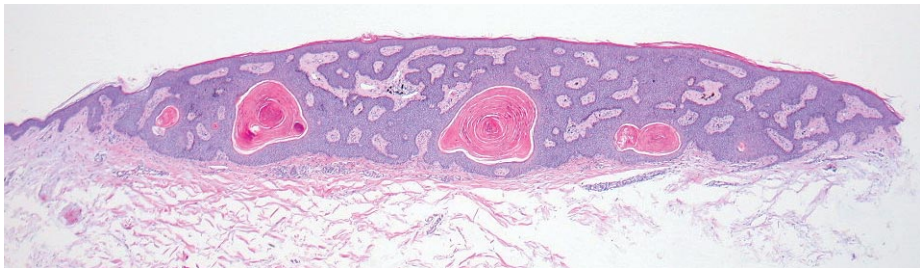


Fig. 1.39 Pigmetned seborrhoeic keratosis. There are elongated interlocking retes consisting of a proliferation of bland and pigmented basaloid and squamous cells with formation of pseudo horn cysts

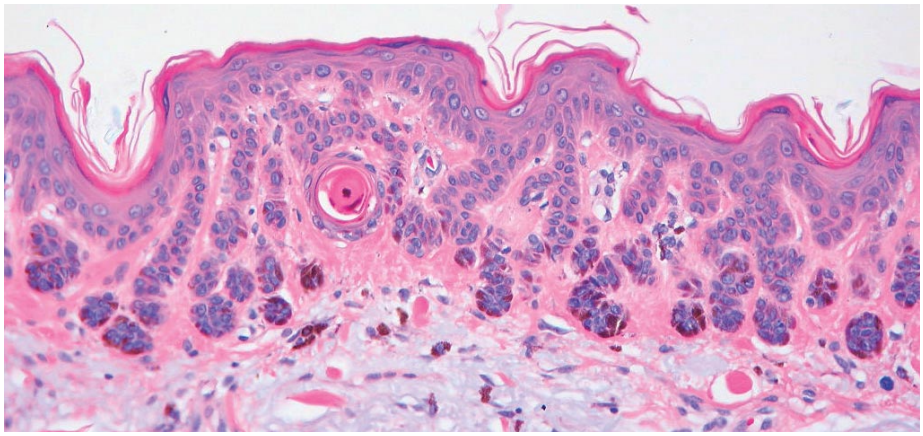


Fig. 1.40 Pigmented reticulated seborrhoeic keratosis. There are slender elongated interlocking rete ridges with hyperpigmentation and no squamous cell atypia, accompanied by focal pseudo horn cyst.

Seborrhoeic keratosis

Definition
Seborrhoeic keratoses are benign hyperplastic tumours of epidermis which are more common in older individuals.

Synonyms
Seborrhoeic wart, senile wart, stucco keratosis, melanoacanthoma.

Epidemiology
Seborrhoeic keratoses are the most common of the cutaneous neoplasms and occur in the majority of elderly Caucasian patients. These lesions are by no means limited to Caucasians, but are present in numerous older individuals of any race. The lesions are unusual in children and even young adults are rarely affected. Identical histological features are seen in certain epidermal naevi.
There is no appreciable sex predilection. In part due to the very widespread incidence of the lesion, most cases are sporadic although several syndromes are associated with seborrhoeic keratosis. Recent studies support the long held belief that seborrhoeic keratosis is a clonal process in the skin {1679}.

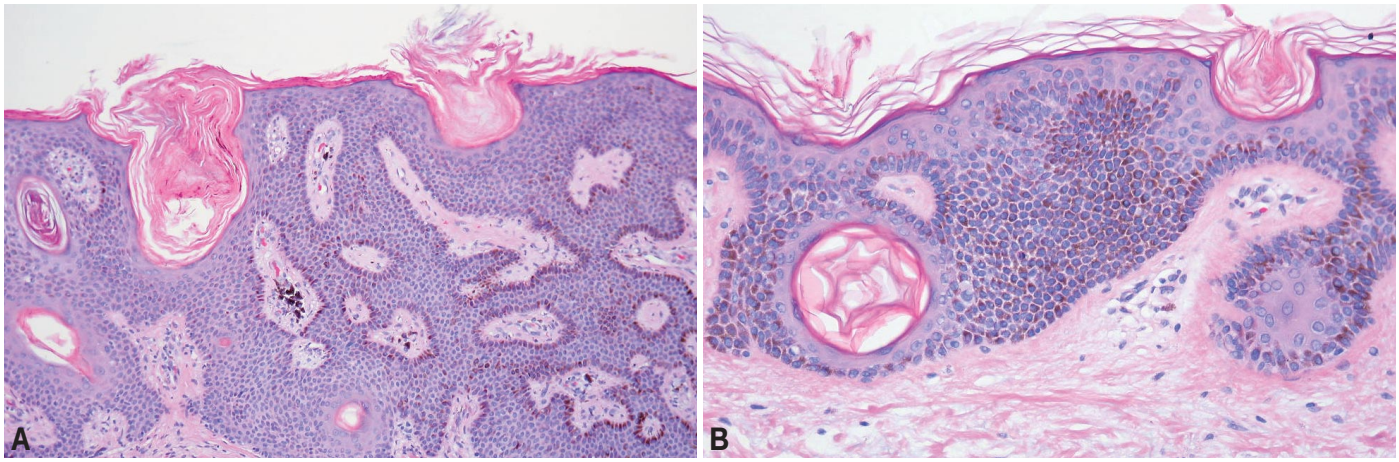


Fig. 1.41 Pigmented seborrhoeic keratosis. **A** and **B** There are elongated interlocking retes consisting of a proliferation of bland and pigmented basaloid and squamous cells with formation of pseudo horn cysts

Clinical features

Seborrhoeic keratoses are slightly raised, tan to brown or black papules. Sun exposed skin is especially affected, but lesions may be present on any site of the skin except for palms or soles. They often have a "stuck on" appearance and may be easily removed. Irritated lesions often demonstrate a crust and prominent hyperkeratosis which diminishes the visibility of the epidermal pigment. Thus, many of these irritated seborrhoeic keratoses are pink to red and quite scaly. Many of these lesions appear more smooth-surfaced and are mistaken for basal cell carcinoma clinically.

While most seborrhoeic keratoses are uniform in colour, speckled examples are common. Pigmented seborrhoeic keratoses may be mistaken clinically for malignant melanoma. There is some correlation between the many described histological variants of seborrhoeic keratosis and the clinical appearance of the tumour.

Keratoses are generally very well circumscribed clinically. Usual lesions are oval in configuration, but linear or unusually shaped lesions are common.

Dermatosis papulosa nigra appears to be a form of multiple seborrhoeic keratoses of the face seen primarily in patients of African descent. This condition is not known to be associated with any type of internal malady {658}.

Leser-Trélat syndrome

This syndrome is the rapid onset of multiple pruritic seborrhoeic keratoses associated with malignancy. The tumours associated have primarily been of gastrointestinal origin, but lymphomas and leukaemias have also been reported. It should be emphasized that some authors dispute the syndrome entirely and favour a coincidental association due to the high frequency of seborrhoeic keratoses in the elderly patients {955, 2110}.

Histopathology

Seborrhoeic keratoses are well-defined proliferations of epidermal keratinocytes which may be endophytic, exophytic or flat. There are seven major types of seborrhoeic keratosis:

Acanthotic (common) seborrhoeic keratosis

The acanthotic type is composed of broad columns or sheets of basaloid or squamoid cells with intervening horn cysts. There may be varying degrees of hyperkeratosis, papillomatosis and acanthosis.

Reticulated seborrhoeic keratosis

This common variant is often sampled histologically because clinical examples are frequently deeply pigmented. They form a net like or retiform pattern of acanthosis.

Pigmented seborrhoeic keratosis

Pimented seborrhoeic keratoses are in every way similar to usual seborrhoeic keratoses, but in addition demonstrate pronounced epidermal melanin pigment.

Clonal seborrhoeic keratosis

Clonal seborrhoeic keratosis is an unusual variant, which demonstrates whorled collections or nests of keratinocytes within the thickened epidermis. These foci of enlarged keratinocytes arranged in circular collections are suggestive of the epidermal collections seen in some cases of in situ squamous carcinoma, but lack the cytological atypia inherent in malignant neoplasms.

Irritated seborrhoeic keratosis

There is a heavy lichenoid inflammatory cell infiltrate in the upper dermis. Apoptotic keratinocytes are usually quite numerous. Features of the hyperkeratotic type (see below) may also be present. Sometimes there is a heavy inflammatory cell infiltrate, including neutrophils, which may not have lichenoid features. Squamous eddies are often present in the epidermis.

Hyperkeratotic seborrhoeic keratosis

This variant shows varying degrees of hyperkeratosis, papillomatosis and acanthosis. Some cases show inflammatory features similar to the irritated variant.

Flat seborrhoeic keratosis

There is mild hyperkeratosis, often mild basal pigmentation ('dirty feet') and only minimal acanthosis. There are no horn cysts. The cells contrast with those of the adjacent normal epidermis by being more compact.

Immunoprofile

All studies confirm the presence of keratins throughout the tumour. Some studies have also demonstrated the presence of carcinoembryonic antigen (CEA) {314,319,665}.

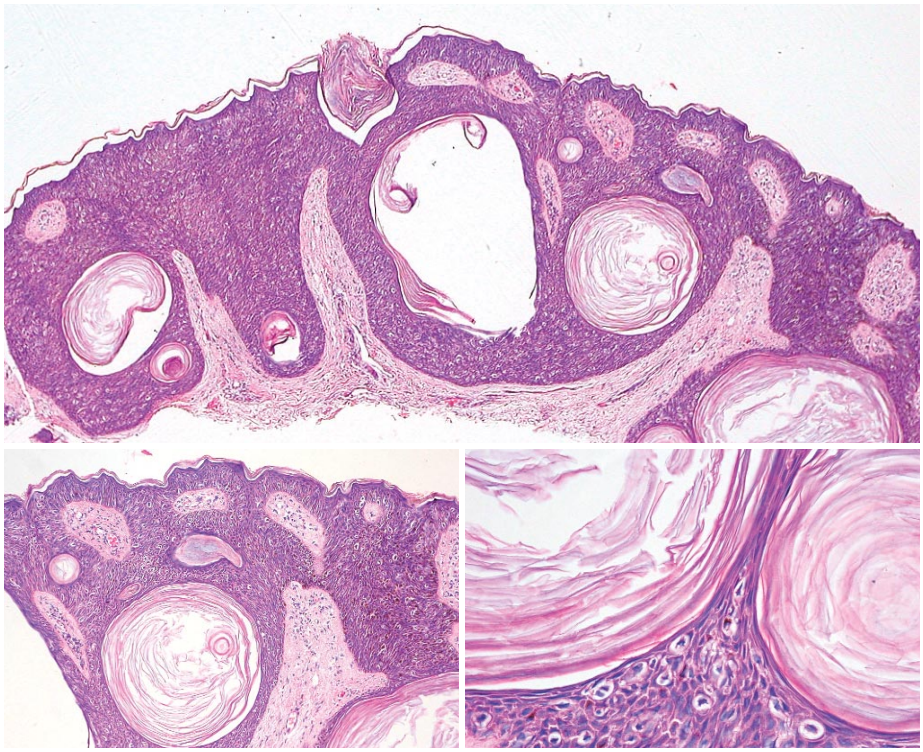


Fig. 1.42 Melanoacanthoma. There are elongated interlocking rete ridges consisting of a proliferation of bland basaloid and squamous cells with formation of pseudo horn cysts, intimately mixed with numerous melanocytes throughout the lesion.

Differential diagnosis
Dowling Degos disease has lesions indistinguishable from seborrhoeic keratosis except for their small size and the presence of a reticulated network of adjacent lesions.
The hyperkeratotic form may resemble a verruca vulgaris. Seborrhoeic keratoses lack parakeratotic columns overlying the digitate hyperkeratosis and there is no haemorrhage, dialated capillaries, koilocytosis or inward turning of the acanthotic downgrowths.

Precursor lesions
Some believe that the solar lentigo (lentigo senilis) is a precursor lesion of reticulated seborrhoeic keratosis. Others regard it as an early form of this lesion.

Prognosis and predictive factors
In a small number of cases Bowen disease coexists with seborrhoeic keratosis.

Melanoacanthoma

Definition
Melanoacanthoma of the skin is a benign mixed proliferation of keratinocytes and melanocytes. It is considered to be a variant of seborrhoeic keratosis.
Melanoacanthoma of the oral mucosa is an unrelated disorder.

Synonyms
Melanoacanthosis, deeply pigmented seborrhoeic keratosis.

Epidemiology
Most patients are adults beyond 40 years of age. Sex predominance is not known. There are no reliable frequency data.

Localization
Most melanoacanthomas are located on the trunk.

Clinical features
Clinically, the lesion resembles a darkly pigmented seborrhoeic keratosis. There are no characteristic symptoms. It may resemble a melanoma with dermatoscopy.

Histopathology
Melanoacanthoma has the same architecture as common seborrhoeic keratoses. However, they stand out by their abundant dendritic melanocytes in virtually all layers of the lesion. The keratinocytes are rich in melanin granules.

Clear cell acanthoma

Definition
Clear cell acanthoma (CCA), is a benign epidermal neoplasm characterized by the presence of glycogen-rich clear/pale cells.

Synonyms
Degos acanthoma, pale cell acanthoma.

Localization
It is usually located on the lower extremities of middle-aged or elderly individuals. Other sites are the upper extremities, head and neck, trunk, buttocks and genital area.

Clinical features
It usually occurs as a solitary, slowly growing, dome-shaped papule, nodule or plaque. The lesion has sharp margins, sometimes with a keratotic scale, and a red or pink colour, giving the tumour a vascular appearance. Clinical variants include multiple, pigmented, giant, atypical, cystic and polypoid CCA {345}.
The clinical differential diagnosis may include pyogenic granuloma, irritated seborrhoeic keratosis, squamous and basal cell carcinoma, melanocytic naevus and nodular amelanotic melanoma.

Histopathology
There is a circumscribed, sharply demarcated epidermal proliferation with psoriasiform elongation of plump and interconnected rete ridges. The keratinocytes differ from those of the adjacent normal epidermis by their pale/clear cytoplasm containing a large amount of glycogen, best demonstrated with a periodic acid-Schiff reaction. The keratinocytes of the basal layer and the intraepidermal portion of the adnexae are not involved. Parakeratosis, infiltration of neutrophils, which may form microabscess in the stratum corneum, and the absence of the granular layer are additional characteristic findings. Dilated capillaries and a scattered inflammatory infiltrate can be observed in the papillary dermis. The presence of melanophages in the papillary dermis and an increased number of melanocytes provide clues to the diagnosis of a pigmented CCA.

Histogenesis
The histogenesis of CCA is not yet completely clear. Initially considered a tumour of sweat gland or hair follicle origin, these sites were later excluded because of the different cytokeratin expression compared to CCA {1743}. Some investigators hypothesized that CCA is a benign epidermal tumour of unknown etiology, probably caused by a specific disturbance of keratinocyte differentiation. The expression of involucrin and epithelial membrane antigen further suggest that CCA is derived from surface epithelium. However, since CCA shows histopathologic findings and cytokeratin expression similar to those observed in psoriasis, others believe that it might represent an inflammatory disease rather than a neoplastic process {742}.

Large cell acanthoma

Definition
Large cell acanthoma, a benign lesion, is now considered to be a stage in the evolution of a solar lentigo to a reticulated seborrhoeic keratosis {1576,1959}. It was thought to represent a particular type of actinic keratosis {1875,2095}, Bowen disease {2038}, or a distinct entity {69,1871,2039}.

Epidemiology
Most patients are middle-aged to elderly persons. Sanchez Yus et al (1988) estimated that approximately 1-2.5 LCAs are diagnosed per 1000 skin biopsies whereas Scholl (1982) saw only 4 cases among > 1000 actinic keratoses and > 3200 seborrhoeic keratoses.

Etiology
Chronic sun exposure is the probable cause of LCA.

Localization
Most lesions tend to occur on the trunk and extremities.

Clinical features
The lesion resembles a solar lentigo, flat seborrhoeic keratosis or stucco keratosis. Most cases are lightly pigmented flat plaques or patches, usually less than 10 mm in diameter. Hyperkeratosis or even verrucous appearance has been described. In Black patients, LCA may present as darkly pigmented lesions {2165}. Hypopigmentation is also seen {69}. Dermatoscopy may rule out melanoma.

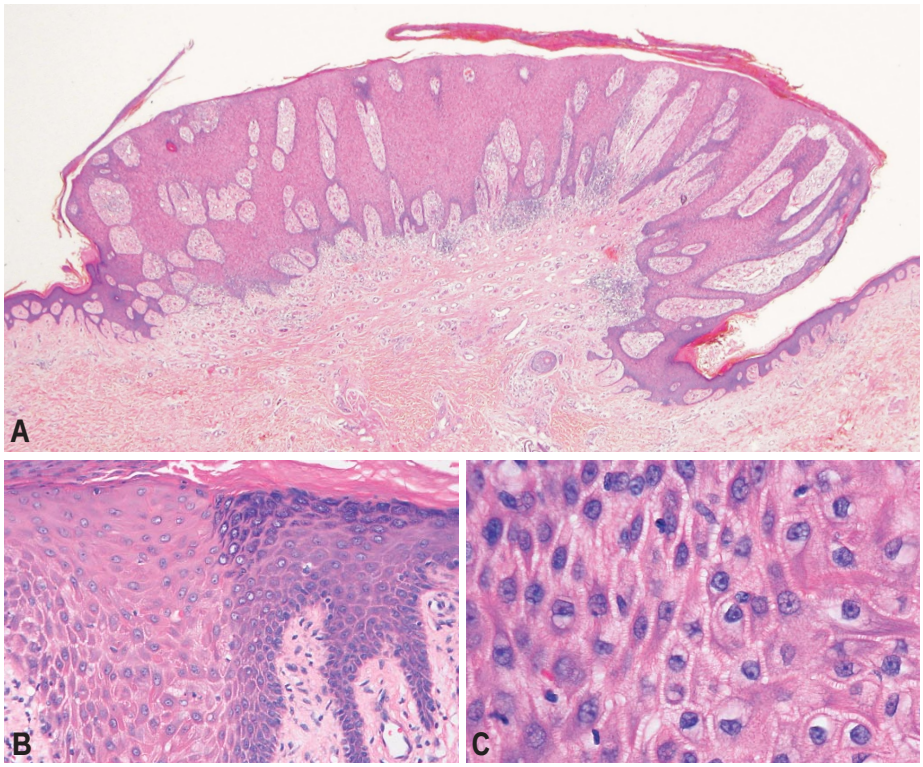


Fig. 1.43 Clear cell acanthoma. **A** There are well circumscribed interlocking columns of pale to clear keratinocytes with absent granular layer and no squamous cell atypia. **B** Note sharp demarcation between normal epidermis (right) and tumour (left). **C** High power view of tumour cells showing pale cytoplasm due to glycogen accumulation.

Histopathology
Large cell acanthoma is a sharply delimited lesion standing out by its unique large keratinocytes that have about double the size both of their cytoplasm and nuclei compared to normal keratinocytes. Often, considerable numbers of melanocytes are present. Three variants have been described: a basic pattern with mild to moderate acanthosis, a verrucous pattern with papillomatosis and hyperkeratosis, and a flat-hyperkeratotic pattern {2039}. The granular layer is thick, there is usually orthohyperkeratosis and the rete ridges may be slightly bulbous.
The growth fraction is low {86,1576} although there is a considerable proportion of both aneuploid and hyperdiploid cells {86}.

Differential diagnosis
Flat seborrhoeic keratoses differ by the smaller size of the constituent cells. Solar keratoses show parakeratosis and greater nuclear pleomorphism.

Keratoacanthoma

Definition
Keratoacanthoma is a squamoproliferative tumour, mainly of hair-bearing skin. Although it has distinctive clinical and histological features, some regard it as a variant of squamous cell carcinoma {190,1701}.

ICD-O code 8071/1

Synonym
Well-differentiated squamous cell carcinoma (keratoacanthoma type).

Epidemiology
Most cases develop in older persons, particularly in the sixth and seventh decades. There is a male preponderance. Keratoacanthomas are more frequent in subtropical areas.

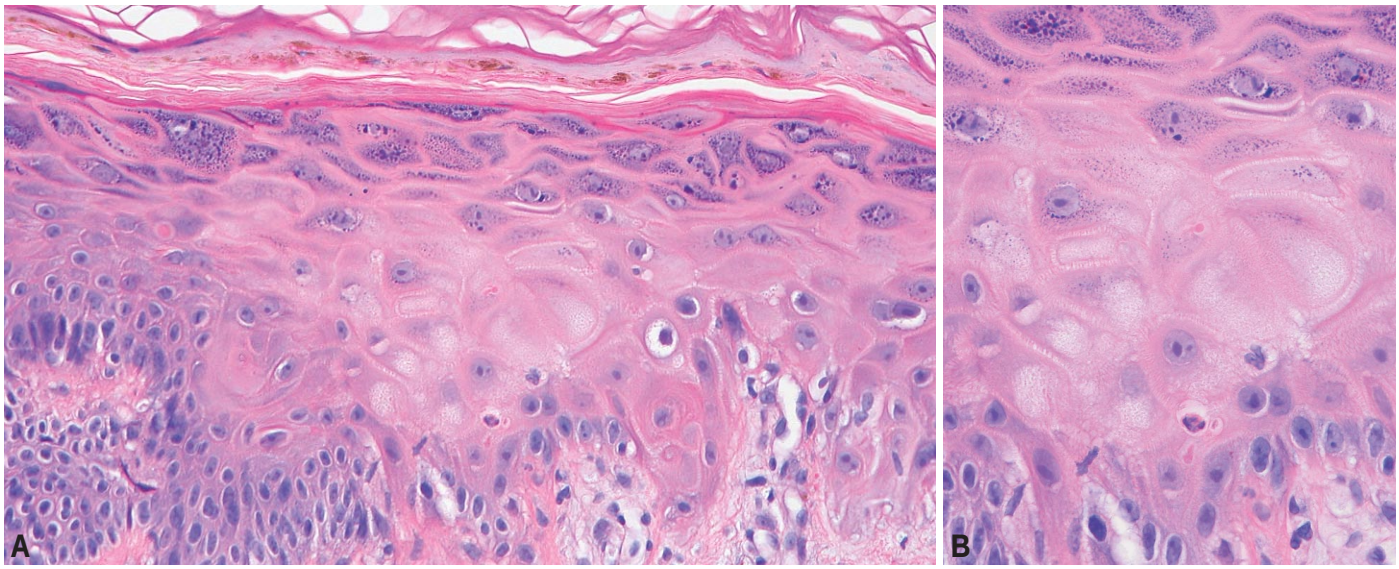


Fig. 1.44 Large cell acanthoma. **A** There is abrupt transition between normal epidermis (left) and large cell acanthoma (right). There is hyperkeratosis, hypergranulosis and markedly enlarged keratinocytes. **B** The tumour cells have enlarged nuclei without hyperchromasia and a low nuclear to cytoplasmic ratio.

Etiology

Exposure to excessive sunlight is the most frequently incriminated factor in their etiology. Viruses have also been implicated, particularly in immunosuppressed patients in whom DNA sequences of HPV have been detected in 20% of cases {2270}. Chemical carcinogens produce similar tumours in some animals, but their role in humans is speculative.

Localization

In temperate climates, up to 70% of lesions develop on the face. In subtropical areas, there is a much greater tendency for lesions to arise on the arms, dorsum of the hands and the lower extremities.

Clinical features

Keratoacanthomas are usually solitary, pink or flesh-coloured, dome-shaped nodules with a central keratin plug. They measure 1-2 cm in diameter. They tend to grow rapidly over 1-2 months with spontaneous involution after 3-6 months. Uncommonly, lesions persist for more than 12 months. Because local tissue destruction can occur during growth and involution, active treatment is usually advocated.

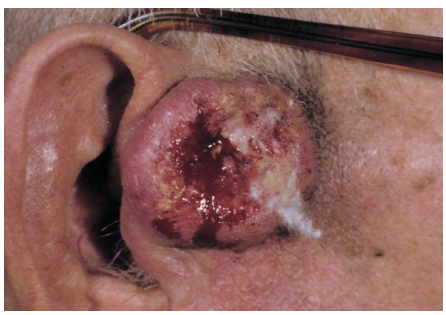


Fig. 1.45 Keratoacanthoma. Typical clinical appearance of exophytic tumour with central crateriform ulceration filled with keratin plug.

Several clinical variants occur:

Giant keratoacanthoma, a lesion greater than 2-3 cm in diameter

Keratoacanthoma centrifugum marginatum, which undergoes progressive peripheral growth with coincident central healing {1740}

Subungual keratoacanthoma, a destructive form that may produce pressure erosion of the distal phalanx. They usually fail to regress spontaneously {146}

Multiple keratoacanthomas, which may be eruptive (Grzybowski type), self-healing (the Ferguson Smith type, which is autosomal dominant in inheritance and caused by an abnormality on chromosome 9q22-q31), and a mixed eruptive and self-healing type (Witten and Zak type).

Multiple lesions can also occur in immunosuppressed patients {625}, in the Muir-Torre syndrome (see below) and at sites of trauma {1789}.

Macroscopy

They are usually pale nodules with a central keratin plug.

Histopathology

Keratoacanthomas are exoendophytic, squamoproliferative nodules with a central, keratin plug. Fully developed lesions show lipping (buttressing) of the edges of the lesion which overlap the central keratin-filled crater, giving it a symmetrical appearance. Blunt downgrowths of squamous epithelium extend into the dermis with an irregular lower border to the tumour. The cells at the periphery of the squamous islands are basaloid in type. As they mature, they become large squamous cells with a distinctive pale eosinophilic cytoplasm. Mitoses may be seen, but atypical mitoses and stromal infiltration suggest a squamous cell carcinoma. SCCs are acknowledged to occur in less than 1% of keratoacanthomas found in subtropical regions. In one series, the reported incidence of a supervening squamous cell carcinoma was approximately one-quarter of all keratoacanthomas {2040}.

A mixed inflammatory cell infiltrate, often including eosinophils and neutrophils may be present in the stroma. Neutrophils may extend into the epithelial nests, producing small microabscesses. Hyperplasia of sweat duct epithelium may be present in some cases.

Perineural invasion is an incidental and infrequent finding, often in facial lesions. It does not usually affect the prognosis or behaviour of the lesions, although local recurrence has been reported in such cases. Several cases with intravenous

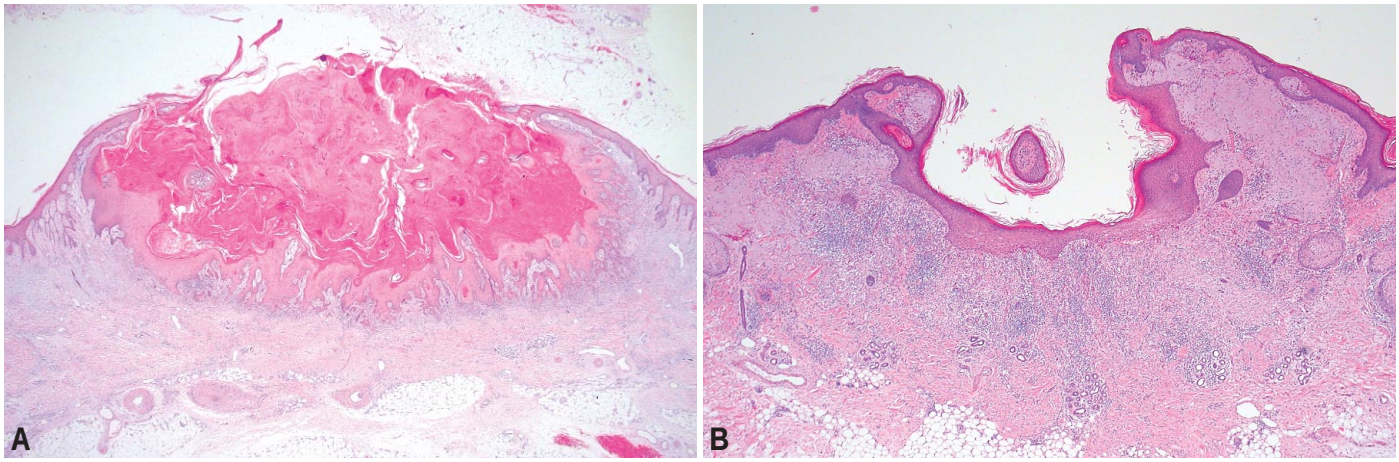


Fig. 1.46 A A low power view of keratoacanthoma demonstrating a central crateriform lesion filled with a keratotic plug and flanked by epidermal buttresses and consisting of tongues and lobules of squamous cells pushing into the deep dermis. **B** Regressed keratoacanthoma. The crateriform architecture remains but the tumour cells are replaced by flattened epidermal keratinocytes, accompanied by dermal fibrous scarring, a lichenoid inflammatory infiltrate and focal foreign body giant cell reaction to keratin in the dermis.

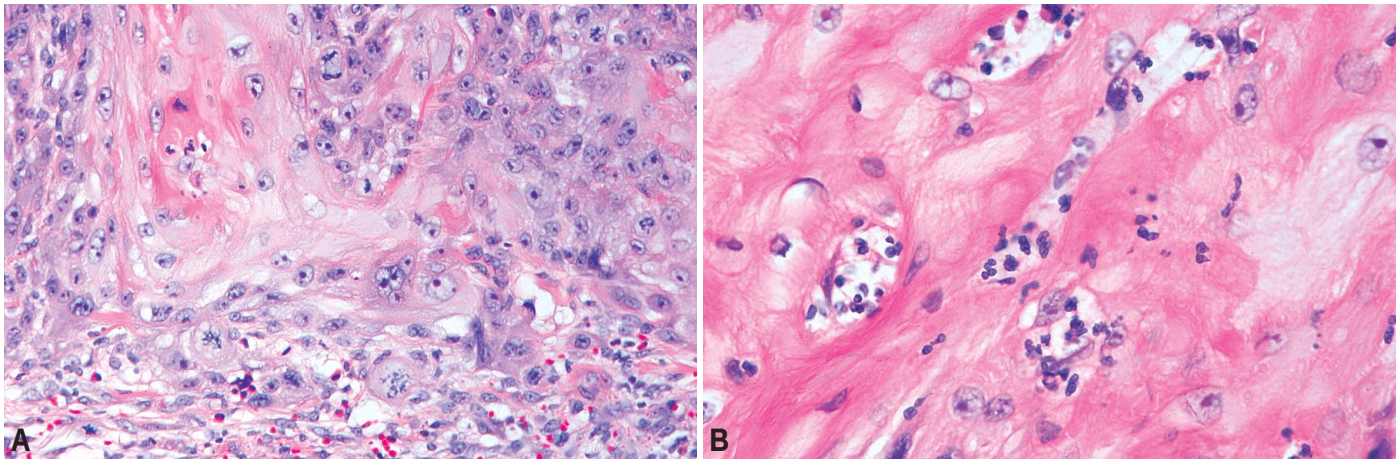


Fig. 1.47 Keratoacanthoma. **A** The tumour cells have abundant pale eosinophilic cytoplasm and pleomorphic nuclei, accompanied by a dermal lymphocytic and eosinophilic infiltrate. **B** Focal neutrophilic aggregates in tumour nests are characteristic of keratoacanthoma.

growth and a favourable outcome have been recorded {842}.

Regressing keratoacanthomas are shallower lesions with a large keratin plug and buttressing at the margins. There is progressive dermal fibrosis and disappearance of tumour nests in the dermis. Foreign body giant cells may be present around residual keratin fragments.

(PCNA / MIB-1 labelled proliferating cells are found in the periphery of the squamous nests in keratoacanthoma, in contrast to a more diffuse pattern in squamous cell carcinoma. Expression of TP53 is found in both tumours. Subungual keratoacanthomas have characteristic dyskeratotic cells, some showing dystrophic calcification, towards the centre of the tumour nests. This variant has fewer neutrophils and eosinophils.

The differential diagnosis from squamous cell carcinoma may be difficult or impossible in superficial shave and punch biopsies. Features favouring keratoacanthoma include the flask-like configuration with a central keratin plug, the pattern of keratinization, the large central squamous cells, the lack of anaplasia and a sharp outline between tumour nests and the stroma {555,2477}.

Histogenesis

The great majority of keratoacanthomas develop on hair-bearing skin {474} and are presumed to be derived from follicular keratinocytes, perhaps with a programmed life span. Those rare tumours that arise on glabrous skin and mucous membranes presumably derive from epithelial keratinocytes.

Genetics

A genetic defect has been reported in patients with the Ferguson Smith type of "multiple self-healing epitheliomas" (keratoacanthomas). The Muir Torre syndrome, in which sebaceous tumours develop in association with visceral tumours, usually gastrointestinal cancers, and often with keratoacanthomas, epidermal cysts and colonic polyps, is inherited as an autosomal dominant trait. Mutations have been found in some cases in one of the DNA mismatch repair genes MLH1 and MSH2.

Prognosis and predictive factors

Most lesions regress spontaneously over several months {260}. This regression may, in part, be immunologically mediated {1782}. Even lesions with perineural and intravenous invasion have a

favourable outcome. Keratoacanthomas can recur in up to 8% of cases. This is more likely with lesions on the fingers, hands, lips and ears. Trauma may be responsible for recurrent lesions in some cases. Rare cases that have developed metastasis have been reported {1038}. Possible explanations include misdiagnosis of the original lesion, the development of a supervening squamous cell carcinoma not recognized in the original material, genuine 'rogue' variants or transformation of the initial lesion into a squamous cell carcinoma in immunosuppressed patients {2476}.

Lichen planus-like keratosis

Definition
Lichen planus-like keratosis (LPLK) is a benign lesion of the skin that represents the attempted immunologic regression of a solar lentigo, seborrhoeic keratosis, large cell acanthoma or other epidermal proliferative lesion {1569,2150}.

Synonyms
Benign lichenoid keratosis.

Epidemiology
LPLK is a relatively common lesion. Most patients are middle-aged to elderly. There is a female predominance.

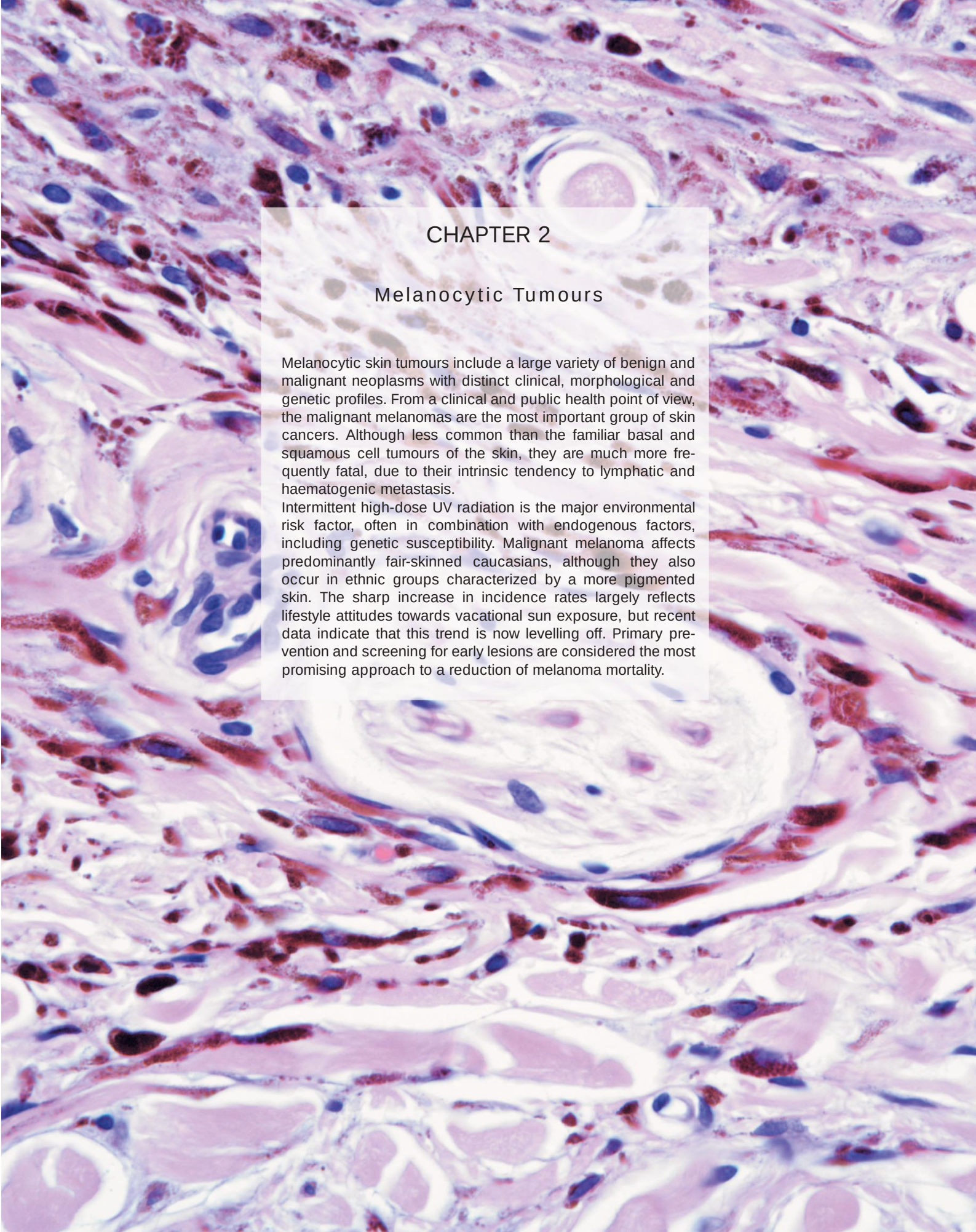
Etiology
The cause of the lesion is not exactly known. However, chronic sunlight exposure appears to be an important factor.

Localization
Most LPLKs are located on the upper trunk and upper extremities.

Clinical features
Clinically, LPLK presents as a flat, irregularly hyperkeratotic plaque with often irregular borders. It may be irregularly pigmented or pale in colour. The lesion resembles a basal cell carcinoma, Bowen disease, actinic keratosis or flat seborrhoeic keratosis. Itching and some pain may occur {1373}. Dermatoscopy can rule out melanocytic lesions.

Histopathology
LPLK is characterized by a lichenoid lymphocytic infiltrate leading to basal vacuolar change and numerous apoptotic cells. There is hypergranulosis and hyperkeratosis, frequently with parakeratotic foci. Actinic elastosis is often present {785}. Features of solar lentigo, large cell acanthoma or early seborrhoeic keratosis may be present at the margins. The inflammatory infiltrate often extends around the superficial vascular plexus.

Differential diagnosis
Lichenoid solar keratosis shows atypia of epidermal keratinocytes. In lichen planus, the inflammatory cells do not usually extend around the superficial vascular plexus. Furthermore parakeratosis, plasma cells and/or eosinophils may be present in LPLK. Similar changes may be seen in lichenoid drug eruptions. Clinical information may be required to separate these entities.



CHAPTER 2

Melanocytic Tumours

Melanocytic skin tumours include a large variety of benign and malignant neoplasms with distinct clinical, morphological and genetic profiles. From a clinical and public health point of view, the malignant melanomas are the most important group of skin cancers. Although less common than the familiar basal and squamous cell tumours of the skin, they are much more frequently fatal, due to their intrinsic tendency to lymphatic and haematogenic metastasis.

Intermittent high-dose UV radiation is the major environmental risk factor, often in combination with endogenous factors, including genetic susceptibility. Malignant melanoma affects predominantly fair-skinned caucasians, although they also occur in ethnic groups characterized by a more pigmented skin. The sharp increase in incidence rates largely reflects lifestyle attitudes towards vacational sun exposure, but recent data indicate that this trend is now levelling off. Primary prevention and screening for early lesions are considered the most promising approach to a reduction of melanoma mortality.

WHO histological classification of melanocytic tumours

Malignant melanoma	8720/3
Superficial spreading melanoma	8743/3
Nodular melanoma	8721/3
Lentigo maligna	8742/2
Acral-lentiginous melanoma	8744/3
Desmoplastic melanoma	8745/3
Melanoma arising from blue naevus	8780/3
Melanoma arising in a giant congenital naevus	8761/3
Melanoma of childhood	
Naevoid melanoma	8720/3
Persistent melanoma	8720/3
Benign melanocytic tumours	
Congenital melanocytic naevi	
Superficial type	8761/0
Proliferative nodules in congenital melanocytic naevi	8762/1
Dermal melanocytic lesions	
Mongolian spot	
Naevus of Ito and Ota	
Blue naevus	8780/0
Cellular blue naevus	8790/0
Combined naevus	
Melanotic macules, simple lentigo and lentiginous naevus	
Dysplastic naevus	8727/0
Site-specific naevi	
Acral	
Genital	
Meyerson naevus	
Persistent (recurrent) melanocytic naevus	
Spitz naevus	8770/0
Pigmented spindle cell naevus (Reed)	8770/0
Halo naevus	8723/0

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for non-invasive tumours, and /1 for borderline or uncertain behaviour.

TNM classification of malignant melanoma

TNM classification[1,2]

T – Primary tumour

The extent of the tumour is classified after excision, see pT.

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1: Metastasis in one regional lymph node
- N1a: only microscopic metastasis (clinically occult)
- N1b: macroscopic metastasis (clinically apparent)

N2: Metastasis in two or three regional lymph nodes or intralymphatic regional metastasis
- N2a: only microscopic nodal metastasis
- N2b: macroscopic nodal metastasis
- N2c: satellite or in-transit metastasis *without* regional nodal metastasis

N3: Metastasis in four or more regional lymph nodes, or matted metastatic regional lymph nodes, or satellite or in-transit metastasis *with* metastasis in regional lymph node(s)

Note: Satellites are tumour nests or nodules (macro- or microscopic) within 2cm of the primary tumour. In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumour but not beyond the regional lymph nodes.

M – Distant metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
- M1a: Skin, subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
- M1b: Lung
- M1c: Other sites, or any site with elevated serum lactic dehydrogenase (LDH)

pT – Primary tumour (pathological classification)

pTX Primary tumour cannot be assessed*
pT0 No evidence of primary tumour
pTis Melanoma in situ (Clark level I) (atypical melanocytic hyperplasia, severe melanocytic dysplacia, not an invasive malignant lesion)

pT1: Tumour 1mm or less in thickness
- pT1a: Clark level II or III, without ulceration
- pT1b: Clark level IV or V, or with ulceration

pT2: Tumour more than 1mm but not more than 2mm in thickness
- pT2a: without ulceration
- pT2b: with ulceration

pT3: Tumour more than 2mm but not more than 4mm in thickness
- pT3a: without ulceration
- pT3b: with ulceration

pT4: Tumour more than 4mm in thickness
- pT4a: without ulceration
- pT4b: with ulceration

Note: *pTX includes shave biopsies and regressed melanomas.

Stage grouping[3]

Stage 0	pTis	N0	M0
Stage I	pT1	N0	M0
Stage IA	pT1a	N0	M0
Stage IB	pT1b	N0	M0
	pT2a	N0	M0
Stage IIA	pT2b	N0	M0
	pT3a	N0	M0
Stage IIB	pT3b	N0	M0
	pT4a	N0	M0
Stage IIC	pT4b	N0	M0
Stage III	Any pT	N1, N2, N3	M0
Stage IIIA	pT1a-4a	N1a, 2a	M0
Stage IIIB	pT1a-4a	N1b, 2b, 2c	M0
	pT1b-4b	N1a, 2a, 2c	M0
Stage IIIC	pT1b-4b	N1b, 2b	M0
	Any pT	N3	M0
Stage IV	Any T	Any N	M1

[1] UICC (2002). TNM classification of malignant tumours. Sixth edition. Wiley, New York
[2] AJCC (2002). Cancer staging manual. Sixth edition. Springer, New York
A help desk for specific questions about the TNM classification is available at http://www.uicc.org (activities, TNM)
[3] Clinical staging includes complete excision of the primary melanoma [pT] with clinical/radiological assessment for regional and distant metastases. Pathologic staging includes complete excision of the primary melanoma [pT] and pathologic assessment of the regional lymph nodes [pN] after partial or complete lymphadenectomy. Stage 0 or stage IA patients do not require pathological evaluation of their lymph nodes.

Malignant melanoma: Introduction

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Incidence and mortality

Approximately 79,000 males and 81,000 females were diagnosed with melanoma world-wide in 2002, of which about 80% occurred in the predominantly white populations of Northern America, Australia, New Zealand and Europe. On a global scale, malignant melanoma was the 16th and 15th most commonly diagnosed cancer in males and females respectively and occurred most frequently in Australia and New Zealand (4th most common males, 3rd in females), North-America (6th in males, 5th in females),and Europe (16th in males, 8th in females) {724}.

In 2002, around 22,000 males and 19,000 females died of the disease worldwide {724}. Melanoma is one of the most important cancers when considered as a cause of loss of life as it is commonly diagnosed in relatively young people {54,310,350,1761}, and can be fatal if untreated. It has been calculated that, in the United States, a person dying of melanoma would die, on average, some 17 years before the age of 65, whereas in Denmark, the mean figure is put at 14-15 years, and in Belgium 6-8 years {54, 310,1761}.

Melanoma had a poor prognosis in the 1950's and 1960's, but from the mid 1970s, mortality rates have been stabilising in many high-risk populations, although incidence rates are still increasing. Survival has improved substantially, mainly in countries with high incidence rates. This is mainly due to early detection of melanomas as a result of an increasing awareness of the disease, probably partly owing to the success of primary and secondary prevention campaigns.

Geographical differences

The levels of both melanoma incidence and mortality vary considerably worldwide. Rates are high in populations where Caucasians predominate, and correspondingly low in countries where inhabitants are of mainly Asian or African origin.

Melanoma in Caucasians

As the most important environmental risk factor in Caucasians is exposure to ultraviolet radiation, incidence within white populations generally increases with increasing proximity to the equator. The highest rates are observed in Australia, where many inhabitants are of Northern European descent and live in a climate with substantially more sunshine than the norm in Northern Europe.

In Western Europe, a diverging pattern is observed: incidence rates are higher in Northern Europe (more distant from the equator) than in the South, reflecting a combination of lighter skin type and higher wealth in the North of Europe. In wealthy populations, a high incidence of melanoma is observed with relatively low mortality rates, due to the fact that melanomas are diagnosed in early stages {609}.

Migrant studies

Groups of migrants from regions of low melanoma incidence to high incidence regions acquire higher rates of melanoma than in their home country, but lower than those in the host country, in both sexes {96,689}. Incidence and mortality rates of native Australians and New Zealanders, who are largely of British origin, are estimated to be roughly twice those of recent British immigrants to these countries {96,1255}. Likewise, native Israelis experience a twofold increased risk of incidence compared to immigrants to Israel from Europe, a risk that remains at least three decades following immigration {2260}. The risk of immigrants has been shown to approach that of the native populations in both Australia and Israel with increasing duration of residence in the host country {96, 533,689,1255,2260}.

Amongst Northern European migrants to Australia, the incidence rates of melanoma have been observed to increase with duration of residence, but decrease with later age of arrival, suggesting that exposure at young ages is important in determining risk {1255}. The lowest risk in immigrants to Australia has been found to be for Southern European and Eastern Asian migrants, reflecting the protective effect of a higher degree of skin pigmentation {1255}. Differences in skin colour are also assumed to be the reason underlying the higher incidence of melanoma in white immigrants to Hawaii from the United States mainland {1031}.

Melanoma in non-Caucasians

U.S. Whites have rates 15 times higher than U.S. Blacks, and a similar contrast in risk is observed in the White and Black populations of South Africa and Zimbabwe {1780}. Melanoma is also relatively uncommon among Asians {1295,

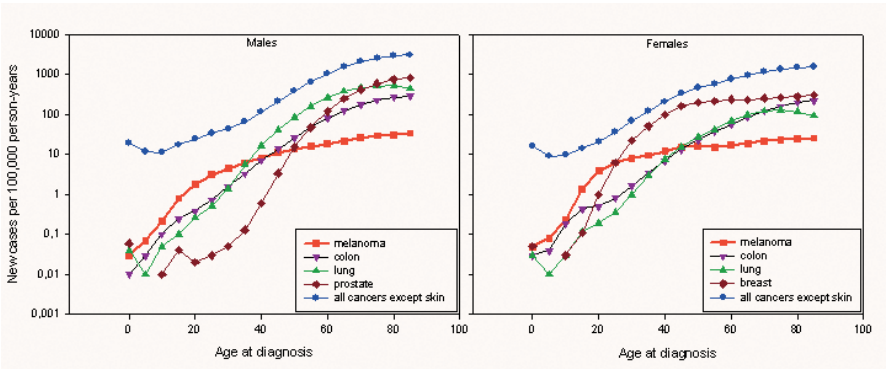

Fig. 2.1 Age-specific incidence of cancer. All data are based on data from Europe 1990-1997. Source: European Network of Cancer Registries. EUROCIM 4.0, Lyon 2001.

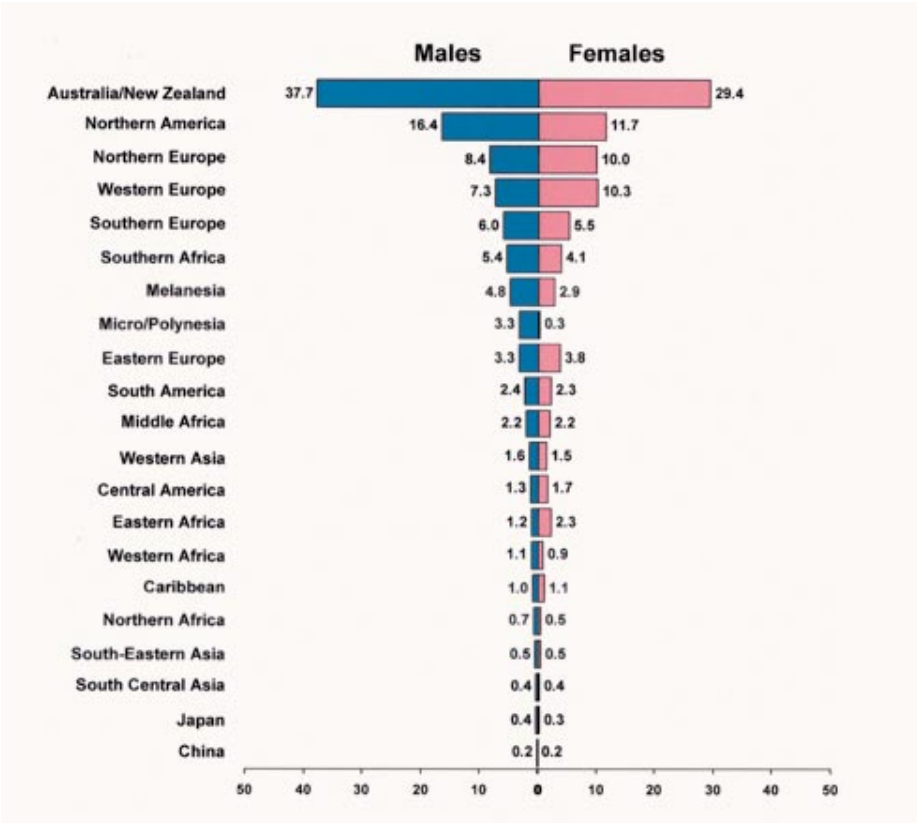

Fig. 2.2 Age-standardized incidence rates for malignant melanoma of skin, per 100 000 population and year, adjusted to the world standard population. From D.M. Parkin et al. {1779}.

1746} and Middle- and South-American populations {891}, probably due to a better protection afforded by a larger amount of pigment in the skin and possibly different ('wiser') sun-exposure patterns. Melanomas appear more often on the non-pigmented areas of the skin in non-Caucasians {940}, are often of the acral lentiginous melanoma type and appear on the palms of hands, soles of the feet and under the nails {200,554}. A common problem in these populations is that pigmented lesions in the skin are often more difficult to notice, and are therefore often detected at relatively late stages, which, at least in part, explain the high case-fatality rates {200,554}. In many African and Asian societies it is considered beautiful to have a light skin. The avoidance of sun-exposure and even more extreme measures, such as bleaching of the skin, have been reported {952,2081}.

Table 2.01
Age-standardized incidence rates per 100 000 person / year in the SEER registry (USA) {1781A}.

Population	Males	Females
Blacks	1.00	0.5
Whites	15.4	11.6

Time trends

Since the 1970's there have been reports of alarming increases in melanoma, initially in terms of mortality {1393} and then in incidence {1481}. These reports observed a doubling in rates every one or two decades (mean annual increments of between 3% and 7%) per annum in populations of European origin for both genders {1761}. The incidence rates increased markedly for intermittently exposed body sites (trunk, legs, etc.) whereas increases in the face and neck were moderate. In males, the largest increases were found on the trunk, and in females on the legs and arms {332,459, 1007,1472,1482,1699,2120,2245,2350}. In an analysis of the SEER data, it was found that melanomas of all stages increased from 1988-1997, but that localized and in situ lesions increased the most {1137}.

In the United States, Australia and Northern Europe, where incidence rates were very high during the 1980s, the rates have been rising less sharply or levelling off since the mid-1990's, especially in younger age groups {516,609, 1137,1353,1472,2144,2244,2245}. In contrast, in Southern and Eastern Europe and in Latin America, rates are increasing {7,609,1353,1579,2144}. Incidence rates in Asia have been rather stable {1142,1295}. There is insufficient data at present to report on time trends in melanoma incidence among African populations. Over the last decades, increases in incidence have mainly been observed for thin melanomas, whereas the rate of thick melanomas seems to be relatively stable {618,1433}. This increase in the number of thin melanomas is mainly observed in countries with high incidence rates, where increases in rates are mainly seen in the superficial spreading melanomas {414, 560,1052,1137,1472,1501}. In countries with lower incidence rates, increases are generally more evenly spread across thickness categories.

Although trends in incidence rates of melanoma vary greatly, mortality rates show less variation. Mortality rates have been levelling off in many populations with high melanoma incidence rates, such as Australia, the United States, and North-western Europe {516,609,827, 1353,1411,1412}. In some countries, a levelling off of incidence rates is now also observed, starting in younger age groups {609}.

Stabilisation of melanoma incidence rates

Age-period-cohort analyses indicate that in Western populations (USA, Australia, New Zealand, Sweden, the Netherlands, Germany) the increasing mortality rates have started to level off, starting in cohorts born in the 1930s and 1940s {534,827,1050,1136,1692,1983,2244, 2352}. In Southern Europe, generally those with lower incidence rates (e.g. Italy and Spain) there has been no sign, as yet, of a downwards trend {1480, 1849,2144}.

A recent plateau in melanoma mortality rates (in some cases followed by incidence rates) is reported in high-incidence countries, such as Australia, USA, Sweden, Norway and Germany {609, 1353,1761,2120,2245}. Only the mortali-

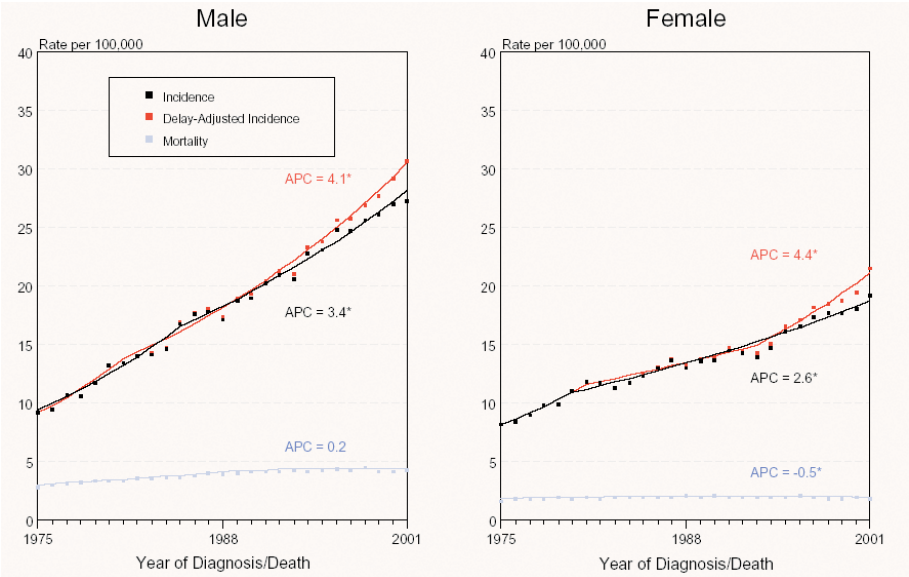

Fig. 2.3 Melanoma of the skin in Whites. SEER Incidence, delay adjusted incidence and US death rates. Despite rising incidence rates, mortality is now stable in men and shows a recent decrease in women. From: L.A.G. Ries et al. {1936}. http://seer.cancer.gov/csr/1975_2001/

ty rates levelled off initially, starting in the late 1970s, with increasing incidence rates. This was most likely because of improving survival {1472, 2245,2351} due to earlier detection, as there were no major advances in systemic treatment. Melanoma incidence rates have been reported to be levelling off, or even decreasing in younger age groups, starting in the 1980s {609}. Furthermore, the mean and median stage or thickness at diagnosis is decreasing {560,618,1433, 1472,2351}, with an increasing registration of thin, superficial spreading melanomas.

Changes in the biology of melanoma, characterized by a tendency towards less aggressive lesions being observed {353} could also be consistent with a continuing rise in melanoma incidence, and a corresponding moderation or stabilisation in the mortality rates.

Etiology

There has been much discussion and debate as to the reasons underlying the dramatic increases in melanoma incidence and mortality, and in particular, whether they are real or due to artefacts, via, for example, increased efforts at screening and diagnosing the disease, changes in diagnostic criteria, or the existence of a non-metastasizing biologically benign form of melanoma. Although some artefacts may have contributed to the increases, a substantial part of the increases is assumed to be genuine {610}.

Both familial and environmental factors play a role in the etiology of melanoma. The familial/genetic components include skin type, number of naevi, having clinical atypical naevi, and having a family history of skin cancer. They are the most important predictors of melanoma risk. As it is not likely that there has been a substantial change over time in familial/genetic risk factors in most populations, these cannot have contributed substantially to the observed increases in melanoma incidence over the past 50 years.

Exposure to UV radiation

Intermittent exposure to UVR is the major environmental risk factor for melanoma, especially in combination with endogenous factors (skin types I and II, immune deficient status, genetic predisposition) {95}. The association between UVR and melanoma is ambiguous, with differences in risks associated with the dose, the way it is delivered (intermittent vs. chronic exposures) and critical time periods (childhood vs. cumulative exposure during life). Intermittent exposure to UVR in white people, especially during childhood, has been postulated to be the main risk factor for the development of melanoma, although exposure in adulthood also plays a part. The relative risk of UV exposure for the development of melanoma is around 2, but when skin characteristics are taken into account, the relative risks increase markedly for those with a sun-sensitive skin. As sunbeds also emit UV-radiation, they most likely also confer a risk for the development of melanoma, as was recently confirmed in a large prospective study {2426}.

Although high sun exposure in childhood is a major determinant {2509}, multiple sunburns {683} and high exposure throughout life {117} raise risk of disease significantly. Cutaneous melanomas appear to arise by different pathways. Those on the head and neck relate mainly to chronic sun exposure while those on the trunk occur in people with many melanocytic naevi {2508}. High numbers of naevi reflect an innate propensity to melanocytic proliferation {2196,2197} and stimulation by sun exposure {591}. The risk of acral melanoma is also increased by exposure to high cumulative UVR and to agricultural chemicals {890}. Occupational sun exposure, especially farming, is associated with risk of ocular melanoma {2401}. Inherited mutations of tumour-suppressor genes (eg CDKN2A) are strongly associated with familial melanoma but probably underlie less than 1% of all cutaneous melanoma {42}.

Occupational vs. recreational exposure

Before the Industrial Revolution, many wealthy people had a pale skin: they worked or stayed indoors, whereas the lower classes tended to work mainly outdoors. During the industrialisation of society (1750-1800), working class people started working indoors and only the rich had the time and money to afford recreational outdoor life. By the early 1920s, daily exposure to sunlight was also advised as a cure for many diseases (acne, rickets, tuberculosis), especially for children. By the 1930s a suntan had become a symbol for wealth and health and since the 1950s, holidays to sunny destinations became popular and affordable to many.

The rising melanoma incidence is most commonly attributed to changes in lifestyle with increasing intermittent exposure to ultraviolet radiation (UVR), due to

the popularity of sunbathing and tanning. Given an induction time of some 20-40 years between exposure and melanoma occurrence, these factors are in accordance with the continuing increases - mainly on the trunk in men and on the legs in women {331,332,619,620,682, 772,2409}.

Ozone layer
Another explanation for the increases is the depletion of the ozone layer, which protects the earth's surface against UVR by filtering out a large part of the UVR from the sunlight before it reaches the earth's surface. Chemical substances released in the earth's atmosphere are slowly breaking down the ozone layer {2199}, increasing the amount of UVR that reaches the earth's surface and likely increasing the risk of skin cancer. Estimates indicate that skin cancer incidence rates could increase dramatically by the end of this century compared to the situation around 2000 {1240}.

Socio-economic status
Melanoma is more common among people with a higher socio-economic status, probably due to a higher excessive intermittent exposure to UVR (outdoor sports, winter sports, sunbathing, getting a tan) in this group. Increasing wealth over the past 6 decades in large parts of the Western (i.e. predominantly Caucasian) populations may indirectly have contributed to the increases in incidence rates of melanoma and other skin cancers.

Melanoma prevention

Sunscreens
An international group of experts convening at the International Agency for Research on Cancer investigated the preventive effects of sunscreen use on the development of skin cancer: They concluded that the use of protective cream could indeed prevent erythema and squamous cell carcinoma after non-intentional sun-exposure (i.e., exposure to the sun without the objective of getting exposed, for example, work-related exposure). Its protective effect for basal cell carcinoma and melanoma, however, is not yet determined, as it is difficult to study due to a long latency period.
Paradoxically, there is inconsistent evidence that the use of sunscreens may increase the risk of melanoma development by increasing sunbathing-time. Of fifteen case-control studies examined by an expert panel, only 3 showed a significantly reduced risk of melanoma, with relative risks between 0.2 and 0.6, the others observing no significant effect (4 studies) or an increased risk (8 studies, RR between 1.7 and 3.5) {2400A}. The increasing use of sunscreens may therefore have contributed to the increases in melanoma incidence.

Vaccination
Vaccination during childhood against tuberculosis with the Bacille Calmette-Guérin (BCG) vaccine or against smallpox with the vaccinia vaccine, or having experienced one or more infectious diseases may decrease the risk of developing melanomas (odds ratios between 0.29 and 0.44) {1303,1330,1331,1821, 1822}. Part of the increases in melanoma incidence could be due to the abolishment of this type of vaccination in Europe.

Clinical features

Sites of involvement
Most commonly affected site per unit surface area of skin in both sexes is the face and male ear head and neck {772,890}, with back and shoulders in men and the lower limbs in females also having high rates per unit area.

Major subtypes
Most classification schemes of melanoma categorize them clinically into four major types, but such classification has little prognostic value and diagnostic relevance, thus being of very limited usefulness in clinical practice.

Lentigo maligna melanoma.
This type of melanoma develops when an invasive tumour arises in a lentigo maligna. It is most common in the head and neck region and in elderly people, and has a relatively favourable prognosis.

Superficial spreading melanoma.
This type of melanoma grows laterally before vertical invasion develops. Increasingly, this is the most common type of melanoma in Caucasians, and has a relatively favourable prognosis being frequently observed in young patients, and on body sites that are intermittently exposed to sunlight.

Nodular melanoma
It usually presents as a rapidly growing pigmented nodule (amelanotic nodular melanomas are rarely observed), which bleeds or ulcerates. This is the most aggressive type of melanoma. It often presents on body sites that are intermittently exposed to sunlight.

Acral lentiginous melanoma
These lesions are pigmented, arising on the palm of the hand, sole of the foot or under the nails. They often present late and represent the most common type of melanoma in heavily pigmented people.

Age distribution
Malignant melanoma (hence referred to as melanoma) is a tumour affecting predominantly adults and elderly patients, with a peak of incidence around the sixth decade of life. In recent years, however, it has been increasingly recognized in middle-aged and young adults, and can be observed in children and adolescents as well. Thus, no age group is spared, and a high level of suspicion should be exerted in examination of any dubious pigmented lesion regardless of the age of the patient.

Origin
The clinical features of melanoma are variable and depend on type and stage of evolution of the tumour, and on location of it. Melanoma may occur de novo, that is, without a precursor lesion, or may develop within a pre-existing benign melanocytic naevus {1168,1750}. It has been estimated that 20-30% of melanomas arise within a pre-existing melanocytic naevus, but this figure in truth may be higher, as in many instances it is very difficult to distinguish histopathologically residual complexes of a benign naevus from those of the melanoma. All types of melanocytic naevi can give rise to a melanoma, but some are more frequently involved, such as congenital melanocytic naevi. Melanoma has only rarely been observed in association with Spitz naevi {1380}, but this may be due also to the difficulty in discerning histopathologically melanocytes of a melanoma from the atypical melanocytes frequently found in

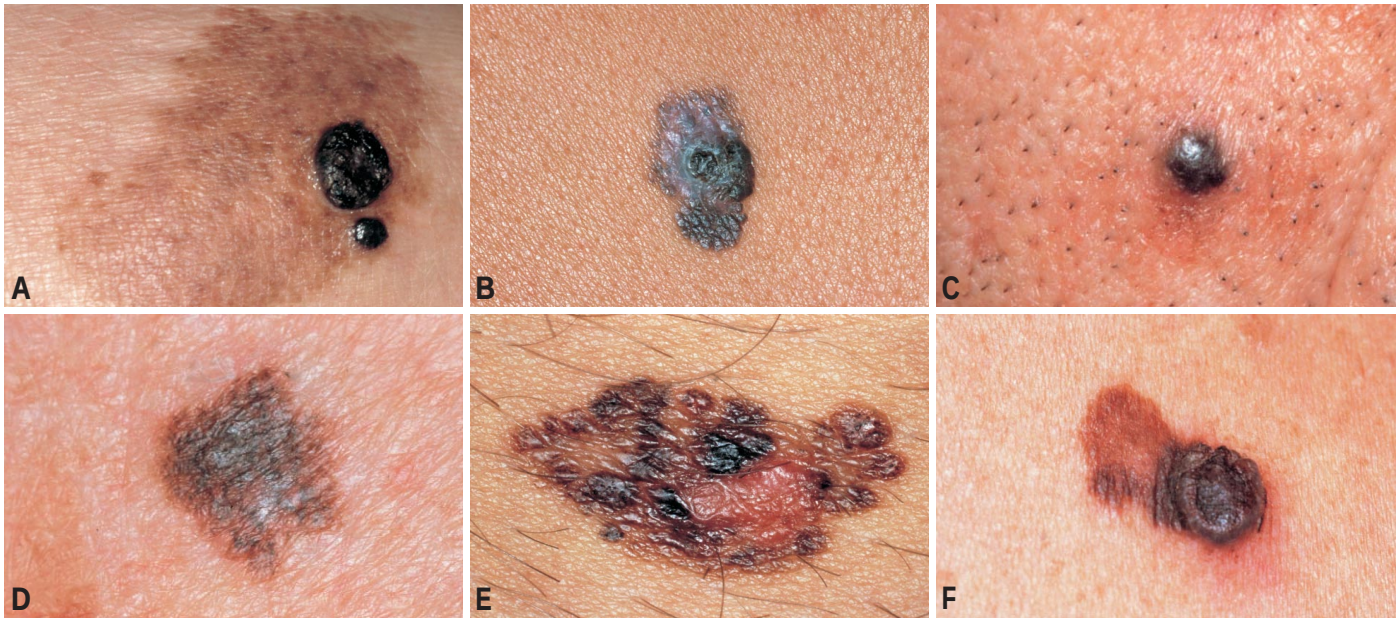

Fig. 2.4 Clinical presentation of melanomas. **A** Malignant melanoma arising in a congenital naevus. **B** Stereotypical cutaneous melanoma characterized by asymmetry, uneven pigmentation, and irregular margins. **C** "Small" melanoma (< 3 mm) characterized by a relatively symmetrical, evenly pigmented small papule. **D** Melanoma in situ. Note flat pigmented lesion with different hues of brown and slightly irregular margins. **E** Early "invasive" melanoma characterized by marked asymmetry and variegations in colour. **F** A nodule of melanoma arising within an in situ component. Note the irregular pigmentation and asymmetry of the flat part of the lesion.

Spitz naevi. Melanoma arising within a pre-existing blue naevus is commonly referred to as malignant blue naevus, an imprecise term that should be avoided.
Melanoma may arise at the site of pre-existing scars (e.g., burn scar) {1758}. Recurrence at the site of a scar from previous biopsy or narrow excision is a sign of incomplete excision of the primary tumour. Recurrence at the site of a complete excision (with negative margins verified histologically) represents locally metastatic disease rather than persistence {1000}.

ABCD rule

The most useful criteria for clinical diagnosis of melanoma are asymmetry and uneven pigmentation of the lesion, and have been integrated in the acronym “ABCD” (Asymmetry, irregular Border, uneven Colour, Diameter > 6 mm) {1552}. Although the “ABCD” mnemonic is considered the standard approach for the clinical diagnosis of melanoma, it has severe limitations when applied to early lesions of it, that may have a relatively homogenous pigmentation, sharp margins, and small diameter. Melanomas less than 5 mm in diameter have been referred to as “small melanomas” in the literature, and may be the source of diagnostic pitfalls both clinically and histopathologically {282}. In addition, when assessed with the ABCD rule many benign melanocytic naevi have atypical features, thus decreasing specificity of this diagnostic criteria, too.

Pigmentation and growth

Most (practically all) de novo melanomas are pigmented lesions that begin as a flat macule, representing the neoplastic growth of malignant melanocytes confined to the epidermis (melanoma in situ) . Lesions in this stage are characterized by a relatively homogenous brown pigmentation with slightly irregular borders. Over time (in most instances probably several years) lesions spread horizontally showing more irregular contours and variegations of the pigmentation, and revealing histopathologically involvement of the superficial (papillary) dermis. When the papillary dermis is filled by neoplastic melanocytes the lesions appear as irregular, unevenly pigmented plaques. In later stages the neoplasms exhibit vertical growth resulting in the formation of papules or nodules, usually confined to one area of the lesion. The papules and nodules represent areas where the tumour grows vertically through the dermis, eventually involving the subcutaneous tissues. In a minority of cases, melanoma exhibits a rapid nodular growth from the outset without horizontal spread, usually within a few months (so-called nodular melanoma). Finally, exceptional cases of dermal melanomas without any intraepidermal component have been recorded {2305}.

Regression

Partial regression of part of the lesion takes place commonly during the entire process of growth of melanoma, resulting in the presence of whitish-grey areas that accentuate the asymmetry and uneven pigmentation of the lesion. In rare cases, complete regression can be observed, leading to the disappearance of all neoplastic melanocytes. Usually, these lesions show uneven pigmentation with whitish, grey and black areas corresponding to the presence of variable fibrosis and infiltrates of melanophages in the dermis. With time, the pigmentation may disappear almost completely. Although regression is an immune-mediated phenomenon corresponding to the elimination of malignant melanocytes by cytotoxic lymphocytes, complete regression of a melanoma can be associated with metastatic spread, thus being a bad rather than a good prognostic sign. The prognostic role (if any) of partial or focal regression has not yet been elucidated, but it seems negligible {764}.

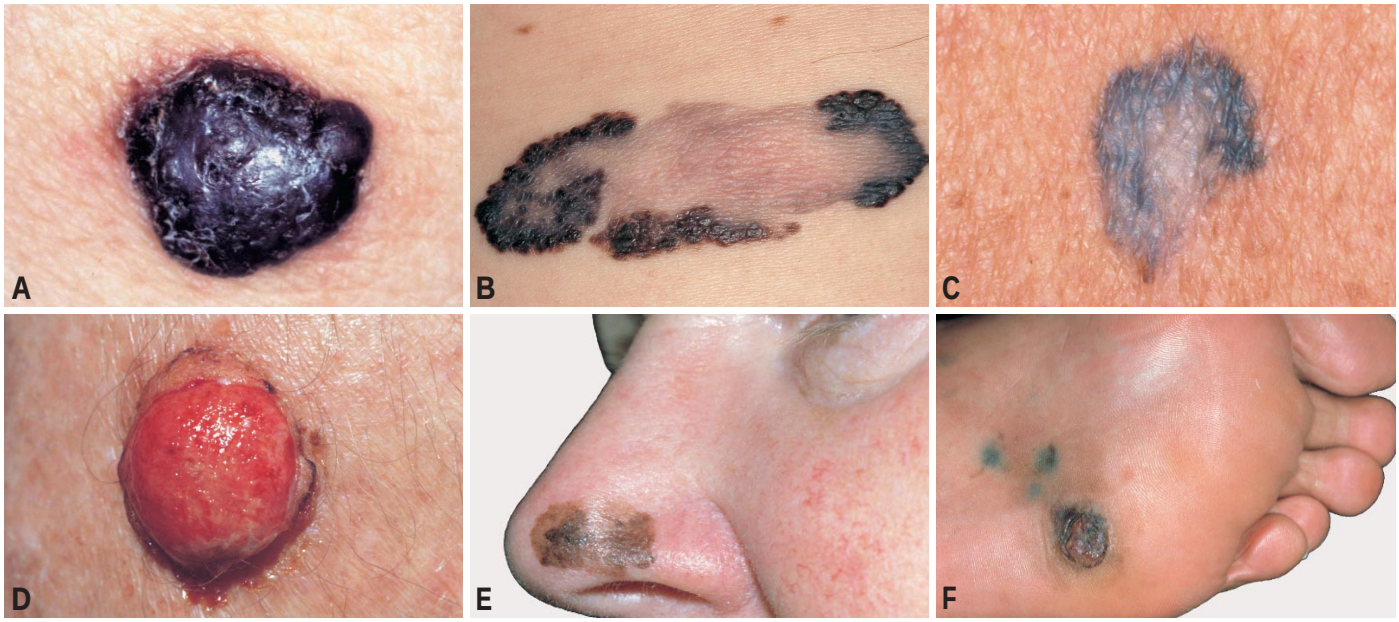

Fig. 2.5 Clinical presentation of melanomas. **A** Nodular melanoma. Large, darkly pigmented tumour practically devoid of a flat component. **B** Melanoma with prominent regression resulting in almost complete disappearance of large part of the lesion. **C** Complete regression of melanoma. The grey pigmentation is due to the presence of heavy infiltrates of melanophages within a fibrotic papillary dermis. The patient had regional lymph node metastases at presentation. **D** Ulcerated nodular melanoma resembling a granuloma pyogenicum. Note focally small areas of slight pigmentation at the margins. **E** So-called "lentigo maligna" (melanoma in situ on sun-damaged skin) arising on the nose. **F** Acral melanoma. Note the marked irregularity of the margins, confering a "multifocal" appearance to the lesion.

Melanoma is more frequent in particular settings (so-called “markers”) including a familial history of melanoma, a previous melanoma in the same patient, presence of many melanocytic naevi, presence of giant congenital naevi, skin type 1 or 2, as well as in rare conditions such as xeroderma pigmentosum among others {53,901,1196,1202,2231,2481}. Patients presenting with one or more of these features should be monitored closely, and suspicious lesions should be biopsied. It is important to remember that multiple primary melanomas may be observed rarely in some patients {1196}.

Clinical variants

Amelanotic melanoma

Although melanoma is a tumour characterized by variable degrees of pigmentation, in rare instances the pigment may be missing altogether (so-called amelanotic melanoma). Amelanotic melanomas are more frequent on the face, where they often display the histopathologic features of desmoplasia (desmoplastic melanoma), but can be observed also on other parts of the body {77,2285}.

Mucosal melanoma

Melanomas arising within a mucosa (oral mucosa, genital mucosa) are often multifocal, and are characterized by dark, uneven pigmentation {670,1963}. Differentiation of early lesions of mucosal melanoma from so-called melanosis (a benign condition characterized by prominent hyperpigmentation of the mucosa without or with only slight increase of melanocytes at the dermo-epidermal junction) may be very difficult or even impossible clinically as well as histopathologically.

Subungual melanomas

In early stages these are sometimes characterized by the presence of a well demarcated, pigmented longitudinal streak (longitudinal melanonychia) {263}. The so-called Hutchinson sign (periungual spread of the pigmentation on the proximal or lateral nail fold) may be absent in early lesions, thus representing a pitfall in the clinical diagnosis.

Ulceration

Rapidly growing, ulcerated melanomas may be misdiagnosed clinically as granuloma pyogenicum. Pigmentation in these cases may be scant and confined only to small areas of the tumour.

Verrucous phenotype

In rare cases, melanoma may present with a verrucous surface similar to what can be observed in seborrhoeic keratoses or common warts (verrucous melanoma) {101}. These cases may be misinterpreted clinically as pigmented seborrhoeic keratoses or other verrucous tumours.

Dermatoscopy

Besides clinical examination, dermatoscopy (dermoscopy, skin surface microscopy, epiluminescence microscopy) has been increasingly regarded as a valuable aid in diagnosis of early melanoma clinically. Dermatoscopic instruments enlarge the lesion 6-100-fold, thus allowing detection of structures and signs not visible to the naked eye. In addition, connection of the dermatoscopic devices to a computer allows one to take standardized digital pictures that can be compared over time, thus being much more sensitive for detection of minimal structural changes of the examined lesion {719}. Finally, computer-assisted diagnostic systems based on dermatoscopic images are available as aids for the evaluation of suspicious pigmented lesions {91}.

Several dermatoscopic diagnostic approaches have been proposed, all of them relying on the examination of distinct patterns and structures. Of particular value in the diagnosis of melanoma are the presence of an irregular pigment

network (uneven thickness of the lines, presence of broad lines at the periphery of the lesion), of black or brown dots irregularly distributed within the lesion, of irregular lines at the periphery of the lesion that are not clearly combined with the pigment network (streaks), of a blue-whitish veil corresponding to infiltrates of melanophages below a thick epidermis with hypergranulosis, of an atypical vascular pattern, and of regression structures. A 7-point checklist for dermatoscopic scoring of atypical melanocytic lesions using the aforementioned criteria has been proposed, and it has been suggested that this approach allows diagnosis of melanoma with a sensitivity of 95% and a specificity of 75% {91,1671}. Other proposed approaches include the Menzies method and the ABCD rule {91}. Besides dermatoscopy, the use of several other devices has been proposed for the early in vivo diagnosis of melanoma, including confocal laser microscopy {1509}.

Staging

Staging investigations depend on stage and extent of the disease and should always include a complete clinical examination {2218A}. Sonography of the superficial lymph nodes and of the abdomen, radiography of the thorax and evaluation of serum markers such as lactate dehydrogenase (LDH), S-100-beta or melanoma-inhibiting activity (MIA) seem to be of little value in asymptomatic patients. Computer tomography (CT) scan, magnetic resonance imaging (MRI), bone scintigraphy and positron emission tomography (PET) are useful methods for evaluation of patients with metastatic disease.

Histopathology

Architectural criteria in the epidermis

Lesional breadth

A proliferation of melanocytes wholly within the epidermis can range in size from >1 mm to a patch many cm in width. Both melanocytic naevi (conventional and Spitz) and melanoma begin as proliferations in which single melanocytes predominate.

By the time most melanomas can be recognized as such clinically they are over 4 mm in diameter, and often far broader {730}. While a large lesional diameter is a finding favouring melanoma, there are many exceptions.

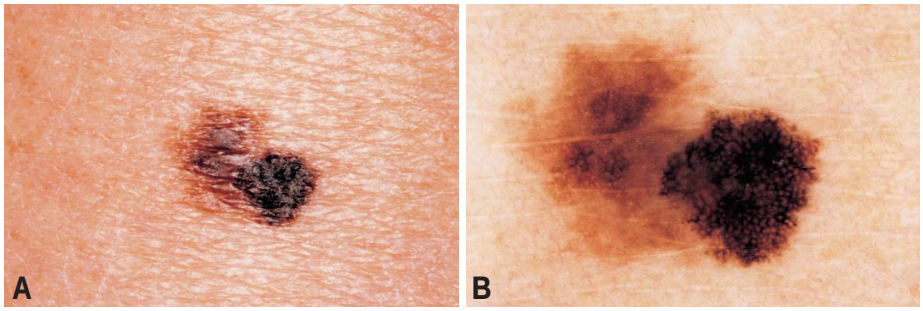

Fig. 2.6 Clinical presentation. **A** and dermatoscopic picture **B** of an early melanoma developing within a "dysplastic" naevus. Note the marked asymmetry of the lesion and the presence of an area with irregular pigment network and broad lines at the periphery, representing melanoma in situ.

Symmetry of changes in the epidermis

The most important attribute of symmetry is in reference to that of melanocytes themselves. The symmetry or lack thereof in terms of the distribution of melanocytes in the epidermis is more difficult to judge than is the overall silhouette of the lesion. It is evaluated by comparing the density of melanocytes on one side of the lesion with the other; pattern of distribution of melanocytes (are they at the junction or above it) on one side of the lesion with the other; disposal as nests or as single cells on one side of the lesion with the other; cytological findings (are melanocytes on one side of the lesion different cytologically with those on the other side). Asymmetry in any of these attributes favours melanoma.

Secondary forms of asymmetry, less important that that of the distribution of melanocytes include asymmetry in pigmentation, epidermal thickness and inflammatory infiltrates. Most of these attributes are not decisive {2506}.

Pigmentation in the epidermis in melanocytic neoplasms is usually in the basal layer (exceptions are particularly dark lesions, such as so-called hypermelanotic naevi) {513}. In such naevi, and in very dark foci of some melanomas, there may be copious melanin in keratinocytes not only in the basal layer but also in the spinous and cornified layers. Either an asymmetrical distribution of melanoma in the basal layer of the epidermis, or melanin above the basal layer on one side of the lesion but not on the other raises the possibility of melanoma. An irregular distribution of epidermal pigment is the cause of one of the “ABCD” rules (variegated colour) of clinical diagnosis of melanoma {8}. The distribution of melanophages also affects pigmentation.

Circumscription

Most melanocytic naevi have sharp borders, and melanomas indistinct ones. A melanocytic neoplasm is easiest to judge as well circumscribed if the edge of the lesion is defined by a nest, rather than by single melanocytes. In such cases, care must be taken that the distances between nests do not exceed or even approximate those between the most peripheral nest and the edge of the section (in other words, one must be sure that the “last” nest is truly the last one). One should also assess whether the nests at the periphery of the lesion are at irregular intervals. A lesion can have an entirely nested junctional component, with small nests at increasingly long intervals at its edges. This is often the cause of a “fuzzy” border in a dysplastic (Clark) naevus.

Predominance of single cells vs. nests

At an early stage in the intraepidermal development of a melanocytic proliferation, benign or malignant, single melanocytes in increased number will be present. Therefore, a 1 or 2 mm lesion, as noted above in which single melanocytes predominate is not necessarily aberrant. In the evolution of most acquired melanocytic naevi, the single melanocytes aggregate into nests by the time the lesion is 2 or 3 mm. in diameter.

The distribution of single melanocytes is also noteworthy. One can imagine a dotted line connecting the tops of dermal papillae with one another. Very few melanocytes should reside in the epidermis above that line.

Confluence of melanocytes is another

clue to the diagnosis of melanoma. Confluent single melanocytes replace the basal layer in a manner such that, at least focally, keratinocytes do not seem to intervene between them. Confluence of nests of melanocytes is a more subjective determination.

Scatter of melanocytes above the junction

If any criterion expounded herein emblemizes intraepidermal melanoma in the minds of pathologists, it is suprabasal scatter of melanocytes. Pagetoid, buckshot and birdshot scatter also describe this distribution of neoplastic cells. It can be difficult to tell if "slight" suprabasal scatter of melanocytes is present.

Physical trauma, such as excoriation or abrasion or by ultraviolet light exposure provokes scatter of melanocytes above the epidermis {2374}. Signs of physical trauma include erosion, necrosis of superficial keratinocytes, parakeratosis, subepidermal fibrin deposits and extravasation of erythrocytes in the papillary dermis. Suprabasal scatter of melanocytes is typical of naevi on acral skin {292}.

Configuration of the epidermis

An uneven epidermal contour is more apt to be present in melanoma than in a naevus. The most typical diagnostic alteration is a thinned epidermis in the area of the melanoma (or melanoma in situ) and elongated rete ridges in an area in which a pre-existent naevus is present. In the case of melanomas in which a large mass of neoplastic cells is present in the dermis, a finding known as "consumption of the epidermis" can occur. The epidermis is thinned, and instead of small cuboidal keratinocytes in the basal layer, one sees large, flat squamous ones, often with vacuolar change. This finding is much more common in melanoma than in naevi {947}.

Kamino bodies

The finding of many large, well formed Kamino bodies favours a Spitz naevus over melanoma. There are few convincing reports of melanomas with Kamino bodies, and these describe few, and smaller bodies. In some such reports, the bodies are not PAS-D positive, suggesting that dyskeratotic cells were mistaken for them. In addition to Spitz naevi, small Kamino bodies occur in some dysplastic (Clark) naevi, and in some halo naevi

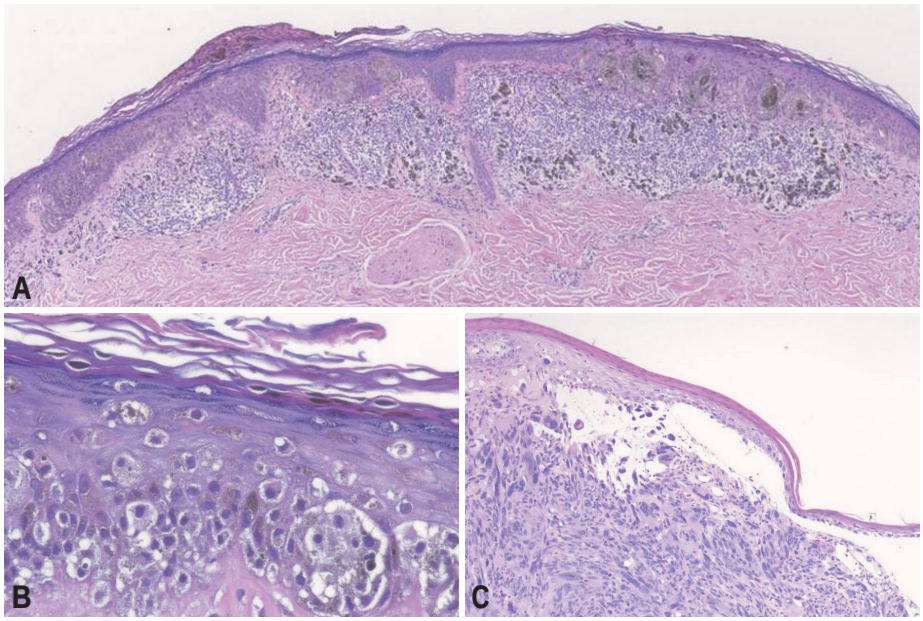

Fig. 2.7 **A** Melanoma with asymmetry. Asymmetry in the distribution of nests and of pigment- which can be within keratinocytes, melanocytes or melanophages is typical of intraepidermal melanoma. **B** Pagetoid scatter of melanocytes is practically emblematic of intraepidermal melanoma. **C** Consumption of the epidermis in melanoma. The epidermis is thinned, with squamous rather than cuboidal cells in the basal layer.

Cytological features of melanoma in the epidermis

Cytologic findings are less of a link to the correct diagnosis in the realm of melanocytic neoplasia than in other tumours. Melanocytes can be large or small, deeply pigmented or amelanotic, and vary from appearing to be round to oval to spindled to thin and dendritic.

Most acquired naevi feature small round, oval or small spindled melanocytes within junctional nests. There may be no visible pigment, or some may be intracytoplasmic. In general, the amount of cytoplasm is scant in most "common" and even in most dysplastic naevi. The nuclei of such cells are usually monomorphous, allowing for different shapes due to various planes of sectioning if the cells are elongated. Melanomas with similar cytologically bland cells do occur, and the diagnosis in such cases must be made via the architectural features of the lesion.

Small melanocytes with scant cytoplasm and angulated, darkly stained nuclei are particularly apt to be found in melanomas in severely sun-damaged skin (lentigo maligna and lentigo maligna melanoma). A similar appearance can be induced by processing artefact, and by the use of some alcohol-based fixatives instead of formalin.

Large round or oval, or epithelioid melanocytes occur in both benign proliferations and in melanoma. Such cells often have abundant pale cytoplasm, with "dusty" (fine and evenly dispersed) melanin. These cells are typically seen in the intraepidermal components of melanomas of all types. Large, pale melanocytes are also present in naevi of the scalp (especially in children and teens), breast and genitalia, and in some dysplastic naevi {1532}.

Spindled melanocytes occur within the epidermis in the junctional nests of dysplastic naevi and in Spitz naevi, as well as in melanoma, where their orientation is haphazard (some nests may be vertical and some horizontal). The nuclei of spindled melanoma cells are more often pleomorphic, and there is heterochromasia, i.e. some may be vesicular and some stain darkly.

Dendritic melanocytes are present in melanomas in dark skin patients in diverse settings, and light skinned ones in so-called lentigo maligna and the lentigo maligna pattern of melanoma, and in melanomas of acral-volar skin, the nail bed and of mucous membranes. The nuclei of dendritic melanocytes may be inconspicuous. The findings of dendrites that ascent to the mid-spinous zone, and

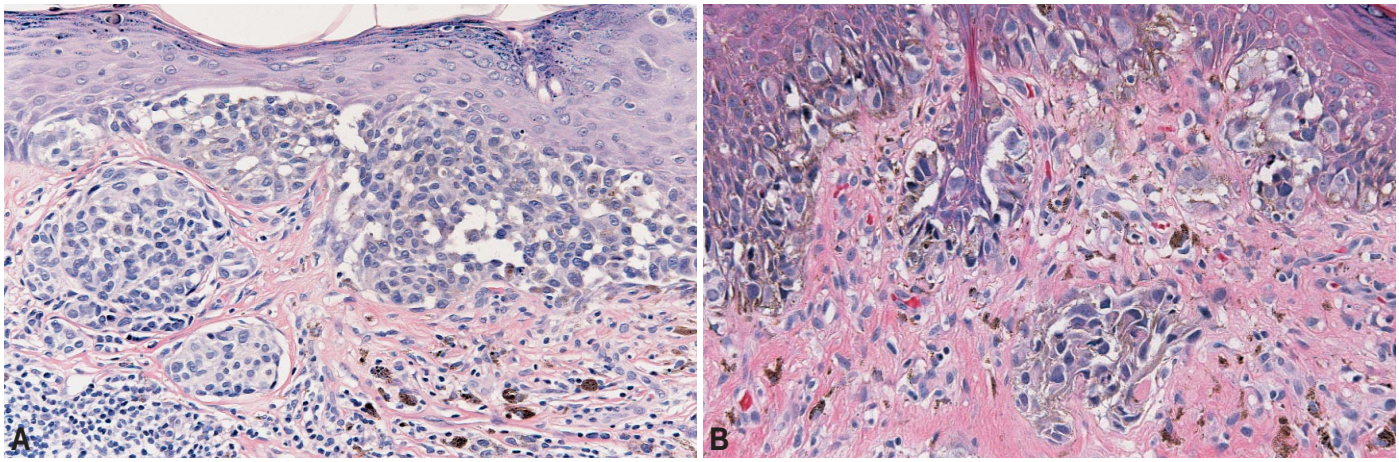

Fig. 2.8 **A** Melanoma, invasive radial growth phase (invasive but non-tumorigenic melanoma). Clusters of cells are present in the dermis (see bottom left) that are not larger than the largest intraepidermal clusters. **B** A thin invasive and tumorigenic melanoma. The cluster of cells in the dermis is slightly larger than the largest cluster in the epidermis, constituting a pattern consistent with a very early tumorigenic melanoma.

especially variability in the widths of dendrites at the same level of the epidermis (anisodendrocytosis) are useful clues to melanoma in these settings.
The extreme cytologic atypia typically seen in thick melanomas in the dermis and in metastases of melanoma, with very large, irregularly shaped and brightly eosinophilic nucleoli is not usually to be found in the intraepidermal component of a melanoma.

Architectural criteria in the dermis
The presence of the intraepidermal changes of melanoma is of course a clue that the dermal component of a melanocytic neoplasm might represent melanoma as well. Again, architectural criteria are more important than cytologic ones, although the balance is more even than in assessing the intraepidermal portion of a melanoma.

Symmetry
The most important aspect of symmetry of the dermal component of a melanocytic neoplasm pertains to its outline, or silhouette.
Other forms of symmetry pertain to what lies within the silhouette- the composition of the neoplasm. The sizes and shapes of nests, the pigmentation and cytologic features of the melanocytes and infiltrates of lymphocytes and melanophages ideally are the same on both sides of the lesion, at the same level of the dermis. A disproportionately large nest of cells with cytologic features that contrast with those on the other side of the lesion may be a clue to melanoma.

Contour
Dysplastic naevi have a flat base at the interface between the papillary and reticular dermis, Spitz naevi have flat or wedge shaped bases, superficial blue naevi are wedge shaped, congenital and congenital-like naevi have an uneven base, with melanocytes clustered around adnexa and sometimes around vessels, and deep (often cellular) blue naevi have a lobulated base, with blunt masses of cells that protrude into the subcutis .
Melanomas that involve the dermis typically have uneven, sometimes jagged bases.

Maturation
Maturation of melanocytes is in some ways a misnomer- a mature melanocyte is dendritic, and synthesizes pigment within an epithelium. The process commonly referred to as maturation is really senescence; it reflects a loss of metabolic activity, reproductive capacity and in some cases a tendency to become fat- just as mammalian senescence does. Maturation of melanocytes occurs in most naevi, with the exception of blue naevi (including deep penetrating naevi). The best-known form of maturation is the progressive diminution in the size of the nuclei of melanocytes at increasing depth within a lesion. Nucleoli also diminish in size, and if they are eosinophilic in the upper part of a lesion they tend to become basophilic at its base. Nuclear maturation in melanocytic lesions can be quantified by morphometric studies {211,1398}.
In addition to nuclear maturation, the amount of cytoplasm is less at the base of a benign melanocytic neoplasm than in its upper nests. If the cytoplasm of the upper cells of a naevus is pigmented, its lower cells tend to be less pigmented or achromic. The sizes of aggregations of melanocytes also should be smaller toward the bottom of a benign neoplasm of melanocytes.
The scientific basis of maturation rests on changes in metabolism (less tyrosinase activity and more acetylcholinesterase activity) and telomeric exhaustion {865,1620}.
Maturation occurs to a limited extent in some melanomas, but in most there are cells at the base of the lesion nearly as large as those at the top, and dispersion from large nests to small ones and single cells is often absent {1989}. Pigmentation near the base of a melanocytic neoplasm can also be a clue to melanoma, but it commonly occurs in blue naevus.

Mitotic activity
Mitoses in the dermal portion of a lesion do not mandate a diagnosis of melanoma. As a rule, the mitotic figures in benign naevi are found in melanocytes within the papillary or superficial reticular dermis. If the lesion in question only extends to this depth, the number of mitoses becomes important, as does the question of whether the mitoses are in clusters (reflecting “hot spots”) or are atypical. Atypical (asymmetric, tripolar or ring) mitotic figures can occur in Spitz naevi, but are rare in other forms of naevus. Ki67 / MIB-1 marks cells that are actively cycling, and the number of such

cells should diminish toward the bottom of a benign melanocytic neoplasm. The finding of a low proliferation rate is no guarantee of benignancy. A high rate in a lesion thought to be benign should trigger reassessment.

Cytologic features of melanoma in the dermis

The cells of a melanoma may be large or small melanocytes, round or spindled, amelanotic or deeply pigmented.

Large spindled melanocytes comprise the dermal component in some melanomas. They often are not reliably demarcated from each other by clefts, as is the case in Spitz naevi. They can form elongated, sometimes sinuous fascicles, especially in melanomas with neuroid differentiation and in desmoplastic melanomas. The spindled melanocytes of desmoplastic melanoma can also be found singly between thickened collagen bundles. They tend to be hyperchromatic, and have irregular nuclear membranes and small nucleoli.

Melanocytes with abundant pale cytoplasm and dusty melanin (large, pale melanocytes) are typically present in the dermis in some dysplastic naevi, naevi at special sites (scalp, breast and genitalia) and in deep penetrating naevi. They are a common cytologic type in melanoma, especially in the superficial spreading and nodular patterns.

Small round melanocytes with scant cytoplasm, resembling those of the mature portion of a naevus can predominate in naevoid melanomas

Radial and vertical growth

Radial growth phase

Most melanomas evolve through an initial stage of tumor progression, as a flat or plaque - like lesion which expands along the radii of an imperfect circle. Because of this clinical analogy, this phase has been termed the “radial growth phase” {494}.

The radial growth phase may be in situ (confined to the epidermis), or in situ and invasive, but in the latter case the cells do not have capacity for proliferation in the dermis {674,832}. Proliferation in the epidermis may give rise to a pattern of single cells, or of clusters or nests of atypical neoplastic melanocytes. Like the cells of junctional nevi, which may migrate into the dermis to form compound nevi, the cells of in situ melanomas may migrate into the papillary dermis. In the dermis, these cells may either undergo apoptosis and disappear {1070}, or may survive without proliferating. In the latter case, the lesional cells may persist in the dermis, but they do not expand to form a tumorigenic nodule.

Vertical growth phase (tumorigenic)

In the next phase of progression, a tumor nodule appears either within the confines of a pre-existing plaque, or, sometimes, de novo in a lesion which is then termed “nodular melanoma” {675} cells.

The key biological feature of vertical growth phase is the ability of the lesional cells to survive and proliferate in the dermis. This ability may be manifested by growth to form a true “tumour” or swelling, or by the presence of mitotic activity. Tumorigenic vertical growth is easily recognized when there is a bulky nodule present. In thin lesions, such as AJCC stage I melanomas, either of two criteria suffices for the diagnosis of vertical growth phase, namely the presence of either “tumorigenicity” or “mitogenicity”. The term "mitogenic" refers to the presence of any mitotic figures in lesional cells in the dermis. The term “tumorigenic” is here defined as the presence of a cluster of cells in the dermis larger than the largest intraepidermal cluster.

Metastatic spread

Most distant metastases from melanoma become evident clinically or are detected during follow-up visits within a few years from excision of the primary tumour. However, it is important to remember that late metastases (> 10 years, sometimes even over 25 years after excision of the primary tumour) are not uncommon in this neoplasm {566, 2088}. The reason why “dormant” metastases begin to grow after such a long time is yet unknown.

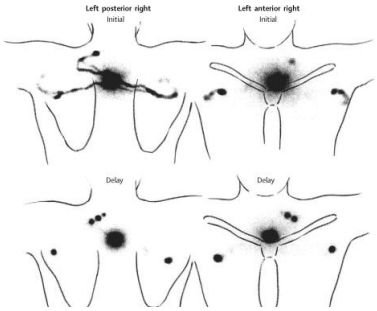

Fig. 2.9 Lymphoscintigraphy in a patient with a melanoma on the central upper back.
Top: summed 10-min dynamic images in posterior and anterior projections after injection of technetium-99m antimony sulphide colloid intradermally at melanoma site. Dominant lymphatic channels pass laterally to both axillae and upwards to interval nodes on back. Delayed scans 2 h later show a single sentinel node in each axilla and three interval nodes (also sentinel nodes in this patient) on upper back. From J.F. Thompson et al. {2348A}, with kind permission of The Lancet.

In most patients with metastatic disease, the regional lymph nodes are affected first, but distant metastases may be observed in patients who do not have obvious lymph node involvement. Besides lymph nodes, the most common site of metastatic spread is the skin. Visceral metastases are more frequently located in the lungs, liver, central nervous system, and bones, but any organ may be affected.

In 1992, sentinel node (SN) biopsy was proposed as a minimally invasive procedure that provided accurate assessment of regional node status in melanoma patients {1655}, allowing full regional node dissection to be avoided in the 80% of patients who had negative SNs. The SN concept is simple: lymph draining from a tumour site passes first to a so-called sentinel node before onward

Table 2.02
Melanoma antigens

Type of antigen	Antigen
Differentiation antigens	Tyrosinase, gp100, Melan-A/MART-1, TRP-1, TRP-2, MC1R, AIM-1
Gangliosides	GM3, GD3, GD2, GM2, 0-acteyl GD3
Mutated proteins	CDK4, ß-catenin, CDC27, MUM-2, triosephosphate isomerase
Products of unusual DNA transcrips	TRP-2, N-acteylglucosaminyl transferase
Cancer / testis antigens (CTAs)	MAGE, BAGE, GAGE, RAGE, NY-ESO-1

Table 2.03
Melanoma markers

Type of marker	Marker[1]			
Differentiation	Tyrosinase, gp100, Melan-A/MART-1	TRP-1, TRP-2, MC1R	AIM-1 S-100	Mitf, HMW-MAA
Progression				
Proliferation	Cyclin A ↑ Cyclin B1 ↑ Cyclin D1/D3 ↑ Cyclin E ↑	Cdk2 ↑ p15 ↓ p16 ↓	p21 ↑ p27 ↓ Ki67 ↑	PCNA ↑ mdm-2 ↑ telomerase ↑
Signaling	c-Kit ↓ c-Myc ↑	N-ras ↑ α-catenin ↓ receptor ↑	EGFR ↑ Transferrin	PTEN ↓
Transcription	ATF-1 ↑	AP-2 ↓		
Adhesion	E-Cadherin ↓ N-Cadherin ↑ VCAM-1 ↓	ICAM-1 ↑ MCAM ↑	ALCAM ↑ αvß3 ↑	α4ß1 ↑ CD44 v6 ↑
Proteases	MMP-1 ↑ MMP-2 ↑ MMP-9 ↑	MMP-13 ↑ MT1-MMP ↑ TIMP-1 ↑	TIMP-3 ↑ EMMPRIN ↑	PA-system ↑ Cathepsin B, D, H, L ↑
Other	ME491/CD63 ↓ HLA Class II ↑	HLA class I ↓ CTAs ↑	Osteonectin ↑	Fas/Fas ligand ↑

[1] ↑ Upregulation with tumour progression; ↓ downregulation with tumour progression

passage to other nodes in the regional node field. Thus the SN is most likely to contain tumour cells, and if none are present in this node, tumour cells are unlikely to be present in other nodes in the node field. Within 3 years of the landmark publication by Morton et al {1915}, confirmation of the accuracy of such assessment was provided by studies in the USA {1915} and Australia {2347}.

It soon became clear that identification of this node was most accurate if three methods were used: a preoperative lymphoscintigram, injection of blue dye around the primary melanoma site immediately preoperatively, and the use of a hand-held gamma probe intraoperatively. Preoperative lymphoscintigraphy for many melanoma patients before SN biopsy provided important new insights into cutaneous lymphatic drainage pathways {2348,2396} and this new information highlighted the importance of preoperative lymphoscintigraphy before undertaking a SN biopsy procedure.

The prognostic value of determining SN status has now been shown in several large studies. All show a large difference in probability of 5-year survival between patients who are SN positive and those who are SN negative, independently of other prognostic variables. Results from the Sydney Melanoma Unit {2565} are typical, with a 5-year survival rate of 56% for SN positive patients (n=145) and 90% for SN negative patients (n=846). Prognostic information from SN biopsies may be further refined by PCR to detect melanoma-specific mRNA in lymph nodes that are negative by standard histopathological techniques {1916}.

SN assessment not only provides important prognostic information; resent clinicla trials suggest that as an removal, with complet regional node field dissecion if micrometastatic melanoma is found, improves the survival of patients {1655A}.

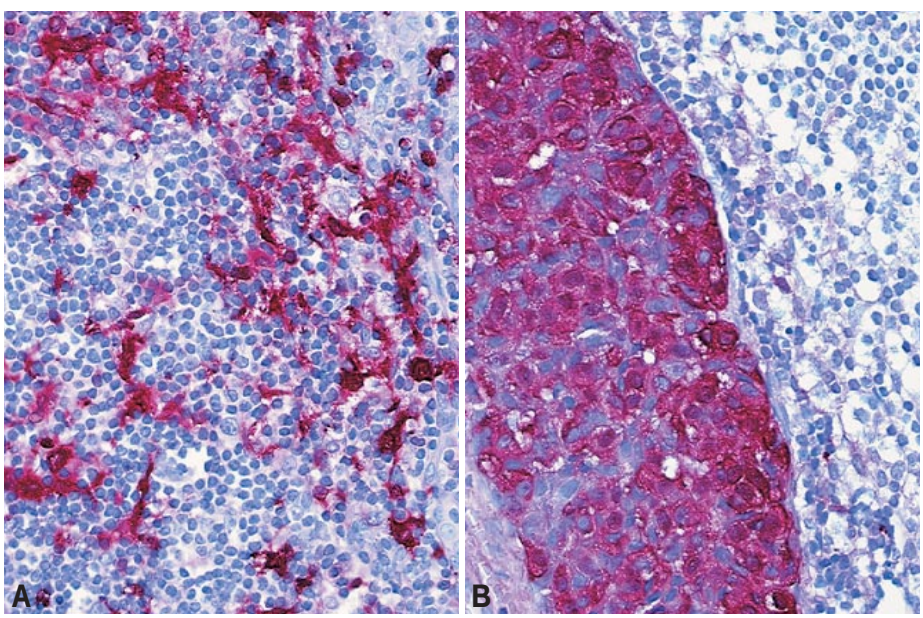

Fig. 2.10 Immunoreactivity of melanoma. **A** Immunohistochemical staining for S-100 of dendritic cells in reactive lymphadenopathy and **B** Melanoma micrometastasis in a sentinel lymph node.

Stage distribution

Survival from melanoma is related to stage at diagnosis. The stage distribution is generally more favourable in high-resource settings, and thus countries with high incidence rates tend to also have better survival than lower incidence (and lower resource) countries {608, 1472,2245,2351}.

Most melanomas are localized in high incidence countries and the proportion that are localized continues to increase with time. Of the cases reported in the U.S. SEER program 1992-1998, 82% had localized disease, 9% regional disease, 4% distant metastases, and 6% were unstaged {186}.

Young patients and women are often diagnosed with melanomas that have a thinner Breslow thickness than older patients and men. Because of the shift in the stage distribution of melanomas towards thinner lesions, together with a disproportionate increase in incidence relative to mortality, some have questioned whether some of these thin lesions that were removed would have ever progressed to metastatic disease {353}.

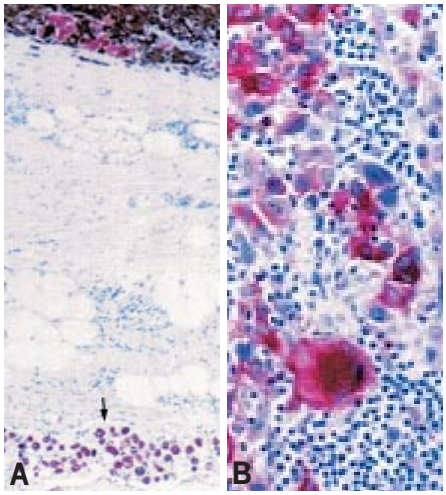

Fig. 2.11 Immunoreactivity for **A** gp100 and **B** MART-1 of metastatic melanoma cells. Note the extranodal tumour embolus in **A** (arrow).

Immunoprofile

Melanoma antigens

The term "melanoma antigen" is used two-fold. Firstly, it refers to a large variety of molecules recognized by (monoclonal) antibodies, that were generated to explore their potential as biological and/or clinical markers. Secondly, melanoma antigen in a strict sense implies a tumour molecule that evokes an immune response in the autologous host {1944}. Some overlap exists between genuine melanoma antigens and melanoma markers. Melanoma antigens currently are used in vaccination trials.

Melanoma markers

Three groups of markers can be distinguished:

Differentiation markers

These markers indicate melanocytic differentiation which is manifested by signs of melanin synthesis. Hereby cells of the melanocytic lineage are identified, but also ectopic melanin synthesis in cells of other lineages. Differentiation markers show a broad expression in many benign melanocytic lesions and (most) primary melanomas. However, in melanoma metastases expression decreases which is accompanied by heterogeneity.

Progression markers

These markers are preferentially expressed in one or few stages in melanocytic tumour progression. Based on their tissue distribution, early, intermediate and late progression markers are discerned. Progression markers include molecules that are involved in key processes in the pathogenesis of metastasis, i.e. proliferation, migration and matrix degradation. They may be derived from the neoplastic cells and/or the stromal cells, and serve as targets for various clinical interventions.

Other markers

These represent molecules that cannot be incorporated into either of the above groups.

Clinical applications

The markers mentioned can be used for several clinical applications {392}. For this purpose currently immunohistochemistry on paraplast embedded tissue sections is applied, preferentially employing a red chromagen in order to contrast with the brown colour of melanin. For some applications RT-PCR is used.

Differential diagnosis of poorly differentiated malignant tumours

In case of a differential diagnosis between poorly differentiated carcinoma, sarcoma, lymphoma and melanoma a panel of various differentiation markers is applied. Melanoma is likely if the tumour is diffusely staining for S-100 and the markers for the other diagnostic options are negative. Given the low specificity of S-100 for melanocytic differentiation the diagnosis has to be substantiated. For this purpose MART-1 (syn. Melan-A) is a powerful marker both having a high sensitivity and specificity. Its sensitivity is higher than gp100 (recognized by HMB45) in cutaneous melanoma and metastasis, although in non-cutaneous melanoma it may be the reverse.

Immunotherapy

Vaccination trials have been started using gp100 and tyrosinase presented by dendritic cells, and MAGE3. Patients are selected on the basis of an appropriate HLA haplotype and extent of antigen expressed {611}. Expression of gp100 and tyrosinase is estimated on immunohistochemically stained melanoma slides; for MAGE3 RT-PCR is used.

Table 2.04
Prognostic indicators for melanoma.

Prognostic factor	Most favourable when:
Breslow thickness	Thin (<1.51 mm)
Histology	Superficial spreading melanoma
Age	Young
Sex	Female
Body site	Not on the trunk, hands, feet
Ulceration	Absent
Mitotic index	Low

Genetic susceptibility

If melanoma runs in the family (i.e. if a parent or sibling was diagnosed with a malignant cutaneous melanoma), the relative risk of developing a melanoma compared to persons without a family history of melanoma is 2-3 {1006} and some melanoma pedigrees have been discovered. Clustering of melanoma in families is however not frequent and the genes implicated in large melanoma families probably only play a small role in population-based melanomas. Two genes have been discovered in melanoma families: CDKN2A (p16) on chromosome 9p21, and CDK4 on chromosome 12. Mutations in the CDKN2A gene have been found in up to 25% of melanoma families worldwide, whereas CDK4 has only been observed in a few rare families. The CDKN2A/p16 gene acts as a tumour suppressor gene and plays a crucial role in cell cycle regulation and senescence. The p16 protein is a cyclin-dependent kinase inhibitor which works by binding to CDK4.The p16 gene tends to be transmitted in an autosomal dominant fashion. Its penetrance varies with population incidence rates, indicating that the same factors that affect population incidence of melanoma may also mediate CDKN2A penetrance. The frequency of mutated p16 in the general population is estimated to be 0.01% {176}.

Other genes, such as *MC1R* (Melanocortin 1 Receptor) and DNA repair genes, are likely to be more important in determining susceptibility for melanoma in the general population. The *MC1R* gene is involved in skin and hair pigmentation and in senescence and immunity {176,251,2385}. Patients with inherited abnormalities in the DNA repair system, like xeroderma pigmentosum patients, are at a 1000-fold increased risk {891}.

Prognosis and predictive factors

Melanoma thickness, body site, histological type of the melanoma, gender of the patient and ulceration are important indicators of patient prognosis {130}. Generally, older patients do less well than younger patients for the same tumour thickness, while females do better than males. Superficial spreading melanomas generally have a better prognosis compared with other histological subtypes, because they usually have a thin Breslow thickness {1471}. One report suggests that sun exposure is associated with increased survival from melanoma {224}.

Reports on prognosis from specialized centres {130}, may contain survival rates lower than reported by population based cancer registries {2051}, possibly because patients with less favourable prognosis are being referred to specialized centres.

Morphological prognostic factors

Several clinical and histologic attributes are useful in predicting the probability of survival for patients with melanoma, and, as targeted therapies begin to be developed, no doubt these or similar attributes may be useful in predicting therapeutic responsiveness. Staging of melanoma has been discussed above, and in the 2002 AJCC classification, this staging includes clinical as well as histologic attributes {130}. The basic purpose of staging is to describe the clinical extent of disease. This may be done by physical exam, by clinical investigations, and by gross and microscopic pathologic examination. The process of predicting prognosis using pathological attributes may be referred to as "microstaging". Some of these attributes useful in prognostication are discussed below.

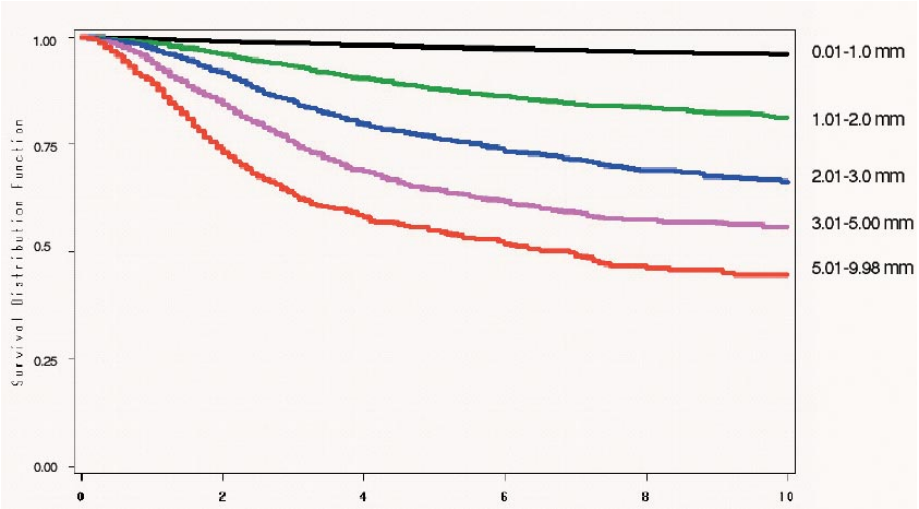

Fig. 2.12 Thickness and prognosis. Kaplan-Meier ten year survival curves by thickness, SEER cohort. Thickness groups presented in various colours are from top to bottom <1.00mm, 1.01-2mm, 2.01-3.0 mm, 3.0-5.0 and >5mm, respectively. Adapted from Gimotty et al, 2005 {830}.

Clark's levels of invasion

First described in 1967, these attributes along with Breslow's thickness measurements are the best known prognostic attributes for melanoma {492}. In Clark's level I, the melanoma is confined to the epidermis (melanoma in situ). In level II, melanoma cells are present in the papillary dermis, which may be expanded but has not filled by tumour. Most level II melanomas are non-tumourigenic, but a few meet criteria for tumourigenicity discussed above. In level III, there is a tumour that fills and expands the papillary dermis. In level IV, tumour cells infiltrate to the collagen fibres of the reticular dermis which unlike the papillary dermis are not specialized maintain epithelium. In level V, the subcutaneous tissue is infiltrated.

Breslow's thickness

According to Breslow's definition, published in 1969, thickness is measured from the top of the granular layer to the deepest invasive tumour cell. This can occasionally be misleading, for example when there is marked epithelial hyperplasia but only a few tumour cells are present in the dermis. In the 2002 AJCC staging system, thickness is grouped in 1 mm intervals {130}. If only one attribute is known, thickness is the single strongest prognostic attribute for melanoma.

Ulceration

Ulceration is a significant stage modifying factor in the 2002 AJCC classification. For any given thickness level, the prognosis is significantly worse when ulceration is present. In "thin" melanomas (Breslow thickness less than 1 mm) this remains true however only a few melanomas are ulcerated. Ulceration loses its significance when mitotic rate is included in a population based multivariable prognostic model {160}.

Mitotic rate

Mitotic rate was the single strongest attribute in the 1989 Clark prognostic model, which was developed in a cohort of patients all of whom had vertical growth phase. Patients with a mitotic rate of six or greater were at approximate twelve-fold greater risk of metastasis than patients whose tumours had no mitoses {491}. In addition, the presence of any mitoses at all in the dermis ("mitogenicity") is predictive not only of survival {831} but also of sentinel lymph node positivity {1251}.

Tumour infiltrating lymphocytes

First demonstrated in the 1989 Clark model {491} and later confirmed by others {502,1609}, the presence of "brisk" tumour infiltrating lymphocytes (lymphocytes present among and in contiguity with tumour cells) is almost as powerful an attribute as mitotic rate.

Lymphovascular invasion

Although not commonly observed, and therefore not found to be an independent factor in most prognostic models, vascu-

lar invasion when present appears to be associated with a worse prognosis {1213}.

Radial growth phase regression
Several studies have demonstrated worse prognosis when radial growth phase regression is present {491}. Possibly in these cases, a small area of tumourigenic vertical growth phase was present before the regression obliterated it.

Microscopic satellites
Like clinical satellites, microscopic satellites are indicative of a lesion with competence for metastasis and are associated with a worse prognosis {962}.

Patient gender and lesional cell location
In most series, even when other prognostic factors are controlled, female patients have better survivals, and the survival is better for patients whose lesions are on the limbs compared to the trunk or extremities {491}.

Immunoprofiling for the assessment of prognosis
Two strategies are followed:
1. Identification of markers suggestive of aggressive subpopulations in primary melanoma {1990}. For this purpose late progression markers are used. Only a limited number of progression markers have prognostic implication independent of the conventional dominant factors, i.e. tumour thickness and ulceration. A list of prognostic markers is presented in Table 2.5. It should be noted here that the clinical relevance of these markers is increasing as the primary melanomas currently diagnosed are relatively thin (1.0-1.5 mm) and rarely show ulceration. It is expected that a set of prognostic markers may help to select melanoma patients for adjuvant therapy. Such a set may be designed on the basis of the outcome of ongoing expression array studies.
2. Microstaging. The presence of melanoma deposits in various stages of the disease is assessed by the demonstration of differentiation markers. However, they may decrease during tumour progression and do not reveal the aggressiveness of the tumour cells. Nevertheless, the extension of the primary tumour that includes thickness measurement and identification of microsallelites, can be facilitated by S-100 or MART-1 immunohistochemistry. This also is applicable for the detection of melanoma cells in sentinel nodes. Immunohistochemistry on serial sections is preferred to molecular staging of sentinel nodes as it has a similar sensitivity, a higher specificity and it preserves morphology.

Table 2.05
Prognostic markers in malignant melanoma

Marker	Expression	Prognosis[1]
Ki67	↑	–
PCNA	↑	–
Cyclin A	↑	–
p16	↓	–
αvβ3	↑	–
ICAM-1	↑	–
CD44	↑	+
MMP-2	↑	–
t-PA	↑	+
gp100	↓	–
Mitf	↑	+
c-kit	↓	–
c-myc	↑	–
p53	↑	+
Osteonectin	↑	–

[1]-: Unfavourable: +: favourable

Superficial spreading melanoma

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Definition
Superficial spreading melanoma (SSM) is a subtype of melanoma which tends to occur on usually covered skin and is characterized by a radial growth phase comprised of large neoplastic melanocytes that extend among keratinocytes in a "buckshot" or pagetoid pattern {493,494}. It is controversial whether SSM is truly different from other melanoma forms of the skin or whether the differences are only due to differences in the skin architecture {22}.

ICD-O 8743/3

Synonym
Pagetoid melanoma.

Epidemiology
SSM makes up almost two thirds of all melanomas in light-skinned people (Fitzpatrick skin types 1–3) and is thus the most frequent subtype of all melanomas. The sex incidence is identical in most areas.

Etiology
Its etiology is not exactly clarified, however, repeated severe sunburns in childhood appear to play an important role. Intermittent sun exposure in adult life is also important.

Localization
SSM may appear on almost the entire body, particularly on sites with acute-intermittent sun exposure. SSM in women is most frequently observed on the legs, in men more commonly on the trunk.

Clinical features
Signs and symptoms
SSM in situ begins as an irregularly pigmented and outlined macule. With the onset of invasion, it develops into a slightly raised plaque. Its borders are usually sharply delimited, often irregular indicating progressive peripheral extension, but they may also be ill-defined. The pigmentation within an individual lesion varies from light to dark brown to even jet-black. Grey or white areas indicate regression. White vitiliginous areas, sometimes even poliosis (white hair) may be observed. Red areas are due to inflammation or increased vascularity. Some SSMs are amelanotic, resembling Bowen or Paget disease. The tumour may reach a considerable diameter until it develops a papule representing the transition from the radial growth to vertical growth phase of SSM. These papules tend to become erosive, ulcerated and crusted with a tendency to easy bleeding. In rare instances satellite nodules are present. Most lesions are asymptomatic, but can present with bleeding once the lesion ulcerates.

Histopathology
SSM in situ or the intraepidermal part of an invasive lesion stands out by pagetoid spread throughout the epidermis of atypical melanocytes that often have large nuclei and nucleoli and abundant pale cytoplasm. Mitoses are frequently absent. The melanocytes may be distributed singly or in nests. The distribution is often irregular and the nests may have irregular shapes or show confluence. Poor lateral circumscription is often present, with single enlarged melanocytes found lateral to the last nest. Hair follicles and eccrine duct epithelium can be involved in a similar pattern. To one side or in the subjacent dermis there may be a residuum of a naevus. In MIS the stromal and inflammatory reaction tends to be inconspicuous and can be absent. An irregular distribution of lymphocytes and/or melanophages may be a diagnostic clue that the lesion is a melanoma. Actinic elastosis may or may not be present.
With development of invasive melanoma, an asymmetric outline becomes a major characteristic. Extensive and highly irregular junctional tumour nests are found at a variable distance to each

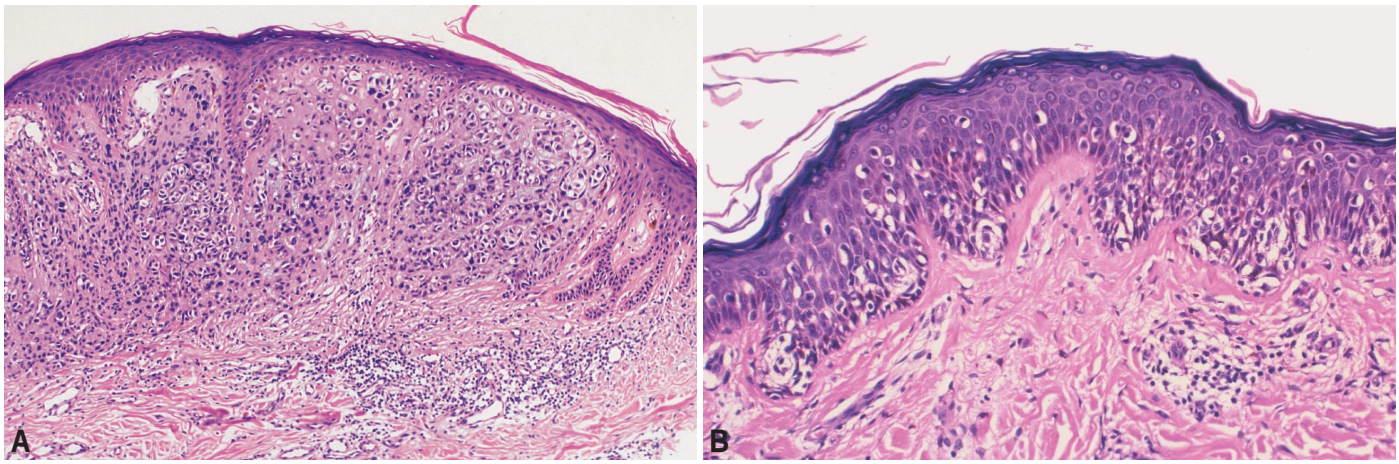

Fig. 2.13 Superficial spreading melanoma. **A** Low power magnification of the papular component. **B** Pagetoid spread of single melanocytes as is typically found in many examples.

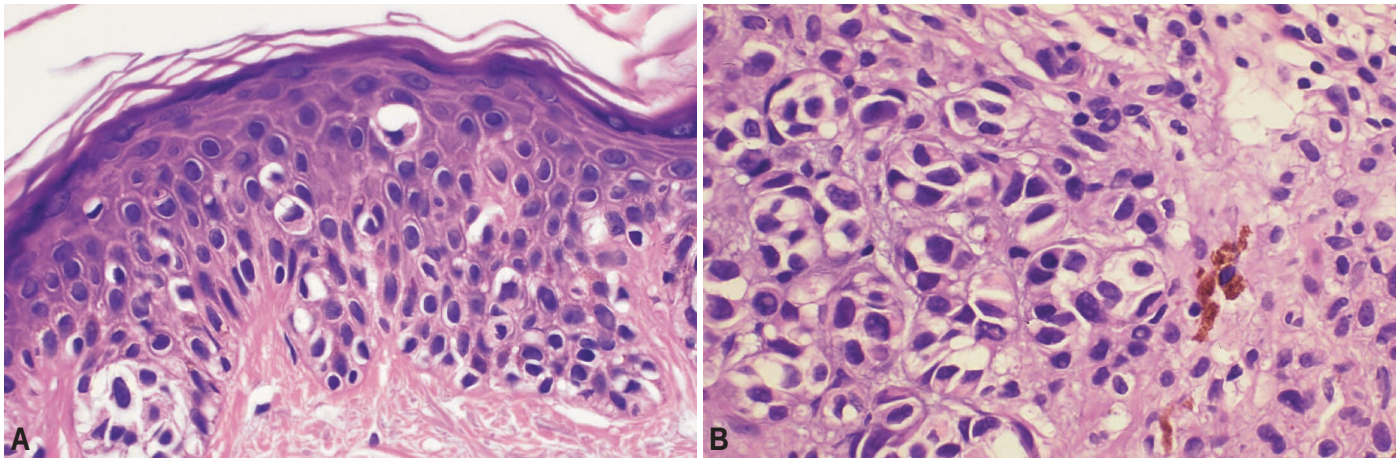

Fig. 2.14 Superficial spreading melanoma. **A** Single cells and small nests are irregualrly arranged along the junction. Toward the centre a large melanocyte is present in mid-spinous layer. A Langerhans cell is in nearly the same position toward the edge but is much smaller. **B** The invasive portion of the melanoma, showing nuclear pleomorphism. At the base there is a lymphocytic infiltrate.

other and may merge. There is often a lack of maturation, manifested by a failure of nests, cells, nuclei or nucleoli to become smaller towards the base of the lesion. Pigment is often irregularly distributed. Mitoses, sometimes atypical, are often seen whereas necrotic melanocytes are rarely identified. A lymphocytic infiltrate may be present at the base of the neoplasm or may infiltrate among its cells (so called tumour infiltrating lymphocytes or TILS). Melanoma may undergo regression, which clinically and grossly most often involves a portion of the lesion, or occasionally its entirety. Histologically this regression may be complete or partial within a given area. Complete regression of a portion of a melanoma ("segmental regression") is manifested by absence of melanocytes in the affected area. In partial regression, there is a strikingly diminished number of melanocytes compared to the remainder of the lesion. In both forms there is fibrosis of the papillary dermis, vascular proliferation and ectasia, and variably dense infiltrates of lymphocytes and melanophages. The epidermis may show loss of rete ridges. The type of regression described above affects the radial growth phase. Occasionally, a vertical growth phase may undergo regression, and sometimes the regressed portion may be replaced by a large mass of melanophages, representing a phenomenon called "tumoural melanosis".

Immunoprofile

There are no specific differences in the immunophenotype of SSM and other forms of melanoma.

Somatic genetics

SSM has a high incidence of mutations in the BRAF oncogene on chromosome 7q34 {1493}. The most common chromosomal aberrations in SSM are losses of chromosomes 9, 10, 6q, 8p and gains of chromosomes 1q, 6p, 7, 8q and 20 {173} Melanomas with increased copies of chromosome 7 that show mutations of B-raf selectively increase the copy number of the mutated allele suggesting that the mutation precedes the chromosomal aberration {1493} The minimal deleted region on chromosome 9 includes the CDKN2A locus on 9p21 as can be seen by high-resolution comparative genomic hybridization (CGH) {876}

Prognosis and predictive factors

The prognosis of SSM does not differ significantly from other forms of melanoma (see Introduction).

Nodular melanoma

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Definition
Nodular melanoma (NM) is a subtype of malignant melanoma (MM) exclusively in vertical growth phase.

ICD-O code 8721/3

Epidemiology
In most parts of the world, NM is the second most common subtype of MM, and accounts for 10 to 15% of all melanomas in Caucasian people {163,436}. NM appears on the average, in older individuals than the common superficial spreading MM (SSM) {436,493}.

Etiology
Most of the skin characteristics and risk factors associated with the development of NM are similar to those of SSM {1364}, including fair or red hair, blue eyes, fair skin, tendency to develop freckles and sunburns, excessive exposure to ultraviolet radiation, numerous common naevi, giant congenital naevi, atypical (dysplastic) naevi, melanoma in a first degree relative, familial atypical mole-melanoma syndrome, immunosuppression, xeroderma pigmentosum and prior melanoma {624,2304}.

Localization
NM may occur in any location, but as for SSM, it is more common on the trunk, head and neck, and lower legs {163}.

Clinical features
NMs typically present as a rapidly expanding papule, nodule or plaque. They are occasionally polypoidal and even pedunculated. They are usually well circumscribed and symmetric and frequently reach a size of approximately 1 cm before diagnosis. The skin markings are often obliterated with frequent ulceration and crust. The colour is often black or blue, although a subset of NM is amelanotic. The amelanotic variety frequently has a subtle blush or peripheral rim of pigment {163,436}.

Macroscopy
As in the clinical features

Tumour spread and staging
The tumour spreads first to the local lymph nodes and then to internal organs. The staging system devised by the American Joint Committee on Cancer includes aspects of the primary tumour, the status of lymph nodes, and the presence and location of any metastases (TNM staging) {130}.

Histopathology
Scanning magnification discloses a raised, dome-shaped, or polypoid tumour, often, but not always, exhibiting some asymmetry. The overlying epidermis may be thin, effaced or ulcerated. Melanoma cells may be present in the overlying epidermis but not beyond the margins of the dermal component (some allow an extension up to 3 adjacent epidermal rete ridges beyond the dermal component). The dermal component is typified by a cohesive nodule or small nests of tumour cells that have a “pushing” or “expansile” pattern of growth. The tumour cells most frequently are epithelioid, but other cell types, including spindle cells, small epithelioid cells resembling naevus cells, and giant mononuclear or multinucleate forms, may predominate or be admixed with other cell types. The cell population usually appears monomorphous but closer examination reveals frequent cellular enlargement, nuclear enlargement, variation in nuclear size and shape, hyperchromatism, and prominent nucleoli.

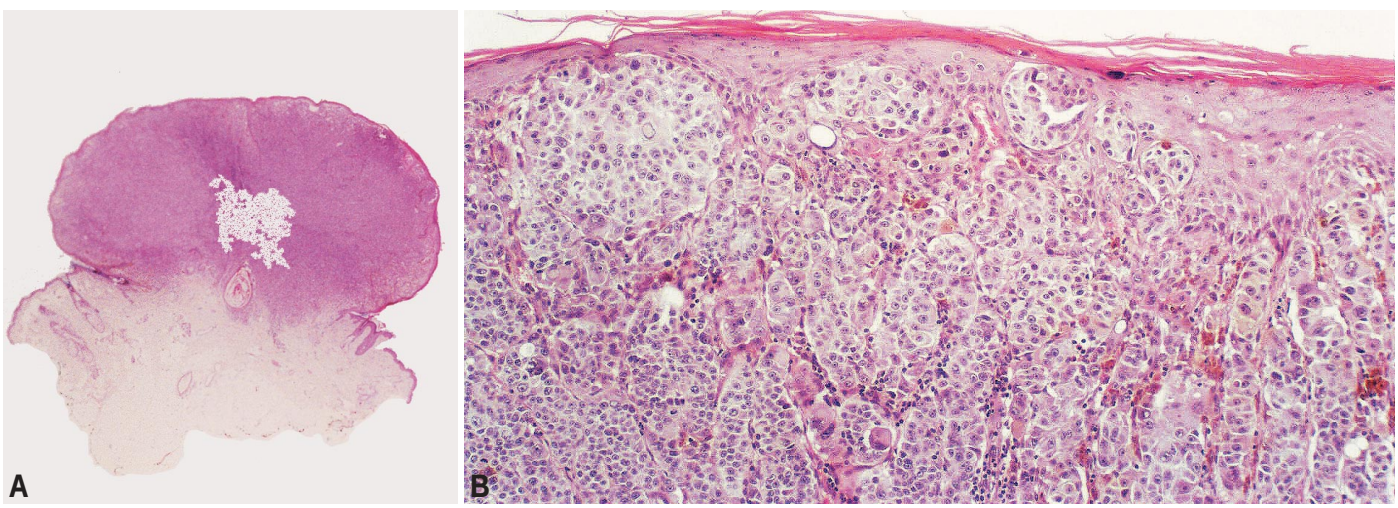

Fig. 2.15 Nodular melanoma. **A** On scanning magnification the tumour has a polypoid configuration with slight asymmetry. Cohesive nodules of tumour cells fill the dermis. **B** Superficial portion of the tumour. Epithelioid melanoma cells are present as single units and in nests that vary in size and shape along the dermoepidermal junction and above it. Similar nests are present in the upper dermis along with numerous melanophages and lymphocytic infiltrates. Some of the epithelioid melanoma cells contain fine melanin granules.

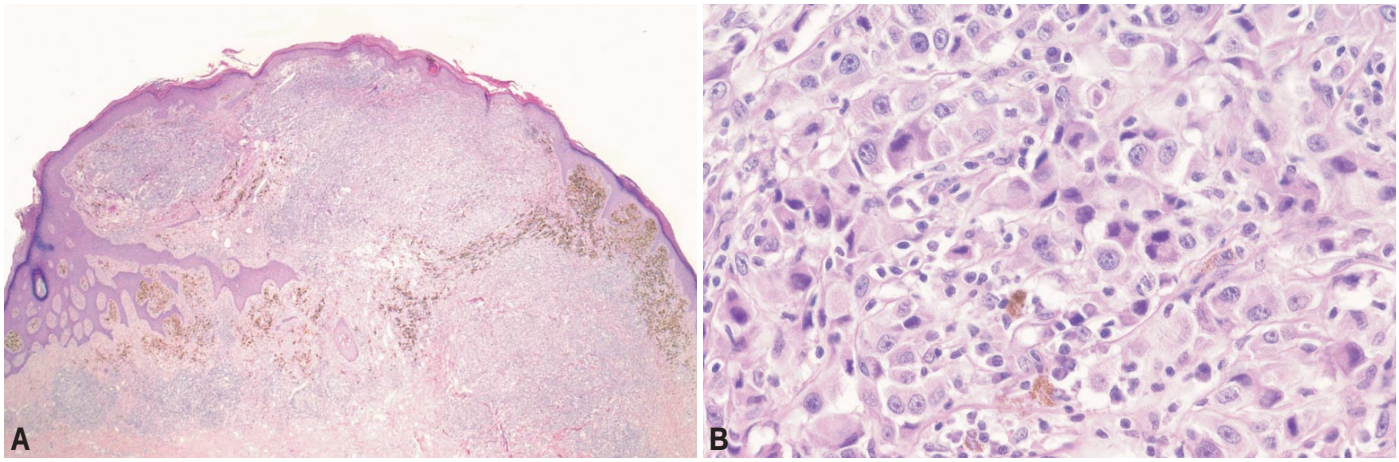

Fig. 2.16 **A** Nodular melanoma with asymmetrical distribution of lesional cells, lymphoctic infiltrates and melanophages. **B** The tumour is composed of melanocytes with large, pleomorphic, vesicular nuclei, some in mitosis.

High nuclear-to-cytoplasmic ratios are often noted. The tumour cells fail to "mature" with progressive descent into the dermis. The cytoplasm of the epithelioid cells often has eosinophilic granular qualities. It may contain melanin granules that vary in size, or appear fine and "dusty". There is absence of melanin in the amelanotic tumours. The surrounding stroma may demonstrate variable mononuclear cell infiltrates, fibroplasia, telangiectasia, and melanophages {154,163}.

Immunoprofile

S-100 protein, HMB-45, Melan A (MART-1), MAGE-1, NKI/C-3, tyrosinase, melanoma cell adhesion molecule (MelCAM) MUC18 and microphthalmia transcription factor (MITF), are expressed by most melanomas {732,1500,1855}. Melanoma cells also express bcl-2 protein, neuron specific enolase and vimentin {626,1861,2131}. Antigens which may demonstrate higher rates of expression in melanoma cells than in naevus cells include Ki-67 (MIB-1), proliferating nuclear antigen (PCNA), p53, cyclin D1, and p21 WAF1(9). The loss of expression of CDKN2A (cyclin dependant kinase inhibitor), and the increased expression of ß3 integrin, have been associated with vertical growth phase and more invasive forms of melanomas {1029,1500,1904,2277,2278,2406}.

Electron microscopy

The demonstration of stage II melanosomes is the hallmark of melanoma diagnosis. They are rarely found in other tumours. Other frequent findings are nuclear pseudoinclusions, prominent nucleoli and cytoplasmic intermediate filaments corresponding morphologically to vimentin filaments. In a minority of melanomas poorly developed intercellular junctions may be present {1016}.

Precursor lesions and histogenesis

It is more common for NM to begin de novo than to arise in a pre-existing naevus {163}. One hypothesis holds that NM represents a final common pathway of very rapid tumour progression from a brief intraepidermal proliferative phase of SSM, lentigo maligna, or acral lentiginous MM {154,163}.

Somatic genetics

Comparative genomic hybridization and mutation analyses have revealed marked differences between melanomas depending on the anatomic site and sun-exposure patterns {173,1493}. These studies did not find unique genetic features in nodular melanomas that justify regarding them as a unique type, supporting the 'common pathway hypothesis {154,163}.

Genetic susceptibility

The proportion of melanomas that have a familial basis ranges from 6% to 14%. Approximately 20% of all individuals with a family history of melanoma have mutations in CDKN2A which maps to chromosome 9p21. In a very few families CDK4 mapping to chromosome 12q14 has been found to be mutated {1851}.

Prognosis and predictive factors

In the T (tumour) category, tumour thickness increased mitotic rate and ulceration are the most powerful predictors of survival, and the level of invasion has a significant impact only within the subgroup of thin (≤1 mm) melanomas {131}. Other adverse prognostic factors include increased tumour vascularity, vascular invasion, microscopic satellites, male gender, increased age, and anatomic location on the head, neck and trunk {122,1528,2597}. In the N (nodes) category the following three independent factors have been identified: the number of metastatic nodes, whether nodal metastases were clinically occult or clinically apparent, and the presence or absence of primary tumour ulceration. In the M (metastases) category, nonvisceral metastases are associated with a better survival compared with visceral metastases {131}.

Lentigo maligna

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Definition
Lentigo maligna (LM) is a form of melanoma in situ that occurs on the sun exposed skin of elderly people, mainly on the face but also, less often, at extrafacial sites including the neck, upper back and forearm. It is characterized histologically by linear and nested proliferation of atypical melanocytes along the dermo-epidermal junction and down the walls of hair follicles and sweat ducts. The melanocytic lesion is associated with severe actinic damage, manifested by epidermal atrophy and solar elastosis. When dermal invasion by atypical melanocytes occurs in association with (LM), the term lentigo maligna melanoma (LMM) is used.

ICD-O code 8742/2

Synonyms and historical annotation
LM has also been known as Hutchinson melanotic freckle, after Hutchinson first described it as "senile freckle" in 1892 {1090} and subsequently as "lentigo-melanosis" {1089}. Dubreuilh {652} described these lesions as "mélanose circonscrite précancereuse" which subsequently came into common use as melanosis circumscripta precancerosa until the classification of Clark {492} in 1967 introduced the category of melanoma commencing in lentigo maligna (Hutchinson's melanotic freckle). That classification was widely but not universally accepted; the World Health Organisation (WHO) classification of 1974 classified superficial spreading melanoma and melanoma arising in Hutchinson melanotic freckle (lentigo maligna melanoma) in one category {2337}. The World Health Organization (WHO) classification of 1996 separated melanoma in-situ into superficial spreading or pagetoid type and lentigo maligna melanoma, whilst acknowledging that there may be no essential biological difference between some or perhaps all categories of melanoma {999}.

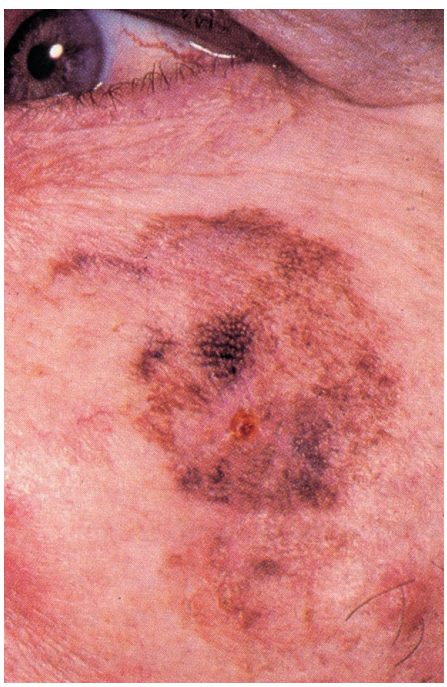

Fig. 2.17 Lentigo maligna. Broad, flat, variably pigmented lesion with a very irregular, ill-defined border on the cheek of a 78-year-old patient.

Etiology
The strong association between LM and its occurrence in the severely sun damaged skin of elderly people has been widely accepted as evidence that LM and LMM represent a distinctive form of melanoma, resembling etiologically the non-melanocytic skin cancers, and suggesting that LM arises in response to accumulated sun exposure, in contrast with the more common forms of melanoma that appear to be related to intermittent sun exposure {1048}. It has also been suggested, however, that differences in body site distribution between the commonly accepted different types of melanoma, through their interaction with amount and pattern of sun exposure, can explain virtually all the observed pathological and epidemiological differences between LM and the more common types of melanoma that occur in widespread anatomical distribution {16,996}. Recent studies have found that LM remains the main histologic type of melanoma in situ on the head and neck and that patients with LM are less likely than patients with melanomas of the trunk to have more than 60 naevi whereas they had a stronger association with the number of solar keratoses {2508}.

Pathogenesis
According to some authorities, the term LM encompasses a phase regarded as a melanoma precursor in which there is proliferation of melanocytes in severely sun damaged skin in intermittent pattern without the confluent growth, pagetoid spread and nesting of atypical melanocytes that, according to this concept, represent malignant melanoma in-situ of LM type, whereas the lesions with less severe, intermittent junctional proliferation are termed atypical melanocytic hyperplasia {759} or, preferably, atypical lentiginous melanocytic proliferation.

Localization
Head and neck are by far the most common sites in both sexes. Extrafacial LMM differs in its site distribution between women and men {549}. A study in Scotland showed that extrafacial LMM in men occurred mainly on the trunk whereas in women 80% occurred on the limbs, mainly the lower leg. The mean age of patients with extrafacial LMM was significantly lower than that of patients with head and neck LM, suggesting that the association between LMM and sunlight may not be related only to the cumulative effects of solar exposure.

Clinical features
LM may be recognized as a small lesion, usually as a mottled light brown macule with irregular margins on the face of a fair skinned elderly patient with evidence of severe solar skin damage, only a few millimetres in diameter, but usually greater than 10 mm. The classical lesions are broad, flat zones of varied pigmentation with an irregular border. With increasing size of the lesion, variation in pigment and irregularity of the border also

become more pronounced, nodules may develop within the lesion and the borders may become difficult or impossible to define where zones of pallor or mottled pigmentation merge imperceptibly with the surrounding skin.

Histopathology

LM is characterized by a predominantly junctional proliferation of atypical melanocytes, frequently extending down the walls of hair follicles and sweat ducts, in association with epidermal atrophy and severe solar elastosis. Although the junctional proliferation may form confluent linear pattern in some areas, elsewhere the atypical melanocytes may be distributed as single units separated by basal cells. Irregular junctional nests of atypical melanocytes are frequently present, as are multinucleate giant cells including those of starburst type {512}. Marked pleomorphism is a feature of the atypical melanocytes which show cytoplasmic retraction artefact and nuclei of stellate, ovoid and crescentic forms, some of them pressed against the cell wall, with a variable chromatin pattern and clear or variably pigmented cytoplasm. Pagetoid foci of atypical epithelioid melanocytes present an appearance indistinguishable from melanoma in situ of so-called superficial spreading type.

A lymphocytic infiltrate and focal fibroplasia are frequently present in the papillary dermis underlying LM, with severe solar elastosis and telangiectasia. Regression, shown by fibrosis, hypervascularity, melanophages and a patchy lymphocytic infiltrate, is a common feature and should prompt a careful search for invasion by atypical melanocytes. The presence of regression at a lateral margin of excision should be emphasized in the report as an indication for re-excision, even when the margins appear clear of atypical melanocytes.

In LMM, dermal invasion occurs in association with LM. The invasive component may consist of atypical melanocytic spindle cells more frequently than is seen in the other common forms of cutaneous melanoma, but epithelioid, small naevoid and tumour giant cells may also be present in varied proportions. The cells of these various types may occur in cohesive groups, strands or as single cells in a diffuse pattern, often associated with lymphocytes and melanophages. The degree of pigmentation varies, including cells with abundant clear cytoplasm adjacent to cells in which the morphologic detail may be obscured by coarse melanin granules.

The invasive component in LMM may be desmoplastic and/or neurotropic with very subtle, diffuse invasion that predisposes to incomplete excision and true local recurrence. Dermal invasion may also originate from atypical melanocytes in the walls of hair follicles and sweat ducts, thus creating a problem in measurement of tumour thickness because it is inappropriate to measure tumour thickness from the granular layer of the epidermis in this instance.

The degree of pigmentation in LM may vary markedly between different examples of the tumour and within one tumour. Zones of amelanosis at the periphery of the lesion may lead to failure by the pathologist to detect atypical cells at the margin of excision, thus leading to persistent growth and “local recurrence” of the tumour.

Differential diagnosis

In cases of extensive amelanosis (amelanotic LM) {60}, the distinction between in-situ squamous cell carcinoma or extramammary Paget disease may be difficult in routine sections, necessitating the use of special stains to demonstrate epithe-

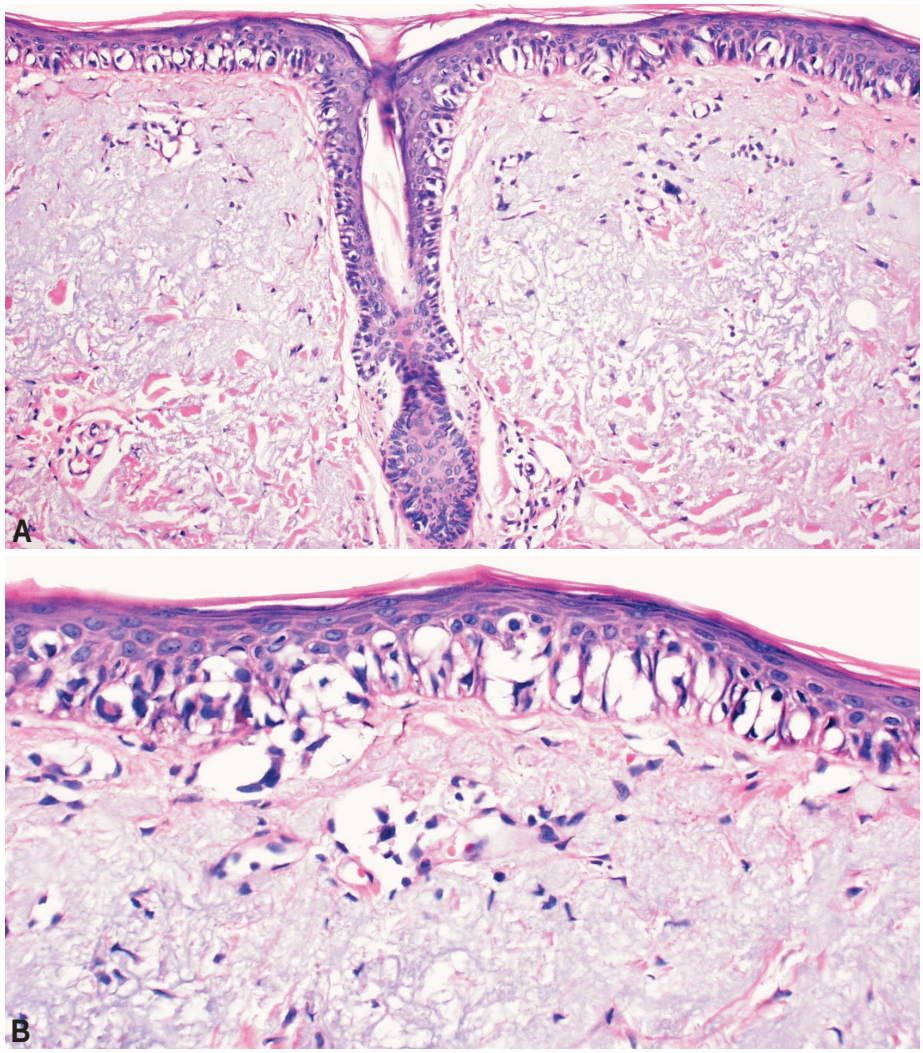

Fig. 2.18 Lentigo maligna. **A** Atypical melanocytes, mainly epithelioid cells with clear cytoplasm, are arranged in confluent pattern along the dermo-epidermal junction and extending down the wall of a central hair follicle. A few single atypical melanocytes are also present above the basal layer. The epidermis is atrophic overlying severe elastosis. **B** Severe nuclear pleomorphism and scattered multinucleate giant cells are present in the junctional proliferation and down the walls of adnexal structures including a sweat duct.

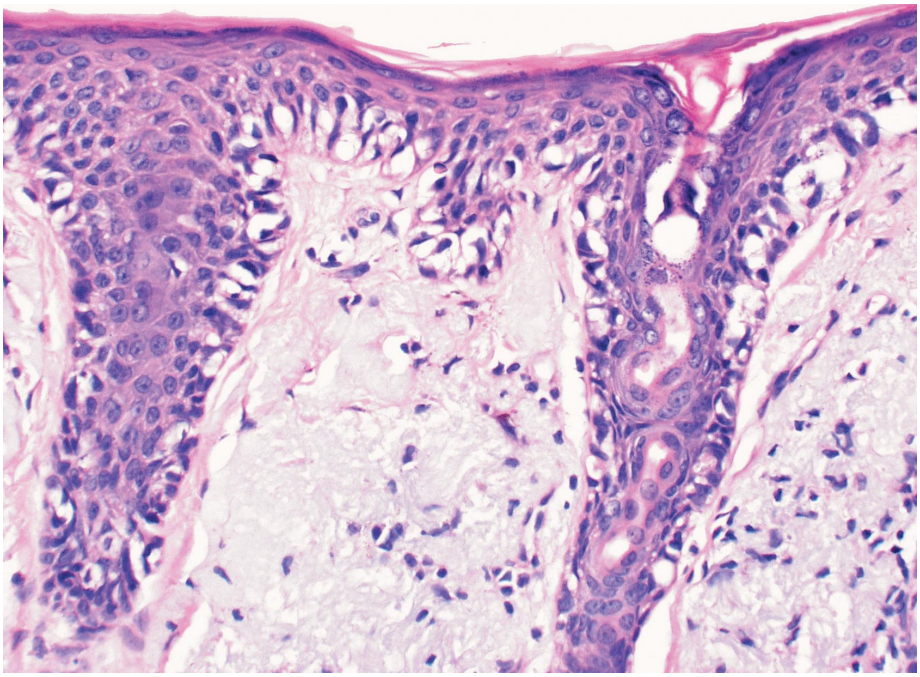

Fig. 2.19 Lentigo maligna. Focal pagetoid growth is present in addition to junctional proliferation including small nests of atypical melanocytes.

lial mucin in extra-mammary Paget disease, and immunostaining, including the use of antibodies to cytokeratins, melan-A and S-100 protein and, as further aids to the diagnosis of Paget disease, carcinoembryonic antigen, and BerEP4.

The distinction between LM and benign forms of junctional melanocytic proliferation is made on the basis of the characteristic cytologic atypia, confluent growth of atypical cells along the junction with frequent extension down the walls of adnexal structures and, commonly, extension of growth above the basal layer in pagetoid pattern.

Histogenesis

LM develops from epidermal melanocytes, most likely due to the cumulative DNA damage resulting from long-term sun exposure {1048}. A recent study of the differential expression of proliferation- and apoptosis-related markers in lentigo maligna and the keratinocytes in solar keratosis has found that the epidermis in LM shows overall low proliferation and a low apoptotic tendency, perhaps aiding aberrant melanocyte proliferation in the early stages of melanoma development {718}.

Somatic genetics

A recent study has shown an association between DNA repair-deficiency and a high level of *TP53* mutations in melanomas of xeroderma pigmentosum patients {2231}. The LMM found in xeroderma pigmentosum patients of the XP complementation group, group XP-C, were associated with an accumulation of unrepaired DNA lesions. Lentigo maligna melanomas have been found to rarely show mutations in BRAF {1493}. Comparative genomic hybridization shows more common losses involving chromosome 13 and less common losses of chromosome 10, when compared to other melanoma types {173}.

Prognosis and predictive factors

Complete excision of lentigo maligna, as a form of melanoma in situ and, therefore, incapable of metastasis, is curative. Prognosis for LMM has been a contentious issue. For many years, it was commonly believed that the prognosis for melanomas of LMM type is better than for other types of melanoma. Most evidence, however, suggests that for melanomas classified as different types according to their histological features, their differences in survival correspond to differences in tumour thickness rather than to their differences in histologic type {20,1296}.

Acral-lentiginous melanoma

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Definition

Acral lentiginous melanoma (ALM) is a distinct variant of cutaneous melanoma, which occurs on the palms, soles, and subungual sites, and has a characteristic histologic picture. Following the three other major clinicopathological subtypes of melanoma, i.e. superficial spreading melanoma, lentigo maligna melanoma, and nodular melanoma, ALM was proposed as the fourth subtype by Reed in 1976 {1905}. In this article, we also use the term acral melanoma and define it as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails. The reason for this usage is described below.

ICD-O code 8744/3

Synonyms

Historically, this type of melanoma has been designated as ALM {1905}, acral melanoma {494}, palmar-plantar-subungal-mucosal melanoma (P-S-M melanoma) {2129}, or unclassified plantar melanoma {100}. Although often considered to be interchangeable, ALM and acral melanoma embody distinct concepts that must be distinguished from each other. ALM is a histologic designation that shows similarities to lentigo maligna melanoma, while acral melanoma is an anatomic designation that refers to melanoma located on the acral sites. Acral melanoma, thus, encompasses both ALM and such subtypes as superficial spreading melanoma and nodular melanoma that may develop in acral locations. Occasionally, the terms acral melanoma and acral lentiginous melanoma are used interchangeably, since the majority of cases of acral melanoma are ALM {1071,1592,1905} and the histological distinction between ALM and superficial spreading melanoma is not always possible {2220}. Even if acral melanoma is an anatomic nomenclature, its use is different among articles. We define it as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails because of presentation of the genetic data. Although P-S-M melanoma was described on the basis of clinical and histologic similarities between the tumours on these sites, the acral melanomas and mucosal ones are recommended to be treated separately, because of their different clinical behaviours {494}.

Epidemiology

Racial differences are quite pronounced in the incidence and predilection sites of melanomas. This is particularly true for acral melanoma wherein acral melanoma comprises 2% and 80% of cutaneous melanomas in Caucasian and dark-skinned patients respectively. In a German study approximately 7% of patients with cutaneous melanoma had

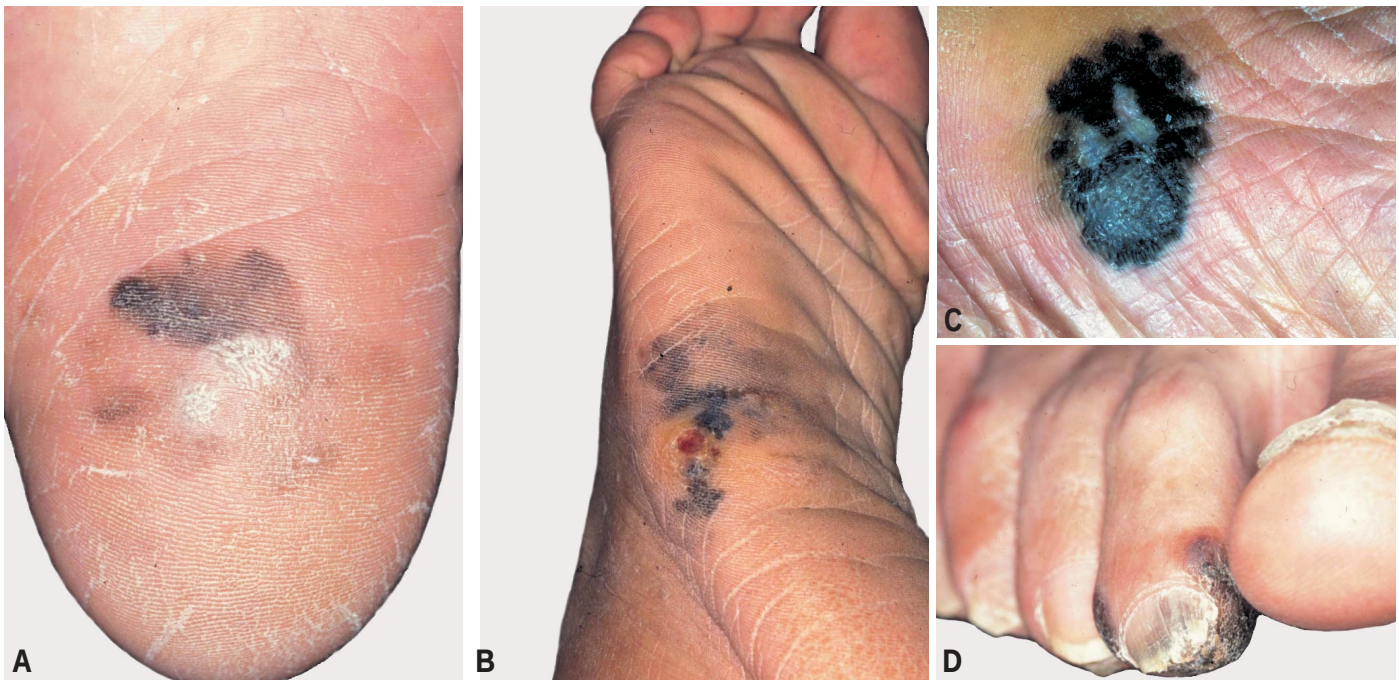

Fig. 2.20 Acral-lentiginous melanoma (ALM). **A** ALM on the heel, showing varying shades of tan to brown pigmentation. **B** ALM on the lateral aspect of the foot, showing irregularly bordered pigmentation with a slightly ulcerated lesion. **C** ALM on the sole, showing an irregularly pigmented macule with notched borders. **D** ALM on the second toe, showing subungual pigmented lesion extending to adjacent skin.

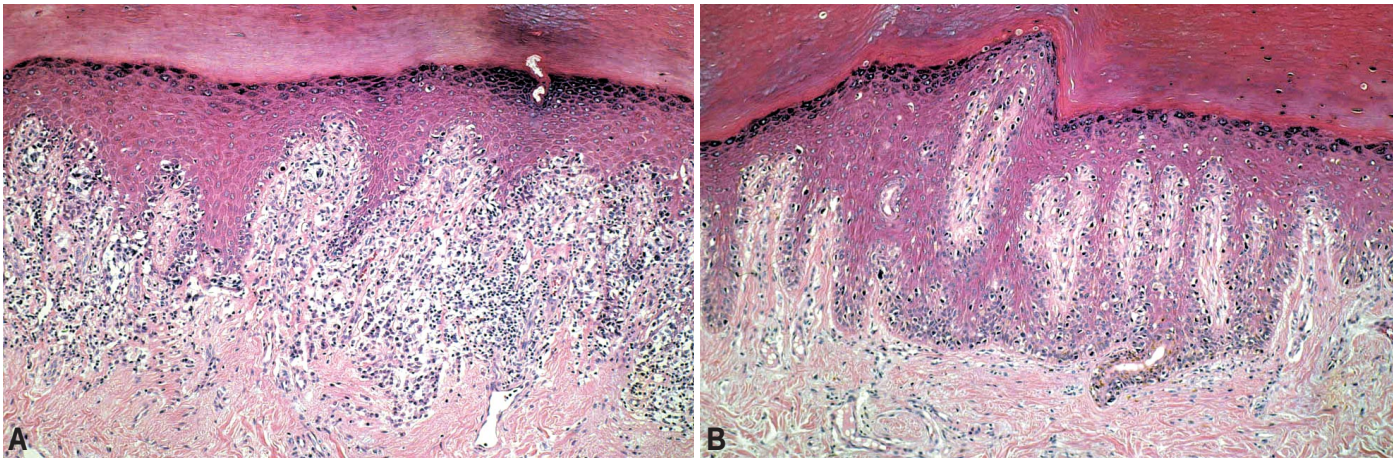

Fig. 2.21 Acral-lentiginous melanoma. **A** ALM, showing marked acanthosis, elongation of the rete ridges, broadened horny layer, and large, atypical melanocytes with large, often bizarre nuclei and nucleoli, and cytoplasm filled with melanin granules. **B** ALM, showing lentiginous proliferation of atypical melanocytes at the border of the tumour.

tumours located on acral sites {1337}. Whereas 77% of cutaneous melanoma in Japanese patients occurs on acral sites {2130}. In African and African-Americans, the highest incidence of cutaneous melanoma has been reported on relatively non-pigmented areas, such as the soles, nail plates, and mucous membranes {1417}. Thus, ALM is the most common type of melanoma in dark-skinned peoples and Asians {1268, 2129}. Nevertheless the absolute incidence of acral melanoma in dark-skinned African and light-skinned Caucasian populations in North America is similar, suggesting that the observed racial difference may relate to a decreased incidence of non-acral melanoma in African American populations {2268}. Compared with the escalating incidence that typifies other melanoma subtypes, the incidence of ALM has remained static {661}.

Overall, ALM occurs in an older patient population than does superficial spreading or nodular melanoma, and, in populations where ALM is common, this tumour more often afflicts men than women. Overall, the age distribution of ALM is similar to that of lentigo maligna melanoma, peaking in the seventh decade of life, whereas superficial spreading melanoma and nodular melanoma peak in the sixth decade {1337}. The mean age of ALM ranges from 55 to 68 years in European countries {767,1337,2123}. In Japanese patients, there is a peak in the sixth decade in both males and females. In Japan, Korea, and Taiwan, men are effected twice as often as women {1220, 1268,1428,2130}. On the other hand in western countries, there is less of a male predominance in patients with ALM {1337,2220}.

Localization

The term acral has been used differently throughout the literature. Most publications use acral for the non-hair bearing, i.e. glabrous skin of the palms and soles, and the nail bed, whereas others also include the dorsal aspect of the hands and feet under this term. In a German study, using the latter definition, acral melanoma occurred on the feet in 87% cases (plantar sites, 57%; subungual, 5%; and dorsum, 9%) and on the hands in 23% (palm, 1%; subungal, 14%; and dorsum, 9%) {1337}. Thus, the plantar sites were greatly more often affected than the palmar sites {1337,2130,2201, 2220,2296}. In contrast to ALM, superficial spreading melanoma occurs more commonly on the sun-exposed dorsal aspects of the hands and feet, whereas nodular melanoma occurs on all acral sites with relatively equal frequency {1337}. In addition to the sole, nail plate is an especially frequent site with a frequency of 16-19% in ALM {1337,2130}. In contrast to the palmar/plantar melanomas, subungual melanomas occur more often on the hands than on the feet {745,1221,2130,2315}. In the Japanese series, the number of subungual melanomas on the fingers is 62-72% and on the toes 28-38%, with an 82% incidence on the thumbs and great toes {1221,2130}. The high percentage of occurrence on the thumbs and great toes may suggest a role for trauma in the etiology of subungual melanoma {2130}. Since sun exposure obviously plays little role in palmoplantar sites, the causative role of ultraviolet light is presumed to be negligible in ALM.

Clinical features

Acral melanomas in the early stages appear as a pigmented macule similar to lentigo maligna. Acral melanomas commonly exhibit clinical evidence of a biphasic growth pattern, with a more rapid evolution from an entirely flat clinical lesion to a lesion containing an elevated focus than is observed in the other types of melanoma. The radial growth phase of ALM is characterized by a macular pigmented lesion with highly irregular, notched borders and varying shades of pigmentation. Within a background pigmented macule, acral melanomas often develop a clinically apparent vertical growth phase. This is manifest as an elevated papule or nodule, sometimes with a verrucous surface, and corresponds to the histological vertical growth phase of malignant melanocytes. Ulceration is more often seen in ALM than in other types of melanoma.

Subungual melanomas often begin as brown to black discolouration of the nail that frequently become bands or streaks of pigmentation. Thickening, splitting, or destruction of the nail plate may occur. The irregular macular hyperpigmentation, coloured tan to dark brown, is also recognized around the nail plate {2130}.

In one study, 17% of the patients noticed

the pre-existence of some pigmented skin lesions, and 21% related a history of trauma {2130}. Pigmented streaks are not uncommon in patients with deeply pigmented skin, nevertheless, a history of a new or recently changing pigmented lesion should prompt the consideration of a biopsy for histological evaluation of the lesion. In this case, reflection of the proximal nail fold to enable biopsy of the nail bed may be necessary for definitive diagnosis.

Unfortunately, clinical misdiagnosis is not uncommon in patients with ALM {409, 767,1327,1592,2222}. Therefore, awareness of atypical presentations of ALM that may contribute to misdiagnosis or diagnostic delay assumes particular importance. ALM lesions are frequently treated or followed for considerable time under the clinical diagnosis of wart, callus, fungal disorder, subungual haematoma, keratoacanthoma, nonhealing ulcer, foreign body, naevus, ingrown toenail, etc {2222}.

Histopathology

The histology of ALM is characteristic but not distinct. In the radial growth phase, the lesions are characterized by marked acanthosis, expanded cornified layer, elongation of the rete ridges, and lentiginous proliferation of atypical melanocytes along the basal epidermis at the border of the tumour {1337,1767}. The intraepidermal component of acral melanoma includes large, atypical melanocytes with large, often bizarre nuclei and nucleoli, and cytoplasm filled with melanin granules {2130}. These melanocytes in the basal layer often exhibit long, elaborate dendritic processes {2130}.

Atypical melanocytes can extend along the sweat ducts into the deep dermis.

In the vertical growth phase, tumour nodules often contain predominantly spindle-shaped cells and are associated with a desmoplastic reaction {2130}. The junctional component of thicker tumours often shows nesting of tumour cells and upward migration to the cornified layer {1337}.

Immunoprofile

As in the other types of melanomas, immunohistochemical stainings for S-100 protein, HMB-45, and MART-1 (also known as Melan-A) are of great diagnostic value in ALM. S-100 protein (positive cases, 95%) is a more sensitive marker than either HMB-45 (80%) or MART-1 (70%) {1268}. However, S-100 protein-negative ALM has been reported {83}. The intesitity of HMB-45 but not of S-100 protein is correlated well with the melanin content. HMB-45-negative cases are all amelanotic, but amelanotic cases are not all negative for HMB-45 {1268}. The melanoma cells also express vimentin {1268}. Focal staining for CAM5.2 or epithelial membrane protein may occasionally be found {1268}.

Somatic genetics

Comparative genomic hybridization (CGH) of melanomas on acral non-hair bearing skin showed distinct differences to melanomas on non-acral skin {171}. A study of 15 acral melanomas and 15 superficial spreading melanomas from non-acral sites showed that all (100%) acral cases had gene amplifications, whereas amplifications were found in two of the superficial spreading melanomas (13%). The most common amplified region is chromosome 11q13 which occurred in 50% of these types of melanoma. A recent study has shown that cyclin D1 is one of several candidate genes in this region. This conclusion was based on the observation that amplification of the cyclin D1 gene was always accompanied with overexpression of the cyclin D1 protein, and that inhibition of cyclin D1 expression in vitro and in xenograft models led to apoptosis or tumour shrinkage {2072}.

FISH studies on primary lesions of acral melanoma showed that the amplifications arise early in acral melanoma and can already be detected at the in situ stage {171}. The *in situ* portion of acral melanoma may extend beyond what is recognizable histopathologically. FISH detected gene amplifications were identified in single basal melanocytes immediately adjacent to the in situ component of acral melanoma; they were equidistantly spaced and looked histopathologically inconspicuous {171}. Based on the observation that these “field cells” were found at the histopathologically uninvolved excision margins of an acral melanoma that recurred multiple times the authors propose that field cells may be a form of minimal residual melanoma that leads to persistence if not removed.

More recent studies using array CGH have confirmed the frequent gene amplifications in acral melanoma preferentially involving chromosome 11q13. In addition, the studies revealed that all melanomas showed these features, independent of their histological growth pattern, as long as they were located on glabrous, i.e. non-hair bearing skin of the palms and soles or subungual sites (Bastian et al, to be published). In addition, melanomas involving these anatomic sites also had a significantly lower mutation rate of the BRAF oncogene (6/39, 15%) than melanomas on the trunk (23/43, 53%) {1493}. The molecular genetic analyses therefore suggest melanomas of the palms of soles and subungual sites represent a genetically distinct form of melanoma, independent of their histological growth pattern.

Prognosis and predictive factors

In general, the prognosis of invasive acral melanoma is poor. This can party be explained by the above described diagnostic delay and increased tumour thickness at the time of diagnosis. However, there are some studies suggesting that acral melanomas may undergo a more aggressive course independent of tumours thickness {151,308, 661,1337}. In a study from Germany, 63 out of 64 patients (98.5%) with melanoma of the sole subsequently developed metastases {775}; a corresponding figure from Japan in 1983 was 35% {2130}. The same hospital recorded that the 5-year survival rate of subungal melanoma increased from 53% in 1969-82 to 83% in 1983-93 {1221}, presumably because of early awareness of lesions and development of treatment {2012}. However, others have reported that ALM is not a significant prognostic indicator {661,2201}, and adjustment for histologic and clinical stage renders the prognostic importance of anatomic location insignificant {151, 308}. These conflicting results can in part be explained by the different definitions used for acral melanomas in the studies. Future studies using refined criteria including genetic information are necessary to assess the prognosis of this melanoma type.

Desmoplastic melanoma and desmoplastic neurotropic melanoma

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K.A. Crotty
R.A. Scolyer

Definition

Desmoplastic melanoma (DM) is a spindle cell melanoma in which the malignant cells are separated by collagen fibres or fibrous stroma. It displays variable cytological atypia, cellularity and stromal fibrosis and more often than not has an accompanying junctional component. Neurotropism is a common associated feature (in at least 30% of cases) and when it occurs such tumours are termed desmoplastic neurotropic melanomas (DNM). The neurotropism may be perineural or intraneural and often extends beyond the desmoplastic component. DM may also present as a recurrence or occasionally as a metastasis from other types of melanoma.

ICD-O code 8745/3

Historical annotations

DM was first described by Conley et al. in 1971 {526} as a clinically inconspicuous superficial melanocytic lesion, mainly on the head and neck, with an atypical junctional component, preceding the development of a bulky dermal and subcutaneous tumour. The latter was composed of atypical melanocytes and spindle cells often with elongated nuclei and a dense collagenous ground substance. Many others subsequently highlighted the frequent neurotropism of DMs.

Epidemiology

Desmoplastic melanomas represent between 1-4% of melanomas. In a large series from the Sydney Melanoma Unit

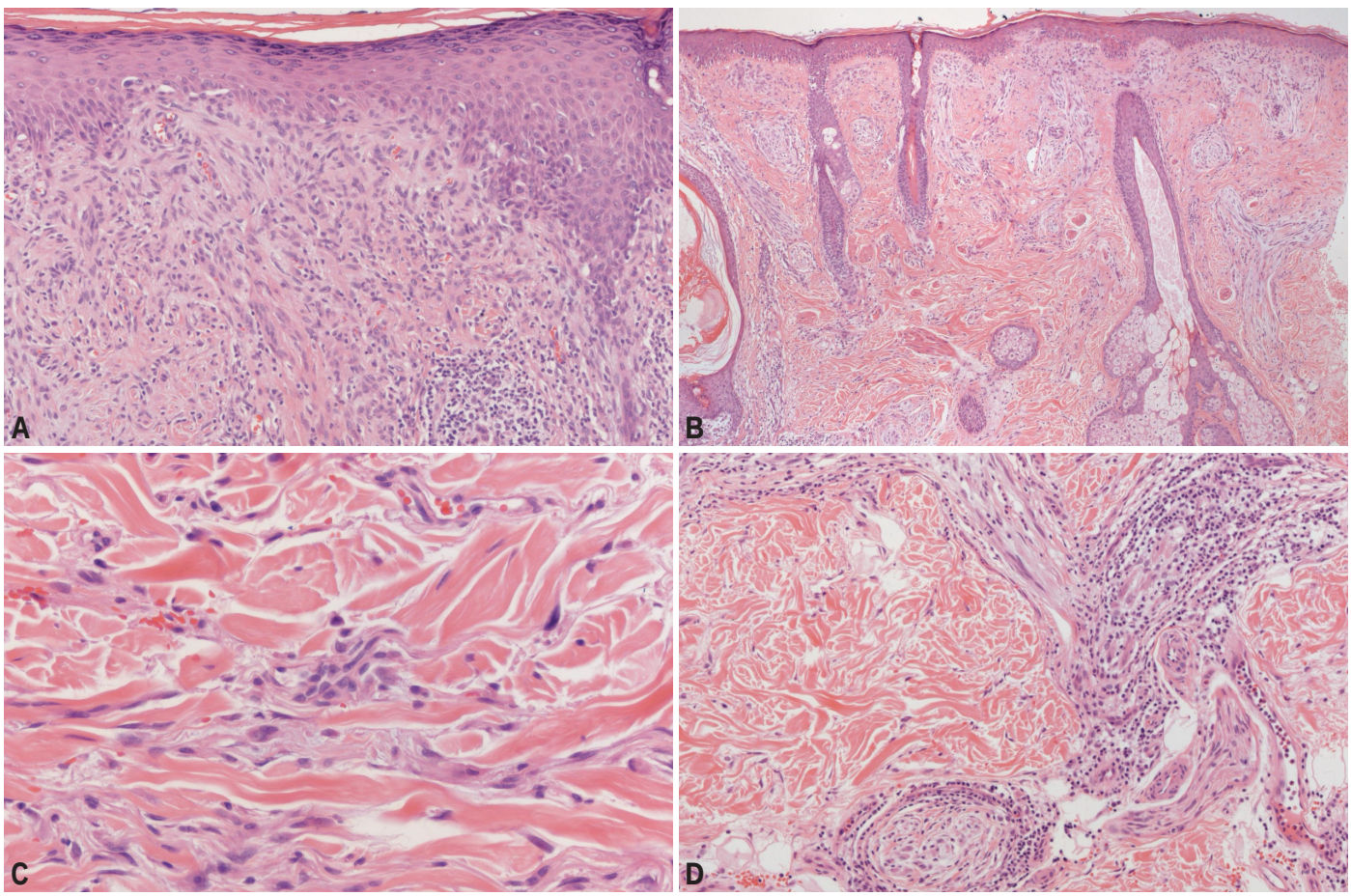

Fig. 2.22 Desmoplastic neurotropic melanoma. **A** Male, 73 yrs, cheek. A few atypical enlarged melanocytes are present in the junctional zone. The fibrohistiocytic pattern is accompanied by scattered lymphocytes, some in clusters. Mitoses are hard to find. **B** Female, 24 yrs, lip. There are "neural transforming" areas with thick neuroid bundles in the upper dermis. Note occasional atypical junctional melanocytes, a few subepidermal spindle cells and scattered lymphocytes. **C** Male, 73 yrs, cheek. Malignant spindle cells with elongated nuclei appear to be within and between collagen bundles. **D** Female, 24 yrs, lip. "Neural transforming" areas with neuroid bundle (top of picture) containing atypical elongated spindle nuclei. Intraneural and perineural involvement of a small nerve is also present. There is a prominent infiltrate of lymphocytes.

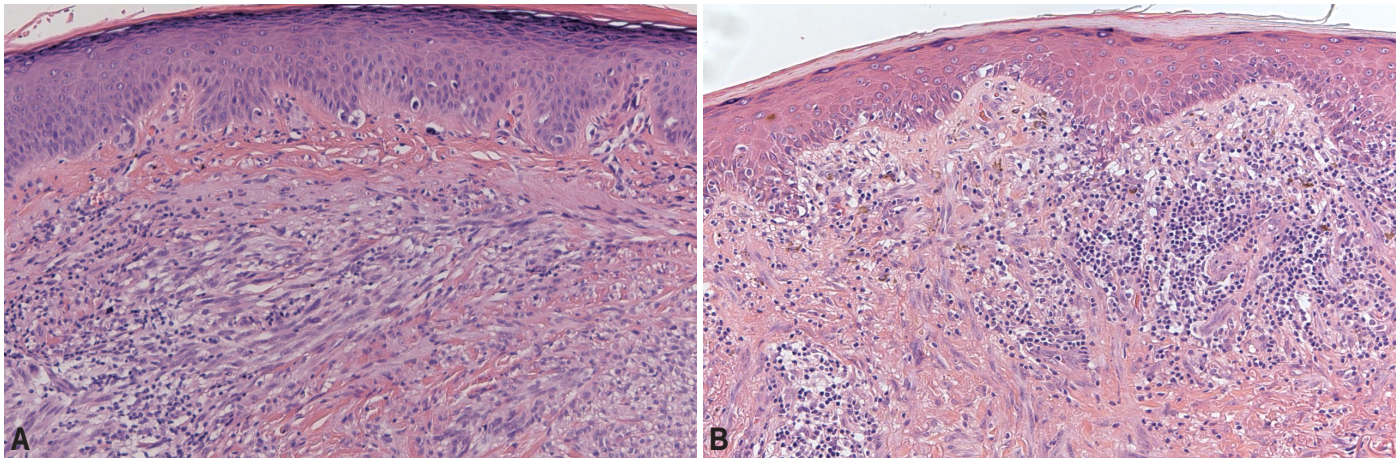

Fig. 2.23 Desmoplastic melanoma. **A** Male, 57 yrs, upper lip. Abnormal junctional melanocytes, spindling dermal melanocytes and a patchy lymphocytic infiltrate. **B** Female, 76 yrs, forearm. Abnormal junctional melanocytes and dermal spindle cells with patchy lymphocytes.

(SMU) the median age at diagnosis was 61.5 years (range 24-91) {1867,1868}. As in other histogenetic types of melanoma, males are more often affected (M:F = 1.75:1) {358A,1867,1868}.

Etiology

The etiology is unknown, but the majority occurs in sun-exposed skin. Some have occurred in irradiated areas {1125}.

Localization

DM may be found in many sites but most commonly involves the head and neck region (37%), including ear, nose and lip {1077}. Males predominate except on the lower limbs. The vulva is a rare site for DM {1664}.

Clinical features

Most present as a painless indurated plaque but some begin as a small papule or nodule {2501}. Almost half lack pigmentation {1867}. Pale lesions are often mistaken for basal cell carcinoma, dermatofibroma or a scar. Pigment is usually due to an associated lentigo maligna (LM)/Hutchinson melanotic freckle (HMF) or superficial spreading melanoma. Unusual presentations include a young age {439,1077}, an erythematous nodule {1326} and alopecia {563}.

Macroscopy

Ulceration is uncommon although it was found in 17% of the SMU cases {1868}.

Tumour spread and staging

The tumours usually infiltrate deeply into the reticular dermis but local spread may involve subcutaneous tissue, deep fascia including periosteum and pericranium, bone and salivary gland. Neurotropic foci may be found well beyond the main tumour. In the SMU series, neurotropism was found only in tumours exceeding 1.5 mm in thickness and Clark level 4 or 5 {1867,1868}. Initial metastases from DM may involve regional lymph nodes or distant sites.

Histopathology

In DM the spindle-shaped melanocytes, which often resemble fibroblasts and are usually non-pigmented, are found in and between mature collagen bundles. The latter may be thickened and/or associated with a mild to marked stromal fibrosis. The distribution of spindle cells is usually haphazard but occasionally they form parallel bundles or storiform areas. The spindle cells often extend into the subcutis diffusely or in fibrous bands and may involve deep fascia, especially pericranium. The overlying epidermis may be thinned or thickened. Characteristically there are accompanying small islands of lymphocytes and plasma cells within and/or at the edge of the tumour. The cytological atypia of the spindle cells usually varies from mild to moderate. However, even in cases with mild atypia, there are usually a few larger or more elongated hyperchromatic nuclei. The cytoplasm of the spindle cells is often poorly defined. In examples where the spindle cells are small, well scattered and associated with solar elastosis, the lymphoid islands may be the main clue to the diagnosis. Paucicellular variants are easily missed on punch and shave biop-

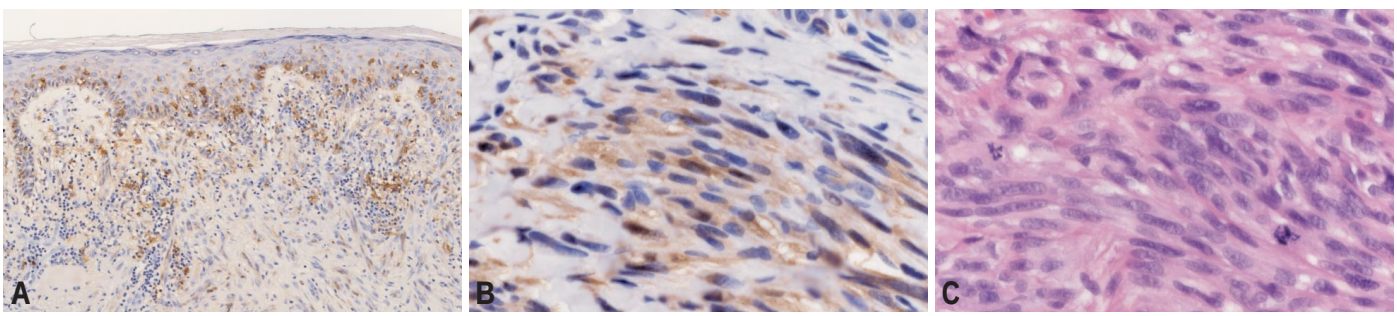

Fig. 2.24 Desmoplastic melanoma. **A** The spindle cells stain poorly with S100 unlike the Langerhans cells and interdigitating cells. **B** Variable S-100 positive nuclear and cytoplasmic staining. **C** Crowded abnormal spindle cells and atypical mitoses.

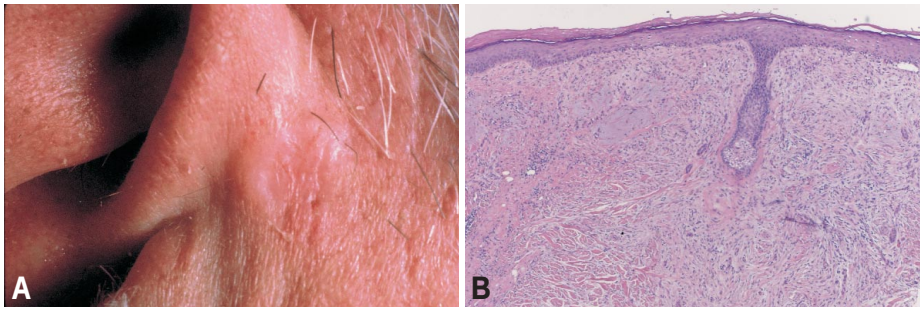

Fig. 2.25 Desmoplastic melanoma. **A** Firm, skin-coloured plaque. **B** Male, 68 yrs, scalp. This punch biopsy was initially diagnosed as a scar. Only an occasional spindle cell was S-100 positive and no abnormal junctional melanocytes were found. A larger desmoplastic melanoma was removed from the same site 6 months later. Clues to the diagnosis are the small foci of lymphocytes and permeation of the band of dermal elastosis by spindle cells.

sies. Junctional change is sometimes minimal or absent {1125}. Occasionally there is an associated banal naevus. Vascular invasion is rare. Even rarer cases show heterotopic bone and cartilage {1644}.

The median Breslow thickness in the SMU series was 2.5 mm (0.2-18 mm) {1867,1868}. The thickness and extent of invasion is usually best determined in S-100 stains. The mitotic rate is variable but is often low. Abnormal mitoses are common in the more cellular tumours.

The neurotropism is characterized by the presence of one or more foci in which the spindle cells extend in a circumferential fashion around nerves in the dermis or deeper and/or thickened nerves containing abnormal cells within their nerve sheath. Spindle cells may also form structures resembling nerves ("neural transforming"). Neurotropism may be present in melanomas without desmoplasia.

Melanomas of any histogenetic type may have desmoplastic areas. The proportion of desmoplasia in a melanoma necessary for the diagnosis of DM has been ill defined in several studies, but proposals for diagnostic criteria have been made {358A,985A,1546A}.

Metastases in lymph nodes may be epithelioid cells, or spindle cells with or without desmoplasia.

Immunoprofile

The spindle cells are positive with S-100 although only a few nuclei are positive in some otherwise typical cases. HMB45 is usually negative except for any foci of epithelioid cells {2476}. NSE, NKI/C-3 and smooth muscle actin {1929} may be positive. Melan A (MART-1) is usually negative. Microphthalmia transcription factor (MTF) is not a sensitive or specific marker {356,885,1294}. Type IV collagen and laminin are frequently expressed in DM {1857}. Vimentin is usually positive although positive staining does not usually assist in diagnosis.

Differential diagnosis

The differential diagnosis includes desmoplastic naevus {958}, which like DM may have perineural extension but lacks asymmetry, mitotic activity, marked nuclear atypia and lymphoid infiltrates. Well established desmoplastic Spitz naevi may have many HMB45 negative spindle cells but these naevi are usually symmetrical with epidermal thickening, include at least a few plump cells and have rare or absent mitoses. Sclerosing cellular blue naevi, which are most frequent on the scalp, also lack mitoses and are more or less diffusely HMB45 positive. Immature scars, especially in re-excision specimens, may focally resemble DM as they may have some S-100 positive spindle cells {476,1951}, foci of lymphocytes and mitoses.

Other differential diagnoses include dermatofibroma/fibrous histiocytoma, fibrosarcoma, "malignant fibrous histiocytoma", malignant peripheral nerve sheath tumour and leiomyosarcoma. These tumours can usually be separated by morphology and appropriate immunohistochemistry.

Histogenesis

It is most likely that the desmoplastic cells are derived from melanocytes that have undergone adaptive fibroplasia. Some authors have suggested that the desmoplasia occurs because of a fibroblastic stromal response and neurofibrosarcomatous differentiation of the tumour cells {2476}. Ultrastructurally, premelanosomes and melanosomes are rare and the spindle cells have the features of fibroblasts. There is abundant rough endoplasmic reticulum and sometimes intracytoplasmic collagen and macular desmosomes {2476}.

Somatic genetics

Chromosomal aberrations and gene mutations have been found in sporadic and familial melanoma {799}. Allelic loss at the neurofibromatosis type 1 (NF1) gene locus is frequent in DM {931}. Basic fibroblast growth factor (bFGF) and other fibrocytokines are often present in the nuclei of DMs {1335}. Loss of heterozygosity of matrix interacting protein 1 (MXI1) is frequent {1893}. No BRAF mutations were found in 12 desmoplastic melanomas {596}, consistent with the finding that melanomas on chronically sun-exposed skin only rarely have BRAF mutations {358B,596,1493}.

Prognosis and predictive factors

Recurrences are common especially after incomplete excision {526}, marginal excision <10 mm or if neurotropism is present {1867,1868}. The conflicting results regarding the risk of regional node field metastases and prognosis of DM patients may be due to a heterogeneity of tumours classified as DM and failure to account for tumour thickness {2115A}. Regional nodal metastases appear to very uncommon in paucicellular DMs with prominent fibrosis and are associated with longer survival {358A, 932A, 985A}. Otherwise, disease free survival rates are similar to other melanomas of comparable thickness {126}. Neurotropism, HMB45 positivity, high mitotic rate, male gender, thickness, ulceration and site all appear to affect survival which overall is 79% at 5 years {1868}. Of patients with a recurrence, 78.2% experienced it within 2 years.

Wide local excision is the treatment of choice {99A}. Radiation therapy has been effective in some cases {71,1125}.

Melanoma arising from blue naevus

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J. A. Carlson

Definition
A melanoma that arises in association with dermal melanocytosis, most frequently cellular blue naevus.

Synonyms
"Malignant blue naevus" or "blue naevus-like melanoma" are terms used to describe melanomas arising in association with a cellular blue naevus or those primary melanomas that resemble blue naevi and lack an in situ component.

ICD-O 8780/3

Epidemiology
Melanoma associated with blue naevus is an exceedingly rare tumour with over 165 reported cases. It affects predominately Caucasians and all age groups with the majority of cases occurring between 20 and 60 years, with a mean age at diagnosis of 44 years {2066, 2332}. Slightly more females than males have been reported (82 females; 76 males). Occasionally, dark-skinned patients develop melanoma in association with a blue naevus {548,1352,1629}.

Localization
In decreasing order, the sites most frequently affected are the scalp (33%), orbit and face (32%), trunk- mostly back and buttocks (19%), extremities (7%) and hands or feet (7%). Involvement of the vulva and vagina have also been reported {422,2233}.

Clinical features
Most melanomas associated with blue naevus (93%) develop in a pre-existing dermal melanocytosis that was congenital (35%), acquired during infancy or childhood (15%) or identified during their adult years (43%). These associated lesions were cellular blue naevi (52%), common blue naevus (16%), naevus of Ota (14%), naevus of Ito (1%) {2066, 2414}, or ocular melanocytosis {542, 1127,2332,2431}. On average, these melanocytoses were present for 24 years before melanoma developed, with a range of 3 months (infant with congenital facial blue naevus {2066}) to 78 years (naevus of Ito {2414}). For congenital and childhood onset melanocytoses, melanoma developed after a mean duration of 34 years (range 3 months to 78 years) whereas for adult onset common or cellular blue naevi, melanoma developed on average after 14 years (range 1 – 56 years). The majority (83%) of affected patients described recent, often rapid, growth or presented with proptosis in the case of orbital melanomas within a year of diagnosis. Other symptoms include colour change or ulceration, and in the case of orbital melanomas, diplopia and blurred vision. The melanoma is typically a large black nodule with mean diameter of 2.1 cm (range 0.5–8.0 cm). In some cases, satellitosis due to cutaneous metastatic deposits appear around the primary nodule {64,276,364,856,1018, 1588,1981,2066}. However, this feature can also represent the well-known phenomenon of satellitosis associated with the common and cellular blue naevus (agminated blue naevus) {616,1059, 1195,2008}. Similarly, cellular blue naevus can also present with regional lymph node deposits {143,1357,2261}. In the former cases, histopathologic examination of the satellite lesions reveals features of benign blue naevus and the lesions present benign biological behaviour with no development of distant lesions.

Etiology
The etiology of melanoma associated with blue naevus is unknown, but the presence of longstanding dermal melanocytosis is likely a risk factor. Ocular and oculodermal melanocytosis (naevus of Ota) is strongly associated with uveal melanoma {2192,2193} and has been reported with meningeal melanocytoma (blue naevus) of the brain {1877} and primary melanomas of the central nervous system {253,569,1104, 1713,1930,2046}. Based on this association and numerous reports of melanoma of the face, orbit or brain associated with oculodermal melanocytosis patients presenting with naevus of Ota should be considered at lifetime risk for melanoma of the skin, orbit or central nervous system, a risk that maybe similar in nature to that identified for large congenital melanocytic naevi with melanoma and neurocutaneous melanocytosis {254}.

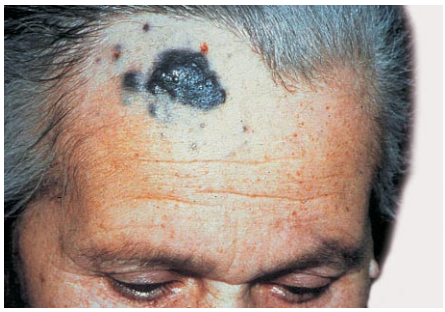

Fig. 2.26 Melanoma arising from blue naevus. Note the presence of satellitosis (Courtesy of Dr. H. Kerl).

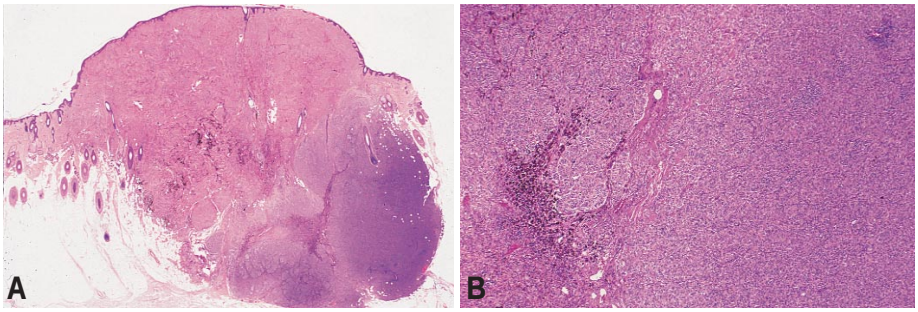

Fig. 2.27 Melanoma arising from blue naevus. **A** Scanning magnification showing a blue naevus with a nodule of malignant melanoma in deeper areas. **B** In deeper areas the nodule of malignant melanoma was composed of sheets of cells destroying pre-existing structures of the dermis.

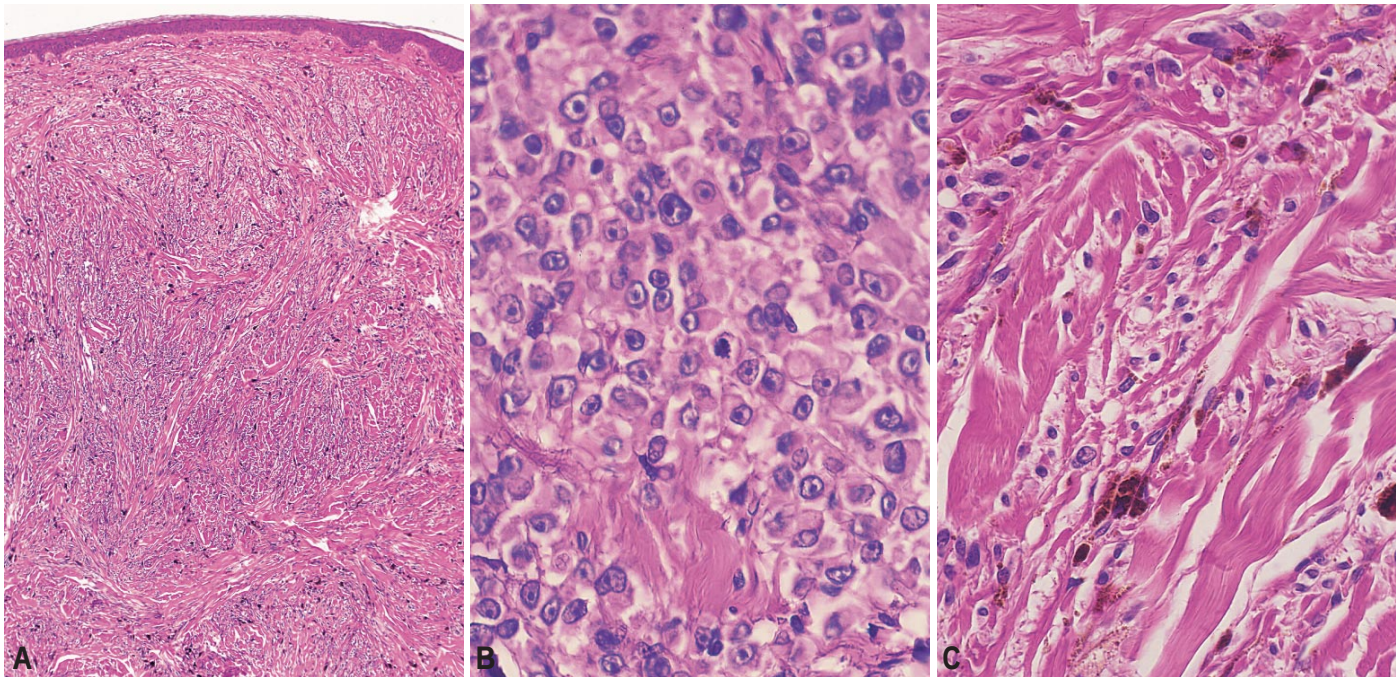

Fig. 2.28 **A** Superficial areas showing stereotypical histopathologic features of a common blue naevus. **B** Higher magnification demonstrated that neoplastic melanocytes of the melanoma showed epithelioid appearance and marked atypia, with large eosinophilic cytoplasm, pleomorphic nuclei and prominent nucleoli. **C** Neoplastic melanocytes of the blue naevus showed small monomorphous nuclei. Note the striking collagenization of the dermis and the abundant number of melanophages.

Additional associations of unknown influence include subacute cutaneous lupus erythematosus, leukoderma, Becker's naevus and prostate adenocarcinoma in one patient {1629}, papillary thyroid carcinoma {94}, acute lymphocytic leukaemia {2119}, psoriasis {238}, and oral contraceptives {1404}. Phototherapy has been associated with cellular blue naevus development {810}.

Histopathology

By definition, a melanoma that develops in a pre-existing blue naevus is a dermal melanoma without the features of melanoma in situ involving the dermoepidermal junction or adnexal epithelium. In fact, 82% of all reported cases described an adjacent common and/or cellular blue naevus. The absence of an identifiable benign naevus component in some reports may be the result of replacement of it by the melanoma or incomplete sampling of the benign element. Although these cases could represent de novo melanomas, a subtle, hypocellular dermal melanocytosis as seen in naevi of Ota and Ito, and Mongolian spots may not have been observed. Reports of orbital, facial and shoulder melanomas associated with naevi of Ota and Ito, and ocular melanocytoses attest to this latter possibility of under-reporting {542,660,1783, 2332,2414}.

At scanning magnification, two histopathologic patterns are evident. One is represented by the benign component of the blue naevus, which may range from very focal to comprising the main bulk of the neoplasm. Often this benign component is represented by a cellular blue naevus and less frequently the lesion contains a common blue naevus. Most cases, however, show a combination of the so-called cellular and common blue naevi, making this distinction useless. The areas of cellular blue naevus consist of solid aggregations of closely arranged monomorphous ovoid cells with abundant pale cytoplasm containing little or no melanin and round vesicular nuclei with inconspicuous nucleoli. In contrast, the areas of common blue naevus are made up of elongated spindled bipolar melanocytes, with long branching dendritic processes most of them filled with abundant granules of melanin. Melanophages and sclerotic bundles of collagen are also frequently observed between the fascicles of dendritic melanocytes.

Although the malignant component may involve the superficial dermis and ulcerate the epidermis, more often it appears as a deep-seated expansile asymmetric nodule involving the reticular dermis and subcutaneous fat. Usually, there is an abrupt transition from the benign blue naevus component to the nodule of melanoma. The nodule or nodules of melanoma show both architectural and cytological features of malignancy. The melanomatous component consists of sheets of cells that involve diffusely the deep dermis destroying the pre-existing structures with pushing margins and sharp demarcation between the neoplasm and adjacent dermis or subcutaneous tissue. Neoplastic melanocytes appear as large spindled to epithelioid cells with abundant cytoplasm and pleomorphic and hyperchromatic nuclei, with prominent nucleoli and frequent mitotic figures. Usually they contain little or no melanin. Without the associated benign component, these dermal nodules would be histopathologically indistinguishable from typical nodular or metastatic melanoma. Necrosis of individual cells as well as necrosis en masse may be also seen in the melanoma component, although this finding seems to be less

frequent than in melanomas arising de novo ("malignant blue naevus") {973}. A perivascular inflammatory infiltrate, mostly composed of lymphocytes, which is usually lacking in blue naevus, is often seen around the melanoma arising in blue naevus.

Melanoma arising in the setting of blue naevus should be differentiated from the so-called atypical cellular blue naevus {118,2371}. These lesions show clinicopathologic features intermediate between typical cellular blue naevus and malignant melanoma associated with blue naevus. The lesions show architectural atypia, characterized by asymmetry and infiltrative margins, as well as cytologic atypia, which consist of hypercellularity, nuclear pleomorphism, hyperchromasia, mitotic figures and necrosis. However, follow-up data of patients with atypical cellular blue naevus demonstrated that no patient experienced either a local recurrence or lymph node or visceral metastasis.

Melanoma associated with blue naevus should be also distinguished from *large plaque-type or giant cellular blue naevus* with subcutaneous cellular nodules {358, 1059}. Large pigmented plaques of childhood onset that show slow enlargement during adolescence and subsequent nodule formation clinically characterize this rare plaque variant of cellular blue naevus. Histopathologically, they exhibit multifocal dermal and subcutaneous proliferations of fusiform and dendritic pigmented melanocytes, with highly cellular nodules located in deeper areas of the plaque. The follow-up of patients with large plaque-type blue naevus with subcutaneous cellular nodules indicates that these lesions behave in a benign fashion.

Metastatic melanoma mimicking blue naevus can also be confused with melanoma associated with a blue naevus {354,2517}. These blue-naevus like metastases occurred in the same anatomic region as the primary tumour or near the skin scar of a dissected lymph node metastasis and were histopathologically characterized by atypical epithelioid melanocytes, mitotic figures, and an associated inflammatory cell infiltrate at the periphery of the lesions. In contrast with melanoma arising in a pre-existing blue naevus, metastatic melanoma to the skin simulating blue naevus lacks the benign blue naevus component.

Animal type melanoma (epithelioid melanocytoma) is a rare variant of primary cutaneous melanoma that may also mimic melanoma associated with blue naevus {567,1917}. Sheets and nodules of heavily pigmented epithelioid melanocytes that tend to aggregate along hair follicles and involve the entire thickness of the dermis with extension into the subcutaneous tissue histopathologically characterize animal-type melanoma. Epithelioid melanocytes in deeper areas show abundant, heavily pigmented cytoplasm and pleomorphic nuclei with prominent eosinophilic nucleoli and mitotic figures. Histopathologic features of melanoma in situ at the dermo-epidermal junction are few or absent, and neoplastic cells do not show evidence of maturation from superficial to deeper dermal areas. The overall architectural and cytologic features of animal-type melanoma closely resemble those of melanoma associated with blue naevus, but animal-type melanoma lacks the benign component of blue naevus or history of a pre-existing melanocytosis.

Metastatic spread

Melanoma associated with blue naevus is an aggressive tumour with frequent metastatic disease to regional lymph nodes (31% of reported cases) and distant sites (42%). Sites of metastasis, in decreasing order of frequency, include liver (36%), lung (22%), brain (16%), skin (13%), bone (9%), and in less than 6% of reported cases, spleen, heart, kidney, pancreas, adrenal, thyroid and parotid glands, ovary, and gastrointestinal tract. Melanuria and generalized melanosis have also been described in its terminal stage {2185}. Metastases can appear as late as 20 years after diagnosis {813}, but the median and mean time of discovery is 1.75 and 3.6 years after diagnosis.

Metastasis to lymph nodes should be differentiated from the presence of blue naevus cells in the capsule of the node {181,392,405,1357,1358}. This well-known pseudo-metastasizing phenomenon seems to be the result of migration arrest during embryogenesis and is characterized by monomorphous melanocytes of blue naevus involving only the capsule and the marginal sinuses of the lymph node. In authentic metastases, nests of atypical melanocytes replace most of the parenchyma of the node, effacing its architecture.

Immunoprofile

Immunohistochemical studies in lesions of melanoma associated with blue naevus have demonstrated a strongly positive reaction of the neoplastic cells, both of the benign and malignant components, for vimentin, S-100 protein, HMB-45 and NKI/C-3 {280,1708,1996}. However, the number of silver positive nucleolar organizer regions (AgNOR score) {813,1826} and growth fraction as measured by proliferating cell nuclear antigen (PCNA) and Ki-67 (MIB-1) are significantly lower in the benign component of blue naevus than in the nodule of melanoma {1708,1826}.

Electron microscopy

Although some authors have interpreted the neoplastic cells of melanoma associated with blue naevus as being related with Schwann cells {1588}, electron microscopic studies have demonstrated the presence of melanosomes in the cells, as well as the lack of cytoplasmic enclosures of unmyelinated axons, which rule out the possibility of Schwann cell differentiation. Although the melanosomes in many cells of the malignant component are devoid of melanin {1014}, incubation with dopa demonstrates that they are strongly dopa-positive {1625}, thus confirming their melanocytic nature.

Somatic genetics

Results of DNA flow cytometry studies in melanoma associated with a blue naevus are variable revealing diploid cell populations in 4 cases {1574,1826} and aneuploid populations in 2 cases {1826}. A molecular analysis failed to demonstrate loss of heterozygosity on microdissected samples in one case of melanoma associated with blue naevus, using a panel of eight genes (MTS1, MXI1, CMM1, p53, NF1, L-myc, hOGG1, and MCC), many of which are commonly associated with conventional melanomas {94}. These findings suggest that melanoma associated with blue naevus may represent a distinct entity with a different molecular pathway to tumourigenesis than that of conventional melanomas. However, in a comparative genomic hybridization study comparing common blue naevi, cellular blue naevi, and atypical cellular blue naevi with melanoma associated with a blue naevus, melanomas associated with blue naevus showed chromosomal abnormalities similar to that of con-

ventional melanoma whereas cellular and atypical cellular blue naevi exhibit infrequent numerical chromosome aberrations similar in character to that identified in proliferative nodules found in congenital melanocytic naevi {1490}.

Prognosis and predictive factors

Some authors have proposed that melanoma associated with blue naevus is a low-grade malignancy {1574}. However, the literature review does not support this opinion. For instance, in a series of 12 cases, metastases developed in 10, and 8 died of metastatic disease {527}, and in another series of 10 cases, 4 patients developed metastases and 3 of them died of disease {883}. Of the 160 cases reported with follow up data, 34% of patients have died due to locally invasive or metastatic melanoma 20 months median, 41 months mean time from diagnosis (range 2–240 months). Therefore, melanoma arising in blue naevus is a highly aggressive tumour with poor prognosis similar to that of thick (>4.00 mm), AJCC stage IIB conventional melanomas {392}. Indeed, the Breslow thickness for this melanoma variant typically is much greater than 4 mm with a mean tumour thickness of 10 mm (range 2.8–45mm){64,640,813,883,1844}. Possible prognostic factors indicative of a poor outcome include the presence of congenital melanocytosis, mixed melanoma cell type (both spindle and epithelioid melanocytes), older age, high mean mitotic count (>4/40 high power field), and lymphocyte count (>100 per 20 high power field) {2332}. These prognostic factors were identified in a study of primary orbital melanoma where 90% of the patients had an associated blue naevus and 47.5% had congenital melanocytosis (naevus of Ota or ocular melanocytosis). The role of sentinel lymph node dissection and postoperative adjuvant therapy remains to be determined. Sentinel lymph node dissection in the staging of melanoma associated with a blue naevus is advocated by some authors {2173} and one patient with metastatic disease to the lymph nodes was alive and without evidence of disease two years after surgery followed by therapy with interferon {640}.

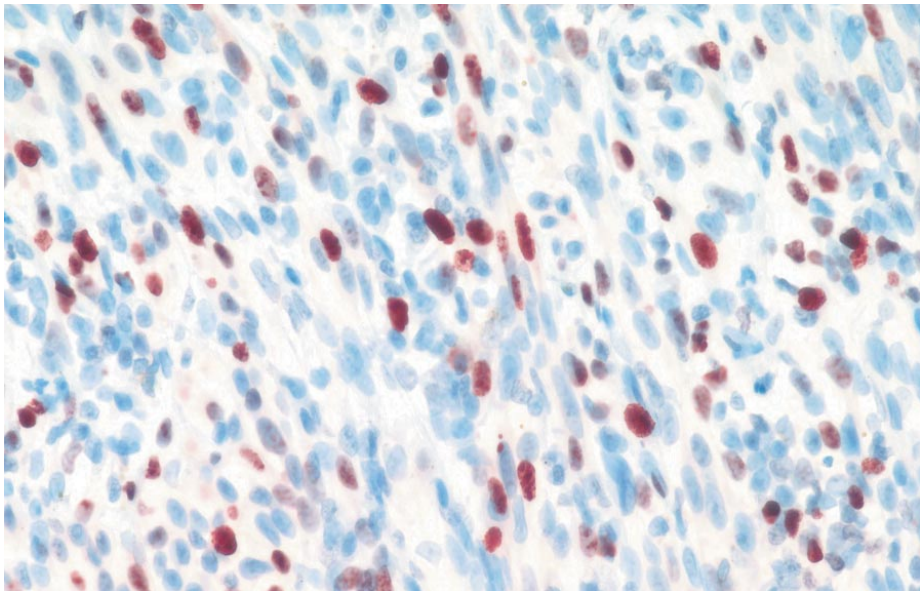

Fig. 2.29 High Ki-67 labelling index in hyperchromatic spindle nuclei of the melanoma arising from blue naevus. The benign portion of the lesion (not shown) had a very low labelling index.

Melanoma arising in giant congenital naevi

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Definition

A proliferation of malignant melanocytes arising either in the epidermal component or the dermal component of a giant congenital naevus associated with risk of metastasis and death.

ICD-O code 8761/3

Synonyms

Malignant melanoma arising in a garment naevus;
malignant melanoma arising in a bathing trunk naevus;
malignant melanoma arising in a giant hairy naevus.

Epidemiology

About 1% of all infants have some kind of a congenital pigmented skin lesion {568}. The giant congenital naevus (GCN) is estimated to occur in around 1 per 20,000 infants {67,411,1306}. The risk of malignant transformation of a GCN has been estimated at from 5-20% but more recent studies based on statistical analyses suggest a figure of 6%. The GCN is a direct precursor of melanoma {1197, 1207,1927,2218}. There is a bimodal distribution to the occurrence of melanoma in GCN. Most develop in childhood before the age of 10 {1508} with a second peak of incidence in adult life.

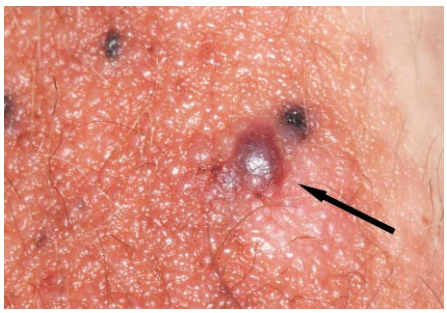

Fig. 2.30 Malignant melanoma presenting as a reddish brown nodule in the midst of the congenital naevus.

Sites of involvement

Malignant melanoma can occur anywhere in a giant congenital naevus. The lesion most commonly arises in lesions on the trunk but can appear in any area even in congenital naevi of the meninges {568,1306,1927}.

Clinical features

The definition of GCN varies and includes a naevus with a diameter larger than 20 cm. Frequently large areas of the body (more than 2% of the body surface) are covered in a garment-like fashion {1306,1927}. The trunk and head and neck are the most common sites for these naevic lesions. The melanoma, very rarely present at birth, usually appears as a rather rapidly growing asymmetrical nodule or plaque of blue-black, reddish or even rarely flesh colouration {568,1009}. Melanoma can occasionally present as a cystic lesion. Therefore, any GCN that develops an apparent subcutaneous cyst must be biopsied. Melanoma is only one of many benign and malignant tumours that may occur in GCN {1009,1928}.

Macroscopy

The lesion usually appears either as a firm nodule, or as a boggy discoloured area, usually dark brown or black in the midst of the naevus. If the lesion arises in the dermis, the tumour can sometimes only be seen on cut surface as a separate nonencapsulated nodule amidst the otherwise tan or pale tan coloured naevus in the dermis or subcutis.

Histopathology

Histologically, the tumours are often asymmetrical and sharply demarcated from the adjacent congenital naevus. If superficial, there is effacement of the rete ridges of the epidermis and often ulceration. The intraepidermal component usually is composed of epithelioid cells with pigmentation. Pagetoid spread is commonly noted. The tumour cells of the dermal component usually form expansile

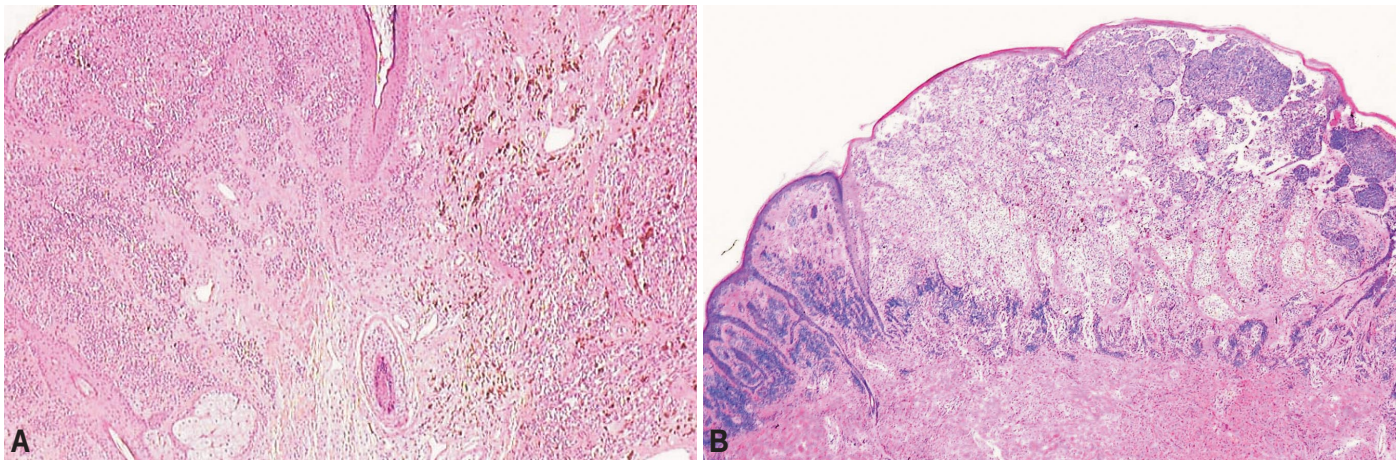

Fig. 2.31 Melanoma arising from large congenital naevus. **A** The melanoma is clearly separate from the naevus cells that are on the left. **B** A protuberant nodule shows the small dark naevus cells to the left and at the base of the melanoma that is composed of nests with dyscohesion.

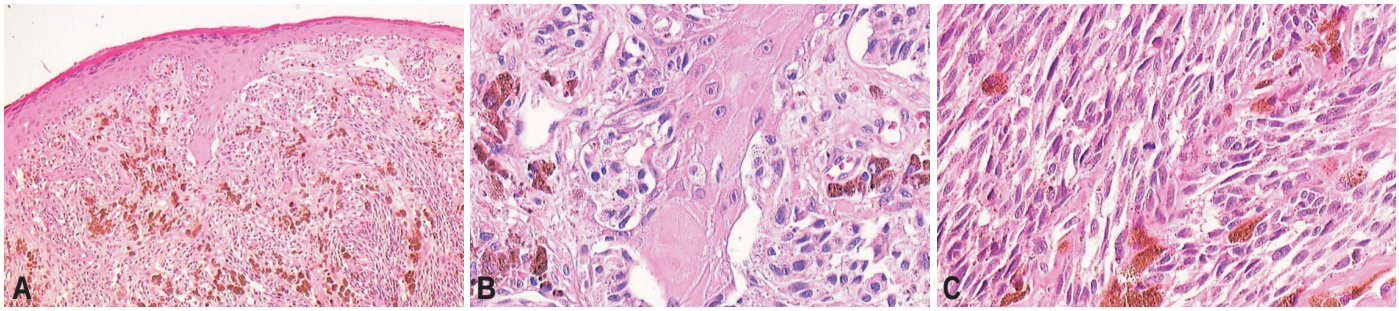

Fig. 2.32 Melanoma arising from large congenital naevus. **A** There is a distinctive proliferation of malignant melanocytes invading the dermis. Note thinning of the rete ridges with a proliferation of malignant melanocytes invading the dermis as spindle cells with an admixed population of melanophages. **B** Reveals epithelioid cells in nests invading the epidermis giving rise to spindle cells in the dermis. **C** The malignant spindle cells show nuclear hyperchromasia and mitoses.

nodules. They exhibit fully transformed malignant characteristics with very irregular chromatin patterns and prominent nucleoli. There is variable pigmentation. Both single cell and zonal necrosis may be observed. The melanoma cells as they abut or infiltrate as cords into the adjacent naevus show no evidence of maturation but maintain their fully malignant characteristics. Mitoses are common and atypical forms are usually present. A lymphocytic host response is often noted. Occasionally, a desmoplastic host response may be observed as well as focal mucinosis. In our experience, the vertical growth phase dermal nodules may exhibit prominent areas of different cell types with different degrees of pigmentation {568,703,1197,1928}.

Histologically, the presence of a residual dermal naevic component with congenital features may be quite difficult to find, particularly, if present in the wall of a vessel.The differential diagnosis includes the proliferative nodules that also arise in large congenital naevi.

Somatic genetics

Comparative genomic hybridization shows that melanomas arising in congenital naevi show similar chromosomal aberrations as melanoma arising independently {175}. By contrast, the proliferative nodules arising in early life do not show chromosomal aberration supporting the view that they are benign {175}.

Childhood melanoma

R.L. Barnhill

Definition

Melanomas developing in individuals prior to the onset of puberty are childhood melanomas and thereafter they are designated as melanomas in adolescents with the age limitation of 18 to 20 years. Childhood melanomas can be further subcategorized as 1) congenital melanoma (onset in utero to birth), 2) infantile melanoma (birth to one-year of age), and 3) childhood melanoma (one year to onset of puberty).

Epidemiology

The incidence of melanoma is exceptionally rare in prepubertal individuals (estimated incidence approximately 0.4% among all melanomas) {269A, 1487A} and uncommon under the age of 20 years (incidence approximately 2%) {123A}. The incidence of melanoma has doubled in patients aged 15 to 19 years over the past decade but has remained unchanged in younger individuals {204A,1037A}. Less than 80 well documented cases of melanoma in children younger than 10 years have been recorded in the literature over a period of 30 years. As in adults, childhood melanomas have a predilection for Caucasians. Individuals with congenital naevi especially large varieties, atypical naevi, family history of melanoma, xeroderma pigmentosum, and immunosuppression are at increased risk for childhood melanoma.

Localization

Melanomas developing in patients up to 16 years of age most commonly involve the trunk (50%), followed by the lower extremities (20%), head and neck (15%), and upper limbs (15%).

Clinical features

Melanomas in individuals under the age of 20, particularly in adolescents, show fairly similar clinical features as compared to melanomas in adults {123A,1916A}. However melanomas in prepubertal individuals are so rare that they are usually unsuspected. Features suggesting melanoma in a pigmented lesion such as a congenital naevus are rapid increase in size, bleeding, development of a palpable nodule (e.g., in a giant congenital naevus), colour change of a nodular lesion, surface changes such as ulceration, and loss of clearly defined margins. Recognition of melanoma appearing de novo requires a high index of clinical suspicion, especially for amelanotic lesions. Utilizing the

conventional ABCDE criteria (Asymmetry, ill-defined Borders, irregular Colour, and large Diameter, Elevation) the clinical detection of melanoma in adults, all such suspicious lesions in children should be evaluated for biopsy and histopathological examination. Melanoma in children also may be associated with pain or pruritus {155,417A,530A, 1037A,1619A,1859A,1930A,1990A, 2003A,2089,2232}.

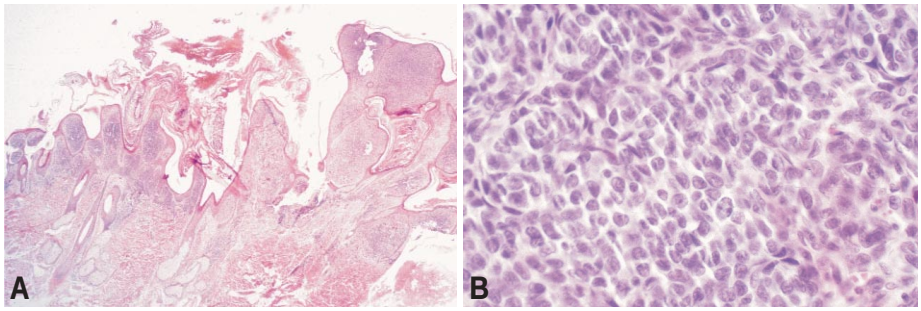

Fig. 2.33 Small-cell melanoma from the scalp of a prepubertal individual. **A** The lesion resembles a conventional melanocytic naevus at scanning magnification. **B** High magnification shows a highly cellular dermal component without maturation. There is a monomorphous population of small round melanocytes with scant cytoplasms resembling the neoplastic cells in lymphoma or neuroendocrine carcinoma. The nuclei are pleomorphic.

Histopathology

The same histopathological criteria should be utilized for diagnosis as have been developed for adult melanomas {155,159A,417A,1990A,2232}. However, clinical information must be strongly considered, particularly age, since cutaneous melanoma is almost nonexistent under the age of two years and especially in the neonatal period.

The important stimulants of melanoma must be excluded: 1) atypical nodular proliferations developing in congenital naevi in infants and young children and 2) Spitz naevi.

Great attention should be given to avoiding over diagnosis melanoma and at the same time to the under recognition of atypical and borderline lesions that require adequate surgery and follow-up for disease recrudescence. Lesions not clearly meeting sufficient criteria for melanoma should be designated as biologically indeterminate. Features appearing to be most useful for the distinction of melanomas from naevi are large size (i.e., >7 mm), ulceration, high mitotic rate (>4 mitoses/mm^2), mitoses in the lower third of the lesion, asymmetry, poorly demarcated lateral borders, lack of maturation, finely-divided melanin, and marked nuclear pleomorphism {155, 159A,2232}. Melanomas in children can be (somewhat artificially) categorized into three principal groups {155, 159A,2232}.

Conventional melanomas

About 40 to 50% of melanomas in children are similar histologically to those in adults {159A,2232}. The intraepidermal components of such melanomas consequently may be pagetoid, lentiginous, or nested. Melanomas of glabrous skin are exceedingly rare in childhood {159A, 2232}. Solar (so-called lentigo maligna) melanomas do not occur in childhood. However, melanomas diagnosed in patients with XP are histologically often similar to solar melanomas except that the actinic damage characteristic of adult tumors is absent {159A,2232}.

Small-cell melanomas

Small-cell melanomas are comprised of monomorphous small cells, reminiscent of small round cell malignancies such as lymphoma, or a melanocytic naevus {155,159A,2232}. These cells are often arranged in sheets or in organoid configurations. The melanocytes contain basophilic round nuclei and condensed chromatin. The high cellular density, lack of maturation, and often prominent mitotic rate are features suggesting melanoma. In children, small cell melanomas may appear de novo or may develop in a congenital naevus. Such melanomas with small-cell phenotypes have often been localized to the scalp, shown striking Breslow thicknesses, and fatal outcome in most patients {159A}.

Melanomas simulating Spitz naevus

On occasion melanomas in both children and adults may exhibit features strongly suggesting a Spitz naevus. These features include both architectural and cytological attributes such as epidermal hyperplasia, wedge-shaped configuration, epidermal clefting about intraepidermal nests, large epithelioid cells and spindle cells arranged in fascicles, etc. {155,159A,2232}.

In addition to conventional melanomas and typical Spitz naevi, there is also an intermediate group of Spitz-like lesions that demonstrate not only some features of Spitz naevi but also varying degrees of atypicality.

Differential diagnosis

Childhood melanomas must be distinguished from congenital and other naevi exhibiting pagetoid melanocytosis, lentiginous melanocytic proliferation, atypical nodular melanocytic proliferation, and from Spitz naevi. Conventional criteria such as age, clinical presentation, size, asymmetry, circumscription, degree of cellular density, maturation, degree of cytological atypia, and mitotic rate should facilitate this discrimination in most cases.

Pagetoid melanocytosis and lentiginous melanocytic proliferation and are features commonly observed in naevi developing in children, particularly in glabrous skin. These changes must not be overinterpreted unless architectural disorder is prominent and cytological abnormalities are present throughout the breadth of the lesion.

Virtually all atypical nodular melanocytic proliferations developing in congenital naevi are biologically benign. Examination of these atypical tumors with reference to karyotype, expression of cell-surface antigens, growth in soft agar, chromosomal aberrations, and other parameters has shown that they have the properties of an immature proliferative but benign tumor {71A,175,1496A}.

Various authors have proposed criteria for distinguishing Spitz naevi from melanomas. Criteria favoring melanoma include asymmetry, ulceration, deep extension (particularly subcutaneous fat), large size (>1 cm), prominent cellular density, lack of maturation, deep mitoses (i.e., more than 3 mitoses in the lower third), high mitotic rate (i.e., >4 to 6/mm^2), abnormal mitoses, and marked nuclear atypia.

Naevoid melanoma

N.S. McNutt
S. Kossard
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Definition

Naevoid melanoma is a subtype of malignant melanoma of the skin that is distinctive in that the primary lesion mimics many of the architectural features of a common compound or intradermal naevus when composed of small melanoma cells, or with Spitz naevus when composed of medium-sized to large melanoma cells. These lesions are defined not as atypical naevi but as melanomas because they involve the dermis and have the potential for metastasis.

ICD-O code 8720/3

Synonym

The term minimal deviation melanoma has been used for some examples.

Epidemiology

Naevoid melanoma is uncommon, being estimated to be approximately 1–2% or less of melanomas {2096,2255}. Due to the low incidence, the small size of series of studies of these tumours, and the slightly different definitions of the lesion, the demographic profiles are not well-established. Naevoid melanomas can occur at any age but often are in young to middle-aged adults. Both men and women are affected, but there is a slight female predominance, perhaps due to early detection in women. In combining data from three similar studies with a total of 65 patients, the distribution of lesions was mostly on the trunk and proximal extremities, specifically on the leg (38.5%), trunk (26.1%), arm (18.5%), head (12.3%), and neck (4.6%) {261, 262,1563,2092,2596}.

Table 2.06
Sex and ages in series of patients with naevoid melanomas.

Reference	Number of subjects		M/F Ratio	Mean Age
	Females	Males		
McNutt {1563}	5/16	11/16	2.2	M 47 (26-75); F 45 (44-57)
Schmoeckel {2092}	25/33	8/33	0.32	M 43 (22-52); F 49 (16-76)
Zembowicz {2596}	10/20	10/20	1	M 41 (19-61); F 44 (26-81)
Blessing 2000 {262}	10/14	4/14	0.4	48.6 (30-77) (small cell MM)
Blessing 1993 {261}	M>F			57 (verrucous MM)

Clinical features

The lesions are generally small papular, nodular, or verrucous, with tan to dark brown colour. The colour may be uniform or irregular. The borders of the lesion are sharp and not very irregular. The lesions often are approximately 5-10 mm in diameter {568}. Clinically apparent inflammation is uncommon. The patient may report that there was a pre-existing macular pigmentation, which became a papule. The lesions are soft and non-tender. They are usually solitary lesions that often are removed because of recent growth or for cosmetic purposes.

Etiology

Unknown. The tumour may arise in clinically normal skin, or in a pre-existing naevus that maintains a naevus pattern of differentiation, or in a lentigo.

Histopathology

The microscopic features of naevoid melanoma are at present restricted by an arbitrary definition to lesions that do not have much intraepidermal spread of tumour cells (pagetoid upward migration) and have a relatively symmetrical profile at low magnification.
There is sharp lateral demarcation of the lesion. Usually there are areas of sheet-like confluent melanocytic proliferation in the dermis. Some lesions have only large nests of cells in the dermis, often larger in the deep portion of the lesion when compared to the upper portion. Mitotic

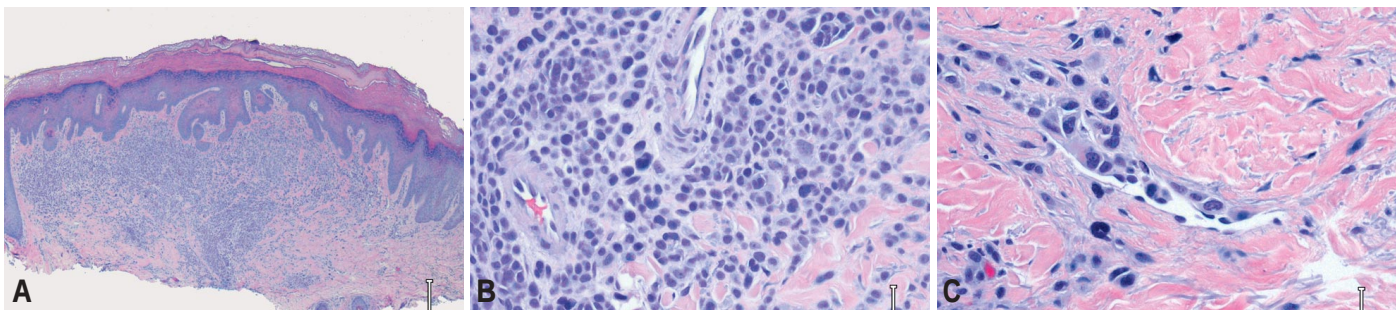

Fig. 2.34 Naevoid melanoma. **A** Naevoid melanoma, papular lesion. (A) At low magnification, note the lack of maturation and the lack of good naevus nest formation in the dermis. **B** Naevoid melanoma, papular lesion. (B) At intermediate magnification, many of the cells are hyperchromatic and atypical. **C** Naevoid melanoma, papular lesion. Perivascular infiltration is at the base of the lesion.

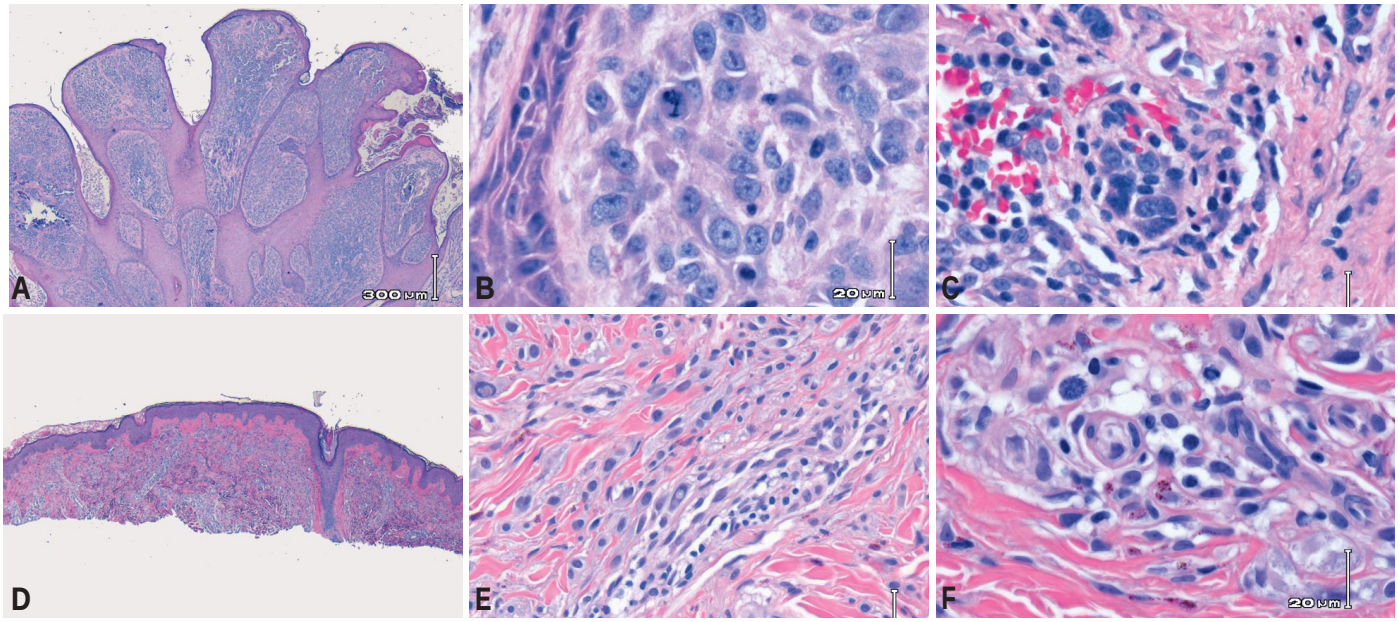

Fig. 2.35 Naevoid melanoma. **A** Verrucous type. Note the crowding of the cells in the dermal papillae. **B** Naevoid melanoma, verrucous type. Note the atypical mitosis in the dermis. **C** Naevoid melanoma, verrucous type. There is vascular invasion at the base of the lesion. **D** Naevoid melanoma with spindle and epithelioid cells. The diffuse dermal pattern with scattered atypical cells, without dermal maturation, shares some features with early desmoplastic melanomas. **E** Naevoid melanoma with spindle and epithelioid cells. Note the nuclear atypia. **F** Naevoid melanoma with spindle and epithelioid cells. Note the lack of maturation of cells in the base of the lesion.

figures can be found in the dermis in most lesions and often multiple mitoses are noted. However, small lesions may have very few mitoses. Naevoid melanomas can occupy a portion of a pre-existing intradermal or compound naevus. The melanomas have a relatively uniform population of small cells with hyperchromatic angulated nuclei or a population of medium-sized to large melanoma cells with more open nuclear chromatin and pale cytoplasm. Inflammatory reaction usually is slight and may be absent. The lesions often are dome-shaped, polypoid, or verrucous in profile {261,568,1562,1563,2092,2543, 2596}.

Immunoprofile and other special stains

HMB-45 reactivity is variable and may be negative or positive {265,1562,1563}. When positive, aberrant patterns of reactivity are common. HMB-45 reactivity may be uniform throughout the dermal portion of the lesion even though there is no junctional component. This reactivity pattern can also be found in blue naevi, some Spitz naevi, and in so-called deep penetrating naevi, and combined naevi {1563,2198}. HMB-45 antibody reacts with the premelanosomal glycoprotein, gp100, and indicates an immature status of the cell with regard to melanin production. A103 antibody, which binds to the antigen Melan-A, reacts with the melanocytic cells throughout the lesion {265}.

The reactivity of the tumour cells with the antibody MIB-1 to detect the protein Ki-67 in cycling cells is positive in both the upper and lower portions of the tumour. In some lesions, the reactivity is slight but greater in the deep portion than in the superficial portion of the lesion. Under controlled conditions, antibodies to detect proliferating cell nuclear antigen (PCNA) have been used to grade melanomas {1160,1934}. In specimens with varied fixation conditions, PCNA has not been found to be reliable because it is sensitive to underfixation and to overfixation in formalin {1563}. Silver staining of nucleolar organizing regions (AgNORs) in 10 small cell melanomas showed an average number of 5.83 (SD+/- 1.69) AgNORs per nucleus. This provided some separation from benign small dermal naevus cells, which had an average of 2.71 (SD+/- 0.50) AgNORs per nucleus. The comparison mean number in 10 superficial spreading melanomas was 8.49 (SD+/- 1.58) AgNORs per nucleus {1316}.

Table 2.07 Histological criteria for metastatic spread of naevoid melanoma.

Metastases	Mean thickness	Mean mitotic index
Without (n=18)	2.24 mm	0.99/mm^2
With (n=15)	1.82 mm	2.96/mm^2

Histogenesis

Naevoid melanomas may arise from the dermal component of small compound or intradermal naevi or from the junctional component of melanocytes in normal skin, or a pre-existing small naevus or lentigo. It is possible that some naevoid melanomas represent early nodular melanomas lacking an evident junctional component.

Prognosis and predictive factors

Predictive features of naevoid melanoma prognosis are tumour thickness, mitotic rate, and large cell type. From 3,500 melanomas, Schmoeckel et al. {2092} selected naevoid melanomas with at least 5 years of follow-up unless there was earlier metastasis. Thirty-three cases were selected: 18 were disease free for at least 5 years. Fifteen had developed metastases. Eight had died of disseminated melanoma. The “most

important criterion was tumour thickness" (but mitoses also seem important {1160}):
McNutt et al. {1562} studied 16 naevoid melanomas and observed that 2 died of melanoma (both large cell type), and one was alive with metastases (10 years, small cell type). Thirteen had wide excisions with no evidence of residual disease or were lost to follow-up.
Zembowicz et al. {2596} selected 20 cases of naevoid melanomas from their files. Three had died and 6 had metastases. There was a three-year follow-up on 8 cases, with a mean follow-up period of 2 years. They conclude: "Naevoid melanoma, as currently defined in the literature and in the present study, seems to have a prognosis similar to that of classical melanoma."
Wong et al. {2543} studied 7 cases of naevoid melanoma (two dome-shaped and five verrucous types) and found local recurrences in 3 and regional metastasis in one patient after 2 years, with a follow-up of 5 months to 5 years.
Lohmann et al. {1444} studied 10 patients with diagnostically controversial lesions who underwent sentinel node biopsy. The differential diagnosis was between Spitz naevus and melanoma. In 5 of the 10 patients, there were sentinel node deposits of tumour in the parenchyma. All patients were alive and free of disease on follow-up of 10 to 54 months.

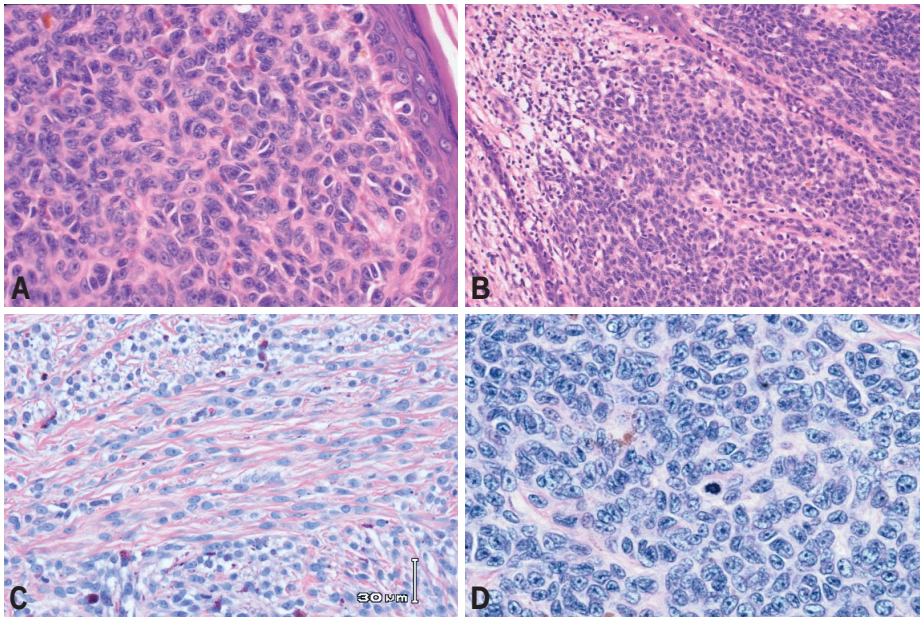

Fig. 2.37 Naevoid melanoma. **A** The melanocytes are arranged as a sheet rather than as discrete nests. **B** The aggregates of melanocytes do not disperse very much at the base of the lesion, where there is a dense lymphocytic infiltrate. **C** Naevoid melanoma and its recurrence. Atypical spindle and epithelioid cells are at the base of the lesion. **D** Mitotic figure among small and monotonous melanocytes.

Variants and differential diagnosis

Minimal deviation melanoma

In the writings of Dr Richard Reed et al. {1911}, this category was analogous to the minimal deviation hepatomas of experimental liver carcinogenesis, which were thought to deviate from the normal cells by only a single enzyme defect, and greatly resembled normal hepatocytes. Initially the minimal-deviation melanomas were characterized as having small cells, without much cytologic atypia, but they all had the architectural patterns of other melanomas. As this concept evolved, minimal deviation melanomas were divided into the following types: blue naevus type, Spitz naevus type, halo naevus type, borderline melanoma, as well as the ordinary minimal deviation melanomas. This created considerable confusion, particularly since the name "minimal deviation" implies a better prognosis, which has not been a consistent finding {2255}. Naevoid melanoma as defined here was mixed into the various types of minimal deviation melanoma and was not recognized as a separate category {1911}. The concept of minimal deviation melanoma has become so vague that the recommendation has been made to stop use of that term. However, there are attempts to clarify the definition of minimal deviation melanoma as distinct from naevoid melanoma {568}.

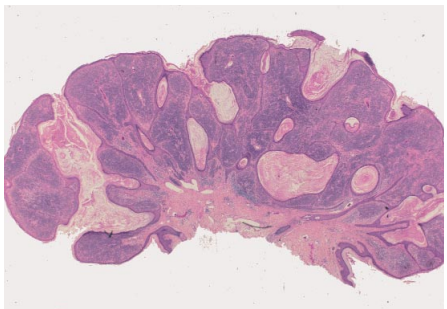
Fig. 2.36 Naevoid melanoma. The lesion has a verrucous profile, easily mistaken for papillomatous naevus.

Small cell melanoma

Melanomas composed of small cells have been studied separately by Kossard and Wilkinson in 1997 {1317}. While some of them are naevoid melanomas, many have the architectural patterns of ordinary superficial spreading melanomas, lentigo maligna melanomas, and acral-lentiginous melanomas. In contrast, naevoid melanomas closely resemble a benign compound or intradermal naevus in architecture. They are all included in the original concept of minimal deviation melanoma. Confusion in terminology arises between small cell melanoma and what we define as naevoid melanoma. This confusion is due to the use of the terms "small naevoid cell type" in small cell melanomas, just on the basis of cell size and without restrictions on the architecture of the lesion. As defined above, a diagnosis of naevoid melanoma requires both architectural and cytological mimicry of a naevus.
Recently a subtype of small-cell naevoid melanoma has been described that develops predominantly in elderly individuals with sun-damaged skin {1313}. This variant has an atypical lentiginous junctional melanocytic proliferation with a nested pattern that may be mistaken for a junctional naevus. This variant has a male predominance and the melanomas occur predominantly on the trunk. The epidemiology suggests that these junctional lesions may be precursors of lentigo maligna or superficial spreading

melanoma in situ. This type of lesion needs further studies as to whether it represents a melanoma sui generis or a lesion with a high propensity to develop further mutations leading to melanoma. It does not fit into the current restricted definition of naevoid melanoma since it has a prominent junctional component and does not involve the dermis in the early stages.

Deep penetrating naevus
This type of naevus has a plexiform growth pattern in the dermis, and despite its name "deep penetrating" most of the lesions are restricted to the upper and middle reticular dermis, giving rise to the concept of the "superficial form of deep penetrating naevus" {2127}. The naevus cells form cords in the dermis composed of large spindled and epithelioid cells resembling a combination of the cells in a blue naevus with cells in a Spitz naevus. Mitotic figures are very rare and are not atypical. They do not have much of an epidermal component unless the deep penetrating naevus component is part of a combined naevus. They must be distinguished from naevoid melanoma, large cell type, which has mitoses in the dermis. However, some lesions given a diagnosis of deep penetrating naevus (with mitoses) have metastasized and may represent examples of naevoid melanomas.

Spitzoid melanoma
This designation is used primarily for melanomas that mimic a Spitz naevus. The presence of a significant junctional component and prominent pagetoid upward migration of large atypical melanocytes distinguish this tumour from a naevoid melanoma. If the Spitzoid melanoma is almost entirely intradermal, it is a variant that would fit into the definition of naevoid melanoma, large cell type.

Metastasizing Spitz naevus
A small number of lesions given the initial diagnosis of Spitz naevi have led to metastases and even the death of patients. Some cases have had only a single lymph node metastasis removed without further evidence of disease on short-term follow-up. The cases with only a single nodal metastasis have been called metastasizing Spitz naevi. Some of these lesions fit the restricted definition of naevoid melanomas if they do not have a significant junctional component. Anecdotal reports indicate that some cases classified as metastasizing Spitz naevus by one institution go to another institution years later with widespread metastases leading to death. The criteria to distinguish between Spitzoid melanoma, melanoma arising in a Spitz naevus, Spitzoid variant of naevoid melanoma, and metastasizing Spitz naevus are controversial and require further investigation. Examination of sentinel lymph nodes in controversial cases of Spitzoid tumours has found a significant number of nodal implants of tumour {1444}.

Proliferative nodules in a congenital naevus
Benign proliferative nodules may arise in the dermis in congenital naevi in some very young patients and may be multiple. Distinction from naevoid melanoma may be difficult since mitotic figures are present in the dermal nodules of naevus cells. Features of benign proliferative nodules that have been emphasized are multiplicity of nodules of similar sizes and appearances, and a gradual blending of the cells of the nodule with the surrounding background congenital naevus cells at the periphery of the nodules. Sharp demarcation of the proliferative nodules is more common in naevoid melanomas arising in the dermal component of a congenital naevus {568}.

Melanoma arising in the dermal component of a large or "giant" congenital naevus
In studies of melanomas arising in giant congenital naevi, many arose from the dermal component {254,1912,1928}. A significant proportion of such melanomas are composed of small, hyperchromatic atypical cells and were interpreted to be similar to melanoblasts, leading to diagnosis of melanoblastoma. These lesions were highly malignant. They are a variant that fits the current definition of naevoid melanoma since they lack an epidermal component and are composed of small epithelioid cells.

Early nodular melanoma
It is most likely that some naevoid melanomas are an early stage in the evolution of nodular melanomas.

Desmoplastic/neurotropic melanoma
Although some of these lesions could fit into the definition of naevoid melanoma, it is conventional to separate them as a distinct entity. Desmoplastic melanomas generally have spindle-shaped cells and naevoid melanomas, as defined here, generally have more epithelioid cells. Both tumours can present as predominantly dermal lesions. Desmoplastic melanomas can resemble desmoplastic naevi, especially hypopigmented blue naevi. Desmoplastic and neurotropic melanomas are best separated from naevoid melanomas since they can be recognized as a distinct group of tumours that has been characterized sufficiently for diagnosis.

Metastatic melanoma
The histologic features of naevoid melanoma can be exactly reproduced in satellite metastatic papules and nodules of melanoma in the skin. The lack of an intraepidermal component, confluent growth patterns, sharp circumscription, symmetry, and dermal mitotic figures can all be found in metastatic melanoma. A diagnosis of naevoid melanoma should be made with great caution in an individual with a known history of melanoma. Misdiagnosis of primary naevoid melanoma as metastatic melanoma can lead to the clinical impression of a metastatic melanoma for which a primary lesion is never found. On the other hand, individuals given a diagnosis of naevoid melanoma, who subsequently rapidly develop extensive metastases, may actually represent patients with a metastatic lesion that resembled a primary naevoid melanoma. Multiplicity of lesions resembling naevoid melanomas simultaneously in the same patient points toward metastatic disease. However multiple naevoid melanomas have been reported in an immunodeficient patient {1804}.

Persistent melanoma and local metastasis of melanoma

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J.C. Maize
M.G. Cook
P.E. LeBoit

Definition
Persistent melanoma is defined as the persistent growth of residual, incompletely excised primary malignant melanoma, of either the epidermal or the invasive component, or both. It represents one form of "local recurrence" of melanoma, the other being local metastasis {30,1001}.

Synonym
Local recurrence of melanoma.

Epidemiology
The epidemiological characteristics are those of the original primary melanoma.

Etiology
The etiological factors are those of the primary melanoma.

Localization
Persistent melanoma may follow removal of melanoma from any site of the body although it seems more common on the head and neck, probably due to the higher incidence of poorly defined variants of melanoma in this site. These include lentigo maligna, in particular the amelanotic variant, and desmoplastic melanoma which is particularly susceptible to incomplete excision because of its poorly defined borders.

Clinical features
The most common clinical presentation is the persistence or recurrence of a flat,

Table 2.08
Histological features of persistent melanoma and local metastases of melanoma.

	Persistent melanoma	Metastatic melanoma
Epidermal component	Usually present, with or without a dermal component .	A. Absent in most cases. B. Epidermotropism uncommonly. The dermal component usually extends beyond a zone of epidermotropism when present. Sometimes the epidermotropic component is more extensive, simulating primary melanoma {998}.
Dermal growth pattern	The full range of patterns associated with primary melanoma.	A. Single or multiple symmetrical dermal and/or subcutaneous nodules. B. Diffuse small groups and strands of neoplastic melanocytes (this pattern occurs in the smallest and presumably earliest metastases).
Inflammation	Lymphocytic inflammation usually present.	Absent or sparse.
Vascular invasion	Sometimes present.	Present in many cases.
Mitotic rate	Variable	High (usually > than 6/mm^2)
Cell type	The full range of cell types seen in primary melanoma, frequently including a mixture of cell types.	Usually monomorphic atypical melanocytic population of epithelioid, spindle or small (naevoid) cells.
Associated naevus	Commonly present.	Rare (coincidental).
Necrosis	Uncommon	Often present in the centres of the nodules.
Epidermal collarette	Uncommon	Usually present, when nodules of metastatic melanoma are in the superficial dermis.
Fibrosis	Frequently present in zones of regression and in desmoplasia.	Little or no reactive fibrosis in the stroma of the tumour.
Scarring	Present in the dermis and often also in the subcutis.	Present when the metastasis occurs at the primary excision site.

NOTE: 1. In cases of persistent melanoma, histological review of the primary excision confirms the presence of in-situ or invasive melanoma (or both) at a margin of excision.
2. The microscopic features of metastatic melanoma involving the scar of the primary excision are the same as those of metastatic melanoma at a site distant from the scar, with the additional feature of the scar at the site of the completely excised primary melanoma {2573}.

variably pigmented patch adjacent to or surrounding the scar of the primary excision site. In some cases there may also be nodule formation when there is persistent dermal invasion, especially of desmoplastic melanoma.

Macroscopy

The lesion frequently is a variably pigmented, often pale macule with poorly defined borders. In many cases of persistent desmoplastic melanoma there is no abnormal pigmentation in the epidermis overlying a firm nodule.

Histopathology

In the uncommon event of incomplete excision of both the epidermal and invasive components of one of the common forms of cutaneous melanoma, the histologic appearances are those of the original tumour, frequently with pagetoid infiltration of the epidermis overlying invasive atypical epithelioid melanocytes, usually with little or no pigmentation, forming an expansile growth pattern adjacent to a zone of scarring. More commonly, the persistent lesion consists of in-situ melanoma with or without focal dermal invasion. Persistence of incompletely excised desmoplastic melanoma may present only sparse, subtle infiltration of a sclerotic nodule in the dermis and/or subcutis, containing atypical spindle cells with hyperchromatic, variably pleomorphic nuclei and sometimes only sparse mitoses, distributed singly and in strands between the collagen bundles. As in the primary tumour, a patchy lymphocytic infiltrate may provide a clue to perineural invasion. Desmoplastic melanoma may very closely simulate a surgical scar in the primary lesion and can be very poorly circumscribed {1194}. However it can be distinguished by its infiltrative pattern beyond the zone usually expected to be involved with scarring following surgery. The features of persistent desmoplastic/neurotropic melanoma may be seen proximal or distal to the scar at the primary excision site, along the line of nerves.

In assessing locally recurrent melanoma it should always be remembered that melanoma metastases may be epidermotropic and simulate primary melanoma {998}.

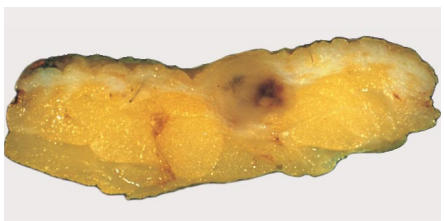

Fig. 2.38 Local melanoma metastasis. So-called "local recurrence" of melanoma in the scar at the excision site of a primary melanoma completely excised with a margin of 25mm.

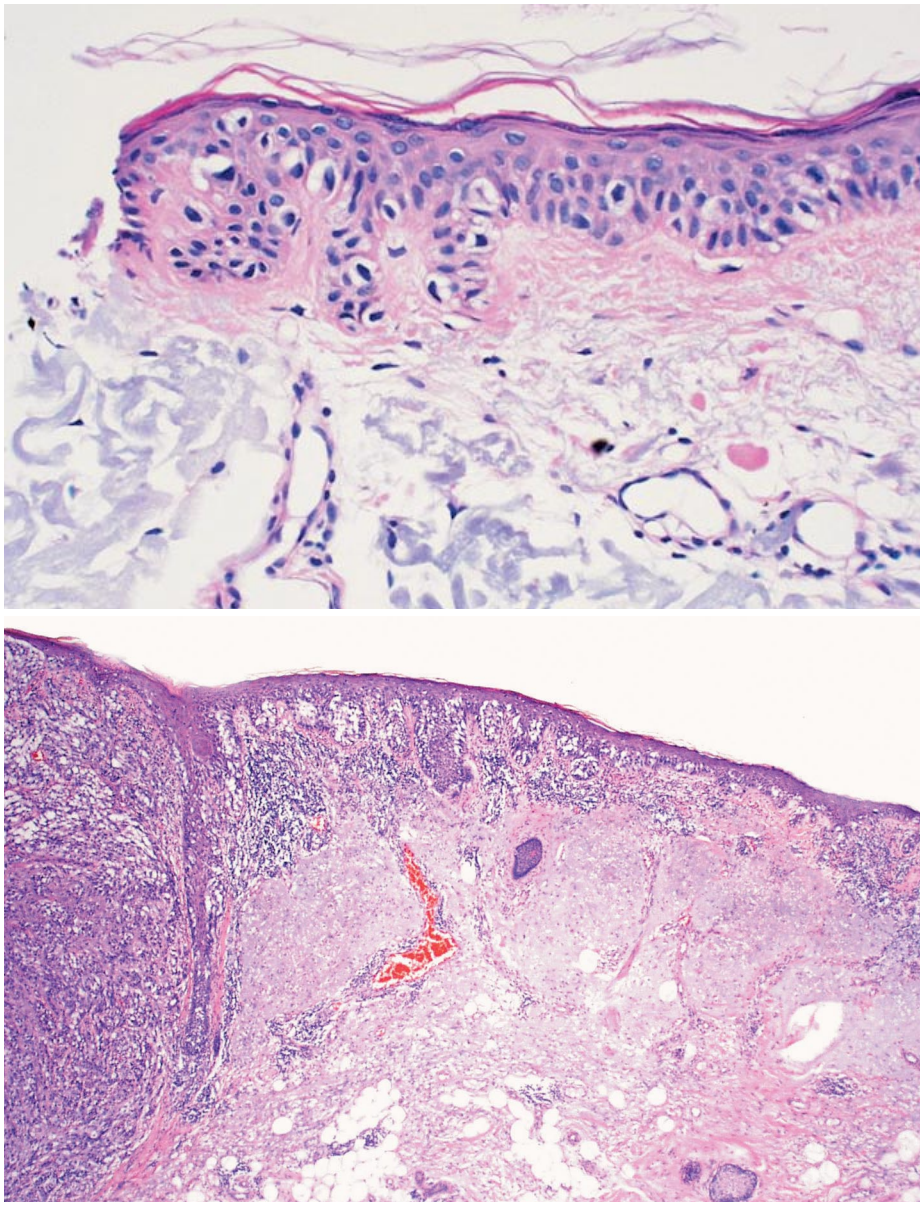

Fig. 2.39 Persistent melanoma. **A** Melanoma in-situ at the lateral margin of the excision of a primary melanoma. **B** "Local recurrence", at the excision site two years later, showing invasive melanoma, extensive adjacent melanoma in-situ and dermal scarring.

Differential diagnosis

Rarely, pigmentation of the epidermis or growth of a nodule at the site of previous excision of melanoma may be due to the coincidental growth of an entirely new and distinct tumour such as dermatofibroma or pigmented basal cell carcinoma. The most important differential diagnosis, however, lies between true persistence of incompletely excised primary melanoma and the other form of “local recurrence” due to metastatic melanoma. Metastatic melanoma in or adjacent to the primary excision scar usually presents as a rapidly growing papule or nodule without pigmentation of the overlying dermis, sometimes associated with

multiple similar, rapidly growing lesions separate from the primary excision site. Histologically, metastases involving the scar present exactly the same features as cutaneous metastases at a distance from the scar {2573}

Histogenesis

Persistent melanoma occurs because a primary melanoma was incompletely excised. The histogenesis, therefore, is essentially that of the original melanoma.

Somatic genetics

The genetic factors are those that apply to the original melanoma.

Prognosis and predictive factors

The prognosis for persistent melanoma is assessed in the same manner as for the original tumour, tumour thickness still being the most important single factor, unlike local recurrence due to metastasis which is a manifestation of systemic metastasis and portends a poor prognosis.

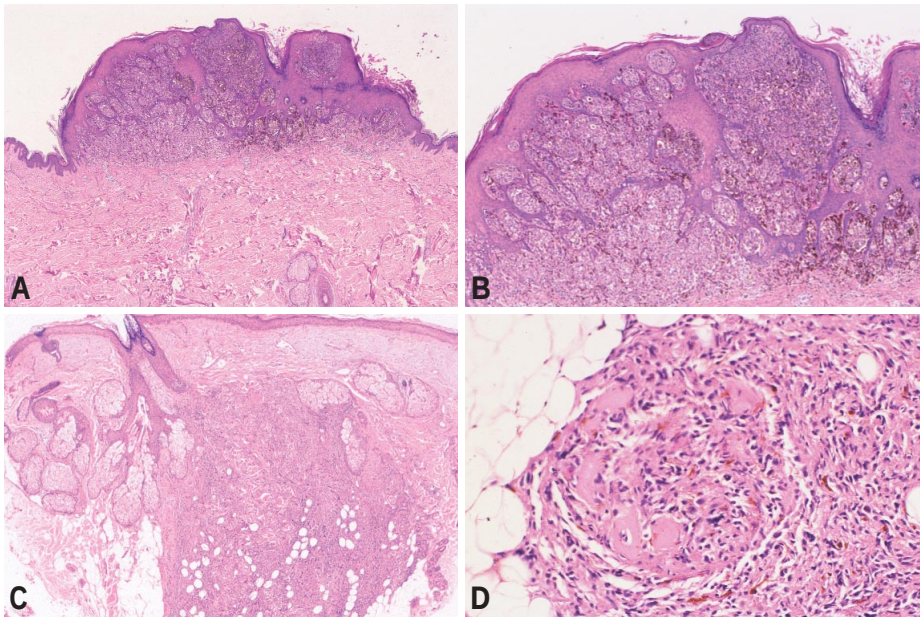

Fig. 2.40 Metastatic melanoma. **A** In this epidermotropic metastatic melanoma, a papule has formed largely due to the irregular epidermal hyperplasia. **B** On the left side of the lesion, one can see sharp circumscription, contributing to resemblance to a Spitz naevus. **C** Metastatic melanoma simulating blue naevus. **D** Irregular nests of melanoma cells are visible at the base of the lesion in the subcutis.

Congenital melanocytic naevus

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Superficial type

Definition
Congenital melanocytic naevi (CMN) of the superficial type are melanocytic proliferations present at birth. The term congenital has been also applied to lesions displaying clinical and histopathological features of congenital melanocytic naevi which may not be apparent at birth. These lesions are designated as tardive congenital melanocytic naevi.

ICD-O code 8761/0

Synonyms
Congenital pattern-like naevus; tardive congenital naevus; congenital naevus-like naevus.

Clinical features
Congenital melanocytic naevi - superficial type are frequently observed. They can be found on any anatomic site and belong to the group of small congenital naevi with a diameter smaller than 1,5 cm.
On gross examination they vary from macules and papules to plaques and reveal different colours from light brown to black. The lesions are usually round or oval with a smooth or papillated surface. They may be hairy or hairless.

Histopathology
In the superficial type of CMN, dense diffuse infiltrates of small monomorphous melano-cytes are found in the upper part of the dermis and the mid-portion of the reticular dermis. The melanocytes are frequently arranged in a band-like pattern and are disposed in single files between collagen bundles ("splaying of melanocytes").
An important criterion for diagnosis is the presence of melanocytes along epithelial structures of adnexa and their angiocentric distribution. They may be found within sebaceous glands, vessels, nerves and in smooth muscles {1168,1531}. In the compound type of a congenital naevus – superficial type, nests of melanocytes are present in the epidermis, mostly at the dermo-epidermal junction.
Melanomas are very rare in newborn and young infants (see chapter on childhood melanoma). Congenital melanocytic naevi, biopsied shortly after birth or in the first years of life can display atypical intraepidermal changes (pagetoid melanocytes arranged as solitary units and nests; single cells present in the upper layers of the epidermis) similar to those of melanoma in situ {1514}. This finding is more commonly found in giant congenital naevi than in small ones.
The clues for diagnosis of this unusual change in a benign naevus are found in the dermis where the large, pale melanocytes merge with smaller ones that have the characteristic features of a congenital melanocytic naevus.

Somatic genetics
Like the majority of melanocytic naevi except Spitz and blue naevi, congenital melanocytic naevi have frequent BRAF mutations and show no chromosomal aberrations {173,1850}.

Prognosis and predictive factors
Recent studies revealed in a significant number of malignant melanomas an association with melanocytic naevi with a congenital histopathologic pattern {159,1245}. However, the pathogenetic role of small congenital melanocytic naevi as precursor lesions of melanoma is controversial {1508, 2323}. Clinical follow-up of 3922 patients with small CMN found no significant risk of melanoma development {205}.

Proliferative nodules in congenital melanocytic naevi

Definition
Proliferative nodules in congenital melanocytic naevi are defined as atypical melanocytic proliferations which manifest predominantly in the neonatal period within a pre-existing large (deep) congenital melanocytic naevus.

ICD-O code 8762/1

Synonyms
Atypical proliferative nodules in giant

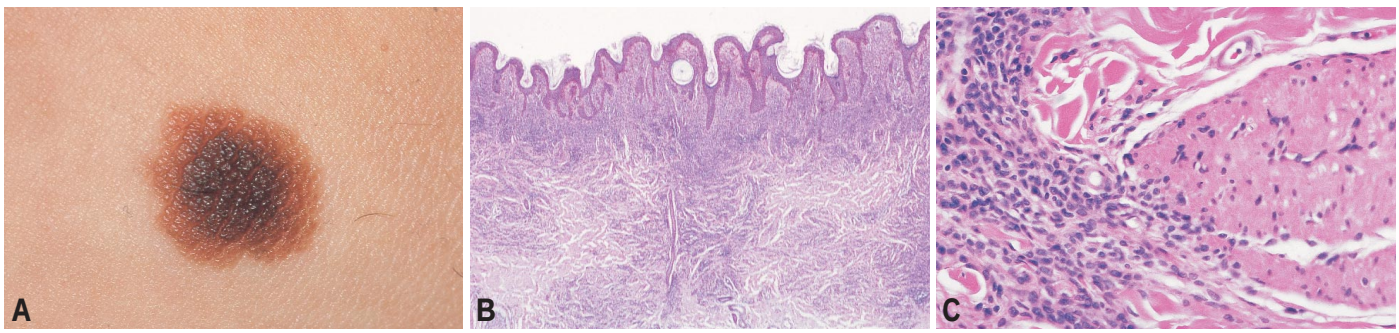


Fig. 2.41 Congenital melanocytic naevus, superficial type. **A** Papule with brown to black colors and a mamillated surface. **B** Band-like infiltrate of melanocytes in the upper dermis. Adnexocentric arragement and "splaying" of melanocytes between bundles of collagen in the upper and mid-portion of the reticular dermis. **C** Monomorphous melanocytes around and focally within an arrector pili muscle.

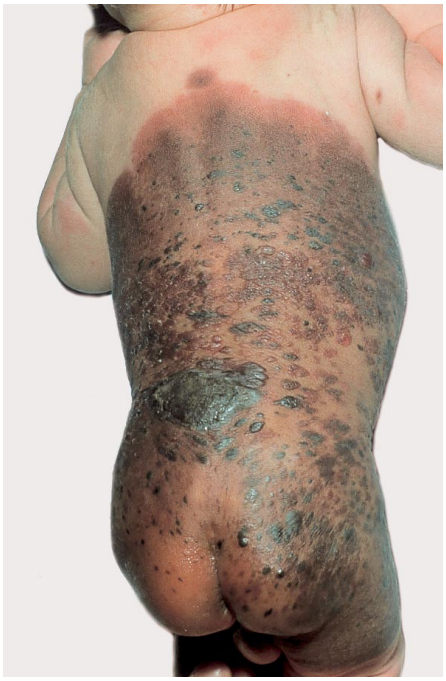


Fig. 2.42 Proliferative nodule in a large congenital melanocytic naevus (garment type). A black plaque above the sacrum representing the proliferative nodule is recognizable.

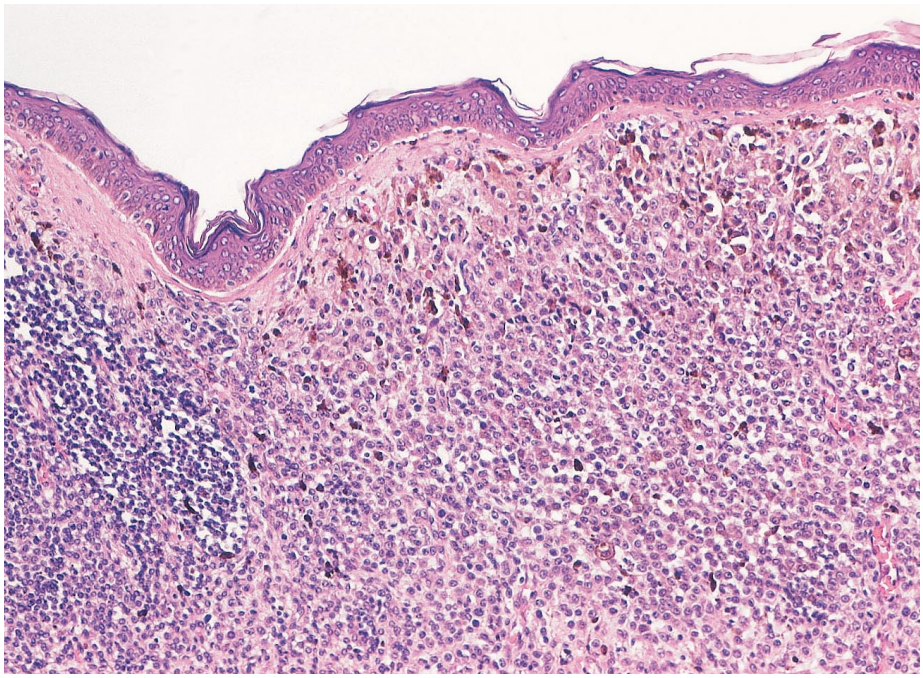


Fig. 2.43 Proliferative nodule in a congenital melanocytic naevus. The congenital melanocytic naevus, with small naevoid cells can be recognized on the left side of the picture. Melanophages are distributed in a uniform fashion in the upper dermis. The profilerative nodule reveals cellularity with relatively monomorphous large cells with prominent nucleoli.

congenital naevi; dermal variant of minimal deviation melanoma in a giant congenital naevus {1907}, dermal melanocytic tumour of uncertain potential in a giant congenital naevus.

Clinical features

There is usually a dark brown to black plaque or nodule above a giant congenital melanocytic naevus. The lesions may become lighter and show regression after years. Occasionally a palpable mass can be found deeply in the skin. These nodular proliferations in congenital melanocytic naevi behave in a benign fashion.

Histopathology

The background congenital melanocytic naevus reveals the characteristic features of a congenital melanocytic naevus of the deep type. A dense diffuse infiltrate of small melanocytes involving the entire dermis and often extending into the septa of the subcutaneous fat can be observed.

The “proliferative“ nodule, which is usually found in the upper and mid dermis consists of roundish epithelioid or spindled melanocytes. The cells are large and appear to blend with the surrounding smaller melanocytes (naevus cells). Atypical nuclei and mitotic figures can be observed.

Differential diagnosis

Proliferative nodules in congenital melanocytic naevi can be misinterpreted as a melanoma that developed in the intradermal component of a congenital naevus (see Melanoma arising in giant congenital naevi) {1009}.

Somatic genetics

In a study of proliferative nodules using comparative genomic hybridization seven out of nine cases showed chromosomal aberrations {175}. Six of the seven cases with aberrations (86%) showed numerical aberrations of whole chromosomes exclusively. This pattern differs significantly from the findings in melanomas arising in congenital naevi or melanoma in general in which the majority (96%) have aberrations involving only partial chromosomes {173}. Loss of chromosome 7 was seen in three of the nine proliferative nodules. Loss of chromosome 7 was not observed in 132 melanomas that were not associated with giant congenital naevi {173}. However, one melanoma arising in a congenital naevus in an eight-year-old boy showed a similar loss of chromosome 7.

A

Blue naevi

E. Calonje
K. Blessing
E. Glusac
G. Strutton

Common blue naevus

Definition
Common blue naevus (BN) is a benign, usually intradermal melanocytic lesion characterized by pigmented dendritic spindle-shaped melanocytes and, more rarely, epithelioid melanocytes. The melanocytes are usually separated by thickened collagen bundles.

ICD-O code 8780/0

Epidemiology
BN is relatively frequent, has predilection for females and presents mainly in young adults between the second and fourth decades. Although most tumours are acquired, congenital examples have been documented {1872}. Familial cases may be seen and usually present with multiple lesions {258,1292}.

Localization
The anatomical distribution is wide but most lesions occur on the distal upper limbs (particularly the dorsum of the hand), followed by the lower limbs, scalp, face and buttocks. Lesions have also been documented in the vagina {1002,2356}, cervix {2393}, prostate {1414}, oral cavity (mainly the hard palate) {327,328} and the capsule of lymph nodes without a primary cutaneous lesion {695,858,1497}.

Clinical features
The most common presentation consists of a single asymptomatic, relatively well-circumscribed, dome-shaped blue or blue-black papule less than 1 cm in diameter. The characteristic blue colour is produced by the Tyndall effect. Tumours may rarely present as a plaque {1025,2494}. Eruptive lesions have rarely been documented. Exceptional clinical presentations include a speckled variant {1044}, hypopigmented lesions {278}, an example with satellite lesions {1195} and a case with widespread lesions. Localized hypertrichosis has been described in a single case {57}.

Histopathology
BN and cellular blue naevus show a wide histological spectrum, frequently overlapping with other melanocytic lesions including deep penetrating naevus and pigmented Spitz naevus {1637}.
BN is typically located in the reticular dermis and only exceptionally extends into the papillary dermis or subcutis. The epidermis appears unremarkable, except in the rare so-called compound blue naevus, in which dendritic junctional melanocytes are identified {733, 1190}. Low power examination reveals a generally symmetric but often ill-defined tumour of variable cellularity. Concentration around adnexa without adnexal destruction is typical. Poorly cellular lesions often display prominent sclerotic stroma making the diagnosis difficult. Lesions with very poor pigmentation are rarely encountered {234,402}. Tumour cells are bland and spindle-shaped or dendritic and usually contain abundant cytoplasmic coarse melanin pigment. Nuclei are small, and an inconspicuous basophilic nucleolus is sometimes present. Numerous melanophages are a relatively constant feature in the vicinity of tumour cells. Extension of tumour cells into nerves and, less frequently, blood vessel walls, may be found. Mitotic figures are exceptional. Rarely, a blue naevus may coexist with a trichoepithelioma {48}.
In some instances, metastatic melanoma may mimic common blue naevus {354}.
Blue naevus may co-exists with other types of naevus (see combined naevus).

Immunoprofile
Tumour cells are usually diffusely positive for melanocytic markers including S-100, HMB45, melan A and microphthalmia transcription factor (MITF-1). Unlike the case in most other benign melanocytic naevi and in melanomas, HMB45 strongly stains the entire lesion in blue naevi.

Somatic genetics
Mutations in the BRAF gene appear to be rare in BN. Chromosomal aberrations are uncommon {1490}.

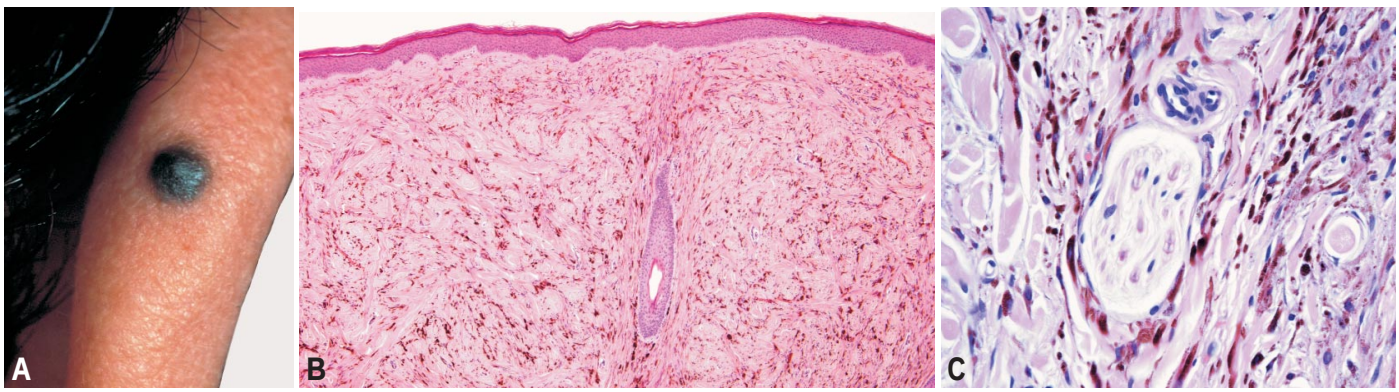


Fig. 2.44 Common blue naevus. **A** Typical clinical appearance of a common blue naevus. **B** A more cellular example with hyalinization of dermal collagen. **C** Melanocytes often extend into the perineurium of dermal nerves.

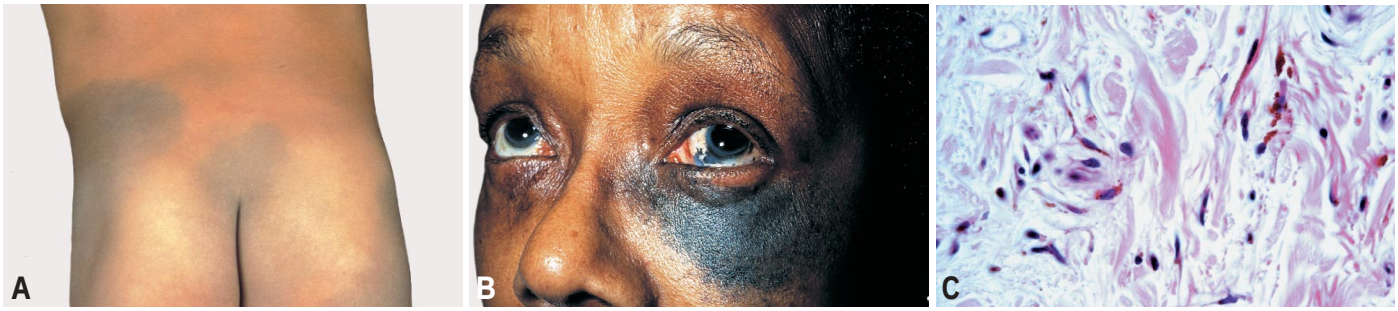


Fig. 2.45 **A** Mongolian spot. Typical prominent macular blue/grey discolouration on lower back and buttocks. **B** Naevus of Ota with involvement of the periorbital skin and conjunctiva. The blue cast is typical. **C** Naevus of Ota. Bipolar, deeply pigmented melanocytes in the reticular dermis.

Prognosis and predictive factors
BN is benign, and malignant transformation is exceptional {883} (see chapter Melanoma arising from blue naevus). Simple excision is curative and local recurrence is very rare {973}.

Mongolian spot

Definition
Mongolian spot (MS) is a form of dermal melanocytosis presenting on the lower back and characterized by scattered pigmented dendritic melanocytes in the reticular dermis.

Epidemiology
MS presents at birth and has marked predilection for Black and Oriental patients with the same sex incidence {1260,1261}. The incidence in Caucasian children is approximately 9.5% {543}.

Localization
Most lesions occur on the lower posterior trunk with predilection for the sacrogluteal region. Lesions identical to MS and naevus of Ito or naevus of Ota may present rarely in other anatomical sites.

Clinical features
MS is characterized by a macular area of blue-green or blue-grey discolouration varying in size from a few to 10 or more cm. Lesions fade gradually, usually disappearing completely when patients reach adolescence.
Association with cleft lip {1096} and the mucopolysaccharidoses, including Hurler and Hunter syndromes) {880, 2063} has been documented. Lesions with the clinical and histological features of MS may rarely present at other body sites.

Histopathology
The epidermis and superficial dermis appear unremarkable. Low power examination reveals a mild increase in cellularity in the deep reticular dermis, consisting of few variably pigmented dendritic melanocytes, which are usually, oriented parallel to the epidermis. Melanophages are occasionally seen.

Naevus of Ito and Naevus of Ota

Definition
Naevus of Ito (NI) and naevus of Ota (NO) are dermal melanocytoses with identical histological features, which differ in their characteristic clinical presentation. NI typically presents in the shoulder region, following the distribution of the lateral brachial and posterior supraclavicular nerves. NO involves the skin and mucosal surfaces (including the conjunctiva), following the distribution of the ophthalmic and maxillary branches of the trigeminal nerve.

Synonyms
Naevus Ota: Oculodermal melanocytosis, Naevus fuscoceruleus ophthalmomaxillaris.

Epidemiology
Both NI and NO are relatively rare, affect mainly patients of Oriental or African origin and have some predilection for females {1027,1307,1626,2243}. Presentation is mainly at birth (up to 50%) or during childhood and adolescence. Adult onset is very rare {447}.

Localization
NI typically involves the supraclavicular, deltoid and less commonly, the scapular area. NO usually involves the sclera, conjunctiva, and skin around the eye and zygomatic and temporal areas. Rarely the nasal and oral mucosa, optic tract and the leptomeninges are involved. Lesions identical to naevus of Ito or naevus of Ota may present rarely in other anatomical sites. A limited form resembling naevus of Ota presenting in the zygomatic area is called naevus of Sun.

Clinical features
Lesions are usually large, macular, ill defined and have a blue or blue-grey colour. A speckled appearance is seen rarely. There is no tendency for spontaneous regression. Bilateral involvement has been documented rarely {1026}. Coexistence between NI and NO is a rare occurrence {615,1026}. Glaucoma is a rare complication of NO {1434}.

Histopathology
The histology of NI and NO is indistinguishable. The epidermis appears unremarkable but may show increased melanin in basal cells and a mild increase in the number of basal melanocytes. In the superficial and mid-dermis there are scattered dendritic or spindle-shaped, often bipolar deeply pigmented melanocytes. Melanophages are rare.

Prognosis and predictive factors
Malignant transformation is exceptional and more common in NO {1783,2194, 2345,2414}. In the latter setting it may occur in the skin, eye or meninges.

Cellular blue naevus

Definition
Cellular blue naevus (CBN) is an acquired dermal/subcutaneous pigmented tumour with prominent cellularity and an expansile growth pattern.

ICD-O code 8790/0

Epidemiology
CBN tends to present between the second and fourth decades of life with female predilection, and it is more common in Caucasians. Congenital cases are exceptional {1095}.

Localization
The anatomical distribution is wide, but CBN have predilection for the buttocks and sacral region (50% of cases), followed by the scalp, face, distal limbs and other sites on the trunk {1957,2336}. Lesions may also rarely occur on the eyes, cervix, vagina, breast and spermatic cord {266,1957,2336}. Aggregates of tumour cells have been reported in the capsules of regional lymph nodes draining an area where an otherwise typical benign cellular blue naevus is present {287,1957,2261,2336}. This phenomenon is regarded as a benign occurrence rather than an ominous finding.

Clinical features
Tumours are usually large, varying from 1 to several centimetres, and the colour varies from light blue-brown to dark blue. Lesions are asymptomatic and grow very slowly, presenting as a non-ulcerated firm nodule {1957,2336}. Exceptional cases present as a large plaque {358}. Rare tumours arising in the scalp have been described with invasion of the underlying bone {1596} and even the brain {854}.
The epithelioid variant of blue naevus is very rare and has mainly been described in patients with Carney complex who usually present with multiple lesions {396,399}. Sporadic lesions are usually solitary and may occur in genital skin {1117,1646,1736}.

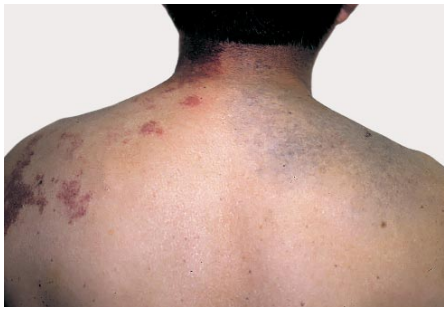


Fig. 2.46 Cellular blue naevi on the upper back.

Macroscopy
The cut surface of a CBN characteristically shows a dark brown to black, well-defined dermal and subcutaneous tumour. In some cases there are areas of haemorrhage and cystic degeneration.

Histopathology
Low-power examination reveals a fairly characteristic picture with a dumbbell-shaped multinodular tumour occupying the reticular dermis and often extending into subcutaneous tissue. A junctional component is not usually found. Areas of pigmentation alternate with poorly pigmented areas and, in a minority of cases, pigment is very scanty {2595}. Cellular areas tend to be more prominent towards the centre of the tumour, and the cellularity may be most marked where the neoplasm protrudes into the subcutis. The cellular areas may alternate with sclerotic or hypocellular areas. In most cases there are focal areas representing or simulating a common blue naevus. High power examination reveals bundles of oval or spindle-shaped cells with pale cytoplasm, alternating with bundles of deeply pigmented spindle-shaped cells. In addition, dendritic melanocytes and/or round, somewhat epithelioid melanocytes may be seen. Cytoplasmic melanin is coarse and granular, and nuclei are regular and vesicular, with a single small inconspicuous basophilic nucleolus. Maturation with depth is not a feature. A frequent finding however, is the focal presence of elongated slender melanocytes resembling Schwann cells, indicative of neurotization as seen in ordinary naevi. Some tumours exhibit a focal alveolar growth pattern {1597} and desmoplasia is occasionally prominent {1599}. Degenerative changes including haemorrhage, cystic change and fibrosis, are seen in some cases. Focal mild or prominent myxoid oedematous change may also be a feature {1598}, and balloon cell change has been documented {1806}.
Occasional cases display a number of unusual features including mitotic figures (1/10 HPFs), focal necrosis, and/or nuclear pleomorphism or hyperchromatism. Such cases show some overlap with the malignant variant of CBN and have been described as atypical CBN {118,2371}.
The epithelioid blue naevus is composed of large round epithelioid and short spindle-shaped deeply pigmented melano-

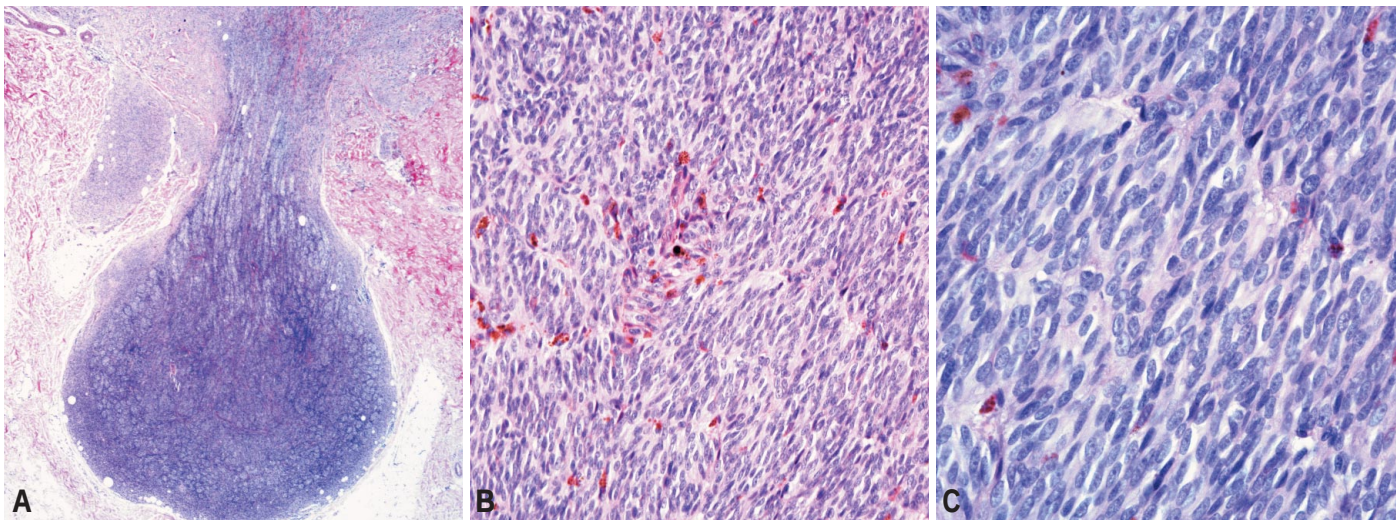


Fig. 2.47 Cellular blue naevus. **A** Typical low-power appearance with a dumb-bell architecture. **B** Bundles of bland spindle-shaped melanocytes alternating with focally pigmented cells. Scattered melanophages are also seen. **C** Typical small vesicular nuclei with a small basophilic nucleolus.

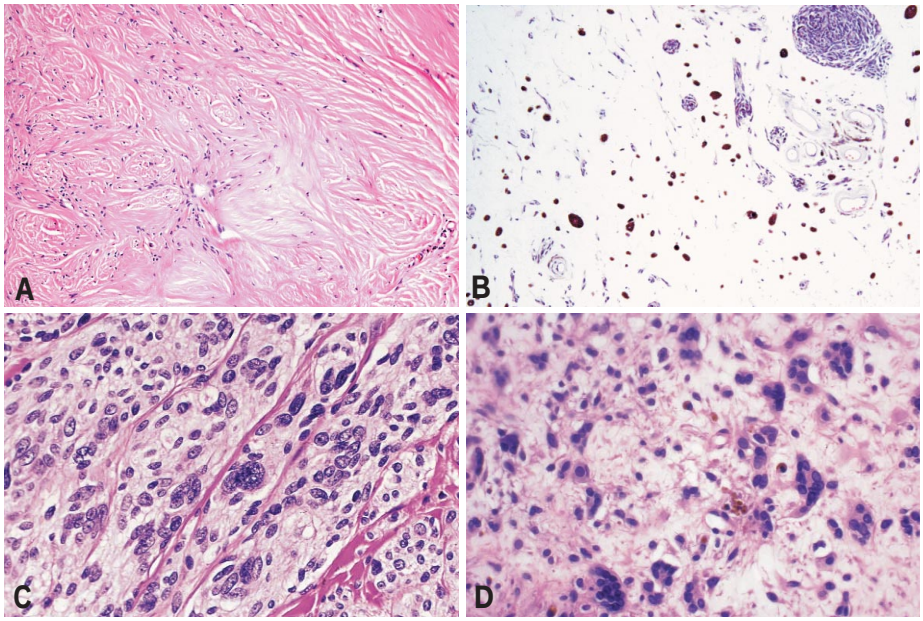


Fig. 2.48 Hypopigmented cellular blue naevus. **A** In some cases, melanin is almost completely absent. **B** Myxoid change may be prominent in some cases. **C** One of the melanocytes is much larger than the others. Some refer to such cases as 'atypical cellular blue naevus'. **D** Large melanocytes are present, some are multinucleated.

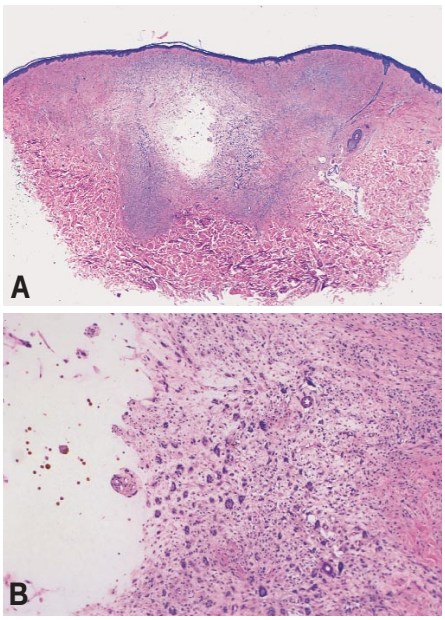


Fig. 2.49 Cellular blue naevus. **A** This lesion has a central focus of cystic change. **B** The edge of the cystic area.

cytes. Some examples of this variant of BN probably represent combined naevi {903}.

Immunoprofile
Tumour cells in CBN are positive for S-100, melan-A and HMB45. In tumours with prominent desmoplasia, and in those with neurotization, staining for melan-A and HMB45 tends to be patchy. CD34 has been reported to be positive in tumour cells in a group of congenital CBN {2204}.

Genetics
Similar to other naevi, cellular blue naevi do not show chromosomal aberrations when analysed by CGH. In a small series of atypical cellular blue naevi, three out of eight cases showed single chromosomal losses with chromosome 3p being affected in two of these cases {1490}.

Prognosis and predictive factors
Although limited case series have characterized these lesions as benign, some cases with atypical features have resulted in recurrences or death from systemic metastasis. They may therefore be regarded as having uncertain malignant potential and treated with complete excision if possible and perhaps long term follow-up. Malignant transformation in CBN is very rare {64,883}.

Deep penetrating naevus

Definition
Deep penetrating naevus (DPN) is a distinctive deeply pigmented lesion showing overlapping features with blue naevus and Spitz naevus.

Synonym
Some cases have been described under the heading of plexiform spindle cell naevus {164}.

Epidemiology
DPN is an acquired lesion presenting mainly between the second and third decades of life with no sex predilection {1953,2127}.

Localization
DPN has a wide anatomical distribution with predilection for the face, upper trunk and proximal limbs {164,537,1575,1953, 2127}.

Clinical features
The tumour presents as a solitary, well-circumscribed blue or dark brown/black dome-shaped papule or nodule usually less than 1 cm in diameter.

Histopathology
Low power examination typically reveals a compound wedge-shaped deeply pigmented dermal and, very rarely, superficial subcutaneous tumour. The base of the lesion parallels the epidermis. The junctional component, which is usually present and may be subtle, consists of small round nests of ordinary naevus cells. In fact, in most cases, a superficial dermal component, representing an ordinary naevus, may be found and therefore these lesions may be regarded as combined naevi {1953}. Much less commonly, focal changes mimicking a Spitz naevus or a blue naevus are found {1953, 2127}. Tumour cells are arranged in nests or bundles and have a short spindle-shaped or, less commonly, round morphology. The cytoplasm contains

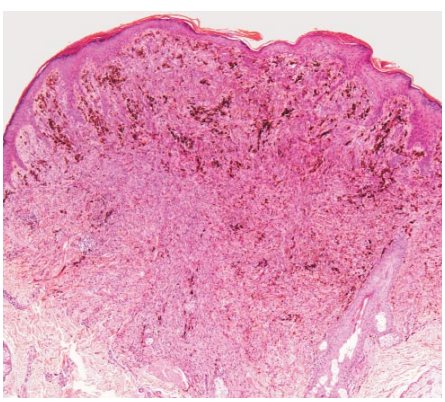


Fig. 2.50 Deep penetrating naevus with a typical wedge-shaped architecture.

abundant melanin and nuclei are vesicular with frequent intranuclear inclusions and a single small basophilic nucleolus. Hyperchromatism and variation in nuclear size may be seen, but as a rule mitotic activity is low or absent (usually not more than 1 per section). The melanocytes follow the path of adnexal structures and blood vessels and there is frequent perineural extension. Maturation is not seen. Some tumours have the cytomorphology of DPN but are superficial and lack the deep penetrating component. Similar changes are seen in a common form of combined naevus.

Prognosis and predictive factors

Local recurrence is exceptional, and only a single case has been reported spreading to a regional lymph node {874}.

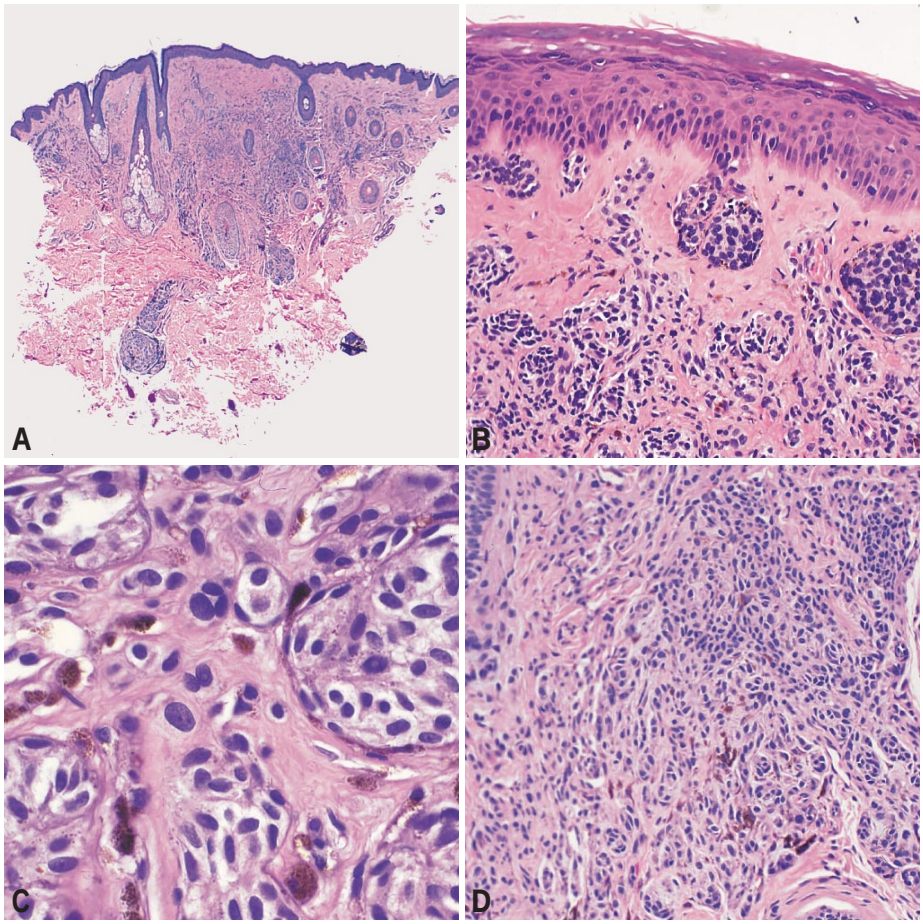


Fig. 2.51 Deep penetrating naevus. **A** A wedge shape and nests of cells around adnexal structures are characteristic findings. **B** The large pale cells in a deep penetrating naevus are arranged as discrete nests. **C** A thin rim of sustentacular cells is present around the edges of many nests. **D** Toward the base of the lesion nests of pale large cells are present near adnexal structures.

Combined naevus

R.L. Barnhill

Definition

A combined naevus or "melanocytic naevus with phenotypic heterogeneity" is a melanocytic naevus either congenital or acquired, containing two or more distinct melanocytic naevus components.

Synonyms and historical annotation

Melanocytic naevus with phenotypic heterogeneity; inverted type A naevus; naevus with focal dermal epithelioid component, and naevi with dermal nodules.

The term combined naevus was used initially to describe the combination of a conventional naevus and blue naevus {61,653,702,1402,2331}. However, the spectrum of combined naevus has been subsequently extended to include components of any type of naevus (Table 2.09){135,156,520,1610}. There may be poor concordance in the interpretation of some cases, because of overlapping features and the difficulty of defining the morphological limits of blue naevi, Spitz naevi, deep penetrating naevi, plexiform pigmented spindle cell naevi, and naevi with dermal epithelioid cell components.

Epidemiology

There are no population-based data available as to the prevalence of combined naevi. However they appear to constitute less than 1% of melanocytic naevi sampled for histopathological examination {2116}. These naevi occur in all age groups (3 to 83 years in a recent study) with a mean age of 30 years {2116}. A slight predominance of women has been consistently reported in several studies {757,1864,1961,2116}.

The developmental biology of combined naevi has not been delineated. Their genesis may be related to more than one pathway of melanocytic differentiation occurring in a single naevus. It cannot be excluded that there is focal neoplastic progression in some proportion of these lesions.

Localization

Scolyer et al. found a predilection for the trunk (chest, back, abdomen) in 35.2% of cases, the head and neck in 23.6%, upper extremities in 22.0%, lower extremities in 9.9%, and perineum and buttocks in 4.4% {2116}. Naevi with a significant blue naevus component commonly involve the face, back, and shoulder {757}. Naevi with prominent components of Spitz naevus often occur on the head and neck (face) or extremities as do conventional Spitz naevi {1961}.

Clinical features

The gross morphological features of combined naevi are probably related to the types of and predominant cellular populations present, e.g., focal dermal pigmented components, blue naevus, Spitz naevus, etc. Most of these naevi measure less than 5 to 6 mm in greatest diameter {156,757,1864,2116}, are reasonably symmetrical, are well-circumscribed papular or dome-shaped lesions, and exhibit dark brown, blue to black colouration. Thus many such naevi are often diagnosed clinically as blue naevi or melanoma because of the predominant dark colour. Some of these naevi may also demonstrate a small well-circumscribed blue or blue-black focus, e.g., often 1–3 mm in diameter, within an otherwise ordinary flesh-coloured, tan, or brown naevus (melanocytic naevi with focal dermal pigmented components) {135,156,520,757,2116}. Some naevi may show irregular borders and pigment patterns also raising concern for melanoma.

Naevi with prominent Spitz components are often diagnosed as an unusual naevus, Spitz naevus, dermatofibroma, or possibly melanoma.

Histopathology

Combined naevi may potentially encompass the entire phenotypic repertoire of melanocytic naevi. By definition two or more distinct naevus components are present. Any combination of naevus components and percentage of the naevus components may occur. However 99% of combined naevi have only two components {2116}. The two components are intimately admixed in 82% of cases whereas they are adjacent in the remainder. The most common pattern of combined naevus is that of a common acquired or congential naevus in combination with discreet foci of pigmented epithelioid and/or spindle cells (which probably includes inverted type A naevus and melanocytic naevus with dermal epithelioid cell components, dermal nodules, or a component of "deep penetrating" or plexiform pigmented spindle cell naevus) {158,164,537,2126}. The latter cells are often enlarged, contain abundant granular melanin, and are disposed in nests or fascicles in the superficial, superficial and deep, or deep portions of or beneath the ordinary naevus, sometimes or commonly in plexiform arrangements. The sizes of the nests or fascicles

Table 2.09 The naevus components potentially occurring in combined naevus

Common acquired naevi
– junctional
– compound
– dermal
Congenital naevi
– junctional
– compound
– dermal
Dysplastic naevi (naevi with architectural disorder and cytological atypia)
– junctional
– compound
Blue naevi
– ordinary or common
– hypercellular
– cellular
– plaque
– epithelioid
Spitz naevi
– junctional
– compound
– dermal
– desmoplastic
Deep penetrating naevi
Plexiform pigmented spindle cell naevi
Naevi with dermal epithelioid cell components (clonal naevus)
– inverted type A naevus
– naevus with dermal nodules
Other

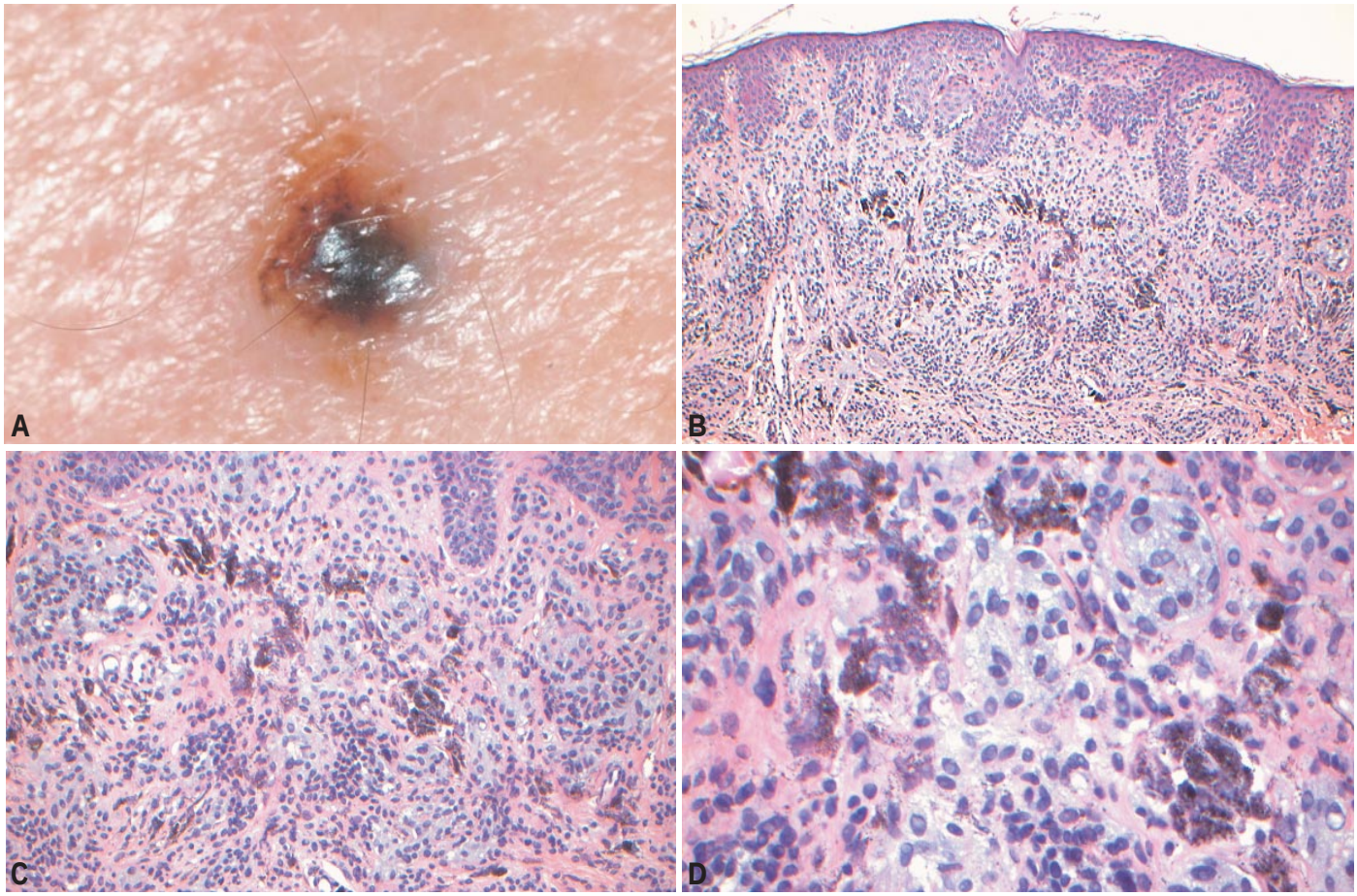


Fig 2.52 Combined naevus. **A** Combined naevus (melanocytic naevus with phenotypic heterogeneity). The lesion is well-defined with central dark brown papule and lighter brown annulus (Courtesy of Harold Rabinovitz, M.D.). **B** There is a conventional compound naevus with small fairly discrete aggregates of heavily pigmented cells in the dermis. **C** This field shows small nests of pigmented polygonal melanocytes and melanophages admixed with the background conventional naevus. **D** The pigmented polygonal melanocytes have abundant cytoplasms and contain nuclei that resemble those in the surrounding small naevus cells. The polygonal cells show transition to the surrounding conventional cells.

may vary from being minuscule to large lobular or digitate aggregates. The nuclei are usually comparable in size to the surrounding conventional naevus cells, or may be slightly enlarged round, oval, or elongate and uniform. On occasion the nuclei may show variable often slight to moderate atypia. Melanophages are also frequently associated with these pigmented foci. This pattern of combined naevus is also probably morphologically identical to that of deep-penetrating naevus and plexiform pigmented spindle cell naevus {158,164,537,2126}.

Another common pattern is that of an ordinary naevus and blue naevus. The ordinary naevus component may be compound or dermal, often overlies or is adjacent to the blue naevus component, and commonly has a congenital pattern. The blue naevus elements most often consist of heavily-pigmented dendritic melanocytes, melanophages, and variable fibrosis. Less commonly, the spindle cells typical of cellular blue naevus may also be present with or without dendritic cells. The component of blue naevus may extend deeply into the reticular dermis as nests or fascicles, often in a plexiform configuration. Despite the two or more components, such naevi are usually symmetric, well-circumscribed, orderly, and display little or no cellular atypia.

Spitz naevi uncommonly are observed in association with ordinary naevus elements {1961}. The topographic relationships of these two components include the Spitz naevus component being adjacent to, beneath, or admixed with the common naevus elements. Such naevi also may have a desmoplastic stroma as in desmoplastic Spitz naevi.

After the above relatively well-recognized forms of combined naevus, almost any combination of cell types is possible {156,2116}. Thus, one may encounter naevi containing various admixtures of ordinary naevus cells, dendritic melanocytes, Spitz naevus cells, and perhaps other transitional cell types. Atypical features may also be observed such as disordered patterns of melanocytes and cytological atypia of both the intraepidermal and dermal components.

Somatic genetics

The conventional naevus component will demonstrate frequent BRAF mutations in contrast to their absence in blue or Spitz naevus components.

Differential diagnosis

The differential diagnosis of combined naevus is dependent on the particular cellular populations present. The histological feature often of most concern is

Table 2.10
Comparison of combined naevus and melanoma

	Combined naevus	Melanoma
Symmetry	Frequent	Uncommon
Size	< 6mm often	> 1cm often
Lateral border	Sharply defined	Poorly-defined
Focus, foci of altered cells*	Present, transition (maturation) to surrounding ordinary naevus	Variable
Cytologic atypia	Usually absent or low-grade	High-grade
Mitotic activity	Absent or minimal (usually < 2/mm^2	Frequent
Mononuclear cell infiltrates	Uncommon	Frequent

*Focus of epithelioid/spindle cells in ordinary naevus (as also observed in inverted type A and clonal naevi)

an aberrant focus of cytologically altered/atypical cells in an otherwise ordinary naevus. Such a finding is of concern for early transformation to melanoma or, even fully-evolved melanoma. The latter histologic alteration is present most commonly in the dermis. However, the development of melanoma in the dermal component of a naevus is highly unusual. Therefore, such a diagnosis must be carefully considered and based on sufficient criteria of atypicality, mitotic activity, nodular (confluent) proliferation, and usually the lack of transition (maturation) to the surrounding naevus.
Although combined naevi are heterogenous, they are usually present in young individuals (< 30 to 40 years), measure less than 5 or 6 mm, and exhibit an overall symmetry and regular appearance. A focal aggregate of pigment-laden epithelioid/spindle cells is usually the feature of concern. Although occasional aggregates of epithelioid cells are large, many are small and well-circumscribed. Cytologic atypia is usually low-grade or insignificant compared to melanoma. The surrounding naevus which commonly is of ordinary type is generally unremarkable with reference to atypicality. An occasional mitosis may be observed in such a focus without undue concern; however, the presence of 2 or more mitoses per high power field should prompt careful inspection for melanoma {156}.

Prognosis and predictive factors
Combined naevi are by definition benign. However it must be acknowledged that as with cellular blue naevi and Spitz naevi, there are unusual variants often characterized by a number of abnormal features. Such atypical lesions rarely may result in metastases and require further study as to more definitive criteria for malignancy. Thus such atypical variants prospectively are best designated as biologically indeterminate and require complete excision and close clinical monitoring.

Melanotic macules, simple lentigo and lentiginous melanocytic naevus

H. Kerl
D. Massi

Melanotic macules

Definition

Melanotic macules are pigmented lesions that occur on skin, mucous membranes, and in nail units {2035}. The lesions are characterized by hyperpigmentation of the epidermal/epithelial basal layer accompanied by a slight increase in number of melanocytes.
There are several syndromes, which are associated with multiple melanotic macules/lentigines (Peutz-Jeghers, NAME, LAMB, LEOPARD, Carney complex (See Chapter 7).

Synonyms

Genital: Genital melanosis/lentiginosis; Vulvar melanotic macule; penile melanotic macule; penile lentigo.
Labial/oral: Labial/oral melanosis; labial melanotic macule; labial lentigo.
Volar: Volar melanosis.
Nail apparatus: Melanosis of the nail bed and matrix; ungual melanosis.
Skin: Reticulated black solar lentigo; "ink spot" lentigo.

Clinical features

Melanotic macule of vulvar and other female genital sites
The condition occurs usually on the vulva as a flat asymmetric macule with a diameter from less than 1–5 cm. Multiple lesions are present in >50% of the cases. The tan-brown to blue-black macules mostly involve the labia minora. But they can also occur on the labia majora, perineum, the introitus, vagina and cervix. They may be difficult to distinguish from melanoma {1400}.

Penile melanotic macule
This lesion usually presents in adult life as a pigmented patch, uniform or variegated in colour with irregular borders, on the glans penis or on the penile shaft. Multiple macules can be observed.

Labial melanotic macule
The lesion occurs in about 3% of persons, mostly in women on the vermilion border of the lower lip. The lesions can be also present on the oral mucosa and on the tongue. A single or multiple (oral melanosis), brownish-black or black macules with irregular sharply demarcated borders can be observed {925}.

Variants

Volar melanotic macule
Clinically a brown, tan, or grey macule (less than 5 mm in diameter) is located on palms and soles usually in Black patients.

Ungual melanotic macule
Pigmented bands (not thicker than 3 mm) are observed in the fingernails of young individuals (longitudinal melanonychia). The lesions are common in dark-skinned races and in the Japanese population. In Laugier-Hunziker syndrome, longitudinal melanonychia is accompanied with labial/oral melanotic macules.

Reticulated melanotic macule
These lesions appear on sun-exposed areas of the trunk or shoulders as a dark-brown or black reticulated macule with irregular borders.
Although the lesion has been named "reticulated black solar lentigo" {277}, it is different from the conventional solar lentigo {1171}.

PUVA-lentigines
PUVA-lentigines are pigmented macules, which develop as a direct response to the effects of long-term therapy with PUVA (psoralens + UVA).

Histopathology

Similar histopathologic changes can be demonstrated in all types of melanotic macules. There is usually no perceptible or a slight increase in the number of melanocytes, which are situated at the dermo-epidermal junction in solitary units. The melanocytes exhibit small and monomorphous nuclei and delicate dendrites. Using Fontana-Masson silver stain, the dendrites are better visible. Atypia is not observed. The basal layer reveals prominent hyperpigmentation. Occasionally hyperplasia of the epidermis can be seen. Melanophages and a mild inflammatory infiltrate are often present in the superficial dermis.
Reticulated melanotic macules show marked hyperpigmentation of the epidermis especially at the tips of the rete ridges whereas the suprapapillary plates are spared and nearly devoid of melanin. A slightly increased number of finely dendritic melanocytes can be observed in the lower layers of the epidermis. In contrast, solar lentigo represents an evolving seborrhoeic keratosis revealing small buds or nubbins of hyperpigmented keratinocytes.
PUVA-lentigines are characterized by an increased number of melanocytes, which are concentrated mostly in pigmented rete ridges as solitary units. Some melanocytes may show atypical nuclei.

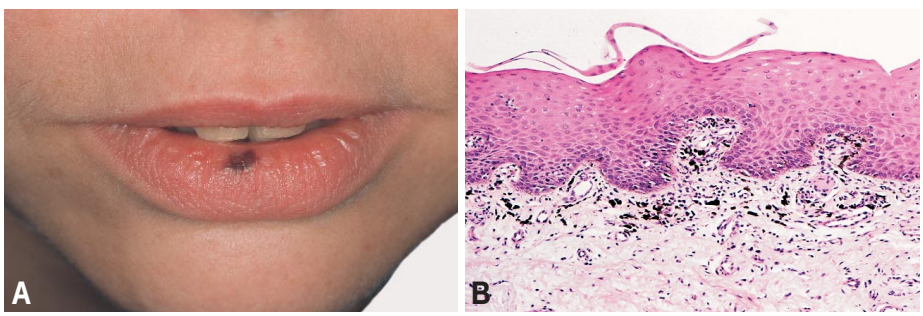


Fig. 2.53 Melanotic macule on the lip. **A** Brown-black macule with irregular margins on the lower lip. **B** Pigmentation of the epithelial basal layer and melanophages in the papillary dermis.

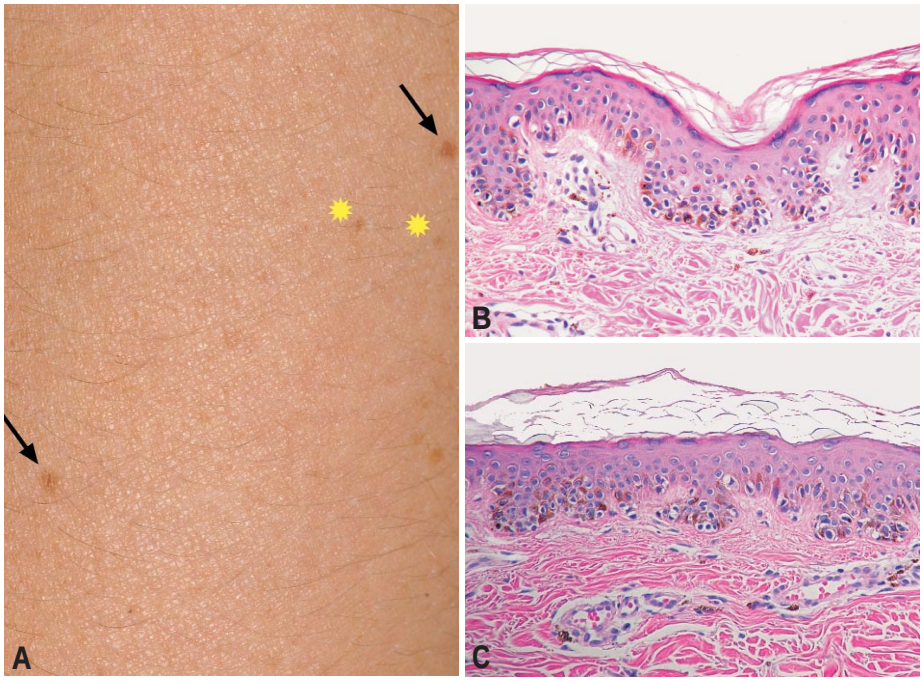


Fig. 2.54 Simple lentigo - Lentiginous melanocytic naevus. **A** Small uniform brown macules; (stars) simple lentigo. (arrows) lentiginous melanocytic naevus. **B** Simple lentigo. Increase in the number of melanocytes in single units along the basal layer - especially around elongated hyperpigmented rete ridges. Distinct nests are absent. **C** Lentiginous melanocytic naevus. Features of lentigo simplex can be recognized. The aggregation of melanocytes in tiny nests indicates the transformation of this lentigo simplex into a lentiginous melanocytic naevus.

Differential diagnosis

Early stages of melanoma in situ must be differentiated from melanotic macules. Melanoma in situ (genital / labial areas) can manifest as a sparsely cellular proliferation of melanocytes. Sometimes in a partial biopsy the only clues are nuclear hyperchromasia or irregularly shaped dendrites. In more fully developed cases, melanocytes are more regularly distributed, can become confluent and may also be situated above the junction. Lesions with more than a slight increase in melanocytes, even without atypia should be carefully evaluated, with additional sampling, over time if indicated. If the problem cannot be resolved complete excision may be appropriate.

Simple lentigo – lentiginous melanocytic naevus

Definition

Simple lentigo and lentiginous melanocytic naevus are pigmented macules representing the early stages in the development of a melanocytic naevus. In simple lentigo, melanocytes are increased in number along the basal layer; lentiginous junctional melanocytic naevus shows in addition formation of small junctional nests. In compound lentiginous melanocytic naevi, small round melanocytes are also present in the papillary dermis.

Synonyms

Lentigo simplex, naevus incipiens.

Clinical features

Small flat roundish uniform brown or black sharply circumscribed macules usually less than 6 mm in diameter, which are most frequently found on the trunk and extremities of children and adults, are observed.

Histopathology

Simple lentigo consists of an increased number of melanocytes disposed as solitary units in the basal layer of variably elongated and hyperpigmented rete ridges. The melanocytes have small round to oval and monomorphous nuclei. They are positioned equidistant from one another and are seen more pronounced at the tips of the rete ridges. Pigment is abundant and found throughout the epidermis including the stratum corneum. Melanophages are usually present in the papillary dermis. Giant melanosomes can be present.

When one or more small nests of melanocytes (i.e. three or more melanocytes per congregation) in such a lesion is observed, it is then called lentiginous naevus (evolving junctional naevus).

The histology of naevus spilus (congenital speckled lentiginous naevus) is indistinguishable from simple lentigo-lentiginous melanocytic junctional naevus.

Prognosis and predictive factors

Melanotic macules have been incorrectly interpreted as premalignant lesions and possible precursors of melanoma {1757A,2394A}. Current evidence supports the notion that melanotic macules, irrespective of their location, should be considered benign in their clinical behaviour, since they tend to remain stable and unchanged when followed over a long period of time.

Simple lentigo and lentiginous melanocytic naevus are wholly benign melanocytic proliferations which have no potential for malignant transformation.

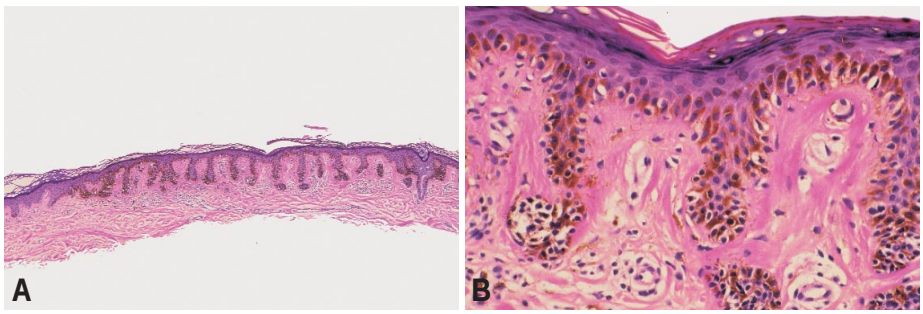


Fig. 2.55 Lentiginous junctional melanocytic naevus. **A** There are elongated rete ridges with increased numbers of single melanocytes at their sides and bases, with some tiny junctional nests. **B** In this example, there are lymphocytic infiltrates and fibroplasia of the papillary dermis.

Dysplastic naevus

C.J. Cockerell
J. Grant-Kels
J.C. Cather
P. LeBoit

Definition
Solitary or multiple naevi, variable in colour, border, and size, with preferential location on the upper trunk and extremities. Dysplastic naevi (DN) occur as sporadic lesions and in a familial setting. They may progress to malignant melanoma.

ICD-O code 8727/0

Synonyms
Atypical naevus {896} has been proposed as a synonym for clinically dysplastic naevus. Other past designations include naevus with architectural disorder {1}, and melanocytic naevus with architectural disorder and cytologic atypia {1,2158}. The concept of Clark naevus includes a large number of junctional and superficial compound naevi of which the dysplastic naevus is a subset.

Historical annotation
Originally, Wallace H. Clark and coworkers described patients with multiple atypical naevi for which they proposed the term "B-K mole syndrome", using the first initial of the surname of two probands {496}. The authors photographically documented two lesions that progressed over time to malignant melanoma. Therefore, the authors considered the "B-K mole" a precursor of melanoma. Soon thereafter, in 1980, Elder et al found lesions similar to those in "B-K mole" patients with non-familial cutaneous malignant melanoma {673}. Subsequently, the "B-K Mole Syndrome" was renamed to 'Dysplastic Naevus Syndrome', with further sub-classification into sporadic or familial types.
In 1992, a U.S. National Institutes of Health Consensus Conference recommended "naevus with architectural disorder" in order to avoid the negative connotation associated with the word "dysplasia" {1}. However, this term has failed to gain wide acceptance {2153}.
In a recent survey by the American Academy of Dermatology, 98% of respondents recognized the dysplastic naevus as a distinct entity {2373}.

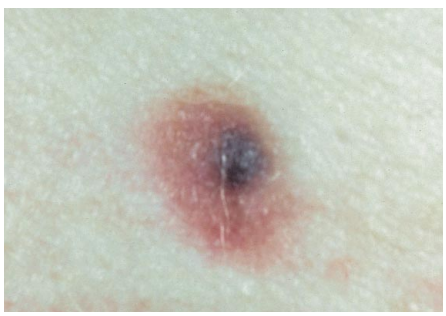


Fig. 2.56 Dysplastic naevus. A solitary leasion on the abdomen. Note the variegated appearance.

Epidemiology
The estimated total number of individuals affected by the familial form is approximately 32 000 in the United States {1320}.
Sporadic, *histologically* dysplastic naevi are seen in up to 50% of White adults, depending on how the lesion is defined. {535,571,1828}. The estimated prevalences of dysplasia in a population based series of naevi ranged from 7-32% {1829}. The prevalence of *clinically* defined dysplastic naevi also varies according to the criteria used, ranging from 5–20%.

Etiology
Ultraviolet radiation has been implicated in the genesis of dysplastic naevi and melanoma. Noz et al found higher in vitro sensitivity to DNA damage by ultraviolet B radiation in melanocytic naevus cells compared to foreskin melanocytes {1732}. One recent study found an increased relative risk for melanoma in a dysplastic naevus group with poor in vitro DNA repair capacity {1360}.

Localization
Dysplastic naevi can occur anywhere on the body but are most commonly found on the trunk {496}. In females, there may be a considerable number on the legs {5559}. A "quadrant" form of dysplastic naevus distribution has been reported where a 59-year-old man had numerous aggregated pigmented lesions (common acquired naevi and dysplastic naevi) confined to the left upper quadrant of his body. Within this quadrant, two malignant melanomas at different stages of progression developed from dysplastic naevi {2266}. Hidden areas such as the scalp and genitalia need thorough evaluation as dysplastic naevi may be seen in these areas {731,2029}. In Greene's original description, it was noted that unlike ordinary moles, dysplastic naevi are often found on the scalp, buttocks and female breast {897}. Lesions on the scalp, genitalia and upper back should be considered for excision due to the difficulty with patient self-examination of these locations {749}, although careful follow-up is a reasonable alternative.

Clinical features
Patients may have one, several or up to hundreds of lesions. In one study, patients who had DN outside the familial melanoma setting had an average of 10 per person {157}. The clinical features originally ascribed to DN included ill-defined or irregular border, irregularly distributed pigmentation, background erythema, and size greater than 5 mm {496,2029}. Lesions often differ from one another in the same individual and in addition, they are often different between individuals {778}. Some lesions may have a central papular component with a macular flare that blends into surrounding tissue resulting in an ill-defined, fuzzy periphery. The surface texture has been described as "pebbly" {2476}. Other lesions are macular or plaque-like without a central papule or nodule. Irregularities in pigment range from tan to dark brown to black. There are often areas of pink and some lesions are amelanotic. Characteristically, lesions first appear around the time of puberty and if they are not apparent by age 20, it is unlikely that an individual has the familial melanoma/dysplastic naevi trait {897}.

Diagnostic criteria
The Dutch Working Group produced five

criteria for the clinical diagnosis of dysplastic naevi: 1) size greater than or equal to 5mm in diameter, 2) vague border, 3) asymmetric shape, 4) irregular pigmentation , and 5) red hue {212}. Additional diagnositic criteria have been advocated by Newton et al. and consist of a scoring system. One point was awarded for the presence of one of five parameters: 1) 100 or more naevi > 2mm, 2) > two atypical naevi, 3) > one naevus on the scalp, 4) one naevus on buttock or > 2 on dorsa of the feet, 5) > one iris naevus. Individuals who have three or more points are considered to have the dysplastic naevus syndrome phenotype {1700}.

Dermoscopy and imaging

Dermoscopy can be used to assist in differentiating a DN from other benign or malignant lesions. A lesion that does not demonstrate features of the predominant type of naevus seen in that individual should be considered atypical and receive special attention {1043}. This is analogous to the "ugly duckling" lesion that refers to one that is distinct from others in a given patient. It has been recommended that such lesions be biopsied as they are more likely to be the ones that demonstrate features suggestive of melanoma {900}.

Several studies have demonstrated the usefulness of regular whole body photographs {1474} and computerized imaging for melanoma surveillance {387, 1286,2440}.

Table 2.12
Dermoscopy findings. From Steiner et al. {2259A}

Dermoscopy finding	Dysplastic naevi	Melanoma
Pigment network	Irregular discrete pigment network 55%	Irregular, prominent (darkly pigmented) in 81%
Overall pigment	Irregular 82%	Irregular (85%)
Brown globules	Irregularly arranged and of variable size (45%)	Irregular arrangement and size (35%)
Margin of pigment network	Irregular margin ends gradually (68%)	Abrupt ending of an irregular margin (63%)
Black dots		Present in 34% with irregular arrangement at periphery in 26%
Radial streaming	1.7%	25%
Pseudopods	1.7%	31%
Depigmentation		Periphery (56%)

Progression to malignant melanoma

Although melanomas in patients with dysplastic naevi may arise within preexisting dysplastic naevi, the vast majority arise de novo. Histologic changes indistinguishable from those of dysplastic naevi are often observed at the peripheries of primary melanomas not associated with naevi and such findings have been interpreted as representing "precursor" dysplastic naevi {672}.

Dysplastic naevi may have chromosomal instability and poor repair mechanisms after sunlight induced injury {1067,2128}. Landi et al demonstrated an increased relative risk for melanoma in a dysplastic naevus group with poor in vitro DNA repair capacity {1360}. Elder classified 6 stages of tumour progression via monoclonal antibodies to melanoma cells or their extracts on frozen tissue sections {675A}.

Table 2.11.
Clinical characteristics of dysplastic naevi

>Variable size (<5mm-over 1 cm): great intralesional variation with respect to size

>Irregular colour: irregular browns, red papule with brown halos, speckled

>Irregular contour: macular or macular with central papular component

>Ill-defined border, often "fuzzy"

>Preferential location on the trunk

Histopathology

Definition and description

The major histopathologic criteria include architectural and cytologic features: size ≥4 mm, junctional component often adjacent to a compound naevic component, nested and single melanocytes mainly near the tips and sides of elongated rete ridges, stromal reactions and mild to moderate cytologic atypia.

There is lack of consensus regarding the histologic classification of dysplastic naevi. Historically, some groups advocate that atypical architecture is all that is required to establish the diagnosis {1943,1980}, while others require cytological abnormalities {1925}. Shea et al recommend evaluating both cytology and architecture in the diagnosis of DN {2158}. More recent descriptions of features common in DN histology included a central dermal naevocytic component with a peripheral extension of a junctional component, elongated epidermal rete ridges, bridging of nests of melanocytes at the dermo-epidermal junction, nests of melanocytes at the sides of rete ridges as well as at their bases, and concentric eosinophilic papillary dermal lamellar fibrosis {1943}. Ackerman and others have placed emphasis on the "shoulder phenomenon" which describes peripheral extension of the junctional component beyond the dermal component in dysplastic naevi {18,1828}.

In general, histologic criteria involving architecture used to describe dysplastic naevi include: circumscription, symmetry, cohesion, suprabasalar melanocytes, confluence and single cell proliferation. Cytologic features include: nuclear shape and staining, nuclear size, nucleolar prominence, and cell size {2158}.

One of the problems in the definition of these lesions is that the histologic changes are non-specific and may be seen in a number of other naevi without clinical features of "dysplastic" naevi such as growing naevi in children and naevi located on certain anatomic sites such as the scalp and flexural areas. Furthermore, the definitions used to describe cytologic atypia are subjective

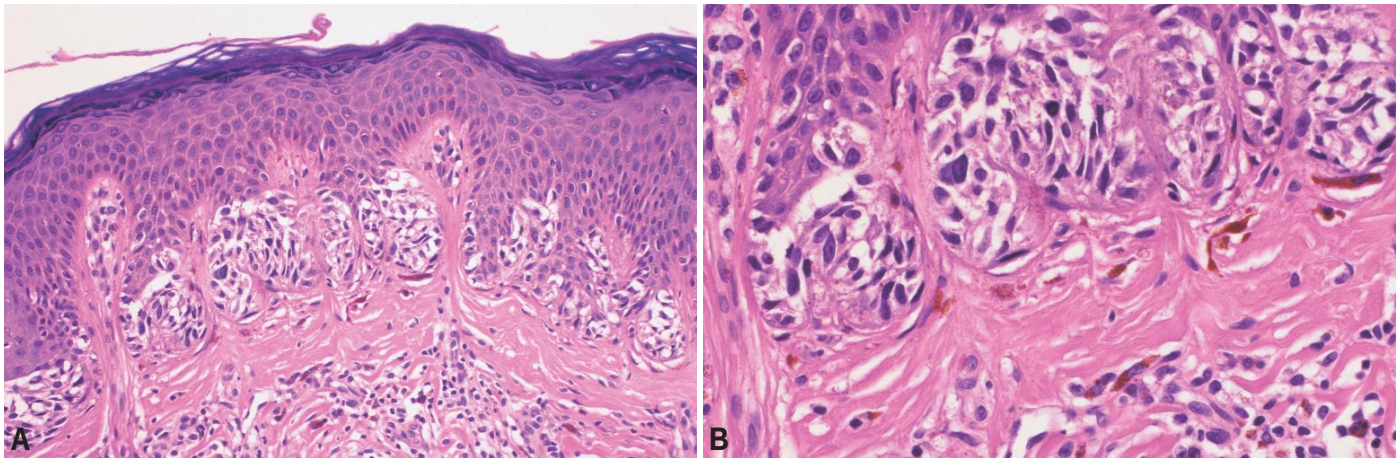


Fig. 2.57 Dysplastic naevus. **A** The naevus cell nests are confined predominantly to the tips of the rete pegs. **B** Note the cytological atypia with nuclear hyperchromasia.

as in no case are the atypical cytologic features as frankly atypical as seen in fully developed melanoma.

Immunoprofile

Mild to moderate staining of dysplastic naevi is observed using antibody to HMB45 antigen. This antibody also often stains intradermal melanocytes within melanomas but not as strongly in common melanocytic naevi {2214}. S-100 is a protein found in the central nervous system that is also present in melanocytes, including melanoma. S-100 protein is found at the dermo-epidermal junction and at all levels of the dermis in dysplastic naevi {1792}. However, S-100 staining is non-specific as it is seen in common naevi, dysplastic naevi as well as malignant melanoma.

Growth fraction / MIB-1 index

Some authors assert that the presence of the proliferation marker Ki-67 in dysplastic naevi indicates that these lesions are precursors to melanoma {760}. The percentage of cells that expressed Ki-67 was an independent prognostic factor {1308}. Kanter et al found that percentages of MIB-1 immunoreactivity in the intradermal portion of the lesions was negligible for benign congenital and acquired naevi, as well as in dysplastic naevi compared to melanomas which exhibited a markedly increased proliferative activity, especially vertical phase melanomas {1201}. At the current time, it is not recommended that proliferation markers be used as a reliable method for distinguishing between naevi and melanoma.

Electron microscopy

The melanosomes in epidermal melanocytes in dyslastic naevi are abnormal, with incompletely developed lamellae and uneven melanization {2476}. Abnormal spherical and partially melanized melanosomes similar to those observed in superficial spreading melanoma have been observed by electron microscopy {672,1363}. Based on these transmission electron microscopy findings, one group suggested that dysplastic naevi lie on a continuum between naevi and superficial spreading melanoma. No correlation has been shown prospectively between ultrastructural findings and progression or predilection to the development of MM.

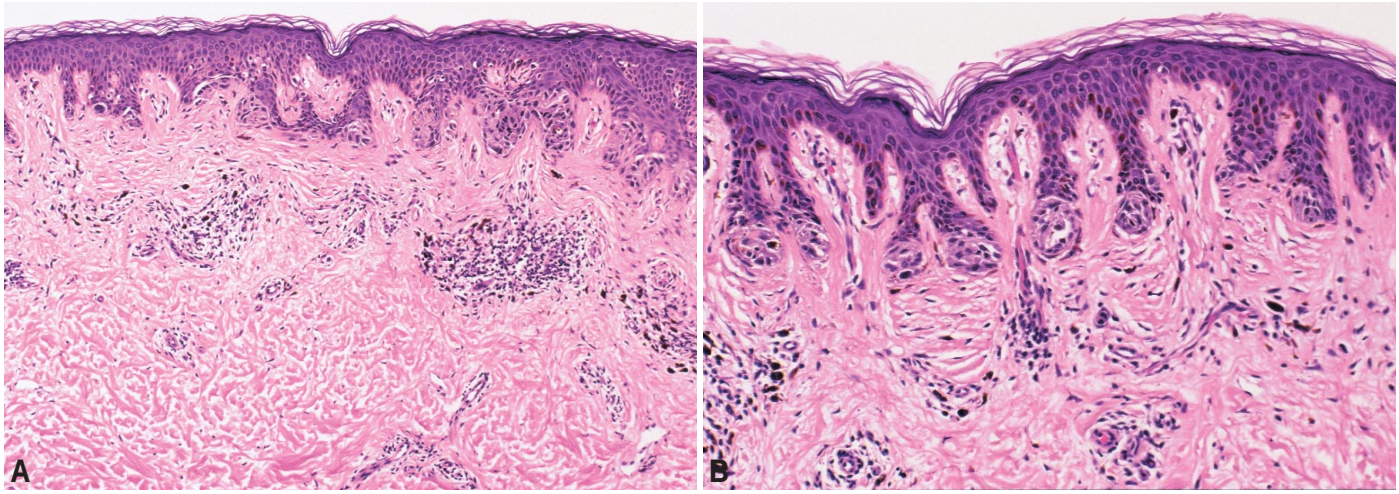


Fig. 2.58 Dysplastic naevus. **A** The junctional component shows both architectural and cytological atypia. There is a mild, superficial perivascular lymphocytic infiltrate. **B** Mild atypia of the junctional nests and dermal papillary fibroplasia.These is some melanin incontinence.

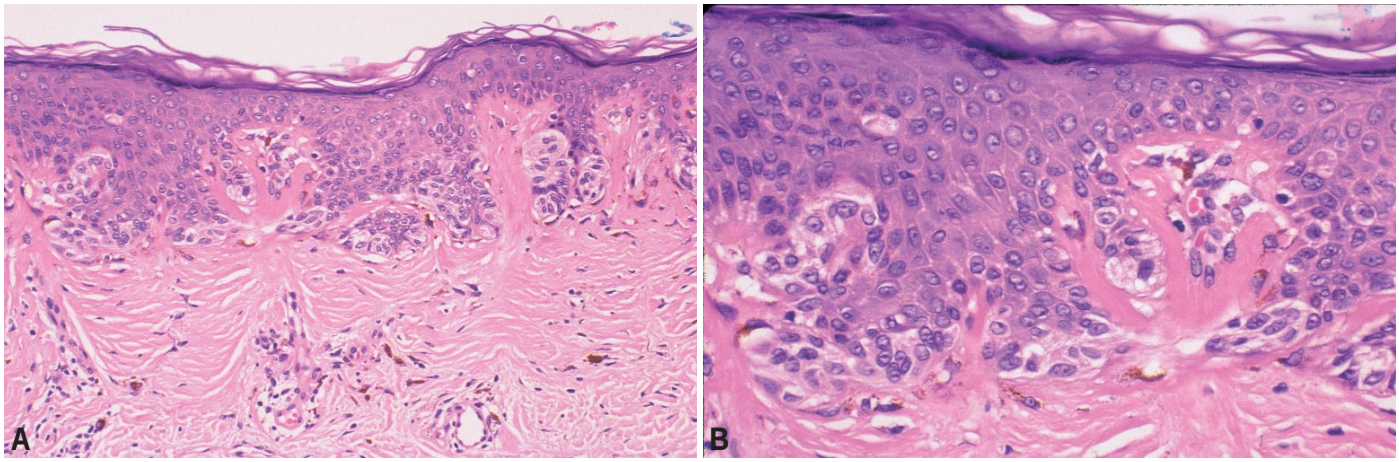


Fig. 2.59 Dysplastic naevus. **A** Some naevus cell nests extend above the the tips of the rete pegs. **B** Mild cytological atypia of the junctional nests.

Variants

Toussaint and Kamino observed histopathologic changes of "dysplastic" naevi in other types of naevi. They also noted that some dysplastic naevi demonstrated features of other varieties of naevi. 2,164 cases of compound melanocytic naevi that fulfilled the histopathologic criteria for the diagnosis of compound dysplastic naevus were reviewed. 87.6% had the histopathologic characteristics of dysplastic naevus, 8.3% showed a dermal component with a congenital pattern, 3.1% demonstrated epidermal and dermal characteristics of Spitz naevus, 0.3% had features of a combined blue naevus, 0.6% had a halo phenomenon and 0.1% showed intradermal naevus. The authors advocate describing dysplastic melanocytic naevi by categorizing them into six groups: 1) dysplastic naevus; 2) dysplastic naevus with a congenital pattern; 3) dysplastic Spitz naevus; 4) dysplastic combined blue naevus; 5) dysplastic halo naevus; and 6) dysplastic neuronaevus {2370}.

Differential diagnosis

The clinical differential diagnosis of dysplastic naevi includes congenital melanocytic naevi, pigmented basal cell carcinoma, Spitz naevus, common acquired melanocytic naevi, melanoma in situ, and superficial spreading malignant melanoma. The histologic differential diagnosis includes melanoma, recurrent naevus, halo naevus, congenital naevus, a growing naevus in a child and Spitz naevus.

Grading

Some authors emphasize cytologic criteria for grading dysplastic naevi {1925}. In 1993, Duncan et al advocated grading dysplatic naevi into groups based on cytology. Dysplastic naevi with slight, moderate and severe cytologic atypia were differentiated. However, concordance between experienced dermatopathologists ranged from 35% to 58%. Because of lack of reproducibility, DeWit et al. did not recommend grading atypia in dysplastic naevi {612}. An analysis of 12 histologic parameters in 123 dysplastic naevi failed to identify parameters useful in differentiating mild from moderate dysplasia {1854}. Despite these considerations, melanoma risk has been associated with the degree of atypia in dysplastic nevi {102}.

Somatic genetics

Cytogenetics and CGH

Jaspers et al performed cytogenetic investigations on lymphocytes and fibroblasts from 25 individuals with dysplastic naevus syndrome and compared the results with a a control population of clinically normal relatives and unrelated individuals. In five DNS patients, increased frequencies of cells with random chromosomal rearrangements including translocations and inversions were observed. These abnormalities were absent in the control population {1134}.

Caporaso analyzed the karyotypes of 163 family members from 13 melanoma-prone families to investigate whether chromosomal instability contributes to familial melanoma. Cutaneous malignant melanoma and dysplastic naevi syndrome patients each had increased structural and numerical abnormalities compared with pooled controls {377}. However, the criteria used to define lesions as "dysplastic" naevi were subjective from the outset so the validity of such studies remains in question.

Park and Vortmeyer examined the frequency of p16 and p53 deletion in nine dysplastic naevi and 13 benign intradermal naevi with five microsatellite markers. Hemizygous deletion was detected in seven of nine dysplastic naevi at one or more loci for p16. No loss of heterozygosity was detected in any of the benign intradermal naevi {1775}.

Molecular genetic alterations

Greene performed an extensive review of the genetics of malignant melanoma and dysplastic naevi in 1998. Many studies demonstrate an autosomal dominant mode of inheritance and speculate pleiotropic manifestations of a proposed melanoma gene on chromosome 1 (1p36). CDKN2A, a tumour suppressor gene localized on chromosome 9, is also reported to be a melanoma gene. The relationship of melanoma to mutation of CDKN2A has been confirmed {895}. Hussein evaluated skin tissue samples of melanoma, dysplastic naevi and benign melanocytic naevi for microsatellite instability. Microsatellites are short single sequence motifs repetitively scattered throughout the human genome. The variation in microsatellite pattern length between tumourous and matching non-tumourous tissues is referred to as microsatellite instability. Microsatellite instability has been associated with other familial and sporadic tumours. Hussein's results demonstrated MSI at 1p and 9p chromosomal regions in dysplastic naevi

and malignant melanoma but not in benign naevi lending further support to others that have speculated on the presence of “melanoma genes” involving the short arm of chromosomes 1 (1p36) and 9 (9p21) {1087}. In 2002, Tucker provided 25-year prospective data regarding 33 families with familial melanoma and dysplastic naevi. Seventeen members were found to have mutations in CDKN2A. Tucker found that the majority of clinically diagnosed dysplastic naevi remained stable or regressed over time. The majority of melanomas detected over the course of the study arose from naevi although some arose de novo {2384}.

Genetic susceptibility

As discussed above, Clark originally described dysplastic naevi in relation to a familial syndrome called the B-K mole syndome {496}. Most dermatologists agree that family members of patients with dysplastic naevi need evaluation {2373}. Familial dysplastic naevi and melanomas have rarely been reported with other systemic malignancies involving the central nervous and digestive system {129,213}.

Prognosis and predictive factors

The incidence of melanoma developing in a given dysplastic naevus has been estimated at 1:3000 per year. Therefore, dysplastic naevi should not be considered as high risk precursors of melanoma, but rather as markers that allow identification of individuals at increased risk for melanoma.

Number of dysplastic naevi and family history

Patients with greater numbers of naevi, dysplastic or otherwise, are at greater risk for melanoma {2386}. Dermatologists acknowledge patients with multiple dysplastic naevi, especially if there is a personal or family history, are at greater risk for developing melanoma {2373}. If patients are from “melanoma-prone families” and have clinically dysplastic naevi, as defined by criteria that include lesional diameter, their individual risk for developing a melanoma is several hundred times that of the general population, with a risk for lifetime incidence of melanoma approaching 100% {744,846}. The significance of a single histologically dysplastic naevus in this context has not been determined. One study evaluated patients with an established diagnosis of melanoma (n=716) compared with normal controls (n=1014) and found that one clinically dysplastic naevus was associated with a 2-fold risk, while 10 or more conferred a 12-fold risk of melanoma {2386}. In the same study, patients who bore 100 or more clinically non-dysplastic naevi had a relative risk of 3.4. Approximately 50% of dysplastic naevi patients with a family history of MM may have multiple primary melanomas {1320}.

Histopathological criteria

There is evidence that histological atypia does correlate with melanoma risk. A recent study of more than 20,000 naevi divided them microscopically into mild, moderate, or severe categories of dysplasia. A personal history of melanoma was present in 5.7 of the patients with mild, 8.1 with moderate and 19.7 with severe atypia. It was concluded that the risk of melanoma was greater for persons who tend to make naevi with high-grade histological atypia {102}.

Genetic predictive factors

Currently, there are no commercially available genetic tests that would be predictive of dysplastic naevi progression to melanoma.

Site specific and Meyerson naevi

H. Kamino
D. Weedon

In some anatomic sites, naevi may have atypical histological features. This chapter discusses three clinicopathologic entities: acral, genital and Meyerson naevi, but other site specific features have been described, including naevi occuring in flexures, umbilicus, ear and scalp.

Acral naevus

Definition
Acral naevi (AN) are benign melanocytic proliferations from the palms and soles.

Synonyms
AN or “naevi on volar skin” include histologic subtypes termed “Melanocytic Acral Naevus with Intraepidermal Ascent of Cells (MANIAC)” {1545} and “atypical or acral lentiginous naevus” {501,1511}.

Epidemiology
Clinical studies which are unable to distinguish lentigines from true naevi, record discrete pigmented volar lesions in less than 1{1763} to 92% {1416} of subjects, with most studies suggesting a range of 3 – 41% of the population {63,519,574, 1338,2223,2418}. In a histologically confirmed study, 3.9% of Caucasians had AN {1473}. Darker patients tend to have a greater percentage {519,1763} and higher total of naevi on acral surfaces {63,519,1553,2418}, though this is not always found {574,1416}. Pigmented acral lesions are generally more common in the second and third decades {63,1338,1415,2418}.

Localization
Plantar naevi are probably more common than palmar naevi {63,574,1473,2418}. AN may occur on both pressure-bearing and pressure-spared surfaces {45,63, 1415}.

Clinical features
AN are usually less than 8 mm with a light to dark brown striated macular component. Congenital AN can be particularly difficult to clinically distinguish from melanoma {289,1511,2013,2017,2018}.
On epiluminesence microscopy (ELM) dermatoscopy), the pigmentation of AN is accentuated in dermal glyphic furrows and occasionally around eccrine ostia, thereby creating reproducible patterns {45,1232,2014,2015}. In acral melanomas the pigment is distributed along the dermatoglyphic ridges {45}.

Etiology
The origin of AN is hypothesized to involve repeated trauma {701,2181, 2182}, foci of “unstable” melanocytes {1416} and racially-correlated variations in melanosome aggregation {1612}.

Histopathology
Distinction of acral naevi from melanoma can be difficult because both may be asymmetric, poorly circumscribed and have intraepidermal ascent of cells {292, 701,984,1545,2181,2182}. Suprabasal melanocytes in AN are relatively more columnar, circumscript and less voluminous than in melanomas {1246}. Signoretti et-al. have shown that symmetry, circumscription, the columnar organization of ascending melanocytes and organization of the junctional component are all influenced by the histologic plane of section; to wit, naevi sectioned perpendicular to dermal glyphics are more likely to have benign attributes {2017, 2018}. Subsequently, severe melanocytic atypia and a dense lymphocytic infiltrate have been found the most reliable features indicative of melanoma {493,707}.

Genital naevus

Definition
Melanocytic naevi on the perineum and genitalia, hereafter “genital naevi (GN)”, include different naevic types distinguished and united by unusual, variably present junctional features.

Synonyms
A subgroup of GN with "unusual histologic features" {480,782} or "atypism" {1608} have been dubbed "atypical melanocytic naevus of the genital type (AMNGT) {495}".

Epidemiology
About 10% of men and women have pigmented genital lesions {574,784,1955}, but many are lentigines {784,1955}. Histologically confirmed GN occur in 2% of women {267,480,1955}.
AMNGT comprise a minority of all GN {267,480,1955}. They typically present by the twenties {1608} and, in contrast to vulvar melanoma, are seen exclusively in premenopausal women {1608,2015}. Dysplastic naevi may also occur on the genitalia but they are usually observed in people with dysplastic naevi elsewhere on their bodies {267,1608}. Vulvar naevi were said to have increased premalignant potential {1763}, though recent data

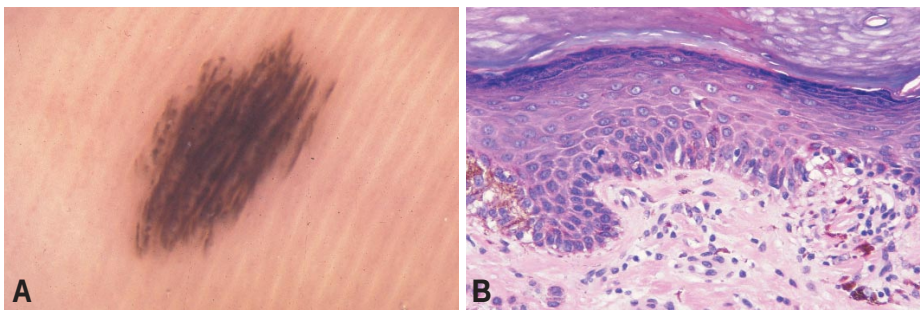


Fig. 2.60 Acral naevus. **A** Epiluminesence microscopy of an acral naevus demonstrating linear hyperpigmentation within the furrows of dermal glyphics. **B** Intraepidermal melanocytes with short dendrites are seen along and above the basal layer.

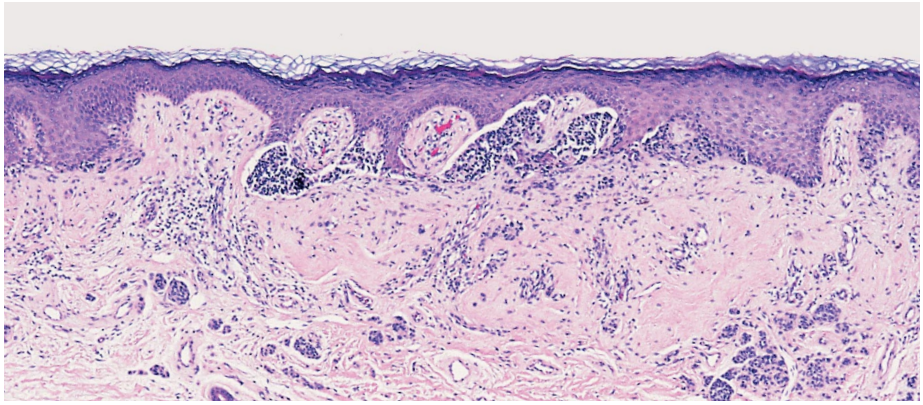


Fig. 2.61 Genital naevus. This example contains features of a dysplastic naevus. Junctional melanocytes are arranged as both nests and single units. There is bridging of rete ridges and lamellar fibroplasia. Dermal melanocytes mature and melanocytes do not ascend above the basal layer.

refutes this {1954}. Histological studies suggest that from 1% {391} to 12% {495} of vulvar melanomas are associated with a naevus.

Localization
AMNGT are more commonly seen on the labia minora and clitoris {495}. Although infrequent, AMNGT may occur on male genitalia {495}. Naevi with histologic features similar to AMNGT may be observed on flexural sites and along the vestigal "milk-line" from the axilla to the upper thighs {1964}. Dysplastic naevi more commonly occur on the labia majora and perineum {495}

Clinical features
Common type GN are dome shaped, evenly pigmented, tan to dark brown papules less than 1 cm {1955}. Both AMNGT and dysplastic GN can be polypoid or flat {495}. They are usually tan-brown, often with some black areas {495}. Clark et-al report a size range from 2 to 24 mm {495}. Despite a long history of advice to the contrary, prophylactic removal of all genital naevi is not recommended {480,784,1955}. AMNGT observed from 1 to 16 years have not recurred or metastasized; yet, their conservative reexicision has been advised {495}.

Etiology
The genesis of GN is poorly understood. Possible influences include repeated superficial trauma, sex hormones, genetic determination and stroma type {391, 495,1964}.

Histopathology
AMNGT are typically "mushroom shaped" with a base composed of maturing melanocytes similar to a common naevus. Melanocytes at the dermal-epidermal junction are arranged in one of three patterns: nests; dyshesive nests; and crowded, ill-defined nests and single melanocytes. In about half of AMNGT there are "skip areas" at the dermo-epidermal junction which lack melanocytes. Thus, it is the junctional component in AMNGT which is worrisome for melanoma. Unlike dysplastic naevi, AMNGT usually lack a lymphocytic infiltrate. The "ill-defined" stroma of AMNGT is different from that typically seen in melanomas or dysplastic naevi {495}. The histopathologic features of dysplastic GN are similar to dysplastic naevi elsewhere {267,495,1955}. Rarely, genital naevi may be distorted by coexistent lichen sclerosus et atrophicus, producing histologic changes similar to those seen in recurrent naevi {17,352,390}.
Unlike melanomas, vulvar naevi are said to lack intraepidermal ascent of melanocytes {17,24,391,782}, though this has been disputed {984,1608}. Regardless of subtype, GN differ from melanoma by circumscription, maturation, and symmetry {17,24,391,782}.

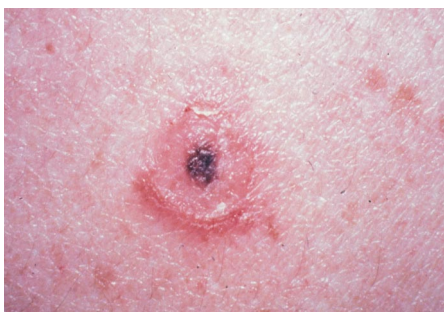


Fig. 2.62 Meyerson naevus. Note the eczemetous halo around a pigmented naevus.

Meyerson naevus

Definition
Meyerson naevus is a benign naevus of junctional, compound or intradermal type surrounded by an eczematous halo {2478}.

Synonyms and historical annotation
"Spongiotic change in melanocytic naevi" {2478}, halo dermatitis {352,2330}, halo eczema {1329} and perinaevic eczema {1816}.
The eponym "Meyerson naevus" (MN) was suggested {1706} to honour the 1971 description of a spongiotic dermatitis involving melanocytic naevi {1595}.

Epidemiology
MN typically occur in young adults {1706} and children {2167}. Affected men have been reported about three times more frequently than women {1706}.

Localization
Eczema may involve one or several naevi {1329,1706} and may spread beyond naevi to previously normal skin {306, 729}. There are no clinical features to suggest which naevi become dermatitic {1329,1706}.

Clinical features
The change may involve one or more naevi simultaneously. The naevus does not usually undergo regression as a result of this change although the transformation of a Meyerson naevus into a halo naevus has been recorded once {1884}. MN are characterized by a pruritic, raised erythematous, scaling and crusted plaque which extends symmetrically 1–2 cm from the central naevus {306, 1329,1595}. Upon resolution the naevus persists unchanged {1595,2330}, though post-inflammatory hypopigmentation may occur {1595,2330}.

Etiology
The inflammation of MN has been likened to pityriasis rosea {564,1595} and allergic contact dermatitis {2478}. One case was triggered by interferon alpha {1328}.

Histopathology
MN are characterized by spongiosis,

microvesiculation, irregular acanthosis, parakeratosis, focal crust and a superficial perivascular infiltrate of lymphocytes and eosinophils {306,676,1595,2478}. There is no histologic regression nor depigmentation {2478}.

There is a naevocellular naevus of junctional, compound or intradermal type with an associated subacute spongiotic dermatitis {1706}. There is variable epidermal acanthosis and a mild to moderate superficial perivascular and interstitial infiltrate of lymphocytes. Usually there are a few eosinophils. There is often mild exocytosis of lymphocytes into the epidermis. There is no regression, although one exception has been recorded (see above). Rarely, dysplastic naevi have been involved {676,1328}.

Immunoprofile

Lymphocytes in MN are predominately CD4 positive {729,1816}. ICAM-1 has been reported to be increased on keratinocytes and endothelium within MN {717}.

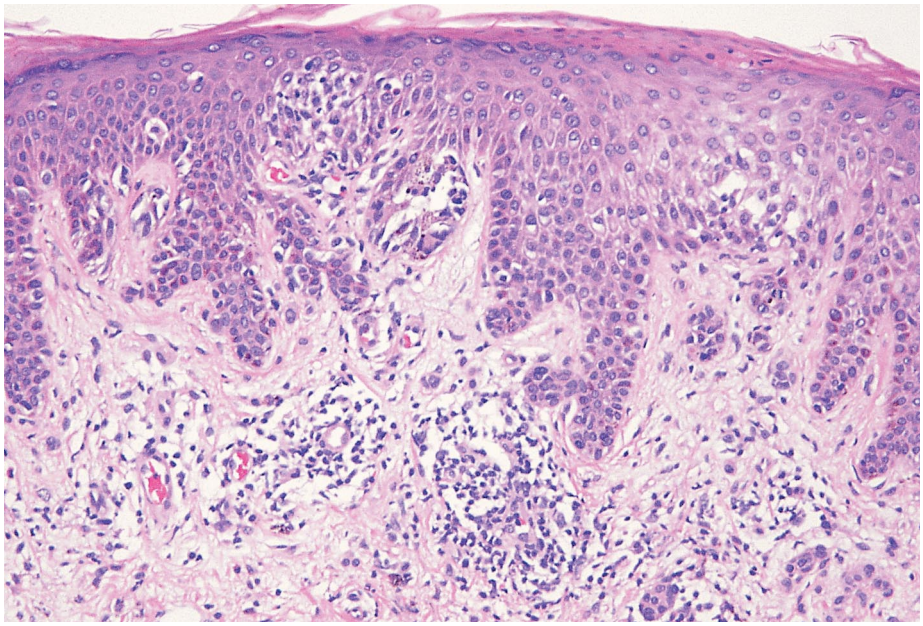


Fig. 2.63 Meyerson naevus. Spongiosis, parakeratosis and irregular acanthosis characterize the epidermis.

Persistent (recurrent) melanocytic naevus

H. Kerl

Definition
Persistent melanocytic naevi are benign compound or intradermal melanocytic naevi that persist (recur) after incomplete excision.

Synonym
Pseudomelanoma {1310}

Clinical features
Persistent melanocytic naevi are the result of incomplete removal after superficial shave technics, dermabrasion or laser treatment {271}. The lesions 'recur' usually after weeks or months after therapy. They are characterized by variably pigmented macules, papules or plaques with irregular borders. A scar from previous surgery can be usually recognized.

Histopathology
Scanning magnification shows commonly above a dermal melanocytic naevus a scar with fibrosis. The intraepidermal changes are characterized by sharp circumscription and confluent nests of melanocytes, that are not equidistant and vary in sizes and shapes. The nests are mostly situated at the dermo-epidermal junction. Melanocytes are also arranged as solitary units at the dermo-epidermal junction and sometimes above it in upper layers of the epidermis {1037}.
Assessment of the original specimen is very important for an accurate diagnosis to ensure that the lesion is really a persistent melanocytic naevus and not a persistent melanoma.

Differential diagnosis
The features within the epidermis and in epithelial structures of adnexa may simulate a melanoma in situ.
However, the sharp circumscription of the intraepidermal component, the presence of melanocytes in nests and as single units mostly at the junction and the typical naevoid cells of the preexisting dermal melanocytic naevus beneath a scar are helpful clues to the diagnosis of persistence (recurrence). Furthermore in persistent melanocytic naevi the melanocytic proliferation within the epidermis is confined to the area above the scar.

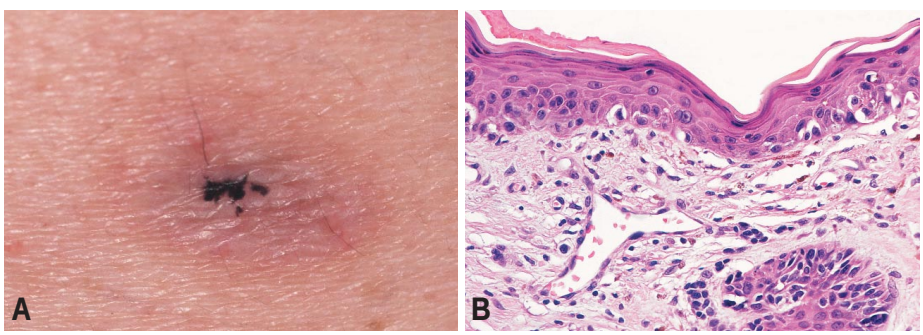


Fig. 2.64 Persistent (recurrent) melanocytic naevus. **A** Small irregular black macule. A scar surrounds the lesion. **B** Persistent (recurrent) melanocytic naevus. Melanocytes are arranged as solitary units along the dermo-epidermal junction and also above it. Atypical nuclei can be observed. Note involvement of the follicle.

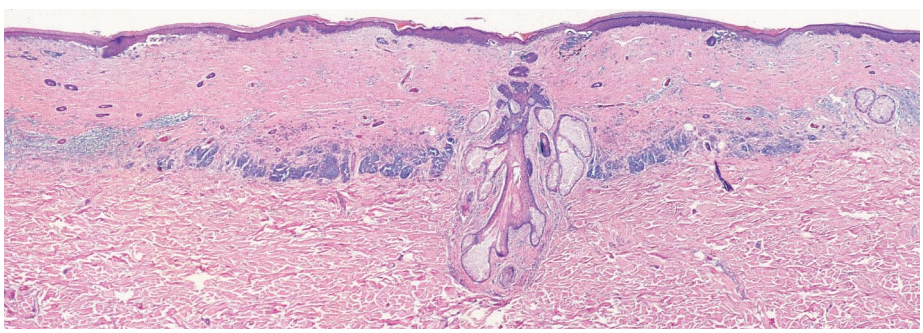


Fig. 2.65 Persistent (recurrent) melanocytic naevus. Trizonal arrangement: 1) Dermal melanocytic naevus. 2) Above the melanocytic naevus a scar revealing fibrosis. 3) Intraepidermal changes with nests of melanocytes with irregular shapes and a tendency to confluence at the dermo-epidermal junction.

Spitz naevus

P.E. LeBoit
B.C. Bastian
W.J. Mooi

Definition
Spitz naevus is a benign proliferation of large spindled, oval or large round (epithelioid) melanocytes that begins in the epidermis, and evolves into compound or intradermal stages. This distinguishes it from some forms of blue naevus, in which the lesion is wholly intradermal from the outset.

ICD code 8770/0

Synonyms
Spindle and epithelioid cell naevus, naevus of spindled and/or epithelioid cells, benign juvenile melanoma {2239}. Pigmented spindle cell naevus (Reed) is probably a distinctive variant of Spitz naevus {158,162,2005}.

Epidemiology
Spitz naevus is most common in the first two decades of life {1015,2155}. Accurate population based studies on its prevalence are not available, and are coloured by the caution shown by pathologists in making an outright diagnosis of Spitz naevus in middle aged or older adults, and in making a diagnosis of Spitz naevus in young adults if there are any unusual microscopic features.
Spitz naevi are mostly recorded in Caucasian patients. However, they occur in all racial groups, and their occurrence in Asians and Africans may be underestimated.

Localization
Spitz naevi can occur on any areas of the body, although the face of children and thighs of young women are stereotypical associations.

Clinical findings
The earliest recognizable Spitz naevi are about a mm. or so in diameter, and the largest recorded are over 2 cm. While the criterion of size has been popularized in the differential diagnosis between Spitz naevus and melanoma, many Spitz naevi are over 1 cm. in diameter. There appears to be an initial period of rapid growth, followed by stabilization. This is in contrast to melanoma, in which the diameter of the lesion is seldom stable.
Most Spitz naevi are lightly pigmented. The classic lesion is a pink to red papule, with an even round border and a domed shape. There is slight scale. The degree of erythema is often such that the clinician considers the diagnosis of haemangioma. However, if one looks at the initial description by Spitz, it is clear that there is considerable heterogeneity, with tan and medium or even dark brown lesions, and verrucous ones also possible {2239}. In dark skinned people, Spitz naevi are usually darker than their normal skin colour. There is usually a uniformity of pigmentation, with the notable exceptions of combined Spitz naevi and Spitz naevi with a halo reaction.
Ulceration is practically never present in Spitz naevi, except in children who traumatize them in play or excoriate them. The presence of an ulcer outside of these settings merits reconsideration as melanoma.
Most Spitz naevi are single lesions. However, groups of Spitz naevi can occur in a single area in agminated Spitz naevus {44,2002}. In such cases, the epidermis in between the papules of Spitz naevus can be normal in appearance, or more commonly is lightly pigmented, resembling a café au lait spot (when it occurs in Caucasian patients). In eruptive Spitz naevus, a patient may have many papules of Spitz naevus appear on a limb or even over the entire integument within a few weeks or months. This obviously distressing situation can be confused with metastasis of melanoma.

Etiology
The cause of Spitz naevus is unknown. Sunburn and biopsy of a single Spitz naevus have been linked to eruptive lesions {597}.

Histopathology
Because the findings of Spitz naevus differ significantly at various stages, we will describe those in detail. Spitz naevus begins as a proliferation of large oval melanocytes at the dermal-epidermal junction. This can occur along a front of only a few mm., and is first recognizable by single, large melanocytes with abundant eosinophilic cytoplasm and large vesicular nuclei. There are often a large number of cells with several nuclei, even in small lesions. Cytoplasm is abundant, and even though the nuclei may be large, they are usually monomorphous. Clefts demarcate the melanocytes from adjacent keratinocytes. Even if single cells are present in number above the junction, they are evenly distributed {355}. As these lesions enlarge, the epidermis above the proliferation thickens, and nests begin to form. The epidermal thickening is largely via hyperplasia of the spinous layer, with squamatization of the basal layer and pointed rete ridges.

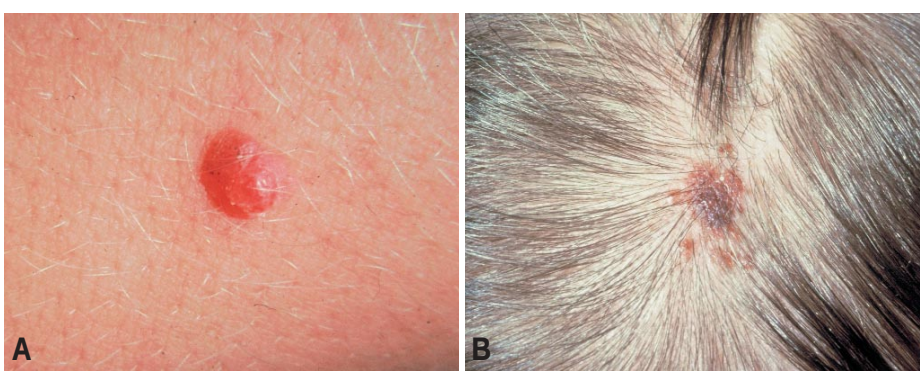


Fig. 2.66 Spitz naevus. **A** A sharply circumscribed, dome-shaped lesion, which may be mistaken for haemangioma. **B** Small brown papules form an agminated lesion. This configuration is often alarming.

There is corresponding hypergranulosis and compact hyperkeratosis.
Within the junctional nests of a Spitz naevus are clefts, separating the melanocytes from one another, and from the epidermis. The clefts tend to be prominent over the apices of junctional nests. The nests may appear to be embedded in the epidermis, rather than lying at the bases of rete ridges. The epidermal hyperplasia of a well developed junctional Spitz naevus, and the nests of the naevus itself are both well circumscribed {19,1636, 1638,1769,2479}. By the time that nests are of substantial size, one may encounter Kamino bodies in the epidermis. Kamino bodies are dull pink staining globules, up to the size of several keratinocytes, often with a scalloped border and a periphery in which there are crescent shaped, compressed appearing keratinocytes {1186}. Unlike dyskeratotic cells, which are more brightly eosinophilic, their major ingredient is basement membrane material. They stain with PAS-D and with immunoperoxidase stains for basement membrane components, such as laminin and type IV collagen {2499}.
Compound Spitz naevus forms when junctional nests become incorporated into the dermis. In early compound lesions, one may see a dense lymphocytic infiltrate, rather than the sparse perivascular one that most authors describe. The dermal nests tend to be smaller than the junctional ones, and as melanocytes descend into the reticular dermis, one can discern a gradient from large nests to smaller ones, and single cells may predominate at the base. Mitotic figures can be present in the upper part of a compound Spitz naevus, but tend to decrease in number toward the base of the lesion. Maturation of melanocytes is also a correlate, with smaller cells that have less cytoplasm, smaller nuclei, and smaller and less eosinophilic nucleoli all findings that reassure the pathologist. If a Spitz naevus is pigmented, the pigmentation lessens in the lower half of the lesion. Fully formed compound lesions often have a domed surface and a wedge shape. Unlike the case in early compound, or even junctional lesions, lymphocytic infiltrates are usually sparse and perivascular.
Intradermal Spitz naevi preserve the domed/wedge shape noted above. The epidermis is often slightly hyperplastic.

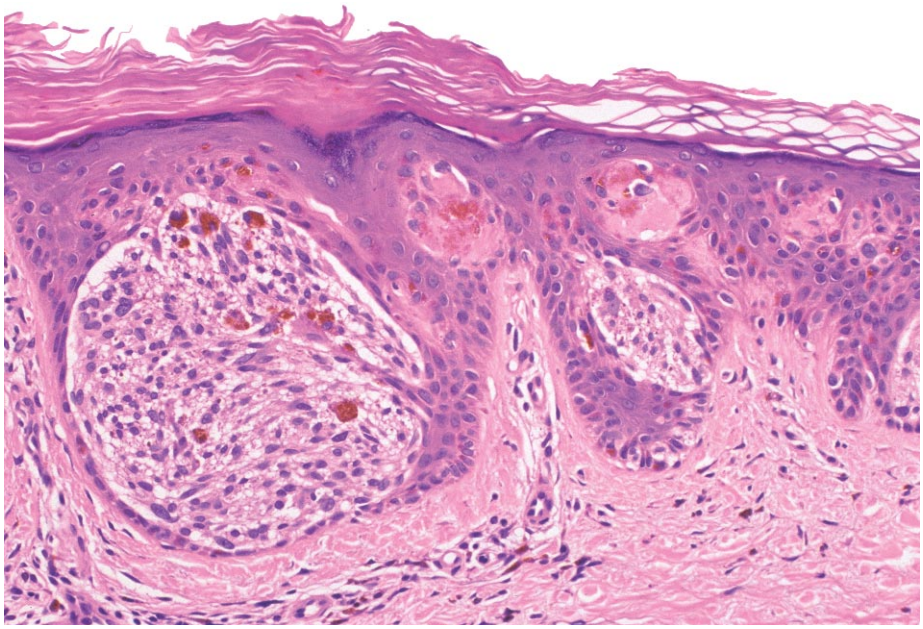


Fig. 2.67 Spitz naevus, junctional type, Clefts separate melanocytes from one another. Several large Kamino bodies are present.

The nests of melanocytes are often present between thickened collagen bundles in the lower part of the lesion. When this is prominent, some apply the term desmoplastic Spitz naevus. Unlike the case in desmoplastic melanoma, there are no markedly elongated fascicles of cells. If the proliferation abuts the subcutis, one may see lymphoid nodules.
For both compound and intradermal lesions, an important finding is that the nests at each level of the lesion should be similar in size, with the cells similar in overall and nuclear size and in pigmentation.
There are many important variants of Spitz naevus. On acral skin, one may see many single melanocytes scattered above the junction. A halo reaction may be present, sometimes accompanied by a clinical halo. The lymphocytes are evenly dispersed throughout the lesion, and some may be apposed to pyknotic melanocytes . The stroma may be sclerotic (hyalinizing Spitz naevus) or highly vascular {2293} . Some nests may have an empty appearing centre (tubular Spitz naevus) {2228}. In combined Spitz naevus, other populations of melanocytes (e.g. small round, bipolar-dendritic, balloon, etc.) may be present {1961}. This is one of the most difficult variants to deal with, as the large cells may not mature and dense lymphocytic infiltrates (up to a halo reaction) may be present {972}.
Another difficult variant is persistent Spitz naevus. The great majority of Spitz naevi do not recur at the biopsy site if the lesion seems to be removed clinically, but goes to a margin. Those that do can show suprabasal scatter of melanocytes (as in other recurrent naevi), a compound Spitz naevus over a scar, a nodule next to a scar, or a picture resembling desmoplastic Spitz naevus {969}.
Lastly, there is a “grey zone” of lesions in which there are many findings of Spitz naevus, but the diagnosis is less certain. For lesions in which the diagnosis is Spitz naevus, but there are a few findings that are unusual, many use the term “atypical Spitz naevus”, although this may be attacked on semantic and functional grounds. If one is not sure of the diagnosis, a descriptive term, such as “proliferation of large melanocytes involving the epidermis and dermis” is preferable. This should be accompanied by a note or comment explaining the difficulties, differential diagnosis, including if appropriate, microstaging parameters that would be appropriate if the lesion were regarded as melanoma, and advising reasonable management. The role, if any for sentinel lymph node biopsy in difficult cases is currently considered controversial {1444,2286}.
Among these “grey-zone” lesions is an emerging, relatively homogeneous group of lesions with a distinctive pattern, often

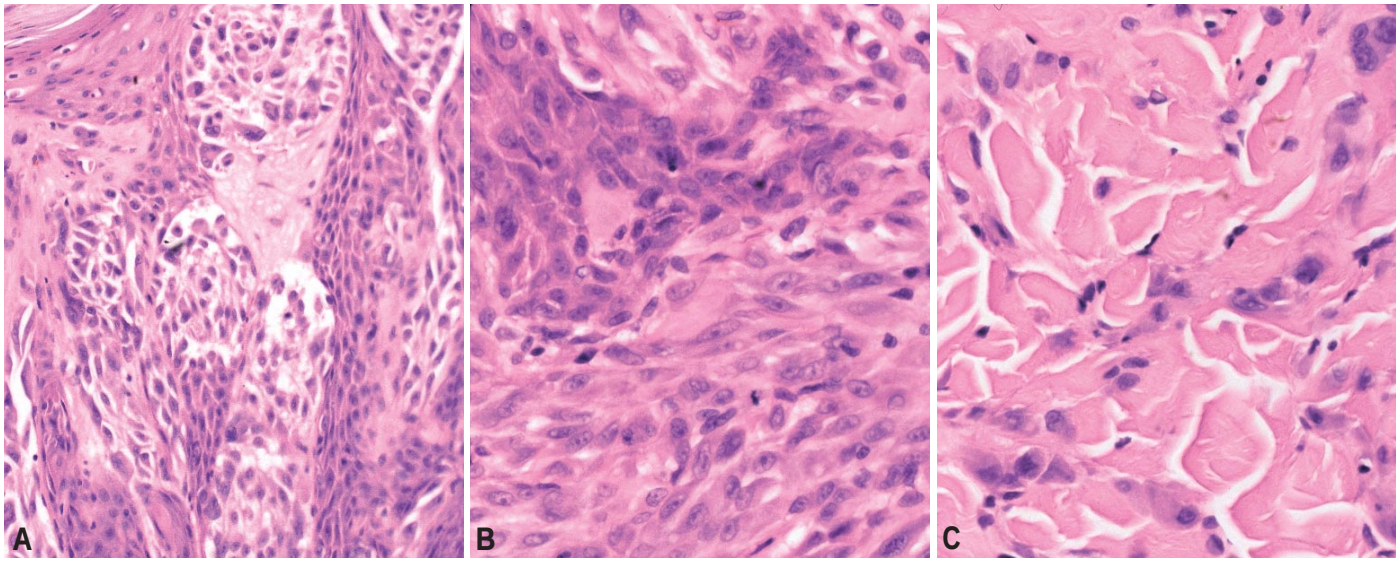


Fig. 2.68 Spitz naevus, compound type. **A** Junctional portion of Spitz naevus with epidermal hyperplasia. **B** The upper part of the lesion is highly cellular. **C** Toward the base single large oval melanocytes are interspersed between thick collagen bundles.

found from early childhood to young adulthood in which there are some features of Spitz naevus and others of melanoma. Common denominators include a vertical orientation, extension into the subcutis with no diminution in cellularity and a blunt, multinodular interface, ulceration, a plasmacytic infiltrate and deep mitotic figures. Such cases have been described as "malignant Spitz naevus" and also simply regarded as melanomas {2205}. In the initial study of "malignant Spitz naevus" there were 3/32 lesions in which palpable lymph node enlargement had occurred, and another 3 in which lymph node involvement was detected on elective dissection. Very similar lesions have been described as melanomas in children {1632}. Follow up data has been presented to the effect that systemic metastasis may not occur, or may be much less frequent than in adults with conventional melanomas matched for thickness. Clearly, further studies are needed to determine if these lesions are fundamentally Spitz naevus, melanoma, or neither.

Somatic genetics

While most cells in most Spitz naevi seem to be diploid, there are a proportion of polyploid cells, at least in the upper part of lesions as judged by image analysis cytometry {1386}. True aneuploidy may be uncommon, as evaluated by flow cytometry {2439}. In an analysis using comparative genomic hybridization the majority of Spitz naevi did not show chromosomal aberrations, whereas 25% showed an isolated gain of chromosome 11p {174}. Preliminary studies indicate that the increased copy number of chromosome 11p is due to the formation of an isochromosome 11p {1494}. About 70% of the Spitz naevi with increased copies of chromosome 11p have mutations in the HRAS gene which maps to this location {172}. HRAS mutations have been found only in a minority of cases (< 10%) with normal copy number of chromosome 11p. Preliminary studies indicate that mutations in BRAF occur infrequently in Spitz naevi.

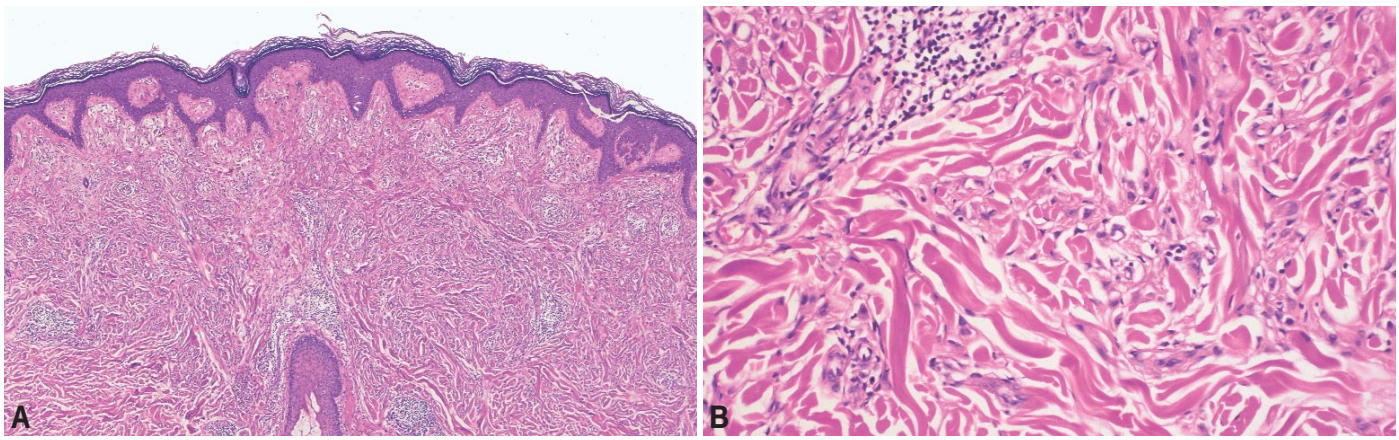


Fig. 2.69 Spitz naevus, desmoplastic type. **A** Rete ridges are uniformly elongated but jagged above the upper part of the lesion. **B** Thin spindle cells are present between collagen bundles.

Pigmented spindle cell naevus (Reed)

L. Cerroni

Definition
Pigmented spindle cell naevus (Reed) is a benign melanocytic naevus showing dark pigmentation clinically, and a proliferation of spindled melanocytes histopathologically.

ICD-O code 8770/0

Synonyms and annotation
This melanocytic naevus has been named eponymously after Richard Reed, who described it in 1975 {1909}. It has also been referred to as Reed naevus or Reed tumour. While some authors regard it as a subtype of the Spitz naevus, pigmented spindle cell naevus (Reed) presents with peculiar clinical and histopathologic features, allowing a reproducible diagnosis and classification to be made.

Epidemiology
Pigmented spindle cell naevus (Reed) is a melanocytic tumour found in children, adults, and, rarely, older patients, with a peak in the third decade. There is a predominance for females.

Clinical features
The patients present with a darkly, homogenously pigmented, flat or slightly dome-shaped, sharply circumscribed papule or plaque located usually on the limbs, especially the thigh {158,2005, 2068}. Less common locations are the trunk and the head and neck region. The lesions are usually of recent onset and smaller than 1 cm. Surface skin microscopy (dermatoscopy, dermoscopy) reveals typically a “starburst” pattern (characterized by the presence of pigmented streaks disposed in a radial arrangement at the edge of the lesion).
A clinical misdiagnosis of malignant melanoma is not infrequent, due to the dark pigmentation and recent onset of the lesions.

Histopathology
Histologically, the tumours are symmetrical and show a sharp lateral circumscription. Spindled, pigmented melanocytes arranged in vertical nests at the dermo-epidermal junction predominate {158,2005,2068}. A few, and in some instances many, melanocytes may be seen above the dermal/epidermal junction, as well as confluence of the nests. The proliferation of melanocytes may be confined to the epidermis, or may extend into the papillary dermis. Occasional mitoses may be found. Cytomorphologically there is a uniform proliferation of elongated, fusiform melanocytes, usually without atypical features. The nuclei are relatively small, with uniform, delicate chromatin. Epithelioid melanocytes are admixed in a minority of cases. Commonly, the epidermis is slightly hyperplastic and shows marked hyperpigmentation of the basal keratinocytes. Intraepidermal eosinophilic globules (so-called “Kamino bodies”) can be observed in about half of the cases. An inflammatory infiltrate composed of lymphocytes and histiocytes with many melanophages is found within the papillary dermis. A subset of cases shows a considerable overlap with Spitz naevi.
Cases with some cytological atypia have been termed “atypical pigmented spindle cell naevus - pigmented spindle cell naevus with architectural and/or cytologic atypia”, and may represent a source of problem in differential diagnosis from malignant melanoma {158}. A variant described as “plexiform pigmented spindle cell naevus” probably represents a pigmnented spindle cells naevus involving the reticular dermis {158}.

Prognosis and predictive factors
Pigmented spindle cell naevus (Reed) is a benign melanocytic proliferation with no potential for distant metastases. Local recurrences may be observed in tumours that were incompletely excised.

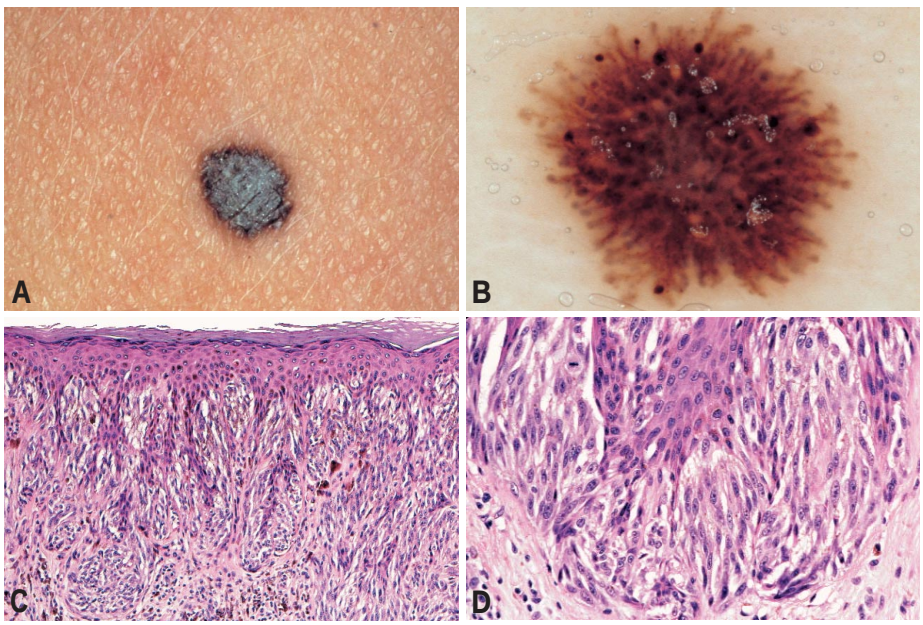


Fig. 2.70 Pigmented spindle cell naevus (Reed). **A** Small, flat, dark papule. **B** Dermoscopy shows the characteristic "starburst" pattern. **C** Elongated nests at the dermoepidermal junction and in the papillary dermis; note pigmentation of the basal keratinocytes and melanocytes, and the presence of numerous melanophages in the papillary dermis. **D** Fusiform melanocytes predominate. Note the mitosis in the upper left corner.

Halo naevus

D. E Elder
X. Xu

Definition
A halo naevus presents as a small circumscribed symmetrical, usually papular pigmented lesion with the appearance of a common benign compound naevus, surrounded by a symmetrical area of depigmentation, representing the "halo" {2469}. The lesion is defined histologically by the presence of a brisk lymphocytic infiltrate among dermal naevus cells, and by loss of pigment in the epidermis adjacent to the naevus. Some naevi with a lymphocytic response of the type seen in halo naevi do not have an obvious clinical or histologic depigmented halo {948}.

ICD-O code 8723/0

Synonyms
Sutton naevus; leukoderma acquisitum centrifugum {2297}.

Clinical features
Halo naevi often present during the summer, perhaps because the halo contrasts better with tanned skin. They are most common in teenagers and young adults. In these cases, they are sometimes associated with dysplastic naevi, and are sometimes multiple. Less often, a solitary halo lesion develops in an older adult, and in this circumstance the possibility of melanoma should be ruled out histologically, especially if the central pigmented lesion is clinically atypical or if the halo is eccentric or asymmetrical in contour.
Serial follow-up of halo naevi demonstrates a characteristic time sequence, beginning with the appearance of the halo around a compound naevus, followed by fading and disappearance of the naevus. The halo then gradually repigments over a year or two, returning to the appearance of normal skin. During this period, especially in teenagers, other similar lesions may develop.
Studies in patients with halo naevi have demonstrated circulating antibodies that are reactive with neoplastic melanocytes including melanoma cells, and the infiltrating cells have been shown to be mainly T lymphocytes {2090}. Antigen-presenting cells and CD8+ T cells have been identified in the inflammatory infiltrates of halo naevi, implicating cytotoxic mechanisms in destruction of naevus cells {2581}. Affected individuals also show activated lymphocytes in their peripheral blood {148} as well as T cell clonal expansion {1670} and anti-naevic IgM antibody production {2359}. These findings are consistent with the idea that halo naevi represent immunologically - mediated rejection of a naevus. The halo develops outside the naevus proper, suggesting that there may be a cross-reaction with a "field" of melanocytes that surrounded the naevus prior to the onset of the intense inflammation in the dermal component.

Histopathology
An early halo naevus presents as a small circumscribed lesion, less then 4 mm in diameter as a rule, composed of naevus cells located in the papillary dermis and usually also in the epidermis. The lesion is symmetrical, and is composed of cells that are uniform from side to side and tend to become smaller (i.e., more "mature") from the top to the bottom of the lesion. The epidermis may be hyperkeratotic with follicular plugging {2469}. The feature that distinguishes a halo naevus from a banal naevus is the presence of a striking dense lymphocytic infiltrate, an appearance that may arouse a suspicion of melanoma in some cases. The lymphocytes extend among the lesional naevus cells, tending to obscure their underlying nested pattern in some cases. Melanin-laden histiocytes and mast cells can be present as well as lymphocytes {2090}. Occasional halo naevi contain a few giant cells or there may be a frankly granulomatous response. Over the ensuing weeks or months, the dermal naevus cells disappear and then the histologic differential diagnosis may include lichenoid inflammatory dermatoses. Over a period of a year or two, the inflammatory cells disappear and histologic examination of the site of a completely resolved halo naevus may disclose essentially normal skin, with little or no evidence of scarring or residual pigment {2469}. In most halo naevi, there is little or no readily observable melanocytic abnormality in the epidermis at the "shoulder" of the lesion beyond the lateral border of the dermal component, even though it is in this region that the striking clinical halo is located. However, DOPA stains for tyrosinase and immunohistochemical (e.g. Melan-A) or argentaffin stains for melanocytes reveal greatly reduced numbers of them in the area of the halo compared to the surrounding skin {2469}.

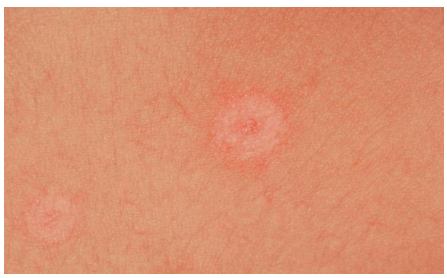


Fig. 2.71 Halo naevus. There are two small naevi surrounded by rims of depigmentation.

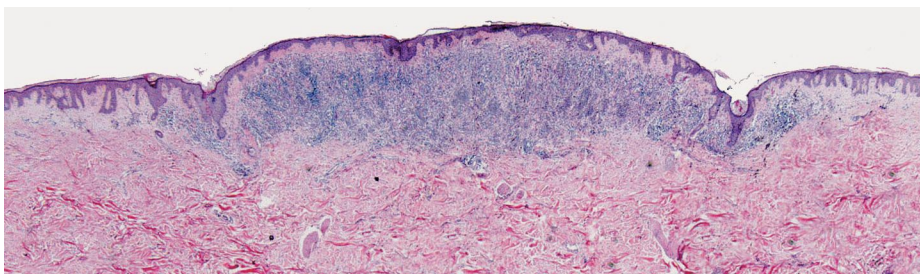


Fig. 2.72 Halo naevus. There is an apparently well circumscribed lesion which at first glance may be mistaken for a lymphocytic infiltrate.

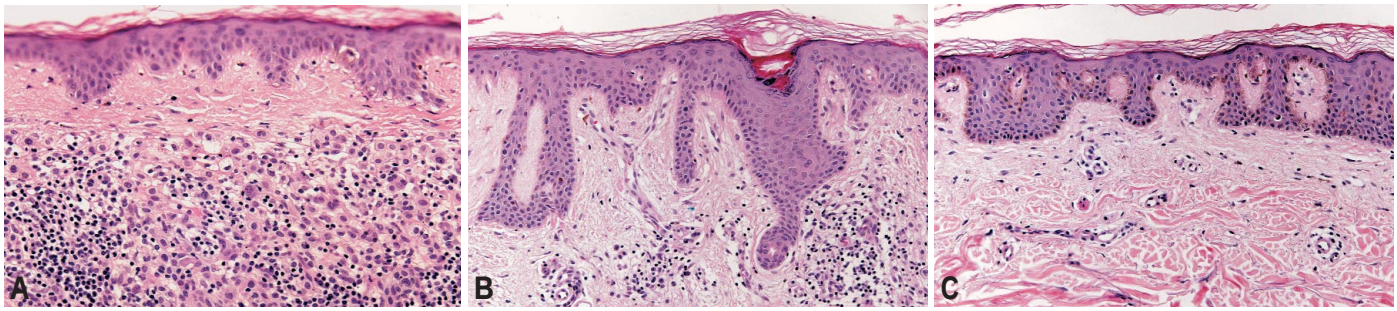


Fig. 2.73 Halo naevus. **A** Infiltrating lymphocytes are intimately admixed with naevus cells, which will lead to apoptosis and ultimate disappearance of the naevus cells. In later examples, naevus cells are more inconspicuous than they are in this field. **B** Extending 1 to 2 mm beyond the lateral border of the dermal naevus component, the papillary dermis is widened with slight fibroplasia, there is a patchy lymphocytic infiltrate, and there is absence of pigment and of melanocytes in the overlying epidermis. This region constitutes the clinical halo. **C** Normal skin adjacent to the halo shows a normal papillary dermis, normal melanin pigment in basal keratinocytes, and the presence of melanocytes, which can be demonstrated if desired with a Melan-A stain.

The lesional cells in most halo naevi are unremarkable dermal naevus cells of the large pigmented (type A) or small non-pigmented (type B) cytology. Pigment is located in naevus cells and in melanophages superficially, and is usually coarse in texture. In some lesions, the dermal cells have nuclei that are larger than is usual in common naevi, and sometimes there is hyperchromatism and a degree of pleomorphism, with or without nucleoli, representing cytologic atypia which is present in about 50% of halo naevi and is usually mild or at worst moderate in degree {1640}. This cytologic atypia may represent a form of "inflammatory" or reactive atypia. Mitotic figures are completely absent in most lesions. However, a few lesions judged to be benign halo naevi have shown one or two mitotic figures {1909}. Such a finding should provoke careful examination of the lesion to rule out melanoma, with deeper sections and embedding of any residual gross tissue. Findings suggestive of melanoma in a lesion simulating a halo naevus include the presence of a separate population of cells with an expansile pattern of growth, severe uniform cytologic atypia, and/or the presence of frequent mitoses, ulceration or necrosis. The halo phenomenon may occasionally involve other types of naevi, including dysplastic naevi {2370}, Spitz naevi {972} and congenital naevi {2359}, as well as melanomas {2090}, and therefore careful inspection of the underlying lesional architecture and cytology in multiple sections may be required for definitive classification.

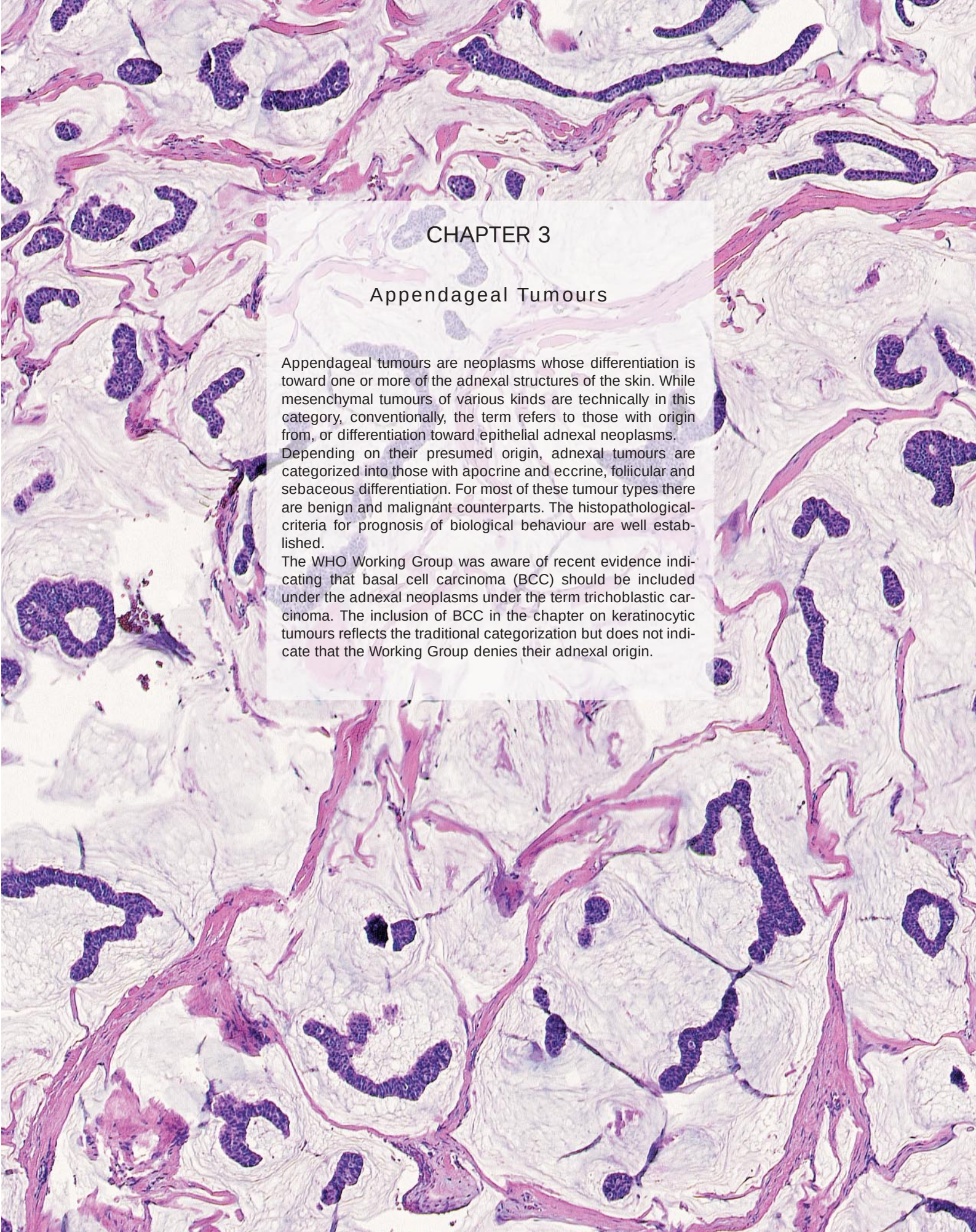
The halo region at the periphery of the dermal component of the lesion may contain a few lymphocytes at the dermal-epidermal interface, with a reduction or an absence of identifiable melanocytes. In comparison with adjacent normal epidermis, pigment may be visibly reduced, and this contrast can be enhanced with a melanin stain. In most lesions, there is no intra-epidermal melanocytic proliferation adjacent to the dermal component, but in a few lesions an adjacent component of melanocytic dysplasia may be observed. If an in situ or microinvasive (" radial growth phase") component diagnostic of melanoma is present adjacent to a dermal lesion simulating halo naevus, the entire lesion is most likely to represent melanoma.

Differential diagnosis

The distinction from common acquired or most other types of naevi is usually easy because of the dense lymphocytic infiltrate. The most important differential diagnosis is with melanoma. Compared to nodular melanoma or to the tumourigenic (vertical growth phase) component of superficial spreading melanoma, a halo naevus is usually smaller (the central naevus is usually less than 4 mm in diameter, while most melanomas are larger than 6 mm, though these values are by no means absolute). However, we have rarely observed small melanomas with naevoid characteristics but with diffuse cellular atypia combined with mitotic activity in which diffuse lymphoid infiltration was a prominent pattern. When pigment is present in a halo naevus, it is usually in the form of coarsely divided granules as is the case in most benign naevi, and if there is a junctional component, its character is that of a naevus rather than a melanoma. Thus, there is usually a discontinuous rather than continuous proliferation of predominantly nested rather than predominantly single naevus cells, and there is little or no tendency to single-cell upward ("pagetoid") intraepidermal spread of the junctional cells.

Some halo naevi may be difficult to distinguish from dysplastic naevi that have an unusually brisk lymphocytic infiltrate. Indeed, not only do halo naevi appear to be common in patients with dysplastic naevi but also a halo response may be seen, clinically and histologically, in dysplastic naevi themselves. If the characteristic patterns of dysplasia are seen at the "shoulder" of the compound portion of a lesion whose other features are consistent with a halo naevus, the diagnosis of dysplastic naevus with halo reaction can be made. Especially if there is a history of other atypical naevi and/or a personal or family history of melanoma, surveillance may be warranted for such individuals.

When naevus cells are inconspicuous among a dense infiltrate of lymphocytes, inflammatory dermatoses such as lichenoid keratoses may be simulated {844}. In these circumstances, an S-100, Melan-A or HMB45 stain may reveal the hidden naevus cells. Care must be taken in interpretation, since histiocytes may weakly express S-100, whereas activated melanocytes and melanoma cells may express HMB45. Finally, there are lesions that have an infiltrative lymphocytic response similar to that of a halo naevus but there is no clinical halo. These lesions may be signed out descriptively as "compound (or dermal) naevi with halo reaction" {1909}. Conversely, some naevi with a clinical halo may lack a lymphocytic infiltrate of the type seen in halo naevi {812}. These may be termed "non-inflammatory halo naevi".



CHAPTER 3

Appendageal Tumours

Appendageal tumours are neoplasms whose differentiation is toward one or more of the adnexal structures of the skin. While mesenchymal tumours of various kinds are technically in this category, conventionally, the term refers to those with origin from, or differentiation toward epithelial adnexal neoplasms.

Depending on their presumed origin, adnexal tumours are categorized into those with apocrine and eccrine, foliicular and sebaceous differentiation. For most of these tumour types there are benign and malignant counterparts. The histopathological-criteria for prognosis of biological behaviour are well established.

The WHO Working Group was aware of recent evidence indicating that basal cell carcinoma (BCC) should be included under the adnexal neoplasms under the term trichoblastic carcinoma. The inclusion of BCC in the chapter on keratinocytic tumours reflects the traditional categorization but does not indicate that the Working Group denies their adnexal origin.

WHO histological classification of appendageal tumours

Tumours with apocrine and eccrine differentiation	
Malignant tumours	
Tubular carcinoma	8211/3
Microcystic adnexal carcinoma	8407/3
Porocarcinoma	8409/3
Spiradenocarcinoma	8403/3
Malignant mixed tumour	8940/3
Hidradenocarcinoma	8400/3
Mucinous carcinoma	8480/3
Digital papillary carcinoma	8408/3
Adenoid cystic carcinoma	8200/3
Apocrine carcinoma	8401/3
Paget disease of breast	8540/3
Extramammary Paget disease	8542/3
Benign tumours	
Hidrocystoma	8404/0
Syringoma	8407/0
Poroma	8409/0
Syringofibroadenoma	8392/0
Hidradenoma	8402/0
Spiradenoma	8403/0
Cylindroma	8200/0
Tubular adenoma	8211/0
Tubular papillary adenoma	8263/0
Syringocystadenoma papilliferum	8406/0
Hidradenoma papilliferum	8405/0
Mixed tumour (chondroid syringoma)	8940/0
Tumours with follicular differentiation	
Malignant tumours	
Pilomatrical carcinoma	8110/3
Proliferating tricholemmal tumour	8103/1
Benign tumours	
Trichoblastoma	8100/0
Pilomatricoma	8110/0
Tricholemmoma	8102/0
Multiple tricholemmomas	8102/0
Trichofolliculoma	8101/0
Fibrofolliculoma / trichodiscoma	8391/0
Tumours with sebaceous differentiation	
Sebaceous carcinoma	8410/3
Sebaceous adenoma	8410/0
Sebaceoma	8410/0
Cystic sebaceous tumour	8410/0

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of skin appendageal carcinomas

TNM classification[1,2]

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but no more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N – Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

[1] {894,2219}.
[2] A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508 .

Appendageal skin tumours: Introduction

P.E. LeBoit

Epidemiology
Most studies on adnexal neoplasms have taken place in western countries with Caucasian populations. Benign adnexal neoplasms tend to occur in younger patients than carcinomas do. Adnexal carcinomas vary from those in which actinic damage is the norm, such as the common basal cell carcinoma (which differentiates toward follicular germ) to those that seem to have little relationship to sun exposure (such as spiradenocarcinoma).

Etiology
No known triggering event is evident in the vast majority of adnexal neoplasms. There are some cases in which the cause is an autosomal dominant mutation in a tumour suppressor gene.

Clinical signs and symptoms
Most benign adnexal neoplasms are smooth surfaced, symmetrical papules or nodules the same colour as the patient's skin or darker. Some, such as sebaceous adenoma and syringocystadenoma papilliferum, have eroded surfaces, but in general, ulceration is a sign of malignancy. Most adnexal carcinomas are irregularly shaped plaques, sometimes ulcerated.

Tumour spread and staging
In general, low-grade carcinomas seldom metastasize; for some, e.g. microcystic adnexal carcinoma, metastasis has not yet been recorded.
A haematogenous pattern seems the rule for a few carcinomas, such as adenoid cystic carcinoma, but most can spread via either lymphatic or haematogenous dissemination. Carcino-mas with eccrine differentiation have a propensity to metastasize to the skin.

Sentinel node biopsy
While a few sentinel node biopsies have been performed for adnexal carcinomas, not enough data have been collected to validate this procedure {274}.

Pathology
Diagnostic criteria of adnexal carcinomas
> Irregular borders, asymmetry at scanning magnification
> Horizontal orientation
> Markedly irrregular aggregates of epithelial cells
> Necrosis en masse
> Infiltration of the dermis or subcutis without the interposition of densely fibrotic stroma
> Mitoses frequent, can be atypical
> Stroma irregular, often scant, sometimes myxoid
> Nuclei pleomorphic. Some neoplasms with monomorphous nuclei, e.g. microcystic adnexal carcinoma, are exceptions.

Diagnostic criteria of benign epithelial adnexal neoplasms {28}:
> Symmetric and smooth bordered at scanning magnification
> Vertically oriented with respect to the surface of the skin
> Aggregates of epithelial cells uniform
> No necrosis en masse (with the excetion of poroma)
> Mitoses variable, but typical
> Densely fibrotic stroma, rich in fibrocytes in the case of trichogenic
> Neoplasms forming a blunt, rounded interface with the native dermis. An exception is poroma, which has vascular, myxoid stroma.
> Nuclei monomorphous; rare exceptions include atypical squamous nuclei in poromas.

Immunoprofile
Most adnexal neoplasms are accompanied by variably dense infiltrates of T-cells. These are intimately admixed with the neoplasm (spiradenoma, cutaneous lymphadenoma, adamantinoid trichoblastoma) and lymphoepithelioma-like carcinoma among malignancies are examples. Syringocystadenoma papilliferum has a complement of plasma cells, many of which secrete IgA.

A complex array of keratins are expressed in adnexal neoplasms. Those with follicular germinative differentiation express cytokeratins seen in follicular germs in embryonic and neonatal life. Those with ductular differentiation have lumens that stain for carcinoembryonic antigen (CEA), and express simple epithelial keratins. Sebaceous differentiation is characterized by expression of epithelial membrane antigen in a microvacuolar pattern.

Precursor lesions
Benign adnexal neoplasms of various sorts can arise in naevus sebaceous, a malformation involving the epidermis, dermis and adnexae. Otherwise, most benign adnexal neoplasms arise de novo. This is also the case for malignant adnexal neoplasms. Rare apocrine carcinomas arise in naevus sebaceous. Rarely, porocarcinoma, spiradenocarcinoma or hidradenocarcinoma may arise in a pre-existent poroma, spiradenoma, or hidradenoma, respectively. The vast majority of basal cell carcinomas arises de novo. Rarely, basal cell carcinomas occur in pre-existent trichoblastomas.

Histogenesis
The origin of most adnexal neoplasms is unknown. It is better to speak of their differentiation. The most clear-cut evidence of differentiation is in follicular neoplasms, where such signs as follicular papillae and germs (as in the trichoblastomas) or trichohyaline granules (as are focally found in pilomatricoma and in matrical carcinomas) can occur. Clear-cut apocrine differentiation, in which decapitation secretion of columnar cells that have brightly eosinophilic cytoplasmic granules is also specific. However, there is a marked similarity between eccrine and apocrine ducts. Also, the columnar cells of eccrine secretory coils can resemble poorly differentiated apocrine secretory cells. Hence, neoplasms with ductular differentiation often have debatable histogenesis {1543}. To some

extent, the differentiation of neoplasms probably reflects their distribution {1544}.

Genetics

Approximately one third of sweat gland carcinomas contain TP53 mutations {239A}. Otherwise, little is known about the genetics of most epithelial neoplasms, with the exception of those that occur in multiplicity as part of autosomal dominant syndromes (see Chapter 7). The mutations found in the germlines of patients with syndromes and multiple tumour suppressor genes tend to be the same as occur as somatic mutations in sporadic adnexal neoplasms. Some trichoblastomas have mutations in the PTCH gene, as found in naevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Trichilemmomas have mutations in PTEN, the same gene as involved in Cowden syndrome. Mutations in DNA repair genes occur in the sebaceous neoplasms of the Muir-Torre syndrome and, to a lesser degree, in sporadic sebaceous neoplasms.

Prognosis and predictive factors

In general, adnexal carcinomas of low cytologic grade have a good prognosis, especially if the lesion is relatively small and completely excised. Those of high cytologic grade may metastasize widely. For many adnexal carcinomas, there are simply insufficient numbers of reported cases to develop much of an idea regarding their prognosis.

Malignant tumours with apocrine and eccrine differentiation

L. Requena
H. Kutzner
M. A. Hurt
D. J. Santa Cruz
A.H. Mehregan
Y. M. Mengesha
S. Kohler
Z B. Argenyi
J. McNiff
P. Rudolph
O. P. Sangüeza

Tubular carcinoma

Definition
Tubular carcinoma is the malignant counterpart of tubular adenoma, featuring apocrine differentiation with prominent tubular structures.

ICD-O code 8211/3

Historical annotation
Probably the first reported examples of tubular carcinoma were included in the series of carcinomas of sweat glands published by Stout and Cooley in 1951 {2274}.

Epidemiology
Tubular carcinoma seems to be slightly more frequent in women. Most patients are middle-aged adults.

Localization
The axilla is the most common location, with rare bilateral involvement. Other sites rich in apocrine glands may also be involved {114,127,1705,1785,2274,2397, 2460,2569}.

Clinical features
Tubular carcinoma usually presents as a firm erythematous nodule, which may be ulcerated or adherent to deeper tissues. Tubular carcinomas may arise in naevus sebaceous {644}.

Histopathology
At scanning magnification, the neoplasm is asymmetric, poorly circumscribed, and infiltrative with prominent and crowded tubular and ductal structures. The lesion often involves the full-thickness of the dermis and it may extend to the subcutaneous tissue. Neoplastic structures show marked variation in size and shape, but, in general, the size of the tubules tends to decrease from superficial to deeper areas. The more superficial larger tubules may show luminal papillations. At higher magnification, epithelial cells lining the tubules show abundant eosinophilic or granular cytoplasm and pleomorphic nuclei, some of them in mitosis. Often the cytoplasm of these cells exhibits signs of decapitation secretion. Lumina are often filled with homogenous eosinophilic material, foamy histiocytes and necrotic debris.
Examples of tubular carcinoma may also exhibit focally solid areas with a combination of cribriform or adenoid cystic patterns as additional morphologic expressions. Areas of necrosis en masse are also frequent, but in contrast with adenoid cystic carcinoma, tubular carcinoma shows no deposits of basement membrane material within the aggregations of neoplastic cells and perineural involvement is usually absent. The stroma is sparse.
Before a diagnosis of primary tubular carcinoma of the skin is established, the possibility of cutaneous metastasis from a visceral tubular carcinoma should be ruled out.

Immunoprofile
Tubular carcinoma shows immunoreactivity with low molecular weight cytokeratins and the luminal cells express EMA and GCDFP-15. Expression of CEA is variable {1785,2569}.

Histogenesis
The presence of decapitation secretion and continuity between neoplastic tubules and follicular infundibula are signs of apocrine differentiation. This is further supported by enzyme histochemistry.

Prognosis and predictive factors
Tubular carcinoma of the skin behaves in a highly malignant fashion. Of the 44 examples reported in the literature, neoplasms from 21 patients metastasized and at least 9 patients died as a result of widespread metastatic disease {1705, 1785,2397,2569}.

Microcystic adnexal carcinoma

Definition
Microcystic adnexal carcinoma {861} is a locally infiltrative and destructive low-

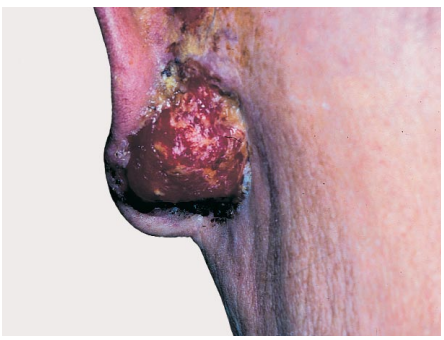


Fig. 3.01 Tubular carcinoma on the retroauricular left region.

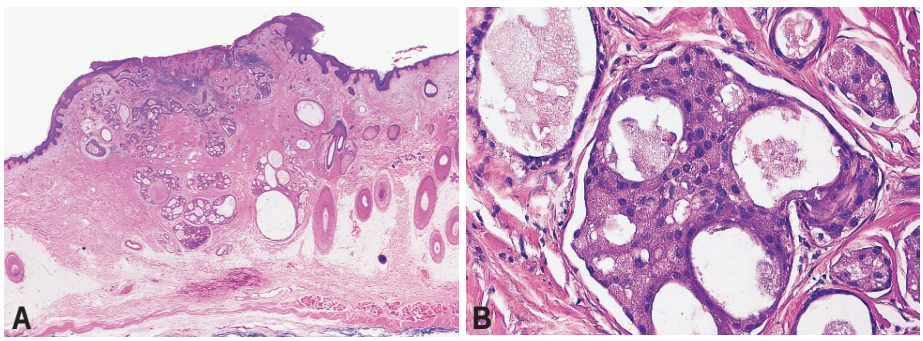


Fig. 3.02 Tubular carcinoma. **A** The neoplasm involves the full-thickness of the dermis and extends into subcutaneous tissue. The stroma is sparse and the epithelium predominates over the stroma. **B** Some neoplastic aggregations of this tubular carcinoma exhibit focally an adenoid cystic pattern.

grade adenocarcinoma differentiated toward ducts. It has little capacity to metastasize.

ICD-O code 8407/3

Synonyms
Sclerosing sweat duct carcinoma {541}, eccrine epithelioma, syringomatous carcinoma.

Clinical features
The carcinoma occurs on the face of adults, more commonly in women. It affects commonly the face {469} and lip, uncommonly other locations, and grows slowly over a period of months to years. It is similar usually to a depressed scar and rarely causes ulceration.

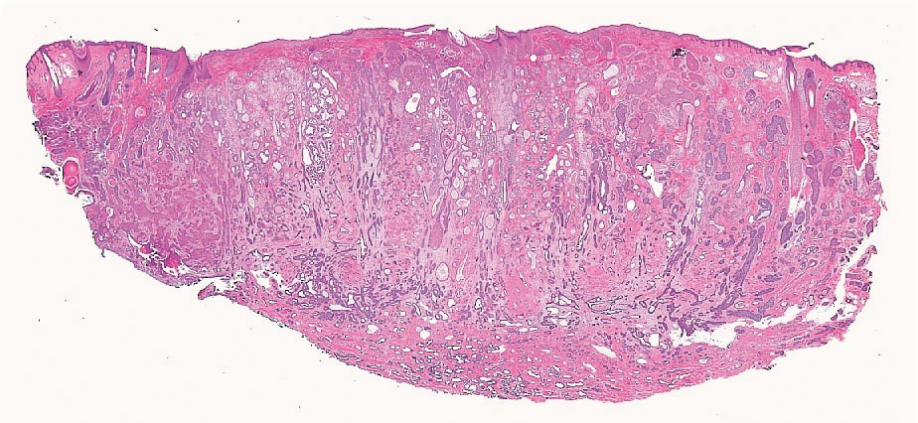


Fig. 3.03 Microcystic adnexal carcinoma. Scanning magnification of microcystic adnexal carcinoma illustrates the zonal effect with solid nests and cysts superficially with complex glands deep.

Histopathology
The classical pattern is that of small, superficial, solid to cystic structures that are similar to small infundibular cysts and ducts. In the middle depth, the lesion is composed completely of small ducts, often in very subtle patterns, frequently with involvement of nerves and perineural spaces. In the deepest areas, “Indian” filing and sclerosis are common findings. Thus, there is a sense that the lesion is stratified from superficial (tubules and cysts) to deep (epithelial cords and sclerosis).
Unusual examples contain sebocytic zones {1862}, and others contain areas similar to follicular sheath, thus suggesting differentiation toward the folliculosebaceous-apocrine unit. In other cases, the lesions are exclusively ductal, causing some authors to designate them as “syringomatous carcinoma” or “sclerosing sweat duct carcinoma” and suggesting that these examples could be derived from eccrine ducts. Some MACs have solid poromatous or clear cell cytology. Cytologically, the lesions are well differentiated, lacking nuclear pleomorphism or mitotic figures. In fact, the finding of nuclear pleomorphism should cause one to reconsider whether the diagnosis of microcystic adnexal carcinoma is correct.

Immunoprofile
There is cytoplasmic staining with AE1/AE3, CK7, and bcl-2. EMA and Ber-EP4 stain in a membranous pattern around ductal cells near the lumen. Alpha SMA and S100 protein stain the

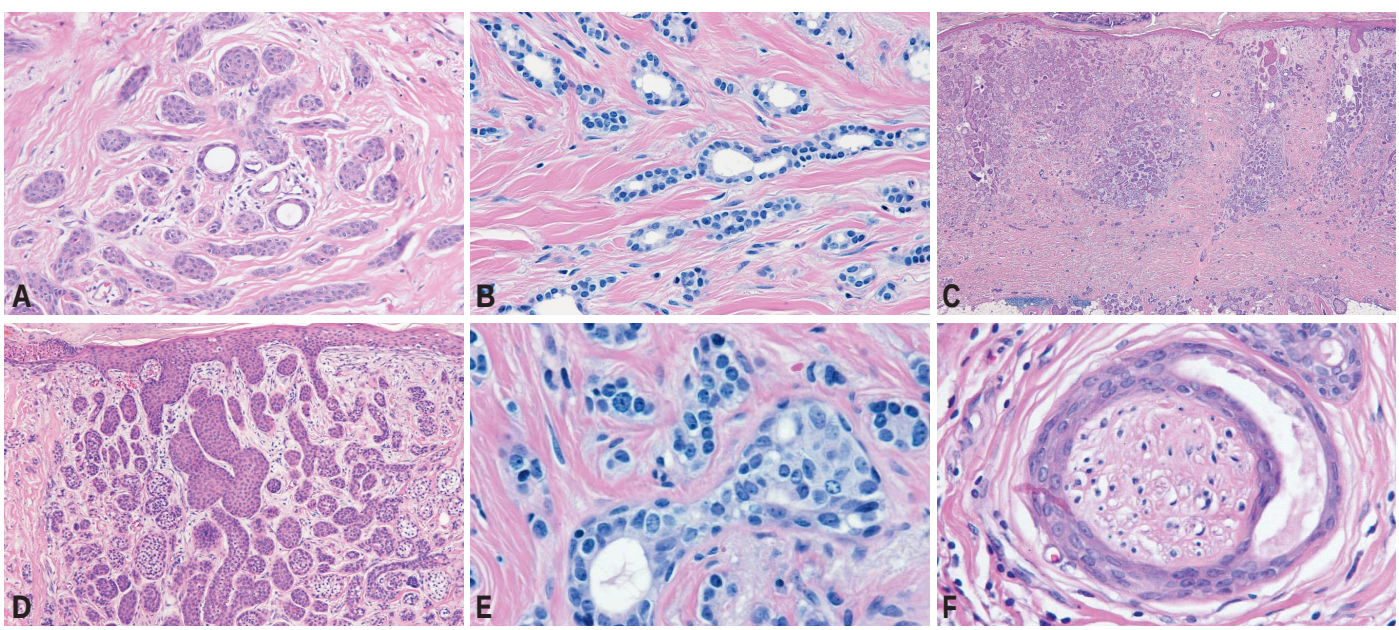


Fig. 3.04 Microcystic adnexal carcinoma. **A** There are a few cysts and solid nests, but no nuclear pleomorphism. The pattern of the lesion helps to recognize it as carcinoma. **B** Not only are there ducts; there are also strands and small nests of neoplastic cells. **C** This example of microcystic adnexal carcinoma again illustrates the zonation pattern, in this case with a few cysts superficially. Note the deep nests that are present in and around the sucutis; not every case will contain compressed ducts exclusively in the deep zones. **D** This example is similar to some poromas. There are solid nests of monomorphous cells as wells as nests of cells with clear cytoplasm. Some authors have designated these lesions "syringomatous" carcinoma. **E** Despite the striking structural patterns of these lesions, most do not contain nuclear pleomorphism. **F** Peripheral nerve, completely encircled by the neoplasm. Note the ductal space.

tubules peripherally. P53 is positive in less than 25% of the neoplastic cells. There is a low proliferative index, as Ki-67 is positive in less than 5% of the neoplastic cells. CK20, c-erb-2, and CD34 are negative {2207}.

Differential diagnosis
The principal differential diagnoses are with superficial biopsies of columnar trichoblastoma (desmoplastic trichoepithelioma) or morpheiform basal cell carcinoma (trichoblastic carcinoma), all of which are CK7 negative. Syringoma is a possible consideration in some cases. Rare examples of metastatic carcinoma to the skin can also mimic it.

Genetics
There is a single report of a 6q deletion {2538}. There is also a report of 2 microcystic adnexal carcinomas, one of which was diploid, and the other, aneuploid, when examined with DNA image cytometry {2437}.

Prognosis
Treatment is surgical, with microscopic control of margins if possible {9}. Radiotherapy has proven successful rarely, but some reported cases have taken on an even more virulent biology after such treatment.

Malignant mixed tumour

Definition
Malignant mixed tumour (MMT) is an exceedingly rare cutaneous adnexal carcinoma with a significant risk for aggressive behaviour and a propensity for metastasis. MMT is regarded as the malignant counterpart of benign mixed tumour {1919} albeit histological diagnosis is foremost based on the biphasic nature of the neoplasm rather than an admixture of benign mixed tumour remnants with carcinomatous tissue {2515}.

ICD-O code 8940/3

Synonyms
Malignant apocrine mixed tumour. Malignant chondroid syringoma.

Epidemiology
MMT represents an exceedingly rare cutaneous adnexal neoplasm which occurs in a wide age range (15 months

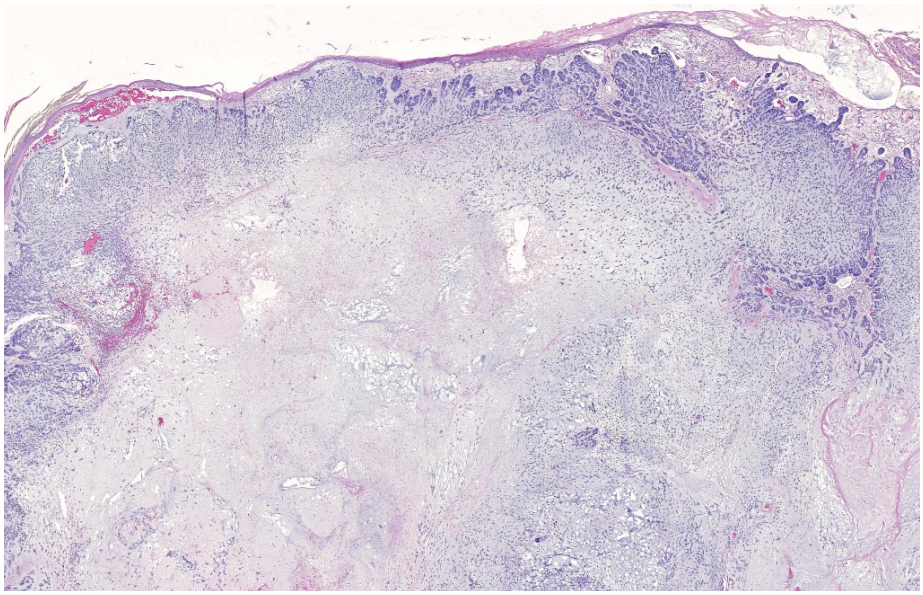


Fig. 3.05 Malignant mixed tumour. Lobulated biphasic tumour consisting of epithelial and mucinous-mesenchymal components. The former predominate at the periphery, while the latter predominate at the center.

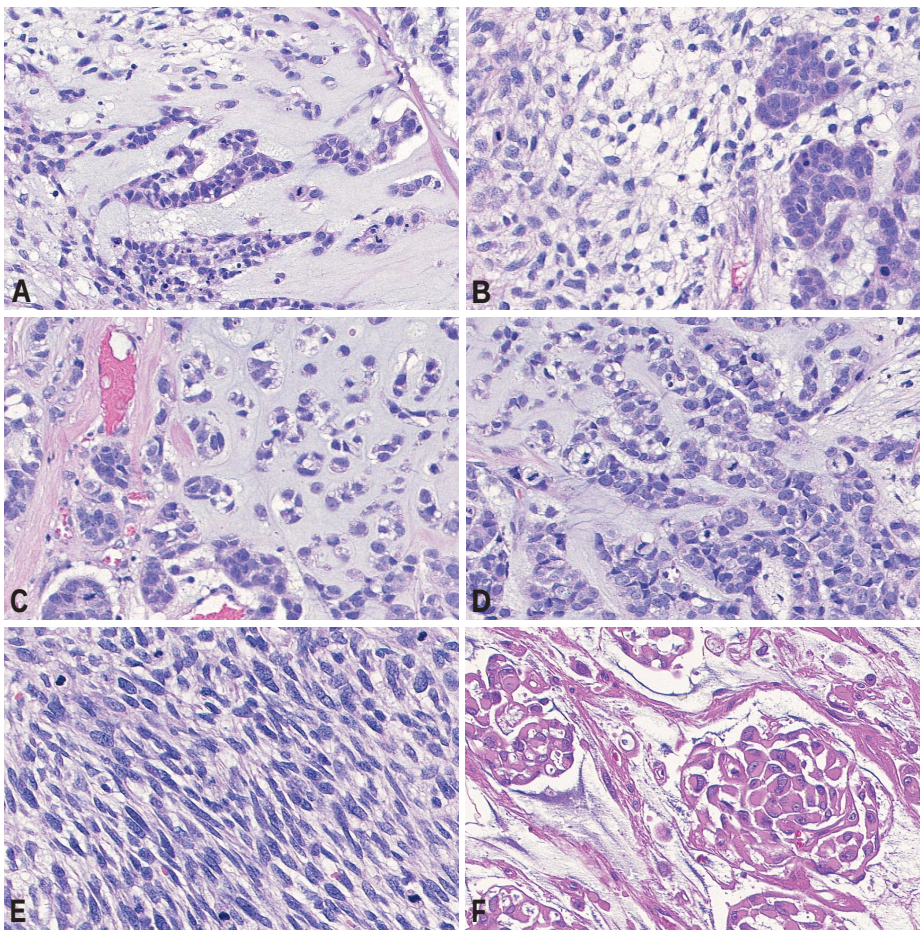


Fig. 3.06 Malignant mixed tumour. **A** Hyperchromatic tumour cells with mitoses. **B** Note variations of cytological differentiation and pleomorphism. **C** Focal zone of tubule formation. **D** Highly pleomorphic tumour lobules with mitoses at the periphery of the tumour. **E** Note the pseudo-sarcomatous pattern with hyperchromatic spindle cells and many mitoses. **F** Nests of plasmacytoid tumour cells amidst a myxoid stroma. Plasmacytoid epithelial differentiation is a hallmark of myoepithelial differentiation.

to 89 years; average 50 years) and is twice more common in women than in men {177,1919}.

Localization
In marked contrast to its benign counterpart MMT shows a predilection for the trunk and the extremities, foremost the hands and feet {177,961,1593,1903, 1919,2177,2377}.

Clinical features
MMT shares most clinical characteristics with its benign counterpart, albeit tumours of the former are much larger at the time of presentation (2-15 cm in diameter). Rarely, rapid growth, ulceration, or pain in a previously indolent skin tumour indicate carcinomatous growth. Most MMT, however, present in a rather bland way with a long history prior to excision. These tumours are well circumscribed and may appear cystic. They are not painful, not ulcerated, and show no distinctive clinical appearance.

Macroscopy
Grossly, most MMT are firm, circumscribed, asymmetrical cutaneous or subcutaneous tumours with a diameter of up to 15 cm. The tumour cut surface may reveal gelatinous material in variable amount {1919}. Because of the infiltrative tumour growth enucleation is not possible.

Histopathology
MMT originates within the dermis or superficial subcutis, and presents as a large, asymmetrical, poorly circumscribed, lobulated biphasic tumour with infiltrative tumour margins and adjacent satellite tumour nodules. Juxtaposed areas of benign and malignant mixed tumour may rarely occur, but are not a prerequisite for the diagnosis of MMT. MMT is composed of both epithelial and mesenchymal components, with epithelial components predominating at the periphery and mesenchymal chondromyxoid elements being more abundant toward the centre {2100}. The chondromyxoid tumour stroma is PAS-negative and consists of hyaluronic acid and sulphated acid mucopolysaccharides {1112}. Stroma ossification is rare {961, 2177}. Epithelial tumour aggregations present as confluent cords and nests of variable size and shape, with interspersed zones of tubule formation. Tubular structures may be either of the elongated apocrine type lined by at least two layers of epithelial cells, with luminal cells exhibiting signs of apocrine secretion and abluminal cells showing plasmacytoid / myoepithelial differentiation, or – more rarely – of the eccrine type showing small round structures lined by a single layer of atypical epithelial cells {961, 1919}. Often, however, MMT consists only of solid aggregations devoid of tubules {928, 1919, 2471}. Epithelial tumour cells may either have a deceptively bland appearance {1112,2100} or show distinctive atypia and pleomorphism of nuclei with a high nuclear-cytoplasmic ratio and numerous mitotic figures {1919}. Zones of necrosis are common. Characteristic epithelial tumour cells are cuboidal with distinctive polygonal or plasmacytoid features {961, 1919}. The latter is considered an indicator of the myoepithelial/apocrine origin of the neoplasm and may be seen as a clue to the diagnosis of MMT {1919}.

Immunoprofile
Tumour cells may show a myoepithelial immunophenotype with coexpression of S100 and cytokeratin {177,976,1839, 2471} and actin expression in a minority of cells {1488}. Spindle cells within the myxoid stroma are vimentin-positive {2117}.

Electron microscopy
Tumour cells exhibit ultrastructural features of myoepithelia with desmosomes and abundant intracytoplasmic filaments {177,1839,2471}. However, ultrastructural studies so far have not presented convincing evidence of either apocrine or eccrine differentiation of MMT {1919}.

Variants
MMT may exhibit deceptively bland cytological features {1112,2100} albeit associated with distinctive architectural criteria of malignancy, e.g. asymmetry, poor circumscription, infiltrative tumour margins, and satellite nodules.
The recently described malignant mixed tumour of soft tissue {1062} shows overlapping histologic criteria with MMT of the skin. The former is considered to be part of the morphological spectrum of myoepithelial tumours of soft tissue.

Differential diagnosis
Extraskeletal myxoid chondrosarcoma consists of non-cohesive elongated tumour nests without ductal or tubular structures. Tumour cells are cytokeratin negative. Mucinous carcinoma and myxopapillary ependymoma show distinct PAS positivity of the extracellular myxoid stroma. Cutaneous myoepithelial carcinoma favours monophasic differentiation with a very discrete myxoid stroma {1585}. MMT and cutaneous myoepithelial carcinoma may fall along a spectrum of tumours with overlapping histologic appearances {1585}.

Histogenesis
MMT probably does not originate in association with its benign counterpart, but develops de novo {1919}. A myoepithelial origin of MMT appears to be most plausible {177,1585,2100}, and MMT may be included in the spectrum of cutaneous myoepithelial neoplasms {1585}.

Prognosis and predictive factors
MMT proliferates in an invasive and destructive fashion, with a high rate of local recurrences and metastases (>50%) into regional lymph nodes, lung, and bone {177,1593}. Death ensues in >25% {177}. However, in >30% MMT neither recurred nor metastasized ("atypical mixed tumour of the skin") {177}. In general, MMT is characterized by its prolonged course {2467}. It is remarkable that non-metastasizing MMTs showed the same histological spectrum as those of proven malignancy {1919}, ranging from bland cytological appearance {961} to marked nuclear pleomorphism and a high mitotic count {2377}. Complete excision before metastasis results in tumour free survival {1919}.

Porocarcinoma

Definition
Eccrine porocarcinoma is a malignant tumour related to the sweat gland duct, showing both intraepidermal and dermal components.

ICD-O code 8409/3

Synonyms and historical annotation
Epidermotropic eccrine carcinoma, malignant eccrine poroma, malignant hidroacanthoma simplex, malignant intraepidermal eccrine poroma, poroepithelioma. The tumour was first described

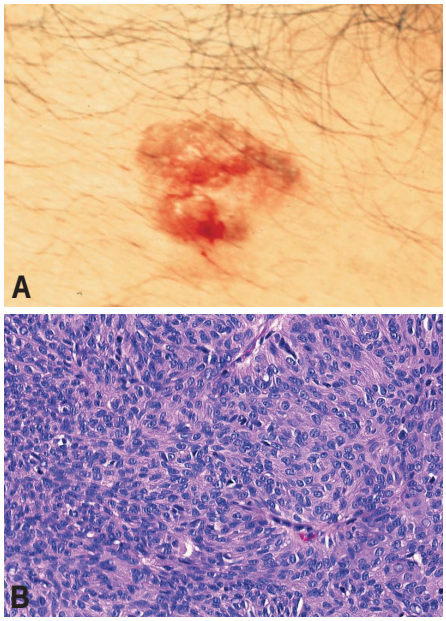


Fig. 3.07 Porocarcinoma. **A** Multinodular ulcerated plaque. **B** Closely arranged polygonal cells with hyperchromasia.

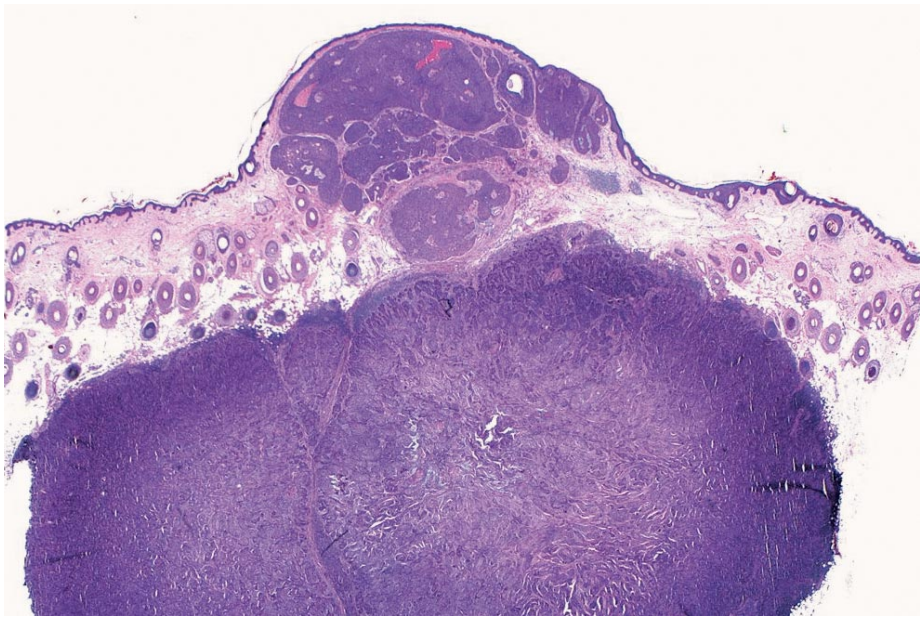


Fig. 3.08 Porocarcinoma. There is a dermal component, partly in apposition with the epidermis, and a large tumour nodule extending into the deep subcutaneous tissues. The lesion is remarkably well demarkated.

by Pinkus and Mehregan in 1963 as epidermotropic eccrine carcinoma {1837}.

Epidemiology

Eccrine porocarcinoma is a rare tumour, predominantly observed in elderly patients with an average age of 67 years {1072}. Women and men are equally affected. The incidence in one large series was 18 per 450,000 cases (0.004%) {1571}.

Etiology

Eccrine porocarcinomas may arise de novo or as a malignant transformation in a pre-existing poroma, hidroacanthoma simplex, or in association with naevus sebaceous {1571,2216,2604}. 18 to 50% of eccrine porocarcinomas are associated with pre-existing eccrine poromas.

Localization

Forty-four to 50% of eccrine porocarcinomas arise on the legs, buttocks, or feet {2216}. The trunk accounts for 24% of the lesions and the head 18% of the lesions with less frequent lesions located on the upper extremities {1072}.

Clinical features

Eccrine porocarcinoma presents as a verrucous nodulo-ulcerative plaque. Clinically the lesions may resemble an eccrine poroma, verruca vulgaris, seborrhoeic keratosis, melanocytic naevus, fibroma, basal cell carcinoma, squamous cell carcinoma, or pyogenic granuloma. Diagnosis is made by skin biopsy.

Histopathology

Eccrine porocarcinoma forms intraepidermal and dermal nests and cords of epithelial cells with pale cytoplasm. The tumour masses form clearly demarcated and frequently rounded nests of polygonal cells with pleomorphic and irregularly-shaped nuclei, prominent nucleoli, and numerous mitotic figures. There is sharp demarcation of the epithelial nests of cells from the adjacent epidermal keratinocytes {1837}. The overlying epidermis may be acanthotic. Both single tumour cells and nests of cells may involve the epidermis in a pagetoid fashion {1359}. Keratinization is usually absent. Intercellular bridging between the tumour cells is inconspicuous. The tumour cells may contain glycogen {2000}. Connection to the intradermal eccrine ducts may be observed. Deep dermal intralymphatic invasion may be observed in up to 15% of the lesions {1952}.

The differential diagnosis includes eccrine poroma, hidroacanthoma simplex, and Paget disease {913}. Eccrine poroma and hidroacanthoma simplex may show focal atypia, but the lesions are symmetrical and well circumscribed. Eccrine porocarcinoma may be differentiated from Paget disease by its relatively sparse epidermal involvement and greater dermal invasion, and the presence of glycogen rather than mucin in tumour cells {913}. In the absence of residual eccrine poroma, it is very difficult to differentiate eccrine porocarcinoma from squamous cell carcinoma {1571}.

Immunoprofile

The tumour nodules stain with antibodies to pan-cytokeratin; tumour cells may stain paler than adjacent epidermal keratinocytes {499,1072}. Ductal structures within the tumour stain strongly positive with CEA and EMA {1359,2216}.

Genetics

Mutation of the p53 gene with loss of its suppressor function has been widely noted with malignant transformation. P53 protein expression has been observed in both eccrine poromas and eccrine porocarcinoma {43,2327}. P16 staining is uniformly negative {914}.

Prognosis and predictive factors

Approximately 20% of eccrine porocarcinomas recur after excision {2216}. Regional lymph node metastasis occurs in 20% of patients, while 12% develop distant metastases {2216}. Patients with metastatic disease have a high mortality rate {170}. Increased number of mitoses,

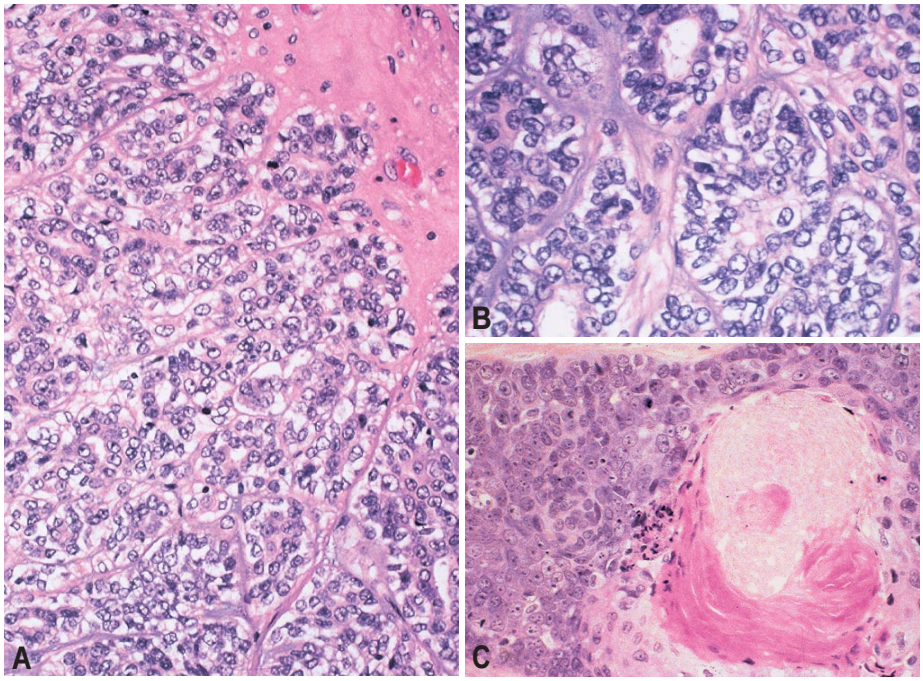


Fig. 3.09 Spiradenocarcinoma. **A** Transitional changes from benign to malignant. Note transitional area with hypercellularity, hyperchromasia and diminished preservation of the usual histologic pattern of a spiradenoma. **B** Spiradenocarcinoma with transitional changes from benign to malignant. Malignant area with occasional residual duct-like structures with clear cell changes and prominent cytologic atypia. **C** Spiradenocarcinoma with unusual cytodifferentiation, squamous "bowenoid" dysplasia.

lymphovascular invasion and tumour depth greater than 7 mm have all been associated with a relatively poor prognosis {1952}.

Spiradenocarcinoma

Definition

Spiradenocarcinoma is a malignant adnexal neoplasm resulting from malignant transformation of a benign spiradenoma.

ICD-O code 8403/3

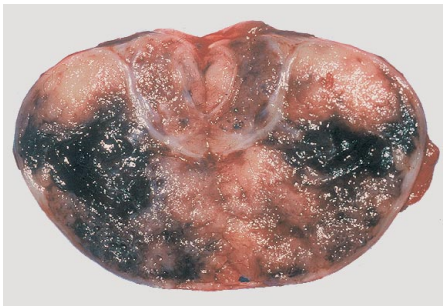


Fig. 3.10 Spiradenocarcinoma. Well-defined, encapsulated mass with areas of solid and cystic changes and haemorrhage.

Synonym

Malignant spiradenoma

Epidemiology

Spiradenocarcinoma is an extremely rare tumour. Approximately 50 well-documented cases have been reported. The tumour mainly affects middle age persons (mean age is 55 yr), and its incidence is similar in both sexes.

Localization

Spiradenocarcinoma can affect any body site, but the most common locations are the upper extremities, followed by the lower extremities, trunk, and the head and neck areas {725,884}.

Clinical features

Typically there is a history of a long-standing lesion that suddenly became enlarged, ulcerated, tender, or changed its colour. The size of the tumour ranges from 0.8-10 cm. The mean duration of a pre-existent lesion is about 20 years before the diagnosis is made {725}. The patient may also have multiple long-standing spiradenomas, which often coexist with cylindromas {89}.

Histopathology

In all cases there are recognizable areas of a benign spiradenoma with the usual well-defined dermal nodules composed of two cell types. Spiradenocarcinoma arising from benign spiradenoma presents two major histologic patterns {89, 725,884}. In one type, there are areas showing gradual transition from benign to a malignant neoplasm. In these lesions the dual cell population of the benign neoplasm imperceptibly merges with the monomorphous cell population of the carcinoma. The usual structural pattern of spiradenoma disappears and is replaced by poorly defined cell nests and cords. Glandular and duct-like structures, as well as hyaline globules, are diminished or may be missing. These changes can be very focal in early lesions and can easily be missed without adequate tissue sampling. In the second type, the malignant changes are adjacent to the spiradenoma without structural or cytological transition. These neoplasms can present a wide spectrum of histologic features including squamous, bowenoid, adenomatous, ductal carcinoma-like, and even histiocyte-like and carcinosarcomatous changes with rhabdomyoblastic or osteosarcomatous differentiation {1391,1548,1958}. In advanced stages of both subtypes, necrosis, haemorrhage, and infiltrative growth can be observed.

Immunoprofile

Spiradenocarcinoma is positive for the majority of cytokeratins, CEA, EMA, and shows a spotty reaction for S-100 protein. Over-expression of P53 has also been reported {89,726,1555,2516}.

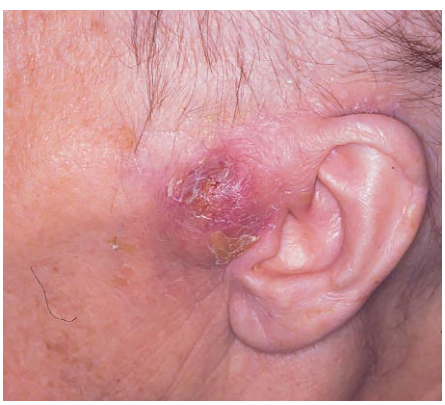


Fig. 3.11 Hidradenocarcinoma involving the left preauricular skin of an elderly male. Note the presence of a retroauricular lymphadenopathy.

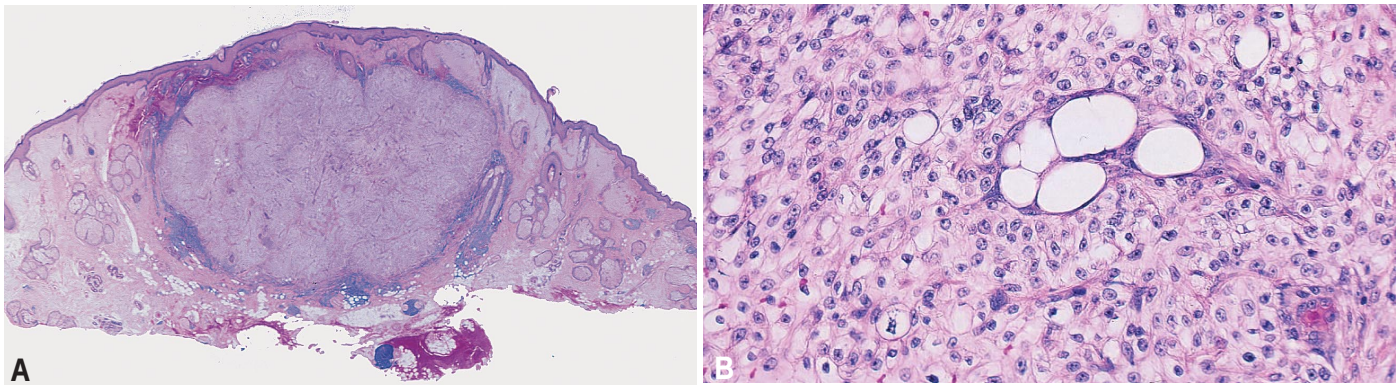


Fig. 3.12 Hidradenocarcinoma. **A** At scanning power the neoplasm appears as a well-circumscribed round nodule involving the full thickness of the dermis. **B** Although the neoplasm is mostly a solid tumour, in some areas there is evidence of ductal differentiation in the form of cytoplasmic vacuoles and small round ducts.

Histogenesis
Theoretically, spiradenocarcinoma can develop de novo. However, the tumour lacks distinctive microscopic features, therefore its histopathologic diagnosis requires recognition of a spiradenoma in association with the malignant changes.

Somatic genetics
TP53 mutations have been identified in carcinomatous portion of spiradenocarcinoma, whereas the spiradenoma part lacked mutations {239A}.

Prognosis and predictive factors
Spiradenocarcinoma is an aggressive neoplasm with multiple local recurrences and eventual widespread metastases, resulting in death. The metastases most often involve lymph nodes, bones, and lungs. Management is primarily surgical; the role of radiation and chemotherapy is still to be defined {1110,1594}.

Hidradenocarcinoma

Definition
Hidradenocarcinoma is the malignant counterpart of hidradenoma.

ICD-O code 8400/3

Synonyms
Clear-cell papillary carcinoma {1436}, clear-cell hidradenocarcinoma {1249, 1470}, malignant clear-cell hidradenoma {578,1237}, malignant clear-cell acrospiroma {992}, malignant eccrine acrospiroma {1741}, primary mucoepidermoid carcinoma of the skin {803, 2497}, nodular hidradenocarcinoma, clear-cell eccrine carcinoma {2300}, mucoepidermoid hidradenocarcinoma {637}, and malignant nodular clear-cell hidradenoma {204}.

Epidemiology
Hidradenocarcinoma seems to be slightly more frequent in women than in men, with the mean age of 50 years, but cases have been also recorded in children {237,477}.

Etiology
Most cases of this carcinoma arise de novo, but some cases are associated with a hidradenoma {237,1013,1237, 1249,1427}.

Localization
This carcinoma may appear in any area.

Clinical features
The neoplasm does not have any distinctive clinical features and usually presents as a slow growing solitary dermal or subcutaneous nodule.

Histopathology
Hidradenocarcinoma is composed of one or several tumour nodules, which vary in size and shape. Focal tubular and ductal structures may be present. Areas of necrosis en masse are common. Usually there is no connection between the epidermis and the tumour, but the surface epithelium may be ulcerated.
The same cell types as seen in hidradenoma are found in hidradenocarcinoma. Atypical cells with pleomorphic nuclei and mitotic figures may be focally prominent, but some tumours lack nuclear atypia. Therefore, the diagnosis can be established only on the basis of architectural characteristics.

Immunoprofile
Neoplastic cells express low molecular weight cytokeratin CAM 5.2 and cytokeratin 19. CEA and EMA decorate the luminal border of ductal structures.

Histogenesis
Most neoplasms have apocrine differentiation, but some show eccrine features.

Prognosis and predictive factors
This carcinoma may metastasize widely and cause death. Of the 76 patients with this carcinoma described in the literature, 22 developed metastases {204,485, 992,1013,1162, 2468}.

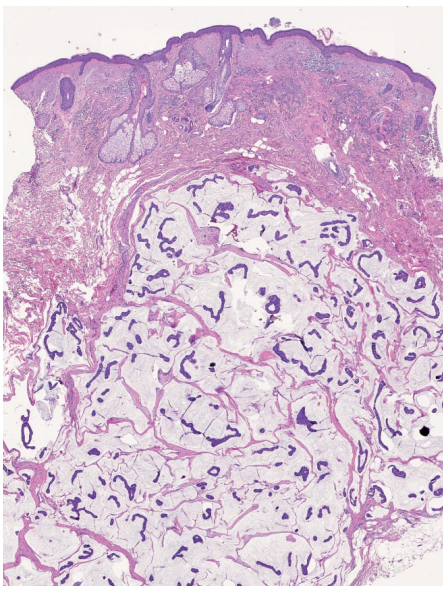


Fig. 3.13 Mucinous carcinoma. Note typical "honeycomb pattern" with small epithelial strands floating in lakes of mucin.

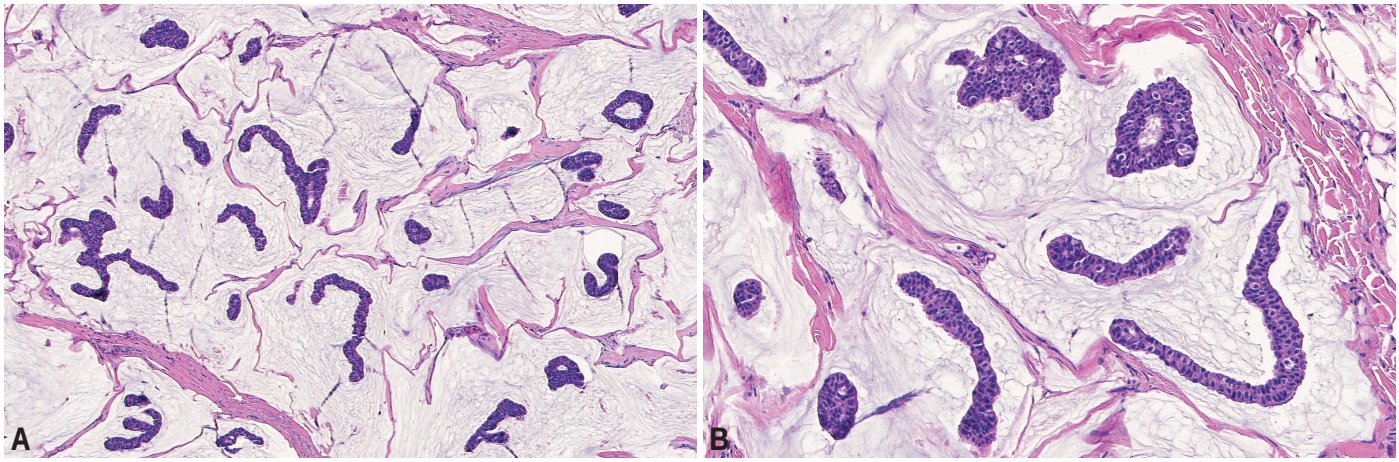


Fig. 3.14 Mucinous carcinoma. **A** Large mucin deposits clearly predominate over epithelial tumour components - in sharp contrast to cutaneous metastasis of mucinous breast carcinoma where epithelial tumour cells predominate and delicate fibrous septa are scarce. **B** Thin strands of epithelial tumour cells with little atypia and very scarce mitoses. Note delicate fibrous septa and incipient tubule formation.

Mucinous carcinoma

Definition

Primary cutaneous mucinous carcinoma (MC) is a rare epithelial neoplasm occurring mostly, but not exclusively, in middle-aged and older patients. Although MC is characterized by destructive local growth and the potential of metastasizing to regional lymph nodes and even beyond them, it generally follows an indolent course with frequent local recurrences. Mucinous carcinoma metastatic to skin from another organ, particularly the breast and gastrointestinal tract, may be histologically indistinguishable from MC.

ICD-O code 8480/3

Synonyms

Primary cutaneous mucinous carcinoma. Colloid, gelatinous and adenocystic carcinoma.

Epidemiology

MC is very rare and occurs mostly between the fifth and seventh decades of life, with an age range between 8 and 84 years. MC is slightly more common in men than in women {1919}.

Localization

Most MC arise on the head, favouring scalp and face with preference of the eyelids {199,305,1212,2217,2319}. Rare sites are axillae, trunk, lower extremities, perianal area and vulva {1919}.

Clinical features

MC presents as a solitary, slowly growing, painless nodular neoplasm. The tumour has a tan, grey, or reddish colour, a smooth surface, and a consistency ranging from soft to firm. Positive transillumination may be a helpful diagnostic tool.

Macroscopy

Grossly, most MC are well-circumscribed, un-encapsulated tumours in the dermis and the subcutaneous fat. Tumour diameters range between 1 and 8 centimetres, albeit larger variants have been reported {1231}. On excision, the tumour appears fixed to the adjacent dermis and does not “shell out” {1919}. The cut surface of excised specimens is gelatinous.

Histopathology

MC presents as an un-encapsulated asymmetric dermal tumour that may extend into the subcutis and even deeper tissue planes {1919}. Tumour satellites may occur at some distance from the main tumour. MC is characterized by large pools of basophilic mucin, which are compartmentalized by delicate fibrous septa, thereby creating a honeycomb pattern. Within the lakes of mucin are small “floating” islands and bizarre clusters of neoplastic epithelial cells, sometimes exhibiting a cribriform arrangement. The epithelial component is denser at the periphery of the tumour. Small glandular or tubular structures containing mucin or showing signs of apocrine secretion occur only rarely. The small neoplastic cells are cuboidal, round, or oval with abundant cytoplasm that may be vacuolated. Nuclei are small with very little atypia. Mitoses are rare. The epithelial mucin is PAS-positive, hyaluronidase and sialinase labile, and consists of non-sulphated acid mucopolysaccharides with sialic acid.

Immunoprofile

Neoplastic cells express low molecular weight cytokeratins, CEA, EMA, GCDFP-15, alpha-lactalbumin, salivary amylase, beta-2-microglobulin. S100 expression is inconstant {199,404,664}. Nuclear expression of oestrogen receptors may be strong, but the pattern of progesteron receptors is more variable {945}. Cytokeratin 20 expression allows differentiation of mucinous gastrointestinal carcinoma metastatic to the skin from primary cytokeratin 20-negative cutaneous MC {664}.

Variants

MC very rarely presents with focal neuroendocrine differentiation {1876}, or with a growth pattern imitating infiltrating carcinoma of the breast {2557}. Epidermotropism of neoplastic cells is unusual.

Electron microscopy

There are less well-differentiated inner pale cells and mucin-containing peripheral dark cells {990}.

Differential diagnosis

Before a diagnosis of MC is established, a primary carcinoma in a breast or another organ (salivary and lacrimal glands, gastrointestinal tract, nose and

paranasal sinuses, bronchi, ovary and renal pelvis) should be specifically sought and excluded as most cases of mucinous carcinoma in the skin are metastatic to it. Histological differentiation between primary cutaneous MC and metastatic mucinous carcinoma to the skin may be impossible, albeit the latter exhibits subtle histological variations {1919}: e.g. larger clusters of cohesive neoplastic cells, less quantities of mucin, a striking predominance of epithelium over mucin, and the absence of delicate fibrous septa that intersect the lakes of mucin.

Malignant mixed tumour of the skin exhibits tubular structures embedded in a myxoid, chondroid, or osteoid stroma, and distinctive polygonal and plasmacytoid neoplastic epithelia. The characteristic honeycomb pattern of MC is not present {1919}.

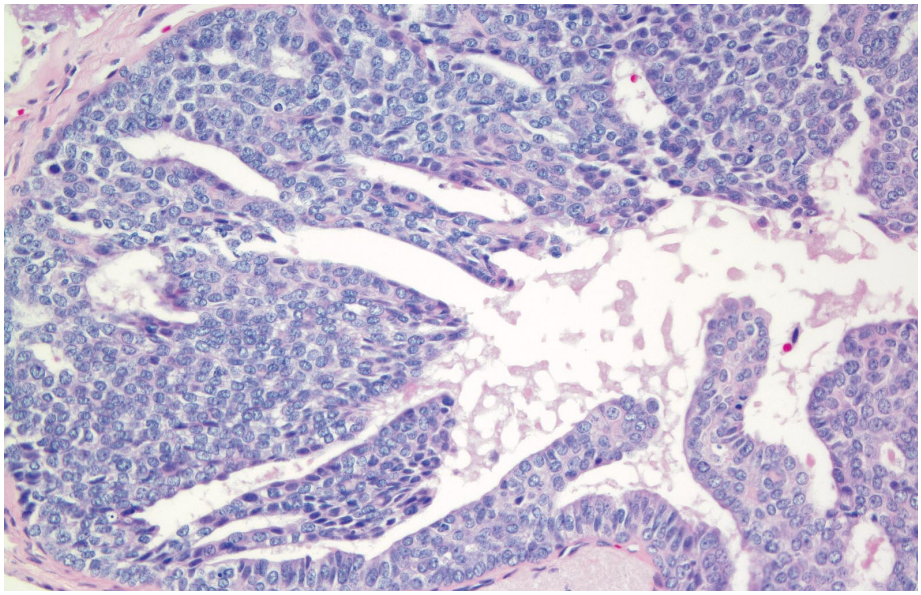


Fig. 3.15 Digital papillary carcinoma. Within the tumour nodules, papillae are formed by heaped up epithelium without stromal cores.

Histogenesis

Histogenesis of MC has not yet been elucidated, but there is strong morphological evidence that MC may be apocrine in nature {1919}.

Prognosis and predictive factors

In contrast to most other sweat gland carcinomas, MC is a low-grade malignant neoplasm with a tendency to persist at the original site but with a low metastatic potential. 10% of the MC so far reported metastasized to regional lymph nodes, but only 3% metastasized in a more widespread fashion {1830}. While multiple recurrences, due to the existence of tumour satellites, are not unusual, death from MC is exceptional {1919}.

Digital papillary carcinoma

Definition

Digital papillary carcinoma is regarded as an uncommon malignant adnexal neoplasm with potential for both recurrence and metastasis.

ICD-O code 8408/3

Synonyms

Aggressive digital papillary adenoma, digital papillary adenocarcinoma

Historically, this group of lesions was divided histologically into aggressive digital papillary adenomas and digital adenocarcinomas {1205}. However, cases originally classified histologically as adenoma developed metastases, demonstrating that histologic parameters do not accurately predict behaviour or allow distinction between adenoma and adenocarcinoma {655}. Therefore, the term aggressive digital papillary adenoma has been abandoned in favour of classification of all such lesions as digital papillary carcinoma.

Epidemiology

Digital papillary carcinomas present almost exclusively on the fingers, toes, palms, and soles. Hands are involved more frequently than feet. There is a male predilection, and most affected individuals are adults in the fifth and sixth decades of life.

Clinical features

Most cases present as a slowly growing deeply seated nodule on a digit. Lesions may be several centimetres in diameter. Pain is occasionally a presenting complaint, and may be related to tumour extension into underlying bone, joint, or nerve. Rarely, metastasis is the first manifestation of disease. Unless underlying bone has been invaded, routine roentgenographic examination may be essentially unremarkable.

Histopathology

Typically, tumours are composed of multi-nodular epithelial aggregates with cystic spaces in the dermis. A cribriform pattern of glands often fills the solid areas of tumour, while papillary epithelial projections are common within cystic spaces. The papillary projections are associated with fibrovascular cores in some areas, while in other areas papillae are formed by heaped up epithelium without stromal support. The epithelium is composed of low columnar or cuboidal cells. Cytologic atypia is usually not marked. Mitoses and necrosis are frequent findings. Cysts contain either necrotic debris or eosinophilic secretory material. Some tumours are well-circumscribed, while others have an infiltrative growth pattern.

Differential diagnosis

The differential diagnosis includes papillary eccrine adenoma, which is usually well-circumscribed, and composed of dilated ducts with a distinct two cell layer and delicate papillae. Malignant adnexal neoplasms such as malignant acrospiroma and malignant spiradenoma are also in the differential, but typically lack the pattern of papillary growth and/or back-to-back glands that characterize digital papillary carcinoma. In addition, malignant spiradenoma usually retains its characteristic two cell population (small basaloid cells and large pale peripheral cells) in at least some foci.

Histogenesis

The occurrence of digital papillary carcinoma on acral sites where eccrine

glands are abundant suggests an eccrine origin of this tumour. Although some cases show decapitation secretion, as is common in apocrine lesions, this phenomenon has also been observed in eccrine tumours. In addition, immunoreactivity for ferritin had led investigators to favour that digital papillary carcinomas derive from eccrine glands {417}.

Prognosis and predictive factors
Complete surgical excision with negative margins is indicated, and sometimes requires amputation. Tumour recurrence is seen in up to 50% of patients, especially in cases without adequate primary excision {1205}. Metastatic disease has been observed in 14% of cases {655}. Metastases may accompany recurrent disease or occur without evidence of local recurrence. Lungs seem a favoured site for metastases, suggesting the probability of haematogenous spread of tumour. Tumour recurrence and metastasis does not seem to correlate with patient age, tumour size, or duration of tumour. Similarly, histologic features such as tumour differentiation, circumscription, or nuclear grade are not predictive of behaviour {655}.

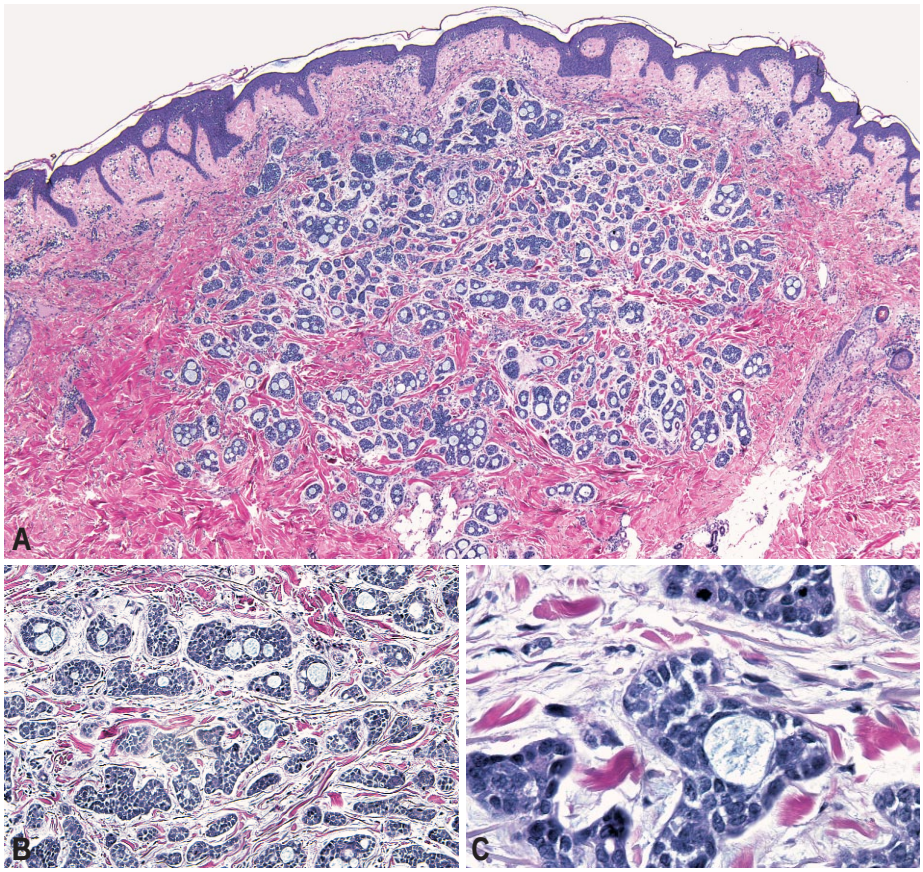


Fig. 3.16 Adenoid cystic carcinoma. **A** Low power view of an adenoid cystic carcinoma demonstrating a poorly circumscribed neoplasm which is composed of collections of basophilic cells arranged in a sieve-like pattern. **B** This photograph highlights the sieve-like pattern with prominent mucin within the glandular spaces. Note also the irregularity of the size and shape of the cellular collections. **C** Mild degree of pleomorphism is seen within the neoplastic cells.

Adenoid cystic carcinoma

Definition
Primary cutaneous adenoid cystic carcinoma is a neoplasm of disputed histogenesis characterized by a cribriform pattern and frequent perineural involvement.

ICD-O code 8200/3

Epidemiology
Over 40 cases have been reported in the literature. Adenoid cystic carcinoma (ACC) affects middle-aged and older individuals (mean age: 58.1) and has a predilection for women {1219}.

Localization
This neoplasm is most common on the scalp (35%) and chest and abdomen (24%) {446,1219}.

Clinical features
Primary cutaneous adenoid cystic carcinoma has an indolent and progressive course. The average duration of the tumour prior to diagnosis is approximately 9.8 years {1219}. The size of the tumour ranges from 0.5-8 cm, with an average size of 3.2 cm. Patients typically present with slowly expanding, firm, skin coloured nodules. Tenderness, ulceration and bleeding are variable and depend on the site of involvement. In the scalp region, alopecia may be an associated finding.

Histopathology
Primary cutaneous ACC is usually poorly circumscribed and is composed of islands, cords and strands of basaloid cells with a glandular, cystic, cribriform and tubular arrangement embedded in a loose fibrous and sometimes mucinous stroma. It typically occupies the mid and deep dermis and may extend into the subcutaneous fat {793}. The epithelial cords have an infiltrative pattern and are not connected to the overlying epidermis. The tumour has a characteristic basophilic appearance on low power due to nuclear hyperchromatism and crowding. Nuclear palisading is absent. The tumour nests are surrounded by a prominent eosinophilic hyaline basement membrane-like material which is periodic acid-Schiff-positive, and diastase-resistant. The cystic spaces often contain abundant mucin {1812}. The mucin is characteristically alcian blue (pH 2.5) positive. The epithelium consists of fairly uniform cells with darkly staining nuclei, which sometimes contain conspicuous, small, solitary nucleoli. Individual tumour cells have a scant amphophilic cytoplasm and an increased nuclear-cytoplasmic ratio. Mitotic activity is usually sparse with 1-2 division figures per high power field (x40) {2514}. Perineural extension, a characteristic feature of salivary gland adenoid cystic carcinoma may be seen, however, not with the frequency seen in other organs.
Before the diagnosis of a primary cutaneous ACC is made, the possibility of a

metastasis from other organs needs to be ruled out on clinico-pathological grounds. The adenoid cystic type of basal cell carcinoma is differentiated by the presence of palisading of the nuclei and stromal retraction.

Immunoprofile
Primary cutaneous adenoid cystic carcinoma stain positively for epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), broad-spectrum keratins, and low-molecular-weight keratins (CAM 5.2). Focal staining with S-100 and vimentin may be seen {210}. Epithelial cells at the periphery of the tumour islands may express actin.

Histogenesis
The eccrine or apocrine origin of this tumour remains disputed. In the past, it has been regarded as an eccrine tumour, although some have been shown to arise from modified apocrine glands {2407}.

Prognosis and predictive factors
An indolent but progressive course is the major characteristic of this tumour. The recurrence rate is high, ranging from 57-70% and therefore wide surgical excision extending well beyond the clinical confines of the tumour is recommended. Recurrences have been reported even with 2 cm margins and may occur many years after excision. For this reason some people favour Mohs micrographic surgery {462}. Only 4 cases have metastasized to the lymph nodes and lungs.

Apocrine carcinoma

Definition
Apocrine carcinoma (AC) is a malignant sweat gland neoplasm with apocrine differentiation. Although an apocrine origin has also been postulated for adenoid cystic carcinoma, hidradenocarcinoma, spiradenocarcinoma, malignant cylindroma, and microcystic adnexal carcinoma, this remains unproven. These entities shall, therefore, be presented separately.

ICD-O code 8401/3

Synonyms
Apocrine adenocarcinoma, apocrine gland carcinoma

Epidemiology
AC is a rare tumour. Both genders are almost equally affected, and there appears to be no racial predilection. {1785,2460}

Etiology
The etiology of AC is unknown. The fact that all patients were over 25 years {824} suggests that full maturity of the apocrine glands is a prerequisite.

Localization
Most AC arise in the axilla and, to a lesser extent, in the anogenital region. Rare locations include the scalp, face, chest, and distal upper extremities. {536,988, 1785,2055,2460} Peculiar variants have been described on the ear (ceruminous gland carcinoma) and the eyelid (Moll gland carcinoma) {2139,2172}.

Clinical features
Because reports are sporadic and may have included a proportion of benign lesions it is difficult to establish a precise clinical profile for AC. Apparently, there are no distinctive features that might enable a confident clinical diagnosis of AC. Most tumours are solitary, but a patient with bilatelal axillary AC has been reported. AC presents as single or multiple, firm or cystic nodules with a reddish or purplish hue of the ovelying skin, sizing between 1.5 and 8 cm {2460}. Ulceration and haemorrhage may be present. The patients' age at presentation ranges from 25 to 91 years, with an average age of 57.9 years {2460}. In many cases, the lesions had been standing for more than 10 years, and even up to 30 years before diagnosis {1650}. Some tumours have arisen within a naevus sebaceous {644}.

Histopathology
AC is typically centred on the deeper dermis and tends to spread into the subcutaneous fatty tissue {1785,2460}. Extension into the epidermis also occurs, occasionally in the form of extramammary Paget disease {1647}. The tumours are usually poorly circumscribed with infiltrating borders. Neighbouring apocrine glands occasionally show in situ carcinoma. {988,2460}. The growth patterns of AC are highly variable, including tubular,

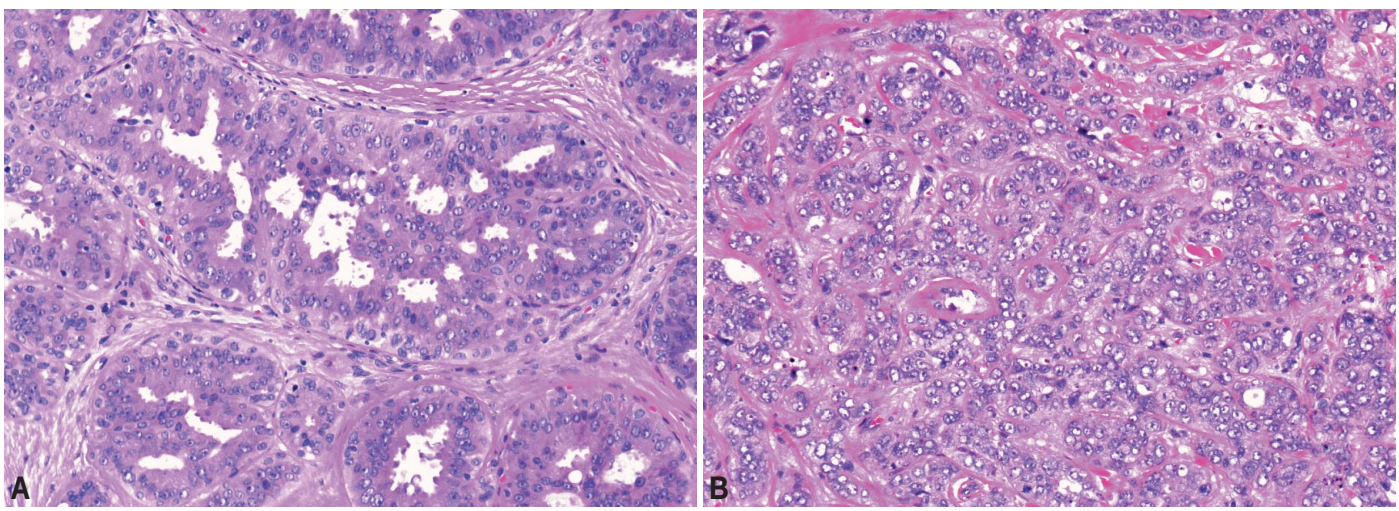


Fig. 3.17 Apocrine carcinoma. **A** Well differentiated cutaneous apocrine carcinoma. Glandular structures with tubulopapillary growth pattern and apical decapitation secretion. **B** Poorly differentiated cutaneous apocrine carcinoma. Micronodular and trabecular growth pattern with hardly any gland formation, hyaline stroma. The cells have scanty amphophilic cytoplasm and contain vesicular nuclei with prominent nucleoli and occasional mitotic figures.

papillary, cystic, cribriform, micronodular, and solid formations {1785,2460}. The cells have abundant eosinophilic cytoplasm and large, round to oval, mostly vesicular nuclei that often contain a single prominent eosinophilic nucleolus {1785}. Intacytoplasmic PAS-positive diastase-resistant granules are characteristic, and intracytoplasmic iron is sometimes demonstrable {988,1785,2139}. A key diagnostic criterion, decapitation secretion in the form of apical snouts {2460} is usually recognizable but may be lacking in poorly differentiated tumours. There is variable mitotic activity, ranging from single mitotic figures in well differentiated tumours and up to 4 mitotic figures per high power field in poorly differentiated carcinomas {2460}. Long standing tumours tend to show increasing anaplasia. The tumour stroma is usually densely fibroblastic or hyaline and may contain prominent lymphoplasmacytic infiltrates.

AC may exhibit focal mucinous carcinoma-like features {2556} or may be composed of signet ring cells {1126}. The latter tumours are mostly located on the eyelid but may occur in the axilla {1343}. Signet ring cell AC show a striking predominance (10:1) in elderly males {1343}.

Immunoprofile

The cells of AC express low molecular weight cytokeratin (CAM5.2), epithelial membrane antigen, carcinoembryonic antigen, cytokeratin15, gross cystic disease fluid protein (GCDFP)-15 {1785} and occasionally S-100 protein {1343, 1785}. Myoepithelial cells, detectable by SMA or CK 5/6 immunostaining, are typically absent {988,2460}.

Differential diagnosis

The main differential diagnosis is with (tubular) apocrine adenoma, and the histologic features that distiguish these two conditions are often subtle. Whilst vascular and neural invasion are diagnostic of carcinoma, stromal invasion is less so and may be difficult to ascertain. Tumour silhouette, cellular pleomorphism and mitotic activity may provide clues to malignancy. As focal squamous differentiation may occur in AC {1785} acantholytic squamous cell carcinoma may have to be considered in the diagnostic differential.

AC is otherwise indistinguishable from apocrine mammary carcinoma metastatic to the skin or apocrine carcinomas arising in ectopic breast tissue in the axilla. Therefore, the diagnosis of primary cutaneous AC rests on a meticulous clinico-pathologic correlation.

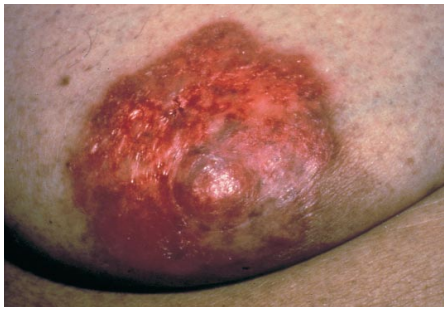


Fig. 3.18 Mammary Paget disease (MPD). Sharply circumscribed erythematous and scaly plaque affecting the nipple and areola.

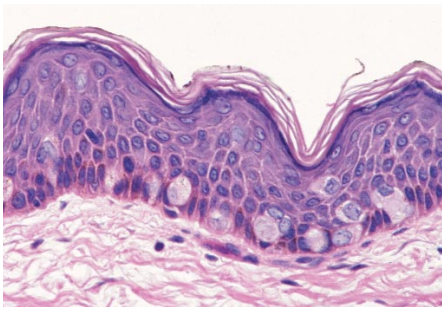


Fig. 3.19 MPD. Cytoplasmic melanin can accumulate in Paget cells and does not indicate melanocytic differentiation.

Histogenesis

AC is thought to arise from preexisting apocrine (sweat) glands {988,1785,2139, 2459}. An interesting alternative origin are the newly described mammary-like sweat glands of the anogenital region, which may also give rise to eccrine tumours {2408}.

Prognosis and predictive factors

The majority of AC are slow growing tumours with a tendency toward a prolonged course. The overall mortality is low, despite frequent recurrences (30%) and metastases to regional lymph nodes (50%) {536,1785,2460}. Wide dissemination and tumour-related deaths have nevertheless been described {437,1785, 2172,2460}. As distant metastases may be a late event in the course of AC a prolonged follow-up is advisable. Reliable predictive factors have not been established.

Paget disease and extramammary Paget disease

Definition

Paget disease of the breast and extramammary Paget disease are intraepidermal adenocarcinomas characterized by large atypical and pale staining cells scattered throughout the epidermis either as single cells or in small clusters. *Mammary Paget disease (MPD)* resembles an eczematous eruption of the nipple and areola, and in almost all cases constitutes skin involvement by an underlying in situ or invasive ductal carcinoma of the breast.

Extramammary Paget disease (EMP) is a scaly erythematous eruption affecting apocrine gland bearing areas of the skin, mainly the female and male genital areas. The majority of cases represent an apocrine adenocarcinoma in situ that has a high recurrence rate and may invade the dermis and then possesses metastatic potential. In a subset of cases EMP is the skin manifestation of an underlying internal malignancy. The skin manifestations of these cases are clinically and histologically indistinguishable from cases not associated with internal malignancy.

ICD-O codes

Paget disease of breast 8540/3

Extramammary Paget disease 8542/3

Historical annotation

In 1874 Sir James Paget first described "about fifteen cases" of a chronic eczematous eruption of the nipple and areola and noted that mammary cancer developed in all patients within two years {1766}. George Thin described the histopathologic features of this condition in 1881. The term Paget disease was coined in 1889 by Radcliffe Crocker when he described a morphologically and histologically similar eruption affecting the penis and scrotum {561}.

Epidemiology

MPD occurs almost exclusively in women. Exceptional cases of men with MPD have been reported {927}. One to two percent of female patients with breast carcinoma develop Paget disease {1971}. Ten to 28% of cases of Paget dis-

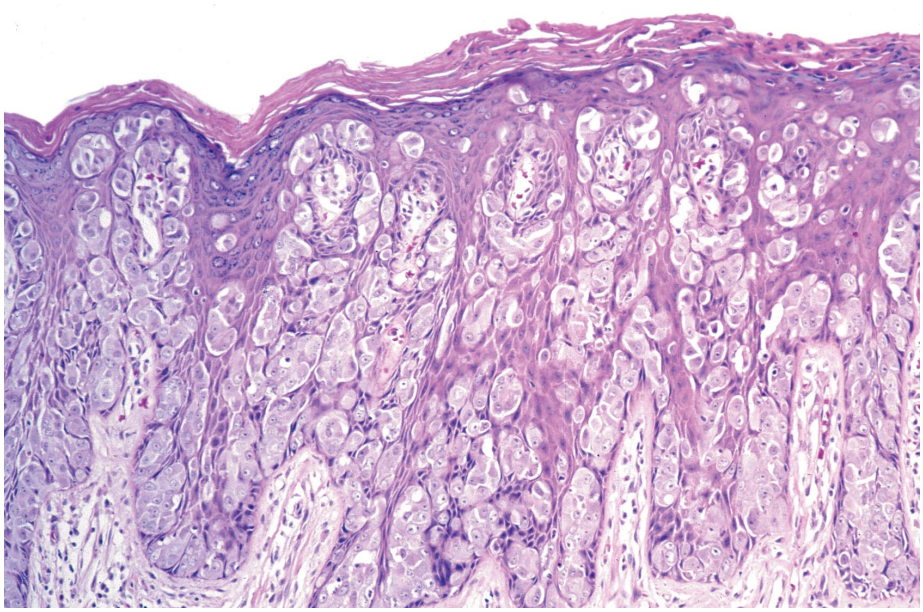


Fig. 3.20 Mammary Paget disease (MPD). Paget cells with large nuclei, prominent nucleoli and abundant pale cytoplasm permeate the entire epidermal thickness.

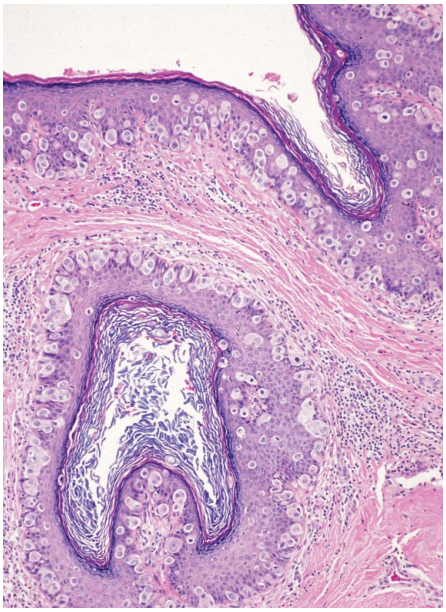


Fig. 3.21 Extramammary Paget disease (EMP). Paget cells often have a propensity for tracking along skin appendages.

ease are detected only on histologic examination of the nipple in a mastectomy specimen, without a clinically apparent lesion {1971}.

No accurate epidemiologic data is available for EMP. It is a rare condition that comprises less than 2% of primary neoplasms of the vulva. EMP occurring in sites other than the vulva is even less common. In genital EMP, women are more commonly affected than men. Most patients are above the age of 60.

Etiology

MPD is almost always associated with an underlying carcinoma of the breast, and the etiology is the same as for breast carcinoma. The inciting factors for primary EMP are unknown. Secondary EMP is an expression of an underlying internal malignancy and the etiology parallels that of the underlying tumour.

Localization

MPD involves the nipple and areola and in advanced cases may extend to the adjacent skin.

EMP involves apocrine gland bearing areas and is most common in the genital area, groin, perineum or perianal region. Axillae, eyelids and external auditory canals rarely may be involved.

Clinical features

Patients who present with MPD initially develop erythema of the nipple and areola. The lesion then progresses to scaly, crusted thick plaques and ultimately to areas of erosion and ulceration. Patches and plaques are almost always unilateral and sharply circumscribed, and sometimes pruritic or painful. In approximately half of the cases a breast mass is palpable. Nipple retraction and serosanguinous discharge may be features of advanced cases with a large underlying carcinoma. Not all patients with MPD have clinical symptoms; 10-28% of cases are detected only on histologic examination in a mastectomy specimen {1971}. The differential diagnosis includes squamous cell carcinoma in situ and eczema. Once a diagnosis of MPD is established the patient needs to be evaluated with imaging studies and other procedures for breast carcinoma. If MPD is associated with a palpable tumour mass, the underlying carcinoma will be invasive in more than 90% of cases. If no tumour mass can be detected clinically, less than 40% of women will have invasive carcinoma.

Patients with EMP most commonly present with pruritus or burning. The skin shows well-demarcated erythematous scaly patches and plaques, which may be ulcerated. Following a diagnosis of EMP the patient needs to undergo thorough examination to rule out an associated internal malignancy.

Tumour spread and staging

MPD without invasive carcinoma on histologic examination is classified as carcinoma in situ (Tis). MPD with a contiguous or non-contiguous invasive component on histology is staged according to the invasive component using the guidelines for staging of breast carcinoma.

Primary EMP is staged either according to the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) or the TNM system of the AJCC (American Joint Committee on Cancer) for vulvar tumours. After a long period of in situ growth EMP can eventually invade the dermis and acquire metastatic potential. Typically, invasive carcinoma associated with EMP first spreads to locoregional lymph nodes and ultimately may develop distant metastases. Secondary EMP is staged according to the criteria for the associated internal malignancy.

Histopathology

On histologic examination MPD and EMP are characterized by neoplastic cells with large nuclei, prominent nucleoli and abundant pale to amphophilic cytoplasm that are scattered throughout the entire epidermal thickness. These cells occur singly and in clusters and often are more numerous in the basal layers of the epidermis. Acinus formation may be present. Paget cells can contain cytoplasmic melanin pigment, a feature that should

not imply melanocytic differentiation. The epidermis is often hyperkeratotic and acanthotic, especially if the disease has been chronic. Particularly in EMP, the tumour cells have a propensity to track along skin appendages. A dermal perivascular lymphohistiocytic infiltrate accompanies the epidermal changes. Paget cells are positive with conventional mucin histochemistry in 40-70% of cases {1297}. In MPD the associated in situ or invasive breast carcinoma is of ductal differentiation in the majority of cases. Lobular carcinoma only rarely gives rise to MPD. Histologically, EMP without an internal malignancy cannot be differentiated from those cases with associated neoplasm.

The histopathologic differential diagnosis includes pagetoid squamous cell carcinoma in situ, superficial spreading malignant melanoma, pagetoid Spitz naevus, clear cells of Toker, pagetoid dyskeratosis, clear cell papulosis, sebaceous carcinoma, intraepidermal Merkel cell carcinoma, eccrine porocarcinoma, cutaneous T-cell lymphoma, Langerhans cell histiocytosis and epidermotropic metastasis.

Immunoprofile

The immunophenotype of MPD closely matches that of the underlying breast carcinoma {511}. Paget cells are practically always positive for low molecular weight cytokeratins (detectable by specific or broad spectrum cytokeratins such as CK7, CAM5.2 and AE1/AE3) and epithelial membrane antigen (EMA), variably positive for polyclonal carcinoembryonic antigen (pCEA) and lack lymphoid markers such as leukocyte common antigen (LCA) and CD3 {1036,1461}. Gross cystic disease fluid protein-15 (GCDFP-15) has been reported in approximately 50% of cases, similar to that of breast carcinoma in general {511}. As in breast carcinoma, reports of S100 reactivity are quite variable, ranging from 0-26% {1757,2548}. Approximately 5% of Paget cases are oestrogen receptor (ER) and/or progesterone receptor (PR) positive {511}.

The tumour cells in primary and secondary EMP are positive for simple cytokeratins (CAM5.2, AE1/AE3), EMA and CEA {1004,1539,1757,2548}. Immunohistochemistry can also suggest the presence of an associated internal malignancy, because primary EMP has the staining characteristics of an apocrine carcinoma and is almost always CK7 positive and gross-cystic disease fluid protein (GCDFP) positive, while CK20 is commonly negative whereas the opposite is true for EMP with associated internal malignancy. The cells in these latter cases are also mostly CK7 positive, but more often express CK20 and do not stain for GCDFP {851,852,1298,1461}. In EMP positive staining with CK20 and lack of staining with GCDFP should prompt an even more thorough evaluation for underlying malignancy.

The most useful keratin markers for MPD and EMP are CAM5.2 and CK7 because they stain >90% of Paget cells but do not react with epidermal or mucosal keratinocytes, a characteristic that makes both antibodies very useful in the evaluation of surgical margins and invasion.

Histogenesis

MPD is almost always associated with an underlying carcinoma of the breast either in situ or invasive. MPD represents the retrograde extension of an underlying carcinoma into the epidermis, either in a contiguous fashion, through spread along the lactiferous ducts or through intraepidermal metastasis. Cases without underlying carcinoma exist but are exceptional {1159}. The etiology of these cases is speculative, but probably they are analogous to primary EMP, representing apocrine adenocarcinomas in situ, derived from Toker cells. Toker cells are cells with bland cytologic features and clear cytoplasm that have been identified by standard light microscopic means in ~10% of normal nipples {1461}. They are derived from lactiferous duct lining cells and preferentially cluster in the epidermis near lactiferous duct ostia. Primary EMP is an apocrine adenocarcinoma in situ that most likely arises from intraepidermal cells of apocrine gland ducts. These cells, analogous to Toker cells of the nipple, have been recently demonstrated in the epidermis of vulvectomy specimens in association with mammary-like glands {2531}. In secondary EMP the disease represents migration of an underlying internal malignancy to the epidermis. Tumours associated with EMP include rectal adenocarcinoma, transitional cell carcinoma of the urethra and bladder, carcinoma of the Bartholins glands, prostate carcinoma, cutaneous adnexal carcinoma and carcinoma of the vagina and cervix.

Prognosis and predictive factors

The prognosis of MPD depends on the size and characteristics of the underlying breast carcinoma. Patients with MPD but without a clinically detectable breast mass have a much better prognosis. In a recent study, 61 patients with MPD and without palpable mass were treated with a cone excision of the nipple-areola complex and radiation therapy. Histologic examination revealed underlying DCIS in 93.3% of patients and Paget disease, only, in 7%. The recurrence rate at a median follow up of 6.4 years was 5.2% (1 patient with DCIS and 3 patients with invasive carcinoma) {242}.

The majority of cases of EMP are not associated with another neoplasm and show a recurrence rate of approximately 30% after surgery, but do not metastasize. Around 10% of patients will develop invasive adenocarcinoma that may progress to metastatic disease {710}. The rate of an associated internal malignancy varies from 15% to 33% and is more common in perianal EMP than vulvar EMP {1024}. In these cases the associated tumour drives the clinical behaviour, treatment and prognosis.

Benign tumours with apocrine and eccrine differentiation

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Hidrocystoma

Definition
Hidrocystomas are cystic proliferations of the sweat glands. They have either apocrine or eccrine differentiation, with the majority being of apocrine nature. Apocrine hidrocystomas are cystic adenomas that arise from the apocrine secretory coil, while eccrine hidrocystomas represent retention cysts of the eccrine cyst duct {607,1919,2047,2188}.

ICD-O code 8404/0

Synonyms
Several and sometimes confusing terms have been used to designate hidrocystomas, to wit: apocrine gland cyst, papillary apocrine gland cyst {1919}, apocrine cystadenoma {1568}.

Epidemiology
Hidrocystomas are relatively rare and account for approximately one per thousand of submitted cutaneous biopsies {607}. They normally present as solitary lesions, however patients with multiple lesions have been observed. Hidrocystomas usually affect middle-aged or older individuals although rare examples have been described in children and adolescents; both sexes are equally affected.

Localization
Hidrocystomas have a predilection for the face and neck, mainly the periorbital area, but may also affect other parts of the body such as the perineum.

Clinical features
Hidrocystomas present as dome-shaped, cystic firm papules or nodules, with a slightly blue colouration. In some cases the content of the cyst is brown or black.

Etiology
The exact cause of hidrocystomas is not known. They have been reported to be exacerbated with high temperatures and to completely disappear with cold weather and atropine therapy {2236}. There is an increased incidence of hidrocystomas in hyperthyroid patients, perhaps related to hyperhidrosis {1270,1673}.

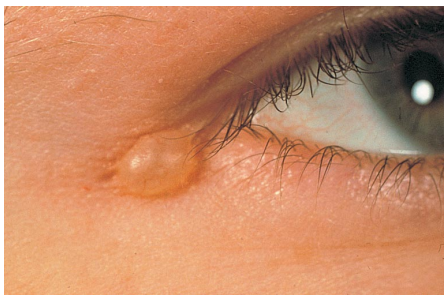


Fig. 3.22 Hidrocystoma presenting as small, dome-shaped lesion on the right side of the face, containing a clear fluid.

Macroscopy
The lesions are of variable size ranging from 0.5-1.0 cm, although lesions of up to 7.0 cm have been reported. Hidrocystomas are usually located in the dermis, but in some cases they may be present in the subcutaneous fat. The cut surface reveals a well-circumscribed, unilocular or multilocular cyst.

Histopathology
Hidrocystomas can be uni or multilocular and are usually lined by a double layer of epithelium. The inner layer contains large columnar cells with eosinophilic cytoplasm which has luminal decapitation secretion, while the outer layer is flat and composed of myoepithelial cells. The term “papillary apocrine gland cyst” has been applied for hidrocystomas with papillary projections of epithelium into the lumen {1919}. Occasionally, hidrocystomas may show a single cystic cavity lined by one or two layers of flattened epithelium as a consequence of the pressure exerted by the contents of the cyst. In this circumstance, distinction from eccrine hidrocystomas, which have a similar lining, becomes impossible {671}.

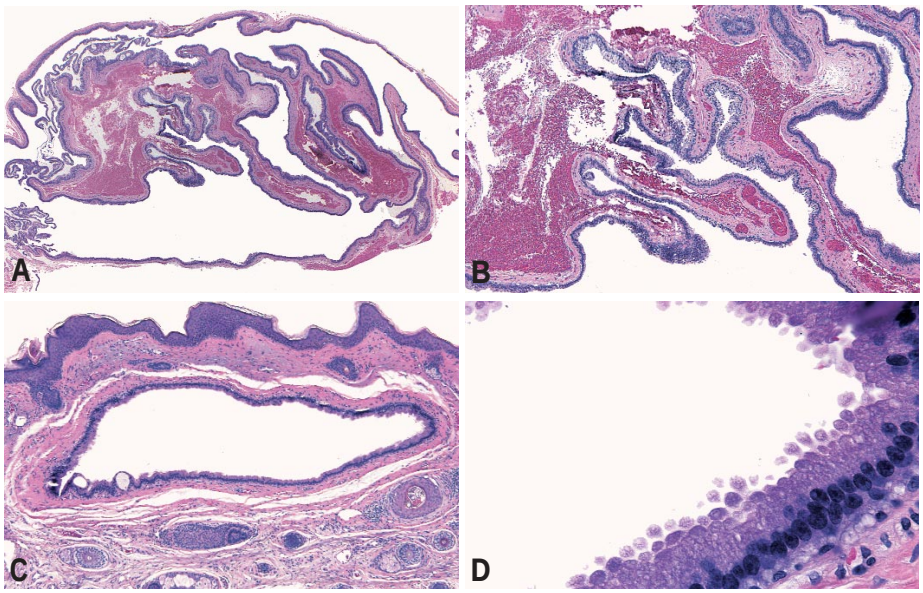


Fig. 3.23 Hidrocystoma, papillary cystadenoma. **A** Example of the so-called "papillary apocrine gland cyst". These lesions are characterized by the presence of papillary projections of epithelium into the lumen. **B** The papillary projections contain a core of connective tissue and are lined by cuboidal epithelium. **C** This picture depicts a typical example of an apocrine hidrocystoma. The lesion is cystic and lined by a cuboidal epithelium. **D** At higher magnification the cyst is lined by a double layer of cuboidal cells with evidence of decapitation and secretion.

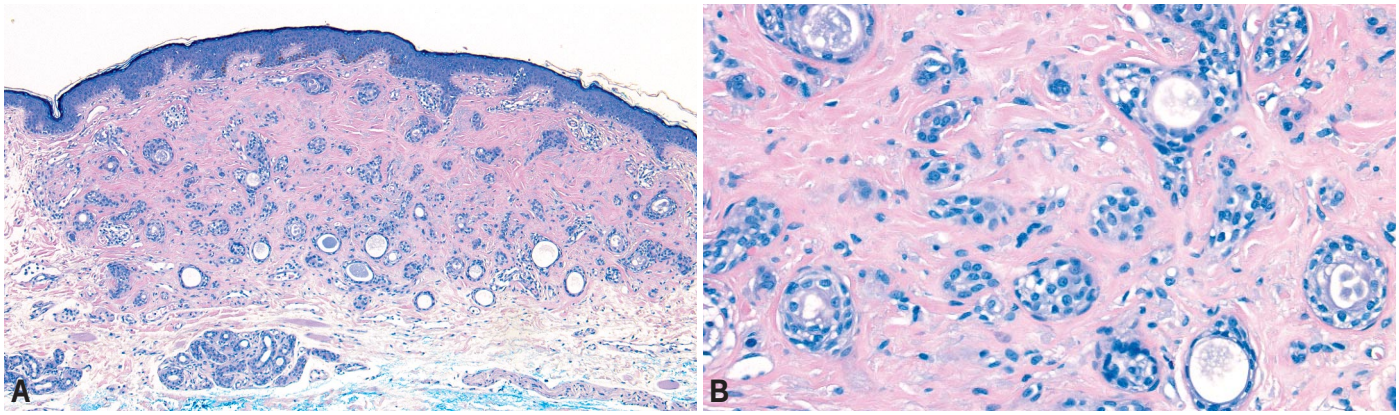


Fig. 3.24 Syringoma. **A** Well circumscribed nodule within the upper dermis. **B** Tubules and cords of uniform epithelial cells in sclerotic stroma.

Immunoprofile
Hidrocystomas express epithelial membrane antigen (EMA) and lysozyme in the cells of the cyst wall; carcinoembryonic antigen (CEA) decorates the luminal cells {1217}. The pattern of cytokeratin expression is variable {607,17444}; there is expression of cytokeratins 7,8,18,19 in the luminal cell layer and cytokeratins 1,5,10,14 in the basal and luminal cell layers.
Smooth muscle actin (SMA) is present in the basal layer {607}. Human milk fat globulin 1 (HMFG) is expressed by the apocrine sweat gland only {607}. S-100 protein is positive in the secretory portion of normal eccrine glands and in the myoepithelial cells of apocrine glands {1678,2358}.

Prognosis and predictive factors
Complete excision is usually curative. Topical atropine or scopolamine has also been used {56,503,2236}. Avoidance of a hot environment or other factors that increase perspiration lessens the severity of these lesions {1668}.

Syringoma

Definition
Syringomas are small benign adnexal neoplasms that are almost always multiple. They are composed of sweat gland epithelium (presumably eccrine) within densely sclerotic stroma.

ICD-O code 8407/0

Synonyms
Eccrine syringoma, lymphangioma tuberosum multiplex.

Epidemiology
Syringomas are common lesions, found more often in women than men. They appear more commonly in Asians than in other races. Syringomas usually arise in adolescence or early adulthood, but are most often biopsied in the 4th decade. Most are sporadic, though some eruptive and disseminated forms may be familial. Syringomas appear to be more common in Down syndrome. A clear cell variant has been associated with diabetes mellitus in many instances {800,2474}.

Localization
By far, the most common sites of involvement are the lower eyelids. Involvement of the upper cheeks is not uncommon. Unusual sites of involvement include the neck, chest, axillae, pubic area, periumbilical region, penis, vulva, hands and forehead. Unilateral linear lesions have been described {552}. Eruptive syringomas are typically numerous, widespread and may appear in crops {1388}.

Clinical features
The lesions are numerous, firm, smooth, dome-shaped, skin coloured or slightly yellowish papules, 1-3 mm in diameter, usually situated in skin of the lower eyelids. Syringomas are rarely solitary.

Histopathology
Syringomas are small lesions, restricted to the upper reticular dermis. They are composed of numerous small solid nests, cords and tubules of epithelial cells within a dense stroma of compactly arranged bundles of collagen, accompanied by relatively few fibrocytes. The epithelial aggregates are usually evenly distributed throughout the lesion. The epithelial cells of syringoma show small nuclei, inconspicuous nucleoli and absent mitotic figures. Cytoplasm ranges from eosinophilic to clear.
The epithelial cells within tubular structures show an inner layer of luminal cells and one or two rows of more peripheral cells. Tubular lumina may be distended, causing flattening of the inner most lining cells. Larger aggregates of cords and nests of cells may exhibit a “comma-like” or “tadpole-like” configuration. The cords, nests and tubules of syringomas branch and anastomose. Milia may be present, and these may rupture producing granulomatous inflammation and subsequent calcification. Syringomas may become confluent. Eruptive syringomas are similar to standard syringomas; however, the stromal component is sometimes less prominent.
In most conventional syringomas some epithelial cells have pale cytoplasm. In some lesions, these cells predominate, and this pattern has been termed “clear-cell syringoma”; it has frequently been associated with diabetes mellitus, but it may be seen sporadically.

Differential diagnosis
Desmoplastic trichoepitheliomas differ from syringomas by being larger, deeper, and composed of epithelial elements that show follicular differentiation. Superficial biopsies of microcystic adnexal carcinoma may greatly resemble syringoma. Microcystic adnexal carcinomas are larger, asymmetric and less circumscribed than syringoma. Virtually all microcystic adnexal carcinomas extend into subcutaneous fat or skeletal muscle, whereas syringomas are restricted to the upper two thirds of the reticular dermis.

Prognosis
Syringomas are benign. Association with or progression towards carcinoma has not been described.

Poroma

Definition
Poromas are benign adnexal neoplasms with terminal ductal differentiation. Although historically considered a neoplasm of eccrine differentiation, poromas can show either eccrine or apocrine lineage.

ICD-O code 8409/0

Synonyms
Eccrine poroma, hidroacanthoma simplex, dermal duct tumour, syringoacanthoma

Epidemiology
Poromas usually present as solitary tumours on acral sites, although they can be seen in virtually any cutaneous location. Most poromas arise in middle age with no sex predilection. Uncommonly, multiple poromas are seen, either limited to palms and soles or in a widespread distribution, for which the term poromatosis has been applied.

Clinical features
Poromas typically manifest as dome-shaped cutaneous papules, nodules or plaques, generally measuring less than 1 cm in diameter. Some lesions are highly vascular and may show a tendency to bleed, particularly on acral sites. Uncommonly, poromas are pigmented. Rapid growth has been reported during pregnancy {920}. Multiple poromas have developed after electron beam therapy for mycosis fungoides {1348} and occurrence in areas of chronic radiation dermatitis has been reported {1802}. Occurrence of poroma within a naevus sebaceous has been documented {1133}.

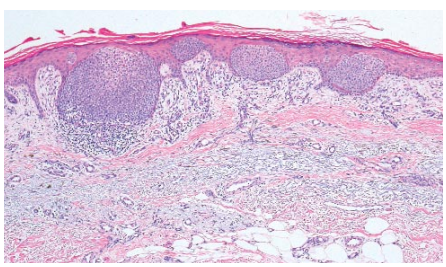


Fig. 3.26 Intraepidermal variant of poroma. There are discrete nests of bland basaloid and cuboidal cells within the epidermis, associated with acrosyringium.

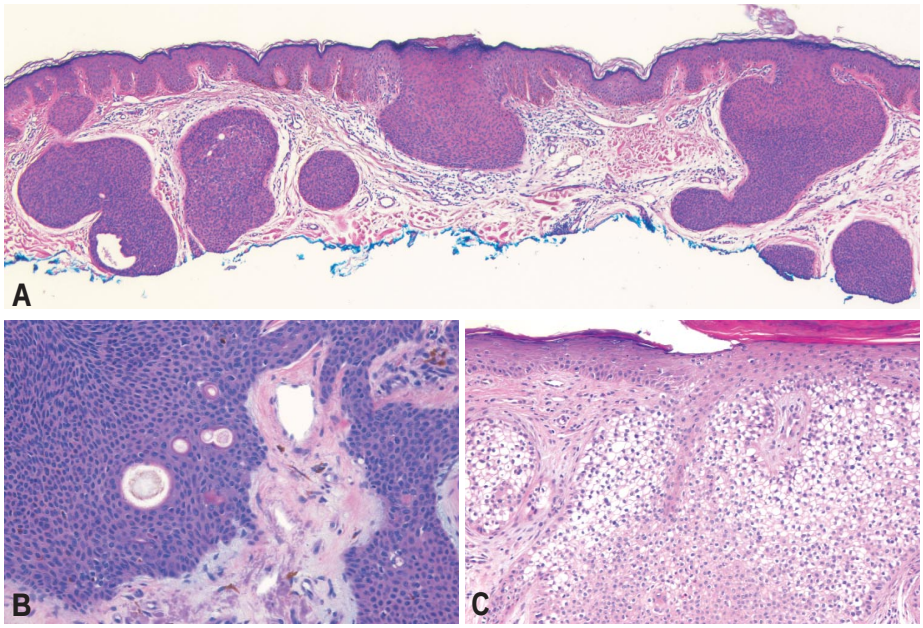


Fig. 3.25 Poroma. **A** Broad tongues of uniform epithelium extend into the dermis from the undersurface of the epidermis. **B** Pigmented poroma illustrating ductal structures and fibrovascular stroma. **C** Clear cell change may be prominent in some poromas.

Histopathology
Poromas are well-circumscribed tumours composed of a proliferation of uniform basaloid, cuboidal cells punctuated by focal ducts and occasional cysts. The epithelial cells of poromas typically extend from the lower epidermis into the dermis in broad columns. The epithelium of poromas is sharply demarcated from adjacent keratinocytes. Nuclei are small and regular, and cytoplasm is modest in amount. The cytoplasm often contains glycogen. Most poromas contain ductal structures lined by PAS positive diastase-resistant cuticles. Small areas of necrosis as well as mitoses are seen in otherwise banal poromas, and are of no prognostic significance. Foci of sebaceous differentiation may be observed. The stroma surrounding poromas is often richly vascular, and may contain granulation tissue.
Architecturally, poromas show a spectrum of change from predominately intraepidermal lesions (hidroacanthoma simplex) to primarily dermal-based neoplasms (dermal duct tumour). Another rare variant has been termed syringoacanthoma, representing a clonal pattern of poroma within an acanthotic epidermis with prominent surface keratinization.

Differential diagnosis
Histologically the differential diagnosis includes seborrheic keratosis, which typically shows keratinization with horn cysts, a more sharply demarcated lower border, and absence of ductal structures. Basal cell carcinoma may sometimes be considered histologically, but shows more obvious peripheral palisading, nuclear variability, and little or no glycogen.

Histogenesis
Poromas may show evidence of either eccrine or apocrine differentiation {970}. Immunohistochemical studies reveal that poroma cells express a cytokeratin phenotype similar to basal cells of the eccrine ducts in some cases {2466}. The absence of myoepithelial cells also suggests differentiation toward the excretory (ductal) component of sweat glands. Occurrence of poromas within follicular sebaceous lesions such as naevus sebaceous, and presence of sebocytes within poroma, implicates origin from apocrine glands in some cases {662, 970}.

Genetics
Some cases of poromatosis have been

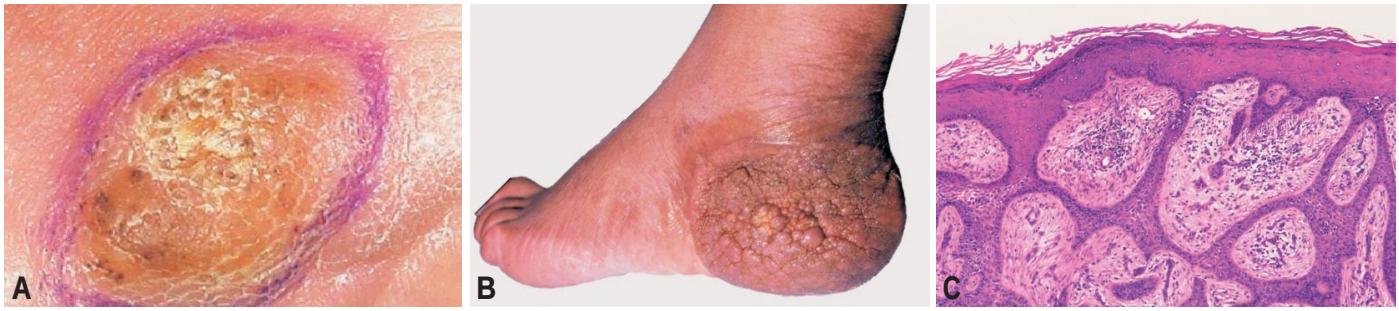


Fig. 3.27 Syringofibroadenoma. **A** Clinical features of the verrucous, solitary type of syringofibroadenoma; a nodule localized on left sole of a 75-years old female, lasting for three years. **B** Eccrine syringofibroadenoma (Mascaro). Presents in many cases as a verrucous plaque. **C** Eccrine syringofibroadenoma (Mascaro). There are branching cords of small keratinocytes attached in multiple foci to the undersurface of the epidermis

associated with hidrotic ectodermal dysplasia {2519}. Rare cases of poroma have occurred in the setting of naevoid basal cell carcinoma syndrome {904}. Studies of p53 protein have shown high expression in some poromas as well as in some porocarcinomas, but staining is not correlated with duration of tumours {43}. Therefore, while p53 mutation may be involved in progression of some poromas to porocarcinoma, other oncogenes or factors are also likely play a role in malignant transformation of poromas.

Prognosis
Poromas are benign and simple excision is curative.

Syringofibroadenoma

Definition
Syringofibroadenoma is a rare benign eccrine tumour with anastomosing strands and fibrovascular stroma, first described by Mascaro {1529}. Multiple lesions of syringofibroadenoma are referred to as eccrine syringofibroadenomatosis {456,2189}.

ICD-O code 8392/0

Synonyms
Eccrine syringofibroadenoma {663}, eccrine syringofibroadenomatous hyperplasia {1721}, eccrine syringofibroadenomatosis {456,2189}, acrosyringeal adenomatosis {950}.

Epidemiology
Syringofibroadenoma is rare, with about 75 reported cases. It occurs primarily in older adults.

Localization
Most of syringofibroadenomas arise on acral areas {498,685,769,2248,2313, 2344,2399}.

Clinical features
The most common clinical presentation is solitary, often verrucous papules or nodules {1529,2248,2313}. Unusual presentations include large plaques, linear lesions, and disseminated tumours {1259,2189,2248}.

Etiology
Occasionally, syringofibroadenoma can be associated with other entities, both inflammatory and neoplastic, including bullous pemphigoid {1720,1721}, lichen planus {780}, ulcers {1092,2399}, squamous cell carcinoma {1399}, sebaceous naevus {1719}, and chronic lymphoedema {806}. Based on the latter association and the presence of fibrous stroma, some authors consider syringofibroadenoma as a hyperplasia rather than a neoplasia {779,780,806,1092,1399,1719, 1720}. It may be associated with Schöpf-Schultz-Passarge syndrome {2189}, an autosomal dominant syndrome with palmoplantar keratoderma, hypodontia, and eyelid hidrocystomas, whose genetic aberration has been localized to chromosome 13q {1259}.

Histopathology
Syringofibroadenoma is characterized by multiple anastomosing cords and strands of monomorphous cuboidal cells {26,1529}. The epithelial cords extend usually into the mid-dermis, and are embedded in a loose fibrovascular stroma. Rarely, a clear cell variant has been observed {781,2415}.

Immunoprofile
Light microscopy usually leads to a specific diagnosis. The tumour cells are usually positive for both keratin 6 and 19 as well as filaggrin {1108,1304,1742,1745, 2314}.

Prognosis and predictive factors
Syringofibroadenoma is a benign condition, and solitary lesions are cured by complete excision, while the treatment of multiple lesions is dependent on the size and location. Cases of syringofibroadenoma with foci of atypical squamous cells have also been described {255, 1215}.

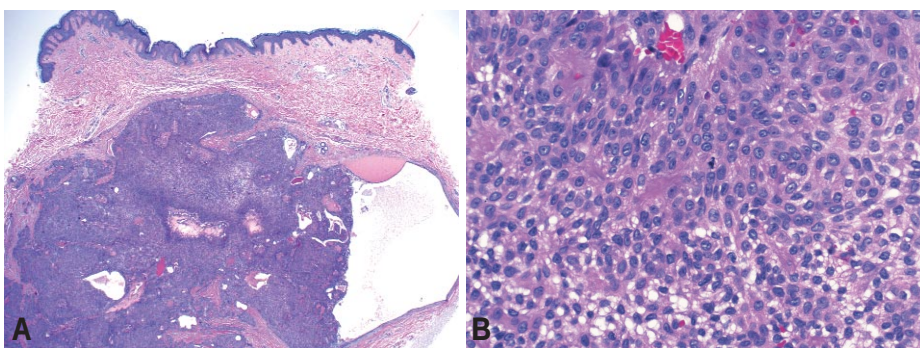


Fig. 3.28 Hidradenoma. **A** There is a multinodular solid and cystic proliferation of monomourphous adnexal keratinocytes. **B** Areas with cytoplasmic pallor are common ('clear cell hidradenoma').

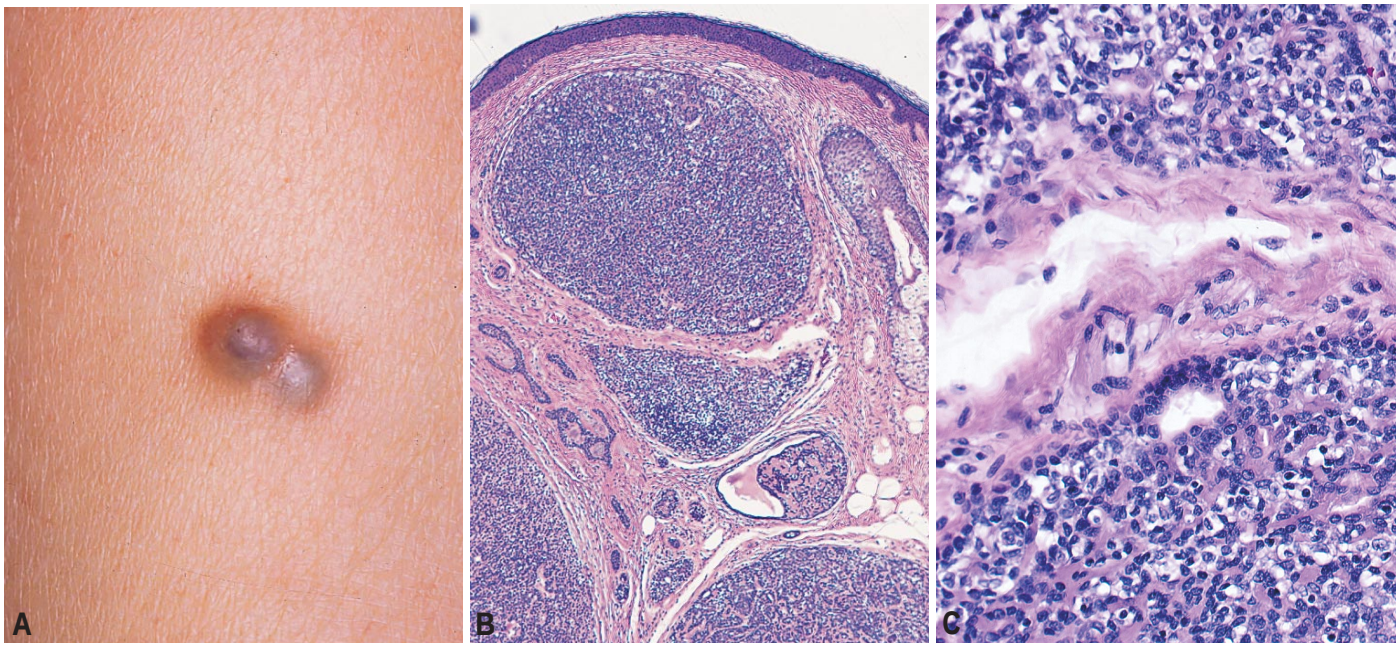


Fig. 3.29 Spiradenoma. **A** A pigmented and painful nodule on the posterior aspect of the arm. **B** These aggregations of neoplastic cells show round shape and smooth borders. **C** At higher magnification, numerous lymphocytes are seen scattered within the nodules of neoplastic epithelial cells. There are two distinct populations of neoplastic epithelial cells, dark and pale. Dark cells are small, basaloid cells with hyperchromatic nuclei and pale cells are larger with vesicular nuclei and ample pale cytoplasm.

Hidradenoma

Definition
Hidradenoma is a benign adnexal neoplasm, closely related to poroma, that displays a limited degree of ductal differentiation. While historically considered eccrine, recent evidence suggests that hidradenoma can be either apocrine or eccrine {825,1543}.

ICD-O code 8402/0

Synonyms
Clear cell hidradenoma, nodular hidradenoma, poroid hidradenoma, acrospiroma, solid-cystic hidradenoma {825,980,1374}.

Epidemiology
Hidradenomas are sporadic with no sex predilection. Most develop in adults, but childhood onset has been documented {715,1652}. Hidradenoma can also arise as a secondary neoplasm with naevus sebaceous.

Localization
Hidradenomas commonly develop on the scalp, trunk, and proximal extremities, and rarely on the hands and feet. Eyelid lesions have also been noted {911}.

Clinical features
Hidradenomas lack any distinctive clinical features, presenting as skin-coloured to red-brown nodules.

Histopathology
Hidradenoma is a mostly dermal neoplasm with a nodular, circumscribed pattern at scanning magnification. Sometimes an epidermal attachment can be identified. The intervening stroma is often sclerotic and may be highly vascularized, with ectatic vascular channels. Hidradenoma is composed of several types of cells:
Clear or pale cells, which contain abundant glycogen, and show distinct cell membranes {578}. The number of clear cells varies from lesion to lesion. When these cells predominate, the name clear-cell hidradenoma is appropriate {2544}.
Squamoid cells are polygonal with a central vesicular nucleus and eosinophilic cytoplasm, and often are arranged in whorls {1774}.
Mucinous cells are the least common component. They are large cells with fine basophilic granular cytoplasm. Cuboidal or columnar cells line the tubules and show evidence of apocrine differentiation {1427}.
Transition between different types of cells is frequent. The cells are arranged in sheets, punctuated by ducts and glandular areas which may show apocrine differentiation. Hybrid lesions including compact poroid cells with prominent ductal differentiation have been referred to as poroid hidradenomas.

Prognosis
Complete excision is curative.

Spiradenoma

Definition
Spiradenoma is a benign dermal neoplasm that can show either eccrine or apocrine differentiation, and significant morphologic overlap with cylindroma.

Historical annotation
Chandeluz, in 1882, probably first described this tumour {765}. Unna first coined the term spiradenoma. In 1956 Kersting and Helwig published the classic paper on spiradenoma in 136 patients {1250}. Additional series of spiradenoma have since been published {12,1496}.

ICD-O code 8403/0

Localization
Most spiradenomas appear on the face

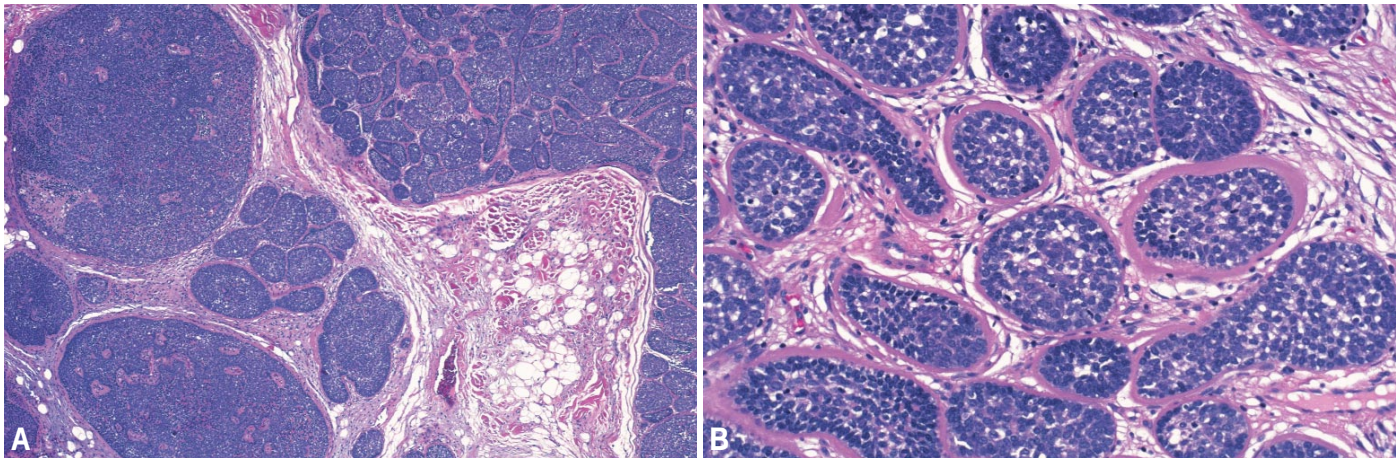


Fig. 3.30 Cylindroma. **A** There is a puzzle-like array of basaloid cells with relatively sharp circumscription of individual nodules. The larger nodules on the left show trabecular internal structure, suggesting overlap with spiradenoma. **B** The nests are outlined by a thick rim of PAS-positive and diastase-resistant basement membrane material.

and upper trunk, but they can also affect other sites.

Clinical features

Usually, spiradenoma appears as a solitary, well-circumscribed, firm nodule, measuring usually less than 1 cm, but giant variants {546} and multiple lesions have also been described {1725}. Unusual cases show multiple spiradenomas arranged in a zosteriform linear pattern {926,2162}. Spiradenoma appears in adult life, although there are also reports of congenital cases {2091}, and in one patient spiradenoma developed within a naevus sebaceous of Jadassohn {2154}. Pain is one of the main clinical characteristics of spiradenoma {926, 2091,2154}. The mechanism of pain or tenderness in spiradenoma is not clear.

Histopathology

At low power magnification, spiradenoma appears as a solid neoplasm composed of a single or few nodules of basaloid cells. These aggregations are round with smooth borders and involve the full thickness of the dermis, sometimes extending into the subcutaneous fat. Often, the intervening stroma is oedematous with ectatic vessels {546}. Dilated vessels rimmed by sclerosis have been interpreted as “ancient” changes due to long-standing lesions {2229}.

Another characteristic finding is the presence of abundant lymphocytes scattered within the tumour nodules. At higher magnification, two distinct populations of neoplastic epithelial cells can be seen, dark and pale. Dark cells are small, basaloid cells with hyperchromatic nuclei located at the periphery, whereas pale cells, which are larger with vesicular nuclei and ample pale cytoplasm, tend to be near the centre of the clusters.

Tubules lined by two rows of epithelial cells may be found within the tumour nodules. A characteristic feature is the presence of eosinophilic PAS positive globules throughout the entire neoplasm, sometimes surrounded by neoplastic cells in pseudorosette fashion. These globules are composed of basement membrane material. Sometimes the stroma shows striking oedema.

Spiradenoma in children may show a different histopathologic pattern. The neoplastic cells appear more immature, making the distinction between clear and dark neoplastic epithelial cells difficult, and the neoplasm may be misinterpreted as a mesenchymal neoplasm {1206}.

Spiradenoma and cylindroma show significant morphological overlap. In some patients with multiple lesions, some tumours show features of spiradenoma, and others features of cylindroma. This supports the notion that spiradenoma and cylindroma are closely related, probably representing two morphologic expressions of the same basic neoplastic process {846,2280}.

Immunoprofile

The tumour cells express cytokeratins, and the tubular structures are CEA positive {1801,2465}. Inflammatory cells scattered within the neoplastic aggregations have been identified as abundant T lymphocytes and Langerhans cells.

Histogenesis

The histochemical and immunohistochemical studies have not clarified the histogenesis of spiradenoma. The frequent association of spiradenoma and cylindroma, a likely apocrine neoplasm, and the sporadic association of spiradenoma with neoplasms with follicular differentiation such as trichoepithelioma {2500}, support an apocrine line of differentiation for spiradenoma on the basis of the common embryologic origin for the three elements of the folliculo-sebaceous-apocrine unit. This is furthermore supported by some examples of spiradenoma that show decapitation secretion in the cells lining the luminal border of the tubular structures. Therefore, the qualifying term of “eccrine” that almost invariably is applied to spiradenoma is inaccurate.

Prognosis and predictive factors

Spiradenoma is a benign neoplasm. Because of the sharp demarcation of the tumour from the surrounding stroma, excision is easily accomplished. Several examples of carcinomas arising in long-standing spiradenomas have been described. In those instances, enlargement of a nodule that had been stable for many years seems to be the sign of malignant transformation {89,240,539, 699,884,2602}. It appears to be accompanied by increased expression of p53 protein {239}.

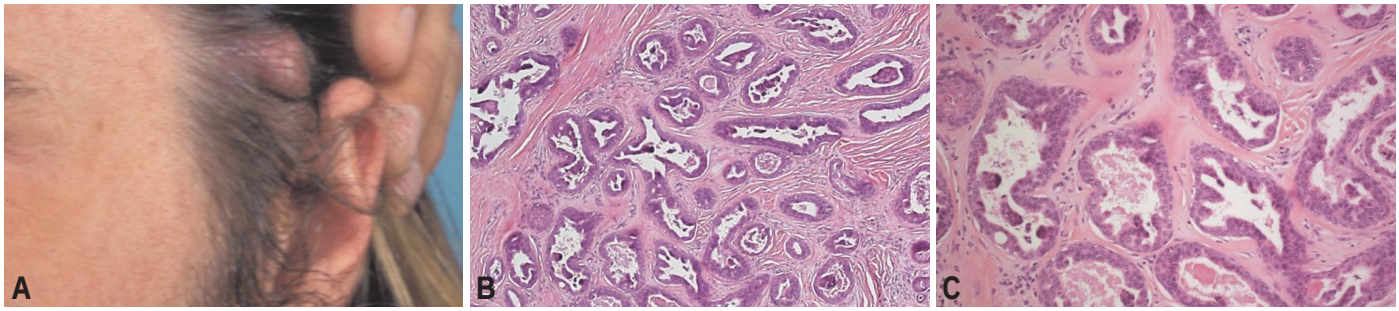


Fig. 3.31 Tubular adenoma. **A** A skin-coloured smooth surfaced nodule on the left parietal scalp. **B** Multiple irregularly shaped tubular glandular structures within a partly sclerosed stroma. **C** Banal appearing tubular glandular elements lined by a double layer of epithelial cells within a sclerosed stroma. The peripheral layer is cuboidal in appearance and the luminal layer demonstrates decapitation secretion. The lumina are filled with cellular debris and granular eosinophilic material.

Cylindroma

Definition
Cylindroma is a relatively undifferentiated benign adnexal neoplasm with a mosaic microscopical pattern. Cylindroma commonly occurs as a hybrid with spiradenoma, an event that has been referred to as cylindrospiradenoma or spiradenocylindroma {301,846,1543,1600}.

ICD-O code 8200/0

Synonyms
Cylindrospiradenoma {301}, spiradenocylindroma {1600}

Epidemiology
Cylindromas may be solitary or multiple, arising on a sporadic basis or as part of Brooke-Spiegler syndrome. There is no sex predilection.

Etiology
The etiology is unknown. A link to chromosome 9 seems likely for multiple spiradenomas and cylindromas in the context of the Brooke-Spiegler syndrome, as the gene has been mapped to 9p21 {951,1538}.

Localization
The vast majority of cylindromas occur on the scalp or face, especially in the vicinity of the ear. Uncommonly, cylindromas develop on the trunk or proximal extremity.

Clinical features
Cylindromas are typically smooth, dome-shaped hairless red-brown papules and nodules. Extensive scalp involvement can create clinical morphology resembling a headpiece (“turban tumour”). Cylindroma can rarely be found as a secondary neoplasm within naevus sebaceous.

Histopathology
Cylindroma is a mostly dermal and sometimes subcutaneous neoplasm with a multinodular, circumscribed pattern at scanning magnification. Individual nodules are composed of mosaic nests of undifferentiated basaloid cells with small darkly-staining nuclei and scant cytoplasm; individual nests fit tightly and neatly within larger nodules in a pattern that has been likened to that of a jigsaw puzzle. The nests of cylindroma are commonly surrounded by a rim of densely eosinophilic PAS-positive basement membrane material, and the nests are also punctuated by small round “droplets” with similar staining qualities. Hybrid lesions with areas of cylindroma and spiradenoma in juxtaposition are not uncommon {301,846,1543,1600}.

Immunoprofile and histogenesis
Refer to the previous chapter on spiradenoma.

Prognosis and predictive factors
Simple excision is usually curative. Malignant transformation is extremely uncommon.

Tubular and tubular papillary adenoma

Definition
Tubular apocrine adenoma is a benign dermal adnexal neoplasm demonstrating apocrine differentiation that typically occurs in a broad age group of women on the scalp region.

ICD-O code
Tubular adenoma 8211/0
Tubular papillary adenoma 8263/0

Synonyms
Apocrine adenoma, tubular adenoma, tubulopapillary hidradenoma, papillary tubular adenoma

Epidemiology
Tubular apocrine adenomas occur sporadically with a female predilection {1361}. A broad age group may be affected {1361}. Some neoplasms may occur in association with a syringocystadenoma papilliferum {76,489,1111, 2364} and can also arise within an organoid naevus {1111,1361,2394}.

Localization
Tubular apocrine adenomas commonly occur on the scalp and less often at other sites including the leg, trunk, axillary and anogenital areas {1361}.

Clinical features
Tubular apocrine adenomas present as asymptomatic solitary nodules that are skin-coloured to pink-red in appearance with either a smooth or irregular appearance {1361}. Most tumours range in overall dimension between 1 to 2 cm but rarely may be as large as 7 cm {1361}.

Histopathology
Tubular apocrine adenomas are well-circumscribed dermal neoplasms that may extend into the subcutis. They have an overall lobular architecture and are typically encased by a fibrous stroma. The lobules consist of multiple irregularly shaped tubular structures that have a double to several layered epithelial lin-

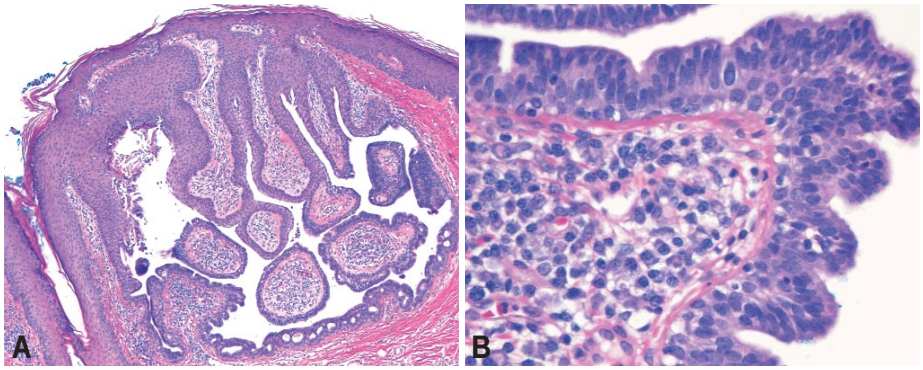


Fig. 3.32 Syringocystadenoma papilliferum. **A** Keratinizing squamous epithelium at the surface merges with columnar epithelium in the deeper portions of the tumour. **B** Papillary projections are lined by pseudostratified columnar epithelium, and plasma cells are typically noted in the stroma.

ing. The peripheral epithelial layer consists of cuboidal to flattened cells (myoepithelial) and the luminal layer of columnar cells that demonstrate decapitation secretion. In some tubules papillary cellular extensions that are devoid of stroma project into the lumina. Additionally, cellular debris and eosinophilic granular material are identified within some lumina {1361}. The neoplasm lacks cytologic atypia and mitotic activity. Overlying epidermal hyperplasia may be present. In those neoplasms that occur in conjunction with syringocystadenoma papilliferum {76,489,2364}, the tubular adenoma component is typically present underlying the syringocystadenoma component. The differential diagnosis includes apocrine adenocarcinoma and papillary eccrine adenoma. In contrast to apocrine adenocarcinoma tubular apocrine adenomas lack cytologic atypia, are well circumscribed and possess a peripheral myoepithelial layer {1751}. Tubular apocrine adenomas resemble papillary eccrine adenomas in many respects and previously these were believed to be related neoplasms {489}. However on the basis of morphologic criteria (papillary eccrine adenomas lack decapitation secretion) and enzyme histochemistry and ultrastructural analysis demonstrating differences in differentiation (apocrine versus eccrine) they are now believed to represent distinct neoplasms. In some instances both eccrine and apocrine differentiation may be observed making a distinction between these neoplasms impossible {771}. The terms tubulopapillary hidradenoma {705} and papillary tubular adenoma {2335} have been suggested for cases with apocrine and eccrine differentiation.

Histogenesis
Enzyme histochemistry {1361} and ultrastructural analysis {1361,2394} have demonstrated tubular apocrine adenomas to be of apocrine differentiation.

Prognosis
Tubular apocrine adenomas are benign slow-growing neoplasms. Simple excision is curative.

Syringocystadenoma papilliferum

Definition
Syringocystadenoma papilliferum is a benign adnexal neoplasm that occurs in association with an organoid naevus such as naevus sebaceous in at least one-third of cases.

ICD-O code 8406/0

Synonmys
Syringoadenoma

Epidemiology
Syringocystadenoma papilliferum occurs with equal frequency in both sexes. It is a tumour of childhood or adolescence, with many examples noted at birth. These lesions tend to increase in size at puberty, and sometimes multiply in number as well as becoming more papillomatous over time.

Clinical features
The majority of syringocystadenomas affect the head and neck area, typically as one or more warty papules, sometimes in a linear array, or as a solitary grey or red plaque. Scalp and neck are favoured sites; those on the scalp are typically alopecic. Syringocystadenomas may develop during puberty in a pre-existing naevus sebaceous, and at least one-third are associated with an underlying organoid naevus.

Histopathology
Histologically, endophytic invaginations of epithelium extend from the epithelial surface into the dermis. Typically squamous epithelium is present at the surface of the invaginations, and is contiguous with a double layer of cuboidal and columnar epithelium in the deeper portions of the lesion. Within the dermis, broad villous projections protrude into cystic spaces. Columnar epithelium is present toward the lumen of the spaces, and simple cuboidal epithelium can be seen at the periphery. Decapitation secretion of luminal cells is a frequent finding. Plasma cells are consistently numerous within the stroma, and are a highly reproducible finding in the stroma of syringocystadenomas.
The differential diagnosis includes hidradenoma papilliferum, which differs clinically by location in the perineal region, and histologically by dermal nodules showing a more complex papillary growth pattern, and absence of plasma cells in the stroma. The epithelial lining of the two lesions shows histologic overlap, however.

Precursor lesions
Approximately one-third of cases arise in organoid naevi.

Histogenesis
Syringocystadenomas show differentiation that is predominantly apocrine in pattern, but eccrine origin has been suggested in some cases, as exemplified by immunohistochemical labelling with eccrine marker IKH-4 {1109}. An intriguing finding is the presence of IgA and secretory component within the epithelial cells in syringocystadenomas, and IgA and well as IgG within the plasma cells {2420}. This observation suggests that plasma cells are attracted to tumour epithelium via a mechanism similar to that used by glands of the normal secretory immune system.

Somatic genetics
Allelic deletions of the patched gene 9q22 and loss of heterozygosity at 9p21

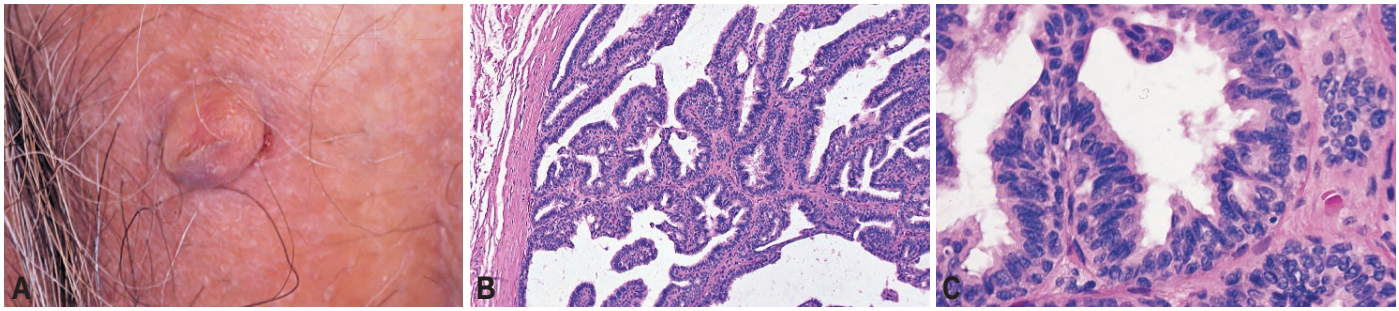


Fig. 3.33 Hidradenoma papilliferum. **A** Hidradenoma papilliferum of the vulva. A polypoid exophytic lesion involving the left labius majus of an elderly woman. **B** The neoplasm shows a prominent papillary pattern. **C** Columnar cells shows evidence of decapitation secretion in their luminal border.

(p16) have been reported in syringocystadenoma papilliferum {281}.

Prognosis and predictive factors
Syringocystadenonas are benign and simple excision is curative.

Hidradenoma papilliferum

Definition
Hidradenoma papilliferum is a benign cystic and papillary neoplasm that almost always develops in the vulval and perianal regions of middle-aged women.

ICD-O code 8405/0

Epidemiology
Most cases appear in women, although there are also reports in males {588, 1441,1697,2421}. The neoplasm is rare in Black patients. The age of presentation ranges from 20-90 years {2428, 2435}.

Localization
The skin of the vulva and perianal regions are the most frequently involved areas {588,1106,1441,1565,1568,1697, 2324,2421}, although rare examples of extra-genital or ectopic hidradenoma papilliferum have been reported on postauricular skin {247}, eyelids {1106, 1697,2056,2421}, external auditory canal {1718}, face {1106,1697} scalp {845}, axilla {1106,2421}, upper limb {2421}, back {727,1106} and thigh {2421}.

Clinical features
The lesion appears as a slow-growing cystic dermal nodule, usually asymptomatic, although it sometimes ulcerates and bleeds. The neoplasm is a unilateral skin-coloured nodule, papule or polypoid exophytic lesion, most commonly located on the labius majus.

Histopathology
At scanning magnification, hidradenoma papilliferum consists of a cystic neoplasm composed of elongated tubules and large papillary structures with a frond-like pattern. The papillae are composed of a central axis of connective tissue lined by two layers of epithelial cells. The basal layer is composed of pale-staining cuboidal myoepithelial cells and the luminal layer is made up by columnar cells with decapitation secretion. The cystic cavity and the lumina of the tubular structures contain apocrine secretions in the form of eosinophilic homogeneous material.
The epithelial cells at the periphery are flattened, and decapitation secretion is less evident, as a consequence of the pressure exerted by the cyst contents. The stroma surrounding the cystic cavity is composed of compressed fibrous tissue that is separated from the normal adjacent dermis by clefts. These clefts are responsible for the tendency of the neoplasm to shell out easily after incision of the epidermis.
In contrast with syringocystadenoma papilliferum, hidradenoma papilliferum is not connected with follicular infundibula and there are not plasma cells in the axis of connective tissue of the papillations. Sometimes, neutrophils are scattered within the connective tissue framework.

Immunoprofile
Immunohistochemical studies demonstrated that epithelial cells lining the papillations express low-molecular weight cytokeratins. The luminal border of the cells lining tubular structures is also decorated by carcinoembryonic antigen, epithelial membrane antigen and gross cystic disease fluid protein-15. Immunostains for S-100 protein and high-molecular-weight keratins are negative {2257}. Neoplastic epithelial cells lining tubules and papillations also express strong immunoreactivity for androgen and oestrogen receptors {1739}.

Histogenesis
Both the histopathologic and ultrastructural characteristics of hidradenoma papilliferum support an apocrine line of differentiation, although some authors have postulated the possibility of origin from Wolffian ducts or accessory mammary glands {576,1633}.

Prognosis and predictive features
Hidradenoma papilliferum is a benign neoplasm cured by simple excision. Malignant transformation is a very uncommon event {588,1730,2274,2460}. A case of adenosquamous carcinoma of the vulva developing from a pre-existing hidradenoma papilliferum has also been reported {142}.

Mixed tumour (chondroid syringoma)

Definition
Cutaneous mixed tumours are benign adnexal tumours of skin composed of epithelial and stromal elements with a wide spectrum of patterns. These tumours are histologically analogous to mixed tumours of the salivary gland, but lack the tendency for local recurrence seen in the latter lesions.

ICD-O code 8940/0

Synonyms
Chondroid syringoma, mixed tumour of skin.

Epidemiology
Mixed tumours most often occur as solitary slowly growing nodules on the head

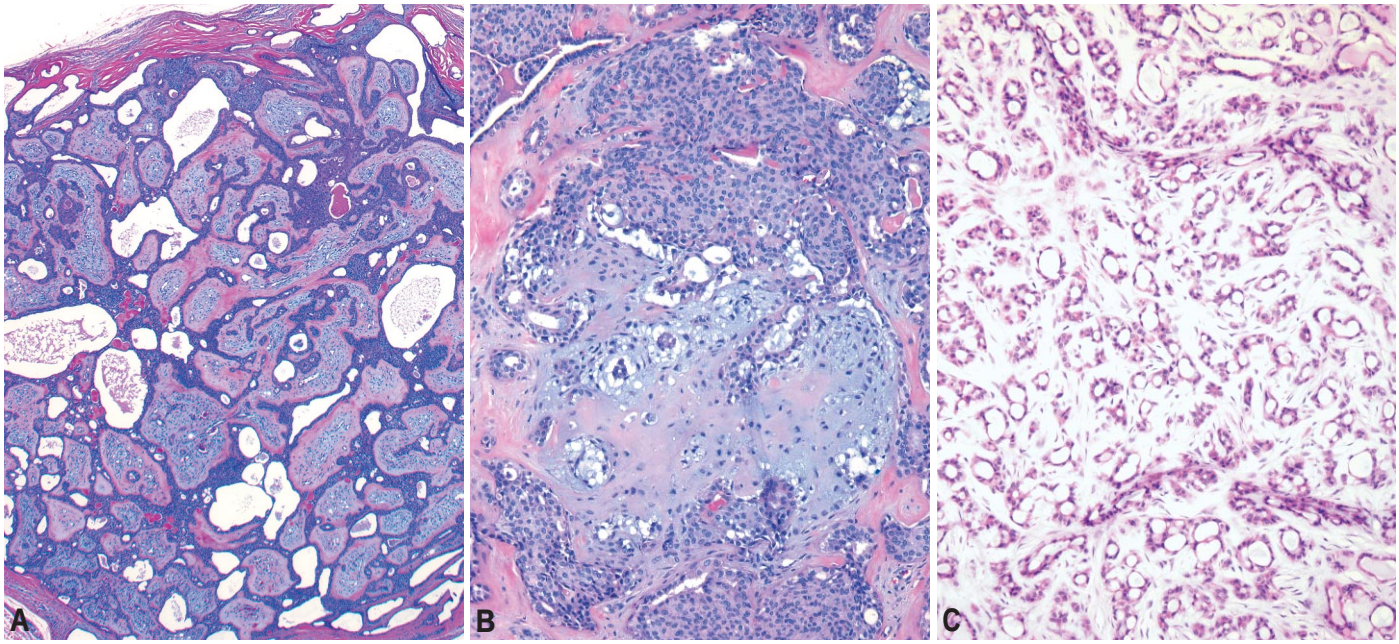


Fig. 3.34 Mixed tumour (chondroid syringoma). **A** Well-circumscribed mixed tumour with branching tubules and myxochondroid stroma. **B** Mixed tumour with epithelial tubules embedded in a myxoid and hyaline stroma. **C** Predominately ductal epithelial pattern of mixed tumour.

and neck of adults, although other sites may be affected. There is a male predilection. Most lesions are between 1-3 cm in diameter, although examples as large as 6 cm have been reported {1182}.

Clinical features

Cutaneous mixed tumours present as asymptomatic dermal nodules, with no specific distinguishing clinical characteristics.

Histopathology

At low power, cutaneous mixed tumours are well-circumscribed lesions located in the dermis and/or subcutis. A biphasic growth pattern can be readily detected, with epithelial elements embedded within a myxoid, chondroid, or fibrous stroma. The epithelium often shows a pattern of branching tubules, sometimes with decapitation secretion suggesting apocrine differentiation. Solid cords and islands of epithelium as well as single cells may also be present. In some cases, the epithelial elements are composed of small non-branching tubules that may contain eosinophilic cuticles. Follicular differentiation occurs in some mixed tumours, in the form of follicular germinative cells, shadow cells, or sebocytes. Mixed tumours may exhibit clear cell change within the epithelial cells. In an estimated 40% of cases, mixed tumours contain hyaline cells characterized by an ovoid shape, dense ground-glass or hyaline-like cytoplasm, and an eccentric nucleus {85}. The cells resemble plasma cells, and have been called plasmacytoid cells. In some cases, hyaline cells are the predominant cell type, leading to the term hyaline-cell rich chondroid syringoma {735}. The presence of hyaline cells appears to be of no prognostic significance, although such cells may present a diagnostic challenge to the unsuspecting pathologist {735}.

Immunoprofile

Immunohistochemical studies reveal staining of the inner layer of epithelial cells with cytokeratin, CEA, and EMA, and staining of the outer cellular layer with S100 and vimentin {2559}.

The stroma of mixed tumours usually comprises at least half of the lesion, and may show variable patterns of differentiation, including myxoid, fibroblastic, fibrocartilagenous, chondroid, and even osteoid components. Combinations of matrix components are the rule. Despite the name chondroid syringoma, chondroid areas may be absent in the stroma. The stroma stains strongly for alcian blue with hyaluronidase resistance.

Differential diagnosis

In mixed tumours where stroma predominates, the differential diagnosis includes entities such as myxoma. In other lesions with abundant epithelial elements, the differential diagnosis includes benign adnexal tumours such as hidradenoma and syringoma, depending on the pattern of epithelial growth.

Histogenesis

It is generally accepted that there are both apocrine and eccrine variants of mixed tumours. Ultrastructural studies confirm that myoepithelial cells surround the epithelial cells, and appear to produce the stromal components of the lesions {2423}. The stroma of mixed tumours contains matrix components such as types II and IV collagen, tenascin, fibronectin, and laminin {773}. Ultrastructural and immunohistochemical studies of hyaline cells in mixed tumours suggest these cells derive from both the epithelial and stromal components of the lesions, possibly representing a regressive process {85}.

Prognosis

Cutaneous mixed tumours are benign lesions cured by simple excision.

Malignant tumours with follicular differentiation

S. Kaddu
L. Requena

Pilomatrical carcinoma

Definition
Pilomatrical carcinoma is the malignant counterpart of pilomatricoma.

ICD-O code 8110/3

Synonyms
Pilomatrix carcinoma, matrical carcinoma, invasive pilomatrixoma, malignant pilomatrixoma, matrix carcinoma.

Epidemiology
Pilomatrical carcinoma is an extremely rare tumour. Most cases present in adults with a broad age range {28,804,954, 2064}. The mean age at the time of diagnosis is about 48 years. The male to female ratio is 2:1.

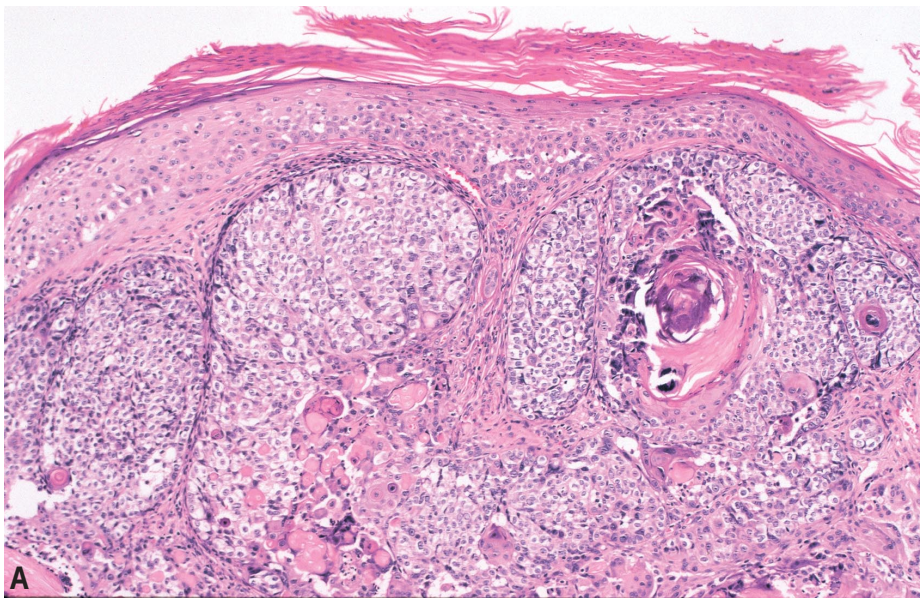
Etiology
The majority of pilomatrical carcinomas develop de novo, although malignant transformation from a pre-existing pilomatricoma has been reported {2064}. It is conceivable that proliferating pilomatricoma, a variant of pilomatricoma that occurs mainly in middle aged and elderly individuals, may represent an intermediate precursor lesion.

Localization
Pilomatrical carcinomas mostly occur in the head and neck, upper extremities and buttocks. Rare tumours have been reported in the axilla and inguinal regions.

Clinical features
The clinical appearance of pilomatrical carcinoma is generally not distinctive. Patients show solitary, occasionally ulcerated or fungating nodules ranging in size from 1-10 cm in diameter. Skin nodules are often of long duration ranging from several months to years before diagnosis, although occasional cases of recent onset and a history of rapid growth have been reported.

Histopathology
The tumour is a large, asymmetrical, poorly circumscribed dermal or dermal-subcutaneous mass composed of several, irregularly shaped and variously sized aggregations of basaloid cells (matrical and supramatrical cells) {28,804,954, 2064}. Foci of cornified material containing shadow cells are characteristically observed within the basaloid cell aggregations. Some neoplasms show a variable desmoplastic stroma surrounding the basaloid cell aggregations. Focal connections of basaloid cell aggregations to the overlying epidermis and/or ulceration are often noted. Basaloid cells exhibit hyperchromatic nuclei, with one or more prominent nucleoli and ill-defined cytoplasmic margins as well as variable numbers of occasionally atypical mitotic figures (up to 10 mitoses per high-power field). Foci of geographical necrosis, calcification and ossification are observed. Mitotic activity is not a reliable indicator of malignancy, because mitoses are common in pilomatricoma. Other parameters, such as an infiltrative growth pattern, as well as angiolymphatic, perineural, and bone invasion, are more reliable features {804,2064}.

Immunoprofile
Immunohistological studies have previ-



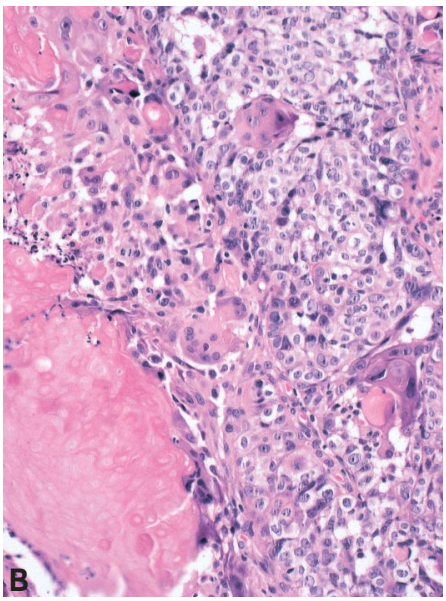


Fig. 3.35 Pilomatrical carcinoma. **A** The neoplastic cells are present in apposition to the epidermis. **B** A large mass of shadow (ghost) cells is present. The clear cells have more nuclear pleomorphism than in the pilomatricoma.

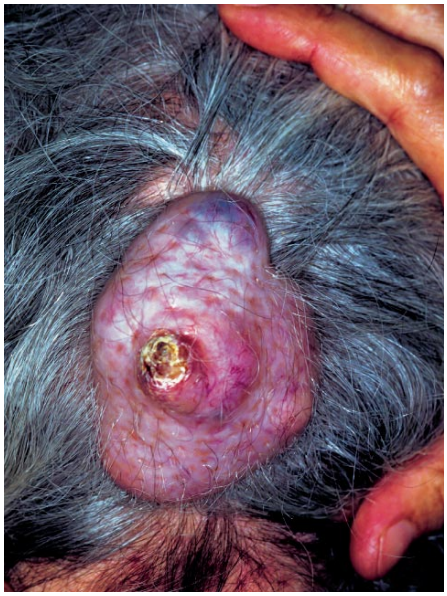


Fig. 3.36 Proliferating tricholemmal tumour. A large tumour on the scalp of an elderly woman.

ously revealed keratin staining in both basaloid and shadow cells {556}.

Prognosis and predictive factors
Treatment of choice is by surgical excision with adequate margins. Mohs micrographic surgery technique may be useful in treating some patients. Pilomatrical carcinoma is a mainly locally aggressive tumour which often recurs if not completely removed but very rarely shows distant metastases. Metastatic spread is evidenced by involvement of regional lymph nodes, lungs and/or bone.

Proliferating tricholemmal tumour

Definition
Proliferating tricholemmal tumour is a solid-cystic neoplasm that shows tricholemmal differentiation similar to that of the isthmus of the hair follicle.

ICD-O code 8103/1

Synonyms and historical annotation
Epidermoid carcinoma in sebaceous cyst {252,416} subepidermal acanthoma {1458}, proliferating epidermoid cyst {1152}, invasive hair matrix tumour of the scalp {1910}, trichochlamydocarcinoma {1053}, giant hair matrix tumour {583}, proliferating tricholemmal cyst {321}, proliferating pilar cyst {68,92}, proliferating follicular cystic neoplasm {23}, proliferating tricholemmal cystic squamous cell carcinoma {1631}, proliferating isthmic cystic carcinoma. These different names reflect the distinct histogenetic and biologic interpretations for this neoplasm among different authors.

Epidemiology
The neoplasm is more frequent in women than in men and most patients are elderly {2069}.

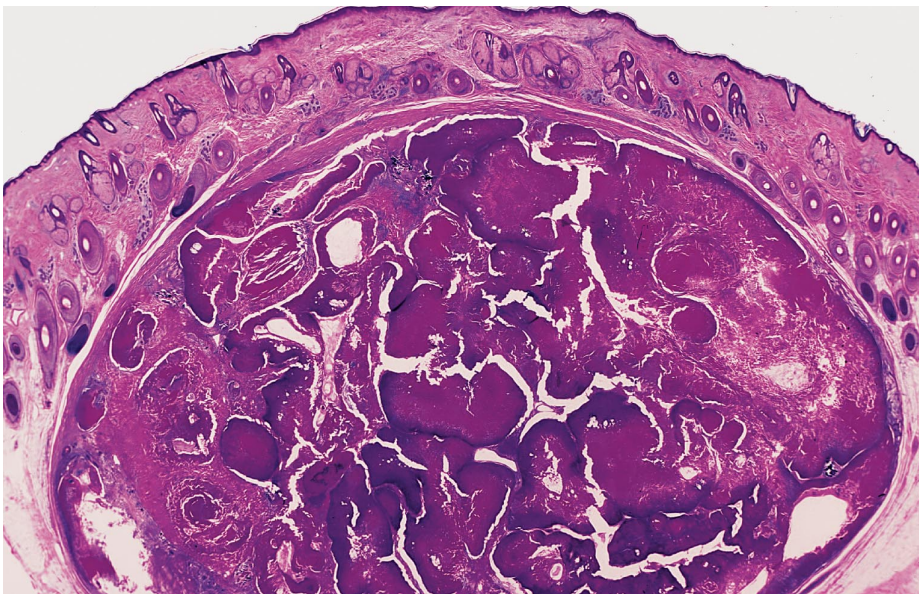


Fig. 3.38 Proliferating tricholemmal tumour. At scanning power the neoplasm appeares as a well-circumscribed cystic neoplasm involving deeper dermis and subcutaneous tissue of the scalp.

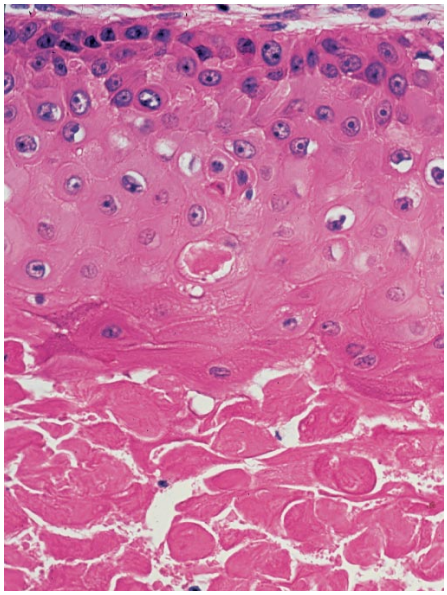


Fig. 3.37 Proliferating tricholemmal tumour. The lobules of the neoplastic epithelium show tricholemmal keratinization, characterized by peripheral palisading of small basaloid cells and large keratinocytes with ample eosinophilic cytoplasm that develop abrupt keratinization without previous granular layer, resulting in compact orthokeratotic eosinophilic keratin. This type of keratinization is similar to that of the outer sheath at the level of the isthmus of the hair follicle.

Localization
More than 90% of the lesions are situated on the scalp. Other described locations, in decreasing order of frequency, include face, trunk, back and forehead {2069}.

Clinical features
The tumour is a solitary, multilobular, large, exophytic mass, which may develop within a naevus sebaceous {866, 1874}. Multiple lesions are very rare. The size ranges from 2-10 cm in diameter, although lesions up to 25 cm in diameter have been described {407}. Alopecia and ulceration can be found.

Macroscopy
The lesions often show a multilobular appearance. The cystic structures often contain compact keratin and calcified material.

Histopathology
Proliferating tricholemmal tumour occurs on a morphologic continuum. On one end of the spectrum, it consists of a well-circumscribed solid and cystic neoplasm which involves the dermis and sometimes extends to the subcutaneous tis-

sue. In addition to the typical features of a tricholemmal (pilar) cyst, this tumour shows prominent epithelial infoldings into the cyst lumen. The epithelium shows peripheral palisading of small basaloid cells arranged along a thick vitreous membrane, differentiating towards large keratinocytes with ample eosinophilic cytoplasm and abrupt keratinization without a granular layer. Often, areas of calcification and abundant cholesterol crystals are seen within the compact eosinophilic keratin. The neoplastic cells are monomorphous without significant cytologic atypia and with only rare mitoses {1135,1724}.

On the other end of the morphologic spectrum are neoplasms with malignant features such as invasive growth extending beyond the confines of the cyst wall coupled with nuclear pleomorphism and high mitotic activity. These areas may be indistinguishable from squamous cell carcinoma. Additional findings include shadow cells as an expression of focal matrical differentiation similar to that of pilomatricoma {1726}, areas of sebaceous and apocrine differentiation {2021}, and spindle cells {1649}.

Differential diagnosis includes tricholemmal cyst, which lacks the multilobular architecture, as well as proliferating epidermoid (infundibular) cyst {2069}. The latter occurs most commonly in the anogenital region of male patients and shows a cystic cavity lined by stratified squamous epithelium with infundibular keratinization. Up to 20% of the lesions may undergo malignant transformation into squamous cell carcinoma {2069}. Differentiation between proliferating tricholemmal tumour and proliferating infundibular cyst is straightforward, because the former shows tricholemmal keratinization, whereas the latter has mainly infundibular keratinization. Tricholemmal carcinoma should also be considered.

Immunoprofile

Proliferating tricholemmal tumour expresses fetal hair root cytokeratin, as well as cytokeratin 7 {933}.

Histogenesis

The pathogenesis remains unknown. In some cases, human papillomavirus has been implicated in the etiology {23}. It is unclear if proliferating tricholemmal tumours arise de novo or from pre-existing tricholemmal cysts {1631,1847}.

Prognosis and predictive factors

Proliferating tricholemmal tumours without atypical features generally behave in a benign fashion {762}. Yet, complete excision is recommended to avoid recurrences, and to allow for complete histopathological evaluation. Tumours with an invasive growth pattern or cytologic atypia have an unpredictable course. They may be locally aggressive, recur, or metastasize {68,178,982,1017,1537,1572,1727,1728,1773,2311,2486}. For this reason, it has been suggested that even the classical benign lesions are squamous cell carcinoma {1631}.

Benign tumours with follicular differentiation

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Trichoblastoma

Definition

Trichoblastoma is a benign neoplasm differentiated toward the trichoblast, i.e., the folliculo-sebaceous-apocrine germ, or follicular germ, for short. In many cases, advanced follicular differentiation can be present also {28,989,1083}.

ICD-O code 8100/0

Synonyms

Trichoepithelioma, trichoblastic fibroma, trichogenic trichoblastoma, lymphadenoma (adamantinoid trichoblastoma), trichogerminoma, sclerosing epithelial hamartoma, Brooke-Fordyce disease, Brooke-Spiegler disease.

Clinical features

Trichoblastomas, as a rule, are solitary, small papules that occur on any hair follicle-bearing location (usually head and neck), at any age, and can affect either sex. They can also present as multiple centrofacial papules or nodules, particularly in the diseases of Brooke-Fordyce and Brooke-Spiegler. The size of an individual neoplasm can vary from a few millimetres to several centimetres, but most are less than 1 cm in diameter. Most are skin-coloured and ulcerated only rarely.

The differential diagnosis is non-specific for solitary lesions, but includes the "angiofibroma" of tuberous sclerosis when multiple.

Histopathology

Trichoblastic epithelial components associated with stereotyped stroma, chiefly the follicular papilla, must be present to establish the diagnosis with surety. There are five patterns; these can be mixed in any given neoplasm.

Large and small nodular trichoblastomas are usually circumscribed, sometimes subcutaneous, and contain a uniform distribution of solid trichoblasts with follicular papillae. In some cases, the follicular "papillae" are not papillary in that they fail to invaginate into the epithelial components of the germ. The epithelial cells are deeply basophilic, uniform, and overlap each other usually. Melanocytes can be prominent within the epithelial areas in some cases. Some cases have nodules that are lymphocyte-rich, a pattern termed originally lymphadenoma {1561,2053}.

It should be noted that, rarely, lesions with a pattern similar to nodular trichoblastoma are really trichoblastic (basal cell) carcinomas that mimic trichoblastoma. While it is not completely understood what are all the factors that differentiate these lesion from trichoblastoma, one seems to be that the carcinomas infiltrate through skeletal muscle or other deep structures while there is a conspicuous absence of the usual stroma present in a classic nodular trichoblastoma. Rare examples with this pattern have metastasized {1960}.

Retiform trichoblastomas are reticulated, with large fenestrations containing follicular stroma.

Cribriform trichoblastoma is the most common pattern when the neoplasms are multiple, characteristic of Brook-Fordyce disease. The trichoblasts are usually fenestrated, but with small fenestrations compared to the retiform pattern.

Racemiform trichoblastoma contains epithelial nests that simulate "clusters of grapes". This results in stromal components that connect with the surrounding stroma rather than being isolated from it in fenestrations.

Columnar trichoblastoma (desmoplastic "trichoepithelioma") occurs most commonly as a solitary depression on the face of a young woman. As a rule, these neoplasms are confined to the superficial dermis. They contain stereotyped, thin strands of epithelium compressed by dense stroma. Small trichoblasts can be seen in some cases, but are less common compared to conventional forms of

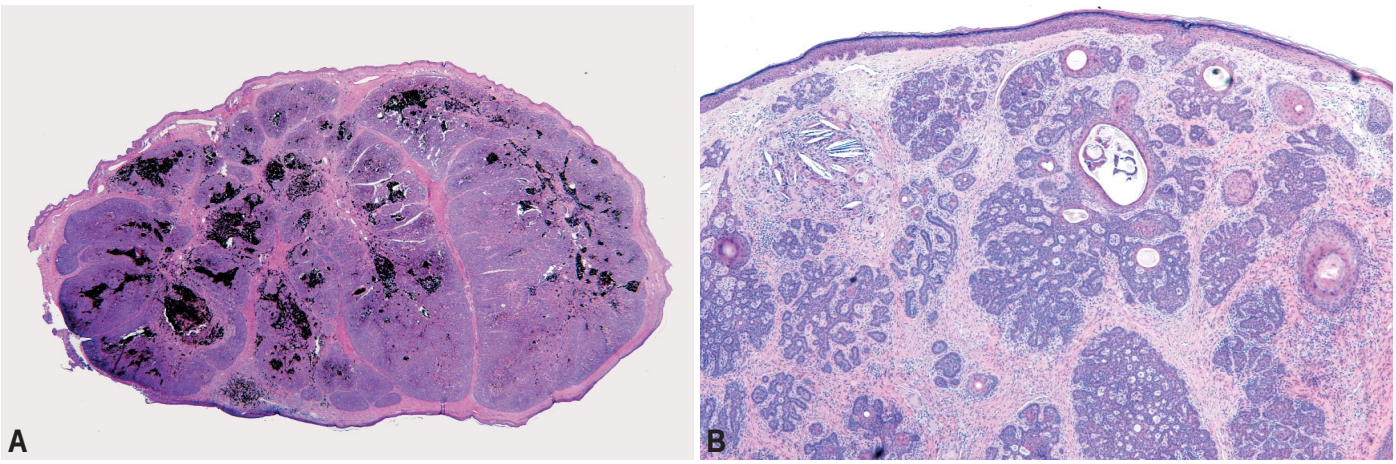

Fig. 3.39 Trichoblastoma. **A** Large nodular trichoblastoma. Note the circumscription. Melanin pigmentation is present in this lesion. **B** Cribriform trichoblastoma. At scanning magnification, there are small groupings of basophilic cells containing small fenestrations of stroma.

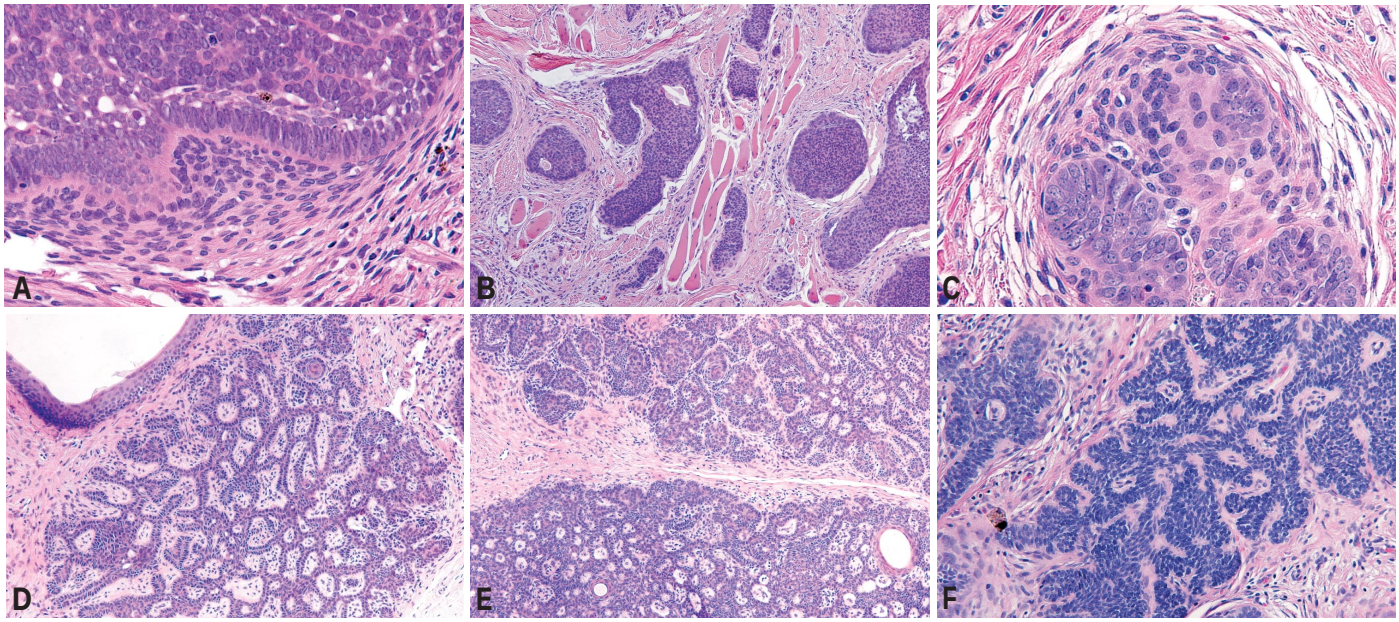

Fig. 3.40 Trichoblastoma. **A** This trichoblast has a typical follicular "papilla" that does not extend cleanly into an invaginated epithelial component of the follicular germ. **B** Compared to the usual types of trichoblasts seen in nodular trichoblastoma, this trichoblastic carcinoma has diminished mesenchymal stroma, specifically diminished mesenchyme of the follicular papilla. **C** Trichoblast containing a superficial follicular papilla that protrudes into an invaginated follicular germ. This is a fundamental finding in trichoblastomas of any pattern. **D** Retiform trichblastoma. This reticulated pattern is seen often in large, solitary lesions. **E** This sieve-like pattern is commonly present in the small centrofacial lesions of Brooke-Fordyce disease and is the pattern known classically "trichoepitheliom". **F** Groupings of follicular germinative cells that branch out, mimicking a "cluster of grapes". Absence of sieve-like areas seen in the cribrifom pattern.

trichoblastoma. The differential diagnosis includes morpheiform basal cell carcinoma, microcystic adnexal carcinoma, and, rarely, metastatic carcinoma from breast. Thus, superficial biopsies of such lesions should be investigated thoroughly, and additional biopsy or excision should be requested for cases in which the diagnosis is uncertain.

Immunoprofile

Trichoblastomas, as a rule, cannot be differentiated from basal cell (trichoblastic) carcinoma based solely on specific expression of cytokeratins. The presence of presumed Merkel cells within a neoplasm, however, does seem to favour trichoblastoma over basal cell carcinoma {1349}. Some trichoblastomas can contain zones of ductal differentiation; when this occurs, markers, such as CEA will highlight those areas {2398} but they will not aid in establishing the diagnosis. Uncommonly, excessive pigmentation is seen in nodular trichoblastoma, and these lesions contain markers for melanocytes {1199}, but they are nonspecific for the diagnosis, as basal cell (trichoblastic) carcinoma can have similar findings.

Desmoplastic trichoepithelioma contains AE14, EMA, and Leu-M1 (CD15) focally, but is negative for CEA and S100 {2511}. CK 5, 8, 14 and 15 have been identified in some cases {2555}. It can be differentiated from morpheiform basal cell carcinoma and microcystic adnexal carcinoma, in most cases, by applying CK20, which marks neuroendocrine cells in desmoplastic trichoepithelioma, but not in basal cell carcinoma or microcystic adnexal carcinoma {13}. Furthermore, CK7 is usually positive in breast carcinoma metastatic to skin and in microcystic adnexal carcinoma, but not in desmoplastic trichoepithelioma. Stromelysin 3 has also been identified in the stroma of morpheiform basal cell carcinoma, but not in the stoma of desmoplastic trichoepithelioma {2346}.

Somatic genetics

Multiple trichoblastomas (Brooke-Fordyce disease) are transmitted as an autosomal dominant trait linked to chromosome 9p21 {6,951}. Solitary (sporadic) trichoblastomas have been linked, in some cases, to 9q22.3 {1538}, the same locus for the naevoid basal cell carcinoma syndrome {4}. Familial multiple trichoblastomas and cylindromas (Brooke-Spiegler disease) have been linked to chromosome 16q12-q13 {5,722}.

Prognosis and predictive factors

Because these are benign neoplasms, no treatment is required, in most cases, if the diagnosis is established with certainty. Because some trichoblastomas may occur, rarely, in association with basal cell (trichoblastic) carcinoma, and because of the difficulty in establishing the diagnosis in superficial biopsies, in some cases, additional biopsy or excision should be considered if there is uncertainty about the diagnosis.

Pilomatricoma

Definition

Pilomatricoma is a relatively common benign cutaneous adnexal neoplasm with differentiation towards the matrix and inner sheath of a normal hair follicle as well as hair cortex {28,1169}.

ICD-O code 8110/0

Synonyms

Pilomatrixoma, calcifying epithelioma of Malherbe, benign calcifying epithelioma

Epidemiology

Pilomatricoma accounts for up to 0.2% of all routine dermatopathologic specimens

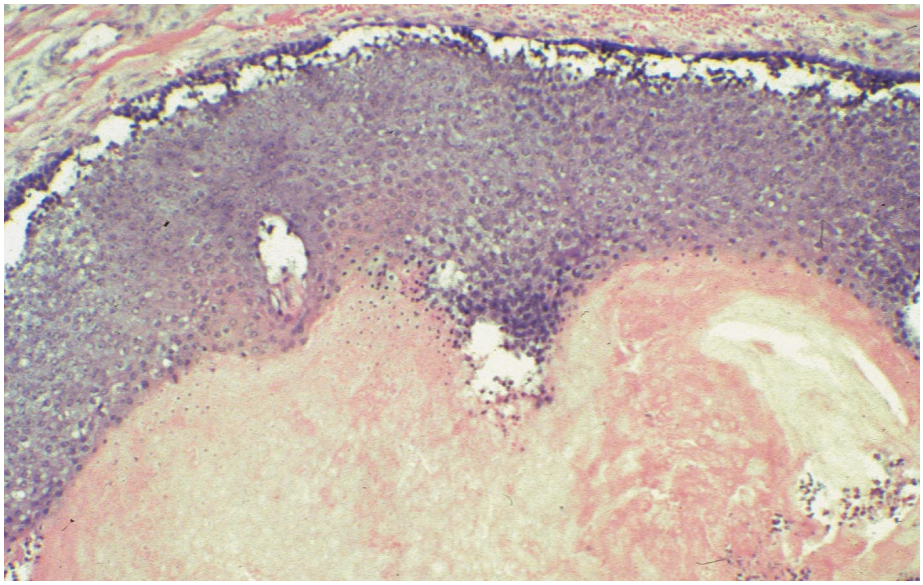

Fig. 3.41 Pilomatricoma. There is a growth component of basolid cells with transition to pilar 'shadow cells'.

in certain centres. The tumour occurs in all age groups {1169}. About 30-50% of cases present in young individuals less than 30 years of age. Previous studies have shown a female predominance.

Localization

Pilomatricomas favour hair-bearing areas, with the majority of cases arising in the head and neck region as well as upper extremities.

Clinical features

Patients present with solitary, asymptomatic, slowly growing, cystic or firm nodules measuring 0.5-3 cm in diameter {28,1169,1170}. Lesions are commonly skin-coloured, but may show a bluish-purple to reddish hue or pigmentation. Unusual presentations include rapidly growing or giant tumours (measuring up to 15 cm in diameter), lesions with overlying striae or anetodermic changes, and multiple tumours. Multiple pilomatricomas are quite rare. They are a marker for myotonic dystrophy, and may rarely be associated with a number of different conditions including Rubinstein-Taybi syndrome, Turner syndrome, Goldenhar syndrome, sternal cleft defects, coagulative defects, and sarcoidosis. Pilomatricoma-like features are an occasional finding in cutaneous cysts removed from patients with Gardner syndrome.

Macroscopy

Grossly, pilomatricomas occur mostly as lobulated masses with variable amounts of chalky white or yellow keratinous material on their cut surfaces. Foci with bone may be observed.

Histopathology

There is usually a relatively well-circumscribed, deep dermal or dermal-subcutaneous, cystic neoplasm surrounded by a variable connective tissue stroma {28, 1169}. A spectrum of histopathologic features reflecting mainly different stages of development is observed in individual lesions. Early and well-developed pilomatricomas are characterized by small to large-sized, cystic lesions lined focally by aggregations of basaloid cells (matrical and supramatrical cells) and few squamoid cells and filled centrally with large masses of eosinophilic cornified material (faulty hair matrix) containing shadow (ghost) cells as well as a few keratin filaments. A transition zone of retained nuclei from basaloid cells to eosinophilic cornified material containing shadow cells is focally observed. Basaloid cells exhibit deeply basophilic oval or round nuclei and a variable number of mitotic figures. Inflamed or regressing pilomatricomas are relatively large cystic tumours with prominent areas of shadow cells and foci of basaloid and/or squamoid cells surrounded by a variable, often dense inflammatory infiltrate with histiocytic giant cells, and occasionally siderophages and/or melanophages. Areas of granulation tissue may be present. Occasional lesions dis-

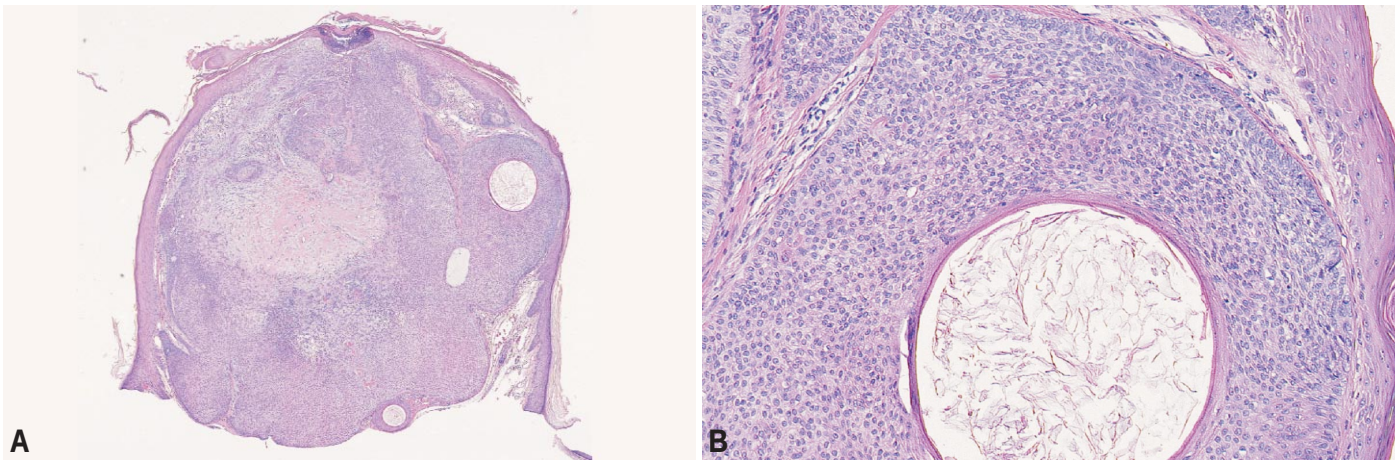

Fig. 3.42 Tricholemmoma. **A** Exo-endophytic tumour with wart-like silhouette and focal desmoplastic stroma. **B** Peripheral epithelia are arranged in a palisade. Small central follicular microcyst.

play features of transepidermal elimination of shadow cells (perforating pilomatricoma) or a keratoacanthoma-like pattern. Old pilomatricoma lesions reveal no epithelial components but show irregularly shaped, partially confluent, focally calcified or metaplastically ossified shadow cell areas embedded in a desmoplastic stroma, with little or no inflammatory infiltrate. Extramedullary haematopoiesis has been observed in some regressing and old pilomatricoma lesions.

A subset of pilomatricomas, also termed "proliferating pilomatricoma", is characterized by the presence of relatively large, solid or solid-cystic basaloid cell areas with small foci of shadow cells {1170}. This variant presents mainly in middle aged and elderly individuals. "Matricoma" represents another unusual pilomatricoma variant characterized by discrete, small, solid aggregations of basaloid cells with several connections to pre-existing infundibula at different points {28}.

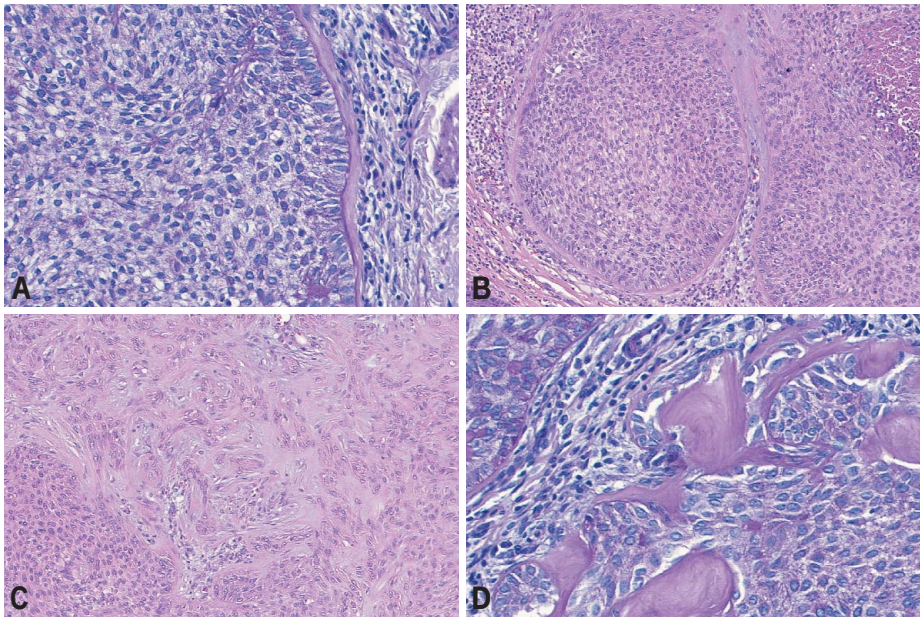

Fig. 3.43 Tricholemmoma. **A** Thick PAS-positive basement membrane. **B** Focal necrosis within bulbous follicular hyperplasia. Thickened basement membrane. **C** Desmoplastic stroma with entrapped bizarre epithelial strands ("pseudoinvasive interface"). **D** PAS-positive desmoplastic stroma and basement membrane.

Molecular and cytogenetics

Derivation of pilomatricomas from the hair matrix has been underlined by recent biochemical studies demonstrating prominent staining of tumour cells with antibodies directed against LEF-1, a marker for hair matrix cells. Mutations in the gene CTNNB1 have been detected in up to 75% of pilomatricomas studied implicating beta-catenin/LEF misregulation as a possible cause of hair matrix cell tumourigenesis {438}. In another study, all 10 pilomatricomas examined were found to display strong bcl-2 immunostaining, a proto-oncogene well known to help in suppressing apoptosis in benign and malignant tumours {712}. This finding supports a role for faulty suppression of apoptosis in the pathogenesis of pilomatricomas.

Prognosis and predictive factors

Treatment is recommended mainly to avoid a foreign body reaction and inflammation with eventual scarring. Surgical excision is usually curative, but occasional recurrences may be observed. Spontaneous regression has been reported in a few cases. Malignant transformation has only been suspected in a single case of pilomatrical carcinoma {2064}.

Tricholemmoma

Definition

Tricholemmoma (TL) is a benign folliculoinfundibular proliferation occurring frequently but not exclusively on the face of adults. Multiple tricholemmomas may be associated with Cowden disease.

ICD-O code

Tricholemmoma	8102/0
Multiple tricholemmomas	8102/0

Synonyms

Trichilemmoma

Epidemiology

TL is a relatively common cutaneous proliferation that occurs mostly in adults and affects both sexes equally {323}. Multiple TLs, often in conjunction with acral keratoses, palmar pits, and oral fibromas, are a cutaneous marker of Cowden disease (multiple hamartoma and neoplasia syndrome) {322,325,681,2025,2247, 2249-2251}.

Localization

TL arises on the head and neck, almost exclusively on the face, favouring the centrofacial area. Rarely, TL may occur in naevus sebaceous {410,1979}.

Clinical features

Patients usually present with a solitary asymptomatic exophytic centrofacial lesion which is either wart-like with verrucous and keratotic features or dome shaped with a smooth surface. Individual lesions are small, varying in diameter between 3 and 8 mm {28}. Multiple facial TLs are almost invariably associated with Cowden disease {2247,2249-2251}.

Histopathology

Most cases of TL present as a sharply circumscribed superficial exo-endophytic proliferation with a papillated surface. There is marked parakeratosis, hyperkeratosis, and wedge-shaped hypergranulosis of the infundibula, in conjunction with a collarette of embracing adnexal epithelium {28,323}. TL does not involve the interfollicular epidermis. The dominating histological pattern of TL is that of a bulbous infundibular hyperplasia with tricholemmal differentiation, akin to the outer root sheath of the hair follicle {28}. There are one or more bulbous lobules, always in continuity with the epidermis. These lobules consist of numerous pale and clear isomorphic epithelia, most of which are PAS positive. At the periphery, pale columnar cells are arranged in a palisade, bordered by a prominent PAS-

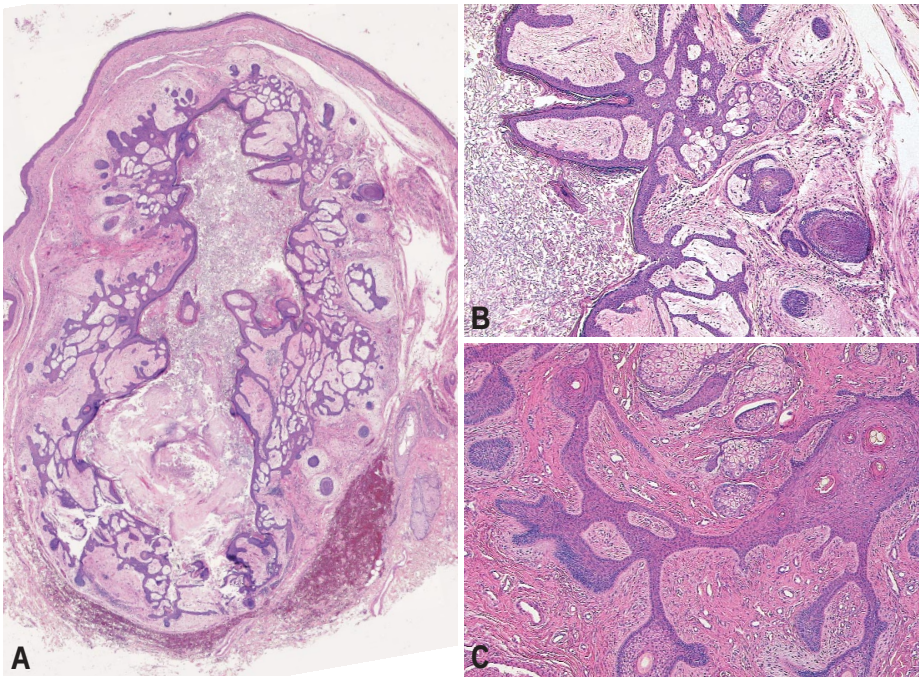

Fig. 3.44 Trichofolliculoma. **A** Note reticulate pattern of vellus follicles in devolution. **B** Detail. Reticulate epithelial strands, sebaceous lobules and few vellus follicles. **C** Note sebaceous lobules and dense fibrotic stroma. Vellus follicles in different stages of devolution.

and type IV collagen-positive basement membrane. Central foci of epidermal / infundibular keratinization, occasional small and inconspicuous squamous eddies, and keratinous microcysts in larger lesions are occasional findings {28}. There are no mitoses.

Desmoplastic tricholemmoma is a variant of TL characterized by a highly desmoplastic stroma with broad zones of sclerosis and distinctive artifactual clefts. Instead of "pushing" smooth lobular contours there may be a pseudoinvasive interface akin to pseudocarcinomatous epithelial hyperplasia, simulating carcinomatous growth {1079,2333}.

Differential diagnosis

Warts, basal cell carcinomas, squamous cell carcinomas, trichoblastomas, seborrhoeic keratoses, and keratosis follicularis inversa may contain areas of tricholemmal differentiation {31,1931}. The tumour of the follicular infundibulum exhibits a plate-like pattern with interconnecting horizontally oriented epithelial strands. Inverted follicular keratosis consists of basaloid and squamous epithelia, associated with large numbers of squamous eddies (i.e. concentric layers of squamous cells in a whorled pattern, sometimes keratinized).

Histogenesis

According to strict topographical anatomical criteria, TL arises from the follicular infundibulum and differentiates toward the outer [tricholemmal] root sheath {28}. Its superficial folliculo-infundibular location militates against the classification of TL as a neoplasm of the lower portion of the hair follicle (i.e. the [outer] tricholemmal sheath).

However, it is still a matter of debate whether TL is of hamartomatous/neoplastic {318,991,1906,1931} or of viral origin {15,28,31}. The detection of HPV DNA in tricholemmomas by PCR {2688} favours the latter view of TL as a resolving verruca vulgaris with tricholemmal differentiation {15,28, 31}.

Prognosis and predictive factors

TL is an entirely benign cutaneous neoplasm. Multiple TLs are a hallmark of Cowden disease and should prompt a search for internal malignancy.

Trichofolliculoma

Definition

Trichofolliculoma (TF) is a follicularly differentiated hamartoma generally appearing during adult life.

ICD-O code 8101/0

Epidemiology

TF represents a rare hamartoma mostly occurring during adulthood (with a wide range of ages between 11 and 77 years {28}) without sex predilection {887}.

Localization

TF favours the head and neck region, foremost the face. Most lesions are situated around the nose {887}.

Clinical features

TF presents as a solitary asymptomatic dome-shaped lesion with a smooth surface and a widely dilated central ostium from which a small tuft of delicate white hairs emerges. Lesions are small, ranging between 0.5 and 1.0 cm in diameter {28}.

Histopathology

The main histological features of TF are reflected by its "Caput Medusae" pattern {28}: embedded in a highly fibrocytic stroma, large numbers of vellus follicles with upper and lower segments like those of normal follicles radiate from the perimeter of a dilated infundibulum.

TF is a symmetrical, well-circumscribed, vertically oriented lesion composed of three components: infundibulo-cystic, follicular, and stromal {28}. The centre of the lesion is occupied by one or more widely dilated infundibulo-cystic structures that are continuous with the epidermis and open to the surface of the skin through an ostium. The cystic lumina may be filled with innumerable corneocytes and vellus hairs. From the epithelial walls of the infundibular cystic spaces smaller infundibula radiate, to which are attached vellus follicles in various numbers. These vellus follicles are not associated with muscles of hair erection or with sebaceous ducts, albeit sebaceous cells arranged as solitary units or in lobules may occur within the lining epithelium of the central infundibulo-cystic structure.

The morphology of the individual vellus follicles may vary from normal to strikingly aberrant {28}. Normal vellus follicles may exhibit all stages of the follicular cycle {2106}. The whole lesion is embedded in a cellular connective tissue sheath, which is separated from the adjacent normal dermis by prominent shrinkage clefts. The highly fibrocytic stroma

which surrounds the individual vellus follicle resembles perifollicular sheath {28}. The existence of considerable numbers of Merkel cells in all trichofolliculomas underlines their classification as hamartomas with follicular differentiation {967}.

Variants

TF is a complex lesion with protean features {28}. Some of these are caused by the evolutionary and devolutionary alteration of the vellus hair follicles in their regular biological cycles {2106}. In this context, folliculo-sebaceous cystic hamartoma {1275,2187} may be interpreted as a TF at its very late stage with nearly complete regression of the transient follicular epithelium, but with concurrent growth and maturation of sebaceous elements {2105}. Sebaceous trichofolliculoma {1846} exhibits distinct sebaceous lobules at its outer circumference, but lacks vellus follicles that radiate from the epithelial lining of the dilated infundibulum. The latter criterion militates against the classification of sebaceous trichofolliculoma as a true TF {28}. Hair follicle naevus is regarded as a TF that was histologically sampled at its periphery {28}. There is a striking predominance of mature vellus follicles and the central infundibular lumen may be quite inconspicuous.

Prognosis and predictive factors

TF represents an entirely benign cutaneous hamartoma with no reports of tumour progression or aggressive clinical course.

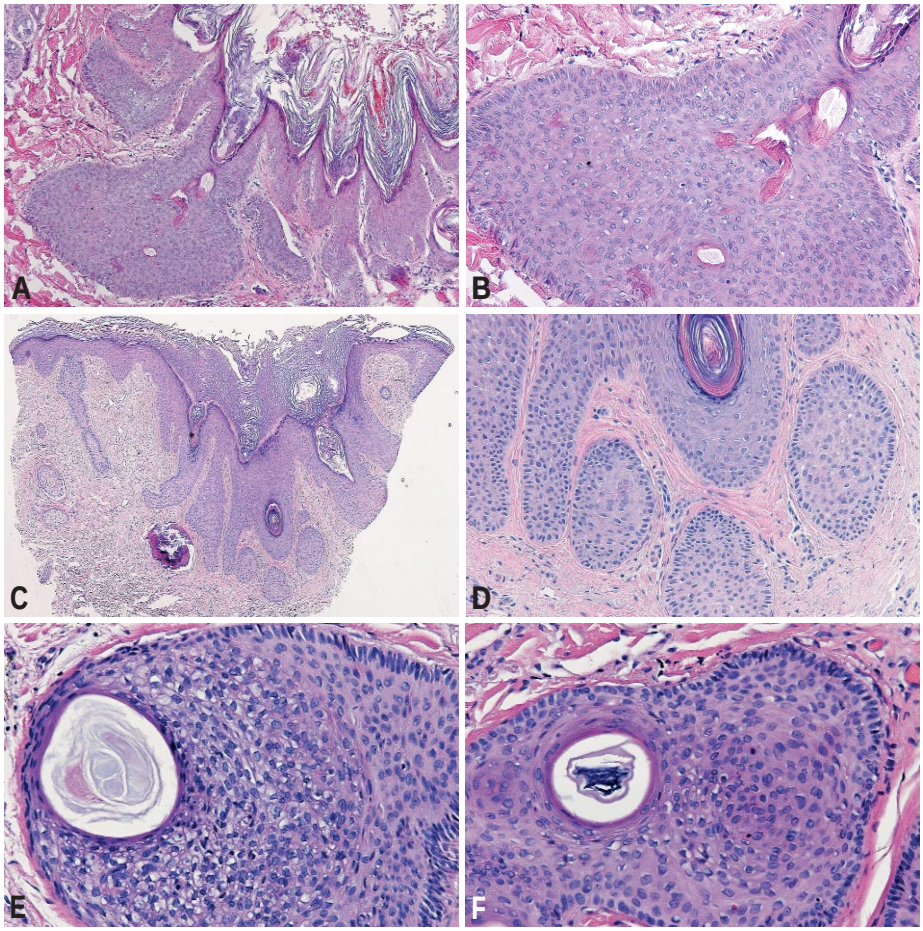

Fig. 3.45 Pilar sheath acanthoma. **A** The characteristic infundibular and isthmic differentiation is stereotyped. Note the lack of a hair filament or inner root sheath. **B** The lobule contains red-pink corneocytes, characteristic of the isthmus. **C** This pilar sheath acanthoma does not have the obvious widened ostium, but it does contain the lobules of isthmic epithelium. **D** The lobules have a nearly syncytial pattern. **E** This lobule has clear-cell changes and syncytial, pink cell changes. Note the lack of inner sheath or hair filament. **F** The small, partly cornified cyst seen here contains no hair filament. Parts of the transient portion of the follicle are rarely seen in pilar sheath acanthoma.

Pilar sheath acanthoma

Definition

Pilar sheath acanthoma is a follicular neoplasm differentiated toward the permanent part of the hair follicle, to wit, the infundibulum and the isthmus. [The infundibulum is an extension of epidermis to meet the isthmus, but both function as part of the follicular sheath].

Synonyms

Infundibuloisthmicoma

Clinical features

Pilar sheath acanthomas affect adults of either sex, and are identified usually on the face. They are small, solitary papules up to 5 mm in diameter, with a central 1-2 mm punctum, lacking hair filaments, and will express corneocytes if squeezed. There are no known associated syndromes and no known genetic abnormalities within the neoplasms {29, 232,473,1570,2212,2402}.

Histopathology

The classical example consists of a patulous infundibulum that connects with lobules of epithelium differentiated toward both the infundibulum and the isthmus. This differentiation results in blue-gray (infundibular) and pink (isthmic) corneocytes that fill the follicular canal. There can be a minor component of stem or bulb (or both) differentiation in some examples. Consequently there is, as a rule, no evidence of hair filaments in these neoplasms.

Differential diagnosis

Pilar sheath acanthoma should be differentiated from dilated pore (Winer), trichofolliculoma, and fibrofolliculoma/trichodiscoma. Dilated pore is an infundibular cyst that has proliferated minimally, but lacks isthmic differentiation.

Trichofolliculoma is a hamartoma and contains fully formed vellus hair follicles that radiate around a centrally positioned cyst. Fibrofolliculoma/trichodiscoma is also a hamartoma found characteristically in the Birt-Hogg-Dubé syndrome and that contains thin strands of infundibular epithelium connected so that fenestrations of delicate fibrous stroma are found within. Additionally, considerable stroma, lacking epithelium, is often identified (trichodiscoma).

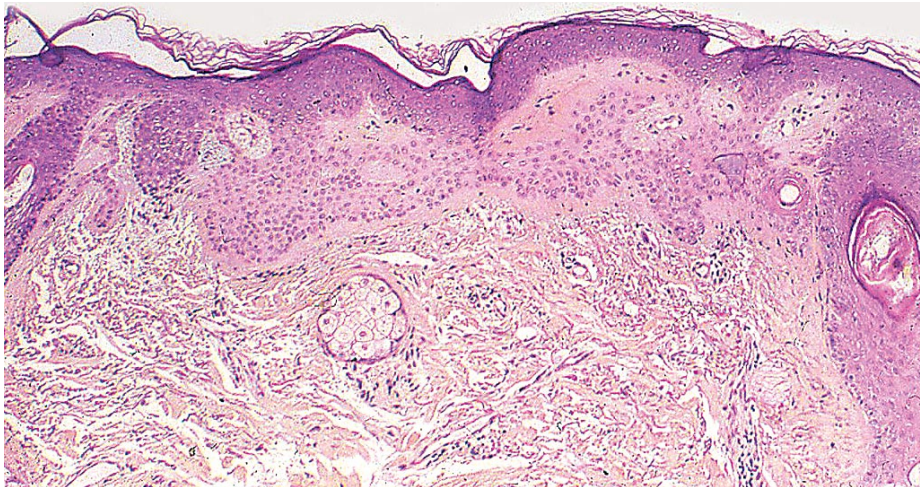

Fig. 3.46 Histopathology of a typical tumour of the follicular infundibulum, with horizontal proliferation of pale keratinocytes in the papillary dermis. Note the connection with the overlying epidermis.

Prognosis and predictive factors
The neoplasm is benign; no treatment is necessary.

Tumour of the follicular infundibulum

Definition
Tumour of the follicular infundibulum (TFI) is a benign epithelial neoplasm of follicular origin.

Synonym
Infundibular tumour.

Epidemiology
TFI is an uncommon tumour occurring in adults, mainly after the age of 50. In two studies, TFI accounted for less than 10 per 100,000 skin samples. They can be observed on the face of patients with Cowden syndrome or on the surface of naevus sebaceous.

Localization and clinical features
Solitary TFI is mainly localized on the face and presents as a small flesh-coloured nodule, resembling basal cell carcinoma. Multiple or eruptive TFI present as hundreds of symmetrically distributed hypopigmented geometric macules localized on the face, neck, trunk, or on the periocular area. Sun exposure increases the contrast between normal skin and the tumours.

Histopathology
TFI is a plate-like horizontal proliferation of pale keratinocytes, which is localized in the papillary dermis and shows multiple connections with the overlying epidermis or with the infundibulum. The cells are paler and larger than normal keratinocytes and their cytoplasm stains with PAS. The tumour is sharply circumscribed and limited by a dense network of elastic fibres easily demonstrated by orcein staining. Desmoplastic and sebaceous variants have been described {557,1485}.

Histogenesis
TFI derives from the normal follicular infundibulum. The occurrence of multiple TFI suggests a possible genetic basis, which remains to be established.

Prognosis and predictive factors
The prognosis is good, except in rare patients with multiple TFI who may develop basal cell carcinomas.

Fibrofolliculoma / trichodiscoma

Definition
Fibrofolliculoma and trichodiscoma are different developmental stages in the life of one single benign appendageal hamartomatous tumour, which differentiates towards the mantle of the hair follicle {27}. Fibrofolliculoma represents the early and trichodiscoma the late stage in the development of this lesion {27}.

ICD-O code 8391/0

Synonyms
Trichodiscoma first was erroneously thought to arise from or to differentiate toward the hair disk (Haarscheibe) and therefore bears this name {1836}. Fibrofolliculoma was often used for perifollicular fibroma in the past. Neurofollicular hamartoma and trichodiscoma are the same {2048}. "Mantleoma" was used as the overall term for both fibrofolliculoma and trichodiscoma {27}.

Epidemiology
Fibrofolliculomas/trichodiscomas are rare appendageal tumours, occurring equally in males and females, usually not before the third decade of life.

Etiology
The etiology of the solitary lesions is unknown. The BHD gene was mapped to 17p11.2 {1256}.

Localization
The preferred sites of location are the face, neck and chest.

Clinical features
Fibrofolliculomas and trichodiscomas cannot be distinguished clinically {248}. The onset of the lesions is mostly in the third to fourth decade of life. They are skin coloured, smooth, dome-shaped papules, measuring 2-4 mm in diameter {248}. The lesions are asymptomatic.

Histopathology
There is a histomorphological continuum between fibrofolliculoma and trichodiscoma. However, most of these presented cases were actually fibrofolliculomas which were merely prepared histologically in an unusual sectioning technique, resulting in misinterpretation as perifollicular fibroma {2107}.

Fibrofolliculoma
The fibrofolliculoma is composed of similar amounts of epithelial as well as mesenchymal elements. At scanning magnification there are one or several adjacent small, vertically oriented infundibulocystic structures, surrounded by a prominent stroma, which is well demarcated from the surrounding normal reticular dermis by clefts. Anastomosing cords and strands of epithelium arise from the dilated infundibulum. Often, cells with sebaceous differentiation are apparent in these epithelial cords. The surrounding

prominent stroma is made up of fine, fibrillary ribbon-like bundles of collagen, often arranged parallel to one another and perpendicular to the epithelial cords. The stroma contains numerous spindled fibrocytes and many venules and capillaries. Elastic fibres are markedly reduced. The stroma is often mucinous, comparable to the stroma of the follicular mantle-region.

Trichodiscoma

Trichodiscoma is a horizontally oriented dome-shaped tumour composed of more mesenchymal tissue than epithelial elements. A prominent tumour stroma of elliptical shape is seen, possessing the same cellular characteristics as in fibrofolliculoma. In peripheral zones of this prominent stroma, small groups of sebaceous lobules may be found. Mantle-like epithelial structures are uncommon. Plaque-like variants of fibrofolliculomas/trichodiscomas with confluence of single lesions and a resulting extension up to several cm in diameter have been described {2103}.

The differential diagnosis of fibrofolliculoma includes trichofolliculoma at a late stage {2105}. Fatty tissue is a typical finding in late stages of trichofolliculoma but not in fibrofolliculoma. Perifollicular fibroma/fibrous papule is also similar to fibrofolliculoma. However, it is usually devoid of mucin and shows no mantle-like epithelial proliferations {27}. Trichodiscomas have to be differentiated from neurofibromas and cutaneous myxomas {521}. However, the latter tumours lack the sebaceous epithelial component, typical of trichodiscoma.

Immunoprofile

The epithelial and mesenchymal parts of the lesions show the common reactivities to cytokeratins and vimentin. The tumour stroma is strongly reactive with antibodies to CD34, reflecting its differentiation towards the follicular mantle region.

Histogenesis

Histologic and immunohistologic data suggest that fibrofolliculoma/trichodiscoma is derived from/differentiated to the mantle region of the hair follicle {27,521}. The mantle region is a specialized epithelial-mesenchymal structure, located at the lower end of the follicular infundibulum {606} and is the source and starting point for the development of the sebaceous glands {27}. Fibrofolliculoma/trichodiscoma is considered to be a hamartomatous lesion. Its mesenchymal part may be responsible for the origin and growth of the whole lesion, leading to the distinctive mesenchymal- epithelial proliferation, reminiscent of a deformed mantle region {2103}. The postulated cell of origin therefore might be a specialized dermal dendritic spindle cell, normally situated in the mantle region {521,2103}.

Genetic susceptibility

Multiple fibrofolliculomas/trichodiscomas are part of the Birt-Hogg-Dubé syndrome (BHD), an autosomal inherited syndrome, also affecting the lung and kidney {248,2579}. The BHD gene is located at 17p11.2 {806} and encodes folliculin whose function is unknown. The patients may have multiple, often bilateral renal carcinomas, frequently representing unusual histological subtypes. They also have an increased frequency of spontaneous pneumothoraces.

Prognosis and predictive factors

Fibrofolliculoma/trichodiscoma is a benign lesion, excised primarily for cosmetic reasons. However, it is an important marker for Birt-Hogg-Dubé syndrome and its associated complications.

Tumours with sebaceous differentiation

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M.R. Wick
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C. Wallace

Sebaceous carcinoma

Definition
Sebaceous carcinoma (SC) is a cytologically- and/or architecturally- malignant neoplasm demonstrating exclusive sebocytic differentiation.

ICD-O code 8410/3

Historical annotation
Historically, SCs have been subcategorized into ocular and extraocular subtypes {1510A, 1696A, 1827A, 1856A, 2511A,2609A}, although there is no inherent biological difference between such lesions.

Epidemiology
SC usually arises in adults, with an average patient age of 62 yrs. and a female predominance, by a factor of roughly 2:1. Tumours of the eyelids are preferentially seen in Asian patients, and also may represent a complication of prior radiotherapy {1067A}.

Clinical features
All SCs present as painless masses, which can be multifocal. In the ocular adnexae, they may be mistaken clinically for chalazions, blepharitis, cicatricial pemphigoid, or conjunctivitis {642,839, 2542}. In extraocular sites, sebaceous malignancies are commonly confused with basal cell carcinomas and squamous cell carcinomas.
Most extraocular SCs are encountered in the skin of the head and neck, followed by the trunk, genitals, and extremities. Rare cases may also be seen in the mouth, salivary glands, lungs, and breasts.

Macroscopy
SCs are nodules that typically enlarge slowly but may occasionally grow rapidly; some become ulcerated. A minority of individuals with this tumour have the Muir-Torre syndrome {2227}.

Histopathology
Sebocytic differentiation, typified by multivesicular and vacuolated clear cytoplasm, is the sine qua non for sebaceous neoplasms including SC. It must be separated from simple cytoplasmic clarity, a microscopic change that is relatively common in cutaneous neoplasms of many other lineages {2294}. SCs are organoid proliferations comprising dermal lobules of variably-atypical polygonal cells, with a fibrovascular stroma that typically lacks desmoplasia. Central portions of the tumour cell nests may be necrotic, yielding a "comedo" growth pattern. The cells of well-differentiated neoplasms show abundant cytoplasm and oval vesicular nuclei with distinct nucleoli; mitotic figures are variable in number. On the other hand, more poorly-differentiated SCs show high nuclear-to-cytoplasmic ratios, nuclear pleomor-

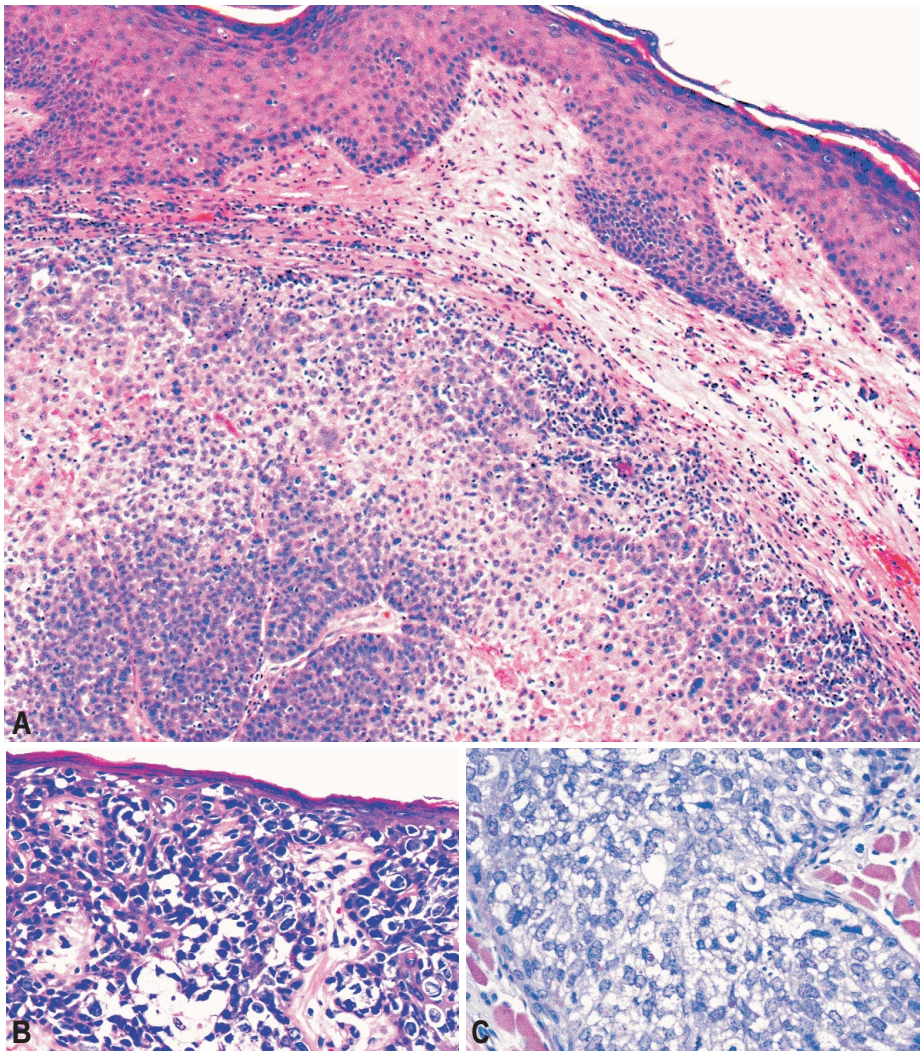


Fig. 3.47 Sebaceous carcinoma. **A** Sebaceous carcinoma, represented by a lobular proliferation of atypical epithelioid cells in the dermis. Multivesicular cytoplasmic vesiculation is present. **B** Extensive in-situ involvement of the surface epithelium is present in this example of sebaceous carcinoma. **C** "Bubbly" cytoplasmic vacuolization is apparent in sebaceous carcinoma.

phism, prominent nucleoli, brisk mitotic activity - sometimes with pathologically-shaped forms - and amphophilic or basophilic cytoplasm. Intracellular vacuoles are sometimes not seen easily in those lesions, and may require the use of special histochemical stains, such as the oil-red-O or Sudan IV methods, to detect them {2540}.

The grading of SCs - into grades I through III - is based on growth patterns rather than on their cytological features {1892}. Tumours that are constituted by well-demarcated, roughly equally-sized cellular lobules are graded as I; those with an admixture of well-defined nests with infiltrative profiles or confluent cell groups are grade II lesions; and grade III SCs exhibit highly-invasive growth or a medullary sheet-like pattern.

All SCs have the potential for an association with overlying carcinoma in-situ (CIS), or extramammary Paget disease (EPD) of the sebaceous type, or both, in the surface epithelium and in other epidermal appendages (especially pilosebaceous units) {448,1702}. The latter lesions are probably marker lesions that represent a cutaneous "field" defect, rather than being direct precursors of, or extensions from, underlying SC. This premise has support from occasional cases in which only intraepithelial sebaceous carcinoma is present, in the absence of an invasive component in the dermis {1510}. In pragmatic terms, however, one should always consider the possibility of infiltrative SC whenever EPD or carcinoma in-situ is seen in a superficial biopsy.

Variants

Selected microscopic variants of SC deserve special comment because they may engender interpretative confusion with other cutaneous tumours {2540, 2542}.

Basaloid SC comprises small cells with scant cytoplasm, and may often show nuclear palisading at the periphery of cellular nests. It commonly manifests a grade III growth pattern, and overtly-sebocytic elements are sparse and difficult to identify as such.

Squamoid SC shows prominent squamous metaplasia, often with keratin pearl formation; some examples may also demonstrate spindle-cell areas, equating with a sarcomatoid image.

Still other examples of SC may demonstrate pseudo-neuroendocrine organoid growth, focally resembling the pattern of "carcinoid" tumours {1235}. Based on these brief descriptions, one could easily predict that basal cell carcinoma, squamous cell carcinoma, neuroendocrine tumours, epithelial malignancies with potential spindle-cell differentiation, and a variety of clear-cell neoplasms in the skin may enter differential diagnostic consideration in selected cases of SC.

Immunoprofile

SC shows immunoreactivity for several generic epithelial markers such as pankeratin, epithelial membrane antigen (EMA), CD15, CU18, CA15.3, and Thomsen-Friedenreich antigen {75}. EMA labeling may enhance the cytoplasmic "bubbliness" of the tumour cells in this neoplasm. That pattern is distinctive, but it is not observed in all examples of SC. Reactivity for androgen receptor protein and human milk fat globule protein-2 also has been reported in SC {182,2191}. However, it is not yet know whether the latter markers are diagnostically helpful in excluding other clear-cell tumours.

Genetic susceptibility

Immunoreactivity in SC for various DNA-mismatch repair gene products, especially for MSH-2, has been correlated with a relationship to the Muir-Torre complex {1468,1536}. However, virtually no systematic data are available on the detailed genetic profiles of either sporadic or syndromic SC.

Prognosis and predicitive factors

Both ocular and extraocular SCs have a 30-40% risk for local tumour recurrence, 20-25% for distant metastases, and 10-20% for tumour-related mortality {1645}. Some reports appear to support the premise that immunoreactivity for mutant p53 protein at a level of >10%, and for proliferating cell nuclear antigen at a level of >25% may be linked to an adverse outcome {977}. A similar comment may apply to those lesions that overexpress the c-erbB-2/HER-2/neu protein {472,977}.

Sebaceous adenoma

Definition

Sebaceous adenoma is a small tumour composed of basaloid cells and fully differentiated sebocytes.

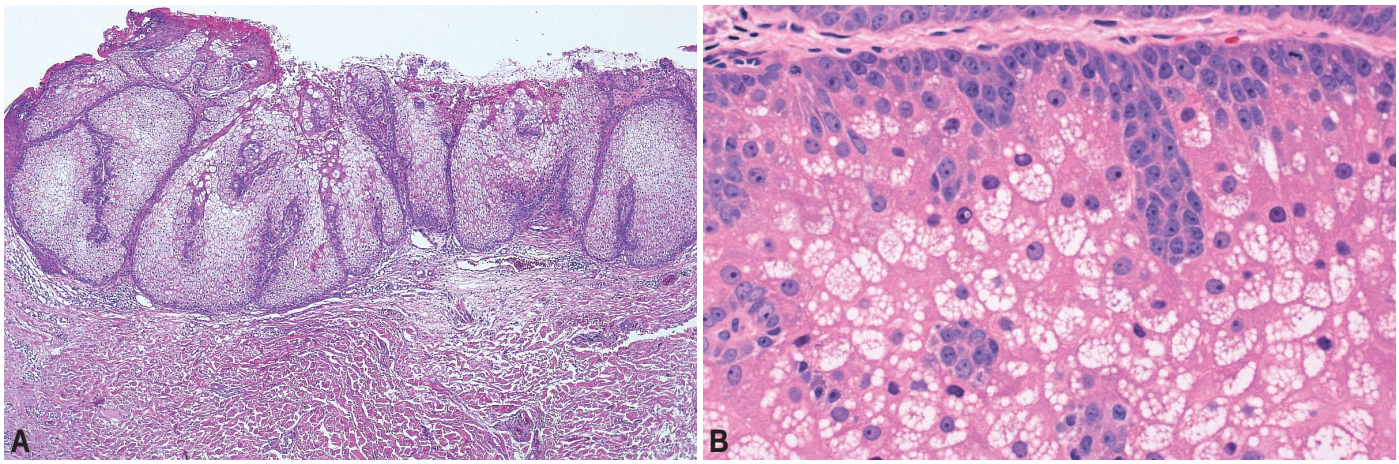


Fig. 3.48 Sebaceous adenoma. **A** Well circumscribed lobulated sebaceous tumour. Fully differentiated sebocytes predominate and epidermis is replaced by the tumour. **B** High magnification of the periphery of the lobule.

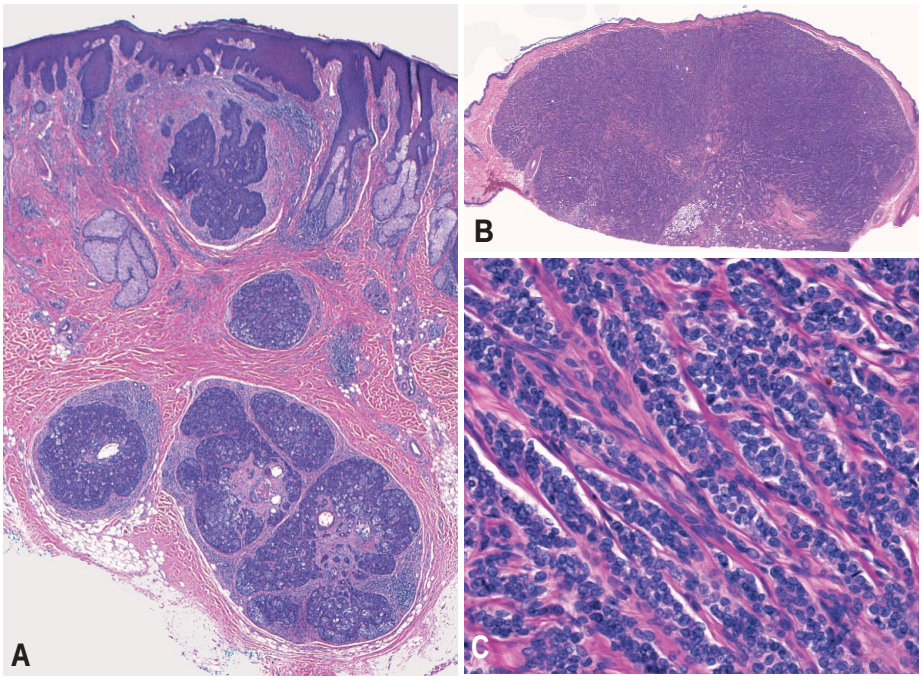


Fig. 3.49 Sebaceoma. **A** Low power view demonstrating a neoplasm with multiple well-circumscribed nodules of different sizes. **B** Example of a reticulated sebaceoma. The neoplasm is composed predominantly of uniform basaloid cells distributed in a reticulated pattern. Please note the presence of cells with sebaceous differentiation at the base of the lesion. **C** Cytologically the basaloid cells are uniform and present between collagen bundles.

ICD-O code 8410/0

Epidemiology
Sebaceous adenomas occur mostly as solitary lesions in persons older than forty years {1993}. Lesions are located usually on sun-damaged skin of the head and neck area. Rarely patients have multiple lesions {2258}, then the possibility of Muir-Torre syndrome should be considered.

Clinical features
Sebaceous adenomas are relatively small yellowish tumours often covered by a scale or crust {2353}.

Histopathology
This well-circumscribed tumour is made up of small lobular aggregations of sebocytes with a rim of basaloid cells at the periphery, recapitulating the maturation of sebocytes from the periphery to the centre comparable to normal sebaceous glands {1542}. Lobules are composed of vacuolated fully differentiated sebocytes and these cells predominate markedly over the basaloid sebocytes. Sebaceous adenoma is often connected to the overlying epidermis, and may be covered by a thick plug of keratin and disintegrated sebocytes. Ductal structures are rare, as are mitotic figures.
Sebaceous adenoma has to be differentiated from sebaceous hyperplasia, where the sebaceous lobules are arranged around a central placed follicular infundibulum that is connected to the epidermis. In sebaceous hyperplasia the epidermis may show changes mimicking seborrhoeic keratosis.
Sebaceomas are nodular lesions of basaloid undifferentiated sebocytes and only a few small groups of vacuolated sebocytes. There may be morphological overlaps between sebaceous adenoma and sebaceoma. The term sebomatricoma was introduced as an attempt to simplify the nomenclature of the different benign sebaceous adnexal tumours and to summarize them under one name {2003}.

Genetics
Little is known about the genetics of sebaceous adenoma. Most of the tumours occur as solitary lesions but a few examples of SA are part of the spectrum of different sebaceous tumours in MTS. By immunohistochemistry it is possible to look for a loss of MSH-2, MLH-1 repair proteins. Tumours related to a mismatch repair gene defect show a microsatellite instability in a high percentage {1334}.

Prognosis and predictive factors
Sebaceous adenomas are benign tumours. If the patient has Muir-Torre syndrome, the prognosis depends on the associated internal malignancies.

Sebaceoma

Definition
Sebaceoma is a benign, adnexal neoplasm with sebaceous differentiation. It is characterized by multiple, smooth-bordered lobules and cystic spaces composed primarily of immature sebaceous cells admixed with randomly scattered mature sebocytes.

ICD-O code 8410/0

Synonyms
Sebaceous epithelioma, basal cell epithelioma with sebaceous differentiation, and sebomatricoma.

Epidemiology
Sebaceomas are rare sebaceous neoplasms that may be associated with the Muir-Torre syndrome {1624,2114}. They typically arise in late adulthood with the mean age of diagnosis being at approximately 70 years of age, but may be seen in early adulthood {2378}. The tumours have a predilection for females.

Localization
Sebaceomas occur mainly on the face and scalp, with rare cases reported on the trunk {226,636,1710,1749,1922, 2258,2378}.

Clinical features
Clinically, sebaceomas present as yellow to orange solitary papules on the head and neck {636,2258,2378}. Those lesions associated with the Muir-Torre syndrome may be multiple {347,1624, 2114}. They are slow-growing neoplasms and do not recur after excision {636, 2258,2378}.

Histopathology
Architecturally sebaceoma is composed of multiple well-circumscribed lobules of various size centred on the dermis. The lobules often contain ducts and cystic

areas containing holocrine secretion and only rarely do they connect with the overlying epidermis. A brightly eosinophilic cuticular material lines both the ducts and cysts, similar to what is seen in the normal sebaceous ducts.
Cytologically the neoplasm is comprised predominantly of small, uniform basaloid cells with bland nuclear features admixed with haphazardly distributed mature-appearing sebaceous cells. The mature sebaceous cells have abundant vacuolated cytoplasm and ovoid nuclei, which often have a scalloped nuclear membrane. Rare typical mitoses may be seen, however, atypical mitosis and necrosis are not features of sebaceoma. The surrounding stroma is dense, eosinophilic connective tissue. There is no cleft seen between the neoplasm and the stroma, as is the case with basal cell carcinoma.
A wide variety of patterns have been described for sebaceoma, sometimes even within the same neoplasm. These include reticulated, cribriform and glandular {634,1710}. There have been reports of a variant with eccrine differentiation, a pigmented variant and a sebaceoma that arose in a seborrhoeic keratosis {226,1749,1922}. Those lesions that arise in Muir-Torre syndrome may have a keratoacanthoma-like architecture {347}.

Immunoprofile
Immunohistochemistry demonstrates positivity with high-molecular weight keratin. EMA stains most mature sebocytes, and thus will only show positivity of the mature vacuolated sebaceous cells scattered amongst the tumour, while the basaloid cell compartment will be negative {1710}. Several reports have demonstrated loss of heterozygosity as well as microsatellite instability in a marker gene located near hMSH2 in patients with sebaceoma and Muir-Torre syndrome {1332,1536}. By immunohistochemistry it is possible to look for a loss of MSH-2, MLH-1 repair proteins {1334}.

Prognosis and predictive factors
Sebaceoma is a benign neoplasm that does not recur after treatment or metastasize. It may be a marker of Muir-Torre syndrome, in which case the patient has a high risk of internal malignancies.

Cystic sebaceous tumour

Definition
Cystic sebaceous tumour is a large distinctive tumour with is almost always associated with Muir-Torre syndrome (MTS) {1999}.

ICD-O code 8410/0

Epidemiology
Cystic sebaceous tumours occur nearly exclusively in MTS, which is a phenotypical variant of the hereditary non polyposis colon cancer syndrome (HNPCC). MTS is inherited in an autosomal-dominant fashion and is caused by genetic alterations within the DNA mismatch repair system. Patients often have a family history of malignancies and most are affected with a variety of internal malignancies such as colon cancer, urothelial cancer, endometrial cancer and others. MTS patients develop a broad spectrum of different sebaceous skin tumours, which may be difficult to classify {347, 1624}, and keratoacanthomas. Among the sebaceous tumours, CSTs are unique because they serve as diagnostic markers for the syndrome. MTS has a male preponderance and is clinically diagnosed mostly in adults older than 40 years.

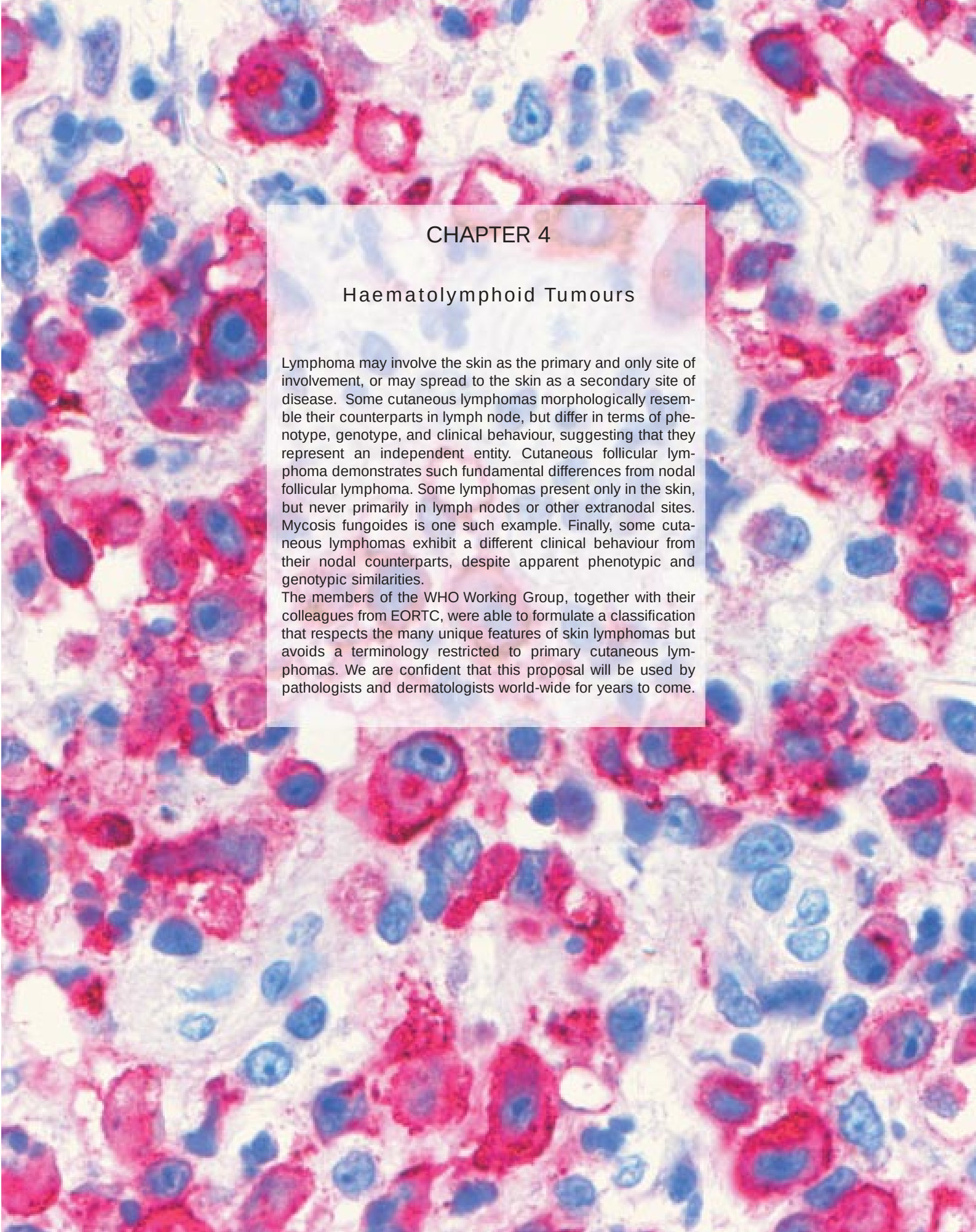
Localization
The upper trunk is the most common location.

Clinical features
CSTs are usually solitary, but rarely can be multiple. They resemble hair follicle cysts and present as dermal nodules. In patients diagnosed with internal malignancies CST is often excised in order to rule out a metastatic skin lesion.

Histopathology
CST are large, well circumscribed dermal tumours which may connect to the upper dermis, and usually extend into the subcutis. The outer surface of the neoplasm may be obscured in cases with an accompanying granulomatous inflammation due to the ruptured cyst wall. Well-differentiated CST show a cystic growth pattern with a small line of basaloid undifferentiated sebaceous matrix cells at the periphery and a broad zone of fully differentiated vacuolated sebocytes towards the centre of the cystic tumour. Well-differentiated CST do not show cytological atypia, and have only few mitoses. Ductal structures may be seen in the cyst wall. Proliferation of tumour cells produces infoldings of the cyst wall in some CST. The more solid variants are predominantly composed of undifferentiated sebaceous cells with mitotic figures and variable cytologic atypia.

Genetics
Germline mutations of the DNA mismatch repair genes are responsible for MTS. In the vast majority of cases the associated tumours show a complete loss of the corresponding mismatch repair protein (MSH2 or MLH1). This can be demonstrated immunohistochemically by antibodies directed against MSH2 and MLH1 protein {1469,1536,2227}. A loss of the nuclear staining for one of these antibodies within the tumour cells accompanied by a positive staining of nuclei in the surrounding tissue strongly suggests loss of the corresponding DNA mismatch repair protein. Typically, these tumours show high microsatellite instability {1332, 1469, 1999}.

Prognosis and predictive factors
Some authors interpret cystic sebaceous adenoma as a variant of sebaceous carcinoma {1733}. So far there is no clinical evidence that these tumours in any case represent malignant sebaceous tumours {872,1624,1999}. Because of these conflicting views, complete excision is recommended.
The prognosis in MTS is determined by the nature of the associated internal malignancies. In most cases CST develops after the first internal malignancy, but in up to 25% of cases they represent the first clinical sign of MTS. Even in a patient with a solitary CST who does not fulfil the clinical criteria for MTS, a molecular genetic analysis may show a germline mutation in a mismatch repair gene {1333}. Because of the specific marker function of CST it is possible to detect patients and families with an inherited DNA mismatch repair defect predisposing to various types of internal cancer.



CHAPTER 4

Haematolymphoid Tumours

Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotype, genotype, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Some lymphomas present only in the skin, but never primarily in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities.

The members of the WHO Working Group, together with their colleagues from EORTC, were able to formulate a classification that respects the many unique features of skin lymphomas but avoids a terminology restricted to primary cutaneous lymphomas. We are confident that this proposal will be used by pathologists and dermatologists world-wide for years to come.

WHO / EORTC classification of cutaneous lymphomas[1]

Mature T-cell and NK-cell neoplasms	
Mycosis fungoides	9700/3
Pagetoid reticulosis (localized disease)	
Follicular, syringotropic, granulomatous variants	
Granulomatous slack skin	
Sezary syndrome	9701/3
CD30+ T-cell lymphoproliferative disorders of the skin	
Lymphomatoid papulosis	9718/1
Primary cutaneous anaplastic large cell lymphoma	9718/3
Subcutaneous panniculitis-like T-cell lymphoma**	9708/3
Primary cutaneous peripheral T-cell lymphoma (PTL), unspecified	9709/3
Subtypes of PTL (provisional)	
Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma	
Cutaneous gamma/delta-positive T-cell lymphoma	
Primary cutaneous small/medium CD4+ T-cell lymphoma	
Extranodal NK/T-cell lymphoma, nasal type	9719/3
Hydroa vacciniformia-like lymphoma (variant)	
*Adult T-cell leukaemia/lymphoma**	9827/3
*Angioimmunoblastic T-cell lymphoma**	9705/3

Mature B-Cell neoplasms	
Cutaneous marginal zone B-cell lymphoma (MALT-type)	9699/3
Cutaneous follicle centre lymphoma	9690/3
Cutaneous diffuse large B-cell lymphoma	9680/3
*Intravascular large B-cell lymphoma**	9680/3
*Lymphomatoid granulomatosis**	9766/1
*Chronic lymphocytic leukaemia**	9823/3
*Mantle cell lymphoma**	9673/3
*Burkitt lymphoma**	9687/3
Immature haematopoietic malignancies	
Blastic NK-cell lymphoma *** / CD4+/CD56+ haematodermic neoplasm	9727/3
Precursor lymphoblastic leukaemia/lymphoma	
*T-lymphoblasic leukaemia**	9837/3
*T-lymphoblastic lymphoma**	9729/3
*B-lymphoblastic leukaemia**	9836/3
*B-lymphoblastic lymphoma**	9728/3
*Myeloid and monocytic leukaemias**	
Hodgkin lymphoma*	

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

* Extracutaneous lymphomas frequently involving the skin as a secondary site are printed in *italics*.

** Definition is restricted to lymphomas of alpha/ beta T-cell origin

*** Recent evidence suggests an origin from a dendritic cell precursor. In recognition of uncertain histogenesis, the term CD4+/CD56+ haematodermic neoplasm" is preferred.

TNM classification of cutaneous T-cell lymphomas (CTCL)

Stage	T	N	M
Ia	T1 Limited lesions covering <10% of the skin surface	N0 no palpable lymph nodes, pathology negative for CTCL	M0 no involvement of visceral organs
Ib	T2 generalized lesions covering 10% and more of the skin surface	N0 no palpable lymph nodes, pathology negative for CTCL	N0 no involvement of visceral organs
IIa	T1 Limited lesions covering <10% of the skin surface,or T2 generalized lesions covering 10% and more of the skin surface	N1 palpable peripheral lymph nodes pathology negative for CTCL	M0 no involvement of visceral organs
IIb	T3 tumours, one or more	N0: no palpable lymph nodes, pathology negative for CTCL or, N1 palpable peripheral lymph nodes, pathology negative for CTCL	M0 no involvement of visceral organs
III	T4 generalized erythroderma	N0: no palpable lymph nodes, pathology negative for CTCL or N1 palpable peripheral lymph nodes, pathology negative for CTCL	M0 no involvement of visceral organs
IVa	T1-4	N2:no palpable peripheral lymph nodes, pathology positive for CTCL or N3:palpable peripheral lymph nodes, pathology positive for CTCL	M0 no involvement of visceral organs
IVb	T1-4	N0-3	M1 involvement of visceral organs

Modified, from Refs. {333,344,2537}.

WHO / EORTC Classification of cutaneous lymphomas

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The skin is the second most common site of extranodal lymphoma, following the gastrointestinal tract {340}. Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Because the clinical implications of primary and secondary cutaneous lymphoma are different, the dermatologist and pathologist should be familiar with both types of neoplasms. For this reason it also is problematic to use a classification system restricted to primary cutaneous lymphomas {2523}. It is important for dermatologists, haematooncologists, and pathologists to use a unified system for the diagnosis and treatment of cutaneous lymphoma {1858}.

Nevertheless, cutaneous lymphomas present some unique clinical aspects. There are some diseases that present only in the skin, and are never primary in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotype, genotype, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities. These differences may be related to stage or tumour burden, or more fundamental biological differences. For example, some lymphomas composed of large centrocytes and centroblasts have an indolent clinical course when presenting as a localized cutaneous tumour, but a similar cytological process in lymph node would be considered aggressive, i.e. diffuse large B-cell lymphoma.

Dermatologists, haematooncologists, and pathologists must use a common language. In this spirit we utilize the WHO classification of lymphoid neoplasms {1121}, but we expand upon the unique features of many cutaneous lymphomas to emphasize their distinctive clinical and biological characteristics {336A,2522}. Additional clinical and morphological variants have been added, where appropriate, in order to comprehensively cover the many manifestations of cutaneous lymphoma. Atypical reactive lesions that may represent precursors of cutaneous lymphoma are discussed where relevant {336A,2522}.

Cutaneous lymphoproliferative disorders (CLD)

These include reactive lymphoid hyperplasias (so called cutaneous “pseudolymphomas”), prelymphomatous conditions and definite malignant lymphoma of low grade or of high grade malignancy. According to their biologic behaviour, CLD can be subgrouped into prognostic categories which are not reflected in the classifications, which however are of special interest for the patient and for the treating physician.

When diagnosing a cutaneous lymphoproliferative disorder, both the clinicopathologic classification and the biologic category should be considered. The advantage of such an approach is to provide the diagnosis according to the current WHO-classification of lymphomas, and in addition, to include essential information about the biologic behaviour, which may be significantly different than that of the nodal counterpart. These data are crucial for the clinician involved in counseling and treatment of the patient.

Reactive lymphoid hyperplasias (RLH) (pseudolymphomas)

These are reactive benign lymphoproliferative processes, localized or disseminated, which heal either spontaneously after elimination of the causative factor (e.g. drugs) or after treatment with non-aggressive (no severe side effects to be expected after long term application) modalities, and which do not recur after removal of the causative agent.

Prelymphomatous (“abortive”) disorders (PLD)

PLD show a chronic long-standing course, no spontaneous regression in most cases, and no extracutaneous spread with involvement of visceral organs. In some cases, clonality of the infiltrate can be demonstrated. However, in most cases the neoplastic cell clone never overcomes host control mechanisms and cannot expand and therefore does not convert into definite malignant lymphoma. Survival time is not affected.

Definite malignant lymphoma of low-grade malignancy (LLM). This category includes cutaneous lymphomas that show a slowly progressive course with systemic spread in later stages and have the potential for transformation into more aggressive high-grade malignant lymphomas. Survival time usually is greater than 5 years.

Definite malignant lymphoma of high-grade malignancy (LHM)

These diseases are characterized by a more rapid course than the low-grade lymphomas and usually exhibit a bad prognosis with survival times less than 5 years.

Mycosis fungoides

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Definition
Mycosis fungoides (MF) is the prototype of cutaneous T-cell lymphomas (CTCL) and can be defined as a peripheral, epidermotropic non-Hodgkin T-cell lymphoma of low grade malignancy initially presenting in the skin and showing stepwise clinical progression from patches to plaques and tumours, and distinct histological (except in early stages), phenotypic and genotypic features.

ICD-O code 9700/3

Synonyms and historical annotation
In 1806 Jean-Louis Alibert (1768-1837) {58} presented an extraordinary skin disease which he described in detail under the name of "Pian fungoides" in 1814 and as "Mycosis fungoides" in 1832 {58}. At his time the etiology of the disease was completely unclear. It is worth noting that Alibert in 1832 copied part of the text from Bontius {283}. Ernest Bazin (1807-1878) published three different stages {184}:
Période érythemateuse (erythematous stage: red colored patches)
Période lichénoide (the lichenoid stage: itching and different plaques with small papules).
Période fongoïdique, mycositique (fungal stage:mushroom-like tumours of different size).

Epidemiology
The incidence of MF from 1973 through 1992 in the USA was 0.36/ 100'000 persons per year {2445}.
Most frequently MF affects adults, usually in their 5th-6th decade, with a male to female ratio of approximately 2:1 and a preponderance of black (1.7) vs white populations.
The increase of frequency paralleled by a decrease of mortality rates between 1979 and 1991 {2485} most probably is due to changing criteria resulting in overdiagnosing MF by including non-neoplastic conditions into this group.
Data collected by the Surveillance, Epidemiology and End Results Program (SEER) of the US National Cancer Institute indicate that the relative survival changed little after 11 years, at which point it was 66% {2485}.

Etiology
The etiology of MF is unknown. The role of environmental antigens, viruses or bacteria is controversial {2605}.

Localization
All parts of the skin may be involved without any predilection site.

Clinical features
Clinically MF is characterised by a stepwise evolution with sequential appearance of patches, plaques and tumours. Patches are circumscribed lesions with discolouration and sometimes little scaling, without palpable infiltration of the skin. Plaques usually evolve out of patches and present with palpable infiltration of various degree (thin and thick plaques). Tumours exhibit an exophytic growth in most of the cases and tend to ulcerate. In advanced stages of the disease there may be spread into the peripheral blood, involvement of lymph nodes, bone marrow and internal organs. Besides physical examination, including mapping of skin lesions and photodocumentation, a skin biopsy for paraffin embedding and for cryo-preservation should be taken, preferentially at multiple sites. Additional investigations include blood cell counts with PAS staining for Sézary cells, chest x-ray and CT-scan of abdomen and of peripheral lymph nodes. There is no need for taking a bone marrow biopsy in early patch and plaque stages of MF without atypical cells in the peripheral blood. Biopsy of enlarged lymph nodes is mandatory.
The current TNM-staging System for CTCL takes into account body surface involved less (T1) or more (T2) than 10%, quality of skin manifestation, i.e. patches/plaques or tumours (T3) or erythroderma (T4) in conjunction with presence or absence of lymph node (N0-N3) or visceral organ involvement (M0-M1) {334}.

Tumour spread and staging
MF, like other cutaneous lymphomas, is a systemic disease with preferential homing and proliferation of neoplastic lymphocytes into the skin. Therefore skin lesions may spread all over the body sur-

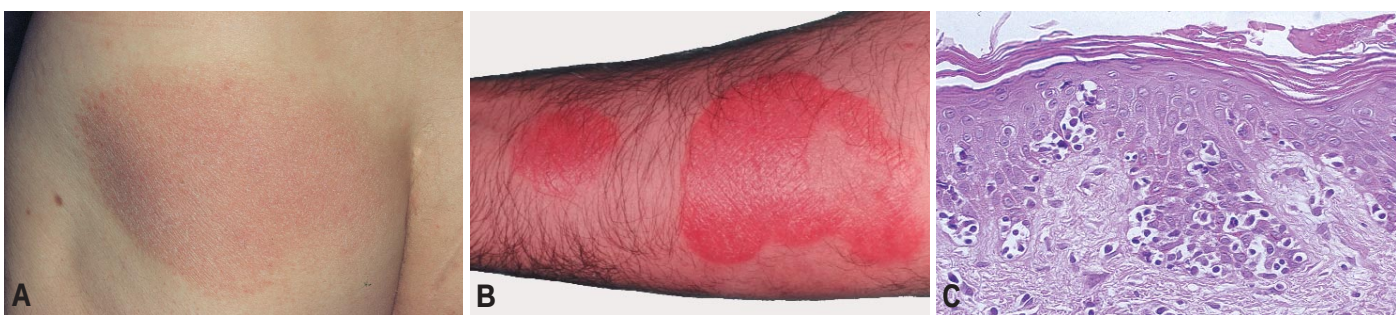

Fig. 4.1 Mycosis fungoides. **A** Large patches involving hip and abdomen. **B** Plaque-stage MF affecting the left arm. **C** Medium-sized hyperconvoluted cerebriform cells with prominent cytoplasmic halos in the epidermis, aligned within the basal layer.

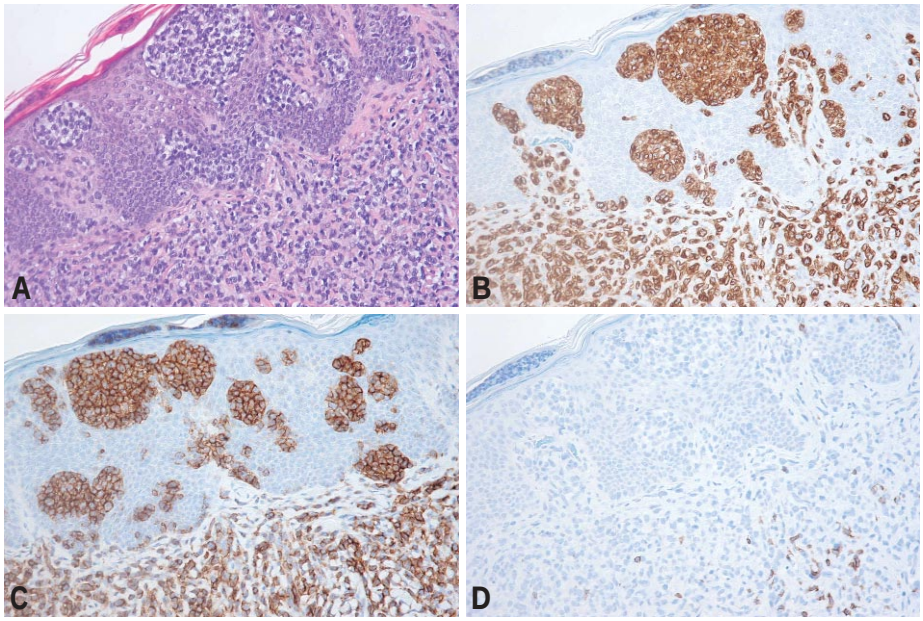

Fig. 4.2 Mycosis fungoides (MF). **A** Typical Pautrier abscesses. The neoplastic cells are strongly positive for **B** CD3 and **C** CD4, while **D** CD8 is negative.

face. Spread to extracutaneous compartments occurs in advanced stages of the disease, due to change or loss of homing receptors, These changes are usually accompanied by a change of cytomorphology of the tumour cells from small cerebriform to medium-sized pleomorphic or large blast-like cells.

Histopathology

The histologic diagnosis of MF is based on numerous subtle changes, most of which may be present to some degree in many inflammatory and neoplastic cutaneous conditions. The most significant criteria, which however in early lesions often are missing or are only present in part, are Pautrier microabscesses, exocytosis of lymphocytes, disproportionate epidermotropism. The presence of cells with hyperconvoluted cerebriform nuclei in the epidermis larger than dermal lymphocytes, or lymphocytes in clusters in the dermis, and lymphocytes aligned within the basal layer without or with only little spongiosis and without prominent vacuolisation in the dermo-epidermal junction are typical but not specific features. Haloed lymphocytes have proved to be the most robust discriminator of MF from non-MF.

Patch stage

The diagnosis is usually based on a combination of specific histologic criteria, without the necessity of confirmatory immunophenotyping {2058,2059,2213}. Whereas in very early "prelymphomatous" patch stages the histological picture often is non-specific, the histological findings become diagnostic in the thin plaque stage, when a denser infiltrate with lymphocytes lining up in the basal layer, especially at the tips of the rete ridges with epidermotropism of single cells is present. The majority of cells are small, differentiated lymphocytes with round or only slightly cerebriform nuclei. Haloed cells may predominate in the epidermis in early patch lesions of patients with otherwise advanced disease. In addition, there can be mild acanthosis, hyperkeratosis, signs of basal layer damage (pigment incontinence), edema or fibrosis of the papillary dermis. There is proliferation of postcapillary venules with prominent endothelial cells, simulating giant cells The infiltrate may contain an admixture of eosinophils, plasma cells, macrophages, and dermal dendritic cells {922,2156}.

Thick plaque stage

This is typified by a dense, subepidermal, usually band-like infiltrate containing a high number of cerebriform cells. Epidermotropism is more prominent with small intraepidermal clusters (2-3 cells) of lymphocytes. Typical Pautrier microabscesses are seen only in approximately one-third of cases. Subcorneal, intraepidermal and subepidermal bullous formation may result from confluence of Pautrier microabscesses {1460}.

Progression to tumour stage

With progression from plaque stage to tumour stage the dermal infiltrates become more diffuse, and epidermotropism may be lost. The proportion of tumour cells increase both in number and size, and may include cells with small, medium-sized and large cerebriform nuclei, blast cells with prominent nuclei and intermediate forms. There is a concomitant decrease in the numbers of reactive T-cells and dendritic cells. In approximately 25% of advanced cases, transformation to a CD30 positive or negative large T-cell lymphoma defined by

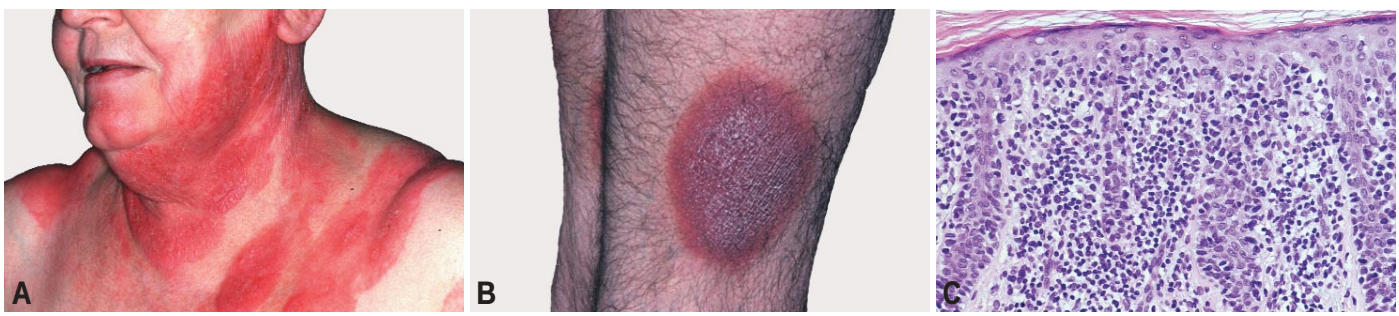

Fig. 4.3 **A** Plaque-stage mycosis fungoides (MF). **B** Thick plaque with haemorrhage in MF. **C** Histopathology of plaque-stage MF. Intra-epidermal and dermal infiltrate.

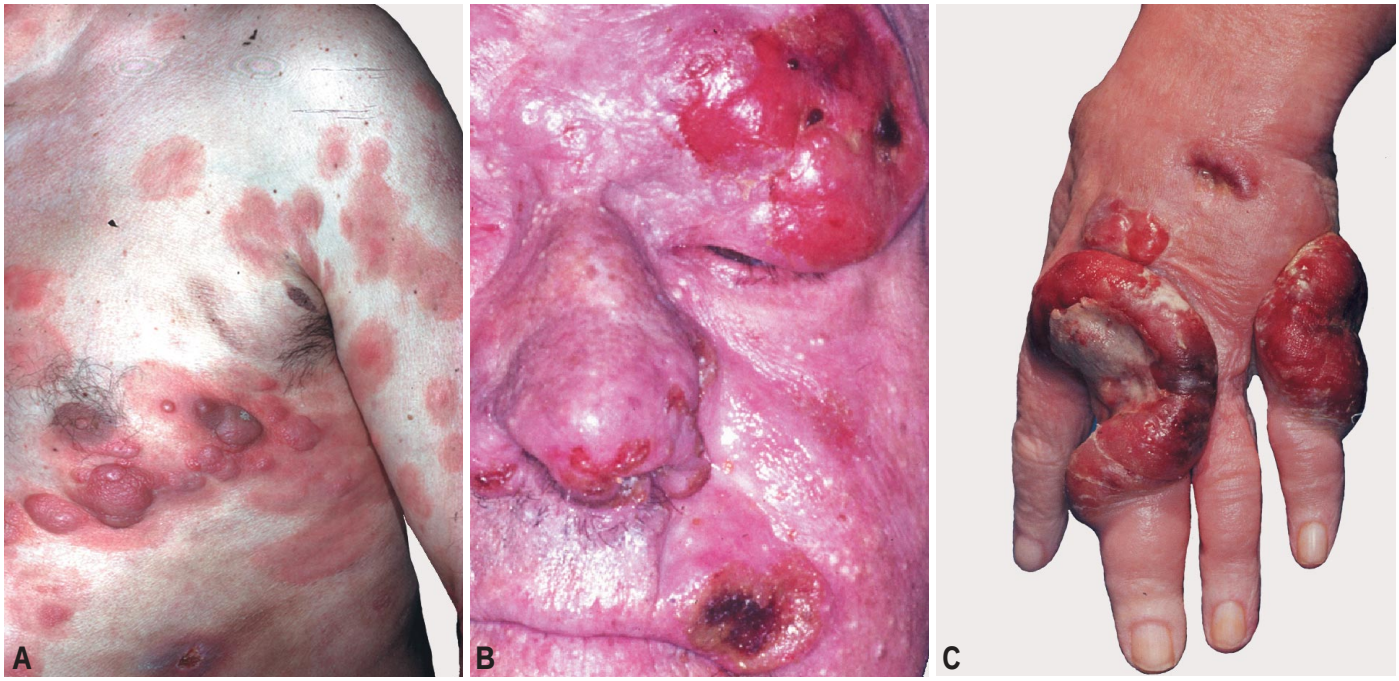

Fig. 4.4 Tumour-stage mycosis fungoides (MF). **A** Patches, plaques and tumours. **B** Ulcerating tumours in the face. **C** 'Fungoid' tumours on the hands.

the presence of more than 25% blast cells may be observed.

Immunoprofile

The immunophenotypical prototype of MF is CD2+, CD3+, CD4+, CD5+, CD45RO+,CD8, TCR-beta +, CD30-. During progression of the disease loss of CD7, 2 and 5 can occur. Helpful in the diagnosis is the loss of CD7, CD2, CD5, or CD4 in the epidermotropic cerebriform cells. During progression of the disease especially when transformation is present CD4 positive epidermotropic cells can have a cytotoxic phenotype (TIA-1, Granzyme B). In the transformed stage the blast cells can express CD30. Besides the CD4 prototype, a small number of MF cases have a CD8 positive cytotoxic phenotype (TIA-1 and granzyme B). These cases have the same clinical behaviour as the CD4 positive cases.

Prelymphomatous precursor lesions

The term "parapsoriasis" is confusing and requires explanation. It encompasses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling lesions {311,312,1375}.

Two groups of parapsoriasis can be differentiated {337}. The benign form 'parapsoriasis en plaques' (Brocq disease), never evolve into malignant lymphoma. The large plaque forms (LPP) with poikiloderma (prereticulotic poikiloderma, parapsoriasis en grandes plaques poikilodermiques, poikiloderma vasculare atrophicans, parapsoriasis lichenoides, parakeratosis variegata) or without poikiloderma (parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples), may after several decades evolve into mycosis fungoides or CTCL in up to 10-50% of cases. Few large (more than 5 cm in diameter) patches show pityriasiform scaling with (poikilodermatous variant) or without telangiectasia and netlike pigmentation. There is no palpable infiltration.

Histologically lesions in large plaque parapsoriasis (LPP) are different from MF or other CTCL. Under patchy parakeratosis there is slight atrophy of the epidermis, due to loss of rete ridges. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, spar-

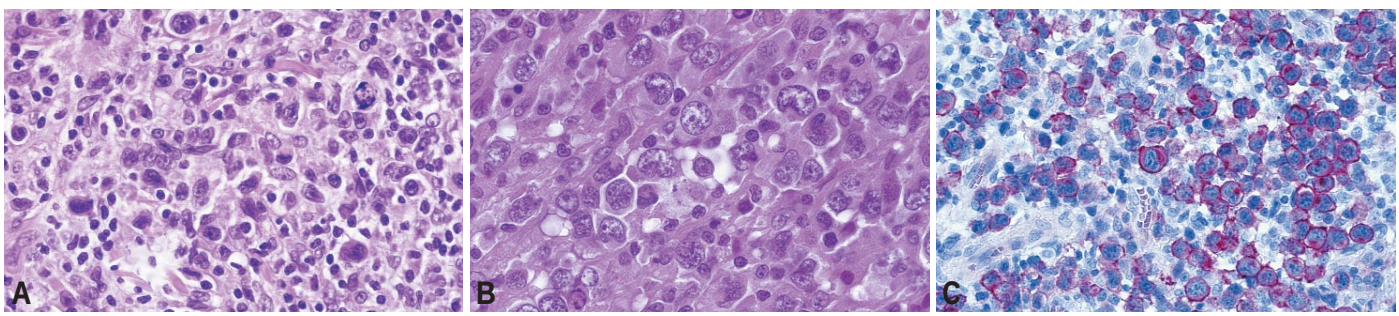

Fig. 4.5 Histopathology of transformed mycosis fungoides(MF). **A** Large-cell pleomorphic transformation. **B** Large cell anaplastic transformation. **C** Immunohistochemistry reveals CD30 positive tumour-cells.

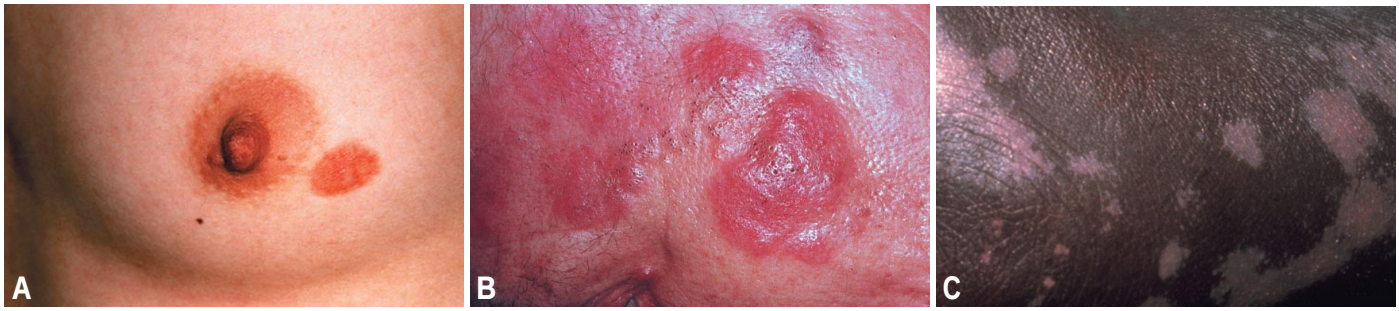

Fig. 4.6 **A** Plaque in mono-lesional mycosis fungoides (MF). **B** Symptomatic mucinosis follicularis in MF. **C** Hypo-pigmented lesions in MF.

ing the papillary region. There is no significant epidermotropism as usually seen in early stages of mycosis fungoides. The poikilodermatous variant of the diseases in addition shows dilated blood vessels in the upper dermis. T-cell receptor gamma gene rearrangement, which is clonal in about half of the patients with LPP, is without any prognostic significance {2186}. There is no significant difference between the observed and expected survivals in patients with LPP.

Histogenesis

Mature skin homing T cells that express the cutaneous lymphocyte antigen (CLA) enabel them to specifically home into the skin. Functionally, the neoplastic cells in MF express TH2 phenotype, which accounts for many systemic changes associated with MF due to the production of a TH2-specific cytokine pattern (IL-4, IL-5, IL-10) leading to fever, oedema, eosinophilia, increase of IgE or IgA, and impaired delayed type reactivity {656,2445}.

Somatic genetics

There have been a few reports on familial occurence of MF or CTCL {2160} and on a possible association of HLA-DR5 with MF {2004}. HLA class II susceptibility alleles, i.e. HLA-DRB1*11, HLA-DQB1*03 and HLA-DRB1*1104 are more prevalent among patients with MF and are likely to be important in the pathogenesis of MF {1039,1118}. T-cell receptor beta and gamma chain genes are clonally rearranged. In advanced cases with extracutaneous involvement, the same clone is usually detected in the skin and in the extracutaneous lesions. In transformed cases the same clone is present in the pre-existing lesions and the high-grade lymphoma {207}.

In advanced stage, the rate of chromosomal aberrations, especially of chromosomes 1, 6 and 11, increase with the activity of the disease and has prognostic significance in patients with MF. Aberrations of chromosomes 8 and 17 are especially associated with active or progressive disease.

Chromosomal abnormality possibly results in increased genetic instability as a basic prerequisite for the development of CTCL. In G-banding studies, numerical aberrations of chromosomes 6, 13, 15, and 17, marker chromosomes, and structural aberrations of chromosomes 3, 9, and 13 were increased in MF {1209}.

In contrast to nodal lymphomas, the large cell transformation in cutaneous T-cell lymphoma (CTCL) is not associated with t(2;5)(p23;q35) chromosomal translocation {613,1420}.

Increased expression of C-myc, p62, TP53 and proliferation markers (PCNA) has been found in advanced stages of MF as compared to early stages of MF suggesting a relationship between levels of these proteins and aggressiveness of CTCL {1192}.

Prognosis and predictive factors

The majority of MF patients show an indolent clinical course over years or decades. The prognosis of the disease is defined by its stage. Patients with early

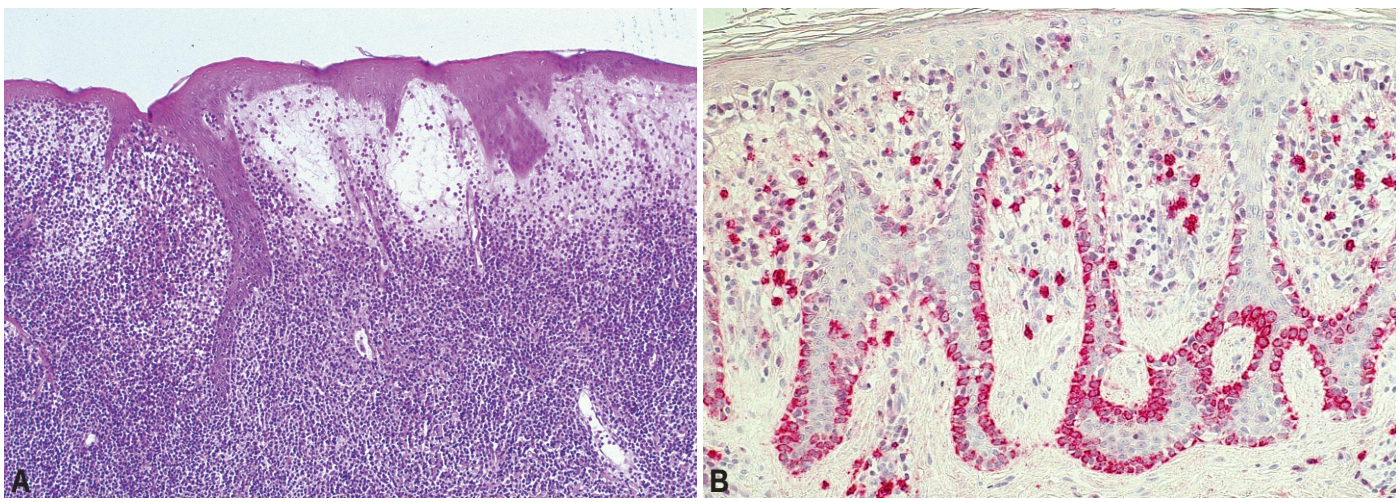

Fig. 4.7 Mycosis fungoides (MF). **A** Bullous variant of MF. **B** Immunohistochemistry shows CD8 positive tumour-cells lining up in the basal layer.

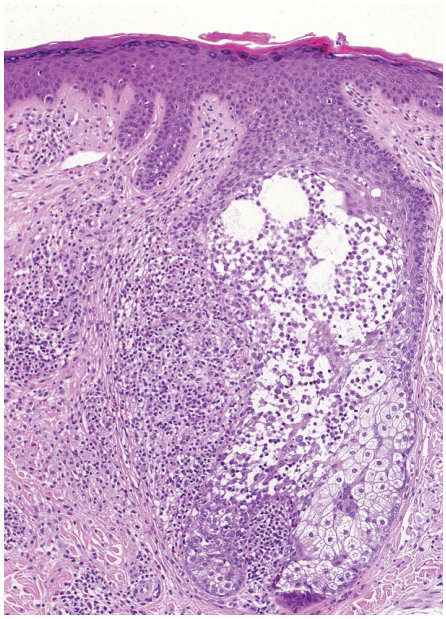

Fig. 4.8 Mucinous follicular variant of MF.

stages, i.e. with patches or thin plaques, without involvement of lymph nodes, peripheral blood or other extracutaneous compartment have an excellent prognosis with survival similar to that of an age, sex, and race-matched population {2575}.
Advanced stage and age above 60 years of age indicate a poor prognosis. When extracutaneous involvement or transformation into high-grade lymphoma occurs, expected survival is usually less than one year {2367,2412}.

Variants
Apart from the classical form of MF, there are several variants of this disease with unusual or atypical clinical and/or histopathological features. These comprise follicular, bullous, dyshidrotic, granulomatous, hypopigmented, poikilodermic, hyperpigmented, pigmented purpura-like, unilesional, palmoplantar, hyperkeratotic/verrucous, vegetating/papillomatous, ichthyosiform, pustular and other forms {1234}.
Pagetoid reticulosis, syringotropic MF, folliculotropic (pilotropic) and granulomatous MF also are variants and deserve special emphasis.

Pagetoid reticulosis

Pagetoid reticulosis, in its localized form also referred to as Woringer-Kolopp disease (WKD) {302,2550} clinically presents as a solitary, slowly growing psoriasiform crusty or hyperkeratotic patch or plaque, typically on a distal limb.
The histological hallmark is the sponge-like disaggregation of the epidermis by small to medium-sized lymphoid cells (pagetoid) which immunophenotypically correspond to those found in MF in most of the cases {336}. However, the neoplastic cells in WKD often demonstrate a higher proliferation rate (>30%) in comparison to lymphocytes in patch or plaque stage MF (<10%), and in some cases infiltrates in WKD may contain high numbers of CD30+ cells {937}. CD8+ {792} variants have also been reported.
There exists a disseminated form featuring the same distinct pagetoid pattern of the infiltrate {1252}, which is now regarded as a separate disease, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

Syringotropic MF

Syringotropic MF represents a rare variant of MF {2586} showing a solitary well circumscribed red-brown plaque with hair loss in the affected area. Histology reveals predominant involvement of

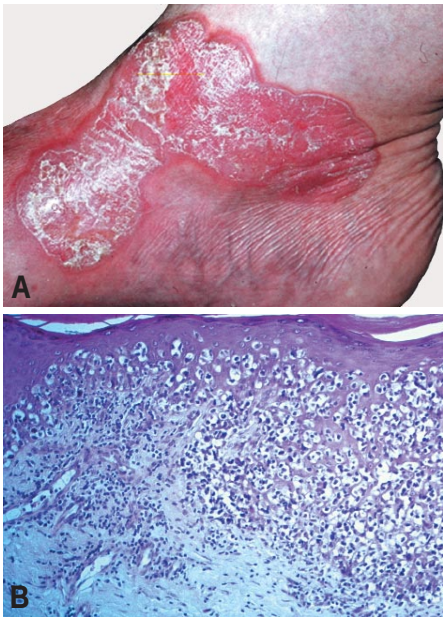

Fig. 4.9 Pagetoid reticulosis. **A** Solitary psoriasiform lesion on the foot. **B** Pagetoid reticulosis showing sponge-like disaggregation of the epidermis by invading haloed lymphoid cells.

irregularly proliferating eccrine sweat glands by small cerebriform lymphocytes {343,2586}.

Folliculotropic MF

Follicular MF, also referred to as pilotropic MF {776} is a rare variant, histopathologically characterized by infiltrates of atypical T lymphocytes around and within the epithelium of the hair follicles with sparing of interfollicular skin. The follicles may show cystic dilatation and/or cornified plugging. There may or may not be mucinosis. When present, mucinous degeneration of the follicular epithelium varies from focal spots of mucin deposition to complete destruction of follicles with mucin lakes. The folliculotropism is

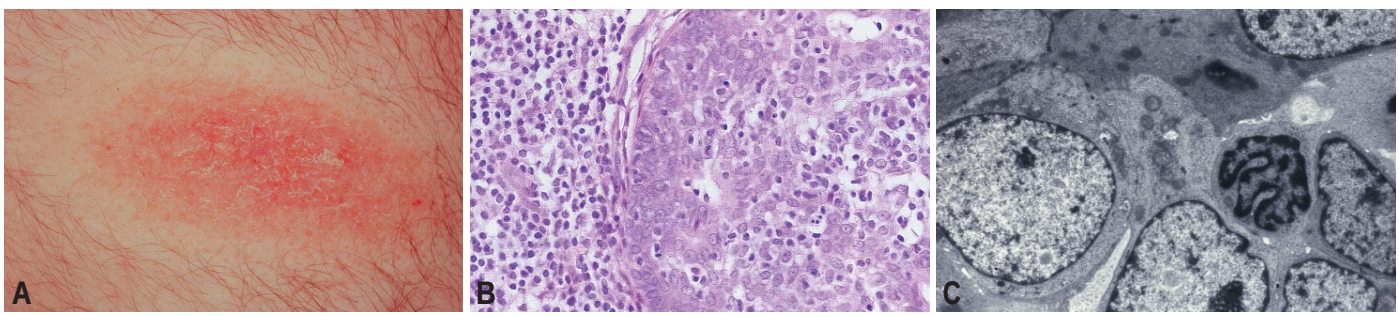

Fig. 4.10 Syringotropic cutaneous T-cell lymphoma (CTCL). **A** Cutaneous patch with hair-loss. **B** Infiltration of a sweat gland. **C** EM showing the convoluted nucleus of a neoplastic cell between acinar cells.

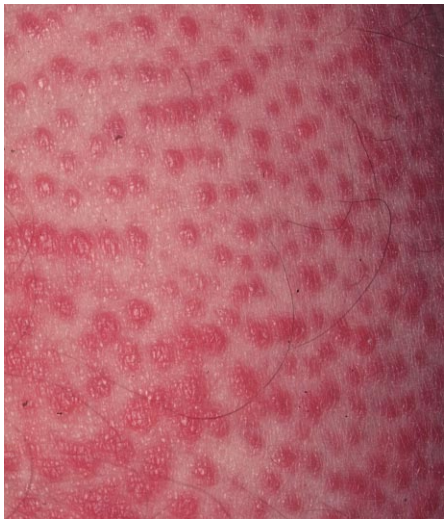

Fig. 4.11 Pilotropic lymphoid infiltrate in follicular mycosis fungoides (MF).

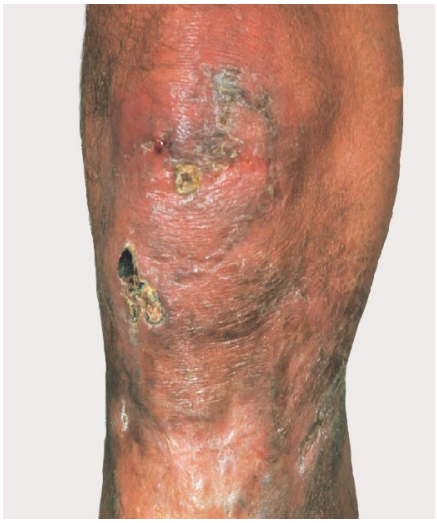

Fig. 4.12 Granulomatous MF. Granulomatous plaques with ulceration on the leg.

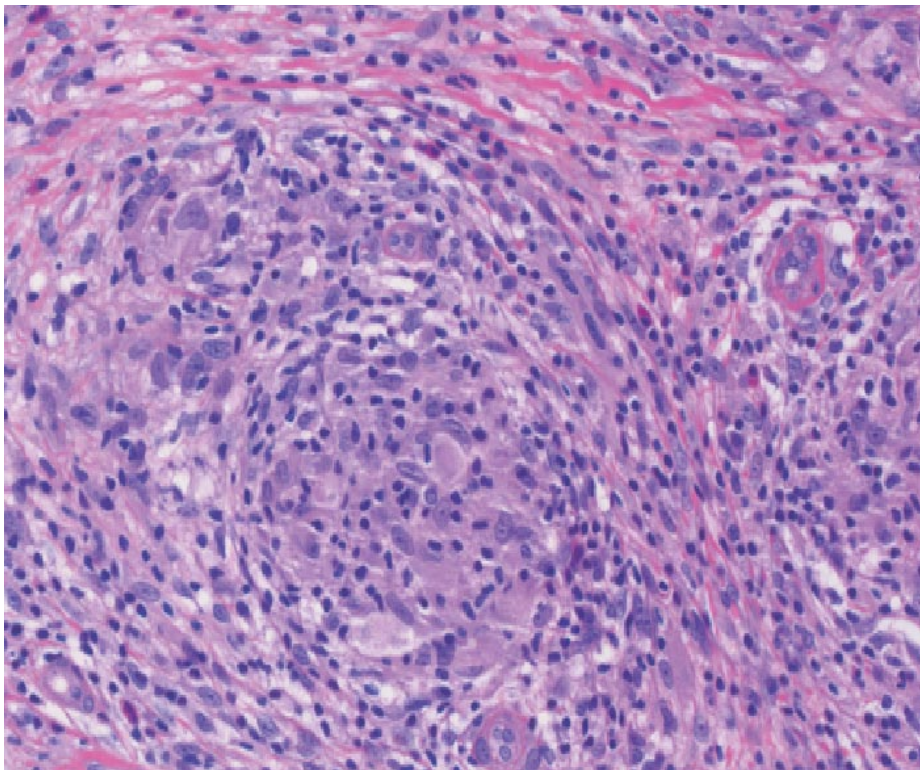

Fig. 4.13 Granulomatous mycosis fungoides (MF) with sarcoidal infiltrate pattern.

possibly due to an increased expression of skin-selective homing receptors and adhesion molecules in the follicular epithelium {1805}. A recent study has demonstrated that follicular MF shows a more aggressive behaviour and a worse prognosis than classical MF {829,2411}.

Granulomatous MF

Granulomatous MF is characterized by the histological presence of a granulomatous reaction {584}, sometimes featuring a sarcoidal or granuloma annulare-like pattern. Multinucleated giant cells may be present {1387}.

The prognostic and clinical significance of a granulomatous reaction in MF remains uncertain {454}.

Sézary syndrome

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Definition

Sézary syndrome (SS) is a rare variant of cutaneous T-cell lymphoma (CTCL), characterized by erythroderma, blood involvement and a poor prognosis. Neoplastic lymphocytes are typically mature T-helper cells with cerebriform nuclei. Criteria for the diagnosis of SS include the demonstration of a peripheral blood T-cell clone by molecular or cytogenetic methods; an expanded CD4+ population resulting in a CD4:CD8 ratio > 10, and immunophenotypic abnormalities such as absent expression of T-cell antigens (CD2, CD3. CD4 and/or CD5). Sézary syndrome (SS) is part of a broader disease spectrum, erythrodermic CTCL. The presence of a clonal T-cell population in the peripheral blood distinguishes SS from reactive disorders that exhibit erythroderma and circulating cells with cerebriform nuclei (pseudo-SS) {777}.

ICD-O code 9701 / 3

Epidemiology

Sézary syndrome accounts for less than 5% of all cutaneous T-cell lymphomas {2523}. It occurs almost exclusively in adults, characteristically presents over the age of 60 and has a male predominance {2523}.

Etiology

SS is of unknown etiology. However, a syndrome clinically indistinguishable from SS is occasionally seen in HTLV-1 associated lymphoma/leukaemia.

Clinical features

SS comprises a clinical triad of pruritus, erythroderma and lymphadenopathy. The pruritus is commonly intractable and sufficiently severe to prevent the patient sleeping or pursuing a normal life. Additional clinical features include alopecia, ectropion, nail dystrophy, palmoplantar keratoderma and leonine facies. Bacterial skin infection is common in Sézary patients and may lead to a marked deterioration in their cutaneous disease. An increased prevalence of secondary malignancies, both cutaneous and systemic, has been reported in SS and attributed to the immunoparesis associated with loss of normal circulating CD4 cells {2075}.

Tumour spread and staging

Haematological involvement was defined in the TNM classification of MF as more than 5% atypical circulating lymphocytes (B1), but was not included as part of the Bunn-Lamberg staging system {1356}. Sézary patients are all T4/B1 (erythroderma with blood involvement) but staging will vary from stage III if there is no lymph node involvement to IVB if there is bone marrow involvement. In practice, most cases of SS are staged as IVA. In 1988, the definition of B1 was increased from 5 to 20%, by the NCI, but was still not included as part of the staging system {2071}.

The problem is that erythrodermic CTCL represents a spectrum and that any attempt to distinguish SS from cases that show a lesser degree of haematological involvement is necessarily arbitrary. An alternative approach is to develop a staging system that incorporates both lymph node status and haematological stage. A haematological staging system

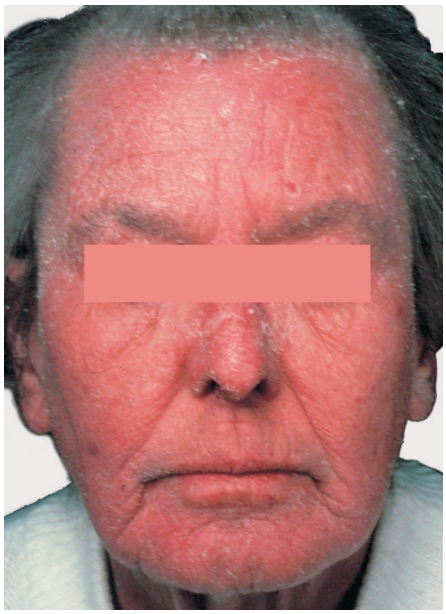

Fig. 4.14 Erythroderma and scaling of the face in Sézary syndrome.

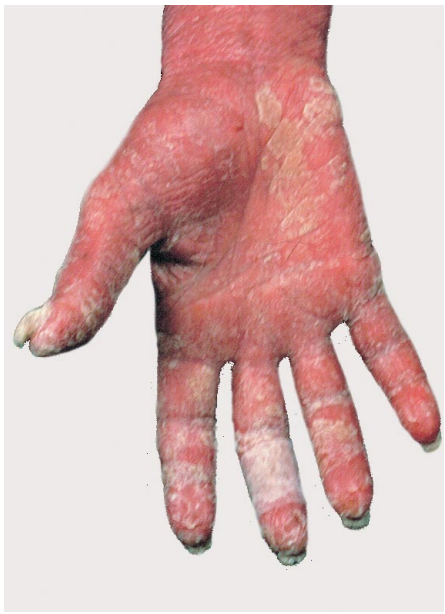

Fig. 4.15 Palmar hyperkeratosis and onychodystrophy in Sézary syndrome.

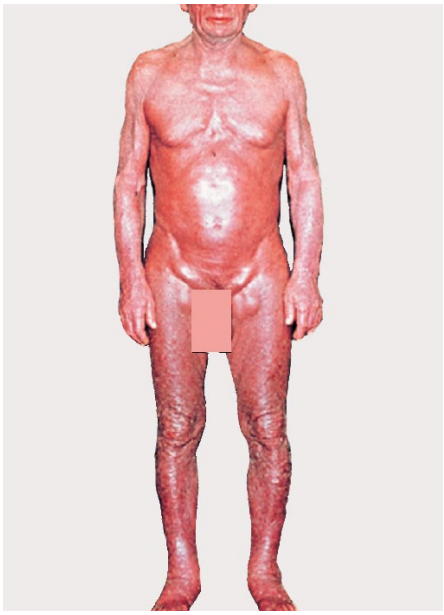

Fig. 4.16 Sézary syndrome. Note erythroderma, oedema of the skin, and swelling of lymph nodes.

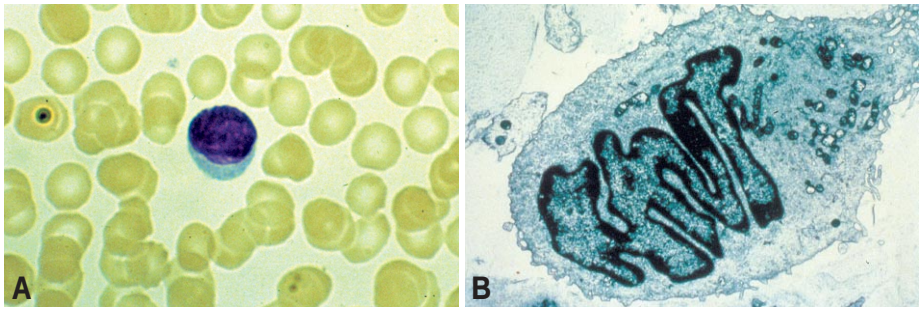

Fig. 4.17 Morphology of Sézary cells. **A** Blood film and **B** Ultrastructure showing a typical convoluted nucleus.

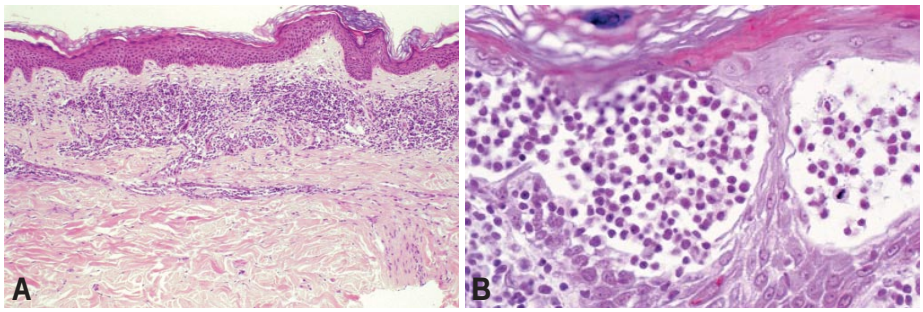

Fig. 4.18 Sézary syndrome. **A** Band-like infiltrate in the epidermis without epidermotropism. **B** Intraepidermal Pautrier micoabscesses.

comprising five categories (H0-H4) was proposed by Russell-Jones and Whittaker {1998}, and subsequent data showed an increase in disease-specific death rates for each category with the most significant change occurring at H2, defined by 5% Sézary cells with a T cell clone demonstrated by PCR, or a T cell clone demonstrated by Southern blot analysis only {2077}. The need for a haematological staging system has also been recognised by the International Society for Cutaneous Lymphoma ISCL {2444}. Currently this is being tested in a larger, multi-centre study under the auspices of the ISCL.

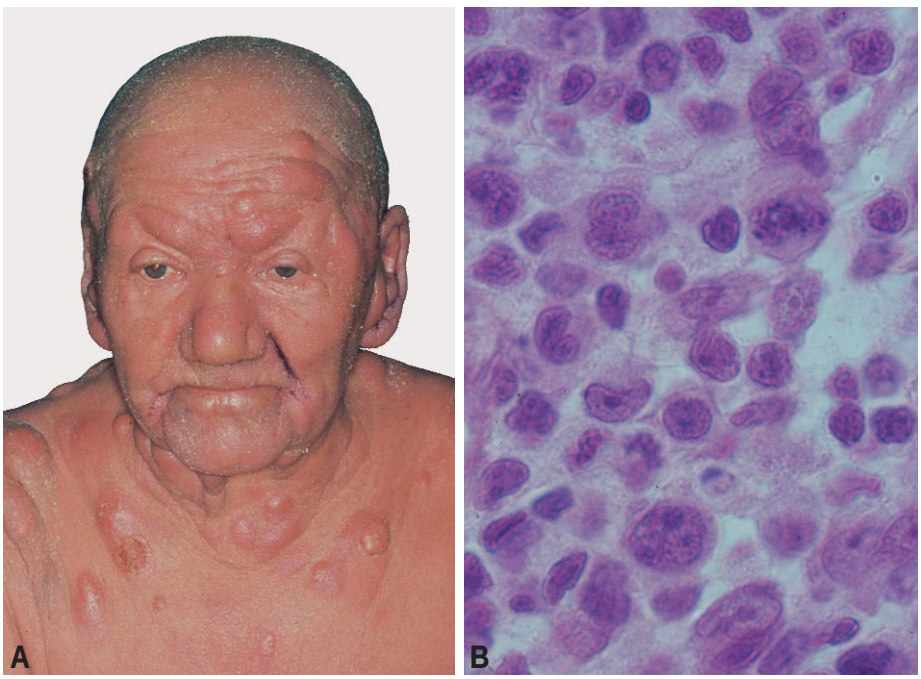

Fig. 4.19 Sézary syndrome transforming into blast-stage. **A** Multiple nodules and tumours. **B** Large atypical cells in blastic transformation of Sézary syndrome.

Histopathology

Despite minor differences {1099}, the range of histological changes in SS are not dissimilar to those seen in patients with mycosis fungoides {2135}. Epidermotropism is a variable feature, and the size of Sézary cells varies in the skin as it does in blood. Only 2/3 of the skin biopsies and 73% of patients had diagnostic changes in the skin biopsies Other causes of erythroderma need to be differentiated from SS, particularly drug induced erythroderma and chronic actinic reticuloid, both of which may show a high proportion of activated lymphocytes with cerebriform nuclei {2135}. In cases with a non-specific histology, the differential diagnosis would include other causes of erythroderma such as eczema or psoriasis.

Immunoprofile

A typical Sézary cell is a mature helper T cell with a memory phenotype. A classic immunoprofile is CD2, CD3, CD4, CD5, CD45RO positive and CD8 negative {1368,2526}. The majority of Sézary cells are also CLA positive {1827} and CD7 negative, and this latter feature has been proposed as a method of distinguishing Sézary cells from normal lymphocytes {957}. However, further studies have shown that the neoplastic cell population is present in both the CD7 positive and CD7 negative subset in the same patient {657}. More recently, Bernengo et al have demonstrated that CD4 positive Sézary cells typically loose the CD26 marker and that a diagnosis of SS or MF with haematological involvement can be made if the CD26 negative subset exceeds 30% of the CD4 positive cells {215}.

Complete loss of T cell antigens such as CD2, CD3, CD4, or CD5 is present in approximately 2/3 of patients with SS {957}. An alternative approach would be the identification of a tumour-specific antigen {669}. Recently two differentiation antigens P140 and SCS have been reported in circulating Sézary cells and P140 was also found in skin-infiltrating cells of patients with SS {1715}.

Histogenesis

The postulated cell of origin is a mature peripheral T cell which has skin-homing properties and exhibits a helper-cell phenotype.

Somatic genetics

Recurrent chromosomal translocations have not been detected in Sézary syndrome, but complex clonal numerical and structural chromosomal abnormalities are common and associated with a poor prognosis {1505,2343}. M-FISH techniques have shown a high rate of unbalanced translocations and associated deletions often involving chromosomes 1p, 10q, 14 and 15 {1505}. CGH studies have identified a consistent pattern of chromosomal gains/deletions (1p, 10q, 13q, 19, 17p losses and 4/4q, 17q and 18 gains) which, with the exception of 17q gains in Sézary syndrome, are identical to mycosis fungoides suggesting a similar pathogenesis {1210,1504}. Allelic losses on 1p, 9p, 10q and 17p have been confirmed by LOH studies and a high rate of microsatellite instability (MSI) has also been detected {2079, 2080}. These findings suggest that dysregulated genes at these chromosomal loci are involved in the pathogenesis {1554,2078}. There is a high rate of genomic instability as indicated by the presence of chromosomal instability {1505}. Constitutive activation of Stat 3 and chromosomal amplification of JUNB, a member of the AP-1 transcription factor complex, have been identified in Sézary syndrome {1089,1506}. A recent cDNA array study in Sézary syndrome has confirmed the presence of JunB overexpression and has also revealed overexpression of other genes associated with a TH2 phenotype such as Gata-3 and RhoB {1211}. These array findings appear to allow the identification of a poor prognostic group {1211}.

Prognosis and predictive factors

Sézary syndrome has a poor prognosis with a median survival of 2 to 4 years depending on the exact definition used {777,1271,2044,2523}. Absolute Sézary cell count and lymph node involvement are independent prognostic factors. In addition, large cell transformation and the development of skin tumours on a background of erythroderma are poor prognostic signs.

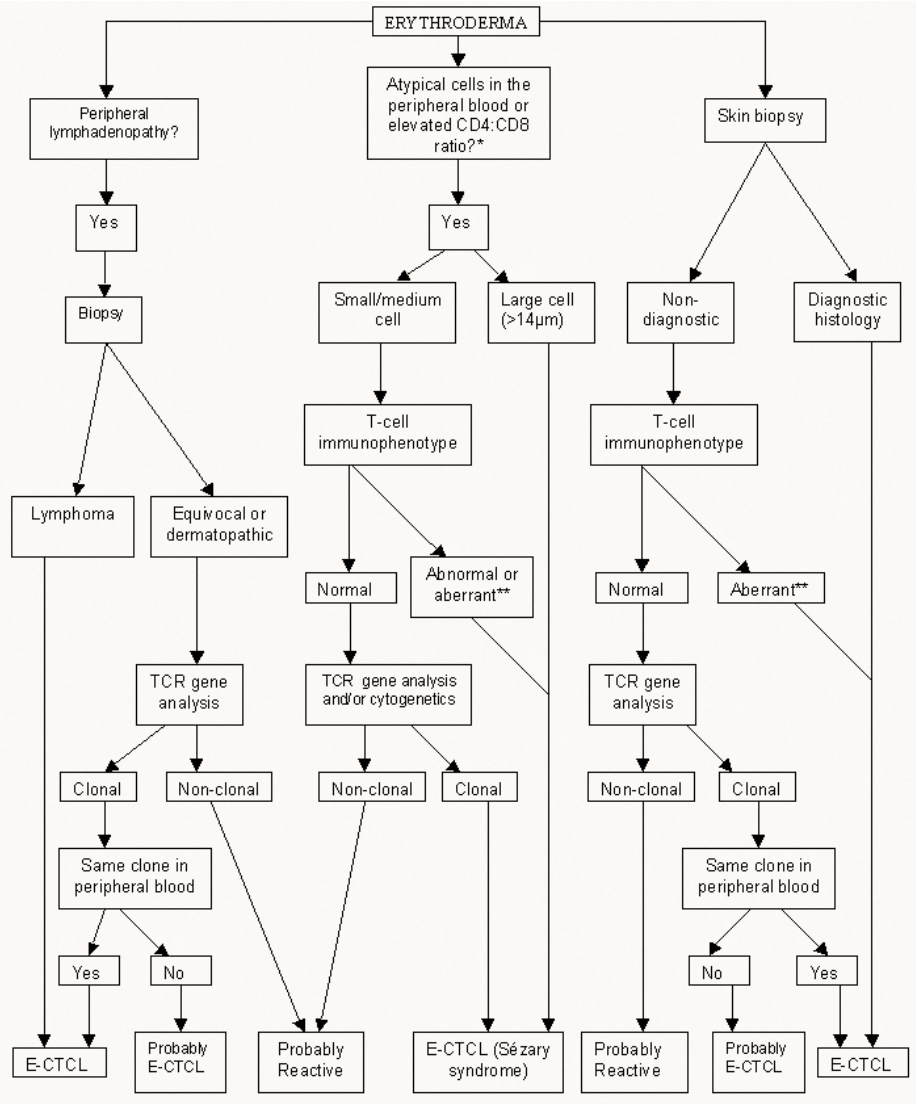

Fig. 4.20 Diagnostic pathways for the differential diagnosis of erythroderma. Algorithm for the evaluation and diagnosis of erythroderma due to cutaneous T-cell lymphoma (E-CTCL) vs. 'reactive' causes of erythroderma. TCR, T-cell receptor. *A CD4/CD8 ratio > 10 or an absolute Sézary cell count of 1 109 L 1 have been proposed as diagnostic criteria for Sézary syndrome (SS), but this algorithm requires additional immunophenotypic or genotypic data. Even so, a Sézary cell count > 1 109 L 1 or a CD4/CD8 ratio > 10 increases the probability of neoplasia, and separates SS from E-CTCL with a lesser degree of blood involvement. **Abnormal T-cell immunophenotype = an increased population of CD4+ cells that are CD26 (> 30%) or p140+. CD7 is less reliable. Aberrant T-cell immunophenotype = loss of pan T-cell markers such as CD2, CD3 or CD5, and/or double-negative T cells (CD4 and CD8). In skin, the loss of CD7 from epidermal lymphocytes is CTCL specific.
From: R. Russell-Jones {1997}.

Granulomatous slack skin

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S. Michaelis
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Definition
Granulomatous slack skin (GSS) is clinically characterized by the development of bulky skin lesions in the major skin folds and histologically by a granulomatous infiltrate composed of small lymphocytes and scattered multinucleated giant cells containing nuclei arranged in a wreath-like fashion.

Synonyms
Progressive atrophying chronic granulomatous dermohypodermitis

Epidemiology
GSS is a rare form of primary cutaneous T-cell lymphoma. GSS usually appears in the third or fourth decade, but can also affect children {373}. GSS occurs almost exclusively in Whites. The male to female ratio is 2:1 to 3:1 {490}.

Clinical features
GSS begins with slightly infiltrated, poikilodermatous sharply demarcated patches and plaques. Predilection sites are the intertriginous areas, especially the axillary and inguinal folds. After years, pathognomonic bulky pendulous skin folds develop as a result of progressive destruction of elastic fibres. The lesions then resemble cutis laxa. Occassionally ulceration occurs. Regional lymphadenopathy may be present. In contrast to granulomatous MF, GSS is in almost all cases confined to intertriginous areas, and runs a more benign course than classic MF {1387}.

Histopathology
Early lesions of GSS display a bandlike infiltrate of small lymphocytes without significant nuclear atypia {1379}. More advanced lesions show a dense lymphocytic infiltrate throughout the entire dermis. Nuclear atypia of lymphocytes is less pronounced than in granulomatous MF. The diagnostic hallmark is numerous multinucleated histiocytic giant cells, which are scattered throughout the background of the dense lymphocytic infiltrate. These giant cells contain 20-30 nuclei located at the periphery of the cytoplasm. Elastophagocytosis and emperipolesis (phagocytosis of lymphoid cells by giant cells) are present. Elastic stains demonstrate the loss of elastic fibres at the sites of the infiltrates in all dermal layers. On occasion, involvement of large vessels occurs. Ultrastructurally, the lymphocytes show hyperchromatic cerebriform nuclei similar to those seen in mycosis fungoides and Sézary syndrome {490}. Specific infiltration of regional lymph nodes or internal organs exhibiting similar features as in the skin has been observed in rare cases.

Immunoprofile
The lymphoid tumour cells display a T helper phenotype with expression of CD3, CD4 and CD45RO. There may be loss of other T-cell markers like CD5 or CD7. In rare cases, the tumour cells express CD30.

Genetics
Clonal rearrangement of TCR genes can be found in most cases and is a useful diagnostic tool in early stages of the disease {1382}. Trisomy 8 has been reported in two cases {136,2442}.

Histogenesis
The tumour cells represent skin-homing T-helper cells.

Prognosis and predictive factors
The disease has a long natural history with a slowly progressive course over decades. Occasionally involvement of regional lymph nodes is found, but does not seem to affect survival. Although life expectancy is not reduced by GSS *per se*, other cutaneous and nodal lymphomas such as mycosis fungoides, Hodgkin lymphoma and peripheral T-cell lymphomas occur in approximately 20 – 50% of the patients, often years or even decades after the manifestation of GSS {202,490,1729,2413}.

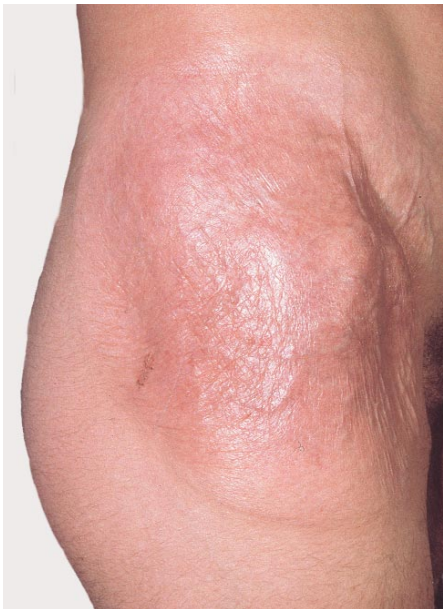

Fig. 4.21 Granulomatous slack skin (GSS). Large slightly infiltrated plaque in the groin.

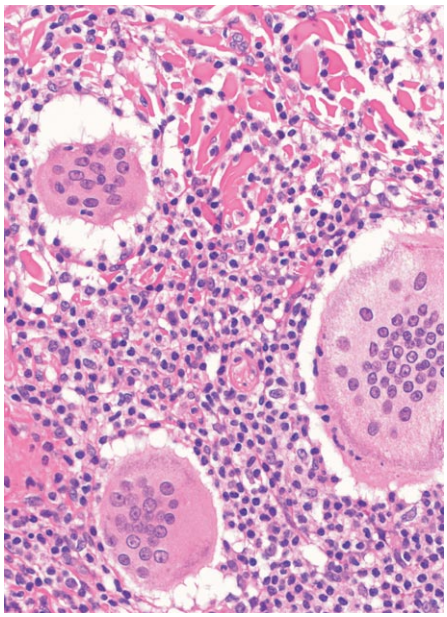

Fig. 4.22 GSS showing characteristic multinucleated giant cells with emperipolesis of lymphocytes.

CD30+ T-cell lymphoproliferative disorders

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R. Willemze
E.S. Jaffe
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M.E. Kadin

CD30-positive T-cell lymphoproliferative disorders (LPD) of the skin (CD30+LPD) represent a distinctive group of primary cutaneous T-cell lymphoma. The spectrum of CD30+ LPD includes lymphomatoid papulosis (LyP), primary cutaneous anaplastic lymphoma (C-ALCL) and borderline cases which differ in their clinical and histological presentations {191, 1174,1225,1795,2520}.
A feature common to all is the expression of CD30, a cytokine receptor belonging to the tumour necrosis factor receptor superfamily.
The term 'borderline lesions' has been applied to lesions that show clinical presentation of one entity (e.g. C-ALCL) but histological features of another one (e.g. LyP). This discrepancy may result in difficulties to assign such lesions to a distinct entity. Clinical presentation plays a crucial role in such discordant cases.

Lymphomatoid papulosis (LyP)

Definition
LyP is a chronic recurrent lymphoproliferative skin disease with self-regressing papulo-nodular skin lesions and atypical lymphoid cells in a polymorphous inflammatory background {1466}.

ICD-O code 9718/1

Epidemiology
LyP is a rare disease with an estimated prevalence of 0.1 to 0.2 cases per 100 000 and a male to female ratio of 1.5:1 {2456}. Mostly people in the third and fifth decades are affected, but children can also be involved.

Localization
Although no definite predilection site has been identified, LyP lesions more often arise on the trunk, especially the buttocks, and extremities.

Etiology
The cause of the disease is unknown. Endogenous retroviral elements have been identified in LyP lesions {1242}. Interaction of CD30 and CD30L as well as TGF-beta and its receptor play an important role in growth regulation, including regression of tumoural lesions {1177,1648}.

Clinical features
LyP is characterized by grouped or disseminated asymptomatic papules and/or nodules, which regress spontaneously after a few weeks sometimes leaving behind varioliform scars {1174}. Often new lesions develop concurrently in the same or another body region. Larger nodules up to 2 cm can develop and persist for months {2524}. Clinicopathologic variants of LyP include regional follicular and pustular forms {2076}.

Histopathology
The histological features of LyP are variable and depend on the stage of the lesions and disease. Three histologic subtypes (types A, B and C) have been delineated {2524} which represent a spectrum with overlapping features {2148}. In fully developed LyP lesions, there is a wedge-shaped diffuse dermal infiltrate which contains medium-sized to large pleomorphic or anaplastic lymphoid cells with irregular nuclei, sparse chromatin and mitotic activity. Some of the large atypical lymphoid cells resemble Reed-Sternberg cells. Ulceration may be present. In type A lesions, scat-

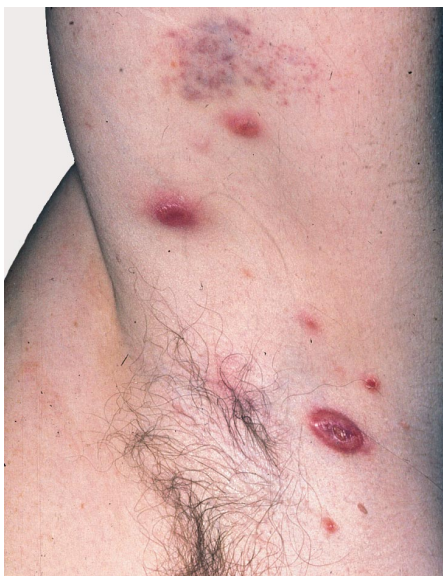

Fig. 4.23 Lymphomatoid papulosis with papules and ulcerating nodules.

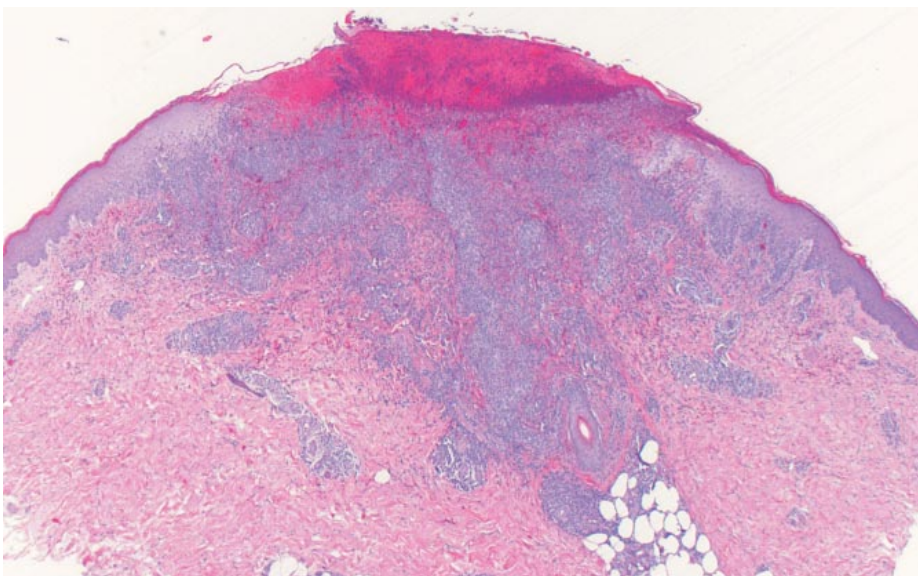

Fig. 4.24 Lymphomatoid papulosis. Wedge-shaped infiltrate with superficial ulceration and crust formation.

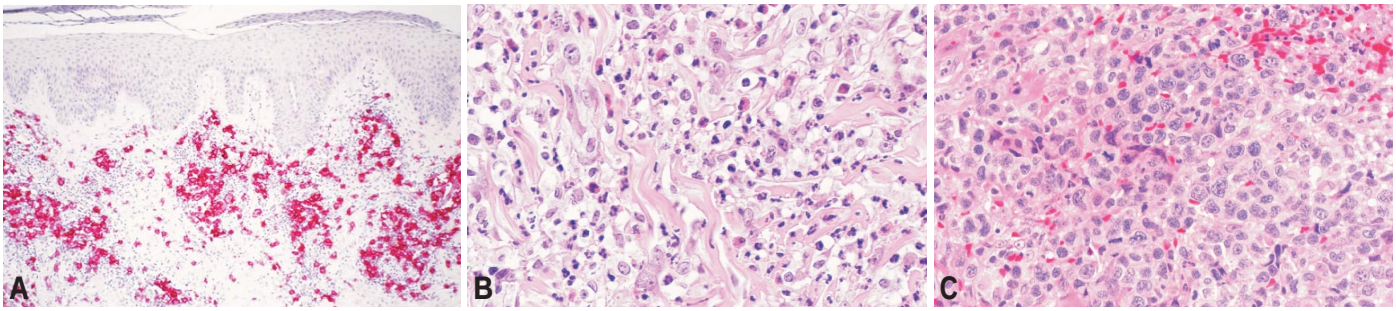

Fig. 4.25 Lymphomatoid papulosis. **A** Grouped and scattered CD30+ lymphocytes of various sizes. **B** Mixed infiltrate consisting of large atypical lymphocytes, eosinophils and neutrophils (LyP, type A). **C** 1325. Cohesive sheets of large atypical lymphocytes with only few neutrophils (LyP, type C).

tered tumour cells are intermingled with numerous inflammatory cells such as neutrophils, eosinophils and histiocytes. Type C lesions show cohesive sheets of large atypical lymphoid cells with only a few intermingled reactive inflammatory cells. The rare type B is characterized by an epidermotropic infiltrate of small atypical lymphoid cells with cerebriform nuclei and histologically resembles mycosis fungoides. Various histologic types may be present in individual patients at the same time.

Due to an overlap of histologic features between LyP and primary as well as secondary cutaneous ALCL, final diagnosis depends on correlation of clinical presentation and histologic findings.

Immunohistochemistry

A hallmark of the large atypical lymphoid cells is their positivity for CD30 {1173, 1227}. The large atypical lymphoid cells in LyP are of T-cell origin with a CD3+, CD4+, CD8-. In 10% of the cases tumour cells express CD56+ {193}. Usually CD2 and CD5 are expressed, whereas often CD7 and sometimes CD3 are absent. In addition, expression of activation markers such as HLA-DR and CD25 (interleukin 2-receptor) is found. Cytotoxic molecules such as TIA-1 and granzyme B are expressed in 70% of the cases {1342}. CD56 is generally negative {968}. CD15, a marker for Reed-Sternberg cells in Hodgkin lymphoma, is usually not expressed in LyP. In contrast to the tumour cells expressing CD30 as in LyP type A and type C, the small atypical lymphocytes present in LyP type B are usually negative for CD30.

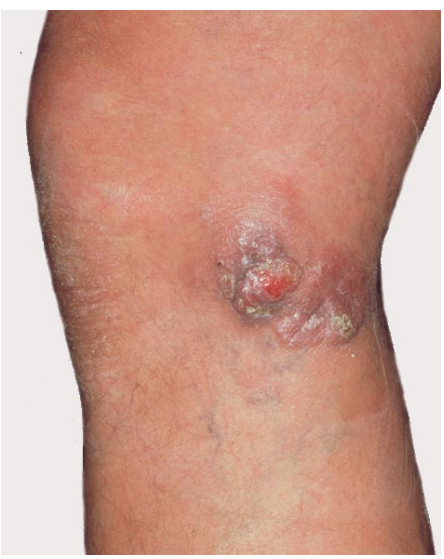

Fig. 4.26 Primary cutaneous anaplastic CD30+ large-cell lymphoma. Solitary large ulcerated nodule on the leg.

Genetics

Clonal rearrangement of T cell receptor genes can be found in at least 40% of LyP lesions. Cytogenetic studies have demonstrated chromosomal deletions and rearrangements of chromosomes 1, 7, 9 and 10 {1813}. The t(2;5)(p23;q35) translocation is not detected in LyP {613}.

Histogenesis

LyP represents a proliferation of activated skin-homing T-cells with a unique cytotoxic phenotype (TIA-1+).

Prognosis and predictive factors

LyP exhibits a favorable prognosis with 5-year-survival rates of 100% {191,1795}. So far, there are no data indicating that any kind of therapeutic intervention in LyP alters the natural history of the disease or prevents progression to other malignant lymphomas {650}. Other cutaneous and nodal lymphomas such as mycosis fungoides, Hodgkin lymphoma and systemic or cutaneous CD30+ large T-cell lymphoma (LTCL) develop in 5-20% of patients with LyP {191,1174}. Long-term follow-up is therefore recommended. These lymphomas are usually referred to as LyP-associated malignant lymphomas. They can develop prior to, concurrent with, or after the manifestation of LyP {1175} and result in a fatal outcome in 2% of patients {191}. No risk factors have been identified which definitely indicate likely progression to associated lymphomas in LyP patients. So far, only fascin expression is found at a significantly higher rate in LyP cases associated with systemic lymphomas {1243}.

Primary cutaneous anaplastic large-cell lymphoma

Definition

Primary cutaneous anaplastic lymphoma (C-ALCL) is a neoplasm composed of large atypical lymphocytes of either pleomorphic, anaplastic or immunoblastic cytomorphology and expression of the CD30 antigen by the majority, i.e. more than 75% of tumour cells. Primary cutaneous and primary nodal CD30+ ALCL are distinct clinical entities that can have similar morphologic features and some overlap in immunophenotype, but differ in age of onset, genetic features, etiology and prognosis {600,2259,2493}.

ICD-O-code 9718/3

Synonyms

Regressing atypical histiocytosis , EORTC: Primary cutaneous large cell T cell lymphoma CD30+

Epidemiology

C-ALCL is the second most common form of cutaneous T-cell lymphoma with an incidence of 0.1-0.2 patients per 100'000. This form of lymphoma affects

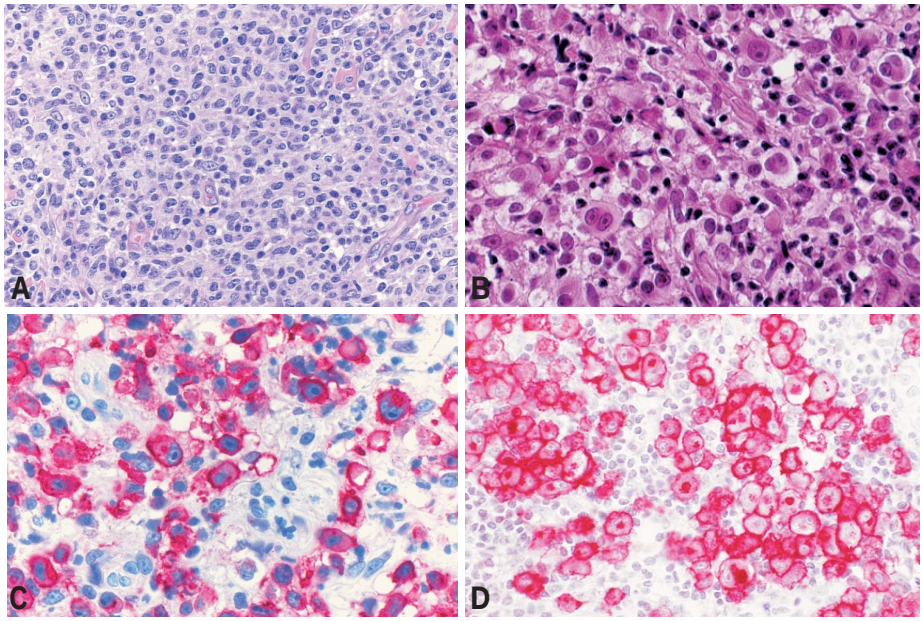

Fig. 4.27 CD30+ Primary cutaneous anaplastic large-cell lymphoma. **A** Large cells in a background of histiocytes, plasma cells and small lymphocytes. **B** Large atypical cells in CD30+ anaplastic large-cell lymphoma. **C** Scattered tumour cells expressing CD30. **D** Expression of CD30 by almost all tumour cells.

mainly people in their sixth decade with a male to female ratio of 2-3:1 {191,1226}, but it can also occur in childhood. C-ALCL is a common form of cutaneous T-cell lymphoma in HIV-infected individuals {1248}.

Localization

The extremities and head are predilection sites {196,1228}.

Clinical features

ALCL usually presents as an asymptomatic, solitary firm nodule which rapidly grows and often ulcerates {1174}. Approximately 20% of the patients have multifocal disease, i.e. two or more lesions at multiple anatomic sites {191}. Involvement of regional lymph nodes can occur. Other extra-cutaneous spread is rare. If there is no therapeutic intervention, spontaneous regression occurs in 10-40% of the tumour lesions {191,1226}.

Histopathology

There is a dense nodular infiltrate extending through all levels of the dermis into the subcutis. Epidermotropism may be found. The infiltrate consists of cohesive sheets of large, cells with irregularly shaped nuclei and one or multiple nucleoli and an abundant, clear or eosinophilic cytoplasm. Mitoses are frequent. Clusters of small reactive lymphocytes are found within and around the tumour. Eosinophils, plasma cells, and accessory dendritic cells usually are not prominent in C-ALCL. Variants of C-ALCL include neutrophil-rich or pyogenic CD30+ ALCL presenting histologically with small aggregations or scattered CD30+ medium to large pleomorphic lymphoid cells within an extensive infiltrate of neutrophils {341,1549}.

Immunohistochemistry

C-ALCL displays an activated T-cell phenotype with expression of T-cell associated antigens CD2, CD3, CD4 and CD45RO, activation markers such as CD25 (IL-2R), CD30, CD71 and HLA-DR, and frequent expression of cytotoxic molecules such as TIA-1, granzyme B and perforin {290,1342}. CD30 must be expressed by at least 75% of the large pleomorphic or anaplastic lymphoid cells. Variable loss of T cell antigens (CD2, CD3, CD5 and CD7) can be found {1228}. In contrast to systemic (nodal) ALCL, C-ALCL does not express EMA, but may express the cutaneous lymphocyte antigen (CLA, HECA-452) and homeobox gene HOXC5 {243}. C-ALCL is consistently negative for the anaplastic lymphoma related tyrosine kinase (ALK).

Genetics

Clonal rearrangement of T cell receptor genes is detected by Southern blot and PCR in most cases (over 90%) of C-ALCL {1467}. The translocation t(2;5) (p23;q35) resulting in expression of npm-alk protein (p80), which is a characteristic feature of systemic anaplastic large cell lymphomas, is rarely if ever found in C-ALCL {228,613}. Systemic ALCL may present with cutaneous disease, and the identification of ALK-expression is helpful in this distinction.

Histogenesis

Activated skin-homing T-cell.

Prognosis and predictive factors

C-ALCL has a favourable prognosis with 5 year-survival rates of 90% {191,1795}. Up to 40% of C-ALCL show spontaneous regression {198}. Regional lymph nodes may be involved, but the survival rate is similar to patients with skin lesions only {191}. Other extracutaneous spread occurs in 10% of the patients, especially in those with multiple grouped or multifocal tumour lesions with a fatal outcome in only a minority of the patients {191}.
Spontaneous regression and age less than 60 years are associated with a better prognosis, while extracutaneous disease and higher age tend to have a worse outcome. Cytomorphology (anaplastic or pleomorphic and immunoblastic) seems not to be a prognostic factor {191,1795}.

Subcutaneous panniculitis-like T-cell lymphoma

E.S. Jaffe
G. Burg

Definition
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a T-cell lymphoma with preferential infiltration of subcutaneous tissue by atypical lymphoid cells of varying size, often with marked tumour necrosis and karyorrhexis.

ICD-O code 9708/3

Historical annotation
In the historical literature, most cases of SPTCL were probably diagnosed as histiocytic cytophagic panniculitis {562, 1527}.

Epidemiology
Subcutaneous panniculitis-like T-cell lymphoma is a rare form of lymphoma, representing less than 1% of all non-Hodgkin lymphomas. It occurs in males and females equally, and has a broad age range. Cases have been reported in children under the age of two years. Most cases occur in adults {1060,1341,2026, 2480}.

Etiology
Unknown. In most patients the disease presents sporadically.

Localization
Patients present with multiple subcutaneous nodules, usually in the absence of other sites of disease. The most common sites of localization are the extremities and trunk.

Clinical features
Clinical symptoms are primarily related to the subcutaneous nodules. The nodules range in size from 0.5 cm to several cm. in diameter. Larger nodules may become necrotic, but ulceration of cutaneous lesions is rare. Systemic symptoms, most commonly fever, are variable but usually present. Some patients may present with a haemophagocytic syndrome with pancytopenias, fever, and hepatosplenomegaly {338,863,2480}. Lymphadenopathy is usually absent.

Histopathology
The infiltrate extends diffusely through the subcutaneous tissue, usually without sparing of septae. The overlying dermis and epidermis are typically uninvolved. The neoplastic cells range in size from small cells with round nuclei and inconspicuous nucleoli to larger transformed cells with hyperchromatic nuclei. The lymphoid cells have a moderate amount of pale-staining cytoplasm. A helpful diagnostic feature is the rimming of the neoplastic cells surrounding individual fat cells {1341}. Admixed reactive histiocytes are frequently present, particularly in areas of fat infiltration and destruction. The histiocytes are frequently vacuolated, due to ingested lipid material. Vascular invasion may be seen in some cases, and necrosis and karyorrhexis are common. However, the infiltrates usually are confined to the subcutaneous tissue, with sparing of the dermis. This feature is helpful in the differential diagnosis from other lymphomas involving skin and subcutaneous tissue. The necrosis is primarily apoptotic in nature, possibly related to the release of cytotoxic molecules {1341,2133}. Cutaneous γδ T-cell lymphomas can have a panniculitis-like component, but commonly show both dermal and epidermal involvement in addition to subcutaneous disease {1060, 1341,2026,2366}. Plasma cells and reactive lymphoid follicles are generally absent, in contrast to lupus profundus panniculitis, and other forms of lobular panniculitis.
In some cases of SPTCL the infiltrates in initial phases may appear deceptively benign, and the differential diagnosis with benign panniculitis may be difficult {338,863}.

Immunoprofile
SPTCL is derived from αß cells, T-cells with a cytotoxic profile.The cells are usu-

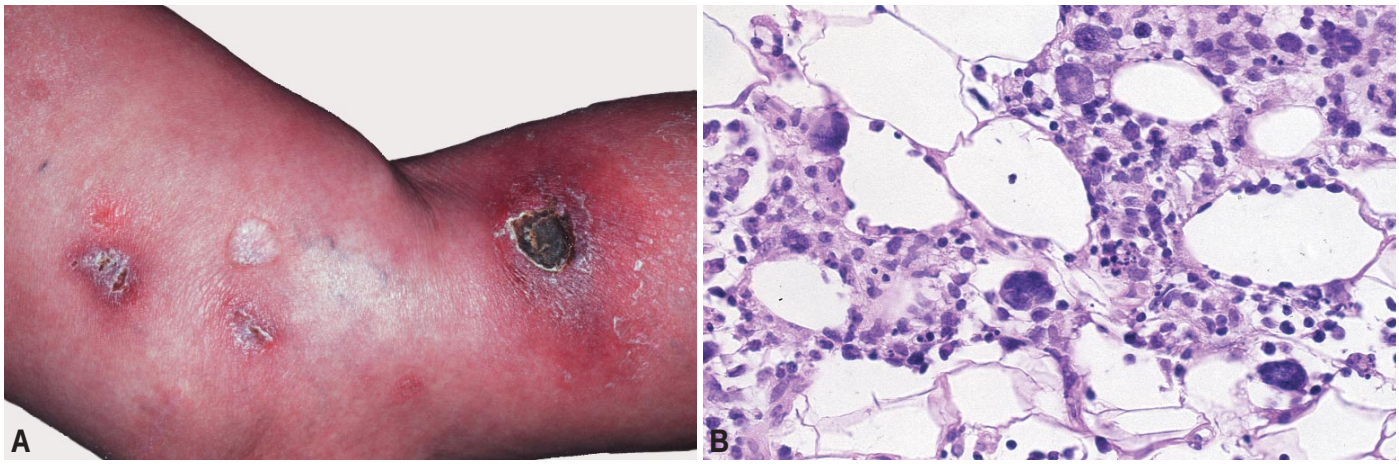

Fig. 4.28 Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL). **A** Erythematous plaques and nodules on the leg with ulceration. **B** Diffuse infiltration of subcutaneous tissue simulating lobular panniculitis. Large atypical cells rimming around fat lobules.

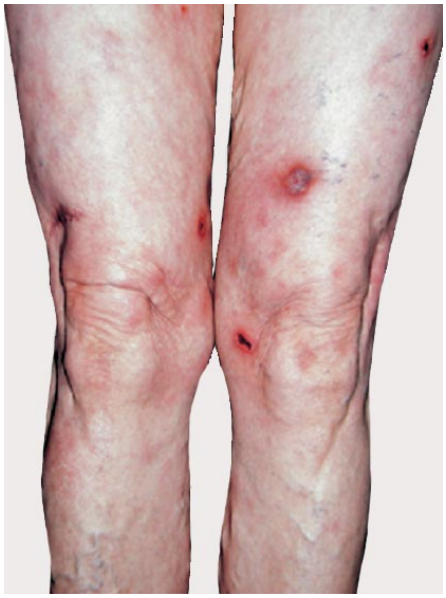

Fig. 4.29 Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL). Subcutaneous erythematous plaques and nodules on the legs.

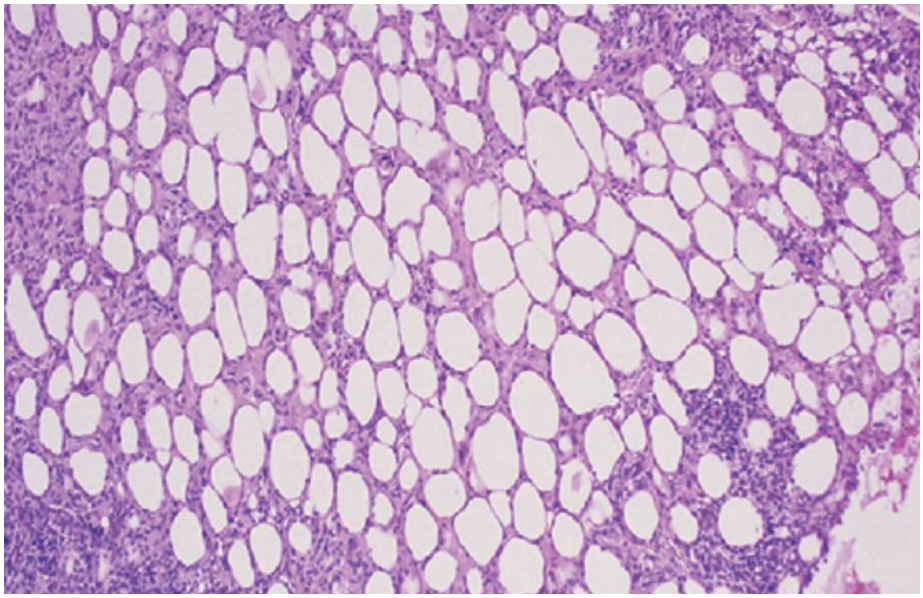

Fig. 4.30 Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL) Lobular panniculitis-like infiltrate of neoplastic lymphoid cells.

ally CD8-positive, with expression of cytotoxic molecules including granzyme B, perforin, and T-cell intracellular antigen (TIA-1) {1341,2026}. However, in contrast to other cytotoxic TCLs related to the innate immune system (enteropathy-type T-cell lymphoma, extranodal NK/T-cell lymphoma), the cells are negative for granzyme M (metase) {694, 1122,1325,2564}. The neoplastic cells are capable of producing a number of cytokines and chemokines, a feature that is related to development of systemic symptoms and the haemopha-gocytic syndrome {338,2340}. Cutaneous γδ T-cell lymphomas {119,338,1341,2026} are distinguished from SPTCL, even if a panniculitis-like component is present.

Histogenesis
Mature cytotoxic T-cell of the adaptive immune system.

Precursor lesions
Oligoclonal T-cell populations may be found in some cases of lobular panniculitis, suggesting the potential for clonal evolution in rare cases {1484}. However, progression from cytophagic panniculitis without monoclonality to SPTCL rarely if ever occurs {1527}.

Somatic genetics
The neoplastic cells show rearrangement of T-cell receptor genes, and are negative for Epstein Barr sequences.

Prognosis and predictive factors
Dissemination to lymph nodes and other organs is uncommon and usually occurs late in the clinical course. The natural history is often aggressive {694,863,917, 1300,2026}. A haemophagocytic syndrome is a frequent complication in αβ cases and usually precipitates a fulminant downhill clinical course. However, if therapy for the underlying lymphoma is instituted and is successful, the haemophagocytic syndrome may remit.

Primary cutaneous peripheral T-cell lymphoma, unspecified

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Definition
A heterogeneous group of cutaneous T-cell lymphomas that do not fit into one of the well-defined subtypes of T-cell lymphoma/leukaemia. Three provisional entities have been separated: Cutaneous γδ T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma and primary cutaneous small-medium CD4+ T-cell lymphoma.

ICD-O code 9709/3

Synonyms and historical annotation
The category of the peripheral T-cell lymphomas, unspecified (PTL) was introduced in the REAL classification {960} and was maintained in the WHO classification {1369}. It encompasses per definition all T-cell neoplasms that do not fit into any of the better defined subtypes of T-cell lymphoma/leukaemia. As such it constitutes a heterogeneous group of diseases. These conditions are most frequently systemic {1121}. Primary cutaneous PTL are rare and constitute less than 10% of all cutaneous T-cell lymphomas (CTCL) in large series {195}. They correspond to the CD30-negative CTCL in the EORTC classification and show an aggressive behaviour in most cases {195,2523}. Therefore, distinction between "primary" and "secondary" cutaneous involvement seems less important for this category.
Although it is still controversial how these tumours can be grouped into separate diseases, recent investigations have suggested that some disorders within this broad group of neoplasms can now be separated out as provisional entities. For the remaining diseases that do not fit into either of these provisional entities (Table 4.1), the designation PTL, unspecified, is maintained.

Table 4.1
Characteristic features of three provisional cutaneous T-cell lymphomas.

	Skin lesion	Pattern of infiltration	Cytology	Phenotype	EBV	Behaviour
γδ-TCL	Patches, plaques, tumours, disseminated	E, D, S	Medium-large, pleomorphic	TCRd1+, CD3+, CD4-, CD8-, CyAg+, CD56 +/-	-	A
AECD8+	Eruptive nodules, hyperkeratotic paches/ plaques, disseminated ,	E	Medium-large pleomorphic	bF1+, CD3+, CD4-, CD8+, CyAg+	-	A
PTL, CD4+	Solitary nodules, tumours	D, S	Small-medium pleomorphic	bF1+, CD3+, CD4+, CD8-	-	I

Abbreviations: γδ-TCL= gamma delta-T-cell lymphoma; AECD8+= aggressive, epidermotopic, CD8+ cytotoxic T-cell lymphoma; E=epidermal; D=dermal; S=subcutaneous; CyAg= cytotoxic antigens (TIA-1, granzyme B, perforin); EBV= Epstein-Barr Virus; A =aggressive; I=indolent.

Cutaneous γδ T-cell lymphoma

Definition
Cutaneous γδ T-cell lymphoma (CGD-TCL) is a lymphoma composed of a clonal proliferation of mature, activated gd T-cells expressing a cytotoxic phenotype. This group includes cases of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with a gamma/delta phenotype. In the WHO classification 2001, these were grouped together with SPTCL of αβ origin {1121}, but they show distinctive features and seem to be more closely related to other CGD-TCL {192,1060, 1533,2026,2366}. A similar and possibly related condition may present primarily in mucosal sites {98}. Whether cutaneous and mucosal γδ TCLs are all part of a single disease, i.e. muco-cutaneous γδ TCL, is not yet clear {1122,2539}.

Epidemiology
CGD-TCLs are rare, with approximately 50 cases reported {1533,1665,2366}. In one series they represented <5% of cutaneous T-cell lymphomas {1879}. Most cases occur in adults. There is no reported sex predilection.

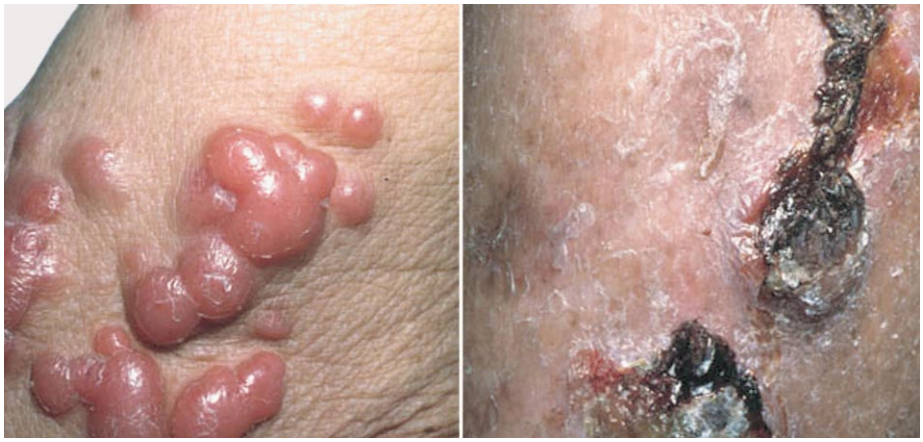

Fig. 4.31 Cutaneous γδ T-cell lymphoma presenting with skin tumours.

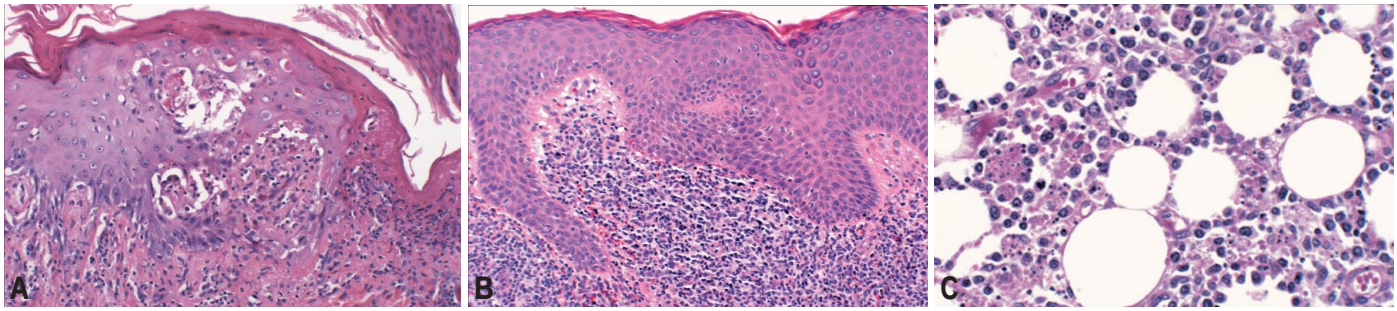

Fig. 4.32 Cutaneous γδ T-cell lymphoma. **A** The infiltrates may be epidemotropic, **B** dermal **C** subcutaneous or combined.

Etiology

The distribution of disease reflects the localization of normal γδ T cells, which are believed to play a role in host mucosal and epithelial immune responses {268}. Impaired immune function associated with chronic antigen stimulation may predispose to the development of mucosal and CGD-TCLs {98,2539}. Epstein-Barr virus (EBV) is generally negative in CGD-TCLs, but may be positive in primary γδ TCL in mucosal sites {98,1191,2366,2539}.

Clinical features

The clinical presentation is variable. The disease may be predominantly epidermotropic and present with patches/plaques, or it may be predominantly deep dermal/subcutaneous with necrotic tumours or nodules, resembling subcutaneous panniculitis-like T-cell lymphoma (SPTCL) of αβ type {192,221,1060,1533, 1665,1879,2026,2366}. The lesions are often mainly present on the extremities {2366}, but other sites may be affected as well {1533,2365}. Patients with CGD-TCL usually lack involvement of lymph nodes, spleen, and bone marrow, but the disease may disseminate to extranodal/mucosal sites. A haemophagocytic syndrome may occur in patients with panniculitis-like tumours {119,2365}.

Histopathology

The neoplastic cells are generally medium to large in size with coarsely clumped chromatin {2366}. Large blastic cells with vesicular nuclei and prominent nucleoli are infrequent. Apoptosis and necrosis are common, often with angioinvasion {1533}. Three major histologic patterns of involvement are present: epidermotropic, dermal, and subcutaneous. However, usually more than one histologic pattern is present in the same patient in different biopsy specimens or within a single biopsy specimen {2366}. Epidermal infiltration may occur as mild epidermotropism to marked pagetoid reticulosis-like infiltrates {221,1665,1879}. Subcutaneous nodules may be panniculitis-like or more solid in appearance and may show rimming of fat cells, similar to SPTCL of alpha/beta origin {1533}. Dermal and epidermal involvement often coexists with subcutaneous disease, in contrast to SPTCL of αβ origin, which is mainly or exclusively subcutaneous in distribution {192,1060,2026}.

Immunoprofile

The cells are CD3+, CD2+, CD7 +/-, but usually negative for CD5 {2539}. Most CGD-TCLs lack both CD4 and CD8, but some are CD8+ {2366}. The cells are positive for TCR-δ, but lack βF1 of the αβ T-cell receptor. The absence of βF1 may be used to infer a γδ origin under appropriate circumstances {1151,2026,2365}. The cells are positive for TIA-1 and the cytotoxic proteins granzyme B, granzyme M, and perforin. {1325,1341, 1533}. CD56 is frequently expressed {1533}.

Histogenesis

Functionally mature and activated cytotoxic γδ T-cells of the innate immune system.

Somatic genetics

The cells show clonal rearrangement of the TCR gamma gene. TCR beta may be rearranged or deleted, but is not expressed. Cases with predominant subcutaneous involvement express Vδ2, but this has not been studied in other CGD-TCL {1860,2026}. EBV is generally negative in primary CGD-TCL {98,119}.

Prognosis and predictive factors

Patients have aggressive disease resistant to multiagent chemotherapy and/or radiation {1665,2366}. In a recent series of 33 patients, 22 (66%) died within 5 years of diagnosis, and in the same study TCRδ1 expression was an independent predictor of survival {2366}. Among 33 patients with CGD-TCL, there was a trend for decreased survival for patients who had subcutaneous fat involvement in comparison with patients who had epidermotropic or dermal disease only. Age, sex, and lymphadenopathy did not have any discernible prognostic impact {2366}.

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Definition

A cutaneous T-cell lymphoma characterized by epidermotropic infiltrates of CD8-positive, cytotoxic T-cells of αβ origin. The behaviour is aggressive in most cases {223}.

Epidemiology

This disease occurs mainly in adults and is rare with approximately 30 cases published worldwide {36,192,223,1533, 2062}.

Clinical features

The clinical presentation is characterized by sudden eruptions of localized or disseminated papules, nodules and tumours, often with central ulceration and necrosis. Superficial, hyperkeratotic patches and plaques may also be present {36,223}. The disease may resemble epidermotropic variants of other cutaneous T-cell lymphomas and is similar, if not identical to cases described as generalized pagetoid reticulosis of the Ketron-Goodman type {1252,1533}. Classical MF, which may express CD8 in rare cases {1456,1880, 2062,2510}, usu-

ally does not show overt destruction and necrosis and has a more protracted behaviour with progression over years from patches to plaques and tumours. The disease may disseminate to other visceral sites (lung, testis, central nervous system, oral mucosa), but lymph nodes are often spared {223}.

Histopathology
The histological and cytological appearance is very variable ranging from a lichenoid pattern with marked, pagetoid epidermotropism and subepidermal edema to deeper, more nodular infiltrates. The epidermis may be acanthotic or atrophic, often with necrosis, ulceration and blister formation {36,223}. Invasion and destruction of adnexal skin structures are commonly seen {1533}. Angiocentricity and angioinvasion may be present {1533}. Tumour cells are small-medium or medium-large with pleomorphic or blastic nuclei {223}.

Immunoprofile
The tumour cell have a βF1+, CD3+, CD8+, Granzyme B+, perforin+, TIA-1+, CD2-, CD4-, CD5-, CD7-/+ phenotype {36,223,2062}. EBV is generally negative {192,1533}.

Histogenesis
Skin homing, CD8-positive, cytotoxic T-cells of αβ type.

Somatic genetics
The neoplastic T-cells show clonal TCR gene rearrangements. Specific genetic abnormalities have not been described.

Prognosis
These lymphomas have an aggressive clinical course with a median survival of 32 months {36,223,1533,2062}.

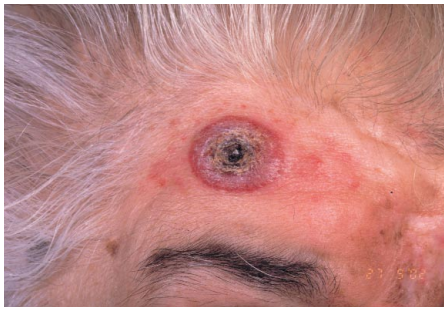

Fig. 4.33 Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma presenting with an ulcerated skin tumour

Primary cutaneous small-medium CD4+ T-cell lymphoma

Definition
A cutaneous T-cell lymphoma characterized by a predominance of small to medium-sized CD4-positive pleomorphic T-cells with clinical features different from MF. Most cases have a favourable clinical course {195,878}.

Epidemiology
A rare disease, accounting for 5-10% of cutaneous lymphomas in large series {195,878}.

Clinical features
Characteristically, these lymphomas present with a solitary plaque or tumour, generally on the face, the neck or the upper trunk {195}. Less commonly, they present with one or several papules, nodules or tumours, but always without patches typical of mycosis fungoides {195,783,2267}.

Histopathology
These lymphomas show dense, diffuse or nodular infiltrates within the dermis with tendency to infiltrate the subcutis. Epidermotropism may be present focally. There is a predominance of small/medium-sized pleomorphic T cells {195,783, 2267}. A small proportion (<30%) of large pleomorphic cells may be present {195}. A considerable admixture with small reactive lymphocytes and histiocytes may sometimes be observed {2074}.

Immunoprofile
By definition these lymphomas have a CD3+, CD4+, CD8-, CD30- phenotype sometimes with loss of pan T-cell markers {195,783}. Cytotoxic proteins are generally not expressed {195}.

Histogenesis
Skin homing, CD4-positive T-cell.

Somatic genetics
The TCR genes are clonally rearranged {783,878}. Demonstration of clonality is a useful criterion for distinction from pseudo-T-cell lymphomas, which may also present with a solitary plaque or nodule. No consistent cytogenetic abnormalities have yet been identified.

Prognosis and predictive factors
These lymphomas have a rather favourable prognosis with an estimated 5-year survival of 60-80% {195,783, 878,2267}. Cases presenting with solitary or localized skin lesions seem to have an especially favourable prognosis {195,878}.

Primary cutaneous PTL, unspecified

Definition
The designation PTL, unspecified is maintained for cutaneous T-cell lym-

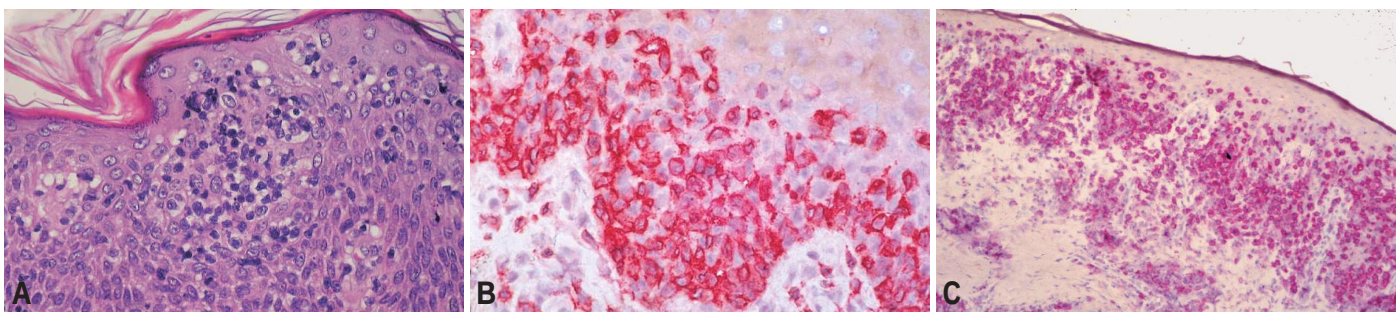

Fig. 4.34 Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. **A** The neoplastic infiltrate is markedly epidermotropic and pleomorphic and is **B** positive for CD3 and **C** for CD8.

phomas that originate from mature, transformed T-lymphocytes and that do not fit into any of the better defined subtypes of mature cutaneous T-cell neoplasms. Hence, other categories of T-cell lymphoma must be excluded. These include the 3 provisional entities described above. Furthermore, given the wide variety of histologic appearances of tumour stage mycosis fungoides (MF), a diagnosis of MF should always be ruled out by complete clinical examination and an accurate clinical history.

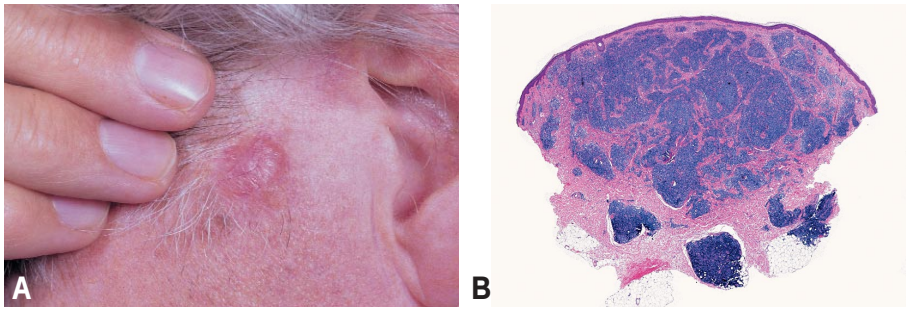

Fig. 4.35 Primary cutaneous small-medium T-cell lymphoma. **A** Small-medium CD4+ T-cell lymphoma with a solitary skin nodule on the face. **B** Nodular infiltrates of lymphocytes involving the entire dermis and superficial part of subcutaneous tissues.

Epidemiology

These tumours account for 5 to 10% of all primary cutaneous T cell or NK cell lymphomas {195}. All ages may be affected, but the disease is most common in adults.

Clinical features

Most lymphomas in this category present with rapidly growing tumours or nodules that may be multiple or (more rarely) solitary or localized {195,197,878,2523}. No sites of predilection have been recorded.

Histopathology

Skin infiltrates are most often diffuse, but nodular or band-like patterns can be seen. Epidermotropism is mild or absent in most cases. The tumour cells are medium to large, usually with markedly pleomorphic nuclei. Rare cases may show a predominance of cells that are more immunoblastic in appearance {197,2523}. Small reactive lymphocytes, eosinophils and plasma cells may be present {195}, but the inflammatory background is usually not as pronounced as it can be in nodal malignancies.

Immunoprofile

The tumour cells express T-cell associated antigens (CD2, CD3, CD5), but usually lack CD7; most cases are CD4+, but rare tumours may be CD8+ or positive (or negative) for both CD4 and CD8 {195}. Cytotoxic antigens (TIA-1+, granzyme B) are usually not expressed {195}. Occasional tumour cells may be CD30-positive.

Histogenesis

Skin homing T-cells.

Precursor lesion

There are no known precursor lesions. As mentioned, cases of transformed MF may closely resemble peripheral T cell lymphoma unspecified and can only be distinguished on clinical grounds.

Somatic genetics

The TCR genes are clonally rearranged. No consistent cytogenetic abnormalities have yet been identified.

Prognosis and predictive factors

The prognosis is poor with 5-year survival rates of less than 20% {195,878}. Cases with immunoblastic morphology may have an even more aggressive behaviour {197,2523}. Cases with solitary/localized lesions seem to behave just as aggressivelys as those with multiple lesions {195}.

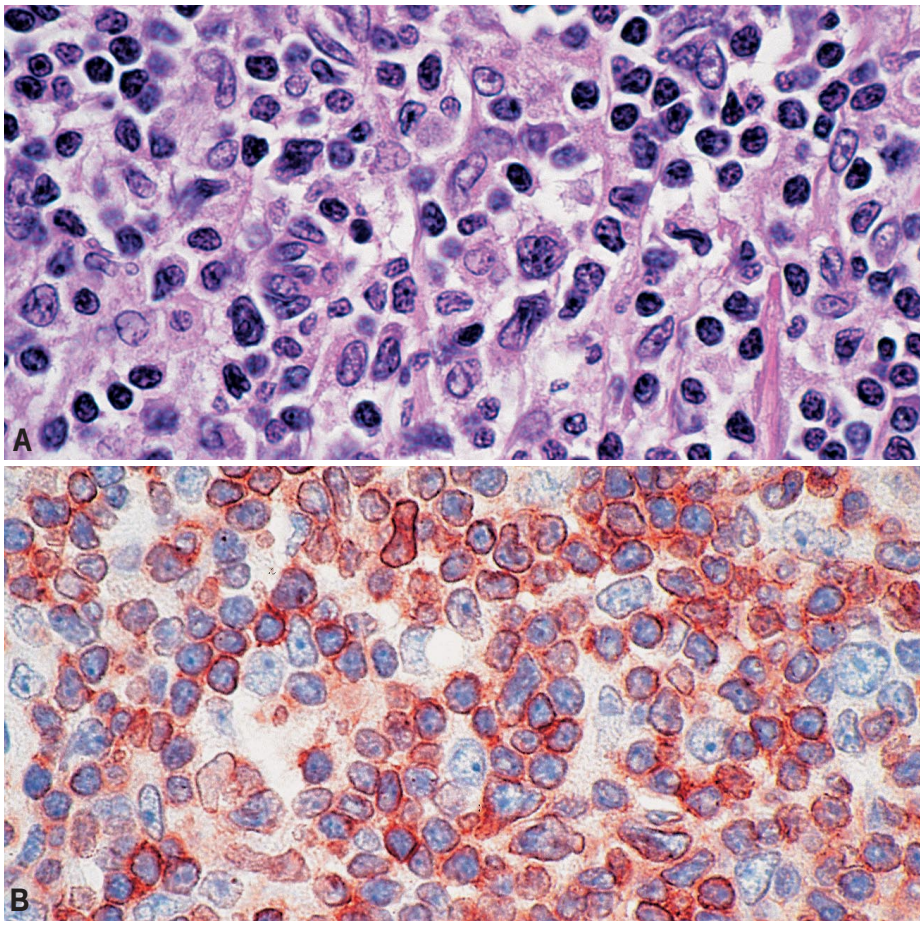

Fig. 4.36 Cutaneous small-medium pleomorphic T-cell lymphoma. **A** Small-medium lymphocytes with pleomorphic nuclei predominating. **B** Staining for CD3 confirms the T-cell lineage of the lymphocytes.

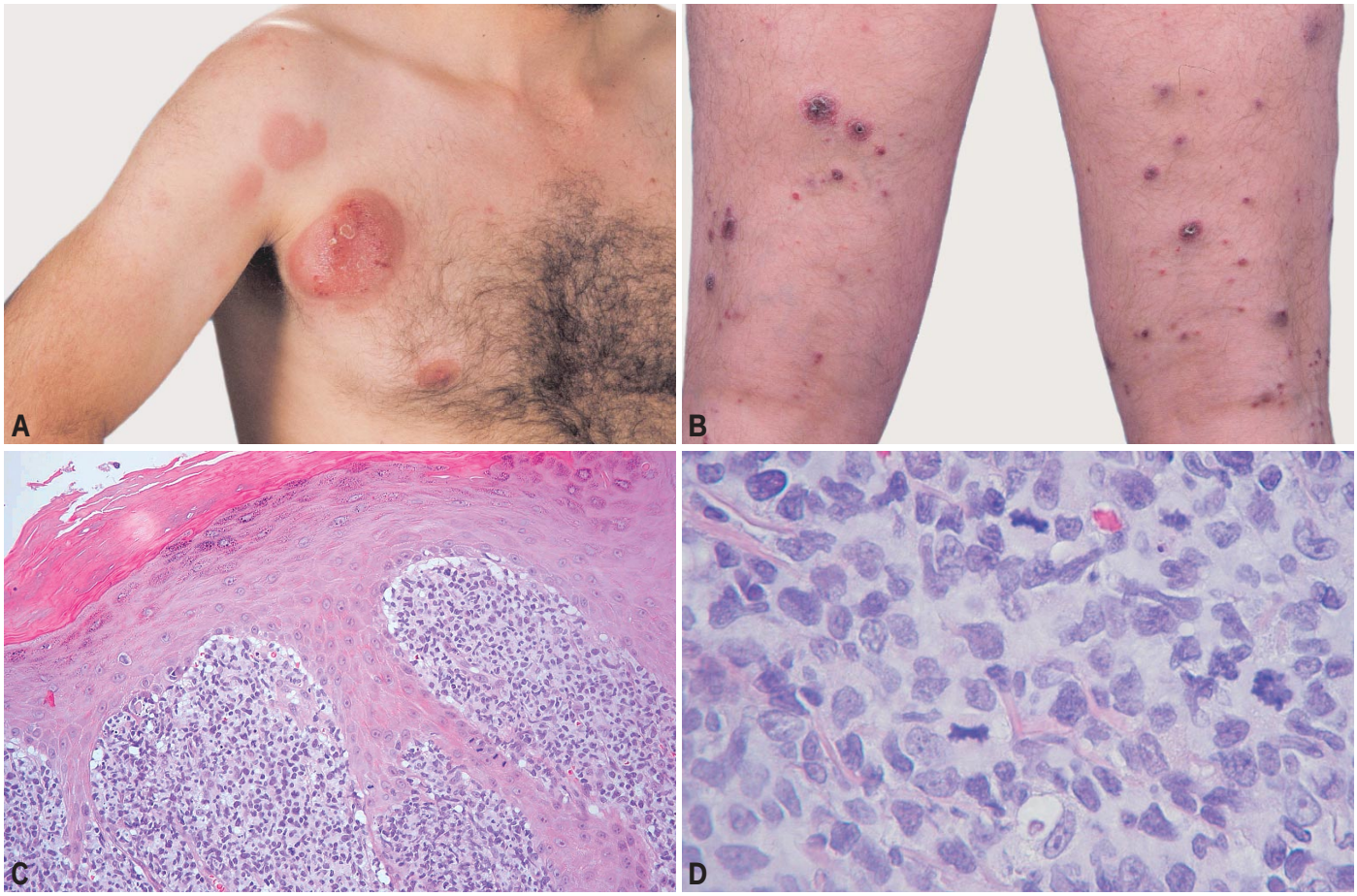

Fig. 4.37 Primary cutaneous peripheral T-cell lymphoma, unspecified. **A** Grouped and **B** disseminated skin lesions. **C** The dermal neoplastic infiltrate is dense and **D** consists of large, pleomorphic cells with irregular nuclei and numerous mitoses.

Cutaneous adult T-cell leukaemia / lymphoma

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C. A. Sander

Definition
Adult T cell leukaemia / lymphoma (ATLL) is a malignancy of mature CD4+ T cells caused by the human T-cell leukaemia virus type I (HTLV-1).

ICD-O code 9827/3

Synonyms
Adult T-cell leukaemia (ATL)

Epidemiology
ATLL is endemic in some regions of the world, especially in southwest Japan, the Caribbean islands, South America, and parts of Central Africa {1848,2392}.

Etiology
ATLL develops in 1% to 5% of individuals infected with HTLV-1 after more than 2 decades of viral persistence. In most patients viral exposure occurs early in life, and incidence figures are related to the place of birth, not residence.
HTLV-1 proviral DNA is monoclonally integrated in the malignant T cell. HTLV-1 encodes the transcriptional activator Tax, which can transform T cells by increasing the expression of a unique set of cellular genes involved in T cell proliferation {1589}.

Localization
Based on organ involvement and severity, ATLL is divided into four clinical categories: acute, chronic, lymphoma, and smoldering types {2171}. Cutaneous involvement is seen in up to 50% of patients. Lymph nodes, liver and spleen are frequently involved.

Clinical features
Patients with ATLL exhibit various cutaneous manifestations. The most frequent manifestation is nodules/tumours (33.9%), followed by red papules (22.6%), erythematous plaques (19.4%) and macules (6.5%) {2142}. Nodules/tumours usually occur as solitary or several lesions on limited sites, whereas multiple papules tend to be distributed over large areas of the body. Subcutaneous tumours (4.8%), erythroderma (3.5%), and purpura (1.6%) are less frequent, and alopecia, folliculitis, erythema multiforme, and prurigo are rarely seen.
In addition to the four clinical types, the cutaneous type of ATLL has been proposed to indicate skin-limited lesions without lymph node involvement or leukaemic involvement {1144}. ATLL limited to the skin may be considered part of the smouldering type. Two patterns of skin involvement are seen; i.e., tumoural and erythematopapular. The tumoural subtype has been reported to have a worse prognosis than the erythematopapular one.

Histopathology
Individual skin lesions of ATLL exhibit varying degrees of tumour cell infiltration from the epidermis to subcutaneous tissue. Epidermotropism of the malignant T-cells is present in the majority of cases,

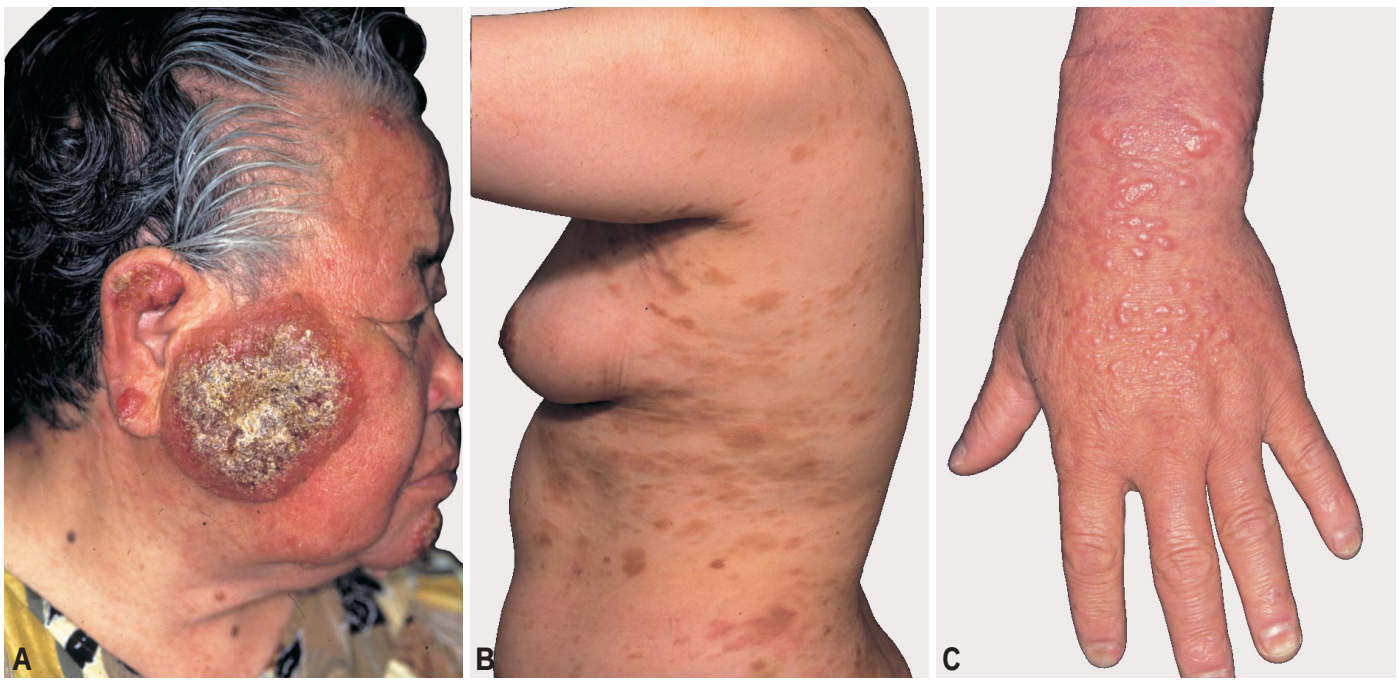

Fig. 4.38 Adult T-cell leukaemia/lymphoma (ATLL) **A** A large tumour on the right cheek. **B** Multiple erythematous plaques on the trunk. **C** Multiple papules on the hand and forearm.

and even Pautrier microabscesses, indistinguishable from those of mycosis fungoides and Sézary syndrome, are often seen. The cells have medium- to large-sized pleomorphic nuclei, and occasionally show mitoses. Nuclear irregularity may be marked, with polylobated flower cells often seen in the blood and tissues. Eosinophils may be intermingled with lymphocytes. In some cases, the tumour cells infiltrate mainly in the subcutaneous tissue {2142,2171}.

Immunohistochemistry

In general, the malignant T cells are positive for CD3, CD4, CD25, and CD45RO but negative for CD7. CD8, CD19, and CD20 {2171}. CD30 expression may be seen in larger transformed cells.

Prognosis and prognostic factors

The prognosis of ATLL patients with skin lesions is dependent on clinical and histological factors, and relates to the four main clinical subtypes. It has been suggested that cases of the smoldering type of ATLL have a poorer prognosis if there are deep dermal cutaneous infiltrates, as compared to cases in which skin manifestations are absent, or only present as superficial infiltration {2142}.

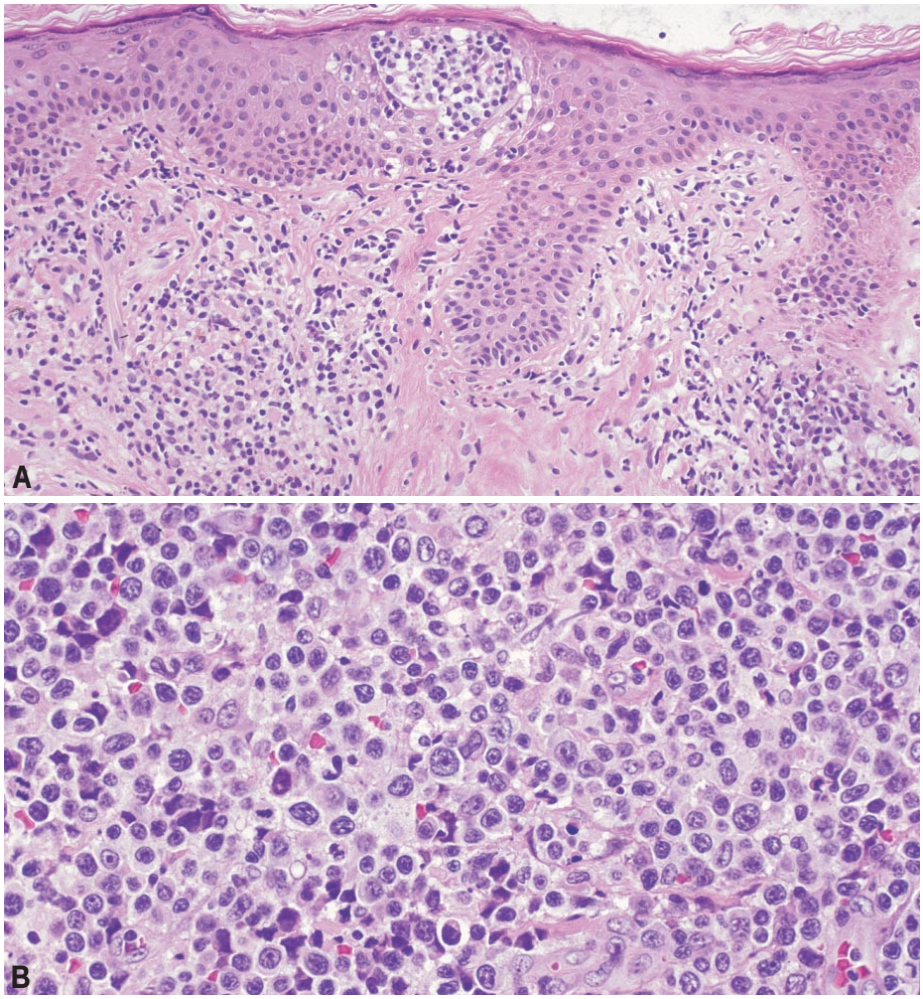

Fig. 4.39 Adult T-cell leukaemia/lymphoma (ATLL). **A** Erythematous macule, showing infiltration of atypical lymphocytes in the upper dermis with Pautrier microabscess. **B** Tumour, massive infiltration of pleomorphic lymphocytes in the dermis.

Extranodal NK/T-cell lymphoma, nasal-type

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J.K.C. Chan

Definition

Extranodal NK/T-cell lymphoma, nasal-type, is an EBV+, nearly always extranodal lymphoma of small, medium or large cells usually with an NK-cell, or more rarely cytotoxic T-cell phenotype. The skin is the second most common site of involvement after the nasal cavity/nasopharynx, and skin involvement may be a primary or secondary manifestation of the disease.

ICD-O code: 9719/3

Synonyms

REAL: angiocentric T-cell lymphoma;
EORTC used to include in CTCL, large cell, CD30- and CTCL, pleomorphic, small/medium-sized

Epidemiology

Extranodal NK/T-cell lymphoma is a rare disease occurring in adults, with a male predominance. This lymphoma is more prevalent in Asia, Central America and South America.

Etiology

It is universally associated with EBV, and genetic factors play a role in susceptibility to the disease {443,1689}.

Localization

The majority of patients present with skin lesions affecting more than one anatomic region, most commonly the trunk and extremities {443,1660}.

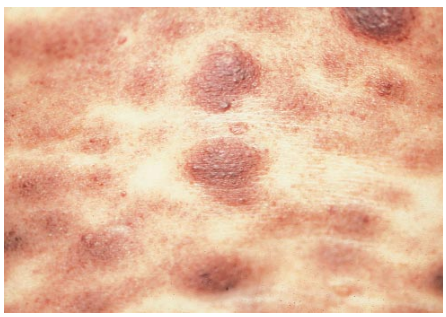

Fig. 4.40 Extranodal NK/T-cell lymphoma, nasal-type. Clinical appearance with violaceous tumour nodules.

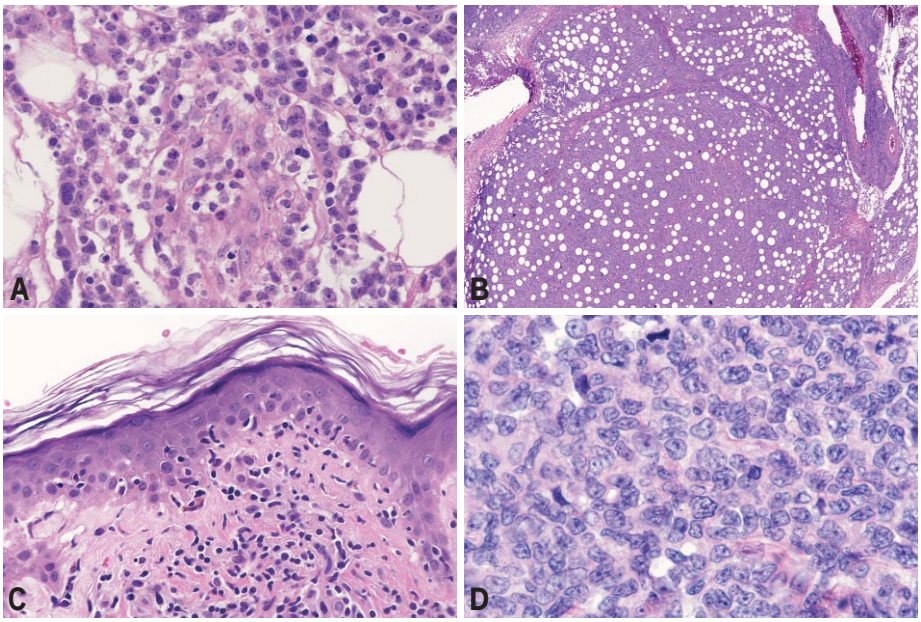

Fig. 4.41 Extranodal NK/T-cell lymphoma, nasal-type. **A** Angiocentricity and angiodestruction. **B** Involvement of the subcutis. **C** Focal epidermotropism, present in approx. 30% of cases. **D** Cytologic detail showing medium sized cells with irregular nuclear foldings.

Clinical features

Cutaneous involvement consists of tumour nodules and plaques. Systemic symptoms such as fever, malaise and weight loss are common. Some cases are accompanied by a haemophagocytic syndrome. The disease is closely related to aggressive NK-cell leukaemia, which also may have cutaneous manifestations, and is also EBV-associated.

Histopathology

A dense dermal infiltrate is often centred on the skin appendages and blood vessels resulting in a column-like low power appearance {1689}. Prominent angiocentricity and angiodestruction are often accompanied by extensive necrosis {443,1689}. Extension into the subcutis is common. Approximately 30% of cases show at least focal epidermotropism {1689}. The mitotic rate is high and apoptotic bodies are numerous. NK/T-cell lymphoma has a broad cytologic spectrum ranging from small to large cells, with most cases consisting of medium sized cells. The cells often exhibit irregular nuclear foldings, moderately dense chromatin, and pale cytoplasm.

Immunoprofile

The most common immunophenotype is: CD2+, CD56+, surface CD3-, cytoplasmic CD3ε+, CD43+ and cytotoxic granules + (TIA-1, granzyme B, perforin) {1325}. Occasional cases are CD56-, but then require EBV positivity or presence of cytotoxic granules for diagnosis;otherwise they should be classified as peripheral T-cell lymphoma, unspecified. LMP-1 is inconsistently expressed, with EBER in situ hybridization preferred for diagnosis.

Genetics

The T-cell receptor is usually in germline configuration.

Prognosis and predictive factors

Extranodal NK/T-cell lymphoma presenting in the skin is a highly aggressive tumour with a median survival of less than 15 months {443,1660}. The most

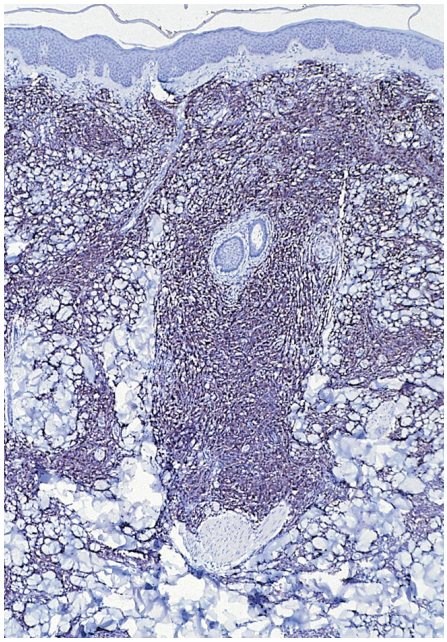

Fig. 4.42 Nasal type NK/T-cell lymphoma (EBV+), immunostained for CD56. Almost all cells are CD56 positive.

important factor predicting poor outcome is the presence of extracutaneous involvement at presentation {1660}. Preliminary data indicate that co-expression of CD56 and CD30 may be associated with a better prognosis {1660,1690}.

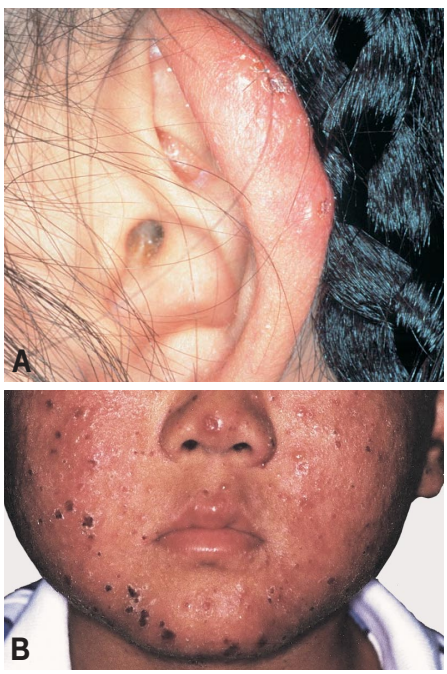

Fig. 4.43 Hydroa vacciniforme-like cutaneous T-cell lymphoma. **A** Infiltrate on the sun-exposed earlobe. **B** Papules, vesicles and crusted erosions on face of young boy.

Hydroa vacciniforme-like cutaneous T-cell lymphoma

Definition

Hydroa-vacciniforme-like cutaneous T-cell lymphoma is a rare EBV-associated lymphoma of cytotoxic T-cell or NK-cell origin that affects children, characterized by a vesiculopapular skin eruption that clinically resembles hydroa vacciniforme.

Synonym

Angiocentric cutaneous T-cell lymphoma of childhood

Epidemiology

Hydroa vacciniforme-like CTCL affects children and teenagers, with almost all reported cases being from Latin America (such as Peru, Bolivia, Mexico) {166, 1479,1991} and Asia (such as Korea and Japan). Boys and girls are affected in an equal ratio {471,765}.

Etiology

The strong association with EBV suggests a pathogenetic role of the virus and genetic predisposition, as in extranodal NK/T-cell lymphoma. The anatomic distribution of the skin lesions suggests sun exposure as a risk factor although tests for minimal erythema doses are usually within normal limits.

Localization

The lesions occur predominantly in sun-exposed areas, particularly the face and limbs.

Clinical features

Patients present with facial and hand oedema and a papulovesicular eruption that affects sun-exposed and to a lesser extent sun-protected areas. Individual lesions start with oedema and erythema and then progress to vesicles, necrosis, ulceration, crusts, and heal as varicelliform scars. Fever, wasting, hepatosplenomegaly, lymphadenopathy and hypersensitivity to insect bites are common. Some cases are accompanied by a haemophagocytic syndrome. The disease may progress to lymph node and visceral involvement.

Histopathology

The infiltrate consists of medium-sized atypical lymphoid cells set in an inflammatory background. The depth of the infiltrate seems related to the age of the lesion {166}. A fully developed lesion shows a dense dermal infiltrate with epidermotropism and extension into the fat in a lobular fashion. Ulceration is common. The infiltrate is often angiotropic/angioinvasive and in addition may display a periadnexal and perineural growth pattern.

Immunoprofile

The tumour cells are cytotoxic T-cells, that have often lost expression of some pan T-cell markers. The most common phenotype is: CD2+, CD3+, CD8+, CD43+, CD45RO+, TIA-1+, Granzyme B+; CD4-, CD5-, CD7-. CD56 is variably positive, but CD57 is negative. CD30 reactivity can be seen in a subset of cells (<30%).

Somatic genetics

The T-cell receptor gene is clonally rearranged {166,1479}, although in cases of NK-cell derivation, T-cell receptor genes are germline.

Prognosis

The prognosis is poor, with a 2-year survival rate of 36% {166}.

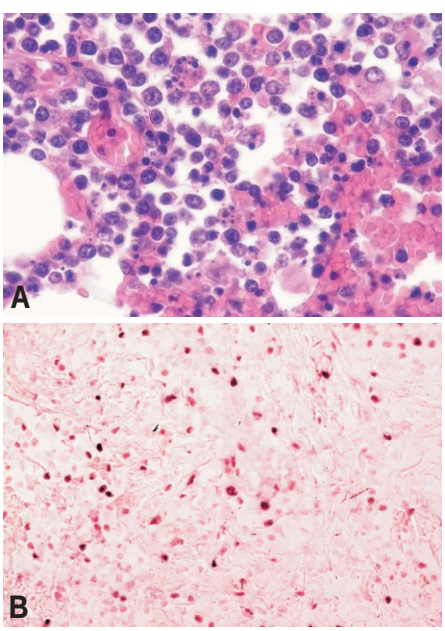

Fig. 4.44 A Subcutaneous infiltrate of tumour cells with prominent cytophagocytosis. **B** In situ hybridisation showing EBER+ tumour cells

Cutaneous involvement in primary extracutaneous T-cell lymphoma

W. Kempf
E. Ralfkiaer
D.V. Kazakov
E.S. Jaffe

Systemic peripheral T-cell lymphoma (PTL), unspecified, involves the skin in approximately 20-30% of the cases {836, 1453}. Skin lesions may be present at diagnosis or can develop during disease progression. Lesions are most often tumours or nodules that may be solitary or multiple. No sites of predilection have been recorded. The histological and phenotypic features are identical to the systemic disease. The prognosis is very poor {104,690,836,1453}.

Systemic anaplastic large cell lymphoma (ALCL)

Primary systemic anaplastic large cell lymphoma affects lymph nodes and extranodal sites, including in 20% of the cases the skin. The skin lesions may be present at diagnosis or can develop at relapse or during disease progression. The skin lesions are usually tumours or nodules that can be solitary or multiple. No sites of predilection have been recorded. The histological, phenotypic and genotypic features are identical in lymph nodes and the skin. The tumour cells are most often large with abundant cytoplasm and characteristic so-called hallmark cells with eccentric, horseshoe- or kidney-shaped nuclei often with an eosinophilic region near the nucleus. The principal morphological variants are the small cell variant and the histiocyte rich variant {809}. It is important to distinguish these lesions from primary cutaneous ALCL. The histological appearance of systemic cases is usually more monomorphic with infrequent tumour giant cells. The tumour cells in systemic ALCL express a cytotoxic phenotype and are positive for CD30 and EMA. CD3 is negative in more than 75% of cases {191, 1121}. CD5 and CD7 are often negative. CD2, CD4 and CD43 are more useful and are expressed in a significant proportion of cases. ALK expression and t(2;5) or variant translocations involving ALK and fusion partners other than NPM are present in the majority of cases {706, 809}. The natural history is aggressive but long term complete remissions can be obtained in most patients with ALK-positive disease {191}.

Angioimmunoblastic T-cell lymphoma (AITL)

ICD-O code 9705/3

Skin lesions in angioimmunoblastic T-cell lymphoma (AITL) occur in half of the cases, usually as a generalized maculopapular eruption simulating viral exanthem or drug eruption, or as urticaria, purpura, erythemato-squamous plaques, prurigo-like lesions, erythroderma, erosions and necrotic lesions. The disease occurs mostly in middle-aged or elderly people without gender preponderance {787}. Other findings are fever, weight loss, night sweats, lymphadenopathy, hepato- and splenomegaly, anaemia, an elevated sedimentation rate, leukocytosis, neutropaenia or thrombocytopaenia, as well as polyclonal hypergammaglobulinemia. AITL exhibits an aggressive course with a median survival ranging from 11 to 30 months and a fatal outcome in 50 to 70% of patients.

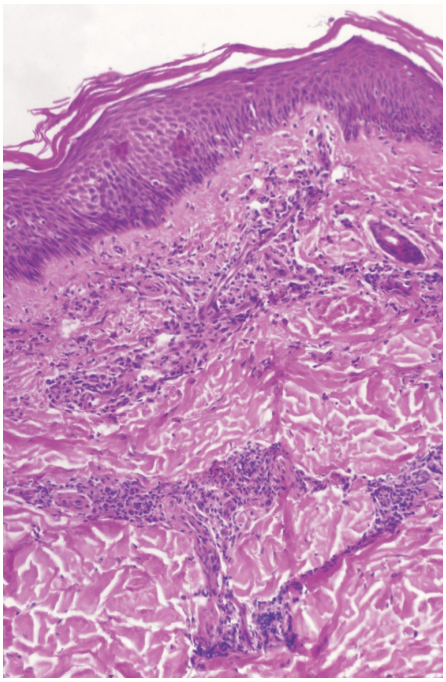

Fig. 4.45 Cutaneous involvement in AITL. A polymorphous perivascular infiltrate is present in the superficial dermis

Histologically, the skin lesions are characterized by nonspecific subtle superficial perivascular infiltrates composed of eosinophils and lymphocytes without atypia accompanied by hyperplasia of capillaries. Admixed plasma cells and histiocytes can be found {2087}. Clonal T cell receptor rearrangement has been reported in some cases {1522}. However, it is not clear whether the cutaneous manifestations are generally due to tumour cell involvement or a secondary phenomenon related to cytokine production.

Cutaneous marginal zone B-cell lymphoma

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L. Duncan
G. Burg
R. Willemze
S.H. Swerdlow
E.S. Jaffe

Definition

Primary cutaneous marginal zone B-cell lymphoma (MZL) is an indolent lymphoma composed of small B cells including marginal zone (centrocyte-like) or monocytoid cells, lymphoplasmacytoid cells and plasma cells. It is considered part of the broad group of extranodal marginal zone B-cell lymphomas commonly involving mucosal sites (mucosa associated lymphoid tissue, MALT). Primary cutaneous immunocytoma, primary cutaneous plasmacytoma and cutaneous follicular lymphoid hyperplasia with monotypic plasma cells are considered variants of MZL.

ICD-O code 9699/3

Synonyms

EORTC (1997): Primary cutaneous immunocytoma / marginal zone B-cell lymphoma

Epidemiology

MZL most commonly affects adults aged over 40 years. There is no clear gender preponderance {132,2141}.

Etiology

In Europe, Borrelia burgdorferi DNA has been identified in some cases of MZL suggesting that it may play an etiological role. {433}. However, no association of Borrelia with CBCL has been found in the United States and Asia {2547}.

Localization

MZL is predominantly localized on the upper extremitites, and less often head and trunk.

Clinical features

In most cases, cutaneous MZL presents with red to violaceous plaques or nodules with an erythematous border {2141}. Ulceration and visceral dissemination are uncommon. MZL with secondary spread to the skin is often multifocal {1418}.

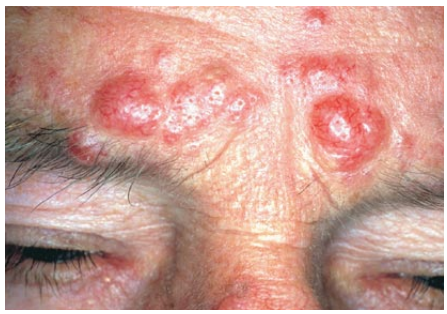

Fig. 4.48 Marginal-zone lymphoma. Firm nodules on the forehead.

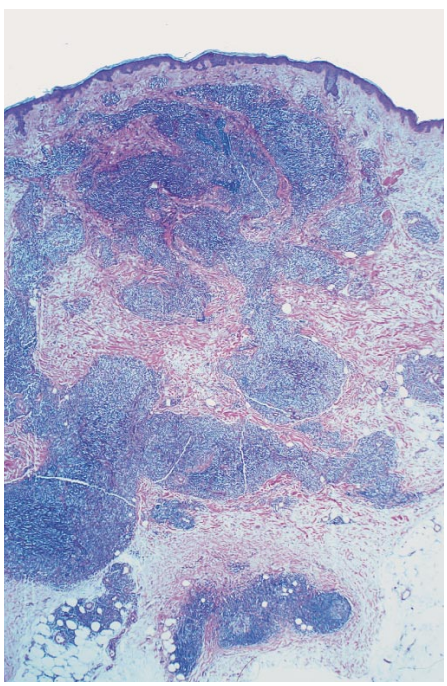

Fig. 4.46 Cutaneous marginal zone B-cell lymphoma. Infiltrate extends through dermis to subcutaneous tissue.

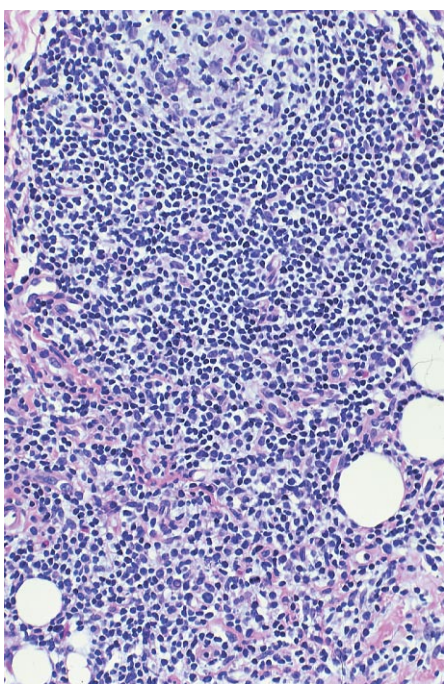

Fig. 4.47 Cutaneous marginal zone B-cell lymphoma. Neoplastic cells surround a residual germinal centre.

Histopathology

The infiltrate is characterized by residual reactive lymphoid follicles surrounded by pale staining cuffs of tumour cells. Reactive germinal centres with distinct mantle zones are commonly found in early lesions but may become colonized by tumour cells as the disease progresses. The interfollicular infiltrate is composed of small to medium-sized, centrocyte-like or monocytoid cells with slightly irregular nuclei, moderately dispersed chromatin, inconspicuous nucleoli and a rim of pale cytoplasm {2234,2362}. Variable numbers of lymphoplasmacytoid cells and plasma cells are typically present at the periphery of the infiltrates or in the subepidermal area. Intranuclear PAS positive pseudoinclusions (Dutcher bodies), are commonly found, particularly in plasma cell rich forms of MZL. Diffuse infiltrates almost completely consisting of monocytoid cells, lymphoepithelial lesions with infiltration of sweat glands and the presence of very immature plasma cells should raise suspicion of secondary cutaneous involvement.

Immunoprofile

The neoplastic cells express CD19+, CD20+, CD22+, CD79a+, but are negative for CD5-, CD10-, bcl-6, CD23-. CD43 may be positive {132}. In contrast to FL, the tumour cells are bcl-2+, but negative for bcl-6 and CD10 {603,1418}. Reactive

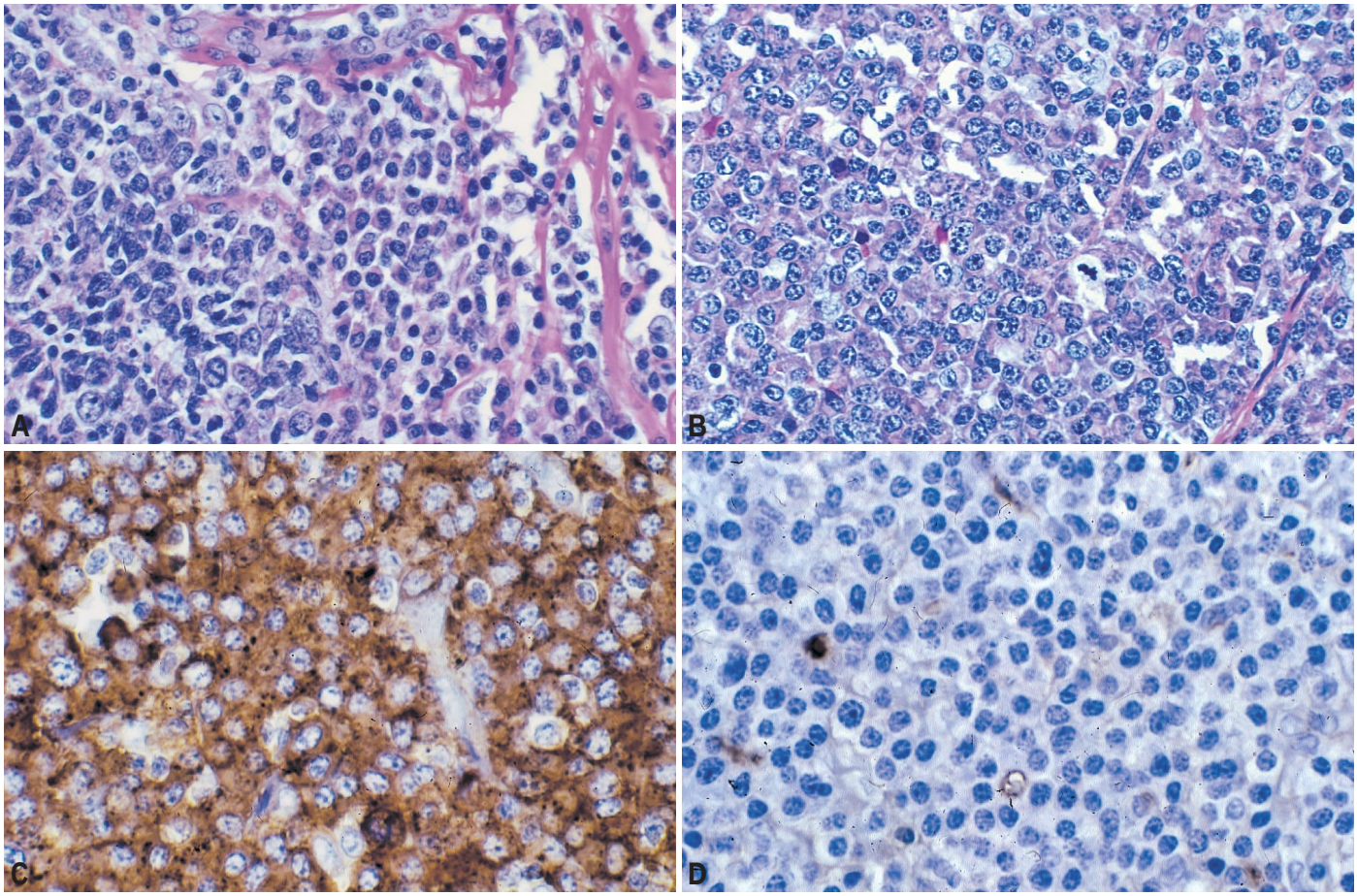

Fig. 4.49 Plasmacytoid cells in cutaneous marginal zone B-cell lymphoma. **A** Monoclonal plasma cells are admixed with cells with monocytoid features. **B** In a subsequent biopsy from the same patient, all of the cells have a plasmacytic morphology and express monoclonal Ig light chains. **C** Kappa. **D** Lambda.

germinal centres are bcl-6+ and bcl-2-. Anti-CD21 staining often reveals regular and irregular networks of follicular dendritic cells (FDC) in reactive follicles, but not associated with tumour cells. The lymphoplasmacytoid cells and the plasma cells show monotypic expression of immunoglobulin light chains. There are numerous admixed reactive T-cells.

Precursor lesion

Cutaneous lymphoid hyperplasia due to Borrelia infection may mimic MZL and has been postulated to represent a precursor lesion in some circumstances.

Histogenesis

Post germinal centre B-lymphocyte with plasmacytic differentiation and gene expression pattern {2273}.

Somatic genetics

IgH genes are clonally rearranged. The most common translocation in gastric MZL, the t(11;18) involving the API2/MLT genes, has not been demonstrated in primary cutaneous MZL {1418,2141,2279}. However, the t(14;18)(q32;q21) involving IGH and MALT1 was reported in approximately one third of cases in a small series. Fas gene mutations are present in a minority of cases, similar to MZL of other extranodal sites. Abnormalities of BCL10 are absent {906}.

Prognosis

MZL shows a protracted clinical course with a tendency for recurrences. However, the prognosis is favourable with 5-year-survival rates between 90 and 100%. Transformation into diffuse large B cell lymphoma occurs infrequently {2141}.

Cutaneous follicle centre lymphoma

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Definition

Primary cutaneous follicle centre lymphoma (PCFCL) is defined as a tumour of neoplastic follicle centre cells (FCC), usually a mixture of small and large cleaved cells (centrocytes) and, to a lesser extent, large noncleaved cells (centroblasts) with prominent nucleoli. The growth pattern varies from follicular to follicular and diffuse to diffuse.

ICD-O Code 9690/3

Synonyms

Kiel: centroblastic-centrocytic (follicular, follicular and diffuse), centroblastic.
Working formulation: follicular, follicular and diffuse (predominantly small cleaved, mixed small cleaved and large cell, predominantly large cell).
WHO: follicular lymphoma, diffuse follicle centre lymphoma, diffuse large B-cell lymphoma.
EORTC (1997): follicular centre cell lymphoma.
Reticulohistiocytoma of the dorsum (Crosti disease): {220}.

Epidemiology

Primary cutaneous B cell lymphoma (CBCL) in Europe account for up to 25% of cutaneous lymphomas, manifesting predominantly in middle aged adults, with no gender predominance {2523}, and having an incidence rate of 0.1-0.2 per 100,000 persons per year {1831}. Among primary CBCL, marginal zone B cell lymphoma and FCL are by far the most common subtypes {744,1281, 2576}.

Etiology

The etiology of primary cutaneous FCL is unknown.

Localization

Most patients have local or regional disease. Trunk and head and neck regions are by far the most frequent localizations {429,744,2061,2523}. Presentation with multifocal skin lesions is observed in a small minority of patients.

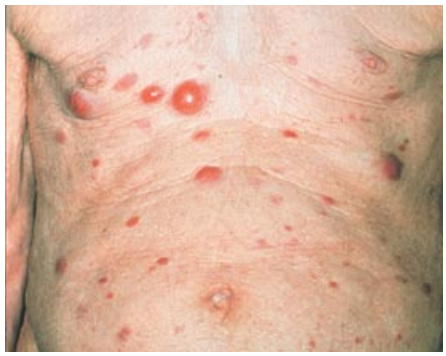

Fig. 4.50 Cutaneous follicle centre lymphoma. Firm nodules on the trunk.

Clinical features

The clinical presentation consists of firm erythematous to violaceous plaques, nodules or tumours of variable size. Larger nodules may be surrounded by small papules and slightly infiltrated, sometimes figurate plaques. The skin surface is smooth. Lesions may be present for months to many years {220, 2061,2523}.

Histopathology

The infiltrates show a spectrum of growth patterns, with a morphologic continuum from follicular to follicular and diffuse to diffuse. The lesions are by definition composed of a mixture of centrocytes (which may be small and/or large) and centroblasts in varying proportion. Small centrocytes and a predominantly follicular growth pattern are more frequently found in small, early lesions. A predominance of large neoplastic cells, particularly large centrocytes or multilobated cells and less frequently centroblasts (not in confluent sheets), are generally found in more advanced lesions (large nodules or tumours) {2523}. When morphologically identifiable, follicles are often ill-defined and show a monotonous population of FCC, lack starry sky histiocytes, and generally have an attenuated or absent mantle zone, different from cutaneous follicular hyperplasias {425, 429,603,864,1397}. The infiltrates are found primarily in the dermis, with extension into subcutaneous tissue seen in larger nodules. The overlying epidermis is generally unaffected.

Immunoprofile

The cells express B-cell markers including CD19, CD20, and CD22, and may show (more often in cryostat sections)

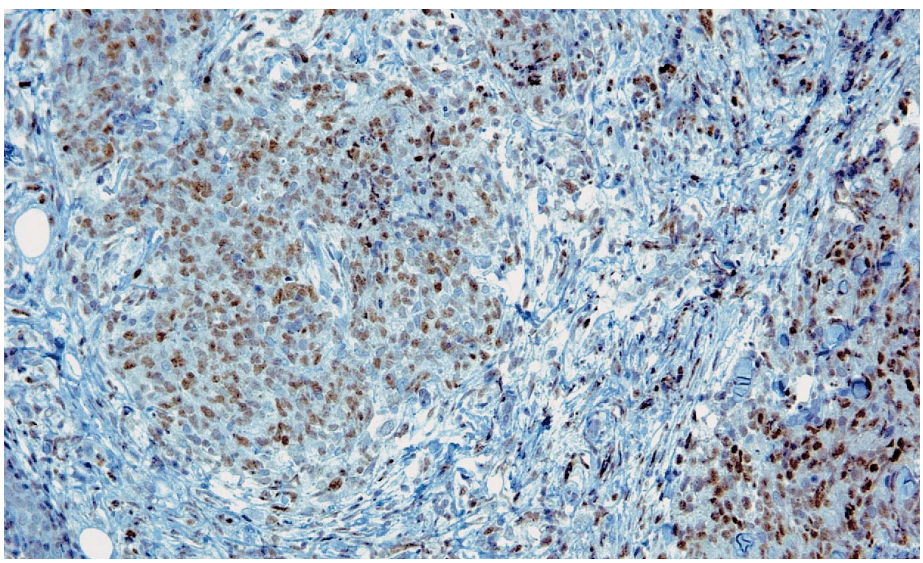

Fig. 4.51 Primary cutaneous follicle centre lymphoma. Neoplastic bcl6+ cells surround and infiltrate a reactive follicle with bcl6+ germinal center.

monotypic staining for surface immunoglobulins (sIg). However, absence of detectable sIg staining is common in tumours showing a diffuse population of large FCC. In PCFCL, neoplastic cells consistently express Bcl-6 protein, while CD10 is variably expressed (often positive in follicular cases and more fequently negative in lesions with diffuse pattern of growth) {425,429,823,1042,1832, 2061}. Bcl-2 protein is usually not expressed but may be faintly positive, less than reactive T-cells {38, 209, 425, 603, 774, 1042,1 622}. The follicles are associated with follicular dendritic cells, positive for CD21, CD23, and CD35. Residual, scattered FDC may be sometimes found in diffuse large cell infiltrates. Neopastic cells are constantly CD5- and CD43-negative. Admixed T-cells may be abundant and sometimes predominant, particularly in small, early lesions.

Histogenesis
Mature germinal centre derived B-lymphocyte {2273,2523}.

Somatic genetics
Clonally rearranged immunoglobulin genes are present. Bcl-2 gene rearrangement and t(14;18) chromosomal translocation are absent in most cases {209,430,467,1622,1820,2523}. Inactivation of p15 and p16 tumour suppressor genes by promotor hypermethylation has been reported in about 10% and 30% of PCFCL, respectively {468}. Chromosomal imbalances have been identified by comparative genomic hybridization (CGH) analysis in a minority of PCFCL, but a consistent pattern has not been emerged {942,1503}.

Prognosis and predictive factors
Primary cutaneous FCL have an excellent prognosis (>95% 5-year survival). Local recurrences, most often near the initial site of cutaneous presentation, may develop but will not influence clinical outcome. Cytologic grade or growth pattern (follicular or diffuse) do not appear to have an impact on prognosis in patients with primary cutaneous disease. Locally directed forms of therapy, most commonly radiation or surgical excision (small, isolated lesions), are generally effective {194, 429, 1283, 1824, 1825, 1938, 2060, 2061, 2202, 2523}.

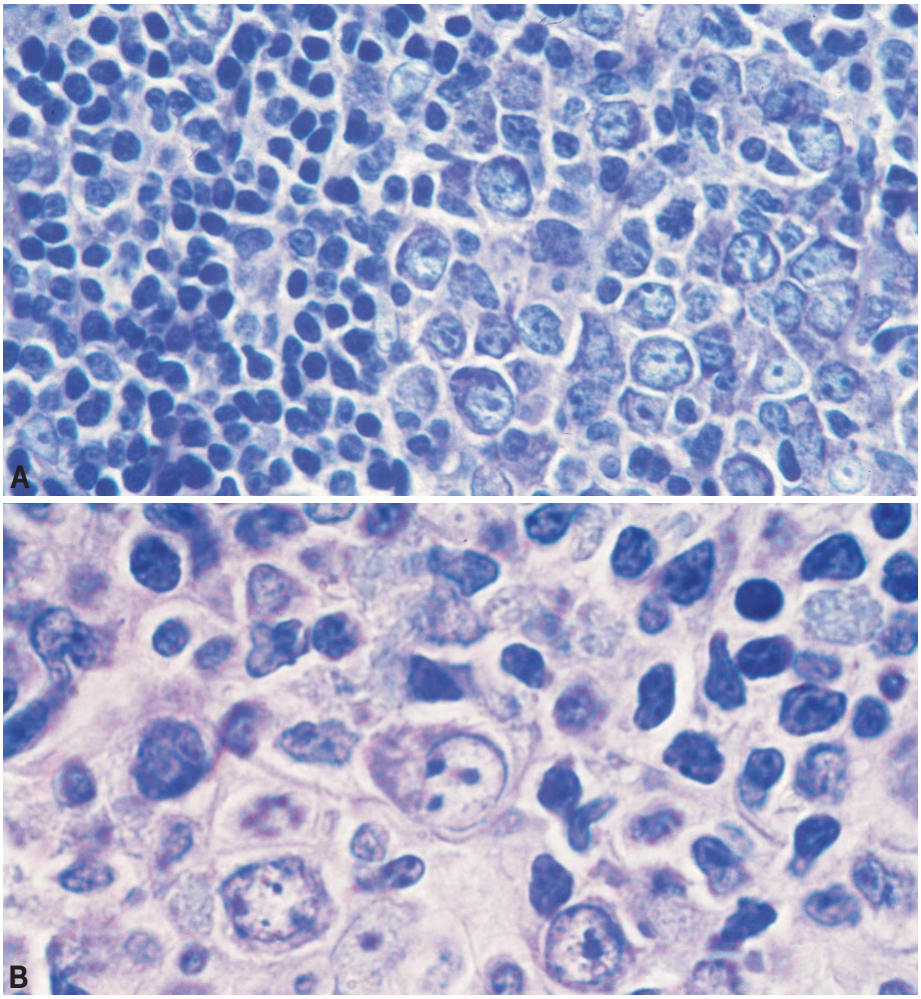

Fig. 4.52 Cutaneous follicle centre lymphoma, follicular growth pattern. **A** Small and large follicle centre cells. **B** Detail of large follicle centre cells

Secondary cutaneous follicular lymphoma (FL)

Patients more often present with multiple lesions in non-contiguous skin sites {429,2060}. Unlike PCFCL, neoplastic cells strongly express CD10 and Bcl2, and show t(14:18) translocation in most cases. These secondary cutaneous forms are managed like a systemic lymphoma. Whether cutaneous involvement by FCL has an impact on prognosis is presently unknown.

Cutaneous diffuse large B-cell lymphoma

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C. Dommann-Scherrer
S.H. Swerdlow
W. Kempf
M Kurrer
H Kutzner
J. Wechsler
N.L. Harris

Definition
Primary cutaneous diffuse large B-cell lymphomas (DLBCLs) are neoplastic proliferations showing a completely diffuse growth pattern consisting of large transformed B-cells without significant admixture of centrocytes.
The most common variant, DLBCL, leg-type, usually occurs on the leg and less frequently at other sites. Other variants are referred to as DLBCL, other and comprise T-cell/histiocyte-rich LBCL, plasmablastic lymphoma and lesions that do not fulfill the criteria for a DLBCL, leg type.

ICD-O code 9680/3

Diffuse large B-cell lymphoma (DLBCL), leg-type

Epidemiology
Approximately 5-10% of cutaneous B-cell lymphomas are classified as DLBCL, leg type. The median age is around 70 years, and the tumours are more common in females than males {2432}. DLBCL of the skin is rare in children {1005}.

Clinical features
DLBCL, leg type occurs primarily in elderly females who present with rapidly developing multiple tumours, most commonly on the leg but sometimes at other localizations. Therefore analogous to the "nasal-type" designation for a distinct extranodal variant of NK/T-cell lymphomas, the term "DLBCL, leg-type" is chosen for all cutaneous diffuse large B-cell lymphomas with the designated cytological and immunophenotypic features. Clinically multiple disseminated or aggregated dome shaped red tumours with a firm consistency and a shiny surface without scaling are seen. Ulceration may occur in advanced stages.

Histopathology
The tumour cells diffusely infiltrate the dermis with a destructive growth pattern, often obliterating adnexal structures. The infiltrate may extend into subcutaneous tissue. The epidermis is often spared, with a Grenz zone. The infiltrate is composed of medium to large sized B cells, which are usually monomorphic in appearance. Cells may resemble immunoblasts, and less commonly centroblasts. There is usually a minimal inflammatory component and little stromal reaction.

Immunohistochemistry
The tumour cells are positive for CD20 and CD79a, negative for CD10 and CD138, have variable BCL-6 expression and are usually strongly positive for BCL-2 protein and MUM-1/IRF-4 {1797}. These features have been shown in nodal DLBCL to correlate with an activated B-cell gene expression profile, which is usually predictive of a more aggressive clinical course {1041, 1977}.

Histogenesis
Transformed peripheral B cell of probable post germinal centre origin {816}.

Somatic genetics
The immunoglobulin genes are clonally rearranged. The BCL-2/JH translocation is absent {814,905,2472}. Recent studies using gene expression profiling have identified increased expression of genes associated with cellular proliferation. The gene expression profile of the leg-type of tumour resembles that of activated B-cell type of nodal or systemic DLBCL {1041} Significant differences have not been identified among tumours of the leg-type arising in different sites {814,1797}.
The primary cutaneous large B-cell lymphoma of the leg-type can be seen in a variety of anatomic locations and is not restricted to the leg {1797}.

Prognosis and Predictive factors
In multivariate analysis, BCL-2 expression, multiple skin lesions, and age remained independent prognostic factors. The 5-year disease-specific survival rates in BCL-2–positive and BCL-2–negative patients were 41% and 89%, respectively (P < .0001). 11,12 13 Thus, these studies support the identification of DLBCL leg type, as a clinically and biologically distinctive group.

Diffuse large B-cell lymphoma, other

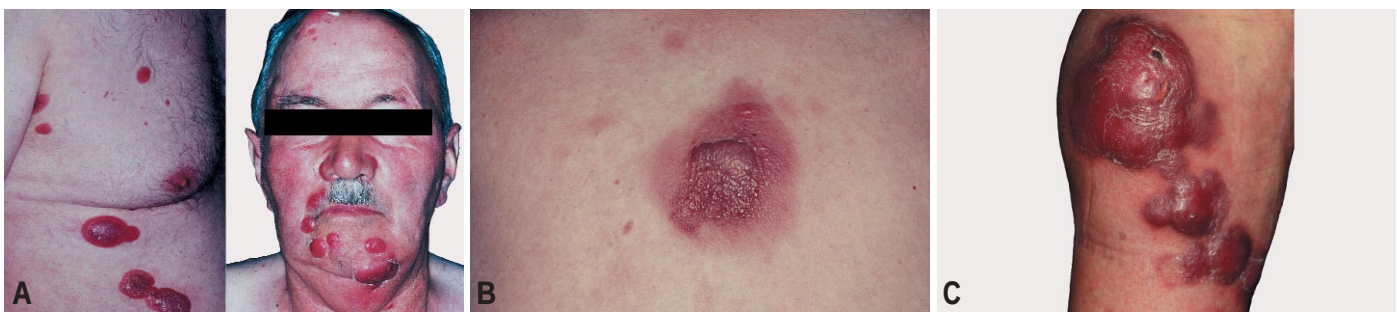

Fig. 4.53 Diffuse large B-cell lymphoma. **A** Dome-shaped nodules and tumours without ulceration on the trunk and in the face. **B** Soft tumour surrounded by an erythematous infiltrate on the back. **C** Aggregation of non-ulcerated nodules and tumours confined to a limited area of the lower leg.

Definition

The term DLBCL, other, refers to diffuse lymphomas composed of large transformed B-cells that lack the typical features of DLBCL, leg-type, and do not conform to the definition of primary cutaneous follicle centre lymphoma. These tumours may be comprised of a monomorphic population of centroblast-like cells, but with a mixed inflammatory background.

BCL-2 protein may be negative, whereas BCL-6 will usually be expressed. The presence of multiple lesions is a poor prognostic indicator; such cases must be distinguished from secondary involvement by DLBCL.

There are some primary cutaneous follicle centre lymphomas in which the majority of tumour cells are centroblasts. Previously these lesions have been categorized as DLBCL by most observers {864,877,879,1263}. These lymphomas invariably contain a population of centrocytes as well as some reactive cells. A focal follicular growth pattern may be seen. Despite the predominance of centroblasts, clinical studies have suggested that these lymphomas have an benign clinical course, and may usually be treated in a conservative manner. Based on the clinical behaviour and the spectrum of cytological composition, these tumours are classified under the single heading of cutaneous follicle centre lymphoma.

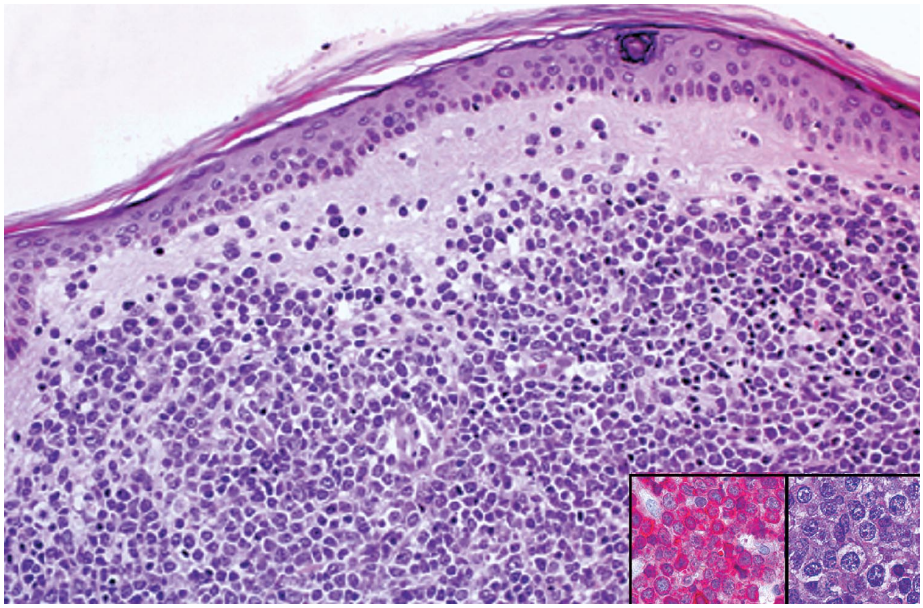

Fig. 4.54 Diffuse large B-cell lymphoma (DLBCL) leg type. Lymphoid cells in the dermis; no infiltration of the epidermis. Left insert: lymphoid cells with strong immunoreactivity for BCL-2. Right insert: large, densely packed lymphoid cells.

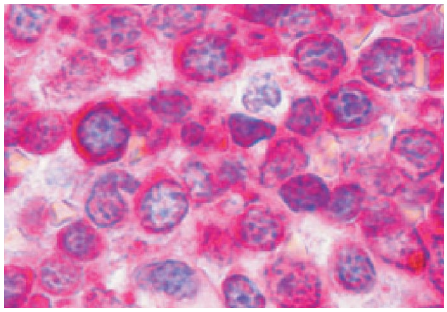

Fig. 4.55 Diffuse large B-cell lymphoma (DLBCL), leg type. BCL-2 staining of atypical lymphoid cells.

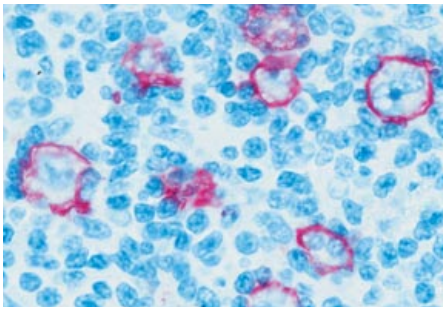

Fig. 4.56 T-cell/histiocyte-rich large B-cell lymphoma. CD20 staining highlights the few neoplastic B-cells intermingled in a dense infiltrate of reactive T-cells.

T-cell / histiocyte-rich large B-cell lymphoma

T-cell / histiocyte-rich large B-cell lymphoma is an unusual morphological variant of “diffuse” LBCL {1886} that rarely occurs primarily in the skin {645,1423}. It is characterized by a small number of large neoplastic B-cells (<10%), scattered within an abundant background of small reactive T-lymphocytes with or without histiocytes. Some T-cell/histiocyte-rich large B-cell lymphomas may represent progression from a more indolent B-cell lymphoma {645,2042}.

Plasmablastic lymphoma

Plasmablastic lymphomas rarely may present as a primary cutaneous lymphoma. The tumour cells can be positive for Epstein Barr virus (EBV), and have a phenotype that reflects terminal stages of B-cell differentiation (CD20-, MUM-1+, CD138+, EMA+). Plasmablastic lymphomas are usually a heterogenous group of disease entities {524} and can be encountered in settings of immunodeficiency, HIV-associated, or iatrogenic {617,985}.

Secondary skin involvement by diffuse large B-cell lymphoma

Secondary skin involvement most commonly shows localisation of the disease on the trunk and the extremities {1263}. The prognosis is worse than in primary DLBCL, which can be controlled by local treatment modalities, particularly if one is dealing with a single lesion.

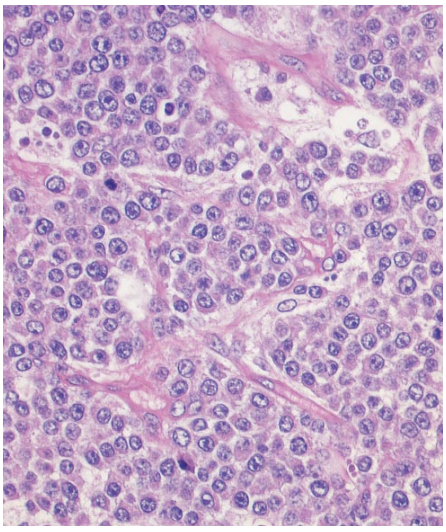

Fig. 4.57 Plasmablastic lymphoma. Tumour displays a spectrum of immunoblasts, plasmablasts, and plasma cells between collagen bundles.

Intravascular large B-cell lymphoma

H. Kutzner
E.S. Jaffe

Definition
Intravascular large B-cell lymphoma (IL) is a rare disease with multiorgan involvement, which also affects the skin. This extranodal subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by the presence of large lymphoid cells within the lumina of small to medium-sized blood vessels, particularly capillaries and postcapillary venules. Skin is a common site of presentation, but most patients have systemic disease at time of diagnosis {696,2523}.

ICD-O code 9680/3

Synonyms
Intravascular lymphomatosis; intravascular lymphoma; angioendotheliomatosis proliferans systematisata; malignant angioendotheliomatosis; angiotropic large cell lymphoma (Lukes-Collins), diffuse large B-cell lymphoma (REAL) intravascular large B-cell lymphoma (WHO).

Epidemiology
IL is rare and can occur at any age, but most patients are in their 6th – 9th decade of life. Male to female ratio is 0.8 (range 0.7 – 5.0) {2566}.

Localization
Dermatological manifestations are present in up to one third of patients. Sites of predilection are the lower extremities, but lesions may involve all parts of the integument. A wide range of organ involvement has been described: central nervous system, skin, adrenal glands, thyroid, gastrointestinal system, kidneys, lungs, genitourinary tract, and eye {275}. At autopsy, involvement of the majority of organs is seen despite the absence of prior clinical manifestations or mass lesions {1257}.

Clinical features
The clinical manifestations are predominantly neurologic (85%) {214} and dermatologic {633} and are attributed to vascular occlusion. There is a notable absence of lymphadenopathy, splenomegaly or circulating lymphoma cells in the majority of cases {631,684, 837, 1257,2387}.
There is a plethora of different skin lesions including tender, indurated nodules, livedo-like reticulate erythema, linear erythematous streaks, and painful indurated telangiectasias. Lesions may imitate phlebitis, panniculitis, or vasculitis {1809}.

Histopathology
The angiotropic lymphoid infiltrate often spares the dermis, requiring deep biopsies including parts of the subcutaneous fat. The large neoplastic lymphoid cells are usually confined to the lumina of capillaries and postcapillary venules {1809, 2513}, albeit extravascular involvement may occur {1257}. Tumour cells are large with vesicular nuclei, prominent nucleoli, and frequent mitoses. Fibrin thrombi in the upper and deep dermal plexus, with partial occlusion of the vascular lumina, and few entrapped hyperchromatic lymphocytes are typical of IL presenting with reticulate and livedoid erythema.

Immunoprofile
Tumour cells usually express B-cell associated antigens and may coexpress CD10 or CD5. {406,697,953,1193,1253, 2566}. Although most IL present with overexpression of theBCL-2 protein {1257} they lack BCL-2 gene rearrangement {1193,2566}. These cases have to be distinguished from other intravascular lymphomas of different lineages {112, 113,633,697,736,1355,2138,2143}.
The precise mechanisms of lymphoid-endothelial interaction leading to vascular occlusion and thrombotic events are

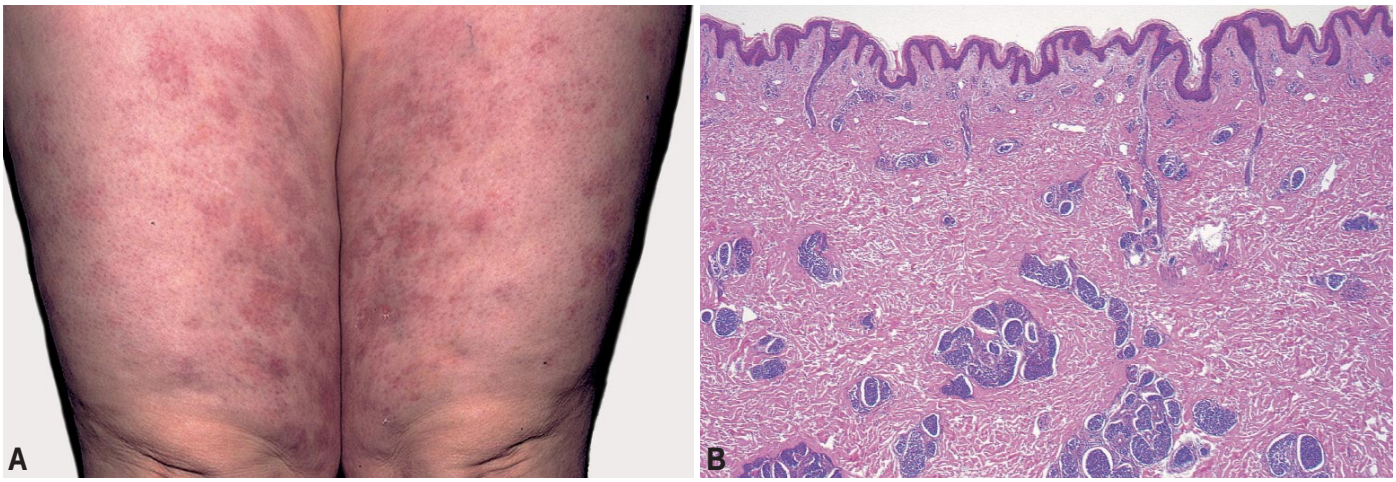

Fig. 4.58 Intravascular large B-cell lymphoma. **A** Involvement of the cutis with livedoid palpable erythema. **B** Dilated dermal vessels filled with densely packed neoplastic lymphoid cells.

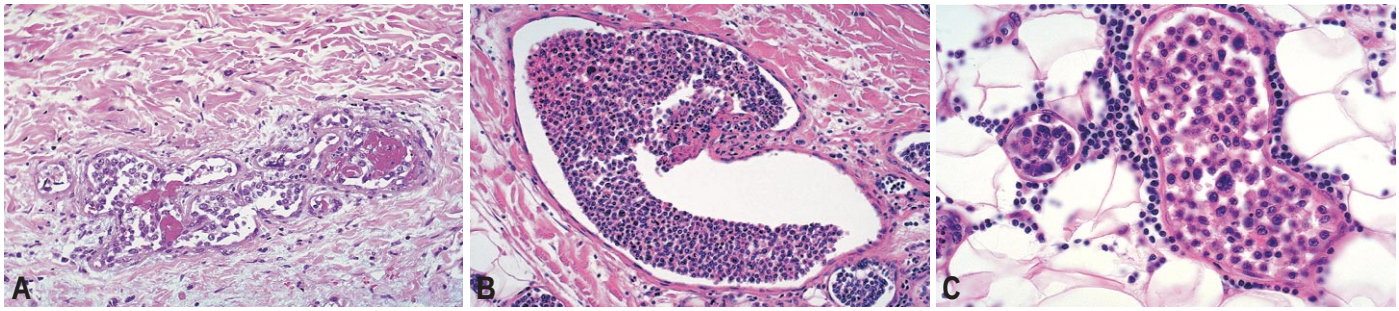

Fig. 4.59 Intravascular large B-cell lymphoma. **A** Tortuous dermal venules with fibrin thrombi and entrapped neoplastic lymphoid cells. **B** Dilated postcapillary venules with intraluminal pleomorphic lymphoid cells. **C** Neoplastic lymphoid cells within lumina of subcutaneous postcapillary venules. Extravascular lymphocytes are distinctly smaller, lacking pleomorphism and mitoses.

not clear. The intravascular trapping of lymphoid tumour cells might be the result of a defect in homing receptors and adhesion molecules on the neoplastic cells and the endothelial cells {737, 1852}.

Histogenesis

The postulated cell of origin is a post follicle centre transformed peripheral B-cell.

Lymphomatoid granulomatosis

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J. Toro
W.H. Wilson

Definition
Lymphomatoid granulomatosis (LYG) is an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of Epstein Barr virus (EBV)-positive B-cells, admixed with numerically predominant T-cells. The skin is the most common extrapulmonary site of involvement.

ICD-0 code 9766/1

Synonyms
Angiocentric immunoproliferative lesion {1432}, angiocentric lymphoma.

Epidemiology
LYG is rare, usually presenting in adult life. It affects males more often than females (at least 2:1) {1223}.

Etiology
Patients with underlying congenital or acquired immunodeficiency are at increased risk for LYG {921,949}. Predisposing conditions include allogeneic organ transplantation, Wiskott-Aldrich syndrome, human immunodeficiency virus infection, and X-linked lymphoproliferative syndrome.
In patients without evidence of underlying immunodeficiency, reduced immune function can usually be demonstrated upon careful clinical or laboratory analysis {2534}.

Localization
Skin is the most common site of involvement outside the lung (25-50%), but cutaneous involvement is rarely seen without pulmonary disease. Extremities and trunk are the most frequent localizations {185,393,1047,1124,1223,1560}.

Clinical features
Patients usually present with signs and symptoms related to the respiratory tract {1124,1223,1426}. Skin lesions consist of multiple erythematous dermal papules and/or subcutaneous nodules {185}. Necrosis and ulceration are generally associated with larger nodules. Indurated plaques, lichen sclerosus et atrophicus-like lesions, and alopecia are less commonly seen {185,1129}. Cutaneous lesions rarely precede pulmonary disease, and are seen either at diagnosis (30%) or later in the course {185}. Other sites of involvement include brain (26%), kidney (32%), liver (29%) {1124}. Lymph nodes and spleen are spared.

Histopathology
LYG is characterized by an angiocentric and angiodestructive lymphohistiocytic infiltrate. Most cutaneous lesions show infiltration of subcutaneous fat, with or without dermal involvement. Lymphocytic vasculitis is frequent, and fibrinoid necrosis may be present {2339}. Well-formed granulomas are usually absent, but a granulomatous reaction may be seen secondary to fat necrosis.

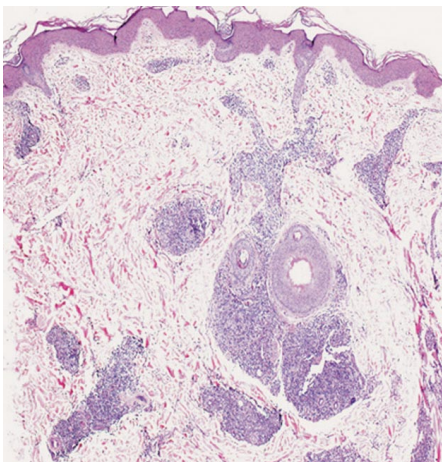

Fig. 4.62 Lymphomatoid granulomatosis. Histological features include perivascular dermal infiltrate.

Immunohistochemistry
While EBV-positive B-cells are readily found in the lung, they are generally rare in skin, with the predominant cell being a CD3+, CD4+ lymphocyte {185}.

Histogenesis
Mature B lymphocyte, transformed by EBV.

Somatic genetics
The ability to detect clonal immunoglob-

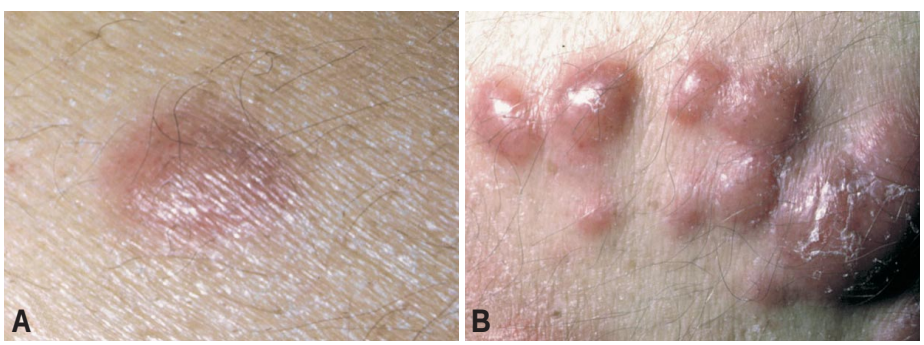

Fig. 4.60 Lymphomatoid granulomatosis. **A** The most common manifestations of LYG in the skin are papules which may grow into nodules. **B** Larger nodules may ulcerate superficially. From M.W. Beaty et al. {185}.

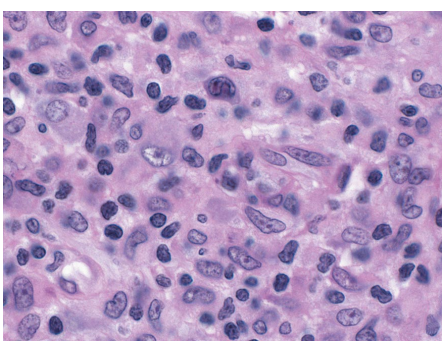

Fig. 4.61 Cutaneous lymphomatoid granulomatosis. Atypical EBV-positive large B-cells represent a minority of infiltrating cells.

ulin heavy chain gene rearrangement is related to grade, with clonal B-cell populations usually found only in grade 2-3 lesions. Southern blot , polymerase chain reaction (PCR), and in situ hybridization techniques can be used to detect EBV sequences {921,1224,1560}.

Prognosis and predictive factors

The natural history of LYG is variable {714,1223}. In some patients it may follow a waxing and waning clinical course, with spontaneous remissions without therapy. However, in most patients the disease is more aggressive, with a median survival of less than two years. Histological grade and clinical aggressiveness relate to the proportion of EBV+ B-cells, but even grade 3 lesions may show spontaneous regression {2534}. The most common cause of death is progressive pulmonary involvement. Skin lesions may appear, without evidence of relapse at other sites {185,2534}.

Cutaneous involvement in primary extracutaneous B-cell lymphoma

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M. Kurrer
M. Bernengo
S. Büchner

Mantle cell lymphoma

Definition
Mantle cell lymphoma is a B-cell lymphoma that almost always overexpresses cyclin D1 and is composed either of small lymphocytes bearing some resemblance to centrocytes or, in the blastoid variant, by cells resembling lymphoblasts or large B-cells. Neither classic centroblasts nor paraimmunoblasts are present.

ICD-O code 9673/3

Epidemiology
MCL occurs in middle aged to older individuals with a male predominance and accounts for up to 10% of all non-Hodgkin lymphomas {2301}.

Clinical features
Most patients present with adenopathy and stage III/IV disease. Hepatosplenomegaly and bone marrow involvement are common and peripheral blood involvement is seen in about 25% of patients. Gastrointestinal disease is also common but often subtle {2254}.

Cutaneous MCL
Skin involvement is rare (2-6% of cases) {2030} but when it occurs, is usually, but not always, seen at initial presentation and associated with extracutaneous disease {654,2132}. Rare cases that appear to be primary are described. Lesions are most common on the thorax and extremities and usually occur as multiple erythematous macules, papules, plaques or nodules {654,2132}.

Histopathology
MCL are usually composed of relatively small lymphocytes with slightly irregular to very clefted nuclei and somewhat dispersed chromatin. In the blastoid variant, which may be relatively more common in cutaneous lesions, the cells either have very dispersed chromatin with inconspicuous nucleoli resembling lymphoblasts, or are larger and more pleomorphic, sometimes with very prominent nucleoli, resembling cells of a diffuse large B-cell lymphoma.
MCL infiltrates in the skin occur in the dermis sometimes with extension to the subcutaneous tissue. A grenz-zone should be present. The infiltrate may be relatively scanty and perivascular/periappendageal, form nodules or be very dense and diffuse. A mantle zone growth pattern with MCL growing around reactive germinal centres may occur {219,654}. Admixed inflammatory cells may be present {654}.

Immunohistochemistry
MCL are distinguished in most cases from other non-Hodgkin lymphomas by their frequent but not invariable CD5+, CD10-, CD23-, cyclin D1+,BCL-6-, CD20+ light chain class restricted phenotype {376,2301,2303}. Cyclin D1 staining can be problematic and CD5 not always positive. With one interesting exception, the cases are negative for the cutaneous lymphocyte-associated antigen {2132}.

Histogenesis
Mature B-cell, probably of the inner mantle zone, usually but not always with unmutated immunoglobulin heavy chain genes.

Somatic genetics
Immunoglobulin genes show clonal rearrangement in all cases and in many, but not all, cases they lack somatic hypermutation {1756,2451}. The vast majority of MCL have a t(11;14)(q13;q32) translocation involving the CCND1 (cyclin D1) and immunoglobulin heavy chain genes with subsequent CCND1/cyclin D1 overexpression {376, 2303}. The most sensitive technique to document the translocation in diagnostic specimens is cytogenetic fluorescence in situ hybridization (FISH) analysis

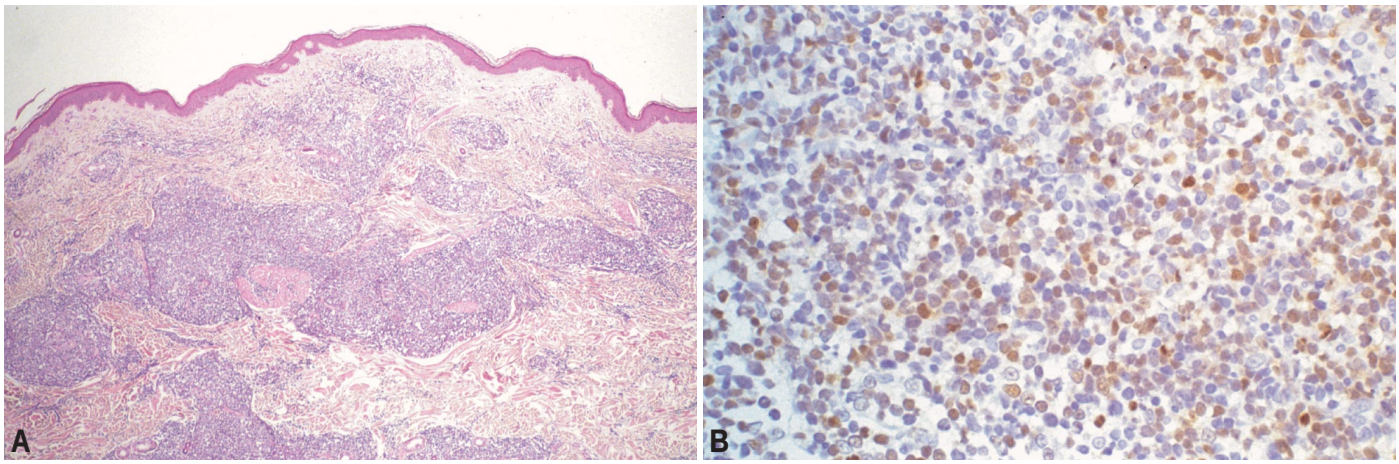

Fig. 4.63 Mantle cell lymphoma. **A** Nodular perivascular and periappendageal infiltrates in all layers of the dermis. A subepidermal grenz-zone is present. **B** Tumour cells show nuclear immunoreactivity for cyclin D1.

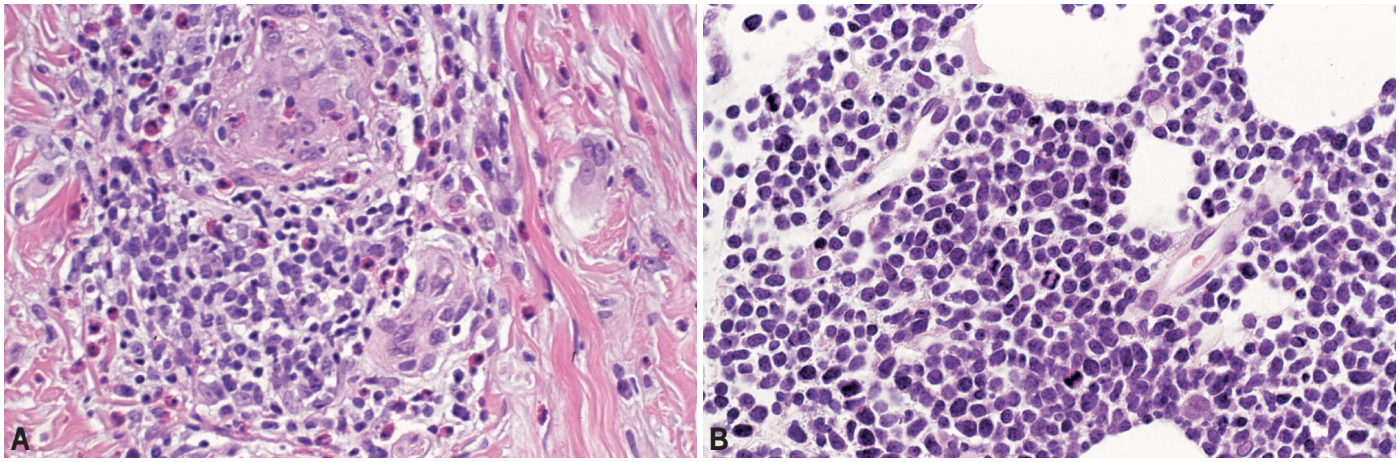

Fig. 4.64 Mantle cell lymphoma. **A** Perivascular infiltrate of small atypical lymphoid cells. **B** Densly packed small atypical lymphoid cells showing polygonal or indented nuclei and homogeneous chromatin staining.

{654,1422}. Gene profiling has suggested the presence of a small subset of cases that lack cyclin D1 abnormalities {1978}. Other primary and mostly secondary abnormalities are also described {376,1045,2303}.

Prognosis and predictive factors
MCL has a median survival of 3-5 years with those having "non-nodal" disease doing better {376,1756,2301,2303}. Adverse prognostic indicators include a high proliferative fraction, probably blastoid morphology, secondary genotypic abnormalities and blood involvement (at least in patients with nodal disease). Whether skin involvement in particular is an independent prognostic indicator is uncertain.

Burkitt lymphoma

Definition
Burkitt lymphoma is a mature B-cell neoplasm composed of relatively uniform medium sized transformed B-cells with a C-MYC translocation {630}.

ICD-O code 9687/3

Epidemiology
BL occurs in children in equatorial Africa (endemic), primarily in children and young adults elsewhere (sporadic) and in immunodeficient patients. There is a male predominance.

Etiology
Endemic BL and a minority of sporadic BL are Epstein-Barr virus positive.

Clinical features
BL usually presents as an extranodal mass often in the abdomen or, in endemic cases, in jaw or other facial bones. Other patients have a leukaemic presentation. Cutaneous involvement in BL appears to be extremely rare and at least usually is associated with disease at other sites {123,141,349,700}. It has rarely been described as occurring with ulceration from direct invasion from underlying bony lesions {349}, as distinct cutaneous lesions at relapse {123} and in 12% of autopsied cases of American BL (2 cases) {141}.

Histopathology
Histologic sections show a diffuse proliferation of medium sized transformed lymphocytes with relatively round nuclei with several nucleoli and a narrow rim of very amphophilic/basophilic cytoplasm. There are many apoptotic bodies and tingible body macrophages creating a starry sky appearance. Skin involvement demonstrates a diffuse but sometimes patchy dermal and subcutaneous infiltrate with a Grenz zone {123,700}.

Immunohistochemistry
Immunophenotypic studies demonstrate CD5-, CD10+,BCL-2-, CD20+ mature B-cells with surface immunoglobulin expression.

Histogenesis
Germinal centre/post germinal centre B-cell

Somatic genetics
All cases have clonal immunoglobulin gene rearrangements and a C-MYC translocation, most often with a t(8;14)(q24;q32) {1483}. Many, if not all, cases also have C-MYC mutations {230, 1483}.

Prognosis and predictive factors
BL is an aggressive but curable neoplasm with a 5 year overall survival of 44% {3}.

Chronic lymphocytic leukaemia / small lymphocytic lymphoma

Definition
Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell neoplasm composed of small, usually CD5+, CD23+, cyclin D1- B-cells with relatively round nuclei having clumped chromatin {1662}. Especially in lymph nodes, there is often an associated minor population of prolymphocytes and paraimmunoblasts that form proliferation centres.

ICD-O code
Chronic lymphocytic leukaemia 9823/3
Small lymphocytic lymphoma 9670/3

Epidemiology
CLL is the most common type of leukaemia in the West and SLL are reported to account for 6.7% of non-Hodgkin lymphomas {3,1064}.

Clinical features
CLL/SLL is seen most commonly in middle aged and older adults with a male predominance. It usually presents with blood and marrow involvement, frequent adenopathy and sometimes hepatosplenomegaly. Skin involvement is reported in 2% of patients without a marked predilection for any region of the body and occurs in patients who also have blood involvement {273,1167}. The face and scalp are frequent sites of involvement. It may be present either at the time of diagnosis or, much more frequently, develops subsequently {431}. Lesions may be single or multiple erythematous macules, papules, violaceous plaques, nodules or tumours either occurring in a limited or less frequently more generalized area {431,1167}. Atypical presentations include chronic paronychia, papulovesicular eruption and finger clubbing. Skin involvement may occur at sites of previous viral (eg, herpes zoster, herpes simplex) or Borrelia burgdorferi infection {427} and at sites of epithelial neoplasms {2215}. Spontaneous regression of CLL infiltrates at least at sites of prior herpetic infection may occur {2449}. In contrast to the absence of virus in at least most of the lesions in viral scars, B. burgdorferi DNA is found in at least some cutaneous CLL lesions {427}.

Histopathology
Histologic sections demonstrate a diffuse proliferation of small relatively round lymphocytes with condensed chromatin with lymph node biopsies typically demonstrating paler (pseudofollicular) proliferation centres where the cells have more abundant pale cytoplasm, more dispersed chromatin and sometimes prominent central nucleoli. The latter cells represent paraimmunoblasts and some of the former cells prolymphocytes.

Cutaneous lesions show a patchy perivascular, nodular, more diffuse or rarely band-like dermal infiltrate of small, usually but not always round, lymphocytes with occasional single lymphocytes in the epidermis and frequent extension into the subcutaneous tissue {431}. Patients with more than one biopsy can demonstrate more than one growth pattern. There may be overlying epidermal changes infrequently including ulceration. Proliferation centres are seen only in a minority of cases although there may be scattered larger cells in other cases {427}. A minority of cases have admixed eosinophils, neutrophils, and/or histiocytes. A granulomatous reaction may be present especially in some of the lesions arising in scars following prior viral infection {432}. Cutaneous CLL associated with granuloma annulare-like changes has also been reported {797}.

Immunoprofile
Immunophenotypic studies demonstrate a characteristic CD5+, CD43+, CD10-, CD23+, FMC7-, cyclin D1-, weakly CD20+ monoclonal B-cell population with weak surface immunoglobulin expression {1662}. In the cutaneous lesions, the admixed T-cells present are mostly of CD4+ type {431}.

Histogenesis
Mature B-cell most likely of memory type (including cases with either mutated or unmutated immunoglobulin heavy chain genes) {586,1288,1976}.

Somatic genetics
All cases have clonal immunoglobulin gene rearrangement although oligoclonal bands suggesting admixed reactive B-cells may also be present in the cutaneous lesions {431}. In some cases the immunoglobulin genes show somatic hypermutation and in others they do not {586,943,1288,1976}. There are no chromosomal abnormalities specific for CLL/SLL; however, the most commonly described abnormalities include 13q and 11q deletions, trisomy 12 and 17q deletion {643}.

Genetic susceptibility
There is an inherited susceptibility to CLL; however, the critical genes remain to be determined {1064}.

Prognosis and predictive factors
CLL/SLL is one of the indolent lymphoid neoplasms. Clinically advanced stage, 17q deletions, unmutated immunoglobulin genes, CD38 and ZAP-70 expression include some of the more important adverse prognostic indicators {553,643, 943,1662,1760,2518}. Most do not believe that skin involvement portends an adverse outcome; however, it has been reported that cases with >5% medium and large-sized B-cells, admixed reactive cells and epidermal changes did worse than those without these features and there are reports in the literature suggesting a poor outcome following any cutaneous involvement {427,432,1167}. Transformation to a large cell lymphoma (Richter syndrome), Hodgkin lymphoma or prolymphocytic leukaemia is also associated with an aggressive course {826}. Richter syndrome can present as cutaneous lesions {427,2578}.

Hodgkin lymphoma

E. S. Jaffe
M. Kadin
H. Kerl

Definition

Hodgkin lymphoma (HL) is a neoplasm characterized by large tumour cells of B-cell lineage in a characteristic inflammatory background. It encompasses two entities distinguishable by their morphology and phenotype, namely nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). Cutaneous involvement by NLPHL has not been reported, and is rare in cHL. For details see the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues {1121}.

ICD-O code

Nodular lymphocyte predominant Hodgkin lymphoma 9659/3
Classical Hodgkin lymphoma 9650/3

Synonym

Hodgkin disease

Epidemiology

Cutaneous involvement by cHL is rare and is seen in <5 % of cases, and <1% of cases at presentation {1076,1457, 2326,2505}. The incidence appears slightly increased in patients infected with the human immunodeficiency virus (HIV) {2094,2157}. cHL has also been reported to occur with increased frequency in patients with mycosis fungoides and cutaneous CD30+ T-cell lymphoproliferative disease (CD30+ LPD), but is usually nodal in localization without cutaneous spread {1123,1176,1324, 2190}.

Etiology

The etiology of cHL is not established. However, an association with the Epstein Barr virus has been suggested, especially in cutaneous cases {1340}.

Localization and Clinical features

Three mechanisms of cutaneous involvement have been implicated: 1) retrograde lymphatic spread from regional lymph nodes; 2) direct extension, usually from a mass lesion; and 3) haematogenous dissemination {2326,2505}. The distribution of cHL lesions relates to the manner of spread. Direct extension is most common in patients with massive mediastinal disease, with involvement of the skin of the chest wall. The lesions are manifested as erythematous papules or nodules. Rare cases of HL presenting as primary disease in the skin have been reported 12 {2195}.

Histopathology, immunoprofile and genotype

The histological features resemble those of cHL in other sites. Classical Reed-Sternberg (RS) cells and variants are seen in an inflammatory background. The immunophenotype also is characteristic of cHL, with the neoplastic cells expressing CD30 and CD15 {426,1340}. However, while most cases of cHL are of B-cell lineage {1340}, cases of cHL with cutaneous involvement may express a T-cell phenotype {595,1176,2527}. Such cases are usually associated with concomitant CD30+ LPD. Common clonal T-cell gene rearrangement has been identified in the atypical cells of CD30+ LPD and cHL involving lymph nodes. Because RS-like cells may be seen in CD30+ LPD, the differential diagnosis between these disorders is often difficult.

Prognostic factors

In patients with cutaneous involvement secondary to haematogenous spread, the prognosis is poor. However, other patterns of cutaneous involvement are not necessarely associated with a poor prognosis {415,1023,1457,1651,1987, 2326,2505}.

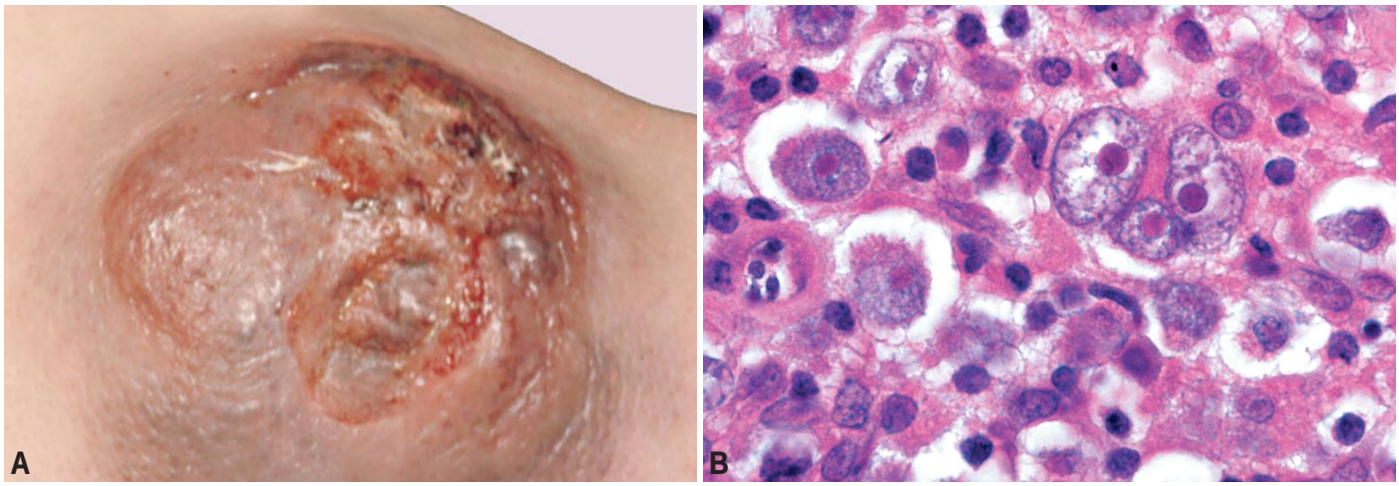

Fig. 4.65 Hodgkin lymphoma. **A** Secondary involvement of the skin often occurs by direct extension, as in this large cutaneous nodule with ulceration. **B** cHL, skin. Classical Reed Sternberg cells are present in a background of reactive lymphocytes.

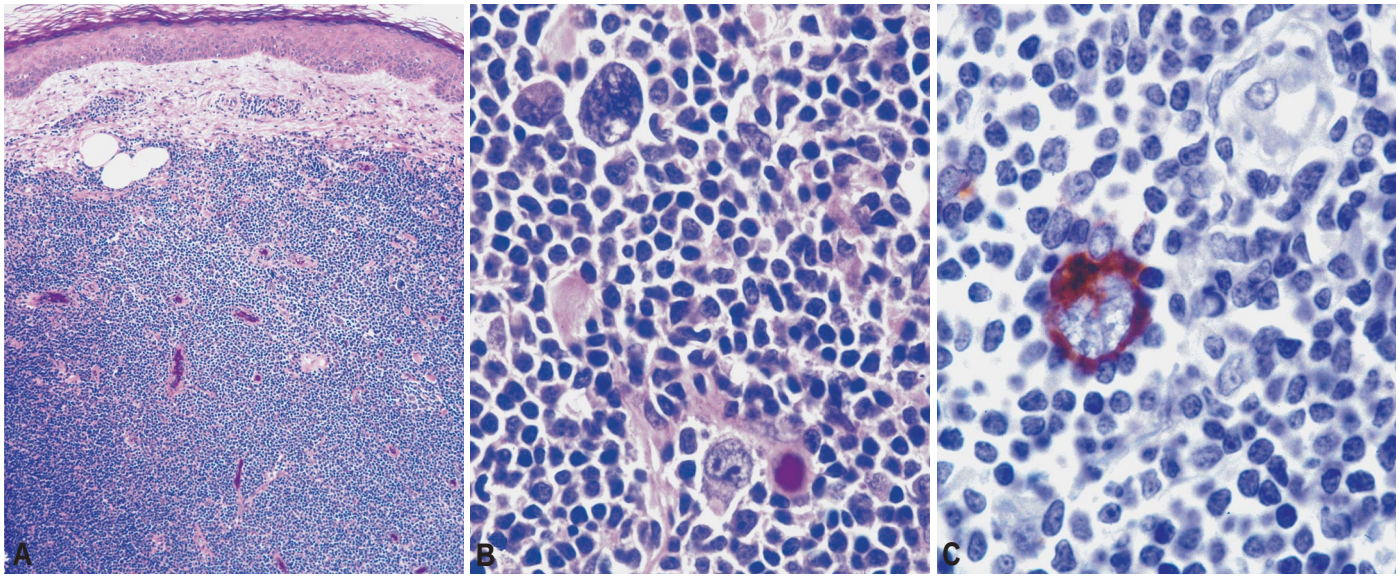

Fig. 4.66 Hodgkin lymphoma. **A** Subcutaneous nodule from primary cutaneous cHL. This patient presented with multiple nodules on the right and left arms. Two years later, she developed a mixed cellularity cHL subtype involving lymph nodes and bone marrow. **B** Reed-Sternberg cells in a background of reactive lymphocytes. **C** Reed-Sternberg cells were strongly CD30-positive, and were positive for CD15 and EBV by in situ hybridization (not shown).

Blastic NK-cell lymphoma

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M.J. Flaig
R. Dummer
D.V. Kazakov
W. Kempf
G. Burg

Definition

Blastic NK-cell lymphoma is a clinically aggressive lymphoma, with a high incidence of cutaneous involvement and risk of leukaemic dissemination. The blastic appearance and CD56 expression initially suggested an NK-precursor origin {632}. More recent studies suggest derivation from a dendritic cell precursor, as reflected in the designation CD4+, CD56+ haematodermic neoplasm.

ICD-O code 9727/3

Synonyms

CD4+, CD56+ agranular haematodermic neoplasm, blastoid NK-cell lymphoma, monomorphic NK-cell lymphoma

Epidemiology

Blastic NK-cell lymphoma is a rare lymphoma. Currently, there are no reports showing any racial or ethnic predilection. Most patients are middle-aged or elderly {632,739,1817}. However, every age can be affected.

Localization

Blastic NK-cell lymphoma has a predilection for skin. At presentation there may be a single tumour, nodule or plaque {632,1817}. Lymph node, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Central nervous system involvement can develop during the course of the disease.

Clinical features

Blastic NK-cell lymphoma frequently involves the skin at presentation with a single tumour, or tumours and plaques. Additionally, lymph nodes, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Most cases of blastic NK-cell lymphoma presenting in the skin progress quickly to develop lymph node, bone marrow, and central nervous system involvement {450,739}. The clinical course is aggressive. There may be initial responses to multiagent chemotherapy, but a high risk of relapse. Regimens for both aggressive lymphomas and acute myeloid or lymphoid leukaemias have been utilized.

Histopathology

The dermis contains a dense, monotonous infiltrate of medium-sized cells with finely clumped chromatin, and absent or indistinct nucleoli resembling lymphoblasts or myeloblasts {632,1121, 1817}. The cells have sparse cytoplasm. Mitotic figures are frequent. The overlying epidermis is spared, with a distinct grenz zone. Inflammatory cells are absent. There is generally no necrosis or angioinvasion.

Immunoprofile

The tumour cells usually express CD4, CD56, and CD43. Expression of CD7, CD2 is variable, whereas surface and cytoplasmic CD3 are negative {632, 1817,2391}. Cytotoxic molecules are generally absent. In some cases TdT and/or CD34 can be positive {313,1681, 2159}. CD68 can be weakly positive, showing focal staining in the Golgi region. Since lymphoblastic and myeloblastic neoplasms can also be positive for CD56, stains for myeloperoxidase, and CD3 should always be performed in order to exclude these entities {2118,2299}. The cells express CD123 and TCL1, both of which support a relationship to dendritic cells {450,1012}. Blastic malignancies of precursor NK-

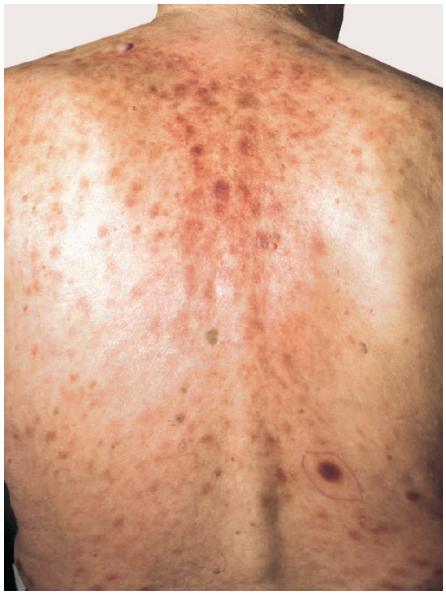

Fig. 4.67 Blastic CD4+ CD56+. NK-cell lymphoma. Brownish haemorrhagic plaques and infiltrates. From D.V. Kazakov et al {1236}.

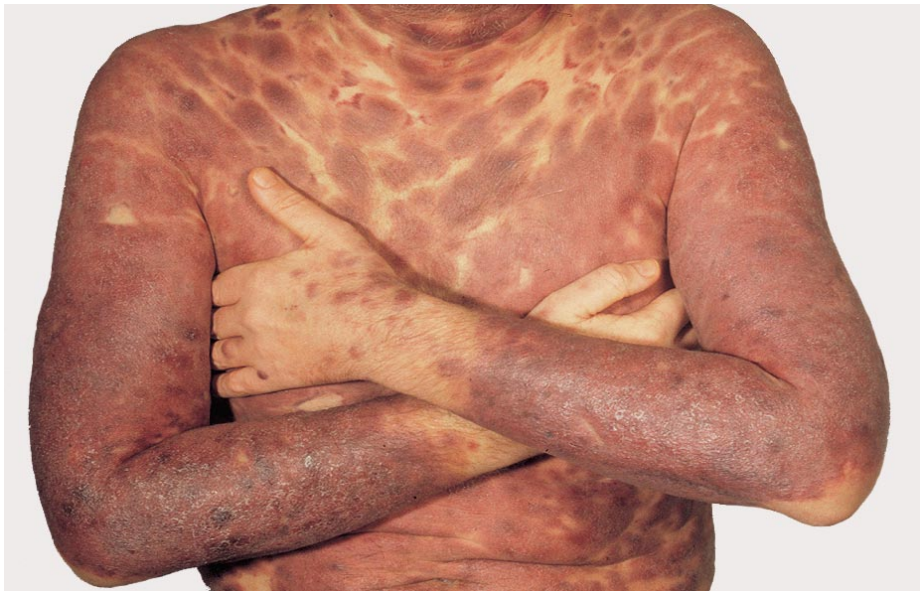

Fig. 4.68 Blastic CD4+ CD56+. NK-cell lymphoma. Diffuse infiltration of the trunk and upper extremities.

cell origin also exist, and may be difficult to distinguish in the absence of specialized techniques {1012,1681,2302}. There has been one report showing expression of KIR receptors {1293}.

Histogenesis

Based on the expression of CD56, an NK-cell derivation was initially proposed. However, the tumour was considered to be of uncertain lineage in the WHO classification. Recently studies have suggested a derivation from plasmacytoid dendritic cells based on gene expression studies and cytokine production. The cells express high levels of interleukin-3 receptor alpha chain (IL-3R-alpha).

Genetics

T-cell receptor genes are in germline configuration. Tumour cells are negative for EBV.

Prognosis and predictive factors

Blastic NK-cell lymphoma is an aggressive disease with a poor prognosis {311,739}. While close to 80% of patients obtained an initial complete remission, the majority of patients relapsed within two years. Patients with single isolated skin lesions appear to have a better prognosis {525}.

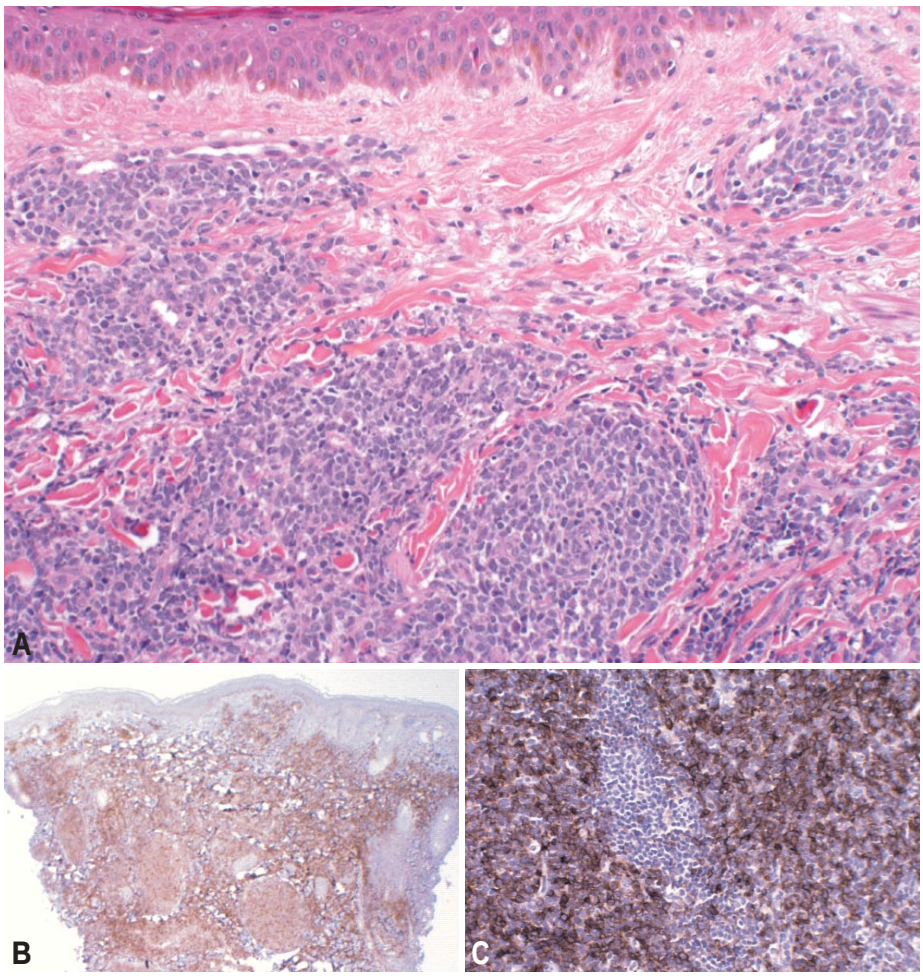

Fig. 4.69 Blastic CD4+ CD56+ NK-cell lymphoma. **A** Tumour cells diffusely infiltrate the dermis, but not epidermis. Note the finely distibuted chromatin and inconspicuous nucleoli. **B** Tumour cells are positive for CD4 and **C** CD56.

Precursor T-lymphoblastic leukaemia/ lymphoma and precursor B-lymphoblastic leukaemia / lymphoma

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Definition

Precursor lymphoblastic leukaemia/ lymphoma is a malignancy derived from precursor cells of either T-cell or B-cell lineage. There is overlap in the clinical presentation, and patients may present with disease primarily in the bone marrow and peripheral blood (leukaemia) or in solid tissues (lymphoma). Because of similarities in stage of differentiation, and manner of presentation, precursor T-cell and B-cell malignancies will be discussed together.

ICD-O code

Precursor T-lymphoblastic leukaemia 9837/3
Precursor T-lymphoblastic lymphoma 9729/3
Precursor B-lymphoblastic leukaemia 9836/3
Precursor B-lymphoblastic lymphoma 9728/3

Synonyms

Acute lymphoblastic leukaemia
Lymphoblastic lymphoma

Epidemiology

Lymphoblastic leukaemia/lymphoma is rare. Approximately 3.5% to 7% of all malignant lymphomas of the skin are of the lymphoblastic type {339,2041}. Most cases are diagnosed in children and young adults. However, every age can be affected. Precursor B-cell malignancies are more common in skin than those of precursor T-cell origin {470,1431,1489, 2043}.

Clinical features

Lymphoblastic lymphoma/leukaemia may initially present in cutaneous or other extranodal sites as a single nodule or tumour {1429,2041}. Frequent sites are the head and neck region, especially for patients with precursor B-cell disease {2043}. However, there is a high likelihood of occult disease in the bone marrow, and patients should be regarded as having systemic disease for therapeutic purposes.

Morphology

The dermis contains a monotonous infiltrate composed of small to medium sized cells with fine chromatin and scant cytoplasm, characteristic of lymphoblasts. Nuclear irregularities are variable, and do not correlate with lineage. The epidermis is uninvolved, with a distinct Grenz zone. The cells are interspersed among dermal collagen fibres, without a stromal or inflammatory response.

Immunoprofile

T-cell lymphoblastic leukaemia/ lymphoma. The tumour cells are positive for terminal transferase (TdT), CD43, CD99 {1489,1949,2043}. They variably express CD1a, CD2, CD3, CD4, CD5, and CD8. CD10 may be positive in some cases. Cytoplasmic CD3 appears before surface CD3. CD7 is nearly always positive {1843}. The phenotype reflects stages in the maturation of a thymic T-cell.

B-cell lymphoblastic leukaemia/ lymphoma. The tumour cells are positive for TdT, CD43, and CD99 {1489,2043}. The cells are usually positive for CD19 and CD79a {326}. CD10 is expressed in most cases. CD20, CD22, and CD24 are variably expressed. LCA may be negative. The cells may contain cytoplasmic μ heavy chain, usually in the absence of light chains.

Histogenesis

Precursor T- or B- lymphoblast.

Somatic genetics

Rearrangement of immunoglobulin heavy chain genes, and T-cell receptor genes usually correlates with B-cell or T-cell lineage, respectively {544,1311}. However, lineage infidelity is common in precursor lymphoid malignancies. Light chain gene rearrangement is a relatively late event in B-cell differentiation.
The classification of lymphoblastic malignancies is closely related to a complex series of genetic abnormalities that correlate with pathogenesis and clinical outcome {1121}.

Prognosis and predictive factors

Precursor lymphoblastic leukaemia/ lymphoma is an aggressive disease. However, cutaneous involvement is not a poor prognostic factor, and response to systemic multiagent chemotherapy may be excellent {2043}.

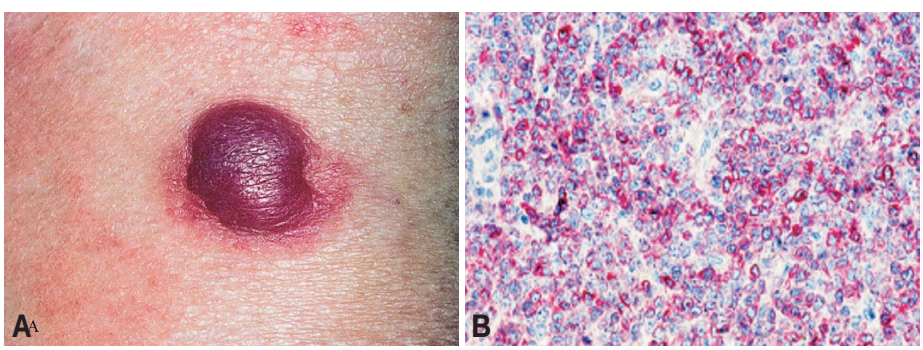

Fig. 4.70 Precursor B lymphoblastic leukaemia/lymphoma. **A** Soft non-ulcerated tumour on an erythematous plaque without scaling. **B** Tumour cells expressing CD79a.

Cutaneous involvement by myeloid leukaemia

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D.W.P. Su
J. Vardiman

Definition
Myeloid leukaemia is a heterogenous malignant disorder of myeloid precursor cells characterized by an increase in blast forms in the peripheral blood and bone marrow. Specific skin involvement results from direct infiltration of the skin by neoplastic cells.

Synonyms
Extramedullary myeloid sarcoma, granulocytic sarcoma, chloroma.

Epidemiology
Acute myeloid leukaemia (AML) accounts for 10-15% of childhood leukaemia but the incidence increases steadily with age. More than 50% of patients are older than 60 years {1838}. Chronic myelogenous leukaemia (CML) is generally a disease of older adults, with a median age between 50 and 60 years at presentation {1183}.
Skin involvement is reported to occur in 2% to 30% of patients with AML {35,125, 649}. Specific skin lesions are equally common among males and females. It is found more frequently in patients with acute myelomonocytic (AMML) and monoblastic/monocytic leukaemias (AMOL). Specific cutaneous lesions are less common in chronic myelomonocytic leukaemia (CMML) and CML.

Clinical features
Specific skin lesions present as solitary or multiple violaceous to red-brown papules, nodules and plaques. The most common sites of involvement are the scalp, face, trunk, and extremities {2288}. Haemorrhagic lesions are common. Leukaemic gingival hyperplasia is a striking feature of AMML and AMOL {649}. In the majority of cases, specific skin lesions develop in the setting of established leukaemia. In rare instances, leukaemic skin infiltrates may precede peripheral blood and bone marrow involvement {445,589,2368}.

Histopathology
There is a moderate or dense, diffuse or nodular infiltrate in the dermis that extends into the subcutaneous fat {329, 1172}. The epidermis usually is spared. The infiltrates typically show perivascular and periadnexal accentuation. A characteristic feature is the presence of rows of atypical cells between collagen bundles {2137}. The infiltrate is composed of medium-sized or large neoplastic cells with round, oval or folded basophilic nuclei. Mitotic figures are usually present. In CML, the infiltrate is more pleomorphic and dominated by mature and immature cells of the granulocytic series. Cutaneous infiltrates of plasmacytoid monocytes may occur in CMML {297}.

Immunoprofile
The majority of the tumour cells shows reactivity for lysozyme, myeloperoxidase, CD45, CD43, and CD74. Staining for chloroacetate esterase and CD68 is variable {1172,1899 }. Staining for CD34 is variable, and often negative in monoblastic leukaemias. The neoplastic cells are negative for CD3, CD20, CD30 and S-100 protein. The presence of CD56 expression in specific skin infiltrates of AML has been reported {1163,1258}.

Histogenesis
Haematopoietic stem cells.

Somatic genetics
Genetic studies of specific cutaneous lesions in AML are scant and limited to isolated cases. An increased incidence of trisomy 8 in AML with skin infiltration has been reported {35}. Rarely, cases of congenital AML may be present with skin lesions.

Genetic susceptibility
Patients with Down syndrome, Fanconi anaemia, ataxia telangiectasia, Bloom syndrome, and Kostmann syndrome are predisposed to AML.

Prognosis and predictive factors
The prognosis of patients with specific skin lesions of AML is generally poor {125,805}. In one series, all patients died within 24 months after onset of skin lesions {1172}.

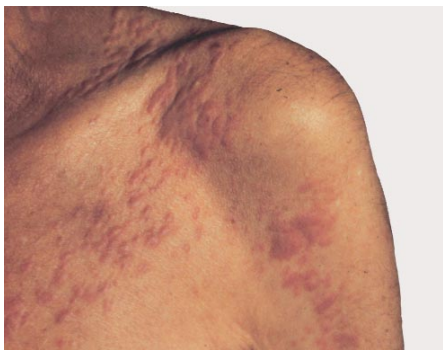

Fig. 4.71 Acute myeloid leukaemia presenting as generalized erythematous papules and plaques.

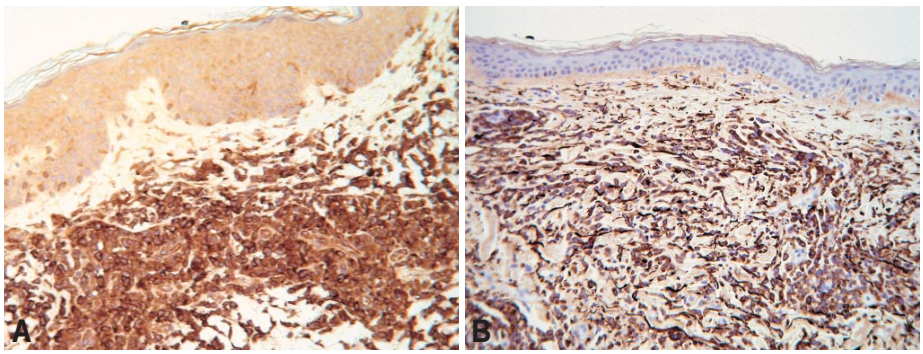

Fig. 4.72 Myeloid and monocytic leukaemias. **A** Acute monocytic leukaemia. Immunohistochemical expression of CD68. **B** Acute myeloid leukaemia. Positive lysozyme stain.

Lymphoid infiltrates of the skin mimicking lymphoma (cutaneous pseudolymphoma)

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W Kempf
C.A. Sander
G Wood
U Schmid
S Cogliatti

Definition

The term pseudolymphoma (PSL) is defined as a reactive polyclonal benign lymphoproliferative process predominantly composed of either B-cells or T-cells, localized or disseminated. It heals spontaneously after cessation of the causative factor (e.g. drugs) or after non-aggressive treatment.

Synonyms and historical annotation

In 1923, Biberstein coined the term lymphocytoma cutis. Since then, a variety of designations have been proposed: lymphadenosis benigna cutis {124}, pseudolymphoma of Spiegler {2237} and Fendt. {721}, cutaneous lymphoid hyperplasia and lymphocytoma cutis {401}. In retrospect, most of these terms were describing cutaneous B-cell pseudolymphomas (B-PSL). The concept of cutaneous T-cell pseudolymphomas (T-PSL) was not widely accepted until the early 1980's.

Epidemiology

Cutaneous pseudolymphomas affect all age groups with a predilection of Borrelia-induced B-pseudolymphomas in children and young adults, whereas drug induced T-pseudolymphomas more frequently are seen in adults. Even though Borrelia-induced pseudolymphomas may be precursors for B-cell lymphomas of the skin, in general cutaneous pseudolymphomas are selfregressing and do not affect survival.

Etiology

Pseudolymphomatous proliferations in the skin may be induced by microbial, physical or chemical agents including Borrelia burgdoferi infection, tattoos and drugs.

Localization

In most cases, skin lesions are confined to the site of external irritation, i.e. tick bite. Due to the preferential "docking" of ticks to body areas where the skin is relatively soft, e.g., scrotum of young boys, the mamilla, ear lobes, large skin folds are preferentially involved.

Clinical features

Several variants of cutaneous PSL exist, presenting with different clinical symptoms.

Pseudolymphoma (PSL) with predominant T-cell infiltrates (T-PSL)
Lymphocytic infiltration (idiopathic or drug induced)
Palpable migratory arciform erythema
Lymphomatoid contact dermatitis
Actinic reticuloid
Persistent nodular arthropod-bite reactions
Inflammatory molluscum contagiosum

The original description of lymphocytic infiltration (idiopathic or drug induced cutaneous T-cell pseudolymphoma) given by Jessner and Kanof in 1953 {1141} is still valid today.

The lesions are flat, discoid, more or less elevated, pinkish to reddish brown, starting as small papules, expanding peripherally, sometimes clearing in the centre, sometimes showing a circinate arrangement. The surface is smooth, occasionally uneven. There is no follicular hyperkeratosis as seen in discoid lupus erythematosus, which may be simulated. There may be only one, a few, or numerous lesions

Histopathology

Characteristic is a sleeve-like, predominantly lymphocytic infiltrate around the vessels of the upper and mid dermis. In addition, some macrophages and eosinophils may be found.

Phenotyping has shown the infiltrate to consist of both B and T cells {423} even though T cells seem to predominate in most cases {2521}.

Palpable migratory arciform erythema clinically shows a circinate or annular slightly elevated erythematous lesion.

Table 4.02 Differentiation between B-pseudolymphoma (B-PSL) and cutaneous B-cell lymphoma (CBCL) Taken from Burg et al. {340}.

	CBCL	PSL
Clinical features		
Number of lesions	solitary or multiple	usually solitary
Extracutaneous involvement	possible	absent
Recurrences	likely	usually no recurrences
Survival time	affected	not affected
Histological features		
Pattern of infiltrate	diffuse or nodular,	nodular (> 90%)
Structure of infiltrate	"bottom-heavy"	"top-heavy"
Border of the infiltrate	convexe, sharply demarcated "infiltrating" between collagen bundles	concave, poorly demarcated
Additional cells	usually absent	eosinophils,plasma cells
Transformation	may occur	never occurs
Immunophenotype		
Immunoglobulin light chains	monotypic (kappa or lambda)	polytypic expression
B-cell marker expressing cells	>50% cells	≤50% cells
T-cell marker expressing cells	usually few	>50% cells
CD21-positive dendritic cells	mostly absent irregular pattern	mostly present regular pattern
Genotype		
Ig heavy chain gene rearrangement	present in most cases	absent in most cases

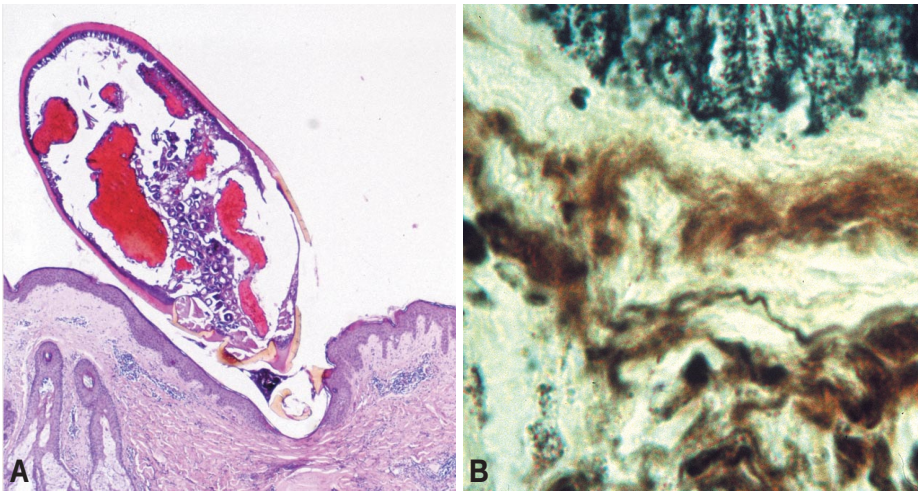


Fig. 4.73 **A** Head of Ixodes ricinus fixed to the skin. **B** 1384. Borrelia burgdorferi in the dermis, silver stain.

Histologically there is a scant sleeve- like perivascular lymphocytic infiltrate in the mid or deep dermis.

Lymphomatoid contact dermatitis has been reported as a reaction to various allergens (i.e. nickel, Peru balsam) or drugs (diphenylhydantoin) inducing mycosis fungoides-like features {1975}. Genotyping has shown clonal rearrangement in some cases. Such cases may be closely related to "clonal dermatitis" some of which develop into overt CTCL {2545,2546}. Histologically, eczematous features with epidermotropism of lymphocytes and accumulations of CD1a-positive Langerhans cells may be found.
Actinic reticuloid is a chronic photoallergic infiltrative dermatitis of light exposed areas associated bearing a clinical and histological resemblance to malignant lymphoma, especially to Sézary syndrome. Histologically there is a dense infiltrate of lymphocytes mixed with many polyclonal plasma cells, eosinophils and macrophages.
There is a considerable overlap between T- and B-PSL in persistent nodular arthropod-bite reaction, nodular scabies and inflammatory molluscum contagiosum which show a dense polymorphous infiltrate consisting of a mixture of T-cells, B-cells, macrophages and predominantly eosinophilic granulocytes.

Lymphomatoid papulosis even though showing biologic features of pseudolymphoma is considered to belong to the group of lymphomas since despite spontaneous regression of single lesions, the disease is not curable and may show transitions to other lymphomas.

PSL with predominant B-cell infiltrates

Lymphadenosis benigna cutis (LABC) {124} -the prototype of this group of B-PSL- is synonymous with lymphocytoma cutis. In Europe it is most commonly caused by infection with Borrelia burgdorferi after a tick bite (Ixodes ricinus). However other microbiological (medicinal leeches, Hirudo medicinalis) {2211}, physical or chemical agents as well may induce lymphocytoma-like reactions.
Two thirds of all lesions are situated on the head, tending to occur on the ear lobes. Other predilections are the nose as well as the nipples, the inguinal area and scrotum. Usually the lesion is a solitary papule or nodule, but several disseminated lesions may occur as well {1068}.
Microscopic examination shows a nodular dermal infiltrate with reactive follicles. In addition, there is a rather diffuse infiltrate containing T cells, histiocytes, eosinophils and polyclonal plasma cells. The presence of macrophages containing ingested nuclear material (tingible body macrophages) within the follicles producing a "starry sky" pattern is a common feature in B-PSL and a hallmark of all reactive germinal centres. The infiltrate is predominantly located in the upper and mid dermis, but may extend into the deep dermis. Small groups of lymphoid cells between collagen bundles may be observed at the periphery of the lesions. This is a helpful histological criterion in the differentiation from cutaneous B-cell lymphoma, in which the nodular infiltrate shows convex rather than concave sharply demarcated borders.
Phenotypically {428} a polyclonal B-lymphocytic infiltrate without light chain restriction of the infiltrate is found in most cases. The cells express the phenotype of mature B-cells (CD 20, CD 79a). In B-PSL, regular and sharply demarcated networks of CD21+ follicular dendritic cells are present, whereas in CBCL these networks are irregularly shaped {342}.

Acral pseudolymphomatous angiokeratoma of children (APACHE) is a rare benign pseudolymphomatous disorder occurring mainly in children {1888}.
The typical clinical presentation is multiple (up to 40), asymptomatic, small papules located unilaterally on the fingers, toes and hands. Their colour is usually red-violet, accounting for their angiomatous appearance {1887}.
Histologically the dermis contains a moderately to very dense, non-epidermotropic infiltrate composed of small well-differentiated lymphocytes admixed with a few plasma cells, histiocytes, and giant cells. Blood vessels show prominent plump endothelial cells {1165,1887}.
Immunohistochemically the cellular infiltrate represents a mixture of polyclonal mature T- and B-lymphocytes {936}.

Inflammatory pseudotumour (IPT) (plasma cell granuloma, inflammatory myofibroblastic pseudotumour) refers to a spectrum of idiopathic benign conditions with unknown etiology that can develop in various organs and deep tissues, particularly in the lung. Cutaneous IPT occurs as a solitary, slowly growing, tender nodule measuring 1-3 cm in diameter. Irrespective the anatomic location, the lesions share common histological features, showing well circumscribed proliferation of myofibroblasts/fibroblasts expressing smooth muscle actin (SMA) and vimentin, a mixed cell infiltrate containing high numbers of plasma cells with prominent germinal centres dispersed throughout the lesion. The plasma cells are polyclonal and are seen in the interfollicular areas (plasma cell granuloma) 21, {508,509}. Later stages show marked fibrosis/sclerosis with thick collagen bundles arranged in concentric whorls.

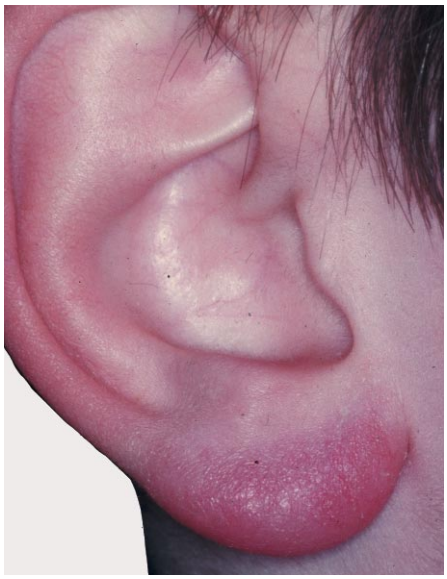


Fig. 4.74 Lymphadenosis benigna cutis (LABC, B-pseudolymphoma) following tick bite in the earlobe.

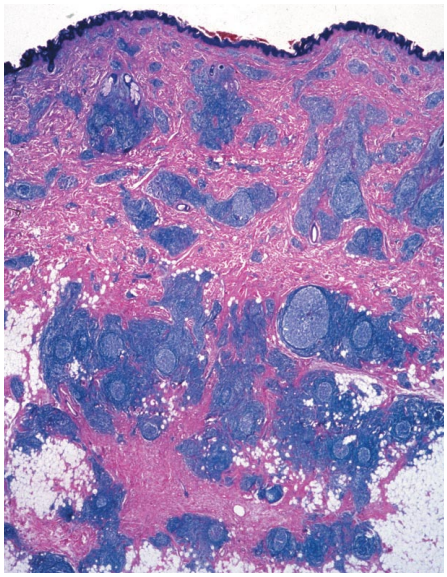


Fig. 4.75 B-PSL. Reactive follicles in lymphadenosis benigna cutis (B-pseudolymphoma).

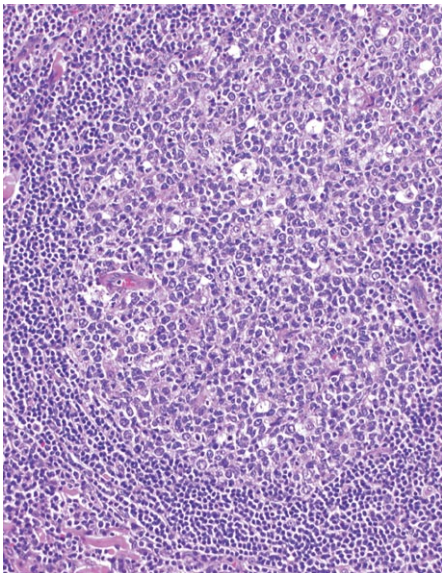


Fig. 4.76 Close up view showing follicular centre with tingible-body macrophages featuring a starry sky pattern.

Histological variations include presence of high endothelial venules, admixture of eosinophils, calcification, psammoma bodies, and presence of large polygonal myofibroblasts (vimentin+, CD15-, CD30-) {1476} with single, double or multiple nuclei and prominent eosinophilic nucleoli resembling Reed-Sternberg cells {388,1084,1476,1881,2561}.
Differential diagnosis of cutaneous IPT includes lymphoma, angiolymphoid hyperplasia with eosinophilia and Kimura and infectious dermatoses (mycobacteria, deep fungal infections). The later stages of cutaneous IPT should be distinguished from erythema elevatum diutinum, granuloma faciale and dermatofibroma with lymphoid infiltrate.

PSL with mixed and unclassified infiltrates

There are reactive lymphocytic infiltrates in the context of other skin disorders that can be referred to as pseudolymphomatous reactions in an even broader sense. Neoplasms, especially squamous cell carcinoma, basal cell carcinoma, and malignant melanoma, or naevi (halo [Sutton] naevi) may show a dense mononuclear infiltrate, composed of T cells or of B cells, sometimes with follicle formation, with polyclonal plasma cells being numerous especially in head and neck localizations.

Histogenesis

Polyclonality is the hallmark of cutaneous pseudolymphomas. Besides T-cells and B-cells, mononuclear phagocytes represent a considerable proportion of the infiltrate. Eosinophils and polytypic plasma cells as well are present in most cases of either B-cell or T-cell pseudolymphomas of the skin {342}.

Somatic genetics

No clonal rearrangement of T-cell receptor genes or of immunoglobulin heavy chain genes or light chain restriction of plasma cells is found.

Prognosis and predictive factors

The prognosis of cutaneous pseudolymphomas by definition is excellent, showing spontaneous regression of the lesions after cessation of the causative factor or due to treatment with non-aggressive treatment modalities. However there is a potential for some cutaneous pseudolymphomas to progress to cutaneous B-cell lymphoma (CBCL) {433,807,1339}, or to cutaneous T-cell lymphoma (CTCL) {2545,2546}.

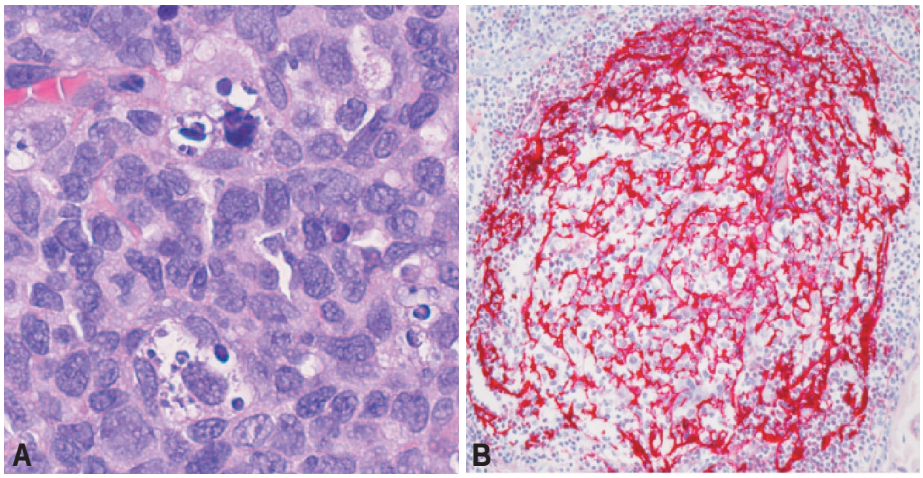


Fig. 4.77 A Tingible body macrophages containing ingested nuclear fragments. **B** Regular network of CD21+ dendritic cells.

Parapsoriasis

G. Burg
M. Santucci
B. Smoller
J. Guitart
M Everett
W. Kempf

Definition
The term “parapsoriasis” is confusing. It encompasses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling skin lesions .
Those diseases which have distinct clinical and histological changes do not fulfill criteria of malignancy, deserve to be labeled with a term which reflects this intermediate situation and labels them as distinct nosologic entities. This term since the days of Brocq has been “parapsoriasis” and there is no reason for changing it {311,312}. Otherwise there will be a bias in epidemiologic data on frequencies, mortality rates and other parameters.
Two groups of parapsoriasis can be differentiated. The benign form (“parapsoriasis en plaques” [Brocq’s disease]), which never evolves into malignant lymphoma and large plaque forms with or without poikiloderma which after several decades may evolve into mycosis fungoides or CTCL in up to 50% of the cases. Table 4.3 summarizes criteria for differentiation of benign and premalignant forms of parapsoriasis en plaques.

Small plaque parapsoriasis

Synonyms
Parapsoriasis, small patch (digitiform) type (Brocq’s disease); Parapsoriasis en plaques, benign type; digitate dermatosis, xanthoerythrodermia perstans; chronic superficial dermatitis

Epidemiology
This form preferentially occurs in young adults and affects males more frequently than females. There are no statistically reliable data on the incidence, which is estimated less than 0.1 per 100.000 per year. There is little tendency to progress. Survival is not affected since SPP never evolves into malignant lymphoma

Clinical Features
Trunk and upper extremities are preferentially involved. Small (2-5cm in diameter), mostly oval or finger-like patches, slightly erythematous, following skin lines. The color is brown red, and fine and powdery (pityriasiform) scaling may be present. The surface is slightly wrinkled resulting in a pseudoatrophic appearance.

Histopathology
The epidermis is normal or slightly spongiotic with patchy parakeratosis. Patchy loose perivascular and disseminated lymphocytic infiltrate, but no edema, are present in the dermis. Significant epidermotropism of lymphoid cells is lacking.

Immunohistochemistry
Lymphoid cells exhibit mostly CD4+ and some CD8+ {935}.

Somatic genetics
Clonal rearrangement for the T-cell receptor genes is not detectable. However clonal rearrangement of lymphoid cells in the peripheral blood of patients has been reported {1661}.

Prognosis and predictive factors
The skin lesions are extraordinarily stable in shape and size over years and decades without spreading to extracutaneous localizations. Lymph nodes, peripheral blood, bone marrow or internal organs are not affected. Life-expectancy is normal. Progression into mycosis fungoides or other CTCL does not occur.

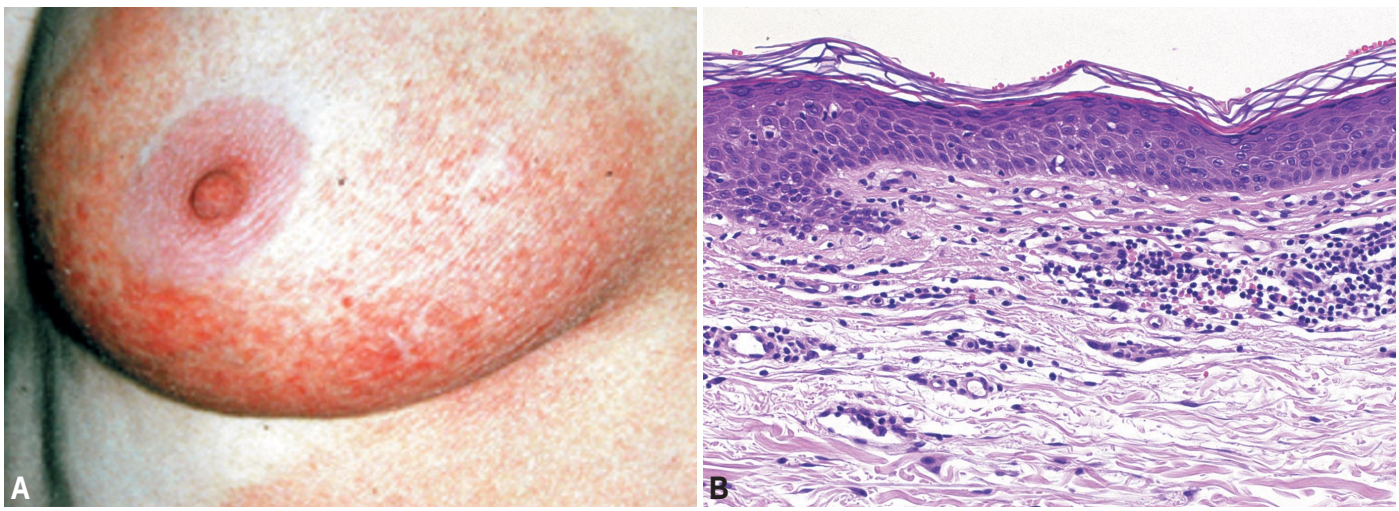


Fig. 4.78 Parapsoriasis. **A** Large plaque parapsoriasis with poikiloderma, showing large teleangiectatic patches and a netlike pigmentation. **B** Flattening of the epidermal rete ridges. Band like lichenoid infiltrate. Dilated small blood vesels in the upper dermis.

Parapsoriasis - Large patch type, with or without poikiloderma

Definition
Pre-malignant inflammatory disorder with tendency to evolve into mycosis fungoides. Some authors consider this lesion a manifestation of early cutaneous T-cell lymphoma (CTCL).

Synonyms
Non-poikilodermatous variant. Parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples.
Poikilodermatous variant : Prereticulotic poikiloderma, parapsoriasis en grandes plaques poikilodermiques; poikiloderma vasculare atrophicans; parapsoriasis lichenoides; parakeratosis variegata

Epidemiology
All age groups may be affected with a slight male preponderance.

Localization
Breast and buttocks are most commonly involved.

Table 4.03
Criteria for distinguishing benign and premalignant forms of parapsoriasis en plaques.

	Benign form (small patch type)	Premalignant form (large patch type) with or without poikiloderma
Age distribution	Adults	All ages
Sex incidence (m:f)	5:1	2:1
Clinical features	Small (2-5cm in diameter), mostly oval, or finger-like patches, slightly erythematous and wrinkled surface (pseudoatrophy) uniformly pinkish or yellowish with pityriasiform scaling	Few large patches (>5cm in diameter) pityriasiform scaling with or without telangiectases and netlike pigmentation, sometimes slightly hyperkeratotic (parakeratosis variegata)
Preferential localizations	Trunk and upper extremities	Breast and buttocks
Histological features	Patchy parakeratosis, slight perivascular patchy infiltrate, no oedema, no significant epidermotropism	Slight epidermal atrophy with loss of rete ridges, significant band-like dermal lymphocytic infiltrate sparing the subepidermal zone, no significant epidermotropism, no oedema; telangiectases may be prominent in the poikilodermatous variant
Prognosis	Life expectancy normal; no progression to mycosis fungoides	Life expectancy normal in most cases; progression to mycosis fungoides occurs

Clinical Features
Few large (more than 5 cm in diameter) patches showing pityriasiform scaling with (poikilodermatous variant), telangiectasia and netlike pigmentation are present. There is no palpable infiltration.

Tumour spread and staging
Lesions may stay unchanged over years and decades, or slowly show enlargement in a few cases. No plaques or tumours occur, except when the disease evolves into CTCL in some of the cases.

Histopathology
Under patchy parakeratosis there is slight atrophy of the epidermis, due to loss of rete ridges, in the poikilodermatous form. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, sparing the papillary region. There is no significant epidermotropism as usually seen in early stages of mycosis fungoides. The poikilodermatous variant of the disease in addition shows dilated blood vessels in the upper dermis.

Somatic genetics
T-cell receptor gamma gene rearrangement,which is clonal in about half of the patients with LPP, is probably without any prognostic significance {2186}.
Increased telomerase activity and shortened telomere length was also detected in CD4+ T cells from patients with parapsoriasis {2552}.

Prognosis and predictive factors
There is no significant difference between the observed and expected survivals in patients with less than 10% skin involved. {2575}. However when skin involvement exceeds10%, as seen in LPP, sporadic cases have an increased risk of transforming into mycosis fungoides after years or decades {2031}.

Langerhans cell histiocytosis

B. Zelger
R.P. Rapini
W Burgdorf
G. Burg

Definition

Langerhans cell histiocytosis (LCH) is a clonal disorder with systemic spread, characterized by proliferation of dendritic cells which bear morphologic and phenotypic markers of Langerhans cells, characterized by Birbeck granules and expression of CD1a and S-100.

ICD-O code 9751/1

Synonyms

Histiocytosis-X, Langerhans cell granulomatosis, Langerhans cell disease

Epidemiology

LCH predominantly occurs in infants. Median age at diagnosis is 3-5 years {2,299}. It has also been reported in patients up to the ninth decade of life {1551,1578,1941}, and occurs equally in men and women. The incidence has been estimated as 0.1–0.5 per 100.000 population per year. There have been reports on familiar cases with autosomal recessive inheritance.

Etiology

The etiology is unknown. Different groups have studied female patients with cutaneous LCH using a variety of x-linked polymorphisms to demonstrate clonality {2530,2574}. In some cases, association with lymphomas, leukaemias and lung tumours {666} has been observed; in others, infections and environmental factors, including El Nino, have been related to childhood LCH {455}. Many view LCH as reactive process {716,2583} because of its tendency toward spontaneous remission and response to mild, non-toxic therapy.

Localization

Two thirds of the sites of involvement diagnosed throughout the course of the disease are present at diagnosis {2}. Initial bone involvement is found in almost all patients. Other organs involved skin (25-100%, depending on subtype), ear, liver, lung, and lymph nodes {299}.

Clinical Features

The clinical presentation of LCH is very diverse and depends on the subtype. Skin lesions may be seen either as single organ involvement or as part of a multiorgan systemic disease in 25-100% of cases. Any anatomic site can be involved including scalp, nails, palms and soles as well as mucous membranes.

Letterer-Siwe Disease

This is the most severe, disseminated form of Langerhans cell histiocytosis. It affects children in their first year of life but occurrence in adults has been reported {1731}. Tiny (0.5 mm in diameter) rose-yellow or brownish-red, translucent papules and patches are found on the scalp, diaper and seborrhoeic sites like nasolabial folds, perioral region, and on the upper trunk . In time, the papules become scaly and crusted and may coalesce into plaques. Petechial and purpuric lesions, pustules and vesicles as

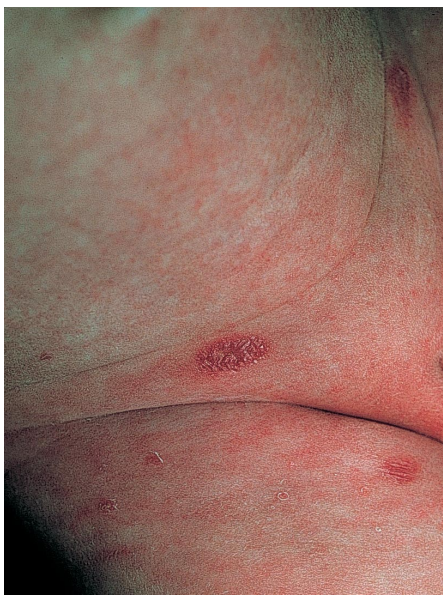


Fig. 4.79 Multiple nodules in a patient with Congenital self-healing reticulohistiocytosis (CSHRH).

Table 4.04
Langerhans cell histiocytoses and their characteristics. This classification has limitations because of the highly variable manifestations of the disease with many overlapping features {340}.

Disease	Age	Skin involvement	Clinical Features	Course	Prognosis
Letterer Siwe	First years of life	~90-100%	Fever, weight loss, lymphadenopathy, hepatosplenomegaly, pancytopenia, bone lesions	Acute	Mortality rate: 50-66%
Hand-Schüller Christian	Children adults	~30%	Osteolytic bone lesions, diabetes insipidus exophthalmos, otitis	Subacute to chronic	Mortality rate: < 50%
Eosinophilic granuloma	Mainly adults	<10%	Solitary bone or skin lesions	Chronic	Favorable
Congenital self-healing reticulohistiocytosis (CSHR)	Congenital	100%	Skin lesions only	Self healing	Excellent*

*Both relapses and conversion to systemic disease can occur, so long-term follow-up is needed {1369}.

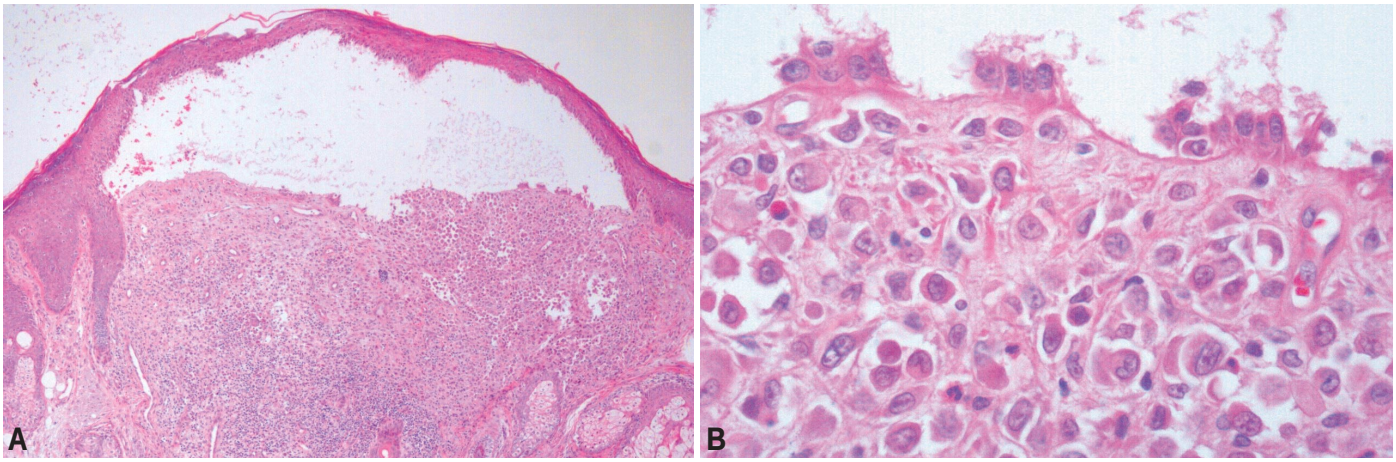


Fig. 4.80 Congenital self-healing reticulohistiocytosis (CSHRH). **A** Papule of CSHRH with **B** Characteristic kidney-shaped nuclei.

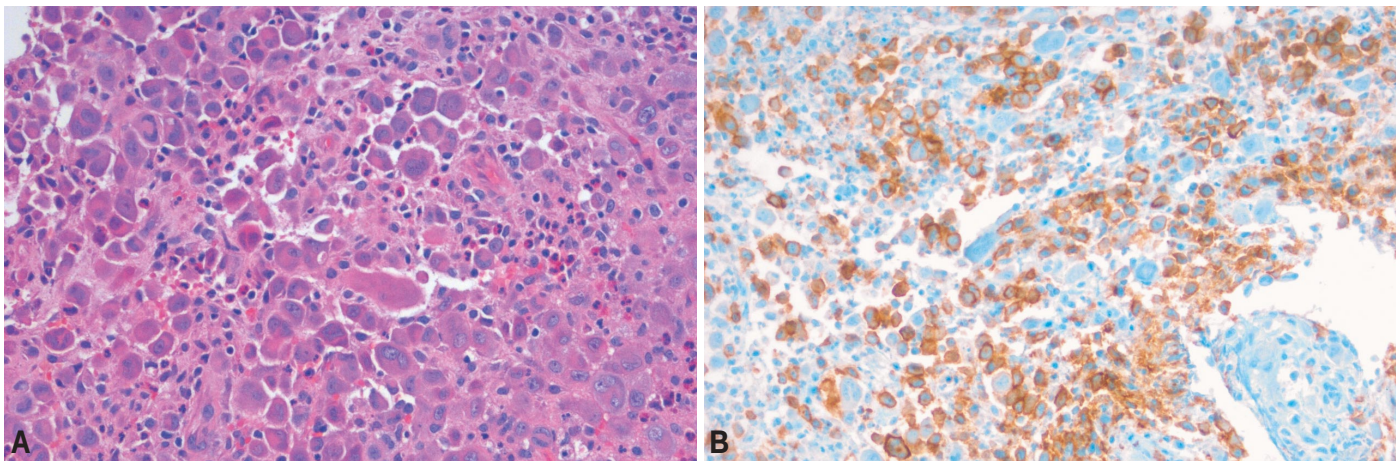


Fig. 4.81 Langerhans cell histiocytosis. **A** Typical ground glass ("reticulocytic"} appearance of Langerhans cells. **B** Langerhans cells with membranous staining for CD1a .

well as small erosions can also be seen. Nodules are uncommon, but may be found on the trunk and tend to ulcerate. Additional symptoms include fever, weight loss, rash, lymphadenopathy, hepatosplenomegaly, pancytopenia and purpura.

Hand – Schüller - Christian disease

The typical triad includes osteolytic skull lesions (100%), hypopituitarism induced diabetes insipidus (50%), and exophthalmos (10%). Otitis media, generalized lymphoadenopathy, hepatosplenomegaly, and pulmonary disease may be additional findings.

Skin lesions occur in about 30% of cases, usually in the intertriginous areas, most often as papules and nodules which may be ulcerated, erosive and superinfected.

Eosinophilic granuloma

The most common site of involvement is bone. The uncommon cutaneous lesions are deep dermal or subcutaneous nodules which are not clinically distinct {818,1956}. Lesions have to be differentiated from granuloma eosinophilicum faciei, a chronic variant of leukocytoclastic vasculitis with variable presence of eosinophils, but usually no extracutaneous manifestation {452}.

Congenital self-healing reticulohistiocytosis (CSHRH)

CSHRH (synonyms: Hashimoto-Pritzker disease; congenital reticulohistiocytosis; congenital self-healing Langerhans cell histiocytosis) {981,2082} is a rare condition (5% of all LCH), initially seen at birth or in the neonatal period, with solitary, localized to generalized papules, vesicles, or nodules on the trunk, head, palms and soles, sometimes showing central ulceration {217}. The skin lesions tend to involute spontaneously within weeks to months leaving behind hypo- or hyperpigmented macules or patches {979,1372}. Affected infants are otherwise well {1369}. Patients should be carefully followed since relapses may occur, including bone involvement, and the occasional case may progress to Letterer-Siwe disease {1445}. Some cases of CSHRH may be clinically confused with the blueberry muffin syndrome, congenital leukaemic infiltrates, xanthogranulomas or mast cell disease, but the microscopic picture brings clarity {360}.

Histopathology

The hallmark and unifying feature of all variants of LCH is a cell with large, pale, folded or lobulated, often reniform, vesic-

ular nucleus and abundant, slightly eosinophilic or amphophilic cytoplasm. Nucleoli are not prominent. Histological variations correlate with the clinical appearance of the lesions. Features may be predominantly proliferative in Letterer-Siwe disease, xanthomatous in Hand-Schüller-Christian-disease, granulomatous as in eosinophilic granuloma, or "reticulocytic" with abundant eosinophilic cytoplasm (ground glass appearance of giant cells) in Hashimoto-Pritzker disease. Fully developed papules and plaques show a dense band-like infiltrate obscuring the dermo-epidermal junction. Epidermotropism of LCs with intraepidermal microabscess formation can be found. In addition to LCs and eosinophils, the infiltrate may contain variable numbers of lymphocytes, epithelioid macrophages including foam cells and giant cells, neutrophils, plasma cells, and extravasated erythrocytes.

Immunohistochemistry

The phenotypic hallmarks in LCH are expression of CD1a, CD4 and S-100 protein, while macrophage markers, including CD68 and lysozyme, are usually negative.

Electron microscopy

Rod- or rocket-shaped granules measuring 200-400 nm (Birbeck granules, Langerhans cell granules) are the ultrastructural hallmark of LCs. The number of Birbeck granules varies, with usually greater prominence in early lesions. Coexistence of myelinoid laminated inclusions or "vermiform" bodies {1372} and Birbeck granules is common in CSHRH.

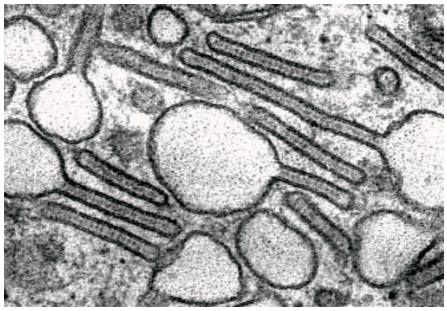


Fig. 4.82 Electron microscopy with numerous Birbeck or Langerhans cell granules. Courtesy Dr. N. Romani, University of Innsbruck, Austria

Genetics

A variety of inconsistent cytogenetic abnormalities have been found in several patients with LCH studied so far using comparitive genomic hybridization, loss of heterozygosity (LOH) and other techniques {107,227,848,1666}. Heterogeneous overexpression of TGFbeta receptor I and II, MDM2, p53, p21, p16, Rb, and BCL2 has been detected in lesional LCH cells {2097}. Familial clustering of two different manifestations of LCH support a role for genetic factor(s) in LCH and raise the possibility of inherited mutations that promote emergence of clonal Langerhans cells {93,134,1200}.
LCH may follow percursor T-cell acute lymphoblastic leukaemia, and in such cases a clonal relationship has been shown for T-cell receptor gene rearrangements {720}.

Prognosis and predictive factors

The biologic behaviour of LCH ranges from spontaneous remission to lethal dissemination, and such behaviour cannot be predicted on the basis of histologic features {1941}. The presence and degree of organ dysfunction, age less than 1 year at diagnosis (except the Hashimoto-Pritzker type), male sex, progressive episodes, and the absence of response to therapy are the most reliable indicators of prognosis {2,1019}. In general, about 10% of patients with multifocal disease die, 30% undergo complete remission, and the remaining 60% embark upon a chronic course {1065, 1425}.

Indeterminate cell histiocytosis

R. Caputo
E. Berti

Definition

Indeterminate cell histiocytosis (ICH) is a proliferative cutaneous disorder of the so-called "indeterminate cells" (IC), i.e. distinct dendritic cells of the skin that display histological, ultrastructural and antigenic features similar to those of Langerhans cells, but do not contain Birbeck granules.

Epidemiology

The disease is very rare (about 15 cases described up to 2003), usually occurs during adulthood, although two cases were in teenagers {1621,2019} and two cases in children {1413,1524}. Both sexes have been affected.

Etiology

The origin of indeterminate cells is still debated. Indeterminate cells may derivate from an arrest of Langerhans cell migration and maturation {1302}, may represent precursors of Langerhans cells which acquire Birbeck granules as they transit from dermal to epidermal sites {1499}. Furthermore it has been suggested {222} that indeterminate cells represent members of the epidermal/dermal dendritic cell system which migrate from skin to regional lymph nodes. According to this concept, indeterminate cell histiocytosis can be considered a disorder due to locally arrested dermal indeterminate cells proliferating prior to their departure for lymph nodes.

Localization

Lesions are usually restricted to the skin. Solitary lesions have been described on the trunk and arms, while multiple lesions are widespread.

Clinical features

The eruption consists of a solitary nodular lesion {222,279,1413,1621} or of multiple papulonodules {279,531,1499,2019, 2179}.
Solitary nodules are soft, red in colour and about 1 cm in diameter, and may be ulcerated. Multiple lesions are firm, asymptomatic papulonodules ranging in size from a few millimetres to 1 cm, varying in colour from dark-red to brownish, and covered by intact skin. These lesions appear in successive crops. Mucous membranes are always spared. Visceral involvement has been observed only in a child. Patients are in good general health.

Histopathology

Light-microscopic evaluation reveals an infiltration of histiocytic cells in the whole dermis and sometimes within the epidermis. The proliferating cells show an abundant pale eosinophilic cytoplasm and large irregular folded or twisted nuclei.
A few mitotic figures and multinucleated giant cells may be observed. Clusters of lymphocytes are admixed.

Immunohistochemistry

Proliferating cells are weakly positive for CD1a, CD68 (KP1), CD11c (Leu M5), CD14 (OKM1), factor XIIIa, lysozyme, α1-antitrypsin, HLA-DR, but negative for CD207 (langerin) {1302,1499,1524,1621, 2179}.

Electron microscopy

The proliferating cells reveal an indented nucleus and an abundant cytoplasm with lysosomes, phagosomes and a well-developed endoplasmic reticulum. Birbeck granules are absent {222,531, 1413}.

Prognosis and predictive factors

Most cases have exhibited complete or partial spontaneous regression of lesions without recurrences. Two cases displayed malignant behaviour {279,1524}. The prognosis is reasonably good, but leukaemia may be associated with this disease {279,1302}.

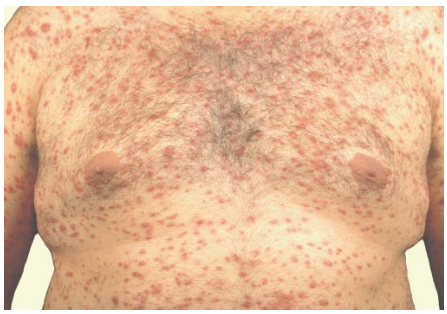


Fig. 4.83 Indeterminate cell histiocytosis. Multiple firm, asymptomatic papulonodules on the trunk, ranging in size from few millimetres to 1 cm, varying in colour from dark red to brownish.

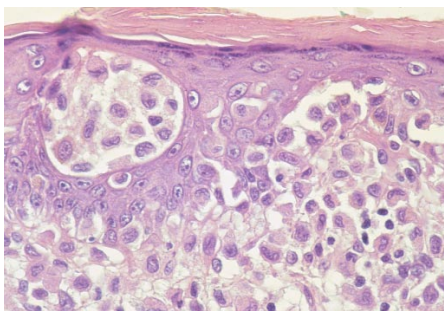


Fig. 4.84 Indeterminate cell histiocytosis. The proliferating cells show an irregular, often reniform, vesicular nucleus, surrounded by abundant pale cytoplasm. From: R. Caputo {378}.

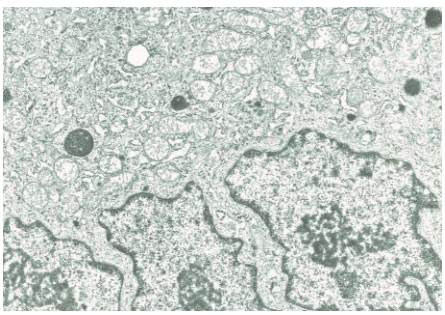


Fig. 4.85 The proliferating cells reveal an indented nucleus and an abundant cytoplasm with lysosomes, phagosomes and a well developed endoplasmic reticulum. Birbeck granules are absent.

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

B. Zelger
S. Kohler
W. Burgdorf

Definition
Sinus histiocytosis with massive lymphadenopathy is a reactive condition of unknown etiology, charactericed by a poliferation of histiocytes which usually exhibit emperipolesis of lymphocytes. The disease can mimic lymphoma. Extranodal involvement is frequent.

Synonyms
Sinus histiocytosis with massive lymphadenopathy, Rosai-Dorfman disease

Epidemiology
Sinus histiocytosis is a rare non-neoplastic disease. Lymph nodes are predominantly affected in children and young male adults; the cutaneous form is particularly seen during the third and fourth decades in female patients {74,307,483}.

Etiology
The etiology is unknown. Lesions are polyclonal, probably the consequence of a cytokine dysregulation {1603}.

Localization
Cervical lymph node involvement is most characteristic. Cutaneous lesions frequently occur on the head and neck, mucous lesions {1105,2498} in the nose and paranasal sinus. Extranodal disease may also affect any other organ {2455}.

Clinical features
Children with massive cervical lymph node swellings frequently suffer from fever and malaise. Laboratory tests show leukocytosis, anemia, polyclonal hypergammaglobulinaemia and an accelerated erythrocyte sedimentation rate. Extranodal involvement is common, up to 40%. Pure cutaneous forms are rare; solitary, clustered or wide-spread, red to brownish papules, rarely plaques and nodules are seen. Regression leaves atrophic, brown macules.

Histopathology
Lymph node architecture is replaced by sheets of faintly stained ("clear") to slightly eosinophilic macrophages. In extranodal location infiltrates frequently simulate lymph node sinuses ("sinusoidal pattern").
Emperipolesis of lymphocytes, erythrocytes or other nuclear debris is prominent, but not specific; it can also be seen in, e.g., subcutaneous T-cell lymphomas. Lymphocytes, plasma cells, neutrophils and fibrosclerosis are found to a variable degree.

Immunohistochemistry
Macrophages are positive for CD68 (PGM1, KP1) and S100 protein; CD1a, factor XIIIa and CD34 are negative {1796}.

Electron microscopy
Macrophages ingest intact lymphocytes. Phagolysosomal structures, but no Birbeck granules are found.

Prognosis and predictive factors
Manifestation in children and lymph node involvement are more readily and rapidly associated with regression than in adults and spread to extranodal sites. The vast majority of lesions is self-limited and benign. Rare fatalities have been associated with immunologic disorders, lymphomas of Hodgkin and non-Hodgkin type, leukaemias {62}, and exceptional cases with solid tumours {1900}.

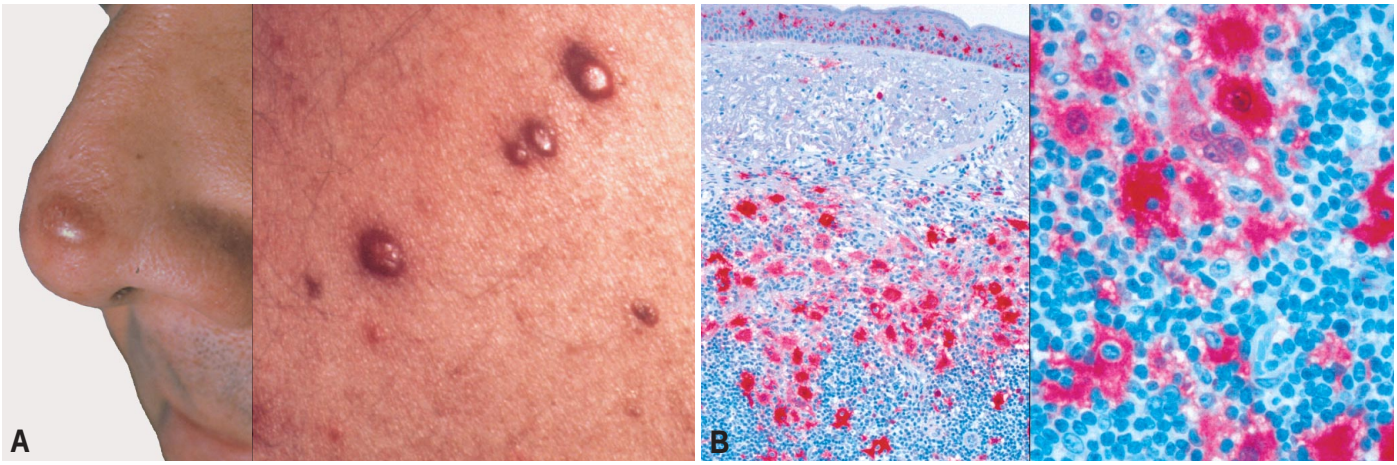


Fig. 4.86 Sinus histiocytosis with massive lymphadenopathy. **A** Left: Brownish nodule of sinus histiocytosis on the nose. 1595 Right: Clustered brownish papules of sinus histiocytosis on the trunk. **B** Left: Sheets of macrophages in sinus histiocytosis positive for S100 protein. Right: Lymphocytes within cytoplasm of histiocytes, i.e,. emperipolesis.

Juvenile xanthogranuloma

R. Caputo
B. Zelger

Definition
Juvenile xanthogranuloma (JXG) is a benign, self-healing, non-Langerhans-cell (LC) histiocytosis most frequently seen in infants and children, characterized by yellowish asymptomatic papules and/or nodules located in the skin and other organs and consisting of an infiltrate of macrophages with a variable degree of lipidization in the absence of a metabolic disorder.

Synonyms
Xanthoma multiplex {33}; Nevoxanthoendothelioma {1551}.

Epidemiology
JXG is the most common form of non LC histiocytosis {378,824}. JXG appears within the first year of life in about 75% of cases; in 15-30% it is present at birth.

Etiology
The etiology is unknown. Foamy cells constitute the main part of the mature lesions of JXG and accumulate lipids, despite normal levels of plasma lipids.
It has been suggested {208} that the uptake of low-density lipoprotein cholesterol and the biosynthesis of intracellular cholesterol are both enhanced; such enhancement might play a role in the process of accumulation of cholesterol esters in the macrophage.

Localization
Cutaneous lesions are irregularly scattered throughout the skin without a tendency to cluster, and are mainly located on the upper part of the body {378,824}. Mucous membranes may rarely be involved.
The most common extracutaneous manifestation of JXG (occurring mainly in the papular and subcutaneous {256} forms) is ocular involvement {256,614,2045, 2603}. Ocular lesions may occur in about 1-10% of affected children and are almost always unilateral and may lead to haemorrhage and glaucoma. Such lesions may precede or follow the cutaneous lesions. The nodular variant of JXG may occasionally be related to systemic lesions of lungs, bones, kidneys, pericardium, colon, ovaries, testes and central nervous system {378,824,2536}.

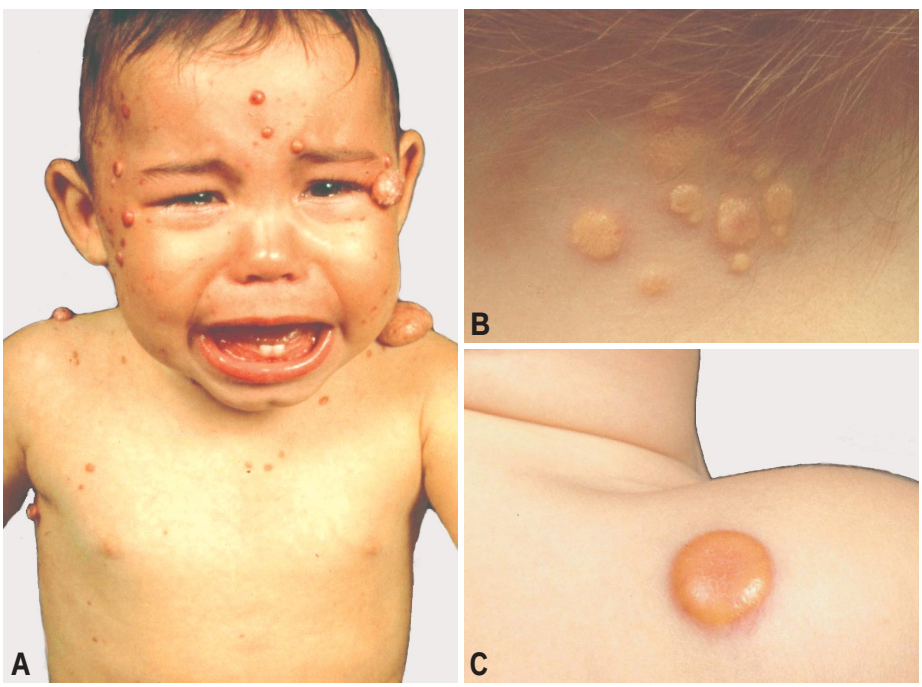


Fig. 4.87 Juvenile xanthogranuloma. **A** Mixed form: this form is characterized by the simultaneous presence of both red brown papules and nodules, irregularly scattered throughout the skin. Previously published by R. Caputo in "Text Atlas of Histiocytic Syndromes. A Dermatological Perspective" , Martin Dunitz, London 1998 {378}. **B** Plaqueform: this cluster of yellow nodules on the back of the neck is the only expression of the disease. **C** Nodular form: a round, high-domed, yellow brown nodule on the right shoulder.

Clinical features
Two main clinical variants can be distinguished: a papular form and a nodular form {824}
The *papular form* is the most frequent and is characterized by numerous (up to 100), firm hemispheric lesions, 2-5 mm in diameter, that are red-brown at first and then quickly turn yellowish. These lesions are associated in perhaps 20% of patients with café-au-lait spots of neurofibromatosis {1140} and may be related to juvenile chronic myeloid leukaemia {538,1650}.
The *nodular form* is less frequent, and is marked by one or a few lesions. The nodules are round to oval, 1-2 cm in diameter, high-domed, shiny, translucent, yellowish or red brown and sometimes show telangectasias on their surface. The term giant JXG has been used to indicate lesions larger than 2 cm. Unusual clinical variants {378,383} are the mixed form (simultaneous presence of both papules and nodules) and the form en plaque, a group of JXG lesions with a tendency to coalesce into a plaque as the only expression of the disease.

Histopathology
Early lesions are characterized by a dense infiltrate of monomorphous, non-lipid containing, macrophages with abundant, slightly eosinophilic, cytoplasm {378,824}. With time the cytoplasm of macrophages becomes laden with lipid and appears foamy.
Mature lesions contain foamy cells, for-

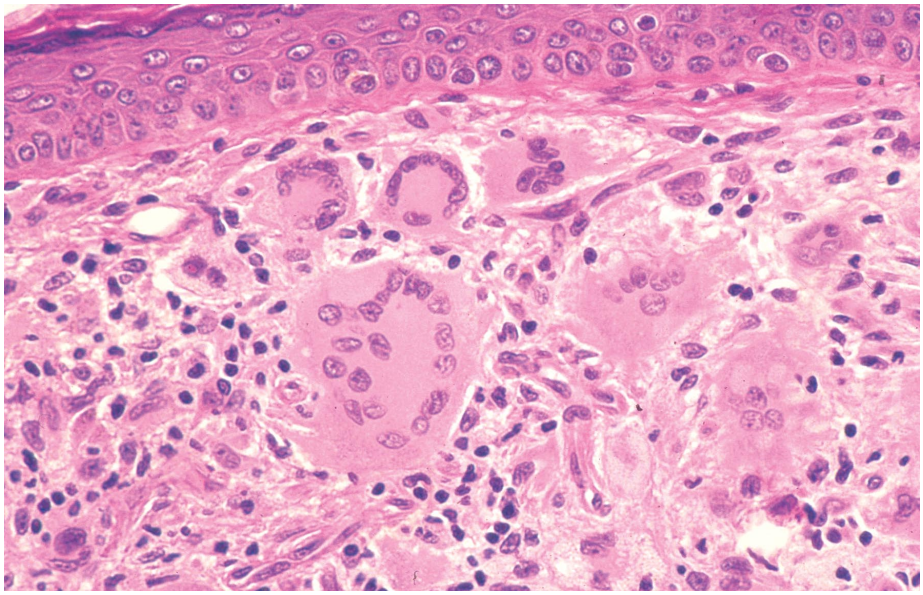


Fig. 4.88 Juvenile xanthogranuloma. Conventional microscopy. In mature lesions, giant cells are mainly distributed in the superficial dermis and on the border of the infiltrate. From: R. Caputo {378}.

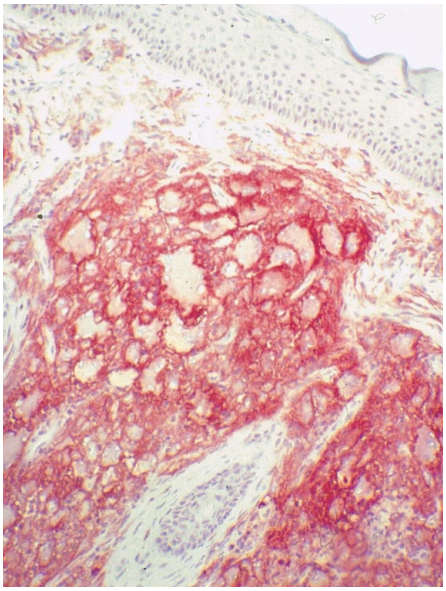


Fig. 4.89 Juvenile xanthogranuloma. Frozen section showing large macrophages stained by CD14 .

eign body giant cells and Touton giant cells, mainly distributed in the superficial dermis and on the border of the infiltrate. In addition to macrophages and foamy cells, there may be lymphocytes, eosinophils, neutrophils and plasma cells scattered throughout the lesion. In older lesions fibrosis replaces the cellular infiltrate, and lipids are not present extracellularly.

Immunohistochemistry

Immunohistochemically {824,2049} macrophages and Touton cells show a uniform positive staining with CD14, CD68, HAM56 (markers with specificity for macrophages) and vimentin, frequent positive staining for factor XIII (markers of dermal dendrocytes) and for cathepisin B and occasional staining for MAC387 (a marker for monocytes and macrophages).

S100 protein, CD1a (OKT6), CD15 (Leu M1) and peanut agglutinin (PNA) are not usually expressed on the macrophages of JXG.

Electron microscopy

Under the electron microscope {378, 824}, the macrophages that characterize the early stage of the disease exhibit pleomorphic nuclei, are rich in pseudopods, and contain many elongated and irregular dense bodies.

Clusters of comma-shaped bodies, but no Langerhans granules (LG) can occasionally be observed. In older lesions there is a predominance of foamy cells, the cytoplasm of which is completely filled with lipid vacuoles, cholesterol clefts, and myeloid bodies. The cells corresponding to Touton giant cells are large (150-250 μm) and sometimes contain more than 10 nuclei. At their periphery, such cells are rich in lipid material, whereas in their centre, mitochondria and lysosomes predominate.

Genetics

JXG is not linked to any genetic locus, but the association with café-au-lait spots of neurofibromatosis (NF1) {2536} and the occasional association with neurilemmomatosis (NF2) {1115} suggests that a JXG locus could reside on chromosome 17q11.2 or 22q12. Clinical {1115} and genetic analyses {1056} indicate that neurilemmomatosis and neurofibromatosis type 2 (NF2) genes are identical.

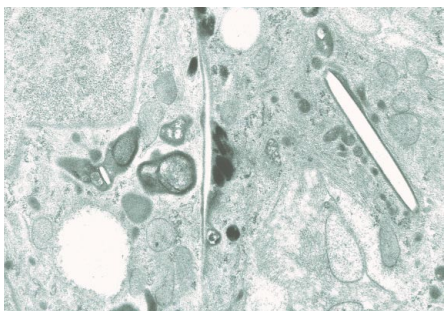


Fig. 4.90 Juvenile xanthogranuloma. Electron microscopy. This large macrophage exhibits lipid droplets, myeloid bodies and cholesterol clefts.

Prognosis and predictive factors

The papules and nodules of the skin tend to flatten with time and both the skin and most of the visceral lesions disappear spontaneously within 3-6 years. A few cases of JXG with fatal evolution, probably due to central nervous system involvement {378} or fatal liver disease {614}, have been reported. In JXG periodic complete blood count and peripheral smears would be judicious during a patient's first two years of life, which is the time of the peak incidence for juvenile chronic myeloid leukaemia.

Reticulohistiocytosis

E. Berti
B. Zelger
R. Caputo

Definition

Reticulohistiocytosis of the skin represents a spectrum of rare clinical entities, ranging from the solitary cutaneous form (SCR) through the generalized cutaneous form without systemic involvement (GCR), to multicentric reticulohistiocytosis with systemic involvement (MR). The skin lesions in all these conditions demonstrate an identical histological pattern, characterized by numerous mononucleated or multinucleated macrophages with abundant, eosinophilic, homogeneous to finely granular cytoplasm with a characteristic ground-glass appearance.

Synonyms

Giant cell reticulohistiocytosis, giant cell histiocytosis; cutaneous reticulohistiocytoma, reticulomatosis with giant cell histiocytes; normocholesterolemic xanthomatosis; lipoid dermatoarthritis; lipoid rheumatism; multicentric reticulohistiocytosis; non-diabetic cutaneous xanthomatosis; reticulohistiocytic granuloma; reticulohistiocytosis of the skin and synovia.

Epidemiology

Reticulohistiocytosis mostly occurs in adults over 40 years of age, but the disease may appear during adolescence: SCR and GCR have been also observed in children. In adults, the most frequent variant is MR, with about 50 and GCR with 10 patients reported in the literature. There is no preference for either sex {167,465,1405,1462}.

Etiology

The etiopathogenesis is unknown. Reticulohistiocytosis may represent an abnormal macrophage response to different stimuli. In solitary forms, local trauma such as insect bites, folliculitis or ruptured infundibular cysts may play a role {379}, while in systemic forms the association with autoimmune disorders and internal malignancies suggests an immunological basis for the initiation of this reaction {1752}.

Localization

SCR involves mainly the head and the neck, but may be found in any cutaneous site {382,1082}. In GCR the lesions are widely scattered on the skin {381,547, 847,2363}. In MR {167,413,465,1405, 1752} skin lesions preferentially affect the fingers, the palms and the back of the hands, the juxta-articular regions of the limbs and the face. Oral, nasal and pharyngeal mucosa are involved in 50% of cases. Osteoarticular lesions involve mainly the hands (80%), knee (70%) and wrists (65%).

Clinical features

The solitary cutaneous reticulohistiocytosis (SCR) or reticulohistiocytoma cutis {382,1082} is characterized by a single, firm, rapidly growing nodule varying in colour from yellow-brown to dark-red. The lesion is often clinically misdiagnosed, it occurs without evidence of systemic involvement, and its onset may be preceded by trauma.

Generalized cutaneous histiocytosis (GCR) {381,547,847,2363} is a purely cutaneous form characterized by the eruption of firm, smooth, asymptomatic papulonodular lesions, 3-10 mm in diameter. The colour of the recent lesions is pink-yellow, while the older lesions show a red-brown colour. Joint and visceral lesions are absent. Possibly, this purely cutaneous form could represent an early stage of multicentric reticulohistiocytosis, before the appearance of joint or visceral lesions.

The term multicentric reticulohistiocytosis {167,413,465,1405,1752} is used to indicate a form of reticulohistiocytosis characterized by the association of a cutaneous and mucous membrane papulonodular eruption with severe arthropathy and other visceral symptoms. The papulonodular lesions range in diameter from a few mm to 2 cm, and are round, translucent and yellow-rose or yellow-brown in colour. Grouping of lesions into plaques can give a cobblestone appearance, but lesions are mostly scattered and isolated. They do not tend to ulcerate, and are pruritic in about one-third of cases. Osteoarticular manifestations cause severe chronic polyarthritis with arthralgias, and are the initial sign of the disease in about 5-65% of cases {167, 465,1405}. The osteoarticular lesions

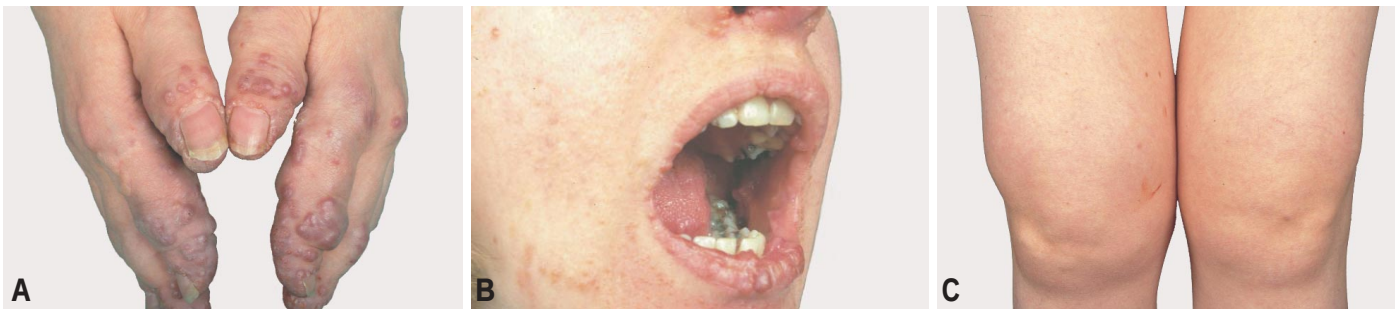


Fig. 4.91 Multicentric reticulohistiocytosis. **A** Purplish-brown, firm nodules characteristically affect the fingers. Periungual papules are arranged about the nail folds. **B** Papulonodular lesions are spread on the face, lips and oral mucosa. Mucous membranes are involved in about 50% of cases. **C** Symmetrical involvement of the knees. In this patient, osteoarticular manifestations were the initial sign of the disease. From: R. Caputo {378}

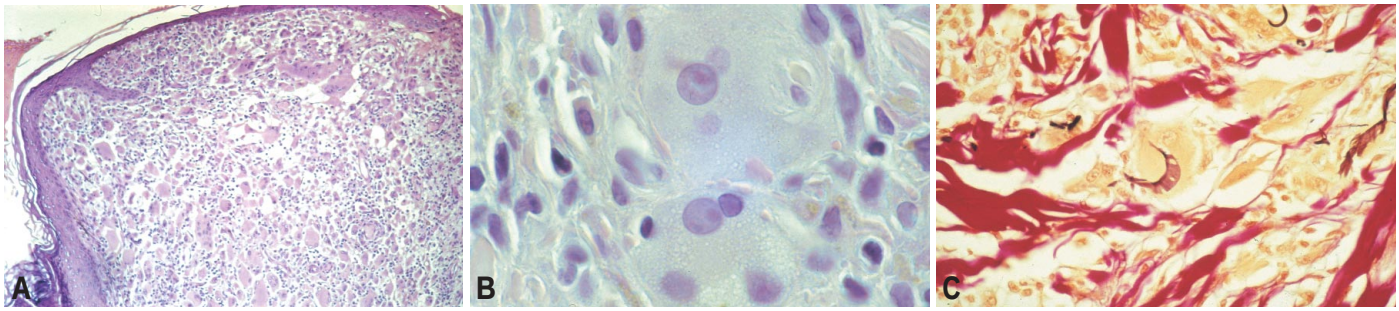


Fig. 4.92 Reticulohistiocytosis. **A** Conventional microscopy: the histological pattern of the lesions is characterized by the presence of numerous, large, mononucleated histiocytes with an abundant eosinophilic, finely granular cytoplasm. **B** Conventional microscopy: in these giant cells showing leukocyte phagocytosis, the typical ground-glass appearance of the cytoplasm is evident. **C** Conventional microscopy: Weigert-Van Gieson staining. Collagen phagocytosis is an occasional finding.

show a progressive destructive course of 6-8 years, and then become stable. Other systemic localizations, histopathologically documented are very rare. Muscular {667} (myositis, myotonia and myoatrophy), cardiopulmonary {532} (pericarditis, cardiac insufficiency, pleuritis, pulmonary infiltration), ocular {667} (exophthalmos, conjunctival infiltration), gastric (gastric ulcer), thyroid (thyroid nodules) and submandibular salivary gland involvements have occasionally been reported. Fever, weight loss and weakness can be present. In MR there is an association with a variety of autoimmune disorders such as dermatomyositis, lupus erythematosus, or Hashimoto thyroiditis as well as internal malignancies in 15-27% of cases {167,413,1405, 1752}. Solid tumours such as bronchial, breast, stomach and cervical carcinomas are most common. Lymphomas and myelodysplastic syndromes have been found less frequently.

Histopathology

The histological findings in the three types of reticulohistiocytosis and in the different tissues are identical {167,465, 1405,1462}. Early lesions are composed of macrophages and lymphocytes, and therefore may be confused with other histiocytoses of the skin. Older lesions show the characteristic histological pattern: the presence of numerous large, mononuclear or multinucleated macrophages with an abundance of eosinophilic, homogeneous to finely granular cytoplasm having a ground glass appearance. At times, phagocytosis of connective tissue and/or cellular components may be seen {379,532}. Histochemically, the granular material in macrophages and giant cells stains with periodic acid-Schiff, Sudan black and scarlet red, indicating the presence of glycolipids and/or glycoproteins and neutral fat {167}.

Immunohistochemistry

Macrophages stain with macrophage markers KP1/PGM1 (CD68), Ki-M1p, and for the mesenchymal epitope of vimentin, and show variable reactivity with HAM56 and for factor XIIIa, lysozyme and α1-antitrypsin {381,382,424,2027,2585}. In contrast, these cells are usually negative for CD1α, S100 protein, Leu-M1 (CD15) and MAC387. Rare exceptions have been reported. According to Zelger et al. {2585}, SCR differs histopathologically and immunohistochemically from MR as lesions are better circumscribed, multinucleated giant cells more prominent, gigantic and bizarre, and macrophages regularly negative for factor XIIIa in the former entity.

Electron microscopy

The infiltrate is formed by large mononuclear to multinucleated cells exhibiting numerous peripheral villi {532,667}. Nuclei are irregular and often polylobated, with nucleoplasm of medium electron density and one or two nucleoli. The cytoplasm contains one or more Golgi apparatus, and is rich in mitochondria, lysosomes, dense bodies, phagosomes and myelin figures. The cytoplasm of about 5-40% of the cells of the infiltrate in many cases contains the so-called pleomorphic cytoplasmic inclusions {380-382,532}, varying in number from cell to cell. The pleomorphic cytoplasmic inclusions are unique and highly complex structures consisting mainly of unit membranes, occasionally surrounding electron-dense areas containing vesicles. Birbeck granules are absent. About 20% of all macrophages show collagenophagic activity {379,766}, but not pleomorphic cytoplasmic inclusions.

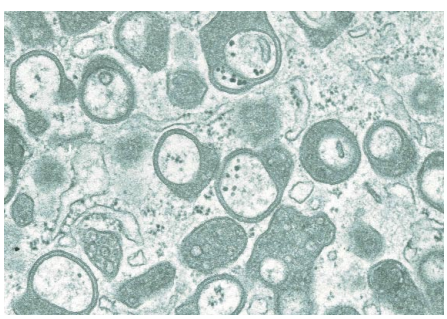


Fig. 4.93 Reticulohistiocytosis. Electron microscopy: the polymorphism of the granules is evident at higher magnification.

Prognosis and predictive factors

The purely cutaneous forms of reticulohistiocytosis (solitary and generalized) may involute spontaneously {382,847}. It is possible that the generalized purely cutaneous form is an early stage of MR, before the appearance of joint and visceral lesions {381,847}, In MR, there is no parallelism between the mucocutaneous and articular manifestations. The mucocutaneous lesions have an unpredictable course, and may remit spontaneously. In half of the patients, the osteoarticular manifestations become stable, while in the other half, they show a progressive destructive course {1405}. The prognosis is favourable for the cutaneous forms. The prognosis of MR is related to the importance of the osteoarticular manifestations and of the underlying immunologic disorders and neoplasms.

Mastocytosis

B.J. Longley
B.M. Henz

Definition

Mastocytosis is a heterogeneous group of disorders characterized by the abnormal growth and accumulation of a clone of mast cells in one or more organ system {1448}. Most patients have cutaneous mastocytosis (CM) with indolent disease that is confined to the skin and that may regress spontaneously.

A minority of patients, usually adults, have systemic mastocytosis (SM) that may rarely be highly aggressive and associated with multi-system involvement and short survival time, or that may be associated with non-mast-cell haematopoietic malignancies {1450, 2372,2405}.

ICD-O Codes

Cutaneous mastocytosis (CM); maculopapular or plaque type mastocytosis, formerly urticaria pigmentosa (UP); telangiectatic mastocytosis, formerly telangiectasia macularis eruptiva perstans (TMEP); diffuse cutaneous mastocytosis (DCL); solitary mastocytoma {965,2405} 9740/1
Indolent systemic mastocytosis 9741/1
Aggressive systemic mastocytosis 9741/3
Mastocytosis with associated haematopoietic disorder 9741/3
Mast cell leukaemia 9742/3

Synonyms

Mast cell disease; mast cell proliferative disease

Epidemiology

Cutaneous mastocytosis may be present at birth and usually first appears before six months of age. A second peak incidence is found in young adults in their 3rd and 4th decades. Paediatric mastocytosis usually regresses by adolescence. Adult mastocytosis is more likely to be persistent and may be associated with SM, rarely also with aggressive systemic mastocytosis. There is no clear gender or ethnic predominance of cases {964,1450}.

Etiology

The KIT protein is a receptor tyrosine kinase that is also known as the mast cell growth factor receptor. Adult mastocytosis and rare pediatric cases are associated with somatic mutations in the c-KIT proto-oncogene that alter the enzymatic site of the KIT protein {361,1449}. Rare kindreds with familial mastocytosis have germ line c-KIT mutations that affect regulatory portions of the KIT protein, also causing constitutive kinase activation. These patients may also have gastrointestinal stromal tumours (GISTs) which are known to be caused by regulatory type c-KIT activating mutations {189,

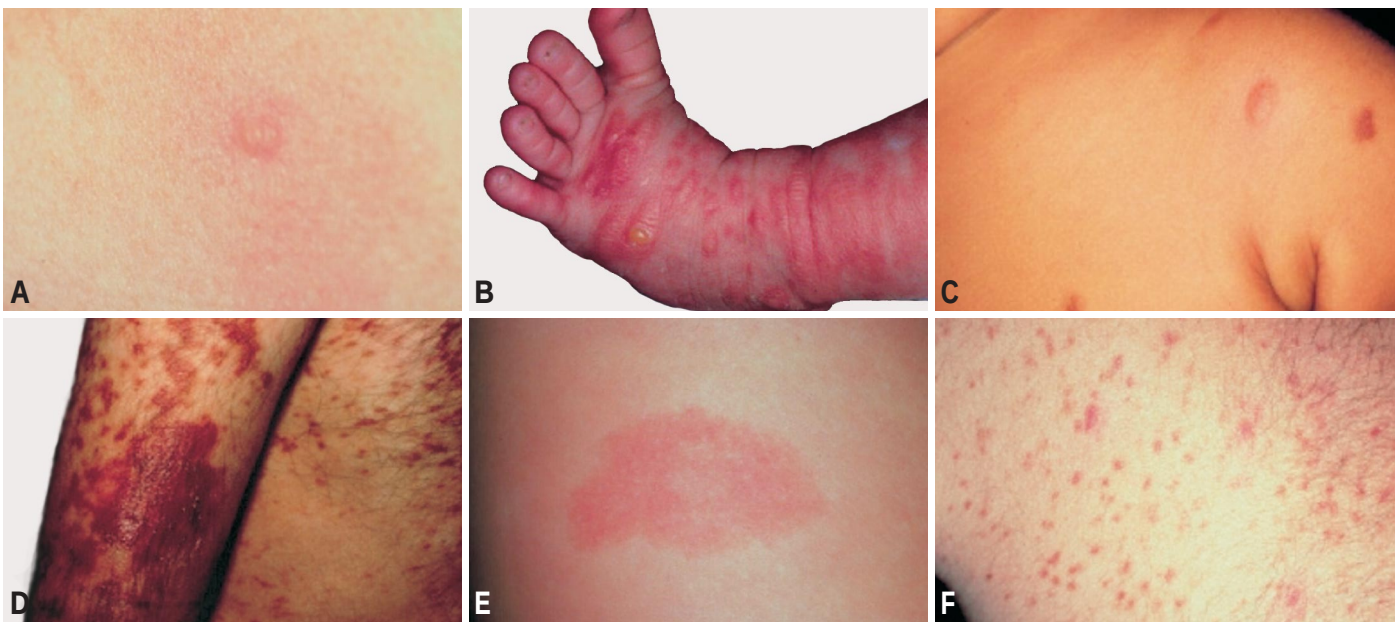


Fig. 4.94 Cutaneous mastocytosis. **A** Wheal and flare of Darier sign. The skin lesions of all forms of cutaneous mastocytosis may urticate when stroked. A palpable wheal appears a few moments after physical stimulation, due to histamine from the mast cells. **B** Tense blister containing clear fluid on skin of infant with diffuse cutaneous mastocytosis. The skin may appear thickened and reddish brown with diffuse involvement. Note the blister caused by mast cell degranulation and histamine release. Blisters may form in infants because the dermal-epidermal junction is not yet well developed. **C** Large pigmented papules of paediatric urticaria pigmentosa. **D** Reddish brown macules, patches and plaques on abdomen and arm of an adult with cutaneous and systemic mastocytosis. **E** Telangiectasia macularis eruptiva perstans form of cutaneous mastocytosis in an adult. **F** Pigmented macules of adult type urticaria pigmentosa. The number of lesions may range from a few to thousands.

1447}. In skin and bone marrow mast cells, there is also an increased expression of anti-apoptotic molecules in both paediatric and adult mastocytosis {963, 966}.

Localization

Eighty percent of patients with mastocytosis have disease confined to the skin. Conversely, of the 20% of patients with systemic mastocytosis, about half have cutaneous involvement. Essentially all patients with SM are adults and have involvement of the bone marrow, but any other organ may also be involved, most commonly the spleen, lymph nodes, or gastrointestinal tract {116,580,2224, 2372}.

Clinical features

Cutaneous mastocytosis includes several distinct clinico-pathologic entities whose morphologies include solitary tumours (Mastocytoma), maculo-papular or plaque-type lesions that are mostly symmetrically distributed (UP/TMEP), and diffuse cutaneous involvement (DCM).

Stroking of any lesion of CM may cause mast cell degranulation with localized swelling or urtication (Darier sign). Clinically normal skin may also urticate when stroked, (so-called dermographism). Moderate itching is present in about half of the patients {579}. Most cutaneous lesions show an increase in epidermal melanin pigment which, combined with the tendency of these lesions to urticate, has led to the term “urticaria pigmentosa”, a historic designation that has recently been proposed to be abandoned {2405}. Blistering or bullous mastocytosis is not a distinct entity but represents an exaggeration of Darier sign seen in infants whose dermo-epidermal junction is not well developed so that accumulation of edema fluid results in the formation of localized blisters {964}.

Other symptoms of mastocytosis may be due to mast cell infiltration of specific organs or due to release of mast cell mediators into the circulation. Organs affected include: the gastrointestinal tract (peptic ulcer disease, diarrhoea and cramping) or the cardio-pulmonary and cardio-vascular systems (flushing, syncope, headache, seizures, hypertension, hypotension including anaphylaxis, tachycardia, and respiratory symptoms). Patients with extensive involvement may have relatively vague constitutional symptoms including fatigue, weight loss, fever, sweats, and non-specific psychiatric symptoms {964,1450}.

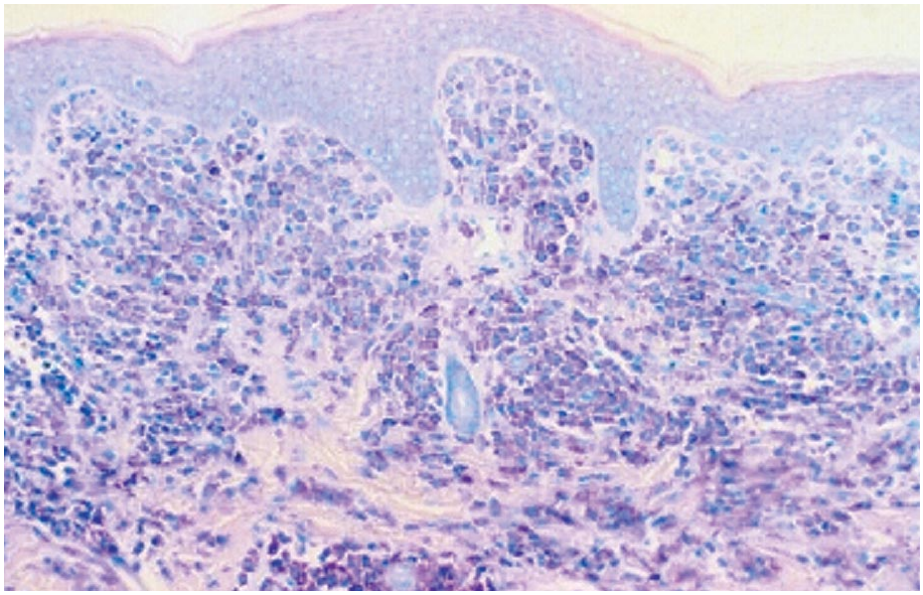


Fig. 4.95 Mastocytoma of the skin. Stains containing toluidine blue stain the mast cell cytoplasmic granules metachromatically purple.

Patients with SM may have also bone-related complaints such as pain, fractures, or arthralgias, secondary to direct mass effects or generalized osteoporosis.

The diagnosis of cutaneous mastocytosis is established by skin biopsy that demonstrates increased numbers of mast cells in the dermis. Imaging studies or biopsy of bone marrow or other internal organs are usually not indicated in the absence of abnormality of the peripheral blood counts or specific signs or symptoms pointing to internal organ involvement.

The clinical presentation of CM may range from subtle diffuse erythema to grossly evident, widespread doughy dermal thickening with accentuation of cutaneous surface markings, giving a so-called “grain leather”, (peau chagrine) or orange skin (peau d’orange) appearance {964,1449,1450,2430,2525}. Tense blisters filled with clear fluid, occasionally slightly-tinged with blood, may be seen overlying lesions of any form of cutaneous mastocytosis in infants.

Individual lesions in young children tend to be lightly pigmented and occur as solitary nodules or multiple papules, or rarely as large heavily pigmented macules, large plaques, or diffuse infiltration of the skin {964}. Large lesions or diffuse involvement in children may point to the presence of c-KIT activating mutations {2405}. In adolescents and adults, the individual lesions tend to be more heavily pigmented and macular, rather than papular, like those of young children. The term TMEP has been used for these macular lesions and for larger, lightly pigmented patches with telangiectasias that may rarely occur in adults {964}. Cutaneous involvement in SM usually appears morphologically identical to CM in adults, but may also show larger plaque like lesions.

Histopathology

In haematoxylin and eosin (H&E) stained sections, normal mast cells have moderately abundant, oval or polygonal shaped cytoplasms with round to oval nuclei, sometimes giving the appearance of a “fried egg”. The nuclei have clumped chromatin and indistinct or inapparent nucleoli. The cytoplasms are filled with small, faintly visible, eosinophilic or amphiphilic granules which stain metachromatically with the Giemsa or toluidine blue stains. Occasionally, mast cells may be spindle shaped or show bi- or multi-lobated nuclei {1401,1450,1607, 2405}.

In normal skin, individual mast cells are found perivascularly and scattered throughout the dermis, without formation of clusters. Mast cells in mastocytosis also tend to accumulate perivascularly, and are most often evident in the super-

ficial dermis, within the dermal papillae {1401,1607}. In solitary mastocytomas and papular, nodular, or diffuse CM, the papillary and/or reticular dermis may show either scanty increases in mast cell numbers or heavy mast cell infiltrates, and there may be extension into the subcutaneous fat. In CM, individual mast cells may rarely be found in the lower epidermis. Unequivocal diagnosis of cutaneous mastocytosis requires the demonstration of aggregates of mast cells within the dermis, and this may be difficult and require multiple biopsies in the TMEP form of adult mastocytosis. Lesions of mastocytosis are usually composed of an infiltrate of monomorphous mast cells, and rarely observed infiltrating eosinophils should raise the possibility of dermal hypersensitivity reaction, parasitosis or an arthropod bite.

Immunohistochemistry

Mast cells are bone-marrow derived cells and therefore express CD45 (CLA). They also express CD117 (the KIT protein) and HLA-DR. Relatively specific mast cell markers include highly sulfated glycosaminoglycans like heparin (toluidine blue stain), tryptase and chymase. CD-2 and/or CD25 may be aberrantly expressed in mast cells of SM {934, 2404, 2405}.

Histogenesis

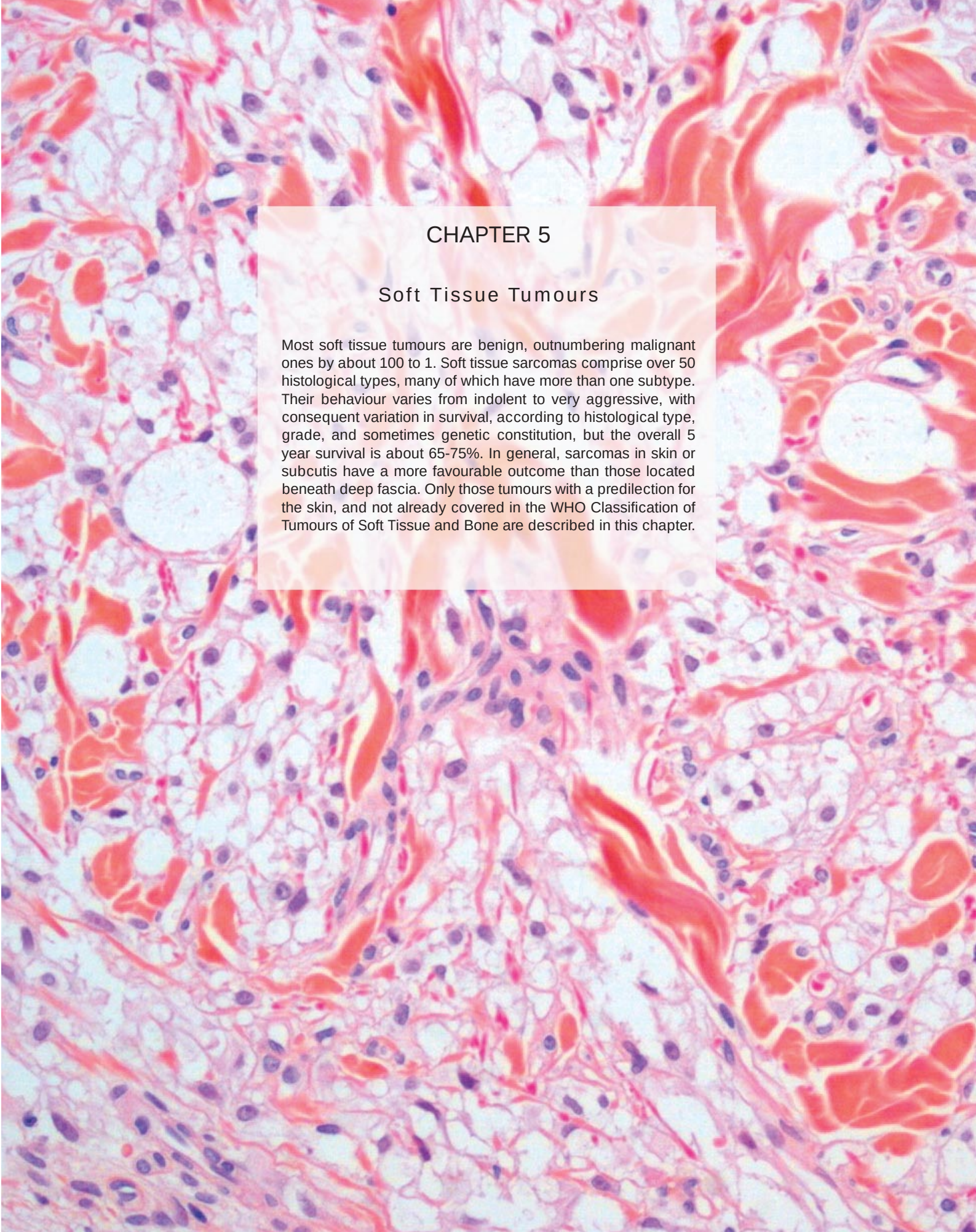
Mast cells are derived from CD34+ haematopoetic precursor cells {1982}.

Somatic genetics

Mastocytosis is a clonal disease in both adults and children {1448,1449}. The tumour cells of almost all cases of adult onset sporadic disease carry somatic point mutations of c-KIT that change the enzymatic site of the KIT protein, causing constitutive activation {361,1449}. Paediatric sporadic mastocytosis has also been shown to be clonal, but c-KIT activating mutations are rare {361,1449}. Very rare cases of familial mastocytosis, usually associated with GISTs tumours, are associated with germ line c-KIT mutations that activate KIT by affecting regulatory portions of the molecule, rather than the enzymatic site {189, 1447}.

Prognosis and predictive factors

Patients with mastocytosis confined to the skin generally have a good prognosis, and cutaneous involvement is usually an indicator of a relatively better prognosis in SM. CM in paediatric patients with solitary mastocytomas or typical papular and macular rashes usually regresses by adolescence. The presence of enzymatic site type KIT activating mutations may indicate persistent disease in this population, and classification of mastocytosis based on both clinical and molecular genetic features may eventually prove to be both prognostically and therapeutically useful {1446, 1465}. In adults, although CM may be symptomatic and persist, overall survival is usually not adversely affected, even in the face of concomitant systemic involvement. Patients having aggressive variants of SM, however, may have a rapidly progressive downhill course with survival measured in months. In patients with associated haematologic malignancies, the prognosis is determined by the course of the related haematologic disease {964}.



CHAPTER 5

Soft Tissue Tumours

Most soft tissue tumours are benign, outnumbering malignant ones by about 100 to 1. Soft tissue sarcomas comprise over 50 histological types, many of which have more than one subtype. Their behaviour varies from indolent to very aggressive, with consequent variation in survival, according to histological type, grade, and sometimes genetic constitution, but the overall 5 year survival is about 65-75%. In general, sarcomas in skin or subcutis have a more favourable outcome than those located beneath deep fascia. Only those tumours with a predilection for the skin, and not already covered in the WHO Classification of Tumours of Soft Tissue and Bone are described in this chapter.

WHO histological classification of soft tissue tumours

Vascular tumour	
Haemangioma of infancy	9131/0
Cherry haemangioma	9120/0
Sinusoidal haemangioma	9120/0
Hobnail haemangioma	9120/0
Glomeruloid haemangioma	9120/0
Microvenular haemangioma	9120/0
Angiolymphoid hyperplasia with eosinophilia	
Spindle cell haemangioma	9136/0
Tufted angioma	9161/0
Arteriovenous haemangioma	9123/0
Cutaneous angiosarcoma	9120/3
Lymphatic tumours	
Lymphangioma circumscriptum	9170/0
Progressive lymphangioma	9170/0
Smooth and skeletal muscle tumours	
Pilar leiomyoma	8890/0
Cutaneous leiomyosarcoma	8890/3
Fibrous, fibrohistiocytic and histiocytic tumours	
Dermatomyofibroma	8824/0
Infantile myofibromatosis	8824/1
Sclerotic fibroma	8823/0
Pleomorphic fibroma	8832/0
Giant cell fibroblastoma	8834/1
Dermatofibrosarcoma protuberans	8832/3
Dermatofibroma (fibrous histiocytoma)	8832/0

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of soft tissue sarcomas

Primary Tumour (T)

TX:	Primary tumour cannot be assessed
T0:	No evidence of primary tumour
T1:	Tumour ≤ 5cm in greatest dimension
	T1a: superficial tumour*
	T1b: deep tumour
T2:	Tumour > 5cm in greatest dimension
	T2a: superficial tumour
	T2b: deep tumour

Regional lymph nodes (N)

NX:	regional lymph nodes cannot be assessed
N0:	no regional lymph node metastasis
N1:	regional lymph node metastasis

Notes: Regional node involvement is rare and cases in which nodal status is not assessed either clinically or pathologically could be considered NO instead of NX or pNX.

Distant metastasis (M)

M0:	no distant metastasis
M1:	distant metastasis

G Histopathological Grading

Translation table for three and four grade to two grade (low vs. high grade) system

TNM two grade system	Three grade systems	Four grade systems
Low Grade	Grade 1	Grade 1
		Grade 2
High Grade	Grade 2	Grade 3
	Grade 3	Grade 4

Stage grouping

Stage IA	T1a	NO,NX	MO	Low grade
	T1b	NO,NX	MO	Low grade
Stage IB	T2a	NO,NX	MO	Low grade
	T2b	NO,NX	MO	Low grade
Stage IIA	T1a	NO,NX	MO	High grade
	T1b	NO,NX	MO	High grade
Stage IIB	T2a	NO,NX	MO	High grade
Stage III	T2b	NO,NX	MO	High grade
Stage IV	Any T	N1	MO	Any grade
	Any T	Any T	M1	Any grade

From references {892,2219}.
Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the supeficial fascia, or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are classified as deep tumours.

Soft tissue tumours: Introduction

C. Fisher

Epidemiology

Age-standardized incidence rates of soft tissue sarcomas, which are fairly constant in most areas covered by cancer registration, range from 1-3 per hundred thousand population {1781}. Sarcomas of cutaneous origin are relatively rare, and are far outnumbered by carcinomas, melanoma and benign mesenchymal neoplasms of skin and subcutis (superficial soft tissue). The most common benign tumours are lipomas, fibrous histiocytomas, vascular or smooth muscle lesions including angioleiomyomas, and nerve sheath tumours (schwannoma, neurofibroma). Some of these tumours are covered elsewhere {756}. The vast majority are located superficially and do not exceed 5 cm in diameter.

Sarcomas are mostly found in older adults. They arise mainly in the extremities, especially the thigh, followed by trunk, head and neck and retroperitoneum.

Etiology

Most soft tissue sarcomas arise spontaneously and are of unknown etiology. A small number arise in rare familial cancer syndromes with germline mutations. A number of other congenital and inherited syndromes are associated with benign and malignant soft tissue tumours; type examples include Mafucci syndrome (chondroid and vascular tumours) and Cowden disease (lipomas, haemangiomas). Further details can be found in the WHO Classification of Tumours of Soft Tissue and Bone {756}.

Non-hereditary genetic factors are also presumed to be pathogenetic in various tumour types which have consistent chromosomal translocations, although it is not known how or in what cell these rearrangements arise. Viruses associated with sarcomas include human herpes virus 8 (HHV8) in Kaposi sarcoma {434,2487}, and EBV in some smooth muscle tumours in children and adults with immunosuppression, including transplant recipients and patients with HIV infection {1390,1547}. Angiosarcoma complicating longstanding lymphoedema, especially after radical mastectomy (Stewart-Treves) might also be due to local immunosuppression {1995}.

An association between exposure to herbicides, including dioxin, and sarcomagenesis is controversial and remains unproven. Sarcomas can arise in the field of prior therapeutic irradiation. This is a dose- and time-related phenomenon, resulting mostly in subfascial, high-grade pleomorphic sarcomas after an interval of 5 or more years. Following irradiation for carcinoma of breast, low-grade cutaneous angiosarcomas have been described after an interval as short as 18 months {1772}.

Clinical features

Benign and malignant tumours present as usually painless masses, with varying growth rate. Cutaneous lesions form a plaque or elevated nodule that can ulcerate when malignant. Large (>5 cm) superficial lesions, and all subfascial or deep-seated tumours, should be referred to a specialist multidisciplinary centre before surgery and preferably before biopsy {180}.

Pathology

In general, malignant soft tissue neoplasms are characterized by nuclear pleomorphism, mitotic activity including abnormal forms, necrosis and vascular invasion. Some benign tumours, however, can show one or more of these features. Examples include nuclear atypia in cutaneous pleomorphic fibroma and atypical benign fibrous histiocytoma (which can also display necrosis), and frequent mitoses in nodular fasciitis. Detailed diagnostic criteria are provided for each subtype.

Diagnostic procedures

Investigation includes clinical assessment of size and depth of tumour, the use of imaging modalities, and biopsy.

Imaging

Imaging is of value for assessing the extent of a primary tumour and its relationship to normal structures, and for revealing metastases. Both computerized tomography (CT) and magnetic resonance imaging (MRI) are used. CT is particularly useful for tumours in body cavities, and for detecting pulmonary metastases. MRI can demonstrate intratumoural heterogeneity, including presence of solid, fatty, fibrous, haemorrhagic or necrotic tissue, and the interface between neoplastic and normal tissue including involvement of neurovascular bundles.

Biopsy

Superficial lesions smaller than 2-5 cm in diameter can be excised in their entirety. Larger ones, and all subfascial and deep-seated tumours need diagnostic sampling. For this, some practitioners prefer open incisional biopsy with an appropriately placed incision that is subsequently excised in continuity with the formal resection. Needle core biopsy, preferably using a Trucut or larger needle can provide diagnostic information for malignancy, subtype and grade, with high sensitivity and specificity in experienced hands {1021,1040}. Fine-needle aspiration cytology is used in a few centres where a large volume of cases allows accrual of sufficient experience {46}; it is not particularly sensitive for diagnosing malignancy in differentiated adipose or in sub-typing low-grade myxoid lesions, partly because the sample might not be representative.

Tumour spread and staging

The recent WHO classification of Tumours of Soft Tissue and Bone {756} recognizes three behavioural categories:

1. Benign tumours. These rarely recur locally, and those that recur do so in a non-destructive fashion and are usually cured by local excision. Exceptionally rarely, an otherwise (and histologically typical) benign tumour, such as cutaneous fibrous histiocytoma, can metastasize.
2. Intermediate tumours are those that

are locally aggressive and/or very occasionally metastasizing. Locally aggressive tumours, such as fibromatosis, recur locally and infiltrate surrounding tissues. Rarely-metastasizing tumours are generally dermal or subcutaneous tumours which have a low (1-2%) but definite risk of metastasis, most often to regional lymph nodes but occasionally to lung. Examples are recorded for plexiform fibrohistiocytic tumour {2028} and angiomatoid fibrous histiocytoma {693}.
3. Malignant tumours infiltrate and recur locally and have an appreciable risk of metastasis (exceeding 20%).

Grading

This is an attempt to predict clinical behaviour based on histological variables. Grading of a tumour should be done on material from a primary untreated neoplasm, though change (increase) of grade can be noted in recurrent or metastatic tumour. It is not applicable to all sarcomas; for example, angiosarcoma, clear cell sarcoma and epithelioid sarcoma are always considered to be of high-grade malignancy. Several grading systems have been proposed, but that of the French Cancer Centres is gaining wide usage {917}. Briefly, tumours are given a score of 1,2 or 3 depending on degree of differentiation; 1, 2 or 3 for number of mitoses per 10 hpf (<10, 11-20, or >20); and 0-2 for amount of necrosis (0, <50%, >50%). A total score count of 2 or 3 is classified as grade 1, a score count of 4 or 5 as 2, and a score of 6, 7 or 8 as grade 3.

Staging

A widely used staging system for soft tissue sarcomas is that of the International Union against Cancer (UICC) (TNM system) and American Joint Commission on Cancer (AJCC) {892,2219}. Unlike for many other tumours, staging of sarcomas includes histological grading as well as tumour size and depth from surface, regional lymph node involvement and distant metastasis.

Prognosis and predictive factors

Completeness of excision (assessed by clear surgical margins in the excision specimen) is the most important factor in prevention of local recurrence {2376}. Some sarcomas, notably epithelioid sarcoma, are relentlessly recurrent, even though they might not metastasize until late in the course of the disease {2238}. For metastasis, general adverse factors are large tumour size and increasing depth from surface. Thus, cutaneous sarcomas have a lower risk of metastasis than those located more deeply {2001}; indeed, histologically malignant leiomyosarcomas confined to skin are essentially non-metastasizing tumours {1164}. In some instances, histological subtype is predictive, but one of the principal factors in assessing prognosis and determining management is the histological grade. Low-grade sarcomas, however, when located in sites where complete surgical excision is difficult, such as retroperitoneum or head and neck, have a worse outcome than similar tumours in the extremities. Molecular genetic findings, especially fusion gene types, might relate to prognosis.

Vascular tumours

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Haemangioma of infancy

Definition
Haemangioma of infancy (HOI) is a proliferation of benign capillaries characterized by perinatal or congenital onset, rapid proliferation in the first year, followed by spontaneous regression. Strong expression of GLUT1 is distinctive.

ICD-O code 9131/0

Synonyms
Infantile haemangioma, juvenile haemangioma.

Epidemiology
HOI is the most common tumour of infancy, affecting up to 10-12% of children {1051,1119}. There is a predilection for females (at least 3:1) {1663}, Caucasians and premature infants {1051,1853}. Presentation is exclusively in infants, although involuting lesions persist into childhood.

Etiology
The unique immunophenotypic resemblance of HOI and placental vessels suggests shared regulatory mechanisms, or possibly a common cellular origin {1723}. Two recent studies have demonstrated endothelial cell clonality in HOI {295,2452}, suggesting a possible role for somatic mutation {2452}.

Localization
It most commonly affects the skin and subcutis of the head and neck, followed by the trunk and extremities. Visceral involvement, although rare, is most common in the liver, followed by the lung, brain, and intestine {746}.

Clinical features
Nascent lesions appear as blanched macules or erythematous patches, often with central telangiectasias, typically around 2 weeks of age. Approximately 30% are congenital. Following a rapid growth phase of 3-18 months, involution occurs over several years, often leaving a fibrofatty residuum. Most develop as focal masses, although some show a diffuse, segmentally distributed pattern {2453}. Although usually solitary, many affected infants have several lesions. Rare cases of "diffuse neonatal haemangiomatosis" have multiple small skin lesions accompanied by visceral lesions {1454}. Large facial haemangiomas may be associated with posterior fossa malformations, aortic coarctation, cardiac defects, arterial abnormalities, eye abnormalities, and sternal clefting (PHACES syndrome) {1591}. Lumbosacral haemangiomas may be associated with spinal dysraphism, tethered cord syndrome, and other caudal abnormalities {850}. MRI in the proliferative phase shows a tumoural mass with flow voids.

Macroscopy
Proliferative phase lesions show solid tan lobules, are well-defined but not encapsulated.

Histopathology
Proliferative phase lesions are cellular masses of plump endothelial cells and pericytes with abundant cytoplasm and enlarged nuclei that together form capillaries with tiny rounded lumina. Investing basement membranes are multilaminated; mast cells are numerous. The capillaries are arranged in delicately defined lobules, separated by thin fibrous septi or normal intervening tissue. Mitotic figures may be numerous; supportive arteries and veins are prominent.
During involution, endothelial cells and pericytes flatten, lumina enlarge, and mitotic figures diminish. Capillaries progressively drop out and are replaced by loose connective tissue. End-stage lesions often show isolated groups of "ghost" vessels composed of thick, acellular basement membrane rings containing apoptotic debris.

Immunohistochemistry
All stages are distinguished from other vascular tumours by their strong endothelial positivity for several antigens, including GLUT1, Lewis Y antigen, FcgRII, and IGF-II {1722,1723,1942}. Basement membranes strongly express merosin {1723}.

Differential diagnosis
Proliferative phase HOI must be distinguished from other cellular vascular proliferations including congenital non-progressive haemangioma, kaposiform haemangioendothelioma, tufted angioma, pyogenic granuloma, and intramuscular haemangioma. Involuting HOI may mimic vascular malformations. The characteristic GLUT1 immunoreactivity of HOI is helpful in routinely fixed specimens {1722}.

Somatic genetics
HOI are generally sporadic, although autosomal dominant inheritance has been suggested in several kindreds {259}. Monozygotic and dizygotic twins show no significant difference in concordance for haemangioma development {464}. No cytogenetic abnormalities have been reported.

Cherry haemangioma

Definition
Cherry haemangioma (CH) is a benign, acquired, well-circumscribed aggregate of dilated capillaries and venules in the superficial dermis.

ICD-O code 9120/0

Synonyms
Campbell de Morgan spots, de Morgan spots, senile haemangioma.

Epidemiology
CH is rare before puberty, with a few lesions developing in early adulthood. Number and incidence increase through adulthood, becoming almost universally present with large numbers in some patients. Sex predilection is not a feature, with the exception of lesions that can occur in pregnancy {169}.

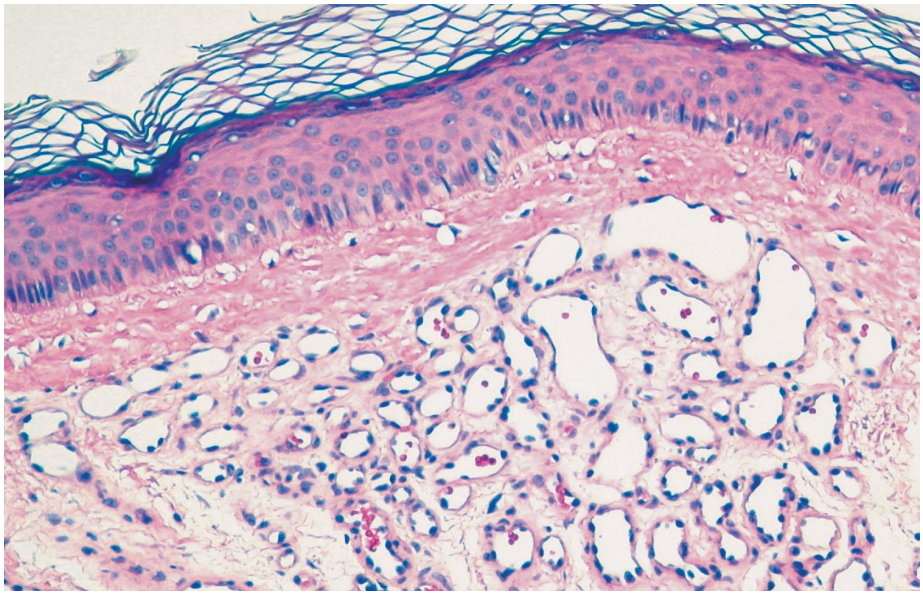

Fig. 5.1 Cherry haemangioma. Thickened basement membrane material around some vessels and protuberant endothelial cells.

Etiology
Age is the most common factor in the development of the majority of lesions. Eruptive cases have been reported after exposure to sulphur, mustard gas, bromide compounds and 2-butoxyethanol solvent {510,747,1901}. There are two reports of outbreaks in populations, without definite causes {1058,2145}. CH lesions that develop in pregnancy can involute in the puerperium and eruptive lesions have been reported in two patients with elevated prolactin levels suggesting a hormonal factor in some lesions {169,1924}.

Localization
The majority of lesions are located on the trunk and upper limbs with relative sparing of the head and neck. There is no predilection for exposed skin.

Clinical features
CH begins as a barely discernible red macule that enlarges to become a slightly elevated erythematous papule 1-5 mm in diameter. It may resist blanching with pressure.

Histopathology
CH is a tightly grouped, well-circumscribed collection of capillary vessels and venules in the superficial dermis with minimal dilatation of some lumena. Elevated lesions show epidermal atrophy with loss of rete ridges and sometimes an epithelial collarette. Endothelial cell nuclei may be protuberant. Sheaths of hyaline multilayered basement membrane material composed of laminin, collagen IV and collagen VI surround most vessels {2317}. Stromal mast cells may be increased compared to normal skin {938}. The endothelial cells are fenestrated and show high levels of carbonic anhydrase {668}. Ki-67 proliferating cell marker is not positive in endothelial cells of CH {2388}.

Histogenesis
Ultrastructural three-dimensional studies show that CH is composed of interconnected spherical and tubular dilatations of venous capillaries and postcapillary venules in the dermal papillae {303}.

Somatic genetics
A genetic or angiogenic factor has not yet been implicated in the development of CH.

Sinusoidal haemangioma

Definition
Sinusoidal haemangioma is a benign vascular neoplasm in which cavernous appearing vascular spaces occur in a well circumscribed, generally small papule or nodule. Most clinicians use the term cavernous haemangioma to refer to much larger and more poorly circumscribed lesions in infants.

ICD-O code 9120/0

Synonym
Cavernous haemangioma (erroneous, in part).

Epidemiology
Most reported cases are in adult women.

Localization
The arms and torso are the most common sites {366}.

Clinical features
Most sinusoidal haemangiomas are freely movable deep dermal or subcutaneous papules or small nodules. When deep, they may be colourless or bluish, but when superficial, they may be red.

Histopathology
Sinusoidal haemangiomas are round or oval and very well circumscribed dermal or subcutaneous neoplasms {366,1680}. They are composed of thin walled vessels with capacious round lumena. The vessels are very closely apposed to one another ("back to back appearance"). Occasional lesions have smooth muscle in their walls. Thrombosis of vascular channels occurs in a proportion of cases. This can lead to intravascular papillary endothelial hyperplasia (a potential stimulant of angiosarcoma in a partial biopsy) and calcification may result {1680}.

Hobnail haemangioma

Definition
Hobnail haemangioma (HH) {389,916, 1584,1896,2052} is a benign vascular proliferation characterized by a wedge-shaped dermal proliferation of irregular vascular channels lined in its superficial portion by endothelial cells with hobnail morphology.

ICD-O code 9120/0

Synonym
Targetoid haemosiderotic haemangioma

Epidemiology
HH is relatively rare and presents mainly in young to middle-aged adults with predilection for males.

Etiology
Trauma may play a role in the formation

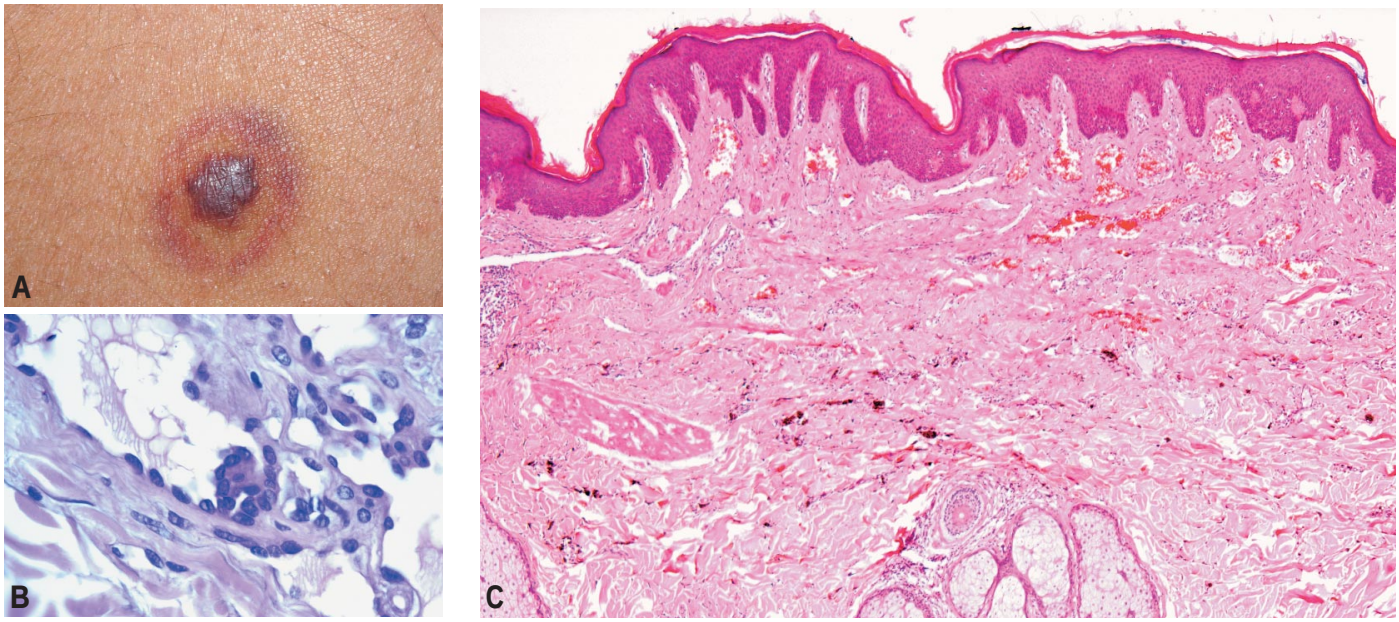

Fig. 5.2 Hobnail haemangioma. **A** Typical targetoid clinical appearance, only seen in a minority of cases. **B** Intravascular papillae lined by hobnail endothelial cells are sometimes seen. **C** Dilated irregular superficial vascular spaces and prominent haemosiderin deposition.

of these lesions {2052}. One possible origin is via trauma to lymphangiomas or angiokeratomas, resulting in dispersion of endothelial cells and erythrocytes into the surrounding dermis.

Localization
Most cases occur on the lower limbs with predilection for the thigh followed by the upper extremities and the trunk. Rare lesions have been reported in the oral cavity including the tongue and gingivae.

Clinical features
Some lesions show a characteristic targetoid clinical appearance with variably pigmented ecchymotic haloes secondary to bleeding and haemosiderin deposition within the tumour {2052}. Most often however, the clinical presentation is non-distinctive and the clinical differential diagnosis includes haemangioma, naevus or fibrous histiocytoma. HH is asymptomatic, usually less than 2 cm in diameter and increases in size very slowly. Patients usually describe cyclic changes {389}. Multiple lesions are exceptional. Similar histological changes may occur after trauma {481}.

Histopathology
The most striking low-power feature is the presence of a wedge-shaped vascular proliferation consisting of superficial, dilated and thin-walled vascular channels lined by bland endothelial cells that appear flat or have hobnail morphology. Some of the vascular channels resemble lymphatics. Focally, intraluminal small papillary projections with collagenous cores are occasionally seen. As the vascular channels descend further into the reticular dermis they gradually become smaller and disappear. Inflammation is not usually a feature. Haemorrhage and haemosiderin deposition are prominent but vary according to the stage of evolution. A Perls stain may be useful in highlighting the haemosiderin.

Immunohistochemistry
The endothelial cells in HH stain diffusely for vascular markers including CD31 and VWF (von Willebrand factor). CD34 is usually negative or very focal. A layer of alpha-smooth muscle actin pericytes surrounds some of the vascular channels. The positive staining for vascular endothelial growth factor receptor-3 (VEGFR-3) in some cases has led to the suggestion that HH displays lymphatic differentiation {1584}. VEGFR-3 is however, not entirely specific for lymphatic endothelium. Staining for human herpes virus 8 is consistently negative {932}.

Differential diagnosis
Kaposi sarcoma differs by the absence of dilated blood vessels lined by hobnail cells.

Prognosis
The lesion is entirely benign and there is no tendency for local recurrence.

Glomeruloid haemangioma

Definition
Glomeruloid haemangioma is a benign vascular proliferation that occurs inside ectatic blood vessels, producing a pattern reminiscent of renal glomeruli.

ICD-O code 9120/0

Epidemiology
This is a very rare vascular proliferation that occurs exclusively in patients with POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal paraproteinaemia and Skin lesions), which is associated with multicentric Castleman disease {440,2562}. Multiple haemangiomas occur in 24-44% of all patients with POEMS syndrome, with most being cherry-type haemangiomas, and only some being glomeruloid haemangiomas {1301,2312,2580}. The reported cases of glomeruloid haemangiomas show female predominance, with patients ranging in age from 40-68 years {440,1278,1285,1965,2083,2380,2562}.

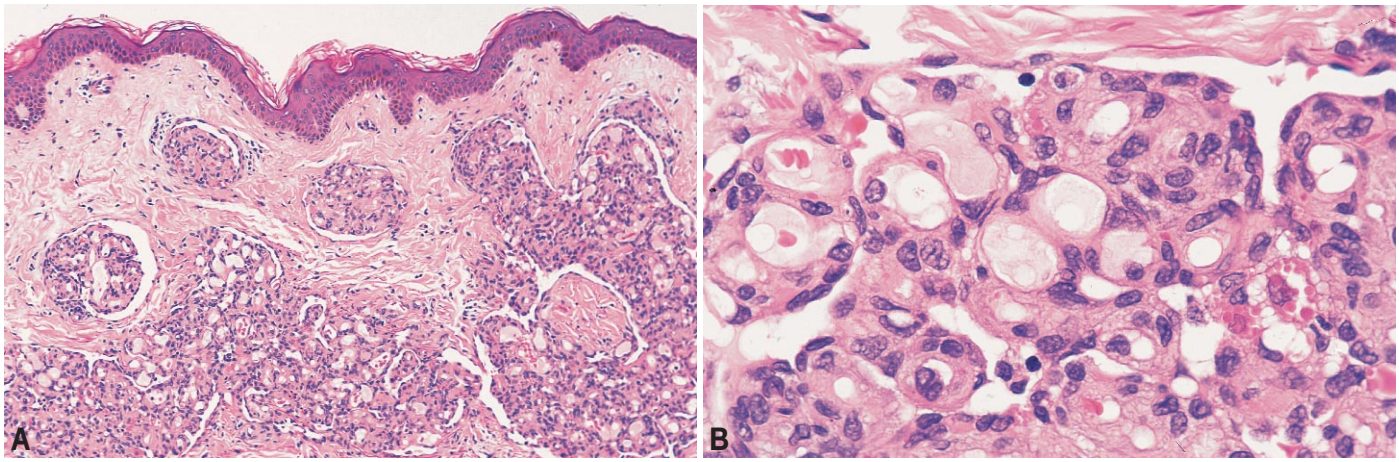

Fig. 5.3 Glomeruloid haemangioma. **A** The dermis shows a vascular proliferation occurring exclusively within thin-walled ectatic vascular spaces, producing a glomerulus-like appearance. **B** The vascular proliferation consists of aggregates of capillaries projecting as a broad tuft into a vascular space. The endothelial cells that line the vascular space and surface of the tuft have dark-staining nuclei ("sinusoidal endothelium"), while those that line the capillaries have plumper and paler nuclei. "Interstitial" cells containing eosinophilic hyaline globules are also seen.

Etiology
Glomeruloid haemangioma has so far only been found in patients with POEMS syndrome. Its development may be mediated by circulating vascular endothelial factor, which is present at high titres in the blood of most patients with POEMS syndrome {2225,2464}.

Localization
The lesions are mainly found on the trunk, face and proximal limb, and exceptionally also in the fingers and deep soft tissues {440,1278,1285, 1965,2380,2562}.

Clinical features
The lesions manifest as multiple purplish-red papules or nodules, ranging in size from a few to 15 mm {1278,1285,1965, 2380,2562}. They occur in patients already known to have POEMS syndrome, or as an early phenomenon before the full-blown syndrome develops {1278,1285,1965,2083,2380,2562}.

Histopathology
Glomeruloid haemangioma is mainly centred in the upper and mid dermis. It is characterized by tufts of proliferated, coiled capillaries projecting inside thin-walled ectatic blood vessels, mimicking renal glomeruli. The "sinusoidal" endothelial cells that line the ectatic vascular spaces and the surface the vascular tufts possess dark round nuclei. These cells also show cleft-like extensions into the cores of the vascular tufts. The capillary loops within the tufts are lined by plump endothelium with slightly larger and paler nuclei, and supported by pericytes. Scattered "interstitial" cells that contain PAS-positive eosinophilic globules are found between the capillary loops, but similar cytoplasmic globules can also be seen in some endothelial cells.

Immunohistochemistry
On immunohistochemical staining, the endothelial cells of the capillary loops stain for CD31 and CD34, and they are well supported by actin-positive pericytes. The sinusoidal endothelial cells covering the tufts are positive for CD31 but not CD34, while those lining the ectatic vascular spaces are strongly CD31 positive but weakly CD34 positive. The eosinophilic globules probably represent immunoglobulin. The cells that contain these globules represent a mixture of histiocytes (CD68+) and endothelial cells (CD31+).

Precursor lesions
Progression from cellular immature, nonspecific, vascular proliferation with slit-like canals reminiscent of tufted angioma to classical glomeruloid haemangioma has been reported {2562}. In addition, cherry-type haemangiomas with miniature glomeruloid structures formation can coexist with glomeruloid haemangiomas in patients with POEMS syndrome {440}. Thus these might represent precursor lesions of glomeruloid haemangioma.

Histogenesis
The currently favoured view is that glomeruloid haemangioma is a reactive vascular proliferation, perhaps representing a distinctive form of reactive angioendotheliomatosis.

Prognosis and predictive factors
Glomeruloid haemangioma per se is a totally innocuous lesion. The outcome of the patients depends on the underlying POEMS syndrome.

Microvenular haemangioma

Definition
Microvenular haemangioma is an acquired, slowly growing asymptomatic lesion with an angiomatous appearance {1080}.

ICD-O code 9120/0

Etiology
A histogenetic relationship between microvenular haemangioma and hormonal factors such as pregnancy and hormonal contraceptives has been postulated {144,2065}, but this feature has not been corroborated by other authors. An example of microvenular haemangioma has developed in a patient with Wiskott-Aldrich syndrome {1939}. Haemangiomas identical to microvenular haemangioma can be seen in patients with POEMS syndrome {25}.

Localization
It most commonly affects the upper limbs, particularly the forearms.

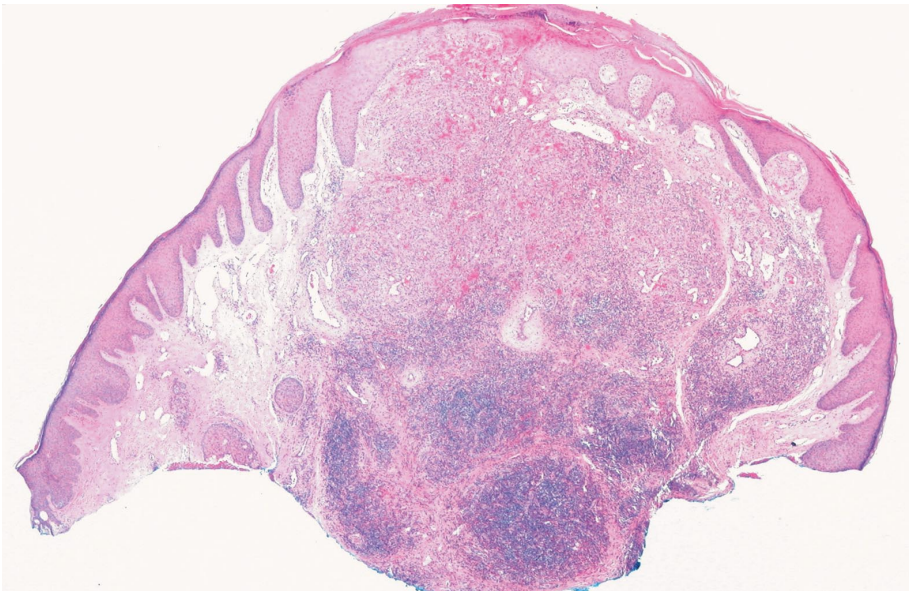

Fig. 5.4 Angiolymphoid hyperplasia with eosinophilia. Lobulated proliferation of small to medium size blood vessels with admixed inflammation and a central prominent vessel.

However, lesions on the trunk, face and lower limbs have also been recorded {65,1061}.

Clinical features

Microvenular haemangiomas appear as sharply circumscribed, bright red, solitary lesions varying in size from 0.5-2 cm.

Histopathology

Microvenular haemangioma appears as a poorly circumscribed proliferation of irregularly branched, round to oval, thin-walled blood vessels lined by a single layer of endothelial cells. They involve the entire reticular dermis and a variable degree of dermal sclerosis is present in the stroma. The lumina of the neoplastic blood vessels are inconspicuous and often collapsed with only a few erythrocytes within them.

The main differential diagnosis is with Kaposi sarcoma in the patch stage. Kaposi sarcoma shows irregular anastomosing vascular spaces, newly formed ectatic vascular channels surrounding pre-existing normal blood vessels and adnexa (promontory sign), plasma cells, hyaline (eosinophilic) globules, and small interstitial fascicles of spindle cells. All of these features are absent in microvenular haemangioma.

Immunohistochemistry

Immunohistochemically, the cells lining the lumina show positivity for factor VIII-related antigen and Ulex europaeus I lectin {144,1080,2065} which qualifies them as endothelial cells. Some smooth muscle actin positive perithelial cells have been also described surrounding this vascular space {65,1061}.

Prognosis

Microvenular haemangioma is a benign neoplasm and it is cured by simple excision.

Angiolymphoid hyperplasia with eosinophilia

Definition

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a benign skin or subcutaneous tumour that is a circumscribed combined proliferation of immature blood vessels and chronic inflammatory infiltrate usually containing eosinophils. Endothelial cells have a distinctive epithelioid or histiocytoid appearance with ample eosinophilic cytoplasm.

Synonyms

Epithelioid haemangioma, cutaneous histiocytoid angioma, pseudo- or atypical pyogenic granuloma, inflammatory angiomatous nodule, intravenous atypical vascular proliferation, nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis {201,1154, 1967,1968,2381}.

Epidemiology

ALHE was originally described as a lesion commonly found in young women on the head and neck {1011}. Recent reviews show a wide age range peaking at 20-50 years without female predominance {738,1753}. There is no predilection for Asian populations.

Etiology

Reactive vascular proliferation and inflammation {2441} in a traumatized vascular structure is a postulated cause of some ALHE lesions. History of antecedent trauma, histologic evidence of

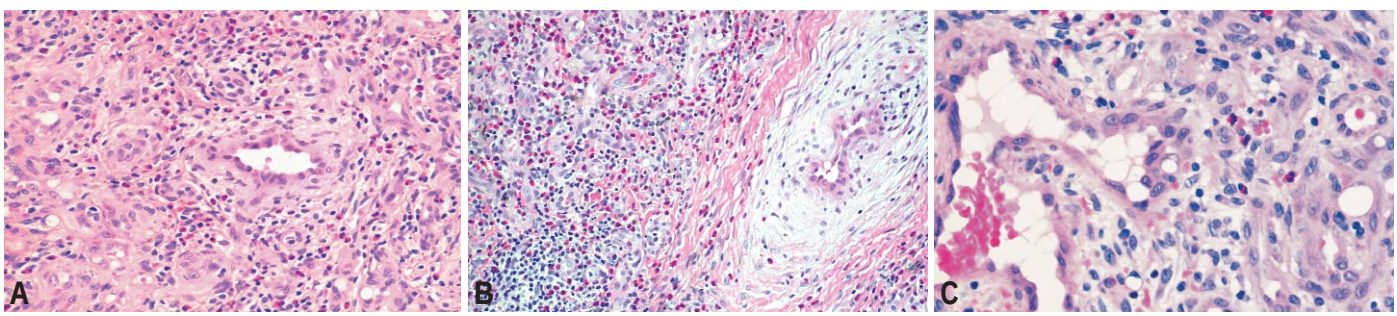

Fig. 5.5 Angiolymphoid hyperplasia with eosinophilia. **A** Epithelioid endothelial cells with abundant cytoplasms, some of which are vacuolated. **B** Proliferating immature vessels with protuberant endothelial nuclei associated with lymphoid and eosinophilic inflammation. **C** Epithelioid endothelial cells with abundant cytoplasms, some of which are vacuolated.

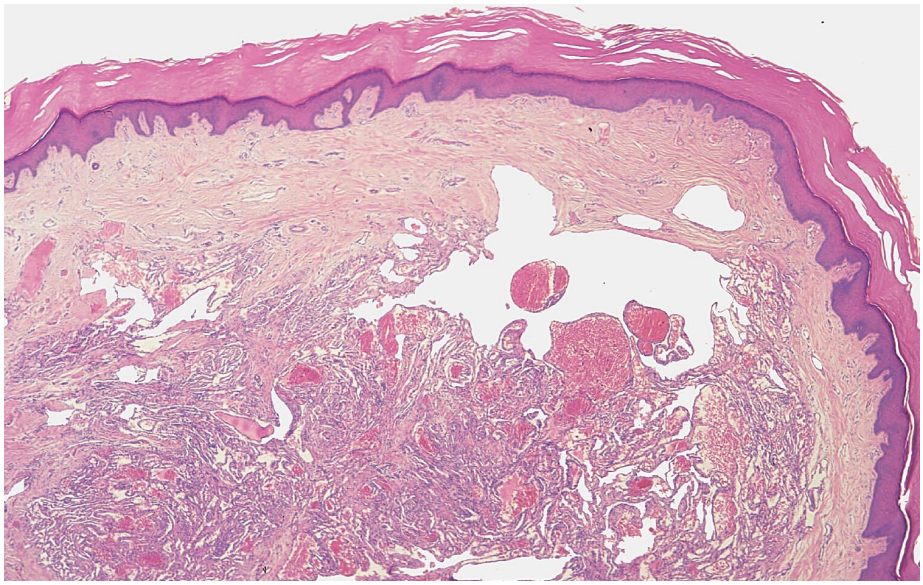

Fig. 5.6 Spindle cell haemangioma. This tumour involving the dermis shows pushing borders, and comprises cavernous vessels intimately intermingled with spindle cells.

adjacent vascular damage {738,2400} and pre-existing arteriovenous malformation {1754} are found in some cases. Although earlier reported, HHV-8 has not been consistently found in ALHE {1130,1241}.

Localization

ALHE most commonly occurs on the head and neck with a predilection for the forehead, scalp and skin around the ear {738,1011,1753}. Occurrence on distal extremities and digits is not uncommon {97}. Multiple other reported sites include trunk, breast {1676}, oral mucosa {1512, 1530,1776}, orbital tissues {145,1513}, vulva {37,2125} and penis {2240}.

Clinical features

ALHE lesions are small red or violaceous papules or plaques with an average size of 1 cm, measuring up to 10 cm. When symptomatic they can be pulsatile, painful and pruritic with scale crust {1011,1753}. When multiple they are usually grouped or zosteriform {647} and may coalesce. In contrast to Kimura disease, lymphadenopathy, eosinophilia, asthma and proteinuria are uncommon and serum IgE is usually normal {97, 441}.

Histopathology

The lobulated, circumscribed dermal or subcutaneous proliferation has a combined vascular and inflammatory component. Sometimes an origin from a medium-sized vessel, usually a vein, is seen. There are arborizing small blood vessels that may surround a larger vascular structure. The vessel walls have smooth muscle cells or pericytes and contain mucin. The endothelial cells have distinct abundant eosinophilic (epithelioid) cytoplasms that can be vacuolated. They protrude into and can occlude vascular lumina or form solid sheets that may mimic angiosarcoma {2582}. Their nuclei have open chromatin, often with a central nucleolus and may protrude into lumina with occasional mitoses.

Multinucleate cells that are endothelial sprouts or histiocyte-like cells can be present {2020}. The density of the inflammatory component between vessels is variable with a prominence of lymphocytes and eosinophils.

Plasma cells, mast cells and lymphoid follicles with reactive germinal centres can be present. Older lesions typically become more fibrotic, less inflammatory and their vascular nature becomes less conspicuous.

Immunoprofile

The endothelial cells are positive for CD31, CD34, VWF (VIIIrAg) and are keratin negative. The proliferative index of the endothelial cells has been reported as 5% using Ki-67 with negative staining for Cyclin D1 and bcl-2. This may support a reactive rather than neoplastic endothelial proliferation {97}. Lymphocytes are a mixture of T- and B-cells. There is no light chain restriction {97, 1753}. One series has shown T-cell clonality in ALHE that may define a subgroup of lesions with a higher incidence of recurrences {1241}.

Differential diagnosis

Kimura disease is a distinct clinicopathological entity, characterized by a more prominent lymphoid proliferation and less prominent vascular component with almost complete absence of epithelioid endothelial cells.

Prognosis and predictive factors

The lesions tend to persist if not completely excised and only rarely will they spontaneously regress. Local recurrence can occur and may be related to persistence of an underlying arteriovenous fistula that is not completely excised {97, 1753,1754}.

Spindle cell haemangioma

Definition

Spindle cell haemangioma is a benign

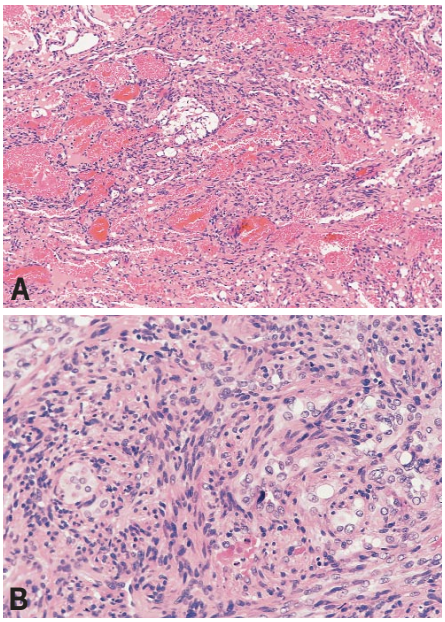

Fig. 5.7 Spindle cell haemangioma. **A** There is intricate mixing of cavernous vessels and spindly cells, with irregular branching narrow vascular spaces coursing through the latter component. **B** Short fascicles of uniform spindly cells are evident. There are interspersed small groups of epithelioid cells with lightly eosinophilic cytoplasm, sometimes with vacuolation.

vascular tumour composed of an intimate admixture of cavernous blood vessels and Kaposi sarcoma-like spindle cell vascular zones.

ICD-O code 9136/0

Synonym
Spindle cell haemangioendothelioma {1807,2488}

Epidemiology
The tumour is uncommon, and mainly affects children and young adults. Those who present late in adulthood usually have long-standing tumours {270,1807}. There is no sex predilection.

Etiology
In a small proportion of cases, spindle cell haemangioma develops in the setting of multiple enchondromas (Maffucci syndrome), Klippel-Trenaunay syndrome, venous malformation, early onset varicose veins, or congenital lymphoedema {709,754,1807}. The onset in young patients and frequent finding of abnormal vessels around the lesion suggest that an underlying vascular malformation may predispose to the development of spindle cell haemangioma {754}.

Localization
They occur on the distal extremities and less commonly on the proximal limb, trunk, head and neck {1807}. Exceptionally, it has been reported in the spleen {709}.

Clinical features
The tumour usually presents as a superficial, slow-growing, painless, solitary purplish mass, or multiple nodules within an anatomical region {1807}. Rare examples may be painful {1784}. The lesion is a discrete red-brown nodule that ranges in size from a few mm to over 10 cm, but most are smaller than 2 cm.

Histopathology
Spindle cell haemangiomas are mostly found in the dermis and subcutis, and occasionally in the deep soft tissues. The tumour is often well-circumscribed but non-encapsulated. It is characterized by intricate blending of cavernous and solid spindle cell zones. The cavernous blood vessels are empty or filled with blood, and may contain organizing thrombi or phleboliths. In the spindle cell regions, short fascicles of spindle cells are interspersed with ramifying narrow vascular spaces. The spindle cells possess uniform, elongated, dark nuclei and eosinophilic cytoplasm. There are scattered single or groups of vacuolated cells or epithelioid cells with lightly eosinophilic cytoplasm.
In about half of the cases, residual vessel walls can be found in the periphery of the lesion, indicating that the lesion is partly or entirely intravascular {754,1807}. Intravascular extension of the lesion can sometimes be seen around the main lesion.

Immunohistochemistry
The cells that line the vascular spaces stain for VWF (VIIIrAg), CD31 and variably for CD34. The spindle cells are negative for the various endothelial markers including CD34, and may show patchy and variable staining for actin {754,796, 1667}.

Differential diagnosis
Spindle cell haemangioma can be distinguished from Kaposi sarcoma by the following features: irregular-shaped, dilated and ramifying vascular spaces rather than short narrow vascular slits among the spindle cells, presence of vacuolated endothelial cells, frequent partial or complete localization within muscular blood vessels, absence of eosinophilic hyaline globules, lack of CD34 immunoreactivity in the spindle cells, and lack of association with HHV-8 {1034}.

Histogenesis
There are controversies on the nature of spindle cell haemangioma, with theories ranging from neoplastic, malformative to hamartomatous {754,1100,1807}. The lesion itself comprises heterogeneous cellular populations, including endothelial cells, pericyte-like cells, fibroblasts, smooth muscle cells and primitive mesenchymal cells.

Somatic genetics
There are no molecular data on spindle cell haemangioma; one studied case shows a normal karyotype {754}. The lesions are diploid on flow cytometric analysis {796,1035}.

Prognosis and predictive factors
Recurrence after local excision occurs in 50-60% of cases, and often results from new lesions developing within the same anatomical region due to intravascular extension. However, there is no metastatic potential.

Tufted angioma

Definition
Tufted angioma is an unusual, acquired, benign vascular neoplasm characterized by slow, indolent growth {1153,1475}.

ICD-O code 9161/0

Synonyms
Tufted haemangioma, progressive capillary haemangioma, angioblastoma of Nakagawa.

Epidemiology
Tufted angioma most commonly affects children and young adults, but both congenital and very late onset cases have been described {995,1264}.

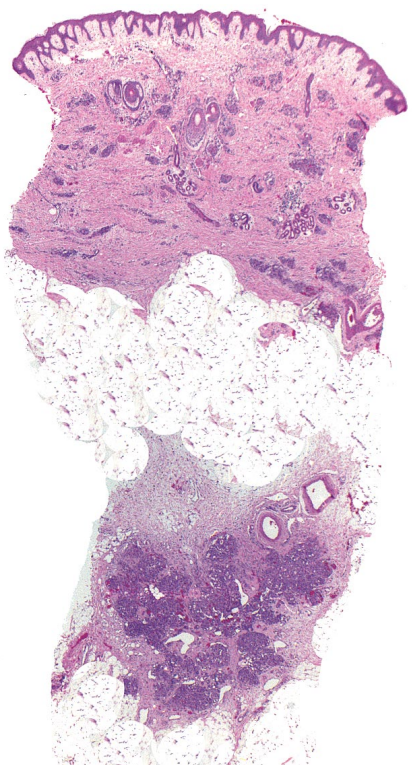

Fig. 5.8 Tufted haemangioma. Another example of a tufted angioma present in the dermis and subcutaneous tissue.

Localization
Tufted angioma favours the shoulders, upper chest, back, and neck {1747}, although examples of these lesions have also been reported on the oral mucosa, extremities and head {1289,2458}.

Clinical features
The most common forms of presentation are enlarging erythematous, brown macules or plaques with an angiomatous appearance. In other instances the lesions resemble granulomas or a connective tissue naevus. Pain and hyperhidrosis have been described {216, 2291}. Raised papules or nodules resembling pyogenic granulomas are sometimes seen within the lesion and occasionally they adopt a linear arrangement {1765}. In some cases the patients present with sclerosing plaques {412}.
Tufted angiomas have been associated with vascular malformations including naevus flammeus {1267,1601}, pregnancy {1272}, non-regressing lipodystrophy centrifugalis abdominalis {1032}, and liver transplant {482}. In some cases of Kasabach-Merritt syndrome the underlying lesion is a tufted angioma {691,692, 2136}. In most cases the growth is halted after some years, and in some cases there is a slight tendency towards spontaneous regression {1131}. Tufted angioma grows slowly and insidiously, and may eventually come to cover large areas of the body.

Histopathology
There are multiple individual vascular lobules within the dermis and subcutaneous fat. These aggregations are more prominent in the middle and lower part of the dermis. Each lobule is composed of aggregates of endothelial cells that whorl concentrically around a pre-existing vascular plexus.
Some lobules bulge into the walls of dilated thin-walled vascular structures, crreating a slit-like or semi-lunar appearance of vessels. This peculiar shape in addition to the angiocentricity of the vascular structures prompted the name “tufted angioma.” Small capillary lumina are identified within the aggregations of endothelial cells. Unusual histopathologic findings in tufted angioma include a mucinous stroma, abundant sweat glands {137}, an intravenous location {795} of the lesion and a proliferation of lymphatic-like channels.

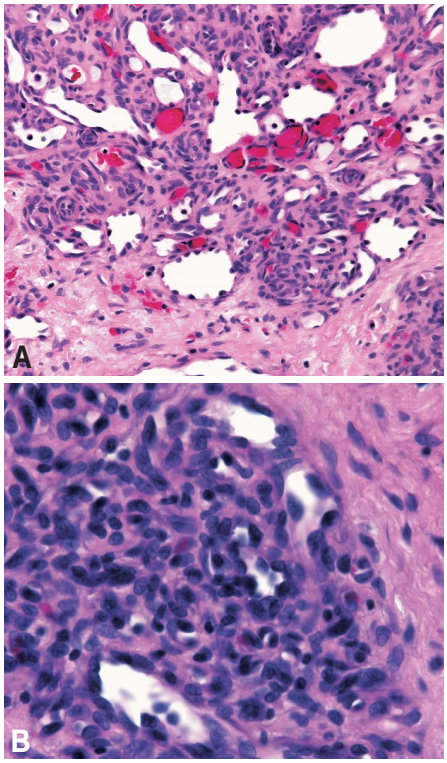

Fig. 5.9 Tufted haemangioma. **A** The vascular lobules in the subcutaneous tissue are composed of irregular vascular spaces, some of them lined with prominent endothelial cells. **B** The neoplastic cells are uniform, in some areas with a slit-like or semilunar appearance.

Immunohistochemistry
Cells in the capillary tufts are weakly positive or negative for VWF (VIIIrAg). They exhibit strong positivity for CD31, CD34 and alpha-smooth muscle actin {1156, 1709}. The cells that show reactivity for smooth muscle actin, most likely represent pericytes.

Electron microscopy
Ultrastructural studies have shown characteristic crystalloid inclusions within endothelial cells in addition to Weibel-Palade bodies {1709}.

Genetics
Most cases are sporadic, although a family with several members affected by tufted angioma has been reported {993}. In this particular family the mode of transmission was autosomal dominant.

Prognosis
Tufted angioma showing spontaneous regression is a rare event. Although benign, symptomatic lesions need to be treated {1131,1709,1948}.

Bacillary angiomatosis

Definition
Bacillary angiomatosis is a reactive vascular proliferation caused by infection with bacteria of the genus Bartonella, most commonly B. henselae and B. quintana {507,855,1383,1845,2492}.

Synonyms
Disseminated pyogenic granulomas (not generally accepted), epithelioid angiomatosis.

Epidemiology
Bacillary angiomatosis most commonly occurs in immunosuppressed patients although there have been a few reports in apparently immunocompetent patients, both adults and children {504,507, 1233,1383,1613,1793,1845,2111,2206, 2325}. Bacillary angiomatosis has most frequently been seen in HIV/AIDS patients.

Localization
Cutaneous involvement may occur at any site and less commonly lesions may involve mucosal surfaces and deeper soft tissue such as muscle, bone, lymph node and liver (peliosis hepatis) {442,507,1383,1845,2085}.

Clinical features
The lesions present as multiple reddish to red-brown cutaneous nodules and occasionally as subcutaneous nodules. In immunocompetent patients there may be fewer nodules {507,1383,1845}.

Histopathology
Sections show a lobular proliferation of well-formed vessels with plump occasionally epitheloid endothelial cells. There is an oedematous to fibrous stroma with a variable infiltrate of neutrophils with nuclear dust, macrophages and ill-defined pale basophilic granular material (representing the bacteria). Diagnosis is made by identifying the characteristic cocco-bacillary organisms with a Warthin -Starry or Giemsa stain {507, 1383,1845}.

Differential diagnosis
Pyogenic granuloma lacks the characteristic basophilic granular material and the dispersed pattern of neutrophils seen in bacillary angiomatosis. Histologically identical lesions can be seen in verruca peruana (verruga peruana).

Prognosis and predictive factors
The infection may be cleared by antibiotics with resolution of the lesions. The overall prognosis depends upon the immune status of the patient and sites of involvement {507,1383,1845}.

Reactive angioendotheliomatosis

Definition
Reactive angioendotheliomatosis (RA) is a relatively rare condition associated with diverse systemic diseases, usually confined to the skin and characterized by a multifocal dermal proliferation of capillaries {1559,2513}.

Synonym
Diffuse dermal angiomatosis. The so-called malignant angioendotheliomatosis represents a form of intravascular lymphoma not related to reactive angioendotheliomatosis {2512}.

Epidemiology
Presentation is mainly in adults with no sex predilection. Occurrence in children is exceptional {304}.

Localization
There is a predilection for the trunk and limbs.

Clinical features
Clinical presentation is variable and consists of fairly widespread erythematous macules, papules, nodules and plaques {1559,2513}. Purpura is a frequent finding. Ulceration is very rare. Many systemic illnesses are related to the development of RA and it can be said that this condition often represents a marker of systemic disease.
Patients affected with RA not uncommonly are immunosuppressed as a result of transplantation. Many conditions have been associated with reactive angioendotheliomatosis including valvular cardiac disease, alcoholic cirrhosis, rheumatoid arthritis, polymyalgia rheumatica, cryoglobulinaemia, the antiphospholipid syndrome, and sarcoidosis {551,1385,1559,2178, 2341,2361}. A more localized variant may be seen in some patients and it is usually associated with peripheral vascular atherosclerosis or iatrogenic arteriovenous fistulas {1266,1276,1918}.

Histopathology
Histologically, the dermis and rarely the superficial subcutaneous tissue show numerous clusters of closely packed capillaries. Many of these capillaries proliferate within pre-existing blood vessels. Cytological atypia is mild or absent but endothelial cells are often prominent and may show focal epithelioid cell change. A layer of pericytes surrounds the newly formed small vascular channels. Extravasation of red blood cells tends to be prominent. PAS positive microthrombi are numerous in cases associated with cryglobulinaemia. Dermal changes resembling fasciitis have also been described.

Differential diagnosis
Distinction from Kaposi sarcoma is easy as in RA there is no proliferation of individual irregular lymphatic-like channels around pre-existing normal blood vessels, proliferating vascular channels are surrounded by a layer of pericytes and inflammatory cells are very rare or absent. Tufted angioma may be distinguished from RA by the typical cannonball appearance at scanning magnification and the presence of slit-like crescent shaped lymphatics around individual tufts in the former. An unusual entity characterized by the presence of aggregates of histiocytes within vascular lumina and described as intravascular histiocytosis has been recently described and may closely mimic reactive angioendotheliomatosis {1935}. Distinction from the later may be difficult and in difficult cases immunohistochemistry is useful in demonstrating the histiocytic nature of the intravascular cells.

Prognosis and predictive factors
RA tends to be self-limiting in the majority of cases with complete spontaneous resolution over weeks or months.

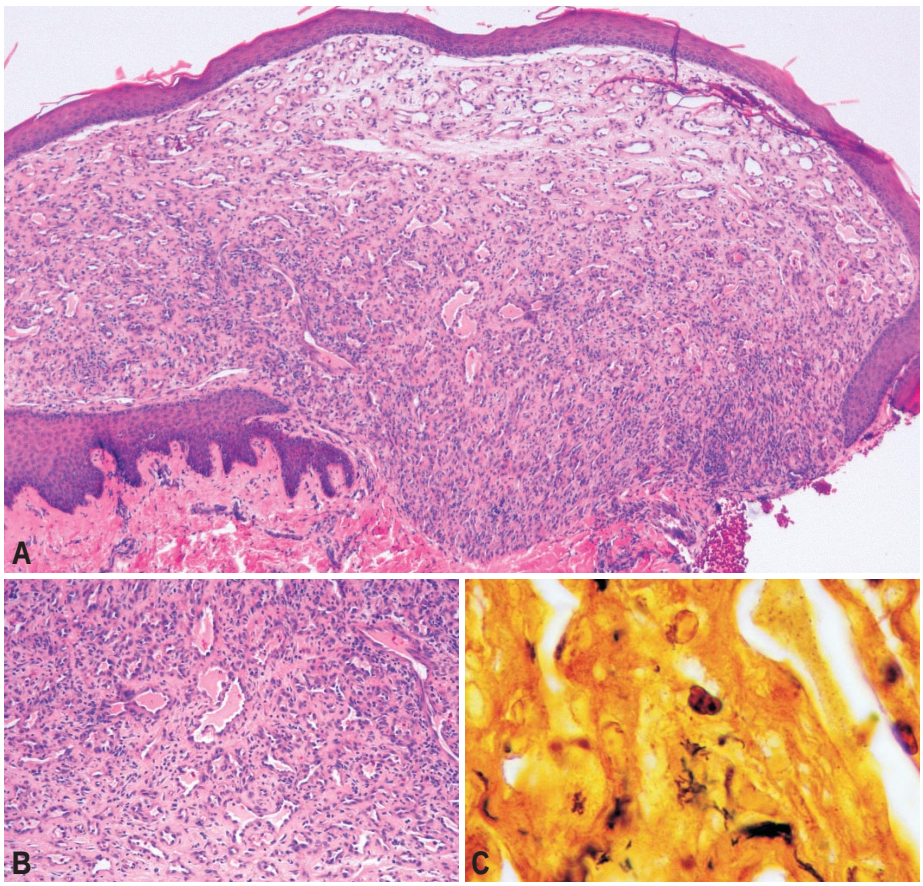

Fig. 5.10 Bacillary angiomatosis. **A** Low power view of a skin lesion of bacillary angiomatosis shows dome shaped expansion of the upper dermis due to a proliferation of small well formed vessels. **B** High power view showing the plump endothelial cells lining the vessels. **C** A Warthin-Starry stain shows the small cocco-bacillary organisms.

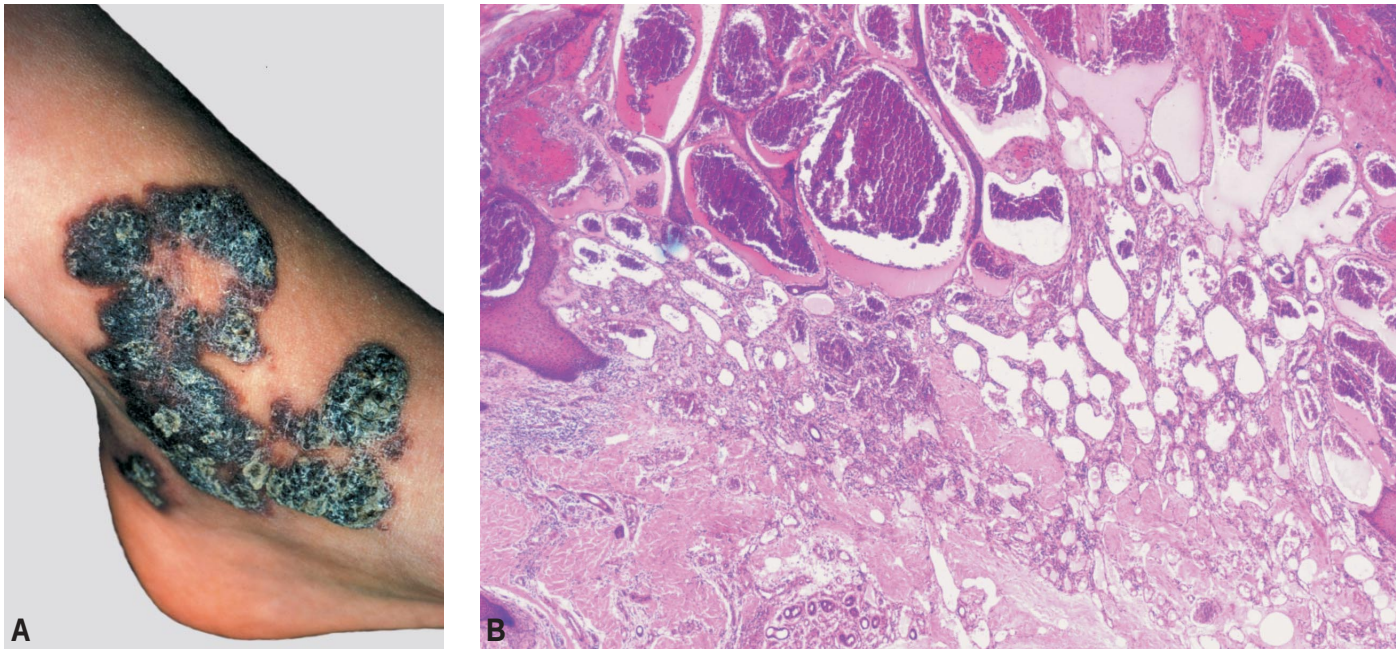

Fig. 5.11 Verrucous haemangioma. **A** A large, irregularly outlined, hyperkeratotic lesion is typical of verrucous haemangioma. **B** This low magnification view of verrucous haemangioma exhibits a superficial and deep proliferation of variously sized blood vessels.

Verrucous haemangioma

Definition
Verrucous haemangioma (VH) is an uncommon variant of haemangioma with capillary or cavernous features {444, 2489}. It is evident at birth or in early childhood and enlarges and becomes hyperkeratotic in later life.

Synonyms
Haemangioma unilateralis naeviforme, unilateral verrucous haemangioma, angiokeratoma circumscriptum naeviforme, naevus vascularis unius lateralis, keratotic haemangioma, naevus angiokeratoticus, naevus keratoangiomatosus {363}.

Epidemiology
VH is usually apparent at birth or in the first few years of life {1102}. The condition is rare, and there is no known gender predilection.

Localization
VH is almost always a unilateral isolated condition, with most cases affecting the leg. Less commonly, it presents on the arm. It is not common on the trunk, but when present on the back in association with underlying spinal malformation, it is a component of Cobb syndrome.

Clinical features
The condition usually presents with lesions that are clustered, discrete to nearly confluent, bluish-red, well demarcated, soft and compressible {363,444, 1102}. The lesions that comprise these clusters may coalesce to form large lesions that cover broad areas over time. Satellite lesions are typical. The condition may show linear or serpiginous distribution. Lesions become hyperkeratotic over time and show a brown to bluish-black appearance. Hyperkeratosis may be so pronounced as to appear verrucous; consequently, the lesion may be mistaken clinically for a wart or keratosis {2560}. Size usually allows distinction from the later two, as verrucous haemangioma tends to be large.

Histopathology
Within the superficial and deep dermis and sometimes the subcutis there are dilated capillaries and venules. Vessels tend to be cavernous in the upper dermis, few in numbers in the deep dermis, and capillary-like in the subcutis. A pseudo-infiltrating pattern may be seen in the subcutis, but close inspection reveals an overall lobulated pattern {444}. There may be thrombosis with secondary papillary endothelial hyperplasia. The vessels are lined by a single layer of endothelial cells without evidence of endothelial proliferation. Inflammatory cells, haemosiderin and fibrosis may be associated. Older lesions show prominent acanthosis, hyperkeratosis with crust and papillomatosis. Ulceration is sometimes present.

Differential diagnosis
Angiokeratoma may also show verrucous epidermal hyperplasia. Verrucous haemangioma differs from angiokeratoma by its large size, involvement of deep vasculature and the presence of vessels that usually vary significantly in size. Angiokeratomas also show a hereditary basis in some cases, are often multiple and show a predilection for the lower trunk, thigh and external genitalia {444}.

Prognosis and predictive factors
VH has a propensity to recur locally {2489}. The condition progresses over time, and superficial therapy has been reported to exacerbate spread {2560}. This may be due, in large part, to the fact that size of the lesion is usually underestimated clinically {444}. Recurrence may also be seen in skin grafts.

Pyogenic granuloma

Definition
Pyogenic granuloma (PG) are rapidly growing, mostly exophytic lesions which may ulcerate.

Synonym
Lobular capillary haemangioma

Epidemiology
An epidemiologic study of 325 cases, {959} showed that 86% of the lesions were cutaneous, while only 12% of the cases affected mucosa. Overall, male patients outnumbered female patients. Pyogenic granuloma is especially common in children and young adults and the peak incidence is around the second decade of life.

Etiology
Most authors consider PG to be a hyperplastic rather than a neoplastic process {598,1615}. Most lesions develop at sites of superficial trauma; in some cases lesions of PG are associated with endocrine alterations or medication and usually regress upon cessation of the stimuli.

Localization
PG preferentially affects the gingiva, lips, mucosa of the nose, fingers, and face {1247,1619}, but examples of pyogenic granuloma have been described in all parts of the skin and mucous membranes including vulva, scrotum, penis, and glans penis {10,929,1477,2360}.

Clinical features
PG presents typically as a papule or polyp with a glistening surface, which bleeds easily. Pyogenic granuloma usually develops at the site of a pre-existing injury. The lesions evolve rapidly over a period of weeks to a maximum size, then shrink and become replaced by fibrous tissue, which disappears within a few months. Epulis gravidarum a gingival lesion that develops during pregnancy, is identical to pyogenic granuloma {1669}. Occasionally, pyogenic granuloma develop within a pre-existing lesion such as a naevus flammeus {1394} or in a spider angioma {1748}. Multiple lesions tend to be localized {1787,2309} but they can also extend in an eruptive and disseminated fashion {2533}. With few exceptions, multiple recurrent lesions are more common in adolescents and young adults, and they usually occur after attempts of electrodesiccation or surgical removal of the primary single lesion. Multiple lesions may also occur after removal of other lesions such as melanocytic neoplasms {621} or in burns {435}. Multiple lesions most commonly affect the trunk, especially the interscapular region. In some cases, eruptive widespread lesions of pyogenic granuloma are a paraneoplastic manifestation {1800}. Rare variants of pyogenic granuloma include the subcutaneous {1777} and intravenous {540} forms.

Histopathology
Early lesions of pyogenic granuloma are identical to granulation tissue, containing, numerous capillaries and venules disposed radially to the skin surface, which is often eroded and covered with scabs. The stroma is oedematous and contains mixed inflammatory infiltrates with lymphocytes, histiocytes, plasma cells, neutrophils and an increased number of mast cells. Fully developed lesions of pyogenic granuloma are polypoid and show a lobular pattern with fibrous septa intersecting the lesion; hence the name lobular capillary haemangioma used by some authors for lesions at this stage. Each lobule is composed of aggregations of capillaries and venules lined by plump endothelial cells. At this stage most lesions have entirely re-epithelialized, and the epidermis forms collarettes of hyperplastic adnexal epithelium at the periphery, partially embracing the lesion; inflammatory infiltrates are sparse and the oedema of the stroma has disappeared. In the late stages of pyogenic granuloma there is a steady increase in the amount of fibrous tissue, so as the fibrotic struts widen, the lobules of capillaries become smaller and, with time, pyogenic granuloma evolves into a fibroma. When the specimen is deep enough, a small feeding artery and one or more veins may be seen ascending from the subcutaneous fat throughout the reticular dermis to directly enter the base of a pyogenic granuloma. The histopathological findings are the same in all variants of pyogenic granuloma.
Uncommon histopathological features in lesions of pyogenic granuloma include intravascular papillary endothelial hyperplasia {1103} and extramedullary haematopoiesis {1986}. When the lesions of PG recur they may show some atypical features which in some cases resemble an angiosarcoma especially in the deeper areas of the lesion. When lesions of PG develop within a vein, they are usually attached to the wall of the vein by a stalk and the lobular pattern is less prominent than in their extravascular counterparts.

Immunohistochemistry
PG lesions express factor VIII related antigen positivity in the endothelial cells lining large vessels, but are negative in the cellular areas {346}, whereas Ulex europaeus I lectin binds to the endothelial cells in both large vessels and cellular aggregates {1606}. There is also expression of inducible nitric oxide synthase {2169}, increased expression of vascular endothelial growth factor {298}, low apoptotic rate expression of Bax/Bcl-2 proteins {1682}, and strong expression of phosphorylated mitogen activated protein kinase {79} in lesions of pyogenic granuloma.
PCR investigations for human papillomavirus {1615} and human herpes virus type 8 (HHV8) {598} have yielded negative results.

Prognosis and predictive factors.
Lesions of PG are benign and easily removed by electrodesiccation and curettage; however lesions may recur, especially in those cases in which the proliferating vessels extend deep within the reticular dermis.

Cavernous haemangioma

Until a few years ago, the term “cavernous haemangiomas” was used to designate venous malformations. These lesions were also erroneously considered to be neoplasms, when in reality they are vascular malformations. They consist of slow-flowing, haemodynamically inactive vascular malformations, which are present at birth and slowly but progressively worsen throughout the lifetime of the patient. In some cases the lesions form a continuum of localized venous malformations, which include blue capillary spongy blebs, “cavernous” lesions (in which the venous lacunae are connected to the venous circulation by capillaries), localized saccular anomalies (connected by veins to the venous circulation) and diffuse venous ectasias. Many of the apparently localized and

superficial venous lesions tend to coexist with venous ectasias and deep vein anomalies.

Angiokeratomas

Definition

Angiokeratomas are acquired vascular lesions that result from the ectatic dilatation of pre-existing vessels in the papillary dermis, accompanied by hyperkeratotic epidermis {1101}. Four clinical variants of angiokeratomas have been recognized, these are: solitary, angiokeratoma corporis diffusum, Mibelli and Fordyce.

Epidemiology

Solitary angiokeratomas affect mainly young adults. Angiokeratoma of Fordyce affects elderly people {34}, however, there are examples of congenital cases {768}. Mibelli angiokeratomas usually appear in childhood or adolescence and they are more common in females {986}. Angiokeratomas of Fabry disease usually appear shortly before puberty and as an X-linked disease, they exclusively affect males; females may be asymptomatic carriers. Fabry disease is a rare error of the metabolism that results in a deficiency of the lysosomal enzyme hydrolase alpha-galactosidase A. It is transmitted as an X-linked recessive trait, the gene responsible for the coding of alpha-galactosidase A has been localized to the middle of the long arm of the X chromosome {250,770}.

Etiology

Solitary angiokeratomas are thought to be the result of injury, trauma, or chronic irritation to the wall of a venule in the papillary dermis.

Fordyce angiokeratomas are usually associated with varicocoele, inguinal hernia and thrombophlebitis {1788}. The lesions may develop after surgical injuries to the genital veins {857}, and there have been cases of angiokeratomas involving the glans penis mucosa of young patients developing after circumcisional surgery {249}. Similar lesions have been described in the vulva of young females {403,857}. These lesions are thought to be the result of increased venous pressure that occurs during pregnancy or develops secondarily to the use of contraceptive pills.

Mibelli angiokeratoma is a condition that is inherited in an autosomal dominant fashion. Angiokeratoma corporis diffusum is the most unusual variant of all the angiokeratomas. It represents a cutaneous manifestation of a group of hereditary enzymatic disorders, but there is also an idiopathic form that presents with no other associated anomalies. Fabry disease is the disease most commonly associated with angiokeratoma corporis diffusum.

Localization

Solitary angiokeratomas may affect any anatomic site, including the oral cavity, although the lower limbs are the most frequent location {1101}. Fordyce angiokeratomas are most common in the scrotum and vulva. Mibelli angiokeratomas usually affect the dorsum of the fingers, toes and interdigital spaces. Lesions of angiokeratoma corporis diffusum in Fabry disease affect the lower part of abdomen, genitalia, buttocks, and thighs in a bathing-trunk distribution.

Clinical features

Although their biologic significance varies greatly, angiokeratomas range from lesions that have very little clinical repercussion to widespread eruptions that are a manifestation of potentially fatal, systemic, metabolic diseases. Solitary angiokeratomas consist of small, warty, black, well-circumscribed papules. Sometimes solitary angiokeratomas develop thrombosis and recanalization with the development of secondary intravascular papillary clinically endothelial hyperplasia. Due to their colour, these lesions may be clinically confused with malignant melanoma {857}. Fordyce angiokeratoma is characterized by the presence of multiple purple to dark papules, measuring 2-4 mm in diameter. In Mibelli angiokeratoma, the lesions consist of several dark papules with a slightly hyperkeratotic surface, and may be associated with acrocyanosis and chilblains. In rare instances, ulceration of the fingertips may appear as a complication of Mibelli angiokeratoma {592}. Lesions of angiokeratoma corporis diffusum are small punctate dark red papules, some of them less than 1 mm in diameter. A frequent and asymptomatic finding is the so-called cornea verticillata, which is a superficial corneal dystrophy. This finding is of diagnostic importance for the detection of mild cases and female carriers. Other cutaneous manifestations include dry skin, anhidrosis, hyperthermic crises {1198}, and acroparaesthesiae secondary to capillary changes in the nail matrix {1132}. In rare instances patients with Fabry disease may also present with concurrent Klippel-Trenaunay-Weber syndrome {821}. Patients with Fabry disease who are devoid of cutaneous lesions have been reported {497}. Angiokeratoma corporis diffusum is not exclusive to Fabry disease and has also been described in association with other rare inherited lysosomal storage diseases. By the same token, rare cases of angiokeratoma corporis diffusum have been described in patients without metabolic anomalies {565,1518}. In some of these patients the angiokeratomas were multiple and presented in a zosteriform distribution.

Histopathology

All variants of angiokeratomas are identical under a conventional microscope. Common features of all angiokeratomas include the presence of dilated thin-walled blood vessels, lined by a layer of endothelial cells, in the papillary dermis and a variable degree of hyperkeratosis {1101}. Occasionally, angiokeratomas may be seen overlying deep vascular malformations {1323}. Hyperkeratosis is usually absent in Fordyce angiokeratomas and in angiokeratoma corporis diffusum (Fabry disease). In patients with Fabry disease there is vacuolization of the cytoplasm of the endothelial cells of the arterioles and smooth muscle cells of the arrector pili. The presence of these vacuoles may be a clue to the specific diagnosis in sections stained with haematoxylin and eosin. However, in most cases the amount of glycolipid in the skin is small making it extremely difficult, if not impossible to identify them, in routinely prepared sections. Special stains such as Sudan black B and PAS highlight the presence of glycolipid deposits within the vacuoles in patients with Fabry disease and related disorders. The lipid material is double refractile, which can be demonstrated by means of polaroscopic examination of unfixed, or formalin fixed frozen sections. Deposits of glycolipids in Fabry disease are not restricted to the lesions of angiokeratoma, but may also be seen in skin that appears to be normal.

Electron microscopy

Ultrastructural studies in angiokeratomas have demonstrated quantitative alterations of cytoplasmic organelles within the endothelial cells {833}. Electron microscopy examination of the skin in Fabry disease show large electron dense lipid deposits in endothelial cells, pericytes, fibroblasts, arrector pili muscles and in secretory, ductal, and myoepithelial cells of the eccrine glands {1683}. These deposits show a characteristic lamellar structure {1366,2438}, not seen in other types of angiokeratomas or in lesions of angiokeratoma corporis diffusum with no enzymatic anomalies. Other ultrastructural findings in patients with Fabry disease consist of intersecting short crescent shaped, tightly packed membranes in the endothelial cells of the small cutaneous blood vessels {679} and cytoplasmic vacuoles in the epithelial cells of the eccrine glands {1094}.

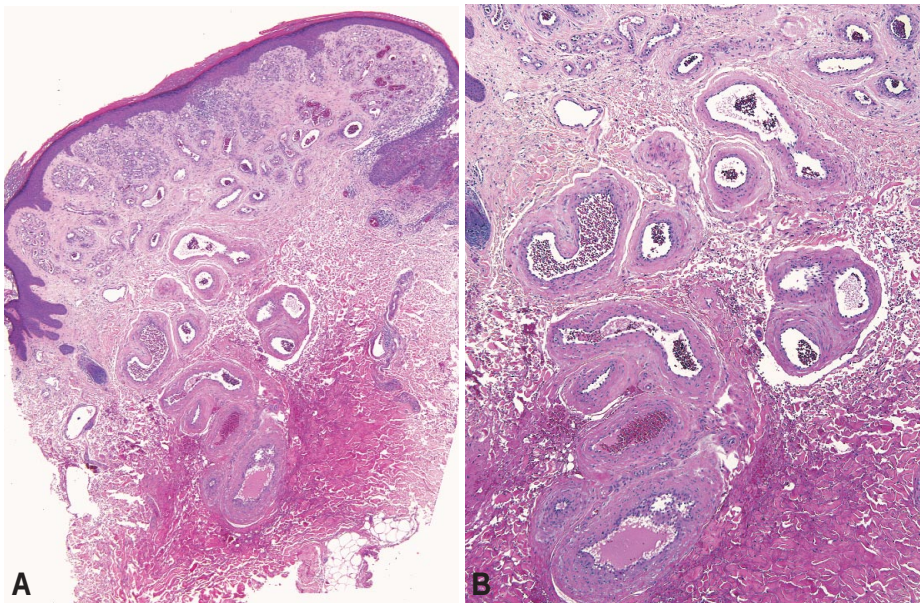

Fig. 5.12 Superficial arteriovenous haemangioma (cirsoid aneurysm). **A** Low power magnification that shows a neoplasm characterized by vessels with thick walls at the base of the lesion and a proliferation of small vessels on the surface. **B** Irregular vessels with thick walls and lined by a single layer of epithelium.

Arteriovenous haemangioma

Definition

Arteriovenous haemangiomas are benign, asymptomatic vascular proliferations. They are not associated with significant arterio-venous shunting.

ICD-O code 9123/0

Synonyms

Cirsoid aneurysm, acral arteriovenous tumour {384,385,528,1811}.

Epidemiology

It occurs mainly in middle-aged adults, with no sex predilection.

Localization

Arteriovenous haemangioma is a neoplasm mainly affecting facial skin. Intraoral and vulvar examples have been also described {1318,1376,1698,1972}.

Clinical features

Arteriovenous haemangioma presents as a red, purple, or skin coloured asymptomatic papule measuring 0.5-1.0 cm. Usually the lesions are solitary, although multiple examples have been cited. When the lesions are multiple they tend to cluster. Occasionally, they are associated with other abnormalities including epidermal naevus syndrome, vascular hamartomas and malformations {372}. Several examples of multiple arteriovenous haemangiomas have been described in patients with chronic liver disease {47}.

Macroscopy

Grossly, lesions of arteriovenous haemangioma present as raised papules and on sectioning there is an admixture of white and red to brown areas, which represent the walls of the thick blood vessels containing blood.

Histopathology

Arteriovenous haemangioma is a well-circumscribed vascular proliferation that involves the upper and mid reticular dermis. The neoplasm is composed mainly of thick-walled muscle-containing blood vessels, lined by a single layer of endothelial cells. Intermingled with the thick-walled blood vessels are thin-walled dilated blood vessels and variable amounts of mucin. Although the thick-walled blood vessels resemble arteries, they lack a well-formed elastic internal membrane, and most likely represent ectatic veins {1318}. In about one-fourth of the studied cases it is possible to identify both the arteriovenous shunts and the spiralled ascending small muscular artery ("feeder" vessel) with serial sections {834}. The lesions recently described as symplastic haemangioma probably represent ancient arteriovenous haemangiomas with atypical cells due to degenerative changes that occur in long-standing lesions {1351}.

Histogenesis

The precise nature of arteriovenous haemangioma is uncertain. Initially it was considered to be a multicentric hamartoma of the sub-papillary vascular plexus with one or more arteriovenous anastomoses {834}. Other authors have suggested that a hamartoma of the Sucquet-Hoyer canal of the glomus body is the cause of this lesion. The latter interpretation, however, is unlikely because glomus cells are usually absent in arteriovenous haemangioma, and to date, they have been identified in only one example of all the reported cases {1318}.

Prognosis

Arteriovenous haemangioma is a benign lesion and local excision suffices.

Cutaneous angiosarcoma

Definition

Angiosarcoma is a malignant neoplasm of endothelial cells. Differentiation between lymphangiosarcoma and sarcomas with blood vascular differentiation appears problematic at the current time.

ICD-O code 9120/3

Synonyms
Lymphangiosarcoma, haemangiosarcoma.

Epidemiology
There are low-grade forms of angiosarcoma that can occur outside the circumscribed clinical settings detailed herein. Almost all high-grade angiosarcomas are in one of the following settings: the head and neck of predominantly male elderly patients (the most common setting) {1046}, the chest of patients who have undergone mastectomy for breast cancer (Stewart-Treves syndrome) {2269}, lymphoedema (congenital or acquired), or post-irradiation {2271}.

Localization
Most of the epidemiologic settings also define the sites of disease.

Clinical features
Angiosarcoma, regardless of its genesis usually begins as a very poorly defined red plaque resembling a bruise {1046}. Lesions can become quite large before metastasis occurs. When it does, the spread is usually haematogenous. Its borders may extend for several centimetres beyond what is visible {1969}. Areas of nodularity arise after a time, but not in all patients. Unless a lesion is detected very early, multiple relapses and death are frequent occurrences.

Histopathology
Angiosarcoma begins as a plaque, with small, jagged thin walled vessels that insinuate themselves between collagen bundles of the reticular dermis. Unlike in Kaposi sarcoma, there is no tendency of spindled cells to first appear in increased number around pre-existent vessels and/or adnexa. The endothelial cells become progressively more protuberant, with enlarged, hyperchromatic nuclei. Lymphoid nodules are sometimes seen. The edges of plaques of angiosarcomas can be very poorly demarcated, making it practically impossible to provide accurate information about the resection margins. Plaques of spindled endothelial cells in the post-mastectomy setting are not necessarily those of angiosarcoma, as Kaposi sarcoma can also occur {59}. The plaque stage of angiosarcoma can give rise to nodules, composed of compact masses of spindled or epithelioid cells, or both. Vascular lumina may be hard to detect in such nodules, and careful inspection may be needed to differentiate these from melanoma and spindle cell squamous carcinoma if only a partial biopsy is submitted. Cytoplasmic vacuoles may be a clue to endothelial differentiation in poorly differentiated cases.

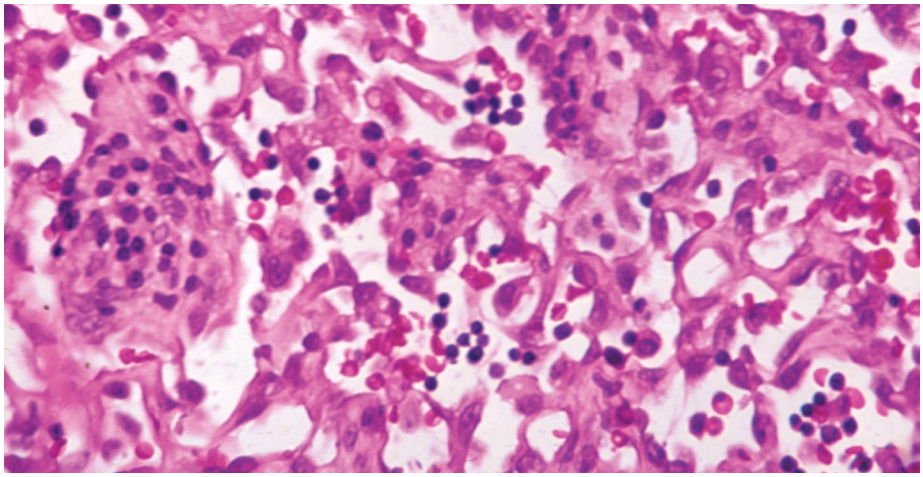

Fig. 5.14 Cutaneous angiosarcoma. The blood vessels have swollen endothelial cells with hyperchromatic nuclei.

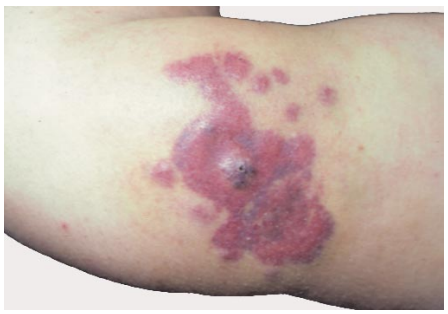

Fig. 5.13 Angiosaroma of the upper arm in a patient with a previous carcinoma of the breast (Stewart-Treves syndrome).

Immunohistochemistry
The cells of angiosarcoma are usually positive for CD31, CD34 or VWF(VIIIrAg). Poorly differentiated tumours can lose one or more of these antigens, necessitating a panel in difficult cases {1755}. Recently FLI-1 has been described as a useful marker with the additional advantage of nuclear staining {761}. Angiosarcoma in the post-mastectomy setting may show blood vascular differentiation, despite a pathogenesis related to lymphoedema {1277}. Angiosarcomas are consistently negative for HHV-8 {1371}.

Differential diagnosis
It includes the atypical vascular proliferation after radiation therapy, Kaposi sarcoma and pseudovascular squamous cell carcinoma.

Genetics
Cytogenetic changes include gains of 5pter-p11, 8p12-qter, and 20pter-q12, losses of 7pter-p15 and 22q13-qter, and –Y {2101}. Insufficient numbers of cases have been analyzed to determine if there are reproducible differences between different types of angiosarcoma.

Prognosis and predictive factors
Metastases to regional lymph nodes and to the lungs occur, often after repeated local recurrences and surgical excisions. The prognosis is poor, and in one series, only 15% of patients survived for 5 years or more after diagnosis {1046}. This, in part, reflects the delayed diagnosis of these lesions. This limited survival is despite the use of various treatment modalities, sometimes involving surgery, radiotherapy, and chemotherapy.

Lymphatic tumours

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Lymphangioma circumscriptum

Definition

Lymphangioma circumscriptum refers to a vascular malformation involving the lymphatic vessels of the superficial dermis. A denomination as superficial lymphatic malformation would be more appropriate to describe this lesion.

ICD-O code 9170/0

Epidemiology

Usually, lymphangioma circumscriptum is present at birth or appears early in life.

Localization

Lymphangioma circumscriptum may be located in any anatomic site, but has predilection for the axillary folds, shoulders, neck, proximal parts of the extremities and tongue {750,1798,2502}. Lesions involving eyelids and conjunctiva {841} and genital skin of males and females {149,419,2006,2436} have also been described.

Clinical features

Clinically, the lesion consists of numerous small vesicle-like lesions, often with a verrucous surface, grouped in a plaque. Sometimes purplish areas within the lesion are seen due to haemorrhage and thrombus formation within the blood vessel component. Probably, the superficial vesicles are the result of saccular dilatations of superficial lymphatics secondary to raised pressure transmitted from the underlying pulsating cisterns {2502}. Magnetic resonance imaging accurately demonstrates the true extent of involvement {1541}. In rare instances, superficial lymphatic malformations are associated with visceral lymphatic malformations involving the mediastinum {1643} or the bladder wall {1107}. Additional associations include Becker naevus {1762}, and superficial lymphatic malformations have been described in patients with Maffucci syndrome {2292} and Cobb syndrome {2168}.

Macroscopy

The excised specimens of lymphangioma circumscriptum show dilated vascular spaces involving both the superficial dermis and deeper subcutaneous tissue, which correspond to the malformed lymphatic vessels.

Histopathology

The stereotypical superficial lymphatic malformation is accompanied by deep lymphatic dilated cisterns with muscular walls situated in the subcutaneous fat, resulting in swelling of the tissue beneath the superficial vesicles {1768}. The superficial component consists of dilated lymph vessels, lined by flat endothelial cells in a discontinuous layer, and situated in the papillary dermis, and the superficial reticular dermis {179,750}.
Sometimes, the lymphatic vessels are arranged in clusters in the papillary dermis, resulting in a papillated or verrucous skin surface. The vessels may contain homogeneous eosinophilic proteinaceous lymph or blood, and occasionally foamy macrophages. Scattered lymphocytes may be seen in the connective tissue stroma between dilated lymphatic vessels. In extensive lesions, large irregular lymphatic channels are usually seen beneath the superficial vessels in deep reticular dermis and subcutaneous fat.

Immunohistochemistry

The usual immunohistochemical markers for endothelial cells, such as factor VIII-related antigen, Ulex europaeus, and CD31 do not differentiate between blood and lymphatic vessels {1799}. In these cases, new endothelial cell markers such as vascular endothelial growth factor receptor-3 (VEGFR-3) {763,1463}, D2-40

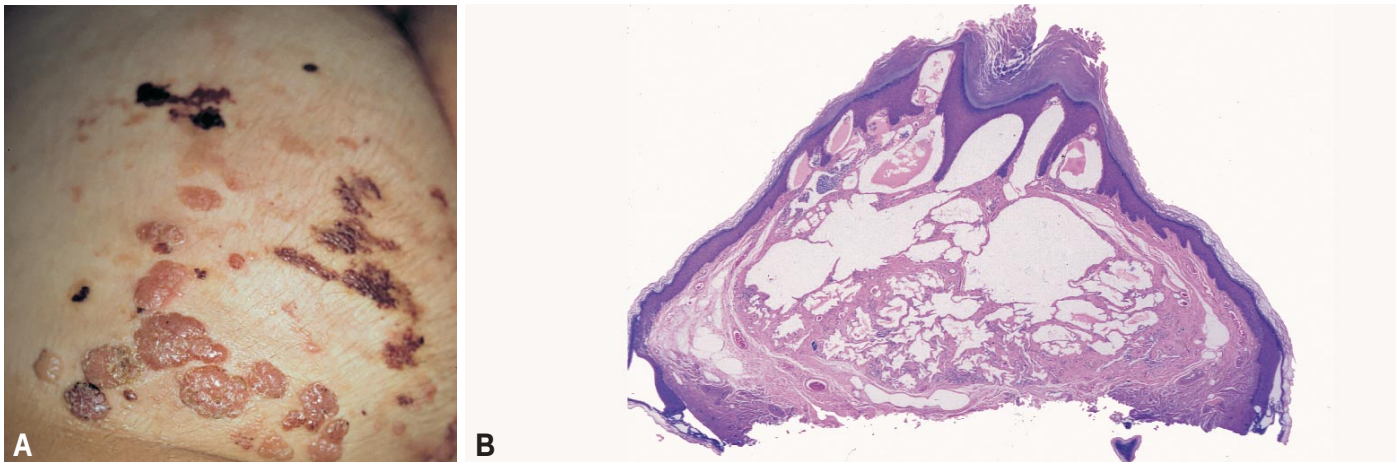

Fig. 5.15 Lymphangioma circumscriptum. **A** Close-up view of the lesions showed that it consisted of numerous vesicle-like lesions, some of them with a verrucous surface, grouped in a plaque. Purplish areas are seen due to haemorrhage and thrombus formation within a blood vessel component. **B** Histopathologically, the lesion consisted of dilated lymph vessels involving the superficial dermis and covered by hyperplastic epidermis with compact hyperkeratosis.

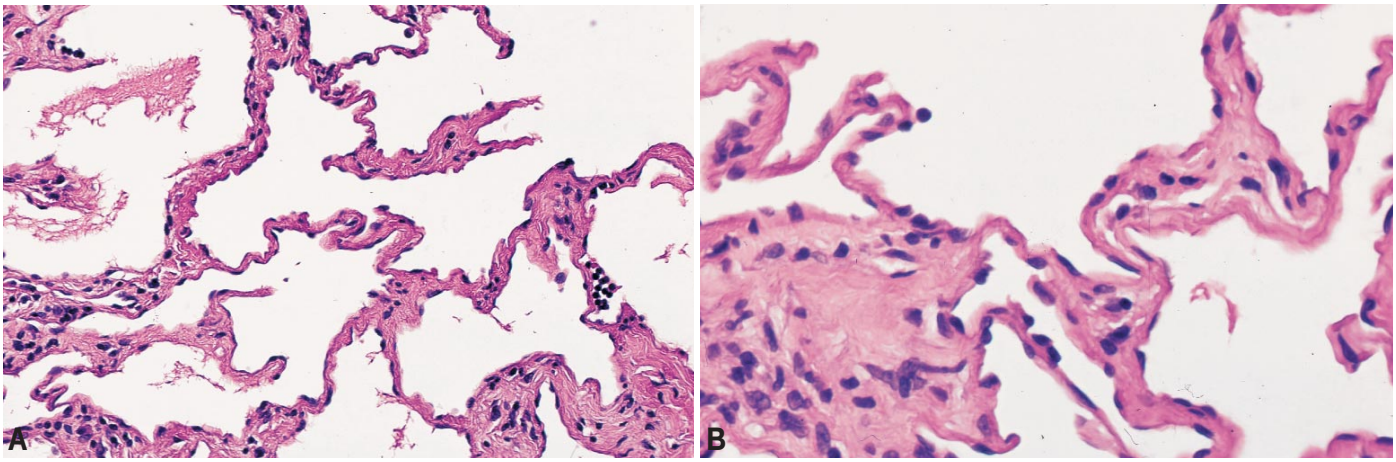

Fig. 5.16 Lymphangioma circumscriptum. **A** The lymphatic channels were lined by a discontinuous layer of flat endothelial cells. **B** The stroma between the lymphatic vessels was scant.

{1179} and Prox1 {2535) may be helpful, since these markers are expressed by lymphatic endothelium {763,1463}.

Histogenesis
Lymphangioma circumscriptum results from abnormalities in the embryologic development of lymphatic vessels of the skin. Lymphangioma circumscriptum probably represents sequestrated dermal lymphatic vessels that failed to link up with the rest of the lymphatic system {2502}. However, an ultrastructural study suggested that lymphangioma circumscriptum was induced by long-standing lymphatic stasis {103}. In some patients, lymphangioma circumscriptum has developed after surgery or radiotherapy on the involved area {1406,1859}.

Prognosis and predictive factors
Usually, lymphangioma circumscriptum is a localized and superficial lymphatic malformation that only causes cosmetic problems and does not require treatment. The presence of a deep component may explain the tendency of the lesions to persist after superficial excision.

Progressive lymphangioma

Definition
Progressive lymphangioma is a benign, localized, slow-growing neoplasm composed of thin-walled, interconnecting vascular channels in the dermis and subcutis.

ICD-O code 9170/0

Synonyms
Acquired progressive lymphangioma, benign lymphangioendothelioma.

Epidemiology
Progressive lymphangioma is rare. It occurs chiefly in middle-aged or older adults and does not show a sex predilection {918}.

Etiology
Progressive lymphangioma has been reported after trauma, such as surgical procedures and tick bites. Inflammation secondary to trauma has been claimed to play a role {2463,2532}.

Localization
Lesions have been reported most commonly on the lower extremities, but any region of the skin may be affected {918}.

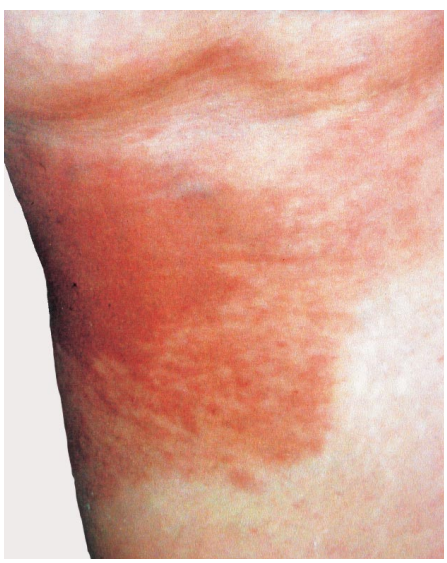

Fig. 5.17 Progressive lymphangioma. Solitary, rather well-circumscribed red patch on the thigh.

Clinical features
Lesions usually present themselves as solitary, well-circumscribed, red or violaceous patches or plaques. Although usually asymptomatic, patients may complain of tenderness, pain, or itching. Because of slow growth over years, lesions may measure several centimetres in diameter {918,1157}.

Histopathology
Progressive lymphangioma is characterized by delicate, often widely dilated vascular spaces lined by a monolayer of monomorphous endothelial cells. In some foci, endothelium-lined papillary stromal projections extend into those spaces. With progressive extension into the deep dermis, vascular spaces become narrower. They tend to dissect between collagen bundles and to surround pre-existing vessels and adnexal structures. Endothelial cells are more numerous than in normal lymphatic vessels and may be closely crowded together. Nuclei may be hyperchromatic, but there is no prominent nuclear atypia.

Immunohistochemistry
Endothelial cells are usually stained by antibodies against CD31 and CD34, whereas other endothelial markers give more inconsistent results. Actin-positive pericytes around vascular lumina are present focally {918,1157}.

Differential diagnosis
Lymphangioma-like Kaposi sarcoma dif-

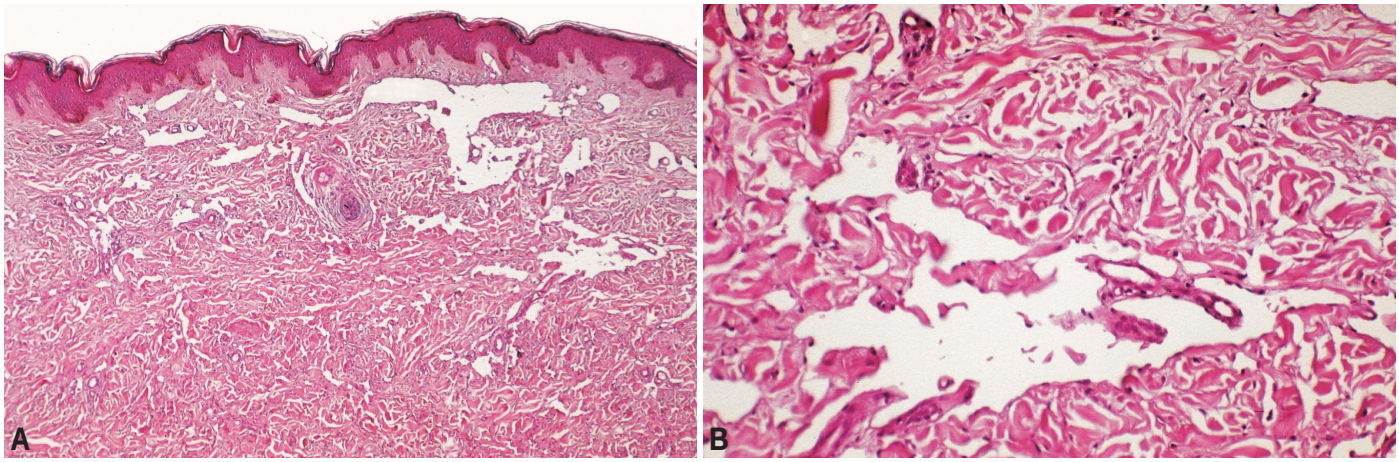

Fig. 5.18 Progressive lymphangioma. **A** Widely dilated, bizarre-shaped vascular spaces dissecting between collagen bundles and surrounding preexisting vessels. Papillary stromal projections extend into vascular lumina. **B** Vascular spaces are lined by a monolayer of monomorphous endothelial cells.

fers from progressive lymphangioma by the presence of plasma cells, the invariable presence of HHV-8 and more classic areas of Kaposi sarcoma elsewhere in the lesion. The so-called atypical vascular proliferation following radiotherapy (benign lymphangiomatous papules) differs from progressive lymphangioma clinically and histopathologically by presenting as tiny vesicles and histopathologically by being associated with much wider spaces in the upper dermis. Moreover, these lesions are thought to represent lymphangiectasias, rather than a neoplastic process {628,1921}.

Histogenesis
Progressive lymphangioma is considered to be a neoplastic proliferation of lymphatic vessels. A neoplastic nature is suggested by its slowly progressive course. Derivation from lymphatic endothelia has been suggested on the basis of rare erythrocytes within and around vascular lumina and absence of a peripheral ring of actin-positive pericytes in most vessels.

Prognosis and predictive factors
Following surgical excision, local recurrences are exceptional. Metastases do not occur. Regression of lesions after systemic therapy with corticosteroids and in the absence of any treatment has been reported {918,1577,2463}.

Lymphangiomatosis

Definition
Lymphangiomatosis is characterized by a diffuse proliferation of lymphatic vessels that may involve bones, parenchymal organs, soft tissue, and skin.

Synonyms
Generalized lymphangioma, systemic cystic angiomatosis, multiple lymphangiectasias.

Epidemiology
Lymphangiomatosis is a rare disease occurring mainly in the first two decades of life. There seems to be no sex predilection {862,1882}.

Localization
Lesions occur in the skin and the superficial soft tissues of the neck, trunk, and extremities. Most cases of lymphangiomatosis affect bones and parenchymal organs, especially the lung, pleura, spleen, and liver. Soft tissue involvement occurs in the mediastinum and retroperitoneum.

Clinical features
Cutaneous and subcutaneous lesions present themselves as soft, fluctuant swellings that can be squeezed from one area to another and that may be associated with tiny vesicles. In patients with involvement of bones and visceral organs, the presenting signs range from pathologic fractures to chylothorax, chylous ascites, and other symptoms related to particular organs affected by the process. The interconnected lymphatic channels can be visualised by lymphangiography or direct injection of contrast media into cystic vascular spaces. Plain x-rays often reveal osteolytic areas as a consequence of involvement of bones {862,1882}.

Histopathology
Cutaneous lesions of lymphangiomatosis are characterized by markedly dilated lymphatic channels throughout the skin and subcutis that are lined by a single attenuated layer of flattened endothelial cells and usually appear empty. Those channels tend to dissect between collagen bundles and to surround pre-existing structures in a manner reminiscent of well-differentiated angiosarcoma. Unlike angiosarcoma, cytologic atypia, endothelial multilayering, and mitotic figures are absent. The stroma often contains numerous siderophages and focal aggregates of lymphocytes. Exceptionally extramedullary haematopoiesis may be seen.

Histogenesis
Lymphangiomatosis probably represents a vascular malformation, rather than a neoplastic process.

Prognosis and predictive factors
When present on the neck and trunk, lymphangiomatosis of soft tissues is usually associated with extensive osseous or visceral involvement and carries a grave prognosis with a high rate of mortality {1882}. In lymphangiomatosis of the limbs, involvement of bones and visceral organs is usually insignificant and prognosis, therefore, favourable {1021}.

Smooth and skeletal muscle tumours

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Smooth muscle is found in the skin in the arrector pili muscles, the walls of blood vessels and in 'genital' skin, which includes the scrotum (dartos muscle), vulva and nipple (areolar smooth muscle). Each of these sites of smooth muscle can give rise to a tumour.
Tumours of striated muscle are exceedingly rare in the skin. Only the rhabdomyomatous mesenchymal hamartoma (striated muscle hamartoma) will be considered below.

Smooth muscle hamartoma

Definition
Smooth muscle hamartoma is a proliferation of dermal smooth muscle bundles that is usually congenital.

Synonyms
Arrector pili hamartoma, congenital pilar and smooth muscle naevus, congenital smooth muscle naevus

Epidemiology
Smooth muscle hamartoma is usually congenital with only occasional reports of lesions with onset in adolescence or adulthood {590,1069}. There is a slight male predominance. The lesion is uncommon {1028}.

Localization
The lesions are most often located on the trunk and extremities, particularly proximally {1145}. Cases have been reported involving the head and neck region {1290}, scrotum {1870} and conjunctiva {1966}.

Clinical features
The typical presentation is as a solitary patch or plaque of varying size, usually between 1 and 10 cm, which may show hyperpigmentation and/or hypertrichosis {1145} and which may increase in size with the growth of the patient {2610}. A positive pseudo-Darier sign is seen in most cases {2610}. Occasional cases have an atrophic appearance {886}. Less common presentations may include papular follicular lesions {659}, multiple lesions {915,2200} and the so-called "Michelin tyre baby", the latter typically in boys. Patients with Michelin tyre syndrome may have various other associated abnormalities {2093}. A clinical classification has been proposed in which type 1 refers to the usual localized form, type 2 the follicular variant, type 3 to multiple lesions and type 4 to the diffuse variant {819}.

Histopathology
There are increased numbers of variably orientated discrete smooth muscle bundles within the dermis and sometimes the subcutis and these may connect to hair follicles {1145,2093}. The overlying epidermis may show acanthosis and basal hyperpigmentation and there may be prominent folliculosebaceous units present, although these do not appear to be increased in number {206,1145}.

Immunohistochemistry
Lesions have been positive for smooth muscle actin and desmin as expected {886,1299,2093}. CD34 positive dendrocytes have been reported to be an integral part of the proliferation {1299}.

Differential diagnosis
Becker naevus may show dermal changes identical to smooth muscle hamartoma. It has been suggested that these lesions may form a spectrum {1145}.
Pilar leiomyoma differs from smooth muscle hamartoma in being acquired, frequently multiple, often painful and comprising less discrete smooth muscle bundles with intervening collagen.

Genetic susceptibility
Rare cases of smooth muscle hamartoma have been described in siblings and in a mother and her children {915}.
Xp microdeletion syndrome is characterized by an unbalanced translocation between the X and Y chromosomes leading to deletion of the distal short arm of the X chromosome. Affected infants show microphthalmia, linear skin defects and sclerocornea. The linear skin defects have been reported to show histological features similar to smooth muscle hamartoma {1794} although this was not described in another case {686}.
A child with a familial paracentric inversion of chromosome 7q and Michelin tyre syndrome with smooth muscle hamar-

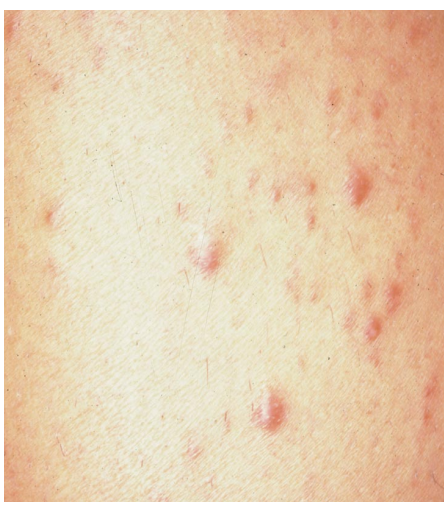


Fig. 5.19 Pilar leomyoma. Multiple pilar leiomyomas of the upper back. The lesions were painful in response to cold.

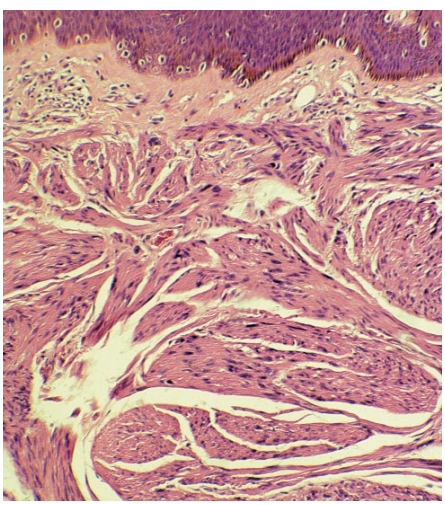


Fig. 5.20 Pilar leiomyoma. There are interlacing bundles of smooth muscle fibres forming a nodule.

toma has been described. The relevance, if any, of the genetic abnormality is unknown {2093}.

Pilar leiomyoma

Definition
Pilar leiomyoma is a benign tumour derived from the arrector pili muscle {1054,1878}.

ICD-O code 8890/0

Synonym
Piloleiomyoma

Epidemiology
Solitary lesions have a female preponderance. They usually develop in adult life. Rarely, they are present at birth. Multiple lesions usually have their onset in the late second or third decades of life.

Localization
Solitary lesions may develop anywhere on hair-bearing skin, particularly the trunk and limbs. Multiple lesions have a predilection for the face, back and extensor surfaces of the extremities.

Clinical features
Pilar leiomyomas may be solitary or multiple, with up to several hundred lesions. Multiple lesions may be grouped, linear, or zosteriform. Solitary lesions may measure up to 2 cm or more in diameter, but multiple lesions are much smaller. Leiomyomas are firm reddish-brown papulonodules. Multiple lesions are usually painful; solitary lesions are infrequently so.

Histopathology
Pilar leiomyomas are circumscribed (but not sharply so), non-encapsulated tumours of the dermis, composed of bundles of smooth muscle arranged in an interlacing or haphazard pattern. The cells have abundant cytoplasm and elongated nuclei with blunt ends. Mitoses are infrequent or absent {1878}. Atypical cells, similar to those seen in the symplastic leiomyoma of the uterus, are uncommon {1486}. Granular cell variants are extremely rare {1586}.
Small amounts of fibrous stroma are present between the muscle bundles in older lesions, but there is usually less stromal collagen than in the smooth muscle hamartoma. Overlying epidermal hyperplasia is sometimes present {1878}. The tumour cells stain for desmin and smooth muscle actin.

Genetics
Some of the multiple cases are familial, with an autosomal dominant inheritance {728}. The syndrome of multiple cutaneous and uterine leiomyomas is also autosomal dominant with the locus on chromosome 1q42.3-q43 {51,1526}.

Cutaneous leiomyosarcoma

Definition
Cutaneous (dermal) leiomyosarcoma is a malignant neoplasm of smooth muscle cells arising in the dermis. Subcutaneous and soft tissue leiomyosarcomas are discussed in the soft tissue monograph.

ICD-O code 8890/3

Epidemiology
Over 100 cases of dermal leiomyosarcoma have now been reported {1164}. Most cases develop in adults, with a peak incidence in the sixth decade. Childhood cases are extremely rare {2563}. There is a male predominance.

Localization
These tumours have a predilection for the extensor surfaces of the extremities and to a lesser extent the scalp and trunk {593}.

Clinical features
Dermal leiomyosarcomas are solitary, firm nodules measuring 0.5-3 cm in diameter. They are usually asymptomatic, but pain and tenderness have been recorded.

Histopathology
By definition, the major portion of the tumour is in the dermis, although subcutaneous extension is present in some cases. They have an irregular outline with tumour cells infiltrating into, or blending with the collagen fibres at the periphery. The tumour is composed of interlacing bundles of elongated spindle-shaped cells with eosinophilic cytoplasm and blunt-ended nuclei. Sometimes there is a suggestion of nuclear palisading. There is at least one mitosis per 10 high-power fields in cellular areas. Pockets of greater mitotic activity (mitotic 'hot spots') are found, usually in areas showing nuclear pleomorphism. Granular cell, epithelioid, inflammatory and desmoplastic variants have all been described {2476}.
Two different growth patterns have been described: A nodular pattern which is quite cellular with nuclear atypia and many mitoses; and a diffuse pattern which is less cellular with well-differentiated smooth muscle cells and inconspicuous mitoses {1164}.

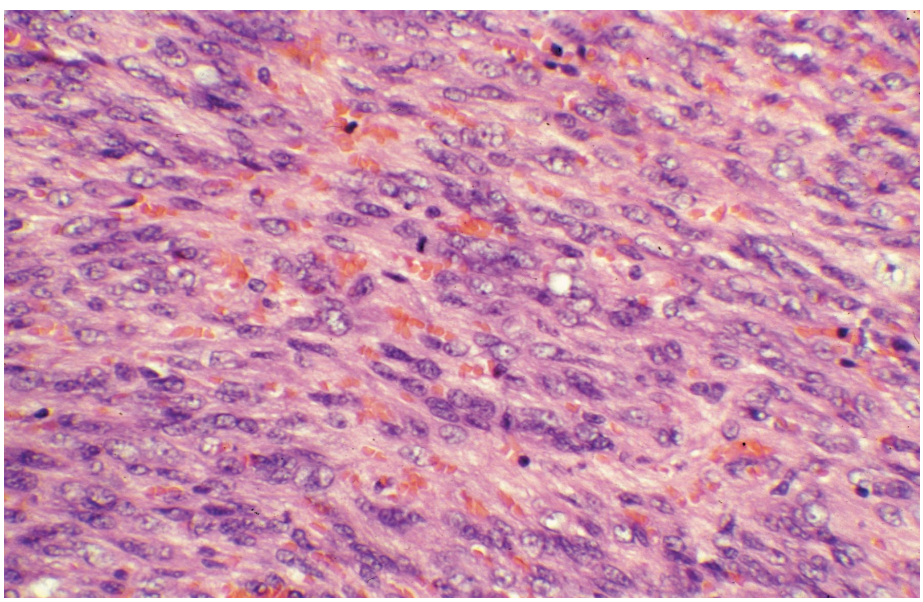


Fig. 5.21 Leiomyosarcoma. confined to the dermis. There are bundles of spindle shaped cells and scattered mitotic figures. Not the nuclear pleomorphism.

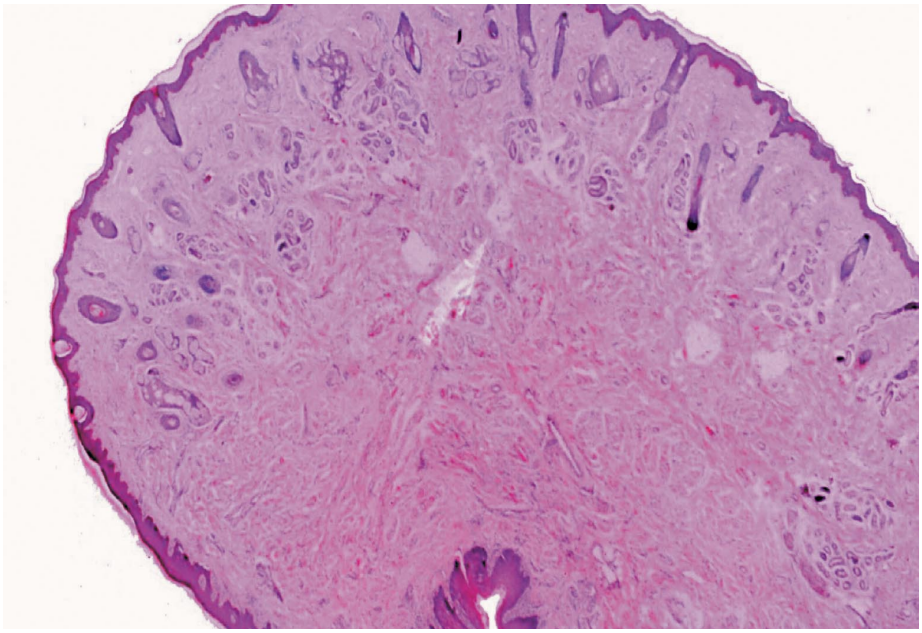


Fig. 5.22 Rhabdomyomatous mesenchymal hamartoma. Low power view of rhabdomyomatous mesenchymal hamartoma, showing polypoid configuration, intact epidermis, numerous small vellus follicles, and a central core containing skeletal muscle.

Immunohistochemistry
The cells express smooth muscle actin. Desmin is present in the majority of cases. Pan-muscle actin (HHF-35) is sometimes present focally.

Histogenesis
The majority of tumours are derived from the arrector pili muscles. Rare cases derived from areolar smooth muscle in the nipple {1452} and dartos muscle in the scrotum {758} have been reported.

Genetics
An unequivocal genetic fingerprint for these tumours is currently lacking {2175}. Various genes have been identified that are expressed differentially in tumour and normal tissue. Soft tissue leiomyosarcomas most often show genomic alterations in the 13q4-q21 region {622}.

Prognosis and predictive factors
Dermal leiomyosarcomas may recur locally, but the reported incidence (5-30%) varies widely {2476}, but metastases of confirmed cases are unknown {1139}.

Rhabdomyomatous mesenchymal hamartoma

Definition
Rhabdomyomatous mesenchymal hamartoma (RMH) refers to single or multiple, congenital, frequently polypoid lesions that typically arise near the midline of the head and neck. They contain skeletal muscle fibres within the dermis {1618}.

Synonyms
Striated muscle hamartoma {1008}, congenital midline hamartoma.

Epidemiology
About 25 examples of this lesion have been reported {1973,2320}. Typically, the lesions have been present since birth or early childhood, and most patients are children. Rare cases have been reported in adults {2037}. Thus far, the male: female ratio is 2:1.

Etiology
These lesions may be derived from striated muscle of the branchial arch {105, 899,1008,1973}.

Localization
RMH typically arises in the midline of the head and neck, with a particular predilection for the nose and chin. There have also been cases involving the preauricular region {1902,2010,2122}, lateral forehead {1973}, and cheek {2320}.

Clinical features
The majority of lesions are described as papules or polyps, but a few have presented as nodules {105,1973,2320} or "sessile masses" {1685}. RMH lesions are generally asymptomatic, but they can demonstrate the interesting property of contractile motion, spontaneously or during crying or feeding {1973,2010}. Most patients lack other congenital anomalies, but there have been associations with cleft lip and palate, ocular abnormalities (coloboma, microphthalmia, limbal dermoid), low-set ears, craniofacial clefts, thyroglossal duct sinus, lipoma of the brain, and upper extremity and syndactyly {1008,1902, 1973,2010,2037}. Histologic features of RMH have been found in the cutaneous polyps {2037} of a case of Delleman syndrome, which consists of orbital cysts, cerebral malformations, and focal dermal hypoplasia as well as cutaneous appendages {723}. In addition, a patient {1902} with RMH in association with ipsilateral limbal dermoid and coloboma (Goldenhar syndrome), has been reported.
Initially, it was believed that RMH might be an X-linked disorder, as the first few cases were reported in males, but this

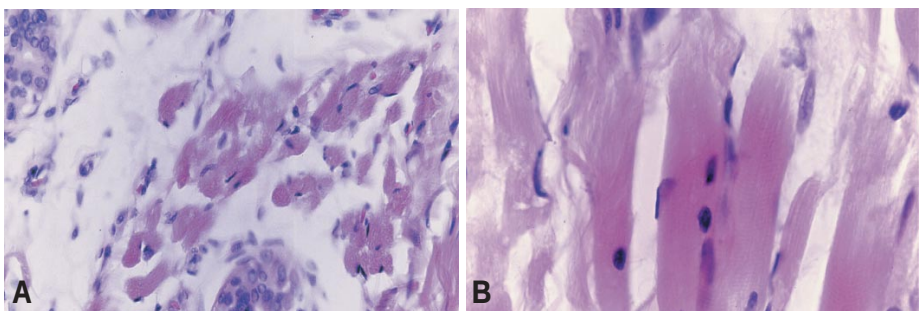


Fig. 5.24 Rhabdomyomatous mesenchymal hamartoma. **A** In the superficial dermis, small skeletal muscle fibers surround eccrine sweat ducts. **B** This high power view shows mature intradermal skeletal muscle fibers with cross-striations.

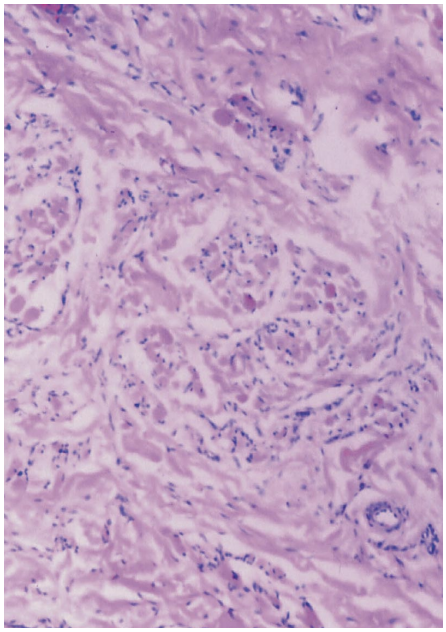


Fig. 5.23 Rhabdomyomatous mesenchymal hamartoma. In the lower part, skeletal muscle fibers among thick collagen bundles of the reticular dermis. In the upper part there are eccrine sweat coils and aggregates of smooth muscle.

was not substantiated when a number of examples were described in girls. Thus far, familial occurrence of this lesion has not been documented.

Histopathology

The most striking feature is the presence of intersecting bundles of mature skeletal muscle fibres, with demonstrable cross striations, and with a general orientation perpendicular to the surface epidermis. Varying amounts of collagen and mature fat surround these muscle fibres {2037}. They extend through the reticular dermis and become attenuated in the papillary dermis {1618}, where they appear to surround adnexal structures, particularly vellus follicles and sebaceous glands {678,713,1618}. Sebaceous and eccrine sweat glands are usually observed, and in one case there were ectopic apocrine glands {2320}. Nerve elements in these lesions vary considerably; in some cases they are not prominent {2010}, but in others there may be numerous small nerve twigs {987} or a large nerve bundle in the central core of the lesion {2037}. One example contained elastic cartilage {2037}, and calcification or ossification have also been reported {2010}. In some cases, elastic fibre distribution has been reported to be normal {1618}, while in others these fibres are markedly decreased {2037}.

Immunoprofile

Skeletal muscle fibres in RMH stain positively for actin, desmin and myoglobin {678,899}.

Differential diagnosis

Although RMH bears a resemblance to fibroepithelial polyp, naevus lipomatosus, and accessory tragus, the combination of midline location and a microscopic skeletal muscle component should permit distinction from those lesions (though small amounts of skeletal muscle have been reported in accessory tragic) {324}). Deeper or more primitive tumours such as fetal rhabdomyoma, fibrous hamartoma of infancy, or neuromuscular hamartoma (benign Triton tumour) should not be difficult to distinguish from RMH {678,2010}.

Somatic genetics

There has been speculation about a human homolog of the mouse disorganization gene (Ds), which is responsible, directly or indirectly, for the development of hamartomas and other defects {1973,2242}.

Fibrous, fibrohistiocytic and histiocytic tumours

W. Weyers
T. Mentzel
R.C. Kasper
A. Tosti
M. Iorizzo
B. Zelger
R. Caputo
H. Kamino
J. D. Harvell
P. Galinier
G.F. Kao
E.J. Glusac
E. Berti
D. Weedon
C. Rose

Keloid scar

Definition
Keloid scars are raised scars that extend beyond the confines of the original wound.

Epidemiology
Keloid scars occur with equal frequency in men and women. They affect all races, but are more common in dark-skinned individuals. In Black, Hispanic, and Asian populations, the incidence ranges between 4.5 and 16%. Keloids occur chiefly in persons under 30 years of age {1711,2149}.

Etiology
There is a genetic predisposition to the formation of keloid scars. Moreover, hormonal and immunological factors may play a role. Keloids often appear in puberty and tend to enlarge during pregnancy; they have been claimed to be more common in patients with signs of allergy and increased serum levels of IgE. Wounds subjected to great tension or become infected are more likely to heal with a keloid scar {1711,2149}.

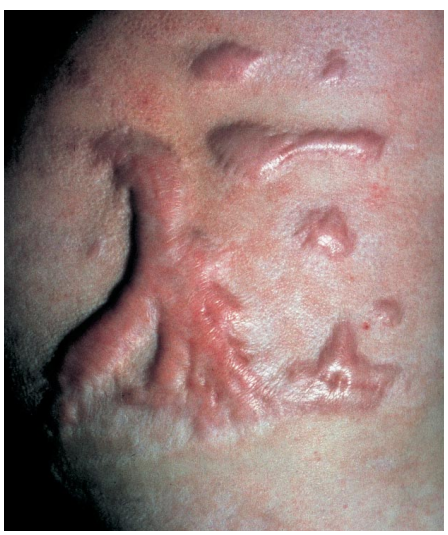


Fig. 5.25 Keloid. Raised erythematous plaques are present.

Localization
Keloids are most common on the earlobes, cheeks, upper arms, upper part of the back, and deltoid and presternal areas. They are seen only rarely on the genitalia, eyelids, and on palms and soles {1711,2149}.

Clinical features
Keloids are well-circumscribed, firm, smooth-surfaced erythematous papules or plaques that occur at the site of an injury. The preceding injury may be only minor and, therefore, not always apparent (e.g., rupture of an inflamed hair follicle). Older lesions may be pale or hyperpigmented. Especially in early stages, keloids are often itchy, tender, or painful {1711,2149}.

Histopathology
After a prolonged period of wound healing thick, homogeneous, strongly eosinophilic bundles of collagen, in haphazard array, develop {1498}. Those “keloidal“ collagen bundles are the histopathologic hallmark of keloid scars, but are not seen in many cases fulfilling the clinical definition of keloids. The border of keloids is often irregular, with tongue-like extensions of bands of thickened collagen underneath normal appearing epidermis and superficial dermis.

Histogenesis
Keloid scars are characterized by an enhanced proliferation and metabolic activity of fibrocytes that seems to result, in part, from the excess of various cytokines produced by inflammatory cells, including transforming growth factor-b1 and platelet-derived growth factor. Moreover, a deficiency of cytokines that down-regulate collagen synthesis and inhibit proliferation of fibrocytes, such as interferon-a, has been noted. There is also evidence of reduced degradation of collagen caused, in part, by inhibition of collagenase activity through acid mucopolysaccharides, proteoglycans, and specific protease inhibitors {1686,1711, 2149,2551}.

Genetic susceptibility
Keloidal scar formation may run in families. It is also more common in Black individuals. A relationship with various human leukocyte antigens has been reported {1711}.

Prognosis and predictive factors
The clinical and histopathologic features of keloid scars indicate a high probability of recurrence following surgical excision alone. Recurrence rates of 45-100% have been described {1711}.

Hypertrophic scar

Definition
Hypertrophic scars are raised scars that do not extend beyond the confines of the original wound. As such, they are closely related to keloids, both being examples of a disturbance of wound healing leading to the formation of exuberant fibrous tissue. Whether hypertrophic scars are simply a less severe variant of keloid scars or represent a different pathologic process is controversial.

Epidemiology
Hypertrophic scars are common. The incidence of hypertrophic scarring (including keloid scars) ranges between 39 and 68% after surgery and between 33 and 91% after burns, depending on the depth of the wound {1711}.

Localization
Hypertrophic scars are most common above the flexor aspects of joints and on the abdomen {2149}.

Clinical features
By definition, hypertrophic scars differ from keloid scars by remaining confined to the original wound. Other distinguishing features are earlier manifestation of

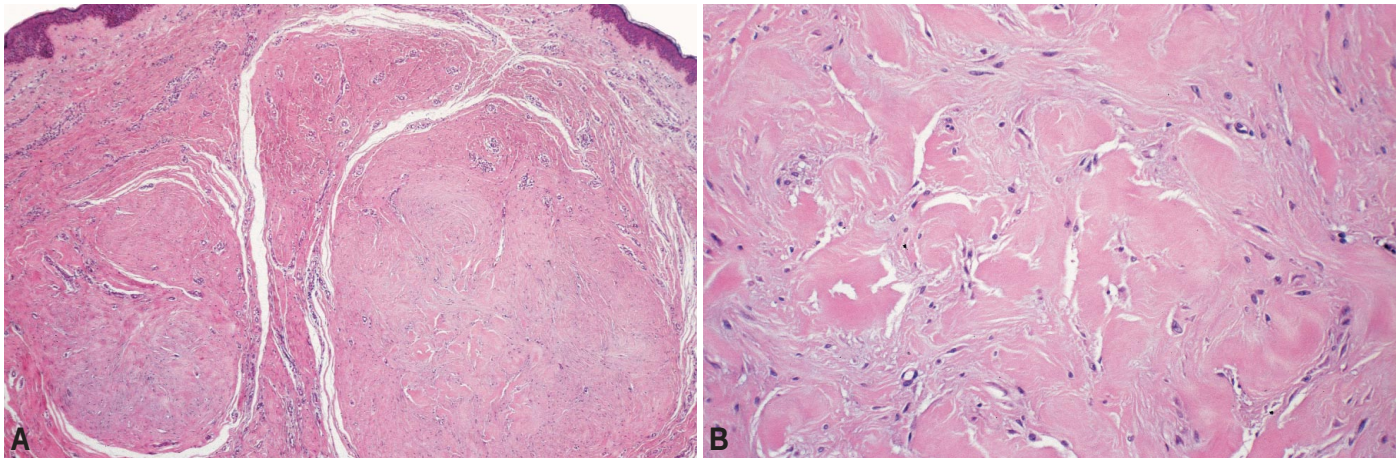


Fig. 5.26 Keloid. **A** Nodular masses of collagen and fibrocytes separated from one another by elongated bands of collagen and containing foci of thick homogeneous, strongly eosinophilic collagen bundles. **B** Thickened homogeneous, strongly eosinophilic bundles of collagen ("keloidal collagen") are the histopathologic hallmark of keloid scars.

hypertrophic scars (usually within 4 weeks after injury, whereas keloids may manifest themselves several months later), a tendency to regression and to contractures not seen in keloid scars, a lower tendency to recur after surgery, and different sites of predilection. In other respects, the clinical features of hypertrophic and keloid scars are essentially the same {2149}.

Histopathology
Hypertrophic scars differ from normal scars chiefly by presence of nodular aggregates of collagen with many fibrocytes. The main distinguishing feature from keloid scars is the absence of keloidal (i.e., thick, strongly eosinophilic) bundles of collagen. Moreover, unlike keloid scars, hypertrophic scars show prominent blood vessels arranged perpendicularly to the skin surface. Borders of hypertrophic scars tend to be more regular, and nodules of collagen tend to be distributed more evenly.

Differential diagnosis
Keloids show thick hyaline collagen bundles. Cases with overlap features between keloids and hypertrophic scars are seen.

Histogenesis
No principal differences have been noted in the histogenesis of hypertrophic scars and keloid scars {1711}.

Prognosis and predictive factors
Although hypertrophic and keloid scars are closely related, the distinguishing features, clinically and histopathologically, allow a judgment to be made about the probability of recurrence following surgical excision. In one series, the recurrence rate of hypertrophic scars was 10%, as opposed to 63% in keloid scars {257}.

Dermatomyofibroma

Definition
Dermatomyofibroma is a distinct biologically benign fibroblastic/myofibroblastic cutaneous proliferation occurring frequently, but not exclusively in young female patients.

ICO-O code 8824/0

Synonym
Plaque-like dermal fibromatosis

Epidemiology
Dermatomyofibroma represents a relatively rare cutaneous mesenchymal neoplasm and usually occurs in young women. Infrequently, dermatomyofibroma is seen in male patients {1073,1189, 1581} and children {1654,1970}.

Localization
Most cases of dermatomyofibroma arise in the shoulder and axilla regions, fol-

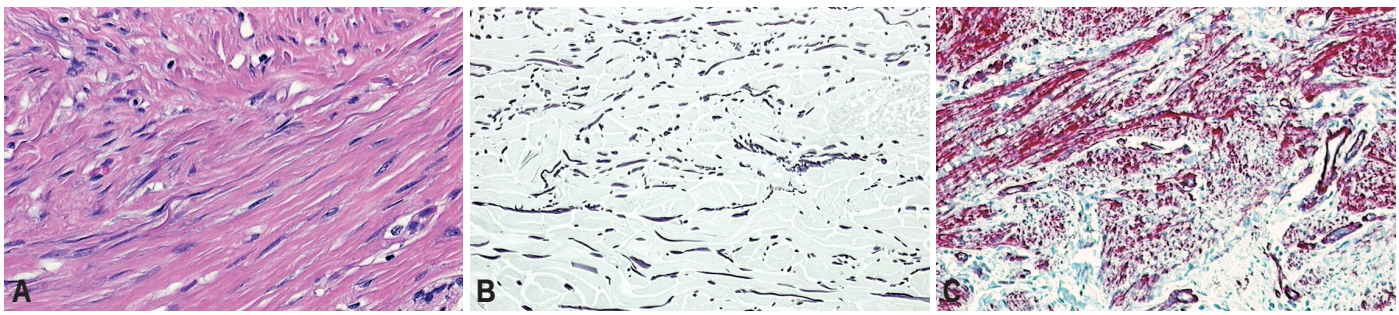


Fig. 5.27 Dermatomyofibroma. **A** Neoplastic cells in dermatomyofibroma have typical cytological features of myofibroblasts with an ill-defined, pale eosinophilic cytoplasm and elongated, tapering nuclei. **B** Characteristically, elastic fibres are slightly increased and fragmented in dermatomyofibroma in comparison to non-neoplastic tissue (bottom). **C** Neoplastic cells in dermatomyofibroma stain variably positive for alpha-smooth muscle actin.

lowed by the trunk, the neck, and the upper arm {523,1073,1189,1581,2322, 2375}; more rarely these lesions are seen on the thigh {1073,1189}.

Clinical features
The patients usually present with a slowly increasing, plaque-like, indurated, often red-brown lesion; rarely these neoplasms may reach a considerable size {1073,2375} or may occur as multiple lesions. Grossly, most neoplasms are circumscribed, oval or annular and present as firm plaques or flat nodules measuring usually 1-2 cm, however, larger lesions have been reported {2375}.

Histopathology
Dermatomyofibroma is characterized by an ill-defined proliferation of cytologically bland spindle-shaped tumour cells arranged mainly in bundles and fascicles oriented parallel to the overlying epidermis.
Adnexal structures are typically spared. In most cases the lesions are confined to the dermis, however, a focal extension into superficial subcutaneous tissue is sometimes noted {1581}. The tumour cells contain an ill-defined pale eosinophilic cytoplasm and uniform fusiform nuclei that are either elongated with tapering edges containing an evenly distributed chromatin or vesicular with small nucleoli.
Tumour cells are set in a collagenous matrix with slightly increased and fragmented elastic fibres, a helpful clue in the distinction of dermatofibroma and scarring processes. The overlying epidermis may show mild acanthosis and focal hyperpigmentation.

Immunoprofile
Tumour cells in dermatomyofibroma stain variably for actin and alpha-smooth muscle actin {1189,1581}. As in other myofibroblastic conditions, the expression of actin seems to be dependent on the age and activity of neoplastic cells, and only approximately 50% of cases are positive for this marker {1582}. Lesional cells are negative for S-100 protein, CD34, desmin, and h-caldesmon {581,1074, 1189,1581}.

Prognosis and predictive factors
Complete excision is advised since these neoplasms may reach a considerable size.

Infantile myofibromatosis

Definition
Infantile myofibromatosis (IM) is a tumour of the skin and soft tissues of disputed histogenesis, which is solitary in two thirds of cases. Multicentric lesions (myofibromatosis) occur {634A}.

ICD-O code 8824/1

Synonyms
Solitary cutaneous myofibroma.

Historical annotation
IM was described by Chung and Enzinger in 1981 as a proliferative disorder of myofibroblasts {486}. Cases had been described earlier as congenital fibrosarcoma {2529}, congenital generalized fibromatosis {1229} and congenital mesenchymal hamartoma {203}.

Epidemiology
Most lesions are present at birth, or appear in the first 2 years of life; onset in adults also occurs {2541}. There is a male predominance.

Clinical features
About a third of lesions are situated in the deep soft tissues and the remainder are located in the skin and/or the subcutananous tissues {1778}. The head, neck and trunk are the usual sites.
They measure 0.5 to 7 cm or more in diameter; they are greyish-white in colour, and fibrous in consistency.

Histopathology
The nodules are reasonably well circumscribed, although there be an infiltrative border in the subcutis. There are plump to elongated spindle cells, grouped in short fascicles. Delicate bundles of collagen separate or enclose the cellular aggregates. Mitoses are variable in number, but not atypical {486,753}.
Vascular spaces resembling those seen in haemangiopericytoma are often found in the centre of the tumour, giving a biphasic appearance. Necrosis, hyalinization, calcification, and focal haemorrhage may be present centrally {753}. For details, see WHO Classification of Tumours of Soft Tissue and Bone {756}.

Immunoprofile
The tumour cells are positive for vimentin and alpha-smooth muscle actin, but negative for S-100, myoglobin, and cytokeratins {2425}. Reports on immunorreactivity for desmin vary {923}.

Histogenesis
Fletcher and colleagues have suggested that the spindle cell component shows smooth muscle differentiation {753}. Requena et al have suggested an origin from myopericytes. {1920}. Recently, the lesion has been included in a spectrum of tumours showing perivascular myoid differentiation {882}.

Genetics
Familial occurrence is too rare to allow any conclusions regarding genetic susceptibility {2427}

Prognosis
The prognosis is excellen, with recurrence unlikely after excision; aggressive variants are rare {849}. There are no features predictive of recurrrence.

Sclerotic fibroma

Definition
Sclerotic fibroma is a benign soft tissue tumour composed of eosinophilic collagen bundles arranged in a storiform pattern {1895}.

ICD-O code 8823/0

Synonym
Storiform collagenoma

Epidemiology
Solitary sclerotic fibroma is rare and occurs in both sexes at any age, from infancy to adulthood. Multiple tumours are typical of Cowden disease, a rare genodermatosis.

Localization
Most frequent sites of involvement are the face, upper and lower extremities and trunk.

Clinical features
Sclerotic fibroma presents as a translucent, white, flesh-coloured or waxy nodule. It is usually unique and measures less than 1 cm. It has a slowly progressive growth, over months or years. The lesion is asymptomatic {1590,1895, 2369}.

Histopathology
The tumour is usually situated in the reticular dermis. It is sharply demarcated and it is composed of hyalinized bands of collagen with a decreased number of fibroblasts. The collagen fibres are thick, glassy and aligned in parallel bundles with a storiform pattern. Elastic fibres are absent. The proliferation tends to expand, pushing aside the normal dermal collagen without engulfing the adnexae {1590,1895,2369}. Alcian Blue staining reveals an increased amount of mucopolysaccharide.

Immunoprofile
Staining for S100 protein, myelin basic protein and neuron specific enolase and desmin are negative {1590,1895}.

Prognosis and predictive factors
Although the lesion is benign, it should be removed due to its tendency to expand.

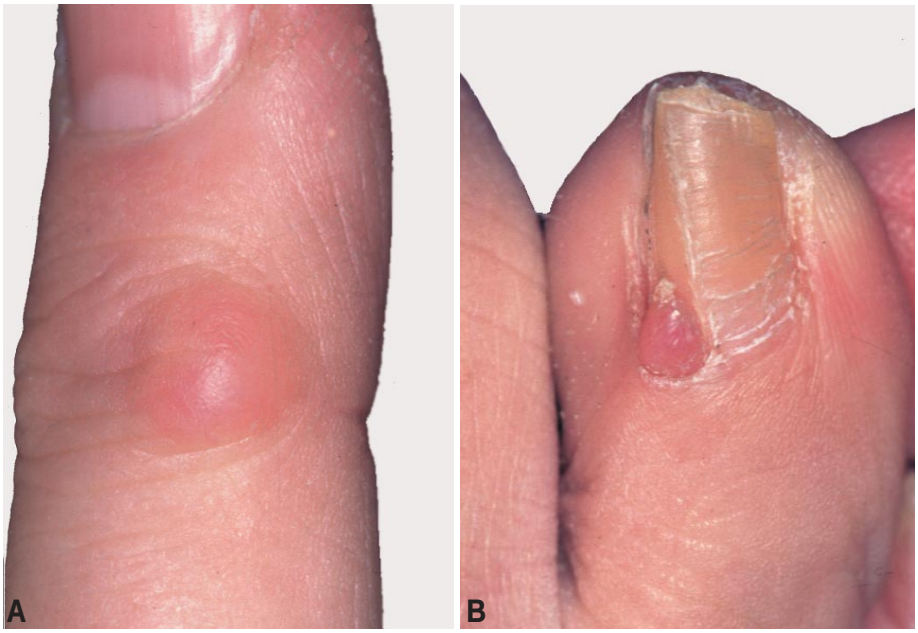


Fig. 5.28 **A** Digital mucous cyst on the dorsum of a finger. **B** Digital fibrokeratoma on a toe.

Digital mucous cyst

Definition
Two types of lesions both with a pseudocystic circumscribed dermal mucin deposition exist. In the more common type a connection with the underlying joint cavity can be demonstrated (ganglion type). The second type represents a focal mucinosis produced by fibroblasts (myxomatous type).

Synonyms
Myxoid pseudocysts of the digits, ganglion of the distal interphalangeal joint, digital focal mucinosis.

Epidemiology
Women are more often affected and patients are middle aged or elderly.

Localization
They typically occur on the dorsum of the fingers near the distal interphalangeal joint or near the proximal nail fold. The index fingers and thumb are primarily affected. The toes are rarely involved {1148,2221}.

Clinical features
The lesions are solitary, soft, smooth surfaced and usually not greater than 1.5 cm. A connection of the pseudocyst to the underlying joint can be demonstrated in the majority of cases by magnetic resonance imaging or injection studies with dye {599,1034}. Osteoarthrosis is sometimes evident.

Histopathology
Myxomatous type: this variant has a large pseudocystic area with a myxomatous stroma with scattered spindle-shaped or stellate fibroblasts analogous to focal mucinosis in other areas of the body. The overlying epidermis is often attenuated. The mucin contains mucopolysaccharides which stain positively with alcian blue and colloidal iron.
Ganglion type: cystic spaces containing mucin with a collagenous fibrous wall characterize these lesions. Occasionally in some areas of the wall a synovial lining can be demonstrated.

Digital fibrokeratoma

Definition
Digital fibrokeratoma is a benign fibrous tumour often accompanied by a hyperplastic epidermis that arises mostly in the periungual area.

Synonyms
Acquired ungual fibrokeratoma, periungual fibromas of tuberous sclerosis (Koenen tumours), subungal and periungual fibromas, acral fibrokeratoma.

Epidemiology
Most patients are adults. Males are affected more frequently than females {2429}. More than half the patients with tuberous sclerosis develop about puberty multiple fibrokeratomas {2470}.

Localization
The majority of lesions occur on a finger or a toe. Occasionally, lesions present on the palms or soles.

Clinical features
The patients usually present with a solitary lesion. Normally, tumours are small and measure 3-5 mm in diameter. A case of a huge lesion measuring up to 5 cm has been described {1181}.

Histopathology
Digital fibrokeratoma is composed of dense collagen fibres, often with vertical orientation, with a variable number of mature fibroblasts and small blood vessels. A few inflammatory cells can be observed. There is often epidermal hyperplasia. In the stroma thin elastic fibres are present and hair follicles are absent. In a rare variant an oedematous and less dense stroma is found {1279,1280}.

Genetics
In patients with tuberous sclerosis mutations in two different genes, TSC1 on

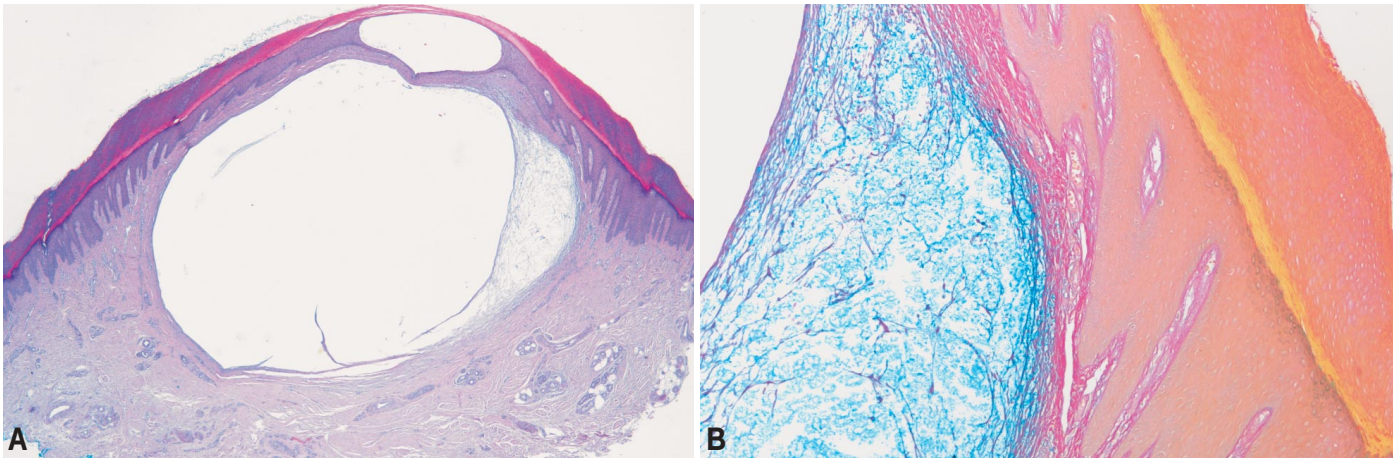


Fig. 5.29 Digital mucous cyst. **A** Low-power view of digital mucous cyst (myxomatous type) shows a cystic lesion with an attenuated epidermis. **B** Colloidal iron stain from this lesion demonstrates the myxomatous stroma.

chromosome 9 and TSC2 on chromosome 16 have been identified {582}.

Pleomorphic fibroma

Definition
Pleomorphic fibroma (PF) is a benign, polypoid or dome-shaped cutaneous neoplasm with cytologically atypical fibrohistiocytic cells {1188}.

ICD-O code 8832/0

Epidemiology
PF occurs mostly in adults {39,1188}.

Localization
They are located on the trunk, extremities, head {39,1188} and rarely the subungal region {983}.

Clinical features
PF are asymptomatic, solitary, slowly growing, flesh coloured and non-ulcerated dome-shaped to polypoid papules from 4-16 mm. The clinical differential diagnosis includes acrochordon, neurofibroma, intradermal naevus and haemangioma. Although clinical behaviour is benign, lesions may locally recur when incompletely removed {1188}.

Etiology
Degeneration, ischemia {808} or the paracrine influence of mast cells {1842} may create the cytologic atypia of PF {1188}.

Histopathology
PF are circumscribed, dome-shaped to polypoid, hypocellular dermal proliferations of spindle and irregularly shaped stellate or multinucleate cells. Lesional cells have scant cytoplasm and large, pleomorphic, hyperchromatic nuclei with small nucleoli and rare mitotic figures. Foam cells are rarely present.
Haphazardly arranged, hyalinized dermal collagen is admixed with moderate mucin. The collagenous bundles in pleomorphic sclerotic fibromas are more storiform and clefted {458,808,1523}. Myxoid {1614} and sclerotic variants have been described {808,1523}.

Immunoprofile
Lesional cells are positive for muscle specific actin, CD34 and rarely alpha-1 antichymotrypsin {1188,1988}.

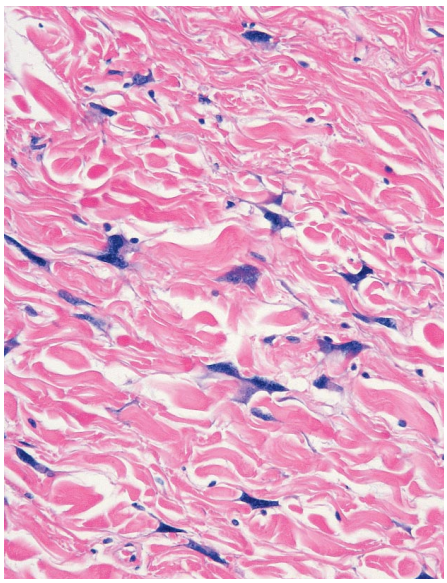


Fig. 5.30 Pleomorphic fibroma. Amid coarse collagen bundles are mesenchymal cells with coarse chromatin and scalloped nuclear borders.

Differential diagnosis
The histologic differential diagnosis includes: atypical fibroxanthoma, variants of dermatofibroma, fibrosarcoma, fibrous papule of the face, angiofibroma, giant cell fibroblastoma, desmoplastic Spitz naevus and fibroepthelial polyp with monster cells {1188}.

Giant cell fibroblastoma

Definition
Giant cell fibroblastoma (GCF) is a histologic variant of DFSP, which primarily affects children.

ICD-O code 8834/1

Epidemiology
GCF is a rare tumour that primarily affects children in the first decade of life, with a strong male predilection.
Occasional cases have also been reported in adults {751}.

Localization
GCF most commonly affects the trunk, shoulder region and groin (similar to DFSP), but other reported sites include the extremities and head and neck {971,2174,2338}.

Clinical features
Giant cell fibroblastoma is described as a slow growing, firm, dermal or subcutaneous mass which is painless and asymptomatic.

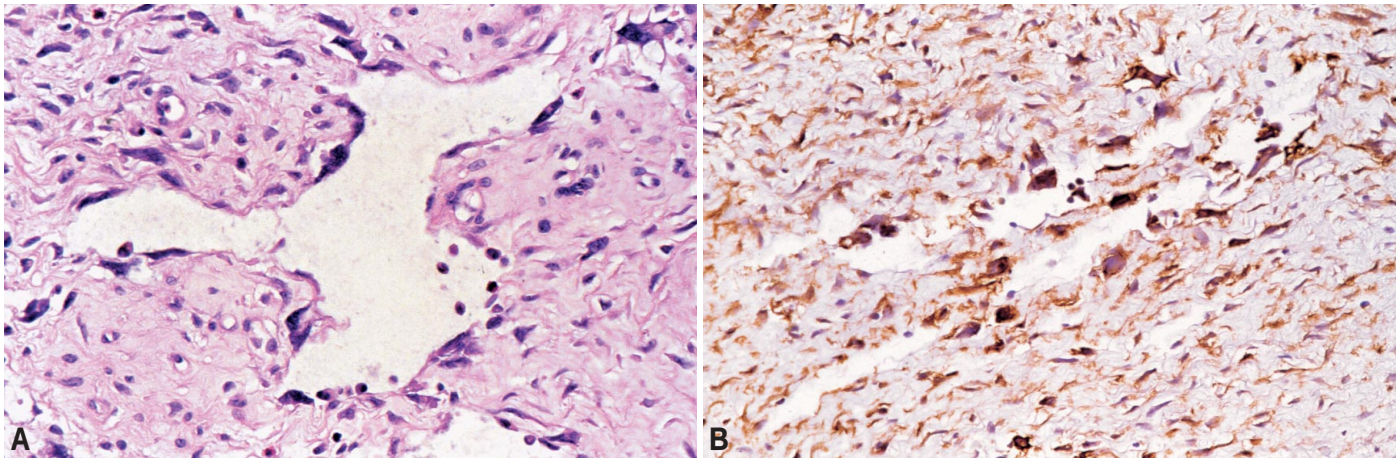


Fig. 5.31 Giant cell fibroblastoma. **A** Angiectoid space lined by hyperchromatic spindle and multinucleate giant cells. **B** CD34 highlights both the giant cells and the surrounding spindle cells.

Macroscopy
Grossly, GCF is a firm yellow or grey tumour with gelatinous or rubbery consistency and without haemorrhage or necrosis {751,2174}.

Histopathology
GCF is usually a subcutaneous tumour, but it often extends into the overlying dermis. Cellularity is variable, but for the most part, GCF is a hypocellular neoplasm composed of wavy spindle shaped cells and scattered giant cells set within a stroma that varies from myxoid to collagenous to sclerotic and contains scattered mast cells. Scattered giant cells with hyperchromatic and angulated nuclei are characteristic. Most giant cells are multinucleated, but some are mononucleated. The nuclei of multinucleate cells are either conglomerated towards the centre of the cell or arranged peripherally, in a characteristic floret pattern. Irregularly branching "angiectoid" spaces which resemble the vascular spaces of lymphangioma are characteristic but are not seen in all cases. These are lined by spindle and multinucleate cells with morphology identical to those seen in the surrounding stroma. Cellular areas representing DFSP or less often pigmented DFSP (Bednar tumour) may be present. Recurrent lesions are uncommon, but when they occur, the lesions may show a pattern of DFSP. Fibrosarcomatous transformation of GCF has been reported in a recurrent lesion originally diagnosed as DFSP {1841}.

Immunoprofile
The stromal and lining cells are CD34 positive, but negative for VWF (VIIIrAg), CD31, S100, actin, desmin, and EMA {971,2338}.

Differential diagnosis
Since CD34 can be focally positive in other soft tissue lesions, finding the characteristic giant cells is important in diagnosing GCF.

Histogenesis
GCF and DFSP are currently classified as neoplasms derived from fibroblasts, but CD34 positivity suggests possible derivation from interstitial dendritic cells {971}.

Somatic genetics
Both GCF and DFSP exhibit an identical t(17;22) (q22;q13) translocation, which in some cases results in a ring chromosome. The t(17;22) translocation fuses the collagen type I alpha 1 gene from chromosome 17q22 to the platelet-derived growth factor β chain gene from chromosome 22q13, resulting in a chimeric COL1A1-PDGFB gene that encodes for a transforming protein with biologic effects similar to normal PDGFB. The neoplastic cells not only harbour the mutation, but also have PDGFB receptors on their cell surface, resulting in an autocrine loop whereby the tumour cells stimulate their own growth {1735}.

Prognosis and predictive factors
Like DFSP, GCF is a locally aggressive tumour of intermediate malignancy, with up to 50% local recurrence in the original series. Metastases from GCF have not been reported.

Dermatofibrosarcoma protuberans

Definition
Dermatofibrosarcoma protuberans (DFSP) is a mesenchymal neoplasm of the dermis and subcutis, generally regarded as a superficial low-grade sarcoma {1605,2491}.

ICD-O code 8832/3

Synonym
Progressive and recurring dermatofibroma.

Epidemiology
DFSP typically presents during early or middle adult life, with male predominance. However, there is evidence that many tumours may have begun during childhood and become apparent during young adulthood.

Localization
The tumour occurs most commonly on the trunk, including chest, back, and abdominal wall. Less commonly, the neoplasm is located on the proximal extremities; it rarely involves the distal extremities. The head and neck, especially the scalp, are also commonly involved. The vulva {1377} and parotid gland are unusual sites of involvement.

Clinical features
DFSP typically presents as a nodular cutaneous mass, with a history of slow but persistent growth, often of several years duration. Early lesions may be sharply demarcated, and may some-

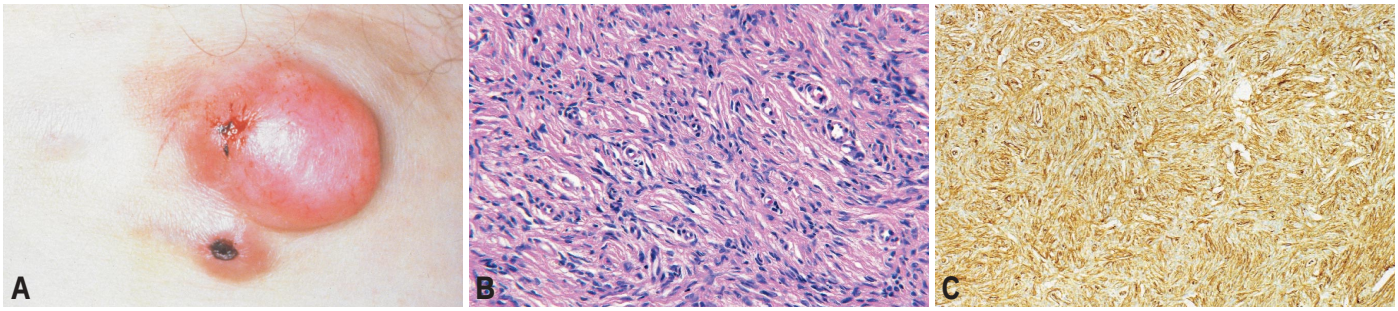


Fig. 5.32 Dermatofibrosarcoma protuberans. **A** DFSP presenting as two reddish nodules with focal ulceration. **B** Compact, uniform, spindle-shaped tumour cells arranged in a storiform pattern. **C** Tumour cells show a strong immunoreactivity for CD34.

times be observed as plaque-like areas of induration, often with peripheral red or blue discolouration. These tumours may resemble morphoea (localized scleroderma) or a morphoeic basal cell carcinoma. The lesion expands slowly, and eventuates in the typical, fully developed protuberant appearance with single or multiple nodules on a plaque-like base. Fungating ulcerated lesions with satellite nodules characterize an advanced neoplasm.

Patients with advanced DFSPs do not exhibit signs and symptoms of chronic wasting, as seen in patients with aggressive, high-grade soft tissue sarcomas. Previous burns, surgical scars, and antecedent trauma have been reported in association with this tumour. There are reports of DFSP occurring at Bacillle-Calmette-Guérin (BCG) vaccination sites {1558}, and in association with chronic arsenism {2176}, acanthosis nigricans, and acrodermatitis enteropathica {2161}. The tumour may show rapid enlargement during pregnancy {2329}.

Macroscopy

Most excised primary DFSPs are indurated plaques with one or more associated nodules. Multiple discrete, protuberant skin and subcutaneous tumours are more characteristic of recurrent neoplasms. Often, there is evidence of a surgical scar on the skin surface of the tumourous tissue. Ulceration may be present. The cut surface of the tumour is grey-white and firm, with occasional areas showing a gelatinous or translucent appearance, corresponding to microscopic areas of myxoid change. Haemorrhage and cystic change are sometimes seen. However, necrosis, a common feature of malignant fibrous histiocytoma, is rarely observed in DFSP. It is unusual to encounter DFSP confined solely to subcutaneous tissue without involvement of the dermis {629}.

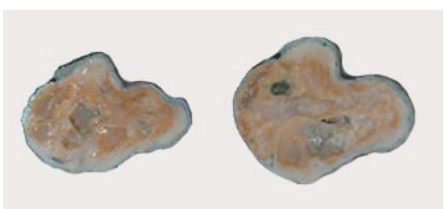


Fig. 5.33 Dermatofibroma (fibrous histiocytoma) Cut surface with distinctive yellow colour.

Histopathology

DFSP diffusely infiltrates the dermis, and invades into subcutaneous tissue, especially along the fibrous septa of fat. The epidermis is usually uninvolved. A grenz zone may be present. In a well-sampled specimen, the tumour shows some variation in histologic features. The centre of the tumour is typically composed of compact, uniform, slender, mildly atypical, spindle-shaped cells, arranged in a whorled, storiform, or cartwheel pattern. The tumour cells tightly encase skin appendages without destroying them. Nuclear pleomorphism is inconspicuous, and mitotic activity is low-to-moderate (<less than 5/10 HPF). Some tumours have a prominent myxoid matrix, and microscopic myxoid changes have been observed in both primary and recurrent tumours {368}. Superficial areas of the neoplasm are less cellular, and spindle cells are separated by dermal collagen. The deep portion of the tumour shows a proliferation of spindle cells which expand fibrous septa and interdigitate with fat lobules, resulting in a honeycomb appearance. In some tumours, giant cells similar to those of giant cell fibroblastoma are seen. At times, peculiar myoid nodules may be present, which represent a nonneoplastic myointimal or myofibroblastic proliferation. Occasional foci may resemble a low-grade fibrosarcoma, with longitudinal fascicles of spindle cells demonstrating more prominent nuclear atypia and mitotic activity (but not greater than 5/10 HPF). Such areas have been seen in a minority of primary or recurrent lesions {853}.

Immunoprofile

DFSP cells label diffusely and strongly with antibodies to CD34 and vimentin. CD34 positivity may be lost in nodular regions. P75 (low-affinity nerve growth factor receptor) has been reported positive in DFSP cells {853}. Tumour cells are negative for S-100 protein, smooth muscle actin, desmin, keratins, and epithelial membrane antigen. Scattered Factor XIIIa positive cells may be present. Tenascin is negative at the dermoepidermal zone (DEZ) in DFSP {1180}. Stromelysin 3 is not expressed in the cells of a DFSP in contrast to dermatofibroma in which it is invariably expressed {558}.

Differential diagnosis

Benign and cellular fibrous histiocytoma or dermatofibroma (DF) can be differentiated from DFSP by the presence of epidermal (sometimes basal cell) hyperplasia, more prominent collagenous stroma, collagen trapping, and infiltration of the fibrous septa, but minimal extension into fat lobules. Immunostains are also helpful. DF contains a focally but not diffusely positive CD34 spindle cell component. P75 and stromelysin 3 are negative, and tenascin is positive at the DEZ in DF.

Diffuse positivity for S-100 protein and the presence of Meissner-like corpuscles separate lesions of diffuse neurofibroma from DFSP.

Malignant fibrous histiocytoma (MFH) exhibits a higher degree of cellular atypia, pleomorphism, and mitotic activity

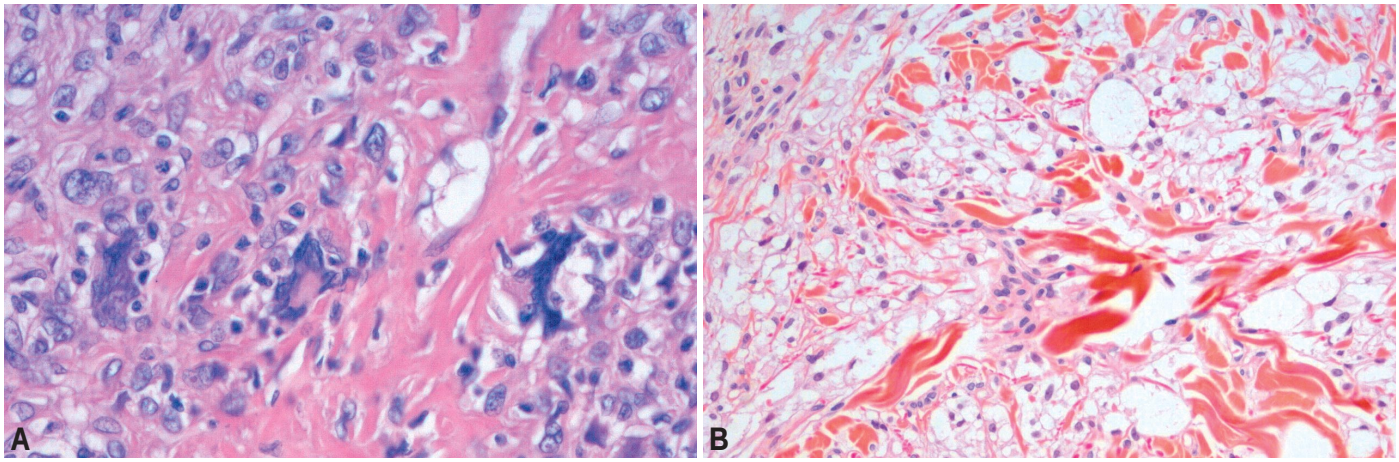


Fig. 5.34 Dermatofibroma (fibrous histiocytoma). **A** Dermatofibroma with monster cells. **B** Clear cell dermatofibroma. Typical cytology with prominent collagen bundles.

than DFSP. Necrosis is usually not a feature of DFSP, but is generally seen in MFH. Myxoid liposarcoma is distinguished from myxoid forms of DFSP by the presence of lipoblasts, negative CD34 staining, and deep soft tissue involvement.

Histogenesis
DFSP and its variant, giant cell fibroblastoma (GCF) are currently classified as neoplasms derived from fibroblasts. CD34 labelling suggests a close linkage to dermal dendrocytes.

Somatic genetics
DFSP and GCF exhibit an identical chromosomal translocation. See page 259.

Prognosis and predictive factors
As with GCF, DFSP has a significant risk of local recurrence. The average recurrence rate in reported cases treated by wide local excision (2-3 cm.) is 18%. A much higher recurrence rate (43%) is reported in tumours treated by superficial or incomplete excisions only {853} Local recurrence usually develops within three years after initial surgery. Metastasis occurs rarely.

Dermatofibroma (fibrous histiocytoma)

Definition
Dermatofibroma (fibrous histiocytoma) {21} is an ill-defined, predominantly dermal lesion characterized by a variable number of spindle and/or rounded cells. A variable admixture of inflammatory cells, coarse collagen bundles in haphazard array, and variable epidermal, melanocytic and folliculosebaceous hyperplasia are present.

ICD-O code
8832/0

Synonyms
Histiocytoma (cutis) {2134}, fibroma durum, subepidermal nodular fibrosis or sclerosis {1602}, sclerotic or sclerosing fibroma {1895}, sclerosing haemangioma {910}.

Epidemiology
Dermatofibroma is a very common lesion and may develop at any age, but particularly during the third and fourth decades. The gender distribution varies among different populations.

Etiology
The etiology has not been established unequivocally. It is controversial whether it is an inflammatory {21,2590,2591} or neoplastic process {365,518,522,919}. Dermatofibroma has been reported following local injuries such as trauma, insect bites or folliculitis, suggesting an inflammatory etiology. By contrast some examples have been reported to be clonal, supportive of a neoplastic etiology {457,1078,2422}.

Localization
Most lesions, including various clinicopathological variants, occur on the extremities {840,1081,1114,1155,1187, 1346,1786,1895,2115,2587,2592-2594} and trunk {187,370,2403}. Rare cases occur on the face {1583}.

Clinical features
Most lesions are single, round, oval to targetoid papules. Early lesions are reddish, but older ones are brown to skin coloured, frequently with a brown rim at the periphery. They usually evolve rapidly. Dermatofibromas are moderately well circumscribed; the consistency usually is hard, but may be cystic, eroded or crusted when secondary changes such as prominent haemorrhage, lipidization or trauma alter the lesions. Most lesions are flat, slightly elevated or show a shallow dell. The “dimpling” sign, when lesions are squeezed between the thumb and index finger, is characteristic.
Occasionally, there may be a few, up to several dozen, sometimes grouped (“agminated”) papules. Multiple dermatofibromas are regarded as a marker of immune suppression; they have been observed in Black females with systemic lupus erythematosus; various other autoimmune disease such as Sjögren syndrome, pemphigus vulgaris, myasthenia gravis and ulcerative colitis treated with immunosuppressive drugs; occasionally in renal graft recipients or AIDS patients. Still other lesions form plaques or nodules to tumours. Dermatofibromas usually are long standing lesions which cause no symptoms.

Macroscopy
Gross examination reveals a moderately well-circumscribed, hard papule, nodule or tumour. The cut surface reveals a skin-coloured to distinctive yellow colour, which may show areas of haemorrhage and lipidization and then become cystic.

Histopathology

Dermatofibromas show a dense infiltrate of spindle-shaped and/or round cells, some of which may be fibrocytes and/or macrophages, centred in the reticular dermis and sometimes, the upper part of the subcutis. Early lesions are rich in macrophages, some of which may be siderophages, and/or lipophages, others multinucleate, e.g. Touton or foreign body giant cells. Established lesions show prominent cellularity and coarse haphazardly arranged collagen bundles. They are frequently arranged in short fascicles that interweave ("storiform"), sometimes with a sclerotic centre.

Lesions are ill-defined and at the periphery there can be collagen trapping by lesional cells ("collagen ball formation"). Epidermal, melanocytic and folliculosebaceous hyperplasia is characteristically found above the lesions, and this can be so prominent that buds of hair follicles mimic superficial basal cell carcinoma. Rare cases show smooth muscle proliferation {1381}. Lymphocytes are often spread throughout the lesion with frequent prominence at the periphery, but may be lacking in later stages. At times foam cells may be prominent in deeper areas adjacent to subcutaneous fat.

A wide number of variants of dermatofibromas have been proposed {369}. Early lesions may show prominent proliferation of blood vessels, previously called sclerosing haemangioma {910}, more recently haemangiopericytoma-like fibrous histiocytoma {2594}. Prominent lipophages and siderophages are seen in the xanthomatous/histiocytic variant {1081,1114} and haemosiderrhotic variant {2036}, respectively. Older lesions become progressively fibrotic, with shrinkage of the lesion, particularly seen in atrophic dermatofibroma. Other variants show a heavy eosinophilic infiltrate {40} or pseudolymphomatous features {150}, respectively. Lichenoid, erosive and ulcerated variants {2034} have also been reported. Deep penetrating variants extend into the subcutis and may be easily confused with dermatofibrosarcoma protuberans {1187,2587}. Other rare variants include dermatofibroma with monster cells {2316}; ossifying dermatofibroma with osteoclast-like giant cells {1345}; granular {2403} and clear cell dermatofibromas {1786,2592}; myofibroblastic dermatofibroma with slender cytoplasmic cell extensions {2593}; myxoid dermatofibromas {2183,2588}; or combined dermatofibromas {2589}, which show a combination of several unusual histopathologic features in one lesion.

Immunoprofile

Dermatofibromas reveal a variable immunohistochemical profile: early lesions are rich in reactivity for macrophage markers such as PGM1 or KP1 (CD68), but also exhibit strong reactivity for factor XIIIa in both macrophages and fibroblasts {2590}. This reactivity is mostly seen at the periphery and continuously diminishes with the ageing of the lesion to be completely absent in atrophic variants. Actin expression is variably seen in dermatofibromas particularly in the myofibroblastic variant {2593}. Occasionally dermatofibromas are focally positive for CD34 {1840,2584}. Recently, stromelysin 3 expression has been reported. It is not expressed in DFSP {558}.

Differential diagnosis

The most important histologic differential diagnoses are dermatofibrosarcoma protuberans (particularly with the cellular variant of dermatofibroma) and Kaposi sarcoma. Dermatofibrosarcoma protuberans is poorly circumscribed, usually much broader and deeper with irregular dissection of subcutis, and shows cells with wavy nuclei in association with delicate fibrillary bundles of collagen frequently arranged in a storiform pattern. In contrast to dermatofibroma it is regularly positive for CD34. Kaposi sarcoma in nodular and tumour stage is characterized by erythrocytes extravasated into slits between interweaving fascicles of spindle-shaped cells; often, tiny pink hyaline globules that represent degenerated erythrocytes are found in these spindle-shaped endothelial cells.

Lesions are positive for CD34 and vascular markers such as CD31.

Variants

Aneurysmal fibrous histiocytoma

This is not uncommon {367,2054}, It may rapidly enlarge because of spontaneous or traumatic haemorrhage into a previously unspectacular lesion or rarely de novo development, and frequently is painful. Clinically, it may mimic nodular melanoma or nodular Kaposi sarcoma. Histology reveals extravasation of erythrocytes, pseudovascular spaces and iron deposits. This histology may occasionally also be confused with melanoma or nodular Kaposi sarcoma, yet the absence of melanocytic as well as vascular markers in the spindle cells easily excludes these simulants.

Epithelioid cell histiocytoma

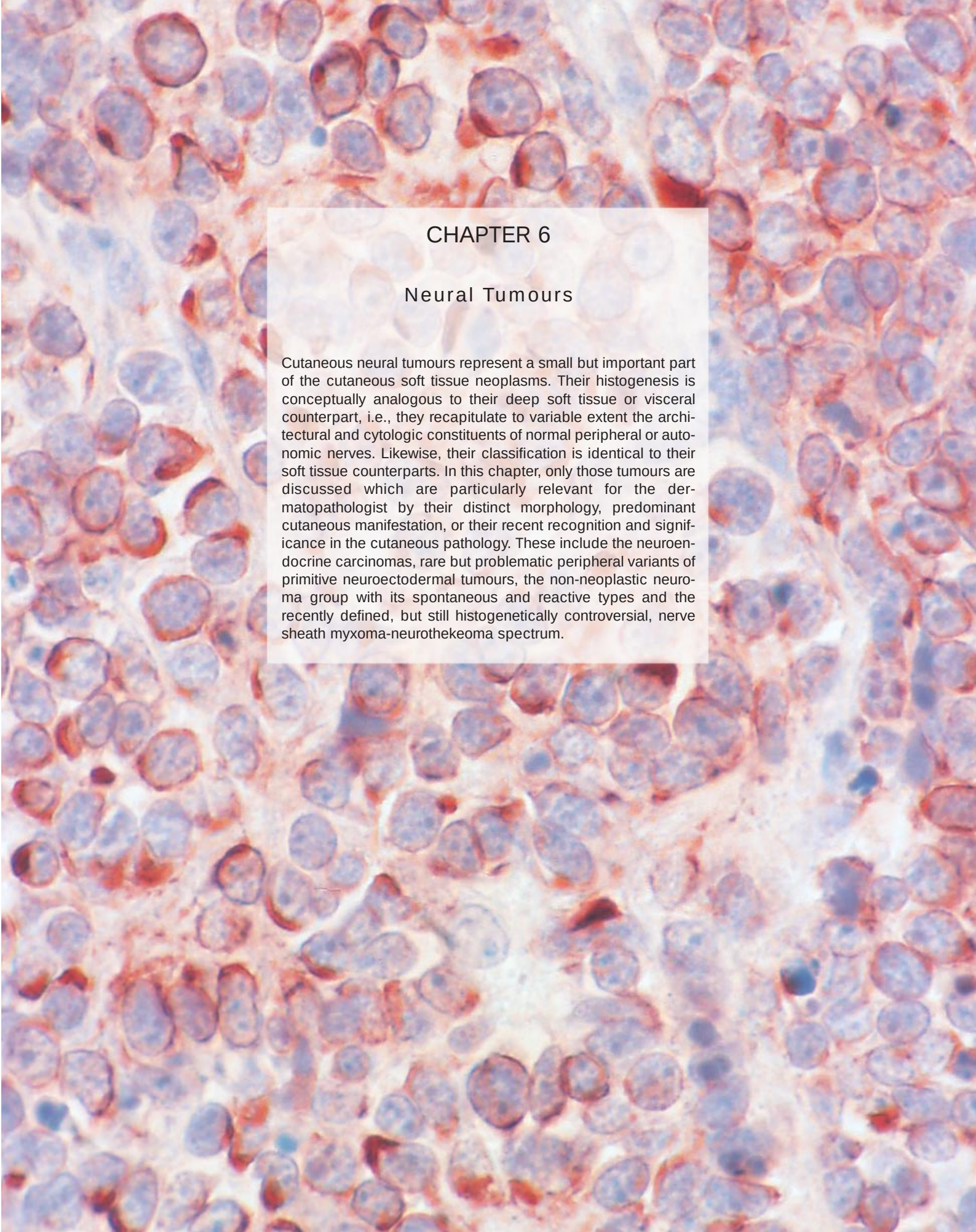
This lesion {840,1155}, including a cellular variant {794} is rare. It occurs on the upper extremities and trunk as a skin-coloured to reddish-brown, hard, exophytic papule, frequently thought to be a Spitz naevus. Histology reveals a lesion mostly restricted to the papillary dermis, prominent epidermal hyperplasia ("collarette") and a sheet-like infiltrate of epithelioid to scalloped fibroblasts. These features may also closely simulate Spitz naevus, yet lesions are negative for melanocytic markers, but positive for factor XIIIa.

Cellular fibrous histiocytoma

This variant is rare {370}. It occurs on the trunk or distal extremities and has a tendency to recur when incompletely excised. Histology reveals a dense, frequently deeply infiltrating lesion of spindle cells in an otherwise typical dermatofibroma. There may be moderate nuclear atypia, occasional mitoses and bizarre giant cells and these lesions have therefore also been called pseudosarcomatous or atypical fibrous histiocytomas {794}. Exceptional cases of this variant have been reported to metastasize and, accordingly, they should always be completely excised.

Prognosis and predictive factors

The vast majority of lesions are benign. Occasionally incomplete excision may result in recurrence. The cellular and aneurysmal variants and lesions of the face may recur in a significant percentage of cases {1583}. Exceedingly rare cases of local aggressive growth or metastases to local or regional lymph nodes or even with wide spread metastases to lung have been recorded in the cellular variant.



CHAPTER 6

Neural Tumours

Cutaneous neural tumours represent a small but important part of the cutaneous soft tissue neoplasms. Their histogenesis is conceptually analogous to their deep soft tissue or visceral counterpart, i.e., they recapitulate to variable extent the architectural and cytologic constituents of normal peripheral or autonomic nerves. Likewise, their classification is identical to their soft tissue counterparts. In this chapter, only those tumours are discussed which are particularly relevant for the dermatopathologist by their distinct morphology, predominant cutaneous manifestation, or their recent recognition and significance in the cutaneous pathology. These include the neuroendocrine carcinomas, rare but problematic peripheral variants of primitive neuroectodermal tumours, the non-neoplastic neuroma group with its spontaneous and reactive types and the recently defined, but still histogenetically controversial, nerve sheath myxoma-neurothekeoma spectrum.

WHO histological classification of neural tumours

Primitive neuroectodermal tumour (PNET)	9364/3
Ewing sarcoma	9260/3
Nerve sheath myxoma	9562/0
Merkel cell carcinoma	8247/3
Granular cell tumour	9580/0

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of skin (Merkel cell) carcinomas[1]

TNM classification[2,3]

T – Primary tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ

T1 Tumour 2 cm or less in greatest dimension
T2 Tumour more than 2 cm but no more than 5 cm in greatest dimension
T3 Tumour more than 5 cm in greatest dimension
T4 Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M – Distant metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

[1] For PNET and Ewing sarcoma see TNM table of soft tissue tumours
[2] {894,2219}.
[3] A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508 .

Palisaded, encapsulated neuroma and traumatic neuroma

Z.B. Argenyi

Palisaded, encapsulated neuroma

Definition
Palisaded, encapsulated neuroma (PEN) is considered a spontaneous proliferation of nerve fibres without evidence of previous trauma.

Synonyms
Solitary circumscribed neuroma, spontaneous neuroma, true neuroma

Historical annotation
The tumour was described by Reed et al. in 1972, who pointed out that despite the occasional nuclear palisading and encapsulation, the tumour is different from Schwannoma {1908}.

Epidemiology
PEN is most common in the 5th and 7th decades and occurs in an approximately equal ratio in both genders. The majority of the lesions, about 90%, are located on the face, but they can occur anywhere on the body. Mucosal involvement has also been recorded {453,752,1908}.

Clinical features
PEN usually manifests as a solitary, small (2-6 cm), skin-coloured or pink, firm or rubbery, dome-shaped, asymptomatic papule or nodule. There is no established association with neurofibromatosis {453,752,1908}.

Macroscopy
On cut sections, the tumour is a yellow-pink, firm ovoid mass in the dermis.

Histopathology
On low magnification, PEN is a well-circumscribed, round or oblong nodule located in the dermis. It is surrounded by a thin fibrous capsule, which is poorly discernible or incomplete near to the epidermal aspect of the tumour. The tumour is composed of tightly woven fascicles which are separated by cleft-like spaces. The proliferating cells are slender spindle cells with ovoid, evenly chromatic nuclei and eosinophilic cytoplasm.
A parallel arrangement of nuclei resembling a palisading pattern or rudimentary Verocay bodies is occasionally present. Mitotic figures are rare or absent. PEN lacks distinct fibrosis, inflammation or granulomatous reaction. A connection with the originating nerve usually requires serial sectioning of the tissue. Silver impregnation reveals numerous nerve fibres (axons), usually in parallel arrangement with the longitudinal axes of the fascicles {55,80,90,453,585,646, 752,1314,1908}.

Immunophenotype
The cells in the capsule stain for epithelial membrane antigen, whereas the spindle cells of the fascicles are positive for S-100 protein and collagen type IV. The axons are labeled with antibodies to neural filaments. Variable myelinization is detected by CD57 (Leu-7) and myelin basic protein {55,80,90}.

Variants
Plexiform and multinodular types.
These rare variants represent unusual growth pattern, but otherwise they retain the usual internal structures and composition of PEN {81,84}.

Spontaneous, non-encapsulated neuromas
These tumours are part of the Multiple Mucosal Neuroma (MMN) syndrome, which is often part of the Multiple Endocrine Neoplasia syndrome (MEN2b), which is associated with pheochromocytoma and medullary carcinoma of the thyroid {815}. The neuromas in MMN manifest as numerous, soft-rubbery, skin-coloured or pink papules and nodules around mucosal orifices, lip, eyelids, and tongue, but scattered cutaneous involvement can also occur {835,1658,1994}. Musculoskeletal abnormalities and intestinal ganglioneuromato-

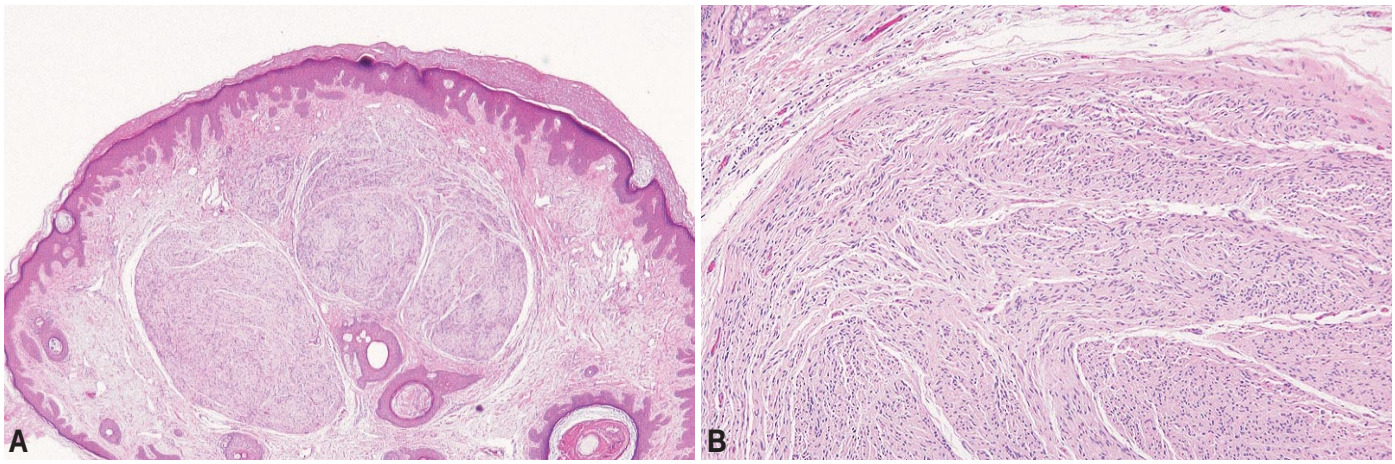


Fig. 6.1 Palisaded, encapsulated neuroma. **A** Multinodular variant of palisaded encapsulated neuroma. **B** The tumour is formed by compactly arranged fascicles separated by artificial clefts.

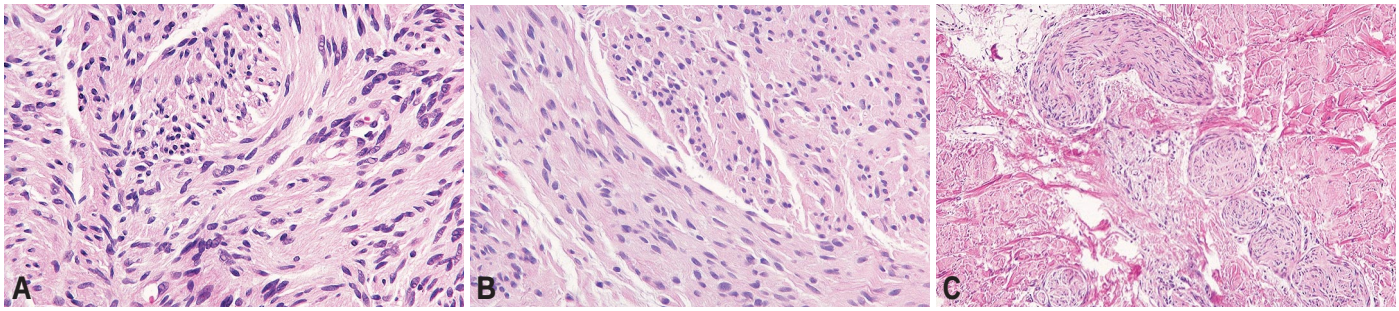


Fig. 6.2 Palisaded, encapsulated neuroma (PEN). **A** Internal structure and cytology correspond to the classical type of PEN. **B** The fascicles are composed of uniform spindle cells without cytologic atypia. Despite the term, no distinct nuclear palisading is present. **C** Spontaneous, non-encapsulated neuromas of Multiple Mucosal Neuroma Syndrome. The tumour is composed of linearly arranged hyperplastic nerve bundles infiltrating the dermis.

sis are also part of the syndrome {236,2504}. Histologically, the tumour is composed of numerous tortuous or fascicular arrangements of hyperplastic nerve bundles infiltrating the submucosa or the dermis, hence the term "non-encapsulated neuroma" has also been applied. The individual fascicles have a linear, elongated appearance instead of the round or oblong structure of PEN; however, the constituent cells are identical to those seen in PEN. Occasionally perineurial and endoneurial increase of mucin can be noted. The immunohistochemical profile of this variant is similar to PEN {815, 835,1658,1994}.

Genetics

Activated mutations of the RET proto-oncogene, involving the somatic or the germinal cell-lineage are found in both the inherited and acquired forms {466, 545,2310}. However, MMN without genetic abnormalities have also been reported {1863,2379}.

Prognostic factors

PEN and its variants are benign, and simple excision is a sufficient treatment. The mucosal neuromas of MEN2b often precede the manifestation of the other endocrine tumours. Therefore their correct recognition is important {1020}.

Traumatic neuroma

Definition

Traumatic neuromas represent reactive or regenerative proliferation of the nerve sheath components as an attempt to reestablish lost nerve integrity after sharp or blunt physical trauma.

Synonyms

Amputation neuroma, supernumerary digit

Epidemiology

Traumatic neuromas can occur at any age or gender. The amputation type is more common on the extremities {1535}. A special variant sometimes referred to incorrectly as "supernumerary digit" occurs on the lateral aspects of hands or feet of newborns. They represent amputation neuromas at the site of the in-utero separated extranumerary digit {487,2152}.

Clinical features

Traumatic neuromas develop at the sites of previous trauma usually as solitary, skin-coloured, broad-based, firm papules and nodules. They are often sensitive or painful on pressure.
Lancinating pain is characteristic of amputation neuromas {351,530,2342}.

Macroscopy

Traumatic neuromas are firm, white-yellow, ill-defined dermal or subcutaneous masses often in a discernible association with the proximal nerve stump.

Histopathology

The tumour is composed of an irregular, haphazardly arranged proliferation of regenerating nerve fascicles of various sizes and shapes embedded in a fibrous stroma. Earlier lesions show acute and chronic inflammation, occasional granulomatous inflammation, whereas more established lesions are markedly fibrotic. Although the tumour is encased in the sclerotic stroma, there is no true encapsulation, and the distal end of the regenerating nerve fascicles often infiltrates the stroma {90,2084}. The individual nerve fascicles appear to recapitulate the architecture of the normal nerve fascicles, but there is considerable variation in their diameter. The constituent cells

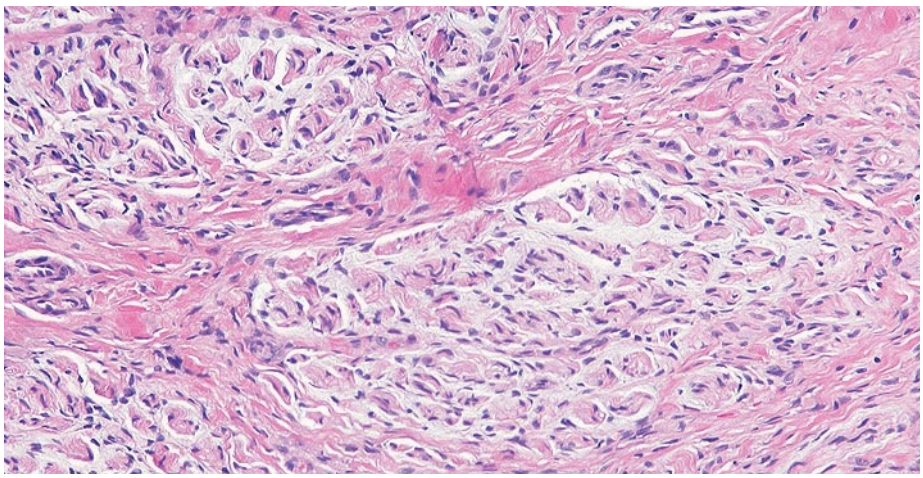


Fig. 6.3 Traumatic neuroma. There is an ill-defined dermal nodule composed of irregularly arranged proliferation of nerve fascicles embedded in a fibrotic (scarred) stroma.

are slender spindle cells (Schwann cells, perineurial cells, and endoneurial fibroblasts). Silver impregnation reveals numerous nerve fibres (axons) in the tumour in a pattern approximating the normal 1:1 ratio of Schwann cells and axons. The “supernumerary digit” is a polypoid lesion covered by thick hyperorthokeratosis with a fibrous stalk containing regenerating nerve fascicles. The morphology of the regenerating nerve fibres is identical to the ones seen in other amputation neuromas.

Immunohistochemistry

The constituent spindle cells of the nerve fascicles are positive for S-100 protein, collagen type IV, whereas the surrounding perineurial cells, when present, stain for epithelial membrane antigen. Antibodies to neural filaments highlight the axons, and myelinization can be demonstrated by antibodies to myelin basic protein and CD57 (Leu-7).

Prognostic factors

Traumatic neuroma is a reactive lesion, however it can cause local interference with adjacent organs and is often symptomatic. The usual treatment is simple excision.

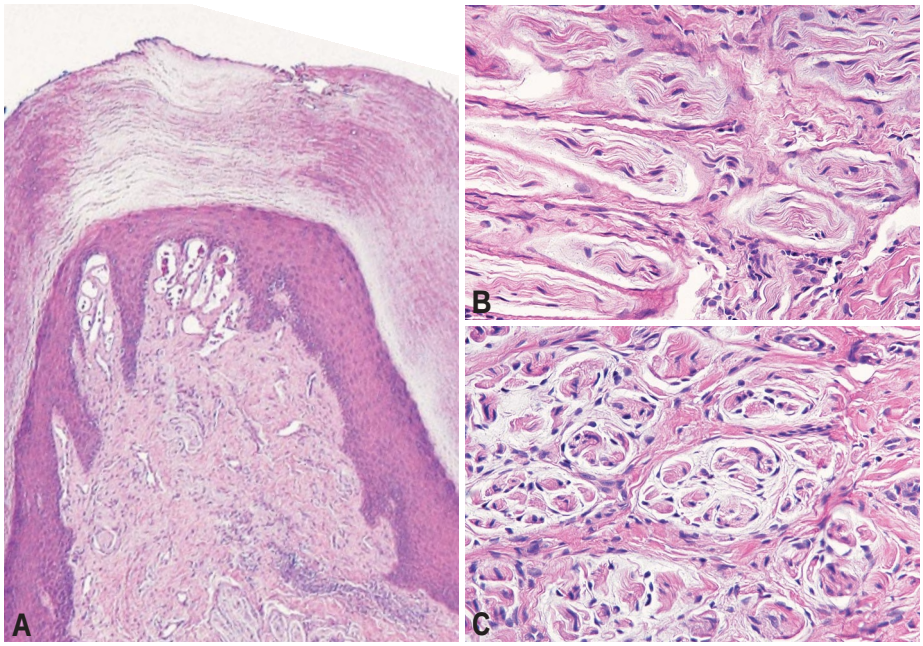


Fig. 6.4 Traumatic neuroma. **A** Supernumerary digit (amputation neuroma). Acral polypoid lesion with proliferation of nerve fascicles at the base of stalk. **B** Higher magnification of the regenerating nerve fascicles in the fibrous stroma. **C** The regenerating nerve fascicles show variation of diameter and orientation. The clear spaces correspond to increased perineurial mucin.

Primary malignant peripheral primitive neuroectodermal tumour (PNET) / Extraskeletal Ewing sarcoma (ES)

S.S. Banerjee

Definition

PNET/ES are malignant small blue round cell tumours, which exhibit varying degrees of neuroectodermal differentiation. In the past, they were regarded as separate entities, but recent cytogenetic and molecular genetic studies have proven that they represent two ends of a phenotypic spectrum of the same tumour type – Ewing sarcoma being relatively undifferentiated and PNET showing morphological (light microscopic/ultrastructural) and/or immunohistochemical features of neuroectodermal differentiation.

ICD-O codes

PNET	9364/3
Ewing sarcoma	9260/3

Synonyms

Peripheral neuroepithelioma, peripheral neuroblastoma

Epidemiology

Primary PNET/ES of skin and subcutaneous tissue are rare neoplasms. These tumours are mainly seen in children and young adults (median age 18 yrs), but they occasionally afflict elderly individuals. There is no significant sex predilection {72,82,138,449,978,1389,1791, 1815,2050,2146,2210,2295,2328,2416}.

Etiology

The etiology of this tumour is unknown.

Localization

These neoplasms have been described on the scalp, face, neck, shoulder, trunk and extremities.

Clinical features

The tumours usually present as ulcerated or non-ulcerated, often painless, but rarely tender, nodules. Occasionally, they appear polypoid {138,978}. Not infrequently, they are clinically misdiagnosed as benign tumours or cysts. A case of cutaneous PNET with numerous tumour nodules that were present for several years has been documented {2050}.

Macroscopic features

The tumours are greyish white and fleshy. Foci of haemorrhage are sometimes noted. Their sizes usually vary from 5 cm to 10 cm.

Histopathology

The tumours usually occupy the dermis with focal extension into subcutis. Some tumours are entirely subcutaneous in location. The overlying epidermis may become ulcerated. The margins may be pushing or infiltrative. The neoplastic cells are small, round to oval and contain hyperchromatic or vesicular nuclei and scanty pale eosinophilic or vacuolated cytoplasm with ill-defined borders. The nucleoli are indistinct or absent. The cells are arranged in sheets, lobules, nests and trabeculae. The mitotic activity and necrosis vary from case to case. Many dark apoptotic cells may be seen. Prominent fibrovascular septa are present in most lesions and some exhibit peritheliomatous or pseudopapillary arrangement of cells. Occasionally, the stromal blood vessels form glomeruloid tufts with prominent endothelial and myointimal cells. Microcystic, pseudoglandular and pseudovascular spaces are observed in many neoplasms. Homer Wright rosettes and neuropil are only rarely present. In atypical examples of this tumour, larger cells with prominent nucleoli, pleomorphic cells with irregular nuclei or groups of mononuclear or binucleate rhabdoid or plasmacytoid cells are seen. Prominent epidermal inclusion cysts within the tumour have been described in one case. Intracytoplasmic glycogen can be demonstrated in most cases. The reticulin stain reveals fibrils around groups of tumour cells. The differential diagnosis of this neoplasm includes deposits of lymphoma/ leukaemia, Merkel cell carcinoma, metastatic small cell neuroendocrine carcinoma, metastatic neuroblastoma, primary or metastatic rhabdomyosarcoma, glomus tumour, small cell melanoma and rare types of sweat gland tumour such as eccrine spiradenoma and non-neuroendocrine small cell carcinoma. Attention to histological detail, immuno- histochemistry, EM studies and genetic analysis help to reach the right diagnosis.

Immunohistochemistry

Characteristically, the neoplastic cells exhibit positivity for CD99 (MIC2 gene product), ß2 microglobulin, FLI-1 gene product, vimentin and one or more puta-

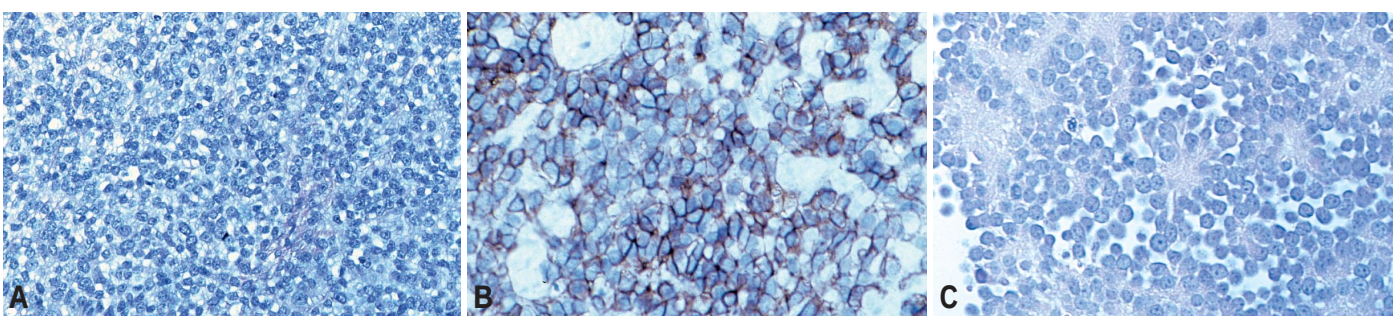


Fig. 6.5 Primary PNET/EES of skin. **A** Tumour composed of sheets of monomorphic small round cells containing hyperchromatic nuclei and scanty cytoplasm. **B** Strong membranous CD99 positivity in the neoplastic cells. **C** Homer-Wright rosettes. They are only rarely seen in these neoplasms.

tive neural/neuroendocrine markers such as NSE, PGP 9.5, neurofilament proteins, synaptophysin and Leu-7. Usually the stain for chromogranin is negative. The CD99 positivity is usually strong, diffuse and membranous. The FLI-1 stains the nuclei of the neoplastic cells. Aberrant cytokeratin, desmin, GFAP, S100 protein and NKIC3 expression may be noted in scattered cells in some cases. The tumour cells are negative for LCA, B&T cell markers, myeloperoxidase, muscle specific actin, MYO-D1, myogenin, EMA and HMB 45 {138}.

Electron microscopy

At the Ewing end of the spectrum, the cells appear rather non-descript with round nuclei and scanty organelles. There is usually abundant glycogen. The PNETs show elongated interdigitating cytoplasmic processes with a few rudimentary junctions, intermediate filaments, microtubules and sparse membrane bound dense core neurosecretory granules (100-250 nm in diameter). No myofilaments, desmosomes or melanosomes are seen {138}.

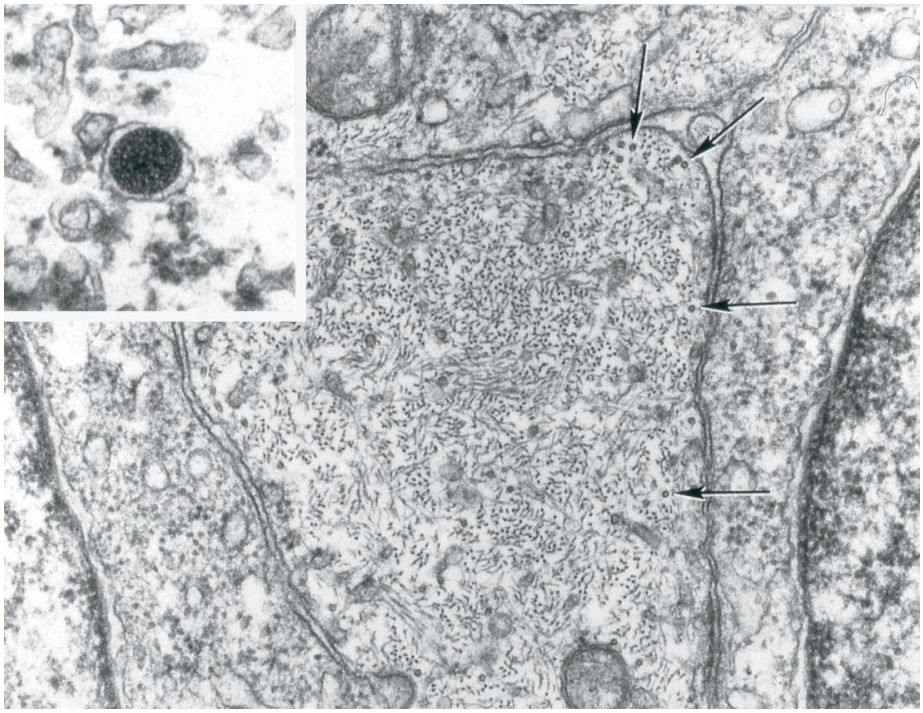


Fig. 6.6 Primary PNET of skin. Electron microscopy of a cutaneous PNET: the cytoplasmic processes of the neoplastic cells contain intermediate filaments and microtubules (arrow). The inset shows a neurosecretory granule.

Genetics

Around 90% of skeletal and extraskeletal PNET/ES exhibit a characteristic chromosomal translocation, t(11;22)(q24;q12). This results in the fusion of EWS gene on chromosome 22q12 with FLI-1 gene on chromosome 11q24. A small number of cutaneous cases have been subjected to cytogenetic/genetic studies and these have also demonstrated the typical genetic defects {978,1389}. An additional copy of chromosome 22 was detected in one case. Conventional cytogenetic study, FISH and RT-PCR techniques have been used to detect these abnormalities.

Prognosis and predictive factors

These neoplasms are aggressive with metastatic potential. The usual sites of metastasis are regional lymph nodes, lung, liver and bones. However, the cutaneous PNET/ES appear to have a better prognosis than their soft tissue counterparts, probably because they are detected early and can be resected adequately. Long term survival has been recorded in a few cases with or without radiotherapy and adjuvant combination chemotherapy {138,478,978,2328}. A prognostically relevant grading or staging system is not yet available for these neoplasms.

Nerve sheath myxoma / neurothekeoma

Z.B. Argenyi

Definition
These tumours encompass a spectrum of neuromesenchymal neoplasms characterized by proliferation of nerve sheath cells in a variable myxomatous stroma. They can be further classified into “classic” and “cellular” types.

ICD-O code 9562/0

Synonyms
Cellular neurothekeoma (used exclusively for the cellular variant), cutaneous lobular neuromyxoma, myxomatous perineuroma

Epidemiology
These tumours are rare. The "classic type" has been reported in middle-aged adults (mean 48.4), with predominance in females, of the head and neck areas and upper extremities {73,1865}. The "cellular type" has been observed in younger adults (mean 24 yrs), more common in females, predominantly on the head and neck areas {88,99,161,371}. However, both types can occur at any age and at any location {229,418,479, 1222,1674,1684,2355}.

Clinical features
The “classic types” manifest as skin-coloured, pink, soft, rubbery papules and nodules, whereas the “cellular types” have a firmer, rather red-tan-brown appearance. Their size ranges between 0.5–2.0 cm. Both types are commonly asymptomatic, but may become sensitive or tender {73,88,99, 161,371,1865}.

Histopathology
The “classic type” is usually a well-defined, multilobular or fascicular tumour located in the dermis with or without extension to the subcutis. The lobules contain abundant myxomatous stroma, which appear to be confined by a thin fibrous encapsulation. The mucin is connective tissue type acidic mucopolysaccharide and stains strongly with colloidal iron, which clears after hyaluronidase treatment. Within the mucinous stroma, there are sparsely distributed spindle, stellate, and polygonal cells without appreciable cytologic atypia. Mitotic figures are rare or absent {73,88,755,1865}. The “cellular variant” shows an ill-defined, often infiltrative growth pattern involving the dermis and subcutis. The proliferating cells form fascicles and nests and are arranged in a plexiform or multilobular pattern. The constituent cells are mainly epithelioid type with ample eosinophilic cytoplasm and indistinct cytoplasmic membranes. The cells have large “bubbly nuclei” with prominent nucleoli. In a smaller percentage of the cases, the tumour is composed of spindle cells with plump or ovoid nuclei forming nests and whorls. In the “cellular type”, cytologic and nuclear atypia are more common and mitotic figures can be conspicuous. Myxoid material is usually scant or present only around the individual nests {88,99,161,371}. In both the “classic” and “cellular types”, associated stromal changes, such as fibrosis, hyalinization of the collagen, patchy chronic inflammation, and angioplasia can occur. Changes showing transition between the “classic” and “cellular types” within the same lesion have been documented. A direct connection with nerve twigs can be demonstrated only rarely.

Immunohistochemistry
The stromal cells in the “classic” type stains strongly for S-100 protein, collagen type IV and weakly for neuron-specific enolase and CD57 (Leu-7). The capsule, when present, may label for epithelial membrane antigen. The “cellular” type does not have a specific or consistent phenotype. The cells show variable expression of PGP9.5, collagen type IV, NK1/C3, CD34, and occasionally smooth muscle specific actin and CD57 (Leu-7). Staining for S-100 protein is rare, and

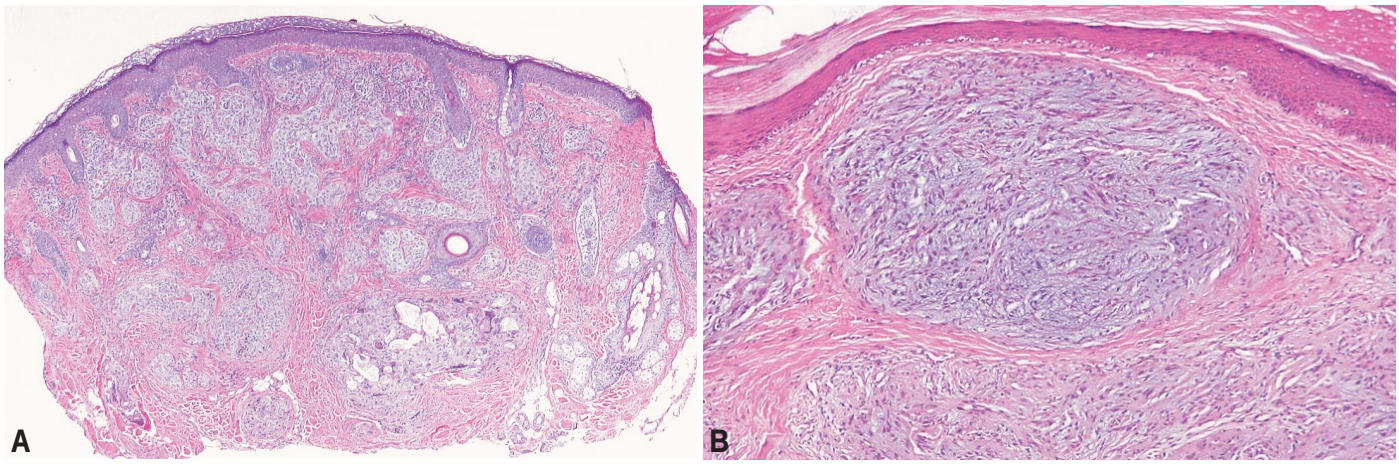


Fig. 6.7 Nerve sheath myxoma (neurothekeoma). **A** Cellular neurothekeoma (cellular variant of nerve sheath myxoma). The tumour cells form nests and strands infiltrating the dermis. **B** Nerve sheath myxoma "classical type". Lobular and fascicular dermal proliferation with myxomatous stroma.

when present it is usually in lesions where there are elements of the "classical" type {87,88,99,161,371,798,1370, 2281,2454}

Prognosis

Both variants are considered benign tumours, although rare cases of the "cellular" type with concerning cytologic atypia and mitotic activity have been reported {231,357}. Both tumours can recur after incomplete removal; therefore, a complete excision is recommended for treatment.

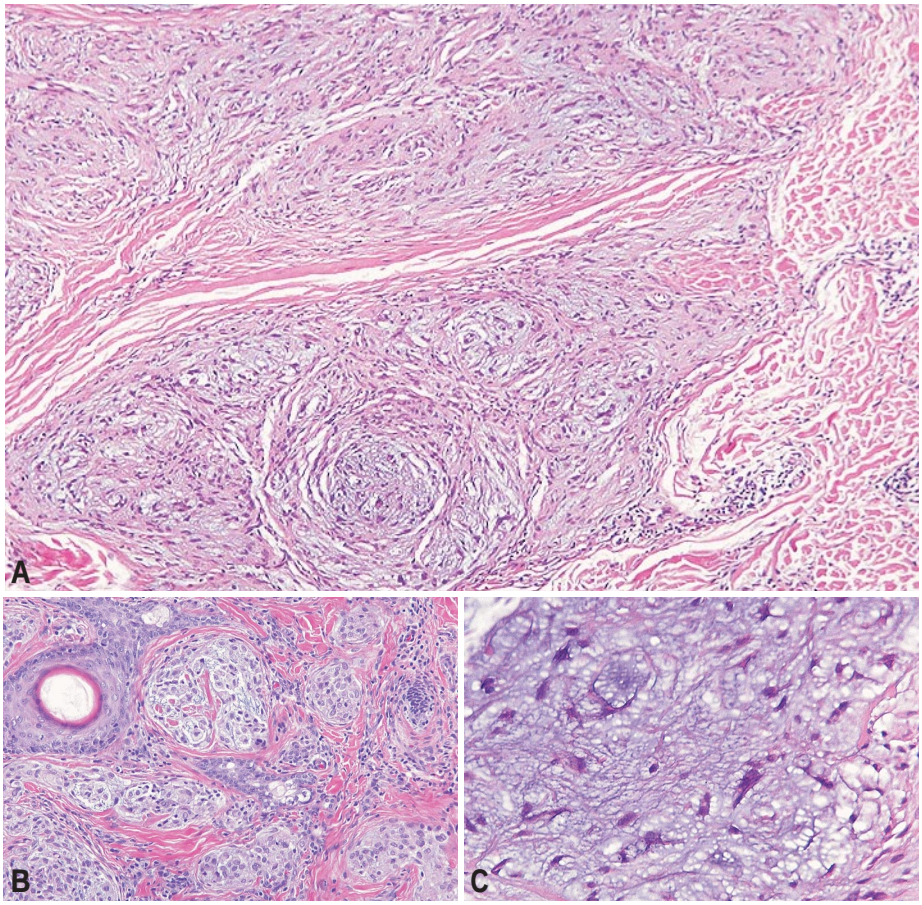


Fig. 6.8 Nerve sheath myxoma (neurothekeoma). **A** Higher magnification of the lobules shows the mixture of variable cellularity and myxomatous changes. **B** The tumour nests are well defined, but not encapsulated and contain minimal or no mucin. The adjacent stroma is hyalinized. **C** Stellate, polygonal, and spindled cells are embedded in a markedly mucinous matrix.

Merkel cell carcinoma

S. Kohler
H. Kerl

Definition
Merkel cell carcinoma is a rare malignant primary cutaneous neoplasm with epithelial and neuroendocrine differentiation. Tumour cells share morphologic, immunohistochemical and ultrastructural features with Merkel cells, but a direct histogenetic link is unproven.

ICD-O code 8247/3

Synonyms
First described in 1972 by Cyril Toker as trabecular carcinoma {2357}. Other synonyms include neuroendocrine carcinoma of the skin, primary small-cell carcinoma of the skin, and cutaneous APUDoma.

Epidemiology
The estimated incidence of Merkel cell carcinoma is about 470 new cases per year in the United States. The tumour most commonly affects Caucasians (0.23 annual age adjusted incidence per 100,000) and is exceptionally rare in black individuals (0.01 annual age adjusted incidence per 100,000) {1616}. Merkel cell carcinoma is more common in men than in women with a ratio of 2.3:1. This tumour typically occurs on the sun- exposed skin of older adults with a median age at presentation of 69 years.

Etiology
Anatomic and geographic distribution of Merkel cell carcinoma imply sun exposure as a major risk factor. A relatively high incidence of this neoplasm in solid organ transplant recipients and in patients with human immunodeficiency virus infection point towards an etiologic role of chronic immunosuppression.

Localization
The majority of Merkel cell carcinomas arise on sun-exposed skin. The most frequently affected sites are the head and neck (50%) and extremities (40%) {843}. The trunk and genitalia are involved in less than 10% of cases. Exceptional cases on mucosal surfaces have been recorded.

Clinical features
Most tumours are solitary and present as a painless dome shaped nodule or indurated plaque that is red, violaceous or skin-coloured and, at times, ulcerated. Growth is typically rapid over a period of weeks to months. Most lesions measure less than 2 cm in diameter.

Tumour spread and staging
Merkel cell carcinoma has a high incidence of local recurrence, regional lymph node metastasis and, ultimately, haematogenous and/or distant lymphatic spread {517}. Clinical staging after histopathologic diagnosis should include at the minimum a chest x-ray and CT of the chest and abdomen to exclude other possible primary sites and to evaluate for the presence of metastatic disease.
Merkel cell carcinoma in locations other

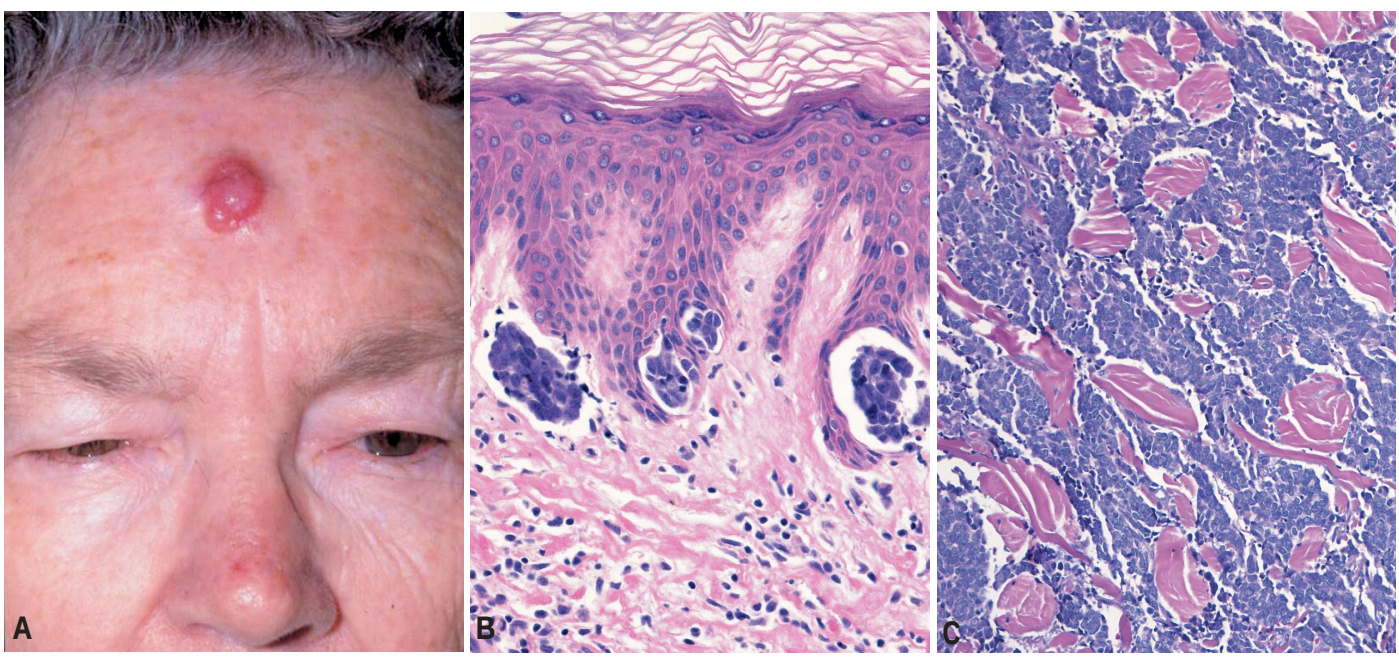


Fig. 6.9 Merkel cell carcinoma. **A** Rapidly growing, violaceous nodule on the forehead (courtesy Dr. Scott Dinehart). **B** Pagetoid involvement of the epidermis. **C** Trabecular growth is one of the architectural patterns of Merkel cell carcinoma.

than the eyelid, vulva and penis is staged according to the TNM system for non-melanoma skin cancers.

Histopathology

Merkel cell carcinoma is a small blue cell neoplasm, composed of cells of uniform size with a round to oval nucleus and scant cytoplasm. Nuclear membranes are distinct, the chromatin is finely dispersed and nucleoli are usually inconspicuous. Mitotic figures and nuclear fragments are numerous. Focal spindle cell differentiation may be present.

The tumour is centred on the dermis and frequently extends into the subcutaneous fat. The epidermis may be involved in a pagetoid fashion {1384} and in exceptional cases the tumour cells are entirely limited to the epidermis. Ulceration of the epidermis occurs in a subset of cases. This neoplasm forms diffuse sheets and solid nests in the dermis. A trabecular growth pattern, ribbons or festoons can be seen mainly in the periphery. Pseudorosette formation is rare. The dermis occasionally shows a desmoplastic response. Larger lesions may show zonal tumour necrosis and angiolymphatic involvement is commonly present around the primary neoplasm. Not infrequently, Merkel cell carcinoma occurs in intimate association with an in situ or invasive squamous cell carcinoma {2450}. Biphenotypic differentiation with squamoid or eccrine foci or even tripartite differentiation with squamoid, glandular and melanocytic foci are described. Areas of partial or complete regression can be found {529}.

The histopathologic differential diagnosis includes basal cell carcinoma, melanoma, lymphoma, eccrine carcinoma, poorly differentiated squamous cell carcinoma, metastatic neuroblastoma, primary peripheral primitive neuroectodermal tumour and metastatic neuroendocrine carcinoma.

Immunohistochemistry

Merkel cell carcinoma shows epithelial and neuroendocrine differentiation. Tumour cells express low molecular weight cytokeratins (detectable by specific or broad spectrum cytokeratins such as AE1/AE3, CAM5.2, pan-cytokeratin), epithelial membrane antigen and the epithelial marker BER-EP4. Cytokeratin 20 is a sensitive and quite specific marker for Merkel cell carcinoma {1604}. The staining pattern for low molecular weight cytokeratins and CK20 typically is as paranuclear dots, but may also show cap-like paranuclear or diffuse cytoplasmic staining {1138}. CK20 is useful in combination with thyroid-transcription factor-1 to differentiate between Merkel cell carcinoma (CK20 positive, TTF-1negative) and small cell carcinoma of the lung (<10% CK20 positive, TTF-1 positive) {463}. CK20 and broad spectrum cytokeratin are also useful for the detection of occult micrometastases in sentinel lymph nodes {2287}. Markers of neuroendocrine differentiation include chromogranin, synaptophysin, neuron-specific enolase, bombesin, somatostatin, calcitonin, gastrin and others. Merkel cell carcinoma also expresses CD117, the KIT receptor tyrosine kinase {2284}, and in approximately a third of cases CD99 {1707}. The tumour cells are negative for leukocyte common antigen and S-100.

Histogenesis

The histogenesis of Merkel cell carcinoma is controversial. A direct histogenetic link between tumour cells and Merkel cells is unproven despite overlap in the morphologic, immunologic and ultrastructural features. Another theory postulates that Merkel cell carcinoma arises from a primitive epidermal stem cell with a capacity to differentiate towards neuroendocrine cells and keratinocytes.

Somatic genetics

A deletion on the short arm of chromosome 1 (1p36) is commonly observed and is shared with other neoplasms of neural crest derivation including neuroblastoma and melanoma {2208}.

Numerous other chromosomal abnormalities are described in Merkel cell carcinoma, the most common being trisomy 6, affecting nearly 50% of tumours. As of yet, no candidate oncogenes or tumour suppressor genes have been identified.

Prognostic factors

Diverse clinical prognostic factors include older age, location on head and neck, size greater than 2 cm, immunosuppression and advanced disease stage {517,843,2208}.

Adverse histopathologic and immunologic features include more than 10 mitotic figures per single high power field, small cell size, angiolymphatic invasion, and immunoreactivity for CD44 {1803}.

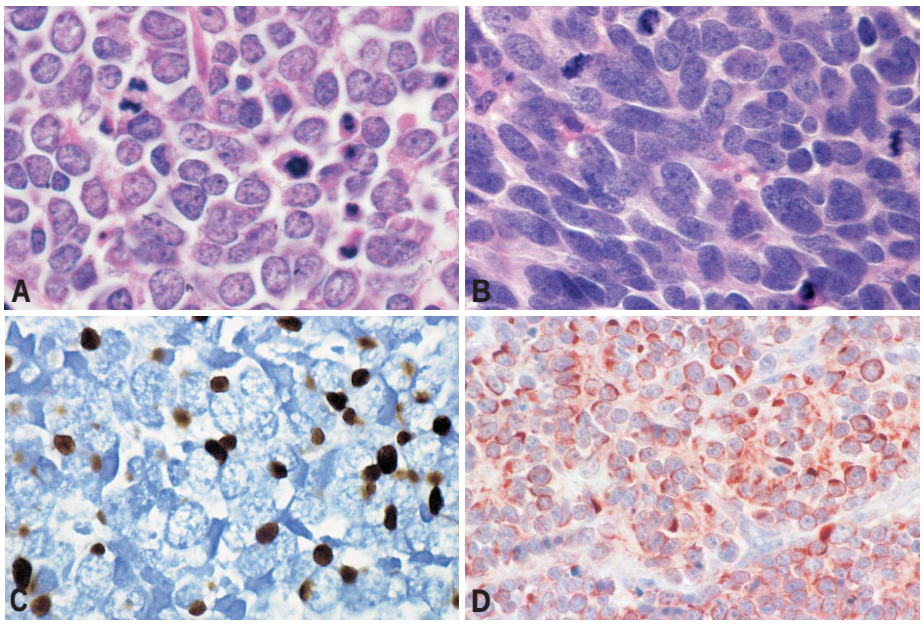


Fig. 6.10 Cutaneous neuroendocrine carcinoma. **A** Cytomorphological details. Note pyknotic nuclei and mitoses. **B** Cytologic detail of Merkel cell carcinoma: Nuclear membranes are distinct, the chromatin is finely dispersed and nucleoli are inconspicuous. Mitotic figures and nuclear fragments are numerous. **C** Punctate perinuclear staining with CK20. **D** Staining with anti-cytokeratin 20 reveals a ring-like and paranuclear dot-like pattern.

Granular cell tumour

Z. B. Argenyi

Definition
Granular cell tumours (GCT) encompass a cytologically similar, but etiologically and clinically diverse group of entities that are characterized by proliferation of large cells with granular-appearing eosinophilic cytoplasm. Herein, only the variant with direct or indirect evidence of peripheral nerve sheath association and common cutaneous manifestation is considered.

ICD-O code 9580/0

Synonyms
Granular cell Schwannoma, granular cell nerve sheath tumour, granular cell myoblastoma, Abrikossoff tumour

Historical annotation
The tumour was thought to be derived from skeletal muscle cells by Abrikossoff (1927). The association with nerve sheath differentiation was proposed by Feyrter (1935).

Epidemiology
GCT affects mainly adults (age 30-50), but can occur at any age. The male to female ratio is about 1:3; it is more common in African Americans than in Whites {78,245,1354}. The tumour is characteristically solitary, and about 70% are located in the head and neck area, including 30% of these in the tongue. Other common locations are the breast and the proximal extremities. GCT usually involves the skin and subcutis; however, visceral involvement can also occur, primarily in the respiratory tract (larynx and trachea) and the gastrointestinal tract (oesophagus, large bowel, and anal area) {245}. In about 10% of the cases GCT is multifocal, simultaneously involv-

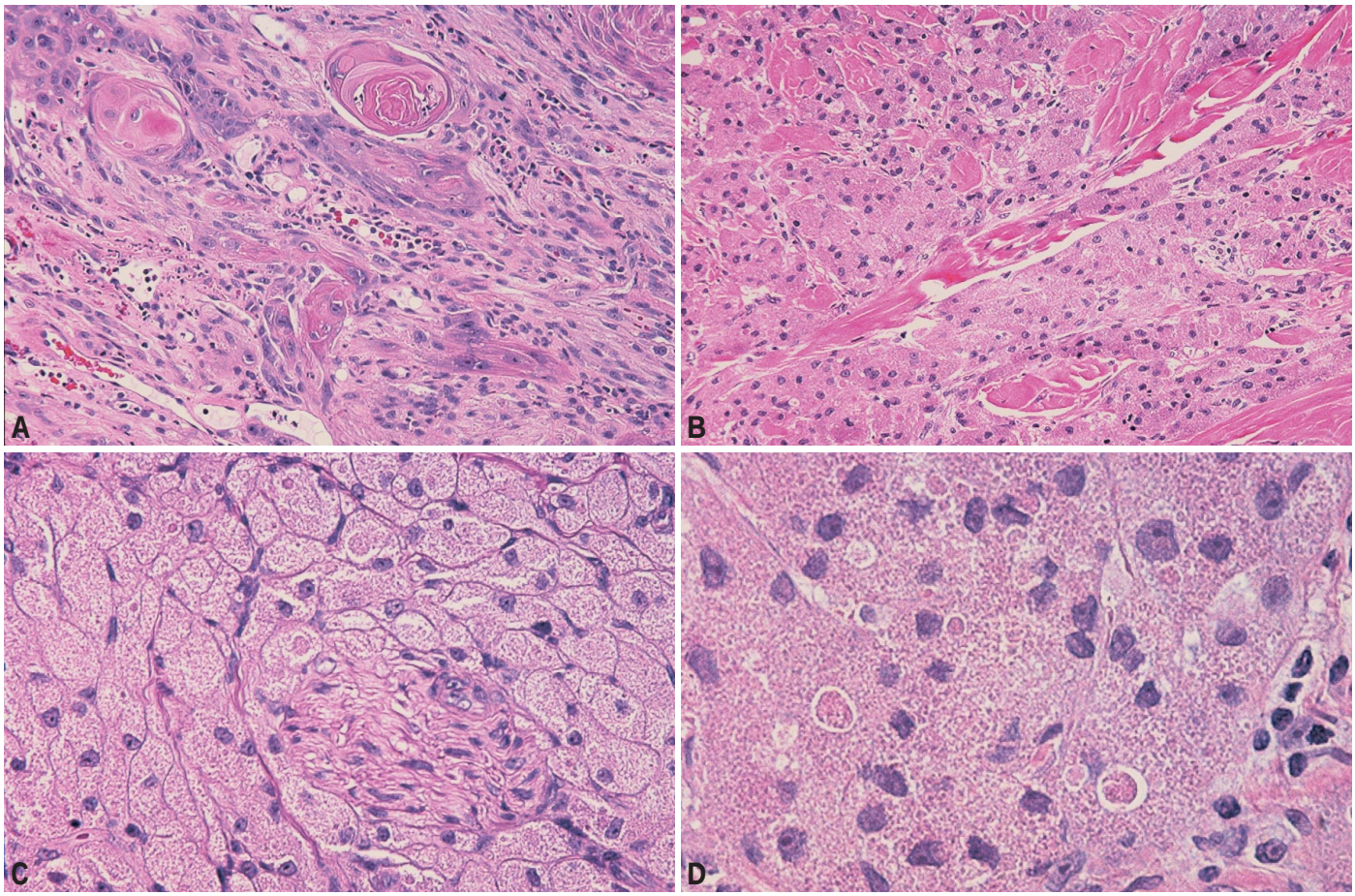


Fig. 6.11 Granular cell tumour. **A** Reactive squamous pseudoepitheliomatous hyperplasia with prominent cytologic atypia mimicking squamous cell carcinoma. The granular cells are intermingled with squamous epithelial cells. **B** Granular cell tumour. The brightly eosinophilic granular cells form solid nests and strands infiltrating the dermis. **C** Granular cell tumour associated with a peripheral nerve. The granular cells have polygonal shape, distinct cytoplasm and eosinophilic granular cytoplasm with round, fairly uniform nuclei. **D** The large, ovoid, brightly eosinophilic globules surrounded by clear halo represent giant lysosomes.

ing the skin, submucosa, and viscera {577}. Congenital presentation has also been reported. No definite association with neurofibromatosis type 1 has been established {1642,2577}.

Clinical features

GCT usually presents as an asymptomatic or occasionally tender or pruritic, skin-coloured or brown-red, firm dermal or subcutaneous papulo-nodule, ranging in size from 0.5-3.0 cm in diameter. Verrucous changes of the surface epithelium are common, whereas ulceration is uncommon. The cutaneous tumours grow slowly; most symptoms are related to visceral locations.

Macroscopy

GCTs are nodular, but not encapsulated, and present as firm dermal or subcutaneous masses with a thickened or verrucous epidermal surface. On cut-surface the tumour has a pink-yellow, finely granular appearance {2084,2490}.

Histopathology

The tumour forms poorly cohesive nests, strands, fascicles, and sheets of polygonal, pale eosinophilic cells in the dermis and subcutis. Commonly, the cells form indistinct delicate fascicles that infiltrate the dermal collagen and extend to the subcutaneous septa. A variant of GCT with a distinctly plexiform growth pattern has been documented {1392}. Perineural spread is a common feature. The cells have an abundant granular, faintly eosinophilic cytoplasm with round, small, hyperchromatic nuclei. The fine, eosinophilic, intracytoplasmic granules correspond to lysosomes, which are PAS positive and diastase resistant.

Occasional larger, brightly eosinophilic ovoid bodies surrounded by a clear halo can be identified within the granules representing residual "giant" lysosomes. Interspersed between the granular cells, there are spindle cells with fibroblast-like features and histiocyte-like cells often with triangular, coarsely granular eosinophilic lysosomes designated as "angulate bodies". Nuclear pleomorphism, prominent nucleoli, and mitotic figures are uncommon. A characteristic feature of most cutaneous GCTs is the overlying pseudoepitheliomatous hyperplasia, which can be so extensive that it can mimic a verruca or a well-differentiated squamous cell carcinoma.

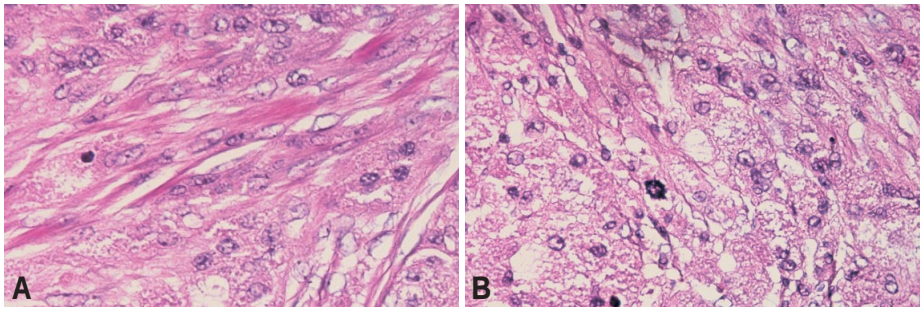


Fig. 6.12 Malignant granular cell tumour. **A** Malignant granular cell tumour shows cells with polygonal and spindled morphology and coarse eosinophilic granularity. **B** Malignant granular cell tumour with pleomorphic cells, single cell necrosis and atypical mitotic figure.

Immunohistochemistry

GCT expresses markers associated with both neural (S-100 protein, PGP 9.5, neuron specific enolase, laminin, NGFR, calretinin, peripheral myelin proteins, P2-P0, myelin basic protein, CD57) and histiocytic (CD68, a-1-antitrypsin) differentiation. The tumour cells are positive for vimentin. Most studies report a negative reaction for neural filaments and GFAP {246,743,1063,1487,1540,1714}.

Variants

Granular cell epulis of infancy

This is a rare, polypoid tumour of the alveolar ridge of the gingiva of the newborn with a predilection for girls. The tumour has cytologic features similar to GCT, but lacks globular cytoplasmic inclusions, angulate body histiocytes, and contains a distinct plexiform capillary pattern. The immunohistochemical profile is also different; the lesions are negative for S-100 protein, NSE, laminin, MBP, CD57, and α-1-ACT {740,1367, 1764,2528}.

Malignant granular cell tumour

These are extremely rare and comprise less than 2% of all granular cell tumours. The age and sex distribution is similar to that of their benign counterparts, but they are more common on the extremities (particularly on the thighs) rather than the head and neck areas, or the oral mucosa. Malignant GCTs grow rapidly, often ulcerate, invade locally and tend to spread via extensive metastases.

Histologically and cytologically two forms can be distinguished: the more common type of malignant GCT is essentially identical to the benign tumour. Since cytologic atypia or mitotic activity are not reliable biologic indicators, correlation of clinical data (large size, rapid growth, ulceration) with the histologic features (necrosis, spindling, and lymphocapillary invasion) should guide in the diagnosis of malignancy. Additional features cited as useful for predicting malignancy are vesicular nuclei with large nucleoli and a mitotic rate greater than 2 mitoses/10 HPF.

The second type of malignant GCT is quite rare; both the primary tumour and its metastases display histologic and cytologic characteristics of malignancy. The immunophenotype of malignant GCT is also similar to that of the benign tumour, however the proliferation markers (Ki-67) show increased labelling indices, and p53 expression is prominent {2084}.

Genetics

Only limited genetic studies have been performed on malignant GCT of the soft tissue. This showed two clonal karyotypes. One atypical tumour was aneuploid and all 11 benign tumours were either diploid (9 cases) or hyperdiploid (2 cases) {627}.

Prognosis and predictive factors

GCT is benign, however local recurrence is common due to incomplete removal complicated by the typical perineural spread. The malignant variants are aggressive tumours and usually have numerous local recurrences before distant spread. Their overall prognosis is poor, with metastases developing within two years in the majority of cases and there is close to 60% mortality within three years {2084,2490}. Because of the potential for recurrence and the morphologic overlap between benign and malignant GCT, complete excision is recommended.

CHAPTER 7

Inherited Tumour Syndromes

The study of familial cancer syndromes has led to the discovery of key genes that are important not only for the understanding of the mechanismsm of genetic susceptibility but also for giving new insights into genetic and signaling pathways involved in sporadic cancers. Investigations into the rare skin disease xeroderma pigmentosum has led to the discovery of 7 DNA repair genes involved in the nucleotide excision repair pathway. Studies of these patients allowed us to understand the mechanism of DNA repair in the general population. Eventually, the in-depth analysis of the activity of these repair genes may allow us to define a subpopulation of individuals at higher risk of developing cancers in different organ sites.

This chapter contains a detailed description of clinical, pathological and genetic data of some major, well characterized inherited syndromes associated with skin cancer or other skin disorders.

Table 7.1
Inherited disorders associated with skin abnormalities

OMIM	Disease	Inheritance	Tumour types	Locus	Gene	Protein	Function
	Xeroderma Pigmentosum	AR	BCC SCC MM				
278700	Complementation group A			9q22.3	XPA	XPA	Damaged DNA-binding interaction with TFIIH and XPF/XPG endonucleases
133510	Complementation group B			2q21	XPB/ERCC3	XPB	3'Δ5' helicase in TFHII
278720	Complementation group C			3p25.1	XPC	XPC	Damaged DNA-binding only involved in global genomic repair. Heterodimer with HHR23B
126340	Complementation group D			19q13.2-3	XPD/ERCC2	XPD	5'Δ3' helicase in TFHII
600045	Complementation group E			11q12-13	DDBI	XPE P127	Damaged DNA-binding only involved in global genomic repair. Heterodimer with DDB2
600811	Complementation group E			11p11-12	DDB2	XPE P48	Damaged DNA-binding only involved in global genomic repair. Heterodimer with DDB1
278760	Complementation group F			16p13.3-13.13	XPF/ERCC4	XPF	5' structure-specific endonuclease heterodimer with ERCC1
133530	Complementation group G			13q32-33	XPG/ERCC5	XPG	3' structure-specific endonuclease. Stabilization of the open complex
603968	Xeroderma pigmentosum variant			6p21.1	POLh	POL h	Translesion DNA polymerase
600160	Familial melanoma		MM	9p21	CDKN2A	P16/INK4 P14ARF	Inhibits CDKs from phosphorylating Rb, thereby freezing cell cycle Stabilizes p53 by inhibiting MDM2, thereby promoting apoptosis
123829	Familial melanoma		MM	12q14	CDK4	CDK4	Activated protein kinase resistant to p16 inhibition ; overphosphorylates Rb, thereby driving cell cycle
155600	Familial atypical mole-malignant melanoma syndrome (FAMMM)/ Dysplastic naevus syndrome (DNS)	AD	MM	1p36(?)	unknown	unknown	CDKN2A and CDK4 genes have been excluded
109400	Naevoid basal cell carcinoma syndrome	AD	BCC	9q22.3	PTCH1	PTCH1	Development gene ; regulates the Sonic Hedgehog signaling pathway
158350	Cowden disease b	AD	MH	10q23	PTEN/ MMAC1	PTEN/TEP1 /MMAC1	Lipid/protein phosphatase
158320	Muir-Torre syndrome	AD	CSN	2p22	hMSH2	hMSH2	Involved in DNA mismatch repair
175100	Gardner syndrome a	AD	EC	5q21	APC	APC	Negatively regulates ß-catenin, a cytoskeletal and growth-promoting protein, and the WNT signaling pathway
131100	Multiple endocrine neoplasia 1	AD	MFA	11q13	MEN1	menin	Inhibitor of Jun D-activated transcription
171400	Multiple endocrine neoplasia 2	AD	CLA	10q11.2	RET	RET	Tyrosine kinase receptor involved in signal transduction
605284	Tuberous sclerosis 1	AD	MSL	9q34	TSC1	hamartin	Interacts with tuberin and exhibits growth-inhibitory activity
191092	Tuberous sclerosis 2	AD	MSL	16p13.3	TSC2	tuberin	GTPase-activating protein for RAP1 and RAB5 ; interacts with hamartin
162200	Neurofibromatosis 1 b (von Recklinghansen disease)	AD	FTK	17q11.2	NF1	neuro-fibromin	Negatively regulates ras-family of signal molecules through GAP function : Tumour suppressor activity
101000	Neurofibromatosis 2 b	AD	ST	22q12.2	NF2	merlin	Integrates cytoskeletal signaling
210900	Bloom syndrome b	AR	ST	15q26.1	BLM/ RECQL3	BLM	DNA helicase ; unwinds DNA at blocked replication forks
175200	Peutz-Jeghers syndrome	AD	MML	19p13.3	STK11	STK11	Serine/threonine protein kinase : Tumour suppressor activity
268400	Rothmund-Thomson syndrome[b]	AR	D	8q24.3	RECQL4	RECQL4	DNA helicase ; unwinds DNA at blocked replication forks/recombination sites
277700	Werner syndrome b	AR	SSC	8p12	WRN/ RECQL2	WRN	DNA helicase ; unwinds DNA at blocked replication forks/recombination sites
135150	Birt-Hogg Dubé Syndrome	AD	HFH	17p11.2	BHD	folliculin	Unknown
132700	Cylindromatosis familial	AD	C	16q12-13	CYLD1	CYLD1	Tumour suppressor gene. Protein with 3 cytoskeletal-associated-protein-glycine-conserved domains implicated in the attachment of organelles to microtubules

Familial cutaneous melanoma

B. Bressac-de Paillerets
F. Demenais

Definition

Familial melanoma is defined as the occurrence in at least two affected blood- relatives up to the third degree on one side of the family. This genetic susceptibility is caused germline mutations in the CDKN2A/p14ARF or CDK4 gene.

OMIM numbers

***600160**:* Cyclin-dependant kinase inhibitor 2A; CDKN2A
Synonyms: CDK4 Inhibitor; multiple tumour suppressor 1, MTS1; TP16; p16(INK4); p16(INK4A); p19(ARF); p14(ARF).

123829 Cyclin-dependant kinase 4; CDK4
Synonyms: Cell Division Kinase 4; Cutaneous malignant melanoma 3, CMM3.

155600 Melanoma, cutaneous malignant; CMM

Table 7.2:
Inherited tumour syndromes
Abbreviations

AR*	Autosomal Recessive
AD	Autosomal Dominant
BCC**	Basal Cell Carcinoma
SCC	Squamous Cell Carcinoma
MM	Malignant Melanoma
MH	Multiple Hamartomatous
CSN	Cutaneous Sebaceous Neoplasms
EC	Epidermoid Cysts
MFA	Multiple Facial Angiofibromas
CLA	Cutaneous Lichen Amyloidosis
MSL	Multiple Skin Lesions
FTK	Fibromatous Tumours of the Skin
ST	Skin Tumours
MML	Melanocytic Macules of the Lip
D	Dermatosis
SSL	Scleroderma-like Skin Changes
HFH	Hair Follicle Hamartomas
C	Cyclindroma

[a] Already described in the WHO Classification of Tumours of the Digestive System {944}
[b] Already described in the WHO Classification of Tumours of Soft Tissue and Bone {756}

Synonyms: Melanoma, malignant; Familial atypical mole-malignant melanoma syndrome, FAMMM; Melanoma familial, MLM; Dysplastic naevus syndrome, hereditary, DNS; Melanoma, cutaneous malignant 1, CMM1; B-K Mole syndrome.

155755 Melanoma-astrocytoma syndrome
Synonyms: Melanoma and neural system tumour syndrome

606719 Melanoma-pancreatic cancer syndrome
Synonyms: Familial atypical multiple mole melanoma pancreatic carcinoma syndrome (FAMMMPC)

Epidemiology

Cutaneous melanoma is a typical example of a multifactorial disease, where both genetic and environmental factors are involved and interact. Genetic factors were first suspected through the existence of familial aggregations of CM. The proportion of familial cases varies from 4-15% across different studies. Within large families, familial aggregation of melanoma was consistent with autosomal, dominant inheritance. In addition to CM family history, numerous epidemiological studies have demonstrated that cutaneous and pigmentary characteristics (the presence of numerous naevi, naevi atypia, skin colour, red hair and freckles), sun exposure (particularly during childhood) and reactions to sun exposure (inability to tan and propensity to develop sunburns) are major CM risk factors. Some melanoma risk factors also show familial aggregations independently of melanoma, suggesting the existence of genetic factors specific to these phenotypes {309}. The various patterns of associations of these different phenotypes (phototype, naevus phenotypes and CM) across families are likely to result from complex interactions of genetic and environmental factors underlying these traits.

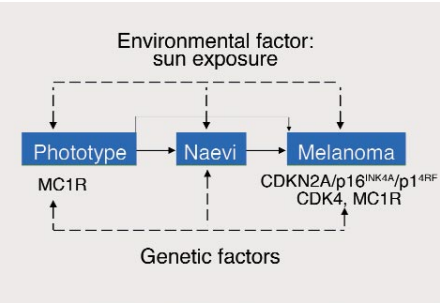


Fig. 7.1 Interaction of environmental (sun exposure) and genetic factors in the evolution of cutaneous melanoma (CM).

Clinical features and neoplastic disease spectrum

Cutaneous melanoma (CM)
Characteristics of familial melanoma include multiple cases of CM among blood-relatives on the same side of the family. Potential genetic predisposition may be suspected also in sporadic cases such as multiple primary CM in the same individual or early age of onset {1239}.

Pancreatic cancer
The existence of an increased risk of pancreatic cancer in a subset of CDKN2A families has been reported {286,859}.

Breast cancer
An excess of breast cancer has been described in two sets of families, Italian and Swedish {286,822}.

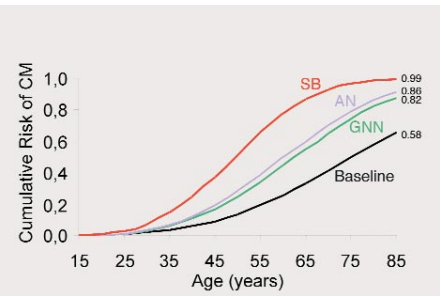


Fig. 7.2 Effect of great number of naevi (GNN), atypical naevi (AN) and sunburns (SB) on cutaneous melanoma (CM) risk in CDKN2A mutation carriers.

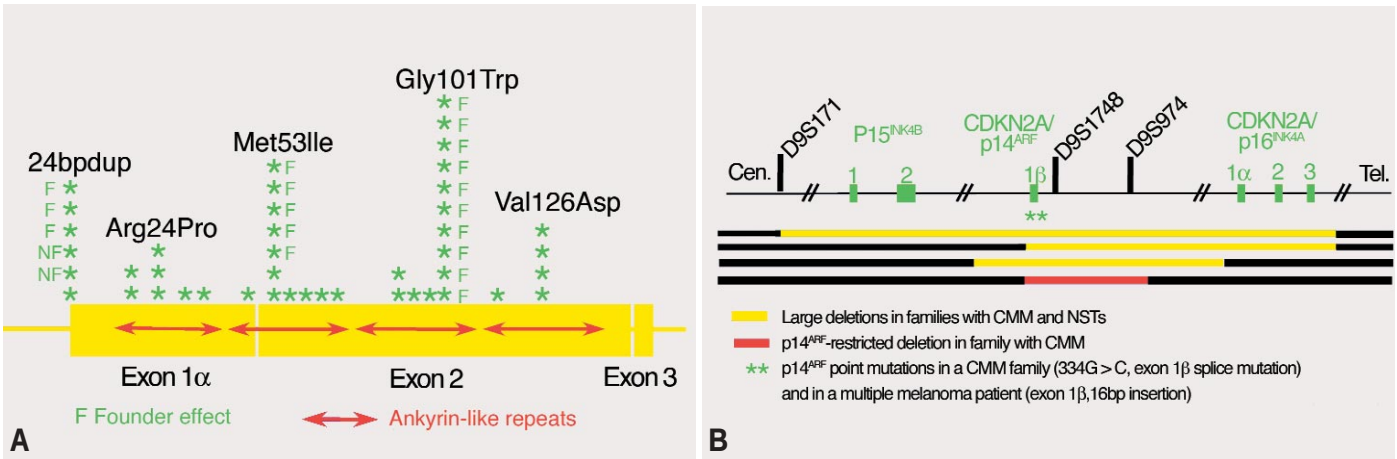


Fig. 7.3 **A**. CDKN2A/p16^{INK4A} germ-like mutations. **B** CDKN2A/p14^{ARF} gene mutations.

Nervous system tumours

Rare families have been described displaying melanoma and neural system tumours (NSTs) over several generations {129,1230}. This has been termed melanoma-astrocytoma syndrome due to the presence of cerebral astrocytomas in the first family described.

Uveal melanoma (UM)

Certain melanoma-prone kindred have members affected by either uveal and/or cutaneous melanoma. The first CDKN2A germline mutation was detected recently in a melanoma-prone family, where one carrier was affected by UM and the other by a CM (Kannengiesser C. et al., Gene Chromosome and Cancer, pending).

Naevus: total number (TN), clinically atypical (AN), histologically dysplastic (DN

These naevus phenotypes are major risk factors for CM but whether they represent precursor lesions in the course of tumour development is still unclear. There are several lines of evidence suggesting that distinct genetic factors may be involved in CM and number of naevi {309}. CDKN2A does not appear to be a "naevus" predisposing gene; this phenotype was found in only half of the subjects with a CDKN2A gene mutation and who had developed melanoma {2226} and a study of Australian twins has reported that a CDKN2A-linked gene may influence flat moles but has no effect on raised or atypical moles {2601}. Naevus phenotypes (TN, AN and/or DN) have been shown to influence the penetrance of CDKN2A in melanoma-prone North-American and French families {860,452A} with a greater effect of DN in non-carriers than in carriers of CDKN2A mutations in the American sample.

Genetics

Gene structure and mutations

Two genes (encoding three proteins) conferring a high risk of developing melanoma have been identified to date, CDKN2A/p14ARF and CDK4. In addition, a low-risk melanoma susceptibility gene has also been identified, the melanocortin-1 receptor gene (MC1R).

CDKN2A/p16INK4A gene

Linkage analyses, cytogenetic studies and loss of heterozygosity (LOH) studies in tumour cells have led researchers to suspect the existence of a CM susceptibility gene at 9p21 locus. The gene, p16INK4A/CDKN2A, was cloned in 1993 {2140} and formally identified as a melanoma susceptibility gene in 1994 {1088,1184}.

The CDKN2A transcript includes exons 1a, 2 and 3. It encodes the 156 amino-acid p16INK4A protein composed of four ankyrin repeats which are motifs involved in protein-protein interactions. P16INK4A binds to cyclin-dependent kinase 4 (CDK4) and 6 (CDK6), therefore preventing binding of cyclin D1 to the CDKs. Cyclin D1/CDK4/6 complexes participate in the phosphorylation of the retinoblastoma protein (RB), allowing the cell to progress beyond the G1 phase of the cell division cycle {2166}. The p16INK4A protein inhibits RB-dependant cell cycle and therefore acts as a tumour suppressor.

The search for mutations of the CDKN2A gene in numerous familial studies around the world shows that the frequency of CDKN2A mutations is about 20% on average but varies from 5-50% depending on the criteria for family selection. Homozygotes for CDKN2A germline mutation have been described in relation to a Dutch founder effect; they display similar phenotypes than heterozygous individuals {912}. Mutations of the CDKN2A gene are detected in approximately 10% of sporadic multiple melanoma cases, without any evidence of de novo mutations up to date but in relation to the existence of a founder effect for some of them {115}. To date, no germ line mutations have been found in cases of childhood melanoma (<18-20 years of age) lacking a family CM context {2507}. Most CDKN2A mutations are missense mutations scattered throughout the coding sequences of exons 1a and 2. Functional studies of mutant p16INK4A proteins have been carried out using several assays displaying various sensitivity: CDK-binding, kinase activity inhibition, growth arrest and protein cellular localisation assays. Two more complex mutations have been also described: a mutation located within CDKN2A 5'UTR, creating an aberrant initiation codon {1435} and a deep intronic mutation (IVS2-105A/G) of CDKN2A, leading to aberrant mRNA splicing {956}. Recurrent mutations described in melanoma-prone families from different continents have been shown to be founder mutations {115,488}.

Within the International Melanoma Consortium, CDKN2A mutation penetrance was estimated to be, in a set of 80

families, 0.58 in Europe, 0.76 in the United States and 0.91 in Australia, by age 80 years {251}. This variation of penetrance by geographical location was found to be similar to the variation of overall population incidence rates among these countries. This suggests that the same risk factors mediate CM risk to the same extent in CDKN2A mutation carriers as in non-carriers. Moreover, CM risk does not change according to whether or not the mutation can simultaneously alter the p16INK4A and p14ARF proteins.

Three MC1R variant alleles also act as modifiers of melanoma risk in families segregating CDKN2A mutations:

MC1Rvar/var genotypes increased the melanoma penetrance in CDKN2A carriers from 50-84% in Australia (sunny country) and from 18–55% in the Netherlands (less sunny country) {291,2410}.

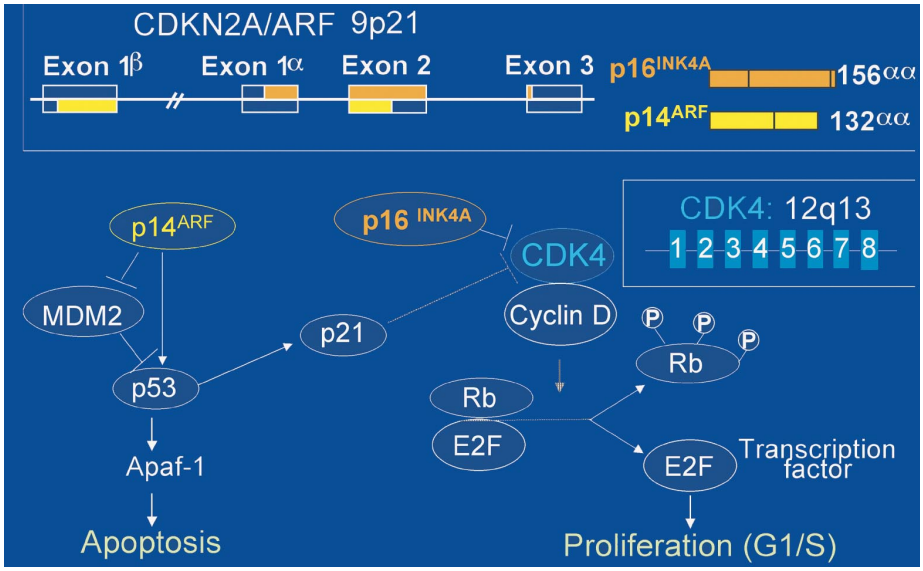


Fig. 7.4 p14ARF and p16INK4A signaling pathways and their role in apoptosis and proliferation of melanocytes.

CDKN2A/p14ARF gene

In 1995, it was discovered that part of CDKN2A gene was common to another transcript. This second transcript (exons 1b, 2 and 3) encodes the human p14ARF protein (ARF meaning "alternative reading frame") composed of 132 amino-acid, encoded by exons 1b and 2. According to the current state of knowledge, p14ARF is involved in regulation of the cell cycle and apoptosis via the p53 and RB pathways, by interacting with MDM2 (leading to p53 protein accumulation and to RB inactivation) and E2F1 proteins {1437}.

Mutations in exon 2 potentially affect p16INK4A and p14ARF proteins at the same time. Despite this dual coding capacity of the INK4A/ARF locus, recent description of three p14ARF germ-line alterations involving only exon 1b suggests a direct role for p14ARF haploinsufficiency in melanoma predisposition : (1) a deletion restricted to exon 1b and segregating with melanoma and neural cell tumours within a family {1890}, (2) a 16bp insertion in exon 1b in a sporadic multiple melanoma case {1945}, (3) a splice mutation in exon 1b in a two melanoma-cases family {1022}.

A role for both p14ARF and p16INK4A/CDKN2A genes?

Germ-line alterations presumably altering both p16INK4A and p14ARF functions, have been described in three CM and NSTs families: two large deletions involving the INK4A locus {128} and a CDKN2A splice point mutation, leading to p16INK4A and p14ARF transcripts lacking exon2 {1818}. However, it cannot be concluded that both p16INK4A and p14ARF inactivation are necessary for melanoma-astrocytoma syndrome as a fourth such family has been also described with a germ line deletion apparently restricted to the p14ARF - specific exon 1b {1890}.

CDK4 gene

The CDK4 gene on chromosome 12q13 is composed of 8 exons within a 5-kilobases (kb) segment. The initiation codon is located in exon 2, the stop codon in exon 8. This gene encodes the cyclin-dependant kinase 4 (CDK4), a 304 amino-acid protein. It has been identified as a melanoma predisposing gene in three families world-wide {2226.2607}. Germline mutations affect Arg-24 residue in exon 2, which plays a key role in p16INK4A binding. The mutation induces the loss of the cell cycle down-regulation signal that p16INK4A exerts through RB phosphorylation. In a "knock-in" Cdk4R24C/R24C mouse model, constitutive Cdk4 activation is oncogenic {1891}.

Application of genetic testing in the clinical testing

There is some evidence that non-carrier of CDKN2A mutations in melanoma-prone families may have a higher incidence of melanoma than the general population, presumably due to co-inheritance of other low-risk susceptibility genes and common environmental risk amongst family members. Therefore, genetic testing for melanoma is of limited clinical utility to date, mainly because a negative genetic test may give dangerously false security. Testing should be done in research protocols and first-degree relatives of high-risk individuals should be engaged in the same programs of melanoma prevention and surveillance, irrespective of the results of any gene testing. However, in countries of low melanoma incidence such as most European countries, DNA testing may improve compliance with sun protection and surveillance in identified mutation carriers. In such situations, CDKN2A testing could be proposed after careful genetic counselling {1238}.

Xeroderma pigmentosum

K.H. Kraemer
A. Sarasin

Definition
Xeroderma pigmentosum (XP) is an autosomal recessive disease with sun sensitivity, photophobia, early onset of freckling, and subsequent neoplastic changes on sun-exposed surfaces {284,778}. There is cellular hypersensitivity to UV radiation and to certain chemicals in association with abnormal DNA repair {2419}. Some of the patients have progressive neurologic degeneration. The XP syndrome is genetically heterogenous. Patients with defective DNA nucleotide excision repair (NER) have defects in one of 7 NER genes, while XP variant patients have normal NER and a defect in a polymerase gene {316,500}.

OMIM Numbers
278700 - XPA
133510 - XPB
278720 - XPC
278730 - XPD
278740 - XPE
278760 - XPF
278780 - XPG
278750 - XP variant

Synonyms
De-Sanctis Cacchione syndrome, pigmented xerodermoid, xeroderma pigmentosum variant

Epidemiology
Incidence
Xeroderma pigmentosum occurs with an estimated frequency of 1:1,000,000 in the United States {1322}. It is more common in Japan, the Middle East and North-Africa. Patients have been reported worldwide in all races including Whites, Asians, Blacks, and Native Americans. Consanguinity is common. There is no significant difference between the sexes.

Clinical features
Abnormalities may be present in the skin, eyes, or nervous system. There is a greatly increased frequency of cancer on sun-exposed sites.

Skin
Approximately half of the patients with XP have a history of acute sunburn reaction on minimal UV exposure {1322}. The other patients give a history of normal tanning without excessive burning. In all patients, numerous freckle-like hyperpigmented macules appear on sun-exposed skin.
The median age of onset of the cutaneous symptoms is between 1 and 2 years {1321}. Repeated sun exposure results in dry and parchment-like skin with increased pigmentation, hence the name xeroderma pigmentosum ("dry pigmented skin"). Pre-malignant actinic keratoses may develop at an early age.

Eyes
Ocular abnormalities are almost as common as the cutaneous abnormalities {801,871,2424}. Clinical findings are strikingly limited to the anterior, UV-exposed structures. Photophobia is often present and may be associated with prominent conjunctival injection.
Continued UV exposure of the eye may result in severe keratitis leading to corneal opacification and vascularization. The lids may develop loss of lashes and atrophy of the skin of the lids results in the lids turning out (ectropion), or in (entropion), or complete loss of the lids in severe cases. Benign conjunctival inflammatory masses or papillomas of

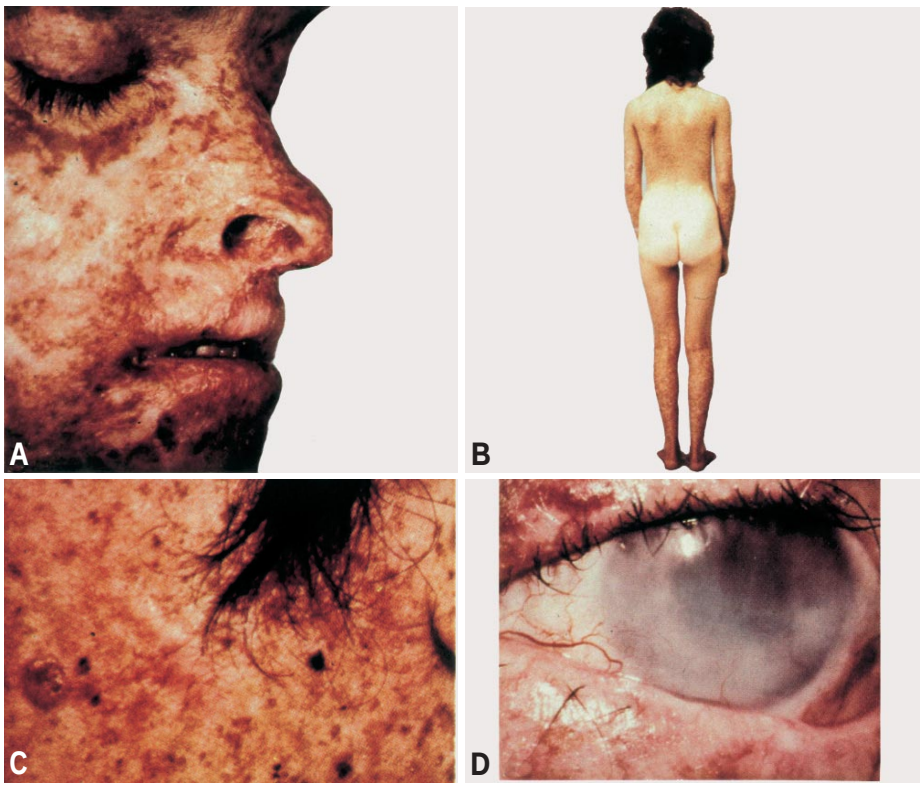


Fig. 7.5 Xeroderma pigmentosum. **A** Face of a 16 year old patient showing dry skin with hyperpigmentation, atrophy and cheilitis. **B** Posterior view of the same patient showing absence of pigmentary changes on areas protected from sunlight. **C** Face of a 14 year old patient showing freckle-like lesions with different amounts of pigmentation, an actinic keratoses, a basal cell carcinoma and a scar with telangiectasia at the site of removal of another neoplasm. **D** Xeroderma pigmentosum. Eye of the 22 year old patient showing secondary telangiectasia invading the cloudy cornea, and atrophy and loss of lashes of the lower lid. Figures from K.H. Kraemer {1319}.

the lids may be present. Basal and squamous cell carcinoma, and melanoma of UV-exposed portions of the eye are common.

Nervous system
Neurologic abnormalities have been reported in approximately 30 percent of the patients. The onset may be early in infancy (the De-Sanctis Cacchione syndrome) or delayed until the second decade. The neurologic abnormalities may be mild (e.g., isolated hyporeflexia) or severe, with progressive mental retardation, sensorineural deafness (beginning with high-frequency hearing loss), spasticity, or seizures. In clinical practice, deep tendon reflex testing and routine audiometry can usually serve as a screen for the presence of XP-associated neurologic abnormalities. The predominant neuropathologic abnormality found at autopsy in patients with neurologic symptoms was loss (or absence) of neurons, particularly in the cerebrum and cerebellum {1894}.

Cancer
Patients with XP under 20 years of age have a greater than 1000-fold increased risk of skin cancer (basal cell or squamous cell carcinoma or melanoma) {1321}. Multiple primary skin cancers are common. The median age of onset of non-melanoma skin cancer reported in patients with XP was 8 years. This 50-year reduction in comparison to the general population is an indication of the importance of DNA repair in protection from skin cancer in normal individuals. There is a greatly increased frequency of cancer of the anterior portion of the eye and of the oral cavity, particularly squamous cell carcinoma of the tip of the tongue. These are presumed sun-exposed sites.
Brain (sarcoma and medulloblastoma), central nervous system (astrocytoma of the spinal cord), lung, uterine, breast, pancreatic, gastric, renal, and testicular tumours and leukaemias have been reported in a small number of XP patients. Overall, these reports suggest an approximate ten to twenty-fold increase in internal neoplasms {1321}.

Diagnosis
There have been no consistent routine clinical laboratory abnormalities in patients with XP. Diagnosis is based on clinical features and confirmed by tests of cellular hypersensitivity to UV damage along with a defect in nucleotide excision repair for classical XP {778}.

Cellular hypersensitivity
Cultured cells from patients with XP generally grow normally when not exposed to damaging agents. The population growth rate or single-cell colony-forming ability is reduced to a greater extent than normal, however, following exposure to UV radiation. A range of post-UV colony-forming abilities has been found with fibroblasts from patients, some having extremely low post-UV colony-forming ability and others having nearly normal survival. XP fibroblasts are also deficient in their ability to repair some UV-damaged viruses or plasmids to a functionally active state. XP variant cells are specifically sensitive killing by UV-irradiation in the presence of caffeine.

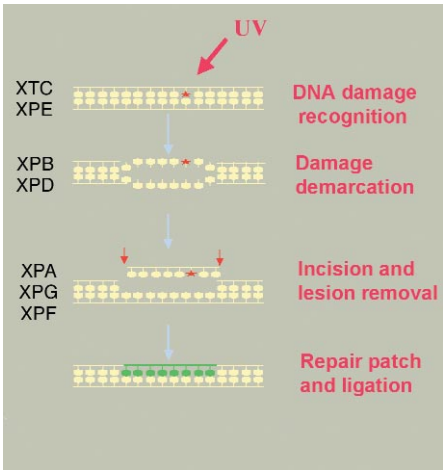


Fig. 7.6 General scheme for nucleotide excision repair (NER). The "classical" XP patients carry mutations in one of the seven XP genes indicated.. Adapted from A. Stary and A. Sarasin {2253}.

DNA repair
Cells from most XP patients have a defect in one of 7 genes (XPA through XPG) involved in the nucleotide excision repair (NER) system {500}. The NER pathway is described in Figure 7.6 {2253}. The DNA repair defect can be measured by post-UV unscheduled DNA synthesis. Host cell reactivation assays can be used to determine the complementation group by use of a panel of cloned DNA repair genes. Cells from XP variant patients have normal NER but have a defect in an error-prone polymerase (pol eta) {316}.
Prenatal diagnosis can be performed by use of unscheduled DNA synthesis assays on cultured amniotic fluid cells and by molecular analysis of trophoblast biopsies {52,1309}.
Most XP cells have a normal response to treatment with x-rays, indicating the specificity of the DNA repair defect.

Genetics
The seven complementation groups found for the classical XP correspond to

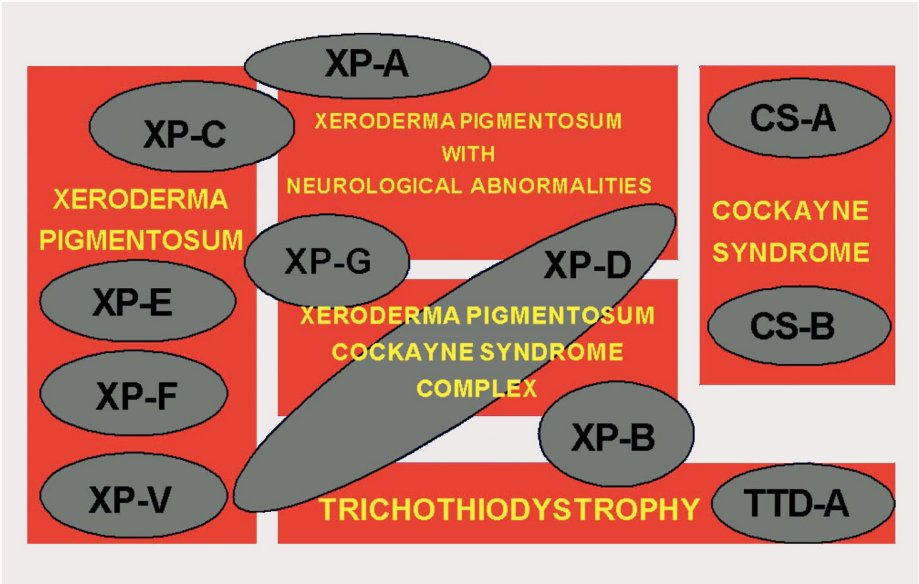


Fig. 7.7 DNA repair diseases. Correlation between clinical disorder (yellow letters) and molecular defects (black letters).

seven genes involved in NER {2253, 2419}; XPC, XPE and XPA code for proteins able to recognize DNA lesions produced by various DNA damaging agents, including UV-radiation. XPB and XPD are two helicases necessary to open the double helix at the site of the lesion. XPF and XPG are two endonucleases able to cut the damaged strand at the 5' and 3' sites, respectively.
Numerous other enzymes are necessary to complete the error-free repair but defects have not yet been identified in these genes in association with human diseases.
There is marked clinical and molecular heterogeneity in XP. Patients in XP complementation groups A, B, D, and G may have neurological abnormalities in addition to skin involvement. Patients with defects in XP complementation group D may have one of at least 5 different clinical phenotypes: XP with skin disease, XP with neurological disease, the XP/Cockayne syndrome complex {1894}, trichothiodystrophy (TTD - a disorder with sulphur deficient brittle hair) {1113} or XP/TTD {315}.

Treatment
Management of patients with XP is based on early diagnosis, life-long protection from UV radiation exposure, and early detection and treatment of neoplasms {778}.

Naevoid basal cell carcinoma (Gorlin) syndrome

R.J. Gorlin
J.C. Ehrhart

Definition

The naevoid basal cell carcinoma syndrome (NBCCS) is a genodermatosis caused by germline mutations of the PTCH gene. It is characterized by numerous basal cell cancers and epidermal cysts of skin, odontogenic keratocysts of jaws, palmar and plantar pits, calcified dural folds, various neoplasms or hamartomas (ovarian fibromas, medulloblastoma, lymphomesenteric cysts, fetal rhabdomyomas, etc.) and various stigmata of maldevelopment (rib and vertebral abnormalities, Sprengel anomaly, enlarged head circumference, cleft lip and/or palate, cortical defects of bones and other lesions.

OMIM number 109400

Synonyms

Naevoid basal cell carcinoma syndrome, Gorlin syndrome, Gorlin-Goltz syndrome, basal cell naevus syndrome.

Epidemiology

The frequency of NBCCS has been variously estimated. It constitutes about 0.4% of all cases of basal cell carcinomas. Evans et al {698} suggested that the minimal prevalence was 1 per 57,000.

Clinical features

Although the syndrome is remarkably variable in sites of involvement, the most persistent problems are the odontogenic keratocysts and the inordinate number of basal cell carcinomas, only a fraction of which become aggressive {867,868, 1273}.

Skull

The head appears large (>60 cm in adults). Relative macrocephaly (occipitofrontal circumference greater than 95th centile for height) is found in 50%. Mild mandibular prognathism, noted as “pouting lower lip”, is seen in 35%.

Basal cell carcinomas

These may appear as early as 2 years of age, especially on the nape, most often proliferate between puberty and 35 years. There appears to be a relationship to increased sun exposure. The basal cell cancers, which vary in number from a few to literally thousands, range in size from 1-10 mm in diameter. They are pearly to flesh coloured to pale brown and may be mistaken for skin tags or naevi. The basal cell carcinomas which most often involve the face and upper chest may become aggressive and invade locally. Increase in size, ulceration, bleeding and crusting indicate invasion. Radiation therapy causes proliferation of basal cell carcinomas and invasion several years later.

Milia

Small keratin-filled cysts (milia) are found intermixed with basal cell carcinomas in 30-50%. Larger, often multiple, epidermal cysts arise on the limbs and trunk in about 35-50% of whites. Multiple cysts are located on the palpebral conjunctiva in about 40%.

Pits

Palmar and, somewhat less often, plantar

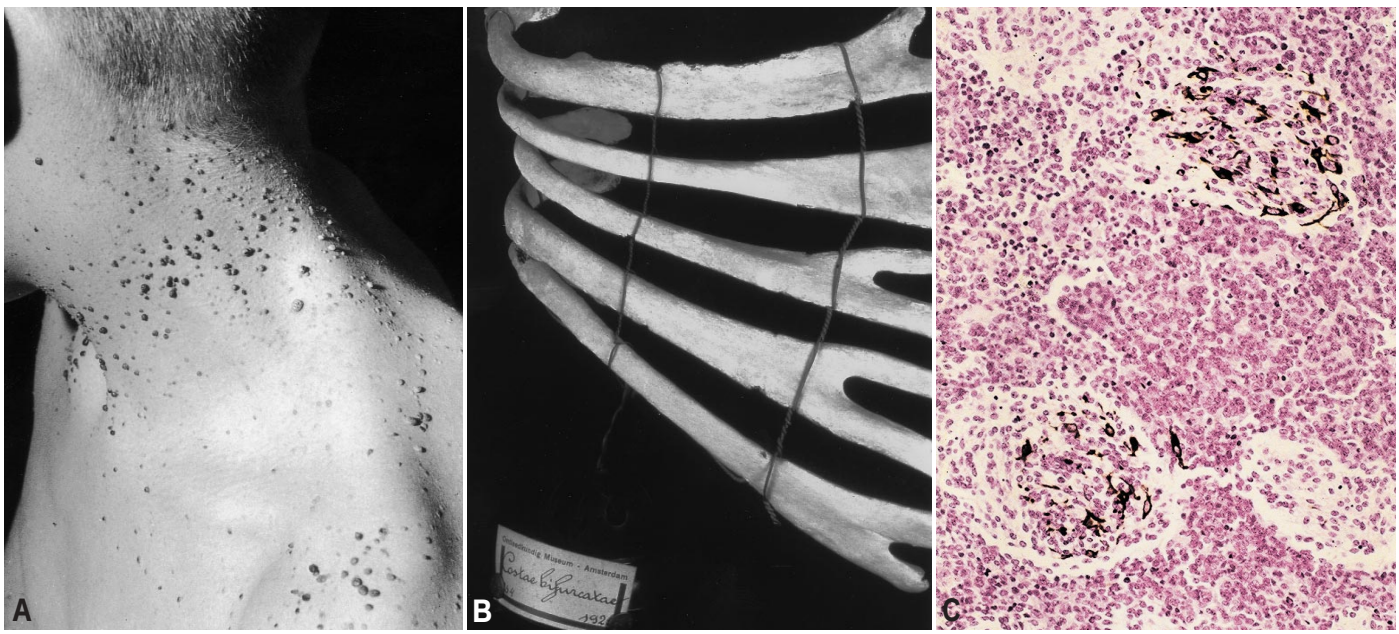


Fig. 7.8 A Multiple naevoid basal cell carcinomas scattered over neck and shoulder. **B** Multiple bifid ribs. **C** Desmoplastic medulloblastoma. The pale, reticulin-free nodules often show focal astrocytic differentiation. GFAP immunohistochemitry. From {1287}. NBCCS is typically associated with this variant.

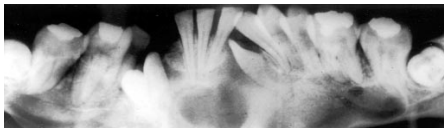


Fig. 7.9 Panoramic radiograph (panorex) showing multiple keratocystic odontogenic tumours / odontogenic keratocysts.

pits (1-2 mm) are asymmetrically present in 65-80%.

Keratocystic odontogenic tumours
Characteristically, multiple (average-6; range 1-30) odontogenic keratocysts, now termed keratocystic odontogenic tumours {153}, of both the upper and more often lower jaws appear after the seventh year of life with an overall frequency of 65%. They effect marked tooth displacement but only rarely cause fracture. There is marked tendency (over 60%) for these cysts to recur following surgery.

Medulloblastoma
This embryonal neoplasm is present in 3-5% of NBCCS patients and characteristically presents during the first 2 years of life as opposed to 7-8 years in the general population {698}. Because medulloblastoma presents early (mean 2.5 years) in patients with NBCCS, children who present with the tumour, especially those less than 5 years, should be carefully examined for signs of the syndrome. Radiation therapy of medulloblastoma results in profuse numbers of invasive basal cell carcinomas appearing in the radiation field (from nape to base of spine).

Table 7.4
Diagnostic criteria for NBCCS
Diagnosis based on two major or one major and two minor criteria.

Major criteria
1. More than 2 BCCs or one under age of 20 yrs
2. Odontogenic keratocyst
3. Three or more palmar pits
4. Bilamellar calcification of falx cerebri
5. Bifid, fused or splayed ribs
6. First degree relative with NBCCS

Minor criteria
1. Macrocephaly adjusted for height
2. Frontal bossing, cleft lip/palate, hypertelorism
3. Sprengel deformity, pectus, syndactyly of digits
4. Bridging of sella turcica, hemivertebrae, flame-shaped radiolucencies
5. Ovarian fibroma
6. Medulloblastoma

Based on V.E. Kimonis et al {1273}.

Fibromas
Cardiac fibromas occur in 3% {698}. Conversely, about 5% of patients with cardiac fibromas have NBCCS. Presentation time has varied from birth to 60 years. Most have been found incidentally. Ovarian fibromas are noted in 25% {698}. The ovarian fibromas associated with NBCCS are most often bilateral (75%).
Minor kidney anomalies and hypogonatrophic hypogonadism are found in roughly 5%. Gorlin {868} reviewed examples of fetal rhabdomyoma.

Imaging
Lamellar calcification of the falx cerebri is found in 55-95% (normal-5%). Calcification of the tentorium cerebelli has been noted in 20-40%, the petroclinoid ligament in 20%, and the diaphragma sellae in 60-80%. Radiographically, this appears as if the sella turcica is bridged, i.e., as if there were fusion of the anterior and posterior clinoid processes {1897,1898}.
Odontogenic keratocysts first appear at about 7-8 years of age and increase in number from puberty onward. They peak during the second and third decades. The cysts cause marked tooth displacement. They may invade the paranasal sinuses and, in the mandible, may extend from the molar-ramus area to the coronoid processes.
Fused, splayed, hypoplastic or bifid ribs have been documented in 45-60%. Kyphoscoliosis with or without pectus is found in 25-40% with spina bifida occulta of the cervical or thoracic vertebrae in 60%. Sprengel deformity and/or unusual narrow sloping shoulders have been described in 10-40%. Other anomalies seen in about 40% include cervical or upper thoracic vertebral fusion, hemivertebra, and lumbarization of the sacrum. Pectus occurs in about 15-25% {1897,1898}.
Small pseudocystic bone lesions (flame-shaped lucencies) have been identified in the phalanges, metapodial bones, carpal and tarsal bones, long bones, pelvis and calvaria in 30%. Calvarial

Table 7.3
Diagnostic findings in adults with naevoid basal cell carcinoma syndrome.
Modified, from R.J. Gorlin {868}.

50% or greater frequency
Enlarged occipitofrontal circumference (macrocephaly, frontal-parietal bossing)
Multiple basal cell carcinomas
Odontogenic keratocysts of jaws
Epidermal cysts of skin
High-arched palate
Palmar and/or plantar pits
Rib anomalies (splayed, fused, partially missing, bifid, etc.)
Spina bifida occulta of cervical or thoracic vertebrae
Calcified falx cerebri
Calcified diaphragma sellae (bridged sella, fused clinoids)
Hyperpneumatization of paranasal sinuses

49-15% frequency
Brain ventricle asymmetry
Calcification of tentorium cerebelli and petroclinoid ligament
Calcified ovarian fibromas
Short fourth metacarpals
Kyphoscoliosis or other vertebral anomalies
Lumbarization of sacrum
Narrow sloping shoulders
Prognathism
Pectus excavatum or carinatum
Pseudocystic lytic lesion of bones (hamartomas)
Strabismus (exotropia)
Syndactyly
Synophrys

14% or less but not random
Medulloblastoma
True ocular hypertelorism
Meningioma
Lymphomesenteric cysts
Cardiac fibromas
Fetal rhabdomyoma
Ovarian fibrosarcoma
Marfanoid build
Anosmia
Agenesis of corpus callosum
Cyst of septum pellucidum
Cleft lip and/or palate
Low-pitched female voice
Polydactyly, postaxial - hands or feet
Sprengel deformity of scapula
Vertebral body fusion
Congenital cataract, glaucoma, coloboma of iris, retina, optic nerve, medullated retinal nerve fibers
Subcutaneous calcifications of skin (possibly underestimated frequency)
Minor kidney malformations
Hypogonadism in males
Mental retardation

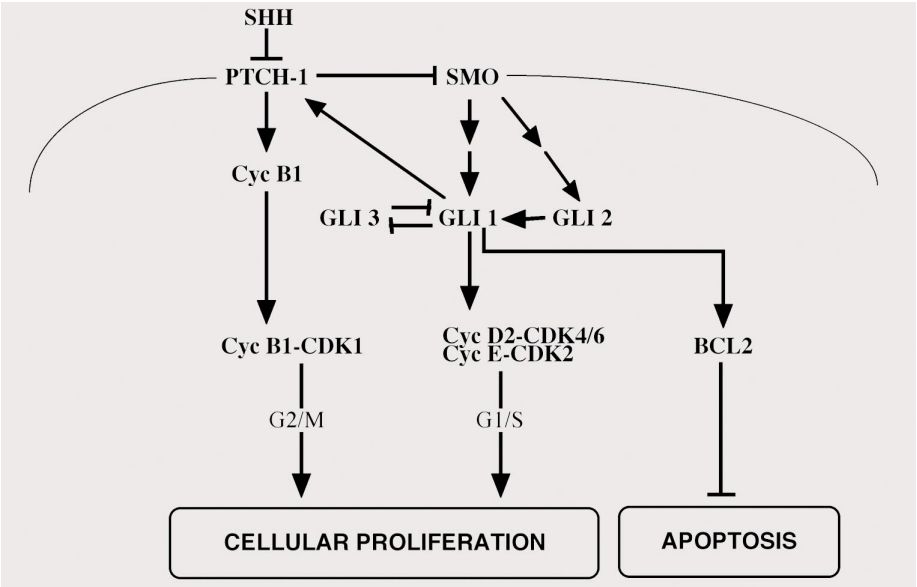


Fig. 7.10 Model of Sonic Hedgehog (SHH) signaling pathway. The function of the pathway is to stimulate cellular proliferation and inhibit apoptosis. The *PTCH-1* gene is predicted to encode a 12-transmembrane receptor with high affinity for the SHH secreted 19 kDa protein ligand. In presence of SHH, the pathway releases the 7-transmembrane protein. Smoothened (SMO) from its inhibition by *PTCH-1*, thus activating target genes through the glioma (GLI) family of zinc-finger transcription factors (GLI1 is the most studied of the three GLI factors). GLI1 may control the G1/S transition checkpoint through activation of the transcription of *Cyclin D2* and *E* genes, and apoptosis through activation of BCL2 expression. *PTCH-1* may also be involved in a G2/M transition checkpoint via Cyclin B1 which localizes to the nucleus upon SHH binding {152}. *PTCH-1* transcription is induced by GLI1, thus generating a negative feedback loop.
Abbreviations : Cyc, cyclin ; CDK, cyclin-dependent kinase.

involvement may give the impression that medulloblastoma has spread to bone. Histologically, the flame-like lesions are hamartomas consisting of fibrous connective tissue, nerves and blood vessels. Subcutaneous calcification of fingers and scalp has been rare. Sclerotic bone lesions have been reported occasionally. Ovarian fibromas are found in about 25% of females. They are bilateral and often calcified, at times overlapping medially.
Prenatal diagnosis by sonography has been accomplished {235}.

Genetics

The first link between the SONIC HEDGEHOG (SHH) signalling pathway and tumour formation in humans was in familial cancers, as 30-40% of NBCCS patients harbour loss-of-function mutations in the PATCHED1 (*PTCH1*) gene {514,939,1992}. That disruption of the SHH signalling pathway is a major determinant of tumour formation, particularly for BCCs, was established from the discovery that *PTCH1* is mutated in 10-38% of sporadic BCCs {514,1992}.
Inactivation of both *PTCH1* alleles also results in the formation of cysts {1408}. Consistent with its pivotal role in embryonic development, aberrant SHH signalling is associated with a range of human developmental anomalies {2434}.
In NBCCS, tumours (BCCs, keratocysts, meningiomas, ovarian fibromas, odontogenic keratocysts) exhibit loss of heterozygosity (LOH) in the *PTCH1* locus (9q22.3) {514}. Various physical anomalies (bifid rib, macrocephaly, cleft lip, etc.) apparently need but one-hit {1407}. LOH in the *PTCH1* locus was observed in 89% of hereditary BCCs. The majority (61-71%) of germline *PTCH1* mutations are rearrangements. Most mutations (>80%) are likely to represent null mutations since they are predicted to result in truncation of the *PTCH1* protein {133, 514,1408,1992}.
The *PTCH1* tumour suppressor gene comprises 23 exons which encode 12 putative transmembrane domains and two large extracellular loops. The function of *PTCH1* is to silence the SHH signalling pathway in absence of active SHH ligand {2308}. In presence of SHH, the pathway acts in at least two ways to regulate target genes. One is to activate GLI 1/2 transcription factors and the other is to inhibit the formation of GLI repressors, mostly from GLI3, to derepress target genes {1992}.

Prognosis and predictive factors

New keratocystic odontogenic tumours (odontogenic keratocysts) and basal cell carcinomas continue for life. Limitation of sun exposure reduces the appearance of the skin cancers. The medulloblastoma appears before the age of 4 years, the ovarian fibromas after puberty.
Therapeutic radiation should be avoided whenever possible due to the high occurrence of basal cell carcinomas in the radiation field.

Cowden syndrome

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Definition

Cowden syndrome (CS) is an autosomal-dominant disorder with age-related penetrance and variable expression, characterized by multiple hamartomas arising in tissues derived from all three embryonic germ cell layers and with a high risk of developing benign and malignant neoplasms in many organ systems, especially in the skin, breast, and thyroid gland. The condition was described in 1963 by Lloyd and Dennis {1439}. It is caused by germline mutations in the tumour suppressor gene *PTEN* located on chromosome 10q23 {1424}.

OMIM number 158350

Synonyms

Multiple hamartoma syndrome, Cowden disease

Epidemiology

Incidence

The incidence of CS, after *PTEN* was identified as the gene, was found to be 1 in 200 000 {1693}. The latter may be an underestimate, since CS has variable expression and often manifests itself only with subtle skin changes, so that this condition may be difficult to recognize {688}. Although the exact proportion of isolated and familial cases is not known, previous and on-going observations suggest that 40-60% are familial {1521, 2448,688A}.

Clinical features

CS is classically characterized as a multiple hamartoma syndrome with a high risk of breast and thyroid cancers. Although the reported age at onset varies from 4–75 years {1451}, CS usually manifests in the second or third decade. More than 90% of individuals affected with CS are likely to manifest a phenotype by the age of 20 years, and 99% develop at least mucocutaneous lesions by the age of 30 years {1694,2448}. CS is characterized by the development of hamartomas, benign and malignant tumours in multiple organ systems including the skin, soft tissues, breast, thyroid gland, gastrointestinal tract, genitourinary tract, and central nervous system. The most common lesions are trichilemmomas (90-100%), breast fibroadenomas (70%), thyroid adenomas (40-60%), multinodular goiter (40–60%), and multiple gastrointestinal polyps (35–40%) {688,1451}. Macrocephaly is seen in 35-40% of cases. Malignant neoplasms develop in the breast in 25–50% of CS females, in the thyroid gland in 3–10% (usually follicular adenocarcinoma) and in the uterus in 3-6%. The most common malignant neoplasm in the breast is ductal adenocarcinoma, which is bilateral in one third of cases {2098}. The average age of CS patients at diagnosis of breast cancer is 10 years younger than in those with sporadic disease {2252}. Male breast cancers also occur, but with unknown frequency {704,1519}. A feature that distinguishes CS from other breast cancer susceptibility syndromes is the occurrence of benign breast disease prior to the development of breast cancer {2098,2099}.

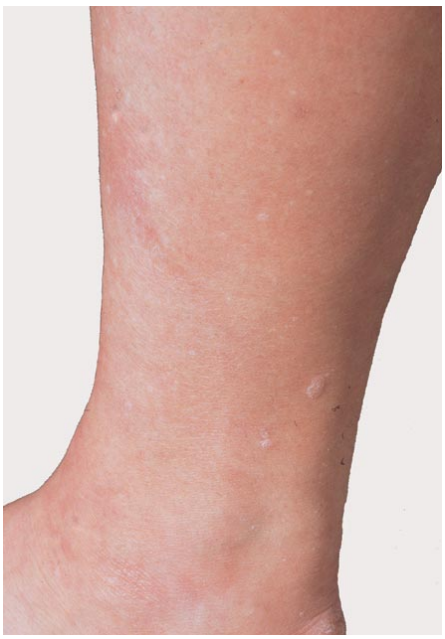

Fig. 7.11 Acral hyperkeratotic papules.

Many other internal malignancies have been reported to occur in individuals affected with CS. There are no data to state whether they are true components of this syndrome or merely coincidental.

Bannayan–Riley–Ruvalcaba syndrome (BRRS)

This pediatric disorder characterized by congenital macrocephaly, multiple lipomatosis and angiomatosis involving the skin and visceral tissues, intestinal hamartomatous polyposis, and pigmented penile lesions, shows a partial clinical overlap with CS {711,1519}.

Diagnostic criteria

The International Cowden Consortium originally proposed a set of operational diagnostic criteria in 1996 {1694}. Because of new data, the Consortium revised the criteria in 2000 {688}, which

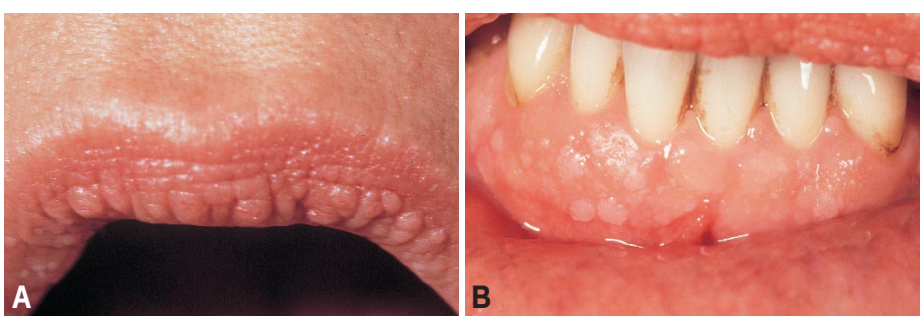

Fig. 7.12 Cowden disease (*PTEN*). **A** Multiple confluent papules on the upper lip. **B** Multiple wart-like lesions on the gingivae.

have also been adopted by the United States' National Comprehensive Cancer Center (NCCN) Practice Guidelines Panel.

Cutaneous and mucosal lesions

Cutaneous lesions are the most important hallmarks for CS, since they are present in almost every patient and frequently appear prior to the development of any internal disease {1030}. Facial papules are the most frequent lesions (85-90%). They are mainly located in periorificial regions, sometimes extending into the nostrils. Histopathologically, the papules frequently show non-specific verrucous acanthomas, trichilemmomas, perifollicular fibromas or may reveal lesions with features intermediate between trichilemmomas, inverted follicular keratosis, and tumour of follicular infundibulum {322,2249-2251}. Although human papilloma virus has not been consistently found in these lesions, some experts believe that trichilemmomas in CS represent verrucae vulgaris with trichilemmal differentiation {28}. Acral verrucous hyperkeratosis on the extensor sides of the extremities and palmoplantar translucent keratoses are seen in approximately 20-30% of cases.

Histopathologically, they show wart-like changes, with prominent compact orthokeratosis, hypergranulosis, and acanthosis, in some cases with trichilemmal differentiation. Involvement of the oral mucosa is present in over 80% of cases. Coalescent lesions produce the characteristic cobblestone-like pattern in 40% of patients. Histopathologically, these lesions are composed of acellular collagen fibres, with a predominantly whorl-like arrangement {2251}. Mucosal papules and nodules with trichilemmoma-like histopathological features are also common. A scrotal tongue is another common finding. Usually mucocutaneous lesions are present in multiple locations, and extension to the oropharynx, larynx, tongue, and nasal mucosa may occur.

Other cutaneous lesions reported to occur in individuals affected with CS include lipoma, angiolipoma, multiple sclerotic fibromas, squamous cell carcinoma, melanoma, basal cell carcinoma, Merkel cell carcinoma, haemangiomas, xanthoma, vitiligo, neuroma, apocrine hidrocystoma, café au lait spots, periorificial and acral lentigines and acanthosis nigricans (reviewed in {748,1030})

Table 7.5
International Cowden Consortium operational criteria for the diagnosis of Cowden syndrome 2000 {688}.

Pathognomonic criteria
Mucocutaneous lesions
- Trichilemmomas, facial
- Acral keratoses
- Papillomatous papules
- Mucosal lesions

Major criteria
- Breast carcinoma
- Thyroid carcinoma (nonmedullary), especially follicular thyroid carcinoma
- Macrocephaly (megalencephaly) (~95th percentile or more)
- Lhermitte-Duclos disease
- Endometrial carcinoma

Minor criteria
- Other thyroid lesions (eg, adenoma or multinodular goitre)
- Mental retardation (IQ~75 or less)
- Gastrointestinal hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genitourinary tumours (eg, renal cell carcinoma, uterine fibroids) or malformation

Operational diagnosis in an individual
1. Mucocutaneous lesions alone if there are:
   - (a) 6 or more facial papules, of which 3 or more are trichilemmoma, or
   - (b) cutaneous facial papules and oral mucosal papillomatosis, or
   - (c) oral mucosal papillomatosis and acral keratoses, or
   - (d) 6 or more palmoplantar keratoses,
2. Two major criteria, one of which is macrocephaly or Lhermitte-Duclos disease
3. One major and three minor criteria
4. Four minor criteria

Operational diagnosis in a family where one individual is diagnosed with Cowden syndrome
1. The pathognomonic criterion or criteria
2. Any one major criterion with or without minor criteria
3. Two minor criteria

Genetics

PTEN/MMAC1/TEP1 on 10q23.3, is the susceptibility gene for CS {1424,1694}.

Gene structure and function

PTEN comprises 9 exons spanning 120-150 kb of genomic distance. It encodes a 1.2 kb transcript and a 403 amino acid lipid dual-specificity phosphatase (it dephosphorylates both protein and lipid substrates) {1419,1421,2256,2448}. A classic phosphatase core motif is encoded within exon 5, which is the largest exon, constituting 20% of the coding region {1419,1421,1519,2256}.

PTEN is the major 3-phosphatase acting in the phosphatidylinositol-3-kinase (PI3K)/Akt pathway {1478,2241}. To date, virtually all naturally occurring missense mutations tested abrogate both lipid and protein phosphatase activity, and one mutant, G129E, affects only lipid phosphatase activity. Overexpression of *PTEN* results, for the most part, in phosphatase-dependent cell cycle arrest at G1 and/or apoptosis, depending on cell type (reviewed in {687,2448}). There is also growing evidence that *PTEN* can mediate growth arrest independent of the PI3K/Akt pathway and perhaps independent of the lipid phosphatase activity {460,1564,2448,2495,2496}.

Mutation spectrum

Approximately 70-85% of CS cases, as strictly defined by the Consortium Criteria, have a germline *PTEN* mutation {1424,1519,2599}. If the diagnostic criteria are relaxed, then mutation frequencies drop to 10-50% {1464,1695,2382}. A

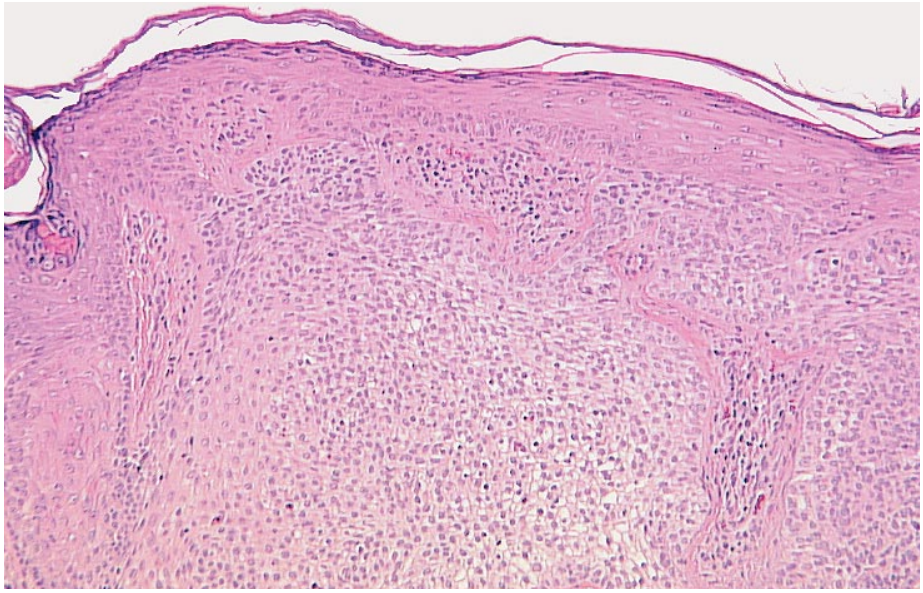

Fig. 7.13 Histopathological appearance of trichilemmoma in a patient with Cowden syndrome (Courtesy of Carl D. Morrison, MD, Ohio State University, USA).

formal study which ascertained 64 unrelated CS-like cases revealed a mutation frequency of 2% if the criteria are not met, even if the diagnosis is made short of one criterion {1519}. A single research centre study involving 37 unrelated CS families, ascertained according to the strict diagnostic criteria of the Consortium, revealed a mutation frequency of 80% {1519}.

As with most other tumour suppressor genes, the mutations found in *PTEN* are scattered throughout all 9 exons. They comprise loss-of-function mutations including missense, nonsense, frameshift and splice-site mutations {1519, 1521,2448}. Approximately 30-40% of germline *PTEN* mutations are found in exon 5. Further, approximately 65% of all mutations can be found in one of exons 5, 7 or 8 {1519,1521}.

Although *PTEN* is the major susceptibility gene for CS, one CS family, without *PTEN* mutations, was found to have a germline mutation in the bone morphogenic protein receptor type 1A gene (*BMPR1A*, MIM 601299), which is one of the susceptibility genes for juvenile polyposis syndrome {1066,2600}.

Whether *BMPR1A* is a minor CS susceptibility gene or whether this family with CS features actually has occult juvenile polyposis is yet unknown.

Genotype-phenotype associations

Clinically useful genotype–phenotype correlations are being intensively investigated. Exploratory genotype-phenotype analyses revealed that the presence of a germline mutation was associated with a familial risk of developing a malignant breast disease. Further, missense mutations and/or mutations 5' of the phosphatase core motif seem to be associated with a surrogate for disease severity (multiorgan involvement) {1519}.

Previously thought to be clinically distinct, BRRS is likely allelic to CS {1519}. Approximately 65% of BRRS families and isolated cases combined carry a germline *PTEN* mutation {420,1520,1521, 2599}. Interestingly, there were 11 cases classified as true CS-BRR overlap families in this cohort, and 10 of the 11 had a *PTEN* mutation. The overlapping mutation spectrum, the existence of true overlap families and the genotype-phenotype associations which suggest that the presence of germline *PTEN* mutation is associated with cancer, strongly indicate that CS and BRR are allelic and are along a single spectrum at the molecular level. The aggregate term "*PTEN* hamartoma tumour syndrome" (PHTS) has therefore been proposed {688,1521}. The clinical spectrum of PHTS has recently been expanded to include also subsets of Proteus syndrome and Proteus-like (non-CS, non-BRR) syndromes {2203,2598}.

Genetics of Cowden syndrome is also reviewed in detail in the WHO Classification of the Tumours of the Nervous System, Tumours of the Digestive System, as well as in the WHO Classification of Tumours of the Breast and Female Genital Organs.

Carney complex

W.H.C. Burgdorf
J.A. Carney

Definition
Carney complex (CNC) is a lentiginosis-multiple endocrine neoplasia syndrome caused by at least two distinct mutations and characterized by multiple often unique tumours including myxomas and schwannomas, endocrine abnormalities, and cutaneous pigmentary lesions {397}.

OMIM numbers
CNC1 160980; CNC2 605244

Synonyms
NAME syndrome {111}, LAMB syndrome {1926}.

Epidemiology
Carney complex is an uncommon disorder, inherited in an autosomal dominant fashion. More than 350 cases are known involving more than 65 families.
The penetrance is high but the expressivity is highly variable. Patients may present with cutaneous, cardiac, or endocrine lesions; often the diagnosis is delayed until multiple manifestations are present.

Localization
The most commonly involved organs are the skin (75%), heart (50%) and adrenal glands (25%).

Clinical features
The cutaneous findings in CNC are often most dramatic. Patients may have multiple flat pigmented lesions that have been described both as ephelides (freckles) with an increased amount of melanin {111} and as lentigines with an increased number of melanocytes {1926}. Blue naevi are another marker of the syndrome; many exhibit epithelioid features on microscopic examination {396}. Pigmented lesions are also common on mucosal surfaces, such as the lips, mouth, conjunctiva and genital mucosa {1244}. Some patients have no pigmentary changes. Another highly specific cutaneous finding is myxomas, especially when they affect the eyelids and the external ear canal {734}. Histologically, these benign tumours often feature strands of lacy epithelium {398}.
The most dramatic systemic finding is cardiac myxoma(s). The CNC-associated myxomas have important differences from sporadic cardiac myxomas; they are more likely to be familial, multiple, occur at a younger age, involve the ventricles and recur {2433}. Recurrent cardiac myxoma(s) may require multiple surgical resections that may result in postoperative arrhythmias and increased mortality.
The most common endocrine finding is primary pigmented nodular adrenal disease, a very rare ACTH-independent cause of Cushing syndrome (25%) {2164}. The adrenal glands show bilateral small, pigmented nodules with internodular cortical atrophy {881,2571}. One of Cushing's first patients, Minnie G., may well have had CNC {395}. Acromegaly and thyroid tumours {2275} are each seen in around 10% of patients. About one-third of male patients have large-cell calcifying Sertoli cell tumours of the testes, often bilateral and sometimes leading to precocious puberty {1734}.
Two other uncommon tumours which should suggest the presence of CNC are psammomatous melanotic schwannomas (20%) of the GI tract, sympathetic chain and skin {394}, and myxoid mammary fibroadenomas (25% of women) {400}.

Diagnostic procedures
Both epithelioid blue naevi and myxomas (the latter sometimes with a characteristic epithelial component) may be identified on skin biopsies and suggest the diagnosis of CNC. When investigation for Cushing syndrome reveals low or undetectable ACTH levels and no adrenal tumour, a diagnosis of primary pigment-

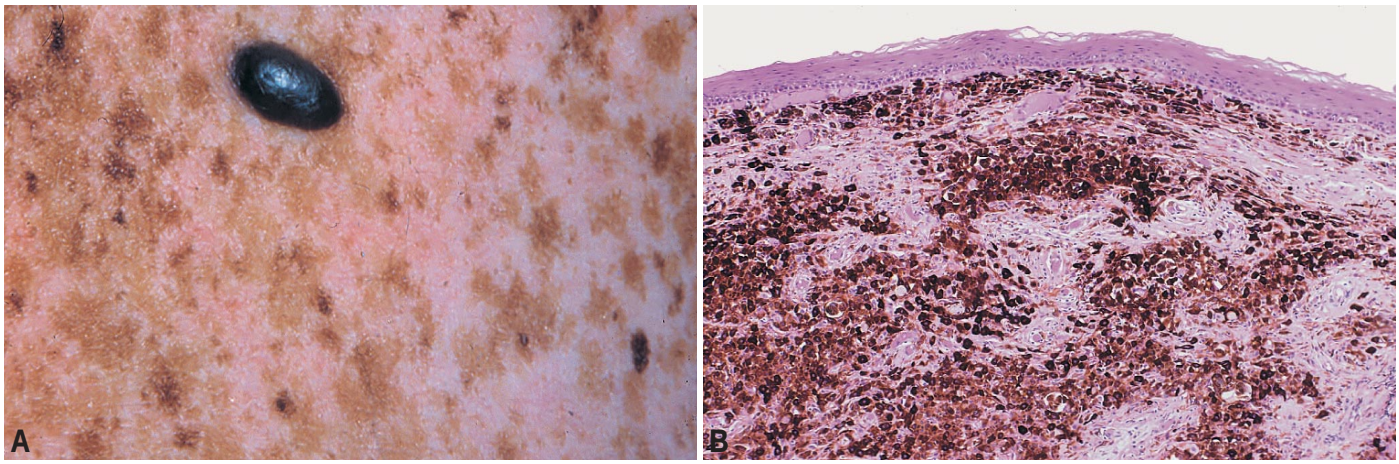

Fig. 7.14 **A** Spotty pigmentation and blue naevus in CNC. Courtesy of Dr. David J. Atherton, London, UK, and reference {111}. **B** Histological specimen of blue naevus showing large epithelioid melanocytes. Courtesy of Dr. Luis Requena, Madrid, Spain.

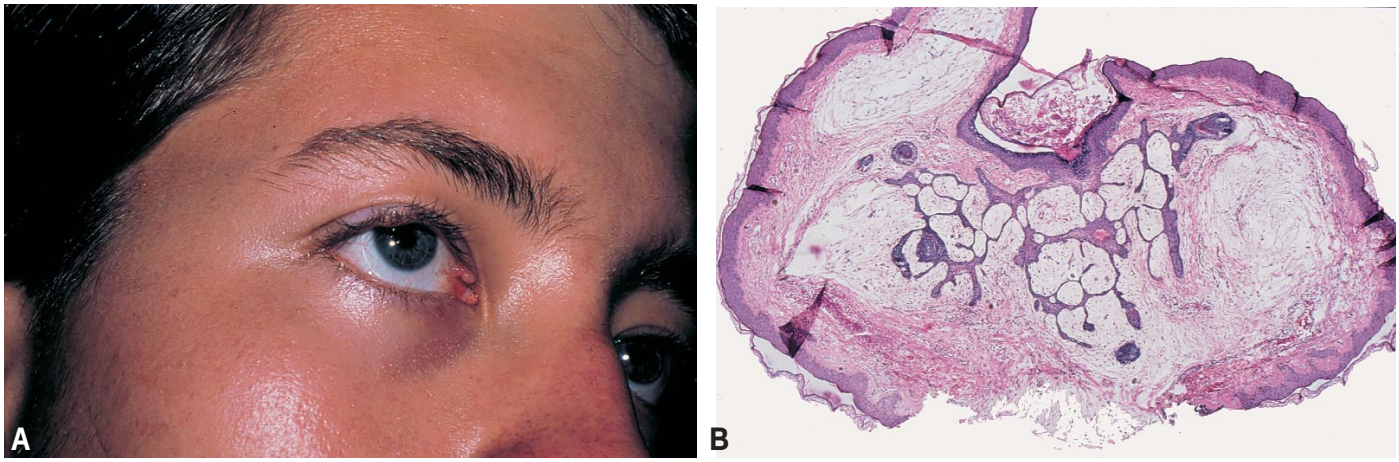

Fig. 7.15 **A** Eyelid myxoma in a young man with CNC and no cutaneous pigmentary changes. **B** Microscopic view of the same lesion, showing lacy epithelial strands amidst deposits of mucin.

ed nodular adrenal disease should be considered and the patient evaluated for CNC, particularly if the patient is young or has multiple pigmented skin spots or lumps. Echocardiography is particularly important {2276}.

Differential diagnosis

When multiple pigmented lesions are present, LEOPARD syndrome should be considered but myxomas are absent in this condition and the systemic manifestations more protean. Mucosal pigmentation strongly resembles that of Peutz-Jeghers syndrome, but intestinal polyps are not part of the usual spectrum of Carney complex.

Genetics

Carney complex is inherited in an autosomal dominant fashion. The gene for CNC1, known as *PRKAR1A*, normally encodes the protein kinase A regulatory subunit R1a {408,1284}. When the mutated gene is present, the regulatory subunit is no longer produced. The patients are heterozygous for the mutation: the tumours tend to have LOH of the wild type allele for this regulatory gene. The *CNC2* gene is less well characterized but appears to be involved in regulating genomic stability, perhaps via the telomeres.

Prognosis and predictive factors

The prognosis depends on detecting cardiac myxoma, the most serious complex of CNC. The average age of 22 patients who died as the result of cardiac causes (cardiac failure from myxoma, cardiac myxoma emboli or cardiac arrhythmia) was 31 years. Timely diagnosis of the neoplasms requires an awareness of the possible significance of the pigmented skin spots, skin tumours, primary pigmented nodular adrenal disease and psammomatous melanotic schwannoma. Patients with lesions suggestive of CNC should be advised to have a general medical evaluation and an echocardiogram. Primary relatives of CNC patients should be similarly advised.

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References

1. Anon. (1993). National Institutes of Health Consensus Development Conference Statement on Diagnosis and Treatment of Early Melanoma, January 27-29, 1992. Am J Dermatopathol 15: 34-43.

2. Anon. (1996). A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. The French Langerhans' Cell Histiocytosis Study Group. Arch Dis Child 75: 17-24.

3. Anon. (1997). A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 89: 3909-3918.

4. Anon. (2004). Basal Cell Nevus Syndrome; BCNS. Online Mendelian Inheritance in Man (OMIM) http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=109400.

5. Anon. (2004). Spiegler-Brooke Syndrome. Online Mendelian Inheritance in Man (OMIM) http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=605041.

6. Anon. (2004). Trichoepithelioma, Multiple Familial. Online Mendelian Inheritance in Man (OMIM) http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=601606.

7. Abarca JF, Casiccia CC (2002). Skin cancer and ultraviolet-B radiation under the Antarctic ozone hole: southern Chile, 1987-2000. Photodermatol Photoimmunol Photomed 18: 294-302.

8. Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy WH, Osman I, Kopf AW, Polsky D (2004). Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. JAMA 292: 2771-2776.

9. Abbate M, Zeitouni NC, Seyler M, Hicks W, Loree T, Cheney RT (2003). Clinical course, risk factors, and treatment of microcystic adnexal carcinoma: a short series report. Dermatol Surg 29: 1035-1038.

10. Abdul Gaffoor PM (1998). Pyogenic granuloma of the scrotum. Cutis 62: 282.

11. Abel EA, Cox AJ, Farber EM (1982). Epidermal dystrophy and actinic keratoses in psoriasis patients following oral psoralen photochemotherapy (PUVA). Follow-up study. J Am Acad Dermatol 7: 333-340.

12. Abenoza P, Ackerman AB (1990). Neoplasms with Eccrine Differentiation. Lea & Febiger: Philadelphia.

13. Abesamis-Cubillan E, Shabrawi-Caelen L, LeBoit PE (2000). Merked cells and sclerosing epithelial neoplasms. Am J Dermatopathol 22: 311-315.

14. Ackerman AB (1970). Histopathologic concept of epidermolytic hyperkeratosis. Arch Dermatol 102: 253-259.

15. Ackerman AB (1978). Trichilemmoma. Arch Dermatol 114: 286.

16. Ackerman AB (1980). Malignant melanoma: a unifying concept. Hum Pathol 11: 591-595.

17. Ackerman AB (1988). Melanocytic proliferations that simulate malignant melanoma histopathologically. In: Pathobiology and Recognition of Malignant Melanoma, Mihm MCJr, Murphy GF, Kaufman N, eds., Williams and Wilkins: Baltimore , p. 167.

18. Ackerman AB (1988). What naevus is dysplastic, a syndrome and the commonest precursor of malignant melanoma? A riddle and an answer. Histopathology 13: 241-256.

19. Ackerman AB (1997). Spitz nevus. Am J Dermatopathol 19: 419-421.

20. Ackerman AB (2000). Mythology and numerology in the sphere of melanoma. Cancer 88: 491-496.

21. Ackerman AB, Chongchitnant N, Sanchez J, Guo Y, Bennin B, Reichel M, Randall MB (1997). Histologic diagnosis of inflammatory skin disorders. An algorithmic method based on pattern analysis. 2nd ed. Lippiniott Williams and Wilkins: Baltimore.

22. Ackerman AB, David KM (1986). A unifying concept of malignant melanoma: biologic aspects. Hum Pathol 17: 438-440.

23. Ackerman AB, de Viragh PA, Chongchitnant N (1993). Proliferating follicular cystic neoplasm. In: Neoplasms with Follicular Differentiation, Ackerman AB, de Viragh PA, Chongchitnant N, eds., Lea & Febiger: Philadelphia , pp. 553-570.

24. Ackerman AB, Guo Y, Lazova R, Kaddu S (2001). Melanocytic nevus on the genitalia vs. Melanoma on the genitalia. In: Differential Diagnosis in Dermatopathology II, Differential Diagnosis in Dermatopathology II, 2nd ed. Ardor Scribendi: New York , pp. 110-113.

25. Ackerman AB, Guo Y, Vitale P (1992). Clues to Diagnosis in Dermatopathology II. ASCP Press: Chicago.

26. Ackerman AB, Mones JM (2001). Resolving Quanderies in Dermatology, Pathology & Dermatopathology. Ardor Scribendi: Philadelphia.

27. Ackerman AB, Reddy VB, Soyer HP (2001). Fibrofolliculoma and trichodiscoma. In: Neoplasms with follicular differentiation, Ackerman AB, Reddy VB, Soyer HP, eds., Ardor Scribendi: New York , pp. 221-244.

28. Ackerman AB, Reddy VB, Soyer HP (2001). Neoplasms with Follicular Differentiation. Ardor Scribendi: New York.

29. Ackerman AB, Reddy VB, Soyer HP (2001). PIlar sheath acanthoma. In: Neoplasms with Follicular Differentiation , Ackerman AB, Reddy VB, Soyer HP, eds., 2nd ed. Ardor Scribendi: New York .

30. Ackerman AB, Scheiner AM (1983). How wide and deep is wide and deep enough? A critique of surgical practice in excisions of primary cutaneous malignant melanoma. Hum Pathol 14: 743-744.

31. Ackerman AB, Wade TR (1980). Tricholemmoma. Am J Dermatopathol 2: 207-224.

32. Ackerman LV (1948). Verrucous carcinoma of the oral cavity. Surgery 23: 670-678.

33. Adamson HG (1905). Congenital xanthoma multiplex in child. Br J Dermatol 17: 222.

34. Agger P, Osmundsen PE (1970). Angiokeratoma of the scrotum (Fordyce). A case report on response to surgical treatment of varicocele. Acta Derm Venereol 50: 221-224.

35. Agis H, Weltermann A, Fonatsch C, Haas O, Mitterbauer G, Mullauer L, Schreiber S, Schwarzinger I, Juretzka W, Valent P, Jager U, Lechner K, Geissler K (2002). A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. Ann Hematol 81: 90-95.

36. Agnarsson BA, Vonderheid EC, Kadin ME (1990). Cutaneous T cell lymphoma with suppressor/cytotoxic (CD8) phenotype: identification of rapidly progressive and chronic subtypes. J Am Acad Dermatol 22: 569-577.

37. Aguilar A, Ambrojo P, Requena L, Olmos L, Sanchez Yus E (1990). Angiolymphoid hyperplasia with eosinophilia limited to the vulva. Clin Exp Dermatol 15: 65-67.

38. Aguilera NS, Tomaszewski MM, Moad JC, Bauer FA, Taubenberger JK, Abbondanzo SL (2001). Cutaneous follicle center lymphoma: a clinicopathologic study of 19 cases. Mod Pathol 14: 828-835.

39. Ahn SK, Won JH, Lee SH, Lee WS, Choi SI (1995). Pleomorphic fibroma on the scalp. Dermatology 191: 245-248.

40. Aiba S, Terui T, Tagami H (2000). Dermatofibroma with diffuse eosinophilic infiltrate. Am J Dermatopathol 22: 281-284.

41. Aird I, Johnson HD, Lennox B, Stanfield AG (1954). Epithelioma cuniculatum: a variety of squamous carcinoma peculiar to the foot. Br J Surg 42: 245-250.

42. Aitken J, Welch J, Duffy D, Milligan A, Green A, Martin N, Hayward N (1999). CDKN2A variants in a population-based sample of Queensland families with melanoma. J Natl Cancer Inst 91: 446-452.

43. Akalin T, Sen S, Yuceturk A, Kandiloglu G (2001). P53 protein expression in eccrine poroma and porocarcinoma. Am J Dermatopathol 23: 402-406.

44. Akasaka T, Imamura Y, Kon S (1993). Multiple agminated juvenile melanoma arising on a hyperpigmented macule. J Dermatol 20: 638-642.

45. Akasu R, Sugiyama H, Araki M, Ohtake N, Furue M, Tamaki K (1996). Dermatoscopic and videomicroscopic features of melanocytic plantar nevi. Am J Dermatopathol 18: 10-18.

46. Akerman M (1997). The cytology of soft tissue tumours. Acta Orthop Scand Suppl 273: 54-59.

47. Akiyama M, Inamoto N (2001). Arteriovenous haemangioma in chronic liver disease: clinical and histopathological features of four cases. Br J Dermatol 144: 604-609.

48. Al Ghamdi AM, Trotter MJ (1999). Trichoepithelioma associated with cellular blue nevus. J Cutan Med Surg 3: 317-319.

49. Alain G, Tousignant J, Rozenfarb E (1993). Chronic arsenic toxicity. Int J Dermatol 32: 899-901.

50. Alam M, Ratner D (2001). Cutaneous squamous-cell carcinoma. N Engl J Med 344: 975-983.

51. Alam NA, Bevan S, Churchman M, Barclay E, Barker K, Jaeger EE, Nelson HM, Healy E, Pembroke AC, Friedmann PS, Dalziel K, Calonje E, Anderson J, August PJ, Davies MG, Felix R, Munro CS, Murdoch M, Rendall J, Kennedy S, Leigh IM, Kelsell DP, Tomlinson IP, Houlston RS (2001). Localization of a gene (MCUL1) for multiple cutaneous leiomyomata and uterine fibroids to chromosome 1q42.3-q43. Am J Hum Genet 68: 1264-1269.

52. Alapetite C, Benoit A, Moustacchi E, Sarasin A (1997). The comet assay as a repair test for prenatal diagnosis of Xeroderma pigmentosum and trichothiodystrophy. J Invest Dermatol 108: 154-159.

53. Albert LS, Rhodes AR, Sober AJ (1990). Dysplastic melanocytic nevi and cutaneous melanoma: markers of increased melanoma risk for affected persons and blood relatives. J Am Acad Dermatol 22: 69-75.

54. Albert VA, Koh HK, Geller AC, Miller DR, Prout MN, Lew RA (1990). Years of potential life lost: another indicator of the impact of cutaneous malignant melanoma on society. J Am Acad Dermatol 23: 308-310.

55. Albrecht S, Kahn HJ, From L (1989). Palisaded encapsulated neuroma: an immunohistochemical study. Mod Pathol 2: 403-406.

56. Alfadley A, Al Aboud K, Tulba A, Mourad MM (2001). Multiple eccrine hidrocystomas of the face. Int J Dermatol 40: 125-129.

57. Algermissen B, Toppe F, Henz BM, Berlien HP, Haas N (2002). Hypertrichotic plaque-type blue naevus—a novel type of dermal melanocytosis: report of an unusual case. Acta Derm Venereol 82: 61-62.

58. Alibert JLM (1806). Description des maladies de la peau : observées à l'hôpital Saint-Louis, et exposition des meilleures méthodes suivies pour leur traitement. Barrois L'Ainé & Fils: Paris.

59. Allan AE, Shoji T, Li N, Burlage A, Davis B, Bhawan J (2001). Two cases of Kaposi's sarcoma mimicking Stewart-Treves syndrome found to be human herpesvirus-8 positive. Am J Dermatopathol 23: 431-436.

60. Allan SJ, Dicker AJ, Tidman MJ, Mclaren KM, Hunter JA (1998). Amelanotic lentigo maligna and amelanotic lentigo maligna melanoma: a report of three cases mimicking intraepidermal squamous carcinoma. J Eur Acad Dermatol Venereol 11: 78-81.

61. Allen AC, Spitz S (1953). Malignant melanoma: A clinicopathologic analysis of the criteria for diagnosis and prognosis. Cancer 6: 1-45.

62. Allen MR, Ninfo V, Viglio A, D'Angelo P, Paulli M, Arico M (2001). Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) in a girl previously affected by acute lymphoblastic

leukemia. Med Pediatr Oncol 37: 150-152.
63. Allyn B, Kopf AW, Kahn M, Witten VH (1963). Incidence of pigmented naevi. JAMA 186: 890-893.
64. Aloi F, Pich A, Pippione M (1996). Malignant cellular blue nevus: a clinicopathological study of 6 cases. Dermatology 192: 36-40.
65. Aloi F, Tomasini C, Pippione M (1993). Microvenular hemangioma. Am J Dermatopathol 15: 534-538.
66. Aloi FG, Molinero A, Pippione M (1988). Basal cell carcinoma with matrical differentiation. Matrical carcinoma. Am J Dermatopathol 10: 509-513.
67. Alper J, Holmes LB, Mihm MCJr (1979). Birthmarks with serious medical significance: nevocullular nevi, sebaceous nevi, and multiple cafe au lait spots. J Pediatr 95: 696-700.
68. Amaral AL, Nascimento AG, Goellner JR (1984). Proliferating pilar (trichilemmal) cyst. Report of two cases, one with carcinomatous transformation and one with distant metastases. Arch Pathol Lab Med 108: 808-810.
69. Ambrojo P, Aguilar A, Requena L, Sanchez YE (1990). Achromic verrucous large cell acanthoma. J Cutan Pathol 17: 182-184.
70. Amonette RA, Salasche SJ, Chesney TM, Clarendon CC, Dilawari RA (1981). Metastatic basal-cell carcinoma. J Dermatol Surg Oncol 7: 397-400.
71. Anderson TD, Weber RS, Guerry D, Elder D, Schuchter L, Loevner LA, Rosenthal DI (2002). Desmoplastic neurotropic melanoma of the head and neck: the role of radiation therapy. Head Neck 24: 1068-1071.
71A. Angelucci D, Natali PG, Amerio PL, Ramenghi M, Musiani P (1991). Rapid perinatal growth mimicking malignant transformation in a giant congenital melanocytic nevus. Hum Pathol 22: 297-301.
72. Angervall L, Enzinger FM (1975). Extraskeletal neoplasm resembling Ewing's sarcoma. Cancer 36: 240-251.
73. Angervall L, Kindblom LG, Haglid K (1984). Dermal nerve sheath myxoma. A light and electron microscopic, histochemical and immunohistochemical study. Cancer 53: 1752-1759.
74. Annessi G, Giannetti A (1996). Purely cutaneous Rosai—Dorfman disease. Br J Dermatol 134: 749-753.
75. Ansai S, Mitsuhashi Y, Kondo S, Manabe M (2004). Immunohistochemical differentiation of extra-ocular sebaceous carcinoma from other skin cancers. J Dermatol 31: 998-1008.
76. Ansai S, Watanabe S, Aso K (1989). A case of tubular apocrine adenoma with syringocystadenoma papilliferum. J Cutan Pathol 16: 230-236.
77. Anstey A, Cerio R, Ramnarain N, Orchard G, Smith N, Jones EW (1994). Desmoplastic malignant melanoma. An immunocytochemical study of 25 cases. Am J Dermatopathol 16: 14-22.
78. Apisarnthanarax P (1981). Granular cell tumor. An analysis of 16 cases and review of the literature. J Am Acad Dermatol 5: 171-182.
79. Arbiser JL, Weiss SW, Arbiser ZK, Bravo F, Govindajaran B, Caceres-Rios H, Cotsonis G, Recavarren S, Swerlick RA, Cohen C (2001). Differential expression of active mitogen-activated protein kinase in cutaneous endothelial neoplasms: implications for biologic behavior and response to therapy. J Am Acad Dermatol 44: 193-197.
80. Argenyi ZB (1990). Immunohistochemical characterization of palisaded, encapsulated neuroma. J Cutan Pathol 17: 329-335.
81. Argenyi ZB (1992). Newly recognized neural neoplasms relevant to the dermatopathologist. Dermatol Clin 10: 219-234.
82. Argenyi ZB, Bergfeld WF, McMahon JT, Goeken JA, Garewal GS (1986). Primitive neuroectodermal tumor in the skin with features of neuroblastoma in an adult patient. J Cutan Pathol 13: 420-430.
83. Argenyi ZB, Cain C, Bromley C, Nguyen AV, Abraham AA, Kerschmann R, LeBoit PE (1994). S-100 protein-negative malignant melanoma: fact or fiction? A light-microscopic and immunohistochemical study. Am J Dermatopathol 16: 233-240.
84. Argenyi ZB, Cooper PH, Santa CD (1993). Plexiform and other unusual variants of palisaded encapsulated neuroma. J Cutan Pathol 20: 34-39.
85. Argenyi ZB, Goeken JA, Balogh K (1989). Hyaline cells in chondroid syringomas. A light-microscopic, immunohistochemical, and ultrastructural study. Am J Dermatopathol 11: 403-412.
86. Argenyi ZB, Huston BM, Argenyi EE, Maillet MW, Hurt MA (1994). Large-cell acanthoma of the skin. A study by image analysis cytometry and immunohistochemistry. Am J Dermatopathol 16: 140-144.
87. Argenyi ZB, Kutzner H, Seaba MM (1995). Ultrastructural spectrum of cutaneous nerve sheath myxoma/cellular neurothekeoma. J Cutan Pathol 22: 137-145.
88. Argenyi ZB, LeBoit PE, Santa Cruz D, Swanson PE, Kutzner H (1993). Nerve sheath myxoma (neurothekeoma) of the skin: light microscopic and immunohistochemical reappraisal of the cellular variant. J Cutan Pathol 20: 294-303.
89. Argenyi ZB, Nguyen AV, Balogh K, Sears JK, Whitaker DC (1992). Malignant eccrine spiradenoma. A clinicopathologic study. Am J Dermatopathol 14: 381-390.
90. Argenyi ZB, Santa CD, Bromley C (1992). Comparative light-microscopic and immunohistochemical study of traumatic and palisaded encapsulated neuromas of the skin. Am J Dermatopathol 14: 504-510.
91. Argenziano G, Fabbrocini G, Carli P, de Giorgi V, Sammarco E, Delfino M (1998). Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. Arch Dermatol 134: 1563-1570.
92. Arico M, La Rocca E, Noto G, Pravata G, Rodolico V (1989). Proliferating tricholemmal tumour with lymph node metastases. Br J Dermatol 121: 793-797.
93. Arico M, Nichols K, Whitlock JA, Arceci R, Haupt R, Mittler U, Kuhne T, Lombardi A, Ishii E, Egeler RM, Danesino C (1999). Familial clustering of Langerhans cell histiocytosis. Br J Haematol 107: 883-888.
94. Ariyanayagam-Baksh SM, Baksh FK, Finkelstein SD, Swalsky PA, Abernethy J, Barnes EL (2003). Malignant blue nevus: a case report and molecular analysis. Am J Dermatopathol 25: 21-27.
95. Armstrong BK, Kricker A (1993). How much melanoma is caused by sun exposure? Melanoma Res 3: 395-401.
96. Armstrong BK, Kricker A, English DR (1997). Sun exposure and skin cancer. Australas J Dermatol 38 Suppl 1: S1-S6.
96A. Arnaudeau-Begard C, Brellier F, Chevallier-Lagente O, Hoeijmakers J, Bernerd F, Sarasin A, Magnaldo T (2003). Genetic correction of DNA repair-deficient/cancer-prone xeroderma pigmentosum groupe C keratinocyts. Hum Gene Ther 14: 983-996.
97. Arnold M, Geilen CC, Coupland SE, Krengel S, Dippel E, Sproder J, Goerdt S, Orfanos CE (1999). Unilateral angiolymphoid hyperplasia with eosinophilia involving the left arm and hand. J Cutan Pathol 26: 436-440.
98. Arnulf B, Copie-Bergman C, Delfau-Larue MH, Lavergne-Slove A, Bosq J, Wechsler J, Wassef M, Matuchansky C, Epardeau B, Stern M, Bagot M, Reyes F, Gaulard P (1998). Nonhepatosplenic gammadelta T-cell lymphoma: a subset of cytotoxic lymphomas with mucosal or skin localization. Blood 91: 1723-1731.
99. Aronson PJ, Fretzin DF, Potter BS (1985). Neurothekeoma of Gallager and Helwig (dermal nerve sheath myxoma variant): report of a case with electron microscopic and immunohistochemical studies. J Cutan Pathol 12: 506-519.
99A. Arora A, Lowe L, Su L, Rees R, Bradford C, Cimmino,VC, Chang AE, Johnson TM, Sabel MS (2005). Wide excision without radiation for desmoplastic melanoma. Cancer (in press, PMID: 16080180).
100. Arrington JHI, Reed RJ, Ichinose H, Krementz ET (1977). Plantar lentiginous melanoma: a distinctive variant of human cutaneous malignant melanoma. Am J Surg Pathol 1: 131-143.
101. Arroyo MP, Chu DH, Mobini N, Park HS (2004). Verrucous plaque on the foot. J Cutan Pathol 31: 271-273.
102. Arumi-Uria M, McNutt NS, Finnerty B (2003). Grading of atypia in nevi: correlation with melanoma risk. Mod Pathol 16: 764-771.
103. Asano S, Endo H, Sagami S (1978). An ultrastructural study of localized lymphangioma circumscriptum. Arch Dermatol Res 262: 301-309.
104. Ascani S, Zinzani PL, Gherlinzoni F, Sabattini E, Briskomatis A, de Vivo A, Piccioli M, Fraternali OG, Pieri F, Goldoni A, Piccaluga PP, Zallocco D, Burnelli R, Leoncini L, Falini B, Tura S, Pileri SA (1997). Peripheral T-cell lymphomas. Clinicopathologic study of 168 cases diagnosed according to the R.E.A.L. Classification. Ann Oncol 8: 583-592.
105. Ashfaq R, Timmons CF (1992). Rhabdomyomatous mesenchymal hamartoma of skin. Pediatr Pathol 12: 731-735.
106. Ashida M, Ueda M, Kunisada M, Ichihashi M, Terai M, Sata T, Matsukura T (2002). Protean manifestations of human papillomavirus type 60 infection on the extremities. Br J Dermatol 146: 885-890.
107. Aslan V, Akay OM, Durak B, Kabukcuoglu S, Gulbas Z (2002). Langerhans cell histiocytosis with transformation to acute leukemia showing 45,X, t(8; 21), 5q-, -Y karyotype. Leuk Lymphoma 43: 1683-1685.
108. Aszterbaum M, Beech J, Epstein EHJr (1999). Ultraviolet light radiation mutagenesis of hedgehog pathway genes in basal cell carcinomas. J Invest Dermatol Symp Proc 4: 41-45.
109. Aszterbaum M, Epstein J, Oro A, Douglas V, LeBoit PE, Scott MP, Epstein EHJr (1999). Ultraviolet and ionizing radiation enhance the growth of BCCs and trichoblastomas in patched heterozygous knockout mice. Nat Med 5: 1285-1291.
110. Aszterbaum M, Rothman A, Johnson RL, Fisher M, Xie J, Bonifas JM, Zhang X, Scott MP, Epstein EHJr (1998). Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. J Invest Dermatol 110: 885-888.
111. Atherton DJ, Pitcher DW, Wells RS, MacDonald DM (1980). A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the NAME syndrome. Br J Dermatol 103: 421-429.
112. Au WY, Shek TW, Kwong YL (2000). Epstein-Barr virus-related intravascular lymphomatosis. Am J Surg Pathol 24: 309-310.
113. Au WY, Shek WH, Nicholls J, Tse KM, Todd D, Kwong YL (1997). T-cell intravascular lymphomatosis (angiotropic large cell lymphoma): association with Epstein-Barr viral infection. Histopathology 31: 563-567.
114. Aurora AL, Luxenberg MN (1970). Case report of adenocarcinoma of glands of Moll. Am J Ophthalmol 70: 984-990.
115. Auroy S, Avril MF, Chompret A, Pham D, Goldstein AM, Bianchi-Scarra G, Frebourg T, Joly P, Spatz A, Rubino C, Demenais F, Bressac de Paillerets B (2001). Sporadic multiple primary melanoma cases: CDKN2A germline mutations with a founder effect. Genes Chromosomes Cancer 32: 195-202.
116. Austen KF (1992). Systemic mastocytosis. N Engl J Med 326: 639-640.
117. Autier P, Dore JF (1998). Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. Int J Cancer 77: 533-537.
118. Avidor I, Kessler E (1977). 'Atypical' blue nevus—a benign variant of cellular blue nevus. Presentation of three cases. Dermatologica 154: 39-44.
119. Avinoach I, Halevy S, Argov S, Sacks M (1994). Gamma/delta T-cell lymphoma involving the subcutaneous tissue and associated with a hemophagocytic syndrome. Am J Dermatopathol 16: 426-433.
120. Azorin D, Lopez-Rios F, Ballestin C, Barrientos N, Rodriguez-Peralto JL (2001). Primary cutaneous adenosquamous carcinoma: a case report and review of the literature. J Cutan Pathol 28: 542-545.
121. Azuma Y, Matsukawa A (1993). Warty dyskeratoma with multiple lesions. J Dermatol 20: 374-377.
122. Azzola MF, Shaw HM, Thompson JF, Soong SJ, Scolyer RA, Watson GF, Colman MH, Zhang Y (2003). Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single center. Cancer 97: 1488-1498.
123. Bachmeyer C, Bazarbachi A, Rio B, Delmer A, Hunault M, Zittoun R, Le Tourneau A, Aractingi S (1997). Specific cutaneous involvement indicating relapse of Burkitt's lymphoma. Am J Hematol 54: 176.
123A. Bader JL, Li FP, Olmstead PM, Strickman NA, Green DM (1985). Childhood malignant melanoma. Incidence and etiology. Am J Pediatr Hematol Oncol 7: 341-345.
124. Baefverstedt B (1944). Über Lymphadenosis benigna cutis. Eine klinische und pathologisch-anatomische Studie. Acta Derm Venereol (Suppl XI) (Stock) 24: 1-102.

125. Baer MR, Barcos M, Farrell H, Raza A, Preisler HD (1989). Acute myelogenous leukemia with leukemia cutis. Eighteen cases seen between 1969 and 1986. Cancer 63: 2192-2200.
126. Baer SC, Schultz D, Synnestvedt M, Elder DE (1995). Desmoplasia and neurotropism. Prognostic variables in patients with stage I melanoma. Cancer 76: 2242-2247.
127. Baes H, Suurmond D (1970). Apocrine sweat gland carcinoma. Report of a case. Br J Dermatol 83: 483-486.
128. Bahuau M, Vidaud D, Jenkins RB, Bieche I, Kimmel DW, Assouline B, Smith JS, Alderete B, Cayuela JM, Harpey JP, Caille B, Vidaud M (1998). Germ-line deletion involving the INK4 locus in familial proneness to melanoma and nervous system tumors. Cancer Res 58: 2298-2303.
129. Bahuau M, Vidaud D, Kujas M, Palangie A, Assouline B, Chaignaud-Lebreton M, Prieur M, Vidaud M, Harpey JP, Lafourcade J, Caille B (1997). Familial aggregation of malignant melanoma/dysplastic naevi and tumours of the nervous system: an original syndrome of tumour proneness. Ann Genet 40: 78-91.
130. Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, Fleming ID, Gershenwald JE, Houghton AJr, Kirkwood JM, McMasters KM, Mihm MF, Morton DL, Reintgen DS, Ross MI, Sober A, Thompson JA, Thompson JF (2001). Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 19: 3635-3648.
131. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, Urist M, McMasters KM, Ross MI, Kirkwood JM, Atkins MB, Thompson JA, Coit DG, Byrd D, Desmond R, Zhang Y, Liu PY, Lyman GH, Morabito A (2001). Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19: 3622-3634.
132. Baldassano MF, Bailey EM, Ferry JA, Harris NL, Duncan LM (1999). Cutaneous lymphoid hyperplasia and cutaneous marginal zone lymphoma: comparison of morphologic and immunophenotypic features. Am J Surg Pathol 23: 88-96.
133. Bale AE, Yu KP (2001). The hedgehog pathway and basal cell carcinomas. Hum Mol Genet 10: 757-762.
134. Baliko Z, Schreiner M, Kishindy KK, Hegedus G, Kosztolanyi G (2000). Different manifestations of langerhans cell histiocytosis affecting two members of a family. Respiration 67: 583-585.
135. Ball NJ, Golitz LE (1994). Melanocytic nevi with focal atypical epithelioid cell components: a review of seventy-three cases. J Am Acad Dermatol 30: 724-729.
136. Balus L, Manente L, Remotti D, Grammatico P, Bellocci M (1996). Granulomatous slack skin. Report of a case and review of the literature. Am J Dermatopathol 18: 199-206.
137. Ban M, Kamiya H, Kitajima Y (2000). Tufted angioma of adult onset, revealing abundant eccrine glands and central regression. Dermatology 201: 68-70.
138. Banerjee SS, Agbamu DA, Eyden BP, Harris M (1997). Clinicopathological characteristics of peripheral primitive neuroectodermal tumour of skin and subcutaneous tissue. Histopathology 31: 355-366.
139. Banerjee SS, Eyden BP, Wells S, McWilliam LJ, Harris M (1992). Pseudoangiosarcomatous carcinoma: a clinicopathological study of seven cases. Histopathology 21: 13-23.
140. Banks ER, Cooper PH (1991). Adenosquamous carcinoma of the skin: a report of 10 cases. J Cutan Pathol 18: 227-234.
141. Banks PM, Arseneau JC, Gralnick HR, Canellos GP, DeVita VTJr, Berard CW (1975). American Burkitt's lymphoma: a clinicopathologic study of 30 cases. II. Pathologic correlations. Am J Med 58: 322-329.
142. Bannatyne P, Elliott P, Russell P (1989). Vulvar adenosquamous carcinoma arising in a hidradenoma papilliferum, with rapidly fatal outcome: case report. Gynecol Oncol 35: 395-398.
143. Bansal RK, Bhaduri AS, Pancholi YJ, Balar DB (1989). Cellular blue nevus with nevus cells in regional lymph nodes: a lesion that mimics melanoma. Indian J Cancer 26: 145-150.
144. Bantel E, Grosshans E, Ortonne JP (1989). [Understanding microcapillary angioma, observations in pregnant patients and in females treated with hormonal contraceptives]. Z Hautkr 64: 1071-1074.
145. Barakova D, Sach J, Kuchynka P, Redinova M, Kocur I (2002). [Angiolymphoid hyperplasia with eosinophilia with bilateral involvement of the lacrimal glands]. Klin Monatsbl Augenheilkd 219: 376-379.
146. Baran R, Goettmann S (1998). Distal digital keratoacanthoma: a report of 12 cases and a review of the literature. Br J Dermatol 139: 512-515.
147. Baran R, Perrin C (1997). Focal subungual warty dyskeratoma. Dermatology 195: 278-280.
148. Baranda L, Torres-Alvarez B, Moncada B, Portales-Perez D, de la Fuente H, Layseca E, Gonzalez-Amaro R (1999). Presence of activated lymphocytes in the peripheral blood of patients with halo nevi. J Am Acad Dermatol 41: 567-572.
149. Bardazzi F, Orlandi C, D'Antuono A, Patrizi A (1998). Lymphangioma circumscriptum of the penis. Sex Transm Infect 74: 303-304.
150. Barker SM, Winkelmann RK (1986). Inflammatory lymphadenoid reactions with dermatofibroma/histiocytoma. J Cutan Pathol 13: 222-226.
151. Barnes BC, Seigler HF, Saxby TS, Kocher MS, Harrelson JM (1994). Melanoma of the foot. J Bone Joint Surg Am 76: 892-898.
152. Barnes EA, Kong M, Ollendorff V, Donoghue DJ (2001). Patched1 interacts with cyclin B1 to regulate cell cycle progression. EMBO J 20: 2214-2223.
153. Barnes L, Eveson JW, Reichart P, Sidransky D (2005). World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours. IARC Press: Lyon.
154. Barnhill RL (1995). Pathology of Melanocytic nevi and Malignant Melanoma. Butterworth-Heineman: Boston.
155. Barnhill RL (1998). Childhood melanoma. Semin Diagn Pathol 15: 189-194.
156. Barnhill RL (2004). Melanocytic nevi with phenotypic heterogeneity. In: Pathology of Melanocytic Nevi and Malignant Melanoma, Barnhill RL, Piepkorn M, Busam KJ, eds., Springer-Verlag: New York , pp. 223-237.
157. Barnhill RL, Albert LS, Shama SK, Goldenhersh MA, Rhodes AR, Sober AJ (1990). Genital lentiginosis: a clinical and histopathologic study. J Am Acad Dermatol 22: 453-460.
158. Barnhill RL, Barnhill MA, Berwick M, Mihm MCJr (1991). The histologic spectrum of pigmented spindle cell nevus: a review of 120 cases with emphasis on atypical variants. Hum Pathol 22: 52-58.
159. Barnhill RL, Fleischli M (1995). Histologic features of congenital melanocytic nevi in infants 1 year of age or younger. J Am Acad Dermatol 33: 780-785.
159A. Barnhill RL, Flotte TJ, Fleischli M, Perez-Atayde A (1995). Cutaneous melanoma and atypical Spitz tumors in childhood. Cancer 76: 1833-1845.
160. Barnhill RL, Katzen J, Spatz A, Fine J, Berwick M (2005). The importance of mitotic rate as a prognostic factor for localized cutaneous melanoma. J Cutan Pathol 32: 268-273.
161. Barnhill RL, Mihm MC, Jr. (1990). Cellular neurothekeoma. A distinctive variant of neurothekeoma mimicking nevomelanocytic tumors. Am J Surg Pathol 14: 113-120.
162. Barnhill RL, Mihm MCJr (1989). Pigmented spindle cell naevus and its variants: distinction from melanoma. Br J Dermatol 121: 717-725.
163. Barnhill RL, Mihm MCJr (1993). The histopathology of cutaneous malignant melanoma. Semin Diagn Pathol 10: 47-75.
164. Barnhill RL, Mihm MCJr, Magro CM (1991). Plexiform spindle cell naevus: a distinctive variant of plexiform melanocytic naevus. Histopathology 18: 243-247.
165. Barr RJ, Graham JH (1979). Granular cell basal cell carcinoma. A distinct histopathologic entity. Arch Dermatol 115: 1064-1067.
166. Barrionuevo C, Anderson VM, Zevallos-Giampietri E, Zaharia M, Misad O, Bravo F, Caceres H, Taxa L, Martinez MT, Wachtel A, Piris MA (2002). Hydroa-like cutaneous T-cell lymphoma: a clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. Appl Immunohistochem Mol Morphol 10: 7-14.
167. Barrow MV, Holubar K (1969). Multicentric reticulohistiocytosis. A review of 33 patients. Medicine (Baltimore) 48: 287-305.
168. Barshack I, Goldberg I, Davidson B, Ravid A, Schiby G, Kopolovic J, Leviav A, Friedman E (1998). Expression of rasGTPase activating protein in basal cell carcinoma of the skin. Mod Pathol 11: 271-275.
169. Barter RH, Letterman GS, Schurter M (1963). Hemangiomas in pregnancy. Am J Obstet Gynecol 87: 625-634.
170. Barzi AS, Ruggeri S, Recchia F, Bertoldi I (1997). Malignant metastatic eccrine poroma. Proposal for a new therapeutic protocol. Dermatol Surg 23: 267-272.
171. Bastian BC, Kashani-Sabet M, Hamm H, Godfrey T, Moore DH, Brocker EB, LeBoit PE, Pinkel D (2000). Gene amplifications characterize acral melanoma and permit the detection of occult tumor cells in the surrounding skin. Cancer Res 60: 1968-1973.
172. Bastian BC, LeBoit PE, Pinkel D (2000). Mutations and copy number increase of HRAS in Spitz nevi with distinctive histopathological features. Am J Pathol 157: 967-972.
173. Bastian BC, Olshen A, LeBoit P, Pinke.D. (2003). Classifying melanocytic tumors based on DNA copy number changes. Am J Pathol 163: 1765-1770.
174. Bastian BC, Wesselmann U, Pinkel D, LeBoit PE (1999). Molecular cytogenetic analysis of Spitz nevi shows clear differences to melanoma. J Invest Dermatol 113: 1065-1069.
175. Bastian BC, Xiong J, Frieden IJ, Williams ML, Chou P, Busam K, Pinkel D, LeBoit PE (2002). Genetic changes in neoplasms arising in congenital melanocytic nevi: differences between nodular proliferations and melanomas. Am J Pathol 161: 1163-1169.
176. Bataille V (2003). Genetic epidemiology of melanoma. Eur J Cancer 39: 1341-1347.
177. Bates AW, Baithun SI (1998). Atypical mixed tumor of the skin: histologic, immunohistochemical, and ultrastructural features in three cases and a review of the criteria for malignancy. Am J Dermatopathol 20: 35-40.
178. Batman PA, Evans HJ (1986). Metastasising pilar tumour of scalp. J Clin Pathol 39: 757-760.
179. Bauer BS, Kernahan DA, Hugo NE (1981). Lymphangioma circumscriptum—a clinicopathological review. Ann Plast Surg 7: 318-326.
180. Bauer HC, Trovik CS, Alvegard TA, Berlin O, Erlanson M, Gustafson P, Klepp R, Moller TR, Rydholm A, Saeter G, Wahlstrom O, Wiklund T (2001). Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register. Acta Orthop Scand 72: 150-159.
181. Bautista NC, Cohen S, Anders KH (1994). Benign melanocytic nevus cells in axillary lymph nodes. A prospective incidence and immunohistochemical study with literature review. Am J Clin Pathol 102: 102-108.
182. Bayer-Garner IB, Givens V, Smoller B (1999). Immunohistochemical staining for androgen receptors: a sensitive marker of sebaceous differentiation. Am J Dermatopathol 21: 426-431.
183. Bayer-Garner IB, Sanderson RD, Smoller BR (1999). Syndecan-1 expression is diminished in acantholytic cutaneous squamous cell carcinoma. J Cutan Pathol 26: 386-390.
184. Bazin P (1870). Leçons sur le traitement des maladies chroniques en général et des affections de la peau en particulier par l'emploi comparé des eaux minérales de l'hydrothérapie et des moyens pharmaceutiques. Delahaye: Paris.
185. Beaty MW, Toro J, Sorbara L, Stern JB, Pittaluga S, Raffeld M, Wilson WH, Jaffe ES (2001). Cutaneous lymphomatoid granulomatosis: correlation of clinical and biologic features. Am J Surg Pathol 25: 1111-1120.
186. Beddingfield FC, III (2003). The melanoma epidemic: res ipsa loquitur. Oncologist 8: 459-465.
187. Beer M, Eckert F, Schmoeckel C (1991). The atrophic dermatofibroma. J Am Acad Dermatol 25: 1081-1082.
188. Beers MH, Berkow R, Burs M (1999). The Merck Manual of Diagnosis and Therapy. Merck & Co.: Whitehouse Station.
189. Beghini A, Tibiletti MG, Roversi G, Chiaravalli AM, Serio G, Capella C, Larizza L (2001). Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and urticaria pigmentosa. Cancer 92: 657-662.
190. Beham A, Regauer S, Soyer HP, Beham-Schmid C (1998). Keratoacan-

thoma: a clinically distinct variant of well differentiated squamous cell carcinoma. Adv Anat Pathol 5: 269-280.
191. Bekkenk MW, Geelen FA, Voorst Vader PC, Heule F, Geerts ML, van Vloten WA, Meijer CJ, Willemze R (2000). Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 95: 3653-3661.
192. Bekkenk MW, Jansen PM, Meijer CJ, Willemze R (2004). CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. Ann Oncol 15: 1097-1108.
193. Bekkenk MW, Kluin PM, Jansen PM, Meijer CJ, Willemze R (2001). Lymphomatoid papulosis with a natural killer-cell phenotype. Br J Dermatol 145: 318-322.
194. Bekkenk MW, Vermeer MH, Geerts ML, Noordijk EM, Heule F, Voorst Vader PC, van Vloten WA, Meijer CJ, Willemze R (1999). Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 17: 2471-2478.
195. Bekkenk MW, Vermeer MH, Jansen PM, Van Marion AM, Canninga-Van Dijk MR, Kluin PM, Geerts ML, Meijer CJ, Willemze R (2003). Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. Blood .
196. Beljaards RC, Kaudewitz P, Berti E, Gianotti R, Neumann C, Rosso R, Paulli M, Meijer CJ, Willemze R (1993). Primary cutaneous CD30-positive large cell lymphoma: definition of a new type of cutaneous lymphoma with a favorable prognosis. A European Multicenter Study of 47 patients. Cancer 71: 2097-2104.
197. Beljaards RC, Meijer CJ, Van der Putte SC, Hollema H, Geerts ML, Bezemer PD, Willemze R (1994). Primary cutaneous T-cell lymphoma: clinicopathological features and prognostic parameters of 35 cases other than mycosis fungoides and CD30-positive large cell lymphoma. J Pathol 172: 53-60.
198. Beljaards RC, Willemze R (1992). The prognosis of patients with lymphomatoid papulosis associated with malignant lymphomas. Br J Dermatol 126: 596-602.
199. Bellezza G, Sidoni A, Bucciarelli E (2000). Primary mucinous carcinoma of the skin. Am J Dermatopathol 22: 166-170.
200. Bellows CF, Belafsky P, Fortgang IS, Beech DJ (2001). Melanoma in African-Americans: trends in biological behavior and clinical characteristics over two decades. J Surg Oncol 78: 10-16.
201. Bendl BJ, Asano K, Lewis RJ (1977). Nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis. Cutis 19: 327-329.
202. Benisovich V, Papadopoulos E, Amorosi EL, Zucker-Franklin D, Silber R (1988). The association of progressive, atrophying, chronic, granulomatous dermohypodermitis with Hodgkin's disease. Cancer 62: 2425-2429.
203. Benjamin SP, Mercer RD, Hawk WA (1977). Myofibroblastic contraction in spontaneous regression of multiple congenital mesenchymal hamartomas. Cancer 40: 2343-2352.
204. Berg JW, McDivitt RW (1968). Pathology of sweat gland carcinoma. Pathol Annu 3: 123-144.
204A. Berg P, Lindelof B (1997). Differences in malignant melanoma between children and adolescents. A 35-year epidemiological study. Arch Dermatol 133: 295-297.
205. Berg P, Lindelof B (2003). Congenital melanocytic naevi and cutaneous melanoma. Melanoma Res 13: 441-445.
206. Berger TG, Levin MW (1984). Congenital smooth muscle hamartoma. J Am Acad Dermatol 11: 709-712.
207. Bergman R (1999). How useful are T-cell receptor gene rearrangement studies as an adjunct to the histopathologic diagnosis of mycosis fungoides? Am J Dermatopathol 21: 498-502.
208. Bergman R, Aviram M, Shemer A, Oiknine Y, Vardi DA, Friedman-Birnbaum R (1993). Enhanced low-density lipoprotein degradation and cholesterol synthesis in monocyte-derived macrophages of patients with adult xanthogranulomatosis. J Invest Dermatol 101: 880-882.
209. Bergman R, Kurtin PJ, Gibson LE, Hull PR, Kimlinger TK, Schroeter AL (2001). Clinicopathologic, immunophenotypic, and molecular characterization of primary cutaneous follicular B-cell lymphoma. Arch Dermatol 137: 432-439.
210. Bergman R, Lichtig C, Moscona RA, Friedman-Birnbaum R (1991). A comparative immunohistochemical study of adenoid cystic carcinoma of the skin and salivary glands. Am J Dermatopathol 13: 162-168.
211. Bergman R, Sabo E, Schafer I (1996). Measurement of the maturation parameter by using computer-assisted interactive image analysis may be helpful in the differential diagnosis between compound Spitz nevus and malignant melanoma. Am J Dermatopathol 18: 567-570.
212. Bergman W, Voorst Vader PC, Ruiter DJ (1997). [Dysplastic nevi and the risk of melanoma: a guideline for patient care. Nederlandse Melanoom Werkgroep van de Vereniging voor Integrale Kankercentra.]. Ned Tijdschr Geneeskd 141: 2010-2014.
213. Bergman W, Watson P, de Jong J, Lynch HT, Fusaro RM (1990). Systemic cancer and the FAMMM syndrome. Br J Cancer 61: 932-936.
214. Beristain X, Azzarelli B (2002). The neurological masquerade of intravascular lymphomatosis. Arch Neurol 59: 439-443.
215. Bernengo MG, Novelli M, Quaglino P, Lisa F, De Matteis A, Savoia P, Cappello N, Fierro MT (2001). The relevance of the CD4+CD26- subset in the identification of circulating Sezary cells. Br J Dermatol 144: 125-135.
215A. Bernerd F, Asselineau D, Vioux C, Chevallier-Lagente O, Bouadjar B, Sarasin A, Magnaldo T (2001). Clues to epidermal cander proneness revealed by reconstruction of DNA repair-deficient xeroderma pigmentosum skin in vitro. Proc Natl Acad Sci USA 98: 7812-7822.
216. Bernstein EF, Kantor G, Howe N, Savit RM, Koblenzer PJ, Uitto J (1994). Tufted angioma of the thigh. J Am Acad Dermatol 31: 307-311.
217. Bernstein EF, Resnik KS, Loose JH, Halcin C, Kauh YC (1993). Solitary congenital self-healing reticulohistiocytosis. Br J Dermatol 129: 449-454.
218. Bernstein SC, Lim KK, Brodland DG, Heidelberg KA (1996). The many faces of squamous cell carcinoma. Dermatol Surg 22: 243-254.
219. Bertero M, Novelli M, Fierro MT, Bernengo MG (1994). Mantle zone lymphoma: an immunohistologic study of skin lesions. J Am Acad Dermatol 30: 23-30.
220. Berti E, Alessi E, Caputo R, Gianotti R, Delia D, Vezzoni P (1988). Reticulohistiocytoma of the dorsum. J Am Acad Dermatol 19: 259-272.
221. Berti E, Cerri A, Cavicchini S, Delia D, Soligo D, Alessi E, Caputo R (1991). Primary cutaneous gamma/delta T-cell lymphoma presenting as disseminated pagetoid reticulosis. J Invest Dermatol 96: 718-723.
222. Berti E, Gianotti R, Alessi E (1988). Unusual cutaneous histiocytosis expressing an intermediate immunophenotype between Langerhans' cells and dermal macrophages. Arch Dermatol 124: 1250-1253.
223. Berti E, Tomasini D, Vermeer MH, Meijer CJ, Alessi E, Willemze R (1999). Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. Am J Pathol 155: 483-492.
224. Berwick M, Armstrong BK, Ben Porat L, Fine J, Kricker A, Eberle C, Barnhill R (2005). Sun exposure and mortality from melanoma. J Natl Cancer Inst 97: 195-199.
225. Betti R, Bruscagin C, Inselvini E, Crosti C (1997). Basal cell carcinomas of covered and unusual sites of the body. Int J Dermatol 36: 503-505.
226. Betti R, Inselvini E, Vergani R, Moneghini L, Crosti C (2001). Sebaceoma arising in association with seborrheic keratosis. Am J Dermatopathol 23: 58-61.
227. Betts DR, Leibundgut KE, Feldges A, Pluss HJ, Niggli FK (1998). Cytogenetic abnormalities in Langerhans cell histiocytosis. Br J Cancer 77: 552-555.
228. Beylot-Barry M, Lamant L, Vergier B, de Muret A, Fraitag S, Delord B, Dubus P, Vaillant L, Delaunay M, Macgrogan G, Beylot C, de Mascarel A, Delsol G, Merlio JP (1996). Detection of t(2;5)(p23;q35) translocation by reverse transcriptase polymerase chain reaction and in situ hybridization in CD30-positive primary cutaneous lymphoma and lymphomatoid papulosis. Am J Pathol 149: 483-492.
229. Bhaskar AR, Kanvinde R (1999). Neurothekeoma of the hand. J Hand Surg [Br] 24: 631-633.
230. Bhatia K, Spangler G, Hamdy N, Neri A, Brubaker G, Levin A, Magrath I (1995). Mutations in the coding region of c-myc occur independently of mutations in the regulatory regions and are predominantly associated with myc/Ig translocation. Curr Top Microbiol Immunol 194: 389-398.
231. Bhatia S, Chu P, Weinberg JM (2003). Atypical cellular neurothekeoma. Dermatol Surg 29: 1154-1157.
232. Bhawan J (1979). Pilar sheath acanthoma. A new benign follicular tumor. J Cutan Pathol 6: 438-440.
233. Bhawan J (1988). Histology of epidermal dysplasia. J Cutan Aging Cosm Dermatol 1: 95-103.
234. Bhawan J, Cao SL (1999). Amelanotic blue nevus: a variant of blue nevus. Am J Dermatopathol 21: 225-228.
235. Bialer MG, Gailani MR, McLaughlin JA, Petrikovsky B, Bale AE (1994). Prenatal diagnosis of Gorlin syndrome. Lancet 344: 477.
236. Bibro MC, Houlihan RK, Sheahan DG (1980). Colonic ganglioneuroma. Arch Surg 115: 75-77.
237. Biddlestone LR, Mclaren KM, Tidman MJ (1991). Malignant hidradenoma—a case report demonstrating insidious histological and clinical progression. Clin Exp Dermatol 16: 474-477.
238. Biernat W, Kordek R, Arkuszewska C, Omulecki A, Wozniak L (1995). Malignant blue nevus with neurosarcoma-like lymph node metastases. Pol J Pathol 46: 51-54.
239. Biernat W, Kordek R, Wozniak L (1995). Over-expression of p53 protein as an indicator of the malignant transformation in spiradenoma. Histopathology 26: 439-443.
239A. Biernat W, Peraud A, Wozniak L, Ohgaki H (1998). p53 mutations in sweat gland carcinomas. Int J Cancer 76: 317-320.
240. Biernat W, Wozniak L (1994). Spiradenocarcinoma: a clinicopathologic and immunohistochemical study of three cases. Am J Dermatopathol 16: 377-382.
241. Biesterfeld S, Pennings K, Grussendorf-Conen EI, Bocking A (1995). Aneuploidy in actinic keratosis and Bowen's disease—increased risk for invasive squamous cell carcinoma? Br J Dermatol 133: 557-560.
242. Bijker N, Rutgers EJ, Duchateau L, Peterse JL, Julien JP, Cataliotti L (2001). Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer 91: 472-477.
243. Bijl JJ, Rieger E, van Oostveen JW, Walboomers JM, Kreike M, Willemze R, Meijer CJ (1997). HOXC4, HOXC5, and HOXC6 expression in primary cutaneous lymphoid lesions. High expression of HOXC5 in anaplastic large-cell lymphomas. Am J Pathol 151: 1067-1074.
244. Billano RA, Little WP (1982). Hypertrophic actinic keratosis. J Am Acad Dermatol 7: 484-489.
245. Billeret-Lebranchu V (1999). [Granular cell tumor. Epidemiology of 263 cases]. Arch Anat Cytol Pathol 47: 26-30.
246. Billeret-Lebranchu V, Martin de la Salle E, Vandenhaute B, Lecomte-Houcke M (1999). [Granular cell tumor and congenital epulis. Histochemical and immunohistochemical of 58 cases]. Arch Anat Cytol Pathol 47: 31-37.
247. Binns JH (1974). A rare case of hidradenoma papilliferum: report of a case and review of the literature. Br J Plast Surg 27: 367-369.
248. Birt AR, Hogg GR, Dube WJ (1977). Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 113: 1674-1677.
249. Bisceglia M, Carosi I, Castelvetere M, Murgo R (1998). [Multiple Fordyce-type angiokeratomas of the scrotum. An iatrogenic case]. Pathologica 90: 46-50.
250. Bishop DF, Calhoun DH, Bernstein HS, et al. (1987). Structure of the human alpha-galactosidase A gene: 5 control elements, intron/exon splice junction sequence and alternative 3' termination. Am J Hum Genet 41(suppl): A208.
251. Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac de Paillerets B, Chompret A, Ghiorzo P, Gruis N, Hansson J, Harland M, Hayward N, Holland EA, Mann GJ, Mantelli M, Nancarrow D, Platz A, Tucker MA (2002). Geographical variation in the penetrance of CDKN2A mutations for melanoma. J Natl Cancer Inst 94: 894-903.
252. Bishop EL (1931). Epidermoid carcinoma in sebaceous cysts. Ann Surg 93: 109-112.
253. Biswas J, Krishnakumar S (2003). Choroidal melanoma in a black patient with oculodermal melanocytosis. Retina 23: 126.

254. Bittencourt FV, Marghoob AA, Kopf AW, Koenig KL, Bart RS (2000). Large congenital melanocytic nevi and the risk for development of malignant melanoma and neurocutaneous melanocytosis. Pediatrics 106: 736-741.
255. Bjarke T, Ternesten-Bratel A, Hedblad M, Rausing A (2003). Carcinoma and eccrine syringofibroadenoma: a report of five cases. J Cutan Pathol 30: 382-392.
256. Black H, Eglick PG, Beerman H (1949). Nevoxanthoendothelioma with ocular involvement. Pediatrics 4: 349-354.
257. Blackburn WR, Cosman B (1966). Histologic basis of keloid and hypertrophic scar differentiation. Clinicopathologic correlation. Arch Pathol 82: 65-71.
258. Blackford S, Roberts DL (1991). Familial multiple blue naevi. Clin Exp Dermatol 16: 308-309.
259. Blei F, Walter J, Orlow SJ, Marchuk DA (1998). Familial segregation of hemangiomas and vascular malformations as an autosomal dominant trait. Arch Dermatol 134: 718-722.
260. Blessing K, al Nafussi A, Gordon PM (1994). The regressing keratoacanthoma. Histopathology 24: 381-384.
261. Blessing K, Evans AT, al Nafussi A (1993). Verrucous naevoid and keratotic malignant melanoma: a clinico-pathological study of 20 cases. Histopathology 23: 453-458.
262. Blessing K, Grant JJ, Sanders DS, Kennedy MM, Husain A, Coburn P (2000). Small cell malignant melanoma: a variant of naevoid melanoma. Clinicopathological features and histological differential diagnosis. J Clin Pathol 53: 591-595.
263. Blessing K, Kernohan NM, Park KG (1991). Subungual malignant melanoma: clinicopathological features of 100 cases. Histopathology 19: 425-429.
264. Blessing K, Mclaren KM, Morris R, Barr BB, Benton EC, Alloub M, Bunney MH, Smith IW, Smart GE, Bird CC (1990). Detection of human papillomavirus in skin and genital lesions of renal allograft recipients by in situ hybridization. Histopathology 16: 181-185.
265. Blessing K, Sanders DS, Grant JJ (1998). Comparison of immunohistochemical staining of the novel antibody melan-A with S100 protein and HMB-45 in malignant melanoma and melanoma variants. Histopathology 32: 139-146.
266. Blicker JA, Rootman J, White VA (1992). Cellular blue nevus of the conjunctiva. Ophthalmology 99: 1714-1717.
267. Blickstein I, Feldberg E, Dgani R, Ben Hur H, Czernobilsky B (1991). Dysplastic vulvar nevi. Obstet Gynecol 78: 968-970.
268. Bluestone JA, Khattri R, Sciammas R, Sperling AI (1995). TCR gamma delta cells: a specialized T-cell subset in the immune system. Annu Rev Cell Dev Biol 11: 307-353.
269. Bocking A, Chatelain R, Salterberg A, Hagedorn M, Gross G (1989). Bowenoid papulosis. Classification as a low-grade in situ carcinoma of the epidermis on the basis of histomorphologic and DNA ploidy studies. Anal Quant Cytol Histol 11: 419-425.
269A. Boddie AW, Jr., Smith JL, Jr., McBride CM (1978). Malignant melanoma in children and young adults: effect of diagnostic criteria on staging and end results. South Med J 71: 1074-1078.
270. Bodemer C, Fraitag S, Amoric JC, Benaceur S, Brunelle F, De Prost Y (1997). [Spindle-cell hemangioendothelioma with monomelic and multifocal form in a child]. Ann Dermatol Venereol 124: 857-860.
271. Boer A, Wolter M, Kaufman R (2003). Pseudomelanoma following laser treatment or laser-treated melanoma. JDDG 1: 47-50.
272. Bogdan I, Burg G, Boni R (2001). Spitz nevi display allelic deletions. Arch Dermatol 137: 1417-1420.
273. Boggs DR, Sofferman SA, Wintrobe MM, Cartwright GE (1966). Factors influencing the duration of survival of patients with chronic lymphocytic leukemia. Am J Med 40: 243-254.
274. Bogner PN, Fullen DR, Lowe L, Paulino A, Biermann JS, Sondak VK, Su LD (2003). Lymphatic mapping and sentinel lymph node biopsy in the detection of early metastasis from sweat gland carcinoma. Cancer 97: 2285-2289.
275. Bogomolski-Yahalom V, Lossos IS, Okun E, Sherman Y, Lossos A, Polliack A (1998). Intravascular lymphomatosis—an indolent or aggressive entity? Leuk Lymphoma 29: 585-593.
276. Boi S, Barbareschi M, Vigl E, Cristofolini M (1991). Malignant blue nevus. Report of four new cases and review of the literature. Histol Histopathol 6: 427-434.
277. Bolognia JL (1992). Reticulated black solar lentigo ('ink spot' lentigo). Arch Dermatol 128: 934-940.
278. Bolognia JL, Glusac EJ (1998). Hypopigmented common blue nevi. Arch Dermatol 134: 754-756.
279. Bonetti F, Knowles DM, Chilosi M, Pisa R, Fiaccavento S, Rizzuto N, Zamboni G, Menestrina F, Fiore-Donati L (1985). A distinctive cutaneous malignant neoplasm expressing the Langerhans cell phenotype. Synchronous occurrence with B-chronic lymphocytic leukemia. Cancer 55: 2417-2425.
280. Boni R, Panizzon R, Huch Boni RA, Steinert H, Dummer R (1996). Malignant blue naevus with distant subcutaneous metastasis. Clin Exp Dermatol 21: 427-430.
281. Boni R, Xin H, Hohl D, Panizzon R, Burg G (2001). Syringocystadenoma papilliferum: a study of potential tumor suppressor genes. Am J Dermatopathol 23: 87-89.
282. Bono A, Bartoli C, Baldi M, Moglia D, Tomatis S, Tragni G, Cascinelli N, Santinami M (2004). Micro-melanoma detection. A clinical study on 22 cases of melanoma with a diameter equal to or less than 3 mm. Tumori 90: 128-131.
283. Bontius J (1642). De medicina Indorum libri IV.
284. Bootsma D, Kraemer KH, Cleaver JE, Hoeijmakers JHJ (2002). Nucleotide excision repair syndromes: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystophy. In: The Genetic Basis of Human Cancer, Vogelstein B, Kinzler KW, eds., 2nd ed. McGraw Hill: New York , pp. 211-237.
285. Borel DM (1973). Cutaneous basosquamous carcinoma. Review of the literature and report of 35 cases. Arch Pathol 95: 293-297.
286. Borg A, Sandberg T, Nilsson K, Johannsson O, Klinker M, Masback A, Westerdahl J, Olsson H, Ingvar C (2000). High frequency of multiple melanomas and breast and pancreas carcinomas in CDKN2A mutation-positive melanoma families. J Natl Cancer Inst 92: 1260-1266.
287. Bortolani A, Barisoni D, Scomazzoni G (1994). Benign "metastatic" cellular blue nevus. Ann Plast Surg 33: 426-431.
288. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV (2002). The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 55: 244-265.
289. Botet MV, Caro FR, Sanchez JL (1981). Congenital acral melanocytic nevi clinically stimulating acral lentiginous melanoma. J Am Acad Dermatol 5: 406-410.
290. Boulland ML, Wechsler J, Bagot M, Pulford K, Kanavaros P, Gaulard P (2000). Primary CD30-positive cutaneous T-cell lymphomas and lymphomatoid papulosis frequently express cytotoxic proteins. Histopathology 36: 136-144.
291. Box NF, Duffy DL, Chen W, Stark M, Martin NG, Sturm RA, Hayward NK (2001). MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. Am J Hum Genet 69: 765-773.
292. Boyd AS, Rapini RP (1994). Acral melanocytic neoplasms: a histologic analysis of 158 lesions. J Am Acad Dermatol 31: 740-745.
293. Boyd AS, Shyr Y, King LEJr (2002). Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. J Am Acad Dermatol 46: 706-709.
294. Boyd AS, Stasko T, Cameron GS, Russell M, King LEJr (2001). Histologic features of actinic keratoses in solid organ transplant recipients and healthy controls. J Am Acad Dermatol 45: 217-221.
295. Boye E, Yu Y, Paranya G, Mulliken JB, Olsen BR, Bischoff J (2001). Clonality and altered behavior of endothelial cells from hemangiomas. J Clin Invest 107: 745-752.
296. Bozdogan O, Erkek E, Atasoy P, Kocak M, Birol A, Caydere M (2002). Bcl-2-related proteins, alpha-smooth muscle actin and amyloid deposits in aggressive and non-aggressive basal cell carcinomas. Acta Derm Venereol 82: 423-427.
297. Braga D, Manganoni AM, Boccaletti V, Pancera C, Marocolo D, Facchetti F, De Panfilis G (1996). Specific skin infiltration as first sign of chronic myelomonocytic leukemia with an unusual phenotype. J Am Acad Dermatol 35: 804-807.
298. Bragado R, Bello E, Requena L, Renedo G, Texeiro E, Alvarez MV, Castilla MA, Caramelo C (1999). Increased expression of vascular endothelial growth factor in pyogenic granulomas. Acta Derm Venereol 79: 422-425.
299. Braier J, Chantada G, Rosso D, Bernaldez P, Amaral D, Latella A, Balancini B, Masautis A, Goldberg J (1999). Langerhans cell histiocytosis: retrospective evaluation of 123 patients at a single institution. Pediatr Hematol Oncol 16: 377-385.
300. Brand D, Ackerman AB (2000). Squamous cell carcinoma, not basal cell carcinoma, is the most common cancer in humans. J Am Acad Dermatol 42: 523-526.
301. Braun-Falco M, Hein R, Ring J (2001). [Cylindrospiradenomas in Brooke-Spiegler syndrome]. Hautarzt 52: 1021-1025.
302. Braun-Falco O, Marghescu S, Wolff HH (1973). [Pagetoide reticulosis—Woringer-Kolopp's disease]. Hautarzt 24: 11-21.
303. Braverman IM, Ken-Yen A (1983). Ultrastructure and three-dimensional reconstruction of several macular and papular telangiectases. J Invest Dermatol 81: 489-497.
304. Brazzelli V, Baldini F, Vassallo C, Borghini F, Chiesa MG, Rosso R, Borroni G (1999). Reactive angioendotheliomatosis in an infant. Am J Dermatopathol 21: 42-45.
305. Breier F, Clabian M, Pokieser W, Feldmann R, Pelzl M, Kosak D, Volc-Platzer B, Kolbabek H, Gschnait F (2000). Primary mucinous carcinoma of the scalp. Dermatology 200: 250-253.
306. Brenan J, Kossard S, Krivanek J (1985). Halo eczema around melanocytic nevi. Int J Dermatol 24: 226-229.
307. Brenn T, Calonje E, Granter SR, Leonard N, Grayson W, Fletcher CD, McKee PH (2002). Cutaneous rosai-dorfman disease is a distinct clinical entity. Am J Dermatopathol 24: 385-391.
308. Breuninger H, Kohler C, Drepper H, Bastian B, Brocker EB, Gohl J, Groth W, Hermanek P, Hohenberger W, Lippold A, Kolmel K, Landthaler M, Peters A, Tilgen W (1994). [Is acrolentiginous melanoma (ALM) more malignant than superficially spreading melanoma (SSM) at a high-risk site? A matched-pair comparison between 113 ALM and SSM within the scope of a multicenter study]. Hautarzt 45: 529-531.
309. Briollais L, Chompret A, Guilloud-Bataille M, Bressac de Paillerets B, Avril MF, Demenais F (2000). Patterns of familial aggregation of three melanoma risk factors: great number of naevi, light phototype and high degree of sun exposure. Int J Epidemiol 29: 408-415.
310. Brochez L, Myny K, Bleyen L, De Backer G, Naeyaert JM (1999). The melanoma burden in Belgium; premature morbidity and mortality make melanoma a considerable health problem. Melanoma Res 9: 614-618.
311. Brocq L (1897). Les érythrodermies pityriasiques en plaques disséminées.
312. Brocq L (1902). Les Parapsoriasis. Ann Dermatol Syphilol 3: 433-468.
313. Brody JP, Allen S, Schulman P, Sun T, Chan WC, Friedman HD, Teichberg S, Koduru P, Cone RW, Loughran TPJr (1995). Acute agranular CD4-positive natural killer cell leukemia. Comprehensive clinicopathologic studies including virologic and in vitro culture with inducing agents. Cancer 75: 2474-2483.
314. Broekaert D, Leigh IM, Lane EB, Van Muijen GN, Ramaekers FC, De Bersaques J, Coucke P (1993). An immunohistochemical and histochemical study of cytokeratin, involucrin and transglutaminase in seborrhoeic keratosis. Arch Dermatol Res 285: 482-490.
315. Broughton BC, Berneburg M, Fawcett H, Taylor EM, Arlett CF, Nardo T, Stefanini M, Menefee E, Price VH, Queille S, Sarasin A, Bohnert E, Krutmann J, Davidson R, Kraemer KH, Lehmann AR (2001). Two individuals with features of both xeroderma pigmentosum and trichothiodystrophy highlight the complexity of the clinical outcomes of mutations in the XPD gene. Hum Mol Genet 10: 2539-2547.
316. Broughton BC, Cordonnier A, Kleijer WJ, Jaspers NG, Fawcett H, Raams A, Garritsen VH, Stary A, Avril MF, Boudsocq F, Masutani C, Hanaoka F, Fuchs RP, Sarasin A, Lehmann AR (2002). Molecular analysis of mutations in DNA polymerase eta in xeroderma pigmentosum-variant patients. Proc Natl Acad Sci U S A 99: 815-820.
317. Brown CI, Perry AE (2000). Incidence of perineural invasion in histologically aggressive types of basal cell carcinoma. Am J Dermatopathol 22: 123-125.
318. Brownstein MH (1980). Trichilemmoma. Benign follicular tumor or viral wart? Am J Dermatopathol 2: 229-231.
319. Brownstein MH (1985). The benign acanthomas. J Cutan Pathol 12: 172-188.
320. Brownstein MH (1988). Acantholytic

acanthoma. J Am Acad Dermatol 19: 783-786.
321. Brownstein MH, Arluk DJ (1981). Proliferating trichilemmal cyst: a simulant of squamous cell carcinoma. Cancer 48: 1207-1214.
322. Brownstein MH, Mehregan AH, Bikowski JB, Lupulescu A, Patterson JC (1979). The dermatopathology of Cowden's syndrome. Br J Dermatol 100: 667-673.
323. Brownstein MH, Shapiro L (1973). Trichilemmoma. Analysis of 40 new cases. Arch Dermatol 107: 866-869.
324. Brownstein MH, Wanger N, Helwig EB (1971). Accessory tragi. Arch Dermatol 104: 625-631.
325. Brownstein MH, Wolf M, Bikowski JB (1978). Cowden's disease: a cutaneous marker of breast cancer. Cancer 41: 2393-2398.
326. Buccheri V, Mihaljevic B, Matutes E, Dyer MJ, Mason DY, Catovsky D (1993). mb-1: a new marker for B-lineage lymphoblastic leukemia. Blood 82: 853-857.
327. Buchner A, Hansen LS (1987). Pigmented nevi of the oral mucosa: a clinicopathologic study of 36 new cases and review of 155 cases from the literature. Part I: A clinicopathologic study of 36 new cases. Oral Surg Oral Med Oral Pathol 63: 566-572.
328. Buchner A, Hansen LS (1987). Pigmented nevi of the oral mucosa: a clinicopathologic study of 36 new cases and review of 155 cases from the literature. Part II: Analysis of 191 cases. Oral Surg Oral Med Oral Pathol 63: 676-682.
329. Buechner SA, Li CY, Su WP (1985). Leukemia cutis. A histopathologic study of 42 cases. Am J Dermatopathol 7: 109-119.
330. Buettner PG, Raasch BA (1998). Incidence rates of skin cancer in Townsville, Australia. Int J Cancer 78: 587-593.
331. Bulliard JL (2000). Site-specific risk of cutaneous malignant melanoma and pattern of sun exposure in New Zealand. Int J Cancer 85: 627-632.
332. Bulliard JL, Cox B (2000). Cutaneous malignant melanoma in New Zealand: trends by anatomical site, 1969-1993. Int J Epidemiol 29: 416-423.
333. Bunn PA, Jr., Lamberg SI (1979). Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas. Cancer Treat Rep 63: 725-728.
334. Bunn PAJr, Lamberg SI (1979). Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas. Cancer Treat Rep 63: 725-728.
335. Bunton TE, Wolfe MJ (1996). N-methyl-N'-nitro-N-nitrosoguanidine-induced neoplasms in medaka (Oryzias latipes). Toxicol Pathol 24: 323-330.
336. Burg G (1977). Pagetoid reticulosis-a cutaneous T-cell lymphoma. J Invest Dermatol 68: 249.
336A. Burg G, Kempf W, Cozzio A, Feit J, Willemze R, Jaffe E, Dummer R, Cerroni L, Berti E, Swerdlow S, Ralfkiaer E, Chimenti S, Diaz-Perez JL,. Duncan LM, Grange F, Harris NL, Kerl H, Kazakov DV, Kurrer M, Knobler R, Meijer CJLM, Pimpinelli N, Russel Jones R, Sander C, Santucci M, Sterry W, Wechsler J, Whittaker S (2005) WHO/EORTC Classification of Cutaneous Lymphomas 2005. Histological and Molecular Aspects. J Cutan Pathol 32 (in press)
337. Burg G, Braun-Falco M (1983). Cutaneous Lymphomas, Pseudolymphomas and Related Disorders. Springer Verlag: Berlin.
338. Burg G, Dummer R, Wilhelm M, Nestle F, Ott MM, Feller A, Hefner H, Lanz U, Schwinn A, Wiede J (1991). A subcutaneous delta-positive T-cell lymphoma that produces interferon gamma. N Engl J Med 325: 1078-1081.
339. Burg G, Kaudewitz P, Klepzig K, Przybilla B, Braun-Falco O (1985). Cutaneous B-cell lymphoma. Dermatol Clin 3: 689-704.
340. Burg G, Kempf W (2005). Cutaneous Lymphomas (Basic and Clinical Dermatology). Marcel Dekker: New York.
341. Burg G, Kempf W, Kazakov DV, Dummer R, Frosch PJ, Lange-Ionescu S, Nishikawa T, Kadin ME (2003). Pyogenic lymphoma of the skin: a peculiar variant of primary cutaneous neutrophil-rich CD30+ anaplastic large-cell lymphoma. Clinicopathological study of four cases and review of the literature. Br J Dermatol 148: 580-586.
342. Burg G, Schmid MH, Kung E, Dommann S, Dummer R (1994). Semimalignant ("pseudolymphomatous") cutaneous B-cell lymphomas. Dermatol Clin 12: 399-407.
343. Burg G, Schmockel C (1992). Syringolymphoid hyperplasia with alopecia—a syringotropic cutaneous T-cell lymphoma? Dermatology 184: 306-307.
344. Burg G, Sterry W (1987). EORTC/BMFI Cutaneous Lymphoma Project Group. Recommendations for staging and therapy of cutaneous lymphomas.
345. Burg G, Wursch T, Fah J, Elsner P (1994). Eruptive hamartomatous clear-cell acanthomas. Dermatology 189: 437-439.
346. Burgdorf WH, Mukai K, Rosai J (1981). Immunohistochemical identification of factor VIII-related antigen in endothelial cells of cutaneous lesions of alleged vascular nature. Am J Clin Pathol 75: 167-171.
347. Burgdorf WH, Pitha J, Fahmy A (1986). Muir-Torre syndrome. Histologic spectrum of sebaceous proliferations. Am J Dermatopathol 8: 202-208.
348. Burkhardt A (1986). [Verrucous carcinoma and carcinoma cuniculatum—forms of squamous cell carcinoma?]. Hautarzt 37: 373-383.
349. Burkitt DP (1970). General features and facial tumours. In: Burkitt's Lymphoma, Burkitt DP, ed., Livingstone: Edinburgh , pp. 6-15.
350. Burnet NG, Jefferies SJ, Benson RJ, Hunt DP, Treasure FP (2005). Years of life lost (YLL) from cancer is an important measure of population burden—and should be considered when allocating research funds. Br J Cancer 92: 241-245.
351. Burtner DD, Goodman M (1977). Traumatic neuroma of the nose. Arch Otolaryngol 103: 108-109.
352. Burton JL, Holden CA (1998). Eczema, lichenification and prurigo. In: Textbook of Dermatology, Champion RH, Burton RT, Burns DA, Breathnach SM, eds., 6th ed. Blackwell Science: Malden, Massachusetts , p. 665.
353. Burton RC, Armstrong BK (1994). Recent incidence trends imply a non-metastasizing form of invasive melanoma. Melanoma Res 4: 107-113.
354. Busam KJ (1999). Metastatic melanoma to the skin simulating blue nevus. Am J Surg Pathol 23: 276-282.
355. Busam KJ, Barnhill RL (1995). Pagetoid Spitz nevus. Intraepidermal Spitz tumor with prominent pagetoid spread. Am J Surg Pathol 19: 1061-1067.
356. Busam KJ, Iversen K, Coplan KC, Jungbluth AA (2001). Analysis of microphthalmia transcription factor expression in normal tissues and tumors, and comparison of its expression with S-100 protein, gp100, and tyrosinase in desmoplastic malignant melanoma. Am J Surg Pathol 25: 197-204.
357. Busam KJ, Mentzel T, Colpaert C, Barnhill RL, Fletcher CD (1998). Atypical or worrisome features in cellular neurothekeoma: a study of 10 cases. Am J Surg Pathol 22: 1067-1072.
358. Busam KJ, Woodruff JM, Erlandson RA, Brady MS (2000). Large plaque-type blue nevus with subcutaneous cellular nodules. Am J Surg Pathol 24: 92-99.
358A. Busam KJ, Mujumdar U, Hummer AJ, Nobrega J, Hawkins WG, Coit DG, Brady MS (2004). Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. Am J Surg Pathol 28: 1518-1525.
358B. Busam KJ, Zhao H, Coit DG, Kucukgol D, Jungbluth AA, Nobrega J, Viale A (2005). Distinction of desmoplastic melanoma from non-desmoplastic melanoma by gene expression profiling. J Invest Dermatol 124: 412-418.
359. Buschke A, Löwenstein L (1925). Über carcinomähnliche Condylomata acuminata des Penis. Klin Wochenschr 4: 1726-1728.
360. Butler DF, Ranatunge BD, Rapini RP (2001). Urticating Hashimoto-Pritzker Langerhans cell histiocytosis. Pediatr Dermatol 18: 41-44.
361. Buttner C, Henz BM, Welker P, Sepp NT, Grabbe J (1998). Identification of activating c-kit mutations in adult-, but not in childhood-onset indolent mastocytosis: a possible explanation for divergent clinical behavior. J Invest Dermatol 111: 1227-1231.
362. Caglar H, Tamer S, Hreshchyshyn MM (1982). Vulvar intraepithelial neoplasia. Obstet Gynecol 60: 346-349.
363. Calduch L, Ortega C, Navarro V, Martinez E, Molina I, Jorda E (2000). Verrucous hemangioma: report of two cases and review of the literature. Pediatr Dermatol 17: 213-217.
364. Calista D, Schianchi S, Landi C (1998). Malignant blue nevus of the scalp. Int J Dermatol 37: 126-127.
365. Calonje E (2000). Is cutaneous benign fibrous histiocytoma (dermatofibroma) a reactive inflammatory process or a neoplasm? Histopathology 37: 278-280.
366. Calonje E, Fletcher CD (1991). Sinusoidal hemangioma. A distinctive benign vascular neoplasm within the group of cavernous hemangiomas. Am J Surg Pathol 15: 1130-1135.
367. Calonje E, Fletcher CD (1995). Aneurysmal benign fibrous histiocytoma: clinicopathological analysis of 40 cases of a tumour frequently misdiagnosed as a vascular neoplasm. Histopathology 26: 323-331.
368. Calonje E, Fletcher CD (1996). Myoid differentiation in dermatofibrosarcoma protuberans and its fibrosarcomatous variant: clinicopathologic analysis of 5 cases. J Cutan Pathol 23: 30-36.
369. Calonje E, Fletcher CDM (1994). Cutaneous fibrohistiocytic tumors: an update. Adv Anat Pathol 1: 2-15.
370. Calonje E, Mentzel T, Fletcher CD (1994). Cellular benign fibrous histiocytoma. Clinicopathologic analysis of 74 cases of a distinctive variant of cutaneous fibrous histiocytoma with frequent recurrence. Am J Surg Pathol 18: 668-676.
371. Calonje E, Wilson-Jones E, Smith NP, Fletcher CD (1992). Cellular 'neurothekeoma': an epithelioid variant of pilar leiomyoma? Morphological and immunohistochemical analysis of a series. Histopathology 20: 397-404.
372. Calzavara Pinton P, Carlino A, Manganoni AM, Donzelli C, Facchetti F (1990). [Epidermal nevus syndrome with multiple vascular hamartomas and malformations]. G Ital Dermatol Venereol 125: 251-254.
373. Camacho FM, Burg G, Moreno JC, Campora RG, Villar JL (1997). Granulomatous slack skin in childhood. Pediatr Dermatol 14: 204-208.
374. Camp RDR (1998). Psoriasis: Psoralen photochemotherapy. In: Textbook of Dermatology, Champion RH, Burton JL, Burns DA, Breathnach SM, eds., 6th ed. Blackwell Science Ltd.: Oxford , pp. 1616-1622.
375. Campbell C, Quinn AG, Ro YS, Angus B, Rees JL (1993). p53 mutations are common and early events that precede tumor invasion in squamous cell neoplasia of the skin. J Invest Dermatol 100: 746-748.
376. Campo E, Raffeld M, Jaffe ES (1999). Mantle-cell lymphoma. Semin Hematol 36: 115-127.
377. Caporaso N, Greene MH, Tsai S, Pickle LW, Mulvihill JJ (1987). Cytogenetics in hereditary malignant melanoma and dysplastic nevus syndrome: is dysplastic nevus syndrome a chromosome instability disorder? Cancer Genet Cytogenet 24: 299-314.
378. Caputo R (1998). Juvenile Xanthogranuloma. In: Text Atlas of Histiocytic Syndromes. A Dermatological Perspective., Text Atlas of Histiocytic Syndromes. A Dermatological Perspective., Martin Dunitz.: London , pp. 39-58.
379. Caputo R, Alessi E, Berti E (1981). Collagen phagocytosis in multicentric reticulohistiocytosis. J Invest Dermatol 76: 342-346.
380. Caputo R, Crosti C, Cainelli T (1977). A unique cytoplasmic structure in papular histiocytoma. J Invest Dermatol 68: 98-104.
381. Caputo R, Ermacora E, Gelmetti C (1988). Diffuse cutaneous reticulohistiocytosis in a child with tuberous sclerosis. Arch Dermatol 124: 567-570.
382. Caputo R, Grimalt R (1992). Solitary reticulohistiocytosis (reticulohistiocytoma) of the skin in children: report of two cases. Arch Dermatol 128: 698-699.
383. Caputo R, Grimalt R, Gelmetti C, Cottoni F (1993). Unusual aspects of juvenile xanthogranuloma. J Am Acad Dermatol 29: 868-870.
384. Carapeto FJ, Armijo M (1978). [Acral arteriovenous tumor]. Ann Dermatol Venereol 105: 977-979.
385. Carapeto FJ, Garcia-Perez A, Winkelmann RK (1977). Acral arteriovenous tumor. Acta Derm Venereol 57: 155-158.
386. Carless MA, Lea RA, Curran JE, Appleyard B, Gaffney P, Green A, Griffiths LR (2002). The GSTM1 null genotype confers an increased risk for solar keratosis development in an Australian Caucasian population. J Invest Dermatol 119: 1373-1378.
387. Carli P, de Giorgi V, Salvini C, Mannone F, Chiarugi A (2002). The gold standard for photographing pigmented skin lesions for diagnostic purposes: contact versus distant imaging. Skin Res Technol 8: 255-259.
388. Carlson JA, Ackerman AB, Fletcher

CD, Zelger B (2001). A cutaneous spindle-cell lesion. Am J Dermatopathol 23: 62-66.
389. Carlson JA, Daulat S, Goodheart HP (1999). Targetoid hemosiderotic hemangioma- a dynamic vascular tumor: report of 3 cases with episodic and cyclic changes and comparison with solitary angiokeratomas. J Am Acad Dermatol 41: 215-224.
390. Carlson JA, Mihm MC (1997). Vulvar nevi, lichen sclerosus et atrophicus, and vitiligo. Arch Dermatol 133: 1314-1316.
391. Carlson JA, Mu XC, Slominski A, Weismann K, Crowson AN, Malfetano J, Prieto VG, Mihm MCJr (2002). Melanocytic proliferations associated with lichen sclerosus. Arch Dermatol 138: 77-87.
392. Carlson JA, Slominski A, Linette GP, Mihm MCJr, Ross JS (2003). Biomarkers in melanoma: staging, prognosis and detection of early metastases. Expert Rev Mol Diagn 3: 303-330.
393. Carlson KC, Gibson LE (1991). Cutaneous signs of lymphomatoid granulomatosis. Arch Dermatol 127: 1693-1698.
394. Carney JA (1990). Psammomatous melanotic schwannoma. A distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing syndrome. Am J Surg Pathol 14: 206-222.
395. Carney JA (1995). The search for Harvey Cushing's patient, Minnie G., and the cause of her hypercortisolism. Am J Surg Pathol 19: 100-108.
396. Carney JA, Ferreiro JA (1996). The epithelioid blue nevus. A multicentric familial tumor with important associations, including cardiac myxoma and psammomatous melanotic schwannoma. Am J Surg Pathol 20: 259-272.
397. Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VL (1985). The complex of myxomas, spotty pigmentation, and endocrine overactivity. Medicine (Baltimore) 64: 270-283.
398. Carney JA, Headington JT, Su WP (1986). Cutaneous myxomas. A major component of the complex of myxomas, spotty pigmentation, and endocrine overactivity. Arch Dermatol 122: 790-798.
399. Carney JA, Stratakis CA (1998). Epithelioid blue nevus and psammomatous melanotic schwannoma: the unusual pigmented skin tumors of the Carney complex. Semin Diagn Pathol 15: 216-224.
400. Carney JA, Toorkey BC (1991). Myxoid fibroadenoma and allied conditions (myxomatosis) of the breast. A heritable disorder with special associations including cardiac and cutaneous myxomas. Am J Surg Pathol 15: 713-721.
401. Caro WA, Helwig HB (1969). Cutaneous lymphoid hyperplasia. Cancer 24: 487-502.
402. Carr S, See J, Wilkinson B, Kossard S (1997). Hypopigmented common blue nevus. J Cutan Pathol 24: 494-498.
403. Carrasco L, Izquierdo MJ, Farina MC, Martin L, Moreno C, Requena L (2000). Strawberry glans penis: a rare manifestation of angiokeratomas involving the glans penis. Br J Dermatol 142: 1256-1257.
404. Carson HJ, Gattuso P, Raslan WF, Reddy V (1995). Mucinous carcinoma of the eyelid. An immunohistochemical study. Am J Dermatopathol 17: 494-498.
405. Carson KF, Wen DR, Li PX, Lana AM, Bailly C, Morton DL, Cochran AJ (1996). Nodal nevi and cutaneous melanomas. Am J Surg Pathol 20: 834-840.
406. Carter DK, Batts KP, de Groen PC, Kurtin PJ (1996). Angiotropic large cell lymphoma (intravascular lymphomatosis) occurring after follicular small cleaved cell lymphoma. Mayo Clin Proc 71: 869-873.
407. Casas JG, Woscoff A (1980). Giant pilar tumor of the scalp. Arch Dermatol 116: 1395.
408. Casey M, Vaughan CJ, He J, Hatcher CJ, Winter JM, Weremowicz S, Montgomery K, Kucherlapati R, Morton CC, Basson CT (2000). Mutations in the protein kinase A R1alpha regulatory subunit cause familial cardiac myxomas and Carney complex. J Clin Invest 106: R31-R38.
409. Cassileth BR, Temoshok L, Frederick BE, Walsh WP, Hurwitz S, Guerry D, Clark WHJr, DiClemente RJ, Sweet DM, Blois MS, Sagebiel RW (1988). Patient and physician delay in melanoma diagnosis. J Am Acad Dermatol 18: 591-598.
410. Castilla EA, Bergfeld WF, Ormsby A (2002). Trichilemmoma and syringocystadenoma papilliferum arising in naevus sebaceous. Pathology 34: 196-197.
411. Castilla EE, da Graca Dutra M, Orioli-Parreiras IM (1981). Epidemiology of congenital pigmented naevi: II. Risk factors. Br J Dermatol 104: 421-427.
412. Catteau B, Enjolras O, Delaporte E, Friedel J, Breviere G, Wassef M, Lecomte-Houcke M, Piette F, Bergoend H (1998). [Sclerosing tufted angioma. Apropos of 4 cases involving lower limbs]. Ann Dermatol Venereol 125: 682-687.
413. Catterall MD (1980). Multicentric reticulohistiocytosis: a review of eight cases. Clin Exp Dermatol 5: 267-279.
414. Cavalieri R, Macchini V, Mostaccioli S, Sonego G, Ferranti G, Corona R, Fucci M, Marzolini F, Rosmini F, Pasquini P (1993). Time trends in features of cutaneous melanoma at diagnosis: central-south Italy, 1962-1991. Ann Ist Super Sanita 29: 469-472.
415. Cavalli F (1998). Rare syndromes in Hodgkin's disease. Ann Oncol 9 Suppl 5: S109-S113.
416. Caylor HD (1925). Epitheliomas in sebaceous cysts. Ann Surg 82: 164-176.
Ceballos PI, Penneys NS, Acosta R (1990).
417. Aggressive digital papillary adenocarcinoma. J Am Acad Dermatol 23: 331-334.
417A. Ceballos PI, Ruiz-Maldonado R, Mihm MCJr (1995). Melanoma in children. N Engl J Med 332: 656-662.
418. Cecchi A, Giomi A, Rapicano V, Apicella P (2000). Cellular neurothekeoma on the left auricle. J Eur Acad Dermatol Venereol 14: 314-315.
419. Cecchi R, Bartoli L, Brunetti L, Pavesi M, Giomi A (1995). Lymphangioma circumscriptum of the vulva of late onset. Acta Derm Venereol 75: 79-80.
420. Celebi JT, Tsou HC, Chen FF, Zhang H, Ping XL, Lebwohl MG, Kezis J, Peacocke M (1999). Phenotypic findings of Cowden syndrome and Bannayan-Zonana syndrome in a family associated with a single germline mutation in PTEN. J Med Genet 36: 360-364.
421. Centeno JA, Mullick FG, Martinez L, Page NP, Gibb H, Longfellow D, Thompson C, Ladich ER (2002). Pathology related to chronic arsenic exposure. Environ Health Perspect 110 Suppl 5: 883-886.
422. Cerez-Pham H, Bertrand G, Tigori J, Simard C (1984). [Association of a malignant vaginal melanoma with vaginal melanosis and a blue nevus of the cervix. Apropos of a case]. Arch Anat Cytol Pathol 32: 48-51.
423. Cerio R, Oliver GF, Jones EW, Winkelmann RK (1990). The heterogeneity of Jessner's lymphocytic infiltration of the skin. Immunohistochemical studies suggesting one form of perivascular lymphocytoma. J Am Acad Dermatol 23: 63-67.
424. Cerio R, Spaull J, Oliver GF, Jones WE (1990). A study of factor XIIIa and MAC 387 immunolabeling in normal and pathological skin. Am J Dermatopathol 12: 221-233.
425. Cerroni L, Arzberger E, Putz B, Hofler G, Metze D, Sander CA, Rose C, Wolf P, Rutten A, McNiff JM, Kerl H (2000). Primary cutaneous follicle center cell lymphoma with follicular growth pattern. Blood 95: 3922-3928.
426. Cerroni L, Beham-Schmid C, Kerl H (1995). Cutaneous Hodgkin's disease: an immunohistochemical analysis. J Cutan Pathol 22: 229-235.
427. Cerroni L, Hofler G, Back B, Wolf P, Maier G, Kerl H (2002). Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia (B-CLL) at sites typical for Borrelia burgdorferi infection. J Cutan Pathol 29: 142-147.
428. Cerroni L, Kerl H (1999). Diagnostic immunohistology: cutaneous lymphomas and pseudolymphomas. Semin Cutan Med Surg 18: 64-70.
429. Cerroni L, Kerl H (2001). Primary cutaneous follicle center cell lymphoma. Leuk Lymphoma 42: 891-900.
430. Cerroni L, Volkenandt M, Rieger E, Soyer HP, Kerl H (1994). bcl-2 protein expression and correlation with the interchromosomal 14;18 translocation in cutaneous lymphomas and pseudolymphomas. J Invest Dermatol 102: 231-235.
431. Cerroni L, Zenahlik P, Hofler G, Kaddu S, Smolle J, Kerl H (1996). Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. Am J Surg Pathol 20: 1000-1010.
432. Cerroni L, Zenahlik P, Kerl H (1995). Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia arising at the site of herpes zoster and herpes simplex scars. Cancer 76: 26-31.
433. Cerroni L, Zochling N, Putz B, Kerl H (1997). Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. J Cutan Pathol 24: 457-461.
434. Cesarman E, Knowles DM (1997). Kaposi's sarcoma-associated herpesvirus: a lymphotropic human herpesvirus associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. Semin Diagn Pathol 14: 54-66.
435. Ceyhan M, Erdem G, Kotiloglu E, Kale G, Talim B, Kanra G, Basaran I (1997). Pyogenic granuloma with multiple dissemination in a burn lesion. Pediatr Dermatol 14: 213-215.
436. Chamberlain AJ, Fritschi L, Kelly JW (2003). Nodular melanoma: patients' perceptions of presenting features and implications for earlier detection. J Am Acad Dermatol 48: 694-701.
437. Chamberlain RS, Huber K, White JC, Travaglino-Parda R (1999). Apocrine gland carcinoma of the axilla: review of the literature and recommendations for treatment. Am J Clin Oncol 22: 131-135.
438. Chan EF, Gat U, McNiff JM, Fuchs E (1999). A common human skin tumour is caused by activating mutations in beta-catenin. Nat Genet 21: 410-413.
439. Chan GS, Choy C, NG WK, Chan KW (1999). Desmoplastic malignant melanoma on the buttock of an 18-year-old girl: differentiation from desmoplastic nevus. Am J Dermatopathol 21: 170-173.
440. Chan JK, Fletcher CD, Hicklin GA, Rosai J (1990). Glomeruloid hemangioma. A distinctive cutaneous lesion of multicentric Castleman's disease associated with POEMS syndrome. Am J Surg Pathol 14: 1036-1046.
441. Chan JK, Hui PK, Ng CS, Yuen NW, Kung IT, Gwi E (1989). Epithelioid haemangioma (angiolymphoid hyperplasia with eosinophilia) and Kimura's disease in Chinese. Histopathology 15: 557-574.
442. Chan JK, Lewin KJ, Lombard CM, Teitelbaum S, Dorfman RF (1991). Histopathology of bacillary angiomatosis of lymph node. Am J Surg Pathol 15: 430-437.
443. Chan JK, Sin VC, Wong KF, Ng CS, Tsang WY, Chan CH, Cheung MM, Lau WH (1997). Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 89: 4501-4513.
444. Chan JKC, Tsang WYW, Calonje E, Fletcher CDM (1995). Verrucous hemangioma. A distinct but neglected variant of cutaneous hemangioma. Int J Surg Pathol 2: 171-176.
445. Chang H, Shih LY, Kuo TT (2003). Primary aleukemic myeloid leukemia cutis treated successfully with combination chemotherapy: report of a case and review of the literature. Ann Hematol 82: 435-439.
446. Chang SE, Ahn SJ, Choi JH, Sung KJ, Moon KC, Koh JK (1999). Primary adenoid cystic carcinoma of skin with lung metastasis. J Am Acad Dermatol 40: 640-642.
447. Chang SE, Kim KJ, Kim ES, Choi JH, Sung KJ, Moon KC, Koh JK (2002). Two cases of late onset Ota's naevus. Clin Exp Dermatol 27: 202-204.
448. Chao AN, Shields CL, Krema H, Shields JA (2001). Outcome of patients with periocular sebaceous gland carcinoma with and without conjunctival intraepithelial invasion. Ophthalmology 108: 1877-1883.
449. Chao TK, Chang YL, Sheen TS (2000). Extraskeletal Ewing's sarcoma of the scalp. J Laryngol Otol 114: 73-75.
450. Chaperot L, Bendriss N, Manches O, Gressin R, Maynadie M, Trimoreau F, Orfeuvre H, Corront B, Feuillard J, Sotto JJ, Bensa JC, Briere F, Plumas J, Jacob MC (2001). Identification of a leukemic counterpart of the plasmacytoid dendritic cells. Blood 97: 3210-3217.
451. Chapman MS, Quitadamo MJ, Perry AE (2000). Pigmented squamous cell carcinoma. J Cutan Pathol 27: 93-95.
452. Chatelain R, Bell SA, Konz B, Rocken M (1998). [Granuloma eosinophilicum faciei simulating rhinophyma. Therapeutic long-term outcome after surgical intervention]. Hautarzt 49: 496-498.
452A. Chaudru V, Chompret A, Bressac-de Paillerets B, Spatz A, Avril MF, Demenais F (2004) J Natl Cancer Inst 96: 785-795
453. Chauvin PJ, Wysocki GP, Daley TD, Pringle GA (1992). Palisaded encapsulated neuroma of oral mucosa. Oral Surg Oral Med Oral Pathol 73: 71-74.
454. Chen KR, Tanaka M, Miyakawa S (1998). Granulomatous mycosis fungoides with small intestinal involvement and a fatal outcome. Br J Dermatol 138: 522-525.
455. Chen RL, Lin KS, Chang WH, Hsieh YL, Chen BW, Jaing TH, Yang CP, Hung IJ, Peng CT, Shu SG, Lu MY, Jou ST, Lin KH, Lin DT, Lin MT, Chen JS, Liu HC, Chen SH, Liang DC, Chiou SS, Chang TT, Sheen JM, Hsiao CC, Cheng SN, Lin JC (2003). Childhood Langerhans cell histiocytosis increased during El Nino 1997-98: a report

from the Taiwan Pediatric Oncology Group. Acta Paediatr Taiwan 44: 14-20.
456. Chen S, Palay D, Templeton SF (1998). Familial eccrine syringofibroadenomatosis with associated ophthalmologic abnormalities. J Am Acad Dermatol 39: 356-358.
457. Chen TC, Kuo T, Chan HL (2000). Dermatofibroma is a clonal proliferative disease. J Cutan Pathol 27: 36-39.
458. Chen TM, Purohit SK, Wang AR (2002). Pleomorphic sclerotic fibroma: a case report and literature review. Am J Dermatopathol 24: 54-58.
459. Chen YT, Zheng T, Holford TR, Berwick M, Dubrow R (1994). Malignant melanoma incidence in Connecticut (United States): time trends and age-period-cohort modeling by anatomic site. Cancer Causes Control 5: 341-350.
460. Cheney IW, Neuteboom ST, Vaillancourt MT, Ramachandra M, Bookstein R (1999). Adenovirus-mediated gene transfer of MMAC1/PTEN to glioblastoma cells inhibits S phase entry by the recruitment of p27Kip1 into cyclin E/CDK2 complexes. Cancer Res 59: 2318-2323.
461. Cherpelis BS, Marcusen C, Lang PG (2002). Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg 28: 268-273.
462. Chesser RS, Bertler DE, Fitzpatrick JE, Mellette JR (1992). Primary cutaneous adenoid cystic carcinoma treated with Mohs micrographic surgery toluidine blue technique. J Dermatol Surg Oncol 18: 175-176.
463. Cheuk W, Kwan MY, Suster S, Chan JK (2001). Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. Arch Pathol Lab Med 125: 228-231.
464. Cheung DS, Warman ML, Mulliken JB (1997). Hemangioma in twins. Ann Plast Surg 38: 269-274.
465. Chevrant-Breton J (1977). La reticulo-histiocytose multicentrique: revue de la litterature recente (depuis 1969). Ann Dermatol Venereol 104: 745-753.
466. Chiefari E, Russo D, Giuffrida D, Zampa GA, Meringolo D, Arturi F, Chiodini I, Bianchi D, Attard M, Trischitta V, Bruno R, Giannasio P, Pontecorvi A, Filetti S (1998). Analysis of RET proto-oncogene abnormalities in patients with MEN 2A, MEN 2B, familial or sporadic medullary thyroid carcinoma. J Endocrinol Invest 21: 358-364.
467. Child FJ, Russell-Jones R, Woolford AJ, Calonje E, Photiou A, Orchard G, Whittaker SJ (2001). Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. Br J Dermatol 144: 735-744.
468. Child FJ, Scarisbrick JJ, Calonje E, Orchard G, Russell-Jones R, Whittaker SJ (2002). Inactivation of tumor suppressor genes p15(INK4b) and p16(INK4a) in primary cutaneous B cell lymphoma. J Invest Dermatol 118: 941-948.
469. Chiller K, Passaro D, Scheuller M, Singer M, McCalmont T, Grekin RC (2000). Microcystic adnexal carcinoma: forty-eight cases, their treatment, and their outcome. Arch Dermatol 136: 1355-1359.
470. Chimenti S, Fink-Puches R, Peris K, Pescarmona E, Putz B, Kerl H, Cerroni L (1999). Cutaneous involvement in lymphoblastic lymphoma. J Cutan Pathol 26: 379-385.
471. Cho KH, Kim CW, Lee DY, Sohn SJ, Kim DW, Chung JH (1996). An Epstein-Barr virus-associated lymphoproliferative lesion of the skin presenting as recurrent necrotic papulovesicles of the face. Br J Dermatol 134: 791-796.
472. Cho KJ, Khang SK, Koh JS, Chung JH, Lee SS (2000). Sebaceous carcinoma of the eyelids: frequent expression of c-erbB-2 oncoprotein. J Korean Med Sci 15: 545-550.
473. Choi YS, Park SH, Bang D (1989). Pilar sheath acanthoma—report of a case with review of the literature. Yonsei Med J 30: 392-395.
474. Choonhakarn C, Ackerman AB (2001). Keratoacanthomas: a new classification based on morphologic findings and on anatomic site. Dermatopathology, practical & conceptual 7: 7-16.
475. Chopra A, Maitra B, Korman NJ (1998). Decreased mRNA expression of several basement membrane components in basal cell carcinoma. J Invest Dermatol 110: 52-56.
476. Chorny JA, Barr RJ (2002). S100-positive spindle cells in scars: a diagnostic pitfall in the re-excision of desmoplastic melanoma. Am J Dermatopathol 24: 309-312.
477. Chow CW, Campbell PE, Burry AF (1984). Sweat gland carcinomas in children. Cancer 53: 1222-1227.
478. Chow E, Merchant TE, Pappo A, Jenkins JJ, Shah AB, Kun LE (2000). Cutaneous and subcutaneous Ewing's sarcoma: an indolent disease. Int J Radiat Oncol Biol Phys 46: 433-438.
479. Chow LT, Ma TK, Chow WH (1997). Cellular neurothekeoma of the hypopharynx. Histopathology 30: 192-194.
480. Christensen WN, Friedman KJ, Woodruff JD, Hood AF (1987). Histologic characteristics of vulvar nevocellular nevi. J Cutan Pathol 14: 87-91.
481. Christenson LJ, Stone MS (2001). Trauma-induced simulator of targetoid hemosiderotic hemangioma. Am J Dermatopathol 23: 221-223.
482. Chu P, LeBoit PE (1992). An eruptive vascular proliferation resembling acquired tufted angioma in the recipient of a liver transplant. J Am Acad Dermatol 26: 322-325.
483. Chu P, LeBoit PE (1992). Histologic features of cutaneous sinus histiocytosis (Rosai-Dorfman disease): study of cases both with and without systemic involvement. J Cutan Pathol 19: 201-206.
484. Chuang TY, Reizner GT (1988). Bowen's disease and internal malignancy. A matched case-control study. J Am Acad Dermatol 19: 47-51.
485. Chung CK, Heffernan AH (1971). Clear cell hidradenoma with metastasis. Case report with a review of the literature. Plast Reconstr Surg 48: 177-180.
486. Chung EB, Enzinger FM (1981). Infantile myofibromatosis. Cancer 48: 1807-1818.
487. Chung J, Nam IW, Ahn SK, Lee SH, Kim JG, Sung YO (1994). Rudimentary polydactyly. J Dermatol 21: 54-55.
488. Ciotti P, Struewing JP, Mantelli M, Chompret A, Avril MF, Santi PL, Tucker MA, Bianchi-Scarra G, Bressac de Paillerets B, Goldstein AM (2000). A single genetic origin for the G101W CDKN2A mutation in 20 melanoma-prone families. Am J Hum Genet 67: 311-319.
489. Civatte J, Belaich S, Lauret P (1979). [Tubular apocrine adenoma (4 cases) (author's transl)]. Ann Dermatol Venereol 106: 665-669.
490. Clarijs M, Poot F, Laka A, Pirard C, Bourlond A (2003). Granulomatous slack skin: treatment with extensive surgery and review of the literature. Dermatology 206: 393-397.
491. Clark WH, Jr., Elder DE, Guerry D, Braitman LE, Trock BJ, Schultz D, Synnestvedt M, Halpern AC (1989). Model predicting survival in stage I melanoma based on tumor progression. J Natl Cancer Inst 81: 1893-1904.
492. Clark WHJr (1967). A classification of malignant melanoma in men correlated with histogenesis and biological behavior. In: Advances in Biology of the Skin. The Pigmentary System, Montagna W, Hu F, eds., 1st ed. Pergamon: London , pp. 621-647.
493. Clark WH Jr, Elder DE, Van Horn M (1986). The biologic forms of malignant melanoma. Hum Pathol 17: 443-450.
494. Clark WHJr, From L, Bernardino EA, Mihm MC (1969). The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 29: 705-727.
495. Clark WHJr, Hood AF, Tucker MA, Jampel RM (1998). Atypical melanocytic nevi of the genital type with a discussion of reciprocal parenchymal-stromal interactions in the biology of neoplasia. Hum Pathol 29: S1-24.
496. Clark WHJr, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ (1978). Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome'. Arch Dermatol 114: 732-738.
497. Clarke JT, Knaack J, Crawhall JC, Wolfe LS (1971). Ceramide trihexosidosis (fabry's disease) without skin lesions. N Engl J Med 284: 233-235.
498. Clarke LE, Ioffreda M, Abt AB (2003). Eccrine syringofibroadenoma arising in peristomal skin: a report of two cases. Int J Surg Pathol 11: 61-63.
499. Claudy AL, Garcier F, Kanitakis J (1984). Eccrine porocarcinoma. Ultrastructural and immunological study. J Dermatol 11: 282-286.
500. Cleaver JE, Thompson LH, Richardson AS, States JC (1999). A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. Hum Mutat 14: 9-22.
501. Clemente C, Zurrida S, Bartoli C, Bono A, Collini P, Rilke F (1995). Acral-lentiginous naevus of plantar skin. Histopathology 27: 549-555.
502. Clemente CG, Mihm MC, Jr., Bufalino R, Zurrida S, Collini P, Cascinelli N (1996). Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. Cancer 77: 1303-1310.
503. Clever HW, Sahl WJ (1991). Multiple eccrine hidrocystomas: a nonsurgical treatment. Arch Dermatol 127: 422-424.
504. Cline MS, Cummings OW, Goldman M, Filo RS, Pescovitz MD (1999). Bacillary angiomatosis in a renal transplant recipient. Transplantation 67: 296-298.
505. Cobb MW (1990). Human papillomavirus infection. J Am Acad Dermatol 22: 547-566.
506. Cockerell CJ (2000). Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). J Am Acad Dermatol 42: 11-17.
507. Cockerell CJ, LeBoit PE (1990). Bacillary angiomatosis: a newly characterized, pseudoneoplastic, infectious, cutaneous vascular disorder. J Am Acad Dermatol 22: 501-512.
508. Coffin CM, Dehner LP, Meis-Kindblom JM (1998). Inflammatory myofibroblastic tumor, inflammatory fibrosarcoma, and related lesions: an historical review with differential diagnostic considerations. Semin Diagn Pathol 15: 102-110.
509. Coffin CM, Humphrey PA, Dehner LP (1998). Extrapulmonary inflammatory myofibroblastic tumor: a clinical and pathological survey. Semin Diagn Pathol 15: 85-101.
510. Cohen AD, Cagnano E, Vardy DA (2001). Cherry angiomas associated with exposure to bromides. Dermatology 202: 52-53.
511. Cohen C, Guarner J, DeRose PB (1993). Mammary Paget's disease and associated carcinoma. An immunohistochemical study. Arch Pathol Lab Med 117: 291-294.
512. Cohen LM (1996). The starburst giant cell is useful for distinguishing lentigo maligna from photodamaged skin. J Am Acad Dermatol 35: 962-968.
513. Cohen LM, Bennion SD, Johnson TW, Golitz LE (1997). Hypermelanotic nevus: clinical, histopathologic, and ultrastructural features in 316 cases. Am J Dermatopathol 19: 23-30.
514. Cohen MMJr (1999). Nevoid basal cell carcinoma syndrome: molecular biology and new hypotheses. Int J Oral Maxillofac Surg 28: 216-223.
515. Cohen PR, Ulmer R, Theriault A, Leigh IM, Duvic M (1997). Epidermolytic acanthomas: clinical characteristics and immunohistochemical features. Am J Dermatopathol 19: 232-241.
516. Cohn-Cedermark G, Mansson-Brahme E, Rutqvist LE, Larsson O, Johansson H, Ringborg U (2000). Trends in mortality from malignant melanoma in Sweden, 1970-1996. Cancer 89: 348-355.
517. Coit DG (2001). Merkel cell carcinoma. Ann Surg Oncol 8: 99S-102S.
518. Colby TV (1997). Metastasizing dermatofibroma. Am J Surg Pathol 21: 976.
519. Coleman WPI, Gately LEI, Krementz AB, Reed RJ, Krementz ET (1980). Nevi, lentigines, and melanomas in blacks. Arch Dermatol 116: 548-551.
520. Collina G, Deen S, Cliff S, Jackson P, Cook MG (1997). Atypical dermal nodules in benign melanocytic naevi. Histopathology 31: 97-101.
521. Collins GL, Somach S, Morgan MB (2002). Histomorphologic and immunophenotypic analysis of fibrofolliculomas and trichodiscomas in Birt-Hogg-Dube syndrome and sporadic disease. J Cutan Pathol 29: 529-533.
522. Colome-Grimmer MI, Evans HL (1996). Metastasizing cellular dermatofibroma. A report of two cases. Am J Surg Pathol 20: 1361-1367.
523. Colome MI, Sanchez RL (1994). Dermatomyofibroma: report of two cases. J Cutan Pathol 21: 371-376.
524. Colomo L, Loong F, Rives S, Pittaluga S, Martinez A, Lopez-Guillermo A, Ojanguren J, Romagosa V, Jaffe ES, Campo E (2004). Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. Am J Surg Pathol 28: 736-747.
525. Cong P, Raffeld M, Jaffe ES (2001). Blastic NK cell lymphoma/leukemia: a clinicopathological study of 23 cases. Mod Pathol 14: 160A.
526. Conley J, Lattes R, Orr W (1971).

Desmoplastic malignant melanoma (a rare variant of spindle cell melanoma). Cancer 28: 914-936.
527. Connelly J, Smith JLJr (1991). Malignant blue nevus. Cancer 67: 2653-2657.
528. Connelly MG, Winkelmann RK (1985). Acral arteriovenous tumor. A clinicopathologic review. Am J Surg Pathol 9: 15-21.
529. Connelly TJ, Cribier B, Brown TJ, Yanguas I (2000). Complete spontaneous regression of Merkel cell carcinoma: a review of the 10 reported cases. Dermatol Surg 26: 853-856.
530. Conolly WB, Goulston E (1973). Problems of digital amputations: a clinical review of 260 patients and 301 amputations. Aust N Z J Surg 43: 118-123.
530A. Conti EM, Cercato MC, Gatta G, Ramazzotti V, Roscioni S (2001). Childhood melanoma in Europe since 1978: a population-based survival study. Eur J Cancer 37: 780-784.
531. Contreras F, Fonseca E, Gamallo C, Burgos E (1990). Multiple self-healing indeterminate cell lesions of the skin in an adult. Am J Dermatopathol 12: 396-401.
532. Coode PE, Ridgway H, Jones DB (1980). Multicentric reticulohistiocytosis: report of two cases with ultrastructure, tissue culture and immunology studies. Clin Exp Dermatol 5: 281-293.
533. Cooke KR, Fraser J (1985). Migration and death from malignant melanoma. Int J Cancer 36: 175-178.
534. Cooke KR, Skegg DC, Fraser J (1983). Trends in malignant melanoma of skin in New Zealand. Int J Cancer 31: 715-718.
535. Cooke KR, Spears GF, Elder DE, Greene MH (1989). Dysplastic naevi in a population-based survey. Cancer 63: 1240-1244.
536. Cooper PH (1987). Carcinomas of sweat glands. Pathol Annu 22 Pt 1: 83-124.
537. Cooper PH (1992). Deep penetrating (plexiform spindle cell) nevus. A frequent participant in combined nevus. J Cutan Pathol 19: 172-180.
538. Cooper PH, Frierson HF, Kayne AL, Sabio H (1984). Association of juvenile xanthogranuloma with juvenile myeloid leukemia. Arch Dermatol 120: 371-375.
539. Cooper PH, Frierson HFJr, Morrison AG (1985). Malignant transformation of eccrine spiradenoma. Arch Dermatol 121: 1445-1448.
540. Cooper PH, McAllister HA, Helwig EB (1979). Intravenous pyogenic granuloma. A study of 18 cases. Am J Surg Pathol 3: 221-228.
541. Cooper PH, Mills SE, Leonard DD, Santa Cruz DJ, Headington JT, Barr RJ, Katz DA (1985). Sclerosing sweat duct (syringomatous) carcinoma. Am J Surg Pathol 9: 422-433.
542. Coppeto JR, Jaffe R, Gillies CG (1978). Primary orbital melanoma. Arch Ophthalmol 96: 2255-2258.
543. Cordova A (1981). The Mongolian spot: a study of ethnic differences and a literature review. Clin Pediatr (Phila) 20: 714-719.
544. Cossman J, Fend F, Staudt L, Raffel M (2001). Application of molecular genetics to the diagnosis and classification of malignant lymphoma. In: Neoplastic Hematopathology, Knowles DM, ed., Lippincott, Williams and Wilkins: Philadelphia , pp. 365-390.
545. Cote GJ, Wohllk N, Evans D, Goepfert H, Gagel RF (1995). RET proto-oncogene mutations in multiple endocrine neoplasia type 2 and medullary thyroid carcinoma. Baillieres Clin Endocrinol Metab 9: 609-630.
546. Cotton DW, Slater DN, Rooney N, Goepel JR, Mills PM (1986). Giant vascular eccrine spiradenomas: a report of two cases with histology, immunohistology and electron microscopy. Histopathology 10: 1093-1099.
547. Coupe MO, Whittaker SJ, Thatcher N (1987). Multicentric reticulohistiocytosis. Br J Dermatol 116: 245-247.
548. Couperus M, Rucker R (1953). Early diagnosis of malignant melanoma of the skin. California Med 78: 21-24.
549. Cox NH, Aitchison TC, MacKie RM (1998). Extrafacial lentigo maligna melanoma: analysis of 71 cases and comparison with lentigo maligna melanoma of the head and neck. Br J Dermatol 139: 439-443.
550. Cox NH, Long ED (1993). Pseudoangiosarcomatous squamous cell carcinoma of skin. Histopathology 22: 295-296.
551. Creamer D, Black MM, Calonje E (2000). Reactive angioendotheliomatosis in association with the antiphospholipid syndrome. J Am Acad Dermatol 42: 903-906.
552. Creamer D, Macdonald A, Griffiths WA (1999). Unilateral linear syringomata. A case report. Clin Exp Dermatol 24: 428-430.
553. Crespo M, Bosch F, Villamor N, Bellosillo B, Colomer D, Rozman M, Marce S, Lopez-Guillermo A, Campo E, Montserrat E (2003). ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. N Engl J Med 348: 1764-1775.
554. Cress RD, Holly EA (1997). Incidence of cutaneous melanoma among non-Hispanic whites, Hispanics, Asians, and blacks: an analysis of california cancer registry data, 1988-93. Cancer Causes Control 8: 246-252.
555. Cribier B, Asch P, Grosshans E (1999). Differentiating squamous cell carcinoma from keratoacanthoma using histopathological criteria. Is it possible? A study of 296 cases. Dermatology 199: 208-212.
556. Cribier B, Asch PH, Regnier C, Rio MC, Grosshans E (1999). Expression of human hair keratin basic 1 in pilomatrixoma. A study of 128 cases. Br J Dermatol 140: 600-604.
557. Cribier B, Grosshans E (1995). Tumor of the follicular infundibulum: a clinicopathologic study. J Am Acad Dermatol 33: 979-984.
558. Cribier B, Noacco G, Peltre B, Grosshans E (2002). Stromelysin 3 expression: a useful marker for the differential diagnosis dermatofibroma versus dermatofibrosarcoma protuberans. J Am Acad Dermatol 46: 408-413.
559. Crijns MB, Bergman W, Berger MJ, Hermans J, Sober AJ (1993). On naevi and melanomas in dysplastic naevus syndrome patients. Clin Exp Dermatol 18: 248-252.
560. Crocetti E, Carli P (2003). Changes from mid-1980s to late 1990s among clinical and demographic correlates of melanoma thickness. Eur J Dermatol 13: 72-75.
561. Crocker HR (1889). Paget's disease affecting the scrotum and penis. Trans Pathol Soc London 40: 187-191.
562. Crotty CP, Winkelmann RK (1981). Cytophagic histiocytic panniculitis with fever, cytopenia, liver failure, and terminal hemorrhagic diathesis. J Am Acad Dermatol 4: 181-194.
563. Crotty KA, McCarthy SW, McCarthy WH, Quinn MJ (2003). Alopecia neoplastica caused by desmoplastic malignant melanoma. Australas J Dermatol .
564. Crovato F, Nazzari G, Gambini C, Massone L (1989). Meyerson's naevi in pityriasis rosea. Br J Dermatol 120: 318-319.
565. Crovato F, Rebora A (1985). Angiokeratoma corporis diffusum and normal enzyme activities. J Am Acad Dermatol 12: 885-886.
566. Crowley NJ, Seigler HF (1990). Late recurrence of malignant melanoma. Analysis of 168 patients. Ann Surg 212: 173-177.
567. Crowson AN, Magro CM, Mihm MCJr (1999). Malignant melanoma with prominent pigment synthesis: "animal type" melanoma—a clinical and histological study of six cases with a consideration of other melanocytic neoplasms with prominent pigment synthesis. Hum Pathol 30: 543-550.
568. Crowson AN, Magro CM, Mihm MCJr (2001). The Melanocytic Proliferations: A Comprehensive Textbook of Pigmented Lesions. First ed. John Wiley & Sons: New York.
569. Croxatto JO, Charles DE, Malbran ES (1981). Neurofibromatosis associated with nevus of Ota and choroidal melanoma. Am J Ophthalmol 92: 578-580.
570. Crum CP, Liskow A, Petras P, Keng WC, Frick HC (1984). Vulvar intraepithelial neoplasia (severe atypia and carcinoma in situ). A clinicopathologic analysis of 41 cases. Cancer 54: 1429-1434.
571. Crutcher WA, Sagebiel RW (1984). Prevalence of dysplastic naevi in a community practice. Lancet 1: 729.
572. Cubilla AL, Ayala MT, Barreto JE, Bellasai JG, Noel JC (1996). Surface adenosquamous carcinoma of the penis. A report of three cases. Am J Surg Pathol 20: 156-160.
573. Cubilla AL, Reuter VE, Gregoire L, Ayala G, Ocampos S, Lancaster WD, Fair W (1998). Basaloid squamous cell carcinoma: a distinctive human papilloma virus-related penile neoplasm: a report of 20 cases. Am J Surg Pathol 22: 755-761.
574. Cullen SL (1962). Incidence of nevi: report of palms, soles and genitalia of 10.000 young men. Arch Dermatol 86: 40-43.
575. Culpepper KS, Granter SR, McKee PH (2004). My approach to atypical melanocytic lesions. J Clin Pathol 57: 1121-1131.
576. Cunningham JA, Hardy J (1947). Hidradenomas of the vulva. South Surg 13: 831-838.
577. Curtis BV, Calcaterra TC, Coulson WF (1997). Multiple granular cell tumor: a case report and review of the literature. Head Neck 19: 634-637.
578. Czarnecki DB, Aarons I, Dowling JP, Lauritz B, Wallis P, Taft EH (1982). Malignant clear cell hidradenoma: a case report. Acta Derm Venereol 62: 173-176.
579. Czarnetzki BM, Behrendt H (1981). Urticaria pigmentosa: clinical picture and response to oral disodium cromoglycate. Br J Dermatol 105: 563-567.
580. Czarnetzki BM, Kolde G, Schoemann A, Urbanitz S, Urbanitz D (1988). Bone marrow findings in adult patients with urticaria pigmentosa. J Am Acad Dermatol 18: 45-51.
581. D'Addario SF, Morgan M, Talley L, Smoller BR (2002). h-Caldesmon as a specific marker of smooth muscle cell differentiation in some soft tissue tumors of the skin. J Cutan Pathol 29: 426-429.
582. Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J, Choy YS, Reeve MP, Thiele E, Egelhoff JC, Kasprzyk-Obara J, Domanska-Pakiela D, Kwiatkowski DJ (2001). Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet 68: 64-80.
583. Dabska M (1971). Giant hair matrix tumor. Cancer 28: 701-706.
584. Dabski K, Stoll HLJr (1987). Granulomatous reactions in mycosis fungoides. J Surg Oncol 34: 217-229.
585. Dakin MC, Leppard B, Theaker JM (1992). The palisaded, encapsulated neuroma (solitary circumscribed neuroma). Histopathology 20: 405-410.
586. Damle RN, Ghiotto F, Valetto A, Albesiano E, Fais F, Yan XJ, Sison CP, Allen SL, Kolitz J, Schulman P, Vinciguerra VP, Budde P, Frey J, Rai KR, Ferrarini M, Chiorazzi N (2002). B-cell chronic lymphocytic leukemia cells express a surface membrane phenotype of activated, antigen-experienced B lymphocytes. Blood 99: 4087-4093.
587. Danaee H, Nelson HH, Karagas MR, Schned AR, Ashok TD, Hirao T, Perry AE, Kelsey KT (2002). Microsatellite instability at tetranucleotide repeats in skin and bladder cancer. Oncogene 21: 4894-4899.
588. Danforth WC (1949). Sweat gland tumors of the vulva. Am J Obstet Gynecol 58: 326-334.
589. Daoud MS, Snow JL, Gibson LE, Daoud S (1996). Aleukemic monocytic leukemia cutis. Mayo Clin Proc 71: 166-168.
590. Darling TN, Kamino H, Murray JC (1993). Acquired cutaneous smooth muscle hamartoma. J Am Acad Dermatol 28: 844-845.
591. Darlington S, Siskind V, Green L, Green A (2002). Longitudinal study of melanocytic nevi in adolescents. J Am Acad Dermatol 46: 715-722.
592. Dave VK, Main RA (1972). Angiokeratoma of Mibelli with necrosis of the fingertips. Arch Dermatol 106: 726-728.
593. Davidson LL, Frost ML, Hanke CW, Epinette WW (1989). Primary leiomyosarcoma of the skin.Case report and review of the literature. J Am Acad Dermatol 21: 1156-1160.
594. Davis MD, Gostout BS, McGovern RM, Persing DH, Schut RL, Pittelkow MR (2000). Large plantar wart caused by human papillomavirus-66 and resolution by topical cidofovir therapy. J Am Acad Dermatol 43: 340-343.
595. Davis TH, Morton CC, Miller-Cassman R, Balk SP, Kadin ME (1992). Hodgkin's disease, lymphomatoid papulosis, and cutaneous T-cell lymphoma derived from a common T-cell clone. N Engl J Med 326: 1115-1122.
596. Davison JM, Rosenbaum E, Barrett TL, Goldenberg D, Hoque MO, Sidransky D, Westra WH (2005). Absence of V599E BRAF mutations in desmoplastic melanomas. Cancer 103: 788-792.
597. Dawe RS, Wainwright NJ, Evans AT, Lowe JG (1998). Multiple widespread eruptive Spitz naevi. Br J Dermatol 138: 872-874.
598. De Aloe G, Rubegni P, Pacenti L, Miracco C, Fimiani M (2001). Human herpesvirus type 8 is not associated with pyogenic granulomas with satellite recurrence. Br J Dermatol 144: 202-203.
599. de Berker D, Lawrence C (2001). Ganglion of the distal interphalangeal joint (myxoid cyst): therapy by identification and repair of the leak of joint fluid. Arch Dermatol 137: 607-610.

600. De Bruin PC, Beljaards RC, van Heerde P, Van D, V, Noorduyn LA, van Krieken JH, Kluin-Nelemans JC, Willemze R, Meijer CJ (1993). Differences in clinical behaviour and immunophenotype between primary cutaneous and primary nodal anaplastic large cell lymphoma of T-cell or null cell phenotype. Histopathology 23: 127-135.

601. De Coninck A, Willemsen M, De Dobbeleer G, Roseeuw D (1986). Vulvar localisation of epidermolytic acanthoma. A light- and electron-microscopic study. Dermatologica 172: 276-278.

602. de Gruijl FR, Longstreth J, Norval M, Cullen AP, Slaper H, Kripke ML, Takizawa Y, van der Leun JC (2003). Health effects from stratospheric ozone depletion and interactions with climate change. Photochem Photobiol Sci 2: 16-28.

603. de Leval L, Harris NL, Longtine J, Ferry JA, Duncan LM (2001). Cutaneous b-cell lymphomas of follicular and marginal zone types: use of Bcl-6, CD10, Bcl-2, and CD21 in differential diagnosis and classification. Am J Surg Pathol 25: 732-741.

604. de Sa BC, Rezze GG, Scramim AP, Landman G, Neves RI (2004). Cutaneous melanoma in childhood and adolescence: retrospective study of 32 patients. Melanoma Res 14: 487-492.

605. de Villiers EM (2001). Taxonomic classification of papillomaviruses. Papillomavirus Report 12: 57-63.

606. de Viragh PA (1995). The 'mantle hair of Pinkus'. A review on the occasion of its centennial. Dermatology 191: 82-87.

607. de Viragh PA, Szeimies RM, Eckert F (1997). Apocrine cystadenoma, apocrine hidrocystoma, and eccrine hidrocystoma: three distinct tumors defined by expression of keratins and human milk fat globulin 1. J Cutan Pathol 24: 249-255.

608. de Vries E, Boniol M, Dore JF, Coebergh JW (2004). Lower incidence rates but thicker melanomas in Eastern Europe before 1992: a comparison with Western Europe. Eur J Cancer 40: 1045-1052.

609. de Vries E, Bray FI, Coebergh JW, Parkin DM (2003). Changing epidemiology of malignant cutaneous melanoma in Europe 1953-1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. Int J Cancer 107: 119-126.

610. de Vries E, Coebergh JW (2004). Cutaneous malignant melanoma in Europe. Eur J Cancer 40: 2355-2366.

611. de Vries TJ, Smeets M, de Graaf R, Hou-Jensen K, Brocker EB, Renard N, Eggermont AM, Van Muijen GN, Ruiter DJ (2001). Expression of gp100, MART-1, tyrosinase, and S100 in paraffin-embedded primary melanomas and locoregional, lymph node, and visceral metastases: implications for diagnosis and immunotherapy. A study conducted by the EORTC Melanoma Cooperative Group. J Pathol 193: 13-20.

612. de Wit PE, van't Hof-Grootenboer B, Ruiter DJ, Bondi R, Brocker EB, Cesarini JP, Hastrup N, Hou-Jensen K, MacKie RM, Scheffer E, Suter L, Urso C (1993). Validity of the histopathological criteria used for diagnosing dysplastic naevi. An interobserver study by the pathology subgroup of the EORTC Malignant Melanoma Cooperative Group. Eur J Cancer 29A: 831-839.

613. DeCoteau JF, Butmarc JR, Kinney MC, Kadin ME (1996). The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30+ lymphoproliferative disorders: comparison with anaplastic large-cell lymphoma of nodal origin. Blood 87: 3437-3441.

614. Dehner P (2003). Juvenile xanthogranuloma in the first two decades. Am J Surg Pathol 27: 579-593.

615. Dekio S, Koike S, Jidoi J (1989). Nevus of ota with nevus of Ito—report of a case with cataract. J Dermatol 16: 164-166.

616. del Rio E, Vazquez Veiga HA, Suarez Penaranda JM (2000). Blue nevus with satellitosis mimicking malignant melanoma. Cutis 65: 301-302.

617. Delecluse HJ, Anagnostopoulos I, Dallenbach F, Hummel M, Marafioti T, Schneider U, Huhn D, Schmidt-Westhausen A, Reichart PA, Gross U, Stein H (1997). Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 89: 1413-1420.

618. Dennis LK (1999). Analysis of the melanoma epidemic, both apparent and real: data from the 1973 through 1994 surveillance, epidemiology, and end results program registry. Arch Dermatol 135: 275-280.

619. Dennis LK (1999). Melanoma incidence by body site: effects of birth-cohort adjustment. Arch Dermatol 135: 1553-1554.

620. Dennis LK, White E, Lee JA (1993). Recent cohort trends in malignant melanoma by anatomic site in the United States. Cancer Causes Control 4: 93-100.

621. Deroo M, Eeckhout I, Naeyaert JM (1997). Eruptive satellite vascular malformations after removal of a melanocytic naevus. Br J Dermatol 137: 292-295.

622. Derre J, Lagace R, Nicolas A, Mairal A, Chibon F, Coindre JM, Terrier P, Sastre X, Aurias A (2001). Leiomyosarcomas and most malignant fibrous histiocytomas share very similar comparative genomic hybridization imbalances: an analysis of a series of 27 leiomyosarcomas. Lab Invest 81: 211-215.

623. Derrick EK, Darley CR, Burge S (1995). Comedonal Darier's disease. Br J Dermatol 132: 453-455.

624. Desmond RA, Soong SJ (2003). Epidemiology of malignant melanoma. Surg Clin North Am 83: 1-29.

625. Dessoukey MW, Omar MF, Abdel-Dayem H (1997). Eruptive keratoacanthomas associated with immunosuppressive therapy in a patient with systemic lupus erythematosus. J Am Acad Dermatol 37: 478-480.

626. Dhillon AP, Rode J (1982). Patterns of staining for neurone specific enolase in benign and malignant melanocytic lesions of the skin. Diagn Histopathol 5: 169-174.

627. Di Tommaso L, Magrini E, Consales A, Poppi M, Pasquinelli G, Dorji T, Benedetti G, Baccarini P (2002). Malignant granular cell tumor of the lateral femoral cutaneous nerve: report of a case with cytogenetic analysis. Hum Pathol 33: 1237-1240.

628. Diaz-Cascajo C, Borghi S, Weyers W, Retzlaff H, Requena L, Metze D (1999). Benign lymphangiomatous papules of the skin following radiotherapy: a report of five new cases and review of the literature. Histopathology 35: 319-327.

629. Diaz-Cascajo C, Weyers W, Rey-Lopez A, Borghi S (1998). Deep dermatofibrosarcoma protuberans: a subcutaneous variant. Histopathology 32: 552-555.

630. Diebold J, Jaffe ES, Raphael M, Warnke RA (2001). Burkitt lymphoma. In: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Jaffe ES, Harris NL, Stein H, Vardiman J, eds., IARC Press: Lyon , pp. 181-184.

631. DiGiuseppe JA, Hartmann DP, Freter C, Cossman J, Mann RB (1997). Molecular detection of bone marrow involvement in intravascular lymphomatosis. Mod Pathol 10: 33-37.

632. DiGiuseppe JA, Louie DC, Williams JE, Miller DT, Griffin CA, Mann RB, Borowitz MJ (1997). Blastic natural killer cell leukemia/lymphoma: a clinicopathologic study. Am J Surg Pathol 21: 1223-1230.

633. DiGiuseppe JA, Nelson WG, Seifter EJ, Boitnott JK, Mann RB (1994). Intravascular lymphomatosis: a clinicopathologic study of 10 cases and assessment of response to chemotherapy. J Clin Oncol 12: 2573-2579.

634. DiLeonardo M (1997). Sebaceous adenoma vs. sebaceoma vs. sebaceous carcinoma. Dermatopathology, practical & conceptual 3: 11.

634A. Dimson OG, Drolet BA, Southern JF, Rock A, Winthrop AL, Esterly NB (2000). Congenital generalized myofibromatosis in a neonate. Arch Dermatol 136: 597-600.

635. Dinehart SM (2000). The treatment of actinic keratoses. J Am Acad Dermatol 42: 25-28.

636. Dinneen AM, Mehregan DR (1996). Sebaceous epithelioma: a review of twenty-one cases. J Am Acad Dermatol 34: 47-50.

637. Dissanayake RV, Salm R (1980). Sweat-gland carcinomas: prognosis related to histological type. Histopathology 4: 445-466.

638. Dixon AY, Lee SH, McGregor DH (1989). Factors predictive of recurrence of basal cell carcinoma. Am J Dermatopathol 11: 222-232.

639. Dixon AY, Lee SH, McGregor DH (1993). Histologic features predictive of basal cell carcinoma recurrence: results of a multivariate analysis. J Cutan Pathol 20: 137-142.

640. Djawari D, Cremer H (1989). [Malignant blue nevus]. Z Hautkr 64: 51-53.

641. Dodson JM, DeSpain J, Hewett JE, Clark DP (1991). Malignant potential of actinic keratoses and the controversy over treatment. A patient-oriented perspective. Arch Dermatol 127: 1029-1031.

642. Dogru M, Matsuo H, Inoue M, Okubo K, Yamamoto M (1997). Management of eyelid sebaceous carcinomas. Ophthalmologica 211: 40-43.

643. Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, Dohner K, Bentz M, Lichter P (2000). Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 343: 1910-1916.

644. Domingo J, Helwig EB (1979). Malignant neoplasms associated with nevus sebaceus of Jadassohn. J Am Acad Dermatol 1: 545-556.

645. Dommann SN, Dommann-Scherrer CC, Zimmerman D, Dours-Zimmermann MT, Hassam S, Burg G (1995). Primary cutaneous T-cell-rich B-cell lymphoma. A case report with a 13-year follow-up. Am J Dermatopathol 17: 618-624.

646. Dover JS, From L, Lewis A (1989). Palisaded encapsulated neuromas. A clinicopathologic study. Arch Dermatol 125: 386-389.

647. Dowlati B, Nabai H, Mehregan DR, Mehregan DA, Khaleel J (2002). Zosteriform angiolymphoid hyperplasia with eosinophilia. J Dermatol 29: 178-179.

648. Drake LA, Ceilley RI, Cornelison RL, Dobes WL, Dorner W, Goltz RW, Lewis CW, Salasche SJ, Turner ML, Lowery BJ, Shama SK, Androphy EJ, Galen WK, Heaton CL, Lynch PJ (1995). Guidelines of care for warts: human papillomavirus. Committee on Guidelines of Care. J Am Acad Dermatol 32: 98-103.

649. Dreizen S, McCredie KB, Keating MJ, Luna MA (1983). Malignant gingival and skin "infiltrates" in adult leukemia. Oral Surg Oral Med Oral Pathol 55: 572-579.

650. Drews R, Samel A, Kadin ME (2000). Lymphomatoid papulosis and anaplastic large cell lymphomas of the skin. Semin Cutan Med Surg 19: 109-117.

651. Dubin N, Kopf AW (1983). Multivariate risk score for recurrence of cutaneous basal cell carcinomas. Arch Dermatol 119: 373-377.

652. Dubreuilh MW (1912). De la melanose circonscrite precancereuse. Ann Dermatol Syphilol 3: 129-151.

653. Dubreuilh W (1912). Le naevus bléu. Ann Dermatol 2: 552.

654. Dubus P, Young P, Beylot-Barry M, Belaud-Rotureau MA, Courville P, Vergier B, Parrens M, Lenormand B, Joly P, Merlio JP (2002). Value of interphase FISH for the diagnosis of t(11:14)(q13;q32) on skin lesions of mantle cell lymphoma. Am J Clin Pathol 118: 832-841.

655. Duke WH, Sherrod TT, Lupton GP (2000). Aggressive digital papillary adenocarcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited). Am J Surg Pathol 24: 775-784.

656. Dummer R, Kohl O, Gillessen J, Kagi M, Burg G (1993). Peripheral blood mononuclear cells in patients with non-leukemic cutaneous T-cell lymphoma. Reduced proliferation and preferential secretion of a T helper-2-like cytokine pattern on stimulation. Arch Dermatol 129: 433-436.

657. Dummer R, Nestle FO, Niederer E, Ludwig E, Laine E, Grundmann H, Grob P, Burg G (1999). Genotypic, phenotypic and functional analysis of CD4+CD7+ and CD4+CD7- T lymphocyte subsets in Sezary syndrome. Arch Dermatol Res 291: 307-311.

658. Dunwell P, Rose A (2003). Study of the skin disease spectrum occurring in an Afro-Caribbean population. Int J Dermatol 42: 287-289.

659. Dupre A, Viraben R (1985). Congenital smooth muscle nevus with follicular spotted appearance. J Am Acad Dermatol 13: 837-838.

660. Dutton JJ, Anderson RL, Schelper RL, Purcell JJ, Tse DT (1984). Orbital malignant melanoma and oculodermal melanocytosis: report of two cases and review of the literature. Ophthalmology 91: 497-507.

661. Dwyer PK, MacKie RM, Watt DC, Aitchison TC (1993). Plantar malignant melanoma in a white Caucasian population. Br J Dermatol 128: 115-120.

662. Eckert F, Betke M, Schmoeckel C, Neuweiler J, Schmid U (1992). Myoepithelial differentiation in benign sweat gland tumors. Demonstrated by a monoclonal antibody to alpha-smooth muscle actin. J Cutan Pathol 19: 294-301.

663. Eckert F, Nilles M, Altmannsberger M (1992). Eccrine syringofibroadenoma: a case report with analysis of cytokeratin expression. Br J Dermatol 126: 257-261.

664. Eckert F, Schmid U, Hardmeier T, Altmannsberger M (1992). Cytokeratin expression in mucinous sweat gland carcinomas: an immunohistochemical analysis of four cases. Histopathology 21: 161-165.
665. Egawa K, Honda Y, Ono T, Kuroki M (1998). Immunohistochemical demonstration of carcinoembryonic antigen and related antigens in various cutaneous keratinous neoplasms and verruca vulgaris. Br J Dermatol 139: 178-185.
666. Egeler RM, Neglia JP, Puccetti DM, Brennan CA, Nesbit ME (1993). Association of Langerhans cell histiocytosis with malignant neoplasms. Cancer 71: 865-873.
667. Ehrlich GE, Young I, Nosheny SZ, Katz WA (1972). Multicentric reticulohistiocytosis (lipoid dermatoarthritis). A multisystem disorder. Am J Med 52: 830-840.
668. Eichhorn M, Jungkunz W, Worl J, Marsch WC (1994). Carbonic anhydrase is abundant in fenestrated capillaries of cherry hemangioma. Acta Derm Venereol 74: 51-53.
669. Eichmuller S, Usener D, Dummer R, Stein A, Thiel D, Schadendorf D (2001). Serological detection of cutaneous T-cell lymphoma-associated antigens. Proc Natl Acad Sci U S A 98: 629-634.
670. Eisen D, Voorhees JJ (1991). Oral melanoma and other pigmented lesions of the oral cavity. J Am Acad Dermatol 24: 527-537.
671. Elder D, Elenitsas R, Ragsdale BD (1977). Eccrine hidrocystoma. In: Lever's Histopathology of the Skin, Elder D, Elenitsas R, Jaworsky C, Johnson BJr, eds., Lippincott Williams & Wilkins: Philadelphia .
672. Elder DE, Elenitsas R, Jaworsky C, Johnson BLJr (1997). Lever's Histopathology of the Skin. 8th ed. Lippincott-Raven: Philadelphia.
673. Elder DE, Goldman LI, Goldman SC, Greene MH, Clark WHJr (1980). Dysplastic nevus syndrome: a phenotypic association of sporadic cutaneous melanoma. Cancer 46: 1787-1794.
674. Elder DE, Guerry D, Epstein MN, Zehngebot L, Lusk E, Van Horn M, Clark WHJr (1984). Invasive malignant melanomas lacking competence for metastasis. Am J Dermatopathol 6 Suppl: 55-61.
675. Elder DE, Murphy GF (1991). Atlas of Tumor Pathology. Melanocytic Tumors of the Skin. 3rd Series ed. AFIP: Washington.
675A. Elder DE, Rodeck U, Thurin J, Cardillo F, Clark WH, Stewart R, Herlyn M (1989). Antigenic profile of tumor progression stages in human melanocytic nevi and melanomas. Cancer Res 49: 5091-5096.
676. Elenitsas R, Halpern AC (1996). Eczematous halo reaction in atypical nevi. J Am Acad Dermatol 34: 357-361.
677. Elgart GW (2001). Seborrheic keratoses, solar lentigines, and lichenoid keratoses. Dermatoscopic features and correlation to histology and clinical signs. Dermatol Clin 19: 347-357.
678. Elgart GW, Patterson JW (1990). Congenital midline hamartoma: case report with histochemical and immunohistochemical findings. Pediatr Dermatol 7: 199-201.
679. Elleder M, Ledvinova J, Vosmik F, Zeman J, Stejskal D, Lageron A (1990). An atypical ultrastructural pattern in Fabry's disease: a study on its nature and incidence in 7 cases. Ultrastruct Pathol 14: 467-474.
680. Elston DM, Bergfeld WF, Petroff N (1993). Basal cell carcinoma with monster cells. J Cutan Pathol 20: 70-73.
681. Elston DM, James WD, Rodman OG, Graham GF (1986). Multiple hamartoma syndrome (Cowden's disease) associated with non-Hodgkin's lymphoma. Arch Dermatol 122: 572-575.
682. Elwood JM, Gallagher RP (1998). Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. Int J Cancer 78: 276-280.
683. Elwood JM, Jopson J (1997). Melanoma and sun exposure: an overview of published studies. Int J Cancer 73: 198-203.
684. Emura I, Naito M, Wakabayashi M, Yoshizawa H, Arakawa M, Chou T (1998). Detection of circulating tumor cells in a patient with intravascular lymphomatosis: a case study examined by the cytology method. Pathol Int 48: 63-66.
685. Endo H, Mikami Y, Sano T (2003). Cervical polyp with eccrine syringofibroadenoma-like features. Histopathology 42: 301-304.
686. Eng A, Lebel RR, Elejalde BR, Anderson C, Bennett L (1994). Linear facial skin defects associated with microphthalmia and other malformations, with chromosome deletion Xp22.1. J Am Acad Dermatol 31: 680-682.
687. Eng C (1998). Genetics of Cowden syndrome: through the looking glass of oncology. Int J Oncol 12: 701-710.
688. Eng C (2000). Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 37: 828-830.
688A. Eng C (2003). PTEN: one gene, many syndromes. Hum Mutat 22: 183-198.
689. English DR, Armstrong BK, Kricker A, Fleming C (1997). Sunlight and cancer. Cancer Causes Control 8: 271-283.
690. English JCI, McCollough ML, Grabski WJ (1996). A pigmented scalp nodule: malignant blue nevus. Cutis 58: 40-42.
691. Enjolras O, Mulliken JB, Wassef M, Frieden IJ, Rieu PN, Burrows PE, Salhi A, Leaute-Labreze C, Kozakewich HP (2000). Residual lesions after Kasabach-Merritt phenomenon in 41 patients. J Am Acad Dermatol 42: 225-235.
692. Enjolras O, Wassef M, Mazoyer E, Frieden IJ, Rieu PN, Drouet L, Taieb A, Stalder JF, Escande JP (1997). Infants with Kasabach-Merritt syndrome do not have "true" hemangiomas. J Pediatr 130: 631-640.
693. Enzinger FM (1979). Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm. Cancer 44: 2147-2157.
694. Epstein JH (1983). Photocarcinogenesis, skin cancer, and aging. J Am Acad Dermatol 9: 487-502.
695. Epstein JI, Erlandson RA, Rosen PP (1984). Nodal blue nevi. A study of three cases. Am J Surg Pathol 8: 907-915.
696. Eros N, Karolyi Z, Kovacs A, Takacs I, Radvanyi G, Kelenyi G (2002). Intravascular B-cell lymphoma. J Am Acad Dermatol 47: S260-S262.
697. Estalilla OC, Koo CH, Brynes RK, Medeiros LJ (1999). Intravascular large B-cell lymphoma. A report of five cases initially diagnosed by bone marrow biopsy. Am J Clin Pathol 112: 248-255.
698. Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA (1993). Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. J Med Genet 30: 460-464.
699. Evans HL, Su D, Smith JL, Winkelmann RK (1979). Carcinoma arising in eccrine spiradenoma. Cancer 43: 1881-1884.
700. Evans HL, Winkelmann RK, Banks PM (1979). Differential diagnosis of malignant and benign cutaneous lymphoid infiltrates: a study of 57 cases in which malignant lymphoma had been diagnosed or suspected in the skin. Cancer 44: 699-717.
701. Evans MJ, Gray ES, Blessing K (1998). Histopathological features of acral melanocytic nevi in children: study of 21 cases. Pediatr Dev Pathol 1: 388-392.
702. Evans RW (1956). Histologic appearance of tumours. Med J Edinb London 1: 230.
703. Everett MA (1989). Histopathology of congenital pigmented nevi. Am J Dermatopathol 11: 11-12.
704. Fackenthal JD, Marsh DJ, Richardson AL, Cummings SA, Eng C, Robinson BG, Olopade OI (2001). Male breast cancer in Cowden syndrome patients with germline PTEN mutations. J Med Genet 38: 159-164.
705. Falck VG, Jordaan HF (1986). Papillary eccrine adenoma. A tubulopapillary hidradenoma with eccrine differentiation. Am J Dermatopathol 8: 64-72.
706. Falini B, Mason DY (2002). Proteins encoded by genes involved in chromosomal alterations in lymphoma and leukemia: clinical value of their detection by immunocytochemistry. Blood 99: 409-426.
707. Fallowfield ME, Collina G, Cook MG (1994). Melanocytic lesions of the palm and sole. Histopathology 24: 463-467.
708. Fan H, Oro AE, Scott MP, Khavari PA (1997). Induction of basal cell carcinoma features in transgenic human skin expressing Sonic Hedgehog. Nat Med 3: 788-792.
709. Fanburg JC, Meis-Kindblom JM, Rosenberg AE (1995). Multiple enchondromas associated with spindle-cell hemangioendotheliomas. An overlooked variant of Maffucci's syndrome. Am J Surg Pathol 19: 1029-1038.
710. Fanning J, Lambert HC, Hale TM, Morris PC, Schuerch C (1999). Paget's disease of the vulva: prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. Am J Obstet Gynecol 180: 24-27.
711. Fargnoli MC, Orlow SJ, Semel-Concepcion J, Bolognia JL (1996). Clinicopathologic findings in the Bannayan-Riley-Ruvalcaba syndrome. Arch Dermatol 132: 1214-1218.
712. Farrier S, Morgan M (1997). bcl-2 expression in pilomatricoma. Am J Dermatopathol 19: 254-257.
713. Farris PE, Manning S, Vuitch F (1994). Rhabdomyomatous mesenchymal hamartoma. Am J Dermatopathol 16: 73-75.
714. Fauci AS, Haynes BF, Costa J, Katz P, Wolff SM (1982). Lymphomatoid Granulomatosis. Prospective clinical and therapeutic experience over 10 years. N Engl J Med 306: 68-74.
715. Faulhaber D, Worle B, Trautner B, Sander CA (2000). Clear cell hidradenoma in a young girl. J Am Acad Dermatol 42: 693-695.
716. Favara BE (2001). Langerhans cell histiocytosis: an identity crisis. Med Pediatr Oncol 37: 545.
717. Feal-Cortizas C, Vargas-Diez E, Buezo GF, Aragues M (1997). Meyerson's nevus immunohistochemical findings in two cases. Australas J Dermatol 38: 222.
718. Feinmesser M, Tsabari C, Fichman S, Hodak E, Sulkes J, Okon E (2003). Differential expression of proliferation- and apoptosis-related markers in lentigo maligna and solar keratosis keratinocytes. Am J Dermatopathol 25: 300-307.
719. Feit NE, Dusza SW, Marghoob AA (2004). Melanomas detected with the aid of total cutaneous photography. Br J Dermatol 150: 706-714.
720. Feldman AL, Berthold F, Arceci RJ, Abramowsky C, Shehata BM, Mann KP, Lauer SJ, Pritchard J, Raffeld M, Jaffe ES (2005). Clonal relationship between precursor T-lymphoblastic leukaemia/lymphoma and Langerhans-cell histiocytosis. Lancet Oncol 6: 435-437.
721. Fendt H (1900). Beiträge zur Kenntnis der sogenannten sarcoiden Geschwülste der Haut. Arch Dermatol Syphilol 53: 212-242.
722. Fenske C, Banerjee P, Holden C, Carter N (2000). Brooke-Spiegler syndrome locus assigned to 16q12-q13. J Invest Dermatol 114: 1057-1058.
723. Ferguson JW, Hutchison HT, Rouse BM (1984). Ocular, cerebral and cutaneous malformations: confirmation of an association. Clin Genet 25: 464-469.
724. Ferlay J, Bray FI, Pisani P, Parkin DM (2001). Globocan 2000: Cancer incidence, mortality and prevalence worldwide. 1 ed. IARC Press: Lyon.
725. Fernandez-Acenero MJ, Manzarbeitia F, Mestre de Juan MJ, Requena L (2001). Malignant spiradenoma: report of two cases and literature review. J Am Acad Dermatol 44: 395-398.
726. Fernandez-Acenero MJ, Manzarbeitia F, Mestre MJ, Requena L (2000). p53 expression in two cases of spiradenocarcinomas. Am J Dermatopathol 22: 104-107.
727. Fernandez-Acenero MJ, Sanchez TA, Sanchez MC, Requena L (2003). Ectopic hidradenoma papilliferum: a case report and literature review. Am J Dermatopathol 25: 176-178.
728. Fernandez-Pugnaire MA, Delgado-Florencio V (1995). Familial multiple cutaneous leiomyomas. Dermatology 191: 295-298.
729. Fernandez Herrera JM, Aragues Montanes M, Fraga Fernandez J, Diez G (1988). Halo eczema in melanocytic nevi. Acta Derm Venereol 68: 161-163.
730. Fernandez EM, Helm KF (2004). The diameter of melanomas. Dermatol Surg 30: 1219-1222.
731. Fernandez M, Raimer SS, Sanchez RL (2001). Dysplastic nevi of the scalp and forehead in children. Pediatr Dermatol 18: 5-8.
732. Fernando SS, Johnson S, Bate J (1994). Immunohistochemical analysis of cutaneous malignant melanoma: comparison of S-100 protein, HMB-45 monoclonal antibody and NKI/C3 monoclonal antibody. Pathology 26: 16-19.
733. Ferrara G, Argenziano G, Zgavec B, Bartenjev I, Staibano S, De Rosa G, Soyer HP (2002). "Compound blue nevus": a reappraisal of "superficial blue nevus with prominent intraepidermal dendritic melanocytes" with emphasis on dermoscopic and histopathologic features. J Am Acad Dermatol 46: 85-89.
734. Ferreiro JA, Carney JA (1994). Myxomas of the external ear and their significance. Am J Surg Pathol 18: 274-280.
735. Ferreiro JA, Nascimento AG (1995). Hyaline-cell rich chondroid syringoma. A tumor mimicking malignancy. Am J Surg Pathol 19: 912-917.
736. Ferreri AJ, Campo E, Ambrosetti A,

Ilariucci F, Seymour JF, Willemze R, Arrigoni G, Rossi G, Lopez-Guillermo A, Berti E, Eriksson M, Federico M, Cortelazzo S, Govi S, Frungillo N, Dell'Oro S, Lestani M, Asioli S, Pedrinis E, Ungari M, Motta T, Rossi R, Artusi T, Iuzzolino P, Zucca E, Cavalli F, Ponzoni M (2004). Anthracycline-based chemotherapy as primary treatment for intravascular lymphoma. Ann Oncol 15: 1215-1221.

737. Ferry JA, Harris NL, Picker LJ, Weinberg DS, Rosales RK, Tapia J, Richardson EPJr (1988). Intravascular lymphomatosis (malignant angioendotheliomatosis). A B-cell neoplasm expressing surface homing receptors. Mod Pathol 1: 444-452.

738. Fetsch JF, Weiss SW (1991). Observations concerning the pathogenesis of epithelioid hemangioma (angiolymphoid hyperplasia). Mod Pathol 4: 449-455.

739. Feuillard J, Jacob MC, Valensi F, Maynadie M, Gressin R, Chaperot L, Arnoulet C, Brignole-Baudouin F, Drenou B, Duchayne E, Falkenrodt A, Garand R, Homolle E, Husson B, Kuhlein E, Le Calvez G, Sainty D, Sotto MF, Trimoreau F, Bene MC (2002). Clinical and biologic features of CD4(+)CD56(+) malignancies. Blood 99: 1556-1563.

740. Filie AC, Lage JM, Azumi N (1996). Immunoreactivity of S100 protein, alpha-1-antitrypsin, and CD68 in adult and congenital granular cell tumors. Mod Pathol 9: 888-892.

741. Filipowicz E, Adegboyega P, Sanchez RL, Gatalica Z (2002). Expression of CD95 (Fas) in sun-exposed human skin and cutaneous carcinomas. Cancer 94: 814-819.

742. Finch TM, Tan CY (2000). Clear cell acanthoma developing on a psoriatic plaque: further evidence of an inflammatory aetiology? Br J Dermatol 142: 842-844.

743. Fine SW, Li M (2003). Expression of calretinin and the alpha-subunit of inhibin in granular cell tumors. Am J Clin Pathol 119: 259-264.

744. Fink-Puches R, Zenahlik P, Back B, Smolle J, Kerl H, Cerroni L (2002). Primary cutaneous lymphomas: applicability of current classification schemes (European Organization for Research and Treatment of Cancer, World Health Organization) based on clinicopathologic features observed in a large group of patients. Blood 99: 800-805.

745. Finley RKI, Driscoll DL, Blumenson LE, Karakousis CP (1994). Subungual melanoma: an eighteen-year review. Surgery 116: 96-100.

746. Finn MC, Glowacki J, Mulliken JB (1983). Congenital vascular lesions: clinical application of a new classification. J Pediatr Surg 18: 894-900.

747. Firooz A, Komeili A, Dowlati Y (1999). Eruptive melanocytic nevi and cherry angiomas secondary to exposure to sulfur mustard gas. J Am Acad Dermatol 40: 646-647.

748. Fistarol SK, Anliker MD, Itin PH (2002). Cowden disease or multiple hamartoma syndrome—cutaneous clue to internal malignancy. Eur J Dermatol 12: 411-421.

749. Fitzpatrick TB, Johnson RA, Wolff K, Suurmond D, Wolf K (2001). Color Atlas & Synopsis of Clinical Dermatology. In: McGraw-Hill: pp. 272-277.

750. Flanagan BP, Helwig EB (1977). Cutaneous lymphangioma. Arch Dermatol 113: 24-30.

751. Fletcher CD (1988). Giant cell fibroblastoma of soft tissue: a clinicopathological and immunohistochemical study. Histopathology 13: 499-508.

752. Fletcher CD (1989). Solitary circumscribed neuroma of the skin (so-called palisaded, encapsulated neuroma). A clinicopathologic and immunohistochemical study. Am J Surg Pathol 13: 574-580.

753. Fletcher CD, Achu P, Van Noorden S, McKee PH (1987). Infantile myofibromatosis: a light microscopic, histochemical and immunohistochemical study suggesting true smooth muscle differentiation. Histopathology 11: 245-258.

754. Fletcher CD, Beham A, Schmid C (1991). Spindle cell haemangioendothelioma: a clinicopathological and immunohistochemical study indicative of a non-neoplastic lesion. Histopathology 18: 291-301.

755. Fletcher CD, Chan JK, McKee PH (1986). Dermal nerve sheath myxoma: a study of three cases. Histopathology 10: 135-145.

756. Fletcher CDM, Unni K, Mertens F (2002). World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC Press: Lyon.

757. Fletcher V, Sagebiel RW (1981). The combined naevus: Mixed patterns of benign melanocytic lesions must be differentiated from malignant melanomas. In: Pathology of Malignant Melanoma, Ackerman AB, ed., Masson Publishing: Philadelphia , pp. 273-283.

758. Flotte TJ, Bell DA, Sidhu GS, Plair CM (1981). Leiomyosarcoma of the dartos muscle. J Cutan Pathol 8: 69-74.

759. Flotte TJ, Mihm MCJr (1999). Lentigo maligna and malignant melanoma in situ, lentigo maligna type. Hum Pathol 30: 533-536.

760. Fogt F, Vortmeyer AO, Tahan SR (1995). Nucleolar organizer regions (AgNOR) and Ki-67 immunoreactivity in cutaneous melanocytic lesions. Am J Dermatopathol 17: 12-17.

761. Folpe AL, Chand EM, Goldblum JR, Weiss SW (2001). Expression of Fli-1, a nuclear transcription factor, distinguishes vascular neoplasms from potential mimics. Am J Surg Pathol 25: 1061-1066.

762. Folpe AL, Reisenauer AK, Mentzel T, Rutten A, Solomon AR (2003). Proliferating trichilemmal tumors: clinicopathologic evaluation is a guide to biologic behavior. J Cutan Pathol 30: 492-498.

763. Folpe AL, Veikkola T, Valtola R, Weiss SW (2000). Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. Mod Pathol 13: 180-185.

764. Fontaine D, Parkhill W, Greer W, Walsh N (2003). Partial regression of primary cutaneous melanoma: is there an association with sub-clinical sentinel lymph node metastasis? Am J Dermatopathol 25: 371-376.

765. Fordyce JA (1895). Adenocarcinoma of the skin originating in the coil glands. J Cutan Dis 13: 41-50.

766. Fortier-Beaulieu M, Thomine E, Boullie MC, Le Loet X, Lauret P, Hemet J (1993). New electron microscopic findings in a case of multicentric reticulohistiocytosis. Long spacing collagen inclusions. Am J Dermatopathol 15: 587-589.

767. Fortin PT, Freiberg AA, Rees R, Sondak VK, Johnson TM (1995). Malignant melanoma of the foot and ankle. J Bone Joint Surg Am 77: 1396-1403.

768. Foucar E, Mason WV (1986). Angiokeratoma circumscriptum following damage to underlying vasculature. Arch Dermatol 122: 245-246.

769. Fouilloux B, Perrin C, Dutoit M, Cambazard F (2001). Clear cell syringofibroadenoma (of Mascaro) of the nail. Br J Dermatol 144: 625-627.

770. Fox MF, DuToit DL, Warnich L, Retief AE (1984). Regional localization of alpha-galactosidase (GLA) to Xpter——q22, hexosaminidase B (HEXB) to 5q13——qter, and arylsulfatase B (ARSB) to 5pter——q13. Cytogenet Cell Genet 38: 45-49.

771. Fox SB, Cotton DW (1992). Tubular apocrine adenoma and papillary eccrine adenoma. Entities or unity? Am J Dermatopathol 14: 149-154.

772. Franceschi S, Levi F, Randimbison L, La Vecchia C (1996). Site distribution of different types of skin cancer: new aetiological clues. Int J Cancer 67: 24-28.

773. Franchi A, Dini M, Paglierani M, Bondi R (1995). Immunolocalization of extracellular matrix components in mixed tumors of the skin. Am J Dermatopathol 17: 36-41.

774. Franco R, Fernandez-Vazquez A, Rodriguez-Peralto JL, Bellas C, Lopez-Rios F, Saez A, Villuendas R, Navarrete M, Fernandez I, Zarco C, Piris MA (2001). Cutaneous follicular B-cell lymphoma: description of a series of 18 cases. Am J Surg Pathol 25: 875-883.

775. Franke W, Neumann NJ, Ruzicka T, Schulte KW (2000). Plantar malignant melanoma — a challenge for early recognition. Melanoma Res 10: 571-576.

776. Fraser-Andrews E, Ashton R, Russell-Jones R (1999). Pilotropic mycosis fungoides presenting with multiple cysts, comedones and alopecia. Br J Dermatol 140: 141-144.

777. Fraser-Andrews EA, Russell-Jones R, Woolford AJ, Wolstencroft RA, Dean AJ, Whittaker SJ (2001). Diagnostic and prognostic importance of T-cell receptor gene analysis in patients with Sezary syndrome. Cancer 92: 1745-1752.

778. Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LO, Katz SI, Fitzpatrick TB (1999). Fitzpatrick's Dermatology in General Medicine. 5th ed. McGraw-Hill: New York.

779. French LE (1997). Reactive eccrine syringofibroadenoma: an emerging subtype. Dermatology 195: 309-310.

780. French LE, Masgrau E, Chavaz P, Saurat JH (1997). Eccrine syringofibroadenoma in a patient with erosive palmoplantar lichen planus. Dermatology 195: 399-401.

781. Fretzin DF, Sloan JB, Beer K, Fretzin SA (1995). Eccrine syringofibroadenoma. A clear-cell variant. Am J Dermatopathol 17: 591-593.

782. Friedman RJ, Ackerman AB (1981). Difficulties in the histological diagnosis of melanocytic nevi on the vulvae of premenopausal women. In: Pathology of Malignant Melanoma, Ackerman AB, ed., Masson Publishing: New York , pp. 119-128.

783. Friedmann D, Wechsler J, Delfau MH, Esteve E, Farcet JP, de Muret A, Parneix-Spake A, Vaillant L, Revuz J, Bagot M (1995). Primary cutaneous pleomorphic small T-cell lymphoma. A review of 11 cases. The French Study Group on Cutaneous Lymphomas. Arch Dermatol 131: 1009-1015.

784. Friedrich EGJr, Burch K, Bahr JP (1979). The vulvar clinic: an eight-year appraisal. Am J Obstet Gynecol 135: 1036-1040.

785. Frigy AF, Cooper PH (1985). Benign lichenoid keratosis. Am J Clin Pathol 83: 439-443.

786. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan S (2000). International Classification of Diseases for Oncology. 3rd ed. World Health Organization: Geneva.

787. Frizzera G, Moran EM, Rappaport H (1975). Angio-immunoblastic lymphadenopathy. Diagnosis and clinical course. Am J Med 59: 803-818.

788. Frost C, Williams G, Green A (2000). High incidence and regression rates of solar keratoses in a Queensland community. J Invest Dermatol 115: 273-277.

789. Frost CA, Green AC (1994). Epidemiology of solar keratoses. Br J Dermatol 131: 455-464.

790. Frost CA, Green AC, Williams GM (1998). The prevalence and determinants of solar keratoses at a subtropical latitude (Queensland, Australia). Br J Dermatol 139: 1033-1039.

791. Fu W, Cockerell CJ (2003). The actinic (solar) keratosis: a 21st-century perspective. Arch Dermatol 139: 66-70.

792. Fujiwara Y, Abe Y, Kuyama M, Arata J, Yoshino T, Akagi T, Miyoshi K (1990). CD8+ cutaneous T-cell lymphoma with pagetoid epidermotropism and angiocentric and angiodestructive infiltration. Arch Dermatol 126: 801-804.

793. Fukai K, Ishii M, Kobayashi H, Chanoki M, Furukawa M, Nakagawa K, Hamada T, Abe Y, Ooshima A (1990). Primary cutaneous adenoid cystic carcinoma: ultrastructural study and immunolocalization of types I, III, IV, V collagens and laminin. J Cutan Pathol 17: 374-380.

794. Fukamizu H, Oku T, Inoue K, Matsumoto K, Okayama H, Tagami H (1983). Atypical ("pseudosarcomatous") cutaneous histiocytoma. J Cut Pathol 10: 327-333.

795. Fukunaga M (2000). Intravenous tufted angioma. APMIS 108: 287-292.

796. Fukunaga M, Ushigome S, Nikaido T, Ishikawa E, Nakamori K (1995). Spindle cell hemangioendothelioma: an immunohistochemical and flow cytometric study of six cases. Pathol Int 45: 589-595.

797. Fullen DR, Jacobson SN, Valdez R, Novice FM, Lowe L (2003). Granuloma annulare-like infiltrates with concomitant cutaneous involvement by B-cell non-Hodgkin's lymphoma: report of a case. Am J Dermatopathol 25: 57-61.

798. Fullen DR, Lowe L, Su LD (2003). Antibody to S100a6 protein is a sensitive immunohistochemical marker for neurothekeoma. J Cutan Pathol 30: 118-122.

799. Fung DC, Holland EA, Becker TM, Hayward NK, Bressac de Paillerets B, Mann GJ (2003). eMelanoBase: an online locus-specific variant database for familial melanoma. Hum Mutat 21: 2-7.

800. Furue M, Hori Y, Nakabayashi Y (1984). Clear-cell syringoma. Association with diabetes mellitus. Am J Dermatopathol 6: 131-138.

801. Gaasterland DE, Rodrigues MM, Moshell AN (1982). Ocular involvement in xeroderma pigmentosum. Ophthalmology 89: 980-986.

802. Gailani MR, Stahle-Backdahl M, Leffell DJ, Glynn M, Zaphiropoulos PG, Pressman C, Unden AB, Dean M, Brash DE,

Bale AE, Toftgard R (1996). The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas. Nat Genet 14: 78-81.
803. Gallager MS, Miller GV, Grampa G (1959). Primary mucoepidermoid carcinoma of the skin. Report of a case. Cancer 12: 286-288.
804. Galvez-Aranda MV, Herrera-Ceballos E, Sanchez-Sanchez P, Bosch-Garcia RJ, Matilla-Vicente A (2002). Pilomatrix carcinoma with lymph node and pulmonary metastasis: report of a case arising on the knee. Am J Dermatopathol 24: 139-143.
805. Gambichler T, Herde M, Hoffmann K, Altmeyer P, Jansen T (2002). Poor prognosis of acute myeloid leukaemia associated with leukaemia cutis. J Eur Acad Dermatol Venereol 16: 177-178.
806. Gambini C, Rongioletti F, Semino MT, Rebora A (1996). Solitary eccrine syringofibroadenoma (or eccrine syringofibroadenomatous hyperplasia?) and diabetic polyneuropathy. Dermatology 193: 68-69.
807. Garbe C, Stein H, Dienemann D, Orfanos CE (1991). Borrelia burgdorferi-associated cutaneous B cell lymphoma: clinical and immunohistologic characterization of four cases. J Am Acad Dermatol 24: 584-590.
808. Garcia-Doval I, Casas L, Toribio J (1998). Pleomorphic fibroma of the skin, a form of sclerotic fibroma: an immunohistochemical study. Clin Exp Dermatol 23: 22-24.
809. Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, Morris SW, Connors JM, Vose JM, Viswanatha DS, Coldman A, Weisenburger DD (1999). Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 93: 3913-3921.
810. Gasior-Chrzan B (2001). Cellular blue nevus in association with phototherapy. Dermatology 202: 140.
811. Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani M (2005). Childhood cancer survival trends in Europe: a EUROCARE Working Group study. J Clin Oncol 23: 3742-3751.
812. Gauthier Y, Surleve-Bazeiile JE, Texier L (1978). Halo nevi without dermal infiltrate. Arch Dermatol 114: 1718.
813. Gayraud A, Lorenzato M, Sartelet H, Grosshans E, Hopfner C, Mehaut S, Bernard P, Durlach A (2002). [Malignant blue nevus: clinicopathologic study with AgNOR measurement. Seven cases]. Ann Dermatol Venereol 129: 1359-1364.
814. Geelen FA, Vermeer MH, Meijer CJ, Van der Putte SC, Kerkhof E, Kluin PM, Willemze R (1998). bcl-2 protein expression in primary cutaneous large B-cell lymphoma is site-related. J Clin Oncol 16: 2080-2085.
815. Gellis SS, Feingold M (1971). Mucosal neuroma syndrome. Syndrome of bilateral pheochromocytoma, medullary thyroid carcinoma, and multiple neuromas. Am J Dis Child 121: 235-236.
816. Gellrich S, Rutz S, Golembowski S, Jacobs C, von Zimmermann M, Lorenz P, Audring H, Muche M, Sterry W, Jahn S (2001). Primary cutaneous follicle center cell lymphomas and large B cell lymphomas of the leg descend from germinal center cells. A single cell polymerase chain reaction analysis. J Invest Dermatol 117: 1512-1520.
817. George E, Swanson PE, Wick MR (1989). Neuroendocrine differentiation in basal cell carcinoma. An immunohistochemical study. Am J Dermatopathol 11: 131-135.
818. Gerbig AW, Zala L, Hunziker T (2000). Tumorlike eosinophilic granuloma of the skin. Am J Dermatopathol 22: 75-78.
819. Gerdsen R, Lagarde C, Steen A, Steen KH, Uerlich M, Bieber T (1999). Congenital smooth muscle hamartoma of the skin: clinical classification. Acta Derm Venereol 79: 408-409.
820. Gerdsen R, Stockfleth E, Uerlich M, Fartasch M, Steen KH, Bieber T (2000). Papular palmoplantar hyperkeratosis following chronic medical exposure to arsenic: human papillomavirus as a co-factor in the pathogenesis of arsenical keratosis? Acta Derm Venereol 80: 292-293.
821. Germain DP (2001). Co-occurrence and contribution of Fabry disease and Klippel-Trenaunay-Weber syndrome to a patient with atypical skin lesions. Clin Genet 60: 63-67.
822. Ghiorzo P, Ciotti P, Mantelli M, Heouaine A, Queirolo P, Rainero ML, Ferrari C, Santi PL, De Marchi R, Farris A, Ajmar F, Bruzzi P, Bianchi-Scarra G (1999). Characterization of ligurian melanoma families and risk of occurrence of other neoplasia. Int J Cancer 83: 441-448.
823. Giannotti B, Santucci M (1993). Skin-associated lymphoid tissue (SALT)-related B-cell lymphoma (primary cutaneous B-cell lymphoma). A concept and a clinicopathologic entity. Arch Dermatol 129: 353-355.
824. Gianotti F, Caputo R (1985). Histiocytic syndromes: a review. J Am Acad Dermatol 13: 383-404.
825. Gianotti R, Alessi E (1997). Clear cell hidradenoma associated with the folliculosebaceous-apocrine unit. Histologic study of five cases. Am J Dermatopathol 19: 351-357.
826. Giles FJ, O'Brien SM, Keating MJ (1998). Chronic lymphocytic leukemia in (Richter's) transformation. Semin Oncol 25: 117-125.
827. Giles GG, Armstrong BK, Burton RC, Staples MP, Thursfield VJ (1996). Has mortality from melanoma stopped rising in Australia? Analysis of trends between 1931 and 1994. BMJ 312: 1121-1125.
828. Giles GG, Marks R, Foley P (1988). Incidence of non-melanocytic skin cancer treated in Australia. Br Med J (Clin Res Ed) 296: 13-17.
829. Gilliam AC, Lessin SR, Wilson DM, Salhany KE (1997). Folliculotropic mycosis fungoides with large-cell transformation presenting as dissecting cellulitis of the scalp. J Cutan Pathol 24: 169-175.
830. Gimotty PA, Botbyl JD, Soong SJ, Guerry DIV (2005). A population-based validation of the AJCC melanoma staging system. J Clin Oncol in press.
831. Gimotty PA, Guerry D, Ming ME, Elenitsas R, Xu X, Czerniecki B, Spitz F, Schuchter L, Elder D (2004). Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. J Clin Oncol 22: 3668-3676.
832. Gimotty PA, Van Belle P, Elder DE, Murry T, Montone KT, Xu X, Hotz S, Raines S, Ming ME, Wahl PM, Guerry DIV (2005). The biologic and prognostic signifi^cance of dermal Ki-67 expression , mitoses and tumorigenicity in thin invasive cutaneous melanoma. J Clin Oncol (in press).
833. Gioglio L, Porta C, Moroni M, Nastasi G, Gangarossa I (1992). Scrotal angiokeratoma (Fordyce): histopathological and ultrastructural findings. Histol Histopathol 7: 47-55.
834. Girard C, Graham JH, Johnson WC (1974). Arteriovenous hemangioma (arteriovenous shunt). A clinicopathological and histochemical study. J Cutan Pathol 1: 73-87.
835. Giroux L, Delorme F, Bettez P (1975). [Multiple mucosal neuroma syndrome]. Union Med Can 104: 605-610.
836. Gisselbrecht C, Gaulard P, Lepage E, Coiffier B, Briere J, Haioun C, Cazals-Hatem D, Bosly A, Xerri L, Tilly H, Berger F, Bouhabdallah R, Diebold J (1998). Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 92: 76-82.
837. Glass J, Hochberg FH, Miller DC (1993). Intravascular lymphomatosis. A systemic disease with neurologic manifestations. Cancer 71: 3156-3164.
838. Glogau RG (2000). The risk of progression to invasive disease. J Am Acad Dermatol 42: 23-24.
839. Gloor P, Ansari I, Sinard J (1999). Sebaceous carcinoma presenting as a unilateral papillary conjunctivitis. Am J Ophthalmol 127: 458-459.
840. Glusac EJ, McNiff JM (1999). Epithelioid cell histiocytoma: a simulant of vascular and melanocytic neoplasms. Am J Dermatopathol 21: 1-7.
841. Goble RR, Frangoulis MA (1990). Lymphangioma circumscriptum of the eyelids and conjunctiva. Br J Ophthalmol 74: 574-575.
842. Godbolt AM, Sullivan JJ, Weedon D (2001). Keratoacanthoma with perineural invasion: a report of 40 cases. Australas J Dermatol 42: 168-171.
843. Goessling W, McKee PH, Mayer RJ (2002). Merkel cell carcinoma. J Clin Oncol 20: 588-598.
844. Goette DK (1980). Benign lichenoid keratosis. Arch Dermatol 116: 780-782.
845. Goette DK (1988). Hidradenoma papilliferum. J Am Acad Dermatol 19: 133-135.
846. Goette DK, McConnell MA, Fowler VR (1982). Cylindroma and eccrine spiradenoma coexistent in the same lesion. Arch Dermatol 118: 274.
847. Goette DK, Odom RB, Fitzwater JEJr (1982). Diffuse cutaneous reticulohistiocytosis. Arch Dermatol 118: 173-176.
848. Gogusev J, Telvi L, Murakami I, Lepelletier Y, Nezelof C, Stojkoski A, Glorion C, Jaubert F (2005). DOR-1, A novel CD10+ stromal cell line derived from progressive Langerhans cell histiocytosis of bone. Pediatr Blood Cancer 44: 128-137.
849. Goldberg NS, Bauer BS, Kraus H, Crussi FG, Esterly NB (1988). Infantile myofibromatosis: a review of clinicopathology with perspectives on new treatment choices. Pediatr Dermatol 5: 37-46.
850. Goldberg NS, Hebert AA, Esterly NB (1986). Sacral hemangiomas and multiple congenital abnormalities. Arch Dermatol 122: 684-687.
851. Goldblum JR, Hart WR (1997). Vulvar Paget's disease: a clinicopathologic and immunohistochemical study of 19 cases. Am J Surg Pathol 21: 1178-1187.
852. Goldblum JR, Hart WR (1998). Perianal Paget's disease: a histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. Am J Surg Pathol 22: 170-179.
853. Goldblum JR, Reith JD, Weiss SW (2000). Sarcomas arising in dermatofibrosarcoma protuberans: a reappraisal of biologic behavior in eighteen cases treated by wide local excision with extended clinical follow up. Am J Surg Pathol 24: 1125-1130.
854. Golden N, Maliawan S, Mulyadi K (2000). Cellular blue naevus of the scalp with brain invasion. J Clin Neurosci 7: 453-454.
855. Goldenberger D, Zbinden R, Perschil I, Altwegg M (1996). [Detection of Bartonella (Rochalimaea) henselae/B. quintana by polymerase chain reaction (PCR)]. Schweiz Med Wochenschr 126: 207-213.
856. Goldenhersh MA, Savin RC, Barnhill RL, Stenn KS (1988). Malignant blue nevus. Case report and literature review. J Am Acad Dermatol 19: 712-722.
857. Goldman L, Gibson SH, Richfield DF (1981). Thrombotic angiokeratoma circumscriptum simulating melanoma. Arch Dermatol 117: 138-139.
858. Goldman RL (1981). Blue naevus of lymph node capsule: report of a unique case. Histopathology 5: 445-450.
859. Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zametkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WHJr, Tucker MA (1995). Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. N Engl J Med 333: 970-974.
860. Goldstein AM, Martinez M, Tucker MA, Demenais F (2000). Gene-covariate interaction between dysplastic nevi and the CDKN2A gene in American melanoma-prone families. Cancer Epidemiol Biomarkers Prev 9: 889-894.
861. Goldstein DJ, Barr RJ, Santa Cruz DJ (1982). Microcystic adnexal carcinoma: a distinct clinicopathologic entity. Cancer 50: 566-572.
862. Gomez CS, Calonje E, Ferrar DW, Browse NL, Fletcher CD (1995). Lymphangiomatosis of the limbs. Clinicopathologic analysis of a series with a good prognosis. Am J Surg Pathol 19: 125-133.
863. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES (1991). T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. Am J Surg Pathol 15: 17-27.
864. Goodlad JR, Krajewski AS, Batstone PJ, McKay P, White JM, Benton EC, Kavanagh GM, Lucraft HH (2002). Primary cutaneous follicular lymphoma: a clinicopathologic and molecular study of 16 cases in support of a distinct entity. Am J Surg Pathol 26: 733-741.
865. Goovaerts G, Buyssens N (1988). Nevus cell maturation or atrophy? Am J Dermatopathol 10: 20-27.
866. Gordon CJ (1991). Proliferating trichilemmal cyst in an organoid nevus. Cutis 48: 49-52.
867. Gorlin RJ (1987). Nevoid basal-cell carcinoma syndrome. Medicine (Baltimore) 66: 98-113.
868. Gorlin RJ (1995). Nevoid basal cell carcinoma syndrome. Dermatol Clin 13: 113-125.
869. Gorlin RJ, Peterson WCJr (1967). Warty dyskeratoma. A note concerning its occurrence on the oral mucosa. Arch Dermatol 95: 292-293.
870. Gottron H (1932). Papillomatosis cutis

beider Unterschenkel. Dermatol Ztschr 63: 409-410.
871. Goyal JL, Rao VA, Srinivasan R, Agrawal K (1994). Oculocutaneous manifestations in xeroderma pigmentosa. Br J Ophthalmol 78: 295-297.
872. Graefe T, Wollina U, Schulz H, Burgdorf W (2000). Muir-Torre syndrome - treatment with isotretinoin and interferon alpha-2a can prevent tumour development. Dermatology 200: 331-333.
873. Graham GJ, Pragnell IB (1992). SCI/MIP-1 alpha: a potent stem cell inhibitor with potential roles in development. Dev Biol 151: 377-381.
874. Graham J (1996). Malignant deep penetrating nevus. J Cut Pathol 23: 76.
875. Graham JH, Helwig EB (1973). Erythroplasia of Queyrat. A clinicopathologic and histochemical study. Cancer 32: 1396-1414.
876. Grammatico P, Binni F, Eibenschutz L, De Bernardo C, Grammatico B, Rinaldi R, De Simone P, Catricala C (2001). CDKN2A novel mutation in a patient from a melanoma-prone family. Melanoma Res 11: 447-449.
877. Grange F, Bekkenk MW, Wechsler J, Meijer CJ, Cerroni L, Bernengo M, Bosq J, Hedelin G, Fink PR, van Vloten WA, Joly P, Bagot M, Willemze R (2001). Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. J Clin Oncol 19: 3602-3610.
878. Grange F, Hedelin G, Joly P, Beylot-Barry M, D'Incan M, Delaunay M, Vaillant L, Avril MF, Bosq J, Wechsler J, Dalac S, Grosieux C, Franck N, Esteve E, Michel C, Bodemer C, Vergier B, Laroche L, Bagot M (1999). Prognostic factors in primary cutaneous lymphomas other than mycosis fungoides and the Sezary syndrome. The French Study Group on Cutaneous Lymphomas. Blood 93: 3637-3642.
879. Grange F, Petrella T, Beylot-Barry M, Joly P, D'Incan M, Delaunay M, Machet L, Avril MF, Dalac S, Bernard P, Carlotti A, Esteve E, Vergier B, Dechelotte P, Cassagnau E, Courville P, Saiag P, Laroche L, Bagot M, Wechsler J (2004). Bcl-2 protein expression is the strongest independent prognostic factor of survival in primary cutaneous large B-cell lymphomas. Blood 103: 3662-3668.
880. Grant BP, Beard JS, de Castro F, Guiglia MC, Hall BD (1998). Extensive mongolian spots in an infant with Hurler syndrome. Arch Dermatol 134: 108-109.
881. Grant CS, Carney JA, Carpenter PC, van Heerden JA (1986). Primary pigmented nodular adrenocortical disease: diagnosis and management. Surgery 100: 1178-1184.
882. Granter SR, Badizadegan K, Fletcher CD (1998). Myofibromatosis in adults, glomangiopericytoma, and myopericytoma: a spectrum of tumors showing perivascular myoid differentiation. Am J Surg Pathol 22: 513-525.
883. Granter SR, McKee PH, Calonje E, Mihm MCJr, Busam K (2001). Melanoma associated with blue nevus and melanoma mimicking cellular blue nevus: a clinicopathologic study of 10 cases on the spectrum of so-called 'malignant blue nevus'. Am J Surg Pathol 25: 316-323.
884. Granter SR, Seeger K, Calonje E, Busam K, McKee PH (2000). Malignant eccrine spiradenoma (spiradenocarcinoma): a clinicopathologic study of 12 cases. Am J Dermatopathol 22: 97-103.
885. Granter SR, Weilbaecher KN, Quigley C, Fletcher CD, Fisher DE (2001). Microphthalmia transcription factor: not a sensitive or specific marker for the diagnosis of desmoplastic melanoma and spindle cell (non-desmoplastic) melanoma. Am J Dermatopathol 23: 185-189.
886. Grau-Massanes M, Raimer S, Colome-Grimmer M, Yen A, Sanchez RL (1996). Congenital smooth muscle hamartoma presenting as a linear atrophic plaque: case report and review of the literature. Pediatr Dermatol 13: 222-225.
887. Gray HR, Helwig EB (1962). Trichofolliculoma. Arch Dermatol 86: 619-625.
888. Green A, Battistutta D, Hart V, Leslie D, Weedon D (1996). Skin cancer in a subtropical Australian population: incidence and lack of association with occupation. The Nambour Study Group. Am J Epidemiol 144: 1034-1040.
889. Green A, Beardmore G, Hart V, Leslie D, Marks R, Staines D (1988). Skin cancer in a Queensland population. J Am Acad Dermatol 19: 1045-1052.
890. Green A, McCredie M, Mackie R, Giles G, Young P, Morton C, Jackman L, Thursfield V (1999). A case-control study of melanomas of the soles and palms (Australia and Scotland). Cancer Causes Control 10: 21-25.
891. Green A, Trichopoulos D (2002). Skin cancer. In: Textbook of Cancer Epidemiology, Adami HO, Hunter D, Trichopoulos D, eds., Oxford University Press: New York , pp. 281-300.
892. Green FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M (2002). AJCC Cancer Staging Manual. 6th ed. ed. Springer: New York.
893. Green PH, Jabri B (2002). Celiac disease and other precursors to small-bowel malignancy. Gastroenterol Clin North Am 31: 625-639.
894. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M (2002). American Joint Committee on Cancer (AJCC). Cancer Staging Manual. 6th ed. Springer Verlag: Heidelberg - New York.
895. Greene MH (1999). The genetics of hereditary melanoma and nevi. 1998 update. Cancer 86: 2464-2477.
896. Greene MH, Clark WHJr, Tucker MA, Elder DE, Kraemer KH, Fraser MC, Bondi EE, Guerry D, Tuthill R, Hamilton R, LaRossa D (1980). Precursor naevi in cutaneous malignant melanoma: a proposed nomenclature. Lancet 2: 1024.
897. Greene MH, Clark WHJr, Tucker MA, Elder DE, Kraemer KH, Guerry D, Witmer WK, Thompson J, Matozzo I, Fraser MC (1985). Acquired precursors of cutaneous malignant melanoma. The familial dysplastic nevus syndrome. N Engl J Med 312: 91-97.
898. Greif C, Bauer A, Wigger-Alberti W, Elsner P (1999). [Giant condylomata acuminata (Buschke-Lowenstein tumor)]. Dtsch Med Wochenschr 124: 962-964.
899. Grilli R, Escalonilla P, Soriano ML, Farina C, Renedo G, Martin L, Requena L (1998). The so-called striated muscle hamartoma is a hamartoma of cutaneous adnexa and mesenchyme, but not of striated muscle. Acta Derm Venereol 78: 390.
900. Grob JJ, Bonerandi JJ (1998). The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. Arch Dermatol 134: 103-104.
901. Grob JJ, Gouvernet J, Aymar D, Mostaque A, Romano MH, Collet AM, Noe MC, Diconstanzo MP, Bonerandi JJ (1990). Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. Cancer 66: 387-395.
902. Grob JJ, Zarour H, Jacquemier J, Hassoun J, Bonerandi JJ (1991). Extra-anogenital HPV16-related bowenoid papulosis. Genitourin Med 67: 18-20.
903. Groben PA, Harvell JD, White WL (2000). Epithelioid blue nevus: neoplasm Sui generis or variation on a theme? Am J Dermatopathol 22: 473-488.
904. Groben PA, Hitchcock MG, Leshin B, White WL (1999). Apocrine poroma: a distinctive case in a patient with nevoid basal cell carcinoma syndrome. Am J Dermatopathol 21: 31-33.
905. Gronbaek K, Moller PH, Nedergaard T, Thomsen K, Baadsgaard O, Hou-Jensen K, Zeuthen J, Guldberg P, Ralfkiaer E (2000). Primary cutaneous B-cell lymphoma: a clinical, histological, phenotypic and genotypic study of 21 cases. Br J Dermatol 142: 913-923.
906. Gronbaek K, Ralfkiaer E, Kalla J, Skovgaard GL, Guldberg P (2003). Infrequent somatic Fas mutations but no evidence of Bcl10 mutations or t(11;18) in primary cutaneous MALT-type lymphoma. J Pathol 201: 134-140.
907. Gross C, Basten D, Langner C (1999). [Squamous cell carcinoma developing from epidermodysplasia verruciformis]. Pathologe 20: 120-124.
908. Gross G, Hagedorn M, Ikenberg H, Rufli T, Dahlet C, Grosshans E, Gissmann L (1985). Bowenoid papulosis. Presence of human papillomavirus (HPV) structural antigens and of HPV 16-related DNA sequences. Arch Dermatol 121: 858-863.
909. Gross GE, Barrasso R (1997). Human papilloma virus infection. Ullstein Mosby: Berlin/Wiesbaden.
910. Gross RE, Wolbach SB (1943). Sclerosing hemangiomas: their relationship to dermatofibroma, histiocytoma, xanthoma and to certain pigmented lesions of the skin. Am J Pathol 19: 533-551.
911. Grossniklaus HE, Knight SH (1991). Eccrine acrospiroma (clear cell hidradenoma) of the eyelid. Immunohistochemical and ultrastructural features. Ophthalmology 98: 347-352.
912. Gruis NA, van der Velden PA, Sandkuijl LA, Prins DE, Weaver-Feldhaus J, Kamb A, Bergman W, Frants RR (1995). Homozygotes for CDKN2 (p16) germline mutation in Dutch familial melanoma kindreds. Nat Genet 10: 351-353.
913. Gschnait F, Horn F, Lindlbauer R, Sponer D (1980). Eccrine porocarcinoma. J Cutan Pathol 7: 349-353.
914. Gu LH, Ichiki Y, Kitajima Y (2002). Aberrant expression of p16 and RB protein in eccrine porocarcinoma. J Cutan Pathol 29: 473-479.
915. Gualandri L, Cambiaghi S, Ermacora E, Tadini G, Gianotti R, Caputo R (2001). Multiple familial smooth muscle hamartomas. Pediatr Dermatol 18: 17-20.
916. Guillou L, Calonje E, Speight P, Rosai J, Fletcher CD (1999). Hobnail hemangioma: a pseudomalignant vascular lesion with a reappraisal of targetoid hemosiderotic hemangioma. Am J Surg Pathol 23: 97-105.
917. Guillou L, Coindre JM, Bonichon F, Nguyen BB, Terrier P, Collin F, Vilain MO, Mandard AM, Le Doussal V, Leroux A, Jacquemier J, Duplay H, Sastre-Garau X, Costa J (1997). Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 15: 350-362.
918. Guillou L, Fletcher CD (2000). Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma: clinicopathologic analysis of a series. Am J Surg Pathol 24: 1047-1057.
919. Guillou L, Gebhard S, Salmeron M, Coindre JM (2000). Metastasizing fibrous histiocytoma of the skin: a clinicopathologic and immunohistochemical analysis of three cases. Mod Pathol 13: 654-660.
920. Guimera Martin-Neda F, Garcia Bustinduy M, Noda CA, Sanchez GR, Garcia Montelongo R (2004). A rapidly growing eccrine poroma in a pregnant woman. J Am Acad Dermatol 50: 124-126.
921. Guinee DJr, Jaffe E, Kingma D, Fishback N, Wallberg K, Krishnan J, Frizzera G, Travis W, Koss M (1994). Pulmonary lymphomatoid granulomatosis. Evidence for a proliferation of Epstein-Barr virus infected B-lymphocytes with a prominent T-cell component and vasculitis. Am J Surg Pathol 18: 753-764.
922. Guitart J, Kennedy J, Ronan S, Chmiel JS, Hsiegh YC, Variakojis D (2001). Histologic criteria for the diagnosis of mycosis fungoides: proposal for a grading system to standardize pathology reporting. J Cutan Pathol 28: 174-183.
923. Guitart J, Ritter JH, Wick MR (1996). Solitary cutaneous myofibromas in adults: report of six cases and discussion of differential diagnosis. J Cutan Pathol 23: 437-444.
924. Guo HR, Yu HS, Hu H, Monson RR (2001). Arsenic in drinking water and skin cancers: cell-type specificity (Taiwan, ROC). Cancer Causes Control 12: 909-916.
925. Gupta G, Williams RE, MacKie RM (1997). The labial melanotic macule: a review of 79 cases. Br J Dermatol 136: 772-775.
926. Gupta S, Jain VK, Singh U, Gupta S (2000). Multiple eccrine spiradenomas in zosteriform distribution in a child. Pediatr Dermatol 17: 384-386.
927. Gupta S, Khanna NN, Khanna S, Gupta S (1983). Paget's disease of the male breast: a clinicopathologic study and a collective review. J Surg Oncol 22: 151-156.
928. Gupta S, Kumar A, Padmanabhan A, Khanna S (1982). Malignant chondroid syringoma: a clinicopathological study and a collective review. J Surg Oncol 20: 139-144.
929. Gupta S, Radotra BD, Kumar B (2000). Multiple, genital lobular capillary haemangioma (pyogenic granuloma) in a young woman: a diagnostic puzzle. Sex Transm Infect 76: 51-52.
930. Gurbuz Y, Apaydin R, Muezzinoglu B, Buyukbabani N (2002). A current dilemma in histopathology: atypical spitz tumor or Spitzoid melanoma? Pediatr Dermatol 19: 99-102.
931. Gutzmer R, Herbst RA, Mommert S, Kiehl P, Matiaske F, Rutten A, Kapp A, Weiss J (2000). Allelic loss at the neurofibromatosis type 1 (NF1) gene locus is frequent in desmoplastic neurotropic melanoma. Hum Genet 107: 357-361.
932. Gutzmer R, Kaspari M, Herbst RA, Kapp A, Kiehl P (2002). Absence of HHV-8 DNA in hobnail hemangiomas. J Cutan Pathol 29: 154-158.
932A. Gyorki DE, Busam K, Panageas K, Brady MS, Coit DG (2003). Sentinel lymph node biopsy for patients with cutaneous desmoplastic melanoma. Ann Surg Oncol

10: 403-407.
933. Haas N, Audring H, Sterry W (2002). Carcinoma arising in a proliferating trichilemmal cyst expresses fetal and trichilemmal hair phenotype. Am J Dermatopathol 24: 340-344.
934. Haas N, Hamann K, Grabbe J, Algermissen B, Czarnetzki BM (1995). Phenotypic characterization of skin lesions in urticaria pigmentosa and mastocytomas. Arch Dermatol Res 287: 242-248.
935. Haeffner AC, Smoller BR, Zepter K, Wood GS (1995). Differentiation and clonality of lesional lymphocytes in small plaque parapsoriasis. Arch Dermatol 131: 321-324.
936. Hagari Y, Hagari S, Kambe N, Kawaguchi T, Nakamoto S, Mihara M (2002). Acral pseudolymphomatous angiokeratoma of children: immunohistochemical and clonal analyses of the infiltrating cells. J Cutan Pathol 29: 313-318.
937. Haghighi B, Smoller BR, LeBoit PE, Warnke RA, Sander CA, Kohler S (2000). Pagetoid reticulosis (Woringer-Kolopp disease): an immunophenotypic, molecular, and clinicopathologic study. Mod Pathol 13: 502-510.
938. Hagiwara K, Khaskhely NM, Uezato H, Nonaka S (1999). Mast cell "densities" in vascular proliferations: a preliminary study of pyogenic granuloma, portwine stain, cavernous hemangioma, cherry angioma, Kaposi's sarcoma, and malignant hemangioendothelioma. J Dermatol 26: 577-586.
939. Hahn H, Wicking C, Zaphiropoulous PG, Gailani MR, Shanley S, Chidambaram A, Vorechovsky I, Holmberg E, Unden AB, Gillies S, Negus K, Smyth I, Pressman C, Leffell DJ, Gerrard B, Goldstein AM, Dean M, Toftgard R, Chenevix-Trench G, Wainwright B, Bale AE (1996). Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell 85: 841-851.
940. Halder RM, Bridgeman-Shah S (1995). Skin cancer in African Americans. Cancer 75: 667-673.
941. Hall JR, Holder W, Knox JM, Knox JM, Verani R (1987). Familial dyskeratotic comedones. A report of three cases and review of the literature. J Am Acad Dermatol 17: 808-814.
942. Hallermann C, Kaune KM, Siebert R, Vermeer MH, Tensen CP, Willemze R, Gunawan B, Bertsch HP, Neumann C (2004). Chromosomal aberration patterns differ in subtypes of primary cutaneous B cell lymphomas. J Invest Dermatol 122: 1495-1502.
943. Hamblin TJ, Orchard JA, Ibbotson RE, Davis Z, Thomas PW, Stevenson FK, Oscier DG (2002). CD38 expression and immunoglobulin variable region mutations are independent prognostic variables in chronic lymphocytic leukemia, but CD38 expression may vary during the course of the disease. Blood 99: 1023-1029.
944. Hamilton SR, Aaltonen LA (2000). World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. IARC Press: Lyon.
945. Hanby AM, McKee P, Jeffery M, Grayson W, Dublin E, Poulsom R, Maguire B (1998). Primary mucinous carcinomas of the skin express TFF1, TFF3, estrogen receptor, and progesterone receptors. Am J Surg Pathol 22: 1125-1131.
946. Hanke CW, Wolf RL, Hochman SA, O'Brian JJ (1983). Chemosurgical reports: perineural spread of basal-cell carcinoma. J Dermatol Surg Oncol 9: 742-747.
947. Hantschke M, Bastian BC, LeBoit PE (2004). Consumption of the epidermis: a diagnostic criterion for the differential diagnosis of melanoma and Spitz nevus. Am J Surg Pathol 28: 1621-1625.
948. Happle R, Echternacht K, Schotola I (1975). ["Halonevus without the halo"]. Hautarzt 26: 44-46.
949. Haque AK, Myers JL, Hudnall SD, Gelman BB, Lloyd RV, Payne D, Borucki M (1998). Pulmonary lymphomatoid granulomatosis in acquired immunodeficiency syndrome: lesions with Epstein-Barr virus infection. Mod Pathol 11: 347-356.
950. Hara K, Mizuno E, Nitta Y, Ikeya T (1992). Acrosyringeal adenomatosis (eccrine syringofibroadenoma of Mascaro). A case report and review of the literature. Am J Dermatopathol 14: 328-339.
951. Harada H, Hashimoto K, Ko MS (1996). The gene for multiple familial trichoepithelioma maps to chromosome 9p21. J Invest Dermatol 107: 41-43.
952. Harada M, Nakachi S, Tasaka K, Sakashita S, Muta K, Yanagida K, Doi R, Kizaki T, Ohno H (2001). Wide use of skin-lightening soap may cause mercury poisoning in Kenya. Sci Total Environ 269: 183-187.
953. Harada S, Suzuki R, Uehira K, Yatabe Y, Kagami Y, Ogura M, Suzuki H, Oyama A, Kodera Y, Ueda R, Morishima Y, Nakamura S, Seto M (1999). Molecular and immunological dissection of diffuse large B cell lymphoma: CD5+, and CD5- with CD10+ groups may constitute clinically relevant subtypes. Leukemia 13: 1441-1447.
954. Hardisson D, Linares MD, Cuevas-Santos J, Contreras F (2001). Pilomatrix carcinoma: a clinicopathologic study of six cases and review of the literature. Am J Dermatopathol 23: 394-401.
955. Hardy RD, Duvic M, Bleyer WA (1997). The sign of Leser-Trelat. Med Pediatr Oncol 28: 234-237.
956. Harland M, Mistry S, Bishop DT, Bishop JA (2001). A deep intronic mutation in CDKN2A is associated with disease in a subset of melanoma pedigrees. Hum Mol Genet 10: 2679-2686.
957. Harmon CB, Witzig TE, Katzmann JA, Pittelkow MR (1996). Detection of circulating T cells with CD4+CD7- immunophenotype in patients with benign and malignant lymphoproliferative dermatoses. J Am Acad Dermatol 35: 404-410.
958. Harris GR, Shea CR, Horenstein MG, Reed JA, Burchette JLJr, Prieto VG (1999). Desmoplastic (sclerotic) nevus: an underrecognized entity that resembles dermatofibroma and desmoplastic melanoma. Am J Surg Pathol 23: 786-794.
959. Harris MN, Desai R, Chuang TY, Hood AF, Mirowski GW (2000). Lobular capillary hemangiomas: An epidemiologic report, with emphasis on cutaneous lesions. J Am Acad Dermatol 42: 1012-1016.
960. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, Wolf-Peeters C, Falini B, Gatter KC, . (1994). A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 84: 1361-1392.
961. Harrist TJ, Aretz TH, Mihm MC, Jr., Evans GW, Rodriquez FL (1981). Cutaneous malignant mixed tumor. Arch Dermatol 117: 719-724.
962. Harrist TJ, Rigel DS, Day CL, Jr., Sober AJ, Lew RA, Rhodes AR, Harris MN, Kopf AW, Friedman RJ, Golomb FM, . (1984). "Microscopic satellites" are more highly associated with regional lymph node metastases than is primary melanoma thickness. Cancer 53: 2183-2187.
963. Hartmann K, Artuc M, Baldus SE, Zirbes TK, Hermes B, Thiele J, Mekori YA, Henz BM (2003). Expression of Bcl-2 and Bcl-xL in cutaneous and bone marrow lesions of mastocytosis. Am J Pathol 163: 819-826.
964. Hartmann K, Henz BM (2001). Mastocytosis: recent advances in defining the disease. Br J Dermatol 144: 682-695.
965. Hartmann K, Henz BM (2002). Classification of cutaneous mastocytosis: a modified consensus proposal. Leuk Res 26: 483-484.
966. Hartmann K, Hermes B, Rappersberger K, Sepp N, Mekori YA, Henz BM (2003). Evidence for altered mast cell proliferation and apoptosis in cutaneous mastocytosis. Br J Dermatol 149: 554-559.
967. Hartschuh W, Schulz T (1999). Immunohistochemical investigation of the different developmental stages of trichofolliculoma with special reference to the Merkel cell. Am J Dermatopathol 21: 8-15.
968. Harvell J, Vaseghi M, Natkunam Y, Kohler S, Kim Y (2002). Large atypical cells of lymphomatoid papulosis are CD56-negative: a study of 18 cases. J Cutan Pathol 29: 88-92.
969. Harvell JD, Bastian BC, LeBoit PE (2002). Persistent (recurrent) Spitz nevi: a histopathologic, immunohistochemical, and molecular pathologic study of 22 cases. Am J Surg Pathol 26: 654-661.
970. Harvell JD, Kerschmann RL, LeBoit PE (1996). Eccrine or apocrine poroma? Six poromas with divergent adnexal differentiation. Am J Dermatopathol 18: 1-9.
971. Harvell JD, Kilpatrick SE, White WL (1998). Histogenetic relations between giant cell fibroblastoma and dermatofibrosarcoma protuberans. CD34 staining showing the spectrum and a simulator. Am J Dermatopathol 20: 339-345.
972. Harvell JD, Meehan SA, LeBoit PE (1997). Spitz's nevi with halo reaction: a histopathologic study of 17 cases. J Cutan Pathol 24: 611-619.
973. Harvell JD, White WL (1999). Persistent and recurrent blue nevi. Am J Dermatopathol 21: 506-517.
974. Harwood CA, Proby CM (2002). Human papillomaviruses and non-melanoma skin cancer. Curr Opin Infect Dis 15: 101-114.
975. Harwood CA, Spink PJ, Surentheran T, Leigh IM, de Villiers EM, McGregor JM, Proby CM, Breuer J (1999). Degenerate and nested PCR: a highly sensitive and specific method for detection of human papillomavirus infection in cutaneous warts. J Clin Microbiol 37: 3545-3555.
976. Hasan N, Baithun SI (1995). Malignant chondroid syringoma with prominent plasmacytoid/hyaline cells. Patologia 28: 303-305.
977. Hasebe T, Mukai K, Yamaguchi N, Ishihara K, Kaneko A, Takasaki Y, Shimosato Y (1994). Prognostic value of immunohistochemical staining for proliferating cell nuclear antigen, p53, and c-erbB-2 in sebaceous gland carcinoma and sweat gland carcinoma: comparison with histopathological parameter. Mod Pathol 7: 37-43.
978. Hasegawa SL, Davison JM, Rutten A, Fletcher JA, Fletcher CD (1998). Primary cutaneous Ewing's sarcoma: immunophenotypic and molecular cytogenetic evaluation of five cases. Am J Surg Pathol 22: 310-318.
979. Hashimoto K, Bale GF, Hawkins HK, Langston C, Pritzker MS (1986). Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker type). Int J Dermatol 25: 516-523.
980. Hashimoto K, DiBella RJ, Lever WF (1967). Clear cell hidradenoma. Histological, histochemical, and electron microscopic studies. Arch Dermatol 96: 18-38.
981. Hashimoto K, Pritzker MS (1973). Electron microscopic study of reticulohistiocytoma. An unusual case of congenital, self-healing reticulohistiocytosis. Arch Dermatol 107: 263-270.
982. Hashimoto Y, Matsuo S, Iizuka H (1994). A DNA-flow cytometric analysis of trichilemmal carcinoma, proliferating trichilemmal cyst and trichilemmal cyst. Acta Derm Venereol 74: 358-360.
983. Hassanein A, Telang G, Benedetto E, Spielvogel R (1998). Subungual myxoid pleomorphic fibroma. Am J Dermatopathol 20: 502-505.
984. Haupt HM, Stern JB (1995). Pagetoid melanocytosis. Histologic features in benign and malignant lesions. Am J Surg Pathol 19: 792-797.
985. Hausermann P, Khanna N, Buess M, Itin PH, Battegay M, Dirnhofer S, Buechner SA (2004). Cutaneous plasmablastic lymphoma in an HIV-positive male: an unrecognized cutaneous manifestation. Dermatology 208: 287-290.
985A. Hawkins WG, Busam KJ, Ben Porat L, Panageas KS, Coit DG, Gyorki DE, Linehan DC, Brady MS (2005). Desmoplastic melanoma: a pathologically and clinically distinct form of cutaneous melanoma. Ann Surg Oncol 12: 207-213.
986. Haye KR, REBELLO DJ (1961). Angiokeratoma of Mibelli. Acta Derm Venereol 41: 56-60.
987. Hayes M, van der Westhuizen N (1992). Congenital rhabdomyomatous mesenchymal hamartoma. Am J Dermatopathol 14: 64-65.
988. Hayes MM, Matisic JP, Weir L (1996). Apocrine carcinoma of the lip: a case report including immunohistochemical and ultrastructural study, discussion of differential diagnosis, and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82: 193-199.
989. Headington JT (1976). Tumors of the hair follicle. A review. Am J Pathol 85: 479-514.
990. Headington JT (1977). Primary mucinous carcinoma of skin: histochemistry and electron microscopy. Cancer 39: 1055-1063.
991. Headington JT (1980). Tricholemmoma. To be or not to be? Am J Dermatopathol 2: 225-226.
992. Headington JT, Niederhuber JE, Beals TF (1978). Malignant clear cell acrospiroma. Cancer 41: 641-647.
993. Heagerty AH, Rubin A, Robinson TW (1992). Familial tufted angioma. Clin Exp Dermatol 17: 344-345.
994. Heaphy MRJr, Ackerman AB (2000). The nature of solar keratosis: a critical review in historical perspective. J Am Acad Dermatol 43: 138-150.
995. Hebeda CL, Scheffer E, Starink TM (1993). Tufted angioma of late onset. Histopathology 23: 191-193.
996. Heenan PJ, Armstrong BK, English DR, Holman CDJ (1987). Pathological and epidemiological variants of cutaneous malignant melanoma. Pigment Cell 8: 107-146.

997. Heenan PJ, Bogle MS (1993). Eccrine differentiation in basal cell carcinoma. J Invest Dermatol 100: 295S-299S.
998. Heenan PJ, Clay CD (1991). Epidermotropic metastatic melanoma simulating multiple primary melanomas. Am J Dermatopathol 13: 396-402.
999. Heenan PJ, Elder DE, Sobin LH (1996). Histological Typing of Skin Tumours. WHO International Histological Classification of Tumours. 2nd ed. Springer: Berlin.
1000. Heenan PJ, Ghaznawie M (1999). The pathogenesis of local recurrence of melanoma at the primary excision site. Br J Plast Surg 52: 209-213.
1001. Heenan PJ, Ghaznawie M (1999). The pathogenesis of local recurrence of melanoma at the primary excision site. Br J Plast Surg 52: 209-213.
1002. Heim K, Hopfl R, Muller-Holzner E, Bergant A, Dapunt O (2000). Multiple blue nevi of the vagina. A case report. J Reprod Med 45: 42-44.
1003. Heim S, Jin Y, Mandahl N, Biorklund A, Wennerberg J, Jonsson N, Mitelman F (1988). Multiple unrelated clonal chromosome abnormalities in an in situ squamous cell carcinoma of the skin. Cancer Genet Cytogenet 36: 149-153.
1004. Helm KF, Goellner JR, Peters MS (1992). Immunohistochemical stains in extramammary Paget's disease. Am J Dermatopathol 14: 402-407.
1005. Hembury TA, Lee B, Gascoyne RD, Macpherson N, Yang B, House N, Medeiros LJ, Hsi ED (2002). Primary cutaneous diffuse large B-cell lymphoma: a clinicopathologic study of 15 cases. Am J Clin Pathol 117: 574-580.
1006. Hemminki K, Zhang H, Czene K (2003). Familial and attributable risks in cutaneous melanoma: effects of proband and age. J Invest Dermatol 120: 217-223.
1007. Hemminki K, Zhang H, Czene K (2003). Incidence trends and familial risks in invasive and in situ cutaneous melanoma by sun-exposed body sites. Int J Cancer 104: 764-771.
1008. Hendrick SJ, Sanchez RL, Blackwell SJ, Raimer SS (1986). Striated muscle hamartoma: description of two cases. Pediatr Dermatol 3: 153-157.
1009. Hendrickson MR, Ross JC (1981). Neoplasms arising in congenital giant nevi: morphologic study of seven cases and a review of the literature. Am J Surg Pathol 5: 109-135.
1010. Hendrix JDJr, Parlette HL (1996). Micronodular basal cell carcinoma. A deceptive histologic subtype with frequent clinically undetected tumor extension. Arch Dermatol 132: 295-298.
1011. Henry PG, Burnett JW (1978). Angiolymphoid hyperplasia with eosinophilia. Arch Dermatol 114: 1168-1172.
1012. Herling M, Teitell MA, Shen RR, Medeiros LJ, Jones D (2003). TCL1 expression in plasmacytoid dendritic cells (DC2s) and the related CD4+ CD56+ blastic tumors of skin. Blood 101: 5007-5009.
1013. Hernandez-Perez E, Cestoni-Parducci R (1985). Nodular hidradenoma and hidradenocarcinoma. A 10-year review. J Am Acad Dermatol 12: 15-20.
1014. Hernandez FJ (1973). Malignant blue nevus. A light and electron microscopic study. Arch Dermatol 107: 741-744.
1015. Herreid PA, Shapiro PE (1996). Age distribution of Spitz nevus vs malignant melanoma. Arch Dermatol 132: 352-353.
1016. Herrera GA, Turbat-Herrera EA (2003). Current role of electron microscopy in the diagnosis of pigmented tumors. Semin Diagn Pathol 20: 60-71.
1017. Herrero J, Monteagudo C, Ruiz A, Llombart-Bosch A (1998). Malignant proliferating trichilemmal tumours: an histopathological and immunohistochemical study of three cases with DNA ploidy and morphometric evaluation. Histopathology 33: 542-546.
1018. Herzberg J, Klein U (1961). Blue nevus with solitary metastasis to the lung and perirenal. Arch Klin Exp Dermatol 212: 158-172.
1019. Herzog KM, Tubbs RR (1998). Langerhans cell histiocytosis. Adv Anat Pathol 5: 347-358.
1020. Heshmati HM, Hofbauer LC (1997). Multiple endocrine neoplasia type 2: recent progress in diagnosis and management. Eur J Endocrinol 137: 572-578.
1021. Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF (1997). Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol 4: 425-431.
1022. Hewitt C, Lee WC, Evans G, Howell A, Elles RG, Jordan R, Sloan P, Read AP, Thakker N (2002). Germline mutation of ARF in a melanoma kindred. Hum Mol Genet 11: 1273-1279.
1023. Heyd J, Weissberg N, Gottschalk S (1989). Hodgkin's disease of the skin. A case report. Cancer 63: 924-929.
1024. Heymann WR (1993). Extramammary Paget's disease. Clin Dermatol 11: 83-87.
1025. Heymann WR, Yablonsky TM (1991). Congenital appearance of plaque-type blue nevi. Arch Dermatol 127: 587.
1026. Hidano A, Kajima H, Endo Y (1965). Bilateral nevus Ota associated with nevus Ito. A case of pigmentation on the lips. Arch Dermatol 91: 357-359.
1027. Hidano A, Kajima H, Ikeda S, Mizutani H, Miyasato H, Niimura M (1967). Natural history of nevus of Ota. Arch Dermatol 95: 187-195.
1028. Hidano A, Purwoko R, Jitsukawa K (1986). Statistical survey of skin changes in Japanese neonates. Pediatr Dermatol 3: 140-144.
1029. Hieken TJ, Farolan M, Ronan SG, Shilkaitis A, Wild L, Das Gupta TK (1996). Beta3 integrin expression in melanoma predicts subsequent metastasis. J Surg Res 63: 169-173.
1030. Hildenbrand C, Burgdorf WH, Lautenschlager S (2001). Cowden syndrome-diagnostic skin signs. Dermatology 202: 362-366.
1031. Hinds MW, Kolonel LN (1980). Malignant melanoma of the skin in Hawaii, 1960-1977. Cancer 45: 811-817.
1032. Hiraiwa A, Takai K, Fukui Y, Adachi A, Fujii H (1990). Nonregressing lipodystrophia centrifugalis abdominalis with angioblastoma (Nakagawa). Arch Dermatol 126: 206-209.
1033. Hirone T, Eryu Y (1978). Ultrastructure of giant pigment granules in lentigo simplex. Acta Derm Venereol 58: 223-229.
1034. Hisaoka M, Hashimoto H, Iwamasa T (1998). Diagnostic implication of Kaposi's sarcoma-associated herpesvirus with special reference to the distinction between spindle cell hemangioendothelioma and Kaposi's sarcoma. Arch Pathol Lab Med 122: 72-76.
1035. Hisaoka M, Kouho H, Aoki T, Hashimoto H (1995). DNA flow cytometric and immunohistochemical analysis of proliferative activity in spindle cell haemangioendothelioma. Histopathology 27: 451-456.
1036. Hitchcock A, Topham S, Bell J, Gullick W, Elston CW, Ellis IO (1992). Routine diagnosis of mammary Paget's disease. A modern approach. Am J Surg Pathol 16: 58-61.
1037. Hoang MP, Prieto VG, Burchette JL, Shea CR (2001). Recurrent melanocytic nevus: a histologic and immunohistochemical evaluation. J Cutan Pathol 28: 400-406.
1037A. Hoang MT, Eichenfield LF (2000). The rising incidence of melanoma in children and adolescents. Dermatol Nurs 12: 188-3.
1038. Hodak E, Jones RE, Ackerman AB (1993). Solitary keratoacanthoma is a squamous-cell carcinoma: three examples with metastases. Am J Dermatopathol 15: 332-342.
1039. Hodak E, Lapidoth M, Kohn K, David D, Brautbar B, Kfir K, Narinski N, Safirman S, Maron M, Klein K (2001). Mycosis fungoides: HLA class II associations among Ashkenazi and non-Ashkenazi Jewish patients. Br J Dermatol 145: 974-980.
1040. Hoeber I, Spillane AJ, Fisher C, Thomas JM (2001). Accuracy of biopsy techniques for limb and limb girdle soft tissue tumors. Ann Surg Oncol 8: 80-87.
1041. Hoefnagel JJ, Dijkman R, Basso K, Jansen PM, Hallermann C, Willemze R, Tensen CP, Vermeer MH (2005). Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 105: 3671-3678.
1042. Hoefnagel JJ, Vermeer MH, Jansen PM, Fleuren GJ, Meijer CJ, Willemze R (2003). Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance. Br J Dermatol 149: 1183-1191.
1043. Hofmann-Wellenhof R, Blum A, Wolf IH, Piccolo D, Kerl H, Garbe C, Soyer HP (2001). Dermoscopic classification of atypical melanocytic nevi (Clark nevi). Arch Dermatol 137: 1575-1580.
1044. Hofmann UB, Ogilvie P, Mullges W, Brocker EB, Hamm H (1998). Congenital unilateral speckled lentiginous blue nevi with asymmetric spinal muscular atrophy. J Am Acad Dermatol 39: 326-329.
1045. Hofmann WK, de Vos S, Tsukasaki K, Wachsman W, Pinkus GS, Said JW, Koeffler HP (2001). Altered apoptosis pathways in mantle cell lymphoma detected by oligonucleotide microarray. Blood 98: 787-794.
1046. Holden CA, Spittle MF, Jones EW (1987). Angiosarcoma of the face and scalp, prognosis and treatment. Cancer 59: 1046-1057.
1047. Holden CA, Wells RS, MacDonald DM (1982). Cutaneous lymphomatoid granulomatosis. Clin Exp Dermatol 7: 449-454.
1048. Holman CD, Armstrong BK (1984). Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenetic types. J Natl Cancer Inst 73: 75-82.
1049. Holman CD, Armstrong BK, Evans PR, Lumsden GJ, Dallimore KJ, Meehan CJ, Beagley J, Gibson IM (1984). Relationship of solar keratosis and history of skin cancer to objective measures of actinic skin damage. Br J Dermatol 110: 129-138.
1050. Holman CD, Mulroney CD, Armstrong BK (1980). Epidemiology of pre-invasive and invasive malignant melanoma in Western Australia. Int J Cancer 25: 317-323.
1051. Holmdahl K (1955). Cutaneous hemangiomas in premature infants. Acta Paediatr Scan 44: 370-379.
1052. Holme SA, Malinovsky K, Roberts DL (2001). Malignant melanoma in South Wales: changing trends in presentation (1986-98). Clin Exp Dermatol 26: 484-489.
1053. Holmes EJ (1968). Tumors of lower hair sheath. Common histogenesis of certain so-called "sebaceous cysts," acanthomas and "sebaceous carcinomas". Cancer 21: 234-248.
1054. Holst VA, Junkins-Hopkins JM, Elenitsas R (2002). Cutaneous smooth muscle neoplasms: clinical features, histologic findings, and treatment options. J Am Acad Dermatol 46: 477-490.
1055. Honda A, Iwasaki T, Sata T, Kawashima M, Morishima T, Matsukura T (1994). Human papillomavirus type 60-associated plantar wart. Ridged wart. Arch Dermatol 130: 1413-1417.
1056. Honda M, Arai E, Sawada S, Ohta A, Niimura M (1995). Neurofibromatosis 2 and neurilemmomatosis gene are identical. J Invest Dermatol 104: 74-77.
1057. Honigsmann H, Wolff K, Gschnait F, Brenner W, Jaschke E (1980). Keratoses and nonmelanoma skin tumors in long-term photochemotherapy (PUVA). J Am Acad Dermatol 3: 406-414.
1058. Honish A, Grimsrud K, Miedzinski L, Gold E, Cherry RR (1988). Outbreak of Campbell de Morgan spots in a nursing home—Alberta. Can Dis Wkly Rep 14: 211-212.
1059. Hoos A, Berho M, Blumencranz PW, Brady MS (2000). Giant cellular blue nevus of the anterior chest wall mimicking metastatic melanoma to the breast: a case report. J Surg Oncol 74: 278-281.
1060. Hoque SR, Child FJ, Whittaker SJ, Ferreira S, Orchard G, Jenner K, Spittle M, Russell-Jones R (2003). Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathological, immunophenotypic and molecular analysis of six patients. Br J Dermatol 148: 516-525.
1061. Horn MS, Stern JB (1995). Small red nodule on the leg of a young woman. Microvenular hemangioma. Arch Dermatol 131: 483, 486.
1062. Hornick JL, Fletcher CD (2003). Myoepithelial tumors of soft tissue: a clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. Am J Surg Pathol 27: 1183-1196.
1063. Hoshi N, Tsu-ura Y, Watanabe K, Suzuki T, Kasukawa R, Suzuki T (1995). Expression of immunoreactivities to 75 kDa nerve growth factor receptor, trk gene product and phosphotyrosine in granular cell tumors. Pathol Int 45: 748-756.
1064. Houlston RS, Sellick G, Yuille M, Matutes E, Catovsky D (2003). Causation of chronic lymphocytic leukemia—insights from familial disease. Leuk Res 27: 871-876.
1065. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ (1999). Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. Cancer 85: 2278-2290.
1066. Howe JR, Bair JL, Sayed MG, Anderson ME, Mitros FA, Petersen GM, Velculescu VE, Traverso G, Vogelstein B (2001). Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. Nat Genet 28: 184-187.
1067. Howell JN, Greene MH, Corner RC, Maher VM, McCormick JJ (1984). Fibroblasts from patients with hereditary

cutaneous malignant melanoma are abnormally sensitive to the mutagenic effect of simulated sunlight and 4-nitroquinoline 1-oxide. Proc Natl Acad Sci U S A 81: 1179-1183.
1067A. Howrey RP, Lipham WJ, Schultz WH, Buckley EG, Dutton JJ, Klintworth GK, Rosoff PM (1998). Sebaceous gland carcinoma: a subtle second malignancy following radiation therapy in patients with bilateral retinoblastoma. Cancer 83: 767-771.
1068. Höfer W (1956). Lymphadenosa benigna cutis. Arch Klin Exp Dermatol 23-40.
1069. Hsiao GH, Chen JS (1995). Acquired genital smooth-muscle hamartoma. A case report. Am J Dermatopathol 17: 67-70.
1070. Hsu MY, Shih DT, Meier FE, Van Belle P, Hsu JY, Elder DE, Buck CA, Herlyn M (1998). Adenoviral gene transfer of beta3 integrin subunit induces conversion from radial to vertical growth phase in primary human melanoma. Am J Pathol 153: 1435-1442.
1071. Hudson DA, Krige JE, Stubbings H (1998). Plantar melanoma: results of treatment in three population groups. Surgery 124: 877-882.
1072. Huet P, Dandurand M, Pignodel C, Guillot B (1996). Metastasizing eccrine porocarcinoma: report of a case and review of the literature. J Am Acad Dermatol 35: 860-864.
1073. Hugel H (1991). [Plaque-like dermal fibromatosis]. Hautarzt 42: 223-226.
1074. Hugel H, Kutzner H, Rutten A, Biess B (1994). [Differences between plaque-like variants of dermatofibrosarcoma protuberans and plaque-like dermal fibromatosis (dermatomyofibroma)]. Hautarzt 45: 299-303.
1075. Hughes JH, Robinson RA (1995). p53 expression in Bowen's disease and in microinvasive squamous cell carcinoma of the skin. Mod Pathol 8: 526-529.
1076. Huhn D, Burg G, Mempel W (1973). [Specific cutaneous changes in Hodgkin's disease (author's transl)]. Dtsch Med Wochenschr 98: 2469-2472.
1077. Hui JI, Linden KG, Barr RJ (2002). Desmoplastic malignant melanoma of the lip: a report of 6 cases and review of the literature. J Am Acad Dermatol 47: 863-868.
1078. Hui P, Glusac EJ, Sinard JH, Perkins AS (2002). Clonal analysis of cutaneous fibrous histiocytoma (dermatofibroma). J Cutan Pathol 29: 385-389.
1079. Hunt SJ, Kilzer B, Santa Cruz DJ (1990). Desmoplastic trichilemmoma: histologic variant resembling invasive carcinoma. J Cutan Pathol 17: 45-52.
1080. Hunt SJ, Santa Cruz DJ, Barr RJ (1991). Microvenular hemangioma. J Cutan Pathol 18: 235-240.
1081. Hunt SJ, Santa Cruz DJ, Miller CW (1990). Cholesterotic fibrous histiocytoma. Its association with hyperlipoproteinemia. Arch Dermatol 126: 506-508.
1082. Hunt SJ, Shin SS (1995). Solitary reticulohistiocytoma in pregnancy: immunohistochemical and ultrastructural study of a case with unusual immunophenotype. J Cutan Pathol 22: 177-181.
1083. Hurt MA (20042). Book review of Neoplasms With Follicular Differentiation, 2nd edition. Am J Dermatopathol 24: 169-179.
1084. Hurt MA, Santa Cruz DJ (1990). Cutaneous inflammatory pseudotumor. Lesions resembling "inflammatory pseudotumors" or "plasma cell granulomas" of extracutaneous sites. Am J Surg Pathol 14: 764-773.
1085. Hurwitz RM, Monger LE (1995). Solar keratosis: an evolving squamous cell carcinoma. Benign or malignant? Dermatol Surg 21: 184.
1086. Hussain M, Rae J, Gilman A, Kauss P (1998). Lifetime health risk assessment from exposure of recreational users to polycyclic aromatic hydrocarbons. Arch Environ Contam Toxicol 35: 527-531.
1087. Hussein MR, Wood GS (2002). Molecular aspects of melanocytic dysplastic nevi. J Mol Diagn 4: 71-80.
1088. Hussussian CJ, Struewing JP, Goldstein AM, Higgins PA, Ally DS, Sheahan MD, Clark WHJr, Tucker MA, Dracopoli NC (1994). Germline p16 mutations in familial melanoma. Nat Genet 8: 15-21.
1089. Hutchinson J (1884). Lentigo-melanosis. Arch Surg (Lond) 5: 252-256.
1090. Hutchinson J (1992). On tissue dotage. Arch Surg (Lond) 3: 315-322.
1091. Huynh PM, Grant-Kels JM, Grin CM (2005). Childhood melanoma: update and treatment. Int J Dermatol 44: 715-723.
1092. Ichikawa E, Fujisawa Y, Tateishi Y, Imakado S, Otsuka F (2000). Eccrine syringofibroadenoma in a patient with a burn scar ulcer. Br J Dermatol 143: 591-594.
1093. Ichikawa E, Watanabe S, Otsuka F (1995). Immunohistochemical localization of keratins and involucrin in solar keratosis and Bowen's disease. Am J Dermatopathol 17: 151-157.
1094. Idoate MA, Pardo-Mindan FJ, Gonzalez Alamillo C (1992). Fabry's disease without angiokeratomas showing unusual eccrine gland vacuolation. J Pathol 167: 65-68.
1095. Iemoto Y, Kondo Y (1984). Congenital giant cellular blue nevus resulting in dystocia. Arch Dermatol 120: 798-799.
1096. Igawa HH, Ohura T, Sugihara T, Ishikawa T, Kumakiri M (1994). Cleft lip mongolian spot: mongolian spot associated with cleft lip. J Am Acad Dermatol 30: 566-569.
1097. Ikegawa S, Saida T, Takizawa Y, Tokuda Y, Ito T, Fujioka F, Sakaki T, Uchida N, Arase S, Takeda K (1989). Vimentin-positive squamous cell carcinoma arising in a burn scar. A highly malignant neoplasm composed of acantholytic round keratinocytes. Arch Dermatol 125: 1672-1676.
1098. Ikenberg H, Gissmann L, Gross G, Grussendorf-Conen EI, zur Hausen H (1983). Human papillomavirus type-16-related DNA in genital Bowen's disease and in Bowenoid papulosis. Int J Cancer 32: 563-565.
1099. Imai S, Burg G, Braun-Falco O (1986). Mycosis fungoides and Sezary's syndrome show distinct histomorphological features. Dermatologica 173: 131-135.
1100. Imayama S, Murakamai Y, Hashimoto H, Hori Y (1992). Spindle cell hemangioendothelioma exhibits the ultrastructural features of reactive vascular proliferation rather than of angiosarcoma. Am J Clin Pathol 97: 279-287.
1101. Imperial R, Helwig EB (1967). Angiokeratoma. A clinicopathological study. Arch Dermatol 95: 166-175.
1102. Imperial R, Helwig EB (1967). Verrucous hemangioma. A clinicopathologic study of 21 cases. Arch Dermatol 96: 247-253.
1103. Inaloz HS, Patel G, Knight AG (2000). Recurrent intravascular papillary endothelial hyperplasia developing from a pyogenic granuloma. J Eur Acad Dermatol Venereol 15: 156-158.
1104. Infante de German-Ribon R, Singh AD, Arevalo JF, Driebe W, Eskin T (1999). Choroidal melanoma with oculodermal melanocytosis in Hispanic patients. Am J Ophthalmol 128: 251-253.
1105. Innocenzi D, Silipo V, Giombini S, Ruco L, Bosman C, Calvieri S (1998). Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): case report with nodal and diffuse muco-cutaneous involvement. J Cutan Pathol 25: 563-567.
1106. Ioannides G (1966). Hidradenoma papilliferum. Am J Obstet Gynecol 94: 849-853.
1107. Irvine AD, Sweeney L, Corbett JR (1996). Lymphangioma circumscriptum associated with paravesical cystic retroperitoneal lymphangioma. Br J Dermatol 134: 1135-1137.
1108. Ishida-Yamamoto A, Iizuka H, Eady RA (1994). Filaggrin immunoreactive composite keratohyalin granules specific to acrosyringia and related tumours. Acta Derm Venereol 74: 37-42.
1109. Ishihara M, Mehregan DR, Hashimoto K, Yotsumoto S, Toi Y, Pietruk T, Mehregan AH, Mehregan DA (1998). Staining of eccrine and apocrine neoplasms and metastatic adenocarcinoma with IKH-4, a monoclonal antibody specific for the eccrine gland. J Cutan Pathol 25: 100-105.
1110. Ishikawa M, Nakanishi Y, Yamazaki N, Yamamoto A (2001). Malignant eccrine spiradenoma: a case report and review of the literature. Dermatol Surg 27: 67-70.
1111. Ishiko A, Shimizu H, Inamoto N, Nakmura K (1993). Is tubular apocrine adenoma a distinct clinical entity? Am J Dermatopathol 15: 482-487.
1112. Ishimura E, Iwamoto H, Kobashi Y, Yamabe H, Ichijima K (1983). Malignant chondroid syringoma. Report of a case with widespread metastasis and review of pertinent literature. Cancer 52: 1966-1973.
1113. Itin PH, Sarasin A, Pittelkow MR (2001). Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. J Am Acad Dermatol 44: 891-920.
1114. Iwata J, Fletcher CD (2000). Lipidized fibrous histiocytoma: clinicopathologic analysis of 22 cases. Am J Dermatopathol 22: 126-134.
1115. Iyengar V, Golomb CA, Schachner L (1998). Neurilemmomatosis, NF2, and juvenile xanthogranuloma. J Am Acad Dermatol 39: 831-834.
1116. Iyer PV, Leong AS (1992). Poorly differentiated squamous cell carcinomas of the skin can express vimentin. J Cutan Pathol 19: 34-39.
1117. Izquierdo MJ, Pastor MA, Carrasco L, Moreno C, Kutzner H, Sangueza OP, Requena L (2001). Epithelioid blue naevus of the genital mucosa: report of four cases. Br J Dermatol 145: 496-501.
1118. Jackow CM, McHam JB, Friss A, Alvear J, Reveille JR, Duvic M (1996). HLA-DR5 and DQB1*03 class II alleles are associated with cutaneous T-cell lymphoma. J Invest Dermatol 107: 373-376.
1119. Jacobs AH (1957). Strawberry hemangiomas: The natural history of the untreated lesion. California Med 86: 8-10.
1120. Jacobs DM, Sandles LG, LeBoit PE (1986). Sebaceous carcinoma arising from Bowen's disease of the vulva. Arch Dermatol 122: 1191-1193.
1121. Jaffe ES, Harris NL, Stein H, Vardiman J (2001). World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon.
1122. Jaffe ES, Krenacs L, Raffeld M (2003). Classification of cytotoxic T-cell and natural killer cell lymphomas. Semin Hematol 40: 175-184.
1123. Jaffe ES, Muller-Hermelink HK (1999). Relationship between Hodgkin's disease and non-Hodgkin's lymphomas. In: Hodgkin's Disease, Mauch P, Armitage J, Diehl V, Hoppe R, Weiss L, eds., Lippincott Raven: Philadelphia , pp. 181-194.
1124. Jaffe ES, Wilson WH (1997). Lymphomatoid granulomatosis: pathogenesis, pathology and clinical implications. Cancer Surv 30: 233-248.
1125. Jain S, Allen PW (1989). Desmoplastic malignant melanoma and its variants. A study of 45 cases. Am J Surg Pathol 13: 358-373.
1126. Jakobiec FA, Austin P, Iwamoto T, Trokel SL, Marquardt MD, Harrison W (1983). Primary infiltrating signet ring carcinoma of the eyelids. Ophthalmology 90: 291-299.
1127. Jakobiec FA, Ellsworth R, Tannenbaum M (1974). Primary orbital melanoma. Am J Ophthalmol 78: 24-39.
1128. James MP, Wells GC, Whimster IW (1978). Spreading pigmented actinic keratoses. Br J Dermatol 98: 373-379.
1129. James WD, Odom RB, Katzenstein AL (1981). Cutaneous manifestations of lymphomatoid granulomatosis. Report of 44 cases and a review of the literature. Arch Dermatol 117: 196-202.
1130. Jang KA, Ahn SJ, Choi JH, Sung KJ, Moon KC, Koh JK, Shim YH (2001). Polymerase chain reaction (PCR) for human herpesvirus 8 and heteroduplex PCR for clonality assessment in angiolymphoid hyperplasia with eosinophilia and Kimura's disease. J Cutan Pathol 28: 363-367.
1131. Jang KA, Choi JH, Sung KJ, Moon KC, Koh JK (1998). Congenital linear tufted angioma with spontaneous regression. Br J Dermatol 138: 912-913.
1132. Jansen W, Lentner A, Genzel I (1994). Capillary changes in angiokeratoma corporis diffusum Fabry. J Dermatol Sci 7: 68-70.
1133. Jaqueti G, Requena L, Sanchez YE (2000). Trichoblastoma is the most common neoplasm developed in nevus sebaceus of Jadassohn: a clinicopathologic study of a series of 155 cases. Am J Dermatopathol 22: 108-118.
1134. Jaspers NG, Roza-de Jongh EJ, Donselaar IG, Velzen-Tillemans JT, van Hemel JO, Rumke P, van der Kamp AW (1987). Sister chromatid exchanges, hyperdiploidy and chromosomal rearrangements studied in cells from melanoma-prone individuals belonging to families with the dysplastic nevus syndrome. Cancer Genet Cytogenet 24: 33-43.
1135. Jaworski R (1987). Unusual proliferating trichilemmal cyst. Am J Dermatopathol 9: 459-461.
1136. Jemal A, Devesa SS, Fears TR, Hartge P (2000). Cancer surveillance series: changing patterns of cutaneous malignant melanoma mortality rates among whites in the United States. J Natl Cancer Inst 92: 811-818.
1137. Jemal A, Devesa SS, Hartge P, Tucker MA (2001). Recent trends in cutaneous melanoma incidence among whites in the United States. J Natl Cancer Inst 93: 678-683.
1138. Jensen K, Kohler S, Rouse RV (2000).

Cytokeratin staining in Merkel cell carcinoma: an immunohistochemical study of cytokeratins 5/6, 7, 17, and 20. Appl Immunohistochem Mol Morphol 8: 310-315.
1139. Jensen ML, Jensen OM, Michalski W, Nielsen OS, Keller J (1996). Intradermal and subcutaneous leiomyosarcoma: a clinicopathological and immunohistochemical study of 41 cases. J Cutan Pathol 23: 458-463.
1140. Jensen NE, Sabharwal S, Walker AE (1971). Naevoxanthoendothelioma and neurofibromatosis. Br J Dermatol 85: 326-330.
1141. Jessner M, Kanoff NB (1953). Lymphocytic infiltration of the skin. Arch Dermatol 68: 447-449.
1142. Jin F, Devesa SS, Chow WH, Zheng W, Ji BT, Fraumeni JF, Jr., Gao YT (1999). Cancer incidence trends in urban shanghai, 1972-1994: an update. Int J Cancer 83: 435-440.
1143. Jin Y, Jin C, Salemark L, Wennerberg J, Persson B, Jonsson N (2002). Clonal chromosome abnormalities in premalignant lesions of the skin. Cancer Genet Cytogenet 136: 48-52.
1144. Johno M, Ohishi M, Kojo Y, Yamamoto S, Ono T (1992). Cutaneous manifestations of adult T-cell leukemia/lymphoma. Gann Monograph Cancer Res 39: 33-41.
1145. Johnson MD, Jacobs AH (1989). Congenital smooth muscle hamartoma. A report of six cases and a review of the literature. Arch Dermatol 125: 820-822.
1146. Johnson RL, Rothman AL, Xie J, Goodrich LV, Bare JW, Bonifas JM, Quinn AG, Myers RM, Cox DR, Epstein EHJr, Scott MP (1996). Human homolog of patched, a candidate gene for the basal cell nevus syndrome. Science 272: 1668-1671.
1147. Johnson TM, Saluja A, Fader D, Blum D, Cotton J, Wang TS, Lowe L (1999). Isolated extragenital bowenoid papulosis of the neck. J Am Acad Dermatol 41: 867-870.
1148. Johnson WC, Graham JH, Helwig EB (1965). Cutaneous myxoid cysts-A clinicopathological and histochemical study. JAMA 191: 15-20.
1149. Johnson WC, Helwig EB (1966). Adenoid squamous cell carcinoma (adenoacanthoma). A clinicopathologic study of 155 patients. Cancer 19: 1639-1650.
1150. Jonason AS, Kunala S, Price GJ, Restifo RJ, Spinelli HM, Persing JA, Leffell DJ, Tarone RE, Brash DE (1996). Frequent clones of p53-mutated keratinocytes in normal human skin. Proc Natl Acad Sci U S A 93: 14025-14029.
1151. Jones D, Vega F, Sarris AH, Medeiros LJ (2002). CD4-CD8-"Double-negative" cutaneous T-cell lymphomas share common histologic features and an aggressive clinical course. Am J Surg Pathol 26: 225-231.
1152. Jones EW (1966). Proliferating epidermoid cysts. Arch Dermatol 94: 11-19.
1153. Jones EW (1976). Dowling oration 1976. Malignant vascular tumours. Clin Exp Dermatol 1: 287-312.
1154. Jones EW, Bleehen SS (1969). Inflammatory angiomatous nodules with abnormal blood vessels occurring about the ears and scalp (pseudo or atypical pyogenic granuloma). Br J Dermatol 81: 804-816.
1155. Jones EW, Cerio R, Smith NP (1989). Epithelioid cell histiocytoma: a new entity. Br J Dermatol 120: 185-195.
1156. Jones EW, Orkin M (1989). Tufted angioma (angioblastoma). A benign progressive angioma, not to be confused with Kaposi's sarcoma or low-grade angiosarcoma. J Am Acad Dermatol 20: 214-225.
1157. Jones EW, Winkelmann RK, Zachary CB, Reda AM (1990). Benign lymphangioendothelioma. J Am Acad Dermatol 23: 229-235.
1158. Jones REJr (1984). What is the boundary that separates a thick solar keratosis and a thin squamous cell carcinoma? Am J Dermatopathol 6: 301-306.
1159. Jones REJr (1985). Mammary Paget's disease without underlying carcinoma. Am J Dermatopathol 7: 361-365.
1160. Jonjic N, Zamolo G, Stifter S, Fuckar D, Gruber F, Sasso F, Rizzardi C, Melato M (2003). Cytomorphological variations, proliferation and angiogenesis in the prognosis of cutaneous melanoma. Clin Exp Dermatol 28: 310-314.
1161. Joshi PC (1998). Copper(II) as an efficient scavenger of singlet molecular oxygen. Indian J Biochem Biophys 35: 208-215.
1162. Junkins-Hopkins JM (2000). Polypoid malignant acrospiroma: a clinical variant with aggressive behaviour. J Cutan Pathol 27: 561.
1163. Kaddu S, Beham-Schmid C, Zenahlik P, Kerl H, Cerroni L (1999). CD56+ blastic transformation of chronic myeloid leukemia involving the skin. J Cutan Pathol 26: 497-503.
1164. Kaddu S, Beham A, Cerroni L, Humer-Fuchs U, Salmhofer W, Kerl H, Soyer HP (1997). Cutaneous leiomyosarcoma. Am J Surg Pathol 21: 979-987.
1165. Kaddu S, Cerroni L, Pilatti A, Soyer HP, Kerl H (1994). Acral pseudolymphomatous angiokeratoma. A variant of the cutaneous pseudolymphomas. Am J Dermatopathol 16: 130-133.
1166. Kaddu S, Dong H, Mayer G, Kerl H, Cerroni L (2002). Warty dyskeratoma—"follicular dyskeratoma": analysis of clinicopathologic features of a distinctive follicular adnexal neoplasm. J Am Acad Dermatol 47: 423-428.
1167. Kaddu S, Smolle J, Cerroni L, Kerl H (1996). Prognostic evaluation of specific cutaneous infiltrates in B-chronic lymphocytic leukemia. J Cutan Pathol 23: 487-494.
1168. Kaddu S, Smolle J, Zenahlik P, Hofmann-Wellenhof R, Kerl H (2002). Melanoma with benign melanocytic naevus components: reappraisal of clinicopathological features and prognosis. Melanoma Res 12: 271-278.
1169. Kaddu S, Soyer HP, Hodl S, Kerl H (1996). Morphological stages of pilomatricoma. Am J Dermatopathol 18: 333-338.
1170. Kaddu S, Soyer HP, Wolf IH, Kerl H (1997). Proliferating pilomatricoma. A histopathologic simulator of matrical carcinoma. J Cutan Pathol 24: 228-234.
1171. Kaddu S, Soyer HP, Wolf IH, Rieger E, Kerl H (1997). [Reticular lentigo]. Hautarzt 48: 181-185.
1172. Kaddu S, Zenahlik P, Beham-Schmid C, Kerl H, Cerroni L (1999). Specific cutaneous infiltrates in patients with myelogenous leukemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. J Am Acad Dermatol 40: 966-978.
1173. Kadin ME (1985). Common activated helper-T-cell origin for lymphomatoid papulosis, mycosis fungoides, and some types of Hodgkin's disease. Lancet 2: 864-865.
1174. Kadin ME (1990). The spectrum of Ki-1+ cutaneous lymphomas. Curr Probl Dermatol 19: 132-143.
1175. Kadin ME (1993). Lymphomatoid papulosis and associated lymphomas. How are they related? Arch Dermatol 129: 351-353.
1176. Kadin ME, Drews R, Samel A, Gilchrist A, Kocher O (2001). Hodgkin's lymphoma of T-cell type: clonal association with a CD30+ cutaneous lymphoma. Hum Pathol 32: 1269-1272.
1177. Kadin ME, Levi E, Kempf W (2001). Progression of lymphomatoid papulosis to systemic lymphoma is associated with escape from growth inhibition by transforming growth factor-beta and CD30 ligand. Ann N Y Acad Sci 941: 59-68.
1178. Kagen MH, Hirsch RJ, Chu P, McCormack PC, Weinberg JM (2000). Multiple infundibulocystic basal cell carcinomas in association with human immunodeficiency virus. J Cutan Pathol 27: 316-318.
1179. Kahn HJ, Bailey D, Marks A (2002). Monoclonal antibody D2-40, a new marker of lymphatic endothelium, reacts with Kaposi's sarcoma and a subset of angiosarcomas. Mod Pathol 15: 434-440.
1180. Kahn HJ, Fekete E, From L (2001). Tenascin differentiates dermatofibroma from dermatofibrosarcoma protuberans: comparison with CD34 and factor XIIIa. Hum Pathol 32: 50-56.
1181. Kakurai M, Yamada T, Kiyosawa T, Ohtsuki M, Nakagawa H (2003). Giant acquired digital fibrokeratoma. J Am Acad Dermatol 48: S67-S68.
1182. Kakuta M, Tsuboi R, Yamazaki M, Sakuma M, Yoshikata R, Ogawa H (1996). Giant mixed tumor of the face. J Dermatol 23: 369-371.
1183. Kalidas M, Kantarjian H, Talpaz M (2001). Chronic myelogenous leukemia. JAMA 286: 895-898.
1184. Kamb A, Shattuck-Eidens D, Eeles R, Liu Q, Gruis NA, Ding W, Hussey C, Tran T, Miki Y, Weaver-Feldhaus J, McClure M, Aitken JF, Anderson DE, Bergman W, Frants R, Goldgar DE, Green A, MacLennan R, Martin NG, Meyer LJ, Youl P, Zone JJ, Skolnick MH, Cannon-Albright LA (1994). Analysis of the p16 gene (CDKN2) as a candidate for the chromosome 9p melanoma susceptibility locus. Nat Genet 8: 23-26.
1185. Kambic V, Gale N, Radsel Z (1982). Warty dyskeratoma of the vocal cord. First reported case. Arch Otolaryngol 108: 385-387.
1186. Kamino H, Flotte TJ, Misheloff E, Greco MA, Ackerman AB (1979). Eosinophilic globules in Spitz's nevi. New findings and a diagnostic sign. Am J Dermatopathol 1: 319-324.
1187. Kamino H, Jacobson M (1990). Dermatofibroma extending into the subcutaneous tissue. Differential diagnosis from dermatofibrosarcoma protuberans. Am J Surg Pathol 14: 1156-1164.
1188. Kamino H, Lee JY, Berke A (1989). Pleomorphic fibroma of the skin: a benign neoplasm with cytologic atypia. A clinicopathologic study of eight cases. Am J Surg Pathol 13: 107-113.
1189. Kamino H, Reddy VB, Gero M, Greco MA (1992). Dermatomyofibroma. A benign cutaneous, plaque-like proliferation of fibroblasts and myofibroblasts in young adults. J Cutan Pathol 19: 85-93.
1190. Kamino H, Tam ST (1990). Compound blue nevus: a variant of blue nevus with an additional junctional dendritic component. A clinical, histopathologic, and immunohistochemical study of six cases. Arch Dermatol 126: 1330-1333.
1191. Kanavaros P, De Bruin PC, Briere J, Meijer CJ, Gaulard P (1995). Epstein-Barr virus (EBV) in extranodal T-cell non-Hodgkin's lymphomas (T-NHL). Identification of nasal T-NHL as a distinct clinicopathological entity associated with EBV. Leuk Lymphoma 18: 27-34.
1192. Kanavaros P, Ioannidou D, Tzardi M, Datseris G, Katsantonis J, Delidis G, Tosca A (1994). Mycosis fungoides: expression of C-myc p62 p53, bcl-2 and PCNA proteins and absence of association with Epstein-Barr virus. Pathol Res Pract 190: 767-774.
1193. Kanda M, Suzumiya J, Ohshima K, Haraoka S, Nakamura N, Abe M, Tamura K, Kikuchi M (2001). Analysis of the immunoglobulin heavy chain gene variable region of intravascular large B-cell lymphoma. Virchows Arch 439: 540-546.
1194. Kaneishi NK, Cockerell CJ (1998). Histologic differentiation of desmoplastic melanoma from cicatrices. Am J Dermatopathol 20: 128-134.
1195. Kang DS, Chung KY (1999). Common blue naevus with satellite lesions: possible perivascular dissemination resulting in a clinical resemblance to malignant melanoma. Br J Dermatol 141: 922-925.
1196. Kang S, Barnhill RL, Mihm MC, Jr., Sober AJ (1992). Multiple primary cutaneous melanomas. Cancer 70: 1911-1916.
1197. Kang S, Milton GW, Sober AJ (1992). Childhood melanoma. In: Cutaneous Melanoma, Balch CM, Houghton AN, Milton GW, eds., 2nd ed. JB Lippincott: Philadelphia , p. 312.
1198. Kang WH, Chun SI, Lee S (1987). Generalized anhidrosis associated with Fabry's disease. J Am Acad Dermatol 17: 883-887.
1199. Kanitakis J, Brutzkus A, Butnaru AC, Claudy A (2002). Melanotrichoblastoma: immunohistochemical study of a variant of pigmented trichoblastoma. Am J Dermatopathol 24: 498-501.
1199A. Kannengiesser C, Avril MF, Spatz A, Laud K, Lenoir GM, Bressac-de-Paillerets B (2003) CDKN2A as a uveal and cutaneous melanoma susceptibility gene. Genes Chromosomes Cancer 38: 265-268
1200. Kanold J, Vannier JP, Fusade T, Drouin V, Thomine E, Prudent M, Tron P (1994). [Langerhans-cell histiocytosis in twin sisters]. Arch Pediatr 1: 49-53.
1201. Kanter L, Blegen H, Wejde J, Lagerlof B, Larsson O (1995). Utility of a proliferation marker in distinguishing between benign naevocellular naevi and naevocellular naevus-like lesions with malignant properties. Melanoma Res 5: 345-350.
1202. Kanzler MH, Mraz-Gernhard S (2001). Primary cutaneous malignant melanoma and its precursor lesions: diagnostic and therapeutic overview. J Am Acad Dermatol 45: 260-276.
1203. Kao GF (1986). Carcinoma arising in Bowen's disease. Arch Dermatol 122: 1124-1126.
1204. Kao GF, Farmer EV (1999). Benign tumors and carcinoma in situ of the skin. In: Pathology of the Skin, Farmer ER, Hood AF, eds., 2nd ed. McGraw Hill Professional: New York , pp. 931-968.
1205. Kao GF, Helwig EB, Graham JH (1987). Aggressive digital papillary adenoma and adenocarcinoma. A clinicopathological study of 57 patients, with histochemical, immunopathological, and ultrastructural observations. J Cutan Pathol 14: 129-146.
1206. Kao GF, Laskin WB, Weiss SW

(1990). Eccrine spiradenoma occurring in infancy mimicking mesenchymal tumor. J Cutan Pathol 17: 214-219.
1207. Kaplan EN (1974). The risk of malignancy in large congenital nevi. Plast Reconstr Surg 53: 421-428.
1208. Karagas MR (1994). Occurrence of cutaneous basal cell and squamous cell malignancies among those with a prior history of skin cancer. The Skin Cancer Prevention Study Group. J Invest Dermatol 102: 10S-13S.
1209. Karenko L, Hyytinen E, Sarna S, Ranki A (1997). Chromosomal abnormalities in cutaneous T-cell lymphoma and in its premalignant conditions as detected by G-banding and interphase cytogenetic methods. J Invest Dermatol 108: 22-29.
1210. Karenko L, Kahkonen M, Hyytinen ER, Lindlof M, Ranki A (1999). Notable losses at specific regions of chromosomes 10q and 13q in the Sezary syndrome detected by comparative genomic hybridization. J Invest Dermatol 112: 392-395.
1211. Kari L, Loboda A, Nebozhyn M, Rook AH, Vonderheid EC, Nichols C, Virok D, Chang C, Horng WH, Johnston J, Wysocka M, Showe MK, Showe LC (2003). Classification and prediction of survival in patients with the leukemic phase of cutaneous T cell lymphoma. J Exp Med 197: 1477-1488.
1212. Karimipour DJ, Johnson TM, Kang S, Wang TS, Lowe L (1997). Mucinous carcinoma of the skin. J Am Acad Dermatol 36: 323-326.
1213. Kashani-Sabet M, Sagebiel RW, Ferreira CM, Nosrati M, Miller JR, III (2001). Vascular involvement in the prognosis of primary cutaneous melanoma. Arch Dermatol 137: 1169-1173.
1214. Kashima M, Adachi M, Honda M, Niimura M, Nakabayashi Y (1994). A case of peculiar plantar warts. Human papillomavirus type 60 infection. Arch Dermatol 130: 1418-1420.
1215. Katane M, Akiyama M, Ohnishi T, Watanabe S, Matsuo I (2003). Carcinomatous transformation of eccrine syringofibroadenoma. J Cutan Pathol 30: 211-214.
1216. Kato N, Onozuka T, Yasukawa K, Kimura K, Sasaki K (2000). Penile hybrid verrucous-squamous carcinoma associated with a superficial inguinal lymph node metastasis. Am J Dermatopathol 22: 339-343.
1217. Kato N, Ueno H (1992). Eccrine hidrocystoma: two cases of Robinson and Smith types. J Dermatol 19: 493-497.
1218. Kato N, Ueno H (1993). Infundibulocystic basal cell carcinoma. Am J Dermatopathol 15: 265-267.
1219. Kato N, Yasukawa K, Onozuka T (1998). Primary cutaneous adenoid cystic carcinoma with lymph node metastasis. Am J Dermatopathol 20: 571-577.
1220. Kato T, Kumasaka N, Suetake T, Tabata N, Tagami H (1996). Clinicopathological study of acral melanoma in situ in 44 Japanese patients. Dermatology 193: 192-197.
1221. Kato T, Suetake T, Sugiyama Y, Tabata N, Tagami H (1996). Epidemiology and prognosis of subungual melanoma in 34 Japanese patients. Br J Dermatol 134: 383-387.
1222. Katsourakis M, Kapranos N, Papanicolaou SI, Patrikiou A (1996). Nerve-sheath myxoma (neurothekeoma) of the oral cavity: a case report and review of the literature. J Oral Maxillofac Surg 54: 904-906.
1223. Katzenstein AL, Carrington CB, Liebow AA (1979). Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. Cancer 43: 360-373.
1224. Katzenstein AL, Peiper SC (1990). Detection of Epstein-Barr virus genomes in lymphomatoid granulomatosis: analysis of 29 cases by the polymerase chain reaction technique. Mod Pathol 3: 435-441.
1225. Kaudewitz P, Burg G (1991). Lymphomatoid papulosis and Ki-1 (CD30)-positive cutaneous large cell lymphomas. Semin Diagn Pathol 8: 117-124.
1226. Kaudewitz P, Burg G, Stein H (1990). Ki-1 (CD30) positive cutaneous anaplastic large cell lymphomas. Curr Probl Dermatol 19: 150-156.
1227. Kaudewitz P, Burg G, Stein H, Klepzig K, Mason DY, Braun-Falco O (1985). Monoclonal antibody patterns in lymphomatoid papulosis. Dermatol Clin 3: 749-757.
1228. Kaudewitz P, Stein H, Dallenbach F, Eckert F, Bieber K, Burg G, Braun-Falco O (1989). Primary and secondary cutaneous Ki-1+ (CD30+) anaplastic large cell lymphomas. Morphologic, immunohistologic, and clinical-characteristics. Am J Pathol 135: 359-367.
1229. KAUFFMAN SL, Stout AP (1965). CONGENITAL MESENCHYMAL TUMORS. Cancer 18: 460-476.
1230. Kaufman DK, Kimmel DW, Parisi JE, Michels VV (1993). A familial syndrome with cutaneous malignant melanoma and cerebral astrocytoma. Neurology 43: 1728-1731.
1231. Kavanagh GM, Rigby HS, Archer CB (1993). Giant primary mucinous sweat gland carcinoma of the scalp. Clin Exp Dermatol 18: 375-377.
1232. Kawabata Y, Tamaki K (1998). Distinctive dermatoscopic features of acral lentiginous melanoma in situ from plantar melanocytic nevi and their histopathologic correlation. J Cutan Med Surg 2: 199-204.
1233. Kayaselcuk F, Ceken I, Bircan S, Tuncer I (2002). Bacillary angiomatosis of the scalp in a human immunodeficiency virus-negative patient. J Eur Acad Dermatol Venereol 16: 612-614.
1234. Kazakov DV, Burg G, Kempf W (2004). Clinicopathological spectrum of mycosis fungoides. J Eur Acad Dermatol Venereol 18: 397-415.
1235. Kazakov DV, Kutzner H, Rutten A, Mukensnabl P, Michal M (2005). Carcinoid-like pattern in sebaceous neoplasms: another distinctive, previously unrecognized pattern in extraocular sebaceous carcinoma and sebaceoma. Am J Dermatopathol 27: 195-203.
1236. Kazakov DV, Mentzel T, Burg G, Dummer R, Kempf W (2003). Blastic natural killer-cell lymphoma of the skin associated with myelodysplastic syndrome or myelogenous leukaemia: a coincidence or more? Br J Dermatol 149: 869-876.
1237. Keasbey LE, Hadley CG (1954). Clear-cell hidradenoma. Report of three cases with widespread metastases. Cancer 7: 934-952.
1238. Kefford R, Bishop JN, Tucker M, Bressac de Paillerets B, Bianchi-Scarra G, Bergman W, Goldstein A, Puig S, Mackie R, Elder D, Hansson J, Hayward N, Hogg D, Olsson H (2002). Genetic testing for melanoma. Lancet Oncol 3: 653-654.
1239. Kefford RF, Newton Bishop JA, Bergman W, Tucker MA (1999). Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. J Clin Oncol 17: 3245-3251.
1240. Kelfkens G, Bregman A, de Gruijl FR, van der Leun JC, Piquet A, van Oijen T, Gieskes WWC, van Loveren H, Velders GJM, Martens P, Slaper H (2002). Ozone layer - climate change interactions: Influence on UV levels and UV related effects. RIVM: Bilthoven.
1241. Kempf W, Haeffner AC, Zepter K, Sander CA, Flaig MJ, Mueller B, Panizzon RG, Hardmeier T, Adams V, Burg G (2002). Angiolymphoid hyperplasia with eosinophilia: evidence for a T-cell lymphoproliferative origin. Hum Pathol 33: 1023-1029.
1242. Kempf W, Kadin ME, Dvorak AM, Lord CC, Burg G, Letvin NL, Koralnik IJ (2003). Endogenous retroviral elements, but not exogenous retroviruses, are detected in CD30-positive lymphoproliferative disorders of the skin. Carcinogenesis 24: 301-306.
1243. Kempf W, Levi E, Kamarashev J, Kutzner H, Pfeifer W, Petrogiannis-Haliotis T, Burg G, Kadin ME (2002). Fascin expression in CD30-positive cutaneous lymphoproliferative disorders. J Cutan Pathol 29: 295-300.
1244. Kennedy RH, Waller RR, Carney JA (1987). Ocular pigmented spots and eyelid myxomas. Am J Ophthalmol 104: 533-538.
1245. Kerl H, Smolle J, Hodl S, Soyer HP (1989). [Congenital pseudomelanoma]. Z Hautkr 64: 564, 567-564, 568.
1246. Kerl H, Trau H, Ackerman AB (1984). Differentiation of melanocytic nevi from malignant melanomas in palms, soles, and nail beds solely by signs in the cornified layer of the epidermis. Am J Dermatopathol 6 Suppl: 159-160.
1247. Kerr DA (21951). Granuloma pyogenicum. Oral Surg Oral Med Oral Pathol 4: 158-176.
1248. Kerschmann RL, Berger TG, Weiss LM, Herndier BG, Abrahms KM, Heon V, Schulze K, Kaplan LD, Resnik SD, LeBoit PE (1995). Cutaneous presentations of lymphoma in human immunodeficiency virus disease. Predominance of T cell lineage. Arch Dermatol 131: 1281-1288.
1249. Kersting DW (2003). Clear cell hidradenoma and hidradenoarcinoma. Arch Dermatol 87: 323-333.
1250. Kersting DW, Helwig EB (1956). Eccrine spiradenoma. Arch Dermatol 73: 199-227.
1251. Kesmodel SB, Karakousis GC, Botbyl JD, Canter RJ, Lewis RT, Wahl PM, Terhune KP, Alavi A, Elder DE, Ming ME, Guerry D, Gimotty PA, Fraker DL, Czerniecki BJ, Spitz FR (2005). Mitotic rate as a predictor of sentinel lymph node positivity in patients with thin melanomas. Ann Surg Oncol 12: 449-458.
1252. Ketron LW, Goodman MH (1931). Multiple lesions of the skin apparently of epithelial origin resembling clinically mycosis fungoides. Arch Dermatol 24: 758-777.
1253. Khalidi HS, Brynes RK, Browne P, Koo CH, Battifora H, Medeiros LJ (1998). Intravascular large B-cell lymphoma: the CD5 antigen is expressed by a subset of cases. Mod Pathol 11: 983-988.
1254. Khanna M, Fortier-Riberdy G, Smoller B, Dinehart S (2002). Reporting tumor thickness for cutaneous squamous cell carcinoma. J Cutan Pathol 29: 321-323.
1255. Khlat M, Vail A, Parkin M, Green A (1992). Mortality from melanoma in migrants to Australia: variation by age at arrival and duration of stay. Am J Epidemiol 135: 1103-1113.
1256. Khoo SK, Bradley M, Wong FK, Hedblad MA, Nordenskjold M, Teh BT (2001). Birt-Hogg-Dube syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12-q11.2. Oncogene 20: 5239-5242.
1257. Khoury H, Lestou VS, Gascoyne RD, Bruyere H, Li CH, Nantel SH, Dalal BI, Naiman SC, Horsman DE (2003). Multicolor karyotyping and clinicopathological analysis of three intravascular lymphoma cases. Mod Pathol 16: 716-724.
1258. Khoury JD, Medeiros LJ, Manning JT, Sulak LE, Bueso-Ramos C, Jones D (2002). CD56(+) TdT(+) blastic natural killer cell tumor of the skin: a primitive systemic malignancy related to myelomonocytic leukemia. Cancer 94: 2401-2408.
1259. Kibar Z, Der Kaloustian V, Brais B, Hani V, Fraser FC, Rouleau GA (1996). The gene responsible for Clouston hidrotic ectodermal dysplasia maps to the pericentromeric region of chromosome 13q. Hum Mol Genet 5: 543-547.
1260. Kikuchi I (1980). Mongolian spots remaining in schoolchildren a statistical survey in Central Okinawa. J Dermatol 7: 213-216.
1261. Kikuchi I, Inoue S (1980). Natural history of the Mongolian spot. J Dermatol 7: 449-450.
1262. Kilkenny M, Merlin K, Young R, Marks R (1998). The prevalence of common skin conditions in Australian school students: 1. Common, plane and plantar viral warts. Br J Dermatol 138: 840-845.
1263. Kim BK, Surti U, Pandya AG, Swerdlow SH (2003). Primary and secondary cutaneous diffuse large B-cell lymphomas: a multiparameter analysis of 25 cases including fluorescence in situ hybridization for t(14;18) translocation. Am J Surg Pathol 27: 356-364.
1264. Kim KJ, Lee MW, Choi JH, Sung KJ, Moon KC, Koh JK (2001). A case of congenital tufted angioma mimicking cavernous hemangioma. J Dermatol 28: 514-515.
1265. Kim MY, Park HJ, Baek SC, Byun DG, Houh D (2002). Mutations of the p53 and PTCH gene in basal cell carcinomas: UV mutation signature and strand bias. J Dermatol Sci 29: 1-9.
1266. Kim S, Elenitsas R, James WD (2002). Diffuse dermal angiomatosis: a variant of reactive angioendotheliomatosis associated with peripheral vascular atherosclerosis. Arch Dermatol 138: 456-458.
1267. Kim TH, Choi EH, Ahn SK, Lee SH (1999). Vascular tumors arising in port-wine stains: two cases of pyogenic granuloma and a case of acquired tufted angioma. J Dermatol 26: 813-816.
1268. Kim YC, Lee MG, Choe SW, Lee MC, Chung HG, Cho SH (2003). Acral lentiginous melanoma: an immunohistochemical study of 20 cases. Int J Dermatol 42: 123-129.
1269. Kim YC, Vandersteen DP, Chung YJ, Myong NH (2001). Signet ring cell basal cell carcinoma: a basal cell carcinoma with myoepithelial differentiation. Am J Dermatopathol 23: 525-529.
1270. Kim YD, Lee EJ, Song MH, Suhr KB, Lee JH, Park JK (2002). Multiple eccrine hidrocystomas associated with Graves' disease. Int J Dermatol 41: 295-297.
1271. Kim YH, Chow S, Varghese A, Hoppe RT (1999). Clinical characteristics and long-term outcome of patients with generalized patch and/or plaque (T2) mycosis fun-

goides. Arch Dermatol 135: 26-32.
1272. Kim YK, Kim HJ, Lee KG (1992). Acquired tufted angioma associated with pregnancy. Clin Exp Dermatol 17: 458-459.
1273. Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ, Bale AE, Bale SJ (1997). Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 69: 299-308.
1274. Kimura S, Hirai A, Harada R, Nagashima M (1978). So-called multicentric pigmented Bowen's disease. Report of a case and a possible etiologic role of human papilloma virus. Dermatologica 157: 229-237.
1275. Kimura T, Miyazawa H, Aoyagi T, Ackerman AB (1991). Folliculosebaceous cystic hamartoma. A distinctive malformation of the skin. Am J Dermatopathol 13: 213-220.
1276. Kimyai-Asadi A, Nousari HC, Ketabchi N, Henneberry JM, Costarangos C (1999). Diffuse dermal angiomatosis: a variant of reactive angioendotheliomatosis associated with atherosclerosis. J Am Acad Dermatol 40: 257-259.
1277. Kindblom LG, Stenman G, Angervall L (1991). Morphological and cytogenetic studies of angiosarcoma in Stewart-Treves syndrome. Virchows Arch A Pathol Anat Histopathol 419: 439-445.
1278. Kingdon EJ, Phillips BB, Jarmulowicz M, Powis SH, Vanderpump MP (2001). Glomeruloid haemangioma and POEMS syndrome. Nephrol Dial Transplant 16: 2105-2107.
1279. Kint A, Baran R (1988). Histopathologic study of Koenen tumors. Are they different from acquired digital fibrokeratoma? J Am Acad Dermatol 18: 369-372.
1280. Kint A, Baran R, De Keyser H (1985). Acquired (digital) fibrokeratoma. J Am Acad Dermatol 12: 816-821.
1281. Kirkham N (2000). Optimal handling and criteria for melanoma diagnosis. Histopathology 37: 467-469.
1282. Kirnbauer R, Lenz P, Okun MM (2003). Human papillomaviruses. In: Dermatology, Bolognia JL, Jorizzo JL, eds., Mosby Publishers: pp. 1217-1233.
1283. Kirova YM, Piedbois Y, Le Bourgeois JP (1999). Radiotherapy in the management of cutaneous B-cell lymphoma. Our experience in 25 cases. Radiother Oncol 52: 15-18.
1284. Kirschner LS, Sandrini F, Monbo J, Lin JP, Carney JA, Stratakis CA (2000). Genetic heterogeneity and spectrum of mutations of the PRKAR1A gene in patients with the carney complex. Hum Mol Genet 9: 3037-3046.
1285. Kishimoto S, Takenaka H, Shibagaki R, Noda Y, Yamamoto M, Yasuno H (2000). Glomeruloid hemangioma in POEMS syndrome shows two different immunophenotypic endothelial cells. J Cutan Pathol 27: 87-92.
1286. Kittler H, Binder M (2001). Risks and benefits of sequential imaging of melanocytic skin lesions in patients with multiple atypical nevi. Arch Dermatol 137: 1590-1595.
1287. Kleihues P, Cavenee WK (2000). World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Nervous System. IARC Press: Lyon.
1288. Klein U, Tu Y, Stolovitzky GA, Mattioli M, Cattoretti G, Husson H, Freedman A, Inghirami G, Cro L, Baldini L, Neri A, Califano A, Dalla-Favera R (2001). Gene expression profiling of B cell chronic lymphocytic leukemia reveals a homogeneous phenotype related to memory B cells. J Exp Med 194: 1625-1638.
1289. Kleinegger CL, Hammond HL, Vincent SD, Finkelstein MW (2000). Acquired tufted angioma: a unique vascular lesion not previously reported in the oral mucosa. Br J Dermatol 142: 794-799.
1290. Knable A, Treadwell P (1996). Pigmented plaque with hypertrichosis on the scalp of an infant. Pediatr Dermatol 13: 431-433.
1291. Knipper JE, Hud JA, Cockerell CJ (1993). Disseminated epidermolytic acanthoma. Am J Dermatopathol 15: 70-72.
1292. Knoell KA, Nelson KC, Patterson JW (1998). Familial multiple blue nevi. J Am Acad Dermatol 39: 322-325.
1293. Knudsen H, Gronbaek K, thor SP, Gisselo C, Johansen P, Timshel S, Bergmann OJ, Hansen NE, Ralfkiaer E (2002). A case of lymphoblastoid natural killer (NK)-cell lymphoma: association with the NK-cell receptor complex CD94/NKG2 and TP53 intragenic deletion. Br J Dermatol 146: 148-153.
1294. Koch MB, Shih IM, Weiss SW, Folpe AL (2001). Microphthalmia transcription factor and melanoma cell adhesion molecule expression distinguish desmoplastic/spindle cell melanoma from morphologic mimics. Am J Surg Pathol 25: 58-64.
1295. Koh D, Wang H, Lee J, Chia KS, Lee HP, Goh CL (2003). Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968-97. Br J Dermatol 148: 1161-1166.
1296. Koh HK, Michalik E, Sober AJ, Lew RA, Day CL, Clark W, Mihm MC, Kopf AW, Blois MS, Fitzpatrick TB (1984). Lentigo maligna melanoma has no better prognosis than other types of melanoma. J Clin Oncol 2: 994-1001.
1297. Kohler S, Rouse RV, Smoller BR (1998). The differential diagnosis of pagetoid cells in the epidermis. Mod Pathol 11: 79-92.
1298. Kohler S, Smoller BR (1996). Gross cystic disease fluid protein-15 reactivity in extramammary Paget's disease with and without associated internal malignancy. Am J Dermatopathol 18: 118-123.
1299. Koizumi H, Kodama K, Tsuji Y, Matsumura T, Nabeshima M, Ohkawara A (1999). CD34-positive dendritic cells are an intrinsic part of smooth muscle hamartoma. Br J Dermatol 140: 172-174.
1300. Koizumi K, Sawada K, Nishio M, Katagiri E, Fukae J, Fukada Y, Tarumi T, Notoya A, Shimizu T, Abe R, Kobayashi H, Koike T (1997). Effective high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation in a patient with the aggressive form of cytophagic histiocytic panniculitis. Bone Marrow Transplant 20: 171-173.
1301. Kojima M, Sakuma H, Mori N (1983). Histopathological features of plasma cell dyscrasia with polyneuropathy and endocrine disturbances, with special reference to germinal center lesions. Jpn J Clin Oncol 13: 557-575.
1302. Kolde G, Brocker EB (1986). Multiple skin tumors of indeterminate cells in an adult. J Am Acad Dermatol 15: 591-597.
1303. Kolmel KF, Grange JM, Krone B, Mastrangelo G, Rossi CR, Henz BM, Seebacher C, Botev IN, Niin M, Lambert D, Shafir R, Kokoschka EM, Kleeberg UR, Gefeller O, Pfahlberg A (2005). Prior immunisation of patients with malignant melanoma with vaccinia or BCG is associated with better survival. An European Organization for Research and Treatment of Cancer cohort study on 542 patients. Eur J Cancer 41: 118-125.
1304. Komine M, Hattori N, Tamaki K (2000). Eccrine syringofibroadenoma (Mascaro): an immunohistochemical study. Am J Dermatopathol 22: 171-175.
1305. Kopf AW, Bart RS (1977). Tumor conference No. 11: multiple bowenoid papules of the penis: a new entity? J Dermatol Surg Oncol 3: 265-269.
1306. Kopf AW, Bart RS, Hennessey P (1979). Congenital nevocytic nevi and malignant melanomas. J Am Acad Dermatol 1: 123-130.
1307. Kopf AW, Weidman AI (1962). Nevus of Ota. Arch Dermatol 85: 195-208.
1308. Korabiowska M, Brinck U, Middel P, Brinkmann U, Berger H, Radzun HJ, Ruschenburg I, Droese M (2000). Proliferative activity in the progression of pigmented skin lesions, diagnostic and prognostic significance. Anticancer Res 20: 1781-1785.
1309. Kore-eda S, Tanaka T, Moriwaki S, Nishigori C, Imamura S (1992). A case of xeroderma pigmentosum group A diagnosed with a polymerase chain reaction (PCR) technique. Usefulness of PCR in the detection of point mutation in a patient with a hereditary disease. Arch Dermatol 128: 971-974.
1310. Kornberg R, Ackerman AB (1975). Pseudomelanoma: recurrent melanocytic nevus following partial surgical removal. Arch Dermatol 111: 1588-1590.
1311. Korsmeyer SJ, Arnold A, Bakhshi A, Ravetch JV, Siebenlist U, Hieter PA, Sharrow SO, LeBien TW, Kersey JH, Poplack DG, Leder P, Waldmann TA (1983). Immunoglobulin gene rearrangement and cell surface antigen expression in acute lymphocytic leukemias of T cell and B cell precursor origins. J Clin Invest 71: 301-313.
1312. Kort R, Fazaa B, Bouden S, Nikkels AF, Pierard GE, Kamoun MR (1995). Perianal basal cell carcinoma. Int J Dermatol 34: 427-428.
1313. Kossard S (2002). Atypical lentiginous junctional naevi of the elderly and melanoma. Australas J Dermatol 43: 93-101.
1314. Kossard S, Kumar A, Wilkinson B (1999). Neural spectrum: palisaded encapsulated neuroma and verocay body poor dermal schwannoma. J Cutan Pathol 26: 31-36.
1315. Kossard S, Rosen R (1992). Cutaneous Bowen's disease. An analysis of 1001 cases according to age, sex, and site. J Am Acad Dermatol 27: 406-410.
1316. Kossard S, Wilkinson B (1995). Nucleolar organizer regions and image analysis nuclear morphometry of small cell (nevoid) melanoma. J Cutan Pathol 22: 132-136.
1317. Kossard S, Wilkinson B (1997). Small cell (naevoid) melanoma: a clinicopathologic study of 131 cases. Australas J Dermatol 38 Suppl 1: S54-S58.
1318. Koutlas IG, Jessurun J (1994). Arteriovenous hemangioma: a clinicopathological and immunohistochemical study. J Cutan Pathol 21: 343-349.
1319. Kraemer KH (1977). Progressive degenerative diseases associated with defective DNA repair: xeroderma pigmentosum and ataxia telangiesctasia. 37-71.
1320. Kraemer KH, Greene MH, Tarone R, Elder DE, Clark WHJr, Guerry D (1983). Dysplastic naevi and cutaneous melanoma risk. Lancet 2: 1076-1077.
1321. Kraemer KH, Lee MM, Andrews AD, Lambert WC (1994). The role of sunlight and DNA repair in melanoma and non-melanoma skin cancer. The xeroderma pigmentosum paradigm. Arch Dermatol 130: 1018-1021.
1322. Kraemer KH, Lee MM, Scotto J (1987). Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol 123: 241-250.
1323. Kraus MD, Lind AC, Alder SL, Dehner LP (1999). Angiomatosis with angiokeratoma-like features in children: a light microscopic and immunophenotypic examination of four cases. Am J Dermatopathol 21: 350-355.
1324. Kremer M, Sandherr M, Geist B, Cabras AD, Hofler H, Fend F (2001). Epstein-Barr virus-negative Hodgkin's lymphoma after mycosis fungoides: molecular evidence for distinct clonal origin. Mod Pathol 14: 91-97.
1325. Krenacs L, Smyth MJ, Bagdi E, Krenacs T, Kopper L, Rudiger T, Zettl A, Muller-Hermelink HK, Jaffe ES, Raffeld M (2003). The serine protease granzyme M is preferentially expressed in NK-cell, gamma delta T-cell, and intestinal T-cell lymphomas: evidence of origin from lymphocytes involved in innate immunity. Blood 101: 3590-3593.
1326. Krenek G, Orengo IF, Baer S, Byrd D (1998). Desmoplastic malignant melanoma presenting as an erythematous nodule tumor. Cutis 61: 275-276.
1327. Krige JE, Isaacs S, Hudson DA, King HS, Strover RM, Johnson CA (1991). Delay in the diagnosis of cutaneous malignant melanoma. A prospective study in 250 patients. Cancer 68: 2064-2068.
1328. Krischer J, Pechere M, Salomon D, Harms M, Chavaz P, Saurat JH (1999). Interferon alfa-2b-induced Meyerson's nevi in a patient with dysplastic nevus syndrome. J Am Acad Dermatol 40: 105-106.
1329. Krivanek JF, Cains GD, Paver K (1977). Halo eczema and junctional naevi: a case report. Australas J Dermatol 18: 81-83.
1330. Krone B, Kolmel KF, Grange JM, Mastrangelo G, Henz BM, Botev IN, Niin M, Seebacher C, Lambert D, Shafir R, Kokoschka EM, Kleeberg UR, Gefeller O, Pfahlberg A (2003). Impact of vaccinations and infectious diseases on the risk of melanoma—evaluation of an EORTC case-control study. Eur J Cancer 39: 2372-2378.
1331. Krone B, Kolmel KF, Henz BM, Grange JM (2005). Protection against melanoma by vaccination with Bacille Calmette-Guerin (BCG) and/or vaccinia: an epidemiology-based hypothesis on the nature of a melanoma risk factor and its immunological control. Eur J Cancer 41: 104-117.
1332. Kruse R, Rutten A, Lamberti C, Hosseiny-Malayeri HR, Wang Y, Ruelfs C, Jungck M, Mathiak M, Ruzicka T, Hartschuh W, Bisceglia M, Friedl W, Propping P (1998). Muir-Torre phenotype has a frequency of DNA mismatch-repair-gene mutations similar to that in hereditary nonpolyposis colorectal cancer families defined by the Amsterdam criteria. Am J Hum Genet 63: 63-70.
1333. Kruse R, Rutten A, Malayeri HR, Gunzl HJ, Friedl W, Propping P (1999). A novel germline mutation in the hMLH1 DNA

mismatch repair gene in a patient with an isolated cystic sebaceous tumor. J Invest Dermatol 112: 117-118.
1334. Kruse R, Rutten A, Schweiger N, Jakob E, Mathiak M, Propping P, Mangold E, Bisceglia M, Ruzicka T (2003). Frequency of microsatellite instability in unselected sebaceous gland neoplasias and hyperplasias. J Invest Dermatol 120: 858-864.
1335. Kubo M, Kikuchi K, Nashiro K, Kakinuma T, Hayashi N, Nanko H, Tamaki K (1998). Expression of fibrogenic cytokines in desmoplastic malignant melanoma. Br J Dermatol 139: 192-197.
1336. Kubo Y, Murao K, Matsumoto K, Arase S (2002). Molecular carcinogenesis of squamous cell carcinomas of the skin. J Med Invest 49: 111-117.
1337. Kuchelmeister C, Schaumburg-Lever G, Garbe C (2000). Acral cutaneous melanoma in caucasians: clinical features, histopathology and prognosis in 112 patients. Br J Dermatol 143: 275-280.
1338. Kukita A, Ishihara K (1989). Clinical features and distribution of malignant melanoma and pigmented nevi on the soles of the feet in Japan. J Invest Dermatol 92: 210S-213S.
1339. Kulow BF, Cualing H, Steele P, VanHorn J, Breneman JC, Mutasim DF, Breneman DL (2002). Progression of cutaneous B-cell pseudolymphoma to cutaneous B-cell lymphoma. J Cutan Med Surg 6: 519-528.
1340. Kumar S, Kingma DW, Weiss WB, Raffeld M, Jaffe ES (1996). Primary cutaneous Hodgkin's disease with evolution to systemic disease. Association with the Epstein-Barr virus. Am J Surg Pathol 20: 754-759.
1341. Kumar S, Krenacs L, Medeiros J, Elenitoba-Johnson KS, Greiner TC, Sorbara L, Kingma DW, Raffeld M, Jaffe ES (1998). Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T lymphocytes. Hum Pathol 29: 397-403.
1342. Kummer JA, Vermeer MH, Dukers D, Meijer CJ, Willemze R (1997). Most primary cutaneous CD30-positive lymphoproliferative disorders have a CD4-positive cytotoxic T-cell phenotype. J Invest Dermatol 109: 636-640.
1343. Kuno Y, Tsuji T, Yamamoto K (1999). Adenocarcinoma with signet ring cells of the axilla: two case reports and review of the literature. J Dermatol 26: 390-395.
1344. Kuo T (1980). Clear cell carcinoma of the skin. A variant of the squamous cell carcinoma that simulates sebaceous carcinoma. Am J Surg Pathol 4: 573-583.
1345. Kuo TT, Chan HL (1994). Ossifying dermatofibroma with osteoclast-like giant cells. Am J Dermatopathol 16: 193-195.
1346. Kuo TT, Hu S, Chan HL (1998). Keloidal dermatofibroma: report of 10 cases of a new variant. Am J Surg Pathol 22: 564-568.
1347. Kurman RJ (2002). Blaustein's Pathology of the Female Genital Tract. 5th ed. Springer: New York Berlin.
1348. Kurokawa M, Amano M, Miyaguni H, Tateyama S, Ogata K, Idemori M, Setoyama M (2001). Eccrine poromas in a patient with mycosis fungoides treated with electron beam therapy. Br J Dermatol 145: 830-833.
1349. Kurzen H, Esposito L, Langbein L, Hartschuh W (2001). Cytokeratins as markers of follicular differentiation: an immunohistochemical study of trichoblastoma and basal cell carcinoma. Am J Dermatopathol 23: 501-509.
1350. Kushida Y, Miki H, Ohmori M (1999). Loss of heterozygosity in actinic keratosis, squamous cell carcinoma and sun-exposed normal-appearing skin in Japanese: difference between Japanese and Caucasians. Cancer Lett 140: 169-175.
1351. Kutzner H, Winzer M, Mentzel T (2000). [Symplastic hemangioma]. Hautarzt 51: 327-331.
1352. Kwittken J, Negri L (1966). Malignant blue nevus. Case report of a Negro woman. Arch Dermatol 94: 64-69.
1353. La Vecchia C, Lucchini F, Negri E, Levi F (1999). Recent declines in worldwide mortality from cutaneous melanoma in youth and middle age. Int J Cancer 81: 62-66.
1354. Lack EE, Worsham GF, Callihan MD, Crawford BE, Klappenbach S, Rowden G, Chun B (1980). Granular cell tumor: a clinicopathologic study of 110 patients. J Surg Oncol 13: 301-316.
1355. Lakhani SR, Hulman G, Hall JM, Slack DN, Sloane JP (1994). Intravascular malignant lymphomatosis (angiotropic large-cell lymphoma). A case report with evidence for T-cell lineage with polymerase chain reaction analysis. Histopathology 25: 283-286.
1356. Lamberg SI, Bunn PAJr (1979). Cutaneous T-cell lymphomas. Summary of the Mycosis Fungoides Cooperative Group-National Cancer Institute Workshop. Arch Dermatol 115: 1103-1105.
1357. Lambert WC, Brodkin RH (1984). Nodal and subcutaneous cellular blue nevi. A pseudometastasizing pseudomelanoma. Arch Dermatol 120: 367-370.
1358. Lamovec J (1984). Blue nevus of the lymph node capsule. Report of a new case with review of the literature. Am J Clin Pathol 81: 367-372.
1359. Landa NG, Winkelmann RK (1991). Epidermotropic eccrine porocarcinoma. J Am Acad Dermatol 24: 27-31.
1360. Landi MT, Baccarelli A, Tarone RE, Pesatori A, Tucker MA, Hedayati M, Grossman L (2002). DNA repair, dysplastic nevi, and sunlight sensitivity in the development of cutaneous malignant melanoma. J Natl Cancer Inst 94: 94-101.
1361. Landry M, Winkelmann RK (1972). An unusual tubular apocrine adenoma. Arch Dermatol 105: 869-879.
1362. Langard S, Rosenberg J, Andersen A, Heldaas SS (2000). Incidence of cancer among workers exposed to vinyl chloride in polyvinyl chloride manufacture. Occup Environ Med 57: 65-68.
1363. Langer K, Rappersberger K, Steiner A, Konrad K, Wolff K (1990). The ultrastructure of dysplastic naevi: comparison with superficial spreading melanoma and common naevocellular naevi. Arch Dermatol Res 282: 353-362.
1364. Langholz B, Richardson J, Rappaport E, Waisman J, Cockburn M, Mack T (2000). Skin characteristics and risk of superficial spreading and nodular melanoma (United States). Cancer Causes Control 11: 741-750.
1365. Lao LM, Kumakiri M, Kiyohara T, Kuwahara H, Ueda K (2001). Sub-populations of melanocytes in pigmented basal cell carcinoma: a quantitative, ultrastructural investigation. J Cutan Pathol 28: 34-43.
1366. Lao LM, Kumakiri M, Mima H, Kuwahara H, Ishida H, Ishiguro K, Fujita T, Ueda K (1998). The ultrastructural characteristics of eccrine sweat glands in a Fabry disease patient with hypohidrosis. J Dermatol Sci 18: 109-117.
1367. Lapid O, Shaco-Levy R, Krieger Y, Kachko L, Sagi A (2001). Congenital epulis. Pediatrics 107: E22.
1368. Laroche L, Bach JF (1981). T cell imbalance in nonleukemic and leukemic cutaneous lymphoma defined by monoclonal antibodies. Clin Immunol Immunopathol 20: 278-284.
1369. Larralde M, Rositto A, Giardelli M, Gatti CF, Santos MA (1999). Congenital self-healing histiocytosis (Hashimoto-Pritzker). Int J Dermatol 38: 693-696.
1370. Laskin WB, Fetsch JF, Miettinen M (2000). The "neurothekeoma": immunohistochemical analysis distinguishes the true nerve sheath myxoma from its mimics. Hum Pathol 31: 1230-1241.
1371. Lasota J, Miettinen M (1999). Absence of Kaposi's sarcoma-associated virus (human herpesvirus-8) sequences in angiosarcoma. Virchows Arch 434: 51-56.
1372. Laugier P, Hunziker N, Laut J, Orusco M, Osmos L (1975). [Reticulohistiocytosis of benign evolution (Hashimoto-Pritzker type). Electron microscopy study]. Ann Dermatol Syphiligr (Paris) 102: 21-31.
1373. Laur WE, Posey RE, Waller JD (1981). Lichen planus-like keratosis. A clinicohistopathologic correlation. J Am Acad Dermatol 4: 329-336.
1374. Laws RA, English JCI, Elston DM (1996). Acrospiroma: a case report and review. Cutis 58: 349-351.
1375. Lazar AP, Caro WA, Roenigk HHJr, Pinski KS (1989). Parapsoriasis and mycosis fungoides: the Northwestern University experience, 1970 to 1985. J Am Acad Dermatol 21: 919-923.
1376. Lazarou G, Goldberg MI (2000). Vulvar arteriovenous hemangioma. A case report. J Reprod Med 45: 439-441.
1377. Leake JF, Buscema J, Cho KR, Currie JL (1991). Dermatofibrosarcoma protuberans of the vulva. Gynecol Oncol 41: 245-249.
1378. Lear JT, Smith AG, Heagerty AH, Bowers B, Jones PW, Gilford J, Alldersea J, Strange RC, Fryer AA (1997). Truncal site and detoxifying enzyme polymorphisms significantly reduce time to presentation of further primary cutaneous basal cell carcinoma. Carcinogenesis 18: 1499-1503.
1379. LeBoit PE (1994). Granulomatous slack skin. Dermatol Clin 12: 375-389.
1380. LeBoit PE (2003). Pictures of a unicorn? Am J Dermatopathol 25: 88-91.
1381. LeBoit PE, Barr RJ (1994). Smooth-muscle proliferation in dermatofibromas. Am J Dermatopathol 16: 155-160.
1382. LeBoit PE, Beckstead JH, Bond B, Epstein WL, Frieden IJ, Parslow TG (1987). Granulomatous slack skin: clonal rearrangement of the T-cell receptor beta gene is evidence for the lymphoproliferative nature of a cutaneous elastolytic disorder. J Invest Dermatol 89: 183-186.
1383. LeBoit PE, Berger TG, Egbert BM, Beckstead JH, Yen TS, Stoler MH (1989). Bacillary angiomatosis. The histopathology and differential diagnosis of a pseudoneoplastic infection in patients with human immunodeficiency virus disease. Am J Surg Pathol 13: 909-920.
1384. LeBoit PE, Crutcher WA, Shapiro PE (1992). Pagetoid intraepidermal spread in Merkel cell (primary neuroendocrine) carcinoma of the skin. Am J Surg Pathol 16: 584-592.
1385. LeBoit PE, Solomon AR, Santa Cruz DJ, Wick MR (1992). Angiomatosis with luminal cryoprotein deposition. J Am Acad Dermatol 27: 969-973.
1386. LeBoit PE, Van Fletcher H (1987). A comparative study of Spitz nevus and nodular malignant melanoma using image analysis cytometry. J Invest Dermatol 88: 753-757.
1387. LeBoit PE, Zackheim HS, White CRJr (1988). Granulomatous variants of cutaneous T-cell lymphoma. The histopathology of granulomatous mycosis fungoides and granulomatous slack skin. Am J Surg Pathol 12: 83-95.
1388. Lee AY, Kawashima M, Nakagawa H, Ishibashi Y (1991). Generalized eruptive syringoma. J Am Acad Dermatol 25: 570-571.
1389. Lee CS, Southey MC, Slater H, Auldist AW, Chow CW, Venter DJ (1995). Primary cutaneous Ewing's sarcoma/peripheral primitive neuroectodermal tumors in childhood. A molecular, cytogenetic, and immunohistochemical study. Diagn Mol Pathol 4: 174-181.
1390. Lee ES, Locker J, Nalesnik M, Reyes J, Jaffe R, Alashari M, Nour B, Tzakis A, Dickman PS (1995). The association of Epstein-Barr virus with smooth-muscle tumors occurring after organ transplantation. N Engl J Med 332: 19-25.
1391. Lee HH, Lee KG (1998). Malignant eccrine spiradenoma with florid squamous differentiation. J Korean Med Sci 13: 191-195.
1392. Lee J, Bhawan J, Wax F, Farber J (1994). Plexiform granular cell tumor. A report of two cases. Am J Dermatopathol 16: 537-541.
1393. Lee JA, Carter AP (1970). Secular trends in mortality from malignant melanoma. J Natl Cancer Inst 45: 91-97.
1394. Lee JB, Kim M, Lee SC, Won YH (2000). Granuloma pyogenicum arising in an arteriovenous haemangioma associated with a port-wine stain. Br J Dermatol 143: 669-671.
1395. Lee PK, Olbricht SM, Gonzalez-Serva A, Harrist TH (1997). rative squamous cell carcinoma: histopathologic and clinical characterizatoin of a newly described skin cancer. J Cutan Pathol 24: 108.
1396. Leffell DJ (2000). The scientific basis of skin cancer. J Am Acad Dermatol 42: 18-22.
1397. Leinweber B, Colli C, Chott A, Kerl H, Cerroni L (2004). Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. Am J Dermatopathol 26: 4-13.
1398. Leitinger G, Cerroni L, Soyer HP, Smolle J, Kerl H (1990). Morphometric diagnosis of melanocytic skin tumors. Am J Dermatopathol 12: 441-445.
1399. Lele SM, Gloster ES, Heilman ER, Chen PC, Chen CK, Anzil AP, Pozner JN, Reardon MJ (1997). Eccrine syringofibroadenoma surrounding a squamous cell carcinoma: a case report. J Cutan Pathol 24: 193-196.
1400. Lenane P, Keane CO, Connell BO, Loughlin SO, Powell FC (2000). Genital melanotic macules: clinical, histologic, immunohistochemical, and ultrastructural features. J Am Acad Dermatol 42: 640-644.
1401. Lennert K, Parwaresch MR (1979). Mast cells and mast cell neoplasia: a review. Histopathology 3: 349-365.
1402. Leopold JG, Richards DB (1968). The interrelationship of blue and common naevi. J Pathol Bacteriol 95: 37-46.
1403. Lerchin E, Rahbari H (1975). Adamantinoid basal cell epithelioma. A histological variant. Arch Dermatol 111: 586-588.
1404. Lerner AB, Nordlund JJ, Kirkwood JM (1979). Effects of oral contraceptives and pregnancy on melanomas. N Engl J Med 301: 47.

1405. Lesher JLJr, Allen BS (1984). Multicentric reticulohistiocytosis. J Am Acad Dermatol 11: 713-723.
1406. Leshin B, Whitaker DC, Foucar E (1986). Lymphangioma circumscriptum following mastectomy and radiation therapy. J Am Acad Dermatol 15: 1117-1119.
1407. Levanat S, Gorlin RJ, Fallet S, Johnson DR, Fantasia JE, Bale AE (1996). A two-hit model for developmental defects in Gorlin syndrome. Nat Genet 12: 85-87.
1408. Levanat S, Pavelic B, Crnic I, Oreskovic S, Manojlovic S (2000). Involvement of PTCH gene in various noninflammatory cysts. J Mol Med 78: 140-146.
1409. Lever L, Marks R (1989). The significance of the Darier-like solar keratosis and acantholytic change in preneoplastic lesions of the epidermis. Br J Dermatol 120: 383-389.
1410. Lever LR, Farr PM (1994). Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. Br J Dermatol 131: 215-219.
1411. Levi F, Erler G, Te VC, Randimbison L, La Vecchia C (2001). Trends in skin cancer incidence in Neuchatel, 1976-98. Tumori 87: 288-289.
1412. Levi F, Te VC, Randimbison L, Erler G, La Vecchia C (2001). Trends in skin cancer incidence in Vaud: an update, 1976-1998. Eur J Cancer Prev 10: 371-373.
1413. Levisohn D, Seidel D, Phelps A, Burgdorf W (1993). Solitary congenital indeterminate cell histiocytoma. Arch Dermatol 129: 81-85.
1414. Lew S, Richter S, Jelin N, Siegal A (1991). A blue naevus of the prostate: a light microscopic study including an investigation of S-100 protein positive cells in the normal and in the diseased gland. Histopathology 18: 443-448.
1415. Lewis MG (1967). Malignant melanoma in Uganda. (The relationship between pigmentation and malignant melanoma on the soles of the feet). Br J Cancer 21: 483-495.
1416. Lewis MG, Johnson K (1968). The incidence and distribution of pigmented naevi in Ugandan Africans. Br J Dermatol 80: 362-366.
1417. Lewis MG, Kiryabwire JW (1968). Aspects of behavior and natural history of malignant melanoma in Uganda. Cancer 21: 876-887.
1418. Li C, Inagaki H, Kuo TT, Hu S, Okabe M, Eimoto T (2003). Primary cutaneous marginal zone B-cell lymphoma: a molecular and clinicopathologic study of 24 asian cases. Am J Surg Pathol 27: 1061-1069.
1419. Li DM, Sun H (1997). TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor beta. Cancer Res 57: 2124-2129.
1420. Li G, Salhany KE, Rook AH, Lessin SR (1997). The pathogenesis of large cell transformation in cutaneous T-cell lymphoma is not associated with t(2;5)(p23;q35) chromosomal translocation. J Cutan Pathol 24: 403-408.
1421. Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, Puc J, Miliaresis C, Rodgers L, McCombie R, Bigner SH, Giovanella BC, Ittmann M, Tycko B, Hibshoosh H, Wigler MH, Parsons R (1997). PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 275: 1943-1947.
1422. Li JY, Gaillard F, Moreau A, Harousseau JL, Laboisse C, Milpied N, Bataille R, Avet-Loiseau H (1999). Detection of translocation t(11;14)(q13;q32) in mantle cell lymphoma by fluorescence in situ hybridization. Am J Pathol 154: 1449-1452.
1423. Li S, Griffin CA, Mann RB, Borowitz MJ (2001). Primary cutaneous T-cell-rich B-cell lymphoma: clinically distinct from its nodal counterpart? Mod Pathol 14: 10-13.
1424. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R (1997). Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 16: 64-67.
1425. Lieberman PH, Jones CR, Steinman RM, Erlandson RA, Smith J, Gee T, Huvos A, Garin-Chesa P, Filippa DA, Urmacher C, Gangi MD, Sperber M (1996). Langerhans cell (eosinophilic) granulomatosis. A clinicopathologic study encompassing 50 years. Am J Surg Pathol 20: 519-552.
1426. Liebow AA, Carrington CR, Friedman PJ (1972). Lymphomatoid granulomatosis. Hum Pathol 3: 457-558.
1427. Lim SC, Lee MJ, Lee MS, Kee KH, Suh CH (1998). Giant hidradenocarcinoma: a report of malignant transformation from nodular hidradenoma. Pathol Int 48: 818-823.
1428. Lin CS, Wang WJ, Wong CK (1990). Acral melanoma. A clinicopathologic study of 28 patients. Int J Dermatol 29: 107-112.
1429. Lin P, Jones D, Dorfman DM, Medeiros LJ (2000). Precursor B-cell lymphoblastic lymphoma: a predominantly extranodal tumor with low propensity for leukemic involvement. Am J Surg Pathol 24: 1480-1490.
1430. Lindelof B, Sigurgeirsson B, Wallberg P, Eklund G (1991). Occurrence of other malignancies in 1973 patients with basal cell carcinoma. J Am Acad Dermatol 25: 245-248.
1431. Link MP, Roper M, Dorfman RF, Crist WM, Cooper MD, Levy R (1983). Cutaneous lymphoblastic lymphoma with pre-B markers. Blood 61: 838-841.
1432. Lipford EHJr, Margolick JB, Longo DL, Fauci AS, Jaffe ES (1988). Angiocentric immunoproliferative lesions: a clinicopathologic spectrum of post-thymic T-cell proliferations. Blood 72: 1674-1681.
1433. Lipsker DM, Hedelin G, Heid E, Grosshans EM, Cribier BJ (1999). Striking increase of thin melanomas contrasts with stable incidence of thick melanomas. Arch Dermatol 135: 1451-1456.
1434. Liu JC, Ball SF (1991). Nevus of Ota with glaucoma: report of three cases. Ann Ophthalmol 23: 286-289.
1435. Liu L, Dilworth D, Gao L, Monzon J, Summers A, Lassam N, Hogg D (1999). Mutation of the CDKN2A 5' UTR creates an aberrant initiation codon and predisposes to melanoma. Nat Genet 21: 128-132.
1436. Liu Y (1949). The histogenesis of clear cell papillary carcinoma of the skin. Am J Pathol 25: 93-103.
1437. Lloyd AC (2000). p53: only ARF the story. Nat Cell Biol 2: E48-E50.
1438. Lloyd KM (1970). Multicentric pigmented Bowen's disease of the groin. Arch Dermatol 101: 48-51.
1439. Lloyd KM, Dennis M (196). Cowden's disease: A possible new symptom complex with multiple system involvement. Ann Intern Med 58: 136-142.
1440. Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ (1991). Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. J Am Acad Dermatol 24: 715-719.
1441. Loane J, Kealy WF, Mulcahy G (1998). Perianal hidradenoma papilliferum occurring in a male: a case report. Ir J Med Sci 167: 26-27.
1442. Lober BA, Lober CW (2000). Actinic keratosis is squamous cell carcinoma. South Med J 93: 650-655.
1443. Lober BA, Lober CW, Accola J (2000). Actinic keratosis is squamous cell carcinoma. J Am Acad Dermatol 43: 881-882.
1444. Lohmann CM, Coit DG, Brady MS, Berwick M, Busam KJ (2002). Sentinel lymph node biopsy in patients with diagnostically controversial spitzoid melanocytic tumors. Am J Surg Pathol 26: 47-55.
1445. Longaker MA, Frieden IJ, LeBoit PE, Sherertz EF (1994). Congenital "self-healing" Langerhans cell histiocytosis: the need for long-term follow-up. J Am Acad Dermatol 31: 910-916.
1446. Longley BJ, Metcalfe DD (2000). A proposed classification of mastocytosis incorporating molecular genetics. Hematol Oncol Clin North Am 14: 697-701, viii.
1447. Longley BJ, Reguera MJ, Ma Y (2001). Classes of c-KIT activating mutations: proposed mechanisms of action and implications for disease classification and therapy. Leuk Res 25: 571-576.
1448. Longley BJ, Tyrrell L, Lu SZ, Ma YS, Langley K, Ding TG, Duffy T, Jacobs P, Tang LH, Modlin I (1996). Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. Nat Genet 12: 312-314.
1449. Longley BJJr, Metcalfe DD, Tharp M, Wang X, Tyrrell L, Lu SZ, Heitjan D, Ma Y (1999). Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. Proc Natl Acad Sci U S A 96: 1609-1614.
1450. Longley J, Duffy TP, Kohn S (1995). The mast cell and mast cell disease. J Am Acad Dermatol 32: 545-561.
1451. Longy M, Lacombe D (1996). Cowden disease. Report of a family and review. Ann Genet 39: 35-42.
1452. Lonsdale RN, Widdison A (1992). Leiomyosarcoma of the nipple. Histopathology 20: 537-539.
1453. Lopez-Guillermo A, Cid J, Salar A, Lopez A, Montalban C, Castrillo JM, Gonzalez M, Ribera JM, Brunet S, Garcia-Conde J, Fernandez dS, Bosch F, Montserrat E (1998). Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol 9: 849-855.
1454. Lopriore E, Markhorst DG (1999). Diffuse neonatal haemangiomatosis: new views on diagnostic criteria and prognosis. Acta Paediatr 88: 93-97.
1455. Lowe D, Fletcher CD, Shaw MP, McKee PH (1984). Eosinophil infiltration in keratoacanthoma and squamous cell carcinoma of the skin. Histopathology 8: 619-625.
1456. Lu D, Patel KA, Duvic M, Jones D (2002). Clinical and pathological spectrum of CD8-positive cutaneous T-cell lymphomas. J Cutan Pathol 29: 465-472.
1457. Lucas P, Bogomeletz WV, Cattan A (1984). [Cutaneous localization of Hodgkin's disease. Description of 4 cases and review of the literature]. Sem Hop 60: 749-754.
1458. Lund HZ (1957). Tumors of the skin. Armed Forces Institute of Pathology: Washington.
1459. Lund HZ (1965). How often does squamous cell carcinoma of the skin metastasize? Arch Dermatol 92: 635-637.
1460. Lund KA, Parker CM, Norins AL, Tejada E (1990). Vesicular cutaneous T cell lymphoma presenting with gangrene. J Am Acad Dermatol 23: 1169-1171.
1461. Lundquist K, Kohler S, Rouse RV (1999). Intraepidermal cytokeratin 7 expression is not restricted to Paget cells but is also seen in Toker cells and Merkel cells. Am J Surg Pathol 23: 212-219.
1462. Luz FB, Gaspar TAP, Kalil-Gaspar N, Ramos-e-Silva M (2001). Multicentric reticulohistiocytosis. J Eur Acad Dermatol Venereol 15: 524-531.
1463. Lymboussaki A, Partanen TA, Olofsson B, Thomas-Crusells J, Fletcher CD, de Waal RM, Kaipainen A, Alitalo K (1998). Expression of the vascular endothelial growth factor C receptor VEGFR-3 in lymphatic endothelium of the skin and in vascular tumors. Am J Pathol 153: 395-403.
1464. Lynch ED, Ostermeyer EA, Lee MK, Arena JF, Ji H, Dann J, Swisshelm K, Suchard D, MacLeod PM, Kvinnsland S, Gjertsen BT, Heimdal K, Lubs H, Moller P, King MC (1997). Inherited mutations in PTEN that are associated with breast cancer, cowden disease, and juvenile polyposis. Am J Hum Genet 61: 1254-1260.
1465. Ma Y, Zeng S, Metcalfe DD, Akin C, Dimitrijevic S, Butterfield JH, McMahon G, Longley BJ (2002). The c-KIT mutation causing human mastocytosis is resistant to STI571 and other KIT kinase inhibitors; kinases with enzymatic site mutations show different inhibitor sensitivity profiles than wild-type kinases and those with regulatory-type mutations. Blood 99: 1741-1744.
1466. Macaulay WL (1968). Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign—histologically malignant. Arch Dermatol 97: 23-30.
1467. Macgrogan G, Vergier B, Dubus P, Beylot-Barry M, Belleannee G, Delaunay MM, Eghbali H, Beylot C, Rivel J, Trojani M, Vital C, de Mascarel A, Bloch B, Merlio JP (1996). CD30-positive cutaneous large cell lymphomas. A comparative study of clinicopathologic and molecular features of 16 cases. Am J Clin Pathol 105: 440-450.
1468. Machin P, Catasus L, Pons C, Munoz J, Conde-Zurita JM, Balmana J, Barnadas M, Marti RM, Prat J, Matias-Guiu X (2002). Microsatellite instability and immunostaining for MSH-2 and MLH-1 in cutaneous and internal tumors from patients with the Muir-Torre syndrome. J Cutan Pathol 29: 415-420.
1469. Machin P, Catasus L, Pons C, Munoz J, Conde-Zurita JM, Balmana J, Barnadas M, Marti RM, Prat J, Matias-Guiu X (2002). Microsatellite instability and immunostaining for MSH-2 and MLH-1 in cutaneous and internal tumors from patients with the Muir-Torre syndrome. J Cutan Pathol 29: 415-420.
1470. Mackenzie DH (1957). A clear-cell hidradenocarcinoma with metastases. Cancer 10: 1021-1023.
1471. MacKie RM (2000). Malignant melanoma: clinical variants and prognostic indicators. Clin Exp Dermatol 25: 471-475.
1472. MacKie RM, Bray CA, Hole DJ, Morris A, Nicolson M, Evans A, Doherty V, Vestey J (2002). Incidence of and survival from malignant melanoma in Scotland: an epidemiological study. Lancet 360: 587-591.
1473. MacKie RM, English J, Aitchison TC,

Fitzsimons CP, Wilson P (1985). The number and distribution of benign pigmented moles (melanocytic naevi) in a healthy British population. Br J Dermatol 113: 167-174.
1474. MacKie RM, McHenry P, Hole D (1993). Accelerated detection with prospective surveillance for cutaneous malignant melanoma in high-risk groups. Lancet 341: 1618-1620.
1475. Macmillan A, Champion RH (1971). Progressive capillary haemangioma. Br J Dermatol 85: 492-493.
1476. MacSweeney F, Desai SA (2000). Inflammatory pseudotumour of the subcutis: a report on the fine needle aspiration findings in a case misdiagnosed cytologically as malignant. Cytopathology 11: 57-60.
1477. Maeda Y, Izutani T, Yonese J, Ishikawa Y, Fukui I (1998). Pyogenic granuloma of the glans penis. Br J Urol 82: 771-772.
1478. Maehama T, Dixon JE (1998). The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem 273: 13375-13378.
1479. Magana M, Sangueza P, Gil-Beristain J, Sanchez-Sosa S, Salgado A, Ramon G, Sangueza OP (1998). Angiocentric cutaneous T-cell lymphoma of childhood (hydroa-like lymphoma): a distinctive type of cutaneous T-cell lymphoma. J Am Acad Dermatol 38: 574-579.
1480. Maggini M, Petrelli G (1984). Malignant melanoma mortality in Italy: 1955-1978. Eur J Cancer Clin Oncol 20: 1321-1323.
1481. Magnus K (1973). Incidence of malignant melanoma of the skin in Norway, 1955-1970. Variations in time and space and solar radiation. Cancer 32: 1275-1286.
1482. Magnus K (1981). Habits of sun exposure and risk of malignant melanoma: an analysis of incidence rates in Norway 1955-1977 by cohort, sex, age, and primary tumor site. Cancer 48: 2329-2335.
1483. Magrath IT, Bhatia K (1997). Pathogenesis of small noncleaved cell lymphomas (Burkitt's lymphoma). In: The Non-Hodgkin's Lymphomas, Magrath IT, ed., Arnold: London , pp. 385-409.
1484. Magro CM, Crowson AN, Kovatich AJ, Burns F (2001). Lupus profundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: a spectrum of subcuticular T-cell lymphoid dyscrasia. J Cutan Pathol 28: 235-247.
1485. Mahalingam M, Bhawan J, Finn R, Stefanato CM (2001). Tumor of the follicular infundibulum with sebaceous differentiation. J Cutan Pathol 28: 314-317.
1486. Mahalingam M, Goldberg LJ (2001). Atypical pilar leiomyoma: cutaneous counterpart of uterine symplastic leiomyoma? Am J Dermatopathol 23: 299-303.
1487. Mahalingam M, LoPiccolo D, Byers HR (2001). Expression of PGP 9.5 in granular cell nerve sheath tumors: an immunohistochemical study of six cases. J Cutan Pathol 28: 282-286.
1487A. Mahre E (1963). Malignant melanomas in children. Arch Pathol Microbiol Scand 59: 184-193.
1488. Maiorana A, Nigrisoli E, Papotti M (1986). Immunohistochemical markers of sweat gland tumors. J Cutan Pathol 13: 187-196.
1489. Maitra A, McKenna RW, Weinberg AG, Schneider NR, Kroft SH (2001). Precursor B-cell lymphoblastic lymphoma. A study of nine cases lacking blood and bone marrow involvement and review of the literature. Am J Clin Pathol 115: 868-875.
1490. Maize JC, Jr., McCalmont TH, Carlson JA, Busam KJ, Kutzner H, Bastian BC (2005). Genomic Analysis of Blue Nevi and Related Dermal Melanocytic Proliferations. Am J Surg Pathol 29: 1214-1220.
1491. Majewski S, Jablonska S (1995). Epidermodysplasia verruciformis as a model of human papillomavirus-induced genetic cancer of the skin. Arch Dermatol 131: 1312-1318.
1492. Majewski S, Jablonska S (2002). Do epidermodysplasia verruciformis human papillomaviruses contribute to malignant and benign epidermal proliferations? Arch Dermatol 138: 649-654.
1493. Maldonado JL, Fridlyand J, Patel H, Jain AN, Busam K, Kageshita T, Ono T, Albertson D, Pinkel D, Bastian BC (2003). Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst 95: 1878-1890.
1494. Maldonado JL, Timmerman L, Fridlyand J, Bastian BC (2004). Mechanisms of cell-cycle arrest in Spitz nevi with constitutive activation of the MAP-kinase pathway. Am J Pathol 164: 1783-1787.
1495. Maloney ME, Jones DB, Sexton FM (1992). Pigmented basal cell carcinoma: investigation of 70 cases. J Am Acad Dermatol 27: 74-78.
1496. Mambo NC (1983). Eccrine spiradenoma: clinical and pathologic study of 49 tumors. J Cutan Pathol 10: 312-320.
1496A. Mancianti ML, Clark WH, Hayes FA, Herlyn M (1990). Malignant melanoma simulants arising in congenital melanocytic nevi do not show experimental evidence for a malignant phenotype. Am J Pathol 136: 817-829.
1497. Mancini L, Gubinelli M, Fortunato C, Carella R (1992). Blue nevus of the lymph node capsule. Report of a case. Pathologica 84: 547-550.
1498. Mancini RE, Quaife JV (1962). Histogenesis of experimentally produced keloids. J Invest Dermatol 38: 143-181.
1499. Manente L, Cotellessa C, Schmitt I, Peris K, Torlone G, Muda AO, Romano MC, Chementi S (1997). Indeterminate cell histiocytosis: a rare histiocytic disorder. Am J Dermatopathol 19: 276-283.
1500. Mangini J, Li N, Bhawan J (2002). Immunohistochemical markers of melanocytic lesions: a review of their diagnostic usefulness. Am J Dermatopathol 24: 270-281.
1501. Mansson-Brahme E, Johansson H, Larsson O, Rutqvist LE, Ringborg U (2002). Trends in incidence of cutaneous malignant melanoma in a Swedish population 1976-1994. Acta Oncol 41: 138-146.
1502. Manstein CH, Gottlieb N, Manstein ME, Manstein G (2000). Giant basal cell carcinoma: a series of seven T3 tumors without metastasis. Plast Reconstr Surg 106: 653-656.
1503. Mao X, Lillington D, Child F, Russell-Jones R, Young B, Whittaker S (2002). Comparative genomic hybridization analysis of primary cutaneous B-cell lymphomas: identification of common genomic alterations in disease pathogenesis. Genes Chromosomes Cancer 35: 144-155.
1504. Mao X, Lillington D, Scarisbrick JJ, Mitchell T, Czepulkowski B, Russell-Jones R, Young B, Whittaker SJ (2002). Molecular cytogenetic analysis of cutaneous T-cell lymphomas: identification of common genetic alterations in Sezary syndrome and mycosis fungoides. Br J Dermatol 147: 464-475.
1505. Mao X, Lillington DM, Czepulkowski B, Russell-Jones R, Young BD, Whittaker S (2003). Molecular cytogenetic characterization of Sezary syndrome. Genes Chromosomes Cancer 36: 250-260.
1506. Mao X, Orchard G, Lillington DM, Russell-Jones R, Young BD, Whittaker SJ (2003). Amplification and overexpression of JUNB is associated with primary cutaneous T-cell lymphomas. Blood 101: 1513-1519.
1507. Marcil I, Stern RS (2000). Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 136: 1524-1530.
1508. Marghoob AA (2002). Congenital melanocytic nevi. Evaluation and management. Dermatol Clin 20: 607-16, viii.
1509. Marghoob AA, Swindle LD, Moricz CZ, Sanchez Negron FA, Slue B, Halpern AC, Kopf AW (2003). Instruments and new technologies for the in vivo diagnosis of melanoma. J Am Acad Dermatol 49: 777-797.
1510. Margo CE, Grossniklaus HE (1995). Intraepithelial sebaceous neoplasia without underlying invasive carcinoma. Surv Ophthalmol 39: 293-301.
1510A. Margo CE, Mulla ZD (1998). Malignant tumors of the eyelid: a population-based study of non-basal cell and non-squamous cell malignant neoplasms. Arch Ophthalmol 116: 195-198.
1511. Margolis RJ, Tong AK, Byers HR, Mihm MCJr (1989). Comparison of acral nevomelanocytic proliferations in Japanese and whites. J Invest Dermatol 92: 222S-226S.
1512. Mariatos G, Gorgoulis VG, Laskaris G, Kittas C (1999). Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) in the oral mucosa. A case report and review of the literature. Oral Oncol 35: 435-438.
1513. Mariatos G, Gorgoulis VG, Laskaris G, Kittas C (2001). Epithelioid haemangioma (angiolymphoid hyperplasia with eosinophilia) in the inner canthus. J Eur Acad Dermatol Venereol 15: 90-91.
1514. Mark GJ, Mihm MC, Liteplo MG, Reed RJ, Clark WH (1973). Congenital melanocytic nevi of the small and garment type. Clinical, histologic, and ultrastructural studies. Hum Pathol 4: 395-418.
1515. Marks R (1987). Nonmelanotic skin cancer and solar keratoses. The quiet 20th century epidemic. Int J Dermatol 26: 201-205.
1516. Marks R, Foley P, Goodman G, Hage BH, Selwood TS (1986). Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 115: 649-655.
1517. Marks R, Rennie G, Selwood TS (1988). Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1: 795-797.
1518. Marsden J, Allen R (1987). Widespread angiokeratomas without evidence of metabolic disease. Arch Dermatol 123: 1125-1127.
1519. Marsh DJ, Coulon V, Lunetta KL, Rocca-Serra P, Dahia PL, Zheng Z, Liaw D, Caron S, Duboue B, Lin AY, Richardson AL, Bonnetblanc JM, Bressieux JM, Cabarrot-Moreau A, Chompret A, Demange L, Eeles RA, Yahanda AM, Fearon ER, Fricker JP, Gorlin RJ, Hodgson SV, Huson S, Lacombe D, LePrat F, Odent S, Toulouse C, Olopade OI, Sobol H, Tishler S, Woods CG, Robinson BG, Weber HC, Parsons R, Peacocke M, Longy M, Eng C (1998). Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 7: 507-515.
1520. Marsh DJ, Dahia PL, Zheng Z, Liaw D, Parsons R, Gorlin RJ, Eng C (1997). Germline mutations in PTEN are present in Bannayan-Zonana syndrome. Nat Genet 16: 333-334.
1521. Marsh DJ, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ, Ahmed SF, Bodurtha J, Crowe C, Curtis MA, Dasouki M, Dunn T, Feit H, Geraghty MT, Graham JMJr, Hodgson SV, Hunter A, Korf BR, Manchester D, Miesfeldt S, Murday VA, Nathanson KL, Parisi M, Pober B, Romano C, Tolmie JL, Trembath R, Winter RM, Zackai EH, Zori RT, Weng LP, Dahia PLM, Eng C (1999). PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet 8: 1461-1472.
1522. Martel P, Laroche L, Courville P, Larroche C, Wechsler J, Lenormand B, Delfau MH, Bodemer C, Bagot M, Joly P (2000). Cutaneous involvement in patients with angioimmunoblastic lymphadenopathy with dysproteinemia: a clinical, immunohistological, and molecular analysis. Arch Dermatol 136: 881-886.
1523. Martin-Lopez R, Feal-Cortizas C, Fraga J (1999). Pleomorphic sclerotic fibroma. Dermatology 198: 69-72.
1524. Martin Flores-Stadler E, Gonzalez-Crussi F, Greene M, Thangavelu M, Kletzel M, Chou PM (1999). Indeterminate-cell histiocytosis: immunophenotypic and cytogenetic findings in an infant. Med Pediatr Oncol 32: 250-254.
1525. Martin RC, Edwards MJ, Cawte TG, Sewell CL, McMasters KM (2000). Basosquamous carcinoma: analysis of prognostic factors influencing recurrence. Cancer 88: 1365-1369.
1526. Martinez-Mir A, Gordon D, Horev L, Klapholz L, Ott J, Christiano AM, Zlotogorski A (2002). Multiple cutaneous and uterine leiomyomas: refinement of the genetic locus for multiple cutaneous and uterine leiomyomas on chromosome 1q42.3-43. J Invest Dermatol 118: 876-880.
1527. Marzano AV, Berti E, Paulli M, Caputo R (2000). Cytophagic histiocytic panniculitis and subcutaneous panniculitis-like T-cell lymphoma: report of 7 cases. Arch Dermatol 136: 889-896.
1528. Masback A, Olsson H, Westerdahl J, Ingvar C, Jonsson N (2001). Prognostic factors in invasive cutaneous malignant melanoma: a population-based study and review. Melanoma Res 11: 435-445.
1529. Mascaro JM (1963). Consideration sur les tumeurs fibro-epitheliales. Le syringofibroadenome. Ann Dermatol Syphilol 90: 146-153.
1530. Massa MC, Fretzin DF, Chowdhury L, Sweet DL (1984). Angiolymphoid hyperplasia demonstrating extensive skin and mucosal lesions controlled with vinblastine therapy. J Am Acad Dermatol 11: 333-339.
1531. Massi D, Carli P, Franchi A, Santucci M (1999). Naevus-associated melanomas: cause or chance? Melanoma Res 9: 85-91.
1532. Massi G, LeBoit PE (2004). Histology of Naevi and Melanoma. Steinkopff Verlag: Darmstadt, Berlin.

1533. Massone C, Chott A, Metze D, Kerl K, Citarella L, Vale E, Kerl H, Cerroni L (2004). Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic, and molecular study of 50 patients. Am J Surg Pathol 28: 719-735.
1534. Mathers ME, O'Donnell M (2000). Squamous cell carcinoma of skin with a rhabdoid phenotype: a case report. J Clin Pathol 53: 868-870.
1535. Mathews GJ, Osterholm JL (1972). Painful traumatic neuromas. Surg Clin North Am 52: 1313-1324.
1536. Mathiak M, Rutten A, Mangold E, Fischer HP, Ruzicka T, Friedl W, Propping P, Kruse R (2002). Loss of DNA mismatch repair proteins in skin tumors from patients with Muir-Torre syndrome and MSH2 or MLH1 germline mutations: establishment of immunohistochemical analysis as a screening test. Am J Surg Pathol 26: 338-343.
1537. Mathis ED, Honningford JB, Rodriguez HE, Wind KP, Connolly MM, Podbielski FJ (2001). Malignant proliferating trichilemmal tumor. Am J Clin Oncol 24: 351-353.
1538. Matt D, Xin H, Vortmeyer AO, Zhuang Z, Burg G, Boni R (2000). Sporadic trichoepithelioma demonstrates deletions at 9q22.3. Arch Dermatol 136: 657-660.
1539. Mazoujian G, Pinkus GS, Haagensen DEJr (1984). Extramammary Paget's disease—evidence for an apocrine origin. An immunoperoxidase study of gross cystic disease fluid protein-15, carcinoembryonic antigen, and keratin proteins. Am J Surg Pathol 8: 43-50.
1540. Mazur MT, Shultz JJ, Myers JL (1990). Granular cell tumor. Immunohistochemical analysis of 21 benign tumors and one malignant tumor. Arch Pathol Lab Med 114: 692-696.
1541. McAlvany JP, Jorizzo JL, Zanolli D, Auringer S, Prichard E, Krowchuk DP, Turner S (1993). Magnetic resonance imaging in the evaluation of lymphangioma circumscriptum. Arch Dermatol 129: 194-197.
1542. McBride SR, Leonard N, Reynolds NJ (2002). Loss of p21(WAF1) compartmentalisation in sebaceous carcinoma compared with sebaceous hyperplasia and sebaceous adenoma. J Clin Pathol 55: 763-766.
1543. McCalmont TH (1996). A call for logic in the classification of adnexal neoplasms. Am J Dermatopathol 18: 103-109.
1544. McCalmont TH (1998). Analysis of the anatomic distribution of adnexal neoplasms suggests a preponderance of lesions of folliculosebaceous lineage. J Cut Pathol 25: 506.
1545. McCalmont TH, Brinsko R, LeBoit PE (1991). Melanocytic acral nevi with intraepidermal ascent of cells (MANIACs): A reappraisal of melanocytic lesions from acral sites. J Cut Pathol 18: 378.
1546. McCalmont TH, Salmon PJM, Geisse JK, Grekin RG (1997). Desmoplastic squamous and adenosquamous carcinoma. 60 examples of an overlooked pattern of epithelial malignancy. J Cutan Pathol 24: 111.
1546A. McCarthy SW, Scolyer RA, Palmer AA (2004). Desmoplastic melanoma: a diagnostic trap for the unwary. Pathology 36: 445-451
1547. McClain KL, Leach CT, Jenson HB, Joshi VV, Pollock BH, Parmley RT, DiCarlo FJ, Chadwick EG, Murphy SB (1995). Association of Epstein-Barr virus with leiomyosarcomas in children with AIDS. N Engl J Med 332: 12-18.
1548. McCluggage WG, Fon LJ, O'Rourke D, Ismail M, Hill CM, Parks TG, Allen DC (1997). Malignant eccrine spiradenoma with carcinomatous and sarcomatous elements. J Clin Pathol 50: 871-873.
1549. McCluggage WG, Walsh MY, Bharucha H (1998). Anaplastic large cell malignant lymphoma with extensive eosinophilic or neutrophilic infiltration. Histopathology 32: 110-115.
1550. McCormack CJ, Kelly JW, Dorevitch AP (1997). Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. Arch Dermatol 133: 593-596.
1551. McDonagh JER (1912). A contribution to our knowledge of the naevoxanthoendothelioma. Br J Dermatol 24: 85-99.
1552. McGovern TW, Litaker MS (1992). Clinical predictors of malignant pigmented lesions. A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. J Dermatol Surg Oncol 18: 22-26.
1553. McGovern VJ (1983). Melanocytic lesions of glabrous skin. In: Melanoma: Histological Diagnosis and Prognosis, McGovern VJ, ed., Raven Press: New York , pp. 125-136.
1554. McGregor JM, Crook T, Fraser-Andrews EA, Rozycka M, Crossland S, Brooks L, Whittaker SJ (1999). Spectrum of p53 gene mutations suggests a possible role for ultraviolet radiation in the pathogenesis of advanced cutaneous lymphomas. J Invest Dermatol 112: 317-321.
1555. McKee PH, Fletcher CD, Stavrinos P, Pambakian H (1990). Carcinosarcoma arising in eccrine spiradenoma. A clinicopathologic and immunohistochemical study of two cases. Am J Dermatopathol 12: 335-343.
1556. McKee PH, Wilkinson JD, Black MM, Whimster IW (1981). Carcinoma (epithelioma) cuniculatum: a clinico-pathological study of nineteen cases and review of the literature. Histopathology 5: 425-436.
1557. McKinley E, Valles R, Bang R, Bocklage T (1998). Signet-ring squamous cell carcinoma: a case report. J Cutan Pathol 25: 176-181.
1558. McLelland J, Chu T (1988). Dermatofibrosarcoma protuberans arising in a BCG vaccination scar. Arch Dermatol 124: 496-497.
1559. McMenamin ME, Fletcher CD (2002). Reactive angioendotheliomatosis: a study of 15 cases demonstrating a wide clinicopathologic spectrum. Am J Surg Pathol 26: 685-697.
1560. McNiff JM, Cooper D, Howe G, Crotty PL, Tallini G, Crouch J, Eisen RN (1996). Lymphomatoid granulomatosis of the skin and lung. An angiocentric T-cell-rich B-cell lymphoproliferative disorder. Arch Dermatol 132: 1464-1470.
1561. McNiff JM, Eisen RN, Glusac EJ (1999). Immunohistochemical comparison of cutaneous lymphadenoma, trichoblastoma, and basal cell carcinoma: support for classification of lymphadenoma as a variant of trichoblastoma. J Cutan Pathol 26: 119-124.
1562. McNutt NS (1998). "Triggered trap": nevoid malignant melanoma. Semin Diagn Pathol 15: 203-209.
1563. McNutt NS, Urmacher C, Hakimian J, Hoss DM, Lugo J (1995). Nevoid malignant melanoma: morphologic patterns and immunohistochemical reactivity. J Cutan Pathol 22: 502-517.
1564. Medema RH, Kops GJ, Bos JL, Burgering BM (2000). AFX-like Forkhead transcription factors mediate cell-cycle regulation by Ras and PKB through p27kip1. Nature 404: 782-787.
1565. Meeker JH, Neubecker RD, Helwig EB (1962). Hidradenoma papilliferum. Am J Clin Pathol 37: 182-195.
1566. Megahed M, Scharffetter-Kochanek K (1993). Acantholytic acanthoma. Am J Dermatopathol 15: 283-285.
1567. Mehlman MA (1991). Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industry: Part I. Carcinogenicity of motor fuels: gasoline. Toxicol Ind Health 7: 143-152.
1568. Mehregan AH (1964). Apocrine cystadenoma. A clinicopathologic study with special reference to pigmented variety. Arch Dermatol 90: 274-279.
1569. Mehregan AH (1975). Lentigo senilis and its evolutions. J Invest Dermatol 65: 429-433.
1570. Mehregan AH, Brownstein MH (1978). Pilar sheath acanthoma. Arch Dermatol 114: 1495-1497.
1571. Mehregan AH, Hashimoto K, Rahbari H (1983). Eccrine adenocarcinoma. A clinicopathologic study of 35 cases. Arch Dermatol 119: 104-114.
1572. Mehregan AH, Lee KC (1987). Malignant proliferating trichilemmal tumors—report of three cases. J Dermatol Surg Oncol 13: 1339-1342.
1573. Mehregan AH, Mehregan DA (1993). Malignant melanoma in childhood. Cancer 71: 4096-4103.
1574. Mehregan DA, Gibson LE, Mehregan AH (1992). Malignant blue nevus: a report of eight cases. J Dermatol Sci 4: 185-192.
1575. Mehregan DA, Mehregan AH (1993). Deep penetrating nevus. Arch Dermatol 129: 328-331.
1576. Mehregan DR, Hamzavi F, Brown K (2003). Large cell acanthoma. Int J Dermatol 42: 36-39.
1577. Mehregan DR, Mehregan AH, Mehregan DA (1992). Benign lymphangioendothelioma: report of 2 cases. J Cutan Pathol 19: 502-505.
1578. Mejia R, Dano JA, Roberts R, Wiley E, CockerelI CJ, Cruz PDJr (1997). Langerhans' cell histiocytosis in adults. J Am Acad Dermatol 37: 314-317.
1579. Mendonca GA (1992). [Increasing risk of skin melanoma in Brazil]. Rev Saude Publica 26: 290-294.
1580. Mene A, Buckley CH (1985). Involvement of the vulval skin appendages by intraepithelial neoplasia. Br J Obstet Gynaecol 92: 634-638.
1581. Mentzel T, Calonje E, Fletcher CD (1993). Dermatomyofibroma: additional observations on a distinctive cutaneous myofibroblastic tumour with emphasis on differential diagnosis. Br J Dermatol 129: 69-73.
1582. Mentzel T, Kutzner H (2003). Haemorragic dermatomyofibroma (plaque-like dermal fibromatosis): clinicopathological and immunohistochemical analysis of three cases resembling Kaposi's sarcoma. Histopathology .
1583. Mentzel T, Kutzner H, Rutten A, Hugel H (2001). Benign fibrous histiocytoma (dermatofibroma) of the face: clinicopathologic and immunohistochemical study of 34 cases associated with an aggressive clinical course. Am J Dermatopathol 23: 419-426.
1584. Mentzel T, Partanen TA, Kutzner H (1999). Hobnail hemangioma ("targetoid hemosiderotic hemangioma"): clinicopathologic and immunohistochemical analysis of 62 cases. J Cutan Pathol 26: 279-286.
1585. Mentzel T, Requena L, Kaddu S, Soares de Aleida LM, Sangueza OP, Kutzner H (2003). Cutaneous myoepithelial neoplasms: clinicopathologic and immunohistochemical study of 20 cases suggesting a continuous spectrum ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and myoepithelial carcinoma. J Cutan Pathol 30: 294-302.
1586. Mentzel T, Wadden C, Fletcher CD (1994). Granular cell change in smooth muscle tumours of skin and soft tissue. Histopathology 24: 223-231.
1587. Menzies SW, Westerhoff K, Rabinovitz H, Kopf AW, McCarthy WH, Katz B (2000). Surface microscopy of pigmented basal cell carcinoma. Arch Dermatol 136: 1012-1016.
1588. Merkow LP, Burt RC, Hayeslip DW, Newton FJ, Slifkin M, Pardo M (1969). A cellular and malignant blue nevus: a light and electron microscopic study. Cancer 24: 888-896.
1589. Mesnard JM, Devaux C (1999). Multiple control levels of cell proliferation by human T-cell leukemia virus type 1 Tax protein. Virology 257: 277-284.
1590. Metcalf JS, Maize JC, LeBoit PE (1991). Circumscribed storiform collagenoma (sclerosing fibroma). Am J Dermatopathol 13: 122-129.
1591. Metry DW, Dowd CF, Barkovich AJ, Frieden IJ (2001). The many faces of PHACE syndrome. J Pediatr 139: 117-123.
1592. Metzger S, Ellwanger U, Stroebel W, Schiebel U, Rassner G, Fierlbeck G (1998). Extent and consequences of physician delay in the diagnosis of acral melanoma. Melanoma Res 8: 181-186.
1593. Metzler G, Schaumburg-Lever G, Hornstein O, Rassner G (1996). Malignant chondroid syringoma: immunohistopathology. Am J Dermatopathol 18: 83-89.
1594. Meyer TK, Rhee JS, Smith MM, Cruz MJ, Osipov VO, Wackym PA (2003). External auditory canal eccrine spiradenocarcinoma: A case report and review of literature. Head Neck 25: 505-510.
1595. Meyerson LB (1971). A peculiar papulosquamous eruption involving pigmented nevi. Arch Dermatol 103: 510-512.
1596. Micali G, Innocenzi D, Nasca MR (1997). Cellular blue nevus of the scalp infiltrating the underlying bone: case report and review. Pediatr Dermatol 14: 199-203.
1597. Michal M (1998). Cellular blue naevi with microalveolar pattern—a type of naevus frequently confused with melanoma. Pathol Res Pract 194: 83-86.
1598. Michal M, Baumruk L, Skalova A (1992). Myxoid change within cellular blue naevi: a diagnostic pitfall. Histopathology 20: 527-530.
1599. Michal M, Kerekes Z, Kinkor Z, Ondrias F, Pizinger K (1995). Desmoplastic cellular blue nevi. Am J Dermatopathol 17: 230-235.
1600. Michal M, Lamovec J, Mukensnabl P, Pizinger K (1999). Spiradenocylindromas of the skin: tumors with morphological features of spiradenoma and cylindroma in the same lesion: report of 12 cases. Pathol Int 49: 419-425.
1601. Michel S, Hohenleutner U, Stolz W, Landthaler M (1999). Acquired tufted

angioma in association with a complex cutaneous vascular malformation. Br J Dermatol 141: 1142-1144.
1602. Michelson HE (1933). Nodular subepidermal fibrosis. Arch Dermatol Syphilol 27: 812-820.
1603. Middel P, Hemmerlein B, Fayyazi A, Kaboth U, Radzun HJ (1999). Sinus histiocytosis with massive lymphadenopathy: evidence for its relationship to macrophages and for a cytokine-related disorder. Histopathology 35: 525-533.
1604. Miettinen M (1995). Keratin 20: immunohistochemical marker for gastrointestinal, urothelial, and Merkel cell carcinomas. Mod Pathol 8: 384-388.
1605. Miettinen M (2003). Malignant and potentially malignant fibroblastic and myofibroblastic tumors. In: Diagnostic Soft Tissue Pathology, Miettinen M, ed., Churchill Livingston: New York , pp. 189-204.
1606. Miettinen M, Holthofer H, Lehto VP, Miettinen A, Virtanen I (1983). Ulex europaeus I lectin as a marker for tumors derived from endothelial cells. Am J Clin Pathol 79: 32-36.
1607. Mihm MC, Clark WH, Reed RJ, Caruso MG (1973). Mast cell infiltrates of the skin and the mastocytosis syndrome. Hum Pathol 4: 231-239.
1608. Mihm MC, Googe PB (1990). Vulvar nevus with atypism. In: Problematic Pigmented Lesions: A Case Method Approach, Mihm MCJr, Googe PB, Tong AK, eds., Lea & Febiger: Philadelphia , pp. 221-239.
1609. Mihm MC, Jr., Clemente CG, Cascinelli N (1996). Tumor infiltrating lymphocytes in lymph node melanoma metastases: a histopathologic prognostic indicator and an expression of local immune response. Lab Invest 74: 43-47.
1610. Mihm MC, Jr., Googe PB (1990). Problematic pigmented lesions. Lea & Febiger: Philadelphia.
1611. Milburn PB, Brandsma JL, Goldsman CI, Teplitz ED, Heilman EI (1988). Disseminated warts and evolving squamous cell carcinoma in a patient with acquired immunodeficiency syndrome. J Am Acad Dermatol 19: 401-405.
1612. Milburn PB, Sian CS, Silvers DN (1982). The color of the skin of the palms and soles as a possible clue to the pathogenesis of acral-lentiginous melanoma. Am J Dermatopathol 4: 429-433.
1613. Milde P, Brunner M, Borchard F, Sudhoff T, Burk M, Zumdick M, Goerz G, Ruzicka T (1995). Cutaneous bacillary angiomatosis in a patient with chronic lymphocytic leukemia. Arch Dermatol 131: 933-936.
1614. Miliauskas JR (1994). Myxoid cutaneous pleomorphic fibroma. Histopathology 24: 179-181.
1615. Miller AM, Sahl WJ, Brown SA, Young SK, Quinlan CM, Patel PR, Benbrook DM, Naylor MF (1997). The role of human papillomavirus in the development of pyogenic granulomas. Int J Dermatol 36: 673-676.
1616. Miller RW, Rabkin CS (1999). Merkel cell carcinoma and melanoma: etiological similarities and differences. Cancer Epidemiol Biomarkers Prev 8: 153-158.
1617. Miller SJ (2000). The National Comprehensive Cancer Network (NCCN) guidelines of care for nonmelanoma skin cancers. Dermatol Surg 26: 289-292.
1618. Mills AE (1989). Rhabdomyomatous mesenchymal hamartoma of skin. Am J Dermatopathol 11: 58-63.
1619. Mills SE, Cooper PH, Fechner RE (1980). Lobular capillary hemangioma: the underlying lesion of pyogenic granuloma. A study of 73 cases from the oral and nasal mucous membranes. Am J Surg Pathol 4: 470-479.
1619A. Milton GW, Shaw HM, Thompson JF, McCarthy WH (1997). Cutaneous melanoma in childhood: incidence and prognosis. Australas J Dermatol 38 Suppl 1: S44-S48.
1620. Miracco C, Pacenti L, Santopietro R, Laurini L, Biagioli M, Luzi P (2000). Evaluation of telomerase activity in cutaneous melanocytic proliferations. Hum Pathol 31: 1018-1021.
1621. Miracco C, Raffaelli M, de Santi MM, Fimiani M, Tosi P (1988). Solitary cutaneous reticulum cell tumor. Enzyme-immunohistochemical and electron-microscopic analogies with IDRC sarcoma. Am J Dermatopathol 10: 47-53.
1622. Mirza I, Macpherson N, Paproski S, Gascoyne RD, Yang B, Finn WG, Hsi ED (2002). Primary cutaneous follicular lymphoma: an assessment of clinical, histopathologic, immunophenotypic, and molecular features. J Clin Oncol 20: 647-655.
1623. Misago N, Ackerman AB (1999). Trichoblastic (basal-cell) carcinoma with trichilemmal (at the bulb) differentiation. Dermatopathology, practical & conceptual 5: 200-204.
1624. Misago N, Narisawa Y (2000). Sebaceous neoplasms in Muir-Torre syndrome. Am J Dermatopathol 22: 155-161.
1625. Mishima Y (1970). Cellular blue nevus. Melanogenic activity and malignant transformation. Arch Dermatol 101: 104-110.
1626. Mishima Y, Mevorah B (1961). Nevus Ota and nevus Ito in American Negroes. J Invest Dermatol 36: 133-154.
1627. Mittelbronn MA, Mullins DL, Ramos-Caro FA, Flowers FP (1998). Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol 37: 677-681.
1628. Miyamoto Y, Ueda K, Sato M, Yasuno H (1979). Disseminated epidermolytic acanthoma. J Cutan Pathol 6: 272-279.
1629. Modly C, Wood C, Horn T (1989). Metastatic malignant melanoma arising from a common blue nevus in a patient with subacute cutaneous lupus erythematosus. Dermatologica 178: 171-175.
1630. Moller R, Reymann F, Hou-Jensen K (1979). Metastases in dermatological patients with squamous cell carcinoma. Arch Dermatol 115: 703-705.
1631. Mones JM, Ackerman AB (1984). Proliferating trichilemmal cyst is a squamous-cell carcinoma. Dermatopathology, practical & conceptual 4: 295-310.
1632. Mones JM, Ackerman AB (2003). Melanomas in prepubescent children: review comprehensively, critique historically, criteria diagnostically, and course biologically. Am J Dermatopathol 25: 223-238.
1633. Montagna W (1962). The Structure and Function of Skin. 2nd ed. Academic Press: New York.
1634. Montagna W, Hu F, Carlisle K (1980). A reinvestigation of solar lentigines. Arch Dermatol 116: 1151-1154.
1635. Montonen O, Ezer S, Laurikkala J, Karjalainen-Lindsberg ML, Thesleff I, Kere J, Saarialho-Kere U (1998). Expression of the anhidrotic ectodermal dysplasia gene is reduced in skin cancer coinciding with reduced E-cadherin. Exp Dermatol 7: 168-174.
1636. Mooi WJ (2001). Histopathology of Spitz naevi and "Spitzoid" melanomas. Curr Top Pathol 94: 65-77.
1637. Mooi WJ (2001). The expanding spectrum of cutaneous blue nevi. Curr Diagn Pathol 7: 56-58.
1638. Mooi WJ (2002). Spitz nevus and its histologic simulators. Adv Anat Pathol 9: 209-221.
1639. Moon TE, Levine N, Cartmel B, Bangert JL, Rodney S, Dong Q, Peng YM, Alberts DS (1997). Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. Cancer Epidemiol Biomarkers Prev 6: 949-956.
1640. Mooney MA, Barr RJ, Buxton MG (1995). Halo nevus or halo phenomenon? A study of 142 cases. J Cutan Pathol 22: 342-348.
1641. Moore AY (2001). Cutaneous warts. In: Human Papillomaviruses: Clinical and Scientific Advances, Sterling JC, Tyring SK, eds., Arnold: London .
1642. Moraillon I, Rybojad M, Chemaly P, Bourrillon A, Morel P (1993). [Congenital multiple cutaneous Abrikossof tumors]. Ann Dermatol Venereol 120: 816-818.
1643. Mordehai J, Kurzbart E, Shinhar D, Sagi A, Finaly R, Mares AJ (1998). Lymphangioma circumscriptum. Pediatr Surg Int 13: 208-210.
1644. Moreno A, Lamarca J, Martinez R, Guix M (1986). Osteoid and bone formation in desmoplastic malignant melanoma. J Cutan Pathol 13: 128-134.
1645. Moreno C, Jacyk WK, Judd MJ, Requena L (2001). Highly aggressive extraocular sebaceous carcinoma. Am J Dermatopathol 23: 450-455.
1646. Moreno C, Requena L, Kutzner H, de la Cruz A, Jaqueti G, Yus ES (2000). Epithelioid blue nevus: a rare variant of blue nevus not always associated with the Carney complex. J Cutan Pathol 27: 218-223.
1647. Morgan JM, Carmichael AJ, Ritchie C (1996). Extramammary Paget's disease of the axilla with an underlying apocrine carcinoma. Acta Derm Venereol 76: 173-174.
1648. Mori M, Manuelli C, Pimpinelli N, Mavilia C, Maggi E, Santucci M, Bianchi B, Cappugi P, Giannotti B, Kadin ME (1999). CD30-CD30 ligand interaction in primary cutaneous CD30(+) T-cell lymphomas: A clue to the pathophysiology of clinical regression. Blood 94: 3077-3083.
1649. Mori O, Hachisuka H, Sasai Y (1990). Proliferating trichilemmal cyst with spindle cell carcinoma. Am J Dermatopathol 12: 479-484.
1650. Morier P, Merot Y, Paccaud D, Beck D, Frenk E (1990). Juvenile chronic granulocytic leukemia, juvenile xanthogranulomas, and neurofibromatosis. Case report and review of the literature. J Am Acad Dermatol 22: 962-965.
1651. Morman MR, Petrozzi JW (1980). Cutaneous Hodgkin's disease. Cutis 26: 483-4, 491.
1652. Morrell DS, Esterly NB (2001). Solitary, lobulated, firm nodule. Pediatr Dermatol 18: 356-358.
1653. Mortier L, Marchetti P, Delaporte E, Martin de Lassalle E, Thomas P, Piette F, Formstecher P, Polakowska R, Danze PM (2002). Progression of actinic keratosis to squamous cell carcinoma of the skin correlates with deletion of the 9p21 region encoding the p16(INK4a) tumor suppressor. Cancer Lett 176: 205-214.
1654. Mortimore RJ, Whitehead KJ (2001). Dermatomyofibroma: a report of two cases, one occurring in a child. Australas J Dermatol 42: 22-25.
1655. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ (1992). Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 127: 392-399.
1655A. Morton DL, Thompson JF, Cochran AJ et al. (2005) Interim results of the multicenter selective lymphadenectomy trial (MSLT-I) in clinical stage melanoma. J Clin Oncol 23: 7500
1656. Motley R, Kersey P, Lawrence C (2002). Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Dermatol 146: 18-25.
1657. Moy RL, Moy LS, Matsuoka LY, Bennett RG, Uitto J (1988). Selectively enhanced procollagen gene expression in sclerosing (morphea-like) basal cell carcinoma as reflected by elevated pro alpha 1(I) and pro alpha 1(III) procollagen messenger RNA steady-state levels. J Invest Dermatol 90: 634-638.
1658. Moyes CD, Alexander FW (1977). Mucosal neuroma syndrome presenting in a neonate. Dev Med Child Neurol 19: 518-534.
1659. Mrak RE, Baker GF (1987). Granular cell basal cell carcinoma. J Cutan Pathol 14: 37-42.
1660. Mraz-Gernhard S, Natkunam Y, Hoppe RT, LeBoit P, Kohler S, Kim YH (2001). Natural killer/natural killer-like T-cell lymphoma, CD56+, presenting in the skin: an increasingly recognized entity with an aggressive course. J Clin Oncol 19: 2179-2188.
1661. Muche JM, Lukowsky A, Asadullah K, Gellrich S, Sterry W (1997). Demonstration of frequent occurrence of clonal T cells in the peripheral blood of patients with primary cutaneous T-cell lymphoma. Blood 90: 1636-1642.
1662. Muller-Hermelink HK, Catovsky D, Montserrat E, Harris NL (2001). Chronic lymphocytic leukaemia/small lymphocytic lymphoma. In: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Jaffe ES, Harris NL, Stein H, Vardiman J, eds., IARC Press: Lyon , pp. 127-130.
1663. Mulliken JB, Fishman SJ, Burrows PE (2000). Vascular anomalies. Curr Probl Surg 37: 517-584.
1664. Mulvany NJ, Sykes P (1997). Desmoplastic melanoma of the vulva. Pathology 29: 241-245.
1665. Munn SE, McGregor JM, Jones A, Amlot P, Rustin MH, Russell JR, Whittaker S (1996). Clinical and pathological heterogeneity in cutaneous gamma-delta T-cell lymphoma: a report of three cases and a review of the literature. Br J Dermatol 135: 976-981.
1666. Murakami I, Gogusev J, Fournet JC, Glorion C, Jaubert F (2002). Detection of molecular cytogenetic aberrations in langerhans cell histiocytosis of bone. Hum Pathol 33: 555-560.
1667. Murakami I, Sarker AB, Teramoto N, Horie Y, Taguchi K, Akagi T (1993). Spindle cell hemangioendothelioma: a report of two cases. Acta Pathol Jpn 43: 529-534.
1668. Murayama N, Tsuboi R, Unno K,

Ogawa H (1994). Multiple eccrine hidrocystomas. Br J Dermatol 131: 585-586.
1669. Musalli NG, Hopps RM, Johnson NW (1976). Oral pyogenic granuloma as a complication of pregnancy and the use of hormonal contraceptives. Int J Gynecol Obstet 14: 187-191.
1670. Musette P, Bachelez H, Flageul B, Delarbre C, Kourilsky P, Dubertret L, Gachelin G (1999). Immune-mediated destruction of melanocytes in halo nevi is associated with the local expansion of a limited number of T cell clones. J Immunol 162: 1789-1794.
1671. Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, Bilek P, Braun-Falco O, Plewig G (1994). The ABCD rule of dermatoscopy. High prospective value in the diagnosis of doubtful melanocytic skin lesions. J Am Acad Dermatol 30: 551-559.
1672. Nadji M (1986). Immunoperoxidase techniques. II. Application to cutaneous neoplasms. Am J Dermatopathol 8: 124-129.
1673. Nagai Y, Ishikawa O, Miyachi Y (1996). Multiple eccrine hidrocystomas associated with Graves' disease. J Dermatol 23: 652-654.
1674. Nagai Y, Ohno Y, Ishikawa O, Miyachi Y (1997). Cellular neurothekeoma on the lower lip. Br J Dermatol 137: 314-315.
1675. Nagore E, Sanchez-Motilla JM, Perez-Valles A, Martinez-Lahuerta C, Alegre V, Aliaga A (2000). Pseudovascular squamous cell carcinoma of the skin. Clin Exp Dermatol 25: 206-208.
1676. Nair M, Aron M, Sharma MC (2000). Angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma) of the breast: report of a case. Surg Today 30: 747-749.
1677. Nakagawa T, Nishimoto M, Takaiwa T (1986). Disseminated epidermolytic acanthoma revealed by PUVA. Dermatologica 173: 150-153.
1678. Nakajima T, Watanabe S, Sato Y, Kameya T, Hirota T, Shimosato Y (1982). An immunoperoxidase study of S-100 protein distribution in normal and neoplastic tissues. Am J Surg Pathol 6: 715-727.
1679. Nakamura H, Hirota S, Adachi S, Ozaki K, Asada H, Kitamura Y (2001). Clonal nature of seborrheic keratosis demonstrated by using the polymorphism of the human androgen receptor locus as a marker. J Invest Dermatol 116: 506-510.
1680. Nakamura M, Miyachi Y (1999). Calcifying sinusoidal haemangioma on the back. Br J Dermatol 141: 377-378.
1681. Nakamura S, Koshikawa T, Yatabe Y, Suchi T (1998). Lymphoblastic lymphoma expressing CD56 and TdT. Am J Surg Pathol 22: 135-137.
1682. Nakamura T (2000). Apoptosis and expression of Bax/Bcl-2 proteins in pyogenic granuloma: a comparative study with granulation tissue and capillary hemangioma. J Cutan Pathol 27: 400-405.
1683. Nakamura T, Kaneko H, Nishino I (1981). Angiokeratoma corporis diffusum (Fabry disease): ultrastructural studies of the skin. Acta Derm Venereol 61: 37-41.
1684. Nakamura Y, Hirakata T, Mukai M (1994). Nerve sheath myxoma of the lower lid. Br J Ophthalmol 78: 729.
1685. Nakanishi H, Hashimoto I, Takiwaki H, Urano Y, Arase S (1995). Striated muscle hamartoma of the nostril. J Dermatol 22: 504-507.
1686. Nakaoka H, Miyauchi S, Miki Y (1995). Proliferating activity of dermal fibroblasts in keloids and hypertrophic scars. Acta Derm Venereol 75: 102-104.
1687. Nappi O, Pettinato G, Wick MR (1989). Adenoid (acantholytic) squamous cell carcinoma of the skin. J Cutan Pathol 16: 114-121.
1688. Nappi O, Wick MR, Pettinato G, Ghiselli RW, Swanson PE (1992). Pseudovascular adenoid squamous cell carcinoma of the skin. A neoplasm that may be mistaken for angiosarcoma. Am J Surg Pathol 16: 429-438.
1689. Natkunam Y, Smoller BR, Zehnder JL, Dorfman RF, Warnke RA (1999). Aggressive cutaneous NK and NK-like T-cell lymphomas: clinicopathologic, immunohistochemical, and molecular analyses of 12 cases. Am J Surg Pathol 23: 571-581.
1690. Natkunam Y, Warnke RA, Haghighi B, Su LD, Le Boit PE, Kim YH, Kohler S (2000). Co-expression of CD56 and CD30 in lymphomas with primary presentation in the skin: clinicopathologic, immunohistochemical and molecular analyses of seven cases. J Cutan Pathol 27: 392-399.
1691. Nebesio CL, Mirowski GW, Chuang TY (2001). Human papillomavirus: clinical significance and malignant potential. Int J Dermatol 40: 373-379.
1692. Nelemans PJ, Kiemeney LA, Rampen FH, Straatman H, Verbeek AL (1992). Trends in mortality from malignant cutaneous melanoma in The Netherlands, 1950-1988. Eur J Cancer 29A: 107-111.
1693. Nelen MR, Kremer H, Konings IB, Schoute F, van Essen AJ, Koch R, Woods CG, Fryns JP, Hamel B, Hoefsloot LH, Peeters EA, Padberg GW (1999). Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. Eur J Hum Genet 7: 267-273.
1694. Nelen MR, Padberg GW, Peeters EA, Lin AY, van den Helm B, Frants RR, Coulon V, Goldstein AM, van Reen MM, Easton DF, Eeles RA, Hodgsen S, Mulvihill JJ, Murday VA, Tucker MA, Mariman EC, Starink TM, Ponder BA, Ropers HH, Kremer H, Longy M, Eng C (1996). Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet 13: 114-116.
1695. Nelen MR, van Staveren WC, Peeters EA, Hassel MB, Gorlin RJ, Hamm H, Lindboe CF, Fryns JP, Sijmons RH, Woods DG, Mariman EC, Padberg GW, Kremer H (1997). Germline mutations in the PTEN/MMAC1 gene in patients with Cowden disease. Hum Mol Genet 6: 1383-1387.
1696. Nelson MA, Einspahr JG, Alberts DS, Balfour CA, Wymer JA, Welch KL, Salasche SJ, Bangert JL, Grogan TM, Bozzo PO (1994). Analysis of the p53 gene in human precancerous actinic keratosis lesions and squamous cell cancers. Cancer Lett 85: 23-29.
1696A. Nelson BR, Metz RD, Majmudar G, Hamilton TA, Gillard MO, Railan D, Griffiths CE, Johnson TM (1996). A comparison of wire brush and diamond fraise superficial dermabrasion for photoaged skin. A clinical, immunohistologic, and biochemical study. J Am Acad Dermatol 34: 235-243.
1697. Netland PA, Townsend DJ, Albert DM, Jakobiec FA (1990). Hidradenoma papilliferum of the upper eyelid arising from the apocrine gland of Moll. Ophthalmology 97: 1593-1598.
1698. Neumann RA, Knobler RM, Schuller-Petrovic S, Lindmaier A, Gebhart W (1989). Giant arteriovenous hemangioma (cirsoid aneurysm) of the nose. J Dermatol Surg Oncol 15: 739-742.
1699. Newnham A, Moller H (2002). Trends in the incidence of cutaneous malignant melanomas in the south east of England, 1960-1998. J Public Health Med 24: 268-275.
1700. Newton JA (1993). Familial melanoma. Clin Exp Dermatol 18: 5-11.
1701. Ng P, Ackerman AB (2001). The major types of squamous-cell carcinoma. Dermatopathology, practical & conceptual 5: 250-252.
1702. Nguyen GK, Mielke BW (1987). Extraocular sebaceous carcinoma with intraepidermal (pagetoid) spread. Am J Dermatopathol 9: 364-365.
1703. Nguyen M, Song S, Liem A, Androphy E, Liu Y, Lambert PF (2002). A mutant of human papillomavirus type 16 E6 deficient in binding alpha-helix partners displays reduced oncogenic potential in vivo. J Virol 76: 13039-13048.
1704. Nguyen P, Vin-Christian K, Ming ME, Berger T (2002). Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. Arch Dermatol 138: 758-763.
1705. Ni C, Wagoner M, Kieval S, Albert DM (1984). Tumours of the Moll's glands. Br J Ophthalmol 68: 502-506.
1706. Nicholls DS, Mason GH (1988). Halo dermatitis around a melanocytic naevus: Meyerson's naevus. Br J Dermatol 118: 125-129.
1707. Nicholson SA, McDermott MB, Swanson PE, Wick MR (2000). CD99 and cytokeratin-20 in small-cell and basaloid tumors of the skin. Appl Immunohistochem Mol Morphol 8: 37-41.
1708. Niederecker C, Sauter B, Furnsinn AM, Rappersberger K (1996). [Malignant blue nevus with metastasis to lymph nodes and brain]. Hautarzt 47: 711-715.
1709. Nielsen H, Nielsen PL (1994). Cutaneous tufted angioma as a differential diagnosis to Kaposi's sarcoma in HIV infection. AIDS 8: 707-708.
1710. Nielsen TA, Maia-Cohen S, Hessel AB, Xie DL, Pellegrini AE (1998). Sebaceous neoplasm with reticulated and cribriform features: a rare variant of sebaceoma. J Cutan Pathol 25: 233-235.
1711. Niessen FB, Spauwen PH, Schalkwijk J, Kon M (1999). On the nature of hypertrophic scars and keloids: a review. Plast Reconstr Surg 104: 1435-1458.
1712. Niizuma K (1979). Isolated epidermolytic acanthoma. A histological study. Dermatologica 159: 30-36.
1713. Nik NA, Glew WB, Zimmerman LE (1982). Malignant melanoma of the choroid in the nevus of Ota of a black patient. Arch Ophthalmol 100: 1641-1643.
1714. Nikkels AF, Arrese Estrada J, Pierard-Franchimont C, Pierard GE (1993). CD68 and factor XIIIa expressions in granular-cell tumor of the skin. Dermatology 186: 106-108.
1715. Nikolova M, Bagot M, Boumsell L, Bensussan A (2002). Identification of cell surface molecules characterizing human cutaneous T-cell lymphomas. Leuk Lymphoma 43: 741-746.
1716. Nilsson M, Unden AB, Krause D, Malmqwist U, Raza K, Zaphiropoulos PG, Toftgard R (2000). Induction of basal cell carcinomas and trichoepitheliomas in mice overexpressing GLI-1. Proc Natl Acad Sci U S A 97: 3438-3443.
1717. Nishigori C (2000). UV-induced DNA damage in carcinogenesis and its repair. J Dermatol Sci 23 Suppl 1: S41-S44.
1718. Nissim F, Czernobilsky B, Ostfeld E (1981). Hidradenoma papilliferum of the external auditory canal. J Laryngol Otol 95: 843-848.
1719. Noguchi M, Akiyama M, Kawakami M, Nagashima T, Niizuma K, Matsuo I (2000). Eccrine syringofibroadenoma developing in a sebaceous naevus. Br J Dermatol 142: 1050-1051.
1720. Nomura K, Hashimoto I (1997). Eccrine syringofibroadenomatosis in two patients with bullous pemphigoid. Dermatology 195: 395-398.
1721. Nomura K, Kogawa T, Hashimoto I, Katabira Y (1991). Eccrine syringofibroadenomatous hyperplasia in a patient with bullous pemphigoid: a case report and review of the literature. Dermatologica 182: 59-62.
1722. North PE, Waner M, Mizeracki A, Mihm MCJr (2000). GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 31: 11-22.
1723. North PE, Waner M, Mizeracki A, Mrak RE, Nicholas R, Kincannon J, Suen JY, Mihm MCJr (2001). A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol 137: 559-570.
1724. Noto G (1999). 'Benign' proliferating trichilemmal tumour: does it really exist? Histopathology 35: 386-387.
1725. Noto G, Bongiorno MR, Pravata G, Arico M (1994). Multiple nevoid spiradenomas. Am J Dermatopathol 16: 280-284.
1726. Noto G, Pravata G, Arico M (1990). "Shadow" cells in proliferating trichilemmal tumors. Am J Dermatopathol 12: 319-320.
1727. Noto G, Pravata G, Arico M (1997). Malignant proliferating trichilemmal tumor. Am J Dermatopathol 19: 202-204.
1728. Noto G, Pravata G, Arico M (1997). Proliferating tricholemmal cyst should always be considered as a low-grade carcinoma. Dermatology 194: 374-375.
1729. Noto G, Pravata G, Miceli S, Arico M (1994). Granulomatous slack skin: report of a case associated with Hodgkin's disease and a review of the literature. Br J Dermatol 131: 275-279.
1730. Novak E, Stevenson RR (1945). Sweat gland tumors of the vulva, benign (hidradenoma) and malignant (adenocarcinoma). Am J Obstet Gynecol 501: 641-659.
1731. Novice FM, Collison DW, Kleinsmith DM, Osband ME, Burdakin JH, Coskey RJ (1989). Letterer-Siwe disease in adults. Cancer 63: 166-174.
1732. Noz KC, Bauwens M, van Buul PP, Vrolijk H, Schothorst AA, Pavel S, Tanke HJ, Vermeer BJ (1996). Comet assay demonstrates a higher ultraviolet B sensitivity to DNA damage in dysplastic nevus cells than in common melanocytic nevus cells and foreskin melanocytes. J Invest Dermatol 106: 1198-1202.
1733. Nussen S, Ackerman AB (1998). Sebaceous "adenoma" is sebaceous carcinoma. Dermatopathology, practical & conceptual 4: 5-14.
1734. Nwokoro NA, Korytkowski MT, Rose S, Gorin MB, Penles Stadler M, Witchel SF, Mulvihill JJ (1997). Spectrum of malignancy and premalignancy in Carney syndrome. Am J Med Genet 73: 369-377.
1735. O'Brien KP, Seroussi E, Dal Cin P, Sciot R, Mandahl N, Fletcher JA, Turc-Carel C, Dumanski JP (1998). Various regions within the alpha-helical domain of the COL1A1 gene are fused to the second exon of the PDGFB gene in dermatofibrosarcomas and giant-cell fibroblas-

tomas. Genes Chromosomes Cancer 23: 187-193.
1736. O'Grady TC, Barr RJ, Billman G, Cunningham BB (1999). Epithelioid blue nevus occurring in children with no evidence of Carney complex. Am J Dermatopathol 21: 483-486.
1737. Obalek S, Jablonska S, Beaudenon S, Walczak L, Orth G (1986). Bowenoid papulosis of the male and female genitalia: risk of cervical neoplasia. J Am Acad Dermatol 14: 433-444.
1738. Odom RB, James WD, Berger TG (2000). Andrews' Diseases of the Skin: Clinical Dermatology. W.B. Saunders: Philadelphia.
1739. Offidani A, Campanati A (1999). Papillary hidradenoma: immunohistochemical analysis of steroid receptor profile with a focus on apocrine differentiation. J Clin Pathol 52: 829-832.
1740. Ogasawara Y, Kinoshita E, Ishida T, Hamamoto Y, Fujiyama J, Muto M (2003). A case of multiple keratoacanthoma centrifugum marginatum: response to oral etretinate. J Am Acad Dermatol 48: 282-285.
1741. Ogilvie JW (1982). Malignant eccrine acrospiroma. A case report. J Bone Joint Surg Am 64: 780-782.
1742. Ohnishi T, Suzuki T, Watanabe S (1995). Eccrine syringofibroadenoma. Report of a case and immunohistochemical study of keratin expression. Br J Dermatol 133: 449-454.
1743. Ohnishi T, Watanabe S (1995). Immunohistochemical characterization of keratin expression in clear cell acanthoma. Br J Dermatol 133: 186-193.
1744. Ohnishi T, Watanabe S (1999). Immunohistochemical analysis of cytokeratin expression in apocrine cystadenoma or hidrocystoma. J Cutan Pathol 26: 295-300.
1745. Ohnishi T, Watanabe S, Nomura K (2000). Immunohistochemical analysis of cytokeratin expression in reactive eccrine syringofibroadenoma-like lesion: a comparative study with eccrine syringofibroadenoma. J Cutan Pathol 27: 164-168.
1746. Ohtsuka H, Nagamatsu S (2003). Changing trends in numbers of deaths from malignant melanoma in Japan, 1955-2000. Dermatology 207: 162-165.
1747. Okada E, Tamura A, Ishikawa O, Miyachi Y (2000). Tufted angioma (angioblastoma): case report and review of 41 cases in the Japanese literature. Clin Exp Dermatol 25: 627-630.
1748. Okada N (1987). Solitary giant spider angioma with an overlying pyogenic granuloma. J Am Acad Dermatol 16: 1053-1054.
1749. Okuda C, Ito M, Fujiwara H, Takenouchi T (1995). Sebaceous epithelioma with sweat gland differentiation. Am J Dermatopathol 17: 523-528.
1750. Okun MR, Di Mattia A, Thompson J, Pearson SH (1974). Malignant melanoma developing from intradermal nevi. Arch Dermatol 110: 599-601.
1751. Okun MR, Finn R, Blumental G (1980). Apocrine adenoma versus pocrine carcinoma. Report of two cases. J Am Acad Dermatol 2: 322-326.
1752. Oliver GF, Umbert I, Winkelmann RK, Muller SA (1990). Reticulohistiocytoma cutis—review of 15 cases and an association with systemic vasculitis in two cases. Clin Exp Dermatol 15: 1-6.
1753. Olsen TG, Helwig EB (1985). Angiolymphoid hyperplasia with eosinophilia. A clinicopathologic study of 116 patients. J Am Acad Dermatol 12: 781-796.
1754. Onishi Y, Ohara K (1999). Angiolymphoid hyperplasia with eosinophilia associated with arteriovenous malformation: a clinicopathological correlation with angiography and serial estimation of serum levels of renin, eosinophil cationic protein and interleukin 5. Br J Dermatol 140: 1153-1156.
1755. Orchard GE, Zelger B, Jones EW, Jones RR (1996). An immunocytochemical assessment of 19 cases of cutaneous angiosarcoma. Histopathology 28: 235-240.
1756. Orchard J, Garand R, Davis Z, Babbage G, Sahota S, Matutes E, Catovsky D, Thomas PW, Avet-Loiseau H, Oscier D (2003). A subset of t(11;14) lymphoma with mantle cell features displays mutated IgVH genes and includes patients with good prognosis, nonnodal disease. Blood 101: 4975-4981.
1757. Ordonez NG, Awalt H, Mackay B (1987). Mammary and extramammary Paget's disease. An immunocytochemical and ultrastructural study. Cancer 59: 1173-1183.
1757A. Orlandini V, Kolb F, Spatz A, Court B, Ortoli JC, Sabourin C, Wechsler J, Mansard S, Souteyrand P, Arigon V, Andry-Benzaquen P, Avril MF (2004). Melanoma of the penis: 6 cases. Ann Dermatol Venereol 131: 541-544.
1758. Orlet HK, Still J, Law E, Gertler C (2001). Malignant melanoma in a burn scar. Ann Plast Surg 46: 59-61.
1759. Ortonne JP (2002). From actinic keratosis to squamous cell carcinoma. Br J Dermatol 146 Suppl 61: 20-23.
1760. Oscier DG, Gardiner AC, Mould SJ, Glide S, Davis ZA, Ibbotson RE, Corcoran MM, Chapman RM, Thomas PW, Copplestone JA, Orchard JA, Hamblin TJ (2002). Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. Blood 100: 1177-1184.
1761. Osterlind A (1992). Epidemiology on malignant melanoma in Europe. Acta Oncol 31: 903-908.
1762. Oyler RM, Davis DA, Woosley JT (1997). Lymphangioma associated with Becker's nevus: a report of coincident hamartomas in a child. Pediatr Dermatol 14: 376-379.
1763. Pack GT, Lenson N, Gerber DM (1952). Regional distribution of moles and melanomas. Arch Surg 65: 826-870.
1764. Packeisen J, Nowak M, Kruger A (2002). [Epulis in a newborn. histogenetic comparison with a granular cell tumor in adults]. Pathologe 23: 145-148.
1765. Padilla RS, Orkin M, Rosai J (1987). Acquired "tufted" angioma (progressive capillary hemangioma). A distinctive clinicopathologic entity related to lobular capillary hemangioma. Am J Dermatopathol 9: 292-300.
1766. Paget J (1874). On disease of the mammary areola preceding cancer of the mammary gland. St Barth Hosp Rep 10: 87.
1767. Paladugu RR, Winberg CD, Yonemoto RH (1983). Acral lentiginous melanoma. A clinicopathologic study of 36 patients. Cancer 52: 161-168.
1768. Palmer LC, Strauch WG, Welton WA (1978). Lymphangioma circumscriptum. A case with deep lymphatic involvement. Arch Dermatol 114: 394-396.
1769. Paniago-Pereira C, Maize JC, Ackerman AB (1978). Nevus of large spindle and/or epithelioid cells (Spitz's nevus). Arch Dermatol 114: 1811-1823.
1770. Papadavid E, Pignatelli M, Zakyn-thinos S, Krausz T, Chu AC (2002). Abnormal immunoreactivity of the E-cadherin/catenin (alpha-, beta-, and gamma-) complex in premalignant and malignant non-melanocytic skin tumours. J Pathol 196: 154-162.
1771. Pappo AS (2003). Melanoma in children and adolescents. Eur J Cancer 39: 2651-2661.
1772. Parham DM, Fisher C (1997). Angiosarcomas of the breast developing post radiotherapy. Histopathology 31: 189-195.
1773. Park BS, Yang SG, Cho KH (1997). Malignant proliferating trichilemmal tumor showing distant metastases. Am J Dermatopathol 19: 536-539.
1774. Park HJ, Kim YC, Cinn YW (2000). Nodular hidradenocarcinoma with prominent squamous differentiation: case report and immunohistochemical study. J Cutan Pathol 27: 423-427.
1775. Park WS, Vortmeyer AO, Pack S, Duray PH, Boni R, Guerami AA, Emmert-Buck MR, Liotta LA, Zhuang Z (1998). Allelic deletion at chromosome 9p21(p16) and 17p13(p53) in microdissected sporadic dysplastic nevus. Hum Pathol 29: 127-130.
1776. Park Y, Chung J, Cho CG (2002). Angiolymphoid hyperplasia with eosinophilia of the tongue: report of a case and review of the literature. Oral Oncol 38: 103-106.
1777. Park YH, Houh D, Houh W (1996). Subcutaneous and superficial granuloma pyogenicum. Int J Dermatol 35: 205-206.
1778. Parker RK, Mallory SB, Baker GF (1991). Infantile myofibromatosis. Pediatr Dermatol 8: 129-132.
1779. Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108.
1780. Parkin DM, Ferlay J, Hamdi-Cherif M, Sitas F, Thomas JO, Wabinga H, Whelan SL (2003). Cancer in Africa: Epidemiology and Prevention. IARC Press: Lyon.
1781. Parkin DM, Whelan SL, Ferley J, Raymond L, Young J (1997). Cancer Incidence in Five Continents. IARC: Lyon.
1782. Patel A, Halliday GM, Cooke BE, Barnetson RS (1994). Evidence that regression in keratoacanthoma is immunologically mediated: a comparison with squamous cell carcinoma. Br J Dermatol 131: 789-798.
1783. Patel BC, Egan CA, Lucius RW, Gerwels JW, Mamalis N, Anderson RL (1998). Cutaneous malignant melanoma and oculodermal melanocytosis (nevus of Ota): report of a case and review of the literature. J Am Acad Dermatol 38: 862-865.
1784. Patel SV, Bass FD, Niemi WJ, Pressman MM (1996). Spindle cell hemangioendothelioma: a case presentation and literature review of a rare lower extremity tumor. J Foot Ankle Surg 35: 309-311.
1785. Paties C, Taccagni GL, Papotti M, Valente G, Zangrandi A, Aloi F (1993). Apocrine carcinoma of the skin. A clinicopathologic, immunocytochemical, and ultrastructural study. Cancer 71: 375-381.
1786. Paties C, Vassallo G, Taccagni GL (1997). Clear cell dermatofibroma. Am J Surg Pathol 21: 250-252.
1787. Patrice SJ, Wiss K, Mulliken JB (1991). Pyogenic granuloma (lobular capillary hemangioma): a clinicopathologic study of 178 cases. Pediatr Dermatol 8: 267-276.
1788. Patrizi A, Neri I, Trevisi P, Landi C, Bardazzi F (1998). Congenital angiokeratoma of Fordyce. J Eur Acad Dermatol Venereol 10: 195-196.
1789. Pattee SF, Silvis NG (2003). Keratoacanthoma developing in sites of previous trauma: a report of two cases and review of the literature. J Am Acad Dermatol 48: S35-S38.
1790. Patterson JW, Kao GF, Graham JH, Helwig EB (1986). Bowenoid papulosis. A clinicopathologic study with ultrastructural observations. Cancer 57: 823-836.
1791. Patterson JW, Maygarden SJ (1986). Extraskeletal Ewing's sarcoma with cutaneous involvement. J Cutan Pathol 13: 46-58.
1792. Paul E, Cochran AJ, Wen DR (1988). Immunohistochemical demonstration of S-100 protein and melanoma-associated antigens in melanocytic nevi. J Cutan Pathol 15: 161-165.
1793. Paul MA, Fleischer ABJr, Wieselthier JS, White WL (1994). Bacillary angiomatosis in an immunocompetent child: the first reported case. Pediatr Dermatol 11: 338-341.
1794. Paulger BR, Kraus EW, Pulitzer DR, Moore CM (1997). Xp microdeletion syndrome characterized by pathognomonic linear skin defects on the head and neck. Pediatr Dermatol 14: 26-30.
1795. Paulli M, Berti E, Rosso R, Boveri E, Kindl S, Klersy C, Lazzarino M, Borroni G, Menestrina F, Santucci M, Gambini C, Vassallo G, Magrini U, Sterry W, Burg G, Geerts ML, Meijer CJLM, Willemze R, Feller AC, Muller-Hermelink HK, Kadin ME (1995). CD30/Ki-1-positive lymphoproliferative disorders of the skin—clinicopathologic correlation and statistical analysis of 86 cases: a multicentric study from the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group. J Clin Oncol 13: 1343-1354.
1796. Paulli M, Rosso R, Kindl S, Boveri E, Marocolo D, Chioda C, Agostini C, Magrini U, Facchetti F (1992). Immunophenotypic characterization of the cell infiltrate in five cases of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Hum Pathol 23: 647-654.
1797. Paulli M, Viglio A, Vivenza D, Capello D, Rossi D, Riboni R, Lucioni M, Incardona P, Boveri E, Bellosta M, Orlandi E, Borroni G, Lazzarino M, Berti E, Alessi E, Magrini U, Gaidano G (2002). Primary cutaneous large B-cell lymphoma of the leg: histogenetic analysis of a controversial clinicopathologic entity. Hum Pathol 33: 937-943.
1798. Peachey RD, Lim CC, Whimster IW (1970). Lymphangioma of skin. A review of 65 cases. Br J Dermatol 83: 519-527.
1799. Pearson JM, McWilliam LJ (1990). A light microscopical, immunohistochemical, and ultrastructural comparison of hemangiomata and lymphangiomata. Ultrastruct Pathol 14: 497-504.
1800. Pembroke AC, Grice K, Levantine AV, Warin AP (1978). Eruptive angiomata in malignant disease. Clin Exp Dermatol 3: 147-156.
1801. Penneys NS (1984). Immunohistochemistry of adnexal neoplasms. J Cutan Pathol 11: 357-364.
1802. Penneys NS, Ackerman AB, Indgin SN, Mandy SH (1970). Eccrine poroma: two unusual variants. Br J Dermatol 82: 613-615.
1803. Penneys NS, Shapiro S (1994). CD44 expression in Merkel cell carcinoma may correlate with risk of metastasis. J Cutan Pathol 21: 22-26.
1804. Pereira F, Carey W, Shibata H, Burnier MNJr, Wang B (2002). Multiple nevoid malignant melanomas in a patient

with AIDS: the role of proliferating cell nuclear antigen in the diagnosis. J Am Acad Dermatol 47: S172-S174.
1805. Pereyo NG, Requena L, Galloway J, Sangueza OP (1997). Follicular mycosis fungoides: a clinicohistopathologic study. J Am Acad Dermatol 36: 563-568.
1806. Perez MT, Suster S (1999). Balloon cell change in cellular blue nevus. Am J Dermatopathol 21: 181-184.
1807. Perkins P, Weiss SW (1996). Spindle cell hemangioendothelioma. An analysis of 78 cases with reassessment of its pathogenesis and biologic behavior. Am J Surg Pathol 20: 1196-1204.
1808. Perkins W, Campbell I, Leigh IM, MacKie RM (1992). Keratin expression in normal skin and epidermal neoplasms demonstrated by a panel of monoclonal antibodies. J Cutan Pathol 19: 476-482.
1809. Perniciaro C, Winkelmann RK, Daoud MS, Su WP (1995). Malignant angioendotheliomatosis is an angiotropic intravascular lymphoma. Immunohistochemical, ultrastructural, and molecular genetics studies. Am J Dermatopathol 17: 242-248.
1810. Person JR (2003). An actinic keratosis is neither malignant nor premalignant: it is an initiated tumor. J Am Acad Dermatol 48: 637-638.
1811. Persson JR (1978). Acral arteriovenous tumor. Acta Derm Venereol 58: 95.
1812. Perzin KH, Gullane P, Conley J (1982). Adenoid cystic carcinoma involving the external auditory canal. Cancer 50: 2873-2883.
1813. Peters K, Knoll JH, Kadin ME (1995). Cytogenetic findings in regressing skin lesions of lymphomatoid papulosis. Cancer Genet Cytogenet 80: 13-16.
1814. Peters MS, Goellner JR (1986). Spitz naevi and malignant melanomas of childhood and adolescence. Histopathology 10: 1289-1302.
1815. Peters MS, Reiman HM, Muller SA (1985). Cutaneous extraskeletal Ewing's sarcoma. J Cutan Pathol 12: 476-485.
1816. Petit A, Viney C, Gaulier A, Sigal M (1994). Coexistence of Meyerson's with Sutton's naevus after sunburn. Dermatology 189: 269-270.
1817. Petrella T, Dalac S, Maynadie M, Mugneret F, Thomine E, Courville P, Joly P, Lenormand B, Arnould L, Wechsler J, Bagot M, Rieux C, Bosq J, Avril MF, Bernheim A, Molina T, Devidas A, Delfau-Larue MH, Gaulard P, Lambert D (1999). CD4+ CD56+ cutaneous neoplasms: a distinct hematological entity? Groupe Francais d'Etude des Lymphomes Cutanes (GFELC). Am J Surg Pathol 23: 137-146.
1818. Petronzelli F, Sollima D, Coppola G, Martini-Neri ME, Neri G, Genuardi M (2001). CDKN2A germline splicing mutation affecting both p16(ink4) and p14(arf) RNA processing in a melanoma/neurofibroma kindred. Genes Chromosomes Cancer 31: 398-401.
1819. Petter G, Haustein UF (2000). Histologic subtyping and malignancy assessment of cutaneous squamous cell carcinoma. Dermatol Surg 26: 521-530.
1820. Pezzella F, Santucci M, et al. (1994). Bcl-2 gene rearrangement and protein expression in primary cutaneous B-cell lymphomas. In: Basic Mechanisms of Physiological and Aberrant Lymphoproliferation in the Skin, van Vloten WA, Lambert WC, Gianotti B, eds., Plenum Press: New York , pp. 343-353.
1821. Pfahlberg A, Botev IN, Kolmel KF, Gefeller O (2002). Vaccination and melanoma risk. Int J Cancer 102: 96-97.
1822. Pfahlberg A, Kolmel KF, Grange JM, Mastrangelo G, Krone B, Botev IN, Niin M, Seebacher C, Lambert D, Shafir R, Schneider D, Kokoschka EM, Kleeberg UR, Uter W, Gefeller O (2002). Inverse association between melanoma and previous vaccinations against tuberculosis and smallpox: results of the FEBIM study. J Invest Dermatol 119: 570-575.
1823. Piamphongsant T (1999). Chronic environmental arsenic poisoning. Int J Dermatol 38: 401-410.
1824. Piccinno R, Caccialanza M, Berti E (2003). Dermatologic radiotherapy of primary cutaneous follicle center cell lymphoma. Eur J Dermatol 13: 49-52.
1825. Piccinno R, Caccialanza M, Berti E, Baldini L (1993). Radiotherapy of cutaneous B cell lymphomas: our experience in 31 cases. Int J Radiat Oncol Biol Phys 27: 385-389.
1826. Pich A, Chiusa L, Margaria E, Aloi F (1993). Proliferative activity in the malignant cellular blue nevus. Hum Pathol 24: 1323-1329.
1827. Picker LJ, Michie SA, Rott LS, Butcher EC (1990). A unique phenotype of skin-associated lymphocytes in humans. Preferential expression of the HECA-452 epitope by benign and malignant T cells at cutaneous sites. Am J Pathol 136: 1053-1068.
1827A. Pickford MA, Hogg FJ, Fallowfield ME, Webster MH (1995). Sebaceous carcinoma of the periorbital and extraorbital regions. Br J Plast Surg 48: 93-96.
1828. Piepkorn M, Meyer LJ, Goldgar D, Seuchter SA, Cannon-Albright LA, Skolnick MH, Zone JJ (1989). The dysplastic melanocytic nevus: a prevalent lesion that correlates poorly with clinical phenotype. J Am Acad Dermatol 20: 407-415.
1829. Piepkorn MW, Barnhill RL, Cannon-Albright LA, Elder DE, Goldgar DE, Lewis CM, Maize JC, Meyer LJ, Rabkin MS, Sagebiel RW, . (1994). A multiobserver, population-based analysis of histologic dysplasia in melanocytic nevi. J Am Acad Dermatol 30: 707-714.
1830. Pilgrim JP, Kloss SG, Wolfish PS, Heng MC (1985). Primary mucinous carcinoma of the skin with metastases to the lymph nodes. Am J Dermatopathol 7: 461-469.
1831. Pimpinelli N, Masala G, et al. (1996). Primary cutaneous lymphomas in Florence: a population-based study 1986-1995. Ann Oncol 7: 130.
1832. Pimpinelli N, Santucci M (2000). The skin-associated lymphoid tissue-related B-cell lymphomas. Semin Cutan Med Surg 19: 124-129.
1833. Pindborg JJ, Reichart PA, Smith CJ, van der Waal I (1997). Histological Typing of Cancer and Precancer of the Oral Mucosa. 2nd ed. Springer: Berlin Heidelberg New York.
1834. Pinkus H (1953). Premalignant fibroepithelial tumours of the skin. Arch Dermatol 67: 598-615.
1835. Pinkus H (1958). Keratosis senilis. A biologic concept of its pathogenesis and diagnosis based on the study of normal epidermis and 1730 seborrheic and senile keratoses. Am J Clin Pathol 29: 193-207.
1836. Pinkus H, Coskey R, Burgess GH (1974). Trichodiscoma. A benign tumor related to haarscheibe (hair disk). J Invest Dermatol 63: 212-218.
1837. Pinkus H, Mehregan AH (1963). Epidermotropic eccrine carcinoma. Arch Dermatol 88: 597-606.
1838. Pinto A, Zagonel V, Ferrara F (2001). Acute myeloid leukemia in the elderly: biology and therapeutic strategies. Crit Rev Oncol Hematol 39: 275-287.
1839. Pinto dM, Herrera GA, Mendonca AM, Estrela RR (1986). Metastatic malignant mixed tumor of the skin. Ultrastructural and immunocytochemical characterization, histogenetic considerations and comparison with benign mixed tumors of skin and salivary glands. Appl Pathol 4: 199-208.
1840. Pitha J, Smoller BR, Somach S, McCalmont TH (2002). A spindled cell CD34+ dermal proliferation. Am J Dermatopathol 24: 85-88.
1841. Pitt MA, Coyne JD, Harris M, McWilliam LJ (1994). Dermatofibrosarcoma protuberans recurring as a giant cell fibroblastoma with subsequent fibrosarcomatous change. Histopathology 24: 197-198.
1842. Pitt MA, Roberts IS (1994). Myxoid cutaneous pleomorphic fibroma. Histopathology 25: 300.
1843. Pittaluga S, Raffeld M, Lipford EH, Cossman J (1986). 3A1 (CD7) expression precedes T beta gene rearrangements in precursor T (lymphoblastic) neoplasms. Blood 68: 134-139.
1844. Plantin P, Le Roy JP, Zagnoli A, Guillet G (1987). [Malignant melanoma developing on a giant congenital nevus of the blue nevus type]. Ann Dermatol Venereol 114: 1243-1246.
1845. Plettenberg A, Lorenzen T, Burtsche BT, Rasokat H, Kaliebe T, Albrecht H, Mertenskotter T, Bogner JR, Stoehr A, Schofer H (2000). Bacillary angiomatosis in HIV-infected patients—an epidemiological and clinical study. Dermatology 201: 326-331.
1846. Plewig G (1980). Sebaceous trichofolliculoma. J Cutan Pathol 7: 394-403.
1847. Poiares Baptista A, Garcia E Silva L, Born MC (1983). Proliferating trichilemmal cyst. J Cutan Pathol 10: 178-187.
1848. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC (1980). Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A 77: 7415-7419.
1849. Pollan M, Lopez-Abente G (1993). Mortality trends in cutaneous malignant melanoma in Spain, 1967-1986. Cancer Epidemiol Biomarkers Prev 2: 545-550.
1850. Pollock PM, Harper UL, Hansen KS, Yudt LM, Stark M, Robbins CM, Moses TY, Hostetter G, Wagner U, Kakareka J, Salem G, Pohida T, Heenan P, Duray P, Kallioniemi O, Hayward NK, Trent JM, Meltzer PS (2003). High frequency of BRAF mutations in nevi. Nat Genet 33: 19-20.
1851. Pollock PM, Trent JM (2000). The genetics of cutaneous melanoma. Clin Lab Med 20: 667-690.
1852. Ponzoni M, Arrigoni G, Gould VE, Del Curto B, Maggioni M, Scapinello A, Paolino S, Cassisa A, Patriarca C (2000). Lack of CD 29 (beta1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. Hum Pathol 31: 220-226.
1853. Powell TG, West CR, Pharoah PO, Cooke RW (1987). Epidemiology of strawberry haemangioma in low birthweight infants. Br J Dermatol 116: 635-641.
1854. Pozo L, Naase M, Cerio R, Blanes A, Diaz-Cano SJ (2001). Critical analysis of histologic criteria for grading atypical (dysplastic) melanocytic nevi. Am J Clin Pathol 115: 194-204.
1855. Prasad ML, Jungbluth AA, Iversen K, Huvos AG, Busam KJ (2001). Expression of melanocytic differentiation markers in malignant melanomas of the oral and sinonasal mucosa. Am J Surg Pathol 25: 782-787.
1856. Price ML, Tidman MJ, Fagg NL, Palmer TJ, MacDonald DM (1988). Distinctive epidermal atypia in immunosuppression-associated cutaneous malignancy. Histopathology 13: 89-94.
1856A. Pricolo VE, Rodil JV, Vezeridis MP (1985). Extraorbital sebaceous carcinoma. Arch Surg 120: 853-855.
1857. Prieto VG, Woodruff JM (1998). Expression of basement membrane antigens in spindle cell melanoma. J Cutan Pathol 25: 297-300.
1858. Prince HM, O'Keefe R, McCormack C, Ryan G, Turner H, Waring P, Baker C (2002). Cutaneous lymphomas: which pathological classification? Pathology 34: 36-45.
1859. Prioleau PG, Santa Cruz DJ (1978). Lymphangioma circumscriptum following radical mastectomy and radiation therapy. Cancer 42: 1989-1991.
1859A. Prosdocimo T, Smith M, Polack EP (2002). The diagnosis and treatment of childhood melanoma. W V Med J 98: 149-151.
1860. Przybylski GK, Wu H, Macon WR, Finan J, Leonard DG, Felgar RE, DiGiuseppe JA, Nowell PC, Swerdlow SH, Kadin ME, Wasik MA, Salhany KE (2000). Hepatosplenic and subcutaneous panniculitis-like gamma/delta T cell lymphomas are derived from different Vdelta subsets of gamma/delta T lymphocytes. J Mol Diagn 2: 11-19.
1861. Puches R, Smolle J, Rieger E, Soyer HP, Kerl H (1991). Expression of cytoskeletal components in melanocytic skin lesions. An immunohistochemical study. Am J Dermatopathol 13: 137-144.
1862. Pujol RM, LeBoit PE, Su WP (1997). Microcystic adnexal carcinoma with extensive sebaceous differentiation. Am J Dermatopathol 19: 358-362.
1863. Pujol RM, Matias-Guiu X, Miralles J, Colomer A, de Moragas JM (1997). Multiple idiopathic mucosal neuromas: a minor form of multiple endocrine neoplasia type 2B or a new entity? J Am Acad Dermatol 37: 349-352.
1864. Pulitzer DR, Martin PC, Cohen AP, Reed RJ (1991). Histologic classification of the combined nevus. Analysis of the variable expression of melanocytic nevi. Am J Surg Pathol 15: 1111-1122.
1865. Pulitzer DR, Reed RJ (1985). Nerve-sheath myxoma (perineurial myxoma). Am J Dermatopathol 7: 409-421.
1866. Quinn AG, Campbell C, Healy E, Rees JL (1994). Chromosome 9 allele loss occurs in both basal and squamous cell carcinomas of the skin. J Invest Dermatol 102: 300-303.
1867. Quinn MJ, Crotty KA (2003). Desmoplastic and neurotropic melanoma. In: Textbook of Melanoma: Pathology, Diagnosis and Management, Thompson JF, Morton DL, Kroon BBR, eds., Martin Dunitz: pp. 387-394.
1868. Quinn MJ, Crotty KA, Thompson JF, Coates AS, O'Brien CJ, McCarthy WH (1998). Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. Cancer 83: 1128-1135.
1869. Quinn TR, Young RH (1997).

Epidermolytic hyperkeratosis in the lower female genital tract: an uncommon simulant of mucocutaneous papillomavirus infection—a report of two cases. Int J Gynecol Pathol 16: 163-168.
1870. Quinn TR, Young RH (1997). Smooth-muscle hamartoma of the tunica dartos of the scrotum: report of a case. J Cutan Pathol 24: 322-326.
1871. Rabinowitz AD, Inghirami G (1992). Large-cell acanthoma. A distinctive keratosis. Am J Dermatopathol 14: 136-138.
1872. Radentz WH, Vogel P (1990). Congenital common blue nevus. Arch Dermatol 126: 124-125.
1873. Rahbari H, Mehregan AH (1982). Basal cell epithelioma (carcinoma) in children and teenagers. Cancer 49: 350-353.
1874. Rahbari H, Mehregan AH (1986). Development of proliferating trichilemmal cyst in organoid nevus. Presentation of two cases. J Am Acad Dermatol 14: 123-126.
1875. Rahbari H, Pinkus H (1978). Large cell acanthoma. One of the actinic keratoses. Arch Dermatol 114: 49-52.
1876. Rahilly MA, Beattie GJ, Lessells AM (1995). Mucinous eccrine carcinoma of the vulva with neuroendocrine differentiation. Histopathology 27: 82-86.
1877. Rahimi-Movaghar V, Karimi M (2003). Meningeal melanocytoma of the brain and oculodermal melanocytosis (nevus of Ota): case report and literature review. Surg Neurol 59: 200-210.
1878. Raj S, Calonje E, Kraus M, Kavanagh G, Newman PL, Fletcher CD (1997). Cutaneous pilar leiomyoma: clinicopathologic analysis of 53 lesions in 45 patients. Am J Dermatopathol 19: 2-9.
1879. Ralfkiaer E, Wollf-Sneedorff A, Thomsen K, Geisler C, Vejlsgaard GL (1992). T-cell receptor gamma delta-positive peripheral T-cell lymphomas presenting in the skin: a clinical, histological and immunophenotypic study. Exp Dermatol 1: 31-36.
1880. Ralfkiaer E, Wollf-Sneedorff A, Thomsen K, Vejlsgaard GL (1993). Immunophenotypic studies in cutaneous T-cell lymphomas: clinical implications. Br J Dermatol 129: 655-659.
1881. Ramachandra S, Hollowood K, Bisceglia M, Fletcher CD (1995). Inflammatory pseudotumour of soft tissues: a clinicopathological and immunohistochemical analysis of 18 cases. Histopathology 27: 313-323.
1882. Ramani P, Shah A (1993). Lymphangiomatosis. Histologic and immunohistochemical analysis of four cases. Am J Surg Pathol 17: 329-335.
1883. Ramdial PK, Madaree A, Reddy R, Chetty R (2000). bcl-2 protein expression in aggressive and non-aggressive basal cell carcinomas. J Cutan Pathol 27: 283-291.
1884. Ramon R, Silvestre JF, Betlloch I, Banuls J, Botella R, Navas J (2000). Progression of Meyerson's naevus to Sutton's naevus. Dermatology 200: 337-338.
1885. Ramos-Caro FA, Sexton FM, Browder JF, Flowers FP (1992). Acantholytic acanthomas in an immunosuppressed patient. J Am Acad Dermatol 27: 452-453.
1886. Ramsay AD, Smith WJ, Isaacson PG (1988). T-cell-rich B-cell lymphoma. Am J Surg Pathol 12: 433-443.
1887. Ramsay B, Dahl MC, Malcolm AJ, Wilson-Jones E (1990). Acral pseudolymphomatous angiokeratoma of children. Arch Dermatol 126: 1524-1525.
1888. Ramsay B, Dahl MCG, Malcolm AJ, Soyer HP, Wilson-Jones E (1988). Acral pseudolymphomatous angiokeratoma of children (APACHE). Br J Dermatol 119 (suppl 33): 13.
1889. Ramzi ST, Maruno M, Khaskhely NM, Khan MA, Takamiyagi A, Uezato H, Nonaka S (2002). An assessment of the malignant potential of actinic keratoses and Bowen's disease: p53 and PCNA expression pattern correlate with the number of desmosomes. J Dermatol 29: 562-572.
1890. Randerson-Moor JA, Harland M, Williams S, Cuthbert-Heavens D, Sheridan E, Aveyard J, Sibley K, Whitaker L, Knowles M, Bishop JN, Bishop DT (2001). A germline deletion of p14(ARF) but not CDKN2A in a melanoma-neural system tumour syndrome family. Hum Mol Genet 10: 55-62.
1891. Rane SG, Cosenza SC, Mettus RV, Reddy EP (2002). Germ line transmission of the Cdk4(R24C) mutation facilitates tumorigenesis and escape from cellular senescence. Mol Cell Biol 22: 644-656.
1892. Rao NA, Hidayat AA, McLean IW, Zimmerman LE (1982). Sebaceous carcinomas of the ocular adnexa: A clinicopathologic study of 104 cases, with five-year follow-up data. Hum Pathol 13: 113-122.
1893. Rao UN, Bakker A, Swalsky PA, Finkelstein SD (1999). Max interacting protein 1: loss of heterozygosity is frequent in desmoplastic melanoma. Mod Pathol 12: 344-350.
1894. Rapin I, Lindenbaum Y, Dickson DW, Kraemer KH, Robbins JH (2000). Cockayne syndrome and xeroderma pigmentosum. Neurology 55: 1442-1449.
1895. Rapini RP, Golitz LE (1989). Sclerotic fibromas of the skin. J Am Acad Dermatol 20: 266-271.
1896. Rapini RP, Golitz LE (1990). Targetoid hemosiderotic hemangioma. J Cutan Pathol 17: 233-235.
1897. Ratcliffe JF, Shanley S, Chenevix-Trench G (1995). The prevalence of cervical and thoracic congenital skeletal abnormalities in basal cell naevus syndrome; a review of cervical and chest radiographs in 80 patients with BCNS. Br J Radiol 68: 596-599.
1898. Ratcliffe JF, Shanley S, Ferguson J, Chenevix-Trench G (1995). The diagnostic implication of falcine calcification on plain skull radiographs of patients with basal cell naevus syndrome and the incidence of falcine calcification in their relatives and two control groups. Br J Radiol 68: 361-368.
1899. Ratnam KV, Su WP, Ziesmer SC, Li CY (1992). Value of immunohistochemistry in the diagnosis of leukemia cutis: study of 54 cases using paraffin-section markers. J Cutan Pathol 19: 193-200.
1900. Ratzinger G, Zelger B, Hobling W, Mikuz G, Zelger BW (2003). Sinus histiocytosis with massive lymphadenopathy Rosai-Dorfman: three unusual manifestations. Virchows Arch 443: 797-800.
1901. Raymond LW, Williford LS, Burke WA (1998). Eruptive cherry angiomas and irritant symptoms after one acute exposure to the glycol ether solvent 2-butoxyethanol. J Occup Environ Med 40: 1059-1064.
1902. Read RW, Burnstine M, Rowland JM, Zamir E, Rao NA (2001). Rhabdomyomatous mesenchymal hamartoma of the eyelid: report of a case and literature review. Ophthalmology 108: 798-804.
1903. Redono C, Rocamora A, Villoria F, Garcia M (1982). Malignant mixed tumor of the skin: malignant chondroid syringoma. Cancer 49: 1690-1696.
1904. Reed JA, Loganzo FJr, Shea CR, Walker GJ, Flores JF, Glendening JM, Bogdany JK, Shiel MJ, Haluska FG, Fountain JW, Albino AP (1995). Loss of expression of the p16/cyclin-dependent kinase inhibitor 2 tumor suppressor gene in melanocytic lesions correlates with invasive stage of tumor progression. Cancer Res 55: 2713-2718.
1905. Reed RJ (1976). Acral lentigineous melanoma. In: New Concepts in Surgical Pathology of the Skin, Harmann W, Kay S, Reed RJ, eds., John Wiley & Sons, Inc.: New York , pp. 89-90.
1906. Reed RJ (1980). Tricholemmoma. A cutaneous hamartoma. Am J Dermatopathol 2: 227-228.
1907. Reed RJ (1993). Giant congenital nevi: a conceptualization of patterns. J Invest Dermatol 100: 300S-312S.
1908. Reed RJ, Fine RM, Meltzer HD (1972). Palisaded, encapsulated neuromas of the skin. Arch Dermatol 106: 865-870.
1909. Reed RJ, Ichinose H, Clark WHJr, Mihm MCJr (1975). Common and uncommon melanocytic nevi and borderline melanomas. Semin Oncol 2: 119-147.
1910. Reed RJ, Lamar LM (1966). Invasive hair matrix tumors of the scalp. Invasive pilomatrixoma. Arch Dermatol 94: 310-316.
1911. Reed RJ, Martin P (1997). Variants of melanoma. Semin Cutan Med Surg 16: 137-158.
1912. Reed WB, Becker SWSr, Becker SWJr, Nickel WR (1965). Giant pigmented nevi melanoma and leptomeningeal melanocytosis - A clinical and histopathological study. Arch Dermatol 91: 100-119.
1913. Rehman I, Quinn AG, Healy E, Rees JL (1994). High frequency of loss of heterozygosity in actinic keratoses, a usually benign disease. Lancet 344: 788-789.
1914. Rehman I, Takata M, Wu YY, Rees JL (1996). Genetic change in actinic keratoses. Oncogene 12: 2483-2490.
1915. Reintgen D, Cruse CW, Wells K, Berman C, Fenske N, Glass F, Schroer K, Heller R, Ross M, Lyman G, . (1994). The orderly progression of melanoma nodal metastases. Ann Surg 220: 759-767.
1916. Reintgen DS, Jakub JW, Pendas S, Swor G, Giuliano R, Shivers S (2004). The staging of malignant melanoma and the Florida Melanoma Trial. Ann Surg Oncol 11: 186S-191S.
1916A. Reintgen DS, Vollmer R, Seigler HF (1989). Juvenile malignant melanoma. Surg Gynecol Obstet 168: 249-253.
1917. Requena L, de la Cruz A, Moreno C, Sangueza O, Requena C (2001). Animal type melanoma: a report of a case with balloon-cell change and sentinel lymph node metastasis. Am J Dermatopathol 23: 341-346.
1918. Requena L, Farina MC, Renedo G, Alvarez A, Yus ES, Sangueza OP (1999). Intravascular and diffuse dermal reactive angioendotheliomatosis secondary to iatrogenic arteriovenous fistulas. J Cutan Pathol 26: 159-164.
1919. Requena L, Kiryu H, Ackerman AB (1998). Neoplasms with apocrine differentiation. Lippincott Williams & Wilkins: Philadelphia.
1920. Requena L, Kutzner H, Hugel H, Rutten A, Furio V (1996). Cutaneous adult myofibroma: a vascular neoplasm. J Cutan Pathol 23: 445-457.
1921. Requena L, Kutzner H, Mentzel T, Duran R, Rodriguez-Peralto JL (2002). Benign vascular proliferations in irradiated skin. Am J Surg Pathol 26: 328-337.
1922. Requena L, Kuztner H, Farina MC (1998). Pigmented and nested sebomatricoma or seborrheic keratosis with sebaceous differentiation? Am J Dermatopathol 20: 383-388.
1923. Requena L, Martin L, Farina MC, Pique E, Escalonilla P (1996). Keloidal basal cell carcinoma. A new clinicopathological variant of basal cell carcinoma. Br J Dermatol 134: 953-957.
1924. Requena L, Sangueza OP (1997). Cutaneous vascular proliferation. Part II. Hyperplasias and benign neoplasms. J Am Acad Dermatol 37: 887-919.
1925. Rhodes AR, Mihm MCJr, Weinstock MA (1989). Dysplastic melanocytic nevi: a reproducible histologic definition emphasizing cellular morphology. Mod Pathol 2: 306-319.
1926. Rhodes AR, Silverman RA, Harrist TJ, Perez-Atayde AR (1984). Mucocutaneous lentigines, cardiomucocutaneous myxomas, and multiple blue nevi: the "LAMB" syndrome. J Am Acad Dermatol 10: 72-82.
1927. Rhodes AR, Weinstock MA, Fitzpatrick TB, Mihm MCJr, Sober AJ (1987). Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. JAMA 258: 3146-3154.
1928. Rhodes AR, Wood WC, Sober AJ, Mihm MCJr (1981). Nonepidermal origin of malignant melanoma associated with a giant congenital nevocellular nevus. Plast Reconstr Surg 67: 782-790.
1929. Riccioni L, Di Tommaso L, Collina G (1999). Actin-rich desmoplastic malignant melanoma: report of three cases. Am J Dermatopathol 21: 537-541.
1930. Rice CD, Brown HH (1990). Primary orbital melanoma associated with orbital melanocytosis. Arch Ophthalmol 108: 1130-1134.
1930A. Richardson SK, Tannous ZS, Mihm MC, Jr. (2002). Congenital and infantile melanoma: review of the literature and report of an uncommon variant, pigment-synthesizing melanoma. J Am Acad Dermatol 47: 77-90.
1931. Richfield DF (1980). Tricholemmoma. True and false types. Am J Dermatopathol 2: 233-234.
1932. Richman T, Penneys NS (1988). Analysis of morpheaform basal cell carcinoma. J Cutan Pathol 15: 359-362.
1933. Riedlinger WF, Hurley MY, Dehner LP, Lind AC (2005). Mucoepidermoid carcinoma of the skin: a distinct entity from adenosquamous carcinoma: a case study with a review of the literature. Am J Surg Pathol 29: 131-135.
1934. Rieger E, Hofmann-Wellenhof R, Soyer HP, Kofler R, Cerroni L, Smolle J, Kerl H (1993). Comparison of proliferative activity as assessed by proliferating cell nuclear antigen (PCNA) and Ki-67 monoclonal antibodies in melanocytic skin lesions. A quantitative immunohistochemical study. J Cutan Pathol 20: 229-236.
1935. Rieger E, Soyer HP, LeBoit PE, Metze D, Slovak R, Kerl H (1999). Reactive angioendotheliomatosis or intravascular histiocytosis? An immunohistochemical and ultrastructural study in two cases of intravascular histiocytic cell proliferation. Br J Dermatol 140: 497-504.
1936. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK (2004). SEER Cancer Statistics Review, 1975-2001. National Cancer Institute.: Bethesda, MD.
1937. Rigel DS, Friedman RJ, Kopf AW (1996). Lifetime risk for development of skin

cancer in the U.S. population: current estimate is now 1 in 5. J Am Acad Dermatol 35: 1012-1013.
1938. Rijlaarsdam JU, Toonstra J, Meijer OW, Noordijk EM, Willemze R (1996). Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: a clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 14: 549-555.
1939. Rikihisa W, Yamamoto O, Kohda F, Hamada M, Yasumoto S, Kiryu H, Asahi M (1999). Microvenular haemangioma in a patient with Wiskott-Aldrich syndrome. Br J Dermatol 141: 752-754.
1940. Rippey JJ, Rippey E (1997). Characteristics of incompletely excised basal cell carcinomas of the skin. Med J Aust 166: 581-583.
1941. Risdall RJ, Dehner LP, Duray P, Kobrinsky N, Robison L, Nesbit MEJr (1983). Histiocytosis X (Langerhans' cell histiocytosis). Prognostic role of histopathology. Arch Pathol Lab Med 107: 59-63.
1942. Ritter MR, Dorrell MI, Edmonds J, Friedlander SF, Friedlander M (2002). Insulin-like growth factor 2 and potential regulators of hemangioma growth and involution identified by large-scale expression analysis. Proc Natl Acad Sci U S A 99: 7455-7460.
1943. Rivers JK, Cockerell CJ, McBride A, Kopf AW (1990). Quantification of histologic features of dysplastic nevi. Am J Dermatopathol 12: 42-50.
1944. Rivoltini L, Carrabba M, Huber V, Castelli C, Novellino L, Dalerba P, Mortarini R, Arancia G, Anichini A, Fais S, Parmiani G (2002). Immunity to cancer: attack and escape in T lymphocyte-tumor cell interaction. Immunol Rev 188: 97-113.
1945. Rizos H, Puig S, Badenas C, Malvehy J, Darmanian AP, Jimenez L, Mila M, Kefford RF (2001). A melanoma-associated germline mutation in exon 1beta inactivates p14ARF. Oncogene 20: 5543-5547.
1946. Ro YS, Cooper PN, Lee JA, Quinn AG, Harrison D, Lane D, Horne CH, Rees JL, Angus B (1993). p53 protein expression in benign and malignant skin tumours. Br J Dermatol 128: 237-241.
1947. Robboy SJ, Anderson MC, Russell P (2002). Pathology of the Female Reproductive Tract. Churchill Livingstone: London, Edinburgh.
1948. Robenzadeh A, Don PC, Weinberg JM (1998). Treatment of tufted angioma with interferon alfa: role of bFGF. Pediatr Dermatol 15: 482.
1949. Robertson PB, Neiman RS, Worapongpaiboon S, John K, Orazi A (1997). 013 (CD99) positivity in hematologic proliferations correlates with TdT positivity. Mod Pathol 10: 277-282.
1950. Robinson JK, Dahiya M (2003). Basal cell carcinoma with pulmonary and lymph node metastasis causing death. Arch Dermatol 139: 643-648.
1951. Robson A, Allen P, Hollowood K (2001). S100 expression in cutaneous scars: a potential diagnostic pitfall in the diagnosis of desmoplastic melanoma. Histopathology 38: 135-140.
1952. Robson A, Greene J, Ansari N, Kim B, Seed PT, McKee PH, Calonje E (2001). Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. Am J Surg Pathol 25: 710-720.
1953. Robson A, Morley-Quante M, Hempel H, McKee PH, Calonje J.E. (2003). Deep penetrating nevus: clinicopathological study of 31 cases with further delineation of histological features allowing distinction from other benign melanocytic lesions and melanoma. Histopathology .
1954. Rock B (1992). Pigmented lesions of the vulva. Dermatol Clin 10: 361-370.
1955. Rock B, Hood AF, Rock JA (1990). Prospective study of vulvar nevi. J Am Acad Dermatol 22: 104-106.
1956. Rodman OG, Cooper PH (1980). Multifocal eosinophilic granuloma of skin and bone. Thirteen year surveillance of a patient. Cutis 26: 487-488.
1957. Rodriguez HA, Ackerman LV (1968). Cellular blue nevus. Clinicopathologic study of forty-five cases. Cancer 21: 393-405.
1958. Roetman B, Vakilzadeh F, Krismann M (2002). [Eccrine spiradenocarcinoma with unusual histiocytic giant cell components. Case report and review of the literature of a rare sweat gland tumor]. Pathologe 23: 149-155.
1959. Roewert HJ, Ackerman AB (1992). Large-cell acanthoma is a solar lentigo. Am J Dermatopathol 14: 122-132.
1960. Rofagha R, Usmani AS, Vadmal M, Hessel AB, Pellegrini AE (2001). Trichoblastic carcinoma: a report of two cases of a deeply infiltrative trichoblastic neoplasm. Dermatol Surg 27: 663-666.
1961. Rogers GS, Advani H, Ackerman AB (1985). A combined variant of Spitz's nevi. How to differentiate them from malignant melanomas. Am J Dermatopathol 7 Suppl: 61-78.
1962. Rohwedder A, Keminer O, Hendricks C, Schaller J (1997). Detection of HPV DNA in trichilemmomas by polymerase chain reaction. J Med Virol 51: 119-125.
1963. Ronan SG, Eng AM, Briele HA, Walker MJ, Das Gupta TK (1990). Malignant melanoma of the female genitalia. J Am Acad Dermatol 22: 428-435.
1964. Rongioletti F, Ball RA, Marcus R, Barnhill RL (2000). Histopathological features of flexural melanocytic nevi: a study of 40 cases. J Cutan Pathol 27: 215-217.
1965. Rongioletti F, Gambini C, Lerza R (1994). Glomeruloid hemangioma. A cutaneous marker of POEMS syndrome. Am J Dermatopathol 16: 175-178.
1966. Roper GJ, Smith MS, Lueder GT (1999). Congenital smooth muscle hamartoma of the conjunctival fornix. Am J Ophthalmol 128: 643-644.
1967. Rosai J, Akerman LR (1974). Intravenous atypical vascular proliferation. A cutaneous lesion simulating a malignant blood vessel tumor. Arch Dermatol 109: 714-717.
1968. Rosai J, Gold J, Landy R (1979). The histiocytoid hemangiomas. A unifying concept embracing several previously described entities of skin, soft tissue, large vessels, bone, and heart. Hum Pathol 10: 707-730.
1969. Rosai J, Sumner HW, Kostianovsky M, Perez-Mesa C (1976). Angiosarcoma of the skin. A clinicopathologic and fine structural study. Hum Pathol 7: 83-109.
1970. Rose C, Brocker EB (1999). Dermatomyofibroma: case report and review. Pediatr Dermatol 16: 456-459.
1971. Rosen PP (2001). Paget's disease of the nipple. In: Rosen's Breast Pathology, Rosen PP, ed., 2nd ed. Lippincott Williams & Wilkins: Philadelphia , pp. 565-579.
1972. Rosen T (1979). Arteriovenous hemangioma. Cutis 24: 57-59.
1973. Rosenberg AS, Kirk J, Morgan MB (2002). Rhabdomyomatous mesenchymal hamartoma: an unusual dermal entity with a report of two cases and a review of the literature. J Cutan Pathol 29: 238-243.
1974. Rosenblatt L, Marks R (1996). Deaths due to squamous cell carcinoma in Australia: is there a case for a public health intervention? Australas J Dermatol 37: 26-29.
1975. Rosenthal CJ, Noguera CA, Coppola A, Kapelner SN (1982). Pseudolymphoma with mycosis fungoides manifestations, hyperresponsiveness to diphenylhydantoin, and lymphocyte disregulation. Cancer 49: 2305-2314.
1976. Rosenwald A, Alizadeh AA, Widhopf G, Simon R, Davis RE, Yu X, Yang L, Pickeral OK, Rassenti LZ, Powell J, Botstein D, Byrd JC, Grever MR, Cheson BD, Chiorazzi N, Wilson WH, Kipps TJ, Brown PO, Staudt LM (2001). Relation of gene expression phenotype to immunoglobulin mutation genotype in B cell chronic lymphocytic leukemia. J Exp Med 194: 1639-1647.
1977. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, Gascoyne RD, Muller-Hermelink HK, Smeland EB, Giltnane JM, Hurt EM, Zhao H, Averett L, Yang L, Wilson WH, Jaffe ES, Simon R, Klausner RD, Powell J, Duffey PL, Longo DL, Greiner TC, Weisenburger DD, Sanger WG, Dave BJ, Lynch JC, Vose J, Armitage JO, Montserrat E, Lopez-Guillermo A, Grogan TM, Miller TP, LeBlanc M, Ott G, Kvaloy S, Delabie J, Holte H, Krajci P, Stokke T, Staudt LM (2002). The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346: 1937-1947.
1978. Rosenwald A, Wright G, Wiestner A, Chan WC, Connors JM, Campo E, Gascoyne RD, Grogan TM, Muller-Hermelink HK, Smeland EB, Chiorazzi M, Giltnane JM, Hurt EM, Zhao H, Averett L, Henrickson S, Yang L, Powell J, Wilson WH, Jaffe ES, Simon R, Klausner RD, Montserrat E, Bosch F, Greiner TC, Weisenburger DD, Sanger WG, Dave BJ, Lynch JC, Vose J, Armitage JO, Fisher RI, Miller TP, LeBlanc M, Ott G, Kvaloy S, Holte H, Delabie J, Staudt LM (2003). The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 3: 185-197.
1979. Roson E, Gomez Centeno P, Sanchez-Aguilar D, Peteiro C, Toribio J (1998). Desmoplastic trichilemmoma arising within a nevus sebaceus. Am J Dermatopathol 20: 495-497.
1980. Roth ME, Grant-Kels JM, Ackerman AB, Elder DE, Friedman RJ, Heilman ER, Maize JC, Sagebiel RW (1991). The histopathology of dysplastic nevi. Continued controversy. Am J Dermatopathol 13: 38-51.
1981. Rothfeld J (1933). Blue nevus with melanosarcoma with metastases to the brain. Nervenarzt 4: 13-16.
1982. Rottem M, Okada T, Goff JP, Metcalfe DD (1994). Mast cells cultured from the peripheral blood of normal donors and patients with mastocytosis originate from a CD34+/Fc epsilon RI- cell population. Blood 84: 2489-2496.
1983. Roush GC, McKay L, Holford TR (1992). A reversal in the long-term increase in deaths attributable to malignant melanoma. Cancer 69: 1714-1720.
1984. Rowe DE, Carroll RJ, Day CLJr (1989). Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol 15: 315-328.
1985. Rowe DE, Carroll RJ, Day CLJr (1992). Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 26: 976-990.
1986. Rowlands CG, Rapson D, Morell T (2000). Extramedullary hematopoiesis in a pyogenic granuloma. Am J Dermatopathol 22: 434-438.
1987. Rubins J (1978). Cutaneous Hodgkin's disease: indolent course and control with chemotherapy. Cancer 42: 1219-1221.
1988. Rudolph P, Schubert C, Zelger BG, Zelger B, Parwaresch R (1999). Differential expression of CD34 and Ki-M1p in pleomorphic fibroma and dermatofibroma with monster cells. Am J Dermatopathol 21: 414-419.
1989. Ruhoy SM, Prieto VG, Eliason SL, Grichnik JM, Burchette JL, Jr., Shea CR (2000). Malignant melanoma with paradoxical maturation. Am J Surg Pathol 24: 1600-1614.
1990. Ruiter D, Bogenrieder T, Elder D, Herlyn M (2002). Melanoma-stroma interactions: structural and functional aspects. Lancet Oncol 3: 35-43.
1990A Ruiz-Maldonado R, Orozco-Covarrubias ML (1997). Malignant melanoma in children. A review. Arch Dermatol 133: 363-371.
1991. Ruiz-Maldonado R, Parrilla FM, Orozco-Covarrubias ML, Ridaura C, Tamayo Sanchez L, Duran McKinster C (1995). Edematous, scarring vasculitic panniculitis: a new multisystemic disease with malignant potential. J Am Acad Dermatol 32: 37-44.
1992. Ruiz i Altaba A, Sanchez P, Dahmane N (2002). Gli and hedgehog in cancer: tumours, embryos and stem cells. Nat Rev Cancer 2: 361-372.
1993. Rulon DB, Helwig EB (1974). Cutaneous sebaceous neoplasms. Cancer 33: 82-102.
1994. Runne U (1977). [Syndrome of multiple neuromas. ("Multiple mucosal neuroma" syndrome)]. Z Hautkr 52: 302-304.
1995. Ruocco V, Schwartz RA, Ruocco E (2002). Lymphedema: an immunologically vulnerable site for development of neoplasms. J Am Acad Dermatol 47: 124-127.
1996. Rupec R, Eckert F, Ruzicka T (1993). [Malignant blue nevus]. Hautarzt 44: 164-166.
1997. Russell-Jones R (2005). Diagnosing erythrodermic cutaneous T-cell lymphoma. Br J Dermatol 153: 1-5.
1998. Russell-Jones R, Whittaker S (1999). T-cell receptor gene analysis in the diagnosis of Sezary syndrome. J Am Acad Dermatol 41: 254-259.
1999. Rutten A, Burgdorf W, Hugel H, Kutzner H, Hosseiny-Malayeri HR, Friedl W, Propping P, Kruse R (1999). Cystic sebaceous tumors as marker lesions for the Muir-Torre syndrome: a histopathologic and molecular genetic study. Am J Dermatopathol 21: 405-413.
2000. Rutten A, Requena L, Requena C (2002). Clear-cell porocarcinoma in situ: a cytologic variant of porocarcinoma in situ. Am J Dermatopathol 24: 67-71.
2001. Rydholm A, Gustafson P, Rooser B, Willen H, Berg NO (1991). Subcutaneous sarcoma. A population-based study of 129 patients. J Bone Joint Surg Br 73: 662-667.
2002. Sabroe RA, Vaingankar NV, Rigby HS, Peachey RD (1996). Agminate Spitz

naevi occurring in an adult after the excision of a solitary Spitz naevus—report of a case and review of the literature. Clin Exp Dermatol 21: 197-200.
2003. Sachez Yus E, Requena L, Simon P, del Rio E (1995). Sebomatricoma: a unifying term that encompasses all benign neoplasms with sebaceous differentiation. Am J Dermatopathol 17: 213-221.
2003A. Saenz NC, Saenz-Badillos J, Busam K, LaQuaglia MP, Corbally M, Brady MS (1999). Childhood melanoma survival. Cancer 85: 750-754.
2004. Safai B, Myskowski PL, Dupont B, Pollack MS (1983). Association of HLA-DR5 with mycosis fungoides. J Invest Dermatol 80: 395-397.
2005. Sagebiel RW, Chinn EK, Egbert BM (1984). Pigmented spindle cell nevus. Clinical and histologic review of 90 cases. Am J Surg Pathol 8: 645-653.
2006. Sah SP, Yadav R, Rani S (2001). Lymphangioma circumscriptum of the vulva mimicking genital wart: a case report and review of literature. J Obstet Gynaecol Res 27: 293-296.
2007. Saha KC (2003). Diagnosis of arsenicosis. J Environ Sci Health Part A Tox Hazard Subst Environ Eng 38: 255-272.
2008. Sahin MT, Demir MA, Yoleri L, Can M, Ozturkcan S (2001). Blue naevus with satellitosis mimicking malignant melanoma. J Eur Acad Dermatol Venereol 15: 570-573.
2009. Sahl WJJr, Snow SN, Levine NS (1994). Giant basal cell carcinoma. Report of two cases and review of the literature. J Am Acad Dermatol 30: 856-859.
2010. Sahn EE, Garen PD, Pai GS, Levkoff AH, Hagerty RC, Maize JC (1990). Multiple rhabdomyomatous mesenchymal hamartomas of skin. Am J Dermatopathol 12: 485-491.
2011. Said JW, Sassoon AF, Shintaku IP, Banks-Schlegel S (1984). Involucrin in squamous and basal cell carcinomas of the skin: an immunohistochemical study. J Invest Dermatol 82: 449-452.
2012. Saida T (2001). Recent advances in melanoma research. J Dermatol Sci 26: 1-13.
2013. Saida T, Ishihara Y, Tokuda Y (1993). Effective detection of plantar malignant melanoma. Int J Dermatol 32: 722-725.
2014. Saida T, Oguchi S, Ishihara Y (1995). In vivo observation of magnified features of pigmented lesions on volar skin using video macroscope. Usefulness of epiluminescence techniques in clinical diagnosis. Arch Dermatol 131: 298-304.
2015. Saida T, Oguchi S, Miyazaki A (2002). Dermoscopy for acral pigmented skin lesions. Clin Dermatol 20: 279-285.
2016. Saida T, Okabe Y, Uhara H (1989). Bowen's disease with invasive carcinoma showing sweat gland differentiation. J Cutan Pathol 16: 222-226.
2017. Saida T, Yoshida N (1990). Guidelines for histopathologic diagnosis of plantar malignant melanoma. Two-dimensional coordination of maximum diameters of lesions and degrees of intraepidermal proliferation of melanocytes. Dermatologica 181: 112-116.
2018. Saida T, Yoshida N, Ikegawa S, Ishihara K, Nakajima T (1990). Clinical guidelines for the early detection of plantar malignant melanoma. J Am Acad Dermatol 23: 37-40.
2019. Saijo S, Hara M, Kuramoto Y, Tagami H (1991). Generalized eruptive histiocytoma: a report of a variant case showing the presence of dermal indeterminate cells. J Cutan Pathol 18: 134-136.
2020. Sakamoto F, Hashimoto T, Takenouchi T, Ito M, Nitto H (1998). Angiolymphoid hyperplasia with eosinophilia presenting multinucleated cells in histology: an ultrastructural study. J Cutan Pathol 25: 322-326.
2021. Sakamoto F, Ito M, Nakamura A, Sato Y (1991). Proliferating trichilemmal cyst with apocrine-acrosyringeal and sebaceous differentiation. J Cutan Pathol 18: 137-141.
2022. Sakamoto F, Ito M, Sato S, Sato Y (1985). Basal cell tumor with apocrine differentiation: apocrine epithelioma. J Am Acad Dermatol 13: 355-363.
2023. Salasche SJ (2000). Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 42: 4-7.
2024. Saldanha G, Fletcher A, Slater DN (2003). Basal cell carcinoma: a dermatopathological and molecular biological update. Br J Dermatol 148: 195-202.
2025. Salem OS, Steck WD (1983). Cowden's disease (multiple hamartoma and neoplasia syndrome). A case report and review of the English literature. J Am Acad Dermatol 8: 686-696.
2026. Salhany KE, Macon WR, Choi JK, Elenitsas R, Lessin SR, Felgar RE, Wilson DM, Przybylski GK, Lister J, Wasik MA, Swerdlow SH (1998). Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. Am J Surg Pathol 22: 881-893.
2027. Salisbury JR, Hall PA, Williams HC, Mangi MH, Mufti GJ (1990). Multicentric reticulohistiocytosis. Detailed immunophenotyping confirms macrophage origin. Am J Surg Pathol 14: 687-693.
2028. Salomao DR, Nascimento AG (1997). Plexiform fibrohistiocytic tumor with systemic metastases: a case report. Am J Surg Pathol 21: 469-476.
2029. Salopek TG (2002). The dilemma of the dysplastic nevus. Dermatol Clin 20: 617-28, viii.
2030. Samaha H, Dumontet C, Ketterer N, Moullet I, Thieblemont C, Bouafia F, Callet-Bauchu E, Felman P, Berger F, Salles G, Coiffier B (1998). Mantle cell lymphoma: a retrospective study of 121 cases. Leukemia 12: 1281-1287.
2031. Samman PD (1972). The natural history of parapsoriasis en plaques (chronic superficial dermatitis) and prereticulotic poikiloderma. Br J Dermatol 87: 405-411.
2032. San Juan J, Monteagudo C, Navarro P, Terradez JJ (1999). Basal cell carcinoma with prominent central palisading of epithelial cells mimicking schwannoma. J Cutan Pathol 26: 528-532.
2033. Sanchez-Carpintero I, Espana A, Idoate MA (1999). Disseminated epidermolytic acanthoma probably related to trauma. Br J Dermatol 141: 728-730.
2034. Sanchez Yus E, Soria L, de Eusebio E, Requena L (2000). Lichenoid, erosive and ulcerated dermatofibromas. Three additional clinico-pathologic variants. J Cutan Pathol 27: 112-117.
2035. Sanchez JL (1998). A unifying concept of melanotic macule. Dermatopathology, practical & conceptual 4: 120-123.
2036. Sanchez RL (1990). The elusive dermatofibromas. Arch Dermatol 126: 522-523.
2037. Sanchez RL, Raimer SS (1994). Clinical and histologic features of striated muscle hamartoma: possible relationship to Delleman's syndrome. J Cutan Pathol 21: 40-46.
2038. Sanchez YE, de Diego V, Urrutia S (1988). Large cell acanthoma. A cytologic variant of Bowen's disease? Am J Dermatopathol 10: 197-208.
2039. Sanchez YE, del Rio E, Requena L (1992). Large-cell acanthoma is a distinctive condition. Am J Dermatopathol 14: 140-147.
2040. Sanchez YE, Simon P, Requena L, Ambrojo P, de Eusebio E (2000). Solitary keratoacanthoma: a self-healing proliferation that frequently becomes malignant. Am J Dermatopathol 22: 305-310.
2041. Sander CA, Flaig MJ, Jaffe ES (2001). Cutaneous manifestations of lymphoma: a clinical guide based on the WHO classification. World Health Organization. Clin Lymphoma 2: 86-100.
2042. Sander CA, Kaudewitz P, Kutzner H, Simon M, Schirren CG, Sioutos N, Cossman J, Plewig G, Kind P, Jaffe ES (1996). T-cell-rich B-cell lymphoma presenting in skin. A clinicopathologic analysis of six cases. J Cutan Pathol 23: 101-108.
2043. Sander CA, Medeiros LJ, Abruzzo LV, Horak ID, Jaffe ES (1991). Lymphoblastic lymphoma presenting in cutaneous sites. A clinicopathologic analysis of six cases. J Am Acad Dermatol 25: 1023-1031.
2044. Sanders C, Pasmooji T, van Vloten WA (1999). The response to therapy and survival in 27 patients with Sezary syndrome. A retrospective study of patints included in the register of the Dutch Cutaneous Lymphoma Working Group (DCLWG). Meeting of the EORTC Cutaneous Lymphoma Project Group Abstract 22.
2045. Sanders TE (1965). Intraocular juvenile xanthogranuloma: a survey of twenty cases. Am J Ophthalmol 60: 1011-1036.
2046. Sang DN, Albert DM, Sober AJ, McMeekin TO (1977). Nevus of Ota with contralateral cerebral melanoma. Arch Ophthalmol 95: 1820-1824.
2047. Sangueza OP (1993). Hidrocistomas. Monogr Dermatol 6: 146.
2048. Sangueza OP, Requena L (1994). Neurofollicular hamartoma. A new histogenetic interpretation. Am J Dermatopathol 16: 150-154.
2049. Sangueza OP, Salmon JK, White CRJr, Beckstead JH (1995). Juvenile xanthogranuloma: a clinical, histopathologic and immunohistochemical study. J Cutan Pathol 22: 327-335.
2050. Sangueza OP, Sangueza P, Valda LR, Meshul CK, Requena L (1994). Multiple primitive neuroectodermal tumors. J Am Acad Dermatol 31: 356-361.
2051. Sant M, Aareleid T, Berrino F, Bielska LM, Carli PM, Faivre J, Grosclaude P, Hedelin G, Matsuda T, Moller H, Moller T, Verdecchia A, Capocaccia R, Gatta G, Micheli A, Santaquilani M, Roazzi P, Lisi D (2003). EUROCARE-3: survival of cancer patients diagnosed 1990-94—results and commentary. Ann Oncol 14 Suppl 5: v61-118.
2052. Santa Cruz DJ, Aronberg J (1988). Targetoid hemosiderotic hemangioma. J Am Acad Dermatol 19: 550-558.
2053. Santa Cruz DJ, Barr RJ, Headington JT (1991). Cutaneous lymphadenoma. Am J Surg Pathol 15: 101-110.
2054. Santa Cruz DJ, Kyriakos M (1981). Aneurysmal ("angiomatoid") fibrous histiocytoma of the skin. Cancer 47: 2053-2061.
2055. Santa Cruz DJ, Prioleau PG (1984). Adnexal carcinomas of the skin. J Cutan Pathol 11: 450-456.
2056. Santa Cruz DJ, Prioleau PG, Smith ME (1981). Hidradenoma papilliferum of the eyelid. Arch Dermatol 117: 55-56.
2057. Santos-Briz A, Antunez P, Lopez-Rios F, Rodriguez-Peralto JL, Garzon A (2002). Human papillomavirus-negative spindle cell carcinoma of the vulva associated with lichen sclerosus: case report and literature review. Am J Dermatopathol 24: 135-138.
2058. Santucci M, Biggeri A, Feller AC, Massi D, Burg G (2000). Efficacy of histologic criteria for diagnosing early mycosis fungoides: an EORTC cutaneous lymphoma study group investigation. European Organization for Research and Treatment of Cancer. Am J Surg Pathol 24: 40-50.
2059. Santucci M, Burg G, Feller AC (1994). Interrater and intrarater reliability of histologic criteria in early cutaneous T-cell lymphoma. An EORTC Cutaneous Lymphoma Project Group study. Dermatol Clin 12: 323-327.
2060. Santucci M, Pimpinelli N (1994). Cutaneous B-cell lymphoma: a SALT-related tumor? In: Basic Mechanisms of Physiological and Aberrant Lymphoproliferation in the Skin, van Vloten WA, Lambert WC, Gianotti B, eds., Plenum Press: New York , pp. 301-315.
2061. Santucci M, Pimpinelli N, Arganini L (1991). Primary cutaneous B-cell lymphoma: a unique type of low-grade lymphoma. Clinicopathologic and immunologic study of 83 cases. Cancer 67: 2311-2326.
2062. Santucci M, Pimpinelli N, Massi D, Kadin ME, Meijer CJ, Muller-Hermelink HK, Paulli M, Wechsler J, Willemze R, Audring H, Bernengo MG, Cerroni L, Chimenti S, Chott A, Diaz-Perez JL, Dippel E, Duncan LM, Feller AC, Geerts ML, Hallermann C, Kempf W, Russell-Jones R, Sander C, Berti E (2003). Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. Cancer 97: 610-627.
2063. Sapadin AN, Friedman IS (1998). Extensive Mongolian spots associated with Hunter syndrome. J Am Acad Dermatol 39: 1013-1015.
2064. Sassmannshausen J, Chaffins M (2001). Pilomatrix carcinoma: a report of a case arising from a previously excised pilomatrixoma and a review of the literature. J Am Acad Dermatol 44: 358-361.
2065. Satge D, Grande-Goburdhun J, Grosshans E (1993). [Microcapillary hemangioma]. Ann Dermatol Venereol 120: 297-298.
2066. Satoh K, Kageshita T, Ono T, Arao T (1985). [A case of malignant blue nevus]. Nippon Hifuka Gakkai Zasshi 95: 1461-1467.
2067. Satti MB, Azzopardi JG (1990). Amyloid deposits in basal cell carcinoma of the skin. A pathologic study of 199 cases. J Am Acad Dermatol 22: 1082-1087.
2068. Sau P, Graham JH, Helwig EB (1993). Pigmented spindle cell nevus: a clinicopathologic analysis of ninety-five cases. J Am Acad Dermatol 28: 565-571.
2069. Sau P, Graham JH, Helwig EB (1995). Proliferating epithelial cysts. Clinicopathological analysis of 96 cases. J Cutan Pathol 22: 394-406.
2070. Sau P, McMarlin SL, Sperling LC, Katz R (1994). Bowen's disease of the nail bed and periungual area. A clinicopathologic analysis of seven cases. Arch Dermatol 130: 204-209.
2071. Sausville EA, Eddy JL, Makuch RW, Fischmann AB, Schechter GP, Matthews M, Glatstein E, Ihde DC, Kaye F, Veach SR (1988). Histopathologic staging at initial

diagnosis of mycosis fungoides and the Sezary syndrome. Definition of three distinctive prognostic groups. Ann Intern Med 109: 372-382.
2072. Sauter ER, Yeo UC, von Stemm A, Zhu W, Litwin S, Tichansky DS, Pistritto G, Nesbit M, Pinkel D, Herlyn M, Bastian BC (2002). Cyclin D1 is a candidate oncogene in cutaneous melanoma. Cancer Res 62: 3200-3206.
2073. Scalzo DA, Hida CA, Toth G, Sober AJ, Mihm MC, Jr. (1997). Childhood melanoma: a clinicopathological study of 22 cases. Melanoma Res 7: 63-68.
2074. Scarabello A, Leinweber B, Ardigo M, Rutten A, Feller AC, Kerl H, Cerroni L (2002). Cutaneous lymphomas with prominent granulomatous reaction: a potential pitfall in the histopathologic diagnosis of cutaneous T- and B-cell lymphomas. Am J Surg Pathol 26: 1259-1268.
2075. Scarisbrick JJ, Child FJ, Evans AV, Fraser-Andrews EA, Spittle M, Russell-Jones R (1999). Secondary malignant neoplasms in 71 patients with Sezary syndrome. Arch Dermatol 135: 1381-1385.
2076. Scarisbrick JJ, Evans AV, Woolford AJ, Black MM, Russell-Jones R (1999). Regional lymphomatoid papulosis: a report of four cases. Br J Dermatol 141: 1125-1128.
2077. Scarisbrick JJ, Whittaker S, Evans AV, Fraser-Andrews EA, Child FJ, Dean A, Russell-Jones R (2001). Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. Blood 97: 624-630.
2078. Scarisbrick JJ, Woolford AJ, Calonje E, Photiou A, Ferreira S, Orchard G, Russell-Jones R, Whittaker SJ (2002). Frequent abnormalities of the p15 and p16 genes in mycosis fungoides and sezary syndrome. J Invest Dermatol 118: 493-499.
2079. Scarisbrick JJ, Woolford AJ, Russell-Jones R, Whittaker SJ (2000). Loss of heterozygosity on 10q and microsatellite instability in advanced stages of primary cutaneous T-cell lymphoma and possible association with homozygous deletion of PTEN. Blood 95: 2937-2942.
2080. Scarisbrick JJ, Woolford AJ, Russell-Jones R, Whittaker SJ (2001). Allelotyping in mycosis fungoides and Sezary syndrome: common regions of allelic loss identified on 9p, 10q, and 17p. J Invest Dermatol 117: 663-670.
2081. Scarpa A, Guerci A (1987). Depigmenting procedures and drugs employed by melanoderm populations. J Ethnopharmacol 19: 17-66.
2082. Schaumburg-Lever G, Rechowicz E, Fehrenbacher B, Moller H, Nau P (1994). Congenital self-healing reticulohistiocytosis—a benign Langerhans cell disease. J Cutan Pathol 21: 59-66.
2083. Scheers C, Kolivras A, Corbisier A, Gheeraert P, Renoirte C, Theunis A, de Saint-Aubain N, Andre J, Sass U, Song M (2002). POEMS syndrome revealed by multiple glomeruloid angiomas. Dermatology 204: 311-314.
2084. Scheithauer BW, Woodruff JM, Erlandson RA (1999). Atlas of Tumor Pathology. Tumors of the Peripheral Nervous System. 3rd ed. AFIP: Washington, DC.
2085. Schinella RA, Greco MA (1990). Bacillary angiomatosis presenting as a soft-tissue tumor without skin involvement. Hum Pathol 21: 567-569.
2086. Schirren CG, Rutten A, Kaudewitz P, Diaz C, McClain S, Burgdorf WH (1997). Trichoblastoma and basal cell carcinoma are neoplasms with follicular differentiation sharing the same profile of cytokeratin intermediate filaments. Am J Dermatopathol 19: 341-350.
2087. Schlegelberger B, Himmler A, Godde E, Grote W, Feller AC, Lennert K (1994). Cytogenetic findings in peripheral T-cell lymphomas as a basis for distinguishing low-grade and high-grade lymphomas. Blood 83: 505-511.
2088. Schmid-Wendtner MH, Baumert J, Schmidt M, Konz B, Holzel D, Plewig G, Volkenandt M (2000). Late metastases of cutaneous melanoma: an analysis of 31 patients. J Am Acad Dermatol 43: 605-609.
2089. Schmid-Wendtner MH, Berking C, Baumert J, Schmidt M, Sander CA, Plewig G, Volkenandt M (2002). Cutaneous melanoma in childhood and adolescence: an analysis of 36 patients. J Am Acad Dermatol 46: 874-879.
2090. Schmitt D, Ortonne JP, Haftek M, Thivolet J (1981). Halo nevus and halo melanoma. Immunocytochemical study of the inflammatory cell infiltrate. In: Pathology of Malignant Melanoma, Ackerman AB, ed., Masson: New York , pp. 333-340.
2091. Schmoeckel C, Burg G (1988). Congenital spiradenoma. Am J Dermatopathol 10: 541-545.
2092. Schmoeckel C, Castro CE, Braun-Falco O (1985). Nevoid malignant melanoma. Arch Dermatol Res 277: 362-369.
2093. Schnur RE, Herzberg AJ, Spinner N, Kant JA, Magnusson M, McDonald-McGinn D, Rehberg K, Honig PJ, Zackai EH (1993). Variability in the Michelin tire syndrome. A child with multiple anomalies, smooth muscle hamartoma, and familial paracentric inversion of chromosome 7q. J Am Acad Dermatol 28: 364-370.
2094. Schoeppel SL, Hoppe RT, Dorfman RF, Horning SJ, Collier AC, Chew TG, Weiss LM (1985). Hodgkin's disease in homosexual men with generalized lymphadenopathy. Ann Intern Med 102: 68-70.
2095. Scholl W (1982). [Large cell acanthoma (author's transl)]. Z Hautkr 57: 1002-1005.
2096. Schon MP, Heisterkamp T, Ahrens C, Megahed M, Ruzicka T (2000). [Presternal verrucous carcinoma]. Hautarzt 51: 766-769.
2097. Schouten B, Egeler RM, Leenen PJ, Taminiau AH, van den Broek LJ, Hogendoorn PC (2002). Expression of cell cycle-related gene products in Langerhans cell histiocytosis. J Pediatr Hematol Oncol 24: 727-732.
2098. Schrager CA, Schneider D, Gruener AC, Tsou HC, Peacocke M (1998). Clinical and pathological features of breast disease in Cowden's syndrome: an underrecognized syndrome with an increased risk of breast cancer. Hum Pathol 29: 47-53.
2099. Schrager CA, Schneider D, Gruener AC, Tsou HC, Peacocke M (1998). Similarities of cutaneous and breast pathology in Cowden's Syndrome. Exp Dermatol 7: 380-390.
2100. Schremmer CN (1970). [Recurrent and metastasing skin tumor of mixed salivary gland tumor type]. Zentralbl Allg Pathol 113: 545-551.
2101. Schuborg C, Mertens F, Rydholm A, Brosjo O, Dictor M, Mitelman F, Mandahl N (1998). Cytogenetic analysis of four angiosarcomas from deep and superficial soft tissue. Cancer Genet Cytogenet 100: 52-56.
2102. Schuller DE, Berg JW, Sherman G, Krause CJ (1979). Cutaneous basosquamous carcinoma of the head and neck: a comparative analysis. Otolaryngol Head Neck Surg 87: 420-427.
2103. Schulz T, Ebschner U, Hartschuh W (2001). Localized Birt-Hogg-Dube syndrome with prominent perivascular fibromas. Am J Dermatopathol 23: 149-153.
2104. Schulz T, Hartschuh W (1997). Merkel cells are absent in basal cell carcinomas but frequently found in trichoblastomas. An immunohistochemical study. J Cutan Pathol 24: 14-24.
2105. Schulz T, Hartschuh W (1998). Folliculo-sebaceous cystic hamartoma is a trichofolliculoma at its very late stage. J Cutan Pathol 25: 354-364.
2106. Schulz T, Hartschuh W (1998). The trichofolliculoma undergoes changes corresponding to the regressing normal hair follicle in its cycle. J Cutan Pathol 25: 341-353.
2107. Schulz T, Hartschuh W (1999). Birt-Hogg-Dube syndrome and Hornstein-Knickenberg syndrome are the same. Different sectioning technique as the cause of different histology. J Cutan Pathol 26: 55-61.
2108. Schwartz RA (1995). Verrucous carcinoma of the skin and mucosa. J Am Acad Dermatol 32: 1-21.
2109. Schwartz RA (1996). Premalignant keratinocytic neoplasms. J Am Acad Dermatol 35: 223-242.
2110. Schwartz RA (1996). Sign of Leser-Trelat. J Am Acad Dermatol 35: 88-95.
2111. Schwartz RA, Gallardo MA, Kapila R, Gascon P, Herscu J, Siegel I, Lambert WC (1996). Bacillary angiomatosis in an HIV seronegative patient on systemic steroid therapy. Br J Dermatol 135: 982-987.
2112. Schwartz RA, Hansen RC, Maize JC (1980). The blue-gray cystic basal cell epithelioma. J Am Acad Dermatol 2: 155-160.
2113. Schwartz RA, Janniger CK (1991). Bowenoid papulosis. J Am Acad Dermatol 24: 261-264.
2114. Schwartz RA, Torre DP (1995). The Muir-Torre syndrome: a 25-year retrospect. J Am Acad Dermatol 33: 90-104.
2115. Schwob VS, Santa Cruz DJ (1986). Palisading cutaneous fibrous histiocytoma. J Cutan Pathol 13: 403-407.
2115A. Scolyer RA, Thompson JF (2005). Desmoplastic melanoma: a heterogeneous entity in which subclassification as "pure" or "mixed" may have important prognostic significance. Ann Surg Oncol 12: 197-199.
2116. Scolyer RA, Zhuang L, Palmer AA, Thompson JF, McCarthy SW (2004). Combined naevus: a benign lesion frequently misdiagnosed both clinically and pathologically as melanoma. Pathology 36: 419-427.
2117. Scott A, Metcalf JS (1988). Cutaneous malignant mixed tumor. Report of a case and review of the literature. Am J Dermatopathol 10: 335-342.
2118. Scott AA, Head DR, Kopecky KJ, Appelbaum FR, Theil KS, Grever MR, Chen IM, Whittaker MH, Griffith BB, Licht JD, Waxman S, Whalen MM, Bankhurst AD, Richter LC, Grogan TM, Willman CL (1994). HLA-DR-, CD33+, CD56+, CD16- Myeloid/Natural Killer-Cell Acute-Leukemia-A Previously Unrecognized Form of Acute-Leukemia Potentiallly Misdiagnosed as French-American-British Acute Myeloid Leukemia-M3. Blood 84: 244-255.
2119. Scott GA, Trepeta R (1993). Clear cell sarcoma of tendons and aponeuroses and malignant blue nevus arising in prepubescent children. Report of two cases and review of the literature. Am J Dermatopathol 15: 139-145.
2120. Scotto J, Pitcher H, Lee JA (1991). Indications of future decreasing trends in skin-melanoma mortality among whites in the United States. Int J Cancer 49: 490-497.
2121. Scrivener Y, Grosshans E, Cribier B (2002). Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 147: 41-47.
2122. Scrivener Y, Petiau P, Rodier-Bruant C, Cribier B, Heid E, Grosshans E (1998). Perianal striated muscle hamartoma associated with hemangioma. Pediatr Dermatol 15: 274-276.
2123. Scrivner D, Oxenhandler RW, Lopez M, Perez-Mesa C (1987). Plantar lentiginous melanoma. A clinicopathologic study. Cancer 60: 2502-2509.
2124. Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson EJ (1994). Histological Typing of Female Genital Tract Tumours. 2nd ed. Springer: Berlin Heidelberg New York.
2125. Scurry J, Dennerstein G, Brenan J (1995). Angiolymphoid hyperplasia with eosinophilia of the vulva. Aust N Z J Obstet Gynaecol 35: 347-348.
2126. Seab JA, Jr., Graham JH, Helwig EB (1989). Deep penetrating nevus. Am J Surg Pathol 13: 39-44.
2127. Seab JAJr, Graham JH, Helwig EB (1989). Deep penetrating nevus. Am J Surg Pathol 13: 39-44.
2128. Seetharam S, Waters HL, Seidman MM, Kraemer KH (1989). Ultraviolet mutagenesis in a plasmid vector replicated in lymphoid cells from patient with the melanoma-prone disorder dysplastic nevus syndrome. Cancer Res 49: 5918-5921.
2129. Seiji M, Mihm MCJr, Sober AJ, Takahashi M, Kato T, Fitzpatrick TB (1979). Malignant melanoma of the palmar-plantar-subungual-mucosal type. Clinical and histopathological features. In: Pigment Cell, Vol. 5, Klaus SN, ed., Karger: Basel , pp. 95-104.
2130. Seiji M, Takematsu H, Hosokawa M, Obata M, Tomita Y, Kato T, Takahashi M, Mihm MCJr (1983). Acral melanoma in Japan. J Invest Dermatol 80 Suppl: 56s-60s.
2131. Sellheyer K, Krahl D, Ratech H (2001). Distribution of Bcl-2 and Bax in embryonic and fetal human skin: antiapoptotic and proapoptotic proteins are differentially expressed in developing skin. Am J Dermatopathol 23: 1-7.
2132. Sen F, Medeiros LJ, Lu D, Jones D, Lai R, Katz R, Abruzzo LV (2002). Mantle cell lymphoma involving skin: cutaneous lesions may be the first manifestation of disease and tumors often have blastoid cytologic features. Am J Surg Pathol 26: 1312-1318.
2133. Sen F, Rassidakis GZ, Jones D, Medeiros LJ (2002). Apoptosis and proliferation in subcutaneous panniculitis-like T-cell lymphoma. Mod Pathol 15: 625-631.
2134. Senear FE, Caro MR (1936). Histiocytoma cutis. Arch Dermatol Syphilol 33: 209.
2135. Sentis HJ, Willemze R, Scheffer E (1986). Histopathologic studies in Sezary syndrome and erythrodermic mycosis fungoides: a comparison with benign forms of erythroderma. J Am Acad Dermatol 15: 1217-1226.
2136. Seo SK, Suh JC, Na GY, Kim IS, Sohn KR (1999). Kasabach-Merritt syndrome:

identification of platelet trapping in a tufted angioma by immunohistochemistry technique using monoclonal antibody to CD61. Pediatr Dermatol 16: 392-394.
2137. Sepp N, Radaszkiewicz T, Meijer CJ, Smolle J, Seewann H, Fritsch P, Kerl H (1993). Specific skin manifestations in acute leukemia with monocytic differentiation. A morphologic and immunohistochemical study of 11 cases. Cancer 71: 124-132.
2138. Sepp N, Schuler G, Romani N, Geissler D, Gattringer C, Burg G, Bartram CR, Fritsch P (1990). "Intravascular lymphomatosis" (angioendotheliomatosis): evidence for a T-cell origin in two cases. Hum Pathol 21: 1051-1058.
2139. Seregard S (1993). Apocrine adenocarcinoma arising in MolI gland cystadenoma. Ophthalmology 100: 1716-1719.
2140. Serrano M, Hannon GJ, Beach D (1993). A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. Nature 366: 704-707.
2141. Servitje O, Gallardo F, Estrach T, Pujol RM, Blanco A, Fernandez-Sevilla A, Petriz L, Peyri J, Romagosa V (2002). Primary cutaneous marginal zone B-cell lymphoma: a clinical, histopathological, immunophenotypic and molecular genetic study of 22 cases. Br J Dermatol 147: 1147-1158.
2142. Setoyama M, Katahira Y, Kanzaki T (1999). Clinicopathologic analysis of 124 cases of adult T-cell leukemia/lymphoma with cutaneous manifestations: the smouldering type with skin manifestations has a poorer prognosis than previously thought. J Dermatol 26: 785-790.
2143. Setoyama M, Mizoguchi S, Orikawa T, Tashiro M (1992). A case of intravascular malignant lymphomatosis (angiotropic large-cell lymphoma) presenting memory T cell phenotype and its expression of adhesion molecules. J Dermatol 19: 263-269.
2144. Severi G, Giles GG, Robertson C, Boyle P, Autier P (2000). Mortality from cutaneous melanoma: evidence for contrasting trends between populations. Br J Cancer 82: 1887-1891.
2145. Seville RH, Rao PS, Hutchinson DN, Birchall G (1970). Outbreak of Campbell de Morgan spots. Br Med J 1: 408-409.
2146. Sexton CW, White WL (1996). Primary cutaneous Ewing's family sarcoma. Report of a case with immunostaining for glycoprotein p30/32 mic2. Am J Dermatopathol 18: 601-605.
2147. Sexton M, Jones DB, Maloney ME (1990). Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. J Am Acad Dermatol 23: 1118-1126.
2148. Shabrawi-Caelen L, Kerl H, Cerroni L (2004). Lymphomatoid papulosis: reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. Arch Dermatol 140: 441-447.
2149. Shaffer JJ, Taylor SC, Cook-Bolden F (2002). Keloidal scars: a review with a critical look at therapeutic options. J Am Acad Dermatol 46: S63-S97.
2150. Shapiro L, Ackerman AB (1966). Solitary lichen planus-like keratosis. Dermatologica 132: 386-392.
2151. Shapiro L, Baraf CS (1970). Isolated epidermolytic acanthoma. A solitary tumor showing granular degeneration. Arch Dermatol 101: 220-223.
2152. Shapiro L, Juhlin EA, Brownstein MH (1973). "Rudimentary polydactyly": an amputation neuroma. Arch Dermatol 108: 223-225.
2153. Shapiro M, Chren MM, Levy RM, Elder DE, LeBoit PE, Mihm MC, Jr., Margolis DJ, Gimotty PA, Ming ME (2004). Variability in nomenclature used for nevi with architectural disorder and cytologic atypia (microscopically dysplastic nevi) by dermatologists and dermatopathologists. J Cutan Pathol 31: 523-530.
2154. Shapiro M, Johnson BJr, Witmer W, Elenitsas R (1999). Spiradenoma arising in a nevus sebaceus of Jadassohn: case report and literature review. Am J Dermatopathol 21: 462-467.
2155. Shapiro PE (1993). Spitz nevi. J Am Acad Dermatol 29: 667-668.
2156. Shapiro PE, Pinto FJ (1994). The histologic spectrum of mycosis fungoides/Sezary syndrome (cutaneous T-cell lymphoma). A review of 222 biopsies, including newly described patterns and the earliest pathologic changes. Am J Surg Pathol 18: 645-667.
2157. Shaw MT, Jacobs SR (1989). Cutaneous Hodgkin's disease in a patient with human immunodeficiency virus infection. Cancer 64: 2585-2587.
2158. Shea CR, Vollmer RT, Prieto VG (1999). Correlating architectural disorder and cytologic atypia in Clark (dysplastic) melanocytic nevi. Hum Pathol 30: 500-505.
2159. Sheibani K, Winberg CD, Burke JS, Nathwani BN, Blayney DW, Van de Velde S, Swartz WG, Rappaport H (1987). Lymphoblastic lymphoma expressing natural killer cell-associated antigens: a clinicopathologic study of six cases. Leuk Res 11: 371-377.
2160. Shelley WB (1980). Familial mycosis fungoides revisited. Arch Dermatol 116: 1177-1178.
2161. Shelley WB (1982). Malignant melanoma and dermatofibrosarcoma in a 60-year-old patient with lifelong acrodermatitis enteropathica. J Am Acad Dermatol 6: 63-66.
2162. Shelley WB, Wood MG (1980). A zosteriform network of spiradenomas. J Am Acad Dermatol 2: 59-61.
2163. Sheng H, Goich S, Wang A, Grachtchouk M, Lowe L, Mo R, Lin K, de Sauvage FJ, Sasaki H, Hui CC, Dlugosz AA (2002). Dissecting the oncogenic potential of Gli2: deletion of an NH(2)-terminal fragment alters skin tumor phenotype. Cancer Res 62: 5308-5316.
2164. Shenoy BV, Carpenter PC, Carney JA (1984). Bilateral primary pigmented nodular adrenocortical disease. Rare cause of the Cushing syndrome. Am J Surg Pathol 8: 335-344.
2165. Sherertz EF, Hess SP, White WL (1991). Perplexing pigmented papules simulating malignant melanoma. Cutis 47: 97-100.
2166. Sherr CJ, Roberts JM (1999). CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev 13: 1501-1512.
2167. Shifer O, Tchetchik R, Glazer O, Metzker A (1992). Halo dermatitis in children. Pediatr Dermatol 9: 275-277.
2168. Shim JH, Lee DW, Cho BK (1996). A case of Cobb syndrome associated with lymphangioma circumscriptum. Dermatology 193: 45-47.
2169. Shimizu K, Naito S, Urata Y, Sekine I, Kondo T, Katayama I (1998). Inducible nitric oxide synthase is expressed in granuloma pyogenicum. Br J Dermatol 138: 769-773.
2170. Shimizu T, Oga A, Murakami T, Muto M (1999). Overexpression of p53 protein associated with proliferative activity and histological degree of malignancy in solar keratosis. Dermatology 199: 113-118.
2171. Shimoyama M (1991). Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 79: 428-437.
2172. Shintaku M, Tsuta K, Yoshida H, Tsubura A, Nakashima Y, Noda K (2002). Apocrine adenocarcinoma of the eyelid with aggressive biological behavior: report of a case. Pathol Int 52: 169-173.
2173. Shirbacheh MV, Mihm MC, Stadelmann WK (2003). The use of selective lymphadenectomy in malignant blue naevus of the scalp. Br J Plast Surg 56: 44-46.
2174. Shmookler BM, Enzinger FM, Weiss SW (1989). Giant cell fibroblastoma. A juvenile form of dermatofibrosarcoma protuberans. Cancer 64: 2154-2161.
2175. Shmulevich I, Hunt K, El Naggar A, Taylor E, Ramdas L, Laborde P, Hess KR, Pollock R, Zhang W (2002). Tumor specific gene expression profiles in human leiomyosarcoma: an evaluation of intratumor heterogeneity. Cancer 94: 2069-2075.
2176. Shneidman D, Belizaire R (1986). Arsenic exposure followed by the development of dermatofibrosarcoma protuberans. Cancer 58: 1585-1587.
2177. Shvili D, Rothem A (1986). Fulminant metastasizing chondroid syringoma of the skin. Am J Dermatopathol 8: 321-325.
2178. Shyong EQ, Gorevic P, Lebwohl M, Phelps RG (2002). Reactive angioendotheliomatosis and sarcoidosis. Int J Dermatol 41: 894-897.
2179. Sidoroff A, Zelger B, Steiner H, Smith N (1996). Indeterminate cell histiocytosis—a clinicopathological entity with features of both X- and non-X histiocytosis. Br J Dermatol 134: 525-532.
2180. Sigel JE, Skacel M, Bergfeld WF, House NS, Rabkin MS, Goldblum JR (2001). The utility of cytokeratin 5/6 in the recognition of cutaneous spindle cell squamous cell carcinoma. J Cutan Pathol 28: 520-524.
2181. Signoretti S, Annessi G (1998). Are histopathological attributes of nevi and melanoma on volar skin related to skin markings? Dermatopathology, practical & conceptual 4: 311-315.
2182. Signoretti S, Annessi G, Puddu P, Faraggiana T (1999). Melanocytic nevi of palms and soles: a histological study according to the plane of section. Am J Surg Pathol 23: 283-287.
2183. Silverman JS, Brustein S (1996). Myxoid dermatofibrohistiocytoma: an indolent post-traumatic tumor composed of CD34+ epithelioid and dendritic cells and factor XIIIa+ dendrophages. J Cutan Pathol 23: 551-557.
2184. Simeonova PP, Luster MI (2000). Mechanisms of arsenic carcinogenicity: genetic or epigenetic mechanisms? J Environ Pathol Toxicol Oncol 19: 281-286.
2185. Simon CA, von Overbeck J, Polla L (1985). [Malignant blue nevus]. Dermatologica 171: 183-188.
2186. Simon M, Flaig MJ, Kind P, Sander CA, Kaudewitz P (2000). Large plaque parapsoriasis: clinical and genotypic correlations. J Cutan Pathol 27: 57-60.
2187. Simon RS, de Eusebio E, Alvarez-Vieitez A, Sanchez YE (1999). Folliculosebaceous cystic hamartoma is but the sebaceous end of tricho-sebo-folliculoma spectrum. J Cutan Pathol 26: 109.
2188. Simon RS, Sanches Yus E (1998). Does eccrine hidrocystoma exist? J Cutan Pathol 25: 182-184.
2189. Simpson EL, Styles AR, Cockerell CJ (1998). Eccrine syringofibroadenomatosis associated with hidrotic ectodermal dysplasia. Br J Dermatol 138: 879-884.
2190. Simrell CR, Boccia RV, Longo DL, Jaffe ES (1986). Coexisting Hodgkin's disease and mycosis fungoides. Immunohistochemical proof of its existence. Arch Pathol Lab Med 110: 1029-1034.
2191. Sinard JH (1999). Immunohistochemical distinction of ocular sebaceous carcinoma from basal cell and squamous cell carcinoma. Arch Ophthalmol 117: 776-783.
2192. Singh AD, De Potter P, Fijal BA, Shields CL, Shields JA, Elston RC (1998). Lifetime prevalence of uveal melanoma in white patients with oculo(dermal) melanocytosis. Ophthalmology 105: 195-198.
2193. Singh AD, Shields CL, Shields JA, De Potter P (1996). Bilateral primary uveal melanoma. Bad luck or bad genes? Ophthalmology 103: 256-262.
2194. Singh M, Kaur B, Annuar NM (1988). Malignant melanoma of the choroid in a naevus of Ota. Br J Ophthalmol 72: 131-133.
2195. Sioutos N, Kerl H, Murphy SB, Kadin ME (1994). Primary cutaneous Hodgkin's disease. Unique clinical, morphologic, and immunophenotypic findings. Am J Dermatopathol 16: 2-8.
2196. Siskind V, Aitken J, Green A, Martin N (2002). Sun exposure and interaction with family history in risk of melanoma, Queensland, Australia. Int J Cancer 97: 90-95.
2197. Siskind V, Darlington S, Green L, Green A (2002). Evolution of melanocytic nevi on the faces and necks of adolescents: a 4 y longitudinal study. J Invest Dermatol 118: 500-504.
2198. Skelton HGI, Smith KJ, Barrett TL, Lupton GP, Graham JH (1991). HMB-45 staining in benign and malignant melanocytic lesions. A reflection of cellular activation. Am J Dermatopathol 13: 543-550.
2199. Slaper H, Velders GJ, Daniel JS, de Gruijl FR, van der Leun JC (1996). Estimates of ozone depletion and skin cancer incidence to examine the Vienna Convention achievements. Nature 384: 256-258.
2200. Slifman NR, Harrist TJ, Rhodes AR (1985). Congenital arrector pili hamartoma. A case report and review of the spectrum of Becker's melanosis and pilar smooth-muscle hamartoma. Arch Dermatol 121: 1034-1037.
2201. Slingluff CLJr, Vollmer R, Seigler HF (1990). Acral melanoma: a review of 185 patients with identification of prognostic variables. J Surg Oncol 45: 91-98.
2202. Smith BD, Smith GL, et al. (2003). Effectiveness of radiotherapy as initial treatment for cutaneous B-cell lymphoma. Int J Radiat Oncol Biol Phys 57: S290.
2203. Smith JM, Kirk EP, Theodosopoulos G, Marshall GM, Walker J, Rogers M, Field M, Brereton JJ, Marsh DJ (2002). Germline mutation of the tumour suppressor PTEN in Proteus syndrome. J Med Genet 39: 937-940.
2204. Smith K, Germain M, Williams J, Skelton H (2001). CD34-positive cellular blue nevi. J Cutan Pathol 28: 145-150.
2205. Smith KJ, Barrett TL, Skelton HGI, Lupton GP, Graham JH (1989). Spindle cell and epithelioid cell nevi with atypia and metastasis (malignant Spitz nevus). Am J

Surg Pathol 13: 931-939.
2206. Smith KJ, Skelton HG, Tuur S, Larson PL, Angritt P (1996). Bacillary angiomatosis in an immunocompetent child. Am J Dermatopathol 18: 597-600.
2207. Smith KJ, Williams J, Corbett D, Skelton H (2001). Microcystic adnexal carcinoma: an immunohistochemical study including markers of proliferation and apoptosis. Am J Surg Pathol 25: 464-471.
2208. Smith PD, Patterson JW (2001). Merkel cell carcinoma (neuroendocrine carcinoma of the skin). Am J Clin Pathol 115 Suppl: S68-S78.
2209. Smith SP, Grande DJ (1991). Basal cell carcinoma recurring after radiotherapy: a unique, difficult treatment subclass of recurrent basal cell carcinoma. J Dermatol Surg Oncol 17: 26-30.
2210. Smolle-Juettner FM, Smolle J, Richtig E, Kraus I, Popper H, Becker H (1992). Primitive neuroectodermal tumor arising in the skin. Differentiation from neuroendocrine carcinoma of the skin. Dermatology 185: 272-275.
2211. Smolle J, Cerroni L, Kerl H (2000). Multiple pseudolymphomas caused by Hirudo medicinalis therapy. J Am Acad Dermatol 43: 867-869.
2212. Smolle J, Kerl H (1983). [Pilar sheath acanthoma - a benign follicular hamartoma.]. Dermatologica 167: 335-338.
2213. Smoller BR, Bishop K, Glusac E, Kim YH, Hendrickson M (1995). Reassessment of histologic parameters in the diagnosis of mycosis fungoides. Am J Surg Pathol 19: 1423-1430.
2214. Smoller BR, McNutt NS, Hsu A (1989). HMB-45 staining of dysplastic nevi. Support for a spectrum of progression toward melanoma. Am J Surg Pathol 13: 680-684.
2215. Smoller BR, Warnke RA (1998). Cutaneous infiltrate of chronic lymphocytic leukemia and relationship to primary cutaneous epithelial neoplasms. J Cutan Pathol 25: 160-164.
2216. Snow SN, Reizner GT (1992). Eccrine porocarcinoma of the face. J Am Acad Dermatol 27: 306-311.
2217. Snow SN, Reizner GT (1992). Mucinous eccrine carcinoma of the eyelid. Cancer 70: 2099-2104.
2218. Sober AJ, Burstein JM (1995). Precursors to skin cancer. Cancer 75: 645-650.
2218A. Sober AJ, Chuang TY, Duciv M, Farmer ER, Grichnik JM, Halpern AC, Ho V, Holloway V, Hood AF, Johnson TM, Lowery BJ; Guidelines/Outcomes Committee (2001). Guidelines of care for primary cutaneous melanoma. J Am Acad Dermatol 45: 579-586.
2219. Sobin LH, Wittekind C (2002). TNM Classification of Malignant Tumours (UICC). 6th ed. ed. Wiley: New York.
2220. Sondergaard K (1983). Histological type and biological behavior of primary cutaneous malignant melanoma. 2. An analysis of 86 cases located on so-called acral regions as plantar, palmar, and sub-/parungual areas. Virchows Arch A Pathol Anat Histopathol 401: 333-343.
2221. Sonnex TS (1986). Digital myxoid cysts: a review. Cutis 37: 89-94.
2222. Soon SL, Solomon AR, Jr., Papadopoulos D, Murray DR, McAlpine B, Washington CV (2003). Acral lentiginous melanoma mimicking benign disease: the Emory experience. J Am Acad Dermatol 48: 183-188.
2223. Sorahan T, Ball PM, Grimley RP, Pope D (1990). Benign pigmented nevi in children from Kidderminster, England: prevalence and associated factors. J Am Acad Dermatol 22: 747-750.
2224. Soter NA (2000). Mastocytosis and the skin. Hematol Oncol Clin North Am 14: 537-55, vi.
2225. Soubrier M, Dubost JJ, Serre AF, Ristori JM, Sauvezie B, Cathebras P, Piette JC, Chapman A, Authier FJ, Gherardi RK (1997). Growth factors in POEMS syndrome: evidence for a marked increase in circulating vascular endothelial growth factor. Arthritis Rheum 40: 786-787.
2226. Soufir N, Avril MF, Chompret A, Demenais F, Bombled J, Spatz A, Stoppa-Lyonnet D, Benard J, Bressac de Paillerets B (1998). Prevalence of p16 and CDK4 germline mutations in 48 melanoma-prone families in France. The French Familial Melanoma Study Group. Hum Mol Genet 7: 209-216.
2227. Southey MC, Young MA, Whitty J, Mifsud S, Keilar M, Mead L, Trute L, Aittomaki K, McLachlan SA, Debinski H, Venter DJ, Armes JE (2001). Molecular pathologic analysis enhances the diagnosis and management of Muir-Torre syndrome and gives insight into its underlying molecular pathogenesis. Am J Surg Pathol 25: 936-941.
2228. Soyer HP, Breier F, Cerroni L, Kerl H (1999). 'Tubular' structures within melanocytic proliferations: a distinctive morphologic finding not restricted to Spitz nevi. J Cutan Pathol 26: 315-317.
2229. Soyer HP, El Shabrawi-Caelen L (2000). A spiradenoma with "ancient" stromal features. Dermatopathology, practical & conceptual 6: 29-32.
2230. Spatz A, Avril MF (1998). Melanoma in childhood: review and perspectives. Pediatr Dev Pathol 1: 463-474.
2231. Spatz A, Giglia-Mari G, Benhamou S, Sarasin A (2001). Association between DNA repair-deficiency and high level of p53 mutations in melanoma of Xeroderma pigmentosum. Cancer Res 61: 2480-2486.
2232. Spatz A, Ruiter D, Hardmeier T, Renard N, Wechsler J, Bailly C, Avril MF, Kwee H, Bastian BC, Hill C, De Potter C, Prade M (1996). Melanoma in childhood: an EORTC-MCG multicenter study on the clinico-pathological aspects. Int J Cancer 68: 317-324.
2233. Spatz A, Zimmermann U, Bachollet B, Pautier P, Michel G, Duvillard P (1998). Malignant blue nevus of the vulva with late ovarian metastasis. Am J Dermatopathol 20: 408-412.
2234. Spencer J, Perry ME, Dunn-Walters DK (1998). Human marginal-zone B cells. Immunol Today 19: 421-426.
2235. Spencer JM, Kahn SM, Jiang W, DeLeo VA, Weinstein IB (1995). Activated ras genes occur in human actinic keratoses, premalignant precursors to squamous cell carcinomas. Arch Dermatol 131: 796-800.
2236. Sperling LC, Sakas EL (1982). Eccrine hidrocystomas. J Am Acad Dermatol 7: 763-770.
2237. Spiegler E (1894). Über die sogenannte Sarkomatosis cutis. Arch Dermatol Syphilol 27: 163-174.
2238. Spillane AJ, Thomas JM, Fisher C (2000). Epithelioid sarcoma: the clinicopathological complexities of this rare soft tissue sarcoma. Ann Surg Oncol 7: 218-225.
2239. Spitz S (1948). Melanomas of childhood. Am J Pathol 24: 591-609.
2240. Srigley JR, Ayala AG, Ordonez NG, van Nostrand AW (1985). Epithelioid hemangioma of the penis. A rare and distinctive vascular lesion. Arch Pathol Lab Med 109: 51-54.
2241. Stambolic V, Suzuki A, de la Pompa JL, Brothers GM, Mirtsos C, Sasaki T, Ruland J, Penninger JM, Siderovski DP, Mak TW (1998). Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. Cell 95: 29-39.
2242. Stanek J, de Courten-Myers G, Spaulding AG, Strub W, Hopkin RJ (2001). Case of complex craniofacial anomalies, bilateral nasal proboscides, palatal pituitary, upper limbs reduction, and amnion rupture sequence: disorganization phenotype? Pediatr Dev Pathol 4: 192-202.
2243. Stanford DG, Georgouras KE (1996). Dermal melanocytosis: a clinical spectrum. Australas J Dermatol 37: 19-25.
2244. Stang A, Jockel KH (2003). Changing patterns of skin melanoma mortality in West Germany from 1968 through 1999. Ann Epidemiol 13: 436-442.
2245. Stang A, Stang K, Stegmaier C, Hakulinen T, Jockel KH (2001). Skin melanoma in Saarland: incidence, survival and mortality 1970-1996. Eur J Cancer Prev 10: 407-415.
2246. Stanley MA (2001). Immune responses to human papillomaviruses. In: Human Papillomaviruses: Clinical and Scientific Advances, Sterling JC, Tyring SK, eds., Arnold: London , pp. 38-49.
2247. Starink TM (1984). Cowden's disease: analysis of fourteen new cases. J Am Acad Dermatol 11: 1127-1141.
2248. Starink TM (1997). Eccrine syringofibroadenoma: multiple lesions representing a new cutaneous marker of the Schopf syndrome, and solitary nonhereditary tumors. J Am Acad Dermatol 36: 569-576.
2249. Starink TM, Hausman R (1984). The cutaneous pathology of extrafacial lesions in Cowden's disease. J Cutan Pathol 11: 338-344.
2250. Starink TM, Hausman R (1984). The cutaneous pathology of facial lesions in Cowden's disease. J Cutan Pathol 11: 331-337.
2251. Starink TM, Meijer CJ, Brownstein MH (1985). The cutaneous pathology of Cowden's disease: new findings. J Cutan Pathol 12: 83-93.
2252. Starink TM, van der Veen JP, Arwert F, de Waal LP, de Lange GG, Gille JJ, Eriksson AW (1986). The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet 29: 222-233.
2253. Stary A, Sarasin A (2002). The genetics of the hereditary xeroderma pigmentosum syndrome. Biochimie 84: 49-60.
2254. Starz H, Balda BR, Bachter D, Buchels H, Vogt H (1999). Secondary lymph node involvement from primary cutaneous large B-cell lymphoma of the leg: sentinel lymph nodectomy as a new strategy for staging circumscribed cutaneous lymphomas. Cancer 85: 199-207.
2255. Stas M, van den Oord JJ, Garmyn M, Degreef H, De Wever I, Wolf-Peeters C (2000). Minimal deviation and/or naevoid melanoma: is recognition worthwhile? A clinicopathological study of nine cases. Melanoma Res 10: 371-380.
2256. Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, Ligon AH, Langford LA, Baumgard ML, Hattier T, Davis T, Frye C, Hu R, Swedlund B, Teng DH, Tavtigian SV (1997). Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 15: 356-362.
2257. Stefanato CM, Finn R, Bhawan J (2000). Extramammary Paget disease with underlying hidradenoma papilliferum: guilt by association? Am J Dermatopathol 22: 439-442.
2258. Steffen C, Ackerman AB (1994). Neoplasms with sebaceous differentiation. Lea and Febiger: Philadelphia.
2259. Stein H, Foss HD, Durkop H, Marafioti T, Delsol G, Pulford K, Pileri S, Falini B (2000). CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 96: 3681-3695.
2259A. Steiner A, Binder M, Schemper M, Wolff K, Pehamberger H (1993). Statistical evaluation of epiluminescence microscopy criteria for melanocytic pigmented skin lesions. J Am Acad Dermatol 29: 581-588.
2260. Steinitz R, Parkin DM, Young JL, Bieber CA, Katz L (1989). Cancer incidence in Jewish migrants to Israel, 1961-1981. IARC Sci Publ 1-311.
2261. Sterchi JM, Muss HB, Weidner N (1987). Cellular blue nevus simulating metastatic melanoma: report of an unusually large lesion associated with nevus-cell aggregates in regional lymph nodes. J Surg Oncol 36: 71-75.
2262. Sterling JC, Tyring SK (2001). Human papillomaviruses, clinical and scientific advances. Arnold: London/New York.
2263. Stern JB, Haupt HM, Smith RR (1994). Fibroepithelioma of Pinkus. Eccrine duct spread of basal cell carcinoma. Am J Dermatopathol 16: 585-587.
2264. Stern RS (1997). Narrowband UV-B and psoriasis. Arch Dermatol 133: 1587-1588.
2265. Stern RS, Laird N (1994). The carcinogenic risk of treatments for severe psoriasis. Photochemotherapy Follow-up Study. Cancer 73: 2759-2764.
2266. Sterry W, Christophers E (1988). Quadrant distribution of dysplastic nevus syndrome. Arch Dermatol 124: 926-929.
2267. Sterry W, Siebel A, Mielke V (1992). HTLV-1-negative pleomorphic T-cell lymphoma of the skin: the clinicopathological correlations and natural history of 15 patients. Br J Dermatol 126: 456-462.
2268. Stevens NG, Liff JM, Weiss NS (1990). Plantar melanoma: is the incidence of melanoma of the sole of the foot really higher in blacks than whites? Int J Cancer 45: 691-693.
2269. Stewart FW, Treves N (1948). Lymphangiosarcoma in pstmastectomy lymphedema. Cancer 1: 64-81.
2270. Stockfleth E, Meinke B, Arndt R, Christophers E, Meyer T (1999). Identification of DNA sequences of both genital and cutaneous HPV types in a small number of keratoacanthomas of nonimmunosuppressed patients. Dermatology 198: 122-125.
2271. Stokkel MP, Peterse HL (1992). Angiosarcoma of the breast after lumpectomy and radiation therapy for adenocarcinoma. Cancer 69: 2965-2968.
2272. Stone DM, Hynes M, Armanini M, Swanson TA, Gu Q, Johnson RL, Scott MP, Pennica D, Goddard A, Phillips H, Noll M, Hooper JE, de Sauvage F, Rosenthal A (1996). The tumour-suppressor gene patched encodes a candidate receptor for Sonic hedgehog. Nature 384: 129-134.
2273. Storz MN, van de Rijn M, Kim YH, Mraz-Gernhard S, Hoppe RT, Kohler S (2003). Gene expression profiles of cutaneous B cell lymphoma. J Invest Dermatol

120: 865-870.
2274. Stout AP, Cooley SGE (1951). Carcinoma of sweat glands. Cancer 4: 521-536.
2275. Stratakis CA, Courcoutsakis NA, Abati A, Filie A, Doppman JL, Carney JA, Shawker T (1997). Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). J Clin Endocrinol Metab 82: 2037-2043.
2276. Stratakis CA, Kirschner LS, Carney JA (2001). Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab 86: 4041-4046.
2277. Straume O, Akslen LA (1997). Alterations and prognostic significance of p16 and p53 protein expression in subgroups of cutaneous melanoma. Int J Cancer 74: 535-539.
2278. Straume O, Sviland L, Akslen LA (2000). Loss of nuclear p16 protein expression correlates with increased tumor cell proliferation (Ki-67) and poor prognosis in patients with vertical growth phase melanoma. Clin Cancer Res 6: 1845-1853.
2279. Streubel B, Lamprecht A, Dierlamm J, Cerroni L, Stolte M, Ott G, Raderer M, Chott A (2003). T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. Blood 101: 2335-2339.
2280. Strobel P, Zettl A, Ren Z, Starostik P, Riedmiller H, Storkel S, Muller-Hermelink HK, Marx A (2002). Spiradenocylindroma of the kidney: clinical and genetic findings suggesting a role of somatic mutation of the CYLD1 gene in the oncogenesis of an unusual renal neoplasm. Am J Surg Pathol 26: 119-124.
2281. Strumia R, Lombardi AR, Cavazzini L (2001). S-100 negative myxoid neurothekeoma. Am J Dermatopathol 23: 82-83.
2282. Strutton GM (1997). Pathological variants of basal cell carcinoma. Australas J Dermatol 38 Suppl 1: S31-S35.
2283. Stubenrauch F, Laimins LA (1999). Human papillomavirus life cycle: active and latent phases. Semin Cancer Biol 9: 379-386.
2284. Su LD, Fullen DR, Lowe L, Uherova P, Schnitzer B, Valdez R (2002). CD117 (KIT receptor) expression in Merkel cell carcinoma. Am J Dermatopathol 24: 289-293.
2285. Su LD, Fullen DR, Lowe L, Wang TS, Schwartz JL, Cimmino VM, Sondak VK, Johnson TM (2004). Desmoplastic and neurotropic melanoma. Cancer 100: 598-604.
2286. Su LD, Fullen DR, Sondak VK, Johnson TM, Lowe L (2003). Sentinel lymph node biopsy for patients with problematic spitzoid melanocytic lesions: a report on 18 patients. Cancer 97: 499-507.
2287. Su LD, Lowe L, Bradford CR, Yahanda AI, Johnson TM, Sondak VK (2002). Immunostaining for cytokeratin 20 improves detection of micrometastatic Merkel cell carcinoma in sentinel lymph nodes. J Am Acad Dermatol 46: 661-666.
2288. Su WP, Buechner SA, Li CY (1984). Clinicopathologic correlations in leukemia cutis. J Am Acad Dermatol 11: 121-128.
2289. Subtil A, LeBoit PE (2000). Lymphocytes + nerves = ? Am J Dermatopathol 22: 362-364.
2290. Suchniak JM, Baer S, Goldberg LH (1997). High rate of malignant transformation in hyperkeratotic actinic keratoses. J Am Acad Dermatol 37: 392-394.
2291. Sumitra S, Yesudian P (1994). Painful tufted angioma precipitated by trauma. Int J Dermatol 33: 675-676.
2292. Suringa DW, Ackerman AB (1970). Cutaneous lymphangiomas with dyschondroplasia (Maffucci's syndrome). A unique variant of an unusual syndrome. Arch Dermatol 101: 472-474.
2293. Suster S (1994). Hyalinizing spindle and epithelioid cell nevus. A study of five cases of a distinctive histologic variant of Spitz's nevus. Am J Dermatopathol 16: 593-598.
2294. Suster S (1996). Clear cell tumors of the skin. Semin Diagn Pathol 13: 40-59.
2295. Suster S, Ronnen M, Huszar M (1988). Extraskeletal Ewing's sarcoma of the scalp. Pediatr Dermatol 5: 123-126.
2296. Sutherland CM, Mather FJ, Muchmore JH, Carter RD, Reed RJ, Krementz ET (1993). Acral lentiginous melanoma. Am J Surg 166: 64-67.
2297. Sutton RL (1916). An unusual variety of vitiligo (leukoderma acquisitum centrifugum). J Cut Dis 34: 797-800.
2298. Suzuki H, Takahashi H, Miyashita M, Takemura T (1995). Persistent actinic epidermolytic hyperkeratosis. J Am Acad Dermatol 32: 63-66.
2299. Suzuki R, Nakamura S (1999). Malignancies of natural killer (NK) cell precursor: myeloid/NK cell precursor acute leukemia and blastic NK cell lymphoma/leukemia. Leuk Res 23: 615-624.
2300. Swanson PE, Cherwitz DL, Neumann MP, Wick MR (1987). Eccrine sweat gland carcinoma: an histologic and immunohistochemical study of 32 cases. J Cutan Pathol 14: 65-86.
2301. Swerdlow SH, Berger F, Isaacson PG, Muller-Hermelink HK, Nathwani BN, Piris MA, Harris NL (2001). Mantle cell lymphoma. In: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Jaffe ES, Harris NL, Stein H, Vardiman J, eds., IARC Press: Lyon , pp. 168-170.
2302. Swerdlow SH, Habeshaw JA, Richards MA, Rainey M, Murray LJ, Stansfeld AG (1985). T lymphoblastic lymphoma with LEU-7 positive phenotype and unusual clinical course: a multiparameter study. Leuk Res 9: 167-173.
2303. Swerdlow SH, Williams ME (2002). From centrocytic to mantle cell lymphoma: a clinicopathologic and molecular review of 3 decades. Hum Pathol 33: 7-20.
2304. Swetter SM (2003). Dermatological perspectives of malignant melanoma. Surg Clin North Am 83: 77-95, vi.
2305. Swetter SM, Ecker PM, Johnson DL, Harvell JD (2004). Primary dermal melanoma: a distinct subtype of melanoma. Arch Dermatol 140: 99-103.
2306. Szymanski FJ (1957). Warty dyskeratoma. A benign cutaneous tumor resembling Darier's disease microscopically. Arch Dermatol 75: 567-572.
2307. Taguchi M, Tsuchida T, Ikeda S, Sekiya T (1998). Alterations of p53 gene and Ha-ras gene are independent events in solar keratosis and squamous cell carcinoma. Pathol Int 48: 689-694.
2308. Taipale J, Cooper MK, Maiti T, Beachy PA (2002). Patched acts catalytically to suppress the activity of Smoothened. Nature 418: 892-897.
2309. Taira JW, Hill TL, Everett MA (1992). Lobular capillary hemangioma (pyogenic granuloma) with satellitosis. J Am Acad Dermatol 27: 297-300.
2310. Takahashi M, Asai N, Iwashita T, Murakami H, Ito S (1998). Molecular mechanisms of development of multiple endocrine neoplasia 2 by RET mutations. J Intern Med 243: 509-513.
2311. Takata M, Rehman I, Rees JL (1998). A trichilemmal carcinoma arising from a proliferating trichilemmal cyst: the loss of the wild-type p53 is a critical event in malignant transformation. Hum Pathol 29: 193-195.
2312. Takatsuki K, Sanada I (1983). Plasma cell dyscrasia with polyneuropathy and endocrine disorder: clinical and laboratory features of 109 reported cases. Jpn J Clin Oncol 13: 543-555.
2313. Takeda H, Mitsuhashi Y, Hayashi M, Kondo S (2000). Eccrine syringofibroadenoma: case report and review of the literature. J Eur Acad Dermatol Venereol 15: 147-149.
2314. Takeda H, Mitsuhashi Y, Yoshikawa K, Katagata Y, Kondo S (1998). Eccrine syringofibroadenoma: report of a case and analysis of cytokeratin expression. Dermatology 196: 242-245.
2315. Takematsu H, Obata M, Tomita Y, Kato T, Takahashi M, Abe R (1985). Subungual melanoma. A clinicopathologic study of 16 Japanese cases. Cancer 55: 2725-2731.
2316. Tamada S, Ackerman AB (1987). Dermatofibroma with monster cells. Am J Dermatopathol 9: 380-387.
2317. Tamm E, Jungkunz W, Marsch WC, Lutjen-Drecoll E (1992). Increase in types IV and VI collagen in cherry haemangiomas. Arch Dermatol Res 284: 275-282.
2318. Tan CY, Marks R (1982). Lichenoid solar keratosis—prevalence and immunologic findings. J Invest Dermatol 79: 365-367.
2319. Tanaka A, Hatoko M, Kuwahara M, Tada H, Muramatsu T (2000). Recurrent mucinous carcinoma of the skin invading to the frontal skull base. Br J Dermatol 143: 458-459.
2320. Tanaka A, Hiroi A, Kanehara S, Yamamoto Y, Uede K, Furukawa F (2002). A case of striated muscle hamartoma on the cheek. J Dermatol 29: 754-756.
2321. Tanay A, Mehregan AH (1969). Warty dyskeratoma. Dermatologica 138: 155-164.
2322. Tani M, Komura A, Ichihashi M (1997). Dermatomyofibroma (Plaqueformige Dermale Fibromatose). J Dermatol 24: 793-797.
2323. Tannous ZS, Mihm MC, Jr., Sober AJ, Duncan LM (2005). Congenital melanocytic nevi: clinical and histopathologic features, risk of melanoma, and clinical management. J Am Acad Dermatol 52: 197-203.
2324. Tappeiner J, Wolff K (1968). [Hidradenoma papilliferum. An enzym histochemical and electron microscopic study]. Hautarzt 19: 101-109.
2325. Tappero JW, Koehler JE, Berger TG, Cockerell CJ, Lee TH, Busch MP, Stites DP, Mohle-Boetani J, Reingold AL, LeBoit PE (1993). Bacillary angiomatosis and bacillary splenitis in immunocompetent adults. Ann Intern Med 118: 363-365.
2326. Tassies D, Sierra J, Montserrat E, Marti R, Estrach T, Rozman C (1992). Specific cutaneous involvement in Hodgkin's disease. Hematol Oncol 10: 75-79.
2327. Tateyama H, Eimoto T, Tada T, Inagaki H, Nakamura T, Yamauchi R (1995). p53 protein and proliferating cell nuclear antigen in eccrine poroma and porocarcinoma. an immunohistochemical study. Am J Dermatopathol 17: 457-464.
2328. Taylor GB, Chan YF (2000). Subcutaneous primitive neuroectodermal tumour in the abdominal wall of a child: long-term survival after local excision. Pathology 32: 294-298.
2329. Taylor HB, Helwig EB (1962). Dermatofibrosarcoma protuberans. A study of 115 cases. Cancer 15: 717-725.
2330. Tegner E, Bjornberg A, Jonsson N (1990). Halo dermatitis around tumours. Acta Derm Venereol 70: 31-34.
2331. Teiche M (1906). Ueber benigne Melanome ("Chromatophorome") der Haut - Blaue Naevi. Virchows Arch 186: 212-229.
2332. Tellada M, Specht CS, McLean IW, Grossniklaus HE, Zimmerman LE (1996). Primary orbital melanomas. Ophthalmology 103: 929-932.
2333. Tellechea O, Reis JP, Baptista AP (1992). Desmoplastic trichilemmoma. Am J Dermatopathol 14: 107-4.
2334. Tellechea O, Reis JP, Domingues JC, Baptista AP (1993). Monoclonal antibody Ber EP4 distinguishes basal-cell carcinoma from squamous-cell carcinoma of the skin. Am J Dermatopathol 15: 452-455.
2335. Tellechea O, Reis JP, Marques C, Baptista AP (1995). Tubular apocrine adenoma with eccrine and apocrine immunophenotypes or papillary tubular adenoma? Am J Dermatopathol 17: 499-505.
2336. Temple-Camp CR, Saxe N, King H (1988). Benign and malignant cellular blue nevus. A clinicopathological study of 30 cases. Am J Dermatopathol 10: 289-296.
2337. Ten Seldam REJ, Helwig EB (1974). Histological Typing of Skin Tumours. WHO International Histological Classification of Tumours. WHO: Geneva.
2338. Terrier-Lacombe MJ, Guillou L, Maire G, Terrier P, Vince DR, de Saint Aubain Somerhausen N, Collin F, Pedeutour F, Coindre JM (2003). Dermatofibrosarcoma protuberans, giant cell fibroblastoma, and hybrid lesions in children: clinicopathologic comparative analysis of 28 cases with molecular data—a study from the French Federation of Cancer Centers Sarcoma Group. Am J Surg Pathol 27: 27-39.
2339. Teruya-Feldstein J, Jaffe ES, Burd PR, Kanegane H, Kingma DW, Wilson WH, Longo DL, Tosato G (1997). The role of Mig, the monokine induced by interferon-gamma, and IP-10, the interferon-gamma-inducible protein-10, in tissue necrosis and vascular damage associated with Epstein-Barr virus-positive lymphoproliferative disease. Blood 90: 4099-4105.
2340. Teruya-Feldstein J, Setsuda J, Yao X, Kingma DW, Straus S, Tosato G, Jaffe ES (1999). MIP-1alpha expression in tissues from patients with hemophagocytic syndrome. Lab Invest 79: 1583-1590.
2341. Thai KE, Barrett W, Kossard S (2003). Reactive angioendotheliomatosis in the setting of antiphospholipid syndrome. Australas J Dermatol 44: 151-155.
2342. Thami GP, Kaur S, Kanwar AJ (2002). Traumatic neuroma following a human bite. Clin Exp Dermatol 27: 76-77.
2343. Thangavelu M, Finn WG, Yelavarthi KK, Roenigk HHJr, Samuelson E, Peterson L, Kuzel TM, Rosen ST (1997). Recurring structural chromosome abnormalities in peripheral blood lymphocytes of patients with mycosis fungoides/Sezary syndrome. Blood 89: 3371-3377.
2344. Theunis A, Andre J, Forton F, Wanet

J, Song M (2001). A case of subungual reactive eccrine syringofibroadenoma. Dermatology 203: 185-187.
2345. Theunissen P, Spincemaille G, Pannebakker M, Lambers J (1993). Meningeal melanoma associated with nevus of Ota: case report and review. Clin Neuropathol 12: 125-129.
2346. Thewes M, Worret WI, Engst R, Ring J (1998). Stromelysin-3: a potent marker for histopathologic differentiation between desmoplastic trichoepithelioma and morphealike basal cell carcinoma. Am J Dermatopathol 20: 140-142.
2347. Thompson JF, McCarthy WH, Bosch CM, O'Brien CJ, Quinn MJ, Paramaesvaran S, Crotty K, McCarthy SW, Uren RF, Howman-Giles R (1995). Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. Melanoma Res 5: 255-260.
2348. Thompson JF, Uren RF, Shaw HM, McCarthy WH, Quinn MJ, O'Brien CJ, Howman-Giles RB (1999). Location of sentinel lymph nodes in patients with cutaneous melanoma: new insights into lymphatic anatomy. J Am Coll Surg 189: 195-204.
2348A Thompson JF, Scolyer RA, Kefford RF (2005). Cutaneous melanoma. Lancet 365: 687-701
2349. Thompson SC, Jolley D, Marks R (1993). Reduction of solar keratoses by regular sunscreen use. N Engl J Med 329: 1147-1151.
2350. Thorn M, Bergstrom R, Adami HO, Ringborg U (1990). Trends in the incidence of malignant melanoma in Sweden, by anatomic site, 1960-1984. Am J Epidemiol 132: 1066-1077.
2351. Thorn M, Ponten F, Bergstrom R, Sparen P, Adami HO (1994). Trends in tumour characteristics and survival of malignant melanoma 1960-84: a population-based study in Sweden. Br J Cancer 70: 743-748.
2352. Thorn M, Sparen P, Bergstrom R, Adami HO (1992). Trends in mortality rates from malignant melanoma in Sweden 1953-1987 and forecasts up to 2007. Br J Cancer 66: 563-567.
2353. Thornton CM, Hunt SJ (1995). Sebaceous adenoma with a cutaneous horn. J Cutan Pathol 22: 185-187.
2354. Tieben LM, Berkhout RJ, Smits HL, Bouwes Bavinck JN, Vermeer BJ, Bruijn JA, Van der Woude FJ, Ter Schegget J (1994). Detection of epidermodysplasia verruciformis-like human papillomavirus types in malignant and premalignant skin lesions of renal transplant recipients. Br J Dermatol 131: 226-230.
2355. Tiffee JC, Pulitzer DR (1996). Nerve sheath myxoma of the oral cavity: case report and review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82: 423-425.
2356. Tobon H, Murphy AI (1977). Benign blue nevus of the vagina. Cancer 40: 3174-3176.
2357. Toker C (1972). Trabecular carcinoma of the skin. Arch Dermatol 105: 107-110.
2358. Tokura Y, Takigawa M, Inoue K, Matsumoto K, Yamada M (1986). S-100 protein-positive cells in hidrocystomas. J Cutan Pathol 13: 102-110.
2359. Tokura Y, Yamanaka K, Wakita H, Kurokawa S, Horiguchi D, Usui A, Sayama S, Takigawa M (1994). Halo congenital nevus undergoing spontaneous regression. Involvement of T-cell immunity in involution and presence of circulating anti-nevus cell IgM antibodies. Arch Dermatol 130: 1036-1041.
2360. Tomasini C, Puiatti P, Bernengo MG (1998). Multiple pyogenic granuloma of the penis. Sex Transm Infect 74: 221-222.
2361. Tomasini C, Soro E, Pippione M (2000). Angioendotheliomatosis in a woman with rheumatoid arthritis. Am J Dermatopathol 22: 334-338.
2362. Tomaszewski MM, Abbondanzo SL, Lupton GP (2000). Extranodal marginal zone B-cell lymphoma of the skin: a morphologic and immunophenotypic study of 11 cases. Am J Dermatopathol 22: 205-211.
2363. Toporcer MB, Kantor GR, Benedetto AV (1991). Multiple cutaneous reticulohistiocytomas (reticulohistiocytic granulomas). J Am Acad Dermatol 25: 948-951.
2364. Toribio J, Zulaica A, Peteiro C (1987). Tubular apocrine adenoma. J Cutan Pathol 14: 114-117.
2365. Toro JR, Beaty M, Sorbara L, Turner ML, White J, Kingma DW, Raffeld M, Jaffe ES (2000). gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. Arch Dermatol 136: 1024-1032.
2366. Toro JR, Liewehr DJ, Pabby N, Sorbara L, Raffeld M, Steinberg SM, Jaffe ES (2003). Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood 101: 3407-3412.
2367. Toro JR, Stoll HLJr, Stomper PC, Oseroff AR (1997). Prognostic factors and evaluation of mycosis fungoides and Sezary syndrome. J Am Acad Dermatol 37: 58-67.
2368. Torok L, Lueff S, Garay G, Tapai M (1999). Monocytic aleukemic leukemia cutis. J Eur Acad Dermatol Venereol 13: 54-58.
2369. Tosti A, Cameli N, Peluso AM, Fanti PA, Peserico A (1999). Storiform collagenoma of the nail. Cutis 64: 203-204.
2370. Toussaint S, Kamino H (1999). Dysplastic changes in different types of melanocytic nevi. A unifying concept. J Cutan Pathol 26: 84-90.
2371. Tran TA, Carlson JA, Basaca PC, Mihm MC (1998). Cellular blue nevus with atypia (atypical cellular blue nevus): a clinicopathologic study of nine cases. J Cutan Pathol 25: 252-258.
2372. Travis WD, Li CY, Bergstralh EJ, Yam LT, Swee RG (1988). Systemic mast cell disease. Analysis of 58 cases and literature review. Medicine (Baltimore) 67: 345-368.
2373. Tripp JM, Kopf AW, Marghoob AA, Bart RS (2002). Management of dysplastic nevi: a survey of fellows of the American Academy of Dermatology. J Am Acad Dermatol 46: 674-682.
2374. Tronnier M, Smolle J, Wolff HH (1995). Ultraviolet irradiation induces acute changes in melanocytic nevi. J Invest Dermatol 104: 475-478.
2375. Trotter MJ, McGregor GI, O'Connell JX (1996). Linear dermatomyofibroma. Clin Exp Dermatol 21: 307-309.
2376. Trovik CS, Bauer HC, Alvegard TA, Anderson H, Blomqvist C, Berlin O, Gustafson P, Saeter G, Walloe A (2000). Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group Register. Eur J Cancer 36: 710-716.
2377. Trown K, Heenan PJ (1994). Malignant mixed tumor of the skin (malignant chondroid syringoma). Pathology 26: 237-243.
2378. Troy JL, Ackerman AB (1984). Sebaceoma. A distinctive benign neoplasm of adnexal epithelium differentiating toward sebaceous cells. Am J Dermatopathol 6: 7-13.
2379. Truchot F, Grezard P, Wolf F, Balme B, Perrot H (2001). Multiple idiopathic mucocutaneous neuromas: a new entity? Br J Dermatol 145: 826-829.
2380. Tsai CY, Lai CH, Chan HL, Kuo TT (2001). Glomeruloid hemangioma—a specific cutaneous marker of POEMS syndrome. Int J Dermatol 40: 403-406.
2381. Tsang WY, Chan JK (1993). The family of epithelioid vascular tumors. Histol Histopathol 8: 187-212.
2382. Tsou HC, Teng DH, Ping XL, Brancolini V, Davis T, Hu R, Xie XX, Gruener AC, Schrager CA, Christiano AM, Eng C, Steck P, Ott J, Tavtigian SV, Peacocke M (1997). The role of MMAC1 mutations in early-onset breast cancer: causative in association with Cowden syndrome and excluded in BRCA1-negative cases. Am J Hum Genet 61: 1036-1043.
2383. Tucker MA, Fraser MC, Goldstein AM, Elder DE, Guerry D, Organic SM (1993). Risk of melanoma and other cancers in melanoma-prone families. J Invest Dermatol 100: S350-S355.
2384. Tucker MA, Fraser MC, Goldstein AM, Struewing JP, King MA, Crawford JT, Chiazze EA, Zametkin DP, Fontaine LS, Clark WHJr (2002). A natural history of melanomas and dysplastic nevi: an atlas of lesions in melanoma-prone families. Cancer 94: 3192-3209.
2385. Tucker MA, Goldstein AM (2003). Melanoma etiology: where are we? Oncogene 22: 3042-3052.
2386. Tucker MA, Halpern A, Holly EA, Hartge P, Elder DE, Sagebiel RW, Guerry D, Clark WHJr (1997). Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. JAMA 277: 1439-1444.
2387. Tucker TJ, Bardales RH, Miranda RN (1999). Intravascular lymphomatosis with bone marrow involvement. Arch Pathol Lab Med 123: 952-956.
2388. Tuder RM, Young R, Karasek M, Bensch K (1987). Adult cutaneous hemangiomas are composed of nonreplicating endothelial cells. J Invest Dermatol 89: 594-597.
2389. Turner RJ, Leonard N, Malcolm AJ, Lawrence CM, Dahl MG (2000). A retrospective study of outcome of Mohs' micrographic surgery for cutaneous squamous cell carcinoma using formalin fixed sections. Br J Dermatol 142: 752-757.
2390. Tyring SK (2000). Human papillomavirus infections: epidemiology, pathogenesis, and host immune response. J Am Acad Dermatol 43: S18-S26.
2391. Uchiyama N, Ito K, Kawai K, Sakamoto F, Takaki M, Ito M (1998). CD2-, CD4+, CD56+ agranular natural killer cell lymphoma of the skin. Am J Dermatopathol 20: 513-517.
2392. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H (1977). Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 50: 481-492.
2393. Uff JS, Hall M (1978). Blue naevus of the cervix: report of two cases and review of the literature. Histopathology 2: 291-299.
2394. Umbert P, Winkelmann RK (1976). Tubular apocrine adenoma. J Cutan Pathol 3: 75-87.
2394A. Umeda M, Komatsubara H, Shibuya Y, Yokoo S, Komori T (2002). Premalignant melanocytic dysplasia and malignant melanoma of the oral mucosa. Oral Oncology 38: 714-722.
2395. Unden AB, Zaphiropoulos PG, Bruce K, Toftgard R, Stahle-Backdahl M (1997). Human patched (PTCH) mRNA is overexpressed consistently in tumor cells of both familial and sporadic basal cell carcinoma. Cancer Res 57: 2336-2340.
2396. Uren RF, Howman-Giles R, Thompson JF (2003). Patterns of lymphatic drainage from the skin in patients with melanoma. J Nucl Med 44: 570-582.
2397. Urso C, Paglierani M, Bondi R (1993). Histologic spectrum of carcinomas with eccrine ductal differentiation (sweat-gland ductal carcinomas). Am J Dermatopathol 15: 435-440.
2398. Usmani AS, Rofagha R, Hessel AB (2002). Trichoblastic neoplasm with apocrine differentiation. Am J Dermatopathol 24: 358-360.
2399. Utani A, Yabunami H, Kakuta T, Endo H, Shinkai H (1999). Reactive eccrine syringofibroadenoma: an association with chronic foot ulcer in a patient with diabetes mellitus. J Am Acad Dermatol 41: 650-651.
2400. Vadlamudi G, Schinella R (1998). Traumatic pseudoaneurysm: a possible early lesion in the spectrum of epithelioid hemangioma/angiolymphoid hyperplasia with eosinophilia. Am J Dermatopathol 20: 113-117.
2400A. Vainio H, Miller AB, Bianchini F (2000). An international evaluation of the cancer-preventive potential of sunscreens. Int J Cancer 88: 838-842.
2401. Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken J, Giles GG, Armstrong BK (2002). Sun exposure predicts risk of ocular melanoma in Australia. Int J Cancer 101: 175-182.
2402. Vakilzadeh F (1987). [Pilar sheath acanthoma]. Hautarzt 38: 40-42.
2403. Val-Bernal JF, Mira C (1996). Dermatofibroma with granular cells. J Cutan Pathol 23: 562-565.
2404. Valent P (1995). 1995 Mack-Forster Award Lecture. Review. Mast cell differentiation antigens: expression in normal and malignant cells and use for diagnostic purposes. Eur J Clin Invest 25: 715-720.
2405. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, Marone G, Nunez R, Akin C, Sotlar K, Sperr WR, Wolff K, Brunning RD, Parwaresch RM, Austen KF, Lennert K, Metcalfe DD, Vardiman JW, Bennett JM (2001). Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 25: 603-625.
2406. Van Belle PA, Elenitsas R, Satyamoorthy K, Wolfe JT, Guerry D, Schuchter L, Van Belle TJ, Albelda S, Tahin P, Herlyn M, Elder DE (1999). Progression-related expression of beta3 integrin in melanomas and nevi. Hum Pathol 30: 562-567.
2407. van der Kwast TH, Vuzevski VD, Ramaekers F, Bousema MT, Van Joost T (1988). Primary cutaneous adenoid cystic carcinoma: case report, immunohistochemistry, and review of the literature. Br J Dermatol 118: 567-577.
2408. Van der Putte SC, van Gorp LH (1994). Adenocarcinoma of the mammary-like glands of the vulva: a concept unifying sweat gland carcinoma of the vulva, carcinoma of supernumerary mammary glands and extramammary Paget's disease. J Cutan Pathol 21: 157-163.
2409. van der Spek-Keijser LM, van der Rhee HJ, Toth G, Van Westering R, Bruijn JA, Coebergh JW (1997). Site, histological

type, and thickness of primary cutaneous malignant melanoma in western Netherlands since 1980. Br J Dermatol 136: 565-571.
2410. van der Velden PA, Sandkuijl LA, Bergman W, Pavel S, van Mourik L, Frants RR, Gruis NA (2001). Melanocortin-1 receptor variant R151C modifies melanoma risk in Dutch families with melanoma. Am J Hum Genet 69: 774-779.
2411. van Doorn R, Scheffer E, Willemze R (2002). Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. Arch Dermatol 138: 191-198.
2412. van Doorn R, Van Haselen CW, Voorst Vader PC, Geerts ML, Heule F, de Rie M, Steijlen PM, Dekker SK, van Vloten WA, Willemze R (2000). Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol 136: 504-510.
2413. Van Haselen CW, Toonstra J, van der Putte SJ, van Dongen JJ, van Hees CL, van Vloten WA (1998). Granulomatous slack skin. Report of three patients with an updated review of the literature. Dermatology 196: 382-391.
2414. van Krieken JH, Boom BW, Scheffer E (1988). Malignant transformation in a naevus of Ito. A case report. Histopathology 12: 100-102.
2415. Van Leeuwen RL, Lavrijsen AP, Starink TM (1999). Eccrine syringofibroadenoma: the simultaneous occurrence of two histopathological variants (conventional and clear-cell type) in one patient. Br J Dermatol 141: 947-949.
2416. Van Nguyen A, Argenyi ZB (1993). Cutaneous neuroblastoma. Peripheral neuroblastoma. Am J Dermatopathol 15: 7-14.
2417. van Praag MC, Bavinck JN, Bergman W, Rosendaal FR, Mommaas AM, Bruynzeel I, Scheffer E, Vermeer BJ, Bruijn JA (1993). PUVA keratosis. A clinical and histopathologic entity associated with an increased risk of nonmelanoma skin cancer. J Am Acad Dermatol 28: 412-417.
2418. Van Scott EJ, Reinerston RP, McCall CB (1957). Prevalence, histological types and significance of palmar and plantar nevi. Cancer 10: 363-367.
2419. van Steeg H, Kraemer KH (1999). Xeroderma pigmentosum and the role of UV-induced DNA damage in skin cancer. Mol Med Today 5: 86-94.
2420. Vanatta PR, Bangert JL, Freeman RG (1985). Syringocystadenoma papilliferum. A plasmacytotropic tumor. Am J Surg Pathol 9: 678-683.
2421. Vang R, Cohen PR (1999). Ectopic hidradenoma papilliferum: a case report and review of the literature. J Am Acad Dermatol 41: 115-118.
2422. Vanni R, Fletcher CD, Sciot R, Dal Cin P, De Wever I, Mandahl N, Mertens F, Mitelman F, Rosai J, Rydholm A, Tallini G, Van Den Berghe H, Willen H (2000). Cytogenetic evidence of clonality in cutaneous benign fibrous histiocytomas: a report of the CHAMP study group. Histopathology 37: 212-217.
2423. Varela-Duran J, Diaz-Flores L, Varela-Nunez R (1979). Ultrastructure of chondroid syringoma: role of the myoepithelial cell in the development of the mixed tumor of the skin and soft tissues. Cancer 44: 148-156.
2424. Varghese R, Raghuveer CV (1997). Oculocutaneous malignancies in xeroderma pigmentosum. Indian J Cancer 34: 12-15.
2425. Variend S, Bax NM, van Gorp J (1995). Are infantile myofibromatosis, congenital fibrosarcoma and congenital haemangiopericytoma histogenetically related? Histopathology 26: 57-62.
2426. Veierod MB, Weiderpass E, Thorn M, Hansson J, Lund E, Armstrong B, Adami HO (2003). A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 95: 1530-1538.
2427. Venencie PY, Bigel P, Desgruelles C, Lortat-Jacob S, Dufier JL, Saurat JH (1987). Infantile myofibromatosis. Report of two cases in one family. Br J Dermatol 117: 255-259.
2428. Veraldi S, Schianchi-Veraldi R, Marini D (1990). Hidradenoma papilliferum of the vulva: report of a case characterized by unusual clinical behavior. J Dermatol Surg Oncol 16: 674-676.
2429. Verallo VV (1968). Acquired digital fibrokeratomas. Br J Dermatol 80: 730-736.
2430. Verbov JL, Borrie PF (1971). Diffuse cutaneous mastocytosis. Br J Dermatol 84: 190-191.
2431. Verdager J (1965). Prepubertal and pubertal melanomas in ophthalmology. Am J Ophthalmol 1002.
2432. Vermeer MH, Geelen FA, Van Haselen CW, Voorst Vader PC, Geerts ML, van Vloten WA, Willemze R (1996). Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group. Arch Dermatol 132: 1304-1308.
2433. Vidaillet HJJr, Seward JB, Fyke FEI, Su WP, Tajik AJ (1987). "Syndrome myxoma": a subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms. Br Heart J 57: 247-255.
2434. Villavicencio EH, Walterhouse DO, Iannaccone PM (2000). The sonic hedgehog-patched-gli pathway in human development and disease. Am J Hum Genet 67: 1047-1054.
2435. Virgili A, Marzola A, Corazza M (2000). Vulvar hidradenoma papilliferum. A review of 10.5 years' experience. J Reprod Med 45: 616-618.
2436. Vlastos AT, Malpica A, Follen M (2003). Lymphangioma circumscriptum of the vulva: a review of the literature. Obstet Gynecol 101: 946-954.
2437. Vogelbruch M, Bocking A, Rutten A, Kapp A, Kiehl P (2000). DNA image cytometry in malignant and benign sweat gland tumours. Br J Dermatol 142: 688-693.
2438. Voglino A, Paradisi M, Dompe G, Onetti MA, Faraggiana T (1988). Angiokeratoma corporis diffusum (Fabry's disease) with unusual features in a female patient. Light- and electron-microscopic investigation. Am J Dermatopathol 10: 343-348.
2439. Vogt T, Stolz W, Glassl A, Abmayr W, Hohenleutner U, Schmoeckel C, Schiffner R, Landthaler M (1996). Multivariate DNA cytometry discriminates between Spitz nevi and malignant melanomas because large polymorphic nuclei in Spitz nevi are not aneuploid. Am J Dermatopathol 18: 142-150.
2440. Voigt H, Classen R (2002). Computer vision and digital imaging technology in melanoma detection. Semin Oncol 29: 308-327.
2441. von den Driesch P, Gruschwitz M, Schell H, Sterry W (1992). Distribution of adhesion molecules, IgE, and CD23 in a case of angiolymphoid hyperplasia with eosinophilia. J Am Acad Dermatol 26: 799-804.
2442. von den Driesch P, Mielke V, Simon MJr, Staib G, Tacke J, Sterry W (1994). ["Granulomatous slack skin"—cutaneous elastolytic lymphoma]. Hautarzt 45: 861-865.
2443. von Domarus H, Stevens PJ (1984). Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. J Am Acad Dermatol 10: 1043-1060.
2444. Vonderheid EC, Bernengo MG, Burg G, Duvic M, Heald P, Laroche L, Olsen E, Pittelkow M, Russell-Jones R, Takigawa M, Willemze R (2002). Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas. J Am Acad Dermatol 46: 95-106.
2445. Vowels BR, Lessin SR, Cassin M, Jaworsky C, Benoit B, Wolfe JT, Rook AH (1994). Th2 cytokine mRNA expression in skin in cutaneous T-cell lymphoma. J Invest Dermatol 103: 669-673.
2446. Wade TR, Ackerman AB (1978). The many faces of solar keratoses. J Dermatol Surg Oncol 4: 730-734.
2447. Wade TR, Kopf AW, Ackerman AB (1978). Bowenoid papulosis of the penis. Cancer 42: 1890-1903.
2448. Waite KA, Eng C (2002). Protean PTEN: form and function. Am J Hum Genet 70: 829-844.
2449. Wakelin SH, Young E, Kelly S, Turner M (1997). Transient leukaemia cutis in chronic lymphocytic leukaemia. Clin Exp Dermatol 22: 148-151.
2450. Walsh NM (2001). Primary neuroendocrine (Merkel cell) carcinoma of the skin: morphologic diversity and implications thereof. Hum Pathol 32: 680-689.
2451. Walsh SH, Thorselius M, Johnson A, Soderberg O, Jerkeman M, Bjorck E, Eriksson I, Thunberg U, Landgren O, Ehinger M, Lofvenberg E, Wallman K, Enblad G, Sander B, Porwit-MacDonald A, Dictor M, Olofsson T, Sundstrom C, Roos G, Rosenquist R (2003). Mutated VH genes and preferential VH3-21 use define new subsets of mantle cell lymphoma. Blood 101: 4047-4054.
2452. Walter JW, North PE, Waner M, Mizeracki A, Blei F, Walker JW, Reinisch JF, Marchuk DA (2002). Somatic mutation of vascular endothelial growth factor receptors in juvenile hemangioma. Genes Chromosomes Cancer 33: 295-303.
2453. Waner M, North PE, Scherer K, Frieden IJ, Mihm MCJr (2003). The nonrandom distribution of facial hemangiomas. Arch Dermatol .
2454. Wang AR, May D, Bourne P, Scott G (1999). PGP9.5: a marker for cellular neurothekeoma. Am J Surg Pathol 23: 1401-1407.
2455. Wang E, Anzai Y, Paulino A, Wong J (2001). Rosai-Dorfman disease presenting with isolated bilateral orbital masses: report of two cases. AJNR Am J Neuroradiol 22: 1386-1388.
2456. Wang HH, Lach L, Kadin ME (1992). Epidemiology of lymphomatoid papulosis. Cancer 70: 2951-2957.
2457. Wang M, Cheng G, Sturla SJ, Shi Y, McIntee EJ, Villalta PW, Upadhyaya P, Hecht SS (2003). Identification of Adducts Formed by Pyridyloxobutylation of Deoxyguanosine and DNA by 4-(Acetoxymethylnitrosamino)-1-(3-pyridyl)-1-butanone, a Chemically Activated Form of Tobacco Specific Carcinogens. Chem Res Toxicol 16: 616-626.
2458. Ward KA, Kennedy CT, Ashworth MT (1996). Acquired tufted angioma frequently develops at sites other than the neck and upper trunk. Clin Exp Dermatol 21: 80.
2459. Warkel RL (1984). Selected apocrine neoplasms. J Cutan Pathol 11: 437-449.
2460. Warkel RL, Helwig EB (1978). Apocrine gland adenoma and adenocarcinoma of the axilla. Arch Dermatol 114: 198-203.
2461. Warner TF, Burgess H, Mohs FE (1982). Extramammary Paget's disease in fibroepithelioma of Pinkus. J Cutan Pathol 9: 340-344.
2462. Wassberg C, Thorn M, Johansson AM, Bergstrom R, Berne B, Ringborg U (2001). Increasing incidence rates of squamous cell carcinoma of the skin in Sweden. Acta Derm Venereol 81: 268-272.
2463. Watanabe M, Kishiyama K, Ohkawara A (1983). Acquired progressive lymphangioma. J Am Acad Dermatol 8: 663-667.
2464. Watanabe O, Maruyama I, Arimura K, Kitajima I, Arimura H, Hanatani M, Matsuo K, Arisato T, Osame M (1998). Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve 21: 1390-1397.
2465. Watanabe S, Hirose M, Sato S, Takahashi H (1994). Immunohistochemical analysis of cytokeratin expression in eccrine spiradenoma: similarities to the transitional portions between secretory segments and coiled ducts of eccrine glands. Br J Dermatol 131: 799-807.
2466. Watanabe S, Mogi S, Ichikawa E, Takahashi H, Minami H, Harada S (1993). Immunohistochemical analysis of keratin distribution in eccrine poroma. Am J Pathol 142: 231-239.
2467. Watson JA, Walker MM, Smith NP, Hunt DM (1991). Malignant chondroid syringoma—a rare cause of secondary bone tumour. Clin Exp Dermatol 16: 306-307.
2468. Waxtein L, Vega E, Cortes R, Hojyo T, Dominguez-Soto L (1998). Malignant nodular hidradenoma. Int J Dermatol 37: 225-228.
2469. Wayte DM, Helwig EB (1968). Halo nevi. Cancer 22: 69-90.
2470. Webb DW, Clarke A, Fryer A, Osborne JP (1996). The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol 135: 1-5.
2471. Webb JN, Stott WG (1975). Malignant chondroid syringoma of the thigh. Report of a case with electron microscopy of the tumour. J Pathol 116: 43-46.
2472. Wechsler J, Bagot M (2000). Primary cutaneous large B-cell lymphomas. Semin Cutan Med Surg 19: 130-132.
2473. Wechsler J, Bastuji-Garin S, Spatz A, Bailly C, Cribier B, Andrac-Meyer L, Vergier B, Fraitag S, Verola O, Wolkenstein P (2002). Reliability of the histopathologic diagnosis of malignant melanoma in childhood. Arch Dermatol 138: 625-628.
2474. Weedon D (1984). Eccrine tumors: a selective review. J Cutan Pathol 11: 421-436.
2475. Weedon D (1997). Tumours of the epidermis: Actinic Keratosis. In: Skin Pathology, Weedon D, ed., Churchill Livingstone: Edinburgh , pp. 643-644.
2476. Weedon D (2002). Skin Pathology. 2nd ed. Churchill Livingstone: London.
2477. Weedon D (2003). Keratoacanthoma: a personal perspective. Curr Diagn Pathol 9: 259-265.

2478. Weedon D, Farnsworth J (1984). Spongiotic changes in melanocytic nevi. Am J Dermatopathol 6 Suppl: 257-259.
2479. Weedon D, Little JH (1977). Spindle and epithelioid cell nevi in children and adults. A review of 211 cases of the Spitz nevus. Cancer 40: 217-225.
2480. Weenig RH, Ng CS, Perniciaro C (2001). Subcutaneous panniculitis-like T-cell lymphoma: an elusive case presenting as lipomembranous panniculitis and a review of 72 cases in the literature. Am J Dermatopathol 23: 206-215.
2481. Wei Q, Lee JE, Gershenwald JE, Ross MI, Mansfield PF, Strom SS, Wang LE, Guo Z, Qiao Y, Amos CI, Spitz MR, Duvic M (2003). Repair of UV light-induced DNA damage and risk of cutaneous malignant melanoma. J Natl Cancer Inst 95: 308-315.
2482. Weidner N, Foucar E (1985). Adenosquamous carcinoma of the skin. An aggressive mucin- and gland-forming squamous carcinoma. Arch Dermatol 121: 775-779.
2483. Weinstock MA (1994). Epidemiologic investigation of nonmelanoma skin cancer mortality: the Rhode Island Follow-Back Study. J Invest Dermatol 102: 6S-9S.
2484. Weinstock MA (1997). Death from skin cancer among the elderly: epidemiological patterns. Arch Dermatol 133: 1207-1209.
2485. Weinstock MA, Reynes JF (1999). The changing survival of patients with mycosis fungoides: a population-based assessment of trends in the United States. Cancer 85: 208-212.
2486. Weiss J, Heine M, Grimmel M, Jung EG (1995). Malignant proliferating trichilemmal cyst. J Am Acad Dermatol 32: 870-873.
2487. Weiss RA, Whitby D, Talbot S, Kellam P, Boshoff C (1998). Human herpesvirus type 8 and Kaposi's sarcoma. J Natl Cancer Inst Monogr 51-54.
2488. Weiss SW, Enzinger FM (1986). Spindle cell hemangioendothelioma. A low-grade angiosarcoma resembling a cavernous hemangioma and Kaposi's sarcoma. Am J Surg Pathol 10: 521-530.
2489. Weiss SW, Goldblum JR (2001). Benign tumors and tumor-like lesions of blood vessels. In: Enzinger and Weiss's Soft Tissue Tumors, Weiss SW, Goldblum JR, eds., 4th ed. Mosby: St. Louis , p. 847.
2490. Weiss SW, Goldblum JR (2001). Benign tumors of the peripheral nerves. In: Enzinger and Weiss's Soft Tissue Tumors, Weiss SW, Goldblum JR, eds., Mosby: St. Louis .
2491. Weiss SW, Goldblum JR (2001). Fibrohistiocytic tumors of intermediate malignancy. In: Enziger and Weiss's Soft Tissue Tumors, Weiss SW, Goldblum JR, eds., 4th ed. Mosby: St. Louis , pp. 491-516.
2492. Welch DF, Pickett DA, Slater LN, Steigerwalt AG, Brenner DJ (1992). Rochalimaea henselae sp. nov., a cause of septicemia, bacillary angiomatosis, and parenchymal bacillary peliosis. J Clin Microbiol 30: 275-280.
2493. Wellmann A, Otsuki T, Vogelbruch M, Clark HM, Jaffe ES, Raffeld M (1995). Analysis of the t(2;5)(p23;q35) translocation by reverse transcription-polymerase chain reaction in CD30+ anaplastic large-cell lymphomas, in other non-Hodgkin's lymphomas of T-cell phenotype, and in Hodgkin's disease. Blood 86: 2321-2328.
2494. Wen SY (1997). Plaque-type blue nevus. Review and an unusual Case. Acta Derm Venereol 77: 458-459.
2495. Weng LP, Brown JL, Baker KM, Ostrowski MC, Eng C (2002). PTEN blocks insulin-mediated ETS-2 phosphorylation through MAP kinase, independently of the phosphoinositide 3-kinase pathway. Hum Mol Genet 11: 1687-1696.
2496. Weng LP, Brown JL, Eng C (2001). PTEN coordinates G(1) arrest by down-regulating cyclin D1 via its protein phosphatase activity and up-regulating p27 via its lipid phosphatase activity in a breast cancer model. Hum Mol Genet 10: 599-604.
2497. Wenig BL, Sciubba JJ, Goodman RS, Platt N (1983). Primary cutaneous mucoepidermoid carcinoma of the anterior neck. Laryngoscope 93: 464-467.
2498. Wenig BM, Abbondanzo SL, Childers EL, Kapadia SB, Heffner DR (1993). Extranodal sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) of the head and neck. Hum Pathol 24: 483-492.
2499. Wesselmann U, Becker LR, Brocker EB, LeBoit PE, Bastian BC (1998). Eosinophilic globules in spitz nevi: no evidence for apoptosis. Am J Dermatopathol 20: 551-554.
2500. Weyers W, Nilles M, Eckert F, Schill WB (1993). Spiradenomas in Brooke-Spiegler syndrome. Am J Dermatopathol 15: 156-161.
2501. Wharton JM, Carlson JA, Mihm MCJr (1999). Desmoplastic malignant melanoma: diagnosis of early clinical lesions. Hum Pathol 30: 537-542.
2502. Whimster IW (1976). The pathology of lymphangioma circumscriptum. Br J Dermatol 94: 473-486.
2503. White GM, Barr RJ, Liao SY (1991). Signet ring cell basal cell carcinoma. Am J Dermatopathol 13: 288-292.
2504. White MP, Goel KM, Connor JM, Coutts NA (1985). Mucosal neuroma syndrome—a phenotype for malignancy. Arch Dis Child 60: 876-877.
2505. White RM, Patterson JW (1985). Cutaneous involvement in Hodgkin's disease. Cancer 55: 1136-1145.
2506. White WL (1990). Sophie's voice, Rorschach's choice. Am J Dermatopathol 12: 630-640.
2507. Whiteman DC, Milligan A, Welch J, Green AC, Hayward NK (1997). Germline CDKN2A mutations in childhood melanoma. J Natl Cancer Inst 89: 1460.
2508. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC (2003). Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst 95: 806-812.
2509. Whiteman DC, Whiteman CA, Green AC (2001). Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 12: 69-82.
2510. Whittam LR, Calonje E, Orchard G, Fraser-Andrews EA, Woolford A, Russell-Jones R (2000). CD8-positive juvenile onset mycosis fungoides: an immunohistochemical and genotypic analysis of six cases. Br J Dermatol 143: 1199-1204.
2511. Wick MR, Cooper PH, Swanson PE, Kaye VN, Sun TT (1990). Microcystic adnexal carcinoma. An immunohistochemical comparison with other cutaneous appendage tumors. Arch Dermatol 126: 189-194.
2511A. Wick MR, Goellner JR, Wolfe JT, III, Su WP (1985). Adnexal carcinomas of the skin. II. Extraocular sebaceous carcinomas. Cancer 56: 1163-1172.
2512. Wick MR, Mills SE, Scheithauer BW, Cooper PH, Davitz MA, Parkinson K (1986). Reassessment of malignant "angioendotheliomatosis". Evidence in favor of its reclassification as "intravascular lymphomatosis". Am J Surg Pathol 10: 112-123.
2513. Wick MR, Rocamora A (1988). Reactive and malignant "angioendotheliomatosis": a discriminant clinicopathological study. J Cutan Pathol 15: 260-271.
2514. Wick MR, Swanson PE (1986). Primary adenoid cystic carcinoma of the skin. A clinical, histological, and immunocytochemical comparison with adenoid cystic carcinoma of salivary glands and adenoid basal cell carcinoma. Am J Dermatopathol 8: 2-13.
2515. Wick MR, Swanson PE (1991). Cutaneous adnexal tumors. A guide to pathologic diagnosis. ASCP Press: Chicago.
2516. Wick MR, Swanson PE, Kaye VN, Pittelkow MR (1987). Sweat gland carcinoma ex eccrine spiradenoma. Am J Dermatopathol 9: 90-98.
2517. Wieselthier JS, White WL (1996). Cutaneous metastasis of ocular malignant melanoma. An unusual presentation simulating blue nevi. Am J Dermatopathol 18: 289-295.
2518. Wiestner A, Rosenwald A, Barry T, Ibbotson RE, Stetler-Stevenson M, Orchard JA, Wilson WH, Hamblin TJ, Oscier DG, Staudt LM (2002). Zap70 expression identifies B-CLL with unmutated immunoglobulin genes, worse clinical outcome and a distinct gene expression profile. Blood 100: 168a.
2519. Wilkinson RD, Schopflocher P, Rozenfeld M (1977). Hidrotic ectodermal dysplasia with diffuse eccrine poromatosis. Arch Dermatol 113: 472-476.
2520. Willemze R, Beljaards RC (1993). Spectrum of primary cutaneous CD30 (Ki-1)-positive lymphoproliferative disorders. A proposal for classification and guidelines for management and treatment. J Am Acad Dermatol 28: 973-980.
2521. Willemze R, Dijkstra A, Meijer CJ (1984). Lymphocytic infiltration of the skin (Jessner): a T-cell lymphoproliferative disease. Br J Dermatol 110: 523-529.
2522. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, Diaz-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ (2005). WHO-EORTC classification for cutaneous lymphomas. Blood 105: 3768-3785.
2523. Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Geerts ML, Goos M, Knobler R, Ralfkiaer E, Santucci M, Smith N, Wechsler J, van Vloten WA, Meijer CJ (1997). EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 90: 354-371.
2524. Willemze R, Meyer CJ, van Vloten WA, Scheffer E (1982). The clinical and histological spectrum of lymphomatoid papulosis. Br J Dermatol 107: 131-144.
2525. Willemze R, Ruiter DJ, Scheffer E, van Vloten WA (1980). Diffuse cutaneous mastocytosis with multiple cutaneous mastocytomas. Report of a case with clinical, histopathological and ultrastructural aspects. Br J Dermatol 102: 601-607.
2526. Willemze R, van Vloten WA, Hermans J, Damsteeg MJ, Meijer CJ (1983). Diagnostic criteria in Sezary's syndrome: a multiparameter study of peripheral blood lymphocytes in 32 patients with erythroderma. J Invest Dermatol 81: 392-397.
2527. Willenbrock K, Ichinohasama R, Kadin ME, Miura I, Terui T, Meguro K, Fukuhara O, DeCoteau JF, Hansmann ML (2002). T-cell variant of classical Hodgkin's lymphoma with nodal and cutaneous manifestations demonstrated by single-cell polymerase chain reaction. Lab Invest 82: 1103-1109.
2528. Williams HK, Williams DM (1997). Oral granular cell tumours: a histological and immunocytochemical study. J Oral Pathol Med 26: 164-169.
2529. WILLIAMS JO, SCHRUM D (1951). Congenital fibrosarcoma; report of a case in a newborn infant. AMA Arch Pathol 51: 548-552.
2530. Willman CL, Busque L, Griffith BB, Favara BE, McClain KL, Duncan MH, Gilliland DG (1994). Langerhans'-cell histiocytosis (histiocytosis X)—a clonal proliferative disease. N Engl J Med 331: 154-160.
2531. Wilma JH, Golitz LE, Fitzpatrick JE (2005). Vulvar clear cells of Toker: precursors of extramammary Paget's disease. Am J Dermatopathol 27: 185-188.
2532. Wilmer A, Kaatz M, Mentzel T, Wollina U (1998). Lymphangioendothelioma after a tick bite. J Am Acad Dermatol 39: 126-128.
2533. Wilson BB, Greer KE, Cooper PH (1989). Eruptive disseminated lobular capillary hemangioma (pyogenic granuloma). J Am Acad Dermatol 21: 391-394.
2534. Wilson WH, Kingma DW, Raffeld M, Wittes RE, Jaffe ES (1996). Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-alpha 2b. Blood 87: 4531-4537.
2535. Wilting J, Papoutsi M, Christ B, Nicolaides KH, von Kaisenberg CS, Borges J, Stark GB, Alitalo K, Tomarev SI, Niemeyer C, Rossler J (2002). The transcription factor Prox1 is a marker for lymphatic endothelial cells in normal and diseased human tissues. FASEB J 16: 1271-1273.
2536. Winkelmann RK (1981). Cutaneous syndromes of non-X histiocytosis. A review of the macrophage-histiocyte diseases of the skin. Arch Dermatol 117: 667-672.
2537. Wittekind C, Henson DE, Hutter RVP, Sobin LH (2003). TNM Supplement: a commentary on uniform use. 3rd ed. Wiley: New York.
2538. Wohlfahrt C, Ternesten A, Sahlin P, Islam Q, Stenman G (1997). Cytogenetic and fluorescence in situ hybridization analyses of a microcystic adnexal carcinoma with del(6)(q23q25). Cancer Genet Cytogenet 98: 106-110.
2539. Wolf-Peeters C, Achten R (2000). Gamma delta T-cell lymphomas: a homogeneous entity? Histopathology 36: 294-305.
2540. Wolfe JT, Wick MR, Campbell RJ (1985). Sebaceous carcinoma of the oculocutaneous adnexa and extraocular skin. In: Pathology of unusual malignant cutaneous tumors, Wick MR, ed., Marcel Dekker: New York , pp. 77-106.
2541. Wolfe JT, III, Cooper PH (1990). Solitary cutaneous "infantile" myofibroma in a 49-year-old woman. Hum Pathol 21: 562-564.
2542. Wolfe JT, III, Yeatts RP, Wick MR, Campbell RJ, Waller RR (1984). Sebaceous carcinoma of the eyelid. Errors in clinical and pathologic diagnosis. Am J Surg Pathol 8: 597-606.

2543. Wong TY, Suster S, Duncan LM, Mihm MCJr (1995). Nevoid melanoma: a clinicopathological study of seven cases of malignant melanoma mimicking spindle and epithelioid cell nevus and verrucous dermal nevus. Hum Pathol 26: 171-179.
2544. Wong TY, Suster S, Nogita T, Duncan LM, Dickersin RG, Mihm MCJr (1994). Clear cell eccrine carcinomas of the skin. A clinicopathologic study of nine patients. Cancer 73: 1631-1643.
2545. Wood GS (1995). Lymphocyte activation in cutaneous T-cell lymphoma. J Invest Dermatol 105: 105S-109S.
2546. Wood GS (2001). Analysis of clonality in cutaneous T cell lymphoma and associated diseases. Ann N Y Acad Sci 941: 26-30.
2547. Wood GS, Kamath NV, Guitart J, Heald P, Kohler S, Smoller BR, Cerroni L (2001). Absence of Borrelia burgdorferi DNA in cutaneous B-cell lymphomas from the United States. J Cutan Pathol 28: 502-507.
2548. Wood WS, Hegedus C (1988). Mammary Paget's disease and intraductal carcinoma. Histologic, histochemical, and immunocytochemical comparison. Am J Dermatopathol 10: 183-188.
2549. Wooldridge WE, Frerichs JB (1971). Multiple adenoid squamous cell carcinoma. Arch Dermatol 104: 202-206.
2550. Woringer MF, Kolopp P (1939). Lesion erythemato-squameuse polycyclique de l'avant-bras evoluant depuis 6 ans chez un garconnet de 13 ans. Ann Dermatol Syphilol 10: 945-958.
2551. Wu J, Wei X, Wu Z, Li S (2002). [An observation of the morphology and the degradation of hypertrophic scar collagen]. Zhonghua Shao Shang Za Zhi 18: 296-298.
2552. Wu KD, Hansen ER (2001). Shortened telomere length is demonstrated in T-cell subsets together with a pronounced increased telomerase activity in CD4 positive T cells from blood of patients with mycosis fungoides and parapsoriasis. Exp Dermatol 10: 329-336.
2553. Xie J, Murone M, Luoh SM, Ryan A, Gu Q, Zhang C, Bonifas JM, Lam CW, Hynes M, Goddard A, Rosenthal A, Epstein EHJr, de Sauvage FJ (1998). Activating Smoothened mutations in sporadic basal-cell carcinoma. Nature 391: 90-92.
2554. Xu XC, Wong WY, Goldberg L, Baer SC, Wolf JE, Ramsdell WM, Alberts DS, Lippman SM, Lotan R (2001). Progressive decreases in nuclear retinoid receptors during skin squamous carcinogenesis. Cancer Res 61: 4306-4310.
2555. Yamamoto O, Hamada T, Doi Y, Sasaguri Y, Hashimoto H (2002). Immunohistochemical and ultrastructural observations of desmoplastic trichoepithelioma with a special reference to a morphological comparison with normal apocrine acrosyringeum. J Cutan Pathol 29: 15-26.
2556. Yamamoto O, Haratake J, Hisaoka M, Asahi M, Bhawan J (1993). A unique case of apocrine carcinoma on the male pubic skin: histopathologic and ultrastructural observations. J Cutan Pathol 20: 378-383.
2557. Yamamoto O, Nakayama K, Asahi M (1992). Sweat gland carcinoma with mucinous and infiltrating duct-like patterns. J Cutan Pathol 19: 334-339.
2558. Yamamoto O, Yasuda H (1997). A case of pseudovascular adenoid squamous cell carcinoma of the skin with spindle cell pattern. J Dermatol 24: 587-594.
2559. Yamamoto O, Yasuda H (1999). An immunohistochemical study of the apocrine type of cutaneous mixed tumors with special reference to their follicular and sebaceous differentiation. J Cutan Pathol 26: 232-241.
2560. Yang CH, Ohara K (2002). Successful surgical treatment of verrucous hemangioma: a combined approach. Dermatol Surg 28: 913-919.
2561. Yang M (1993). Cutaneous inflammatory pseudotumor: a case report with immunohistochemical and ultrastructural studies. Pathology 25: 405-409.
2562. Yang SG, Cho KH, Bang YJ, Kim CW (1998). A case of glomeruloid hemangioma associated with multicentric Castleman's disease. Am J Dermatopathol 20: 266-270.
2563. Yanguas I, Goday J, Gonzalez-Guemes M, Lozano M, Soloeta R (1997). Cutaneous leiomyosarcoma in a child. Pediatr Dermatol 14: 281-283.
2564. Yashiro K, Nakagawa T, Takaiwa T, Inai M (1999). Actinic keratoses arising only on sun-exposed vitiligo skin. Clin Exp Dermatol 24: 199-201.
2565. Yee VS, Thompson JF, McKinnon JG, Scolyer RA, Li LX, McCarthy WH, O'Brien CJ, Quinn MJ, Saw RP, Shannon KF, Stretch JR, Uren RF (2005). Outcome in 846 cutaneous melanoma patients from a single center after a negative sentinel node biopsy. Ann Surg Oncol 12: 429-439.
2566. Yegappan S, Coupland R, Arber DA, Wang N, Miocinovic R, Tubbs RR, Hsi ED (2001). Angiotropic lymphoma: an immunophenotypically and clinically heterogeneous lymphoma. Mod Pathol 14: 1147-1156.
2567. Yeh S (1973). Skin cancer in chronic arsenicism. Hum Pathol 4: 469-485.
2568. Yeh S, How SW, Lin CS (1968). Arsenical cancer of skin. Histologic study with special reference to Bowen's disease. Cancer 21: 312-339.
2569. Yoshida A, Kodama Y, Hatanaka S, Takasaki T, Kuriwaki K, Yoshida H (1991). Apocrine adenocarcinoma of the bilateral axillae. Acta Pathol Jpn 41: 927-932.
2570. Young RH, Srigley RJ, Amin MB, Ulbright TM, Cubilla AL (2000). Atlas of Tumor Pathology. Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra, and Penis. AFIP: Washington, DC.
2571. Young WFJr, Carney JA, Musa BU, Wulffraat NM, Lens JW, Drexhage HA (1989). Familial Cushing's syndrome due to primary pigmented nodular adrenocortical disease. Reinvestigation 50 years later. N Engl J Med 321: 1659-1664.
2572. Yu HS, Lee CH, Jee SH, Ho CK, Guo YL (2001). Environmental and occupational skin diseases in Taiwan. J Dermatol 28: 628-631.
2573. Yu LL, Heenan PJ (1999). The morphological features of locally recurrent melanoma and cutaneous metastases of melanoma. Hum Pathol 30: 551-555.
2574. Yu RC, Chu C, Buluwela L, Chu AC (1994). Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet 343: 767-768.
2575. Zackheim HS, Amin S, Kashani-Sabet M, McMillan A (1999). Prognosis in cutaneous T-cell lymphoma by skin stage: long-term survival in 489 patients. J Am Acad Dermatol 40: 418-425.
2576. Zackheim HS, Vonderheid EC, Ramsay DL, LeBoit PE, Rothfleisch J, Kashani-Sabet M (2000). Relative frequency of various forms of primary cutaneous lymphomas. J Am Acad Dermatol 43: 793-796.
2577. Zaenglein AL, Meehan SA, Orlow SJ (2001). Congenital granular cell tumors localized to the arm. Pediatr Dermatol 18: 234-237.
2578. Zarco C, Lahuerta-Palacios JJ, Borrego L, Toscano R, Gil R, Iglesias L (1993). Centroblastic transformation of chronic lymphocytic leukaemia with primary skin involvement—cutaneous presentation of Richter's syndrome. Clin Exp Dermatol 18: 263-267.
2579. Zbar B, Alvord WG, Glenn G, Turner M, Pavlovich CP, Schmidt L, Walther M, Choyke P, Weirich G, Hewitt SM, Duray P, Gabril F, Greenberg C, Merino MJ, Toro J, Linehan WM (2002). Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. Cancer Epidemiol Biomarkers Prev 11: 393-400.
2580. Zea-Mendoza AC, Alonso-Ruiz A, Garcia-Vadillo A, Moreno-Caparros A, Beltran-Gutierrez J (1984). POEMS syndrome with neuroarthropathy and nodular regenerative hyperplasia of the liver. Arthritis Rheum 27: 1053-1057.
2581. Zeff RA, Freitag A, Grin CM, Grant-Kels JM (1997). The immune response in halo nevi. J Am Acad Dermatol 37: 620-624.
2582. Zeitouni NC, Hanna S, Loree TR, Brooks J, Cheney RT (2002). Angiolymphoid hyperplasia with eosinophilia: a classic clinical presentation with histologic features of angiosarcoma. Dermatol Surg 28: 772-775.
2583. Zelger B (2001). Langerhans cell histiocytosis: a reactive or neoplastic disorder? Med Pediatr Oncol 37: 543-544.
2584. Zelger B (2002). It's a dermatofibroma, CD34 is irrelevant! Am J Dermatopathol 24: 453-454.
2585. Zelger B, Cerio R, Soyer HP, Misch K, Orchard G, Wilson-Jones E (1994). Reticulohistiocytoma and multicentric reticulohistiocytosis. Histopathologic and immunophenotypic distinct entities. Am J Dermatopathol 16: 577-584.
2586. Zelger B, Sepp N, Weyrer K, Grunewald K, Zelger B (1994). Syringotropic cutaneous T-cell lymphoma: a variant of mycosis fungoides? Br J Dermatol 130: 765-769.
2587. Zelger B, Sidoroff A, Stanzl U, Fritsch PO, Ofner D, Zelger B, Jasani B, Schmid KW (1994). Deep penetrating dermatofibroma versus dermatofibrosarcoma protuberans. A clinicopathologic comparison. Am J Surg Pathol 18: 677-686.
2588. Zelger BG, Calonje E, Zelger B (1999). Myxoid dermatofibroma. Histopathology 34: 357-364.
2589. Zelger BG, Sidoroff A, Zelger B (2000). Combined dermatofibroma: co-existence of two or more variant patterns in a single lesion. Histopathology 36: 529-539.
2590. Zelger BG, Zelger B (1998). [Dermatofibroma. A clinico-pathologic classification scheme]. Pathologe 19: 412-419.
2591. Zelger BG, Zelger B (2001). Dermatofibroma (fibrous histiocytoma): an inflammatory or neoplastic disorder? Histopathology 38: 379-381.
2592. Zelger BW, Steiner H, Kutzner H (1996). Clear cell dermatofibroma. Case report of an unusual fibrohistiocytic lesion. Am J Surg Pathol 20: 483-491.
2593. Zelger BW, Zelger BG, Rappersberger K (1997). Prominent myofibroblastic differentiation. A pitfall in the diagnosis of dermatofibroma. Am J Dermatopathol 19: 138-146.
2594. Zelger BW, Zelger BG, Steiner H, Ofner D (1996). Aneurysmal and haemangiopericytoma-like fibrous histiocytoma. J Clin Pathol 49: 313-318.
2595. Zembowicz A, Granter SR, McKee PH, Mihm MC (2002). Amelanotic cellular blue nevus: a hypopigmented variant of the cellular blue nevus: clinicopathologic analysis of 20 cases. Am J Surg Pathol 26: 1493-1500.
2596. Zembowicz A, McCusker M, Chiarelli C, Dei Tos AP, Granter SR, Calonje E, McKee PH (2001). Morphological analysis of nevoid melanoma: a study of 20 cases with a review of the literature. Am J Dermatopathol 23: 167-175.
2597. Zettersten E, Shaikh L, Ramirez R, Kashani-Sabet M (2003). Prognostic factors in primary cutaneous melanoma. Surg Clin North Am 83: 61-75.
2598. Zhou X, Hampel H, Thiele H, Gorlin RJ, Hennekam RC, Parisi M, Winter RM, Eng C (2001). Association of germline mutation in the PTEN tumour suppressor gene and Proteus and Proteus-like syndromes. Lancet 358: 210-211.
2599. Zhou XP, Waite KA, Pilarski R, Hampel H, Fernandez MJ, Bos C, Dasouki M, Feldman GL, Greenberg LA, Ivanovich J, Matloff E, Patterson A, Pierpont ME, Russo D, Nassif NT, Eng C (2003). Germline PTEN promoter mutations and deletions in Cowden/Bannayan-Riley-Ruvalcaba syndrome result in aberrant PTEN protein and dysregulation of the phosphoinositol-3-kinase/Akt pathway. Am J Hum Genet 73: 404-411.
2600. Zhou XP, Woodford-Richens K, Lehtonen R, Kurose K, Aldred M, Hampel H, Launonen V, Virta S, Pilarski R, Salovaara R, Bodmer WF, Conrad BA, Dunlop M, Hodgson SV, Iwama T, Jarvinen H, Kellokumpu I, Kim JC, Leggett B, Markie D, Mecklin JP, Neale K, Phillips R, Piris J, Rozen P, Houlston RS, Aaltonen LA, Tomlinson IP, Eng C (2001). Germline mutations in BMPR1A/ALK3 cause a subset of cases of juvenile polyposis syndrome and of Cowden and Bannayan-Riley-Ruvalcaba syndromes. Am J Hum Genet 69: 704-711.
2601. Zhu G, Duffy DL, Eldridge A, Grace M, Mayne C, O'Gorman L, Aitken JF, Neale MC, Hayward NK, Green AC, Martin NG (1999). A major quantitative-trait locus for mole density is linked to the familial melanoma gene CDKN2A: a maximum-likelihood combined linkage and association analysis in twins and their sibs. Am J Hum Genet 65: 483-492.
2602. Ziegler A, Jonason AS, Leffell DJ, Simon JA, Sharma HW, Kimmelman J, Remington L, Jacks T, Brash DE (1994). Sunburn and p53 in the onset of skin cancer. Nature 372: 773-776.
2603. Zimmerman LE (1965). Ocular lesions of juvenile xanthogranuloma. Nevoxanthoedothelioma. Am J Ophthalmol 60: 1011-1035.
2604. Zina AM, Bundino S, Pippione MG (1982). Pigmented hidroacanthoma simplex with porocarcinoma. Light and electron microscopic study of a case. J Cutan Pathol 9: 104-112.
2605. Zucker-Franklin D, Pancake BA (1994). The role of human T-cell lymphotropic viruses (HTLV-I and II) in cutaneous T-cell lymphomas. Semin Dermatol 13: 160-165.
2606. Zuckerman R, Maier JP, Guiney WB, Jr., Huntsman WT, Mooney EK (2001). Pediatric melanoma: confirming the diagnosis with sentinel node biopsy. Ann Plast Surg 46: 394-399.

2607. Zuo L, Weger J, Yang Q, Goldstein AM, Tucker MA, Walker GJ, Hayward N, Dracopoli NC (1996). Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. Nat Genet 12: 97-99.
2608. zur Hausen H (2000). Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst 92: 690-698.
2609. zur Hausen H (2001). Oncogenic DNA viruses. Oncogene 20: 7820-7823.
2609A. Zurcher M, Hintschich CR, Garner A, Bunce C, Collin JR (1998). Sebaceous carcinoma of the eyelid: a clinicopathological study. Br J Ophthalmol 82: 1049-1055.
2610. Zvulunov A, Rotem A, Merlob P, Metzker A (1990). Congenital smooth muscle hamartoma. Prevalence, clinical findings, and follow-up in 15 patients. Am J Dis Child 144: 782-784.

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