Histopathology of Skin Cancer

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Core Messages

› The different histologic patterns of skin cancer are vital for the proper diagnosis and treatment of skin malignancies. This chapter reviews histologic findings of multiple skin malignancies, as well as their different histologic patterns. The use of immunohistochemical stains is also reviewed.

2.1 Basal Cell Carcinoma

G. Goldenberg, L.E. Golitz, and J. Fitzpatrick

Basal cell carcinoma (BCC) is an epithelial neoplasm that is believed to derive from the basal layer of the epidermis or follicular epithelium. The classic histologic presentation of BCC is that of nodules and/or strands of atypical basaloid cells that show nuclear palisading, cellular apoptosis, and scattered mitotic activity (Fig. 2.1). Artifactual cleft formation may be seen between the tumor lobules and its surrounding stroma, which may be mucinous. Solar elastosis, a manifestation of chronic actinic damage, is usually present in the dermis. Tumor calcification may be seen, especially in long standing tumors, although this phenomenon has been reported to be more commonly associated with more aggressive BCC subtypes [1]. Multiple growth patterns of BCC have been described, and these act as prognosticators of biologic behavior [2].

Superficial basal cell carcinoma presents with nodules and strands of basaloid cells that proliferate parallel to the epidermis and demonstrate slit-like retraction

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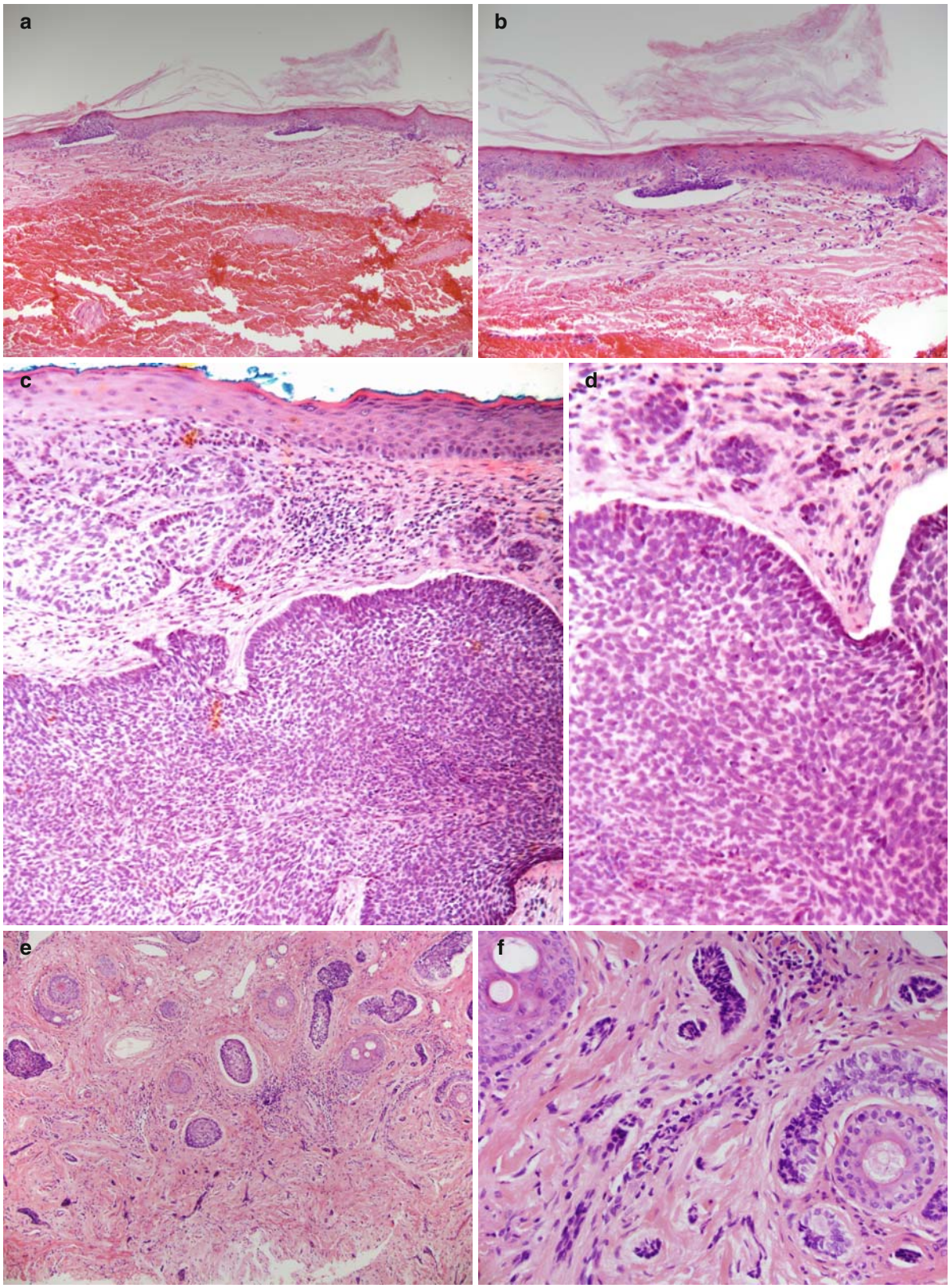

Fig. 2.1 (continued)

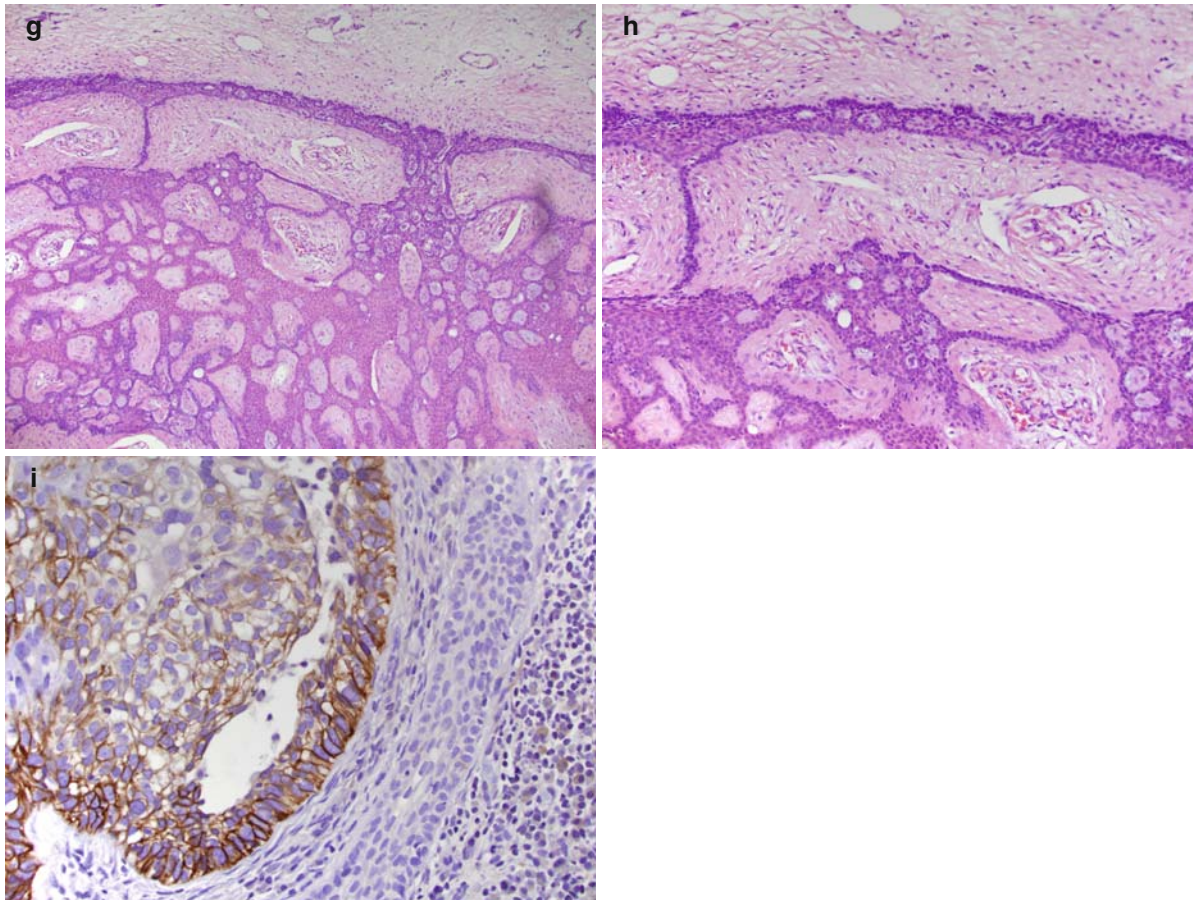

Fig. 2.1 Basal Cell Carcinoma, showing classic feature of nuclear palisading, artifactual cleft formation, and nuclear apoptosis; (**a**, **b**) Superficial growth patter; (**c**, **d**) Nodular growth pattern; (**e**, **f**) Morpheaform (sclerosing) growth patter; (**g**, **h**) Fibroepithelioma of Pinkus growth pattern; and (**i**) Positive Ber-EP4 immunohistochemical stain

from the surrounding stroma (Fig. 2.1a, b) [3]. Tumor cells may also proliferate along follicular structures.

Nodular basal cell carcinoma (NBCC) presents with discrete, well-defined nodules and strands of basaloid cells in the papillary and reticular dermis, which may focally show a connection to the overlying epidermis (Fig. 2.1c, d). Roughly one-third of NBCC's will show a coexistent superficial component [2]. Artifactual stromal retraction is usually present in these cases. Central tumor necrosis and/or mucin deposition may be seen within the individual nodules, giving the neoplasm a "cystic" appearance.

Morpheaform (sclerosing) basal cell carcinoma presents with thin strands of atypical basaloid cells in the dermis (Fig. 2.1e, f). These neoplastic strands are usually one-to-two strands thick and are enmeshed in a densely collagenized stroma with proplastic fibroblasts [2]. Individual tumor cell necrosis and mitotic activity may be more common with this growth pattern. Stromal retraction may still be seen, but is less common than in other types of BCC. This neoplasm is usually poorly circumscribed and shows an infiltrating growth pattern, invading into reticular dermis and subcutaneous fat.

Fibroepithelioma of Pinkus is a rare type of BCC that typically presents above the natal cleft or on the lower trunk with a pink or flesh colored nodule that may mimic seborrheic keratosis [4]. This tumor presents with elongated basaloid epithelial strands, which usually show multiple connection points to the overlying epidermis (Fig. 2.1g, h). Retraction from the distinct fibromyxoid stroma is usually seen. Histologically, the most important differential diagnosis is eccrine syringofibroadenoma of Mascaro, which presents with

elongated basaloid strands containing central eccrine ductal cells with a well-defined cuticle [5].

Immunohistochemical staining is rarely required in order to diagnose a BCC. Ber-EP4, a monoclonal antibody which recognizes two glycopolypeptides (34 and 39 kDa) found in most human epithelial cells, has recently been utilized to distinguish BCC from squamous cell carcinoma (Fig. 2.1i) (SCC) [6–10]. All BBCs, regardless of the subtype, stain positive with Ber-EP4, whereas SCC do not show positive staining. This marker can also be reliably used to differentiate BCC from microcystic adnexal carcinoma [11].

2.2 Squamous Cell Carcinoma In Situ

J. Roewert-Huber

SCC in situ has many diverse clinical presentations (see Table 2.1) and includes numerous distinct subtypes with a wide range of clinical manifestation. Histologically, squamous cell carcinoma in situ is composed of atypical keratinocytes, which can be identified throughout the full thickness of the epidermis. The atypical keratinocytes exhibit eosinophilic, sometimes pale or vacuolated cytoplasm, a sign of faulty cornification, as well as whorls of parakeratosis within aggregates of neoplastic cells ("horn pearls"). An increased number of atypical mitoses and dyskeratotic or necrotic keratinocytes can be found throughout the epidermis. The nuclei of the atypical keratinocytes are crowded, pleomorphic, and often large and hyperchromatic. By definition, the atypical keratinocytes throughout the epidermis do not penetrate into the dermis. SCC in situ may develop into invasive SCC.

Histologically, the different types of SSC exhibit the same morphology; however, their architectural patterns are different. It is very important to differentiate between these lesions because they present with a wide range of different clinical manifestations covering benign types of bowenoid papulosis, as well as tumors with possible invasive growth potential. Examples of the more aggressive of the latter tumor types are actinic keratosis and Bowen's disease with a tendency towards invasive, and frequently metastatic, growth.

Table 2.1 Squamous cell carcinoma in situ

Actinic keratosis
Bowen's disease
Bowenoid papulosis
Erythoplasia of Qeuyrat

2.2.1 Actinic Keratosis (AK)

For the last approximately 100 years, a controversial discussion regarding the terminology of actinic keratosis has been ongoing. Actinic keratosis lesions are categorized by some authors as precancerous because a subset appears to have low individual potential for invasive malignancy or for spontaneous regression.

However, other authors have postulated that AK lesions have to be regarded as early squamous cell carcinomas. The reason for this is that the morphology of atypical cells in the epidermis in both actinic keratosis and cutaneous squamous cell carcinoma is identical and represents histological aspects of the same disease. Today, AK is considered as early squamous cell carcinoma. Recent studies of molecular, biochemical pathogenesis confirm this pathogenitic classification.

2.2.1.1 Histology Appearance

Histologically, AK is characterized by the loss of orderly cell maturation with atypical keratinocytes in the epidermis. The atypical keratinocytes reveal a loss of polarity, and the nuclei of the atypical keratinocytes are crowded, pleomorphic, and often large, hyperchromatic with cytologic atypia. These cells are characterized eosinophilic, sometimes pale or vacuolated cytoplasm. The number of mitosis is increased. Dyskeratotic or necrotic keratinocytes are found in the epidermis. The presence of atypical keratinocytes varies from very few atypical cells in size and amount at the basal cell layer of the epidermis to more advanced lesions with moderate keratocytic atypia in the epidermis that does not involve the granular cell layer. Fully developed lesions contain atypical keratinocytes, which involve the entire epidermis reaching the granular cell layer. These histological changes are equivalent to previously called SCC in situ. The epidermal keratinocytes of the acrosyringia and acrotrichia are spared, showing normal appearance and keratinization patterns, thereby reflecting a normal orthokeratotic cornified layer. The cytoplasm of keratinocytes of the acrosyringia and acrotrichia is more basophilic or blue and shows a sharp demarcation to the atypical epidermal keratinocytes, which have a more eosinopihlic or pink cytoplasm. There are often small round buds at the basal layer which protrude into the papillary dermis. The epidermal keratinocytes are immature, thereby contributing to parakeratosis alternating with hyperkeratosis. Actinic keratoses almost always show solar elastosis in the dermis and often contains a cell infiltrate, composed mostly of lymphocytes and plasma cells.

AKs can be divided into the following six histological types: hypertrophic, atrophic, bowenoid, acantholytic, lichenoid, and pigmented. Overlapping between these subtypes may be noticed within the same lesion.

The hypertrophic type shows prominent hyperkeratosis and acanthosis. The atrophic variant has a thinned epidermis, rete ridges are missing. The bowenoid type of actinic keratosis is difficult to distinguish from Bowen's disease. In contrast to actinic keratosis, Bowen's disease shows parakeratosis, which may be strikingly predominate, and no distinct alternation of orthokeratosis and parakeratosis. The process spares acrosyringia, but not acrotrichia; suprabasal clefts or acantholytic cells are not found. The acantholytic variant reveals focal acantholysis, sometimes being accompanied by clefts similar to other acantholytic diseases. The lichenoid type shows a dense band-like infiltrate of lymphocytes in the papillary dermis and vacuolar alteration at the dermoepidermal junction. The pigmented variant has increased melanin pigmentation in the epidermis.

In 2007, Roewert-Huber et al. [1] published a classification of actinic keratoses, which categorizes the AK into three histological types based on the extent of atypical keratinocytes in the epidermis.

Early In Situ SCC-Type I (Mild)

Atypical keratinocytes are found in the basal and suprabasal layer of the epidermis, and could extend to the lower one-third of the epidermis.

The nuclei are hyperchromatic, variable in size, and have mild irregularities in nuclear outline. Often, a loss of nuclear polarity occurs, with many of the cells that have oval nuclei oriented at obtuse angles, instead of perpendicular to the epidermis. The follicular infundibulum is not involved.

Early In Situ SCC-Type II (Moderate) (Fig. 2.2a)

Atypical keratinocytes extend to the lower two-thirds of the epidermis alternating with zones of normal epidermis of the acrotrichia and acrosyringia in particular. Buds of keratinocytes in the upper papillary dermis can be found.

In Situ SCC-Type III (Severe) (Fig. 2.2b)

Atypical keratinocytes extend more than two-thirds to full thickness within the epidermis including involvement of the epithelia of the hair follicle

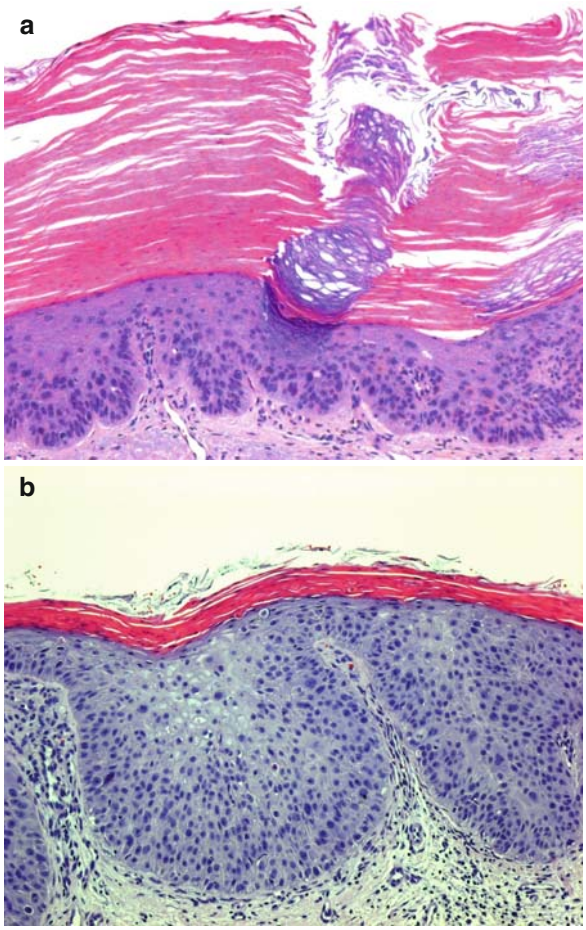

Fig. 2.2 (**a**) Early in situ SCC-type II (moderate) with atypical keratinocytes extending to the lower two thirds of the epidermis alternating with zones of normal epidermis of the acrotrichia and acrosyringia in particular. Alternation of pink parakeratosis and blue orthokeratosis. (**b**) In situ SCC-type III (severe) with atypical keratinocytes extending more than two thirds to full thickness of the epidermis including involement of the epithelia of the hair follicle infundibula and acrosyringia as seen in SCC in situ

infundibula and acrosyringia as seen in SCC in situ. Buds of keratinocytes can also be found in the upper papillary dermis.

Grade III lesions are equivalent to lesions previously called SCC in situ.

This creation of a grading system for epithelial tumors, similar to that for other neoplasms, was warranted and long overdue. Tumor classifications according to severity and extent are important. The classification of AK will provide the clinician with a very improved prognostic tool of the malignant potential of the lesion, helping him with the selection of the most specific therapeutic option. Without a grading system, the clinician does not have the tools to accurately judge the amount of atypical keratinocytes in the epidermis; with this information, the physician has the information to choose more precisely the appropriate therapy for these types of early squamous cell carcinomas.

Reference

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2.2.2 Bowen's Disease

J. Röwert-Huber

The term Bowen's disease refers to a particular type of intraepidermal squamous cell carcinoma, the so-called squamous cell carcinoma in situ. Nevertheless, it is a clinical and histopathological distinct entity.

The lesion may occur on any skin surface.

The epidermis shows acanthosis with increased cellularity and hyper – and parakeratosis as signs of aberrant cornificiation. The keratinocytes are crowded and are arranged in complete disorder, reflecting a "windblown" appearance. The specific histological features of Bowen's disease are cells with more prominent cytologic atypia characterized by large, pleomorphic and hyperchromatic nuclei, By loss of normal polarity, and by absence of maturation to the surface in together with dyskeratotic and occasionally multinucleated cells. Numerous mitoses including atypical bizarre forms are noted. Below the otherwise intact dermoepidermal basement membrane, there is a chronic inflammatory infiltrate in the upper corium (Fig. 2.3).

In the pigmented variant of Bowen's disease, is characterized by the presence of more pigment in the atypical keratinocytes along with numerous melanophages.

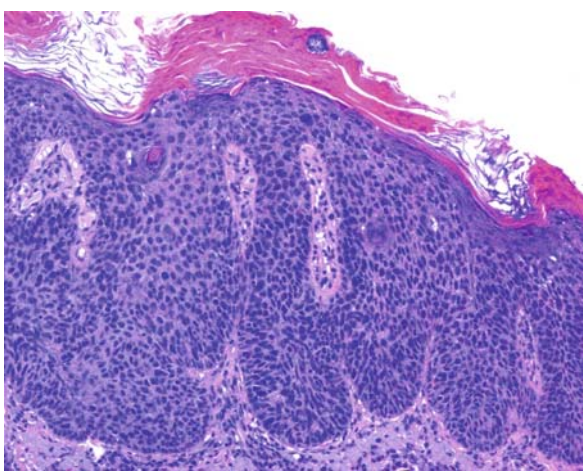

Fig. 2.3 Bowen's disease. Acanthosis with increased cellularity and hyper – and parakeratosis. Crowding of keratinocytes and arrangement in complete disorder giving them a "windblown" appearance. Promiment cytologic atypia characterized by large, pleomorphic and hyperchromatic nuclei, a loss of normal polarity and no maturation to the surface in association with dyskeratotic and occasionally multinucleated cells. Numerous mitoses including atypical bizarre forms are noted.

2.2.2.1 Erythroplasia of Queyrat

Similar lesions located on the glans penis are referred to as Erythroplasia of Queyrat. They have the identical histological features as does Bowen's disease. The term Bowen's disease has been replaced in gynaecological pathology by the term vulvar interepithelial neoplasia (VIN) and is equivalent to VIN grade III.

2.2.2.2 Bowenoid Papulosis

Bowenoid papulosis is characterized by the same cytopathological changes as Bowen's disease, except that in low power the lesions resemble condylomata acuminata. In contrast to Bowen's disease, Bowenoid papulosis exhibits multiple verrucous papules, which are frequently pigmented.

2.3 Invasive Squamous Cell Carcinoma

J. Roewert-Huber

Invasive Squamous cell carcinoma is an epithelial tumor infiltrating into the dermis, characterized by signs of cornification. The histological picture of squamous cell carcinoma reveals proliferation of anastomosing nests, sheets, and strands of atypical keratinocytes originating in the epidermis and infiltrating into the dermis. Prominent intercellular bridges are characteristic. Epithelial cells exhibit glassy eosinophilic cytoplasm and frequently a large nucleus. Dyskeratotic cells, parakeratosis, and horn pearl formation are sign of abnormal cornification (Fig. 2.4). These morphologic features of squamous cell differentiation are variably present in the tumor. Sometimes, in lesions with complete anaplastic transformation, it may be difficult to determine the tumor origin. Immunohistochemical examinations play an important role, because these transformed cells will characteristically show a type of keratin expression with higher molecular weight and particular epithelial membrane antigen (EMA).

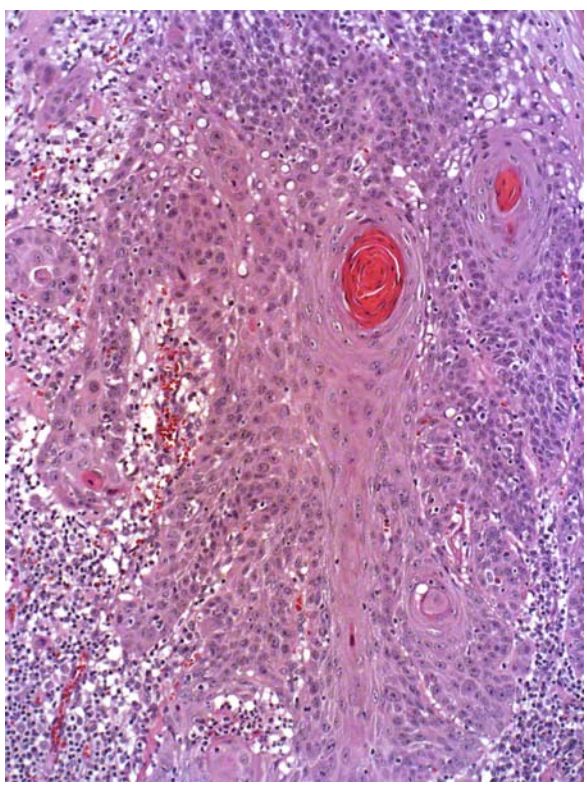

Fig. 2.4 Invasive squamous cell carcinoma: Proliferation of anastomosing nests, sheets and strands of atypical keratinocytes originating in the epidermis and infiltrating into the dermis. Epithelial cells exhibit glassy eosinophilic cytoplasm and frequently a large nucleus. Dyskeratotic cells, parakeratosis and horn pearl formation are also observed.

SCC is categorized into well-differentiated, moderately, or poorly differentiated subtypes. The extent of differentiation varies with the extent of keratinization. In well-developed, well-differentiated SSC the majority of the tumor cells are highly differentiated and exhibit squamous eddies or horn pearls and show minimal pleomorphism. Poorly-differentiated SCC, which is a more aggressive tumor type, contains very few keratin horn pearls in comparison and exhibits a more advanced anaplastic appearance. The moderately differentiated SCC exhibits a histopathology pattern with features of both the well-differentiated and the more anaplastic type.

Broders' classification, originally published in 1932, devises a four-tiered system: grade I, tumors in which more than 75% of cells are differentiated; grade II, tumors with 50–75% differentiation; grade III, tumors with 25–50% differentiation; and grade IV, tumors with less than 25% differentiation. This classification was never really accepted and used by pathologists, because it was perceived as being rather subjective. Clinically, the most important are the two extremes of well vs. poorly differentiated squamous cell carcinoma. Today, the TNM classification system (see Table 2.2) is used for squamous cell carcinoma of the skin. Together with the clinical staging grouping, the TNM classification system allows physicians to compare tumor stages across patients, assess prognosis, and design appropriate treatment regimens.

An important additional prognostic factor besides tumor size and histological differentiation is the depth of infiltration. With increasing depth of invasion of the primary tumor, the risk of metastatic spread increases significantly. In addition, anatomic site, perineural invasion, as well as histological variants are important influencing contributors toward a more aggressive course of tumor progression. If signs of spindle-cell differentiation, glandular differentiation, or basal-cell differentiation are present as part of the squamous cell tumor, these will be described appropriately and thus

Table 2.2 TNM clinical classification

Primary tumor (T) – T refers to tumor size at the primary site			
Tx Primary tumor cannot be assessed			
T0 No evidence of primary tumor			
Tis Carcinoma in situ			
T1 Tumor 2 cm or less in greatest dimension			
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension			
T3 Tumor more than 5 cm in greatest dimension			
T4 Tumor with extension to deep extradermal structures, i.e., cartilage, muscle, or bone			
Regional lymph nodes (N) – N refers to the status of the cervical chain of lymph nodes			
NX Regional lymph nodes cannot be assessed			
N0 No evidence of regional lymph node involvement			
N1 Regional lymph nodes metastasis			
Distant metastases (M) – M refers to the presence or absence of distant metastases			
MX Distant metastases cannot be assessed			
M0 No evidence of distant metastases			
M1 Evidence of distant metastases			
Staging grouping			
Stage 0	Tis,	NO,	MO
Stage 1	T1,	N0,	M0
Stage 2	T2, T3	N0,	M0
Stage 3	T4	N0	M0
	Any T	N1	M0
Stage 4	Any T	Any N	M1

Table 2.3 The major variants of squamous cell carcinoma

Acantholytic squamous cell carcinoma/Pseudovascular squamous cell carcinoma
Spindle cell (Sarcomatoid) carcinoma
Verrucous squamous cell carcinoma,
Keratoacanthoma
Adenosquamous carcinoma

recognized as distinctive features. The major variants are listed in Table 2.3.

2.3.1 Acantholytic Squamous Cell Carcinoma

It is also named adenoid SCC (pseudoglandular) based on its gland-like pattern related to prominent acantholysis. Acantholyse is characterized by a loss of cohesion (desmosomes) between cells. These cells typically are round and can contribute to the formation of clefts, gland-like cell aggregates, or tubular spaces. The acantholytic areas may mimic types of adenocarcinoma or sweat gland carcinoma or may be forming a pseudovascular pattern resembling angiosarcoma. Clinically, this type of tumor is indistinguishable from other SCCs. In the literature, discussion is controversial whether this variant may be more aggressive than conventional SCC.

2.3.2 Spindle Cell Squamous Cell Carcinoma

It is an uncommon variant of SCC, also named spindle-cell carcinoma, carcinosarcoma, or sarcomatoid carcinoma. This tumor variant appears almost always on sun-damaged or irradiated skin of elderly patients. The incidence is increased in immunosuppressed patients. Histologically, the tumor is composed of atypical spindle cells with no or miminal components of keratinization and no evidence of epidermal origin. The spindle cells show scant eosinophilic cytoplasm and large nuclei. Many Mitotic figures and bizarre pleomrohic giant cells are usually found. Distinction between this tumortype, sarcomas, or other spindle cell tumors may be difficult. Thus, in cases of doubt, immunohistochemistry is helpful because it allows identification of particularly high-molecular keratin and EMA antibodies.

2.3.3 Verrucous Squamous Cell Carcinoma

It has been described under different synonyms. In the skin, it is named epithelioma cuniculatum, or in anogenitial region, Buschke-Löwenstein tumor, and the oral cavitiy, Ackermann tumor. It is extremely rare, and a well-differentiated variant of SCC with low malignant potential. All the different kinds of verrucous squamous cell carcinoma have the same histologic features, exhibiting endo-oxophytic growth with hyperkeratosis, papillomatosis, and acanthosis resembling a verruca vulgaris. The well-proliferating keratinocytes in these lesions are more pushing with broad, rounded borders, rather than infiltrating the tissue.

Only very little atypia and no atypical mititoc figures are present in this tumor. Draining sinuses and crypt-like spaces as well as interaepidermal neutrophils usually forming an intraepidermal abscess are also an important diagnostic clue.

2.3.4 Adenosquamous Carcinoma

It is a rare variant of squamous cell carcinoma related to acrosyringia. These lesions are characterized by the formation of mucin secreting true glandular differentiation within well-differentiated squamous cell nest. A moderate number of mitosis can be found. The tumor cells might have their origin in pluripotent epithelial cells near or within the acrosyringical portions of sweat ducts because they secrete diastase resistant mucins of sweat gland tumors. The glands forming cells express also carcinoembryonic (CEA) antigen, which are normally found in eccrine and apocrine glands.

The tumor occurs on the head, neck, and penis in elderly patients. The behavior of this tumor is aggressive and is associated with a high rate of recurrence and metastasis rate.

2.3.5 Keratoacanthoma (KA), Variants of SCC

Keratoacanthoma (KA) is considered by most physicians as a variant of SCC.

The morphological appearance, clinical course, and the potential for spontaneous regression are unique features of Keratoacanthoma. Histologically, many features overlap with SCC. Definitive histologic distinction from a well-differentiated SCC could be very difficult or may be impossible to achieve with confidence if the lesion is incompletely excised.

The architecture of the fully developed lesion is symmetrical, well circumscribed with a central keratin-filled crater. The epidermis consists of exo-endophytic nodules, which infiltrate the dermis. The tumor is poorly demarcated and is usually surrounded by a mixed inflammatory infiltrate. Neutrophils may be seen in the epidermis producing small microabscesses. The keratinocytes have an abundant hyalinated cytoplasm. Typical mitotic figures, perineural invasion, and intravenous growth may be seen incidentally.

2.4 Malignant Melanoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

The histologic diagnosis of malignant melanoma (MM) requires a constellation of specific architectural and cytologic findings. The atypical architectural features seen in MM are listed in Table 2.4 and atypical cytologic features are listed in Table 2.5. MM may develop *de novo* or within a preexisting melanocytic nevus, which is present in approximately one-third of MM. It has also been demonstrated that almost all primary MM begin as proliferations of melanocytes initially present at the dermoepidermal junction (DEJ) [12]. This stage or phase of MM progression has been termed "nontumorigenic" or radial growth phase [13]. MM becomes invasive as atypical melanocytes invade into the papillary dermis, as single cells or atypical nests. This phase of tumor progression has been termed as "tumorigenic" or vertical growth phase (VGP). Some have described the VGP as invasion of melanoma cells in cohesive aggregates [14]. The depth of invasion of MM into the dermis can be measured by Clark's level

Table 2.4 Atypical architectural finding seen in malignant melanoma

Large size
Asymmetry
Poor circumscription
Predominance of single cell melanocytes over nests of melanocytes along the dermoepidermal junction
Pagetoid (upward) migration of single cell melanocytes
Confluent spread of melanocytes
Cellular dyscohesion
Lack of uniform melanin distribution
Lack of melanocyte maturation with descent in the dermis
Dermal regression

Table 2.5 Atypical cytologic findings seen in malignant melanoma

Nuclear hyperchromasia with coarse chromatin
Nuclear enlargement
Nuclear pleomorphism
Prominent nucleoli
Mitosis, dermal, including atypical mitosis
Cellular necrosis
Dusty melanin
High nuclear to cytoplasmic ratio
Thickened nuclear membrane

Table 2.6 Clark's level of invasion

Level I:	Melanoma in situ
Level II:	Microinvasion into papillary dermis
Level III:	Expansion into papillary dermis
Level IV:	Invasion into reticular dermis
Level V:	Invasion into subcutaneous fat

Table 2.7 Selected stains utilized in MM

S100
HMB-45
Melan-A/MART-1

(Table 2.6) and Breslow's depth, which is measured in millimeters. Multiple special stains have been utilized in MM, and these are listed in Table 2.7.

Malignant melanoma in situ (MMIS), including lentigo maligna (LM) type, presents with atypical melanocytes confined to the epidermis (Fig. 2.5a, b). The epidermis is typically atrophic in LM type of MMIS. The presence of single cell melanocytes, junctional nests of atypical melanocytes, extension of melanocytes above the basal layer of the epidermis, confluent spread of atypical cells, and follicular extension have been used as criteria for diagnosis of MMIS [15, 16]. Solar elastosis and melanophages are often found in the dermis. Lentigo maligna melanoma (LMM) arises from LM, and is characterized by the same findings within the epidermis as LM, with dermal invasion by atypical melanocytes.

Superficial spreading malignant melanoma (SSMM) presents with atypical melanocytes at all levels of the epidermis, with significant pagetoid spread (Figs. 2.5c–e). Atypical melanocytes found in the dermis may be present singly and in nests. Atypical dermal melanocytes show failure of maturation with descent. While the majority of atypical melanocytes are epithelioid, spindle cell melanocytes may also be seen.

Nodular malignant melanoma (NMM) presents with atypical melanocytes within the epidermis, with pagetoid spread, and in the underlying dermis (Fig. 2.5f–h). This MM subtype is characterized by the lack of atypical melanocytes within the epidermis adjacent to the dermal component. Dermal melanocytes fail to mature and may show significant mitotic activity.

Acral lentiginous malignant melanoma (ALMM) initially presents with a lentiginous radial growth phase of melanocytes within the epidermis, but as the tumor becomes thicker, nests on melanocytes with pagetoid spread may be seen (Fig. 2.5i, j) [17]. Halos surrounding melanocytes may be seen, giving the atypical cells a lacunar appearance. Invasive dermal melanocytes may be seen singly or in nests, composed of epithelioid or spindle-shaped cells.

Desmoplastic malignant melanoma (DMM) is a rare type of MM that presents with dermal elongated spindle-shaped melanocytes, which may show nuclear hyperchromasia, bizarre nuclei, and lack melanin pigment (Fig. 2.5k, l). Melanocytes in DMM usually lack pigment and may be highlighted by immunochemical stains (Fig. 2.5m). Fascicles of atypical melanocytes may show an infiltrative growth pattern, extending into subcutaneous fat. Abundant desmoplastic collagen bundles are usually present in the dermis. Lesions which present with less collagen and more spindle-shaped cells are referred to as spindle cell malignant melanoma (SCMM), although it has been shown that SCMM and DMM form a continuum without discrete separation [18]. An intraepidermal atypical melanocytic proliferation is also observed in the majority of DMM [19].

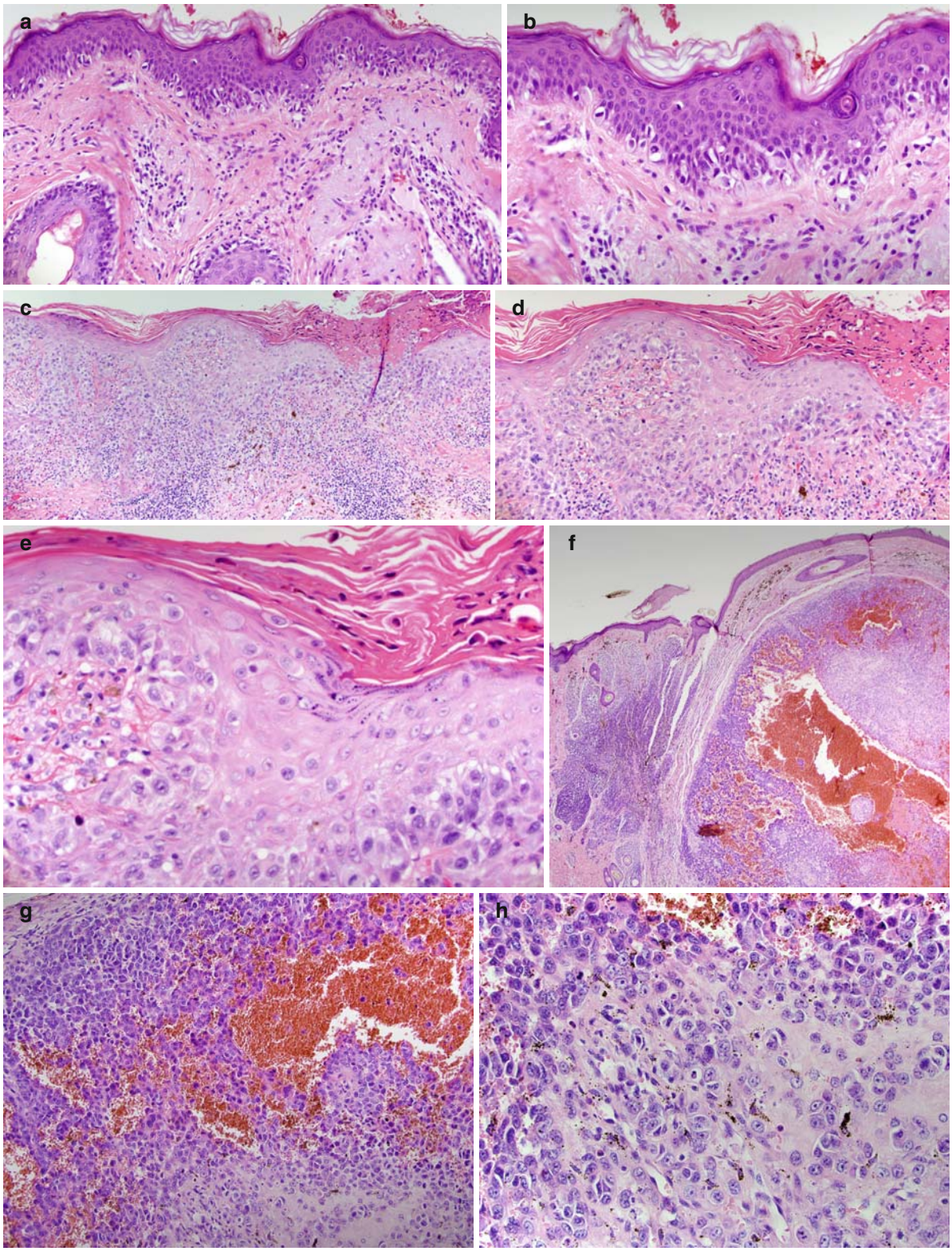

Fig. 2.5 (continued)

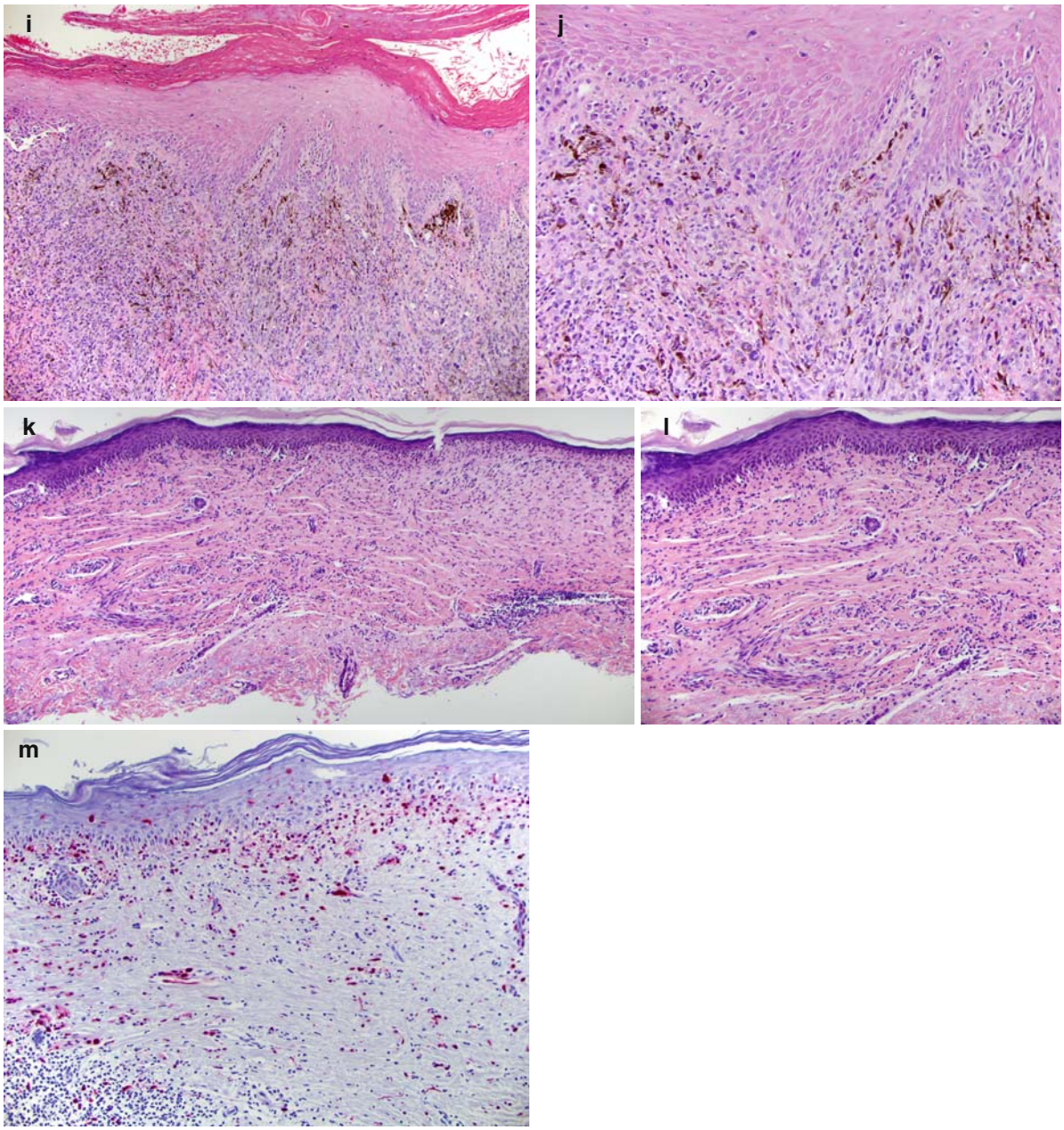

Fig. 2.5 Malignant melanoma. (**a**, **b**) Lentigo maligna type showing single cell spread of melanocytes along the dermal-epidemal junction; (**c**, **e**) Superficial spreading malignant melanoma showing significant pagetoid spread; (**f**, **h**) Nodular malignant melanoma showing dermal invasion without significant later spread along the dermal-epidermal junction; (**i**, **j**) Acral lentiginous malignant melanoma showing an atypical melanocytic proliferation on acral skin; (**k**, **l**) Desmoplastic malignant melanoma showing atypical melanocytes embedded in a desmoplastic stroma; and (**m**) S100 stain highlights atypical melanocytes in this Desmoplastic malignant melanoma

2.5 Merkel cell carcinoma

Martina Ulrich, Jean Kanitakis

The diagnosis of Merkel cell carcinoma (MCC) is usually made by histologic examination as the clinical features are rather nonspecific. Histopathologically, MCC represents a dermal tumor composed of round, small basophilic monomorphous cells with large nuclei, prominent nucleoli, and inconspicuous cytoplasm. Mitotic figures are commonly seen, and necrosis and ulceration may occur. The tumor usually spares the papillary dermis and the epidermis, and extends from the reticular dermis to the subcutaneous tissue. However, spread to the hypodermis and epidermis with pagetoid infiltration might occur [1]. Three pathological subtypes of MCC have been described, i.e., the trabecular, the small cell, and the intermediate type, which is the commonest one [2].

The differential diagnosis includes other tumors made of small cells, namely small cell lung cancer metastasis, lymphoma, or melanoma. Immunohistochemistry is needed for the confirmation of diagnosis. MCC cells express CK20 (and occasionally also neurofilaments) with a typical perinuclear dot pattern (Fig. 2.6), Neuron Specific Enolase, chromogranin A, and synaptophysin. Contrasting with small cell lung cancer, MCC does not express the Thyroid Transcription Factor 1 (TTF-1) (Table 2.8).

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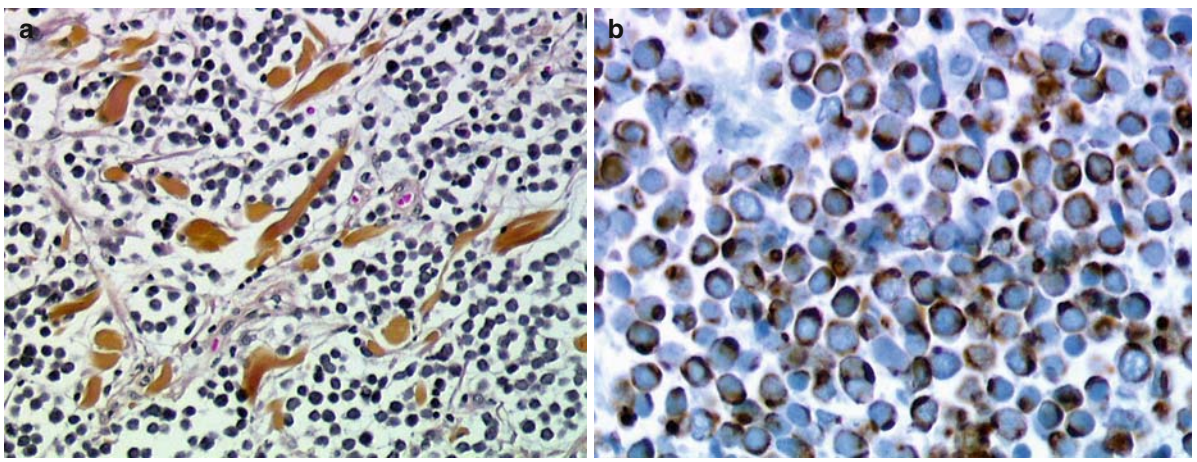

Fig. 2.6 (**a**) Pathology of Merkel cell carcinoma: the tumour is made of uniform, large round cells with basophilic nuclei, invading diffusely the dermis(haematoxylin-eosin stain). (**b**) Merkel cell carcinoma: tumor cells express CK20 in a dot-like or signet-tring-like pattern (immunoperoxidase)

Table 2.8 Immunohistochemical features of MCC in comparison with other small cell tumors

	CK20	TTF-1	Vimentin	NSE	Chromogranin	S100 protein	LCA
Merkel cell carcinoma	+	–	–	+	+/–	–	–
Small cell lung cancer	+/–	+	–	+/–	+/–	–	–
Melanoma	–	–	+	+/–	–	+	–
Lymphoma	–	–	+	–/+	–	–	+

CK20 cytokeratin 20; *TTF-1* thyroid transcription factor-1; *NSE* neuron-specific enolase; *LCA* leucocyte common antigen

2.6 Kaposi's Sarcoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

The histologic presentation of Kaposi's sarcoma (KS) is similar, regardless of the clinical disease presentation [20, 21]. The unifying histologic features of KS are the presence of atypical, irregular, and angulated vascular channels (Fig. 2.7a,b). The promontory sign is often described in KS and refers to irregular vascular channels that partially surround preexisting blood vessels. The presence of plasma cells in the surrounding stroma is also a classic finding.

The histologic presentation of KS evolves through patch, plaque, and tumor stages, similar to clinical disease [22]. Patch stage KS present with irregular, angulated vascular channels in the reticular dermis. While ectatic vascular channels may be seen in this stage, the vessels may be very subtle and present with slit-like spaces and spindle-shaped cells. Plaque stage KS presents with obvious vascular channels filling the entire dermis and extending into the superficial subcutaneous fat. The presence of a significant spindle cell component is the most characteristic feature of this stage of KS. These cells intercalate between collagen bundles, forming slit-like, irregular vascular channels. Hemosiderin deposits and PAS-positive hyaline globules are commonly seen in this stage of KS. Fascicles and sheets of spindle-shaped cells characterize the tumor stage of KS, along with a variable number of slit-like vascular channels. Mitotic figures vary in number, but may be frequent in this stage of KS.

Evidence of human herpesvirus 8 (HHV-8) has been found by polymerase chain reaction in approximately 95% of KS lesions, and appears to be independent of the type of the disease (i.e., endemic type vs. AIDS-associated type and etc.) [23]. An immunohistochemistry stain for HHV-8 is available, and has been shown to be 99% sensitive and 100% specific for KS lesions (Fig. 2.7c) [24]. Immunohistochemical staining with CD-31, CD-34, factor VIII antigen, and CD-40 has also been found useful.

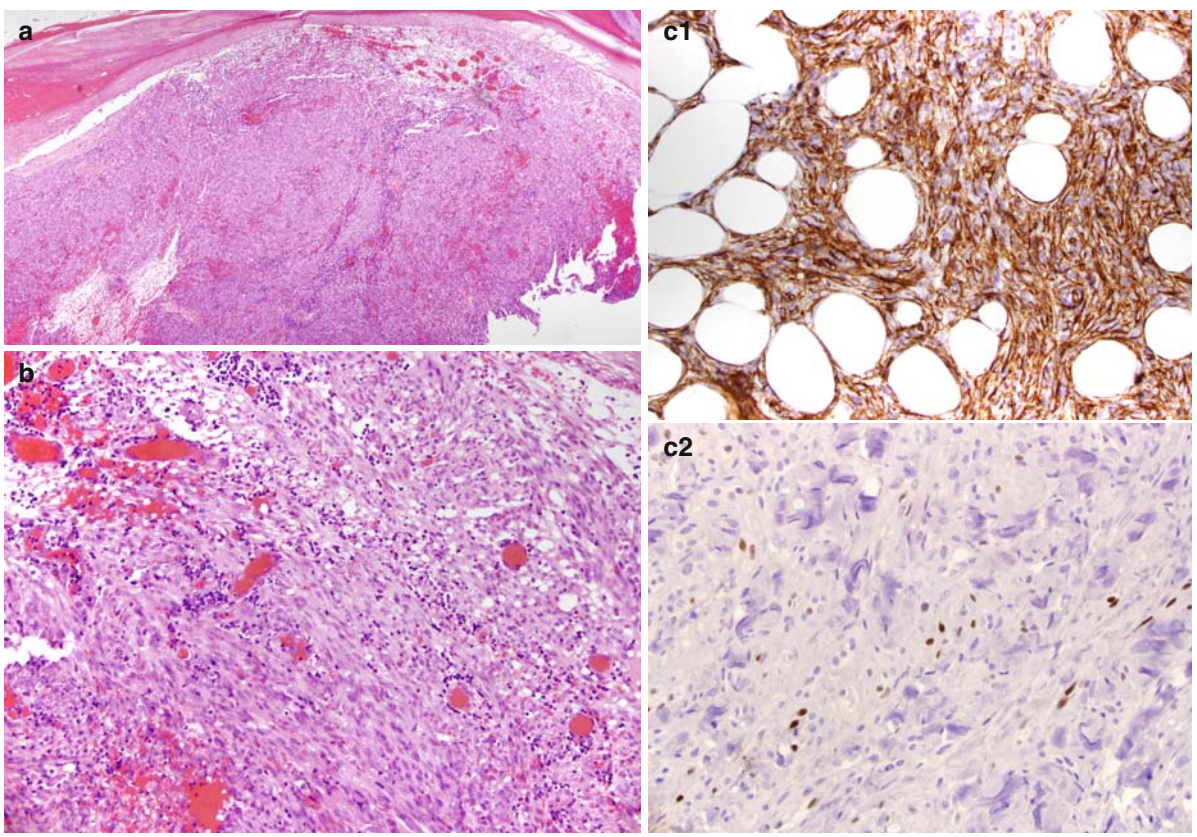

Fig. 2.7 Kaposi's sarcoma. (**a**, **b**) Numerous atypical, irregular, and angulated vascular channels; (**c**) positive staining with human herpesvirus 8 immunohistochemical stain

2.7 Dermatofibrosarcoma Protuberans

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

Dermatofibrosarcoma protuberans (DFSP), which is associated with the rearrangement of chromosomes 17 and 22 with the fusion between the collagen type I1 gene and the platelet-derived growth factor β-chain gene, is a spindle cell neoplasm that shows an infiltrative growth pattern (Fig. 2.8a, b) [25]. The main portion of this neoplasm shows a storiform arrangement with extension into the subcutaneous fat, with fat entrapment creating a honeycomb pattern [26]. Cytologically, there is usually little nuclear pleomorphism and a low-to-moderate mitotic index. DFSP is a highly cellular malignancy with scant collagen. Several histologic variants of DFSP have been reported, including myxoid, granular cell, and pigmented types.

Expression of CD-34 antigen (human progenitor cell antigen) in DFSP (Fig. 2.8c) is well described and has been used to support the view that these lesions are variants of nerve sheath tumors, which are distinct from benign fibrous histiocytomas that do not express CD-34 [27]. Immunohistochemical staining with vimentin, and more recently CD-10, has also been reported [28, 29].

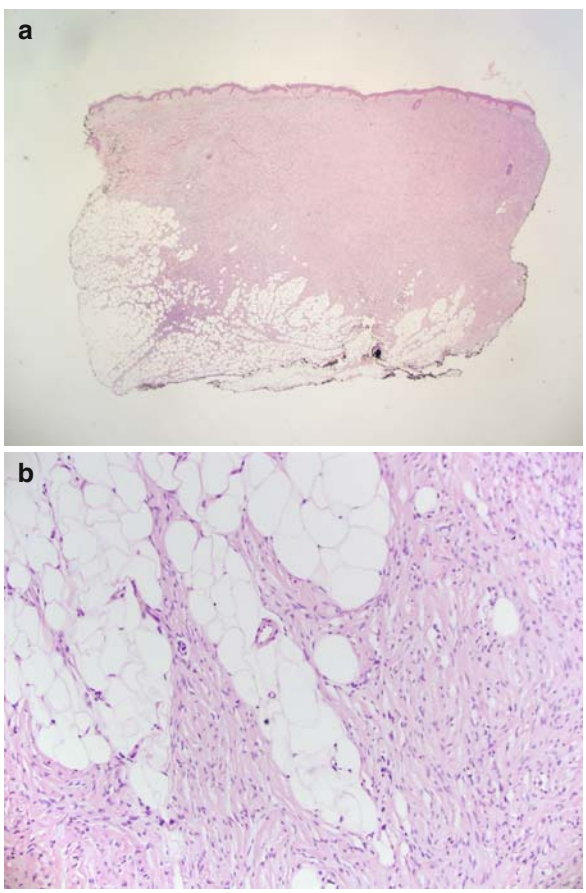

Fig. 2.8 Dermatofibrosarcoma protuberans. (**a**, **b**) Atypical spindle cells show an infiltrative growth patters and storiform arrangement, with extension into the subcutaneous fat; (**c**) Positive CD-34 immunohistochemical stain

2.8 Atypical Fibroxanthoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

Atypical fibroxanthoma is a dermal neoplasm usually separated from the overlying epidermis by a thin Grenz. It is composed of multiple cell-types, including spindle, polyhedral, giant, clear, granular and osteoid cells (Fig. 2.9a, b) [30]. Spindle cells may predominate, show pleomorphism, contain vesicular nuclei, and often form fascicles. Polyhedral cells usually show a vacuolated lipid-containing cytoplasm, and are large and haphazardly arranged. Giant cells are multinucleated and pleomorphic, and bizarre mitosis are common in his variant. By definition, this is a superficial neoplasm, without the involvement of the deep dermis and subcutis. The overlying epidermis is usually effaced and the surrounding dermis usually shows solar elastosis.

Immunohistochemically, AFX stains positive with vimentin, and staining with CD10 and procollagen-1 (Fig. 2.9c) has also been recently described [31, 32].

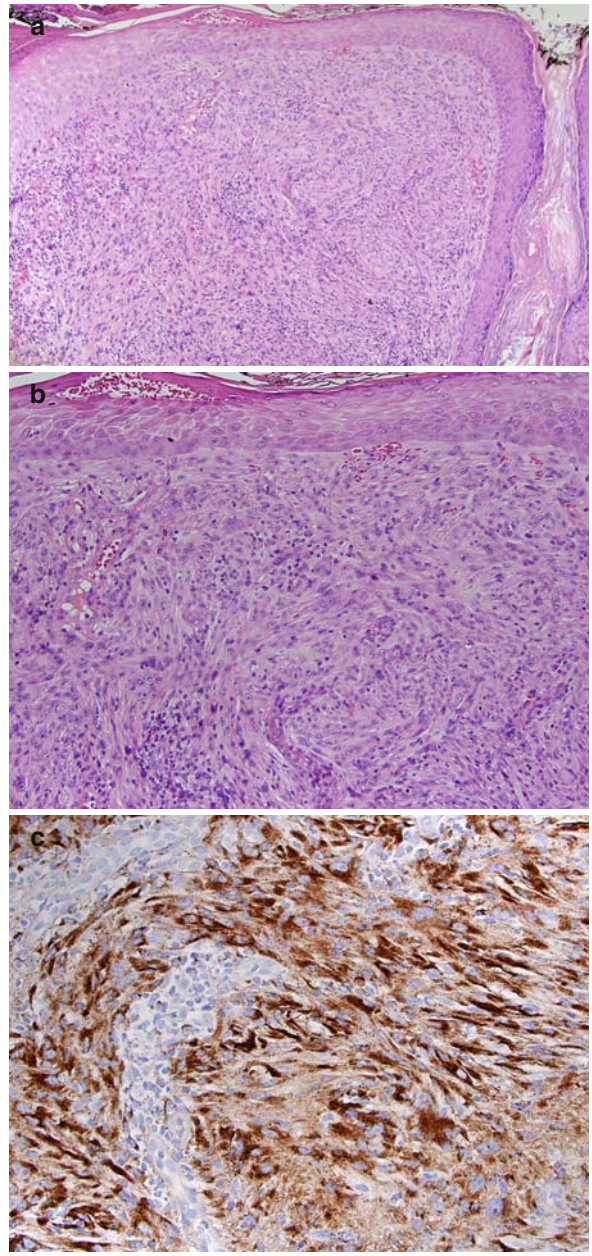

Fig. 2.9 Atypical fibroxanthoma. (**a**, **b**) Spindle cells showing pleomorphism, nuclear hyperchromasia, numerous mitosis, and arranged in fascicles; (**c**) Positive Procollogen I immunohistochemical stain

2.9 Malignant Fibrous Histiocytoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

The term "malignant fibrous histiocytoma" (MFH) has fallen out of favor, and most of these tumors have been reclassified in the latest World Health Organization Classification of soft tissue tumors [33]. A recent study that utilized comparative genomic hybridization demonstrated that most MFHs do not constitute a homogeneous entity, but could correspond other sarcomas, particularly leiomyosarcoma and liposarcoma [34, 35]. The classic histologic presentation of MFH has been divided into five types: pleomorphic, angiomatoid, myxoid, giant cell, and inflammatory. Architecturally, MFH is a dermal neoplasm with an infiltrative border. The pleomorphic type is most common, and presents with plump, atypical spindle cells that may be arranged in a storiform pattern, bizarre giant cells, and nodules and sheets of histiocytes. The angiomatoid variant shows large blood filled spaces, admixed with atypical spindle-shaped cell.

Immunohistochemical staining is usually positive with vimentin, and staining with CD74 and CD68 has also been described [36–38].

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