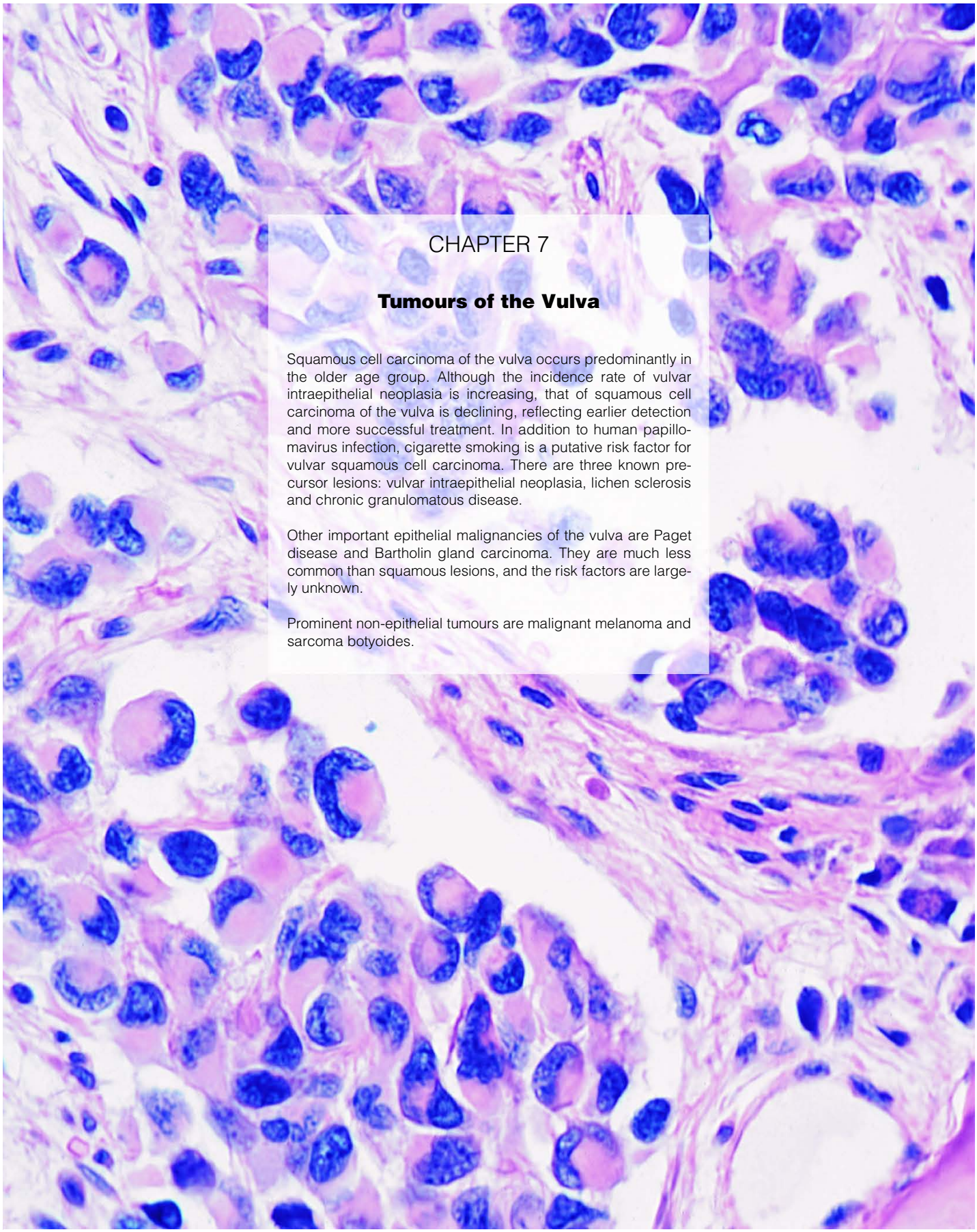

CHAPTER 7

Tumours of the Vulva

Squamous cell carcinoma of the vulva occurs predominantly in the older age group. Although the incidence rate of vulvar intraepithelial neoplasia is increasing, that of squamous cell carcinoma of the vulva is declining, reflecting earlier detection and more successful treatment. In addition to human papillomavirus infection, cigarette smoking is a putative risk factor for vulvar squamous cell carcinoma. There are three known precursor lesions: vulvar intraepithelial neoplasia, lichen sclerosis and chronic granulomatous disease.

Other important epithelial malignancies of the vulva are Paget disease and Bartholin gland carcinoma. They are much less common than squamous lesions, and the risk factors are largely unknown.

Prominent non-epithelial tumours are malignant melanoma and sarcoma botyoides.

WHO histological classification of tumours of the vulva

Epithelial tumours	
Squamous and related tumours and precursors	
Squamous cell carcinoma, not otherwise specified	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Basaloid	8083/3
Warty	8051/3
Verrucous	8051/3
Keratoacanthoma-like	
Variant with tumour giant cells	
Others	
Basal cell carcinoma	8090/3
Squamous intraepithelial neoplasia	
Vulvar intraepithelial neoplasia (VIN) 3 /	8077/2
squamous cell carcinoma in situ	8070/2
Benign squamous lesions	
Condyloma acuminatum	
Vestibular papilloma (micropapillomatosis)	8052/0
Fibroepithelial polyp	
Seborrheic and inverted follicular keratosis	
Keratoacanthoma	
Glandular tumours	
Paget disease	8542/3
Bartholin gland tumours	
Adenocarcinoma	8140/3
Squamous cell carcinoma	8070/3
Adenoid cystic carcinoma	8200/3
Adenosquamous carcinoma	8560/3
Transitional cell carcinoma	8120/3
Small cell carcinoma	8041/3
Adenoma	8140/0
Adenomyoma	8932/0
Others	
Tumours arising from specialized anogenital mammary-like glands	
Adenocarcinoma of mammary gland type	8500/3
Papillary hidradenoma	8405/0
Others	
Adenocarcinoma of Skene gland origin	8140/3
Adenocarcinomas of other types	8140/3
Adenoma of minor vestibular glands	8140/0
Mixed tumour of the vulva	8940/0
Tumours of skin appendage origin	
Malignant sweat gland tumours	8400/3
Sebaceous carcinoma	8410/3
Syringoma	8407/0
Nodular hidradenoma	8402/0
Trichoepithelioma	8100/0
Trichilemmoma	8102/0
Others	
Soft tissue tumours	
Sarcoma botryoides	8910/3
Leiomyosarcoma	8890/3
Proximal epithelioid sarcoma	8804/3
Alveolar soft part sarcoma	9581/3
Liposarcoma	8850/3
Dermatofibrosarcoma protuberans	8832/3
Deep angiomyxoma	8841/1
Superficial angiomyxoma	8841/0
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Leiomyoma	8890/0
Granular cell tumour	9580/0
Others	
Melanocytic tumours	
Malignant melanoma	8720/3
Congenital melanocytic naevus	8761/0
Acquired melanocytic naevus	8720/0
Blue naevus	8780/0
Atypical melanocytic naevus of the genital type	8720/0
Dysplastic melanocytic naevus	8727/0
Miscellaneous tumours	
Yolk sac tumour	9071/3
Merkel cell tumour	8247/3
Peripheral primitive neuroectodermal tumour /	9364/3
Ewing tumour	9260/3
Haematopoetic and lymphoid tumours	
Malignant lymphoma (specify type)	
Leukaemia (specify type)	
Secondary tumours	

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {921} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

[2] Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are only available for lesions categorized as squamous intraepithelial neoplasia grade 3 (e.g. intraepithelial neoplasia/VIN grade 3) = 8077/2; squamous cell carcinoma in situ 8070/2.

TNM classification of carcinomas of the vulva

TNM Classification[1,2]

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ (preinvasive carcinoma)
T1	Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension
T1a	Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion no greater than 1 mm
T1b	Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion greater than 1 mm
T2	Tumour confined to vulva or vulva and perineum, more than 2 cm in greatest dimension
T3	Tumour invades any of the following: lower urethra, vagina, anus
T4	Tumour invades any of the following: bladder mucosa, rectal mucosa, upper urethra; or is fixed to pubic bone

Note: The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

N – Regional Lymph Nodes[3]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral regional lymph node metastasis
N2	Bilateral regional lymph node metastasis

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (including pelvic lymph node metastasis)

Stage Grouping (TNM and FIGO)

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IVB	Any T	Any N	M1

[1] {51,2976}.
[2] A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
[3] The regional lymph nodes are the femoral and inguinal nodes.

Epithelial tumours

E.J. Wilkinson
M.R. Teixeira

Squamous tumours

Definition
Malignant or benign epithelial tumours composed primarily of squamous cells.

ICD-O codes

Squamous cell carcinoma	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Basaloid	8083/3
Warty	8051/3
Verrucous	8051/3
Basal cell carcinoma	8090/3
Vulvar intraepithelial neoplasia (VIN), grade 3 /	8077/2
squamous cell carcinoma in situ	8070/2
Vestibular papilloma	8052/0

Squamous cell carcinoma

Definition
An invasive carcinoma composed of squamous cells of varying degrees of differentiation.

Epidemiology
Squamous cell carcinoma is the most common malignant tumour of the vulva.
Primary squamous cell carcinoma of the vulva occurs more frequently in the older age group; the reported incidence rates are 1:100,000 in younger women and 20 in 100,000 in the elderly {2804}.

Table 7.01
Currently recognized precursors of vulvar squamous cell carcinoma.

(1) Vulvar intraepithelial neoplasia (VIN) and associated human papillomavirus (HPV) infection.
(2) The simplex (differentiated) type of VIN not associated with HPV infection {1621,3175}.
(3) Lichen sclerosus {1621} with associated squamous cell hyperplasia {403}.
(4) Chronic granulomatous vulvar disease such as granuloma inguinale {2628}.

Aetiology
In addition to human papillomavirus (HPV), cigarette smoking is a risk factor for vulvar carcinoma {611}. However, the specific aetiology of most vulvar epithelial tumours is unknown. The carcinomas associated with HPV include warty and basaloid carcinomas with the corresponding intraepithelial precursor lesions {584,1106,1541,2180,2936}. Verrucous carcinoma is associated with HPV, usually of type 6 or 11. In some cases there is no recognized precursor lesion. Squamous cell hyperplasia per se is apparently not a precursor of vulvar squamous cell carcinoma {1461}.
There are currently four recognized precursor of vulvar carcinoma (See table 7.1). Vulvar intraepithelial neoplasia (VIN) of the simpex (differentiated) type is usually associated with lichen sclerosus. The latter is also considered to be a precursor of keratinizing squamous cell carcinoma and is not HPV associated {3175}.
In the retrospective evaluation of vulvectomy specimens from women with vulvar squamous cell carcinoma, the frequency of identifying associated lichen sclerosus ranges from 15-40%, the higher rate being observed in deeply invasive carcinomas {403,1621,3240}. The lifetime risk of squamous cell carcinoma arising in vulvar lichen sclerosus is unknown but may exceed 6% {403,1621,1824,2369, 2606}. The squamous cell carcinomas associated with lichen sclerosus involving the vulva are usually of the keratinizing type.

Localization
Vulvar squamous cell carcinoma is usually solitary and is found most commonly on the labia minora or majora; the clitoris is the primary site in approximately 10% of cases.

Clinical features
Signs and symptoms
Squamous cell carcinoma may present as an ulcer, nodule, macule or pedunculated mass. Symptoms may be similar to those seen with VIN, although in more advanced cases discharge, bleeding, pain, odour or self-palpation of a mass may bring the patient to the physician.

Imaging
Imaging studies are generally not applicable for the detection of vulvar tumours. When the regional lymph nodes are clinically suspicious, imaging studies, including computed tomography or magnetic resonance, are employed, where available, to evaluate pelvic and paraaortic lymph nodes. Dye and technetium-99m labelled colloid have been used to detect inguino-femoral sentinel lymph nodes {646}.

Colposcopy
Colposcopic examination employing topically applied 3% acetic acid to enhance visualization of lesions and photographic recording of vulvar lesions may be of value in clinical management and follow-up {3124}

Exfoliative and aspiration cytology
Although exfoliative cytology has been applied to the evaluation of primary tumours of the vulva, this practice is not commonly used, and directed biopsy of identified lesions is the most effective method of primary diagnosis.
Fine needle aspiration cytology is of value in assessing suspicious lymph nodes or subcutaneous nodules {1283}.

Macroscopy
Most vulvar squamous carcinomas are solitary. The tumours may be nodular, verruciform or ulcerated with raised firm edges.

Tumour spread and staging
The staging of vulvar tumours is by the TNM/FIGO classification {51,2976}.
Superficially invasive vulvar carcinoma, stage 1A as defined by FIGO, is a single focus of squamous cell carcinoma having a diameter of 2 cm or less and a depth of invasion of 1 mm or less. The definition includes cases that have capillary-like space involvement by tumour. The term "microinvasive carcinoma" is not recommended.

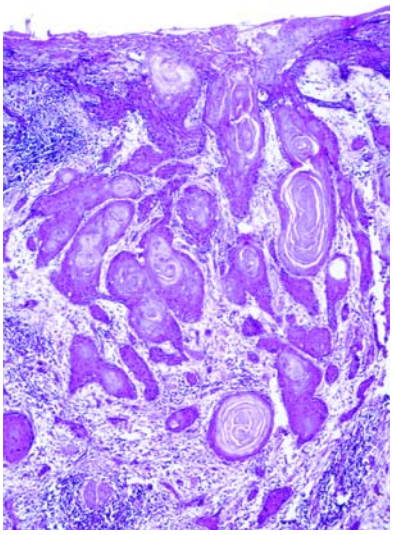

Fig. 7.01 Squamous cell carcinoma, keratinizing type. Keratin pearls are prominent. Invasion is confluent with a desmoplastic stromal response.

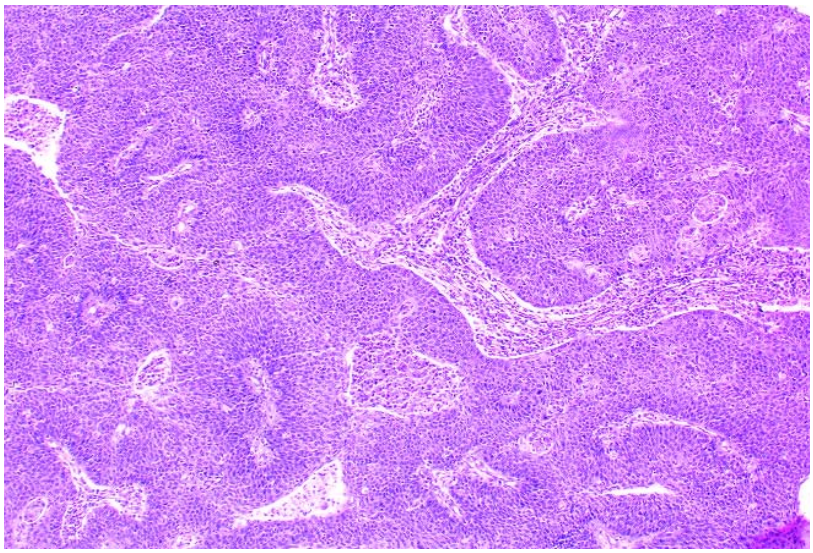

Fig. 7.02 Squamous cell carcinoma, basaloid type. Irregular aggregates of poorly differentiated squamous cells without keratinization infiltrate the stroma in the form of interconnecting columns. The tumour is composed of poorly differentiated basaloid type cells.

Histopathology

Squamous cell carcinoma is an invasive neoplasm composed of squamous cells of varying degrees of differentiation. Several morphological variants have been described:

Keratinizing

Keratinizing squamous cell carcinoma contains keratin pearls.

Non-keratinizing

Non-keratinizing squamous cell carcinoma does not form appreciable keratin; it may contain small numbers of individually keratinized cells but lacks keratin pearls. Rarely, the tumour is composed predominantly of spindle-shaped cells {2529}. In some cases the carcinoma may have a sarcoma-like stroma {2778}.

Basaloid

Basaloid squamous cell carcinoma is composed of nests of immature, basal type squamous cells with scanty cytoplasm that resemble closely the cells of squamous carcinoma in situ of the cervix. Some keratinization may be evident in the centres of the nests, but keratin pearls are rarely present. This tumour may be associated with HPV infections, predominantly type 16 {1541, 2936}.

Warty

Warty (condylomatous) squamous cell carcinoma has a warty surface and cellular features of HPV infection {720, 1541,2936}.

Verrucous

Verrucous carcinoma is a highly differentiated squamous cell carcinoma that has a hyperkeratinized, undulating, warty surface and invades the underlying stroma in the form of bulbous pegs with a pushing border.

Verrucous carcinoma accounts for 1-2% of all vulvar carcinomas and has little or no metastatic potential. The cellular features include minimal nuclear atypia and abundant eosinophilic cytoplasm. Mitotic figures are rare and, when present, are typical. There is usually a prominent chronic inflammatory cell infiltrate in the stroma. HPV, especially type 6, has been identified in a number of cases. Giant condyloma (Buschke-Lowenstein tumour) is considered by some to be synonymous with verrucous carcinoma {100, 348,1336,1501}.

Keratoacanthoma-like

These tumours, often referred to as keratoacanthoma, may arise on the hair-bearing skin of the vulva. They are rapidly growing but are usually self-limited. Histologically, they consist of a central crater filled with a glassy squamous epithelial proliferation in which horny masses of keratin are pushed upward, while tongues of squamous epithelium invade the dermis. Metastasis of so-called keratoacanthoma has been described {1227}. Complete excision with a clear histological margin is the recommended treatment.

Variant with tumour giant cells

Squamous cell carcinoma with a prominent tumour giant cell component is a highly aggressive neoplasm that can be confused with malignant melanoma {3122}.

Tumour measurements

It is recommended that the following features should be included in the pathology report {2601,3119}:

(1) Depth of invasion (mm).
(2) Tumour thickness.
(3) Method of measurement of depth of invasion and thickness of the tumour.
(4) Presence or absence of vascular space involvement by tumour.
(5) Diameter of the tumour, including the clinically measured diameter, if available.

In the event that invasion is equivocal

even with additional sectioning, it is recommended that invasion should not be diagnosed {3119}.
The following criteria apply to the measurement of vulvar squamous cell carcinoma:
(1) Thickness: measurement from the surface, or the granular layer if keratinized, to the deepest point of invasion.
(2) Depth of invasion: measurement from the epithelial-stromal junction of the adjacent most superficial dermal papillae to the deepest point of invasion.
The preferred measurement is the depth of invasion, as defined above.

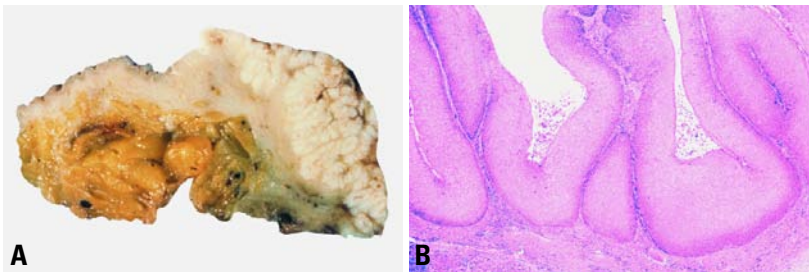

Fig. 7.03 Verrucous carcinoma. **A** The characteristic exophytic and endophytic growth pattern is evident in the sectioned surface of the tumour on the right side of the field. **B** The tumour is composed of well differentiated squamous epithelium with an undulating surface, minimal cytological atypia and a pushing border.

Somatic genetics

Cytogenetic data exist on 11 squamous cell carcinomas of the vulva {2897,3156}. The most common karyotypic changes are loss of 3p, 8p, 22q, Xp, 10q and 18q and gain of 3q and 11q21. There is an inverse correlation between histological differentiation and karyotypic complexity. Furthermore, a comparative genomic hybridization study of 10 cases revealed losses of 4p, 3p, and 5q and gains of 3q and 8p {1338}. Loss of 10q and 18q seems to be particularly associated with a poor prognosis in squamous cell carcinoma {2897,3156}. On the other hand, the only cytogenetically analysed squamous cell carcinoma in situ of the vulva (VIN 3) had a rearrangement of 11p as the sole anomaly {2818}.
TP53 mutation or HPV can independently lead to cell cycle disruption relevant to vulvar squamous cell carcinogenesis. Besides mutational inactivation, *TP53* can be inactivated through binding of HPV protein E6. *PTEN* is another gene that is frequently mutated in carcinomas of the vulva {1234}. Both *TP53* and *PTEN* mutations have also been detected in VIN, indicating that they are early events in vulvar carcinogenesis {1234,1866}. High frequencies of allelic imbalance have been detected at 1q, 2q, 3p, 5q, 8p, 8q, 10p, 10q, 11p, 11q, 15q, 17p, 18q, 21q and 22q, most of these irrespective of HPV status {2256}. This finding suggests that despite a different pathogenesis both HPV-positive and HPV-negative vulvar squamous cell carcinomas share several genetic changes during their progression.

Prognosis and predictive factors

Risk factors for recurrence include advanced stage, tumour diameter >2.5 cm, multifocality, capillary-like space involvement, associated VIN 2 or VIN 3 and involved margins of resection {1235,2004}. The extent of lymph node involvement and mode of treatment may also influence survival {721}. Patients whose tumours have a "spray" or finger-like pattern of invasion have a poorer survival than those with a "pushing" pattern {1235}.
For patients with stage 1A carcinoma, the therapy is usually local excision with at least a 1-cm margin of normal tissue {3, 1428}. Inguinofemoral lymph node dissection is usually unnecessary {247,373,374,1105, 1428}. The risk of recurrence in stage 1A cases is very low, with 5 and 10-year recurrence-free tumour specific survivals of 100% and 94.7%, respectively {1732}. Late recurrence or "reoccurrence" of a second squamous carcinoma in another site within the vulva is rare but can occur, and therefore long-term follow-up is warranted.
For tumours greater than stage 1A partial or total deep vulvectomy with ipsilateral or bilateral inguino-femoral lymph node resection may be required. If superficial lymph nodes contain tumour, radiotherapy to the deep pelvic nodes or chemoradiation may be necessary {360,373, 1749,2783}.

Basal cell carcinoma

Definition

An infiltrating tumour composed predominantly of cells resembling the basal cells of the epidermis.

Clinical features

This tumour presents as a slow growing, locally invasive, but rarely metastasizing lesion in the vulva {218,833,1872, 2260}.

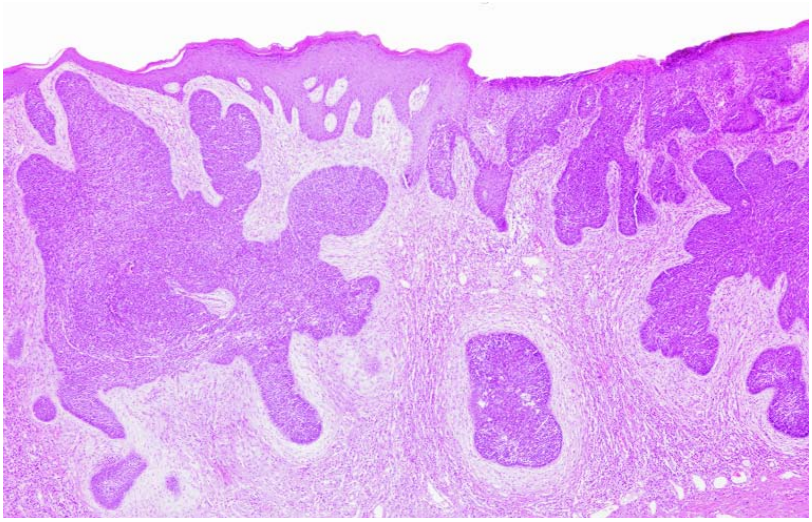

Fig. 7.04 Basal cell carcinoma. Aggregates of uniform basaloid cells with peripherial palisading arise from the basal layer of the overlying squamous epithelium and infiltrate the stroma.

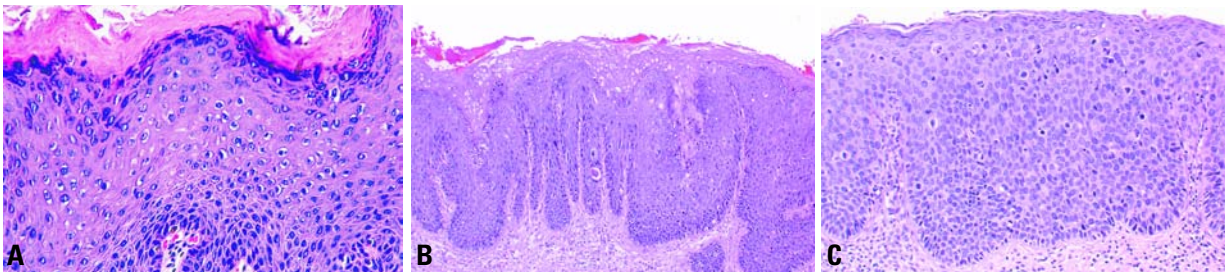

Fig. 7.05 Vulvar intraepithelial neoplasia (VIN). **A** VIN 1. Hyperkeratosis is prominent. Nuclear crowding is confined to the lower third of the epithelium. **B** VIN 3, warty type (severe displasia). Beneath a hyperkeratotic surface the epithelial cells are crowded and show minimal maturation. **C** VIN 3 (carcinoma in situ, basaloid type). Nearly the entire epithelium is composed of closely packed basaloid cells.

Histopathology
The tumour is composed of aggregates of uniform basal cells with peripheral palisading. Squamous cell differentiation may occur at the centre of the tumour nests. Tumours containing gland-like structures are referred to as "adenoid basal cell carcinoma" {1850}. Those containing infiltrating malignant-appearing squamous cells may be diagnosed as metatypical basal cell carcinoma or basosquamous carcinoma. Immunohistochemical findings reflect these histological subtypes {183}. Basal cell carcinoma has been reported in association with vulvar Paget disease {1084}.

Histogenesis
This tumour is derived from the basal cells of the epidermis or hair follicles.

Prognosis and predictive factors
Basal cell carcinoma of the vulva is usually treated by local excision; however, groin metastases have been reported {1017}.

Vulvar intraepithelial neoplasia

Definition
An intraepithelial lesion of the vulvar squamous epithelium characterized by disordered maturation and nuclear abnormalities, i.e. loss of polarity, pleomorphism, coarse chromatin, irregularities of the nuclear membrane and mitotic figures, including atypical forms.

Synonym
Dysplasia/carcinoma in situ.

Epidemiology
The incidence of VIN, unlike that of vulvar carcinoma, has been increasing over the past 20 years, especially in women of reproductive age, with the highest frequency reported in women 20-35 years old {538,1312,2804}.

Aetiology
VIN is predominately of the warty or basaloid types, and both are associated with HPV, most commonly type 16 {1106, 1197,1663,2936}. Women with HPV-related vulvar disease have an increased risk of associated cervical intraepithelial neoplasia (CIN) {2766}. Women infected with human immunodeficiency virus (HIV) have a high frequency of HPV infection of the lower genital tract and associated CIN and/or VIN {2766}.

Clinical features
Women with VIN may present with vulvar pruritus or irritation or may observe the lesions and seek medical assistance {919}. VIN is typically a macular or papular lesion or lesions, which in approximately one-half of the cases are white or aceto-white. Approximately one-quarter of VIN lesions are pigmented. VIN is multifocal in approximately two-thirds of the cases. The remaining patients usually present as a solitary lesion, a more common finding in older women {431}. Large confluent lesions are uncommon {919, 3123}.

Tumour spread and staging
Up to one-fifth of the women presenting with VIN are found to have an associated squamous cell carcinoma {431,1197, 1272}. In most cases these squamous cell carcinomas are superficially invasive.

Histopathology
The epithelial cells are typically crowded, and acanthosis may be present. A prominent granular layer may be associated with parakeratosis, hyperkeratosis or both. Involvement of skin appendages is seen in over one-third of the cases, which in hairy skin may be as deep as 2.7 mm. Skin appendage involvement should not be misinterpreted as invasion {219,2636}. There may be associated HPV changes. The term "bowenoid papulosis" should not be used as a histological diagnosis (see below).
The grading of HPV-related VIN is similar to that used in the cervix. The simplex type of VIN (carcinoma in situ, simplex

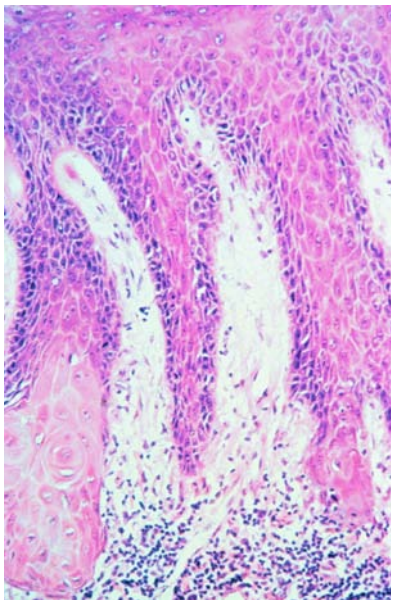

Fig. 7.06 Vulvar intraepithelial neoplasia, differentiated (simplex) type. The atypia is confined to the basal and parabasal layers. The squamous cells have nuclear abnormalities with prominent eosinophilic abortive pearl formations in the deeper portions of the epithelium. The presence of paradoxical maturation abutting on the epithelial-stromal junction is suggestive of impending invasion.

type) is a highly differentiated lesion resembling well differentiated squamous cell carcinoma in which the atypia is most prominent in or confined to the basal and parabasal layers of the epithelium, where the cells have abundant cytoplasm and form pearls and the nuclei are relatively uniform in size and contain coarse chromatin and prominent nucleoli {3175}.

Somatic genetics

The only cytogenetically analysed case of VIN 3 (squamous cell carcinoma in situ) of the vulva had a rearrangement of 11p as the sole anomaly {2818}.
Genomic deletions have been demonstrated in the simplex (differentiated) form of VIN and its subsequent squamous carcinoma unrelated to HPV infection {1663}. These also express TP53 {1824,3175}.

Prognosis and predictive factors

VIN is usually treated by local excision. Laser or other ablative procedure may also have a role {1197,1369,3124}. Spontaneous regression of VIN 2 and 3 in younger women with papular pigmented lesions is recognized, and such lesions are referred to clinically as bowenoid papulosis by some investigators {1369}. The recurrence of VIN is well recognized, especially in women who are heavy cigarette smokers or positive for HIV.

Condyloma acuminatum

Definition

A benign neoplasm characterized by papillary fronds containing fibrovascular cores and lined by stratified squamous epithelium with evidence of HPV infection, usually in the form of koilocytosis.

Tumour spread and staging

Co-infection of the vulva and cervix is well recognized {1528}. Vulvar carcinoma in young women has been associated with genital condyloma {2945}.

Histopathology

The lesions are typically multiple and papillomatous or papular. The epithelium is acanthotic with parabasal hyperplasia and koilocytosis in the upper portion. Hyperkeratosis and parakeratosis are usual, and binucleated and multinucleated keratinocytes are often present. The rete ridges are elongated and thickened. A chronic inflammatory infiltrate is usually present within the underlying connective tissue.
HPV infection in the vulvar epithelium is expressed in three broad categories:
(1) Fully expressed, with morphological features of HPV infection, as seen in condyloma acuminatum
(2) Minimally expressed, with only mild morphological changes, e.g. koilocytosis
(3) Latent, in which no characteristic morphological changes are seen, although HPV can be detected with the use of molecular techniques {1013}.

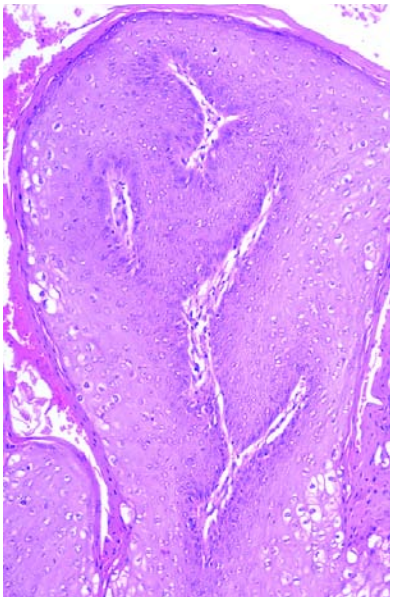

Fig. 7.07 Condyloma acuminatum. Papillary fronds with fibrovascular cores are lined by squamous epithelium with hyperkeratosis, acanthosis and koilocytosis.

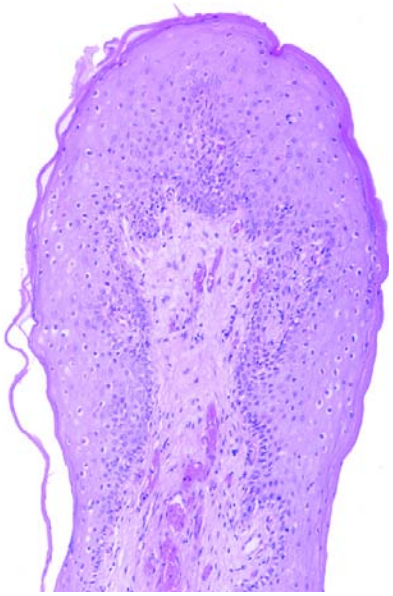

Fig. 7.08 Vestibular papilloma. Smooth surfaced squamous epithelium without acanthosis or koilocytotic atypia lines a delicate fibrovascular stalk.

Vestibular papilloma

Definition

A benign papillary tumour with a squamous epithelial mucosal surface that overlies a delicate fibrovascular stalk.

Synonyms

Micropapillomatosis labialis, vestibular micropapillomatosis.
These terms are applicable when numerous lesions are present.

Clinical features

The lesions may be solitary but frequently are multiple, often occurring in clusters near the hymenal ring, resulting in a condition referred to as vestibular papillomatosis or micropapillomatosis or micropapillomatosis labialis {238,644, 980,1930,2277}. They are less than 6 mm in height. Unlike condylomas, they do not typically respond to podophyllin and/or interferon {2277}.

Histopathology

These lesions have papillary architecture and a smooth surface without acanthosis or koilocytotic atypia. They lack the complex arborizing architecture of condyloma.

Aetiology

The great majority of studies of vestibular micropapillomatosis as defined above have demonstrated no relationship of these lesions to HPV {238,644,1856, 2118,2277}.

Fibroepithelial polyp

Definition

A polypoid lesion covered by squamous epithelium and containing a central core of fibrous tissue in which stellate cells with tapering cytoplasmic processes and

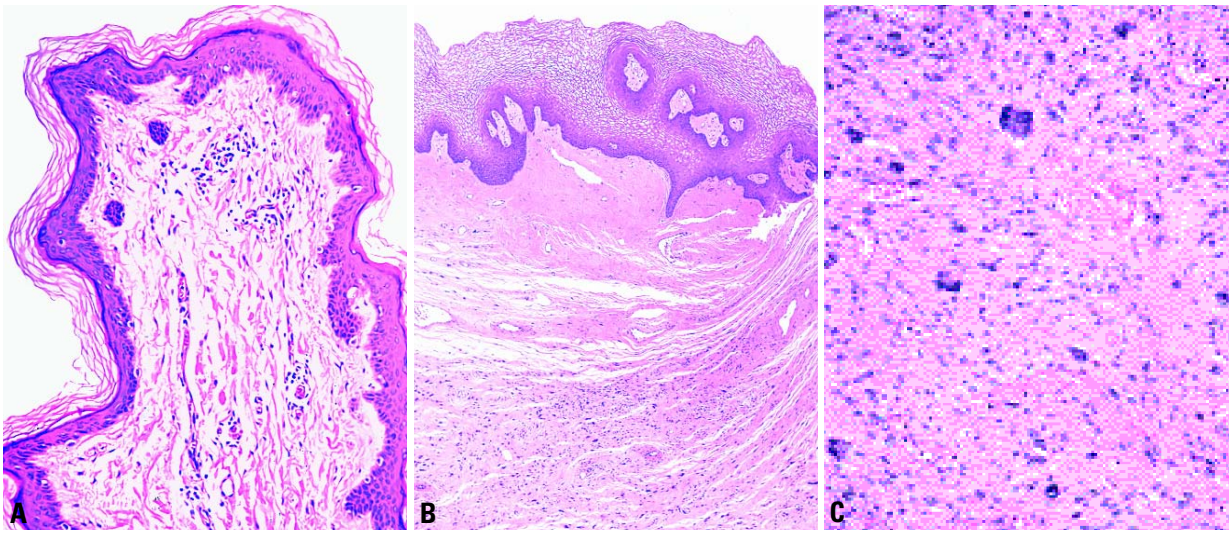

Fig. 7.09 Fibroepithelial polyp of the vulva. **A** The central core of fibrous tissue contains thin-walled vessels. The epithelium is not acanthotic. **B** Stratified squamous epithelium covers dense fibrous stroma. **C** Note the scattered bizarre multinucleated giant cells in the stroma.

irregularly shaped thin-walled vessels are prominent features.

Histopathology

These polypoid lesions are characterized by a prominent fibrovascular stroma covered by squamous epithelium without evidence of koilocytosis. In contrast to vulvar condylomas, fibroepithelial polyps do not show epithelial acanthosis or papillary architecture. Bizarre stromal cells have been described in these polyps that do not influence behaviour {416}.

Aetiology

In contrast to condylomas, fibroepithelial polyps appear unrelated to HPV infection and rarely contain HPV nucleic acids {1837}.

Prognosis and predictive factors

Although benign, the lesion may recur if incompletely excised {2141}.

Seborrheic keratosis and inverted follicular keratosis

Definition

A benign tumour characterized by proliferation of the basal cells of the squamous epithelium with acanthosis, hyperkeratosis and the formation of keratin-filled pseudohorn cysts. Some cases may have an incidental HPV infection {3263}. Inverted follicular keratosis is a seborrheic keratosis of follicular origin and contains prominent squamous eddies. An inverted follicular keratosis of the vulva has been reported that may have been related to close shaving {2467}.

Keratoacanthoma

This rare squamoproliferative lesion commonly occurs on sun-exposed skin. It is thought to arise from follicular epithelium and was originally considered to be benign. It has a central keratin-filled crater and focal infiltration at its dermal interface. In some instances the lesion regresses spontaneously {2361}. Two cases have been described in the vulva {997}. At present the lesion originally described as keratoacanthoma is generally accepted as a well differentiated squamous cell carcinoma, keratoacanthoma type {1227}, and the latter diagnosis is recommended (see section on squamous cell carcinoma).

Glandular tumours

ICD-O codes

Paget disease	8542/3
Bartholin gland tumours	
Adenocarcinoma	8140/3
Squamous cell carcinoma	8070/3
Adenoid cystic carcinoma	8200/3
Adenosquamous carcinoma	8560/3
Small cell carcinoma	8041/3
Transitional cell carcinoma	8120/3
Adenoma	8140/0
Adenomyoma	8932/0
Papillary hidradenoma	8405/0
Adenocarcinoma of Skene gland origin	8140/3
Adenoma of minor vestibular glands	8140/0
Mixed tumour of the vulva	8940/0

Vulvar Paget disease

Definition

An intraepithelial neoplasm of cutaneous origin expressing apocrine or eccrine glandular-like features and characterized by distinctive large cells with prominent cytoplasm referred to as Paget cells. It may also be derived from an underlying skin appendage adenocarcinoma or anorectal or urothelial carcinoma {3121}.

Epidemiology

Primary cutaneous Paget disease is an uncommon neoplasm, usually of postmenopausal White women. In approximately 10-20% of women with vulvar Paget disease, there is an invasive component or an underlying skin appendage adenocarcinoma {825,3121}.

Clinical features

Paget disease typically presents as a symptomatic red, eczematoid lesion that may clinically resemble a dermatosis {1028,3121,3267}. Paget disease that is related to anorectal adenocarcinoma

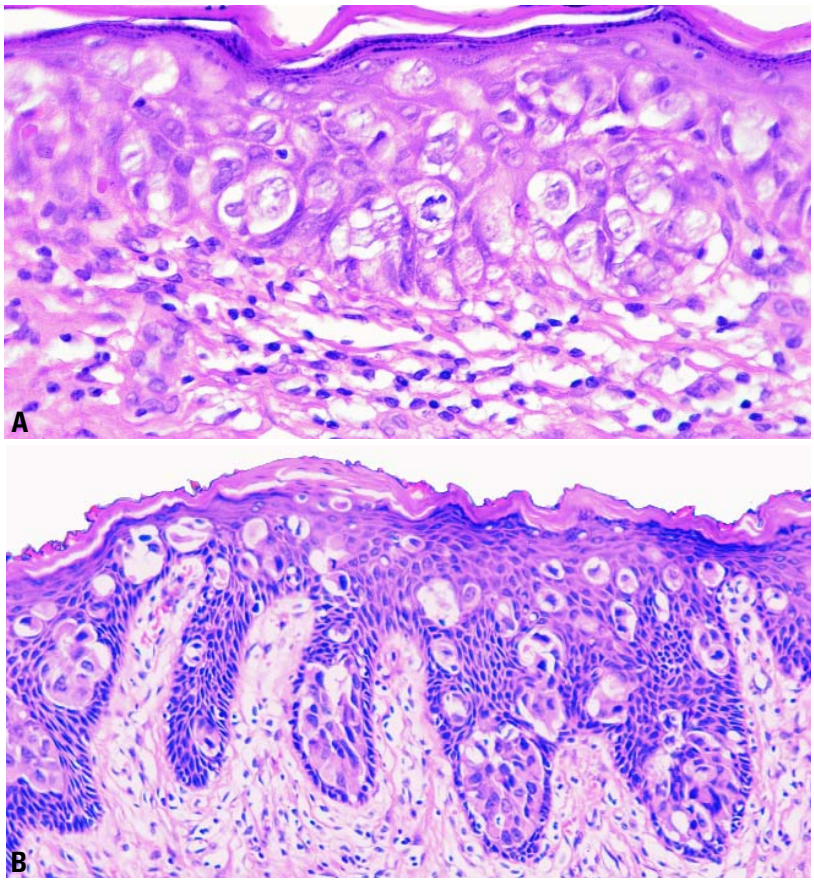

Fig. 7.10 Paget disease of the vulva. **A** Paget disease of cutaneous origin. Clusters of large pale Paget cells with atypical nuclei are present within the epidermis. A mitotic figure is evident. **B** Paget disease of urothelial origin. Clusters of large pale cells resembling transitional cell carcinoma involve predominantly the parabasal area of the epidermis with sparing of the basal layer.

clinically involves the perianal mucosa and skin, as well as the adjacent vulva.

Histopathology

The Paget cell of cutaneous origin is typically a large, round cell with a large nucleus and prominent nucleolus. The cytoplasm is pale on routine hematoxylin and eosin stain, is often vacuolated and stains with mucicarmine. The cytoplasm contains PAS-positive material that is resistant to diastase. The Paget cells may also express CA125 and Her-2/neu but do not express estrogen receptor {573,3119,3121}.

Paget disease that is related to urothelial neoplasia contains cells with the morphological features of high grade urothelial neoplasms {1746,3121}. It may histologically resemble primary cutaneous Paget disease, though it has a different immunohistochemical profile.

Somatic genetics

Three cytogenetically abnormal clones were detected in Paget disease of the vulva {2897}, a finding consistent with the view that this disease may arise multicentrically from pluripotent stem cells within the epidermis. DNA aneuploidy in Paget disease is associated with an increased risk of recurrence {2553}.

Bartholin gland carcinoma

Definition

Primary carcinoma of diverse cell types located at the site of the Bartholin gland.

Clinical features

Bartholin gland carcinoma occurs predominantly in women over 50 years of age and presents as an enlargement in the Bartholin gland area that may clinically resemble a Bartholin duct cyst.

Tumour spread and staging

Approximately 20% of cases are associated with ipsilateral inguinofemoral lymph node metastases at presentation {556,1634,3108}.

Histopathology

The tumour is typically solid and deeply infiltrative. A transition from an adjacent Bartholin gland to tumour is of value in identifying its origin. Various types of carcinoma have been described.

Adenocarcinoma

Adenocarcinoma accounts for approximately 40% of Bartholin gland tumours {556,1634}. Adenocarcinomas may be mucinous, papillary or mucoepidermoid in type. They are usually carcinoembryonic antigen immunoreactive.

Squamous cell carcinoma

This tumour accounts for approximately 40% of Bartholin gland tumours and is composed of neoplastic squamous cells.

Adenoid cystic carcinoma

Adenoid cystic carcinoma accounts for approximately 15% of Bartholin gland tumours {556,675}. It is composed typically of rounded islands of uniform malignant epithelial cells with a cribriform pattern. A hyaline stroma may form cylinders separating rows of tumour cells. The intraluminal material is basement membrane-like rather than a secretion, supporting a squamous rather than glandular origin.

The cytogenetic analysis of an adenoid cystic carcinoma of Bartholin gland revealed a complex karyotype involving chromosomes 1, 4, 6, 11, 14 and 22 {1457}.

Adenosquamous carcinoma

Adenosquamous carcinoma accounts for approximately 5% of Bartholin gland tumours. It is composed of neoplastic mucin-containing glandular and neoplastic squamous cells.

Transitional cell carcinoma

Transitional cell carcinoma is a rare tumour of Bartholin gland composed of

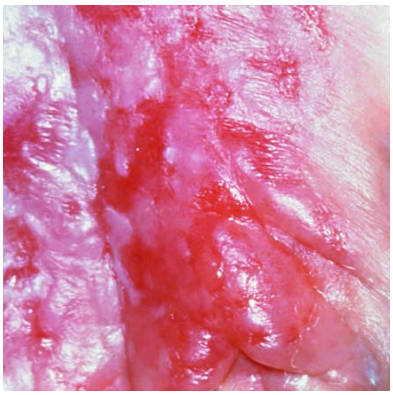

Fig. 7.11 Paget disease of the vulva. Note the red, eczematous appearance.

Table 7.02
Immunohistochemical findings of Paget disease.

Type of Paget disease	CK-7	CK 20	GCDFP-15	CEA	UP-III
Primary skin neoplasm	+	-	+	+	-
Related to anorectal carcinoma	+	+	-	+	-
Related to urothelial carcinoma	+	(+)	-	-	+

Abbreviations for antibodies used as follows:
CK = cytokeratin; CEA = carcinoembryonic antigen; GCDFP-15 = gross cystic disease fluid protein-15; UP-III = uroplakin III {2088,3121}.

neoplastic urothelial-type cells, occasionally with a minor component of glandular or squamous cells.

Small cell carcinoma
This rare highly malignant neoplasm is composed of small neuroendocrine cells with scant cytoplasm and numerous mitotic figures {1361}.

Benign neoplasms of Bartholin gland

Adenoma and adenomyoma

Bartholin gland adenoma is a rare benign tumour of Bartholin gland characterized by small clustered closely packed glands and tubules lined by columnar to cuboidal epithelium with colloid-like secretion arranged in a lobular pattern and contiguous with identifiable Bartholin gland elements. Bartholin gland adenoma has been reported in association with adenoid cystic carcinoma {1487}. Bartholin gland nodular hyperplasia can be distinguished from adenoma by the preservation of the normal duct-acinar relationships present in hyperplasia. Bartholin gland adenomyoma has a fibromuscular stromal element that is immunoreactive for smooth muscle actin and desmin as well as a lobular glandular architecture with glands lined by columnar mucin-secreting epithelial cells adjacent to tubules {1487}.

Tumours arising from specialized anogenital mammary-like glands

Definition

Malignant and benign tumours, usually of glandular type and resembling neoplasms of the breast, may arise in specialized anogenital mammary-like glands. These glands and the tumours that arise from them are usually identified in or adjacent to the intralabial sulcus. Adenocarcinoma with morphological features of breast carcinoma has been reported as a primary vulvar tumour {687}. Such tumours are currently thought to arise from the specialized anogenital glands and not from ectopic breast tissue {2991,2992}. The papillary hidradenoma is an example of a benign neoplasm {2991,2992}. Intraductal adenocarcinoma of mammary-type within a hidradenoma has been reported {2212}.

Papillary hidradenoma

Definition
A benign tumour composed of epithelial secretory cells and underlying myoepithelial cells lining complex branching papillae with delicate fibrovascular stalks.

Epidemiology
This tumour is rare in the vulva but is the most common benign glandular neoplasm at this site.

Clinical features
It usually presents as an asymptomatic mass within or adjacent to the intralabial sulcus and may cause bleeding resembling carcinoma if the gland prolapses and/or ulcerates.

Histopathology
The tumour is distinctly circumscribed and composed of complex papillae and

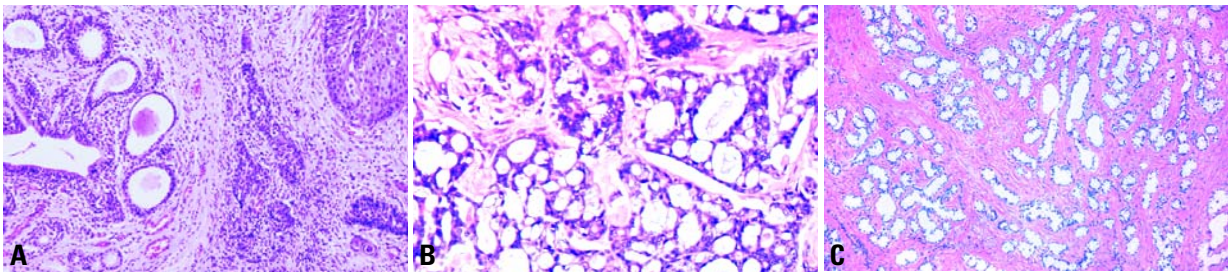

Fig. 7.12 Bartholin gland neoplasms. **A** Squamous cell carcinoma. Aggregates of neoplastic squamous cells infiltrate Bartholin gland seen on the left. **B** Adenoid cystic carcinoma. Note the cribriform pattern with the lumens containing basophilic mucin. **C** Bartholin gland adenoma. A nodule is composed of clustered glands lined by mucinous epithelium.

glandular elements surrounded by fibrous tissue. Relatively uniform columnar epithelial secretory cells with underlying myoepithelial cells cover the glands and papillary stalks.

Adenocarcinoma of Skene gland origin

An adenocarcinoma of Skene gland with associated metastasis has been reported {2726}. Skene gland is the female homologue of the male prostate, and the tumour expresses prostate antigens by immunohistochemistry {2726}. A carcinoma of Skene duct origin was associated with systemic coagulopathy {2895}.

Adenocarcinomas of other types

These tumours may arise from endometriosis or ectopic cloacal tissue {307,3126,3237}.

Adenoma of minor vestibular glands

Adenoma of minor vestibular glands is a rare benign tumour composed of clusters of small glands lined by mucin-secreting columnar epithelial cells arranged in a lobular pattern without intervening Bartholin duct elements. It is usually an incidental finding measuring 1-2 mm in diameter, although one example was as large as 10 mm. Nodular hyperplasia of the minor vestibular glands may also occur {141,2295}

Mixed tumour of the vulva

Definition
A benign epithelial tumour composed of epithelial cells arranged in tubules or nests mixed with a fibrous stromal component that may include chondroid, osseous and myxoid elements.

Synonyms
Pleomorphic adenoma, chondroid syringoma.

Clinical features
Mixed tumour of the vulva usually presents as a subcutaneous nodule involving the labum majus and/or the Bartholin gland area.

Histopathology
The histological features are similar to those of mixed tumours of salivary glands. The tumour with its stromal-like elements is believed to arise from pluripotential myoepithelial cells that are present in Bartholin gland, sweat glands and the specialized anogenital (mammary-like) glands of the vulva {2410}.

Prognosis and predictive factors
Although these tumours are considered benign, insufficient cases of vulvar mixed tumours have been reported to determine their natural history at this site. The tumour may recur locally. A carcinoma arising in a mixed tumour has been described {2117}. Complete local excision with free margins is the recommended therapy for the primary tumour as well as for local recurrences.

Tumours of skin appendage origin

Definition
Benign or malignant tumours differentiating towards hair follicles or sweat or sebaceous glands.

ICD-O codes

Malignant sweat gland tumour	8400/3
Sebaceous carcinoma	8410/3
Syringoma	8407/0
Nodular hidradenoma	8402/0
Trichoepithelioma	8100/0
Trichilemmoma	8102/0

Malignant sweat gland tumours

Vulvar malignant sweat gland tumours include eccrine adenocarcinoma, porocarcinoma, clear cell hidradenocarcinoma, and apocrine adenocarcinoma, the last of which may be associated with Paget disease {3112}.

Sebaceous carcinoma

Vulvar sebaceous carcinoma resembles its cutaneous counterpart. It is a malignant tumour composed of cords and nests of basaloid appearing neoplastic glandular elements with cellular features of sebaceous epithelium. The tumour may be associated with neoplastic sebaceous cells present in pagetoid nests within the parabasal component of the overlying epithelium and in larger clusters near the epithelial surface {405,795}. Sebaceous carcinoma of the vulva may be associated with VIN {1318}.

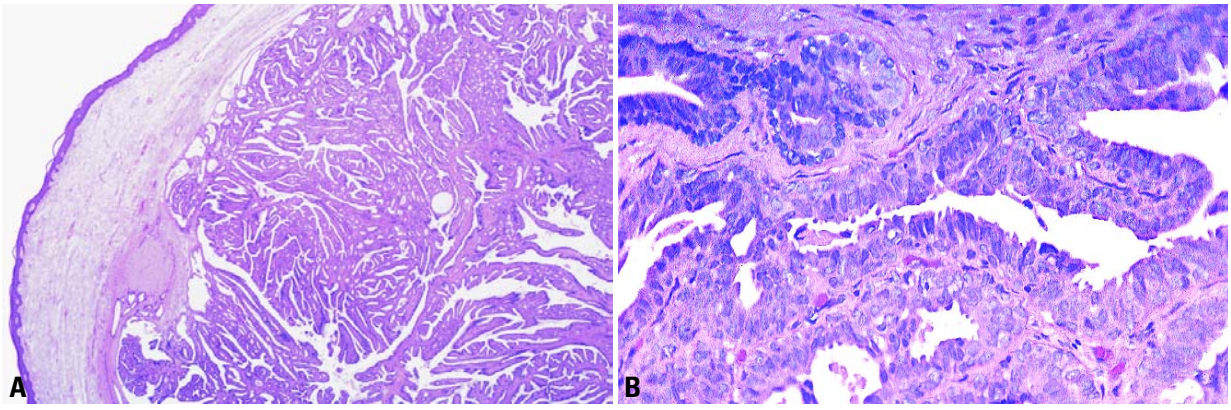

Fig. 7.13 Papillary hidradenoma of the vulva. **A** Note the circumscribed tumour composed of complex branching papillae. **B** The epithelial lining is composed of a double layer of cells, an inner layer of secretory cells and an outer layer of myoepithelial cells.

Syringoma

Definition
A benign epithelial tumour believed to arise from eccrine ducts that is composed of small and relatively uniform epithelial-lined tubules and cysts within a densely fibrous dermis.

Clinical findings
It presents as asymptomatic or pruritic papules that are small, clustered and non-pigmented and involve the deeper skin layers of the labia majora. The nodules are often bilateral {415}.

Histopathology
Histologically, small epithelial cysts and dilated duct-like spaces lined by two rows of cells, an inner epithelial and an outer myoepithelial, are seen. The ductular structures typically form comma-like shapes. The tumour lacks a clearly defined capsule or margin; the dermis surrounding the neoplastic ducts has a fibrotic appearance.

Nodular hidradenoma

Definition
Nodular hidradenoma is an infrequent benign tumour of sweat gland origin composed of epithelial cells with clear cytoplasm arranged in lobules and nests.

Synonym
Clear cell hidradenoma.

Histopathology
It is composed of epithelial cells with clear cytoplasm arranged in lobules and nests {1950}.

Prognosis and predictive factors
Complete local excision is considered adequate therapy.

Trichoepithelioma

Definition
A benign tumour composed of complex interconnected nests of basaloid cells that form small "horn cysts" (cysts containing keratin).

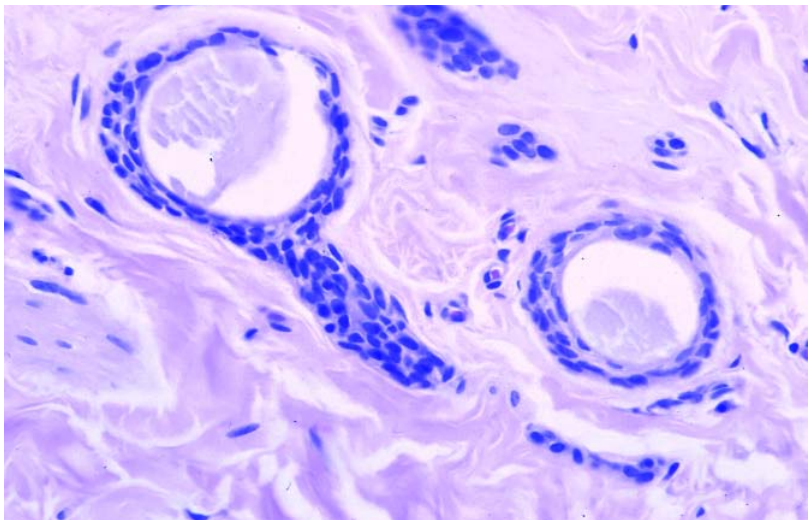

Fig. 7.14 Syringoma of the vulva. The tumour is composed of well differentiated ductal elements of eccrine type consisting of irregular, sometimes comma-shaped, cord-like and tubular structures that infiltrate the dermis.

Clinical features
On clinical examination single or multiple cutaneous nodules with overlying skin abnormalities are identified.

Histopathology
Nests of cells form small keratin-containing cysts. The neoplastic epithelial cells are monomorphic without nuclear hyperchromasia or atypia. The tumour has a defined dermal interface and lacks an infiltrative appearance. Rupture of the keratin-containing cysts may result in a granulomatous reaction with foreign body giant cells. Hair follicles may be identified in some cases.

Histogenesis
The tumour is considered to be of follicular origin {478}.

Prognosis and predictive factors
The treatment is complete local excision.

Trichilemmoma

Definition
A benign epithelial tumour composed of relatively uniform epithelial cells with pale-staining cytoplasm that may have some nuclear pleomorphism. It is thought to arise from the proliferation of outer root sheath epithelial cells of the hair follicle.

Synonym
Proliferating trichilemmal tumour.

Clinical findings
Clinically, these tumours have been reported in the dermis of the labium majus, presenting as a slow-growing solid mass {140}.

Histopathology
The tumour has a lobulated appearance with a dermal pushing border that may show no connection with the overlying epithelium. The cells show peripheral palisading and increased clear cytoplasm as they stratify toward the centre. Amorphous keratin is present in the lumens, although no granular layer is formed. Calcification may occur.

Uncommon vulvar skin appendage tumours

Proliferating trichilemmal cysts (pilar tumours) {2329}, trichoblastic fibroma {1003} and apocrine cystadenoma {1021} have been described on the vulva. A local excision is therapeutic.

Mesenchymal tumours

R.L. Kempson
M.R.Teixeira
M.R. Hendrickson

Definition
A variety of benign and malignant soft tissue tumours that occur in the vulva.

Malignant soft tissue tumours

Definition
Malignant soft tissue tumours that arise in the vulva.

ICD-O codes

Sarcoma botryoides	8910/3
Leiomyosarcoma	8890/3
Proximal-type epithelioid sarcoma	8804/3
Alveolar soft part sarcoma	9581/3
Liposarcoma	8850/3
Dermatofibrosarcoma protuberans	8832/3

Sarcoma botryoides

Definition
A malignant neoplasm exhibiting striated muscle differentiation that occurs almost exclusively in children younger than 10 years of age {555,558,2002}.

Synonym
Embryonal rhabdomyosarcoma.

Clinical features
In girls the neoplasm typically arises from the labial or perineal area and presents with bleeding and ulceration. The neoplasm usually presents as a solid vulvar mass; the distinctive "bunch of grapes" appearance is more characteristic of vaginal primaries.

Tumour spread and staging
When both the vulva and vagina are involved, the tumour is regarded as vaginal for staging purposes.

Histopathology
For the typical histological features of sarcoma botryoides see the chapter on the vagina. Vulvar rhabdomyosarcoma sometimes exhibits an alveolar pattern, usually a focal finding, but occasionally diffuse. In this pattern tumour cells grow in loosely cohesive nests separated by fibrous septa. Towards the centre of the nests, the cells show loss of cohesion and float freely within a space, whilst the cells at the periphery are adherent to the septa, a pattern that simulates pulmonary alveoli. The tumour cell cytoplasm stains with a variety of muscle markers including actin, myosin, desmin, myogenin and myoD-1.

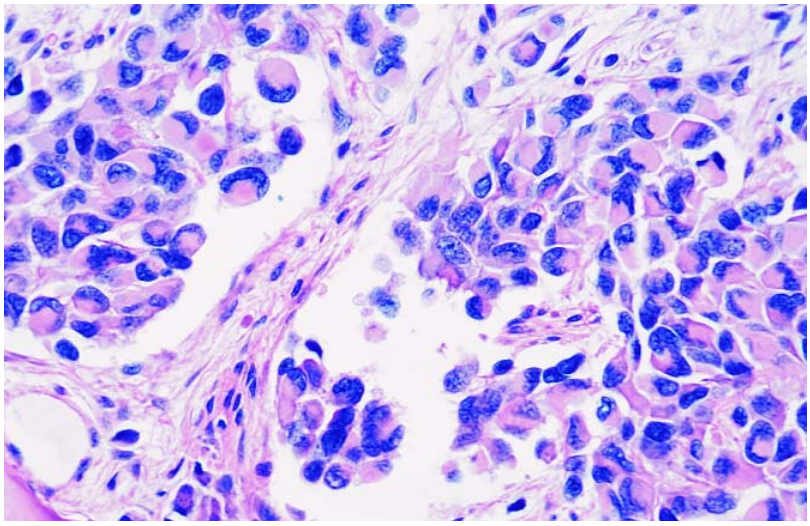

Fig. 7.15 Sarcoma botryoides, alveolar type. The tumour cells grow in loosely cohesive nests separated by fibrous septa that simulate pulmonary alveoli.

Prognosis and predictive factors
The prognosis depends both upon the clinical stage and the histological type {99}. An alveolar histology, even when focal, is an unfavourable prognostic feature, whereas classic botryoid embryonal rhabdomyosarcoma is associated with a greater than 90% survival {558}.

Leiomyosarcoma

Definition
A rare malignant neoplasm showing smooth muscle differentiation.

Clinical features
These neoplasms occur in adults in any part of the vulva and present as a rapidly enlarging mass, sometimes with pain.

Histopathology
Most reported cases are high grade neoplasms with the usual features of necrosis, infiltrative margins, cytological atypia and mitotic indices in excess of 10 mitotic figures per 10 high power fields. Problematic tumours are those with no necrosis and a low mitotic index {2880}.

Differential diagnosis
Leiomyosarcoma should be differentiated from postoperative spindle cell nodule {1397}. The latter is mitotically active and may infiltrate the underlying tissue. The distinction from leiomyosarcoma or other malignant spindle cell tumours depends to a large extent on the history of a recent operation at the same site {1762}.

Proximal-type epithelioid sarcoma

Definition
A malignant tumour histologically similar to epithelioid sarcoma of soft parts.

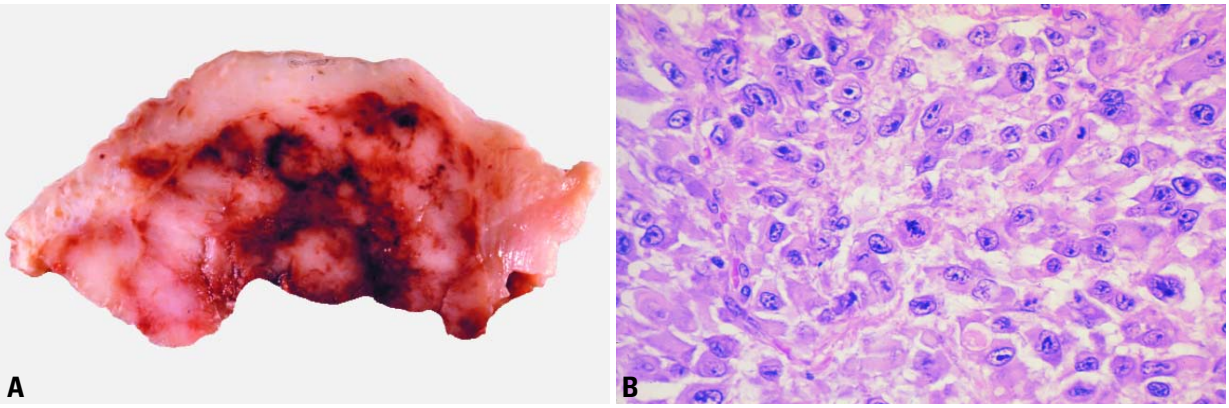

Fig. 7.16 Epithelioid sarcoma of the vulva. **A** The tumour forms a multinodular mass beneath the skin with areas of haemorrhage. **B** The neoplasm is composed of large epithelioid cells with pleomorphic nuclei, prominent nucleoli and frequent mitotic figures.

Synonym
Malignant rhabdoid tumour, adult type.

Histopathology
This tumour, which has histological and immunological features similar to epithelioid sarcoma of the extremities, has a predilection for the vulva {1078}. The growth pattern is frequently nodular, and the tumour cells are large with abundant amphophilic cytoplasm. The nuclei are either large and pleomorphic with small nucleoli or vesicular with prominent nucleoli. Keratin and vimentin stains are positive in essentially all tumours, and CD34 is positive in approximately one-half of the cases.

Prognosis and predictive factors
Frequent recurrences and a high incidence of metastasis mark the clinical course.

Alveolar soft part sarcoma

Definition
A sarcoma characterized by solid and alveolar groups of large epithelial-like cells with granular, eosinophilic cytoplasm.

Histopathology
The rare cases of alveolar soft part sarcoma reported in the vulva have the same distinctive histology as those neoplasms occurring in more conventional soft tissue locations {2639}. The tumour is composed of large uniform cells with abundant granular to vacuolated eosinophilic cytoplasm; the cells are compartmentalized into packets by thin-walled often sinusoidal vessels. Most of the tumours contain characteristic intracytoplasmic PAS-positive, diastase resistent, rod-shaped crystals.

Liposarcoma

Liposarcomas are extremely rare in this location {354,2062}. Both atypical lipomatous tumours (well differentiated liposarcomas) and myxoid liposarcomas have been reported.

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans is a highly recurrent low grade cutaneous sarcoma that is usually located on the trunk. Although rare, more than 10 cases have been reported in the vulva, and in one such case a supernumerary ring chromosome with the characteristic *COL1A1/PDGFB* fusion gene was found {3004}.

Benign soft tissue tumours

Definition
Benign soft tissue tumours that arise in the vulva.

ICD-O codes

Deep angiomyxoma	8841/1
Superficial angiomyxoma	8841/0
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Leiomyoma	8890/0
Granular cell tumour	9580/0

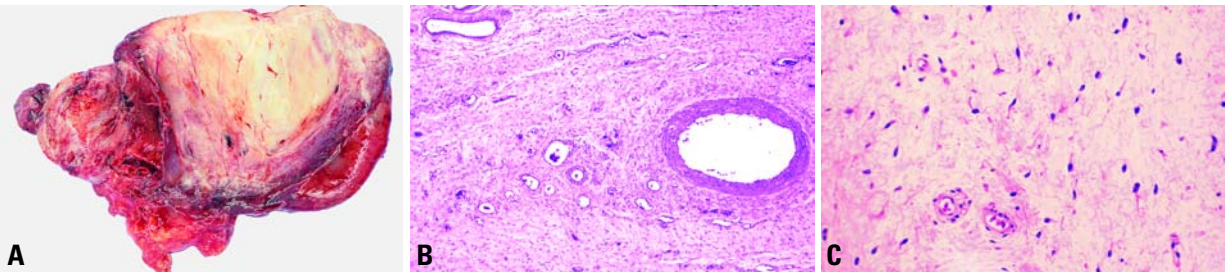

Fig. 7.17 Deep angiomyxoma. **A** The tumour forms a large bulging mass with a pale myxoid surface. **B** The neoplasm contains vessels of variable calibre, some of which are thick-walled. **C** The tumour is sparsely cellular and composed of uniform stellate cells set in a myxoid matrix.

Table 7.03
Differential diagnosis of myxoid soft tissue lesions of the vulva.

	Sarcoma botryoides	Deep angiomyxoma	Angiomyofibro-blastoma	Superficial angiomyxoma	Fibroepithelial polyp
Age at presentation	Pre-pubertal	Reproductive years	Reproductive years	Reproductive years	Reproductive years
Size, site and macroscopic configuration	Polypoid, exophytic or mass	Often larger than 5 cm, never exophytic	Subcutaneous, less than 5 cm	Small, dermal lobulated, superficial	Small, subepithelial, exophytic
Margins	Infiltrative	Infiltrative	Compressive		Poorly circumscribed
Cellularity and cells	Largely paucicellular with a variably pronounced cambium layer Spindle shaped cells including rhabdomyoblasts in the myxoid zones	Paucicellular Cytologically bland, stellate	More cellular than DA Perivascular concen-tration of cells is usual. Cytologically bland Plasmacytoid or epithelioid cells may be prominent.		Bland spindle cells in addition to enlar-ged, pleomorphic stromal cells with smudged chromatin
Vessels	Inconspicuous	Medium calibre, thick-walled vessels; pinwheel collagen	Smaller vessels than DA Perivascular concen-tration of stromal cells	Elongated thin-walled vessels	
Matrix		Paucicellular, myxoid			
Mitotic index	Usually easily found	Rare	Rare	Rare	Rare
Immunohistochemistry	Actin and desmin positive. Myogenin and myoD positive.	Actin, desmin and vimentin positive.	Strongly desmin positive. Minority of cells in occasional cases show positivity for either smooth muscle actin or panmuscle actin (HHF35). Negative for S-100 protein, keratin, fast myosin and myoglobin.	Desmin negative	Often desmin positive
Associated findings				Stromal neutrophils When multiple, consider Carney syndrome	Overlying epithelium may demonstrate intraepithelial neoplasia
Clinical course	Fully malignant neoplasm Alveolar histology adverse prognostic factor	Local recurrence common; never metastasizes	Does not recur Occasional lesions have hybrid features of DA and AMFB and should be treated as DA		Benign, no recurrences

Abbreviations: DA = Deep angiomyxoma; AMFB = Angiomyofibroblastoma

Deep angiomyxoma

Definition
A locally infiltrative tumour composed of fibroblasts, myofibroblasts and numerous, characteristically thick-walled, blood vessels embedded in an abundant myxoid matrix.

Synonym
Aggressive angiomyxoma.

Clinical features
Most patients present with a relatively large, often greater than 10 cm, slowly growing, painless mass in the pelviperineal region that may give rise to pressure effects on the adjacent urogenital or anorectal tracts. Imaging studies often show the mass to be substantially larger than clinically suspected.

Macroscopy
Macroscopically, the tumour is lobulated but poorly circumscribed due to finger-like extensions into the surrounding tissue. The neoplasm is grey-pink or tan and rubbery or gelatinous.

Tumour spread and staging
Deep angiomyxoma is a locally infiltrative but non-metastasizing neoplasm that occurs during the reproductive years {198,853,2779}.

Histopathology
The constituent cells of this paucicellular neoplasm are small, uniform, spindle-shaped to stellate with poorly defined, pale eosinophilic cytoplasm and bland, often vesicular nuclei. The abundant myxoid matrix contains a variable number of rounded medium-sized to large vessels that possess thickened focally hyalinized walls. Multinucleated cells may be present, and occasionally there is morphological overlap with angiomyo -fibroblastoma (see below). Actin and desmin stains are positive in almost all cases, whereas S-100 protein is consistently negative {1431,2082}.

Differential diagnosis
The differential diagnosis includes angiomyofibroblastoma, fibroepithelial polyp (so-called pseudosarcoma botryoides) and superficial angiomyxoma {1054,2063}.
Other less common lesions that may enter the differential diagnosis are:
(1) Myxoid neurofibroma, which has more buckled or wavy nuclei and whose cells are S-100 protein positive.
(2) Low grade myxofibrosarcoma, which has thin–walled curvilinear vessels, shows more nuclear atypia and is essentially always desmin negative.
(3) Myxoid liposarcoma, which contains delicate arborizing vessels and small lipoblasts.
(4) Cellular angiofibroma, which is well circumscribed.

Somatic genetics
A single case of vulvar deep angiomyxoma showed a loss of one X chromosome as the only cytogenetic aberration, a chromosomal change that is uncommon in this neoplasm {1438}.

Prognosis and predictive factors
The treatment for this locally aggressive but non-metastasizing proliferation is primarily surgical with close attention to margins. Approximately 30% of patients develop one or more local recurrences.

Superficial angiomyxoma

Definition
A multilobulated, dermal or subcutaneous lesion composed of fibroblasts and thin-walled vessels in a myxoid matrix that occurs in adults.

Clinical features
The tumour occurs as a subcutanous mass during the reproductive years.

Histopathology
Scattered multinucleated fibroblasts are often seen {389,854}. There is no cytological atypia or pleomorphism, but scattered mitoses may be found. The stroma generally contains an inconspicuous mixed inflammatory infiltrate that is notable for the presence of neutrophils despite the absence of ulceration or necrosis. Up to one-third contain an epithelial component, usually squamous epithelium.

Prognosis and predictive factors
Approximately one-third of the lesions recur locally in a non–destructive fashion, usually as a consequence of an incomplete or marginal excision. Less than 5% of cases recur repeatedly.

Angiomyofibroblastoma

Definition
A benign, non-recurring, well circumscribed, myofibroblastic lesion composed of spindle-shaped to round cells

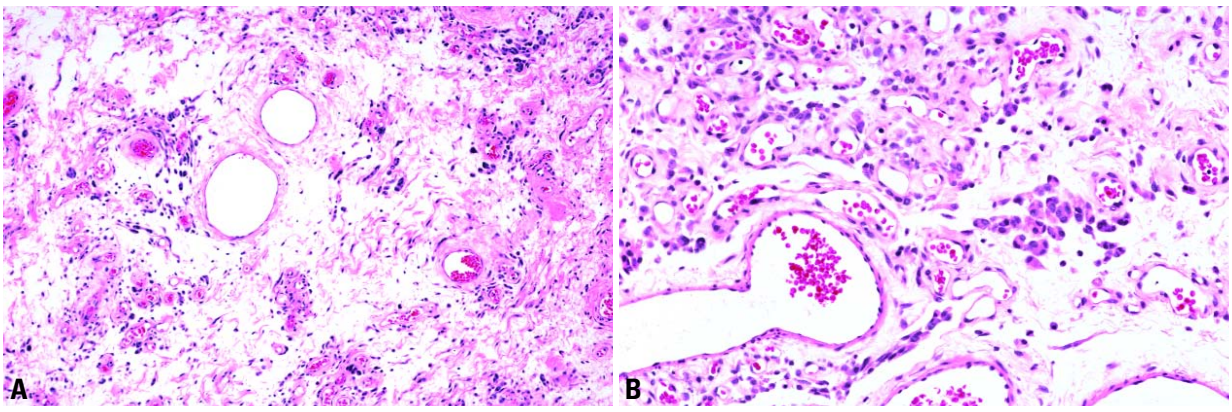

Fig. 7.18 Angiomyofibroblastoma. **A** Alternating hypercellular and hypocellular areas are associated with a prominent vascular pattern. **B** Binucleate and trinucleate tumour cells are common, and some cells have a plasmacytoid appearance.

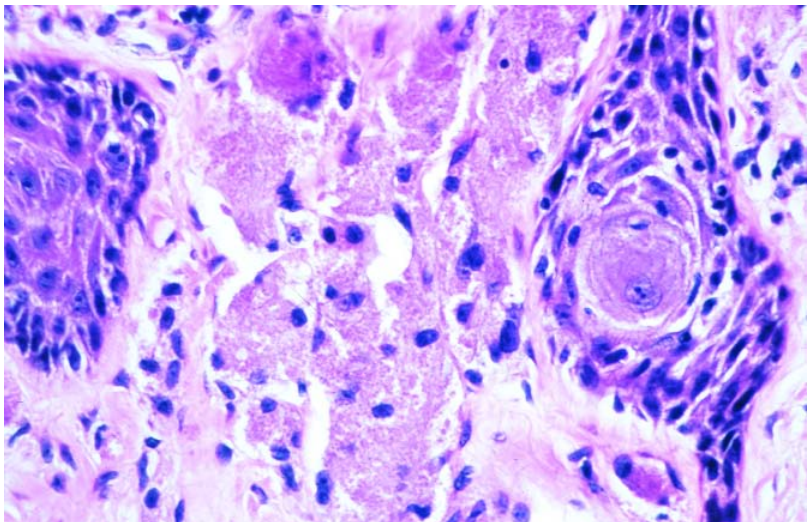

Fig. 7.19 Granular cell tumour of the vulva. The neoplasm is composed of cells with abundant granular cytoplasm and small uniform nuclei between pegs of proliferative squamous epithelium.

that tend to concentrate around vessels {890,1054,2019,2082}.

Clinical features
Angiomyofibroblastoma occurs in the reproductive years and usually presents as a slowly growing, painless, well circumscribed, subcutaneous mass measuring less than 5 cm in maximum diameter.

Macroscopy
Macroscopically, a narrow fibrous pseudocapsule delimits these tumours.

Histopathology
At low power angiomyofibroblastoma shows alternating hypercellular and hypocellular areas associated with a prominent vascular pattern throughout. Binucleate or multinucleate tumour cells are common, and some cells have denser, more hyaline cytoplasm, imparting a plasmacytoid appearance. Mitoses are very infrequent. The constituent cells are desmin positive. The major differential diagnostic considerations are deep angiomyxoma and fibroepithelial polyp.

Cellular angiofibroma

Definition
A recently described distinctive benign mesenchymal tumour composed of bland spindle-shaped cells admixed with numerous hyalinized blood vessels.

Clinical features
The tumour typically presents as a circumscribed solid rubbery vulvar mass in middle-aged women.

Histopathology
Cellular angiofibroma is usually a well circumscribed cellular lesion that is composed of bland spindle-shaped cells interspersed with medium to small blood vessels, which typically have thick hyalinized walls {597,1818,2063}. Mature adipocytes, especially around the periphery of the lesion, are a characteristic feature.
Cellular angiofibroma is vimentin-positive and desmin-negative, an immunoprofile that differentiates this tumour from deep angiomyxoma and angiomyofibroblastoma.

Prognosis and predictive factors
A local recurrence following excision has been described in a single case {1818}.

Leiomyoma
These benign neoplasms do not differ macroscopically or histologically from leiomyomas encountered elsewhere in the female genital tract and are treated by simple excision. Problematic smooth muscle neoplasms are those that are greater than 7.0 cm in greatest dimension, have infiltrative margins and a mitotic index in excess of 5 per 10 high power fields {2880} (see section on leiomyosarcoma).

Granular cell tumour

Definition
A tumour composed of cells with uniform central nuclei and abundant granular, slightly basophilic cytoplasm.

Histopathology
These have the same appearance as in other more common sites. A proliferation of cells with small uniform nuclei and abundant, granular, slightly basophilic cytoplasm diffusely involves the superficial connective tissue {2554}. The tumour cells are uniformly S-100 protein positive. Of particular importance in the vulva is the tendency for the overlying squamous epithelium to undergo pseudoepitheliomatous hyperplasia and simulate a well differentiated squamous carcinoma {3138}. Malignant varieties are rare and show high cellularity, nuclear pleomorphism, tumour cell necrosis and frequent mitotic figures {824}.

Other benign tumours and tumour-like conditions
Other benign tumours and tumour-like conditions that occur in the vulva include lipoma, haemangioma, angiokeratoma, pyogenic granuloma (lobular capillary haemangioma), lymphangioma, neurofibroma, schwannoma, glomus tumour, rhabdomyoma and post-operative spindle cell nodule {1762}. The histological features are similar to their appearance in more common sites.

Melanocytic tumours

E.J. Wilkinson
M.R. Teixeira

Malignant melanomas account for 2-10% of vulvar malignancies {2316} and occur predominantly in elderly White women. A variety of naevi that must be distinguished from melanoma also occur in the vulva.

ICD-O codes

Malignant melanoma	8720/3
Congenital melanocytic naevus	8761/0
Acquired melanocytic naevus	8720/0
Blue naevus	8780/0
Atypical melanocytic naevus of the genital type	8720/0
Dysplastic melanocytic naevus	8727/0

Malignant melanoma

Definition

A malignant tumour of melanocytic origin.

Clinical features

Signs and symptoms

Symptoms include vulvar bleeding, pruritus and dysuria. Although vulvar malignant melanoma usually presents as a pigmented mass, 27% are non-pigmented {2320}. Satellite cutaneous nodules occur in 20% of cases {2320}. Melanoma may arise in a prior benign or atypical appearing melanocytic lesion. {1912, 3151}. The majority present as a nodule or polypoid mass. Approximately 5% are ulcerated {2320}. They occur with nearly equal frequency in the labia majora, labia minora or clitoris.

Imaging

Radiological, magnetic resonance imaging and/or radiolabelled isotope scan studies may be used to assess tumour that is present outside the vulva.

Histopathology

Three histological types of melanoma are identified: superficial spreading, nodular and mucosal/acral lentiginous {216, 1355,2261,2864}. Approximately 25% of the cases are unclassifiable {2320}. Melanomas may be composed of epithelioid, spindle, dendritic, nevoid or mixed cell types. The epithelioid cells contain abundant eosinophilic cytoplasm, large nuclei and prominent nucleoli. The dendritic cells have tapering cytoplasmic extensions resembling nerve cells and show moderate nuclear pleomorphism. Spindle-shaped cells have smaller, oval nuclei and may be arranged in sheets or bundles. Certain cell types may predominate within a given tumour. The amount of melanin within the tumour cells is highly variable, and cells may contain no melanin.

Both mucosal/acral lentiginous and superficial spreading melanomas can be entirely intraepithelial. When invasive, both histological types have vertical and radial growth phases, the vertical growth component representing the invasive focus of tumour. Nodular melanomas display predominately a vertical growth phase. Atypical melanocytes characteristic of melanoma in situ usually can be identified within the epithelium adjacent to mucosal/acral lentiginous and superficial spreading melanomas.

Superficial spreading melanomas have malignant melanocytic cells within the area of invasion that are typically large with relatively uniform nuclei and prominent nucleoli, similar to the adjacent intraepithelial melanoma. The intraepithelial component is considered to be the radial growth portion of the tumour.

Nodular melanomas may have a small neoplastic intraepithelial component adjacent to the invasive tumour and are generally not considered to have a significant radial growth phase. The cells of nodular melanomas may be epithelioid or spindle-shaped. These tumours are typically deeply invasive.

Mucosal/acral lentiginous melanomas are most common within the vulvar vestibule, including the clitoris. They are characterized by spindle-shaped neoplastic melanocytes within the junctional zone involving the adjacent superficial stroma in a diffuse pattern. The spindle-shaped cells are relatively uniform, lacking significant nuclear pleomorphism. Within the stroma the tumour is usually associated with a desmoplastic response.

There is some variation in the reported frequency of melanoma types involving the vulva; however, in a large series of 198 cases mucosal/acral lentiginous melanoma comprised 52% of the cases, nodular melanoma 20% and superficial

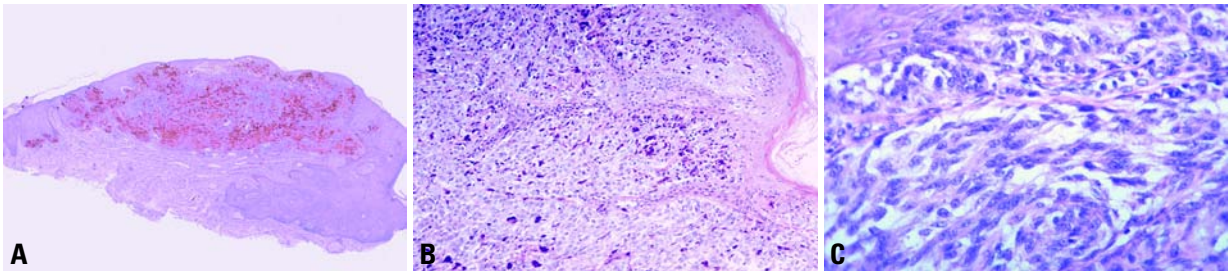

Fig. 7.20 Malignant melanoma of the vulva. **A** Low power micrograph of a heavily pigmented melanoma. **B** The neoplastic cells involve the epithelium and the junctional areas as well as the adjacent dermis. Note the large, pleomorphic nuclei with prominent nucleoli. Some cells contain melanin. **C** This neoplasm is composed of spindle-shaped cells with elongated nuclei resembling a spindle cell sarcoma.

Table 7.04
Clark levels of cutaneous melanoma {3120}.

Level I	Melanoma in situ
Level II	Superficial papillary dermis
Level III	Fills and expands papillary dermis
Level IV	Reticular dermis
Level V	Deeper than reticular dermis into fat or other deeper tissue

spreading melanoma 4%, with the remainder of the cases being unclassifiable {2320,3120}.

Immunoprofile
Melanomas usually are immunoreactive for S-100 protein, HMB-45 and Melan A {3119}. Unlike some tumours of epithelial origin, including Paget disease, they are not immunoreactive for AE1/3, cytokeratins 7 and 20, epithelial membrane antigen, carcinoembryonic antigen or gross cystic disease fluid protein-15 {3120}.

Somatic genetics
The only two malignant melanomas of the vulva so far karyotyped showed trisomy 20 and del(18)(p11), respectively {2897}.

Prognosis and predictive factors
Clinical criteria
Treatment for a vulvar melanoma with a thickness of 0.75 mm or less is usually a wide local excision with a 1-cm circumferential margin and a 1-2 cm deep margin. Melanomas with a thickness of 1-4 mm require a 2 cm circumferential margin and a deep margin of at least 1-2 cm {2949}. Melanomas with a thickness greater than 4 mm are usually treated by radical vulvectomy {2950}. Depending on the tumour size, bilateral inguinofemoral lymphadenectomy may also be performed {1912,2261,2864, 3151}.

Histopathological criteria
Clark levels and Breslow thickness measurements are used to assess cutaneous vulvar melanomas.
Breslow thickness measurements for cutaneous malignant melanoma require measurement from the deep border of the granular layer of the overlying epithelium to the deepest point of tumour invasion. If a melanoma is less than 0.76 mm in thickness, it has little or no metastatic potential {1694,3120}.
Survival following a diagnosis of vulvar melanoma is adversely influenced by numerous factors including a tumour thickness exceeding 2 mm, a tumour interpreted as Clark level IV or greater, a mitotic count within the tumour exceeding 10 mitoses per square mm, surface ulceration of the tumour and advanced tumour stage {3120}.

Congenital melanocytic naevus

The congenital melanocytic naevus is a benign tumour of melanocytes that is present at birth. Tumours may be small or involve a large area.

Acquired melanocytic naevus

The acquired melanocytic naevus appears in childhood and continues to grow with increasing age. This lesion may be junctional, i.e. at the epidermal-dermal junction, intradermal or compound (junctional and intradermal).

Blue naevus
The blue naevus is located entirely within the dermis and is composed of spindle-shaped or dendritic melanocytes that are typically heavily pigmented. A subtype known as the cellular blue naevus has a low potential for metastasis.

Atypical melanocytic naevus of the genital type

Definition
One type of atypical melanocytic proliferation in the genital area that forms a distinctive clinicopathological entity that can be distinguished from melanoma and dysplastic naevus.

Synonym
Atypical vulvar naevus.

Clinical features
The atypical melanocytic naevus of the genital type occurs primarily in young women of reproductive age. Unlike the dysplastic naevus, it is not associated with dysplastic naevi in other sites.
Vulvar naevi can be influenced by hormonal changes and may appear more active or atypical during pregnancy.

Histopathology
The atypical melanocytic naevus of the genital type has junctional melanocytic nests that are variably sized and include some atypical superficial melanocytes, These lesions lack significant atypia or mitotic activity in the deeper dermal melanocytes and do not involve skin appendages. In addition the lesion is small, well circumscribed and lacks pagetoid spread or necrosis {31,498}.

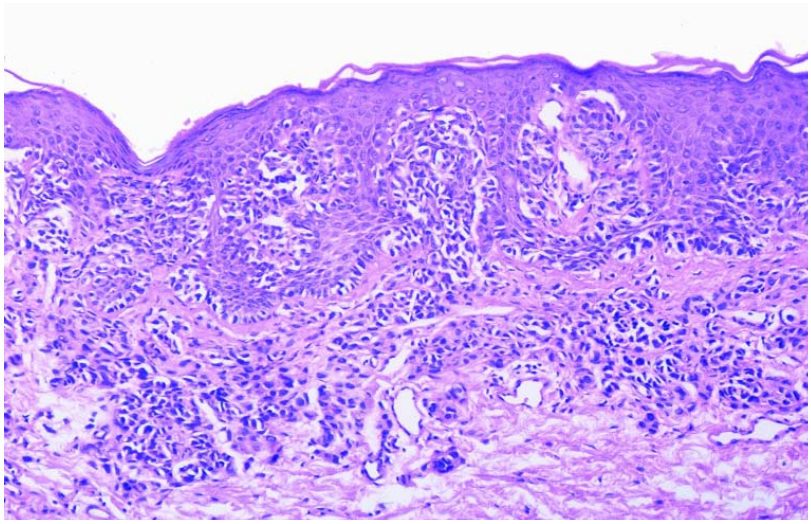

Fig. 7.21 Atypical melanocytic naevus of the genital type. The tumour is a compound naevus with variably sized melanocytic nests and atypia confined to the superficial melanocytes..

Dysplastic melanocytic naevus

Definition
A naevus that exhibits slight to moderate nuclear atypia that occurs only in the cells in the superficial portion.

Clinical features
These naevi occur predominantly in young women of reproductive age and present as elevated pigmented lesions with irregular borders typically exceeding 0.5 cm in diameter. Dysplastic naevi are rare on the vulva and may be associated with similar naevi elsewhere on the trunk and extremities.

Histopathology
They are composed of large epithelioid or spindle-shaped naevus cells with nuclear pleomorphism and prominent nucleoli. The atypical naevus cells are clustered in irregularly spaced junctional nests and involve hair shafts and the ducts of sweat glands and other skin appendages {31,498}. The dysplastic naevus may be compound or junctional. Features that distinguish a dysplastic naevus from malignant melanoma include symmetrical growth evident on full cross-section and the predominance of atypical cells in the superficial cellular component of the naevus. Limited pagetoid spread of single melanocytes with minimal or no involvement of the upper one-third of the epithelium may also be seen {31,498,2362}.

Genetic susceptibility
These vulvar naevi may occur in patients with the dysplastic naevus syndrome.

Germ cell, neuroectodermal, lymphoid and secondary tumours

E.J. Wilkinson

Definition
Primary tumours of the vulva that are not epithelial, mesenchymal or melanocytic in type, as well as secondary tumours.

ICD-O codes

Yolk sac tumour	9071/3
Merkel cell tumour	8247/3
Peripheral primitive neuroectodermal tumour/ Ewing tumour	9364/3 9260/3

Yolk sac tumour

Definition
A primitive malignant germ cell tumour characterized by a variety of distinctive histological patterns, some of which recapitulate phases in the development of the normal yolk sac.

Synonym
Endodermal sinus tumour.

Epidemiology
Yolk sac tumour is rare in the vulva and has been reported primarily in children and young women {888}.

Histopathology
For the histological features see the chapter on the ovary.

Prognosis and predictive factors
Vulvar yolk sac tumour is treated by local wide excision and chemotherapy, which is usually platinum-based {888}.

Merkel cell tumour

Definition
A malignant tumour composed of small neuroendocrine type cells of the lower epidermis.

Synonym
Neuroendocrine carcinoma of the skin.

Epidemiology
Merkel cell tumours are rare in the vulva and aggressive {324,554,996}.

Histopathology
The neoplastic cells have scanty cytoplasm and nuclei with finely stippled chromatin. Glandular and squamous differentiation has been reported {2607}.

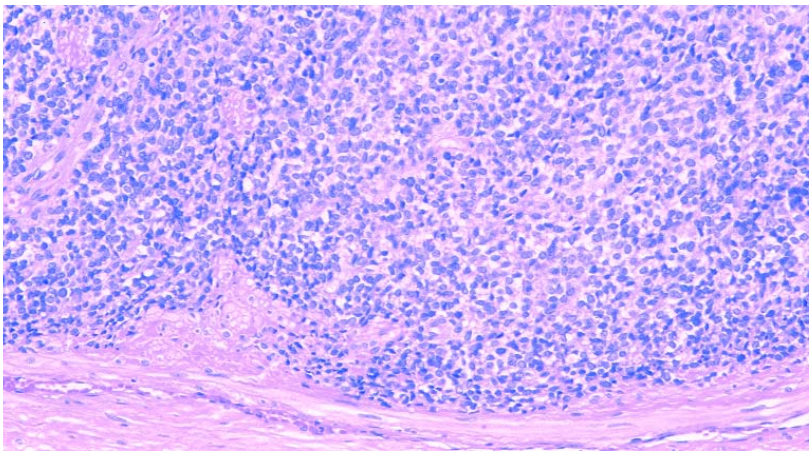

Fig. 7.22 A highly cellular peripheral primitive neuroectodermal tumour of vulva in an 18 year old.

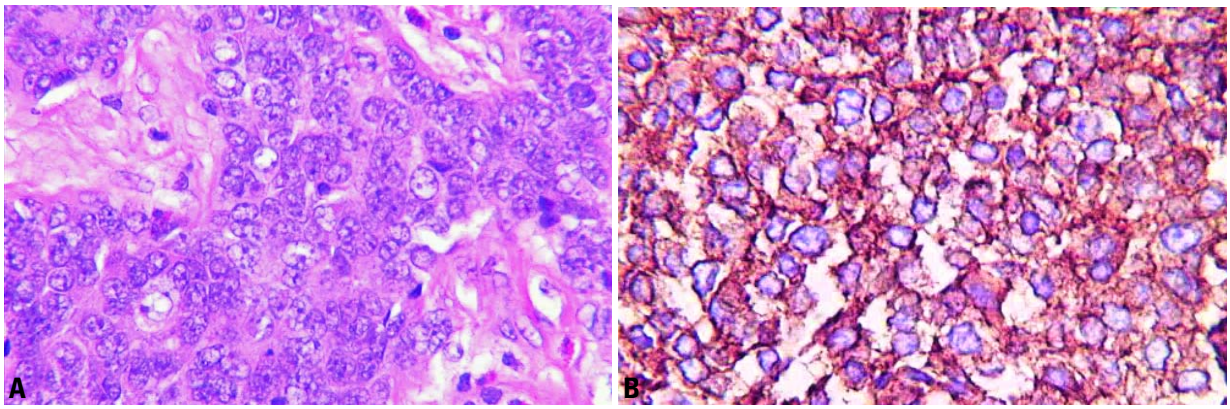

Fig. 7.23 Vulvar peripheral primitive neuroectodermal tumour. **A** The neoplasm is composed of relatively small, somewhat irregularly shaped cells with minimal cytoplasm. The nuclei are pleomorphic with granular chromatin and occasional small nucleoli. **B** Intense immunoreactivity for MIC 2 (CD99) is evident.

Immunohistochemical stains for cytokeratin demonstrate a distinctive perinuclear globular cytoplasmic pattern, and markers of neuroendocrine differentiation are usually positive {1209}. Electron microscopic examination demonstrates intermediate filaments in a globular paranuclear arrangement and dense core granules {554,996,1209}.

Histogenesis

These neoplasms are derived from small, neuroendocrine cells of the lower epidermis.

Peripheral primitive neuroectodermal tumour / Ewing tumour

Definition

An embryonal tumour arising outside of the central nervous system composed of undifferentiated or poorly differentiated neuroepithelial cells.

Clinical features

This is a rare primary tumour of the vulva that has been in reported in children and adult women of reproductive age {2839, 3002} and presents as a subcutaneous mass.

Histopathology

It is circumscribed but not encapsulated and composed of relatively small cells with minimal cytoplasm and ill defined cell borders. The nuclei are hyperchromatic with finely granular chromatin. Small nucleoli are evident. The mitotic count is variable, with an average of 3 per 10 high power fields reported {3002}. The tumour is usually multilobulated but is variable in appearance with solid areas, sinusoidal-appearing areas with cystic spaces containing eosinophilic proteineaceous material and Homer Wright rosettes {2839,3002}.

The tumour cells are immunoreactive for CD99 and vimentin and may be reactive for synaptophysin. Pan-cytokeratin may be focally positive in some cases. Dense core neurosecretory granules are not identified by electron microscopy.

Somatic genetics

A vulvar peripheral primitive neuroectodermal tumour/Ewing tumour has been shown to express the *EWS/FLI1* chimeric transcript due to the chromosome translocation t(11;22)(q24;q12), which is pathognomonic for this tumour type and is present in approximately 90% of tumours of this type {3002}.

Malignant lymphoma

Definition

A malignant lymphoproliferative neoplasm that may be primary or secondary.

Clinical features

This is a rare neoplasm that presents as a vulvar mass {1279,2266,3002}.

Histopathology

In the largest series two-thirds of the cases were diffuse large B-cell lymphomas {3002}.

Prognosis and predictive factors

Malignant lymphoma of the vulva is usually an aggressive disease {3002}.

Leukaemia

Definition

A malignant haematopoetic neoplasm that may be primary or secondary.

Clinical features

Rarely, granulocytic sarcoma presents as a vulvar mass {1583}

Histopathology

See chapters on the cervix and vagina.

Secondary tumours of the vulva

Definition

Tumours of the vulva that originate outside the vulva.

Incidence and origin

The vulva is a rare site of secondary involvement by tumour. Tumours may involve the vulva by lymphatic spread or contiguous growth. The primary site of a secondary tumour of the vulva is most commonly the cervix, followed by the endometrium or ovary. Occasionally, breast carcinoma, renal cell carcinoma, gastric carcinoma, lung carcinoma, and, rarely, gestational choriocarcinoma, malignant melanoma or neuroblastoma spread to the vulva. Vaginal, urethral, urinary bladder and anorectal carcinomas may extend directly into the vulva {1631, 1802,3121}.