Penis and Scrotum Pathology

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Frequently Asked Questions and Answers

What Is the World Health Organization (WHO) 2016 Classification of Squamous Cell Carcinoma of Penis?

The vast majority of malignant tumors of the penis are squamous cell carcinomas (SCCs) originating in the inner mucosal lining of the glans, coronal sulcus, or foreskin. Less than 50% of the subtypes of SCCs are of the conventional type, and the majority belongs to special categories. Compared to previous exclusively morphology-based classification schemes, the 2016 WHO classification presents a new classification based on clinicopathologic properties and relation to human papillomavirus (HPV) infection (Table 7.1). The mixed category is introduced in the new classification for tumors with more than one histological pattern. The new classification also clarifies the relationships between some neoplasms. Some entities that were originally described as specific tumor types have been shown to be morphological variants. For example, carcinoma cuniculatum is a variant of verrucous carcinoma; pseudoglandular and pseudohyperplastic carcinomas are variants of usual SCC; warty-basaloid carcinoma, clear cell carcinoma, and the papillary variant of basaloid carcinoma are variants of warty carcinoma.

Table 7.1 2016 WHO classification of squamous cell carcinoma of the penis

Non-HPV-related penile SCCs	HPV-related penile SCCs	Others
SCC - Usual carcinoma - Pseudohyperplastic carcinoma - Pseudoglandular carcinoma Verrucous carcinoma - Pure verrucous carcinoma - Carcinoma cuniculatum Papillary carcinoma, NOS Adenosquamous carcinoma Sarcomatoid squamous cell carcinoma Mixed carcinoma	Basaloid carcinoma - Papillary-basaloid carcinoma Warty carcinoma - Warty-basaloid carcinoma - Clear cell carcinoma Lymphoepithelioma-like carcinoma	Unclassified carcinoma

Non-HPV-Related Squamous Cell Carcinomas

Non-HPV-related subtypes of SCC include SCC of the usual type, pseudohyperplastic carcinoma, pseudoglandular carcinoma, verrucous carcinoma and carcinoma cuniculatum and variant types of SCC (papillary, adenosquamous, and sarcomatoid SCC) (Table 7.1).

Pseudohyperplastic carcinoma occurs in older patients (typically 70–80 years old) and is associated with lichen sclerosus. Pseudoglandular carcinoma is an aggressive tumor simulating adenocarcinoma. Verrucous carcinoma is a nonmetastasizing low-grade neoplasm with carcinoma cuniculatum as a variant. Carcinoma cuniculatum is a rare low-grade tumor with a labyrinthine growth pattern with no metastatic potential. Among all penile carcinomas, sarcomatoid SCC is the most aggressive, and is associated with the worst prognosis.

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HPV-Related Squamous Cell Carcinomas

HPV-related carcinomas are basaloid and warty (condylomatous) SCC, and rare variants, including warty-basaloid, papillary-basaloid, and clear cell carcinoma. Very unusual HPV-related tumors are lymphoepithelioma-like and medullary SCC (Table 7.1). Basaloid SCC has a high rate of nodal metastasis, whereas warty (condylomatous) carcinoma is rarely associated with regional nodal metastasis.

Precursor Lesions

Penile intraepithelial neoplasia (PeIN) is a precursor lesion of invasive SCC. It is a penile squamous epithelial proliferation characterized by dysplastic changes and an intact basement membrane.

Differentiated PeIN is non-HPV-related. It is characterized by parakeratosis and elongation of rete ridges. Lesional cells are enlarged, with abundant eosinophilic cytoplasm, and are located predominantly in the basal layers. Differentiated PeIN is commonly associated with lichen sclerosus.

Basaloid and warty (*or mixed basaloid-warty*) *PeINs* are usually associated with HPV infection. They are typically composed of atypical small basaloid cells involving full epithelial thickness and exhibiting strong p16 immunostaining.

References: [1–4]

What Are the Microscopic Features of HPV-Related Penile Carcinomas?

HPV is frequently found in tumors with predominant basaloid cells and also in those with predominantly koilocytic cells. There is high prevalence of HPV positivity in high-grade penile carcinomas, in lesions dominated by small tumor cells, in tumors with a high number of multinucleated cells and mitoses, and in tumors with small amounts of parakeratosis.

Reference: [3]

What Is the Relationship between HPV and Histologic Subtypes of Penile Carcinoma?

HPV is frequently found in

- Basaloid and warty carcinomas and their mixtures
- Lymphoepithelioma-like
- Clear cell carcinomas
- PeIN with similar basaloid or warty morphology is frequently identified in tissues adjacent to HPV-related invasive neoplasms.

HPV is usually negative in

- Usual SCC
- Pseudoglandular carcinoma
- Sarcomatoid carcinoma
- Pseudohyperplastic carcinomas

These tumors are frequently associated with differentiated PeIN and lichen sclerosus.

What Are the Types of Non-HPV-Related Variants of Penile Carcinomas?

Squamous Cell Carcinoma, Usual Type

- Invasive SCC with a varying degree of differentiation and keratinization that cannot be classified as other histologic subtypes morphologically, also termed SCC, not otherwise specified (NOS).
- Most common histological subtype of penile SCC (60–65%).
- It is subdivided into well differentiated (Fig. 7.1a–c), moderately differentiated (Fig. 7.2a–c), and poorly differentiated (Fig. 7.3a–c) based on nuclear pleomorphism and variable amounts of keratin production.
- Tumors are usually well-differentiated or moderately differentiated SCC similar to other sites.
- Keratinization is evident in most cases.
- Squamous hyperplasia and differentiated penile intraepithelial neoplasia (PeIN) are commonly found in adjacent mucosa in the great majority of cases.
- Lichen sclerosus is present in almost 1/2 of patients.
- Tumor invasion into penile erectile tissues and multiple compartments including corpora and urethra is frequently noted.
- Assessment of depth of invasion, perineural and vascular invasion, involvement of the corpora, glans, and multifocality should be addressed in all reports.
- Usually negative for HPV by in situ hybridization and p16 by immunostain.
- Most important prognostic factors: histologic grade, anatomical level of infiltration, vascular invasion, and perineural invasion.
- Inguinal nodal metastases occur in 1/3 of patients.

Verrucous Carcinoma

- A subtype of extremely well-differentiated SCC with hyperkeratosis and acanthosis, broad papillary fronds and pushing base.
- Accounts for 3–8% of penile carcinomas.
- Usually involves the glans or foreskin, and presents as slow growing exophytic cauliflower-like gray-white mass (Fig. 7.4a).
- Extremely well differentiated, composed of acanthotic papillae with slender fibrovascular cores, with prominent keratin craters identified between papillae (Fig. 7.4b).
- Tumor is usually confined to lamina propria, with broad and pushing base (Fig. 7.4b).

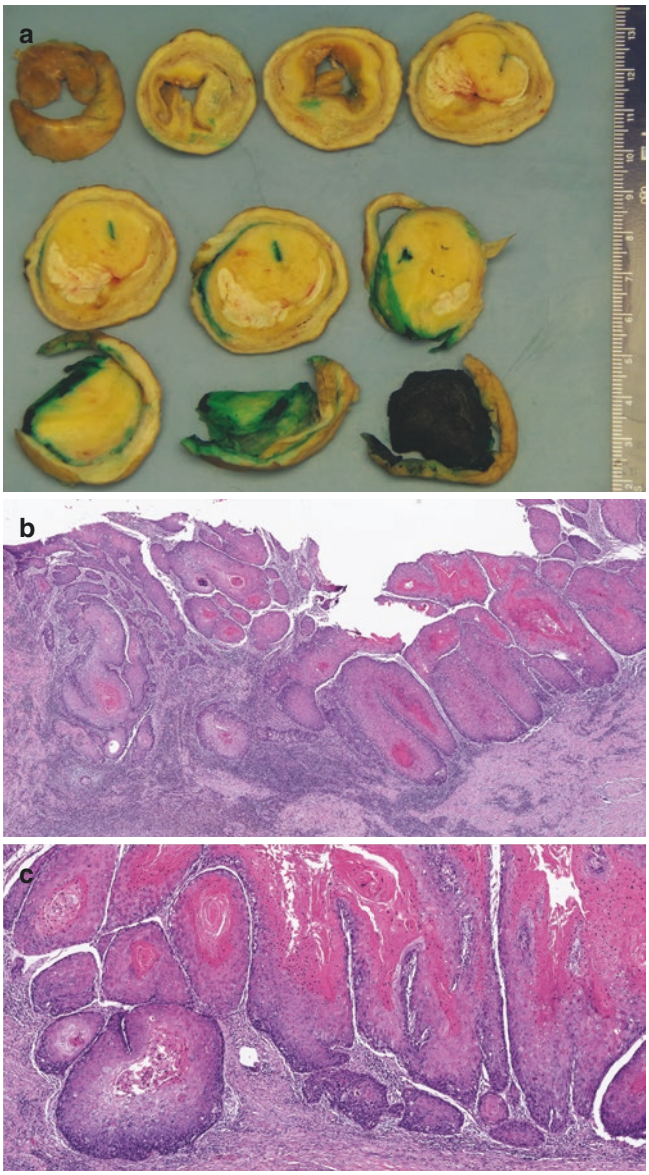

Fig. 7.1 Well-differentiated squamous cell carcinoma. (**a**) Cut surface shows a well-demarcated, pearly-white appearance. (**b**) Multiple invading tumor nests composed of well-differentiated squamous cells (**c**)

- Koilocytosis, higher-grade areas, necrosis, or infiltrative borders are absent.
- Locally aggressive but biologically indolent. No metastases reported with pure verrucous carcinoma.
- Standard recommended treatment is complete local excision with clear margins, or partial or total penectomy.
- Treatment with radiation must be avoided, as transformation to a frankly invasive squamous cell carcinoma can occur, which will have metastatic potential.

Carcinoma Cuniculatum

- Rare variant of verrucous carcinoma characterized by a deeply burrowing growth pattern mimicking rabbit burrows (cuniculi) (Fig. 7.5a).

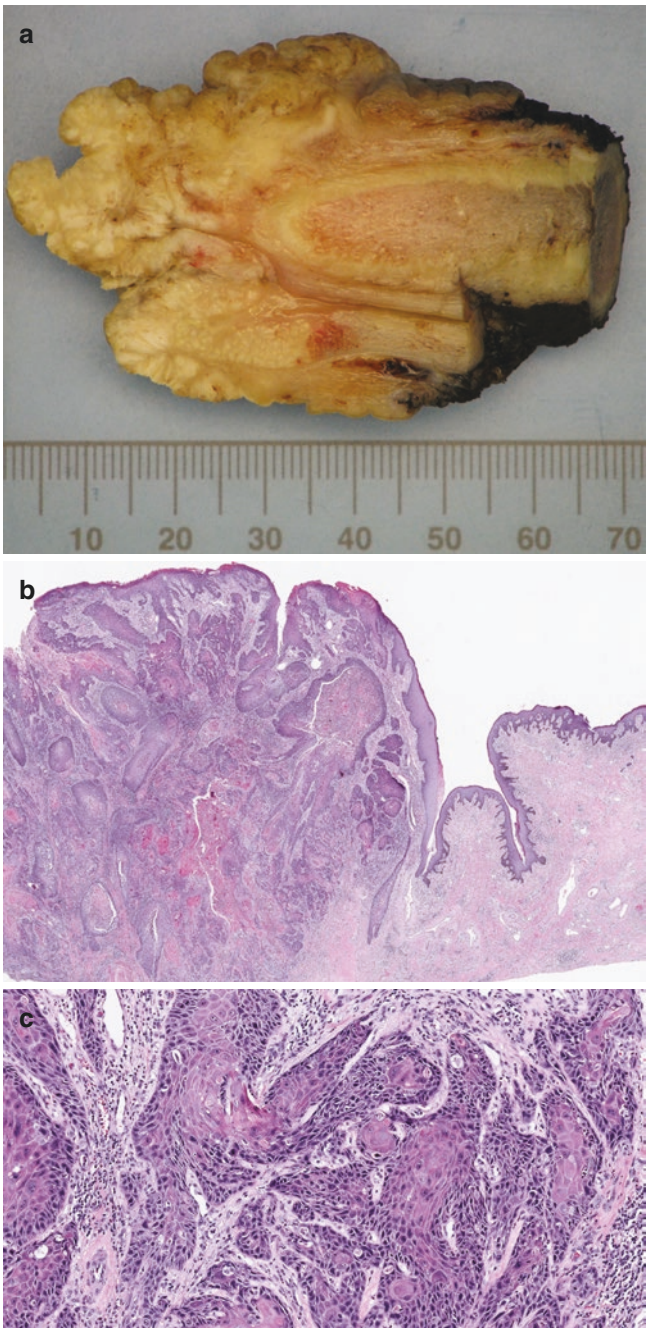

Fig. 7.2 Moderately differentiated squamous cell carcinoma. (**a**) The tumor exhibits infiltrating whitish-gray cut surface with an irregular tumor front. (**b**) Irregular nests of tumor cells with keratinization and nuclear atypia (**c**)

- Large exoendophytic tumor with cobblestone appearance.
- Deep endophytic and interanastomosing pattern of sinus tracts mimicking rabbit burrows (Fig. 7.5b).
- Most cases show hybrid (mixed) verrucous carcinoma with peculiar deep growth pattern.
- Extremely well differentiated (verrucous carcinoma) (Fig. 7.5c).
- Acanthotic papillae separated by abundant keratin.

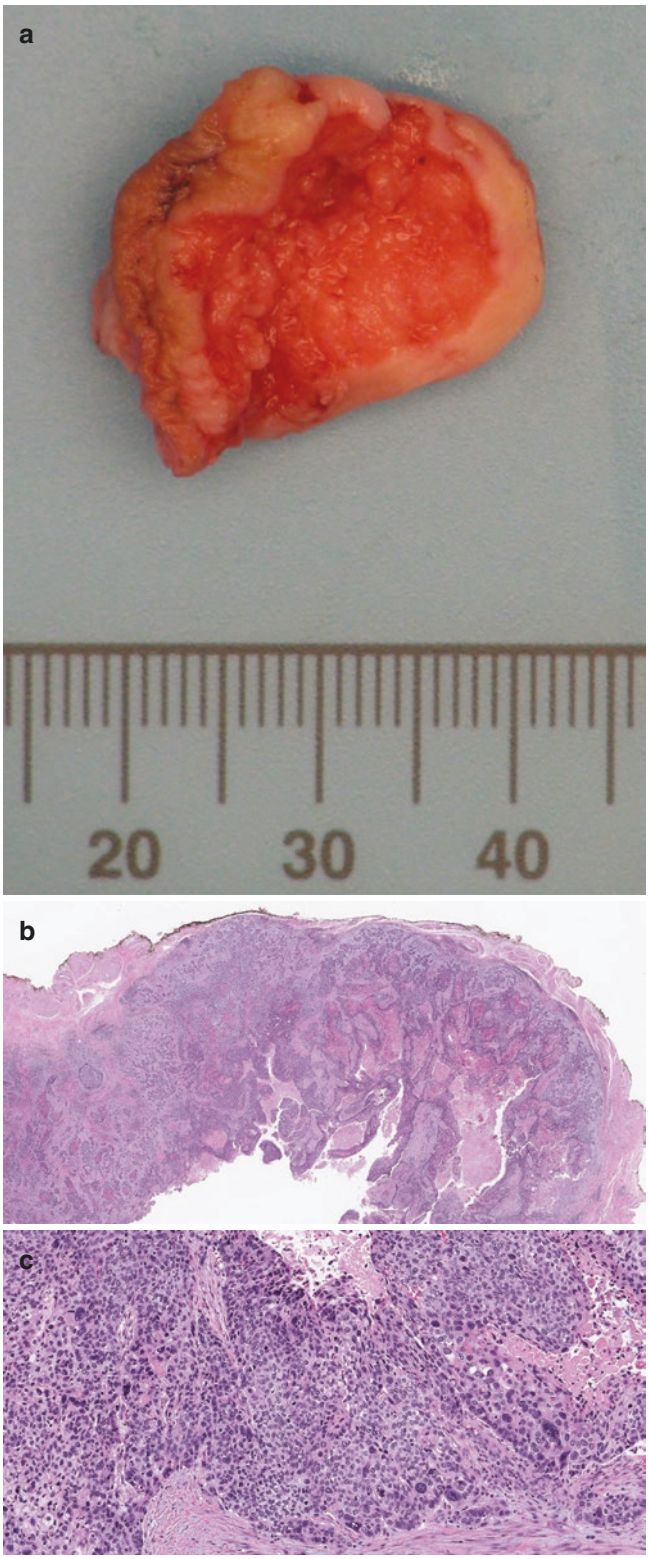

Fig. 7.3 Poorly differentiated squamous cell carcinoma. (**a**) An endophytic tumor displays tan firm cut surface with infiltrating border. (**b**) Invasive tumor composed of angulated tumor nests. (**c**) Tumor cells show poor keratinization, hyperchromatic nuclei, marked nuclear pleomorphism, and stromal reaction

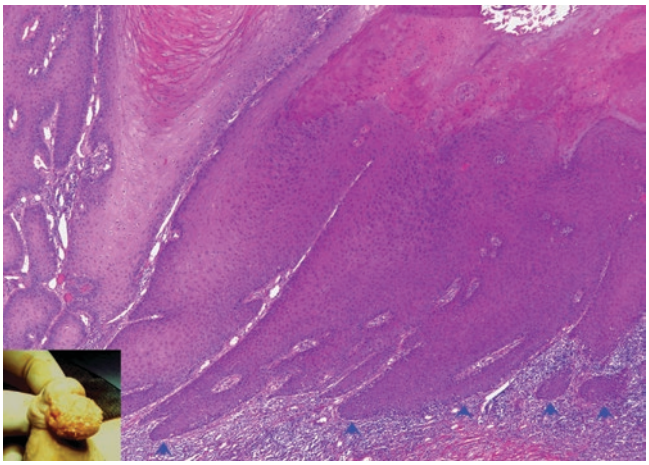

Fig. 7.4 Verrucous carcinoma. An exophytic cauliflower-like gray-white mass involving glans, coronal sulcus, and foreskin (as shown in inset). Well-defined broad-based pushing border (arrow heads) with prominent inflammatory cells present at the tumor margin. Tumor cells are well differentiated with minimal basal cell atypia

- Interanastomotic channels contain abundant keratin (Fig. 7.5b).
- Sinus tracts are commonly seen.
- Broad based pushing border.
- Focal higher-grade areas and infiltrative pattern are common.
- Lack of koilocytosis.

Papillary Carcinoma, NOS

- A variant of SCC
- A papillomatous, verruciform low-grade keratinizing neoplasm without koilocytosis
- Accounts for 5–8% of penile SCC
- Associated with lichen sclerosis, not associated with HPV infection
- Presents as a slow-growing, bulky, cauliflower-like, whitish-gray mass, most commonly involving the glans
- Irregular, complex, exophytic papillary growth (Fig. 7.6a)
- Well-to-moderately differentiated with prominent keratinization (Fig. 7.6b)
- No koilocytosis
- Less aggressive than usual penile SCC
- Standard recommended treatment is wide local excision or partial penectomy

Pseudoglandular Carcinoma

- High-grade carcinoma with prominent acantholysis and pseudoglandular features.
- Accounts for 1–2% of penile SCC.
- Unicentric large destructive, ulcerated and deeply invasive carcinoma.

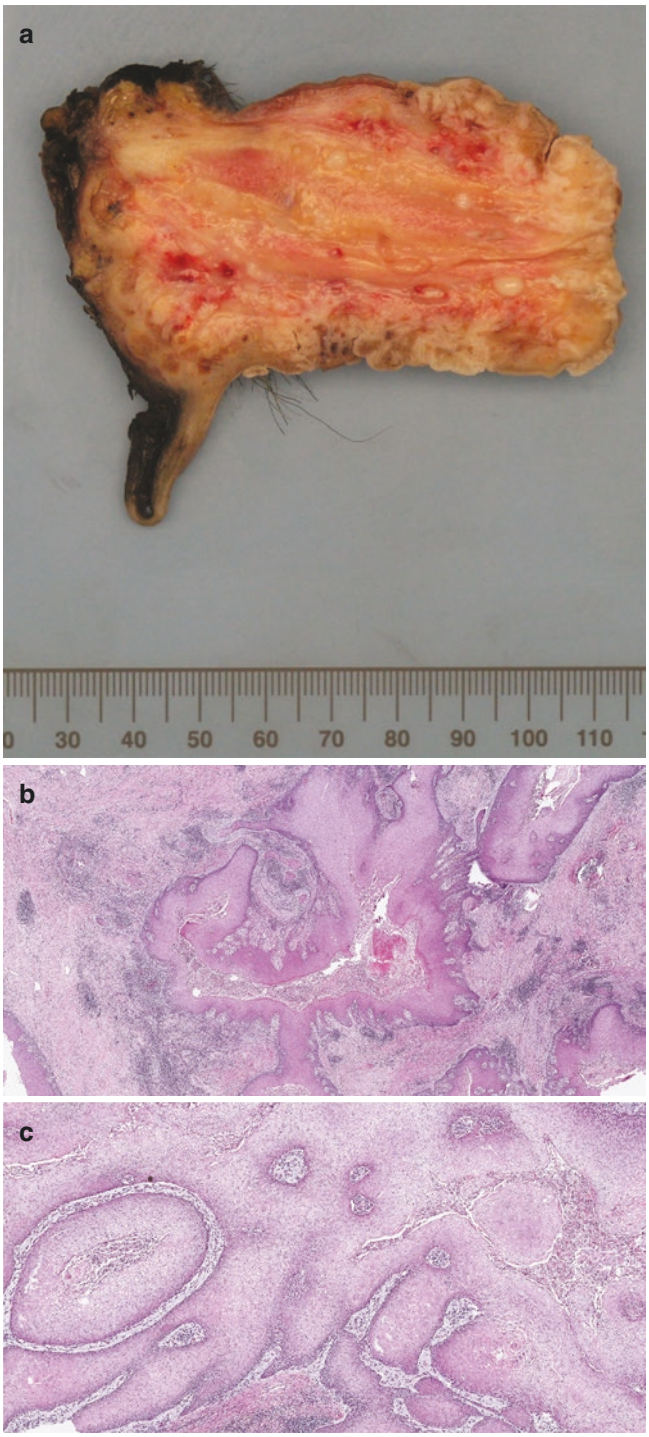

Fig. 7.5 Carcinoma cuniculatum. (**a**) A deeply burrowing growth pattern mimicking rabbit burrows. (**b**) Deep endophytic and interanastomosing pattern of sinus tracts containing abundant keratin. (**c**) Tumor cells are extremely well differentiated with minimal cytologic atypia

- Honeycomb or multicystic appearance at low magnification.
- Pseudoglandular features are noted in 30–85% of specimens.

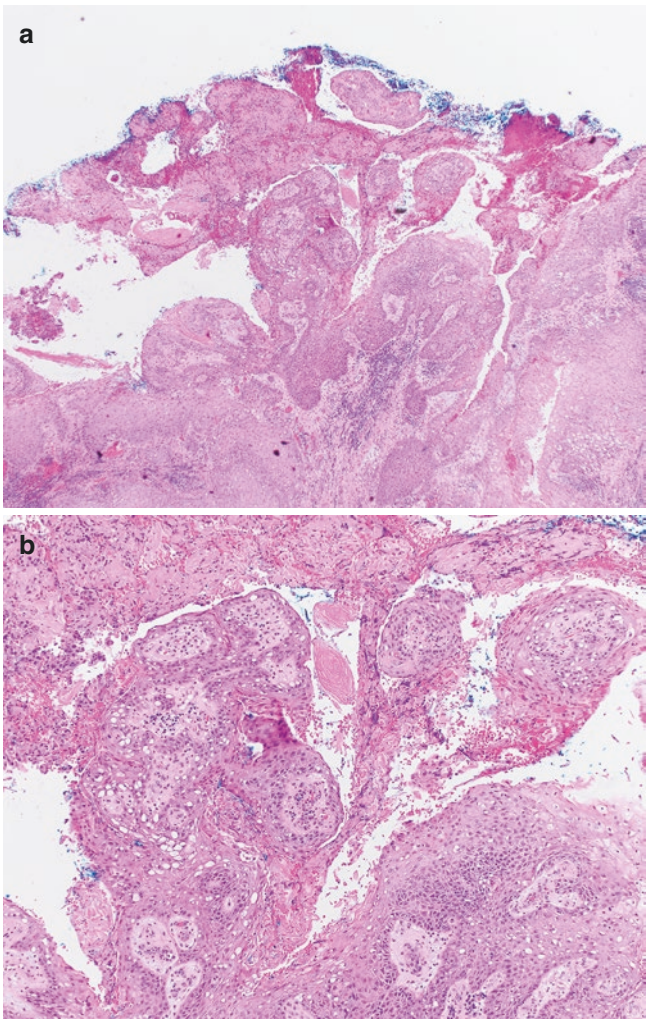

Fig. 7.6 Papillary carcinoma. (**a**) Low-power view reveals a complex papillary growth pattern with hyperkeratosis. Irregular fibrovascular cores are evident. (**b**) Papillae are lined by maturing keratinocytes with minimal to moderate nuclear atypia

- Open spaces are surrounded by high-grade cylindrical to flat squamous cells.
- Cellular debris, microabscesses, keratin, or acantholytic cells fill central pseudoglandular spaces (comedocarcinoma-like pattern).
- Deeply invasive carcinoma; most cases invade into the corpora cavernosa.
- Local recurrence and regional metastasis have been reported.
- Mortality rate is ~40%, higher than usual SCC.

Sarcomatoid Squamous Cell Carcinoma

- Squamous cell carcinoma with a malignant spindle cell or sarcomatoid component.
- ~4% of penile SCCs.
- White-gray, mixed exophytic and endophytic mass on the glans penis (Fig. 7.7a).

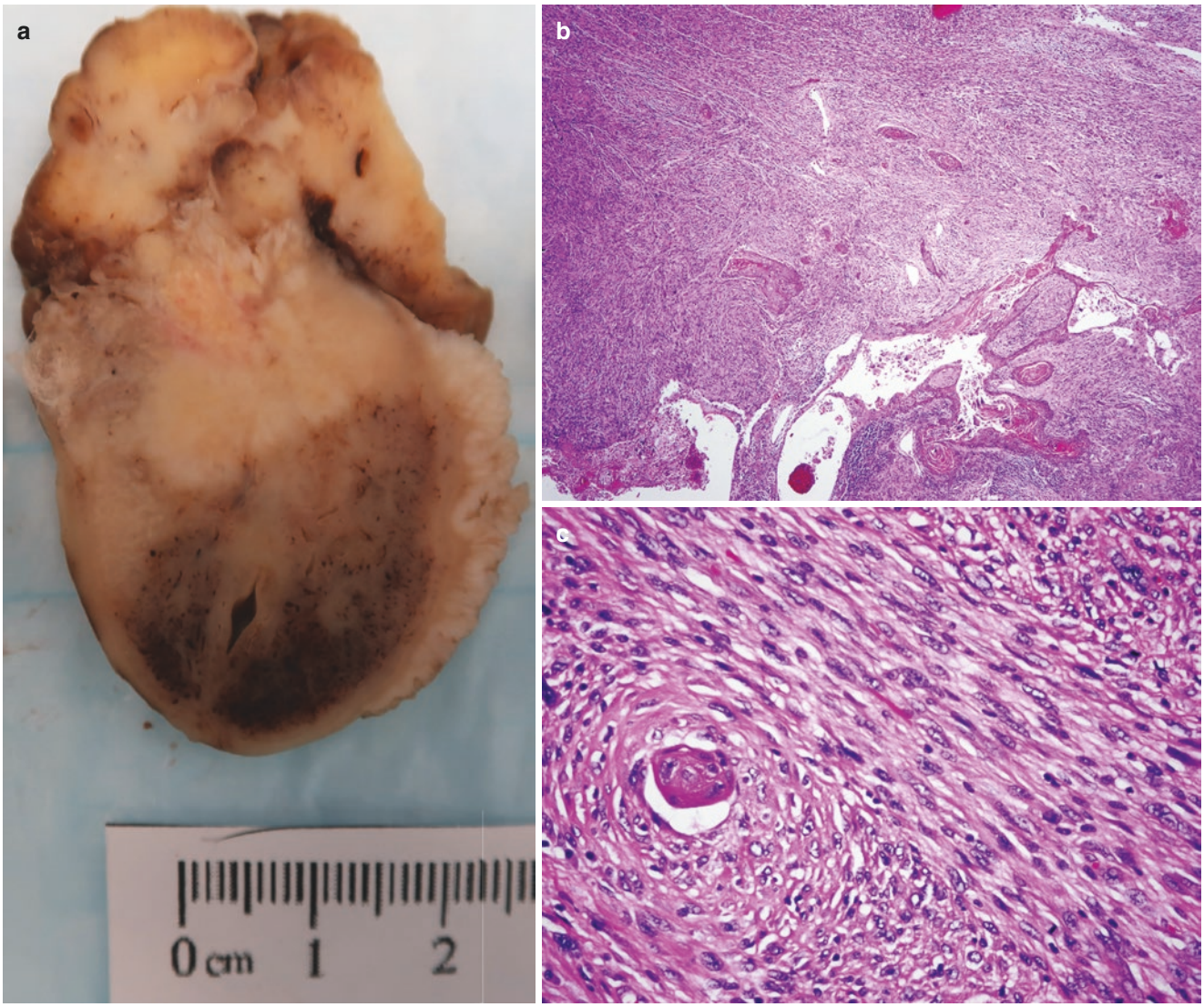

Fig. 7.7 Sarcomatoid squamous cell carcinoma. (**a**) Infiltrating tumor show tan firm cut surface, covering foreskin, coronal sulcus, and glans. (**b**) A biphasic carcinomatous and sarcomatoid spindle cell tumor. (**c**) Spindle cell component shows fibrosarcoma-like features

- The tumor is composed of high-grade SCC and a spindle cell (≥30%) component (Fig. 7.7b).
- Spindle cell component shows various histologic features, including myxoid, pseudoangiomatous, malignant fibrous histiocytoma-like, and fibrosarcoma-like (Fig. 7.7c).
- Heterologous differentiation into bone, cartilage, and muscle may be found.
- Mitotic figures are numerous, and necrosis may be prominent.
- Lymphovascular and perineural invasion are common.
- High-molecular-weight cytokeratin and p63 may be positive in sarcomatoid area.
- Clinical course usually aggressive with early lymph node metastasis and distant metastasis (e.g., lung, skin, bone, pleura).
- Most aggressive carcinoma of all penile carcinomas, with high mortality (45–75%).

Adenosquamous Carcinoma

- Biphasic malignant tumor with both squamous and adenocarcinoma components (Fig. 7.8a).
- Rare, only 11 cases reported.
- The squamous component predominates over the glandular component.
- Squamous component consists of warty or usual types of squamous carcinoma (Fig. 7.8b).
- Glandular component should have definitive gland formation (Fig. 7.8c), with or without mucin production.
- Can be deeply invasive and may show vascular invasion.

References: [5–10]

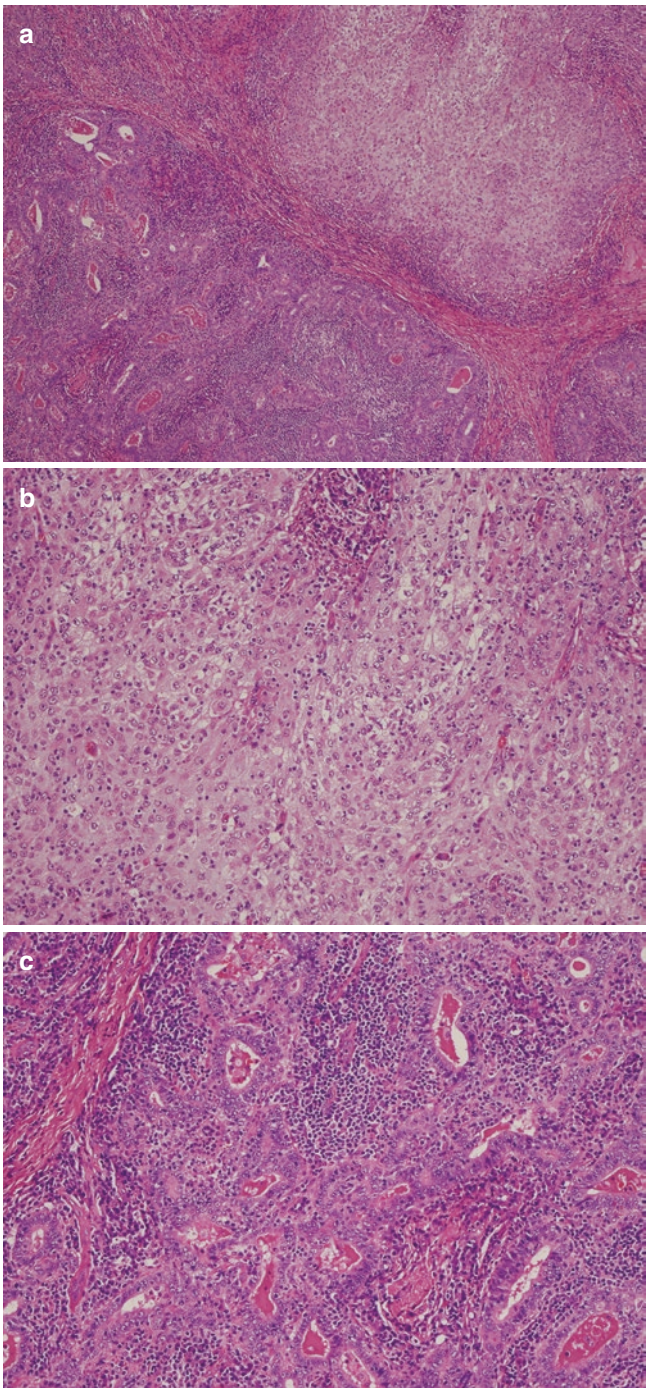

Fig. 7.8 Adenosquamous carcinoma. (**a**) Biphasic malignancy with squamous cell carcinoma and adenocarcinoma features. (**b**) Squamous component consists of usual types of squamous carcinoma. (**c**) Glandular component shows definitive gland formation

What Are the Types of HPV-Related Variants of Penile Carcinoma?

Basaloid Squamous Carcinoma

- Solid, aggressive tumor with endophytic solid growth pattern and basaloid features.

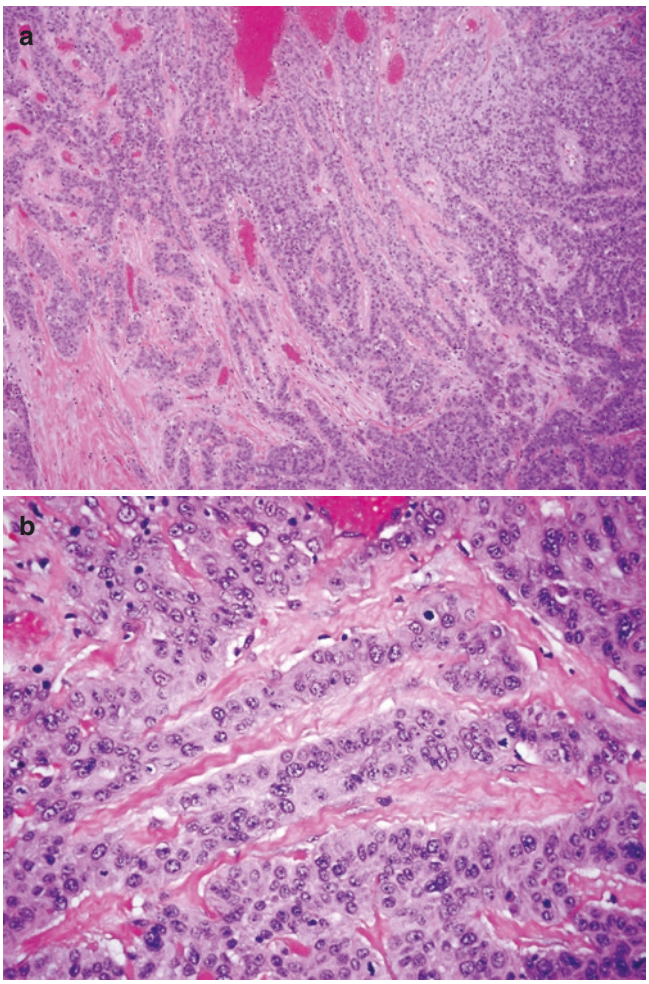

Fig. 7.9 Basaloid squamous carcinoma. (**a**) Tumor grows in a nesting pattern. (**b**) Monotonous small- to medium-sized tumor cells with high nuclear/cytoplasmic ratio and scant cytoplasm

- Most common HPV-related penile carcinoma (HPV16 most common).
- Accounts for 5–10% of penile carcinomas.
- Affects males in their 50s, ~10 years younger than patients with usual SCC.
- Grossly presents as a deeply infiltrative tumor mass with surface ulceration.
- Tumor grows in a nesting pattern with frequent comedonecrosis (Fig. 7.9a).
- Monotonous small- to medium-sized tumor cells with high nuclear/cytoplasmic ratio and scant cytoplasm (Fig. 7.9b).
- Frequent mitotic figures and apoptotic cells may impart a "starry sky" appearance.
- Focally abrupt keratinization.
- Vascular invasion and deep invasion are frequent.
- p16 immunostain is strong and diffuse.
- Approximately half of patients may present with regional nodal metastasis.
- Mortality varies from 20% to 30%.

Papillary-Basaloid Carcinoma

- Rare variant of basaloid carcinomas, 1–2% of all penile SCCs.
- HPV-related (HPV16 most common).
- Villous exophytic tumor entirely composed of small basophilic cells indistinguishable from basaloid cells.
- Papillary configuration with a central fibrovascular core (Fig. 7.10a).
- Invasive tumor is similar to typical basaloid carcinoma (Fig. 7.10b).
- p16 immunostain is strong and diffuse.
- Prognosis depends on the stage of the carcinoma.

Warty (Condylomatous) Carcinoma

- Exophytic verruciform tumor affecting the glans, sulcus, or foreskin, accounts for 5–10% penile SCCs.
- HPV-related (HPV16 most common).
- Cauliflower or cobblestone-like gross appearance. Cut surface reveals multinodular tan to white papillomatous growth with a darker center (Fig. 7.11a).
- Condylomatous papillae with prominent central fibrovascular cores (Fig. 7.11b).
- Nuclear pleomorphism and cytoplasmic clear cells with koilocytic morphology (Fig. 7.11c).
- Commonly invasive with jagged border, moderately differentiated.
- p16 immunostain is strong and diffuse.
- Inguinal metastases are unusual, and mortality is low. Local recurrence in 17–18% cases.

Warty-Basaloid Carcinoma

- Variant of warty carcinoma of the penis and is a mixed tumor with condylomatous and basaloid features.
- HPV-related (HPV16 most common).
- Grossly large exo-/endophytic tumors. Cut surface shows a biphasic papillomatous tumor on the surface and a solid and micronodular deeply invasive tumor in erectile tissues.
- Warty and basaloid features are present and intermixed in various proportions (Fig. 7.12a, b).
- p16 immunostain is strong and diffuse.
- Inguinal metastases are present in 50% of patient and mortality is between that of basaloid and warty carcinoma, closer to that of basaloid carcinoma.

Clear Cell Carcinoma

- Aggressive, poorly differentiated variant of warty carcinoma that affects the glans or foreskin.
- HPV-related.
- Composed predominantly of clear cells, with distinctive nesting pattern.

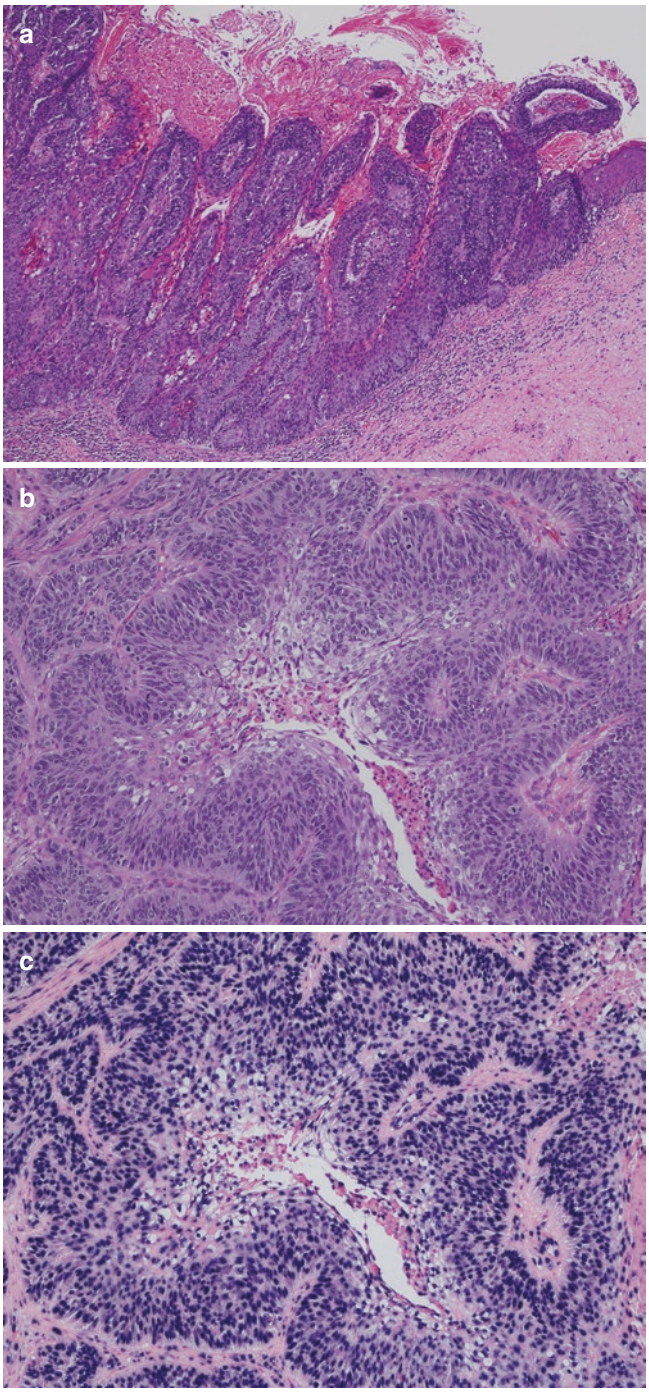

Fig. 7.10 Papillary basaloid carcinoma. (**a**) Papillary configuration with a central fibrovascular core. (**b**) Invasive tumor is similar to typical basaloid carcinoma. (**c**) Diffuse and dense staining of high-risk HPV RNA by in situ hybridization

- Comedo-like necrosis and geographic necrosis are common.
- p16 immunostain is strong and diffuse.
- Nodal metastases are present in the majority of cases.

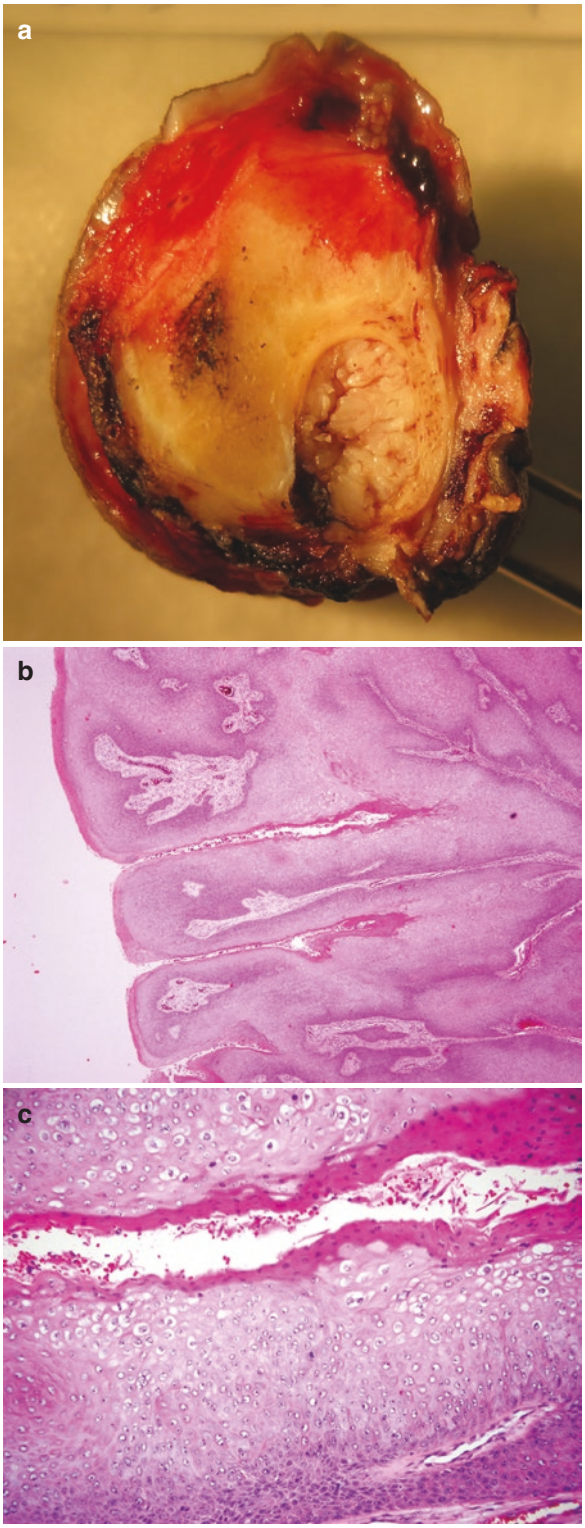

Fig. 7.11 Warty carcinoma. (**a**) Cauliflower or cobblestone-like gross appearance. Cut surface reveals multinodular tan to white papillomatous growth with a darker center. (**b**) Condylomatous papillae with prominent central fibrovascular cores. (**c**) Nuclear pleomorphism and cytoplasmic clear cells with koilocytic morphology

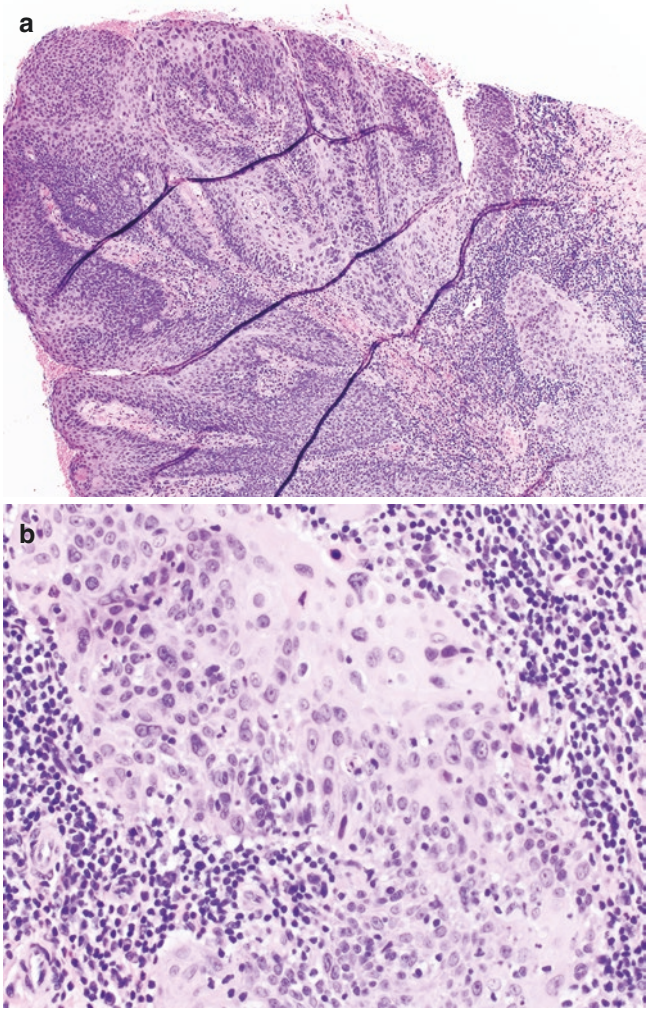

Fig. 7.12 Warty-basaloid carcinoma. (**a**) Papillomatous growth with superficial invasion of lamina propria invasion. (**b**) Dual populations of basophilic cells and clear cells. Both clear cell warty and basaloid features are present in the same invasive carcinoma nest

Lymphoepithelioma-like Carcinoma

- Poorly differentiated invasive squamous cell carcinoma resembling lymphoepithelioma or undifferentiated nasopharyngeal carcinoma.
- HPV-related.
- Large exophytic tumor located mainly in glans with extension to the foreskin.
- Invasive cords, trabeculae, nest, or sheets (Fig. 7.13a).
- Syncytial growth pattern of poorly differentiated to undifferentiated cells with indistinct cellular borders (Fig. 7.13b).
- Intermixed dense lymphoplasmacytic and eosinophilic infiltrate obscuring tumor cell boundaries.
- p16 immunostain is strong and diffuse.

References: [5, 11–16]

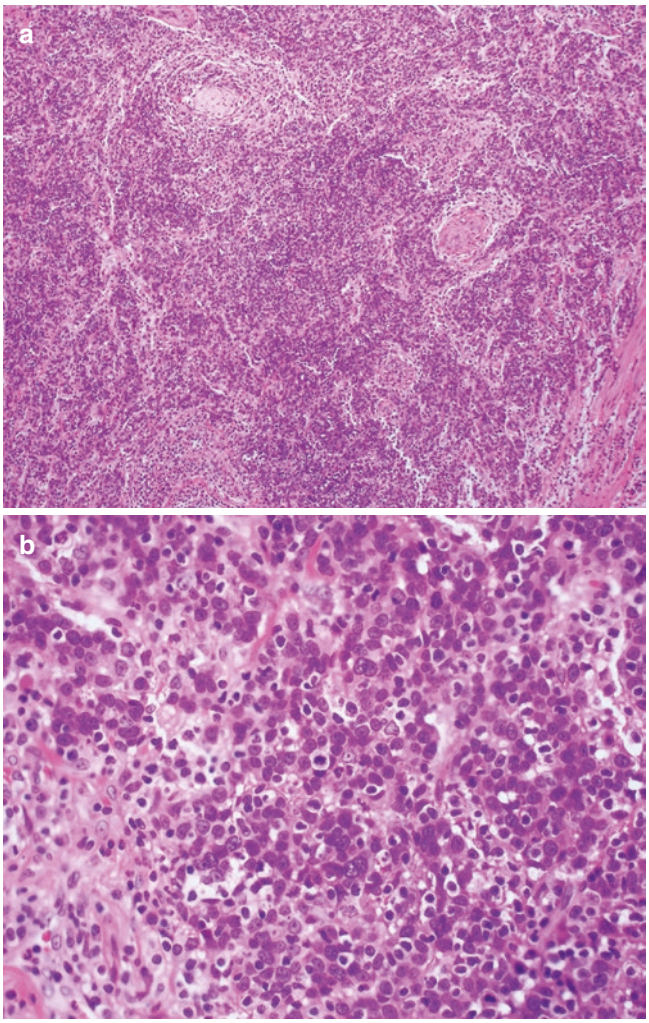

Fig. 7.13 Lymphoepithelioma-like carcinoma. (**a**) Irregular nests and trabeculae of undifferentiated tumor cells within dense lymphoplasmacytic infiltrate. (**b**) Syncytial tumor cells intermixed with inflammatory cells. (Reproduced with permission from Dr. Helen P. Cathro, University of Virginia)

What Is the Histologic Classification of Penile Intraepithelial Neoplasia (PeIN)?

PeIN is regarded as an intraepithelial (in situ) precursor lesion of invasive SCC. Synonyms include squamous cell carcinoma in situ (SCCIS), squamous intraepithelial lesion (SIL), erythroplasia of Queyrat and Bowen disease. PeIN is further subclassified into differentiated and undifferentiated types, with the latter being subdivided into basaloid, warty, and warty-basaloid subtypes.

Differentiated PeIN

- Thickened epithelium with hyperkeratosis, parakeratosis, and hypergranulosis (Fig. 7.14)
- Elongated and anastomosing rete ridges
- Subtle abnormal maturation (enlarged keratinocytes with abundant eosinophilic cytoplasm)

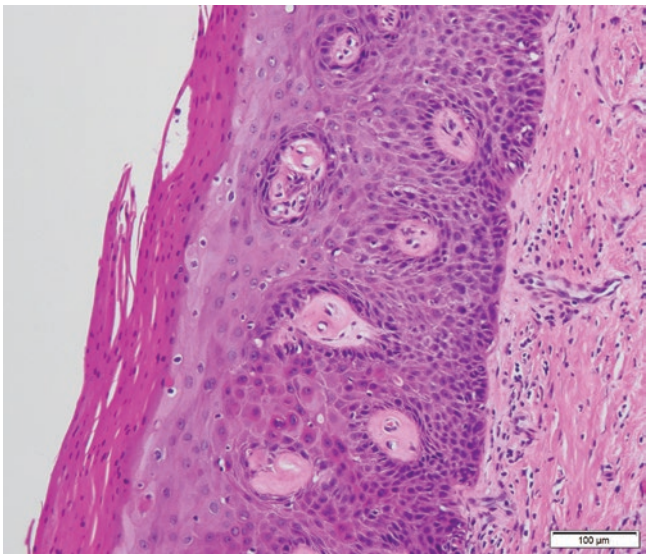

Fig. 7.14 Differentiated PeIN. Thickened epithelium with elongated rete ridges, enlarged keratinocytes with abundant eosinophilic cytoplasm, and atypical basal cells with hyperchromatic nuclei

- Keratin pearl formation
- Prominent intercellular bridges (lack of cohesion)
- Dysplastic hyperchromatic basal cells
- Unrelated to HPV infection
- p16 negative or non-block expression; p53 overexpression (suprabasal extension) or total lack of expression

Undifferentiated PeIN, Subtypes

Basaloid PeIN (Fig. 7.15)

- Epithelium replaced by a monotonous population of small- to intermediate-sized blue cells with a high nuclear/cytoplasmic ratio
- Parakeratosis with a flat surface
- Abundant mitotic figures and apoptotic bodies
- Isolated koilocytes in the superficial layers
- HPV-related, with strong/diffuse block-staining pattern of p16 positivity (Fig. 7.16a, b)

Warty PeIN (Fig. 7.17)

- Thickened epithelium with an undulating and spiking surface and striking cellular pleomorphism
- Atypical parakeratosis and dyskeratosis
- Conspicuous koilocytosis (hyperchromatic wrinkled nuclei, perinuclear halos, multinucleation)
- Abundant mitotic figures
- HPV-related, strong/diffuse block p16 positivity

Warty-basaloid PeIN (Fig. 7.18)

- Overlapping features of both warty and basaloid types

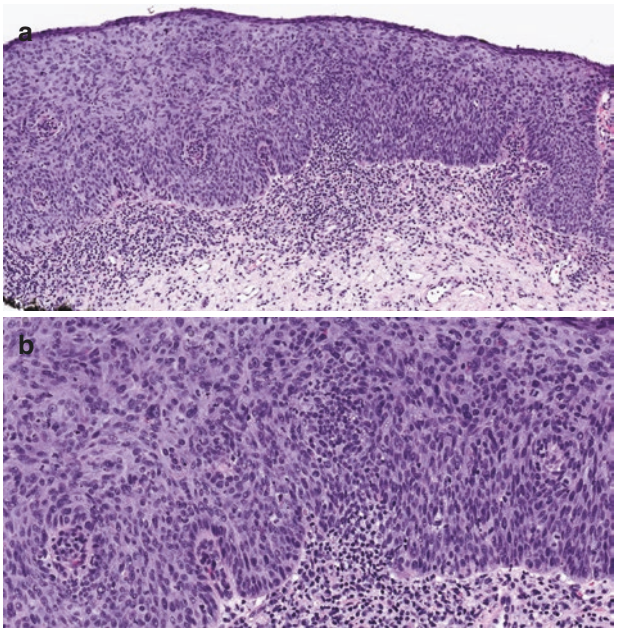

Fig. 7.15 Basaloid PeIN. (**a**) At low-power view, the lesion has flat or slightly irregular surface with parakeratosis. (**b**) At high-power view, the squamous epithelium is replaced by basophilic tumor cells with scant cytoplasm and indistinct cell borders. High mitotic rate is present

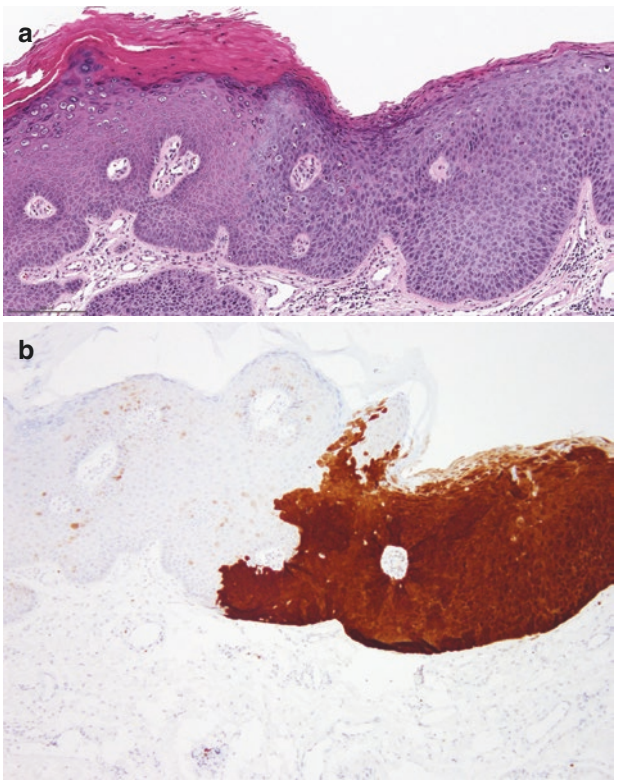

Fig. 7.16 Basloid PeIN, p16 stain. The immunopositivity for p16 is accepted as such only a dense, complete, "en block," nuclear, and cytoplasmic staining in contrast to the scattered staining pattern in normal squamous epithelium

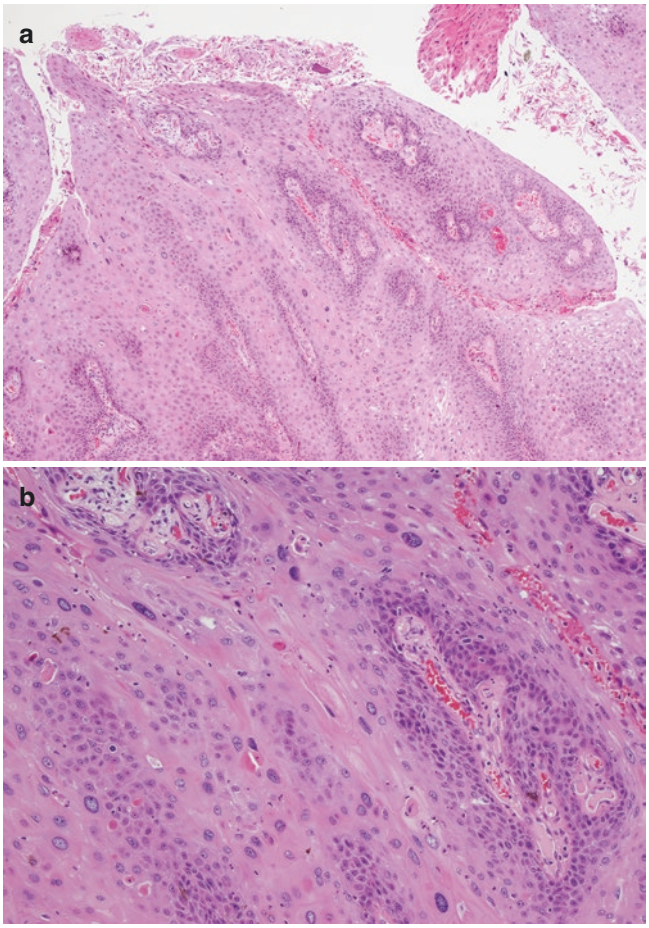

Fig. 7.17 Warty PeIN. (**a**) At low-power view, spiky or papillary parakeratotic surface is observed. (**b**) Nuclear pleomorphism is commonly found

- Spiking surface with koilocytic changes on the upper part of the epithelium
- Lower half of the epithelium is predominantly composed of small basaloid cells
- HPV-related, strong/diffuse block p16 positivity

The Lower Anogenital Squamous Terminology Standardization project (LAST) recommends a two-tiered nomenclature system for HPV-related PeIN:

- Low-grade squamous intraepithelial lesion (LGSIL): cytologic atypia limited to the lower third of the epithelium.
- High-grade squamous intraepithelial lesion (HGSIL): cytologic atypia involving more than one-third of the epithelium. When atypia involves the full thickness, it is equivalent to SCC in situ.

There is a significant association of the different types of PeIN with specific invasive SCC variants. Differentiated PeIN is seen preferentially associated with usual, papillary, pseudohyperplastic, verrucous, and sarcomatoid carcinomas.

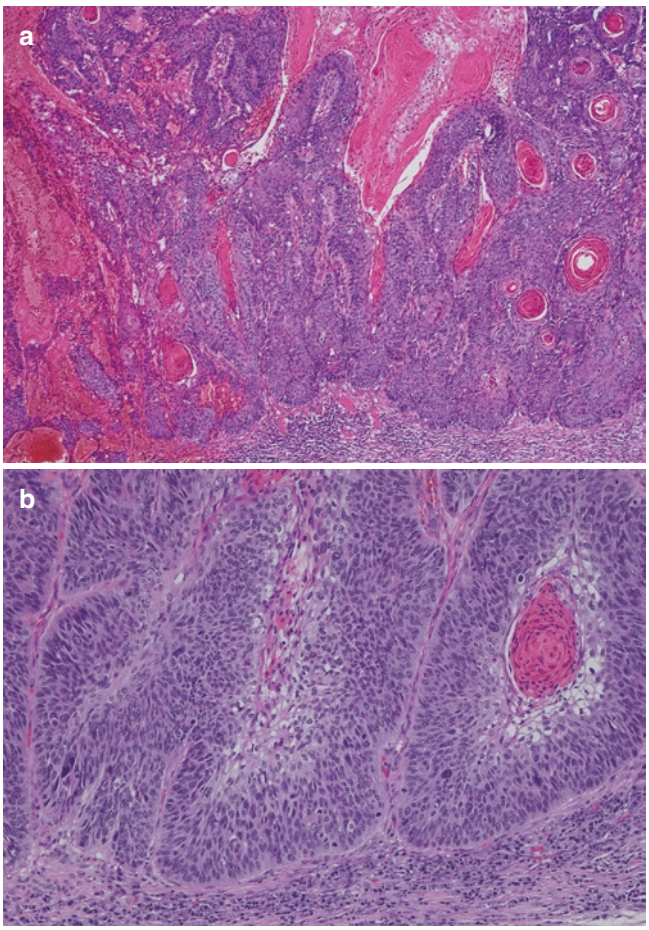

Fig. 7.18 Warty-basaloid PeIN. (**a**) Warty features in the upper third of the epithelium (spiky parakeratotic surface with koilocytosis). (**b**) Basaloid cells present in the middle and lower third of the epithelium

Undifferentiated PeIN is distinctively associated with warty, basaloid, and mixed warty-basaloid carcinomas.

References: [17, 18]

What Features Distinguish Differentiated PeIN from Undifferentiated PeIN?

Distinguishing clinicopathologic features between differentiated PeIN and undifferentiated PeIN are listed in Table 7.2.

What Features Distinguish Differentiated PeIN from Lichen Simplex Chronicus?

Distinguishing clinicopathologic features between differentiated PeIN and Lichen simplex chronicus are listed Table 7.3.

Table 7.2 Distinguishing features between differentiated PeIN and undeffirentiated PeIN

	Differentiated PeIN	Undifferentiated PeIN
Location	Foreskin	Glans
Multifocality	Sometimes	Often
HPV related	No	Yes
p16	Negative	Positive
Association with lichen sclerosus	Yes	No
Associated invasive SCC	NOS, verrucous, pseudohyperplastic, papillary, sarcomatoid SCC	Warty, basaloid, warty-basaloid SCC

What Features Distinguish Warty/Basaloid PeIN from Bowenoid Papulosis?

Distinguishing clinicopathologic features between warty/basaloid PeIN and Bowenoid papulosis are listed Table 7.4.

What Features Distinguish Penile Squamous Cell Carcinoma from Urothelial Carcinoma of Distal Urethra?

Distinguishing pathologic features and immunophenotype between penile squamous cell carcinoma and urothelial carcinoma of distal urethra are listed Table 7.5.

What Features Distinguish Papillary Squamous Cell Carcinoma, NOS, from Verrucous and Warty Carcinoma?

Distinguishing pathologic features among papillary, verrucous, and warty squamous cell carcinoma are listed in Table 7.6.

What Features Distinguish Papillary Squamous Cell Carcinoma from Papillary Basaloid Carcinoma?

Distinguishing pathologic features between papillary squamous cell carcinoma and papillary basaloid carcinoma are listed in Table 7.7.

Table 7.3 Distinguishing features between differentiated PeIN and lichen simplex chronicus

	Differentiated PeIN	Lichen simplex chronicus
Pathogenesis	Precancerous	Inflammatory/reactive
Thickened epithelium	Present	Present
Hyperkeratosis, parakeratosis and hypergranulosis	Present	Present
Basal cell atypia	Prominent	None/minimal
HPV	–	–
p16	–	–
p53	Overexpression/total loss of expression (mutated)	Basilar expression (wild type)

Table 7.4 Distinguishing features between warty/basaloid PeIN and Bowenoid papulosis

	Warty/basaloid PeIN	Bowenoid papulosis
Pathogenesis	Precancerous	<1% progress to SCC, often regresses spontaneously
Age	Older (40–60 yo)	Young, sexually active (30 yo mean)
Presentation	Solitary/multifocal	Small, multiple lesions
Regression	–	+
Basaloid cells	Present	Present
Koilocytosis	Present	Present
Spiking surface	Present	Present
HPV	+ (HPV16)	+ (HPV16)
p16	+	+
p53	Overexpression/total loss of expression (mutated)	Basilar expression (wild type)

Table 7.5 Distinguishing features between squamous cell carcinoma and urothelial carcinoma of distal urethra

	Penile squamous cell carcinoma	Urothelial carcinoma of distal urethra
Adjacent urothelial carcinoma	Absent	Present
PeIN	Present	Absent
Squamous hyperplasia	Present	Absent
p63	+	+
GATA-3	±	+
CK20	–	+
Uroplakin	–	+

Table 7.6 Distinguishing features among papillary carcinoma, verrucous carcinoma, and warty carcinoma

	Papillary carcinoma, NOS	Verrucous carcinoma	Warty carcinoma
Cauliflower-like exophytic growth	Present	Present	Present
Differentiation	Well to moderate	Well	Moderate
Papillomatosis	Present	Present	Absent
Fibrovascular core	Present	Absent	Present
Broad pushing border	Absent	Present	Absent
Koilocytosis	Absent	Present	Present
PeIN	Differentiated	Differentiated	Undifferentiated
Squamous hyperplasia	Present	Present	Present
Lichen sclerosis	Present	Present	Absent
HPV-associated	No	No	Yes
p16 immunostain	–	–	+

Table 7.7 Distinguishing features between papillary carcinoma and papillary-basaloid carcinoma

	Papillary carcinoma, NOS	Papillary-basaloid carcinoma
Cauliflower-like exophytic growth	Present	Present
Papillomatosis	Present	Present
Fibrovascular core	Present	Present
Papillae lining cells	Well-differentiated cells with eosinophilic cytoplasm (pink cells)	Poorly differentiated basophilic small cells with scanty cytoplasm (blue cells)
Broad pushing border	Absent	Absent
Koilocytosis	Absent	Absent
PeIN	Differentiated	Undifferentiated
Squamous hyperplasia	Present	Present
Lichen sclerosis	Present	Absent
HPV-associated	No	Yes
p16 immunostain	–	+

What Features Distinguish Sarcomatoid Squamous Cell Carcinoma from Primary Sarcoma of Penis?

The distinguishing clinic–pathologic features and immunophenotype between sarcomatoid squamous cell carcinoma and primary sarcoma of the penis are listed in Table 7.8.

Table 7.8 Distinguishing features between sarcomatoid squamous carcinoma and primary sarcoma

	Sarcomatoid squamous cell carcinoma	Primary sarcoma
Occurrence	1–4% of penile carcinomas	Exceedingly rare
MC location	Glans	Shaft (corpora cavernosa), deeply located
History of penile carcinomas	Present	Absent
Epithelial differentiation	Present	Absent
Connection to surface epithelium	Present	Absent (deeply located)
High-grade spindle cells	Present	Present
Heterologous elements	±	±
PeIN	Present	Absent
p63/CK5/6/HMWCK	+ (less in spindle area)	–
AE1/AE3/CAM5.2 immunostains	± (may be negative in spindle area)	–

What Features Distinguish Verrucous Carcinoma from Giant Condylomas?

The distinguishing morphologic features between verrucous carcinoma and giant condylomas are listed in Table 7.9.

Table 7.9 Distinguishing features between verrucous carcinoma and giant condyloma

	Verrucous carcinoma	Giant condyloma
Low-grade nuclei	Present	Present
Noninvasive, pushing border	Present	Present
Exophytic growth	Present	Present
Endophytic growth	Present	Absent
Koilocytosis	Absent	Present

What Features Distinguish Warty-Basaloid Carcinoma from Warty Carcinoma and Basaloid Carcinoma?

The distinguishing morphologic and immunophenotypical features among warty carcinoma, basaloid squamous carcinoma, and warty-basaloid carcinoma are listed in Table 7.10.

Table 7.10 Distinguishing features among warty carcinoma, basaloid squamous cell carcinoma, and warty-basaloid carcinoma

	Warty carcinoma	Basaloid squamous cell carcinoma	Warty-basaloid carcinoma
Warty (condylomatous) component	Present	Absent	Present
Basaloid component	Absent	Present	Present
Koilocytosis	Present	Absent	Present
HPV-associated	Yes	Yes	Yes
p16 immunostain	+	+	+

What Features Distinguish Clear Cell Carcinoma from Warty Carcinoma with Prominent Clear Cells?

The distinguishing morphologic and immunophenotypical features between clear cell carcinoma and warty carcinoma with prominent clear cells are listed in Table 7.11.

What Features Distinguish Clear Cell Carcinoma from Metastatic Renal Cell Carcinoma?

The distinguishing pathologic and immunophenotypical features between clear cell carcinoma and metastatic renal cell carcinoma are listed in Table 7.12.

Table 7.11 Distinguishing features between clear cell carcinoma and warty carcinoma with prominent clear cells

	Clear cell carcinoma	Warty carcinoma with prominent clear cells
Papillomatosis	Absent	Present
Fibrovascular core	Absent	Present
Warty PeIN	Present	Present
HPV-associated	Yes	Yes
p16 immunostain	+	+

Table 7.12 Distinguishing features between clear cell carcinoma and metastatic renal cell carcinoma

	Clear cell carcinoma	Metastatic renal cell carcinoma
MC location	Foreskin, coronal sulcus or glans (penile mucosal compartments)	Corpus cavernosum
Lymphovascular invasion	±	Extensive
Warty/basaloid PeIN	Present	Absent
HPV-associated	Yes	No
p16 immunostain	+	–
Pax-8 immunostain	–	+

What Features Distinguish Clear Cell Carcinoma from Sweat Gland Carcinoma?

The distinguishing morphologic and immunophenotypical features between clear cell carcinoma and sweat gland carcinoma are listed in Table 7.13.

What Features Distinguish Carcinoma Cuniculatum from Verrucous Carcinoma?

The distinguishing morphologic and immunophenotypical features between carcinoma cuniculatum and verrucous carcinoma are listed in Table 7.14.

Table 7.13 Distinguishing features between clear cell carcinoma and sweat gland carcinoma

	Clear cell carcinoma	Sweat gland carcinoma
MC location	Foreskin, coronal sulcus or glans (penile mucosal compartments)	Skin shaft
Warty/basaloid PeIN	Present	Absent
HPV-associated	Yes	No
p16 immunostain	+	–

Table 7.14 Distinguishing features between carcinoma cuniculatum and verrucous carcinoma

	Carcinoma cuniculatum	Verrucous carcinoma
Cauliflower-like exophytic growth	Present	Present
Differentiation	Well to moderate	Well
Papillomatosis	Present	Present
Fibrovascular core	Absent	Absent
Burrowing pattern	Present	Absent
Focal high-grade area	Present	Absent
Focal infiltrative pattern	Present	Absent
PeIN	Differentiated	Differentiated
Squamous hyperplasia	Present	Present
Lichen sclerosis	Present	Present
HPV-associated	No	No
p16 immunostain	–	–

What Features Distinguish Pseudoglandular Carcinoma from Adenosquamous Carcinoma?

The distinguishing morphologic and immunophenotypical features between pseudoglandular carcinoma and adenosquamous carcinoma are listed in Table 7.15.

What Is the Value of P16 in the Diagnosis of HPV-Related Penile Tumors?

Although the majority of HPV-related penile tumors can be identified with routine hematoxylin and eosin (H&E) staining, p16 immunohistochemical staining can serve as a surrogate of HPV infection, which is recommended by the WHO. In a study comparing p16 with HPV detection by PCR, p16 is frequently associated with high-risk HPV, with an overall concordance of 84%. The highest rate of positivity was identified in basaloid and mixed basaloid carcinomas, while intermediate rates were present in warty and usual carcinomas.

p16 immunostaining may be helpful for accurate classification in morphologically challenging cases. For example, warty carcinoma (p16-positive) can be distinguished from papillary carcinoma, NOS and giant condylomas, both of which are p16-negative. p16 may prove to be useful as a prognostic marker as more outcome data becomes available in the future. It has been well demonstrated that patients with p16-positive carcinomas in the head and neck region have a better prognosis than those with p16-negative carcinomas. For penile carcinoma, there are fewer studies, and there is lack of consensus currently about the prognostic value of p16 immunostaining status of these tumors. In some studies, HPV presence is a good prognostic marker, whereas in other studies the findings are inconclusive.

References: [19–24]

Table 7.15 Distinguishing features between pseudoglandular carcinoma and adenosquamous carcinoma

	Pseudoglandular carcinoma	Adenosquamous carcinoma
True glandular differentiation	Absent	Present
Honeycombing (multicystic)	Present	Present/Absent
Biphasic pattern	Absent	Present
Cyst lining	High-grade cylindrical to flat squamous cells	Glandular cells
Mucin	–	+
PeIN	Differentiated	Differentiated
Squamous hyperplasia	Present	Present
Lichen sclerosis	Present	Present
HPV-associated	No	No
p16 immunostain	–	–

What Is the Prevalence Distribution of HPV Types in Penile Carcinomas?

HPV is detectable in 30–50% of penile SCCs. Most HPV infections in this setting are classified as high-risk genotypes, and the majority of these correspond to HPV-16, accounting for about 60% of HPV-attributable cases. HPV-related tumors affect younger patients, whereas tumors unrelated to HPV tend to be seen in older patients with lichen sclerosus or squamous hyperplasia (Table 7.16).

Reference: [3, 25]

What Are the Ancillary Tests for HPV Detection and Genotyping?

The detection of HPV infection in genital samples may increase the sensitivity of primary and secondary screenings of penile as well as cervical cancer. HPV testing may also improve the specificity of screening programs, resulting in the prevention of overtreatment and cost savings for confirmatory procedures.

Nucleic acid-hybridization assays

- Southern blotting
- In situ hybridization
- Dot-blot hybridization ViraPap/ViraType test (Digene Corporation, USA)

Signal-amplification assays

- Cervista HPV (Hologic, Inc., Marlborough, MA)
- Hybrid Capture II system (HC-2, Digene Corp., USA)
- *Nucleic acid-amplification methods*
- Microarray analysis
- PapilloCheck
- Polymerase chain reaction (PCR)

Table 7.16 HPV-type prevalence distribution in penile carcinomas[a]

Genotype	Frequency (%)	Relative contribution among HPV(+) cases (%)
Any type	47.0	100
HPV-16	28.3	60.23
HPV-18	6.3	13.35
HPV-6/11	3.8	8.13
HPV-31	0.5	1.16
HPV-45	0.5	1.16
HPV-33	0.4	0.87
HPV-52	0.3	0.58
Other types	1.2	2.47

[a]Data is based on a meta-analysis of 31 studies including 1466 penile carcinomas [25]

- Real-time PCR
- Abbott real time
- PCR-RFLP
- HPV genome sequencing
- INNO-LiPA (LiPA HBV GT; Innogenetics N.V., Ghent, Belgium)
- COBAS 4800 HPV test
- Linear Array HPV Genotyping (Roche Molecular Diagnostics, Pleasanton, CA)
- CLART human papillomavirus 2
- Microplate colorimetric hybridization assay (MCHA)
- PreTect Proofer (HPV-mRNA detection)
- APTIMA HPV assay (HPV-mRNA detection)

Reference: [26]

What Are the Grading Parameters for Penile Squamous Cell Carcinoma?

A three-tiered histological grading is recommended for penile SCCs: grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. In penile cancers, grades 1, 2, and 3 occur with approximately equal frequency. When more than one grade is identified in the same specimen, a grade is assigned on the basis of the worst observed grade. Any proportion of grade 3 is sufficient to place the tumor in this category.

Grade 1: Well Differentiated

Tumors show extreme differentiation, keratinization, and maturation. Nuclear atypia is minimal or absent. Tumors grow in large nests. The grade of verrucous carcinoma, with minimal deviation from the histology of the normal squamous epithelium, may be used as a model for grade 1 tumors.

Grade 2: Moderately Differentiated

Tumors are intermediate in their histological features between the features of grades 1 and 3 carcinomas. They grow in irregular nests with obvious keratinization and partial cell maturation. Nuclear atypia is moderate.

Grade 3: Poorly Differentiated

Tumors are usually solid or trabecular. They show scant keratinization and are predominantly composed of undifferentiated or anaplastic cells. There is no maturation. Cells are pleomorphic and show numerous mitotic figures. Basaloid and sarcomatoid carcinomas are prototypical examples of grade 3 tumors. Any percentage of anaplastic cells (grade 3) is important in increasing the risk of inguinal metastasis.

Table 7.17 Correlation of histological grades and subtypes of penile SCCs

Grade 1	Grade 2	Grade 3
Verrucous	Warty (condylomatous)	Sarcomatoid
Papillary NOS Cuniculatum	Moderately differentiated usual	Pseudoglandular Basaloid
Pseudohyperplastic		Clear cell
Well differentiated usual		Lymphoepithelioma-like
		Poorly differentiated usual

Histological grades can be correlated with specific subtypes of penile SCCs. Many of the histological subtypes of SCC of the penis are associated with distinct grades based on the histological features of the subtypes. Usual SCC exhibits the widest range in grading (Table 7.17).

References: [27, 28]

What Are the Staging Parameters for Penile Squamous Cell Carcinoma?

The following stages are from the American Joint Committee on Cancer Staging Manual, eighth edition:

Primary Tumor (T)

- TX: primary tumor cannot be assessed.
- T0: no evidence of primary tumor.
- Tis: carcinoma in situ (preinvasive carcinoma).
- Ta: noninvasive localized carcinoma (broad pushing penetration or invasion is permitted; destructive invasion is against this diagnosis).
- T1a: tumor invades subepithelial connective tissue without lymphovascular or perineural invasion and is not high grade (ie, grade 3 orsarcomatoid).
- T1b: tumor invades subepithelial connective tissue with lymphovascular invasion and/or perineural invasion or is high grade (ie, grade 3 orsarcomatoid).
- T2: tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion.
- T3: tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion.
- T4: tumor invades into adjacent structures (i.e., scrotum, prostate, pubic bone).

Regional Lymph Nodes (N) (Pathological Classification)

- pNX: regional lymph nodes cannot be assessed.
- pN0: no regional lymph node metastasis.

- pN1: ≤2 unilateral inguinal metastases, no extranodal extension.
- pN2: ≥3 unilateral inguinal metastases or bilateral metastases, no extranodal extension.
- pN3: Extranodal extension of lymph node metastases or pelvic lymph node metastases.

Distant Metastasis (M)

- M0: no distant metastasis.
- M1: distant metastasis (including lymph node metastasis outside of the true pelvis).

Note: Staging of squamous cell carcinoma of the skin of the shaft or glans of the penis is different from cancer arising in the urethra.

- If the erectile tissue (corpus cavernosa, spongiosum) is involved, the tumor is pT3 or pT2.
- If the urethra is involved by cancer invading to it from the surface, through the erectile tissue, the tumor is pT3.
- If involved by surface spread via the urethral meatus, this is not pT3.
- Invasive carcinoma involving neither of these structures is pT1 [i.e., tumor only involves the lamina propria (dermis) of the penile skin].
- T1 is subdivided into T1a and T1b based on the presence or absence of lymphovascular invasion, perineural invasion or poorly differentiated cancers.
- Prostatic invasion is considered T4.
- Metastasis to lymph nodes outside of the true pelvis is M1.

Reference: [29]

What Are the Staging Parameters for Penile Urethral Carcinoma?

Urethral carcinomas are staged using a different TNM system than carcinomas that arise on the penile shaft skin or on the glans penis. Most malignant tumors of the urethra are SCCs, followed by urothelial carcinomas and adenocarcinomas. Clear cell adenocarcinomas are rare but more common in female patients.

The following stages are from the American Joint Committee on Cancer Staging Manual, eighth edition:

Primary Tumor (T)

- pTX: primary tumor cannot be assessed.
- pTa: noninvasive carcinoma.
- pTis: carcinoma in situ.
- pT1: tumor invades subepithelial connective tissue.
- pT2: tumor invades corpus spongiosum, prostate, periurethral muscle.
- pT3: tumor invades corpus cavernosum, beyond prostatic capsule, anterior vaginal wall, bladder neck.
- pT4: tumor invades other adjacent organs.

Regional Lymph Node Metastasis (pN Stage)

- pNX: regional lymph nodes cannot be assessed.
- pN0: no regional lymph node metastasis.
- pN1: metastasis in a single lymph node 2 cm or less in greatest dimension.
- pN2: metastasis in a single node more than 2 cm in greatest dimension, or in multiple nodes.

Distant Metastasis (pM Stage)

- pM0: no distant metastasis
- pM1: distant metastasis

Note: In the prostatic urethra, carcinoma of the urethral lining with invasion into subepithelial connective tissue is staged as pT1; invasion arising from the prostatic ducts is designated as at least pT2.

Reference: [29]

What Are the Updates for Penile Cancer in the 8th ed. AJCC TMN Staging Manual?

Significant changes in nonurethral penile cancer have been proposed over past editions; see summary below:

- Ta Broadened to noninvasive localized squamous cell carcinoma
- T1 Tumor invasion to layers superficial to corporal tissues specified according to region's histoanatomy (glans, foreskin, or shaft)
  - Perineural invasion included to divide T1a and T1b
  - Sarcomatoid change clarified as one high-grade variable to divide T1a and T1b
- T2 Confined to tumor invasion into corpus spongiosum
  - Tumor invasion of corpus cavernosum excluded
- T3 Tumor invasion into corpus cavernosum
  - Urethral involvement no longer the determinant and can be T2 or T3
- pN1 Increased to up to two unilateral inguinal lymph node metastases without extranodal extension
- pN2 Increased to >2 unilateral or bilateral inguinal lymph node metastases without extranodal extension

Ta is now significantly expanded to all noninvasive localized squamous cell carcinoma (SCC) from the previous noninvasive verrucous carcinoma. Most verrucous carcinomas exhibit a broad pushing deep aspect, and the presence, depth and extent of invasion are often difficult to assess. The new definition does not permit any overt destructive invasion in well-sampled verrucous carcinoma. The new Ta category also includes other noninvasive SCC types such as basaloid, warty, papillary, and mixed types. Ta is analogous to noninvasive papillary urothelial

carcinoma of the urinary tract, while Tis designates penile carcinoma in situ just as it designates urothelial carcinoma in situ.

The definition of T1 or noncorporal invasive cancers is revised according to penile region-specific anatomy. The corpora are covered externally by varying tissue layers in the different regions of the penis (glans, foreskin, and shaft). Having precise definitions facilitates more consistent categorization of T1 disease, as compared to previous editions which used nonspecific subepithelial tissue layers as a general definition.

T1 is subcategorized into T1a and T1b, which have different risks for lymph node (LN) metastasis (10.5–18.1% vs 33.3–50%). This subcategorization is of considerable importance in the clinical consideration of performing inguinal LN dissection.

High-grade (G3) histology is one variable used to separate T1b from T1a cancers.

Sarcomatoid carcinoma, a known aggressive histology of SCC, is now considered as a high-grade feature of T1b cancer.

Perineural invasion is recognized as a predictor for regional LN metastasis and is now added as another separation criterion between T1a and T1b tumors.

T2 is now restricted to invasion into corpus spongiosum while invasion into corpus cavernosum is upstaged to T3. In previous editions, invasion of corpus spongiosum and corpus cavernosum were grouped together as T2. Recent studies have shown that corpus spongiosum invasion is associated with a lower incidence of inguinal LN involvement than corpus cavernosum invasion (33–35.8% vs 48.6–52.5%) and better survival.

Urethral invasion, previously defined as T3 disease, can now be either T2 or T3 depending on the more important level of corporal invasion. Penile cancer near the meatus may invade directly into the distal urethra bypassing the corpora and is not associated with worse outcome.

pN1 is now increased to up to two unilateral inguinal LN metastases, while pN2 is now modified as more than three unilateral or bilateral inguinal LN metastases. The shift to the lower pN1 may avoid adjuvant chemotherapy to some patients with (two positive) LN disease since this treatment has been recommended to pN2 patients. The AJCC 7th edition pN1 (single inguinal LN) and pN2 (multiple or bilateral inguinal LNs) categories were shown in some clinical scenarios to have no significant difference in risk for death from disease. However, metastasis involving three or more unilateral or bilateral inguinal LNs have poorer outcomes compared with metastasis involving one or two unilateral inguinal LNs (60.5% vs 90.7% 3-year cancer-specific survival).

The three-tiered WHO/ISUP grading system has now replaced the four-tiered modification of the Broder's grading system for SCC (level of evidence III). Histologic grade in penile SCC is a significant predictor of regional LN metastasis and has been shown to improve the ability of the AJCC stage to predict cancer-specific mortality.

The WHO/ISUP grading for SCC considers any amount of anaplasia as grade 3 (G3). Poorly differentiated histology or anaplasia particularly when >50% is a strong predictor for LN metastasis.

The two grade extremes (G1 and G3) facilitate prognostic categorization of penile SCC.

Reference: [29]

What Are the Prognostic Markers for Penile Carcinoma?

Histologic tumor type, grade, TNM classification, and perineural invasion are the most important factors in assessing prognosis in penile cancer. A prognostic index combining tumor grade, anatomic level of tumor infiltration, and perineural invasion has been proposed. The index correlates well with incidence of nodal metastases and patient survival.

Beyond conventional pathologic parameters, no single prognostic marker has gained widespread acceptance in penile carcinoma. Expression of p16 has been shown to be associated with a better prognosis, whereas the expression of p53 indicated a dismal clinical course. At the tumor boundary, an infiltrative pattern is associated with a higher risk for lymph node metastasis as compared with a pushing pattern. Markers that indicate an epithelial-mesenchymal transition (e.g., E-cadherin) and markers that are associated with stromal degradation (e.g., metalloproteinases) are therefore also promising candidates for assessment as prognostic indicators.

Metastasis to the inguinal lymph nodes is among the most important prognostic factors in cancer of the penis. A meticulous processing of inguinal lymph node specimens is therefore mandatory. The sentinel technique with radioactive tracers can be adopted to modify the extent of inguinal dissection.

References: [30, 31]

What Is the Management of Penile Cancer?

Treatment is dependent on tumor type and staging. Traditionally, the primary management of advanced invasive carcinoma involved radical or partial penile amputation with a 2-cm margin for oncologic efficacy. When penile tumors extend into the corporeal bodies, urethra, and adjacent structures (T2–T4), a more extensive resection was typically elected. Partial penectomy has demonstrated excellent oncologic control and is the gold standard for distal invasive tumors. When a negative margin cannot be achieved or a large fungating tumor is present, total amputation with perineal urethrostomy is recommended with penile reconstruction in select cases. For patients with evidence of inguinal lymph node metastasis, lymphadenectomy is mandatory.

For small low-grade, noninvasive (PeIN, Ta, T1a) and small carefully selected high-grade or even higher stage invasive tumors, conservative excision with attempted penile preservation may be elected. Techniques include wide local excision, laser ablation, partial or total glansectomy, glans resurfacing, Mohs microsurgery, partial amputation, and radiation therapy.

Reference: [32]

What Is the Protocol for the Examination of Specimens from Patients with Carcinoma of the Penis?

Penectomy Specimen

Take measurements, describe specimen, and identify and describe tumor. Most SCCs of the penis arise from the epithelium of the distal portion of the organ (glans, coronal sulcus, and mucosal surface of the prepuce; the tumor may involve one or more of these anatomic compartments).

Take a complete cross section (shave) of the proximal shaft amputation margin, making sure to include the entire circumference of the urethra. If the urethra has been retracted, it is important to identify its resection margin and submit it entirely. The resection margin can be divided in three important areas that need to be analyzed: the skin of the shaft with underlying dartos and penile fascia; corpora cavernosa with albuginea; and urethra with periurethral cylinder that includes lamina propria, corpus spongiosum, albuginea, and penile fascia (Fig. 7.1). Since this is a large specimen, it may need to be included in several cassettes to include the entire resection margin.

Fix the rest of the specimen overnight. Then, in the fixed state and if the tumor is large and involves most of the glans, cut longitudinally and centrally by using the meatus and the proximal urethra as reference points. Separate the specimen into halves, left and right. Then bread-loaf the shaft of the penis at 3 mm intervals beginning distally and stopping 1 cm from corona. Document the size and depth of any invasive neoplasm. Indicate whether the tumor invades the landmark structures, including corpus spongiosum, corpus cavernosum, and urethra. Submit sections of tumor to demonstrate its depth of invasion and relationship to urethra, corpora cavernosa, and corpus spongiosum. A section should include the tumor and adjacent unremarkable epithelium. Sections of the foreskin and glans and shaft mucosa should also be included. For tumors involving the urethra, indicate the extent of gross involvement and submit sections to indicate this.

Sample Dictation

Specimen is received [in formalin/fresh], labeled with the patient's name and "[ ]", and consists of a [partial/total] penectomy specimen with[out] attached foreskin, measuring [ ] × [ ] × [ ] cm. There is a [ ] × [ ] × [ ] cm tumor arising in the [foreskin/glans/coronal sulcus/shaft/or a combination of these]. The lesion is [color] and [ulcerative/flat/nodular/verrucous]. Upon sectioning, the tumor invades [subepithelium/corpora cavernosa/corpus spongiosum/urethra] to a depth of [ ] cm. The tumor is [not] present at the soft tissue margin, which is inked [ ]. The remaining [foreskin/glans/shaft] appears [unremarkable/remarkable] with [describe].

Summary of Sections

- 1A Shaft shave margin (including urethra)
- 1B Foreskin shave margin (if present)
- 1C Tumor with deepest invasion
- 1D Tumor in relation to urethra, corpora cavernosa, and spongiosum
- 1E Sections of normal-appearing foreskin, glans, and shaft

What Is the Proper Way to Report the Pathologic Findings in Penile Squamous Cell Carcinoma?

The report should contain the following information: primary tumor (tumor site or sites), size in centimeters, histologic subtype, histologic grade, anatomic level of invasion, tumor thickness in millimeters, and vascular and perineural invasion.

In penectomy specimens, the margins of resection to be reported are urethral/periurethral, corporal, and skin of the shaft. In circumcision specimens, margins include coronal sulcus mucosal margin and cutaneous margin. Commonly associated lesions to be reported are penile intraepithelial neoplasia (differentiated or undifferentiated), lichen sclerosus, and other "inflammatory dermatologic" conditions. If the specimen is accompanied by inguinal nodes, the number and size of nodes should be described. All nodes should be included for microscopic examination. The number of positive nodes and total number of nodes examined should be reported as well as the presence of extracapsular extension and the number and site (e.g., inguinal vs pelvic) of metastatic nodes. The distinction between superficial and deep inguinal lymph nodes has been removed in the 8th edition TNM classification.

Case Studies

Sclerosing Lipogranuloma

Case Presentation

A 35-year-old man presented with a hard mass invading the skin and subcutaneous tissues, which had progressively

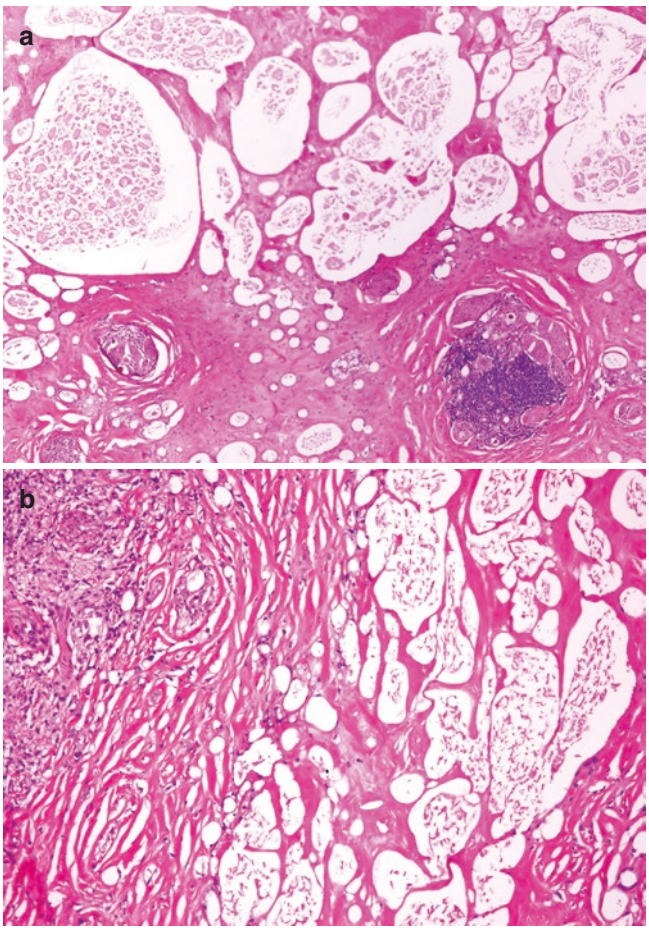

Fig. 7.19 Sclerosing lipogranuloma. (**a**) Numerous variably sized vacuolated spaces adjacent to characteristic sclerotic stroma. (**b**) Foreign body giant cells and lipid vacuoles with marked variation in size

enlarged over 3-month period. He denied the history of injecting foreign material into his external genitalia. There was no trauma to the groin. On physical examination, there were multiple non-tender, irregular masses on the penile shaft dorsally without pus discharge per meatus. The histopathology shows numerous, variably sized vacuolated spaces adjacent to characteristic sclerotic stroma (Fig. 7.19a) and foreign body giant cells and lipid vacuoles with marked variation in size (Fig. 7.19b)

Final diagnosis: sclerosing lipogranuloma

Case Report

Sclerosing lipogranuloma of the penis, also commonly referred to as penile paraffinoma, lipogranuloma, and Tancho's nodules, is a rare benign disease and presents as a peculiar granulomatous reaction that occurs after injury of the adipose tissue. It has been reported to involve many different organs. The term sclerosing lipogranuloma first appeared in Smetana and Bernhard's abstract in 1948 [33]. Subsequently, they expanded their case series to 14 cases, 9 of which involved external male genitalia [34]. They also proposed that it resulted from the reaction to endogenously broken down lipids following trauma provoking a fibrosis and foreign body reaction. Several years later, the other theory advocated by Newcomer [35] and supported by Arduino [36] was that the reaction followed the injection of foreign vegetable or mineral oils. Since then, a considerable number of cases have been reported in the English literature. Nowadays, the disease is subdivided into primary and secondary types based on precipitating factors. The primary type is caused by the reaction to endogenously broken down lipids, in which no possible etiologic factors can be identified, and is rare in Western countries. The secondary type is caused by injection of exogenous foreign bodies for variable reasons from premature ejaculation and impotence to sexual deviance. A wide variety of foreign materials, including silicone, paraffin, mineral oil, metallic mercury, petroleum jelly, vaseline, and cod liver oil, have been reported [37–40].

Clinically, patients usually present with penile deformity, painful erections and eventually, the inability to achieve sexual activities [37, 41]. Other manifestations of foreign body reaction are in the form of inflammation, induration, edema, scarring, necrosis, and ulceration. In some instance clinical presentations are alarming. Tsili et al. reported a patient presenting with painless enlargement of the penis shaft due to the presence of a hard mass invading the skin and subcutaneous tissues [42]. Reactive regional lymphadenopathy and gross deformity may lead to clinical concern for a neoplasia and often warrants biopsy.

An imaging technique accurately characterizing and assessing the extent of the disease would be valuable in the appropriate preoperative planning of these patients, although radiographical features are only described in limited number of case reports. The sonographic features include a poorly defined mass with a high level of echogenicity and an elongated appearance on a longitudinal plane [43]. Computerized tomography (CT) and multiparametric magnetic resonance imaging (MRI) findings of primary sclerosing lipogranuloma were reported in case reports. The lesion was reported to show symmetrically Y-shaped, with the arms of the Y surrounding the penile shaft. The mass showed similar and moderately high signal intensity when compared to muscles on T1- and T2-weighted images, respectively, with irregular enhancement after gadolinium administration, were often described as "Y-shaped" and were unlikely to recur. No fatty components were revealed within the mass.

Sclerosing lipogranulomas usually present indurated and sometimes tender plaque or tumor with variable sizes ranging from few centimeters to massive replacement of genital area. Correspondingly, the lesion is ill-defined with firm, yellow, granular, and gelatinous cut surfaces. Invading into adjacent skin and subcutaneous tissue and underlying muscles can be seen. Histopathological examination demonstrates lipid

vacuoles embedded in a sclerotic stroma composed of epithelioid cells and a mixture of inflammatory cells infiltrates in the interstitium, including multinucleated giant cells, lymphocytes, macrophages, and monocytes. Eosinophils may be present, but usually mild. Inflammatory cells infiltrates may be multinodular or diffuse. If foreign bodies related, vacuoles of variable size corresponding to exogenous substances embedded in collagenous tissue may be obvious, which may mimic adipose tumor at lower power view. It becomes more obvious that many vacuoles are within mono- and multinucleated histiocytes at higher power examination. Immunohistochemical stain can be utilized to rule out neoplastic process, including CD68 and CD163 to confirm histiocytic nature of infiltrate. Oil Red O staining on frozen sections may be helpful to confirm the diagnosis.

Top differentials considerations include malakoplakia, liposarcoma, metastatic carcinoma with clear or signet ring cells, adenomatoid tumor and lymphangioma. Making the distinction among these differentials is critical, in view of the different therapeutic options for them. In most cases careful examination of morphologic features with H&E stain is the key to distinct sclerotic lipogranuloma from aforementioned entities. In cases that are challenging to diagnose with H&E sections, readily available immunohistochemical stains can aid in the distinction. Liposarcoma usually lacks of foreign body type giant cell reaction and foamy histiocytes, which are seen in sclerotic lipogranulomas. Metastatic carcinomas have atypical nuclei and immunoreactivity for keratin. Adenomatoid tumor is a benign mesothelial tumor and characterized by cystic or slit-like spaces lined by flattened or cuboidal cells and immunopositivity for keratin and mesothelial markers, including calretinin. Lymphangioma is another benign entity with the proliferation of dilated lymphatic vessels and positive for vascular or lymphatic markers, CD31 or D2-40, if needed, to clarify diagnosis.

Clinical management of secondary penile sclerosing lipogranuloma usually requires an aggressive treatment including partial or total excision of granulomas, with or without reconstructive skin flaps depending on the extent of excision.

Scrotal Calcinosis

Case Presentation

A 30-year-old man reports multiple itchy bumps on scrotum, which present for years. His physical examination revealed multiple and bilateral calcified cutaneous lesions of the scrotum. The lesions were completely surgically excised. Histological examination reveals basophilic granular and globular materials, which is consistent with calcium deposition (Fig. 7.20a), in various intensity and sizes in dermis and upper part of dartos. Palisading histiocytes and multinucleated giant cells are found at the periphery (Fig. 7.20b).

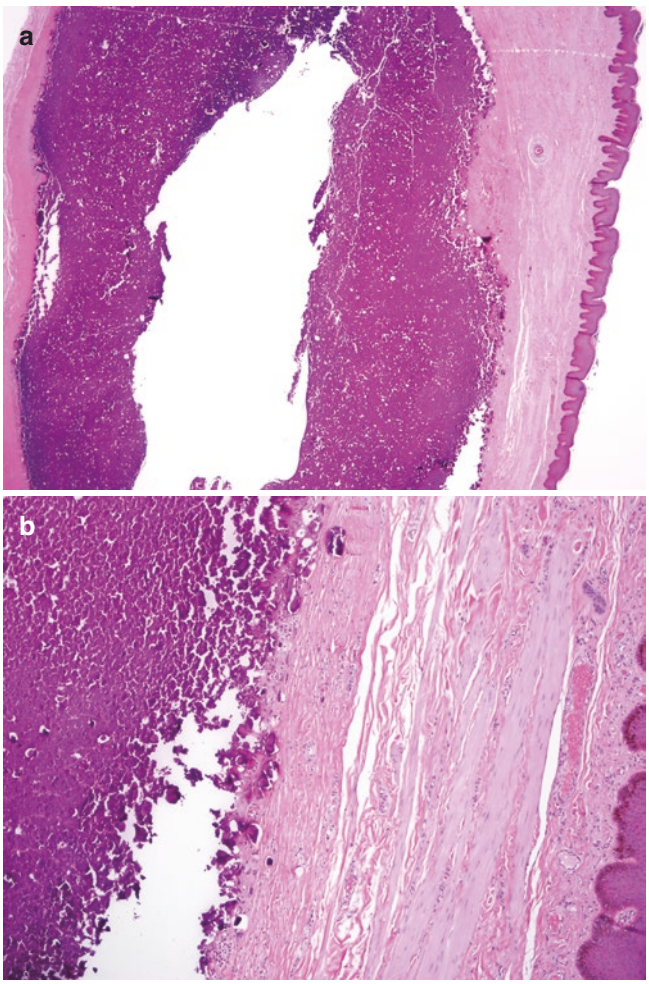

Fig. 7.20 Scrotal calcinosis. (**a**) Basophilic granular and globular materials with various intensity and size are seen in dermis, which is consistent with calcium. (**b**) Palisading histiocytes and multinucleated giant cells are present at the periphery

Final diagnosis: scrotal calcinosis

Case Report

Scrotal calcinosis is a rare, yet benign, disease of the scrotal skin with uncertain etiology, which was first described in 1883 by Lewinski [44]. Clinically, it usually presents as gradual growth of brown-yellow firm solitary or multiple nodules on the scrotal skin in the absence of abnormalities in calcium and phosphate metabolism [45]. Sometimes it produces a white, chalky material. Scrotal calcinosis typically begins in adolescence or early adulthood. Although it tends to increase in size and number over time [46], lesions remain discrete and do not become confluent. In addition, nodules are movable and do not attach to underlying structures. Some

patients complain about pain and itching and there have also been reports of infections associated with scrotal calcinosis. Unusual presentations include pedunculated forms [47] and perineal/suprapubic pain consistent with chronic prostatitis [48]. To relieve symptoms and to preserve scrotal cosmesis are the indication for surgery [49]. Although it is controversial, surgery is still considered to be the treatment of choice and provides a good clinical outcome. The laxity of the scrotal skin, along with the decision to perform multiple elliptical excisions, allowed for good scrotal coverage and excellent cosmetic outcome. However, there are considerable controversies among clinicians as to the risk of recurrence after surgery. Some clinicians believe that all patients with scrotal calcinosis should undergo surgical intervention, in contrast, other disagree with surgical excision considering the high probability of recurrence [50].

Controversy regarding the pathogenesis of scrotal calcinosis still exists, despite its rarity and benign clinical behavior. Some investigators believe that it is truly a late presentation of epidermal inclusion cysts with dystrophic calcification [51–53]. It was previously proposed that it has been attributed to sebaceous cysts, calcified steatocystoma, fibroma, atheroma, and xanthoma [54]. More recently, it has been suggested that scrotal calcinosis is resulting dystrophic calcification from dartos muscle necrosis and degeneration [47].

Macroscopically, scrotal calcinosis shows hard white calcified deposits located in dermis and dartos. Histologically, it is characterized by basophilic granular and globular materials, which is consistent with calcium deposition, in various intensity and sizes in dermis and upper part of dartos. Palisading histiocytes and multinucleated giant cells are usually found at the periphery. Remnants of preexisting cystic lesion or adnexal neoplasm may be identified adjacent to the lesion. Calcified material can be highlighted with von Kossa stain though it is rarely necessary [55].

There almost no histologic differential diagnosis owing to very distinctive morphology of scrotal calcinosis. Nodular amyloidosis is only consideration. In contrast to scrotal calcinosis, amyloidosis exhibits homogeneous and eosinophilic material, which is positive for Congo red and crystal violet and negative for von Kossa [56].

Although the consensus on the management is still lacking, surgical intervention is the only treatment recommendation, especially for patients with multiple nodules. Nonsurgical treatment includes the use of corticosteroids and a low-calcium diet with cellulose phosphate supplementation. Surgical management corrects cosmetic deformity and enable to provide tissue sample for confirmation of the diagnosis on histologic examination.

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