Vulvar Glandular and Other Neoplasms

6

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Abstract

This chapter will address vulvar neoplasms with glandular differentiation as well as neuroendocrine carcinoma and metastatic tumors. These entities are rare, as the vast majority of malignancies of the vulva are squamous in origin. Careful consideration of the differential diagnosis, as well as knowledge of any pertinent clinical history, is essential when evaluating these lesions.

Keywords

Adenosquamous carcinoma · Adenocarcinoma · Bartholin Merkel · Cloacogenic · Metastasis

6.1 Adenosquamous Carcinoma of the Vulva

6.1.1 Clinical Features

Adenosquamous carcinoma of the vulva is uncommon, comprising just 18 of 135 cases of vulvar cancer in one large study [1]. The mean age of diagnosis is 65–70 years, and this entity may be associated with chronic vulvar inflammatory disease [2]. Adenosquamous carcinoma of the vulva is not associated with human papilloma virus (HPV), though this is based on the study of relatively few cases [2, 3]. In a study by Carson et al., only one of 16 cases was positive for an undetermined type of HPV DNA [3]. This tumor involves the labium majus, and many also involve the labium minus [1]. Adenosquamous carcinoma has been proposed to arise from mucin-secreting glands of the hair shaft [4], Bartholin glands [5], and, in one report, a hidradenoma papilliferum [6].

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6.1.2 Microscopic Findings

Adenosquamous carcinoma is characterized by a blend of tumor cells showing squamous and glandular differentiation. The glandular areas are usually lined by a single layer of cells, while multilayering results in a squamoid appearance with frequent areas of keratinization, dyskeratosis, and acantholysis (Fig. 6.1). Solid areas within the tumor frequently consist of spindled squamoid cells. The tumor is deeply invasive in many cases and may involve the vagina and other adjacent perineal structures.

6.1.3 Immunohistochemistry

The lesional cells are diffusely positive for a high-molecular-weight keratin stain, and carcinoembryonic antigen (CEA) stain can be used to highlight glandular differentiation.

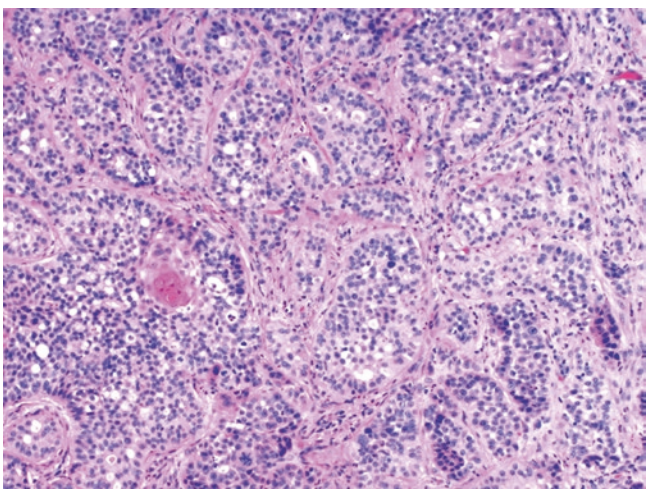

Fig. 6.1 Adenosquamous carcinoma, showing areas of dyskeratosis adjacent to gland formation (original magnification, 100×)

W. Zheng et al. (eds.), *Gynecologic and Obstetric Pathology, Volume 1*, https://doi.org/10.1007/978-981-13-3016-2_6

6.1.4 Differential Diagnosis

The growth pattern of the acantholytic, or pseudoglandular, variant of *squamous cell carcinoma* can mimic that of adenosquamous carcinoma (Fig. 6.2). Careful examination for the presence of true glandular differentiation is necessary for the latter diagnosis [2]. *Invasive Paget disease* and *amelanotic melanoma* are also considerations on the differential diagnosis. This differential can be narrowed down through the use of appropriate immunohistochemistry, if necessary. These entities as well as their immunohistochemical profiles are discussed separately in this chapter.

6.1.5 Prognosis and Treatment

Vulvar adenosquamous carcinoma has a worse prognosis than squamous cell carcinoma of a comparable stage [1] and is associated with a higher rate of metastasis [7]. Patients with adenosquamous carcinoma typically present at a clinically more advanced stage of disease than those with conventional squamous cell carcinoma; Underwood et al. observed that 2/3 of the patients in their study were T3 or higher when diagnosed [1]. Treatment varies depending on the extent of disease. Surgical treatment includes wide local excision or partial radical vulvectomy with lymphadenectomy; however, advanced- or late-stage disease may require the combination of surgery and chemoradiation.

6.1.6 Adenocarcinoma

This section discusses extramammary Paget disease, carcinoma arising in ectopic breast tissue, skin appendage adenocarcinoma, and carcinoma of the Bartholin gland.

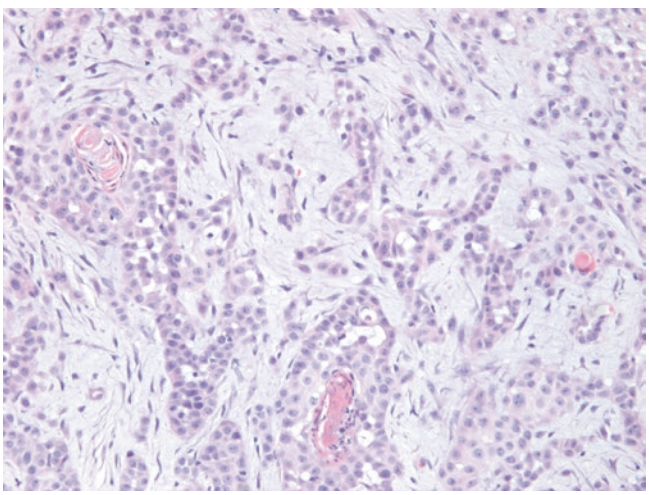

Fig. 6.2 Squamous cell carcinoma with acantholytic features (original magnification, 200×)

6.2 Extramammary Paget Disease

6.2.1 Clinical Features

Extramammary Paget disease (EMPD) is a rare intraepithelial adenocarcinoma that may arise from primary or secondary spread of malignant cells. EMPD comprises 1–2% of all vulvar malignancies [8], but in terms of EMPD sites, the vulva is the most common. Other less common areas of involvement include the perianal region, eyelids, groin, and scrotum [9]. Secondary EMPD represents spread of an internal malignancy, often a genitourinary or gastrointestinal source, and may represent up to 30% of EMPD cases [10]. Ruling out internal malignancy is vital as this portends different prognostic and therapeutic implications.

Women affected by EMPD of the vulva are usually between 50 and 80 years old [11]. Clinically, lesions present as multicentric moist, red pruritic plaques with or without ulceration. Erythema with hyperkeratotic scale may lead to a clinical differential diagnosis of more common conditions such as eczema, *Candida albicans* infection, or vulvar intraepithelial neoplasia. While pruritus is the most common symptom, up to 10% of patients may be asymptomatic, and diagnosis may not occur until 2 years after symptom onset [12].

6.2.2 Microscopic Findings

EMPD is characterized by large, atypical cells with pale cytoplasm, namely, Paget cells, arranged singly or in nests, occupying the lower level of the epidermis (Fig. 6.3). Cytologically, Paget cells display pale cytoplasm and enlarged vesicular nuclei with prominent nucleoli.

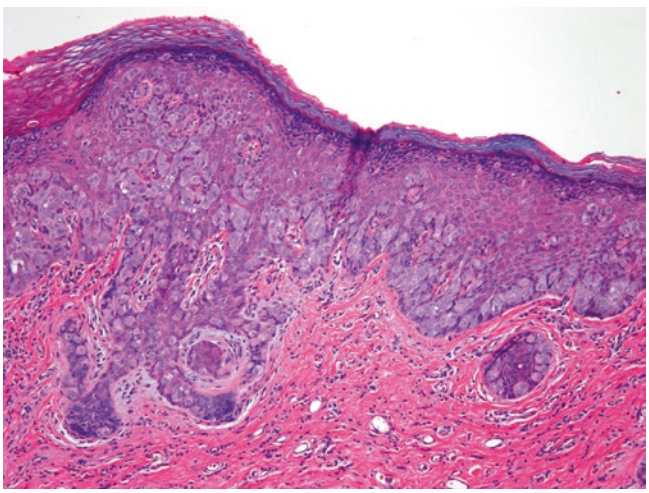

Fig. 6.3 Extramammary Paget disease, lower third of the epidermis is involved by small clusters or single cells with noticeably fainter cytoplasm staining (original magnification, 100×)

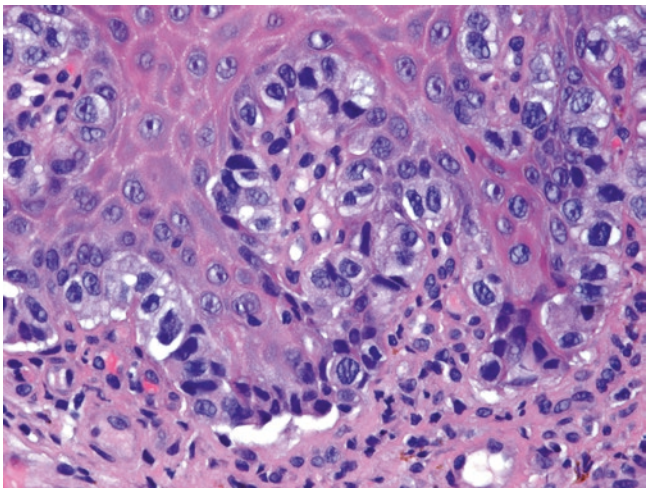

Fig. 6.4 Extramammary Paget disease, the presence of cytoplasmic vacuoles aids in the diagnosis of an adenocarcinoma (original magnification, 400×)

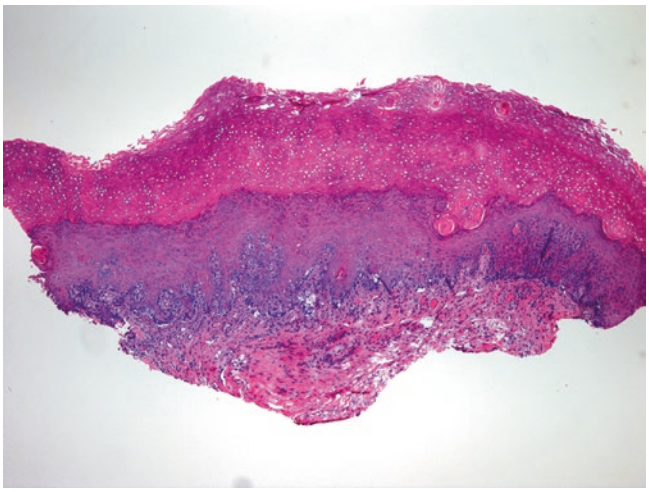

Fig. 6.5 Extramammary Paget disease. Overlying epidermal changes, including squamous hyperplasia as seen here, are often encountered in EMPD (original magnification, 40×)

Cytoplasmic vacuoles may be seen (Fig. 6.4). Occasionally, Paget cells may be found in the upper layers of the epidermis or extending along adnexal structures. Similar to other cutaneous tumors, adnexal extension does not equate invasive disease, and preservation of the basal keratinocytes is a key clue to ruling out invasion [11]. Direct stromal invasion may be difficult to find given the multicentric nature of EMPD, but its incidence may be as high as 47% [13].

Other histologic patterns can be observed in EMPD and include glandular and acantholysis-like patterns [14]. The glandular pattern is uncommon but shows intraepidermal glands with polarization of tumor cells around a central lumen. The acantholytic pattern demonstrates tumor cells falling apart within the epidermis and creating spaces; this lack of cohesion between tumor cells and neighboring keratinocytes imparts a pseudoglandular appearance. Invasion is characterized by malignant cells located in the dermis as nests or single cells with clear delineation from the basement membrane. Rare reports have described invasion presenting as mucinous carcinoma [10]. Some studies have found correlation between the presence of invasion and the histologic pattern of EMPD, but these studies are limited in sample size and not restricted to vulvar EMPD [14].

Epidermal changes are commonly encountered in association with EMPD. Hyperplasia and anastomosis of the epidermal rete ridges have been described in EMPD of the perianal region [15]. Other epidermal proliferations include papillomatous hyperplasia, fibroepithelioma-like hyperplasia, and squamous hyperplasia (Fig. 6.5). Concurrent in situ and invasive squamous cell carcinoma have also been observed in cases of vulvar EMPD [16]. One must be aware of these benign and malignant epidermal changes as they may obscure or distract from a diagnosis of EMPD.

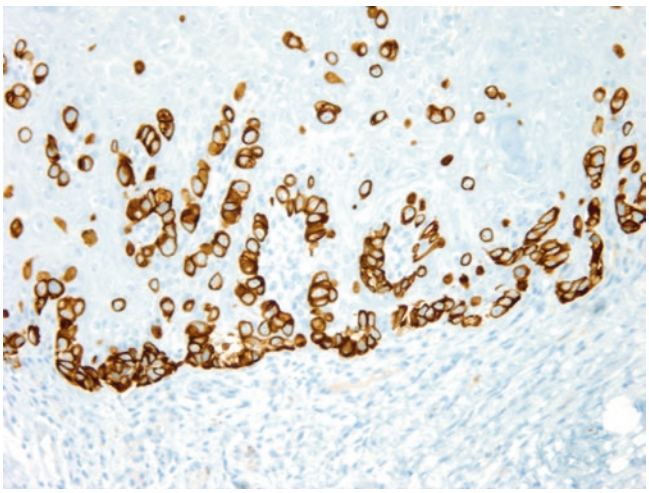

Fig. 6.6 Extramammary Paget disease. Immunohistochemical staining for cytokeratin 7 shows positivity in the EMPD cells that are predominantly found in the lower epidermis. Note the negativity for CK7 in the normal keratinocytes (original magnification, 200×)

6.2.3 Immunohistochemistry

Immunohistochemical staining patterns are useful when attempting to differentiate between primary and secondary EMPD. EMPD tumor cells typically express low molecular weight cytokeratin, epithelial membrane antigen (EMA), gross cystic disease fluid protein 15 (GCDFP-15), and carcinoembryonic antigen (CEA). Primary EMPD has an immunoprofile of CK7+/CK20-/GCDFP15+ (Fig. 6.6). Positivity for Her2/neu may be seen in 30–50% of primary EMPD. Secondary EMPD immunophenotypes depend upon the primary site. Secondary EMPD from an anorectal primary will be CK7-/CK20+/GCDFP15- as well as MUC2+ and CDX2+. EMPD from a urothelial primary is usually

CK7+/CK20 +/GCDFP-15-, and additional positive staining can be seen with uroplakin-3 and GATA-3 [17, 18]. However, some studies have found GATA-3 positivity in primary EPMD, which may make it a less reliable stain when ruling out a urothelial primary [19]. A summary of an immunohistochemical panel which may be useful in distinguishing primary from secondary EMPD is provided in (Table 6.1).

Intracellular mucin is highlighted by the use of special stains such as periodic acid Schiff, Alcian blue, or mucicarmine [20]. In terms of hormone receptor status, primary EMPD is characteristically negative for estrogen and progesterone receptors; androgen receptor can be immunopositive in approximately half of cases. Interestingly, this hormone phenotype is similar to that of benign apocrine glands and apocrine carcinoma [21].

6.2.4 Differential Diagnosis

Superficial spreading melanoma and *melanoma in situ* may have similar cytological and architectural features. Large cells with prominent nucleoli can form nests and show pagetoid spread throughout the epidermis; however, melanoma will typically involve the basal layer, whereas EMPD shows an intact basal layer with displacement of keratinocytes (Fig. 6.7). Melanin pigment may be more prominent in variants of melanoma, but occasional melanin may be seen in Paget cells [11]. Paget cells are usually negative for melanocytes markers such as S-100, HMB45, Melan-A, and SOX10 [20]. In addition, melanoma is negative for mucins by various special stains.

Squamous cell carcinoma (SCC), in situ or invasive, is a much more common entity that may show pagetoid spread of neoplastic cells (Fig. 6.8). A histologic clue is full-thickness atypia with effacement of the basal layer in squamous lesions. SCC will lack glandular formation and intracellular mucin and is usually negative for CK7 and GCDFP-15 and positive for CK5/CK6, p63, and p16 [22]. *Usual-type vulvar intraepithelial neoplasia* (uVIN) falls on the premalignant spectrum of SCC, and, like SCC, pagetoid spread has been described. Diffuse, full-thickness positivity with p16 aids in the diagnosis of uVIN.

Sebaceous carcinoma, which typically involves the head and neck, is another rare malignancy which may show cytologic and architectural overlap with EMPD. Sebaceous carcinoma is cytologically characterized by atypical basaloid cells showing foci of sebocytic differentiation in the form of multiple lipid-filled vacuoles with nuclear indentation. Architecturally, the intraepidermal portion often shows pagetoid spread, and dermal invasion is apparent (Fig. 6.9). Immunohistochemistry is a useful tool in cases of superfi-

Table 6.1 Immunophenotypes of EMPD

		Secondary EMPD		
	Primary EMPD	Anorectal	Urothelial	Cervical
Cytokeratin 7	+	–	+	+
Cytokeratin 20	–	+	+	–
GCDFP-15	+	–	–	–
Additional positive stains	Her-2/neu	MUC-2 CDX-2	GATA-3 Uroplakin-3	p63 p16

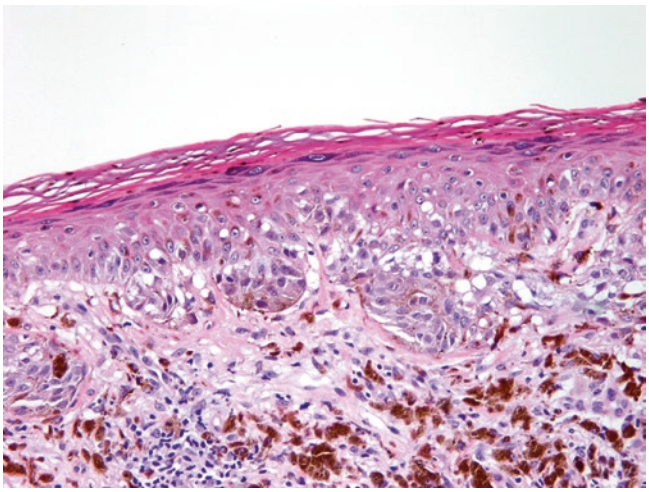

Fig. 6.7 Superficial spreading melanoma with basally located melanocytes. Note the grayish cytoplasm, lack of mucin vacuoles, and presence of melanin (original magnification, 200×)

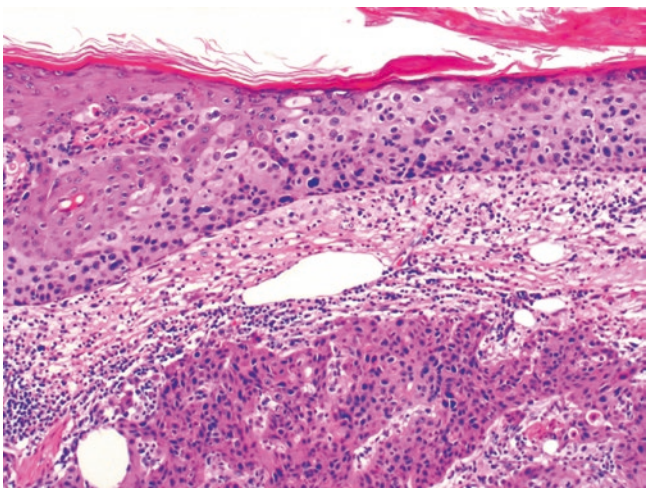

Fig. 6.8 Squamous cell carcinoma with pagetoid spread (original magnification, 100×)

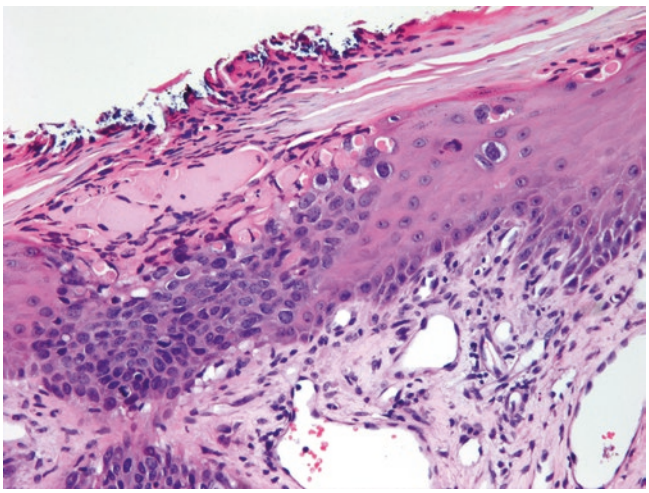

Fig. 6.9 Sebaceous carcinoma with intraepidermal spread (original magnification, 200×)

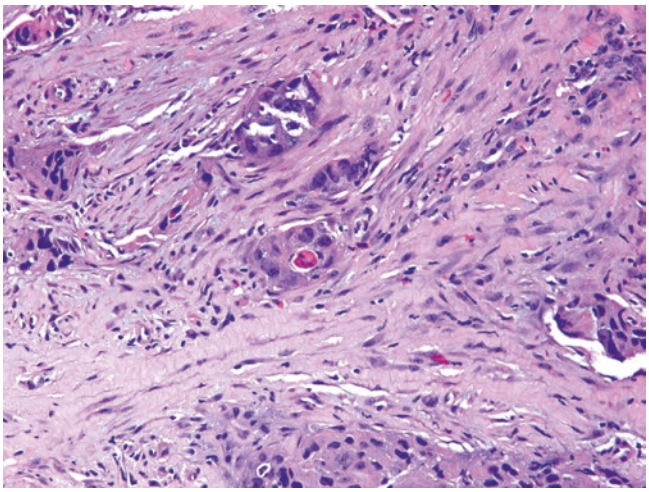

Fig. 6.10 Ductal adenocarcinoma showing high-grade nuclear features with surrounding desmoplastic stroma (original magnification, 200×)

cially sampled sebaceous carcinoma in which the dermal component is not readily visualized. Sebaceous carcinoma shows membranous positivity for adipophilin around lipid vesicles, and staining for nuclear factor XIIIa has been proposed as a sensitive marker of sebaceous differentiation [23, 24]. Sebaceous tumor cells will be negative for GCDFP-15 and CEA.

6.3 Carcinoma Arising in Ectopic Breast Tissue

6.3.1 Clinical Features

Ectopic breast tissue is the result of incomplete ectodermal involution and may be found anywhere from the axilla to the vulva [25]. Clinically, palpable ectopic breast tissue may be mistaken as a lipoma due to a predominance of adipose tissue. As with other ectopic tissue, there remains a small but present risk for malignancy. Only a few dozen cases of carcinoma arising from ectopic breast tissue have been reported. Patients tend to be in their late 60s, but patients as young as 44 years old have been reported [26]. Lesions may be slightly tender and average 3 cm in size. As with any vulvar mass in a postmenopausal woman, vulvar lesions should be approached with a high suspicion for malignancy.

6.3.2 Microscopic Findings

Breast carcinoma arising from ectopic breast tissue has the same morphologic variants as seen in breast primaries. *Ductal carcinoma* is characterized by infiltrating angulated glands with varying degrees of nuclear atypia (Fig. 6.10).

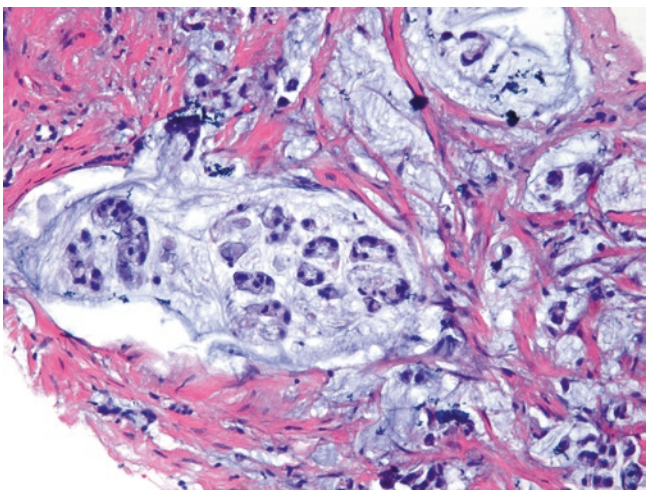

Fig. 6.11 Mucinous carcinoma is comprised of islands of low-grade neoplastic cells floating in mucin (original magnification, 200×)

Tumors can range from well-formed glands (low-grade) to sheets of tumor cells with high mitotic activity (high-grade). Ductal carcinoma in situ may be identified by distended glands filled with a monotonous population of cells with or without comedonecrosis.

Mucinous carcinoma is another variant of breast carcinoma that may be seen in the vulva. This variant features an abundance of extracellular mucin with floating islands of tumor cells (Fig. 6.11). Tumor cells are typically well-differentiated with low-grade nuclear features. Thin fibrous septa traverse the mucin pools and form compartments.

Lobular carcinoma is typically low-grade and shows invasion as single cells arranged in cords.

It is essential to assess lymphovascular invasion and subsequent lymph node metastasis in cases of breast carcinoma aris-

ing from ectopic tissue. Previous reviews of the literature have reported lymph node metastasis in up to 66% of cases [26].

Normal benign changes of the breast may also be found in ectopic breast tissue [27]. An example is lactational change, which features closely packed glands with cytoplasmic blebs and vacuoles. Relative increases in cellularity and prominent nucleoli raise the suspicion for malignancy, but overall well-circumscribed architecture and clinical awareness are key in recognizing benign mimics.

6.3.3 Immunohistochemistry

Similar to primary breast carcinoma, carcinoma arising out of ectopic breast tissue will stain positively for pancytokeratin, CK7, mammoglobin, and gross cystic disease fluid protein (GCDFP-15) [26]. Over half of cases will stain estrogen receptor (ER) and progesterone receptor (PR) positive. Her2/neu, human epidermal growth factor receptor 2, is typically negative in these carcinomas. Given the infrequency of Her2/neu positivity, many authors only require positivity in ER or PR as part of their diagnostic criteria for breast carcinoma arising from the vulva [28].

6.3.4 Differential Diagnosis

Other patterns of primary breast carcinoma are less likely but should be considered in the differential diagnosis.

6.3.5 Prognosis and Therapy

Given the rarity of breast carcinoma arising from ectopic breast tissue, there are no widely accepted treatment guidelines at this time. In the event of a positive sentinel node, lymph node mapping with subsequent lymphadenectomy has been researched and strongly supported by some authors [29]. Treatment plans for vulvar primaries may mirror those of breast primaries: personalization of surgical, chemotherapeutic, and hormonal therapies [26].

6.4 Phyllodes Tumor

The lesional transformation of mammary-like tissue is not restricted solely to the ductal epithelium as stromal lesions, while rare, can also occur. Typically, lesions present as solitary, mobile, and painless nodules involving the labia majora [30]. Prior literature review of vulvar phyllodes tumor characterized the gross findings as a well-circumscribed white lesion with a pushing margin and papillary-like fronds [30]. The histologic features are similar to that of a primary breast phyllodes tumor and include leaflike fronds of stromal overgrowth covered by a bilayer of epithelium and myoepithelial cells. Higher power view of the stroma demonstrates bland spindle cells in a collagenized background; hyalinization may be focal when present [31].

Immunohistochemical staining shows the ductal epithelial cells are positive for ER and PR, which in contrast, are negative in the stromal spindle cells [30]. The myoepithelial cells are positive for SMA and S-100. The stromal spindle cells are also positive for CD34, vimentin, and SMA; ER and PR are usually negative.

6.5 Skene's Gland Adenocarcinoma

While the periurethral Skene's gland is part of the genitourinary system, it is important to recognize that the exceedingly rare Skene's gland adenocarcinoma may be encountered as a vulvar lesion. This tumor typically affects women in their 60s, and median tumor size has been reported to be 3.0 cm. Pain may be elicited by the perineural invasion of the tumor.

Gross features include poor circumscription with invasive borders; the surface is usually solid, although necrosis may be present [32]. Histologic features may vary widely as the tumor may show features similar to prostatic, intestinal, or adenoid cystic carcinomas. Prostatic differentiation will show highly atypical cells with cribiforming or tubular formation, and immunostaining may show positivity for PSA, CA-125, and P504S [33]. Intestinal differentiation will show cribiforming with glandular areas and signet rings. Similar to other tumor that show intestinal features, immunostaining will show positivity for CDX2 and MUC2 [32].

6.6 Skin Appendage Adenocarcinoma

Due to the presence of hair, apocrine glands, and sebaceous glands found throughout the vulvar skin, the malignant counterparts of these cell lines have been reported in the vulva. Approximately half of malignant vulvar adnexal tumors are some form of EMPD, and the other less frequent malignant tumors include sebaceous carcinoma, apocrine carcinoma, and microcystic adnexal carcinoma [34]. Adenoid cystic carcinoma is discussed later in this chapter as a carcinoma of the Bartholin gland.

6.6.1 Clinical Features

Due to a higher density of skin appendages, cutaneous adnexal malignancies are much more common on the head and neck of patients in their 50s and 60s. However, there are multiple case reports of such lesions affecting the vulva. Typically, these lesions present as a slowly growing papule

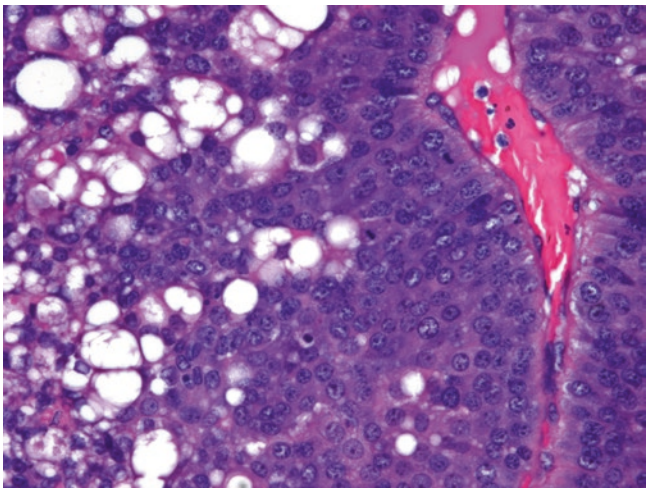

Fig. 6.12 Sebaceous carcinoma. Oftentimes focal, the presence of lipid vacuoles that indent the nucleus is useful in identifying sebaceous carcinoma and differentiating it from basal cell carcinoma (original magnification, 400×)

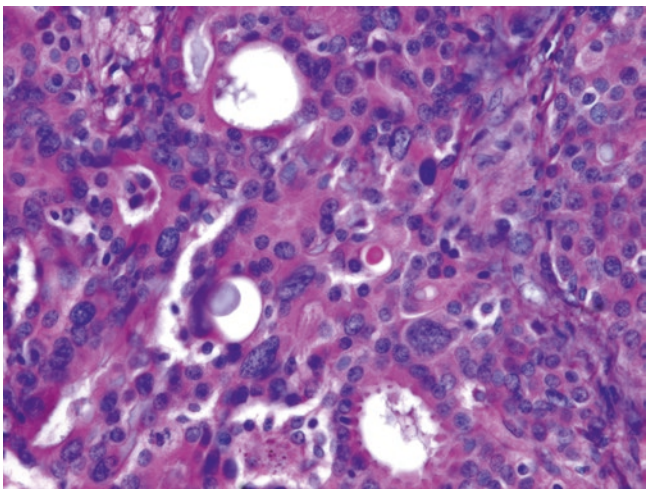

Fig. 6.13 Apocrine carcinoma showing marked nuclear atypia with areas of gland formation and apical snouting (original magnification, 400×)

with various degrees of pain or paresthesia, which is likely secondary to nerve involvement [35]. Ulceration and pain are variable, and lesions average 3.0 cm in size [35, 36].

Coloration varies from flesh-colored to slightly yellow as is the case for *sebaceous carcinoma* due to its increased lipid content [37].

6.6.2 Microscopic Findings

Sebaceous carcinoma is characterized by lobules of basaloid cells with marked atypia and mitoses. Well-differentiated tumors will display clear cell change in the center of the tumor nodules, and tumor cells will have multiple lipid vacuoles that indent the nucleus (Fig. 6.12). Within the tumor nodules, central comedonecrosis is a common finding. With poorly differentiated tumors, there are less obvious malignant sebocytes and more basaloid cells with prominent atypia. Occasionally, these cells may have a squamous appearance, which may lead to confusion with much more common entities such as squamous cell carcinoma.

Apocrine carcinoma features large eosinophilic cells arranged in cords and nests within the dermis. At scanning magnification, these tumors can appear benign as there may be an overall nodular growth of tightly packed glands. Higher power viewing reveals these glands dissecting through collagen fibers with various degrees of cribiforming. Tumor cells may showed marked atypia and have characteristic decapitation secretion and apical snouting (Fig. 6.13) [38].

Microcystic adnexal carcinoma (MAC) is a slow growing but locally aggressive sweat gland tumor that may be confused with benign syringoma, desmoplastic trichoepithelioma, or infiltrative basal cell carcinoma, especially when interpreting a superficial biopsy. At low power, MAC is asymmetric and poorly circumscribed and usually extends into the deep dermis and subcutis. The superficial aspect of the tumor shows keratinous cysts and basaloid strands with variable ductal differentiation. The stroma displays a desmoplastic response. MAC may also grow as nests and cords, and there is a characteristic "tadpole-like" trailing of the ductal component, which is architecturally similar to syringoma (Fig. 6.14) [35]. Key histologic features to distinguish MAC from syringoma are the presence of perineural invasion and extension of the low-grade ductal structures into the subcutaneous tissue or muscle (Fig. 6.15). As opposed to MAC, syringomas and desmoplastic trichoepitheliomas are sharply demarcated laterally at the base of the lesion. As such, a sufficiently deep biopsy is required for accurate diagnosis.

6.6.3 Immunohistochemistry

Sebaceous carcinoma can be readily identified on routine staining in well-differentiated cases. For cases with poor differentiation, immunohistochemistry has more utility. Epithelial membrane antigen (EMA) positivity is helpful in well-differentiated sebaceous carcinomas, as positivity helps rule out basal cell carcinoma, which is EMA negative [39]. Adipophilin, which is a protein found within lipid droplets in cells, is a highly sensitive and specific immunostain for sebaceous neoplasms [40]. Nuclear positivity for androgen receptor can be seen even in poorly differentiated sebaceous carcinomas, but this does not rule out basal cell carcinoma as over half of BCC may be androgen receptor positive [41]. Positivity for nuclear factor XIIIa may be helpful in supporting sebaceous differentiation [24].

Apocrine carcinoma expresses gross cystic disease fluid protein-15 (GCDFP-15), estrogen receptor, and androgen

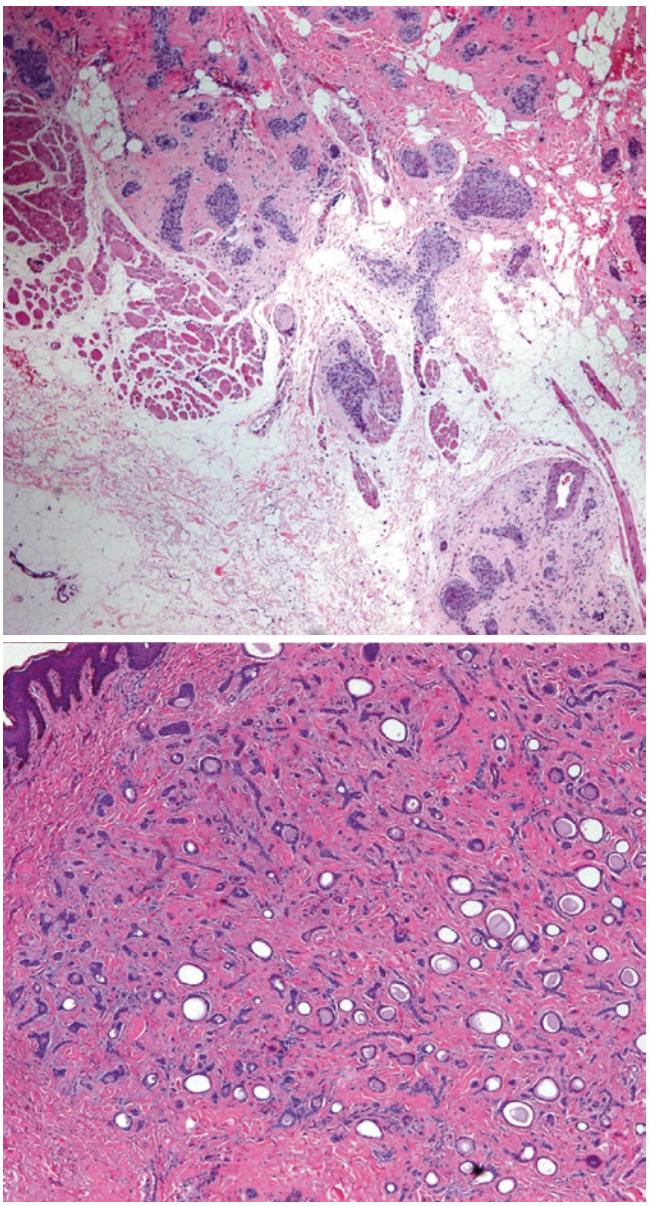

Fig. 6.14 Microcystic adnexal carcinoma (top) is composed of low-grade cells forming nests and cords with occasional lumen formation. Invasion into the subcutis and perineural invasion are key to the diagnosis. Syringoma (bottom) has the same nested and corded architecture, but involvement is limited to the dermis and usually well-circumscribed (original magnification, 40×)

receptor [42]. One must be careful when relying on histology or immunohistochemistry for the diagnosis of cutaneous apocrine carcinoma versus breast carcinoma. Hormone receptors and GCDFP-15 are positive in both entities, and immunostaining patterns with mammoglobin may not fully elucidate tumor origin. Thorough review of clinical history and searching for neighboring mammary-like glands are helpful in making this rare diagnosis.

Pancytokeratin may be useful to highlight the extent of tumor spread in *MAC*. BerEP4 negativity may be useful to differentiate MAC from an infiltrative or morpheaform basal cell carcinoma, which shows intense BerEP4 positivity [43]. Cytokeratin 15 negativity and cytokeratin 19 positivity helps distinguish MAC from desmoplastic trichoepithelioma; although, some studies have found various degrees of CK15 positivity in MAC [43, 44]. CK20-positive Merkel cells are present as colonizing desmoplastic trichoepitheliomas but are absent in basal cell carcinomas and microcystic adnexal carcinomas [45].

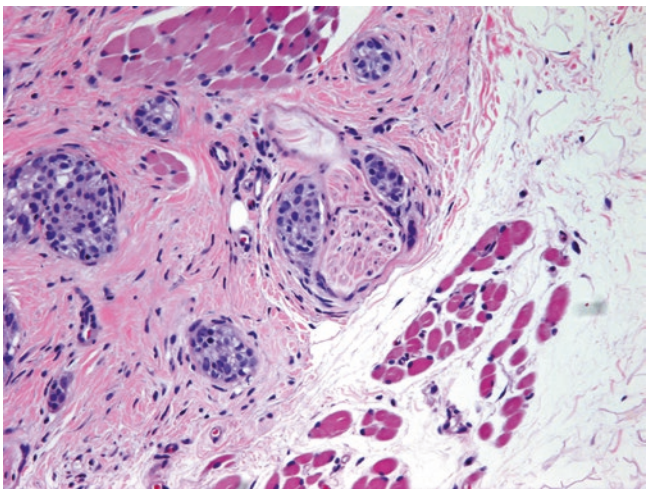

Fig. 6.15 Microcystic adnexal carcinoma. The presence of subcutaneous or, in this case, perineural invasion is essential feature to make the diagnosis of MAC (original magnification, 200×)

6.7 Carcinoma of the Bartholin Gland

6.7.1 Clinical Features

Carcinomas of the Bartholin gland comprise less than 5% of vulvar carcinomas and less than 1% of all gynecologic cancers. The most common histologic subtype is squamous cell carcinoma, followed by adenocarcinoma and less common tumors such as adenoid cystic carcinoma and small cell neuroendocrine carcinoma [46, 47]. Such tumors typically present as a painless mass of the posterolateral vulva in postmenopausal females. Patients may complain of pruritus, vulvodynia, or abnormal bleeding. One should be cautious when diagnosing any Bartholin gland "cyst" reported in a postmenopausal female and approach such lesions with a high suspicion for malignancy [48]. The biopsy should provide appropriate depth, and one must exclude more common diagnoses such as metastasis.

6.7.2 Pathologic Features

6.7.2.1 Gross Findings

Bartholin gland carcinoma is usually an ill-defined mass that has an average size of 4.0 cm [49]. The lesion may be cystic or firm, and focal areas of necrosis may be identified on the cut surface.

6.7.2.2 Microscopic Findings

Squamous Cell Carcinoma

The most common histologic subtype of Bartholin gland carcinoma is squamous cell carcinoma (SCC). Similar to SCC of other organs, various degrees of differentiation and keratinization can be seen. Identification of carcinoma in situ within the Bartholin gland duct is a histologic clue to tumor origin.

Adenocarcinoma

The second most common histologic subtype, adenocarcinoma, may show papillary or solid patterns. Intraductal adenocarcinoma features markedly atypical cells tracking along the Bartholin gland duct extending to the squamous-lined surface. Other features include cribiforming and intraductal necrosis similar to that seen in intraductal carcinoma in situ of breast origin. Invasion is noted by angulated glands with adjacent desmoplastic stroma. Cytologically, tumor cells are hyperchromatic with irregular nuclear borders and increased N:C ratio.

Adenoid Cystic Carcinoma

Morphologic features of adenoid cystic carcinoma of the Bartholin gland are identical to those seen in the salivary gland and other sites. The tumor is composed of infiltrating glands with a characteristic cribiforming pattern, commonly described as "cookie-cutter" (Fig. 6.16). Morphology is commonly a mixture of tubuloglandular and nested patterns [50]. Eosinophilic basement membrane-like material is found within these cribiforming neoplastic glands. Similar to a primary salivary gland malignancy, perineural invasion is commonly found in adenoid cystic carcinoma [51].

Small Cell Carcinoma

Small cell carcinoma is a poorly differentiated neuroendocrine carcinoma that shows "small blue cells" at low power. Architectural features include tumor cells arranged in nests or trabeculae. Tumor cells show enlarged nuclei with a thin rim of cytoplasm, and nuclear molding is abundant. Extensive crush artifact is present, which may raise suspicion for lymphoma.

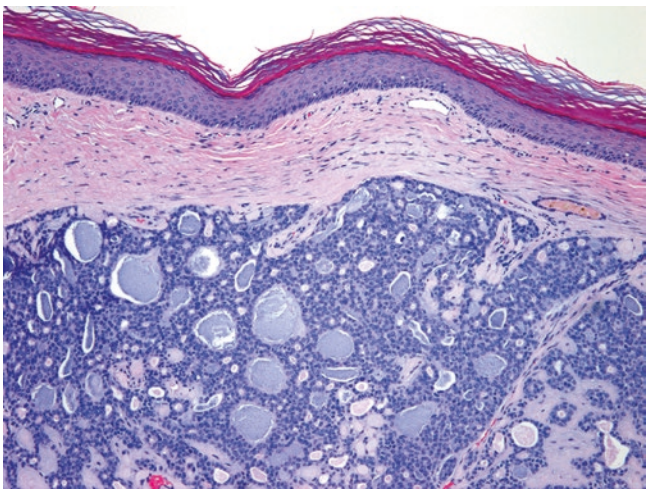

Fig. 6.16 Adenoid cystic carcinoma showing punched out luminal spaces characteristic of adenoid cystic carcinoma (original magnification, 100×)

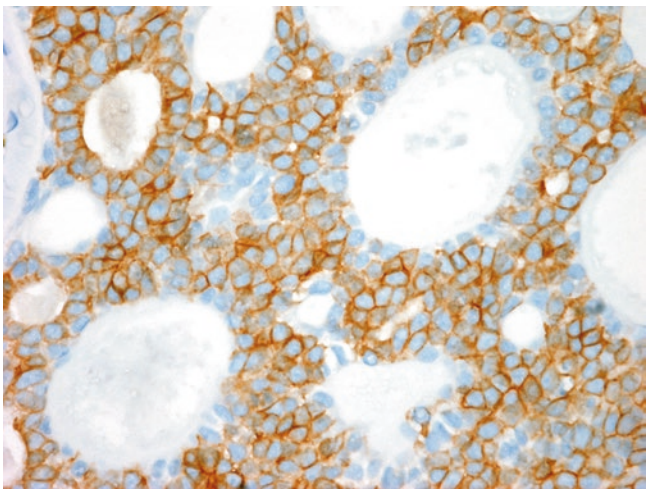

Fig. 6.17 Adenoid cystic carcinoma. Membranous and cytoplasmic immunopositivity for CD117 (c-kit) may be restricted to luminal cells or involve all tumor cells (original magnification, 400×)

6.7.2.3 Immunohistochemistry

In cases of poorly differentiated neoplasms, immunohistochemistry may play a vital role (Table 6.1). SCC will stain positively for p63, high molecular weight cytokeratin, CEA, and EMA. Infection with HPV type 16 in cases of Bartholin gland SCC makes diffuse p16 positivity a surrogate marker for HPV infection [47, 52].

Adenoid cystic carcinoma shows membrane and cytoplasmic positivity for c-kit (CD117) in the luminal cells; although, the pattern of immunopositivity may differ by tumor pattern (Fig. 6.17) [53]. Peripheral myoepithelial cells show p63 nuclear positivity (Fig. 6.18) and variable nuclear and cytoplasmic S-100 positivity, which demonstrates the myoepithelial component of this tumor [54]. Luminal tumor cells are also positive for CK 8/18, AE1/AE3, and EMA [52].

Small cell carcinoma shows variable membrane and cytoplasmic positivity, if any, for keratins. Nuclear TTF-1 positivity is not site-specific, and positivity has been described to vary by tumor origin [55]. Oftentimes, cytoplasmic positivity for neuroendocrine markers, such as synaptophysin and chromogranin, is essential to determine neuroendocrine origin.

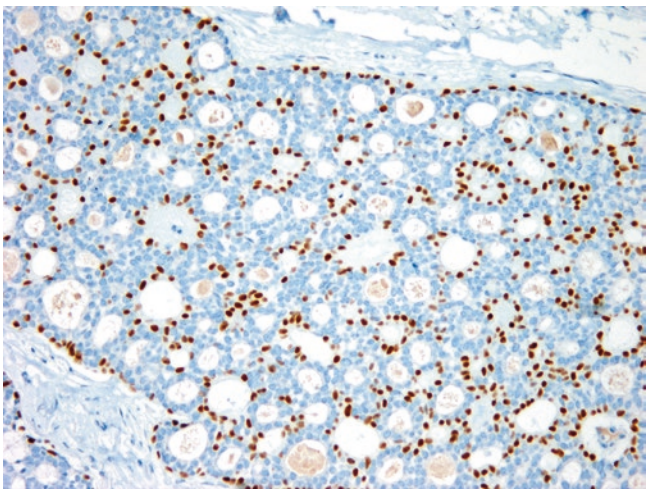

Fig. 6.18 Adenoid cystic carcinoma. Nuclear positivity for p63 highlights myoepithelial cells within adenoid cystic carcinoma (original magnification, 200×)

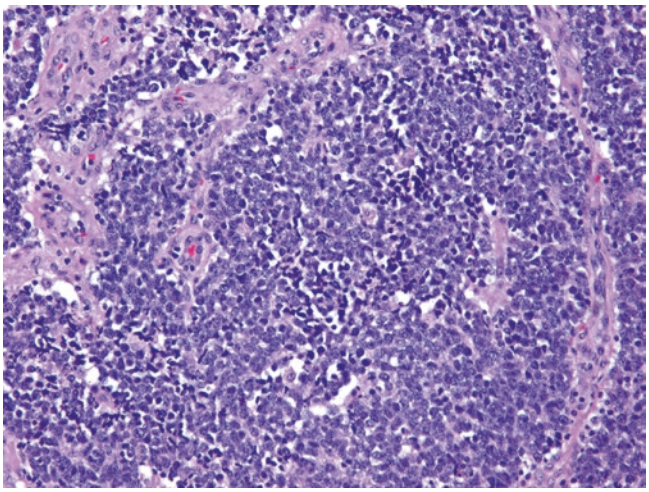

Fig. 6.19 Merkel cell carcinoma consists of sheets of tumor cells that give a "blue" appearance due to high N:C ratio (original magnification, 200×)

6.8 Merkel Cell Carcinoma

6.8.1 Clinical Features

Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine carcinoma that typically affects sun-exposed areas with over half located on the head and neck. A vast majority of patients are Caucasians with an average age of 69 years [56]. Vulvar MCC is quite rare, which makes clinical behavior more difficult to predict [57]. Similar to MCC of the head and neck, vulvar MCC is marked by aggressive clinical behavior and recurrence. Clinically, vulvar MCC presents as a rapidly growing red-blue mass at the labia majora [58]. Tumor size can average 7.5 cm, and patients commonly complain of tenderness, pruritus, and ulceration. Time to presentation can be delayed, and overall disease duration can range from 1 to 18 months [58]. Similar to other mass lesions of the vulva, MCC may be clinically mistaken for a Bartholin gland cyst or abscess. As mentioned earlier in this chapter, one should have a high index of suspicion for malignancy when encountering a suspected Bartholin gland cyst in a postmenopausal patient.

6.8.2 Microscopic Findings

MCC is characterized by nests and trabeculae of cells with high nuclear to cytoplasmic ratio (Fig. 6.19) [59]. The tumor may show areas of invasion with adjacent mucinous and mucin-filled spaces similar to that seen in basal cell carcinoma [60]. Larger tumors tend to display geographic necrosis. Increased mitoses and apoptotic debris can be found throughout the tumor [61]. Lymphovascular invasion is commonly present and usually best appreciated at the tumor periphery. MCC tumor cells have been reported to display pagetoid spread in up to 20% of cases [60, 62].

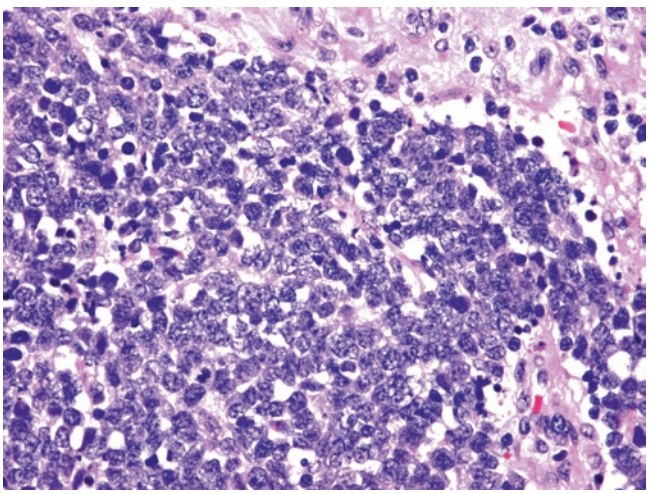

Fig. 6.20 High nuclear/cytoplasm ratio with "salt and pepper" chromatin and nuclear molding are characteristic features of Merkel cell carcinoma (original magnification, 400×)

Similar to neuroendocrine carcinomas arising from other locations, nuclear features of MCC exhibit homogeneous "salt and pepper" chromatin, nuclear molding, and inconspicuous nucleoli (Fig. 6.20) [60]. These nuclear features are key factors to distinguish from basal cell carcinoma, which would show well-developed peripheral palisading of tumor cells. Crush artifact is typically present, and the extent of crush may raise suspicion for a hematolymphoid neoplasm.

6.8.3 Immunohistochemistry

Given the histologic overlap of MCC with other entities, immunohistochemistry plays a vital role in excluding other

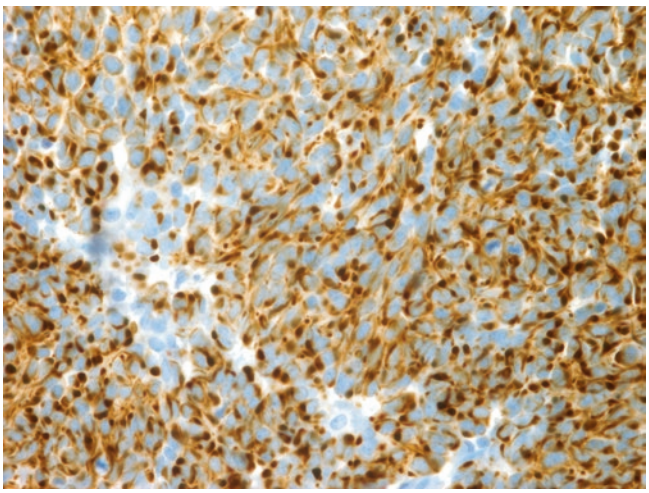

Fig. 6.21 Immunohistochemical staining for cytokeratin 20 shows perinuclear "dot-like" staining (original magnification, 400×)

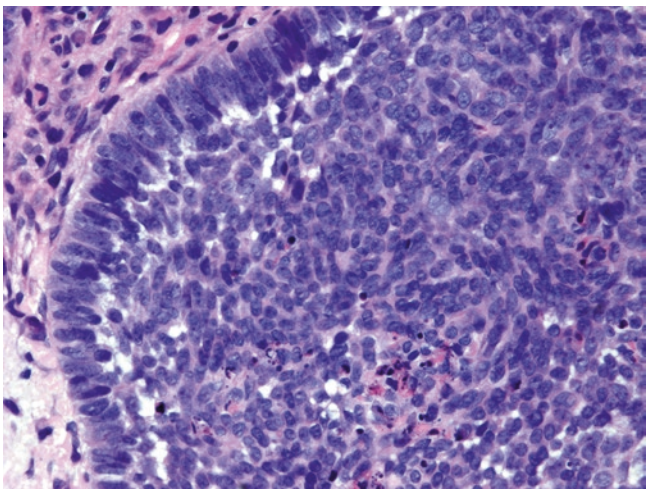

Fig. 6.22 Basal cell carcinoma has characteristic palisading of tumor cells at the tumor-stroma interface (original magnification, 400×)

high-grade tumors. Pancytokeratin is positive in approximately half of cases of vulvar MCC, and low molecular weight keratin can be positive in as few as 20% of cases [58]. Typically, MCC stains negative for CK7 and positive for CK20, but a subset of MCC with CK20-/CK7+ has been reported [63, 64]. In the setting of CK20 positivity, MCC has a classic perinuclear dot-like positivity (Fig. 6.21) [58]. Like other neuroendocrine tumors, there must be some degree of positivity for chromogranin, synaptophysin, or neuron-specific enolase. As with all immunostains, caution must be used when dealing with areas of crush artifact.

6.8.4 Differential Diagnosis

Basal cell carcinoma, when considering overall cutaneous distribution, is the most common cutaneous malignancy [65]. The correlation between basal cell carcinoma and cumulative UV exposure is well established, and the majority is found at the head and neck [66]. Once thought to be rare as a vulvar neoplasm, approximately 2% of basal cell carcinomas arise in the vulva [67]. The average age of affected patient is 70 years old, and lesions typically average 2.0 cm with ulceration a common finding. Clinical symptoms are non-specific and include bleeding, pruritus, and pain [67]. Histologically, basal cell carcinoma is characterized by peripheral palisading of basaloid cells with high nuclear/chromatin ratio (Fig. 6.22). Common morphologic patterns include superficial invasion, nodular, and infiltrative. Similar to MCC, basal cell carcinoma has mucinous stroma, but basal cell carcinoma exhibits artifactual retraction of the tumor-stroma interface. Mitotic activity is less frequent than in MCC. Immunostaining for basal cell carcinoma will show positivity for Ber-EP4 and negativity for CK20, synaptophysin, and chromogranin-A.

Lymphoma can rarely affect the gynecologic tract, and the most common type affecting the vulva is diffuse large B-cell lymphoma [68]. Lymphomas may be histologically distinguished from MCC in various ways. Unlike the trabecular and nested patterns of invasion seen in MCC, lymphomas tend to form sheets of dyscohesive cells. Similar to MCC, crush artifact and necrosis may be common, but lymphomas will not have the "salt and pepper" chromatin pattern seen in neuroendocrine tumors. A broad stain such as CD45 will stain positively in lymphomas, while cytokeratins and neuroendocrine markers will be negative. Lymphoblastic lymphoma, which may lack CD45, is a notable exception.

Extrapulmonary small cell carcinoma is rare and occurs in approximately 2% of all cases of small cell carcinoma [69]. Small cell carcinoma arising from the gynecologic tract commonly involves the cervix, but areas of less frequent involvement include the ovary, fallopian tube, and vulva. Histologically, small cell carcinoma of the gynecologic tract is identical to that of other sites, including lung primaries. Tumor cells are arranged in sheets or trabeculae, and there is frequently necrosis with increased mitotic rate [69]. A thorough clinical and radiologic history is essential when determining primary versus secondary small cell carcinoma. It should be noted that TTF-1 expression is not specific for small cell carcinoma of pulmonary origin and should not be used to distinguish primary from metastatic small cell carcinomas involving extrapulmonary sites. However, TTF-1 expression may be useful in distinguishing TTF-1 negative Merkel cell carcinomas from cutaneous metastasis of small cell carcinomas, which are TTF-1 positive [55, 70]. Small cell carcinoma is usually negative for CK20, which aids in distinguishing it from MCC.

6.9 Cloacogenic Neoplasms

6.9.1 Clinical Features

Cloacogenic carcinoma of the vulva is an extremely rare variant of primary adenocarcinoma of the vulva with as few as 20 cases reported in the literature [71]. The average age of presentation is 51 years old with a range of 35 to 67 years old [71, 72]. Anatomically, primary adenocarcinomas of the vulva are thought to arise from the Bartholin glands that are normally present in the vulvar area [73–76]. Other possible origins are sweat glands, Skene's glands, minor vestibular glands, or endometriotic implants. Cloacogenic carcinoma is thought to arise from embryonic or ectopic rests of cloacogenic tissue [77]. Rare multicentric cases have been described [78].

6.9.2 Microscopic Findings

Histologically, these lesions resemble colonic adenocarcinoma. A feature found in the majority cases is direct continuity of the tumor with the epidermis [71, 73–77, 79]. The neoplastic cells form glands, and the cells lining the acini are columnar and often stratified. Proliferation into gland-in-gland patterns, varying numbers of goblet cells, and a prominent brush border may be observed [77, 80].

6.9.3 Immunohistochemistry and Histochemistry

Reported cases have shown positive staining with CEA, broad-spectrum cytokeratin, CDX-2, and p53 antigen [72, 73] and variable staining for CK7 and CK20 [79]. A recent case report described diffuse positivity for p53 and only focal positivity for p16INK4a [81]. Neuroendocrine markers such as synaptophysin may highlight endocrine cells [77]. Alcian blue, mucicarmine, and PAS with diastase decorate goblet cells, indicating the presence of enteric-type sialomucins [77].

6.9.4 Differential Diagnosis

As the morphology and potentially the immunophenotype of the tumor are essentially identical to that of colonic adenocarcinoma, a thorough clinical workup is necessary to exclude metastasis from a colonic origin [71, 72, 80].

6.9.5 Prognosis and Treatment

Treatment typically includes wide local excision or, less often, radical vulvectomy with or without local lymph node excision. Most of these tumors are indolent in nature with excision seemingly curative [71, 75, 76, 79]; however, local recurrence has been reported [77] as well as rare more aggressive forms with distant metastasis [72, 74].

6.10 Metastatic Tumors

6.10.1 Clinical Features

Metastatic tumors of the vulva are rare, accounting for 5–8% of vulvar malignancies [2]. These lesions present in females with a median age of 55 years old and are most common in perimenopausal or postmenopausal women; however, the age range of presentation is wide, with patients presenting anywhere from 18 to 84 years of age [82]. In a study of 66 cases of metastatic tumors to the vulva, Neto et al. found that in roughly half of cases, the tumor was of gynecologic origin; 43.9% were from nongynecologic origin, and the remaining had unknown primaries [82]. Primary sites reported in the literature include the anogenital squamous lesions, anal adenocarcinoma, endometrium, lung, and breast [83–87]. Clinical presentation varies from multiple nodules to a single mass. Some less frequent presentations include bleeding, pruritus, swelling, local discomfort, or a cystic lesion [82]. Anatomically, the labium majus is the most commonly involved site [82].

6.10.2 Microscopic Findings

Histologically, metastatic disease resembles the primary tumor.

6.10.3 Immunohistochemistry

Immunohistochemistry varies by the tumor origin; therefore, a wide panel may be necessary to evaluate these lesions depending on the histologic appearance, especially in the absence of a known primary tumor (Table 6.2). CK7 and CK20 are widely used markers in this setting, and PAX-8 (nuclear), which has a moderate to high sensitivity and high specificity for diagnosing carcinomas of Mullerian origin, may also be useful [88]. Table 6.3 provides a summary of immunohistochemical stains which are useful in pinpointing the origin of a metastatic tumor.

Table 6.2 Positive immunohistochemical staining patterns of Bartholin gland carcinoma subtypes [52]

Squamous cell carcinoma	p16 (HPV positive), p63, CEA, CK19
Adenocarcinoma	CAM 5.2, CA 19–9, CEA, EMA
Adenoid cystic carcinoma	Epithelial cells: AE1/AE3, CK 8/18, EMA Myoepithelial cells: CD117, p63, S-100
Small cell carcinoma	CAM 5.2, CD56, neuron-specific enolase, chromogranin, synaptophysin

Table 6.3 Useful immunohistochemical stains for working up metastatic tumors to the vulva [2, 18]

	CK7	CK20	TTF-1	GCDFP-15	ER	PR	Vimentin	p16	CEA
Endometrium	+	–			+		+	Patchy +	–
Lung	+	–	+						
Breast	+	–	–	+	+/–	+/–			
Primary EMPD	+	–		+					
Urothelial	+	+		–					

6.10.4 Differential Diagnosis

Primary Paget Disease must be distinguished from metastasis or direct extension of urothelial carcinoma [89]. Immunohistochemistry is necessary in this circumstance – the immunoprofile of vulvar Paget disease is GCDFP+/CK7+/CK20-, while urothelial neoplasia is GCDFP-/CK7+/CK20+ (Table 6.1).

Primary breast carcinoma arising in ectopic breast tissue versus metastatic breast carcinoma is a particularly challenging differential diagnosis and usually cannot be made on histologic and immunohistochemical grounds alone. Metastatic breast carcinoma to the vulva has been described only 20 times in the literature [86, 87, 90–97], and one case of synchronous vulvar metastasis arising from a low-grade ductal carcinoma has been reported [95]. The diagnosis of metastatic disease is supported by a known history of breast malignancy, with the vulvar tumor demonstrating identical histological, immunohistochemical, and hormone receptor status – with the exception that in some cases the hormone receptor status may change due to spontaneous mutations [91, 93]. On the other hand, the presence of normal ectopic breast tissue in the vulvar specimen would suggest a primary lesion.

The knowledge of a preexisting malignancy and the absence of intraepithelial involvement aid in the diagnosis of metastasis. Thorough clinical history, relevant imaging, and physical examination are often necessary to determine the tumor of origin (Table 6.3).

6.10.5 Prognosis and Treatment

A variety of therapeutic methods have been used including any combination of surgery, chemotherapy, and/or radiation, depending on the extent of disease and tumor of origin. Prognosis is usually poor as distant metastases often suggest late-stage disease.

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