

Mai P. Hoang and Dmitry V. Kazakov

Introduction

The vulva contains a wide range of constituents including adnexal structures as seen in nongenital skin (e.g., apocrine and eccrine glands and folliculosebaceous units) and glands only seen in the anogenital region (e.g., anogenital mammary-like glands, major and minor vestibular glands). The modified mucous membrane of the labia minora contains apocrine glands and ectopic sebaceous glands. Other glandular elements that are present in the vulva include the Skene glands (paraurethral glands), the major vestibular glands or Bartholin glands (mucus-producing vestibular glands), and minor vestibular glands [1]. Mammary-type tissue in the vulva was first described by Hartung in 1892 [2]. Previously thought to represent ectopic breast tissue, anogenital mammary-like glands are now regarded by many as normal structures of the anogenital region. They are typically found in the sulcus between the labia minora and majora and extend through the perineum to the anal region [2, 3]. The superficial portion of the gland's excretory duct possesses an outer myoepithelial layer and transitional cell epithelium [4]. As the duct enters

the epidermis, the myoepithelial layer is lost, and it is lined by squamous epithelium [4]. Toker cells (cytokeratin 7-positive clear cells which may occur singly and in small clusters in the lower epidermis), similar to those described by Toker in the normal nipples, may be apparent within the ductal epithelium of the anogenital mammary-like glands at the site of insertion [5]. These Toker cells were first documented in the vulva by Willman et al. [6].

Lesions of Anogenital Mammary-Like Glands

Fibroadenoma and Phyllodes Tumor

Vulvar fibroadenoma was first reported in 1932 by Friedel [7]. These rare fibroepithelial lesions and phyllodes tumors arise from the anogenital mammary-like glands which microscopically appears identical to their more common mammary counterparts [8–13] (see Chap. 1, Fig. 1.8). They present as asymptomatic nodules with sizes ranging from 0.8 to 6 cm. The ages of the patients ranged from 20 to 69 years [8–13]. Local recurrence has been reported in phyllodes tumors [11]. Exceptionally, simultaneous appearance of vulvar and mammary fibroadenoma as well as bilateral presentation has been reported [14, 15]. Local excision appears to be the treatment of choice.

M.P. Hoang, M.D. (✉)

Department of Pathology, Harvard Medical School,
Massachusetts General Hospital, Boston, MA, USA
e-mail: mhoang@mg.harvard.edu

Histologic Features

Fibroadenoma is a circumscribed tumor composed of branching and anastomosing glandular structures surrounded by a fibrous paucicellular stroma (Fig. 11.1). Cystic dilatation and intraluminal papillary projections can be seen. Although with a similarly biphasic pattern, phyllodes tumor exhibits leaflike projections and a more cellular

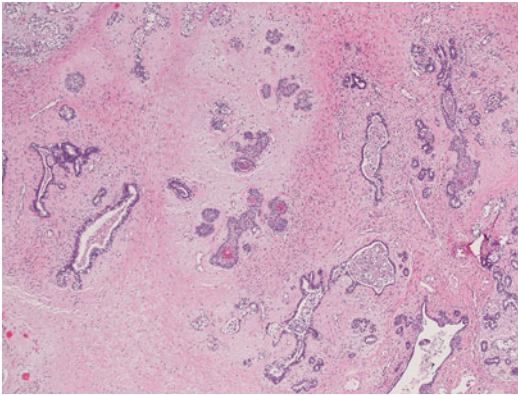


Fig. 11.1 *Fibroadenoma*. A biphasic tumor comprised of branching glandular structures within a fibrous stroma (Courtesy of Dr. Payal Kapur, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas)

stromal component, often with periductal stromal condensation (Fig. 11.2a, b). Similar to the mammary counterpart, depending on the degree of pleomorphism of the stroma, phyllodes tumor in the anogenital areas can be classified into benign, low-grade, and high-grade variants. It appears that most reported cases belonged to either benign or low-grade variant, with a single case of high-grade neoplasm showing a rhabdomyosarcomatous stroma being documented [16]. In both fibroadenoma and phyllodes tumor, unusual features can be seen in the form of pseudoangiomatic stromal hyperplasia (PASH), hyperplastic and metaplastic epithelial and stromal changes, and lactation-like changes [11]. PASH characterized by open, slit-like, often anastomosing channels devoid of erythrocytes and lined by discontinuous, often attenuated, inconspicuous cells without atypia or mitotic activity may simulate low-grade angiosarcoma [17].

Similar to the mammary counterpart, the epithelial component expresses epithelial markers (AE1/AE3, CK7), estrogen receptor (ER) and progesterone receptor (PR); and smooth muscle markers highlight the myoepithelial layer [8, 13]. Human papillomavirus (HPV) DNA has been shown to be negative in three vulvar fibroadenomas [18].

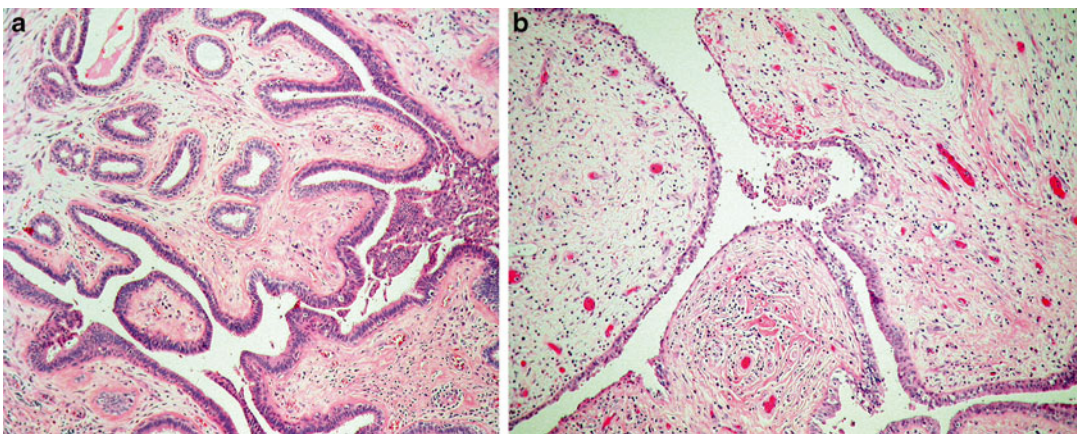


Fig. 11.2 (a, b) *Phyllodes tumor*. (a). Leaflike projections are seen at low magnification. (b). A cellular stroma is seen at higher magnification (Courtesy of Dr. Venetia

Sarode, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas)

Differential Diagnosis

The architecture and stroma would be the main differentiating features between fibroadenoma and benign phyllodes tumor. Fibroadenoma would exhibit a fibrous paucicellular stroma, whereas benign phyllodes tumor has a more cellular stroma. PASH should be differentiated from its mimicker, the low-grade angiosarcoma, by the lack of cytologic atypia, mitotic activity, and erythrocytes [17].

Summary

Clinical Presentation

- Present as asymptomatic nodules

Histologic Features

- Fibroadenoma: a circumscribed tumor composed of branching glandular structures surrounded by a fibrous paucicellular stroma
- Phyllodes tumor: leaflike projections and cellular stromal component with variable number of pleomorphic cells and mitosis

Differential Diagnosis

- Vascular neoplasm for lesion with pseudoangiomatous stromal hyperplasia

Lactating Adenoma

Associated with pregnancy, lactating adenoma arises from the anogenital mammary-like glands in rare occasions [19]. They can be solitary or multiple and present as masses [20, 21].

Histologic Features

The lesion is circumscribed and comprised of densely packed round tubules lined by cells with cytoplasmic vacuoles and intraluminal eosinophilic secretion (Fig. 11.3a, b). The stromal component does not compress the ducts. Mitotic figures may be identified.

Differential Diagnosis

Other lesions of anogenital mammary-like glands can exhibit lactational changes such as a fibroadenoma [11, 22].

Summary

Clinical Presentation

- Rare lesion that presents as a mass during pregnancy

Histologic Features

- Well-circumscribed lesion
- Epithelial cells with cytoplasmic vacuoles

Differential Diagnosis

- Other lesions of anogenital mammary-like glands with lactational changes

Takeaway Essentials

Clinical Relevant Pearls

- Vulvar fibroadenoma and phyllodes tumor are rare lesions arising from the anogenital mammary-like glands.
- Enlargement during pregnancy may be seen due to lactating-like changes.

Pathology Interpretation Pearls

- The number of stromal mitosis is the determining criterion in distinguishing benign from low-grade phyllodes tumor.

Immunohistochemical/Molecular Findings

- The epithelial component expresses estrogen receptor.

Takeaway Essentials

Clinical Relevant Pearls

- Most of these lesions are alarming because of the detection of significant clinical changes in a short period of time.

Pathology Interpretation Pearls

- Mitotic figures are not associated with aggressive behavior.

Immunohistochemical/Molecular Findings

- In practice rarely are immunohistochemical stains used to diagnose these lesions.

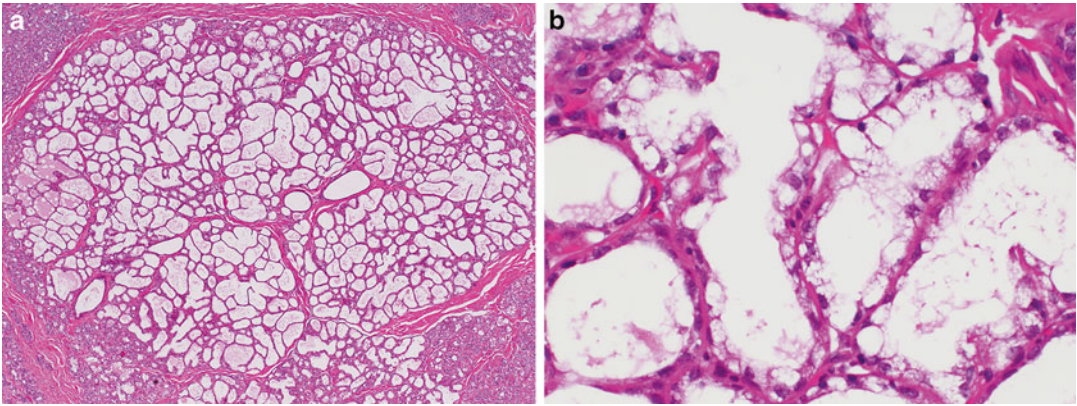


Fig. 11.3 (a, b) *Lactating adenoma*. A circumscribed proliferation of round tubules which are lined by cells with cytoplasmic vacuoles (Courtesy of Dr. M. Angelica

Selim, Department of Pathology, Duke University Medical Center, Durham, NC)

Hidradenoma Papilliferum and Hidradenocarcinoma Papilliferum

Hidradenoma papilliferum was first reported by Worth in 1878 and characteristically occurs in the vulvar and perianal regions [23]. Initially thought to be derived from the apocrine glands [24], subsequent reports support that hidradenoma papilliferum (as well as tubular adenoma) are derived from anogenital mammary-like glands [25, 26]. Therefore, the term “mammary-like gland adenoma of the vulva” has been proposed; however, hidradenoma papilliferum is best conceptually compared to intraductal papilloma of the breast [4, 27]. In a recent review [28], hidradenoma papilliferum was the most common benign vulvar glandular neoplasm accounting for 60 % of the benign lesions.

It often presents as a solitary and asymptomatic nodule. The ages of the patients in large series range from 29 to 90 years with the mean of 50 years [27]. The sites of involvement include labia minora (50 %), labia majora (40 %), fourchette (7 %), and clitoris (3 %) [27]. This distribution mirrors that of anogenital mammary-like glands. Although HPV types 16, 31, 33, 53, and 56 have been identified within lesional tissue, the virus does not appear to play a causative role [17].

Histologic Features

Histopathologically, the tumor exhibits both a papillary and glandular architecture with interconnected anastomosing tubules. The inner epithelial cells are typically columnar with pale eosinophilic cytoplasm and are surrounded by a myoepithelial layer (Fig. 11.4a, b). Oncocytic (oxyphilic) metaplasia, clear cell change, predominantly solid growth, cystic change, sclerosing adenosis-like changes, and others can be seen [4, 17, 29]. Mitoses can be identified in both the epithelial as well as the myoepithelial components and are not indicative of aggressive behavior [30].

The epithelial component is highlighted by a variety of keratins (AE1/AE3, CK5/6, CK15) [31, 32], ER [33], and GCDFP-15 [34]. The myoepithelial component would be stained with a number of myoepithelial markers (S100, smooth muscle actin, calponin) and interestingly nestin [32].

The literature cites five cases of ductal carcinoma in situ arising in association with hidradenoma papilliferum [35–38]. Histopathologically, these tumors are described to possess foci of crowded pleomorphic epithelial cells with hyperchromatic nuclei, prominent nucleoli, and abnormal mitotic figures. However, the retention of a myoepithelial layer is indicative of its in situ nature [36, 38].

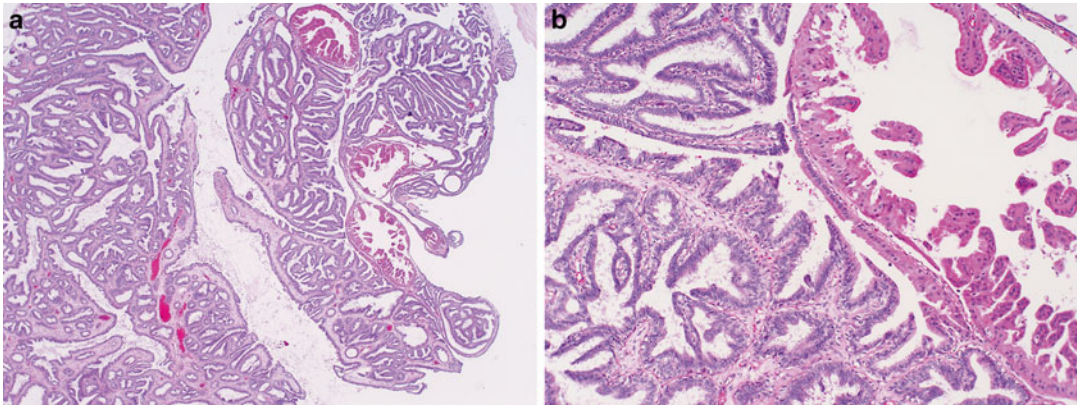


Fig. 11.4 (a, b) *Hidradenoma papilliferum*. (a). An intradermal tumor comprised of branching and anastomosing tubules which are lined by inner epithelial columnar cells and an outer myoepithelial cells. (b). Prominent apocrine

metaplasia can be seen (Courtesy of Dr. M. Angelica Selim, Department of Pathology, Duke University Medical Center, Durham, NC)

Differential Diagnosis

When there is connection to the overlying epidermis, epidermal hyperplasia and prominent plasma cells infiltrate can mimic syringocystadenoma papilliferum.

Summary

Clinical Presentation

- A solitary and asymptomatic nodule

Histologic Features

- A papillary and glandular architecture with interconnected anastomosing tubules.
- An inner epithelial and an outer myoepithelial layer.
- Oncocytic metaplasia, clear cell change, predominantly solid growth, and cystic change can be seen.

Differential Diagnosis

- Syringocystadenoma papilliferum

Pathology Interpretation Pearls

- Mitoses can be seen in both the epithelial as well as the myoepithelial components and are not indicative of aggressive behavior.
- When cellular pleomorphism and severe cytologic atypia are seen, the diagnosis of hidradenocarcinoma papilliferum should be considered.

Immunohistochemical/Molecular Findings

- The retention of a myoepithelial layer highlighted by smooth muscle actin or calponin is indicative of the in situ nature of the lesion.

Takeaway Essentials

Clinical Relevant Pearls

- Derived from anogenital mammary-like glands

Extramammary Paget Disease

First reported by Crocker [39] to affect the scrotum and penis, extramammary Paget Disease (EMPD) has since been documented in the vulva and perianal region [40]. EMPD can be either primary or secondary. Primary EMPD can be either an intraepithelial neoplasm with or without invasion, or as a manifestation of an underlying primary adenocarcinoma. The implicated cells of origin for primary EMPD include skin adnexa (eccrine or apocrine glands) and anogenital

mammary-like glands [6], or possibly pluripotential stem cells [4, 41–43]. Chanda et al. [44] identified that 29 % of 197 EMPD cases were associated with an underlying malignancy arising in organs in proximity to the vulva. Through a mechanism reminiscent of mammary Paget disease, secondary EMPD is thought to originate from epidermotropic spread of malignant cells or within contiguous epithelium [45]. Many cases of vulvar secondary EMPD have been described in association with other gynecologic and genitourinary (bladder) neoplasms [40]. Furthermore, perianal Paget disease, which accounts for 20 % of EMPD cases [46], is strongly associated with adenocarcinoma of the anus and colorectum [47].

EMPD of the vulva predominantly affects women in the seventh decade [48–50]. The primary symptoms are pruritus and burning [48]. The labia majora is the most frequently involved site followed by labia minora and clitoris [50]. It presents as a relatively well-demarcated flat or slightly elevated erythematous or gray-white lesion, 1–20 cm in size [50, 51] (Fig. 11.5). “Triple” EMPD is a rare presentation in which the genital lesions are associated with synchronous or metachronous, uni- or bilateral axillary involvement [52]. The primary EMPD is with a high recurrence rate and rarely metastasizes, contrary to the secondary form [48]. Noninvasive EMPD has an excellent prognosis [53]. Studies have shown conflicting data regarding the presence of invasion and prognosis [54, 55]. A recent study using the SEER (Surveillance, Epidemiology, and End Results) Program identified a long-term increased risk of developing secondary malignancies in patients with invasive EMPD [56]. Surgical excision is currently the standard treatment [49].

Histologic Features

The histologic features are similar in both primary and secondary forms, characterized by large pale cells arranged as single units and clusters or glands formed within the epidermis (Fig. 11.6a–c). The involvement of adnexa, most commonly hair follicles and ducts, is frequently seen in EMPD. A signet-ring appearance can be seen due to marked intracytoplasmic mucin accumulation. In EMPD in situ, the neoplastic cells



Fig. 11.5 Extramammary Paget disease. An erythematous plaque is seen bilaterally on the vulva and extends to the perianal region

are localized within the epidermis. Invasive EMPD is classified as microinvasive or invasive. In microinvasive cases, the tumor cells are seen in the stroma no deeper than 1 mm below the basement membrane [57].

Rarely, mammary-type ductal carcinoma, invasive or in situ, can be seen in EMPD. In the latter case, ductal carcinoma in situ (DCIS) appears to involve anogenital mammary-like glands, thus complicating the accepted terminology EMPD in situ used for designation of carcinoma cells confined to the epidermis.

The tumor cells in EMPD are usually positive for mucicarmine, Alcian blue, and periodic acid-Schiff with diastase. Primary EMPD lesions would typically exhibit a sweat gland phenotype (cytokeratin (CK) 7+/CK20-/gross cystic disease fluid protein (GCDFFP)-15+), whereas secondary EMPD lesions would exhibit an endodermal phenotype (CK7+/CK20+/

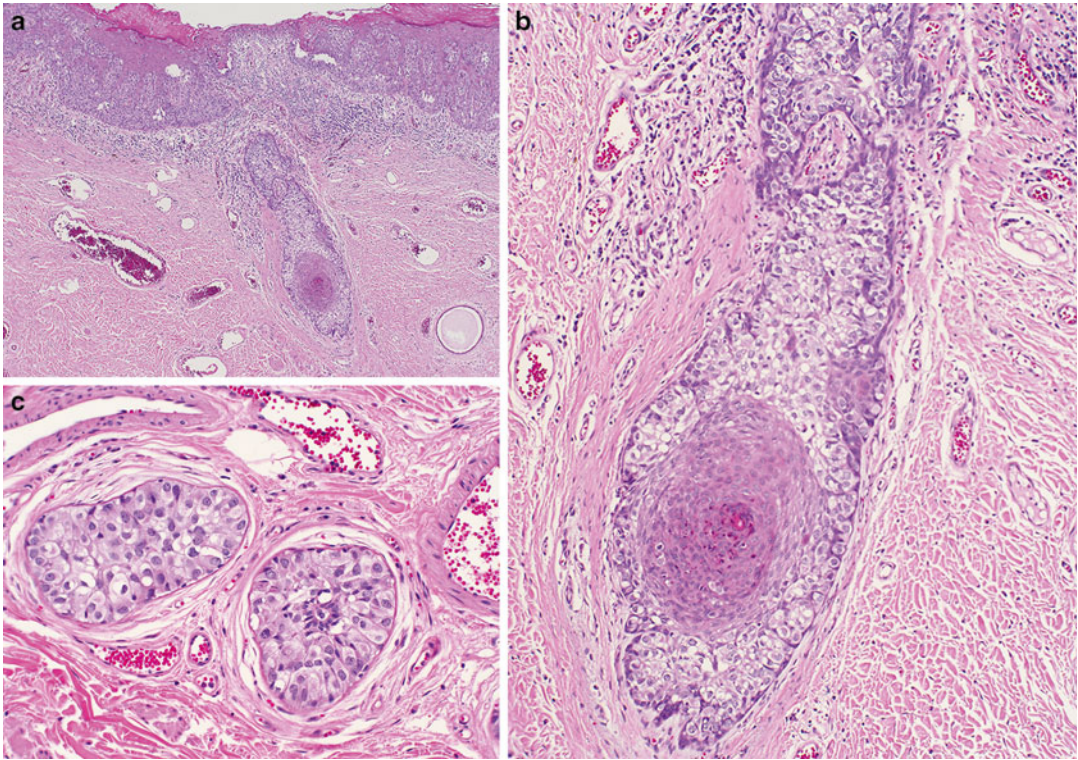


Fig. 11.6 (a–c) *Extramammary Paget disease*. (a, b) A proliferation of polygonal neoplastic cells is seen within the epidermis and extending into hair follicular epithelium. (c). Tumor cells with abundant pale cytoplasm and vesicular nuclei are seen replacing the eccrine glands.

Residual lumen is still visible in one of the glands – a clue for not misdiagnosis adnexal extension as invasion (Courtesy of Dr. M. Angelica Selim, Department of Pathology, Duke University Medical Center, Durham, NC)

GCDFP-15-) [58] (Fig. 11.7). Co-expression of CK20 and CDX2 is indicative of secondary EMPD of colorectal origin [59, 60]. HER-2/neu and CDX2 have been found to be useful in distinguishing primary EMPD from secondary EMPD of anorectal adenocarcinoma [61, 62]. Although the expression can be variable, mucin core proteins such as MUC2 and MUC5AC might be helpful in distinguishing primary from secondary EMPD (see *Vignette 3* at the end of this chapter) (Table 11.1). Uroplakin III has been demonstrated to be of help in identifying metastatic urothelial carcinomas [63]. It should be emphasized however that the burden of

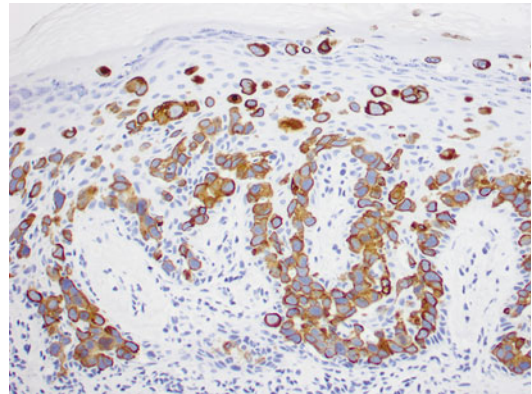


Fig. 11.7 *Extramammary Paget disease*. The intraepidermal tumor cells strongly express cytokeratin 7

Table 11.1 Immunoprofile of primary and secondary extramammary Paget disease

Immunostain	Primary	Secondary colorectal	Secondary urothelial
Cytokeratin 7	+	-/+	-/+
Cytokeratin 20	-	+	+
GCDFP-15	+	-	-
HER-2/neu	+	-	-
CDX2	-	+	-
Uroplakin III	-	-	+
p63	-	-	+
MUC5AC	+	-	-
MUC-2	-	+	-

GCDFP-15 gross cystic disease fluid protein-15

delineation between primary and secondary EMPD lies on the clinician.

Our understanding of the genetic basis for EMPD is currently limited. The expression of HER-2/neu and androgen receptor indicates potential benefit from targeted therapy [62, 64]. However, fluorescence in situ hybridization demonstrates no evidence of HER-2 gene amplification [65]. Recently, the deleted in liver cancer-1 gene (*DLCL1*) hypermethylation and mutations in oncogene *PIK3CA* with overexpression of PI3K protein have been shown in EMPD cases [66–68].

Differential Diagnosis

The differential diagnosis of EMPD includes both benign conditions such as vulvar Toker cells, mucinous metaplasia, vulva intraepithelial neoplasia, and malignant melanoma [69]. In a recent study of 56 patients, Shaco-Levy et al. [50] reported that a panel of pan-cytokeratin, CK7, CEA, and EMA labels 100 % of primary EMPD cases, while no cases stained with S100, HMB-45, and MART-1 distinguishing EMPD from malignant melanoma. The mucinous cells in mucinous metaplasia would lack cytologic atypia and replace rather than infiltrate the squamous epithelium as in EMPD (see Chap. 12). Careful examination would show that the neoplastic cells in EMPD are round and often with cytoplasmic mucin in contrast to the dysplastic keratinocytes seen in VIN.

Summary

Clinical Presentation

- Affects mainly women in the seventh decade.
- The labia majora is the most frequently involved site followed by labia minora and clitoris.
- It presents as a relatively well-demarcated flat or slightly elevated erythematous or gray-white lesion.

Histologic Features

- Large pale cells arranged in singly or in clusters within the epidermis.
- Extension along the adnexal structures can be seen.
- Microinvasion is defined when the tumor cells are seen less than one millimeter below the basement membrane.

Differential Diagnosis

- Vulvar Toker cells
- Mucinous metaplasia
- Vulvar intraepithelial neoplasia with mucinous differentiation
- Secondary EMPD
- Malignant melanoma

Takeaway Essentials

Clinical Relevant Pearls

- Primary EMPD is slowly progressive and rarely metastasizes, in contrast to the secondary form.
- EMPD is frequently confused with eczematous process delaying the diagnosis.

Pathology Interpretation Pearls

- Minimal inflammation is seen in association with EMPD.
- Cytoplasmic mucin is seen only in EMPD and not in squamous cell carcinoma or malignant melanoma.

Immunohistochemical/Molecular Findings

- Panel for primary EMPD: CK7, CK903, and S100
- Panel for secondary EMPD: CK7, CK20, CDX2, and p63

Other Lesions of Anogenital Mammary-Like Glands

Uncommon benign lesions of the anogenital mammary-like glands include fibrocystic-like changes in the form of sclerosing adenosis, columnar cell lesions, ductal lesions, and various metaplastic changes affecting the epithelium and myoepithelium.

Other Carcinomas of Anogenital Mammary-Like Glands

Adenocarcinoma of Anogenital Mammary-Like Glands

First reported by Greene in 1936, there have been approximately 30–40 cases of adenocarcinoma of anogenital mammary-like glands reported in the literature to date [4, 70–76]. Anogenital mammary-like glands have been suggested in those cases as a likely origin due to their marked similarity to homologous mammary carcinomas. The labia majora is the most commonly involved site, and the mean tumor size is 2.5 cm [71]. Because of the rarity, varying treatment modalities, and relatively short follow-up periods in the original publications, it is difficult to draw firm conclusions regarding the natural history and prognosis of these neoplasms. As a group, primary

mammary-type adenocarcinomas appear to be locally aggressive tumors. In one review, 60 % (12/20) of patients were found to have regional lymph node metastasis at the time of presentation [71]. Radical or hemivulvectomy has been the primary treatment in most cases [71].

Histologic Features

The presence of an in situ component, remarkable similarity to a mammary counterpart, or a transition zone between normal mammary-like glands and the carcinoma component is necessary to establish a diagnosis. The histopathology of these tumors varies from predominantly ductal to lobular, mixed ductal and lobular, tubulolobular, mucinous, and adenoid cystic-like [71, 73, 74, 77, 78]. The morphology of most cases is that of an invasive ductal carcinoma [71] (Fig. 11.8a, b).

Differential Diagnosis

The differential diagnosis includes extramammary Paget disease, sweat gland carcinoma, and metastatic adenocarcinoma to the vulva. Without clinical history, it would be difficult to distinguish adenocarcinoma of anogenital mammary-like glands from metastatic carcinoma from the breast since both have similar histology. Expression of ER and PR has been variable in adenocarcinoma of mammary-like glands [71, 76].

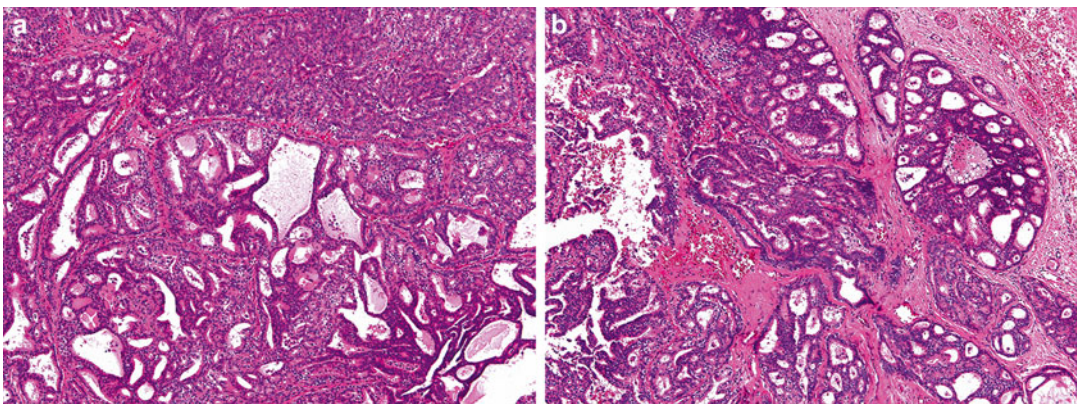


Fig. 11.8 (a, b) *Adenocarcinoma of mammary-like glands.* An infiltrative carcinoma resembling mammary ductal carcinoma is seen

Summary*Clinical Presentation*

- The labia majora is the most commonly involved site.

Histologic Features

- Varied from predominantly ductal to lobular, mixed ductal and lobular, tubulolobular, mucinous, and adenoid cystic-like

Differential Diagnosis

- Extramammary Paget disease, sweat gland carcinoma, and metastatic adenocarcinoma to the vulva

Takeaway Essentials*Clinical Relevant Pearls*

- An aggressive tumor with 60 % of patients presented with nodal metastasis

Pathology Interpretation Pearls

- Transition zone between normal mammary-like glands and the carcinoma component confirms the diagnosis.
- The histology of most cases is that of an invasive ductal carcinoma.

Immunohistochemical/Molecular Findings

- Can express estrogen and progesterone receptors

patients [81]. Pruritus was the most commonly presenting symptom [81]. The size has been reported to increase during summer month or menstruation. Rare report of familial history has been documented [80].

Some have hypothesized that the growth of syringoma is under hormonal influence [82, 83]; however, staining for estrogen receptor (ER) and progesterone receptor (PR) was negative for all 15 studied cases by Huang et al. [81] and the case reported by Trager et al. [84]. Reported treatment for vulvar syringomas includes carbon dioxide laser treatment [81, 86], cryotherapy [87], electrosurgery [88], and excision [83].

Histologic Features

The lesion is typically a well-circumscribed proliferation of small ductal structures that are evenly distributed in a collagenous stroma (Fig. 11.9). The geometric ductal structures such as “comma-like” or “tadpole-like” are characteristic features. Clear cell change can be seen in tumors associated with diabetes mellitus and Down syndrome [89]. Extension into the deep dermis and subcutaneous tissue is typically seen in the plaque-type syringoma. Vulvar syringoma can be encountered as an incidental finding in association with melanocytic nevi, lichen sclerosis, and lichen simplex chronicus.

Syringoma are reported to express cytokeratin (CK) 6 and CK10 [90] and variable expression

Other Adnexal Neoplasms**Syringoma**

Syringoma was first described in 1874 by Kaposi and Biesiadeki as “lymphangioma tuberosum multiplex”; however vulvar involvement was not reported until 1972 [79]. Since then isolated cases and small case series of syringomas on the genital region have been reported [80–88].

Vulvar syringomas mostly occurred in young women in the third decade [81]. In a series of 18 vulvar syringomas from Taiwan, 11 lesions presented as multiple skin-colored, smooth-surfaced or brownish papules on the labia majora [81]. Discrete whitish cystic papules were seen in three

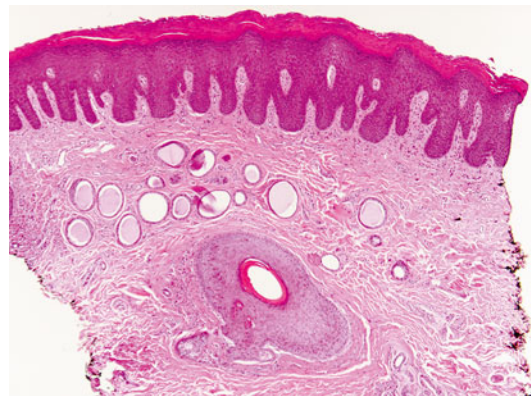


Fig. 11.9 *Syringoma*. A proliferation of small ductal structures is seen evenly distributed in a collagenous stroma. The overlying epidermis exhibits lichen simplex chronicus changes – hyperkeratosis, epidermal hyperplasia, and hypergranulosis

for epithelial membrane antigen, CK1, CK5, CK11, CK14, and CK19 [91–94].

Differential Diagnosis

The differential diagnosis of deep or plaque-type vulvar syringoma would include microcystic adnexal carcinoma [95, 96]. (See *Vignette 1* at the end of this chapter.) A sharp demarcation between the deep syringoma and the adjacent dermis or subcutaneous tissue would not be seen in microcystic adnexal carcinoma.

Summary

Clinical Presentation

- Multiple skin-colored or brownish papules on the labia majora

Histologic Features

- A well-circumscribed superficial proliferation of small ductal structures that are evenly distributed in a collagenous stroma

Differential Diagnosis

- Microcystic adnexal carcinoma

Takeaway Essentials

Clinical Relevant Pearls

- Pruritus is the most common presenting symptom worsening in summertime and menstruation.
- It can be confused with HPV lesions.

Pathology Interpretation Pearls

- Often an incidental finding in association with melanocytic nevi, lichen sclerosis, and lichen simplex chronicus

Hidradenoma

Clear cell hidradenoma usually presents as a solid and cystic nodule with no site predilection, though is only rarely reported to occur on the vulva [28, 97–99]. There have been rare case reports of vulvar hidradenocarcinoma [100–102]. Approximately 50 % of hidradenoma possesses the t(11;19) translocation [102]. HER-2/neu

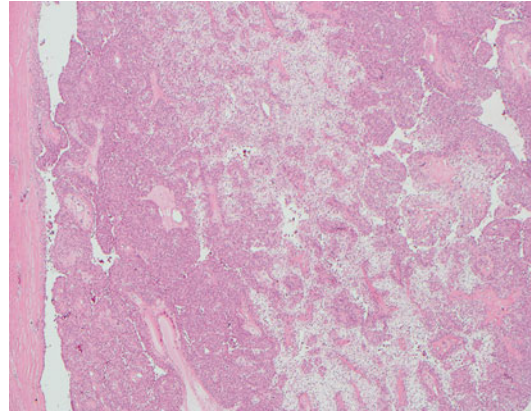


Fig. 11.10 *Hidradenoma*. A cystic and solid neoplasm comprised of clear as well as eosinophilic neoplastic cells is seen

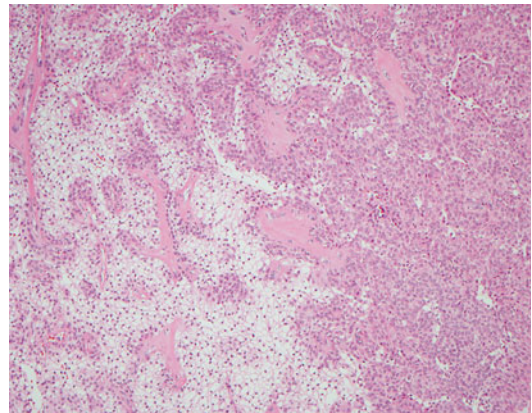


Fig. 11.11 *Hidradenoma*. A cystic and solid neoplasm comprised of clear as well as eosinophilic neoplastic cells is seen

amplification has been reported in a case of metastasizing hidradenocarcinoma [103]; however, this finding has not been confirmed by subsequent studies [102, 104, 105]. Mutations of *TP53* [102, 104, 105], *PIK3CA* [105], and *AKT-1* [105] have been documented in rare cases of hidradenocarcinomas.

Histologic Features

Hidradenoma is characterized by multilobulated, circumscribed yet unencapsulated tumor (Figs. 11.10 and 11.11). Glandular structures can be seen, and in some cases these are striking. The tumor cells are diverse and can be clear, eosino-

philic, squamoid/epidermoid, mucinous, oxyphilic/oncocytic, and transitional/intermediate [24]. Stroma is often hyalinized and sclerotic.

Differential Diagnosis

When focal infiltrative architecture and increased mitotic figures are seen, it is classified as atypical hidradenoma [106], whereas hidradenocarcinomas are characterized by infiltrative growth pattern, deep extension, necrosis, nuclear pleomorphism, and greater than 4 mitoses per 10 high-power fields [106]. Although in some rare instances, metastasizing hidradenocarcinomas do not show these histopathologic features [102]. Apparently, both high-grade and low-grade variants of hidradenocarcinoma exist [107].

Summary

Clinical Presentation

- A solid and cystic nodule

Histologic Features

- Glandular structures and tumor cells with eosinophilic, clear, or mucinous cytoplasm.
- Stroma is frequently sclerotic and hyalinized.

Differential Diagnosis

- Atypical hidradenoma
- Hidradenocarcinoma

Takeaway Essentials

Pathology Interpretation Pearls

- Hidradenocarcinomas are characterized by infiltrative growth pattern, deep extension, necrosis, nuclear pleomorphism, and greater than 4 mitoses per 10 high-power fields.

Immunohistochemical/Molecular Findings

- Ki-67 index can be helpful in distinguishing atypical and malignant from benign hidradenoma.

Sebaceous Carcinoma

Although sebaceous glands can be prominent on the vulva, there have been only few cases of sebaceous carcinoma reported at this site [108–114]. The case reported by Jacobs et al. [110] was associated with colonic adenocarcinoma, likely in the setting of Muir-Torre syndrome. Two cases were associated with overlying Bowen's disease [110, 111].

Histologic Features

Histologically, sebaceous carcinoma is characterized by an infiltrative proliferation comprised of pleomorphic basaloid cells with focal sebaceous differentiation. Ductal structures with eosinophilic cuticle, characteristic of sebaceous ducts, can be seen in well-differentiated sebaceous tumors (Fig. 11.12a, b). Vascular and perineural

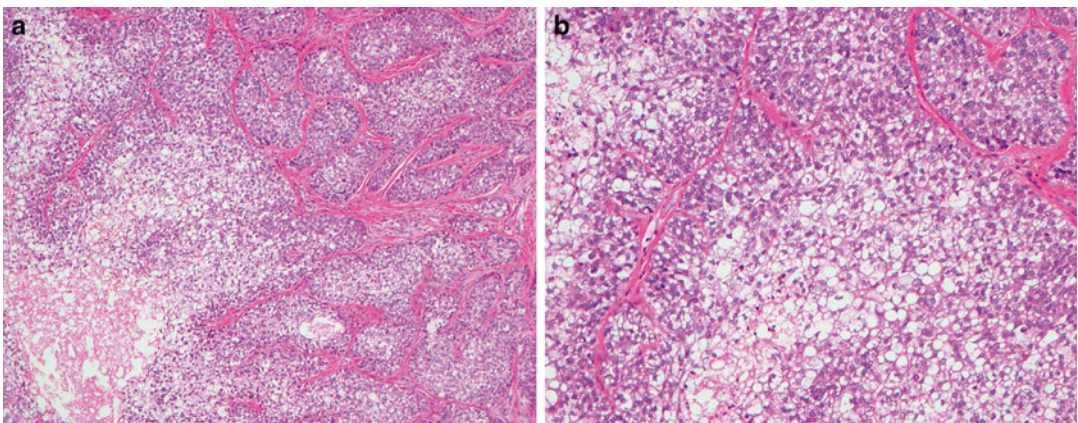


Fig. 11.12 (a, b) *Sebaceous carcinoma*. (a). An infiltrative carcinoma with sebaceous differentiation is seen. (b). Cytoplasmic lipid vacuoles are noted at higher magnification

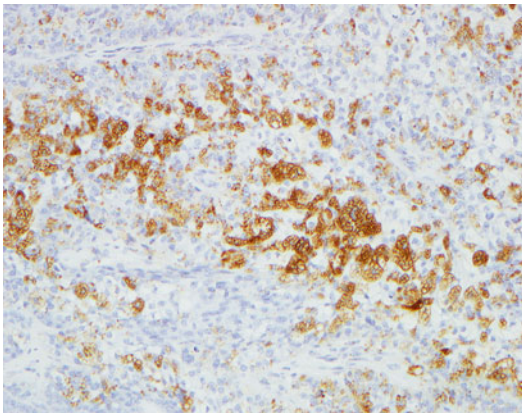


Fig. 11.13 *Sebaceous carcinoma.* The abundant cytoplasmic lipid vacuoles are highlighted by adipophilin immunostain

invasion can be seen. A panel of 2 mismatch repair proteins (PMS2 and MSH6) has been shown by one group to be as effective as a four-antibody panel (PMS2, MSH6, MSH2, and MLH1) as screening panel in detecting Lynch or Muir-Torre syndromes [115]. Vulvar sebaceous lesions however are rarely, if ever, associated with the syndrome. Recently, adipophilin has been shown to be a helpful marker in distinguishing sebaceous carcinomas from mimics [116, 117] (Fig. 11.13).

Differential Diagnosis

Sebaceoma has rarely been reported in the vulva [28]. When a tumor exhibits multiple nests of basaloid cells with scattered mitoses but lacks the atypia of sebaceous carcinoma, it is classified as a sebaceoma.

Summary

Clinical Presentation

- Rarely present on the vulva

Histologic Features

- An infiltrative tumor comprised predominantly of basaloid cells and focally sebaceous differentiation

Differential Diagnosis

- Sebaceoma

Takeaway Essentials

Clinical Relevant Pearls

- Vulvar sebaceous lesions however are rarely, if ever, associated with Muir-Torre syndrome.

Pathology Interpretation Pearls

- The sebaceous changes can be focal; therefore, examination of the entire lesion increases the chance of finding the diagnostic areas.

Immunohistochemical/Molecular Findings

- PMS2 and MSH6 have been shown to be as effective as a four-antibody panel (PMS2, MSH6, MSH2, and MLH1) as screening panel in detecting Lynch or Muir-Torre syndrome.
- Adipophilin can be helpful in highlighting the sebaceous differentiation.

Poroma

Poroma is often present on plantar or palmar skin; however, it may be found on any area containing sweat glands [118]. Rare cases of vulvar poroma have been reported with the frequency of 2.2 % of benign vulvar adnexal neoplasms [28].

Histologic Features

The tumor exhibits a proliferation of uniformly round (poroid) cells and eosinophilic squamoid (cuticular) cells (Fig. 11.14). Small ductal structures lined by an eosinophilic cuticle (highlighted by periodic acid-Schiff (PAS), epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA)) are often seen. It is generally accepted that poromas encompass the following tumors: classic poroma, hidroacanthoma simplex, dermal duct tumor, and poroid hidradenoma depending on the architecture of the neoplasm.

Studies have suggested that poroma derives from the basal keratinocytes of the sweat duct ridge and of the lower acrosyringium [119]. A panel of CK7 and CK19 has been shown to be helpful in differentiating porocarcinoma from squamous cell carcinoma [120].

Loss of heterozygosity in the *APC* gene has been shown in 3/7 poromas; however, this finding is of uncertain significance [121].

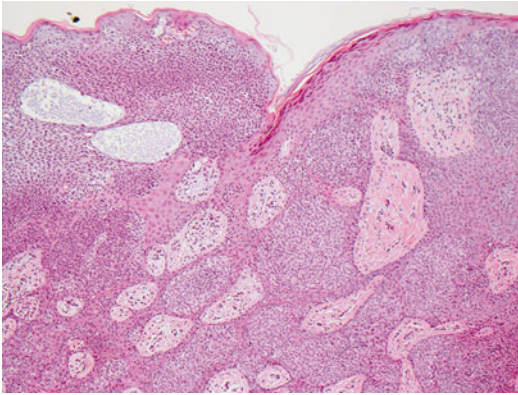


Fig. 11.14 *Poroma*. An intraepidermal proliferation of uniformly round cells

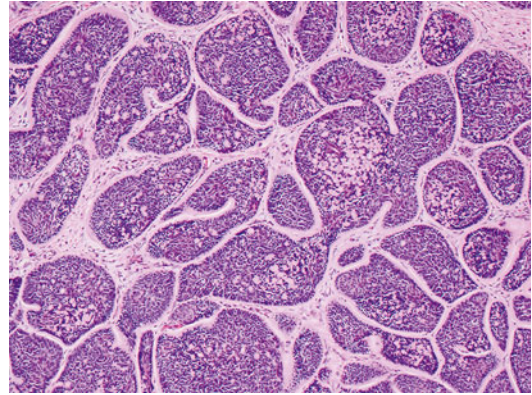


Fig. 11.15 *Cylindroma*. Nodules of basaloid tumor cells are surrounded by eosinophilic basement membrane material

Differential Diagnosis

Porocarcinoma of the vulva is very rare with few cases reported in the literature [122–125]. They often affect women in the sixth decade. Similar to porocarcinomas at nongenital sites, they are associated with frequent nodal metastases [122–125]. One should keep in mind that porocarcinoma is likely to be overdiagnosed or even misdiagnosed, as the analysis of the histological images and descriptions of published “porocarcinomas” strongly suggests.

Summary

Clinical Presentation

- Poroma may be found on any skin area with sweat glands.

Histologic Features

- Comprised of uniform poroid cells and squamoid cuticular cells

Differential Diagnosis

- Porocarcinoma

Takeaway Essentials

Clinical Relevant Pearls

- This tumor needs to be in the differential diagnosis of a mass in postmenopausal women.

Pathology Interpretation Pearls

- Small cytoplasmic vacuoles within the cuticular cells are evidence of primitive ductal differentiation.

Immunohistochemical/Molecular Findings

- EMA and CEA are useful diagnostic tools in highlighting the ductal differentiation.

Cylindroma

Cylindromas are typically found on the head and neck region [126]. Multiple lesions together with spiradenoma and/or trichoepitheliomas are found in the inherited Brooke-Spiegler syndrome [127, 128]. In the vulva, rare cases of cylindroma including those occurring in the setting of Brooke-Spiegler syndrome have been reported [28, 126].

Histologic Features

Nodules of basaloid cells are surrounded by eosinophilic basement membrane material arranged in a jigsaw pattern (Fig. 11.15).

Differential Diagnosis

The malignant counterpart, commonly termed cylindrocarcinoma, has been documented in one rare case at this site [129]. Histologically, several malignant patterns have been documented in cases of malignant transformation of a preexisting benign cylindroma (please refer to differential

diagnosis section of spiradenoma). Cylindroma-like or spiradenocylindroma-like basaloid (cloacogenic) carcinoma can also be a differential diagnostic consideration from a histological point of view, but this lesion usually occurs on the perianal and anal area [130].

Summary

Clinical Presentation

- Solitary or multiple skin-colored nodules

Histologic Features

- Nodules of basaloid cells are surrounded by eosinophilic basement membrane material arranged in a jigsaw pattern.

Differential Diagnosis

- Spiradenoma

Takeaway Essentials

Clinical Relevant Pearls

- Multiple lesions together with spiradenoma and/or trichoepitheliomas are indicative of Brooke-Spiegler syndrome.

Pathology Interpretation Pearls

- Transition between the preexisting benign tumor and the malignant neoplasm is typically gradual.

Spiradenoma

Spiradenoma often presents as a nodule on the head and neck, trunk, or extremities [131]. Rare cases of spiradenoma have been reported in the vulva [28].

Histologic Features

Histologically, spiradenoma presents as a well-circumscribed tumor is composed of two cell populations – central cluster of large cells surrounded by small dark basaloid cells with hyperchromatic nuclei (Fig. 11.16a, b). Ductal differentiation can often be seen, and in rare cases, authentic adenomatous or adenomyoepitheliomatous structures with glands possessing a peripheral myoepithelial cell layer can be recognized [132, 133]. Intratumoral lymphocytes are an essential component of the neoplasm.

Differential Diagnosis

The main differential diagnosis would be a related tumor, the cylindroma. In fact, cylindroma and spiradenoma are thought to comprise a morphological spectrum, with a hybrid or intermediate lesion, the spiradenocylindroma in between, making the strict separation of cylindroma and spiradenoma at some point artificial. On the other hand, considering the microscopic heterogeneity of the malignant counterpart, the terms spiradenocarcinoma and malignant spiradenoma, although often used, are too generic and fail to reflect the range of microscopic appearances that may be indicative

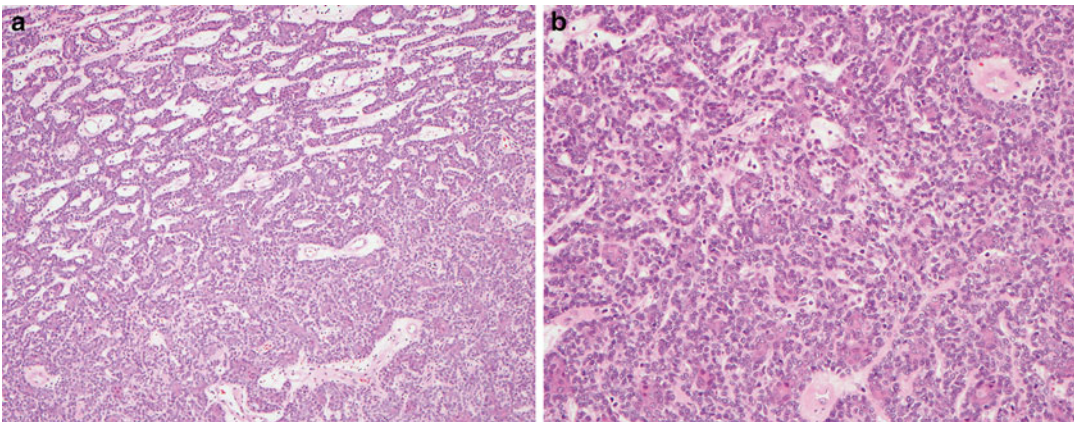


Fig. 11.16 (a, b) *Spiradenoma*. A tumor comprised of central pale large cells and outer small dark basaloid cells with hyperchromatic nuclei

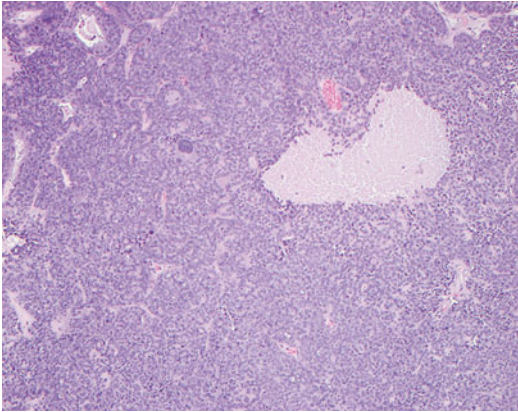


Fig. 11.17 *Spiradenocarcinoma*. Necrosis is noted in this cellular tumor

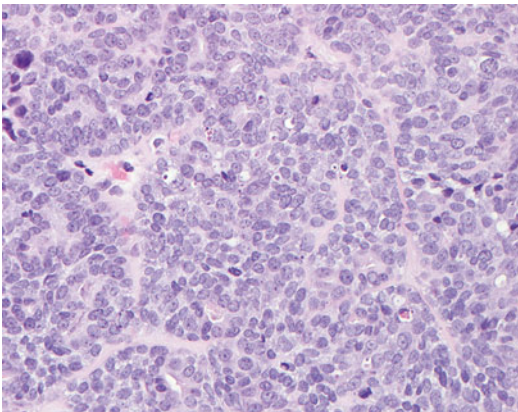


Fig. 11.18 *Spiradenocarcinoma*. Prominent mitotic figures are noted

of behavior and prognosis. Malignant lesions evolving from spiradenoma are classified based on at least four histopathological patterns: salivary gland-type basal cell adenocarcinoma, low grade; salivary gland-type basal cell adenocarcinoma, high grade; apocrine adenocarcinoma, not otherwise specified, in situ or infiltrative; and sarcomatoid (metaplastic) carcinoma [134] (Figs. 11.17 and 11.18). The lesions mostly occur as sporadic solitary neoplasms, or as a component of Brooke-Spiegler syndrome. Only rare cases have been documented arising in the vulva [135–137]. The clinical course of malignant tumors correlates to some extent to the histological pattern and the clinical phenotype. Low-grade neoplasms resembling basal cell adenocarcinoma of salivary glands have been shown to have a less aggressive course,

with local recurrences but no distant metastases, whereas analogous high-grade lesions followed a highly aggressive course. Patients with sarcomatoid (metaplastic) carcinoma had a relatively good survival, an unexpected feature noted by various authors. It appears that the tumor occurring in patients with Brooke-Spiegler syndrome demonstrates a more aggressive behavior compared to their sporadic counterparts, but this should be validated in large series.

Summary

Clinical Presentation

- A nodule on the head and neck, trunk, or extremities

Histologic Features

- A well-circumscribed tumor composed of two cell populations – central cluster of pale large cells surrounded by small dark basaloid cells with hyperchromatic nuclei
- Intratumoral presence of lymphocytes

Differential Diagnosis

- Spiradenocylindroma

Takeaway Essentials

Clinical Relevant Pearls

- The lesions mostly occur as sporadic solitary neoplasms, or as a component of Brooke-Spiegler syndrome

Pathology Interpretation Pearls

- Cylindroma and spiradenoma are thought to comprise a morphological spectrum, with a hybrid or intermediate lesion, the spiradenocylindroma in between.
- The malignant component of spiradenocarcinoma can be:

Salivary gland-type basal cell adenocarcinoma, low grade

Salivary gland-type basal cell adenocarcinoma, high grade

Apocrine adenocarcinoma, not otherwise specified, in situ or infiltrative

Sarcomatoid (metaplastic) carcinoma

Mixed Tumors (Chondroid Syringoma)

Two types of mixed tumors are recognized in the skin, namely apocrine mixed tumor and eccrine mixed tumor. Chondroid syringoma, also known as benign mixed tumor and pleomorphic adenoma, is a rare tumor of the vulva with only a few cases reported in the literature [138–142]. The rarity of mixed tumors in the vulva is underscored by the absence of a single vulvar case in a series of 244 cases [143]. With exception of a single case of eccrine mixed tumor, reported examples of vulvar mixed tumors were of the apocrine variety [144].

Histologic Features

Histologically, the tumor contains a mixture of epithelial and myoepithelial cells associated with a myxoid or cartilaginous stroma [140] (Fig. 11.19).

Differential Diagnosis

The malignant counterpart or malignant chondroid syringoma is characterized by infiltrative growth, greater cellularity and nuclear pleomorphism, mitotic activity, and necrosis [145]. Malignant chondroid syringoma can recur and metastasize to regional lymph nodes and distant sites. However, if strict diagnostic criteria of malignant mixed tumor are applied (presence of a residuum of benign mixed tumor which also contains an

unquestionable malignant component), malignant apocrine or eccrine mixed tumor of the skin is an extremely rare neoplasm with no convincing cases documented in the vulva so far [146].

Summary

Clinical Presentation

- Erythematous to skin-colored nodule

Histologic Features

- A mixture of epithelial and myoepithelial cells associated with a myxoid or cartilaginous stroma

Differential Diagnosis

- Malignant chondroid syringoma

Takeaway Essentials

Clinical Relevant Pearls

- As clinical presentation is nonspecific, the differential diagnosis of an erythematous to skin-colored mass in the vulva needs to include this adnexal tumor.

Pathology Interpretation Pearls

- With exception of a single case of eccrine mixed tumor, reported examples of vulvar mixed tumors were of the apocrine variety.

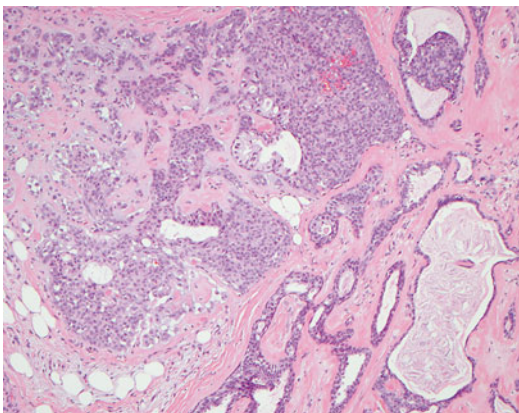


Fig. 11.19 *Chondroid syringoma.* A mixture of epithelial and myoepithelial cells associated with a myxoid or cartilaginous stroma

Metastatic Carcinoma

Metastatic tumors involving the vulva are rare, and the literature is comprised of a few series and case reports [147–150]. In the largest series of 66 cases, approximately equal numbers of the metastases were from genital and extragenital sites [149] (Table 11.2). The most frequent extragynecologic primaries are colorectal in origin [147, 149]. Metastatic tumors usually present as multiple erythematous firm nodules and are associated with postmenopausal women, widespread disease, and poor clinical course [149]. They portend poor prognosis since approximately 90 % of these patients also have multiple simultaneous metastases to other sites [149].

Table 11.2 Genital and extragenital primary sites of 63 metastases in the descending order of frequency

<i>Genital primary</i>	
Cervix	15 (24 %)
Ovary	8 (13 %)
Endometrium	6 (9.5 %)
Vagina	2 (3 %)
<i>Extragenital primary</i>	
Colorectal and anal	12 (19 %)
Breast	4 (6 %)
Skin	4 (6 %)
Lung	3 (5 %)
Urethra	1 (2 %)
Bladder	1 (2 %)
Pancreas	1 (2 %)
Uncertain	6 (9.5 %)

Data from: Neto et al. [149]

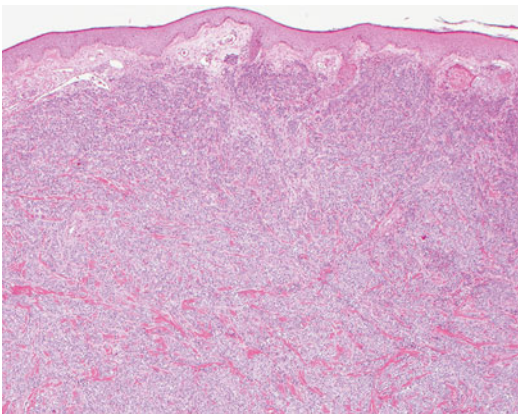


Fig. 11.20 *Metastatic carcinoma from the endometrium.* A nodule of epithelioid neoplastic cells is seen replacing the entire dermis

Histologic Features

The histologic appearance of the metastases would correspond to the primary tumors (Figs. 11.20 and 11.21). A panel of immunohistochemical stains is helpful in distinguishing primary versus metastatic carcinoma to the vulva. CDX2 and CK20 expression would be helpful in ruling a colorectal metastasis; whereas CK7 and ER/PR expression would suggest an ovarian primary.

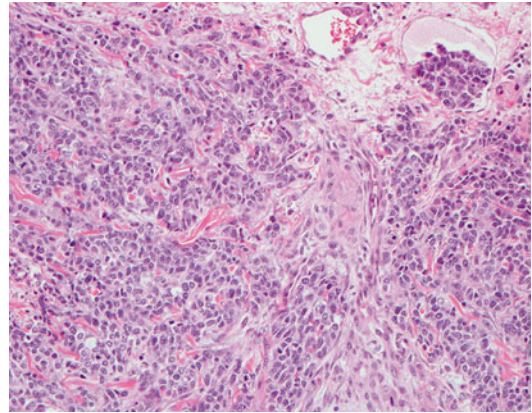


Fig. 11.21 *Metastatic carcinoma from the endometrium.* Lymphovascular invasion is noted at the upper right-hand corner

Summary

Clinical Presentation

- Multiple erythematous firm nodules
- Seen in postmenopausal women, widespread disease, and poor prognosis

Histologic Features

- Histologic appearance of these metastases would correspond to the primary tumors.

Differential Diagnosis

- Broad and depend on the organ of origin

Takeaway Essentials

Clinical Relevant Pearls

- Often with simultaneous metastases to other sites.
- Clinical history is essential to reach a definitive diagnosis.

Pathology Interpretation Pearls

- Prominent lymphovascular invasion is often indicative of a metastasis.

Immunohistochemical/Molecular Findings

- Colonic adenocarcinoma: CDX2+, CK20+, and MUC5AC–
- Ovarian adenocarcinoma: CK7+, ER/PR+, CK20–, and MUC5AC+
- Endometrial adenocarcinoma: CK7+ and vimentin+

Case Vignettes

Vignette 1

Clinical History: A 28-year-old woman presented with multiple, small, pearly white nodules whose sizes ranging from 1 to 4 mm. These nodules were seen on an area measuring 2.0×7.0 cm on her left vulva. An excision was performed.

Microscopic Description: The majority of these lesions show well-circumscribed nodules of tumor in the dermis and some extending into subcutaneous tissue. A sharply demarcated border is seen between the deep aspect of the lesion and the subcutaneous tissue (Fig. 11.22). Small ductal structures are seen evenly distributed in a collagenous stroma (Fig. 11.23).

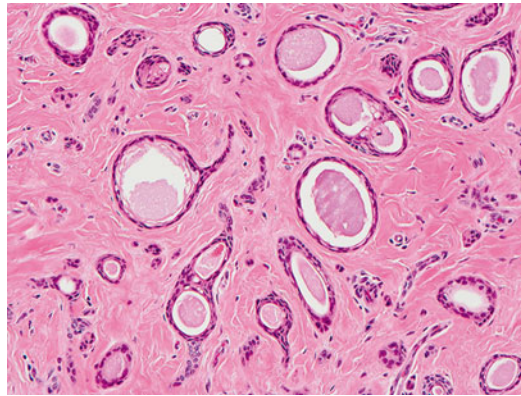


Fig. 11.22 Vignette 1. A circumscribed nodule of tumor in the dermis exhibiting sharply demarcated border between its deep aspect and the subcutaneous tissue

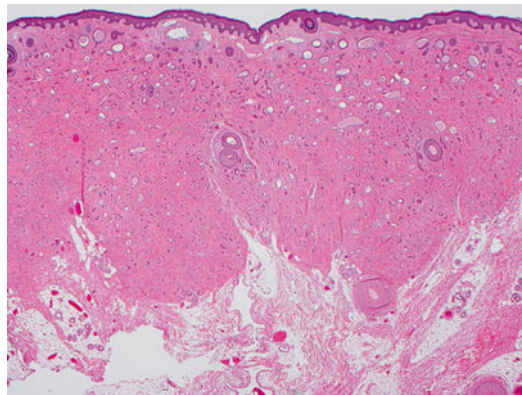


Fig. 11.23 Vignette 1. Small ductal structures are seen evenly distributed in a collagenous stroma

(continued)

Diagnosis: Deep syringoma

Discussion: The deep extension of this syringoma is unusual, and there have been rare cases reported in the literature [95, 96]. Although one “giant” vulvar syringoma has been reported, there has been no mention as to whether there was deep extension of the tumor [151]. The main differential diagnosis of a deep syringoma is a microcystic adnexal carcinoma which is typically a solitary lesion. Syringomas are typically multiple, and solitary presentation would be very unusual [152].

Vignette 2

Clinical History: An 80-year-old female presented with a nodule on her right labium majus. The clinical impression was acrochordon versus neurofibroma versus others.

Microscopic Description: The skin biopsy shows a nodular proliferation of basaloid neoplastic cells exhibiting follicular differentiation, peripheral palisade, and extracellular mucin (Figs. 11.24 and 11.25).

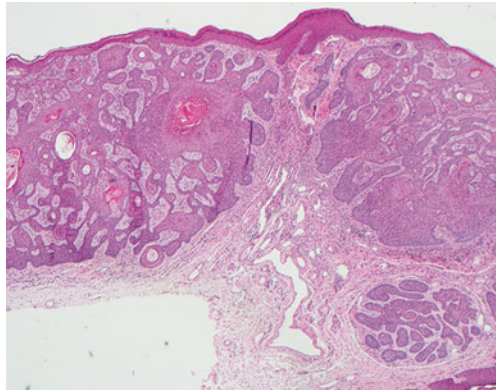


Fig. 11.24 Vignette 2. A nodular proliferation of basaloid neoplastic cells exhibiting follicular differentiation

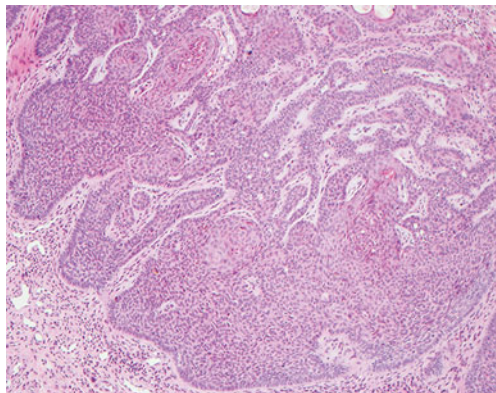


Fig. 11.25 Vignette 2. Peripheral palisade and extracellular mucin are seen

(continued)

Diagnosis: Basal cell carcinoma

Discussion: Basal cell carcinoma (BCC) is the most common cutaneous cancer in the U.S. [153]. However, only approximately 300 cases of anogenital BCC have been reported [153–158], accounting for less than 1 % of all BCC [150] and 3 % of vulvar cancer [155]. The median age appears to be the seventh decade [155, 158]. Only rarely do the patients develop nodal metastases. The occurrence of BCC in non-sun-exposed area raises the possibility of other etiologic agents such as chronic irritation, chronic infection, trauma, irradiation, and arsenical compounds [157]. HPV testing by in situ hybridization for serotypes 6, 11, 16, 18, 31, 33, and 51 was reported negative in five tested cases [158]. This review identified two cases of vulvar BCC (4 % of malignant vulvar adnexal neoplasms), both of which were nodular type, the most common histopathologic subtype [158].

Germ line mutations in the patched or patched 1 (PTCH) gene, a tumor suppressor gene, and the human homolog of the *Drosophila* patched gene, on chromosome 9q22.3, were demonstrated in BCCs of basal cell nevus syndrome (60–70 %) as well as in sporadic BCCs [159, 160].

Vignette 3

Clinical History: An 82-year-old woman presented with 1-year history of perianal itching that has recently started to spread anteriorly. Physical examination revealed an erythematous plaque extending bilaterally from her anal verge laterally towards both buttocks and anteriorly to the perineal body. Anoscopy showed no obvious intra-anal extension of the lesion.

Microscopic Description: Multiple skin biopsies obtained from her anal as well as right and left labia showed similar histologic findings. There is a proliferation of single and polygonal neoplastic cells within the epidermis (Fig. 11.26). Intracytoplasmic mucin is noted in many of these tumor cells, some with a signet-ring appearance (Fig. 11.27). The tumor cells are strongly positive for cytokeratin 20 (Fig. 11.28), carcinoembryonic antigen, and CDX2 (Fig. 11.29). They are negative for cytokeratin 7 and gross cystic disease fluid protein-15.

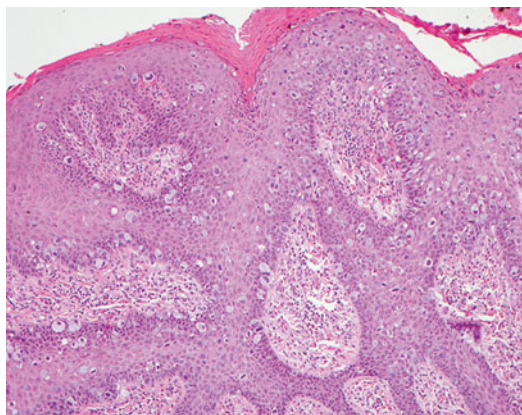


Fig. 11.26 Vignette 3. A proliferation of single polygonal neoplastic cells is seen within the epidermis

(continued)

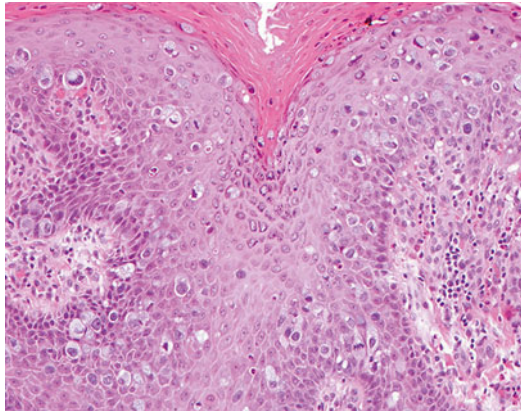


Fig. 11.27 Vignette 3. Intracytoplasmic mucin is noted

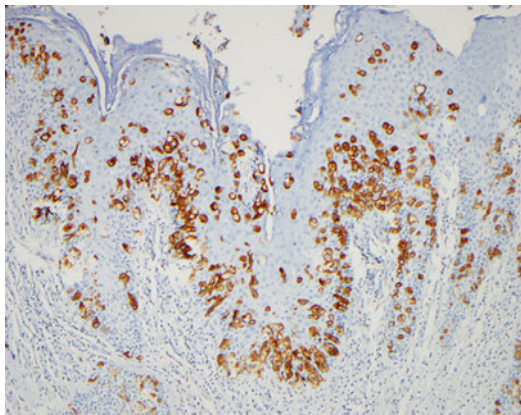


Fig. 11.28 Vignette 3. The tumor cells are positive for cytokeratin 20

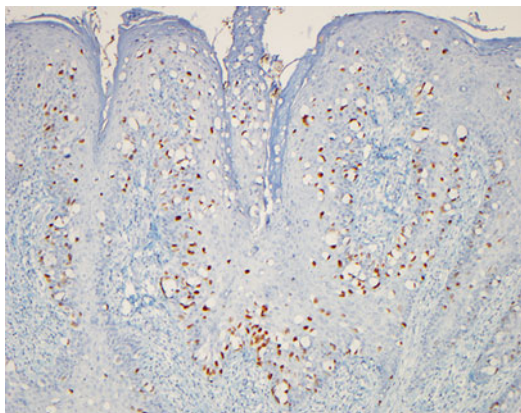


Fig. 11.29 Vignette 3. Nuclear CDX2 expression is noted within the tumor cells

(continued)

Diagnosis: Secondary EMPD from a colorectal primary

Discussion: In a large meta-analysis of 650 reported cases of vulvoperineal EMPD by Preti et al. [161], 10 % of the cases are associated with an underlying visceral malignancy, most commonly colorectal and urothelial carcinomas. Although the definitive diagnosis would depend on clinical pathologic correlation, an immunohistochemical panel would be very helpful in narrowing the differential diagnosis (Table 11.2). Whereas primary EMPD lesions would typically have an immunoprofile of CK7+ CK20- GCDFP-15+ (Fig. 11.7); secondary EMPD lesions would likely be CK7-/+CK20+ GCDFP-15- [58]. As illustrated in this case, the co-expression of CK20 and CDX2 is indicative of secondary EMPD of a colorectal primary [59, 60]. HER-2/neu would be seen in 65 % of primary EMPD in contrast to only 15 % of secondary EMPD, while CDX2 would be seen in 100 % and 33 % of secondary and primary EMPD, respectively [61, 62]. In addition, MUC5AC is commonly expressed in the majority of primary EMPD, whereas MUC2 would be positive in secondary EMPD from a colonic primary [162, 163]. Secondary EMPD of urothelial origin would express Uroplakin III and p63 [63].

References

- Williams PL, Bannister LH, Berry MM. Gray's anatomy. 38th ed. New York: Churchill Livingstone; 1995.
- Van der Putte SC. Anogenital "sweat" glands. Histology and pathology of a gland that may mimic mammary glands. *Am J Dermatopathol.* 1991;13(6):557-67.
- Van der Putte SC. Mammary-like glands of the vulva and their disorders. *Int J Gynecol Pathol.* 1994;13(2):150-60.
- Kazakov DV, Spagnolo DV, Kacerovska D, Michal M. Lesions of anogenital mammary-like glands: an update. *Adv Anat Pathol.* 2011;18(1):1-28.
- Toker C. Clear cells of the nipple epidermis. *Cancer.* 1970;25(3):601-10.
- Willman JH, Golitz LE, Fitzpatrick JE. Vulvar clear cells of Toker: precursors of extramammary Paget's disease. *Am J Dermatopathol.* 2005;27(3):185-8.
- Friedel R. Ein Fibroadenom einer nebenbrustdruese im rechten labium maius. *Virchows Arch F Path Anat.* 1932;286:62-9.
- Sington JD, Manek S, Hollowood K. Fibroadenoma of the mammary-like glands of the vulva. *Histopathology.* 2002;41(6):563-5.
- Carter JE, Mizell KN, Tucker JA. Mammary-type fibroepithelial neoplasms of the vulva: a case report and review of the literature. *J Cutan Pathol.* 2008;35(2):246-9.
- Vella JE, Taibjee SM, Sanders DS, Stellakis M, Carr RA. Fibroadenoma of the anogenital region. *J Clin Pathol.* 2008;61(7):871-2.
- Kazakov DV, Spagnolo DV, Stewart CJ, Thompson J, Agaimy A, Magro G, et al. Fibroadenoma and phylloides tumors of anogenital mammary-like glands: a series of 13 neoplasms in 12 cases, including mammary-type juvenile fibroadenoma, fibroadenoma with lactation changes, and neurofibromatosis-associated pseudoangiomatous stromal hyperplasia with multinucleated giant cells. *Am J Surg Pathol.* 2010;34(1):95-103.
- Mannan AA, Kahvic M, Aziz AH. Phylloides tumor of the vulva: report of a rare case and review of the literature. *Am J Dermatopathol.* 2010;32(4):384-6.
- Heffernan TP, Sarode VR, Hoffman B, Lea J. Recurrent phylloides tumor of the vulva: a case report with review of diagnostic criteria and differential diagnosis. *Int J Gynecol Pathol.* 2010;29(3):294-7.
- Audisio T, Crespo-Roca F, Giraudo P, Ramallo R. Fibroadenoma of the vulva - simultaneous with breast fibroadenomas and uterine fibroma. *J Low Genit Tract Dis.* 2011;15(1):75-9.
- Hassim AM. Bilateral fibroadenoma in supernumerary breasts of the vulva. *J Obstet Gynaecol Br Commonw.* 1969;76(3):275-7.
- Fu L, Lau S, Roy I, Ferenczy A. Phylloides tumor with malignant stromal morphology of the vulva: a case report and review of the literature. *Int J Gynecol Pathol.* 2011;30(2):198-202.
- Kazakov DV, Bisceglia M, Mukensnabl P, Michal M. Pseudoangiomatous stromal hyperplasia in lesions involving anogenital mammary-like glands. *Am J Surg Pathol.* 2005;29(9):1243-6.
- Kazakov DV, Nemcova J, Mikyskova I, Belousova IE, Vazmitel M, Michal M. Human papillomavirus in lesions of anogenital mammary-like glands. *Int J Gynecol Pathol.* 2007;26(4):475-80.
- Gugliotta P, Fibbi ML, Fessia L, Canevini P, Bussolati G. Lactating supernumerary mammary

- gland tissue in the vulva. *Appl Pathol.* 1983;1(2): 61–5.
20. Lee ES, Kim I. Multiple vulvar lactating adenomas. *Obstet Gynecol.* 2011;118(2 Pt 2):478–80.
 21. O'Hara MF, Page DL. Adenomas of the breast and ectopic breast under lactational influences. *Hum Pathol.* 1985;16(7):707–12.
 22. Lev-Cohain N, Kapur P, Pedrosa I. Vulvar fibroadenoma with lactational changes in ectopic breast tissue. *Case Rep Obstet Gynecol.* 2013;2013:924902.
 23. Woodworth H, Docketty MB, Wilson RB, Pratt JH. Papillary hidradenoma of the vulva: a clinicopathologic study of 69 cases. *Am J Obstet Gynecol.* 1971;110(4):501–8.
 24. Requena L, Kiryu H, Ackerman AB. Neoplasms with apocrine differentiation. Philadelphia: Lippincott-Raven; 1998.
 25. Parks A, Branch KD, Metcalf J, Underwood P, Young J. Hidradenoma papilliferum with mixed histopathologic features of syringocystadenoma papilliferum and anogenital mammary-like glands: report of a case and review of the literature. *Am J Dermatopathol.* 2012;34(1):104–9.
 26. Nishie W, Sawamura D, Mayuzumi M, Takahashi S, Shimizu H. Hidradenoma papilliferum with mixed histopathologic features of syringocystadenoma papilliferum and anogenital mammary-like glands. *J Cutan Pathol.* 2004;31(8):561–4.
 27. Scurry J, van der Putte SC, Pyman J, Chetty N, Szabo R. Mammary-like gland adenoma of the vulva: review of 46 cases. *Pathology.* 2009;41(4): 372–8.
 28. Baker GM, Selim MA, Hoang MP. Vulvar adnexal lesions: a 32-year, single-institution review from Massachusetts General Hospital. *Arch Pathol Lab Med.* 2013;137(9):1237–46.
 29. Kazakov DV, Mikyskova I, Kutzner H, Simpson RHW, Hes O, Mukensnabl P, et al. Hidradenoma papilliferum with oxyphilic metaplasia: a clinicopathological study of 18 cases, including detection of human papillomavirus. *Am J Dermatopathol.* 2005;27(2):102–10.
 30. Sington J, Chandrapala R, Manek S, Hollowood K. Mitotic count is not predictive of clinical behavior in hidradenoma papilliferum of the vulva: a clinicopathologic study of 19 cases. *Am J Dermatopathol.* 2006;28(4):322–6.
 31. Plumb SJ, Argenyi ZB, Stone MS, De Young BR. Cytokeratin 5/6 immunostaining in cutaneous adnexal neoplasms and metastatic adenocarcinoma. *Am J Dermatopathol.* 2004;26(6):447–51.
 32. Mahalingam M, Srivastava A, Hoang MP. Expression of stem-cell markers (cytokeratin 15 and nestin) in primary adnexal neoplasms – clues to etiopathogenesis. *Am J Dermatopathol.* 2010;32(8):774–9.
 33. Swanson PE, Mazoujian G, Mills SE, Campbell RJ, Wick MR. Immunoreactivity for estrogen receptor protein in sweat gland tumors. *Am J Surg Pathol.* 1991;15(9):835–41.
 34. Mazoujian G, Margolis R. Immunohistochemistry of gross cystic disease fluid protein (GCDPF-15) in 65 benign sweat gland tumors of the skin. *Am J Dermatopathol.* 1988;10(1):28–35.
 35. Castro CY, Deavers M. Ductal carcinoma in-situ arising in mammary-like glands of the vulva. *Int J Gynecol Pathol.* 2001;20(3):277–83.
 36. Pelosi G, Martignoni G, Bonetti F. Intraductal carcinoma of mammary-type apocrine epithelium arising within a papillary hidradenoma of the vulva. Report of a case and review of the literature. *Arch Pathol Lab Med.* 1991;115(12):1249–54.
 37. Shah SS, Adelson M, Mazur MT. Adenocarcinoma in situ arising in vulvar papillary hidradenoma: report of 2 cases. *Int J Gynecol Pathol.* 2008;27(3):453–6.
 38. Vazmitel M, Spagnolo DV, Nemcova J, Michal M, Kazakov DV. Hidradenoma papilliferum with a ductal carcinoma in situ component: case report and review of the literature. *Am J Dermatopathol.* 2008;30(4):392–4.
 39. Crocker H. Paget's disease affecting the scrotum and penis. *Trans Pathol Soc Lond.* 1889;40:187–91.
 40. Lam C, Funaro D. Extramammary Paget's disease: summary of current knowledge. *Dermatol Clin.* 2010;28(4):807–26.
 41. Belousova IE, Kazakov DV, Michal M, Suster S. Vulvar Tokel cells: the long-awaited missing link: a proposal for an origin-based histogenetic classification of extramammary Paget disease. *Am J Dermatopathol.* 2006;28(1):84–6.
 42. Lloyd J, Flanagan AM. Mammary and extramammary Paget's disease. *J Clin Pathol.* 2000;53(10):742–9.
 43. Regauer S. Extramammary Paget's disease – a proliferation of adnexal origin? *Histopathology.* 2006; 48(6):723–9.
 44. Chanda JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. *J Am Acad Dermatol.* 1985;13(6):1009–14.
 45. Shepherd V, Davidson EJ, Davies-Humphreys J. Extramammary Paget's disease. *BJOG.* 2005;112(3): 273–9.
 46. Kanitakis J. Mammary and extramammary Paget's disease. *J Eur Acad Dermatol Venerol.* 2007;21(5): 581–90.
 47. Goldblum JR, Hart WR. Perianal Paget's disease: a histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. *Am J Surg Pathol.* 1998;22(2):170–9.
 48. De Magnis A, Checcucci V, Catalano C, Corazzesi A, Pieralli A, Taddei G, Frambrini M. Vulvar paget disease: a large single-centre experience on clinical presentation, surgical treatment, and long-term outcomes. *J Low Genit Tract Dis.* 2013;17(2): 104–10.
 49. Cai Y, Sheng W, Xiang L, Wu X, Yang H. Primary extramammary Paget's disease of the vulva: the clinicopathological features and treatment outcomes in a series of 43 patients. *Gynecol Oncol.* 2013;129(2): 412–6.

50. Shaco-Levy R, Bean SM, Vollmer RT, Papalas JA, Bentley RC, Selim MA, Robboy SJ. Paget disease of the vulva: a histologic study of 56 cases correlating pathologic features and disease course. *Int J Gynecol Pathol.* 2010;29(1):69–78.
51. Siesling S, Elferink MA, van Dijk JA, Pierie P, Blokk WA. Epidemiology and treatment of extramammary Paget disease in the Netherlands. *Eur J Surg Oncol.* 2007;33(8):951–5.
52. Kawatsu T, Miki Y. Triple extramammary Paget's disease. *Arch Dermatol.* 1971;104(3):316–9.
53. Jones ISC, Crandon A, Sanday K. Paget's disease of the vulva: diagnosis and follow-up key to management; a retrospective study of 50 cases from Queensland. *Gynecol Oncol.* 2011;122(1):42–4.
54. Parker LP, Parker JR, Bodurka-Bevers D, Deavers M, Bevers MW, Shen-Gunther J, Gerhenson DM. Paget's disease of the vulva: pathology, pattern of involvement, and prognosis. *Gynecol Oncol.* 2000;77(1):183–9.
55. Kodama S, Kanedo T, Saito M, Yoshiya N, Honma S, Tanaka K. A clinicopathologic study of 30 patients with Paget's disease of the vulva. *Gynecol Oncol.* 1995;56(1):63–70.
56. Karam A, Dorigo O. Increased risk and pattern of secondary malignancies in patients with invasive extramammary Paget disease. *Br J Dermatol.* 2014;170(3):661–71.
57. Feuer GA, Shevchuk M, Calanog A. Vulvar Paget's disease: the need to exclude an invasive lesion. *Gynecol Oncol.* 1990;38(1):81–9.
58. Goldblum JR, Hart WR. Vulvar Paget's disease: a clinicopathologic and immunohistochemical study of 19 cases. *Am J Surg Pathol.* 1997;21(10):1178–87.
59. De Nisi MC, D'Amuri A, Toscano M, Lalinga AV, Pirtoli L, Miracco C. Usefulness of CDX2 in the diagnosis of extramammary Paget disease associated with malignancies of intestinal type. *Br J Dermatol.* 2005;153(3):677–9.
60. Ohnishi T, Watanabe S. The use of cytokeratins 7 and 20 in the diagnosis of primary and secondary extramammary Paget's disease. *Br J Dermatol.* 2000;142(2):243–7.
61. Perrotto J, Abbott JJ, Ceilley RI, Ahmed I. The role of immunohistochemistry in discriminating primary from secondary extramammary Paget's disease. *Am J Dermatopathol.* 2010;32(2):137–43.
62. Plaza JA, Torres-Cabala C, Ivan D, Prieto VG. HER-2/neu expression in extramammary Paget disease: a clinicopathologic and immunohistochemistry study of 47 cases with and without underlying malignancy. *J Cutan Pathol.* 2009;36(7):729–33.
63. Brown HM, Wilkinson EJ. Uroplakin-III to distinguish primary vulvar Paget disease from Paget disease secondary to urothelial carcinoma. *Hum Pathol.* 2002;33(5):545–8.
64. Liegl B, Horn HC, Moinfar F. Androgen receptors are frequently expressed in mammary and extramammary Paget's disease. *Mod Pathol.* 2005;18(10):1283–8.
65. Hikita T, Ohtsuki Y, Maeda T, Furihata M. Immunohistochemical and fluorescence studies on noninvasive and invasive extramammary Paget's disease. *Int J Surg Pathol.* 2012;20(5):441–8.
66. Kang Z, Xu F, Zhang QA, Lin J, Wu Z, Zhang X, et al. Correlation of DLC1 gene methylation with oncogenic PIK3CA mutations in extramammary Paget's disease. *Mod Pathol.* 2012;25(8):1160–8.
67. Kang Z, Xu F, Zhang QA, Wu Z, Zhang X, Xu J, et al. Oncogenic mutations in extramammary Paget's disease and their clinical relevance. *Int J Cancer.* 2013;132(4):824–31.
68. Qian Y, Zhang N, Chen S, Chu S, Feng A, Liu H. PI3K, Rac1 and pPAK1 are overexpressed in extramammary Paget's disease. *J Cutan Pathol.* 2012;39(11):1010–5.
69. McCluggage WG. Recent developments in vulvovaginal pathology. *Histopathology.* 2009;54(2):156–73.
70. Abbott JJ, Ahmed I. Adenocarcinoma of mammary-like glands of the vulva: report of a case and review of the literature. *Am J Dermatopathol.* 2006;28(2):127–33.
71. Wick MR, Ockner DM, Mills SE, Ritter JH, Swanson PS. Homologous carcinomas of the breast, skin, and salivary glands. *Am J Clin Pathol.* 1998;109(1):75–84.
72. Van der Putte SC, van Gorp LH. Adenocarcinoma of the mammary-like glands of the vulva: a concept unifying sweat gland carcinoma of the vulva, carcinoma of supernumerary mammary glands and extramammary Paget's disease. *J Cutan Pathol.* 1994;21(2):157–63.
73. Tanaka H, Umekawa T, Nagao K, Ishihara A, Toyoda N. Adenocarcinoma of mammary-like glands in the vulva successfully treated by weekly paclitaxel. *Int J Gynecol Cancer.* 2005;15(3):568–71.
74. Alsaad KO, Obaidat N, Dube V, Chapman W, Ghazarian D. Vulvar apocrine adenocarcinoma: a case with nodal metastasis and intranodal mucinous differentiation. *Pathol Res Pract.* 2009;205(2):131–5.
75. Benito V, Arribas S, Martinez D, Medina N, Lubrano A, Arencibia O. Metastatic adenocarcinoma of mammary-like glands of the vulva successfully treated with surgery and hormonal therapy. *J Obstet Gynaecol Res.* 2013;39(1):450–4.
76. Kazakov DV, Belousova IE, Sima R, Michal M. Mammary type tubulolobular carcinoma of the anogenital area: report of a case of a unique tumor presumably originating in anogenital mammarylike glands. *Am J Surg Pathol.* 2006;30(9):1193–6.
77. Fernandez-Figueras MT, Michal M, Kazakov DV. Mammary-type tubulolobular carcinoma of anogenital mammary-like glands with prominent stromal elastosis. *Am J Surg Pathol.* 2010;34(8):1224–6.
78. Carneiro SJ, Gardner HL, Knox JM. Syringoma: three cases with vulvar involvement. *Obstet Gynecol.* 1972;39(1):95–9.

79. Young Jr AW, Herman EW, Tovell HM. Syringoma of the vulva: incidence, diagnosis, and cause of pruritus. *Obstet Gynecol.* 1980;55(4):515–8.
80. Huang YH, Chuang YH, Kuo TT, Yang LC, Hong HS. Vulvar syringoma: a clinicopathologic and immunohistologic study of 18 patients and results of treatment. *J Am Acad Dermatol.* 2003;48(5):735–9.
81. Wallace ML, Smoller BR. Progesterone receptor positivity supports hormonal control of syringomas. *J Cutan Pathol.* 1995;22(5):442–5.
82. Yorganci A, Kale A, Dunder I, Ensari A, Sertcelik A. Vulvar syringoma showing progesterone receptor positivity. *BJOG.* 2000;107(2):292–4.
83. Trager JD, Silvers J, Reed JA, Scott RA. Neck and vulvar papules in an 8-year-old girl. *Arch Dermatol.* 1999;135(2):203. 206.
84. Chandler WM, Bosenberg MW. Autoimmune acrosyringitis with ductal cysts: reclassification of case of eruptive syringoma. *J Cutan Pathol.* 2009;36(12):1312–5.
85. Tay YK, Tham SN, Teo R. Localized vulvar syringomas – an unusual cause of pruritus vulvae. *Dermatology.* 1996;192(1):62–3.
86. Belardi MG, Maglione MA, Vighi S, di Paola GR. Syringoma of the vulva: a case report. *J Reprod Med.* 1994;39(12):957–9.
87. Zhu WY. Vulvar syringoma associated with epidermal cyst. *Int J Dermatol.* 1989;28(2):142–3.
88. Furue M, Hori Y, Nakabayashi Y. Clear-cell syringoma. Association with diabetes mellitus. *Am J Dermatopathol.* 1984;6(2):131–8.
89. Missall TA, Burkemper NM, Jensen SL, Hurley MY. Immunohistochemical differentiation of four benign eccrine tumors. *J Cutan Pathol.* 2009;36(2):190–6.
90. Eckert F, Nilles M, Schmid U, Altmannsberger M. Distribution of cytokeratin polypeptides in syringomas. An immunohistochemical study on paraffin-embedded material. *Am J Dermatopathol.* 1992;14(2):115–21.
91. Ohnishi T, Watanabe S. Immunohistochemical analysis of keratin expression in clear cell syringoma. A comparative study with conventional syringoma. *J Cutan Pathol.* 1997;24(6):370–6.
92. Kim BC, Park EJ, Kwon IH, Cho HJ, Park HR, Kim KH, Kim KJ. An immunohistochemical study of the origin of the solid strand in syringoma, using carcinoembryonic antigen, epithelial membrane antigen, and cytokeratin 5. *Int J Dermatol.* 2012;51(7):817–22.
93. Langbein L, Cribier B, Schirmacher P, Praetzel-Wunder S, Peltre B, Schweizer J. New concepts on the histogenesis of eccrine neoplasia from keratin expression in the normal eccrine gland, syringoma and poroma. *Br J Dermatol.* 2008;159(3):633–45.
94. Kazakov DV, Bouda Jr J, Kacerovska D, Michal M. Vulvar syringomas with deep extension: a potential histopathologic mimic of microcystic adnexal carcinoma. *Int J Gynecol Pathol.* 2011;30(1):92–4.
95. Suwattee P, McClelland MC, Huiras EE, Warshaw EM, Lee PK, Kaye VN, et al. Plaque-type syringoma: two cases misdiagnosed as microcystic adnexal carcinoma. *J Cutan Pathol.* 2008;35(6):570–4.
96. Kersting DW. Clear cell hidradenoma and hidradenocarcinoma. *Arch Dermatol.* 1963;87:323–33.
97. Bondi R, Ambrosi L. Clear cell hidradenoma (with special reference to the usual localization in the vulva. *Arch De Vecchi Anat Patol.* 1963;41:201–25.
98. Messing MJ, Richardson MS, Smith MT, King L, Gallup DG. Metastatic clear-cell hidradenocarcinoma of the vulva. *Gynecol Oncol.* 1993;48(2):264–8.
99. Biedrzycki OJ, Rufford B, Wilcox M, Barton DPJ, Jameson C. Malignant clear cell hidradenoma of the vulva: report of a unique case and review of the literature. *Int J Gynecol Pathol.* 2008;27(1):142–6.
100. Webb JB, Beswick IP. Eccrine hidradenocarcinoma of the vulva with Paget's disease. Case report with a review of the literature. *Br J Obstet Gynaecol.* 1993;90(1):90–5.
101. Kazakov DV, Ivan D, Kutzner H, Spagnolo DV, Grossmann P, Vanecek T, et al. Cutaneous hidradenocarcinoma: a clinicopathological, immunohistochemical, and molecular biologic study of 14 cases, including Her2/neu gene expression/amplification, TP53 gene mutation analysis, and t(11;19) translocation. *Am J Dermatopathol.* 2009;31(3):236–47.
102. Nash JW, Barrett TL, Kies M, Ross MI, Sneige N, Diwan AH, Lazar AJ. Metastatic hidradenocarcinoma with demonstration of Her-2/neu gene amplification by fluorescence in situ hybridization: potential treatment implications. *J Cutan Pathol.* 2007;34(1):49–54.
103. Dias-Santagata D, Lam Q, Bergethon K, Baker GM, Iafrate AJ, Rakheja D, Hoang MP. A potential role for targeted therapy in a subset of metastasizing adnexal carcinomas. *Mod Pathol.* 2011;24(7):974–82.
104. Le LP, Dias-Santagata D, Pawlak AC, Cospser AK, Nguyen AT, Selim MA, et al. Apocrine-eccrine carcinomas: molecular and immunohistochemical analyses. *PLoS One.* 2012;7(10):e47290.
105. Nazarian RM, Kapur P, Rakheja D, Piris A, Duncan LM, Mihm Jr MC, Hoang MP. Atypical and malignant hidradenomas: a histologic and immunohistochemical study. *Mod Pathol.* 2009;22(4):600–10.
106. Stefanato CM, Ferrara G, Chaudhry IH, Guevara Pineda C, Waschkowski G, Rose C, Calonje E. Clear cell nodular hidradenoma involving the lymphatic system: a tumor of uncertain malignant potential or a novel example of “metastasizing” benign tumor? *Am J Surg Pathol.* 2012;36(12):1835–40.
107. Carlson JW, McGlennen RC, Gomez R, Longbella C, Carter J, Carson LF. Sebaceous carcinoma of the vulva: a case report and review of the literature. *Gynecol Oncol.* 1996;60(3):489–91.
108. Rulon DB, Helwig EB. Cutaneous sebaceous neoplasms. *Cancer.* 1974;33(1):82–102.
109. Jacobs DM, Sandles LG, Leboit PE. Sebaceous carcinoma arising from Bowen's disease of the vulva. *Arch Dermatol.* 1986;122(10):1191–3.
110. Escalonilla P, Grilli R, Canamero M, Soriano ML, Farina MC, Manzarbeitia F, et al. Sebaceous

- carcinoma of the vulva. *Am J Dermatopathol.* 1999; 21(5):468–72.
111. Pusiol T, Morichetti D, Zorzi MG. Sebaceous carcinoma of the vulva: critical approach to grading and review of the literature. *Pathologica.* 2011;103(3): 64–7.
112. Khan Z, Misra G, Fiander AN, Dallimore NS. Sebaceous carcinoma of the vulva. *BJOG.* 2003; 110(2):227–8.
113. Kawamoto M, Fukuda Y, Kamoi S, Sugisaki Y, Yamanaka N. Sebaceous carcinoma of the vulva. *Pathol Int.* 1995;45(10):767–73.
114. Mojtahed A, Schrijver I, Ford JM, Longacre TA, Pai RK. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. *Mod Pathol.* 2011; 24(7):1004–14.
115. Ostler DA, Prieto VG, Reed JA, Deavers MT, Lazar AJ, Ivan D. Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases. *Mod Pathol.* 2010;23(4):567–73.
116. Boussahmain C, Mochel MC, Hoang MP. Perilipin and adipophilin expression in sebaceous carcinoma and mimics. *Hum Pathol.* 2013;44(9):1811–6.
117. Pinkus H, Rogin JR, Goldman R. Eccrine poroma. Tumors exhibiting features of the epidermal sweat duct unit. *AMA Arch Dermatol.* 1956;74(5): 511–21.
118. Battistella M, Langbein L, Peltre B, Cribier B. From hydroacanthoma simplex to poroid hidradenoma: clinicopathologic and immunohistochemic study of poroid neoplasms and reappraisal of their histogenesis. *Am J Dermatopathol.* 2010;32(5):459–68.
119. Mahalingam M, Richards JE, Selim MA, Muzikansky A, Hoang MP. An immunohistochemical comparison of cytokeratin 7, cytokeratin 15, cytokeratin 19, CAM5.2, carcinoembryonic antigen, and nestin in differentiating porocarcinoma from squamous cell carcinoma. *Hum Pathol.* 2012;43(8): 1265–72.
120. Ichihashi N, Kitajima Y. Loss of heterozygosity of adenomatous polyposis coli gene in cutaneous tumors as determined by using polymerase chain reaction and paraffin section preparations. *J Dermatol Sci.* 2000;22(2):102–6.
121. Adegboyega PA. Eccrine porocarcinoma of the vulva: a case report and review of literature. *Int J Gynecol Pathol.* 2011;30(1):95–100.
122. Katsanis WA, Doering DL, Bosscher JR, O’Conner DM. Vulva eccrine porocarcinoma. *Gynecol Oncol.* 1996;62(3):396–9.
123. Liegl B, Regauer S. Eccrine carcinoma (nodular porocarcinoma) of the vulva. *Histopathology.* 2005; 47(3):324–6.
124. Stephen MR, Matalka I, Hanretty K. Malignant eccrine poroma of the vulva. *Br J Obstet Gynaecol.* 1998;105(4):471–2.
125. Crain RC, Helwig EB. Dermal cylindroma (dermal eccrine cylindroma). *Am J Clin Pathol.* 1961;35: 504–15.
126. Young AL, Kellermayer R, Szigeti R, Teszas A, Azmi S, Celebi JT. CYLD mutations underlie Brooke-Spiegler, familial cylindromatosis, and multiple familial trichoepithelioma syndromes. *Clin Genet.* 2006;70(3):246–9.
127. Grossmann P, Vanecek T, Steiner P, Kacerovska D, Spagnolo DV, Cribier B, et al. Novel and recurrent germline and somatic mutations in a cohort of 67 patients from 48 families with Brooke-Spiegler syndrome including the phenotypic variant of multiple familial trichoepitheliomas and correlation with the histopathologic findings in 379 biopsy specimens. *Am J Dermatopathol.* 2013;35(1):34–44.
128. Sayre GP. Cylindroma of the vulva; adenocarcinoma, cylindroma type, of the vulva; report of a case of 27 years’ duration. *Proc Staff Meet Mayo Clin.* 1949;24(9):224–33.
129. Kacerovska D, Szepe P, Vanecek T, Nemcova J, Michal M, Mukensnabl P, Kazakov DV. Spiradenocylindroma-like basaloid carcinoma of the anus and rectum: case report, including HPV studies and analysis of the CYLD gene mutations. *Am J Dermatopathol.* 2008;30(5):472–6.
130. Nambo NC. Eccrine spiradenoma: clinical and pathologic study of 49 tumors. *J Cutan Pathol.* 1983;10(5):312–20.
131. Kacerovska D, Kazakov DV, Kutzner H, Michal M. Spiradenoma with marked adenomyoepitheliomatous features. *Am J Dermatopathol.* 2010;32(7):744–6.
132. Kazakov DV, Magro G, Kutzner H, Spagnolo DV, Yang Y, Zaspas O, Mukensnabl P, Michal M. Spiradenoma and spiradenocylindroma with an adenomatous or atypical adenomatous component: a clinicopathological study of 6 cases. *Am J Dermatopathol.* 2008;30(5):436–41.
133. Kazakov DV, Zelger B, Rütten A, Vazmitel M, Spagnolo DV, Kacerovska D, et al. Morphologic diversity of malignant neoplasms arising in preexisting spiradenoma, cylindroma, and spiradenocylindroma based on the study of 24 cases, sporadic or occurring in the setting of Brooke-Spiegler syndrome. *Am J Surg Pathol.* 2009;33(5):705–19.
134. Chen G, Cheuk W, Cheung JS, Chan JK. Carcinosarcoma ex eccrine spiradenoma of the vulva: report of the first case. *Int J Gynecol Pathol.* 2011;30(3):301–5.
135. Emam EE, Sawan AS, Al-Tamimi SR, Molah RM. Malignant spiradenoma/cylindroma of the vulva. *Saudi Med J.* 2012;33(11):1229–33.
136. Chase DM, Basu T, Saffari B, Ries S, Berman ML. Malignant eccrine spiradenoma of the vulva: a case report and review of the literature. *Int J Gynecol Cancer.* 2006;16(3):1465–9.
137. Su A, Apple SK, Moatamed NA. Pleomorphic adenoma of the vulva, clinical reminder of a rare occurrence. *Rare Tumors.* 2012;4(1):e16.

138. Ordonez NG, Manning JT, Luna MA. Mixed tumor of the vulva: a report of two cases probably arising in Bartholin's gland. *Cancer*. 1981;48(1):181–6.
139. Dykgraaf RH, van Veen MM, van Bekkum-de Jonge EE, Gerretsen J, de Jong D, Burger CW. Pleomorphic adenoma of the vulva: a review illustrated by a clinical case. *Int J Gynecol Cancer*. 2006;16(2):920–3.
140. Rorat E, Wallach RC. Mixed tumors of the vulva: clinical outcome and pathology. *Int J Gynecol Pathol*. 1984;3(3):323–8.
141. Wilson D, Woodger BA. Pleomorphic adenoma of the vulva. *J Obstet Gynaecol Br Commonw*. 1974;81(12):1000–2.
142. Chome J, Giard R. Case report of an unusual tumor of the vulva: epithelioma of rearranged stroma or so-called mixed tumor. *Bull Fed Soc Gynecol Obstet Lang Fr*. 1956;8(5):562–5 [Article in French].
143. Kazakov DV, Belousova IE, Bisceglia M, Calonje E, Emberger M, Grayson W, et al. Apocrine mixed tumor of the skin ("mixed tumor of the folliculosebaceous-apocrine complex"). Spectrum of differentiations and metaplastic changes in the epithelial, myoepithelial, and stromal components based on a histopathologic study of 244 cases. *J Am Acad Dermatol*. 2007;57(3):467–83.
144. Kazakov DV, Kacerovska D, Hantschke M, Zelger B, Kutzner H, Requena L, et al. Cutaneous mixed tumor, eccrine variant: a clinicopathologic and immunohistochemical study of 50 cases, with emphasis on unusual histopathologic features. *Am J Dermatopathol*. 2011;33(6):557–68.
145. Gemer O, Piura B, Segal S, Inbar IY. Adenocarcinoma arising in a chondroid syringoma of vulva. *Int J Gynecol Pathol*. 2003;22(4):398–400.
146. Kazakov DV, Michal M, Kacerovska D, McKee PH. Cutaneous adnexal tumors. Philadelphia: William & Wilkins Lippincott; 2012.
147. Mazur MT, Hsueh S, Gersell DJ. Metastases to the female genital tract. Analysis of 325 cases. *Cancer*. 1984;53(9):1978–84.
148. Dehner LP. Metastatic and secondary tumors of the vulva. *Obstet Gynecol*. 1973;42(1):47–57.
149. Neto AG, Deavers MT, Silva EG, Malpica A. Metastatic tumors of the vulva: a clinicopathologic study of 66 cases. *Am J Surg Pathol*. 2003;27:799–804.
150. Thomakos N, Rodolakis A, Akrivos N, Skampardonis N, Sotiropoulou M, Biliatis I, et al. Metastatic medullary carcinoma of the vulva in a patient with MEN IIb syndrome. *In Vivo*. 2010; 24(5):791–4.
151. Blasdale C, McLelland J. Solitary giant vulval syringoma. *Br J Dermatol*. 1999;141(2):374–5.
152. Henner MS, Shapiro PE, Ritter JH, Leffell DJ, Wick MR. Solitary syringoma: report of five cases and clinicopathologic comparison with microcystic adnexal carcinoma of the skin. *Am J Dermatopathol*. 1995;17(5):465–70.
153. Miller SJ. Biology of basal cell carcinoma (part 1). *J Am Acad Dermatol*. 1991;24(1):1–13.
154. De Giorgi V, Salvini C, Massi D, Raspollini M, Carli P. Vulvar basal cell carcinoma: retrospective study and review of literature. *Gynecol Oncol*. 2005;97(1): 192–4.
155. Benedet JL, Miller DM, Ehlen TG, Bertrand MA. Basal cell carcinoma of the vulva: clinical features and treatment results in 28 patients. *Obstet Gynecol*. 1997;90(5):765–8.
156. Betti R, Brusca C, Inselvini E, Crosti C. Basal cell carcinomas of covered and unusual sites of the body. *Int J Dermatol*. 1997;36(7):503–5.
157. Feakins RM, Lowe DG. Basal cell carcinoma of the vulva: clinicopathologic study of 45 cases. *Int J Gynecol Pathol*. 1997;16(4):319–24.
158. Gibson GE, Ahmed I. Perianal and genital basal cell carcinoma: a clinicopathologic review of 51 cases. *J Am Acad Dermatol*. 2001;45(1):68–71.
159. Johnson RL, Rothman AL, Xie J, Goodrich LV, Bare JW, Bonifas JM, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science*. 1996;272(5268):1668–71.
160. Hahn H, Wicking C, Zaphiropoulos PG, Gailani MR, Shanley S, Chidambaram A, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. *Cell*. 1996;85(6):841–51.
161. Preti M, Micheletti L, Massobrio M, Ansai S-I, Wilkinson EJ. Vulvar Paget disease: one century after first reported. *J Low Genit Tract Dis*. 2003; 7(2):122–35.
162. Kuan SF, Montaq AG, Hart J, Krausz T, Recant W. Differential expression of mucin genes in mammary and extramammary Paget's disease. *Am J Surg Pathol*. 2001;25(12):1469–77.
163. Yoshii N, Kitajima S, Yonezawa S, Matsukita S, Setoyama M, Kanzaki T. Expression of mucin core proteins in extramammary Paget's disease. *Pathol Int*. 2002;52(5–6):390–9.