Vulvar Ectopic Tissues, Cysts, and Benign Adnexal Tumors

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Anastasia M. Konstantinova, Michal Michal, and Dmitry V. Kazakov

Abstract

The vulva represents the female external genitalia external to the hymen, extending anteriorly to the mons pubis, posteriorly to the anus, and laterally to the inguinal-gluteal folds. It contains various histological structures including hair follicles, sebaceous, sweat, anogenital mammary-like, vestibular, and periurethral glands, which can give rise to various benign adnexal tumors. This chapter addresses the recent literature and our personal experience on benign cystic lesions, ectopic tissues, lesions of major and minor vestibular glands, benign lesions of anogenital mammary-like glands, and benign adnexal tumors of the vulva. Discussed are the normal anatomy and histology of the vulva as well as the clinical presentation, histopathological and immunohistochemical features and the differential diagnosis of paraurethral and Bartholin's gland cyst, mesonephric-like and mesothelial cyst, prostatic-type tissue of the vulva, endometriosis, hidradenoma papilliferum, fibroadenoma and benign phyllodes tumor, lactating adenoma, adenosis tumor, mammary-type fibrocystic disease and hamartoma, syringoma, cylindroma, spiradenoma, spiradenocylindroma, apocrine and eccrine mixed tumors and others.

Keywords

Vulva · Histology · Benign · Adnexal · Anogeniltal mammary-like glands

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4.1 Anatomy and Histology

The vulva represents the female external genitalia external to the hymen, extending anteriorly to the mons pubis, posteriorly to the anus, and laterally to the inguinal-gluteal folds. The main anatomic structures comprising of the vulva include the mons pubis, labia majora, labia minora, clitoris, vulvar vestibule and vestibulovaginal bulbs, urinary meatus, vaginal opening and hymen. Apart from the epidermis and adnexa, major and minor vestibular glands and anogenital mammary-like glands are histological constituents of the vulva [1, 2].

The mons pubis is a rounded prominence of fatty tissue located over the pubic symphysis of the pubic bones. It is covered by the skin with a stratified squamous keratinized epithelium, hair follicles, eccrine glands, and sensory receptors [2]. Hair follicle depth within the vulva is greatest in the mons pubis, with the depth up to 2.72 mm [3].

The labia majora are two large longitudinal folds of the skin that extend from the mons pubis, merge with the inguinal-gluteal folds laterally and with the perineal body posteriorly. The labia majora lie laterally and parallel to the labia minora, separated from the latter by the intralabial sulcus. Each labium majus has two surfaces, an outer one, pigmented and covered with pubic hair, containing apocrine and eccrine sweat glands, and an inner one, containing an abundance of sebaceous glands. These glands are not associated with hair follicles and open directly onto the epithelial surface. Sebaceous glands within the labia majora may have a depth of up to 2.03 mm [3]. The labia majora are covered with a squamous epithelium (Fig. 4.1) and contain a thin layer of smooth muscle that vaguely resemble the dartos muscle of the scrotum and a large amount of subcutaneous adipose tissue fat [1, 2, 4].

Medial to the labia majora, mainly within the sulcus between the labia majora and minora, *anogenital mammary-like glands* (AGMLG) are present (Fig. 4.1). Long regarded as ectopic or supernumerary breast tissue, anogenital mammary-like glands are now considered a

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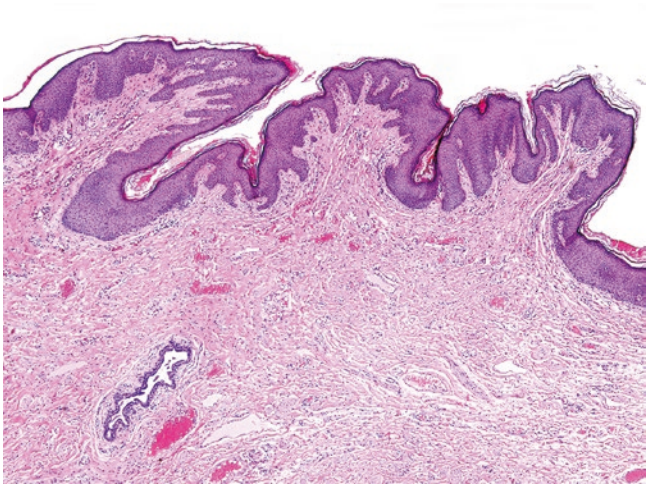

Fig. 4.1 The medial part of labia majora is covered by the squamous pigmented epithelium with a thin keratin layer. Note an anogenital mammary-like gland in the dermis

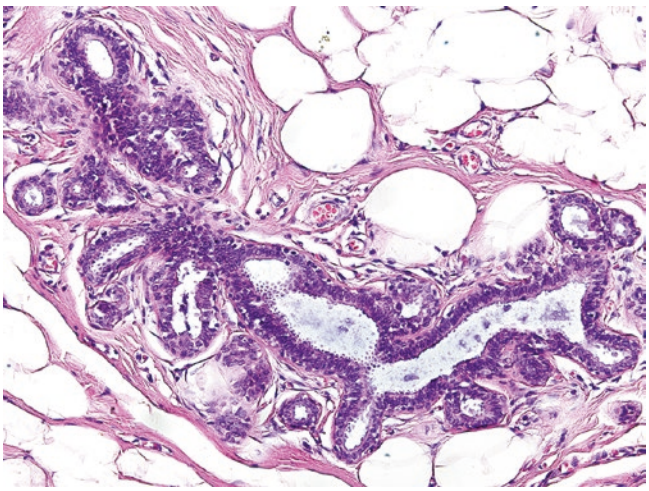

Fig. 4.2 An anogenital mammary-like gland with more complex structures showing outpouchings

normal constituent of the anogenital area [5–9]. Normal AGMLG exhibit a varying cytoarchitectural complexity and lined by a simple cuboidal to columnar epithelium surrounded by an outer myoepithelial layer. These glands vary from simple glandular structures with round lumina surrounded by a loose or dense fibrotic stroma, to more complex units closely imitating breast tissue (Fig. 4.2) [5, 7, 10]. Elastic fibers around anogenital glands can be found. The maximal depth of AGMLG is 3.9 mm, with a range of 0.64–3.9 mm [11]. Immunohistochemically, luminal cells show intermediate to strong expression of low molecular weight CKs ("luminal" keratins), ER (nuclear), PR (nuclear), AR (nuclear), and intermediate to strong expression of EMA (membranous, cytoplasmic), GCDFP-15 (cytoplasmic), mammaglobin (cytoplasmic), MUC1 (membranous, cytoplasmic), and GATA3 (nuclear). Furthermore, some cells in the luminal layer were positive for the high molecular weight CKs (cytoplasmic), CK5 (cytoplasmic), CK5/6 (cytoplasmic), CK14 (cytoplasmic), and CK17 (cytoplasmic), and p16 (nuclear, cytoplasmic). The outer cells of AGMLG are positive for myoepithelial markers and mostly for high molecular weight CKs ("basal" keratins"). The positivity for E-cadherin (membranous), CD138 (membranous), and MSH2 (nuclear) is seen in both layers of cells [12].

The excretory system of AGMLG opens to the epidermal surface and lined with columnar epithelium surrounded by myoepithelial cell layer which merges into a squamous epithelium. In some cases, elastic fibers surrounding excretory ducts of AGMLG can be found. Vulvar small clear cells (Toker cells), similar to Toker cells of the nipple, are arranged as single cells, in small clusters, or rarely form gland-like structures, can be detected in the lower epidermis around the openings of AGMLG ducts (Fig. 4.3a). Toker cells can be highlighted by using immunohistochemical staining with CK7 (membranous, cytoplasmic) (Fig. 4.3b) [10, 11, 13].

The labia minora are paired flaps of skin medial to the labia majora that bordered the vulvar vestibule. Anteriorly, each labium minus divides into two portions surrounding the clitoris: the upper part of each lip passes above the clitoris forming a prepuce and the lower part passes beneath the glans clitoridis and becomes the frenulum. Hart's line seen on the inner aspect of the labia minora represents the sides of the vestibule and marks the change from the vulvar skin covered by the epithelium of the stratified squamous type with thin keratin layer to the smoother transitional skin of the vulva covered by a not keratinized, generally highly glycogenated epithelium. Most of the epithelium of the labia minora is pigmented and the dermis does not contain skin appendages [1, 2].

4.1.1 Clitoris

The clitoris is a complex erectile structure located at the front of the vulva, containing attached root and free body and covered by protective fold of skin—preputium clitoridis. The visible portion of the clitoris is the clitoral glans. The clitoral crura are composed of erectile tissue similar to that seen in the penile corpora cavernosa (Fig. 4.4). They consist of cavernous veins surrounded by longitudinal smooth muscle as well as small centrally placed muscular arteries enveloped by the tunica albuginea. The glans clitoridis is highly sensitive, containing many nerve endings with abundant numbed of Pacinian corpuscles and covered by a squamous mucosa without glands (Fig. 4.4) [1, 2, 4].

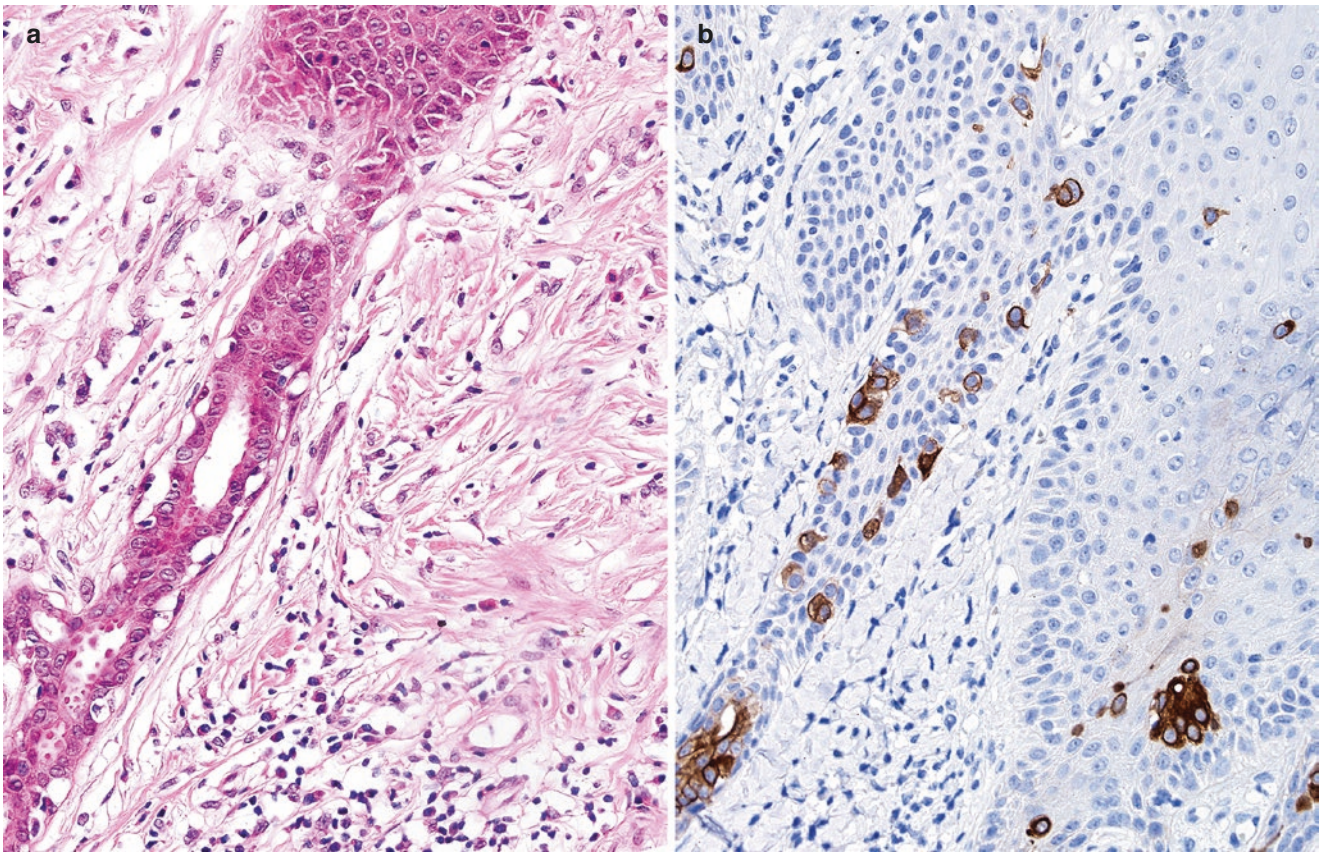

Fig. 4.3 Vulvar Toker cells in the lower epidermis around the openings of AGMLG duct (**a**). Positive immunohistochemical staining with CK7 (**b**)

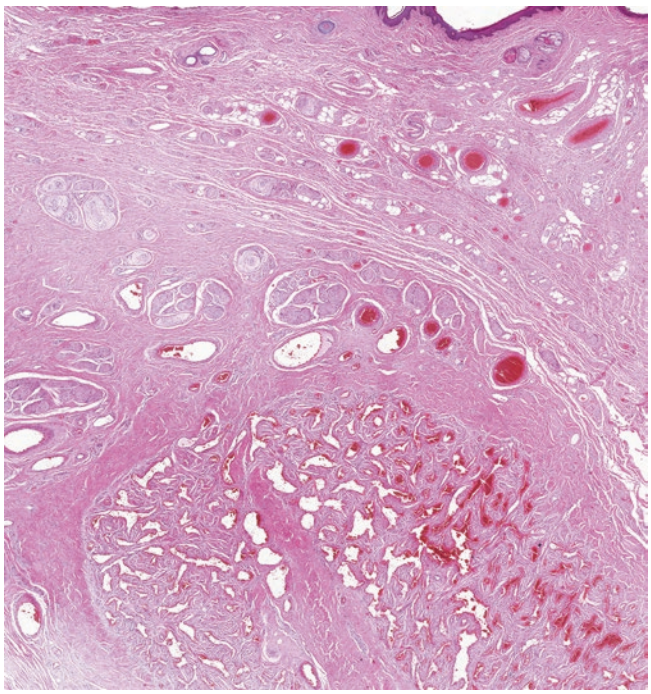

Fig. 4.4 The clitoris is covered by the squamous epithelium and contains erectile tissue, Pacinian corpuscles, and nerve bundles

4.1.2 Vulvar Vestibule

The vulvar vestibule is part of the vulva between the Hart's line inside the labia minora and the hymen. Both the vaginal opening and urethral orifice are within the vestibule. Additionally, within the vulvar vestibule are gland openings from both the major and minor vestibular glands, as well as the paired opening of the periurethral Skene's ducts. The external urethral orifice is placed behind the clitoris and in front of the vagina. Urethral meatus is lined by a transitional epithelium that merges with the stratified squamous epithelium of the vestibule. The vaginal orifice, the most proximal boundary of the vulvar vestibule, is a median slit below and behind the opening of the urethra. The vaginal introitus is lined by a nonkeratinized and glycogen-rich stratified squamous epithelium [1, 2].

4.1.2.1 Vestibular Glands

The major vestibular glands (Bartholin's glands) are paired glands which correspond to the male bulbourethral glands (Cowper's glands). They are located in the posterolateral area of the vulva and open into the vestibule. Bartholin's gland is composed of acini lined by mucus-secreting columnar cells surrounded by a peripheral layer of myoepithelial cells

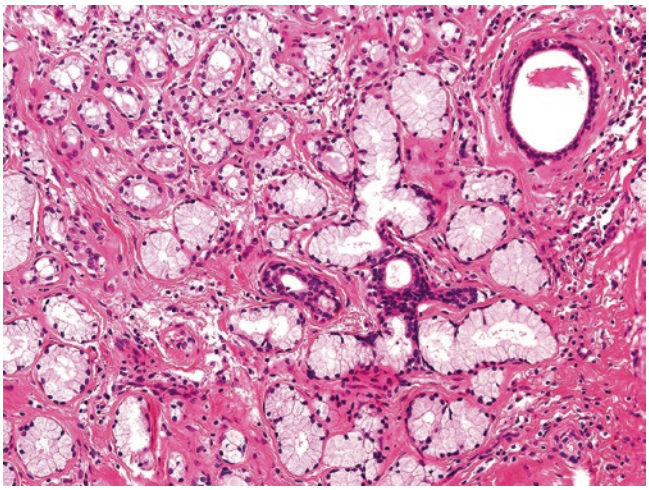

Fig. 4.5 Normal major (Bartholin's) vestibular glands acini lined by columnar mucin-producing cells with an adjacent duct

(Fig. 4.5). The secretion of these acini empties into Bartholin's duct, which is lined by a transitional-like epithelium. At the vestibular surface the distal part of the duct is lining by a non-keratinized squamous epithelium [1, 14, 15].

Minor vestibular glands, the analogue to the glands of Littre of the male urethra, are small simple glands that enter directly to the mucosal surface of the posterior vestibule. Majority of women have from 2 to 10 glands with a maximum depth of 2.27 mm. These glands have a mucus-secreting epithelium which changes to a stratified squamous epithelium near their exit at the vestibular surface [1, 15, 16].

4.1.2.2 Periurethral Glands

The major periurethral (Skene) glands are a paired organ located on either side of the urethral meatus and represent the female homologue of the male prostate. The glands are lined by mucinous pseudostratified columnar epithelial cells, whereas ducts are lined by a transitional epithelium that merges with the vestibular squamous epithelium [17].

Immediately adjacent to most of urethra are the periurethral glands of Huffman (minor periurethral glands) composed of a columnar mucinous epithelium [1, 2, 17].

Blood supply to the vulva is via the femoral artery and the internal iliac artery. Nerve supply to the vulva is via the pudendal nerve, iliohypogastric, ilioinguinal, and genitofemoral nerves. Parasympathetic innervation of erectile tissue occurs via pelvic splanchnic nerves [1, 2].

4.2 Benign Cystic Lesions

4.2.1 Paraurethral (Skene's) Gland Cyst

Skene's gland cyst results from dilatation of the duct of the paraurethral gland. The infection or inflammation is thought to be the cause of the ductal occlusion. The lesion is usually asymptomatic, measuring 1–2 cm, and involves the upper lateral introitus. Skene's duct cysts are a rare cause of an interlabial mass, especially in newborns [18, 19].

4.2.1.1 Histopathology

The Skene's gland cysts are lined by either a stratified squamous or transitional epithelium with rare mucinous cells [2, 15, 20].

4.2.2 Mesonephric-like (Gartner) Cyst

Mesonephric-like cysts are derived from the Wolffian ducts and involve the lateral aspect of the vulva. Clinically, the cyst presents as a thin-walled, translucent cyst containing clear fluid [21].

4.2.2.1 Histopathology

The cyst is lined by a cuboidal to columnar non-ciliated epithelium [2, 15, 20].

4.2.3 Cyst of the Canal of Nuck (Mesothelial Cyst)

The Canal of Nuck is a cystic remnant of the processus vaginalis, the rudimentary sac of peritoneal mesothelium that accompanies the round ligament as it traverses the inguinal canal, ending in the labium majus. Failure of closure of this structure results in blockage and cystic dilatation (female hydrocele) [22]. Clinically, patients present with an asymptomatic, nontender swelling in the groin, rarely in the labium majus or mons pubis. The condition is seen mainly in girls and young female patients.

4.2.3.1 Histopathology

The wall of the cyst is lined by low cuboidal cells of the mesothelial origin, which can be confirmed immunohistochemically with calretinin (nuclear and cytoplasmic staining) and D2–40 (membranous and cytoplasmic staining). The wall is surrounded by a loose fibrous tissue. Trauma may result in rupture; stromal fibrosis and hemosiderin deposition can be observed [2, 15, 20].

4.2.4 Epidermal Inclusion Cyst

Epidermoid (infundibular) cysts are usually solitary, asymptomatic, slow-growing lesions that are commonly present on the scalp, neck, and face; rarely they are located in the clitoris and labium majus. It is thought that the formation of the cysts results from the embedding and invagination of a squa-

mous epithelium in the line of the scar. Then the epithelium desquamates and produces a cystic mass. These cysts could develop many years after the initial injury, e.g., surgical excision, circumcision, and genital piercing.

4.2.4.1 Histopathology

The wall of the cyst is formed by a keratinizing epithelium with the presence of a granular layer and the lumen contains abundant laminated keratin [20, 23, 24]. In some cases, the lumina are filled with calcium deposits and show hair shafts, suggesting that some of the lesions represent true infundibular cysts rather than epidermal invaginations [15].

4.3 Ectopic Tissues

4.3.1 Prostatic-Type Tissue of the Vulva

Skene's glands are thought to represent the female homologue of the male prostate. Occurrence of prostatic-type tissue in the lower female genital tract is rare and probably derived from the Skene's glands misplaced during embryologic development. Only isolated cases of prostatic-type tissue of the vulva have been reported in the literature [25, 26]. The ages of these three patients ranged from 43 to 58 years. In one case, the lesion presented with intermittent pea-sized swellings on the labia majora, whereas in other two cases the prostatic tissue was an incidental microscopic finding [25, 26].

4.3.1.1 Histopathology

Microscopically, small lobular clusters of benign glands and nests of epithelial cells were seen in the superficial dermis (Fig. 4.6). In two cases, these small glands were lined by a double-layered epithelium and there were bright, eosinophilic cytoplasmic granules in some of the luminal cells, resembling Paneth cell-like change reported in the male prostate. In the remaining case, the epithelial elements were predominantly squamous with tubules located around the periphery. In all three cases, the glands were positive for PSA (cytoplasmic) and in two cases they were positive for prostatic acid phosphatase (PrAP) (cytoplasmic) [25, 26].

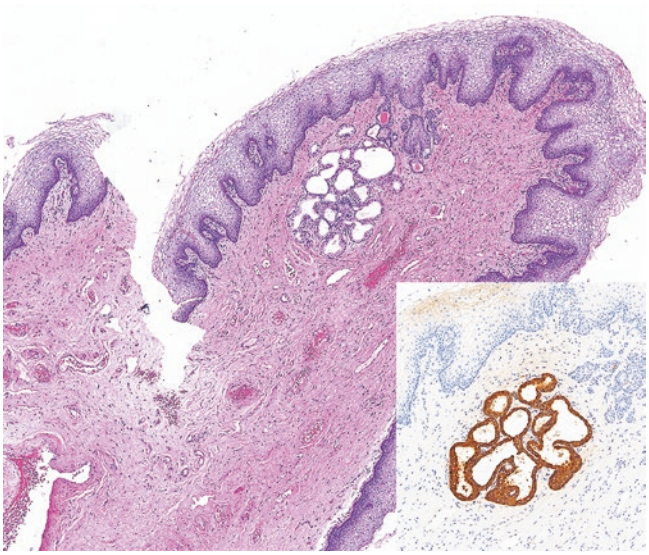

Fig. 4.6 Prostatic-type tissue in the vulva presented as small lobular cluster of benign glands within the superficial dermis. Insets: the glands manifest positivity for prostatic acid phosphatase (Courtesy of Colin J.R. Stewart, FRCPA, Perth, Western Australia, Australia)

Fig. 4.7 Vulvar endometriosis in the cutaneous scar (Courtesy of Dr. Jiří Bouda, Pilsen, Czech Republic)

4.3.2 Endometriosis

Endometriosis of the vulva is rare condition wherein endometrial-type glands and stroma occur within the vulva. It can be seen at sites of trauma, cutaneous scars after episiotomy, Bartholin's gland cyst removal, etc., supporting the implantation theory of origin (Fig. 4.7). Endometriosis of the vulva may present as a mass lesion, or may bleed or swell with the menstrual cycle [27–29].

4.3.2.1 Histopathology

Histologically, both the endometrial glandular epithelium and the endometrial stroma with hemosiderin-laden macrophages are present (Fig. 4.8). In women under progesterone treatment and pregnancy the decidualization can be observed. A wide spectrum of microscopic changes, including hyperplasia and many types of metaplastic alterations of the Müllerian epithelium can be found [2, 15].

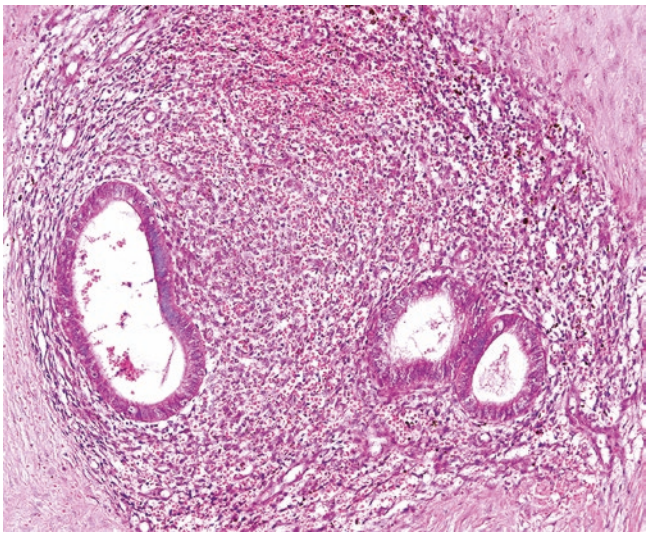

Fig. 4.8 Vulvar endometriosis. Both the endometrial glands and stroma are evident

Fig. 4.9 Bartholin's gland cyst. Translucent nodular-cystic lesion in the vulva (Courtesy of Dr. Jiří Bouda, Pilsen, Czech Republic)

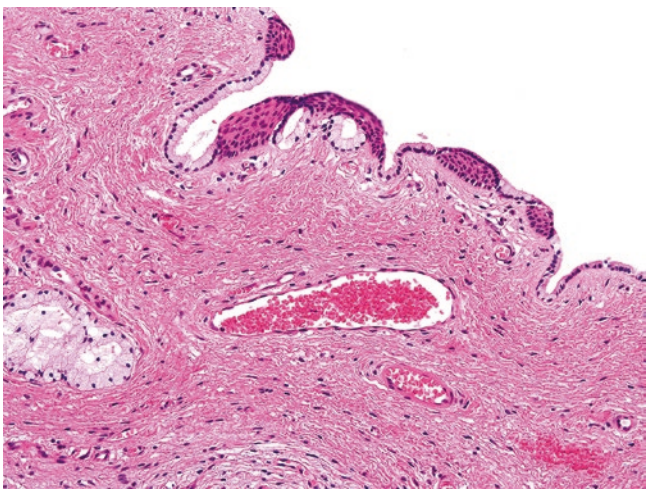

Fig. 4.10 Bartholin's gland cyst is lined by a squamous and mucinous epithelium

4.4 Lesions of Major and Minor Vestibular Glands

4.4.1 Bartholin's Gland Cyst

Bartholin's gland (duct) cyst results from dilatation of Bartholin's duct due to obstruction of its vestibular orifice. It occurs in 3% of adult women and usually asymptomatic. Patients present with cystic or nodular lesion of variable size located in the posterolateral introitus (Fig. 4.9) [15, 30, 31].

4.4.1.1 Histopathology

Bartholin's gland cysts are lined by a transitional, squamous, ciliated, or mucinous epithelium or by any combination of these epithelial types (Fig. 4.10). Rarely, areas resembling the fallopian tube epithelium or apocrine-type secretion can be noticed. A portion of Bartholin's glands tissue is almost always present near the cyst or attached to the cystic wall. Inflammation is common and can result in the destruction of the cyst.

4.4.1.2 Differential Diagnosis

Mucous cysts are smaller than Bartholin's gland cyst. Also, Bartholin's gland cysts are distinguished from cysts of mesonephric origin by staining for mucin, which is negative in mesonephric lesions. Epidermoid cyst most frequently located in the labia majora and clitoris is lined by a stratified squamous epithelium. Cyst of the canal of Nuck can be differentiated from Bartholin's gland cyst by its position in the superolateral position of the labia majora and lining by flattened mesothelial cells [2, 15].

4.4.2 Mucous Cyst

Mucous cysts probably result from occlusion of a minor vestibular gland. It is mostly observed in adult women. The majority of these cysts are small and present no symptoms, while some may grow larger causing discomfort.

4.4.2.1 Histopathology

Mucous cysts appear as smaller cysts lined by columnar mucinous cells resting on the basement membrane and filled with mucin. Squamous cells may also be seen [2, 15].

4.4.3 Nodular Vestibular Gland Hyperplasia

Nodular hyperplasia is a rare benign lesion of major vestibular gland. It is probably the most common solid lesion of Bartholin's glands [32]. Nodular hyperplasia presents as an asymptomatic or slightly painful small nodular lesion.

4.4.3.1 Histopathology

Nodular hyperplasia displays a lobular architecture with an increased number of secretory acini with preservation of the normal duct structures (Fig. 4.11). Areas with a diffuse growth of acini can be seen. The acinar cells are cuboidal or columnar, with mucin-filled cytoplasm and bland nuclei. Duct dilatations, squamous metaplasia of the ductal epithelium, mild lymphohistiocytic infiltrate, and duct rupture with extravasated stromal mucin have been reported in nodular hyperplasia [15, 31–33].

4.5 Benign Lesions of Anogenital Mammary-Like Glands

Benign and malignant lesions affecting anogenital mammary-like glands, including authentic neoplasms and various epithelial or stromal changes, are histopathologically very similar or identical to their mammary counterparts [5, 7, 11, 34–42]. Some lesions involving AGMLG demonstrate a stromal change identical to that known in mammary pathology as pseudoangiomatous stromal hyperplasia (PASH) [35]. It appeared as slit-like, open anastomosing channels devoid of erythrocytes and lined by discontinuous, inconspicuous cells without atypia or mitotic activity (Fig. 4.12) [35]. Areas of PASH have been described in anogenital fibroadenomas, phyllodes tumors, in complex neoplastic lesions and in one case of mild hyperplasia of anogenital mammary-like glands, stromal sclerosis and substantial lipomatous metaplasia [35, 41, 43–45]. Multinucleated cells associated with PASH were detected in one patient who suffered from neurofibromatosis [43]. PASH is distinguished from low-grade angiosarcoma by the lack of cytologic atypia, mitotic activity, intraluminal erythrocytes, and negativity for CD31 [35, 41].

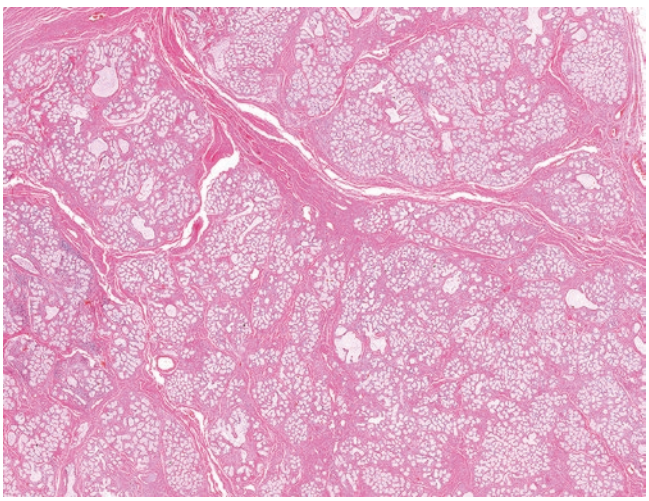

Fig. 4.11 Nodular hyperplasia of Bartholin's glands displays an increased number of acini with preservation of normal duct-acinar relationship

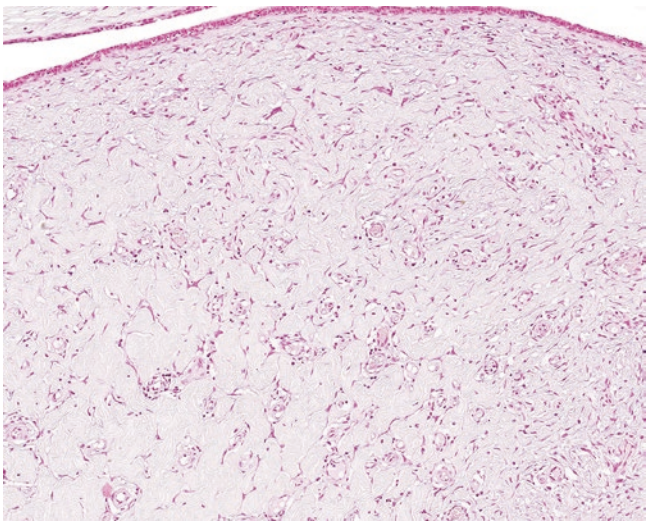

Fig. 4.12 Pseudoangiomatous stromal hyperplasia in the fibroepithelial lesion of anogenital mammary-like glands characterized by slit-like, open anastomosing channels devoid of erythrocytes and lined by discontinuous, inconspicuous cells without atypia or mitotic activity

4.5.1 Hidradenoma Papilliferum

Hidradenoma papilliferum (HP), also known as papillary hidradenoma, is the most common benign glandular neoplasm of the vulva which can be compared conceptually as the cutaneous counterpart of mammary intraductal papilloma [40, 46–49]. The lesion often presents as a small (from 0.5 to 2 cm) solitary asymptomatic nodule or cyst-like lesion on the labia minora and labia majora. The age of the patients ranges from 29 to 90 years. This is a benign tumor, but it may recur if incompletely excised [31].

4.5.1.1 Histopathology

HP is characterized by a cytoarchitectural variability, sometimes within the same tumor: some tumors are solid and composed of papillary and tubular areas, whereas others are predominantly cystic [10, 40, 46, 47, 49, 50]. Some HP have a connection to the epidermis or follicular infundibulum [51–53]. The neoplasm exhibits a complex pattern of branching and anastomosing tubules interconnected in a labyrinthine manner, with bands of fibrous tissue between them, focally forming papillae (Fig. 4.13a). A luminal layer of the tubules and papillae is formed by epithelial cells surrounded by a layer of myoepithelial cells. Decapitation secretion is a common feature. Epithelial metaplastic changes (oxyphilic (Fig. 4.13a, b), mucinous and squamous metaplasia, clear cell change), morphological features analogous to those occurring in benign breast disease (sclerosing adenosis-like

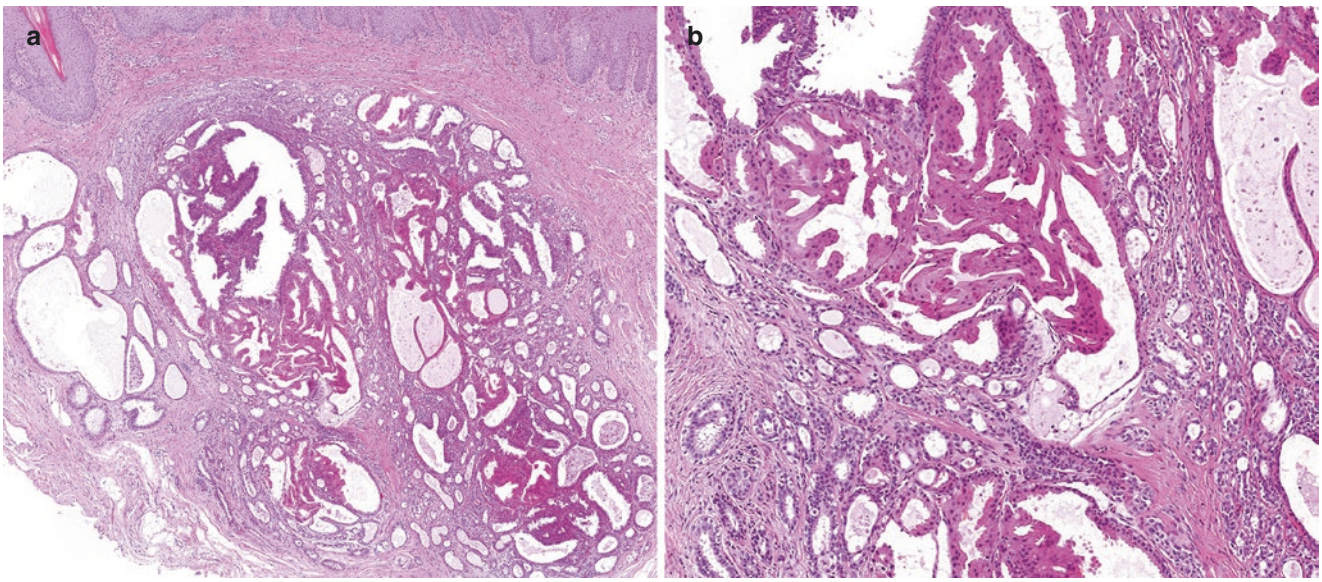

Fig. 4.13 Hidradenoma papilliferum. Intradermal solid-cystic neoplasm with a complex pattern of branching and anastomosing tubules and papillae (**a**). Prominent oxyphilic metaplasia (**b**)

changes, atypical and usual ductal hyperplasia and solid and "streaming" growth patterns can be seen [15, 40]. The mitotic index in HP can be up to 13/10 HPF, but it does not predict a more aggressive outcome [48]. Several cases of ductal carcinoma in situ arising in HP have been reported [42, 54]. In some cases, remnants of AGMLGs may be seen adjacent to the HP [40]. Two cases with mixed histopathological features of fibroadenoma and hidradenoma papilliferum and PASH have been reported [41, 44]. In addition, HP can rarely be seen in association with various benign and malignant lesions, including Bartholin's gland abscess, squamous cell carcinoma, and extramammary Paget disease [40, 55–57].

4.5.1.2 Differential Diagnosis

Prominent oxyphilic metaplasia, accompanied by nuclear enlargement, especially in areas with solid growth, may bear a resemblance to adenocarcinoma. In fact, such changes are analogous to atypical apocrine adenosis of the breast [47]. In cases with a connection to the overlying epidermis with reactive epidermal hyperplasia and prominent plasma cell infiltrate, HP may simulate syringocystadenoma papilliferum. Prominent, yet focal hyperplasia of stromal myofibroblast-like cells (HP) should not be confused with sarcomatoid carcinoma [15].

4.5.2 Fibroadenoma and Benign Phyllodes Tumor

Fibroadenoma and benign phyllodes tumor arising in AGMLGs are biphasic, circumscribed, epithelial-stromal neoplasms identical to homonymous mammary neoplasms. These lesions are rare, with approximately 40 cases of vulvar fibroadenoma and 11 cases of vulvar benign phyllodes tumor and reported to date [58] and affect predominately women of reproductive age, but they may be found in postmenopausal women and rarely in prepubertal girls [59]. These fibroepithelial neoplasms present as solitary, firm, asymptomatic nodules with an average size of 3 cm [43]. Multiple cases of fibroadenoma [60–62] and phyllodes tumors [63–65] have been reported. Enlargement may occur during pregnancy [66, 67]. Local recurrence after surgical excision can occur in phyllodes tumors [63, 68].

4.5.2.1 Histopathology

Fibroadenomas are well-circumscribed neoplasms composed of branching and anastomosing glandular structures surrounded by a paucicellular stroma showing low or no mitotic activity (Fig. 4.14). The pericanalicular growth pattern is typified by retention of round or oval duct lumina, whereas the intracanalicular growth pattern is characterized by stromal compression of the lumina sometimes producing slit-like structures. Cystic dilatation of duct lumina, apocrine secretion, and intraluminal papillary projections may be seen [10, 15, 43]. A case of mammary-type juvenile fibroadenoma has been reported [43].

Phyllodes tumor shows a growth pattern with leaf-like projections (Fig. 4.15a). The stroma is usually hypercellular, with periglandular condensation; cellularity commonly varies within a neoplasm (Fig. 4.15a, b). Three categories of the phyllodes tumor are recognized: benign, low grade, and high grade. The grade is defined by the atypia in the stroma. Except for a single case of high-grade neoplasm showing a rhabdomyosarcomatous stroma [69], the reported examples of vulvar phyllodes tumor were either benign or low grade [10, 43].

Columnar cell change, usual and florid ductal hyperplasia, pseudoangiomatous stromal hyperplasia, metaplastic changes in epithelial and stromal changes and lactation-like changes are rare features occurring in fibroadenoma and benign phyllodes tumor involving AGMLGs [15].

These neoplasms show overlapping features and in some cases the differentiation between fibroadenoma and benign or low-grade malignant phyllodes tumor may be very difficult. The stroma in phyllodes tumor is more cellular than fibroadenomas and variable in different foci of the lesion. Additionally, phyllodes tumor has less regular outlines than fibroadenoma which is usually a sharply demarcated lesion [15].

Fibroepithelial foci resembling fibroadenoma may rarely be found in other "complex" lesions of AGMLGs [41, 44].

4.5.2.2 Differential Diagnosis

Focal lactation-like change in a lesion of AGMLGs can be confused with malignancy. The clue to the diagnosis is the presence of intracytoplasmic vacuoles and intraluminal secretion. In lactating adenoma, the whole lesion manifests this feature.

Areas of PASH should be distinguished with low-grade angiosarcoma, which shows at least mild nuclear pleomorphism and immunopositivity for vascular markers [2, 15].

4.5.3 Lactating Adenoma

Lactating adenoma arising from AGMLGs is extremely rare and associated with pregnancy. The lesion can be solitary or multiple presenting as masses [70–73].

4.5.3.1 Histopathology

The lesion is well circumscribed and composed of densely packed round tubules lined by large cells with hyperchromatic nuclei and containing intracytoplasmic vacuoles and intraluminal secretion. Additionally, cystic changes, duct ectasia, and apocrine metaplasia have been described [71].

4.5.3.2 Differential Diagnosis

Lactating adenoma can be misdiagnosed as adenocarcinoma [15]. Rarely, lactation-like changes may occur in other lesions of AGMLGs, such as fibroadenoma [10, 66].

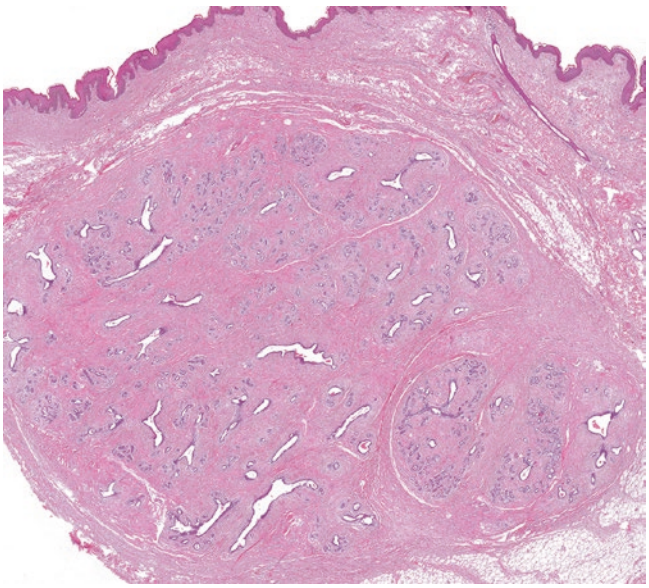

Fig. 4.14 Whole mount histological section evidencing a fibroadenoma arising in anogenital mammary-like glands

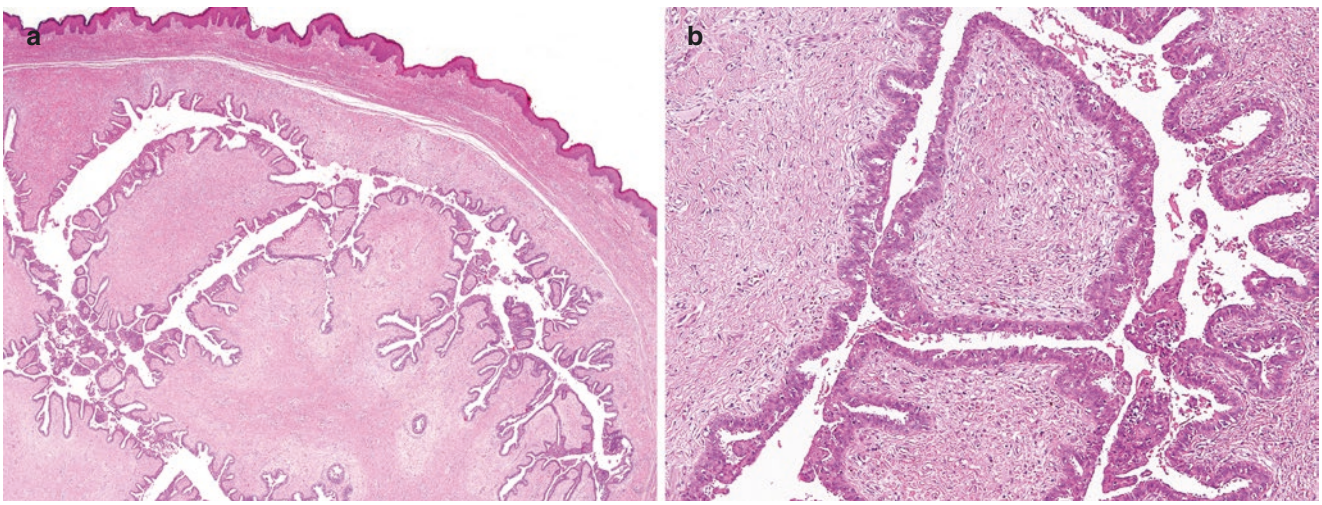

Fig. 4.15 Benign phyllodes tumors of the vulva with a leaf-like intracanalicular growth pattern and stromal hypercellularity (**a**, **b**)

4.5.4 Adenosis Tumor

Sclerosing adenosis may occur as a component of different lesions of AGMLG, including hidradenoma papilliferum, phyllodes tumor, and fibroadenoma [10, 40]. In addition, sclerosing adenosis can itself produce a clinically detectable lesion, the adenosis tumor. It is a very rare condition, with two reported lesions located in the perianal area and one in the vulva, ranging in size from 7 to 20 mm. The ages of these three patients were from 46 to 60 years [36, 74].

4.5.4.1 Histopathology

Sclerosing adenosis is a compact proliferation of small ductal structures with luminal epithelial cells which are often atrophic and attenuated with the preservation of the peripheral myoepithelial cell layer in a sclerotic stroma. Lesions are well demarcated, unencapsulated with irregular distribution of the glands (Fig. 4.16a). The luminal cells showed no cytological and nuclear atypia and visible is only minimal regular mitotic activity. Decapitation secretion is seen (Fig. 4.16b). Different patterns, including variably sized microcysts and cysts, some with papillary projections having hyalinized cores, areas reminiscent of usual ductal hyperplasia, various metaplastic changes in the epithelial and myoepithelial components can be noted. Isolated, typical AGMLG can be found in the periphery of the lesion.

4.5.4.2 Differential Diagnosis

Vulvar sclerosing adenosis can be confused with an invasive adenocarcinoma, but in the adenosis the myoepithelial cells at the periphery of the glands is a constant feature and can be highlighted by myoepithelial markers (actin S (membranous, cytoplasmic), calponin (cytoplasmic), CD10 (cytoplasmic, membranous), and others) [36, 74].

4.5.5 Mammary-Type Fibrocystic Disease

Mammary-type fibrocystic disease is rare condition clinically presenting as a cutaneous nodule simulating a tumor.

4.5.5.1 Histopathology

The changes are identical to those seen in the homonymous lesions in the breast and include cysts, oxyphilic (apocrine) metaplasia, fibrosis, calcification, chronic inflammation, and epithelial hyperplasia which are the basic morphological changes seen in fibrocystic disease (Fig. 4.17) [39].

4.5.6 Mammary-Type Hamartoma

A single case of mammary-type hamartoma in the anogenital area had been reported. It was a well-circumscribed 4.5-cm nodule in a patient with bilateral gigantomastia and nodular pseudoangiomatous stromal hyperplasia in the axilla [38]. The cutaneous lesion was located in the perianal area, but it presumably can be found in the vulva where AGMLG are more numerous.

4.5.6.1 Histopathology

Microscopically, the lesion demonstrated circumscribed margins, dense stromal fibrosis, islands of adipose tissue, cystic dilatation of ducts, scattered benign breast-type lobules, and a sparse focal infiltrate of lymphocytes (Fig. 4.18). In addition, adjacent intact AGMLGs were found [38].

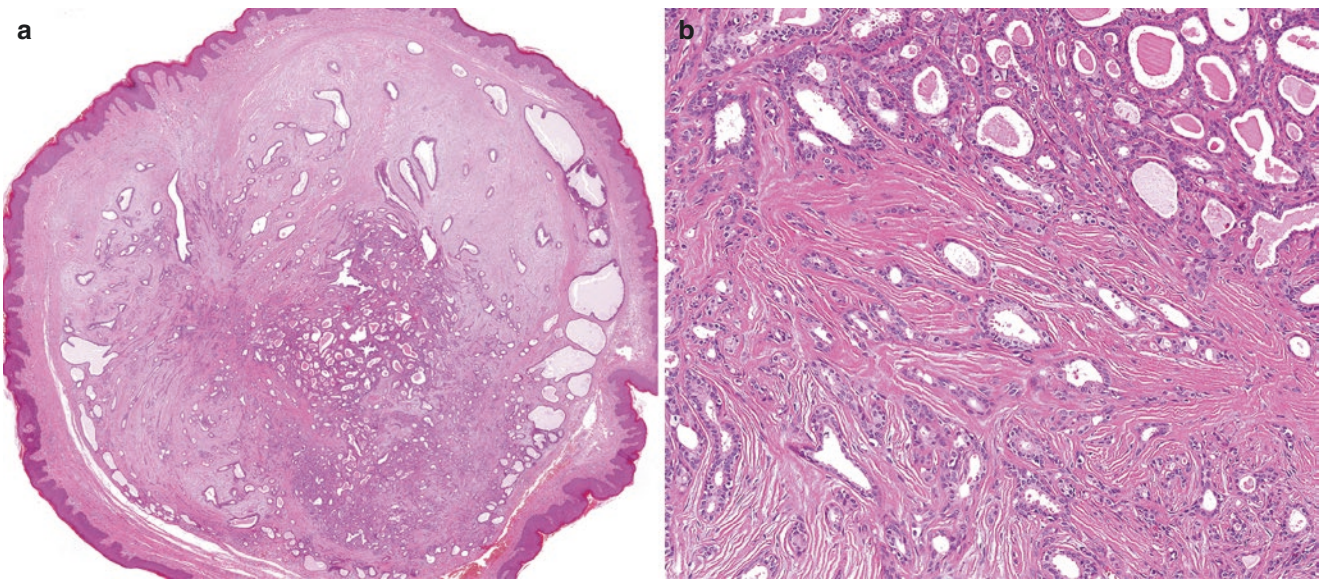

Fig. 4.16 Adenosis tumor. A well-demarcated, unencapsulated lesion (**a**). Areas of sclerosing adenosis composed of compressed tubular structures with a preserved myoepithelial layer in a sclerotic stroma (**b**)

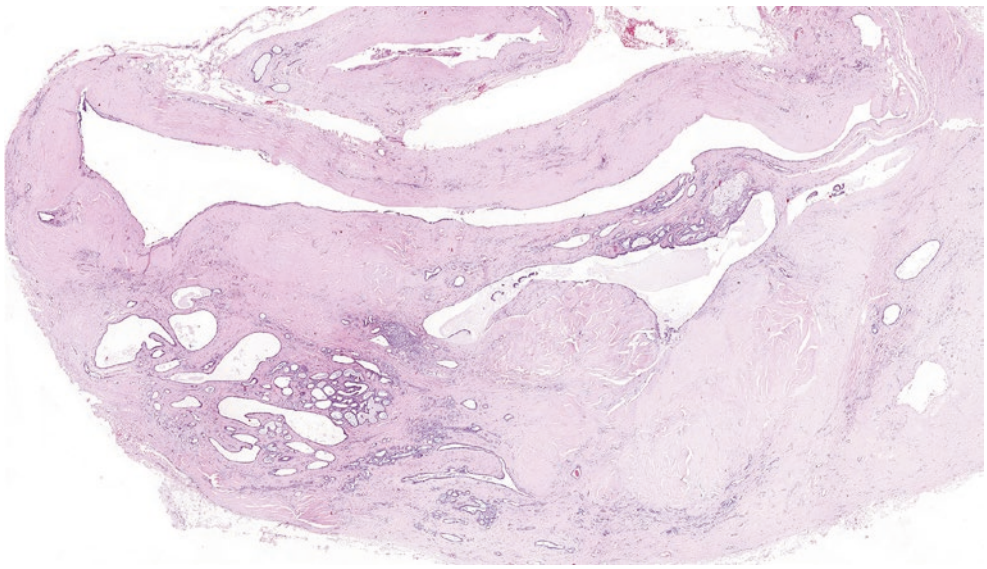

Fig. 4.17 Mammary-type fibrocystic disease. The lesion is well circumscribed but not encapsulated and displays marked stromal sclerosis and variably sized cysts

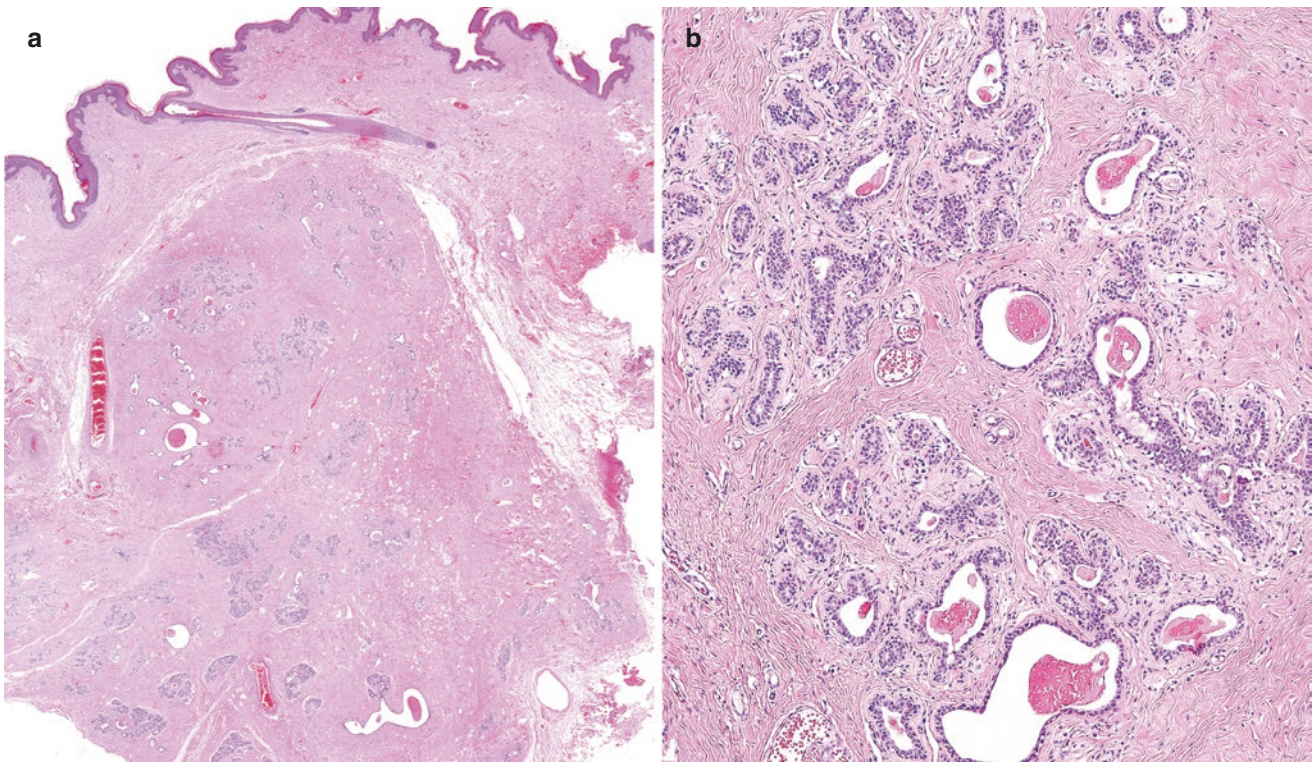

Fig. 4.18 Mammary-type hamartoma. The lesion is a sharply demarcated mass composed predominantly of dense sclerotic collagen, containing numerous well-developed mammary-type lobules, some of which ducts exhibit cystic dilatation (**a**, **b**)

4.6 Benign Adnexal Tumors

4.6.1 Syringoma

Syringoma is a small benign adnexal neoplasm usually presenting in the vulva as multiple, asymptomatic, small, smooth-surfaced, skin-colored, pink or brownish papules (Fig. 4.19). Adolescents and young adults are mostly affected. Familial cases of syringoma and coexistence with Down's syndrome have been reported [31]. The most common sites of involvement are the lower eyelids. Vulva is also a common site wherein syringomas present with symptom of pruritis and occur on an erythematous background. Vulvar

Fig. 4.19 Vulvar syringomas. Multiple small papules in the vulva (Courtesy of Dr. Jiří Bouda, Pilsen, Czech Republic)

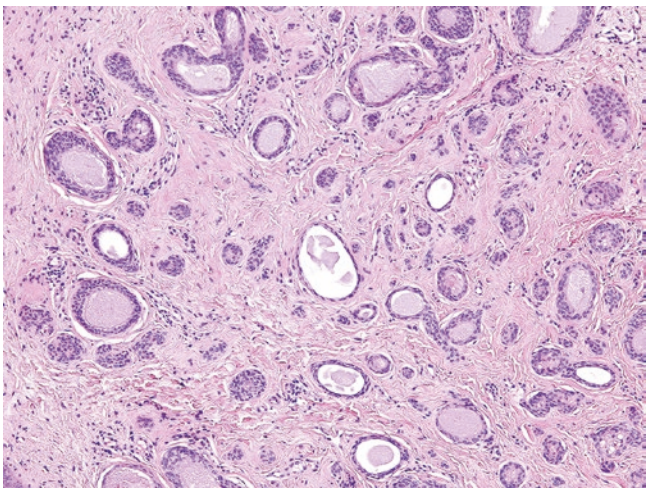

Fig. 4.20 Vulvar syringoma. The lesion consists of small solid and ductal structures in sclerotic collagenous stroma. "Comma-like" or "tadpole-like" elements can be seen

syringomas have commonly been described in association with extragenital lesions [75, 76].

4.6.1.1 Histopathology

Histopathologically, syringoma is usually a small, well-circumscribed neoplasm confined to the upper part of the dermis consisting of small solid and ductal structures that have peculiar geometric shapes (comma-like or tadpole-like) and are relatively evenly distributed in sclerotic collagenous stroma (Fig. 4.20). The cords, nests, and tubules of syringomas branch and anastomose. The epithelial aggregates are composed of monomorphous cuboidal cells with small nuclei and inconspicuous nucleoli. In most conventional syringomas most epithelial cells are eosinophilic and some cells have pale cytoplasm. The deep location of vulvar syringoma is unusual [77]. Clear cell change, prominent keratinization (squamous metaplasia), extension into the deeper dermis or subcutis, and presence of numerous mast cells in the stroma can be seen in syringoma. A clear cell variant has been associated with diabetes mellitus in many instances [31].

4.6.1.2 Differential Diagnosis

Syringomatous ductal proliferations and syringoma-like structures can be associated with several inflammatory and neoplastic conditions including extramammary Paget's disease (EMPD), basal cell carcinoma, reexcision specimens, prurigo nodularis, and others. A particular pitfall in the vulva are syringomatoid structures occurring in EMPD [78]. Microcystic adnexal carcinoma (MAC) and syringoma can have a morphological overlap but have different clinical presentation. MAC is extremely rare in the vulva. Moreover, microcystic adnexal carcinomas is usually a deeply infiltrative neoplasm with perineural extension which is larger, asymmetric, and less circumscribed than syringoma, although exceptionally rare vulva syringoma may show deep extension [2, 15, 20, 31, 77].

4.6.2 Spiradenoma, Cylindroma, and Spiradenocylindroma

Spiradenoma, cylindroma, and spiradenocylindroma are closely related entities comprising of a morphological spectrum. All three neoplasms occur either sporadically or may be part of Brooke-Spiegler syndrome with the head and neck area is the predilection side, but rare lesion has been reported in the vulva [79]. Clinically, sporadic tumors are solitary asymptomatic nodules affecting adult or elderly patients. In patients with Brooke-Spiegler syndrome lesions are multiple in various combinations with other adnexal neoplasms, mostly trichoepitheliomas [80–84].

4.6.2.1 Histopathology

Tumors are well circumscribed, sometimes encapsulated, and may be multi- or uninodular. Histologically, spiradenoma presents as a nodule composed of pale large cells and lymphocytes intermixed with small basaloid cells. Within the nodules the epithelial cells are arranged in a trabecular, reticular, or solid fashion (Fig. 4.21a). Focal ductal differentiation can be evident.

Cylindroma represents multinodular lesions composed of a basaloid cells surrounded by eosinophilic basement membrane material arranged in a jigsaw puzzle (mosaic-like). The peripheral cells are often darker than those cells located in the center and show palisading (Fig. 4.21b).

Spiradenocylindroma demonstrate areas typical of both spiradenoma and cylindroma, with at least 10% of its volume conforming to either of the two patterns. The elements of these two tumors are either closely intermingled or sharply demarcated [15].

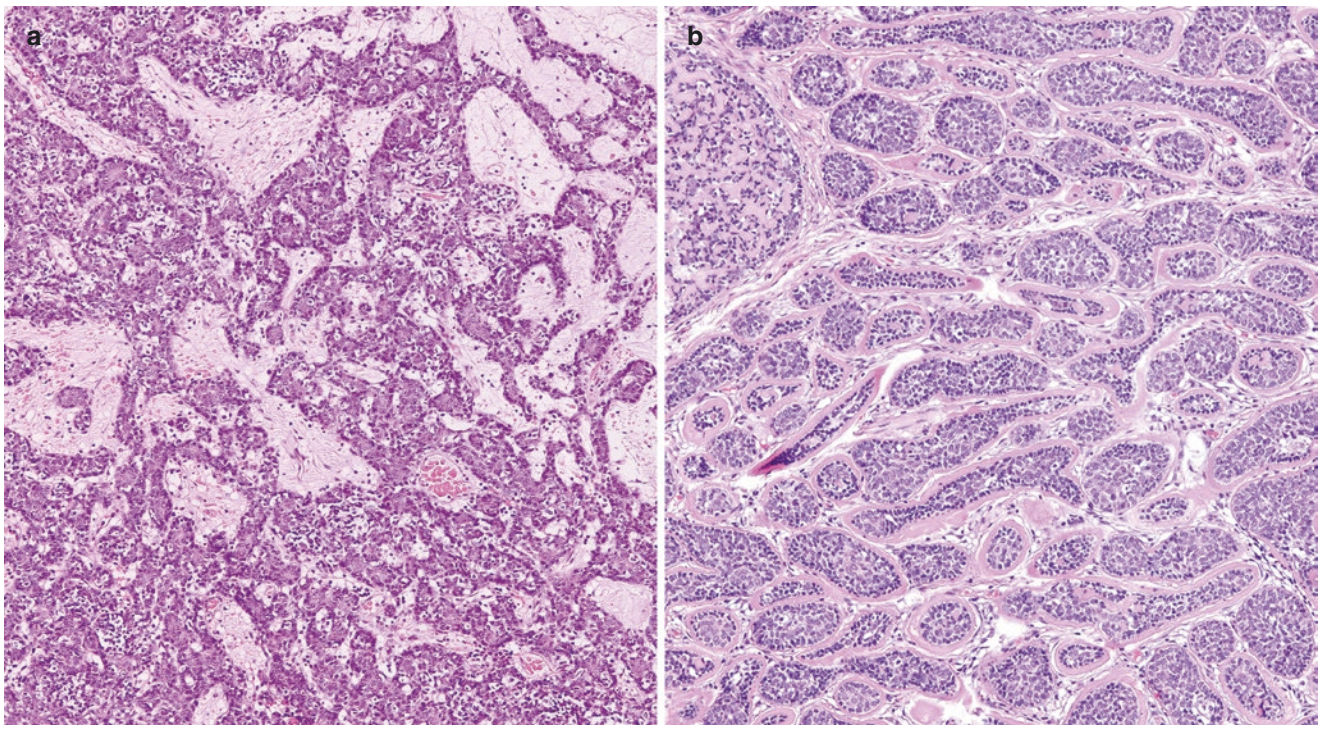

Fig. 4.21 Spiradenoma. Small basaloid neoplastic cells are arranged in a trabecular pattern. Note intratumoral lymphocytes (**a**). Cylindroma. A neoplasm manifesting jigsaw puzzle arrangement of islands of basaloid cells surrounded by eosinophilic basement membrane material (**b**)

Marked cystic changes, a poorly developed jigsaw puzzle pattern in cylindroma, other lines of adnexal differentiation, adenomatous component, adenoid cystic carcinoma-like pattern, metaplastic changes in the epithelial component, prominence of lymphocytes, and others can be seen [2, 15, 20, 31].

4.6.2.2 Differential Diagnosis

Spiradenoma with a prominent trabecular pattern can be confused with sebaceous neoplasms with a carcinoid-like or labyrinthine/sinusoidal pattern but the clue to the diagnosis is the presence of intratumoral lymphocytes.

Cylindroma and spiradenocylindroma may resemble basaloid (cloacogenic) carcinoma of the anus, but carcinoma have cellular atypia, in situ component, and common positivity for p16 [2, 15, 31].

4.6.3 Apocrine and Eccrine Mixed Tumors (Chondroid Syringoma)

Mixed tumors of the skin (pleomorphic adenoma) are usually classified into the more common apocrine type and the rare eccrine type. Usually they are slowly growing solitary nodules on the head or extremities of the middle-aged and elderly persons [2, 85]. Only a few vulvar cases of chondroid syringoma of both types have been reported in the literature [86–90]. The tumor may recur if not completely excised [31].

4.6.3.1 Histopathology

Apocrine mixed tumors show considerable variation in their epithelial, myoepithelial, and stromal components and usually characterized by branching tubular structures, often manifesting apocrine secretion, embedded in a chondromyxoid cartilaginous or osseous stroma (Fig. 4.22a). In contrast to its apocrine counterpart, eccrine mixed tumors do not display signs of decapitation secretion, sebaceous or follicular differentiation. The epithelial component of eccrine mixed tumors is composed of simple monolayered tubular elements, small epithelial nests, strands and cords, or singe cell units set in myxohyaline and cartilaginous stroma (Fig. 4.22b) [85].

4.6.3.2 Differential Diagnosis

Rare cases of chondroid syringoma with predominance of stromal component can be confused with mesenchymal neoplasms. In such cases it is important to recognize a minor epithelial component which can by highlighted by cytokeratin immunostaining.

Prominent myoepithelial differentiation may require distinction from myoepithelioma, but myoepithelioma is composed entirely of myoepithelial cells without any glandular or ductal differentiation.

So-called vulvar microglandular adenosis-like neoplasm described by Raiguru et al. represents an example of eccrine mixed tumor [91].

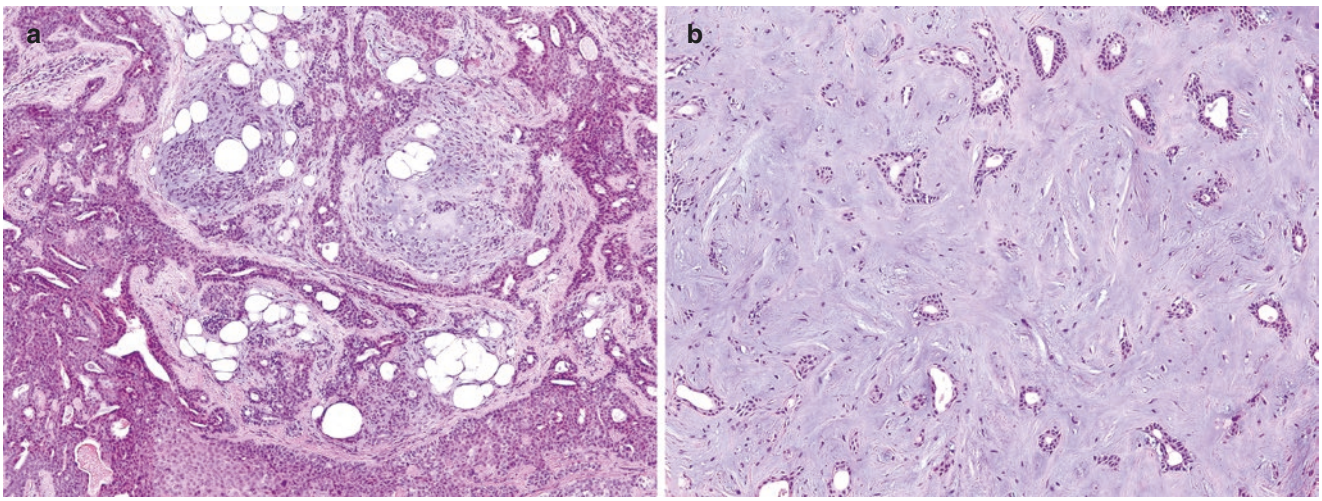

Fig. 4.22 Apocrine mixed tumor. Interconnected, double-layered ductal structures and myoepithelial cells set in fibromyxoid stroma (**a**) Eccrine mixed tumor. Ductal elements are monolayered and are surrounded by myxoid and hyalinized stroma (**b**)

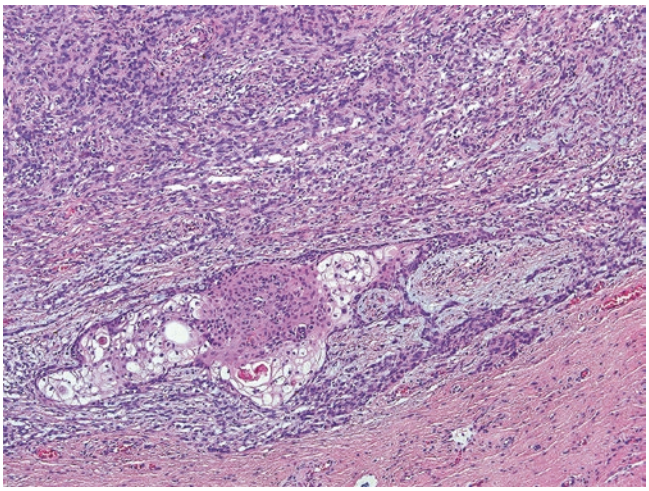

Fig. 4.23 Mixed tumor of the vagina. The neoplasm is composed of epithelial elements and stromal-type spindled cells

The malignant counterpart of chondroid syringoma, the malignant chondroid syringoma is characterized by infiltrative growth, nuclear pleomorphism, mitotic activity, and necrosis [2, 15].

One should keep in mind a distinctive neoplasm occurring in or near the hymen or its remnants, the mixed tumor of the vagina. Microscopically, it is composed of benign epithelial (islands of mature squamous, mucinous glands, or clear cell epithelium) and stromal-type spindled elements (Fig. 4.23) [92, 93].

4.6.4 Other Benign Adnexal Neoplasms

Other benign adnexal neoplasms, including poroma, pilomatricoma, hidradenoma, sebaceoma, and trichoepithelioma have been identified in the vulva [83]. Rare cases of vulvar myoepithelioma and trichofolliculoma have been reported [94–97]. Yoshida et al. described nine cases of "myoepithelioma-like tumors of the vulvar region" with the deficiency of SMARCB1 expression in all cases [98].

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