Benign Vulvar and Vaginal Pathology

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Abstract

Benign vulvar and vaginal pathology is common, consisting of a wide variety of lesions which include inflammatory conditions, pigmented lesions, neoplastic and nonneoplastic masses, and cysts. Women of all ages are affected. The majority of these lesions are clinically insignificant unless symptomatic or when they mimic malignancy. Rare lesions with premalignant potential are also present.

Keywords

Lichen sclerosus • Papillary hidradenoma • Vulvar melanosis • Atypical melanocytic nevi of genital type • Fibroepithelial polyp • Dysplastic nevi • Bartholin's gland cyst • Mullerian cyst • Epithelial inclusion cyst

Contents

1 Introduction

The high prevalence of benign lesions of the vulva and vagina makes the clinical and pathologic recognition of these entities important. Some of these lesions can lead to significant morbidity, and some are even considered premalignant. Successful treatments are available for most all these lesions. We discuss the most common and clinically relevant of these in this chapter.

2 Lichen Sclerosus

2.1 Introduction

Lichen sclerosus (LS) is a chronic, progressive, and debilitating dermatosis which remains poorly understood despite its recognition in the late

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nineteenth century. The hallmark of the disease is progressive scarring of the skin manifested grossly as white plaques and epidermal atrophy and histologically as dermal sclerosis with chronic inflammation. It affects males and females, adults and children, and all races but has a predilection for postmenopausal Caucasian women. It can involve any part of the skin but predominantly affects the anogenital region with only 6% of cases presenting as pure extragenital lesions. Of the vulvar dermatoses, it is the most common accounting for 39% of all cases. The prevalence of LS is estimated to be 0.1–1.7% but is likely an underestimate due to patient's presenting to numerous clinical settings, lack of clinical diagnosis, and underreporting by patients due to lack of symptoms or embarrassment.

The etiology of LS remains unknown and controversial. Interplay between immunologic alterations and chronic inflammation is believed to result in the formation of sclerosis. The development of LS in patients after surgery, trauma, instrumentation, and genital piercings supports this theory. Autoimmune and genetic components are strongly favored to play a part. Autoantibodies against extracellular matrix 1 (ECM1) protein and the basement membrane zone (BMZ) [BP180 and BP230] have been described in. *Borrelia burgdorferi* and Epstein Barr virus have been implicated as causative agents, but no strong evidence exists to support their involvement. Other possible causes include hormonal influences due to the presence of decreased dihydrotestosterone in affected females and the presentation of the disease at times of low estrogen (peak incidences in prepubertal and postmenopausal women).

2.2 Clinical Features

The diagnosis of LS is clinical, presenting as a constellation of symptoms, gross features, and clinical sequelae. In a prospective cohort study of 225 patients, the most common complaints were itching (90.2%), burning (74.3%), and dyspareunia (47.5%). On examination pallor, scarring sclerosis, and atrophy were seen in half the patients. Hyperkeratosis, purpura, itching related excoriations, and erythema were also present to a lesser degree (Virgili et al. 2014). Sites of involvement include the interlabial sulci, labia minora and majora, clitoris and hood, and perineum and perianal area; mucosal sites are spared.

LS usually starts as nonspecific erythema, edema, and fragility (erosions, fissuring, purpura, and ecchymoses) and progresses to large porcelain white plaques and papules. These evolve into dry, hypopigmented, sclerotic and atrophic lesions resulting in a crinkling or cellophane paper type appearance which is pathognomonic of LS. The progressive scarring of LS can result in fusion of the labia minora, obliteration of the clitoris, and stenosis of the introitus. Although controversial, LS is considered a risk factor for invasive squamous cell carcinoma (SCC) with a reported lifetime risk of 0.3–5%. It is not considered a premalignant lesion.

2.3 Histology

LS has been divided into an early and late stage clinically and histologically although this designation is debated due to lack of correlation between clinical duration and histologic findings. Early LS is histologically nonspecific. Findings include a lichenoid interface dermatitis and basement membrane thickening. Luminal hyperkeratosis and hypergranulosis of the adnexal structures; mild irregular, occasionally psoriasiform acanthosis; subepithelial edema; dermal homogenized collagen; and dilated blood vessels immediately under the basement membrane may also be seen. The differential includes lichen planus, psoriasis, and Zoon's vulvitis. Late LS has a classic histologic picture of hyperkeratosis, epidermal atrophy with flattening of the rete ridges, vacuolar interface changes, loss of elastic fibers, and hyalinization of the lamina propria with or without an underlying lymphocytic infiltrate. However, a not uncommon hyperplastic variant has been described and may increase risk of development of SCC (Scurry et al. 2001; Weyers 2013). An atypical variant that may be a

precursor to differentiated vulvar intraepithelial neoplasia (VIN) has also been described (Chiesa-Vottero 2006). The nonspecific features of early LS and variants of more typical late LS often make histologic diagnosis of LS difficult; clinical correlation is a must.

3 Fibroepithelial Polyp

3.1 Clinical Features

Fibroepithelial polyps (FEP) are benign indolent lesions found most commonly in the genital region of premenopausal reproductive aged women. The most common site is the vagina followed by the vulva, cervix, and extragenital sites. In the vulva, they are usually present on hair-bearing skin but involvement of the labia minora has been described. The median age in one study was 32 years, (Nucci et al. 2000) but they have been reported in a wide age range of patients, including infants and the elderly. FEP typically presents as a polypoid or pedunculated exophytic mass that is usually solitary but can be multiple with multiple lesions being seen more often in pregnant patients (Nucci et al. 2000). Symptoms include bleeding, discharge, general discomfort, and sensation of a mass. Their clinical significance stems from their gross and clinical overlap with malignant neoplasms resulting in the alternative terminology of pseudosarcoma botyroides. Biopsy or excision with histologic examination is necessary to exclude malignancy.

FEP is thought to be a hyperplastic process rather than true neoplasm. Features supporting this theory are the presence of multinucleate cells in normal adjacent tissue and the presence of estrogen (ER) and progesterone receptors (PR) in normal stromal cells (see Sect. 3.2 below). The etiology is unknown and includes origin from a regressing nevus, irritation, skin aging, and hormones. Findings to support hormones as a cause include the fact that 20% of patients with FEP are pregnant, 10% are on hormone replacement therapy (HRT), multiple lesions are seen in pregnant patients, and spontaneous regression after birth has been reported.

The gross appearance of FEP is variable. It is often <5 cm in size, but the literature contains examples of 10, 15, and 18.5 cm lesions (Madueke-Laveaux et al. 2013; Navada et al. 2011). Gross features range from small fleshy colored to pigmented papillomatous resembling condyloma to large pedunculated lesions which are often hypopigmented. They have also been described as edematous, mucoid, rubbery, and hard with increased vascularity and as a gelatinous cyst. The differential includes numerous benign lesions such as sebaceous cyst, condyloma, fibroid, and hymenal ring as well as malignant neoplasms.

3.2 Histology

The typical histologic features of FEP include a fibrovascular core, loose edematous stroma, prominent dilated thick walled vessels, overlying intact squamous epithelium, multinucleate stromal cells throughout including at the epithelial stromal interface, and spindle or stellate stromal cells with tapering cytoplasmic processes. The squamous epithelium may be hyperplastic, acanthotic, parakeratotic, attenuated, and rarely even ulcerated (Navada et al. 2011; Nucci et al. 2000). The lesion lacks circumscription, merging with normal tissue at the margins. The constituent stromal cell is fibroblastic/myofibroblastic by immunohistochemistry and ultrastructurally and has been shown to be positive for ER, PR desmin, actin, and vimentin. The typical histologic appearance is easy to diagnose, but variants of these features pose diagnostic dilemmas. Focal myxoid stroma may lead to a misdiagnosis of aggressive angimyxoma (AA). However, AA is subcutaneous not exophytic and uniformly myxoid not focally. A cellular variant of FEP that has been described is particularly worrisome because it can be mistaken for sarcoma. It consists of a hypercellular stroma and can have cytologic pleomorphism, up to 10 mitoses per 10 high power fields, and atypical mitoses which can lead to a misdiagnosis of sarcoma. The presence of multinucleate cells should help exclude sarcoma as they are strictly a feature of FEP (Nucci et al. 2000).

4 Vulvar Melanosis

Vulvar melanosis (VM), also known as vulvar lentiginosis or vulvar melanotic macules, is the most common pigmented disorder of the vulva. It is a benign disorder that typically affects perimenopausal Caucasian women with a reported median age of 40–44 years in one study (Murzaku et al. 2014). It accounts for 68% of all pigmented lesions in reproductive aged women. The typical presentation is of single or multiple asymmetric macules or patches of varying shades of tan to black color that vary in size and have poorly demarcated irregular borders. The lesions can be longstanding and grow in size (Rudolph 1990). They arise most often on mucosal surfaces with the most common sites being the labia minora followed by the labia majora (Cengiz et al. 2015). Hair-bearing skin is spared. The etiology is unknown but lichen sclerosus, human papilloma virus, and hormones have all been implicated (Murzaku et al. 2014) although one study of 23 cases failed to demonstrate common strains of HPV (Jih et al. 1999).

The most common histologic finding in VM is increased melanin pigment in the basal layer of the epidermis. It is usually accompanied by no or mild proliferation of melanocytes. If proliferation is present, it is as single cells confined to the basal layer; nesting or confluent proliferation should not be seen. Other less common findings include acanthosis, pigment incontinence with melanophages in the papillary dermis, and dendritic melanocytes at the dermal-epidermal junction. Atypia is absent or very mild (Jackson 1984; Kanj et al. 1992; Rudolph 1990; Jih et al. 1999).

Despite its benign prognosis, VM is important clinically due to its gross similarity to malignant melanoma (MM). Conservative treatment consists of baseline photography followed by sequential imaging. If melanoma cannot be excluded biopsy must be performed. Dermoscopy can also help to determine the benign nature of the lesion (Murzaku et al. 2014). VM has been proposed as a risk factor for development of MM, but no strong evidence to support this has yet been identified.

5 Nevus

5.1 Clinical Features

Vulvar nevi are present in 2% of the female population and account for 23% of all pigmented vulvar lesions. The median age of diagnosis is 28–33 years although a significant number can be seen in the pediatric population (<18 years of age). The most common nevus diagnosed is the typical variant that is found at other sites in the body. It is most often acquired and can be junctional, compound, or intradermal. Other variants described are congenital, dysplastic, blue, and spitz nevus. An important variant due to its histologic similarity to malignant melanoma (MM) is atypical melanocytic nevi of genital type (AMNGT). AMNGT is considered a nevus with site specific features and accounts for 5% of vulvar nevi. Its median age of presentation is less than that of typical nevi and ranges from 17 to 26 years. A family history of dysplastic nevi or MM is more common in these patients.

Typical nevi present as symmetric macules or flat topped or dome-shaped papules with well-demarcated, regular borders. They are usually <1 cm in size and have uniform color ranging from pink, dark brown-black, and rarely blue. Common sites of involvement are the labia majora followed by the labia minora and clitoral hood. Involvement of hair-bearing sites is less common. AMNGT present with dark pigmentation, irregular borders, and larger size (up to 2 cm in diameter). They present more often on the labia minora and have an equal distribution between mucosal and hair-bearing sites. In children, AMNGT predominate at mucosal sites.

5.2 Histology

Typical nevi are histologically identical to typical nevi anywhere else on the body. They consist of nests of cytologically bland melanocytes at the dermal-epidermal junction (DEJ) (junctional nevus), in the dermis (intradermal nevus), or both

(compound nevus). Confluent or merging nests, lentiginous or pagetoid spread, mitoses, and atypia are absent. Dermal components often show maturation. AMNGT, although worrisome to the unexperienced pathologist, has a characteristic histologic appearance enabling accurate diagnosis. It is a compound nevus with well-demarcated, symmetric contours. On low power it appears large, nodular, and has increased cellularity. The junctional component consists of florid, large, irregularly distributed nests of mild to moderately atypical melanocytes that may show confluence and often have retraction artifact. These nests often are fusiform or oval shaped with their long axis parallel to the DEJ (Brenn 2011). Lentiginous and pagetoid spread into the granular layer is usually a focal finding in the center of the lesion only (Ribe 2008). Hyperchromatic and multinucleate forms may be seen as well as mitotic activity up to 2 mitoses/HPF. If melanocytic atypia is random rather than uniform, deep dermal or atypical mitoses present or necrosis seen, a diagnosis of dysplastic nevus must be ruled out.

6 Papillary Hidradenoma

6.1 Clinical Features

Papillary hidradenoma (PH), also known as hidradenoma papilliferum, is a benign neoplasm that most often affects the vulva of postpubescent Caucasian women. Rare incidents of lesions in males, other races, and extragenital sites have been reported (Scurry et al. 2009; Duhan et al. 2011). The mean age in one study of 46 patients was 52 years with a reported age range in the literature of 20–89 years (Scurry et al. 2009). The most common sites of involvement in the vulva are the labia majora (38%) and labia minora (26%). PH usually presents as an asymptomatic, small (2 mm to 3 cm), solitary, slow growing, dome or spherical shaped freely movable mass. It can be solid or cystic; ulcerated; pedunculated; and blue, red, or skin colored. When symptoms are present they include a nodule increasing in size, pruritus, bleeding, and very rarely tenderness. PH can rarely be multifocal; when it is, it is usually unilateral (Parks et al. 2012). The largest reported case is 8 × 5 cm (Kaufmann et al. 1987).

The histogenesis of PH was believed to be from apocrine and eccrine glands. Currently it is thought to be from mammary-like glands (MLG) in the vulva prompting some authors to advocate a name change to MLG adenoma (Scurry et al. 2009). Features supporting this theory are the analogous distribution of the lesion to vulvar MLGs, their immunophenotypic (see below) and histologic overlap, and the presence of MLGs adjacent to or in close proximity to PH on histologic sections. An association with human papilloma virus has been reported, but causation has not been proven (Vazmitel et al. 2008). PH is also thought to be a cause of Bartholin's cyst due to a reported and its typical anatomical proximity to Bartholin's duct (Docimo et al. 2008).

6.2 Histology

PH is an adenoma that arises in the dermis with no connection to the epidermis. At low power it can mimic adenocarcinoma due to the presence of a fibrotic pseudocapsule which entraps epithelium at the periphery mimicking an invasive pattern. High power shows anastomosing tubules and cystic spaces with papillary folds projecting into the lumen reminiscent of an intraductal papilloma of the breast. If tubules predominate, rare solid areas can also be seen (Scurry et al. 2009). The tubules and papillae are composed of two cell layers: an inner layer of tall, columnar ductal cells and outer layer of flat or cuboidal myoepithelial cells. Sometimes only a single layer is present. The ductal cells can have apical snouts and faint eosinophilic cytoplasm imparting an apocrine look. Rare examples of clear, mucinous and foam cells have also been described (Scurry et al. 2009). Pleomorphism and mitoses can be present but only mildly. Ductal cells are positive for estrogen receptor (ER), progesterone receptor (PR),

GCDFP-15, CK7, PanK, and EMA. Myopeithelial cells are positive for actin and p63 (Parks et al. 2012; Vazmitel et al. 2008; Shah et al. 2008).

7 Vaginal Cysts

7.1 Introduction

Vaginal cysts are clinically common lesions affecting an estimated 1/200 reproductive aged women. The cysts are often asymptomatic leading to an underestimate in not only prevalence but also a lack of pathologic examination and unfamiliarity with histologic designation. Although histologic distinction between the different cysts is not clinically important, it can be done with relative ease by understanding of embryogenesis of the vagina. The vagina is derived from mullerian, mesonephric, and urogenital sinus tissues. The common cysts can be divided into embryonic (Mullerian, Gartner's duct, and Bartholin's gland) and nonembryonic (epidermal inclusion cyst (EIC)).

7.2 Cysts of Embryonic Origin

7.2.1 Mullerian Cysts

Mullerian cysts are derived from the mullerian ducts which form the majority of the vagina. They are the most common of the benign vaginal cysts accounting for up to 44% of cysts. They can be located almost anywhere within the vagina but are usually found in the anterolateral aspect. They range in size from 1 to 7 cm and are often asymptomatic and clinically undetectable, especially if small.

Mullerian cysts can be comprised of any of the normal mullerian tissues including endocervical (mucinous), tubal, or endometrial. The most common finding is an admixture of endocervical and tubal with admixed squamous metaplasia. Endocervical epithelium consists of tall columnar cells, basally located nuclei, and cytoplasmic and luminal mucin. Tubal epithelium consists of ciliated tubal cells with admixed tubal peg and secretory cells. Endometrial epithelium is rare and if present is usually focal. If abundant luminal mucin is present, the epithelium may become compressed or flattened making distinction between Gartner's duct cysts difficult. Confirmation of mucin with mucicarmine stain can help differentiate as Gartner's duct cysts are nonmucinous. Abundant squamous metaplasia can make distinction from EIC almost impossible but distinction is not clinically significant.

7.2.2 Gartner's Duct Cysts

Gartner's duct, or mesonephric, cysts arise from the Wolffian ducts. They are less common than their mullerian counterpart comprising approximately 10% of benign vaginal cysts. They are often smaller than mullerian cysts and usually found along the lateral wall of the vagina. They are lined by a nonmucinous low columnar or cuboidal epithelium. They can be distinguished from mullerian cysts by the lack of ciliated epithelium, squamous metaplasia, and negative mucicarmine confirming the absence of mucin.

7.2.3 Bartholin's Gland Cysts

Bartholin's gland cysts arise due to blockage of Bartholin's duct, a 2.5 cm duct which drains into the vaginal vestibule adjacent to the hymen posteriolaterally. The gland itself is located in the posteriolateral vulva beneath the labia majora and minora. Blockage is usually a result of infection or increased viscosity of the secreted mucin. The cysts are found in the lateral introitus, range in size from 1 to 4 cm, and are usually unilateral, nontender, and asymptomatic.

Bartholin's duct is comprised of three types of epithelium: mucinous proximally and in gland acini, transitional in the middle, and squamous distally and at the entrance into the vestibule. Following this pattern, Bartholin's gland cysts can contain one, two, or all three epithelial types depending on size and location along the duct. Luminal contents consist of a clear mucoid liquid. Acute and chronic

inflammations are not uncommon, and infection with resultant abscess can also be seen.

7.3 Nonembryonic Cysts

7.3.1 Epithelial Inclusion Cysts

EICs are the most common of the nonembryonic vaginal cysts. They are most often located in areas of previous surgery or trauma and are believed to be a result of traumatic inclusion of the normal vaginal mucosa. They range in size from a few millimeters to several centimeters. They are lined by stratified nonkeratinizing squamous epithelium lacking rete ridges. The lumen contains keratinaceous debris and desquamated cells. Rupture of the cyst can result in an exuberant chronic inflammatory or granulomatous reaction.

7.3.2 Endometriosis

Endometriotic cysts of the vagina can be superficial or deep. When superficial, they are located in the vaginal vault, are not associated with pelvic endometriosis, and are usually present at a site of previous surgery. Deep cysts are more common, are associated with pelvic endometriosis, and are most often located in the posterior fornix. Endometriotic cysts present as friable erythematous masses ranging in color from red to blue. Histologically, they are lined by endometrioid epithelium surrounded by endometrial stroma, hemosiderin pigment, and hemosiderin-laden macrophages.

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