Lesions of the Bartholin Gland: A Review

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Abstract: Most lesions of the Bartholin gland are cysts or abscesses. Clinicians are taught that lesions of the Bartholin gland occurring in older women should raise the differential diagnosis of malignancy, although these are uncommon. A variety of more unusual and rare lesions of the Bartholin gland have been reported. This review focuses on these less common entities, which must be considered as well when encountering pathology of the Bartholin gland.

Key Words: Bartholin gland, female, vulvar diseases

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The Bartholin glands (BG) were named after Caspar Bartholin the younger,[1] who dissected them in cattle and described them in 1677, postulating their presence in human females as well. Other authors[2] ascribe the detection in cattle to Duverney, and the term *Duverney glands* may be encountered. The younger Bartholin was a member of a prominent medical family, 4 of whom were on the faculty of the University of Copenhagen and whose achievements are sometimes confused with each other. An interesting history of this medical family was published by Hill.[1] Although most lesions of the BG are cysts and abscesses, which may not generate a surgical pathology specimen, there are a variety of less common lesions that occur in the gland and may lead to biopsy or excision. The following is a short review of diagnoses that may be rendered on such a specimen. Lesions of the BG are listed in Table 1.

THE NORMAL BARTHOLIN GLAND

The normal BG is unusual in that it is composed of several epithelial types. The body of the gland is composed of mucinous acini. The duct is predominantly transitional epithelium (although a mix of mucinous, transitional, and squamous may occur in the duct), and the orifices, opening at the 4:00- and 8:00-o'clock positions, are lined with squamous epithelium, blending into the squamous epithelium of the vulvar vestibule (see Figure 1). It is for this reason that carcinomas of the BG may be of any of these types of epithelium.

CYSTS AND ABSCESSES

Bartholin duct (BD) cysts, which are due occlusion of the orifice, and abscesses, which may be multimicrobial and due to gonorrheal or chlamydial infections,[3] are common reasons for emergency department patient visits. Marsupialization or incision and drainage may not generate a specimen for surgical pathology evaluation (see Figure 2); however, a few of these inflammatory lesions are more unusual.

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Goetsch[4] reported a 9% rate of occlusion of the BG ostium after superficial localized vestibulectomy, noting that approximately half had symptoms. The lesions manifested as small blisters, which were unroofed in some of the cases. The exceptionally rare occurrence of a BG abscess in a neonate has been reported[5] and should be considered in the differential diagnosis of vulvar swelling in a prepubertal female. In 1 highly unusual case,[6] a BG abscess led to a rectovaginal fistula.

OTHER INFLAMMATORY LESIONS

Tuberculosis

Dhall et al.[7] described a patient with a tuberculous ulcer occurring in the BG region after excision of a BD cyst and suggested consideration of this diagnosis for a nonhealing genital ulcer, particularly in areas of the world where genital tuberculosis is not rare, such as this case, which occurred in India.

Malakoplakia

Malakoplakia, an unusual inflammatory lesion usually seen in the genitourinary or gastrointestinal tract, has been described in the BG. The 2 cases of Paquin et al.[8] occurred in postmenopausal women presenting with BG swelling: 1 with an asymptomatic lesion and 1 tender. Malakoplakia is composed of sheets of histiocytes containing small intracytoplasmic Michaelis-Gutmann bodies, thought to be due to a defect with incompletely phagocytosed bacteria.

BENIGN TUMORS AND TUMOR-LIKE LESIONS

Endometriosis/Endometrioma

There are several theories relating to the dissemination of endometriosis, including retrograde menses, vascular or lymphatic dissemination, and metaplasia. Cases occurring in BG give some insight into these theories, but without a definitive conclusion. Although it is well recognized that endometriosis can be seen within an episiotomy scar, where seeding is thought to be the etiology, the occurrence in a scar associated with previous BG surgery is rare. Buda et al.[9] presented such a case, in a 39-year-old woman with a history of multiple procedures on a recurrent Bartholin abscess. Bilateral endometriomas of BG were reported as occurring 2 weeks after excision of an ovarian endometrioma,[10] and vascular dissemination was suggested as an etiology.

Arteriovenous Malformation

An unusual cause of intermittent vaginal bleeding was described by Lal et al.[11] This arteriovenous malformation occurred in a 43-year-old woman and was composed of abnormally configured tortuous arteries and veins. Clinically, the patient had a compressible cystic mass with dilated duct opening, and milking of the mass expressed blood. One of the cases of Foushee et al.[12] in a series of benign BG masses was described as being either thrombosed varices or cavernous hemangioma.

Crohn Disease

Crohn disease may involve the BG and may mimic an abscess. The disease either may be in direct continuity with the

TABLE 1. Lesions of the Bartholin Gland

Inflammatory
Cysts/abscesses
TB
Malakoplakia
Benign tumors and tumor-like lesions
Hamartoma
Endometrioma
Crohn disease
Hyperplasia
Adenoma
Papilloma
Arteriovenous malformation
Primary epithelial premalignant lesions and malignancies
Squamous intraepithelial neoplasia
Squamous cell carcinoma
Adenoid cystic carcinoma
Adenocarcinoma-papillary, mucinous, colloid
Adenosquamous carcinoma
Transitional cell carcinoma
Undifferentiated carcinoma
Epithelioid-myoepithelial carcinoma
Neuroendocrine carcinoma
Merkel cell carcinoma
Lymphoepithelioma-like carcinoma
Mesenchymal lesions
Leiomyoma
Leiomyosarcoma
Epithelioid sarcoma
Lymphoma
Lesions metastatic to Bartholin gland

gastrointestinal tract, forming a cololabial fistula, which can be demonstrated on MRI, or may be isolated from the gastrointestinal tract.[13] Amu et al.[14] linked their 56-year-old patient's squamous cell carcinoma of the BG to her long-standing Crohn disease, the course of which involved 7 rectovaginal fistula repairs.

Hyperplasia, Adenoma, and Hamartoma

Two cases of nodular hyperplasia thought to be BG cysts were reported by Kazakov et al.[15] This lesion was described histologically as a proliferation of acini and dilated ducts with inspissated secretions, in their normal relationship. The literature is unclear in distinguishing this lesion from adenoma.[12, 15] The dilated ducts may rupture, and there may be inflammation, which may relate to the pathogenesis of this lesion.[15] Criteria to distinguish hyperplasia from adenoma have been set forth by Koenig and Tavassoli[16]; however, Kazakov et al.[15] emphasized the difficulties in distinction, emphasizing how their 2 cases fit the criteria for nodular hyperplasia but, by being monoclonal, might actually be neoplastic.

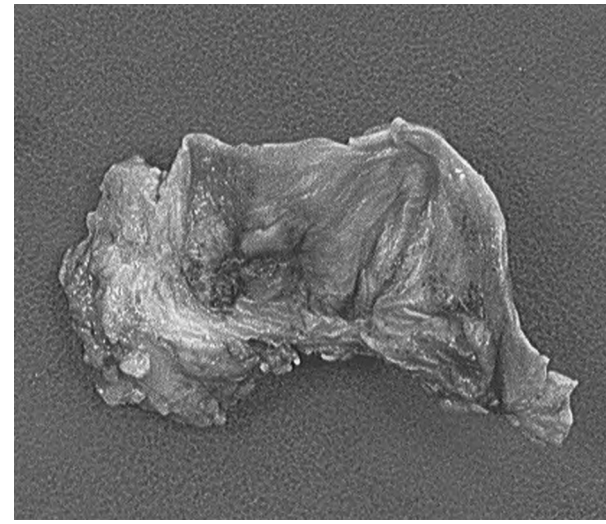

FIGURE 2. Bartholin duct cyst completely excised. Note the flat lining of the cyst.

Adenomas are rare benign solid lesions of the BG. They may be asymptomatic or painful nodules.[17] Mandsager et al.[17] reported the case of a 31-year-old woman with bilateral adenomas leading to pain during sexual response, which resolved after excision. The histologic finding resembled normal glandular acini and small ducts; however, there were many more of them per unit area. These lesions have also been referred to as hamartomas, questioning their neoplastic character.[12,18]

"Mucinous cystadenoma," a clinically cystic lesion but histologically solid lesion, has also been reported, with focal epithelial hyperplasia and partial encapsulation; however, the authors acknowledge that these may be in the spectrum of hyperplasia or hamartoma as discussed by others.

The rarity of these lesions limits the ability to further characterize these lesions.[12,19] Clinically, the significance is minimal, as excision resolves the problem.

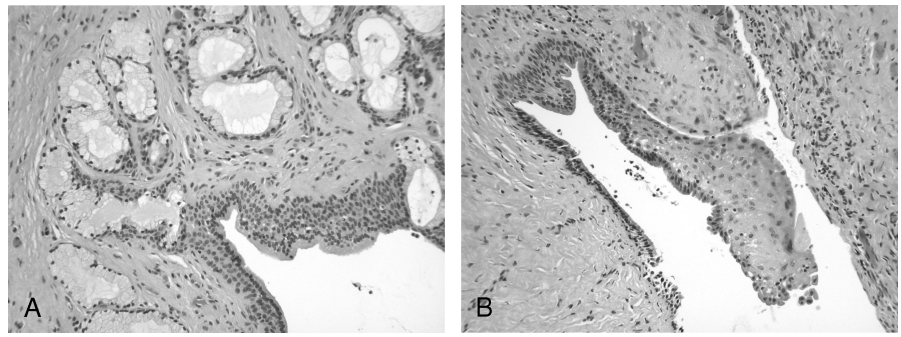

FIGURE 1. Normal Bartholin gland is composed of mucinous acini and ducts lined predominantly by transitional epithelium (lower right) (A) with an admixture of squamous and mucinous epithelium (B). The duct orifice (not shown) is usually squamous, blending with the epithelium of the vestibule.

Papilloma

Enghardt et al.[20] presented a case of a 50-year-old woman who presented with an asymptomatic vaginal cyst. Attempted extirpation was discontinued owing to the large size (6 cm) and adherence of this cyst, and the patient underwent unroofing, marsupialization, and excision of a polypoid nodule seen at the distal end of the cyst. This was found to be a papilloma, with a mixture of mucinous columnar, squamous, and transitional epithelium, analogous to the composition of the normal gland and duct. At the time, the authors were unable to find a similar case in the literature.

PREMALIGNANT AND MALIGNANT LESIONS OF THE BARTHOLIN GLAND

Bartholin gland carcinomas are rare, comprising less than 1% of gynecologic malignancies[21] and 0.1% to 5% of vulvar carcinomas.[22] Bartholin gland carcinoma was first documented in 1864.[2] Previous cysts or inflammation of the gland have occurred in less than 10% of cases.[21] In order for a neoplasm to be considered of BG origin, there must be normal gland identified adjacent to the tumor, with histologic transition, have compatible histologic features for a BG origin, and the patient must not have another primary tumor concurrently.[22,23] Because of the rarity of these lesions, treatment is individualized, with no prospective randomized trials available.[2] Many of these lesions are in the literature as single case reports. Again because of the rarity of these lesions, as well as the lack of specific symptoms, clinical suspicion tends to be low, with lesions thought to initially be cysts or abscesses, delaying diagnosis and treatment.[2] Presenting symptoms include painless mass, bleeding, pruritus, and rarely pain.[24] Biopsies must be sufficiently large and deep to be diagnostic. Treatment plans tend to be similar to usual vulvar carcinoma.[2] Ouldamer et al.[2] described a detailed therapeutic approach, encouraging gynecologic oncology involvement. Awareness and early diagnosis are critical because overall 5-year survival without inguinal lymph node metastases is only 50%, decreasing to 18% with 2 or more metastatic inguinal nodes.[25]

SQUAMOUS INTRAEPITHELIAL NEOPLASIA

Because almost half of BG carcinomas are squamous cell carcinoma, it is not surprising to find that intraepithelial neoplasia can occur in the BG. A case of high-grade squamous intraepithelial lesion (SIL) was reported in a 53-year-old woman who presented with a history of recurrent painless cyst over a 30-year period, never surgically treated. Of significance in this case was a previous cone biopsy for high-grade SIL/cervical intraepithelial neoplasia grade 3 (HSIL/CIN3). The cyst, measuring 5 × 5 cm, was completely excised and showed focal squamous differentiation, with an area of high-grade SIL. The authors were only able to locate 1 previous reported case in the literature, in association with human papillomavirus type 16 (HPV-16).[26,27]

PRIMARY EPITHELIAL MALIGNANCIES

Approximately 80% of BG carcinomas are either squamous cell carcinomas or adenocarcinomas, of approximately equal frequency.[2] Given the mixture of epithelial types in the gland and duct, it is not surprising that the histologic type of carcinomas varies.

Squamous Cell Carcinoma

The most common malignancy arising in the BG is squamous cell carcinoma (see Figure 3). Felix et al.[21] have demonstrated HPV-16 in 6 of 7 of the squamous cell carcinomas they evaluated by polymerase chain reaction. They postulated that squamous and adenocarcinomas arise in a transitional zone in the BG, similar to cervical carcinoma. Seward et al.[28] reported a case of squamous cell carcinoma metastatic to the lung. The lung lesion was confirmed to be metastatic by allelotyping, and both the BG and lung lesions were positive for high-risk HPV.

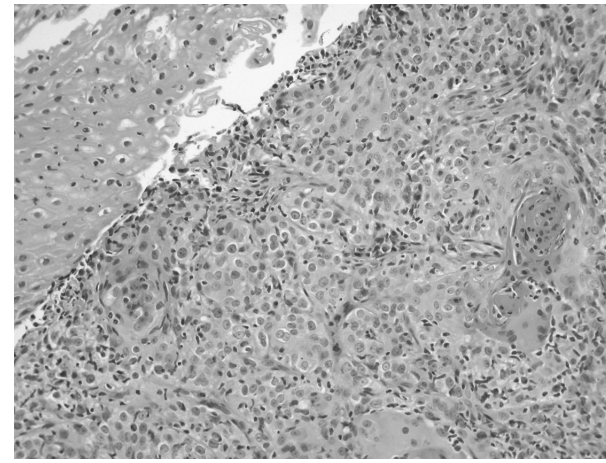

FIGURE 3. Squamous cell carcinoma of the Bartholin gland shown in this tru-cut needle biopsy. Note the overlying benign squamous epithelium.

Adenocarcinoma

Most vulvar adenocarcinomas are of BG origin and often show positive inguinofemoral nodes and deep invasion, with aggressive behavior.[29] Adenocarcinomas of BG have been shown to have estrogen and progesterone receptors.[30] They may be papillary, mucinous, or colloid lesions. Adenosquamous carcinomas are reported to be more aggressive than adenocarcinomas, owing to more frequent nodal involvement.[25] In 1 unusual case,[29] the BG adenocarcinoma, present in multiple inguinofemoral nodes at hemi-vulvectomy, spread to the patient's skull during postoperative chemotherapy, and the patient died of the disease 9 months after the initial surgery. Adenocarcinoma of the BG has occurred in association with Paget disease of the vulva as well.[31]

Adenoid Cystic Carcinoma

Approximately 60 cases of adenoid cystic carcinoma of the BG were reported as of 2009.[23] They represent approximately 10% to 15% of malignancies of the BG.[22,25] Adenoid cystic carcinomas are usually seen in salivary glands and have a very characteristic cribriform pattern containing basement membrane-like material (see Figure 4). Some of the reported BG cases have had long-term survival, up to 33 years in the case of DePasquale et al.,[22] although recurrence is common. Extremely rarely, liver metastasis has occurred.[32] There is a propensity for perineural invasion, which may be a cause of recurrence, which has also been postulated to be the cause of pruritus and burning associated with the lesion, even before a palpable mass is detected.[22]

Epithelioid-Myoepithelial Carcinoma

McCluggage et al.[23] described 2 cases of a distinct neoplasm of the BGs composed of a predominantly tubular tumor with 2 cell layers, inner epithelial and outer myoepithelial, confirmed by immunohistochemistry and were histologically similar to breast or salivary tissue. The authors believed

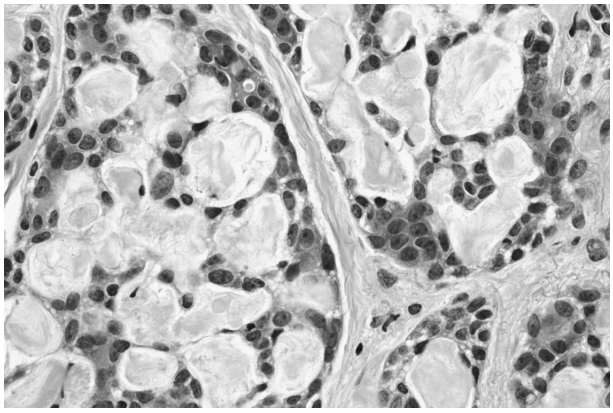

FIGURE 4. Adenoid cystic carcinoma of the Bartholin gland shows characteristic ''cookie-cutter'' spaces containing basement membrane-like material.

the lesion was clinically similar to salivary gland epithelial-myoepithelial carcinoma and represented a low-grade carcinoma. The patients were 44 and 51 years old, and the lesions were 2 and 3 cm. Both lesions were well circumscribed but unencapsulated and locally infiltrative. Both patients underwent more radical surgery after initial diagnosis, with a partial vulvovaginectomy and bilateral inguinal lymph node dissection in one and a partial vulvectomy and ipsilateral inguinal lymph node dissection in the other. Although no follow-up was available, the authors postulated that these would behave similarly to the salivary gland counterpart, be potentially locally recurrent, but unlikely to metastasize.

Neuroendocrine Carcinoma

Small cell neuroendocrine carcinomas, histologically similar to those seen in lung, are exceptionally rare in the BG. Jones et al.[33] report the case of a 30-year-old woman who had a 3-month history of an enlarging painful nodule and had positive inguinal nodes found during the workup. The histologic differential diagnosis of this rare lesion is lymphoma, which has also occurred in the BG and has similar appearing "small blue cells." The differential also includes Merkel cell tumor,[34] a neuroendocrine tumor of skin, which could occur in the squamous epithelium overlying the gland. The authors[33] also suggest that a poorly differentiated small cell sarcoma such as an alveolar rhabdomyosarcoma might also be confused owing to the small blue cell histologic finding.

Merkel Cell Carcinoma

Merkel cell carcinoma is a cutaneous small cell neuroendocrine carcinoma most often seen in the skin of the head and neck and exceptionally rare in the BG and vulva in general. It has shown aggressive behavior in reported lower genital cases,[34] although the case reported by Khoury-Collado et al.[34] was that of a 49-year-old woman who survived 24 months at the time of the report, after radical surgery. The tumor most closely resembles lymphoma, from which it can be distinguished by immunohistochemistry, with positivity for keratins and neuroendocrine markers. The cells also exhibit nuclear molding, a feature not associated with lymphoma.

Lymphoepithelioma-Like Carcinoma

Kacerovska et al.[35] reported a lymphoepithelioma-like carcinoma of the BG in a 52-year- old woman. This is an exceptionally rare lesion in the vulva at any location and does not seem to be secondary to Epstein-Barr virus, as it is in the nasopharynx.[35] Clinically, the diagnosis was initially "fibroma." After the nodule was excised and the diagnosis was made, the patient underwent a partial radical vulvectomy with bilateral inguinal node dissection and was disease free 6 months later. Histologically, this lesion is composed of sheets of large epithelial cells within a heavy background of chronic inflammatory cells. Neither Epstein-Barr virus nor HPV was detected.

Transitional Cell Carcinoma

Transitional epithelium lines part or most of the BG duct, so it is not unexpected that transitional cell carcinoma (TCC) would be seen in this location. However, TCC of the BG represents less than 5% of BG carcinomas, with only a few reported cases.[2,36] Fujiwaki et al.[36] report a case in a 66-year-old Japanese woman, seen in association with "low-grade dysplasia." Despite local excision and unilateral inguinal lymphadenectomy for what was found to be metastatic disease (less aggressive surgery was due to the patient's comorbid heart disease), and chemotherapy, she died of disease 14 months later.

OTHER RARE BENIGN AND MALIGNANT EPITHELIAL LESIONS

Rare benign lesions include the mixed tumor (pleomorphic adenoma), a lesion usually seen in salivary gland, but occurring in vulva. Two cases were reported attributed to BG origin.[37]

Felix et al.[38] described a salivary gland–type basal cell adenocarcinoma of BG, which is more analogous to salivary tumors than primary vulvar adenocarcinoma. The 75-year-old patient underwent incomplete excision and subsequent radiotherapy and had local residual tumor but no metastases 18 months later.

Lim et al.[25] reported a primary clear cell adenocarcinoma of the BG in a 46-year-old woman who underwent excision with subsequent bilateral inguinal lymphadenectomy and was disease free at 9 months.

Skin appendage neoplasms may also occur in the region of the BG. A malignant clear cell hidradenoma was diagnosed in a case initially thought to be a BD cyst.[39]

Fluorine-18 fluorodeoxyglucose positron emission tomography–computed tomography (F-18 FDG PET-CT) scan was suggested as a useful modality for staging and evaluation of treatment efficacy in a case of an advanced undifferentiated carcinoma of the BG.[40]

MESENCHYMAL LESIONS

Leiomyoma and Leiomyosarcoma

Francis et al.[41] report the case of a BG leiomyoma in a 56-year-old woman complaining of a genital "lump." There was initial clinical concern for carcinoma, and the mass was excised. The authors emphasize the importance of considering enlarged gland excision in women older than 50 years and viewing any BG mass in a woman older than 40 years with suspicion warranting biopsy.

A case of low-grade myxoid leiomyosarcoma was reported[42] where the presumed cyst was excised at the time of a vaginal delivery. More extensive excision performed at 8 weeks postpartum was negative for tumor; however, local recurrence occurred 10 months later.

A 52-year-old woman presented with a 6-cm leiomyosarcoma initially diagnosed as BG cyst.[43] The patient underwent radical hemi-vulvectomy with ipsilateral inguinal lymphadenectomy followed by chemotherapy and radiation. She had a local recurrence excised a year later and remained disease free for the next 4 years of available follow-up. The authors did a literature search and reported that their patient was the seventh

patient in the literature with a BG leiomyosarcoma. For vulvar smooth muscle neoplasms, size greater than 5 cm, infiltrative margins, more than 5 mitoses per 10 high-power fields and moderate to severe cytologic atypia are criteria for consideration of malignancy, with 3 or more being malignant, 2 leading to a diagnosis of benign atypical leiomyoma, and 1 feature considered benign.[43,44] Local recurrence is not unexpected, and features such as larger size, anaplasia, more than 10 mitoses per 10 high-power fields, tumor cell necrosis, or involved margins are considered risk factors for more aggressive behavior and possible indicators for consideration of more than wide local excision.[43]

Epithelioid Sarcoma

Sarcomas of the vulva are extremely rare, and only a few vulvar epithelioid sarcomas have been reported, several in young white females.[45] One of these was a case of epithelioid sarcoma originally clinically diagnosed as a BD cyst and pathologically as an epithelial carcinoma in a 49-year-old woman. The case was staged at T2 N2 M0, and despite aggressive therapy, the patient died within 8 months. Characteristically, epithelioid sarcomas form sheets of polygonal epithelioid cells with vesicular nuclei, which stain for both epithelial membrane antigen and vimentin.[46] Vulvar lesions have behaved more aggressively than the classic distal type of epithelioid sarcoma seen in the extremities.[46]

LYMPHOMA

Tjalma et al.[47] have reported a 73-year-old woman with a primary non–Hodgkin lymphoma (NHL) in the BG, noting that lower genital tract NHL is most often associated with systemic disease.

LESIONS METASTATIC TO BD

A case of endometrial adenocarcinoma recurred in the site of a marsupialization of a BD cyst in a 53-year-old woman who had undergone the marsupialization simultaneous to the initial diagnostic dilatation and curettage, lending credence to the theory of tumor seeding as the etiology.[48]

Metastatic medullary carcinoma of the thyroid to the BG was reported in a patient with multiple endocrine neoplasia IIb (MEN IIb) and history of pheochromocytoma, neuroma, and medullary thyroid carcinoma.[49] She had been treated for 9 months with antibiotics for BG "inflammation" before wide local excision. She had been treated for medullary thyroid carcinoma approximately 18 years before the BG lesion.

Bilateral metastases of renal cell carcinoma to the 2 BGs was reported by Leiman et al.,[50] with primary diagnosis by fine needle aspiration biopsy. Breast carcinoma has also been reported metastatic to the BG.[51]

LESIONS MIMICKING BG ABSCESS OR CYST

Large or recurrent "BG" lesions may not be what they appear clinically, and malignancy must always be considered, particularly in the postmenopausal women, but in premenopausal women as well. Rarely, adolescents may have such lesions, as in the case of a 16-year-old with what was thought to be a BG cyst/abscess and turned out to be a myeloid sarcoma (also termed *granulocytic sarcoma*), a tumoral mass of the cells associated with leukemia. This lesion is exceptionally rare in the vagina, and has been reported before this case in adults.[52] Koc et al.[53] reported a case of a perineal leiomyoma thought to be a complex BG abscess on magnetic resonance imaging. Other lesions that occur on the vulva may also be mistaken for BG cysts/abscesses, such as the case of cellular angiofibroma described by Micheletti et al.[54] A vulvar cloacogenic adenocarcinoma presented as a recurrent BG infection as well.[55]

The very rare and potentially aggressive myoepithelial carcinoma of the vulva, not to be confused with the low-grade epithelial-myoepithelial carcinoma described by McCluggage et al.,[23] was reported to mimic a BG abscess in a pregnant woman.[56] Mirhashemi et al.[57] reported a vaginal small cell carcinoma in a 32-year-old mimicking a BG abscess. These lesions of myoepithelial cells usually arise in salivary glands but may also be seen in breast, skin, and soft tissue.[56]

Advanced Kaposi sarcoma of the vulva in a 38-year-old HIV-positive woman was clinically interpreted as a BG abscess initially. She had had 2 previous episodes of vulvar swelling, with incision and drainage and antibiotics, and underwent biopsy confirmation at final diagnosis, at which point she had metastatic disease.[58]

Benign neoplasms may also mimic BG cysts/abscesses. A schwannoma was reported in a 59-year-old woman[59] and a cellular blue nevus was reported in a 15-year-old woman,[60] both of whom were thought to have a BG abscess.

Bilateral new-onset hemorrhagic BD cysts were reported after cesarean delivery in a patient.[61] It is unclear why these lesions developed suddenly at this time.

One of the more unusual lesions masquerading as a BD cyst was the complete hydatidiform mole reported by Fambrini et al.[62] The patient had had a spontaneous abortion of a reportedly nonmolar gestation 8 weeks before undergoing laser carbon dioxide therapy for a presumed BD cyst. When grape-like tissue was seen on unroofing the supposed cyst, suction curettage and laser vaporization of the cyst was performed. The patient's β-human chorionic gonadotropin regressed to normal spontaneously after this therapy.

In summary, a variety of unusual lesions can occur in the BG. Owing to the rarity of BG malignancies in general, and some of the malignant lesions here described in particular, clinical suspicion may be low, and there may not be well-supported evidence for therapy. Because early diagnosis is the key for some of these potentially aggressive lesions, clinicians should have a low threshold for biopsy when a BG lesion occurs in an older woman or in any woman where the lesion recurs or fails to resolve.

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