Diagnosis and management of vulvar cancer: A review

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Vulvar malignancies represent a serious gynecologic health concern, especially given the increasing incidence over the past several decades. Squamous cell carcinoma and melanoma are common subtypes, although other neoplasms, such as basal cell carcinoma and Paget disease of the vulva, might be seen. Many vulvar cancers are initially misdiagnosed as inflammatory conditions, delaying diagnosis and worsening prognosis. It is essential that dermatologists are familiar with characteristic findings for each malignancy to ensure appropriate diagnosis and management. Herein, we review the unique epidemiologic and clinical characteristics of each major vulvar malignancy, as well as discuss their respective prognoses and current management recommendations. (J Am Acad Dermatol 2019;81:1387-96.)

Key words: basal cell carcinoma; melanoma; Paget disease; squamous cell carcinoma; vulva; vulvar cancer.

Over the past few decades, the overall incidence of vulvar cancer has increased by an average of 4.6% every 5 years; vulvar cancer caused 1200 deaths in 2018, and 6190 new cases are estimated to occur every year.[1,2] Although historically vulvar cancer peaks during the 7th decade of life, recent trends have been largely driven by increasing incidence of vulvar squamous cell carcinoma (SCC) in younger women.[3,4]

SCC is by far the most common vulvar malignancy, followed by melanoma.[3] Less commonly seen vulvar neoplasms include basal cell carcinoma (BCC) and Paget disease of the vulva. Diagnosis can be challenging, but early identification and management of these clinical entities is essential, as prognosis is generally favorable if diagnosed at an early stage. Herein, we review the epidemiology, clinical characteristics, prognosis, and treatment of major vulvar malignancies.

SQUAMOUS CELL CARCINOMA

Terminology

Vulvar carcinoma encompasses both invasive SCC and its precursor lesions. In the older nomenclature, precursor lesions (including high-grade premalignant disease and SCC in situ) were referred to as vulvar intraepithelial neoplasia (VIN)[5] and were subdivided into 2 categories. Usual-type VIN was associated with human papillomavirus (HPV) and observed mostly in younger women, and differentiated VIN (dVIN) was HPV-independent and predominantly seen after menopause.[5,6]

In 2015, the terminology was modified to be consistent with other HPV-associated lesions of the lower genital tract.[7] Under the current classification, HPV-associated precursors (formerly usual-type VIN) are called vulvar high-grade squamous intraepithelial lesions (HSILs), and non-HPV–associated precursors remain designated dVIN. Flat lesions associated with basal atypia and koilocytic changes (condyloma or HPV effect) are termed vulvar low-grade squamous intraepithelial lesions (LSILs).[7]

Vulvar HSILs are associated with risk for invasive SCC development in younger women because of its oncogenic HPV-related pathway. However, dVIN, which arises in the background of chronic inflammatory dermatoses, such as lichen sclerosus, is associated with an even higher risk for invasive malignant progression.[7]

Epidemiology

Vulvar SCCs (vSCCs) represent 90% of vulvar cancers and occur in 2-7 of every 100,000 women.[8,9] As mentioned, the incidence of vSCC has been

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increasing in younger women, with in situ lesions increasing at a faster rate than invasive SCC.[8,10] Proposed explanations for this trend include temporal shifts in sexual practices, changes in disease classification, and screening tests.[11] Vulvar HSILs, associated with oncogenic HPV subtypes in younger women, account for 43%-60% of vSCC.[12,13] Risk factors for progression include immunosuppression, smoking, and history of cervical cancer.

CAPSULE SUMMARY

- Many vulvar cancers are initially misdiagnosed as inflammatory conditions, delaying appropriate treatment. Given the steadily increasing incidence, misdiagnosis represents a serious gynecologic concern.
- Dermatologists should be familiar with vulvar malignancies and maintain a high threshold for suspicion during skin examinations. Early treatment and intervention generally lead to more favorable prognosis.

Clinical presentation and pathogenesis

Grossly, vSCC (including invasive and premalignant disease) can present as a raised, flat ulcerated plaque-like, polypoid, or warty mass on the vulva (Fig 1). Lesions might be skin-colored, white, erythematous, or pigmented.[12] Although many patients are asymptomatic at diagnosis, some experience pruritus, burning, pain, or bleeding, especially with invasive disease.[12,14] Vulvar HSILs tend to be multifocal, slow-growing, and have the potential for spontaneous regression.[15] The histologic subtypes are warty, basaloid, or mixed. If presenting as multicentric, 3-5 mm violaceous or erythematous papules, Bowenoid papulosis (which frequently self-resolves) might be suspected.[16] In contrast, dVIN arises in the setting of chronic inflammatory dermatoses and has a higher recurrence rate, worse prognosis, and more rapid progression to invasive vSCC than vulvar HSILs.[6,15,17]

vSCC is thought to have 2 distinct pathogeneses related to its subclassification. In HPV-positive vSCC, oncoproteins E6 and E7 lead to inactivation of tumor suppressor proteins p53 and Rb, respectively, and cell cycle protein p16ink4a is overexpressed.[18] In contrast, in HPV-negative vSCC, p16ink4a is not overexpressed, and p53 is expressed.[15,18]

Prognosis and management

vSCC has a combined clinical, surgical, and pathologic staging system on the basis of the American Joint Committee on Cancer and the International Federation of Gynecology and Obstetrics staging systems.[19] Lymph node involvement is the most significant prognostic indicator. Because of the prognostic implications of HPV infection, initial workup should include immunohistochemical staining for p53 and p16ink4a. Historically, the gold standard for treatment of vSCC was en bloc radical vulvectomy with bilateral inguinofemoral lymphadenectomy. Given the significant morbidity of this procedure, current practice involves wide local excision and sentinel lymph node biopsy with possible lymphadenectomy, which has comparable efficacy with decreased morbidity.[12,20] Adjuvant chemotherapy and radiation are also considered on an individualized basis, especially in patients who cannot be treated surgically.

Treatment of vulvar LSILs and HSILs varies depending on classification. As vulvar LSILs have low risk of malignant transformation, treatment is symptomatic or to prevent autoinoculation and sexual transmission. For vulvar HSILs, surgical excision, ablative therapy, and topical imiquimod are all comparable in efficacy.[7,21] Surgical excision remains the treatment of choice for dVIN, given its higher risk for malignant transformation.[15]

Current preventative efforts focus on immunization with the quadrivalent or 9-valent HPV vaccine, which has been demonstrated to decrease the risk of vulvar HSILs; the quadrivalent vaccine is protective against HPV genotypes 6, 11, 16, and 18 and the 9-valent vaccine against 6, 11, 16, 18, 31, 33, 45, 52, and 58.[7,22] As of October 2018, the 9-valent vaccine is approved by the US Food and Drug Administration for women and men aged 9-45 years. Addressing other risk factors, such as smoking and chronic vulvar dermatoses, also plays an important role in preventing vSCC.

MELANOMA

Epidemiology

After vSCC, vulvar melanoma is the second most common vulvar cancer, accounting for 5%-10% of all vulvar malignancies.[23] Incidence has been reported at <0.2 cases/100,000 women.[23] Though the vulva represents just 0.7% of total body surface area, ~2% of all melanomas in female patients occur on the vulva, making the vulva ~2.5 times more likely to develop a melanoma than other locations of the same surface area.[24] White women are most commonly affected, usually in their 5th to 7th decades of life.[23]

Abbreviations used:

BCC:	basal cell carcinoma
dVIN:	differentiated vulvar intraepithelial neoplasia
EMPD:	extramammary Paget disease
HPV:	human papillomavirus
HSIL:	high-grade squamous intraepithelial lesion
LSIL:	low-grade squamous intraepithelial lesion
SCC:	squamous cell carcinoma
VIN:	vulvar intraepithelial neoplasia
vSCC:	vulvar squamous cell carcinoma

Clinical presentation and pathogenesis

Vulvar melanoma commonly presents as a macule, papule, or nodule >6 mm in length, with markedly irregular borders and coloration (Fig 2).[24] Pruritus, bleeding, discharge, ulceration, or lymphadenopathy might occur.[23] The labia majora and clitoral area are the most common sites. In a study of 219 cases, nearly half of vulvar melanomas occurred on mucosal skin, 12% on hair-bearing skin, and 35% at the junction between mucosal and hair-bearing skin; 25% of cases were clinically amelanotic and more frequently in mucosal than hair-bearing skin.[24]

A study of 11 mucosal melanomas showed that the dermoscopic combination of structureless zones and blue, gray, or white coloration is highly predictive of melanoma,[25] but features such as polymorphous vessels and multiple colors should also raise suspicion.[26] Nonmucosal vulvar melanomas have been noted in small case series to have peripheral radial lines and thick reticular lines on dermoscopy.[27,28] Benign vulvar nevi typically show globular, homogeneous, and reticular patterns on dermoscopy, and vulvar melanosis can demonstrate parallel and ring-like patterns.[26,29] These benign entities are common, and not all pigmented vulvar lesions require biopsy.

Because the vulva is sun-protected, ultraviolet radiation is not thought to be a driver of vulvar melanoma. Histopathologic and genetic studies suggest that vulvar melanoma is more similar to acral lentiginous melanoma than to cutaneous melanoma.[29] Over half of vulvar melanomas are of the mucosal lentiginous subtype, 22% are nodular, and 4% are superficial spreading; this is the reverse of the order observed for other melanomas.[24] Vulvar melanomas also have a molecular profile distinct from that of cutaneous melanomas. Approximately 25% of lesions harbor *KIT* mutations, and *BRAF* and *NRAS* mutations are less common (although *BRAF* mutation rates as high as 26% have been reported).[30,31]

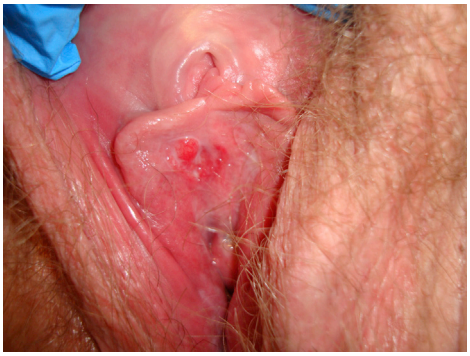

Fig 1. Invasive vulvar squamous cell carcinoma.

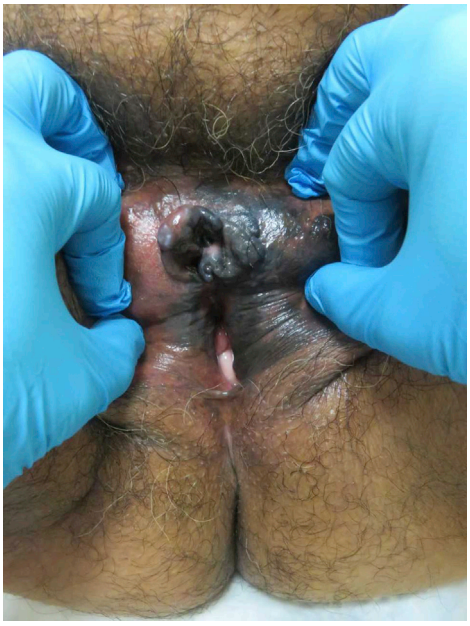

Fig 2. Vulvar melanoma.

Prognosis and management

Diagnosis of vulvar melanoma is often delayed due to its location and nonspecific symptoms. High recurrence rates and tendency to metastasize are commonly seen, and prognosis is generally poor with mean 5-year survival of 27%-60%.[9,32] Because vulvar melanoma typically develops in postmenopausal women who might no longer see a gynecologist, dermatologists are the first line of defense for screening and diagnosis. By offering a genital examination during regular skin examinations, vulvar melanomas might be detected earlier and poor prognosis improved. As with cutaneous melanoma, prognostic factors include tumor thickness, ulceration, and lymph node status.[33]

Surgery after histopathologic confirmation remains the mainstay of treatment. Despite the shift toward more conservative surgeries to decrease

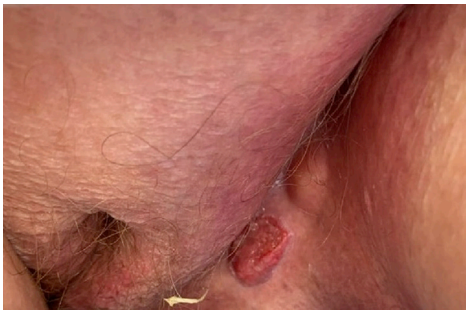

Fig 3. Vulvar basal cell carcinoma.

morbidity, the 5-year survival rate has remained relatively unchanged.[34] Data on adjuvant chemotherapy and immunotherapy have shown mixed results.[34-36] An improved understanding of molecular genetics has led to the development of targeted therapies for mucosal melanoma; though data is still limited, imatinib, a small-molecule inhibitor of KIT, could be a promising option.[37,38]

BASAL CELL CARCINOMA

Epidemiology

Although BCC is the most common skin cancer, vulvar lesions are rare; <0.4% of all BCCs occur in this region, and vulvar BCC accounts for only 2%-4% of all vulvar cancers.[39,40] Affected women are typically white, with a mean age of 70 years.[41]

Clinical presentation and pathogenesis

Vulvar BCC most commonly presents as a solitary pink or flesh-colored papule or plaque on the labium majus, but bilateral and multifocal lesions can occur (Fig 3).[42] Pigmentation is possible; 3% of vulvar BCCs in white women and up to 81% of vulvar BCCs in Chinese women are pigmented.[43] Symptoms, if present, are nonspecific and include pruritus, irritation, discomfort, pain, ulceration, and bleeding.[41] Dermoscopy of vulvar BCC reveals structures characteristic of extragenital lesions, such as blue-gray ovoid nests and globules, arborizing telangiectasias, leaf-like structures, white shiny areas, and ulceration.[43,44]

Although BCCs typically correlate with cumulative ultraviolet radiation, development on sun-protected areas like the vulva suggests other etiologies yet to be determined.[41] Immunosuppression, chronic irritation, pelvic radiation, and trauma might be contributing factors.[39] There are reports of vulvar BCC arising in the setting of Paget disease of the vulva,[42,45,46] lichen sclerosus,[42,47] and nevoid BCC syndrome.[48]

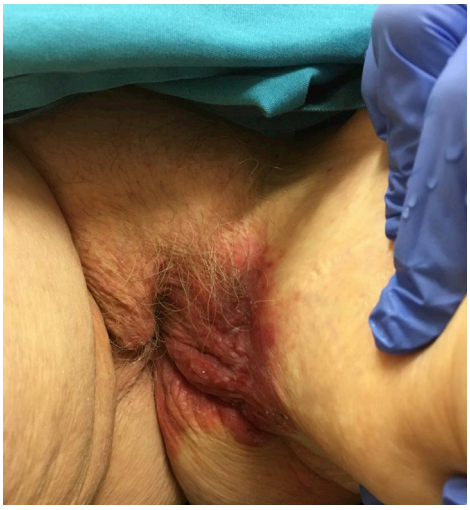

Fig 4. Paget disease of the vulva.

Prognosis and management

Like BCCs elsewhere, vulvar BCC has an extremely good prognosis and is characterized by indolent growth and low propensity for metastasis.[49] However, lesions can become locally invasive and destructive, if left untreated. Vulvar BCC can mimic inflammatory and infectious conditions, such as eczema, psoriasis, and chronic candidiasis.[39,43] Misdiagnosis can lead to inappropriate treatment and delay in intervention. In a clinicopathologic review of 51 lesions, mean size upon diagnosis was 1.85 cm, and 29.4% were ulcerated, suggesting delayed diagnosis is common.[39] Suspected lesions should be biopsied promptly.

As with cutaneous BCC, most vulvar BCCs are treated with surgical excision. Local recurrence has been reported at 10%-25%, possibly because of incomplete excision, inadequate surgical margins, or low overall incidence of vulvar BCC.[49,50] Given these high recurrence rates, Mohs micrographic surgery should be considered. Of the 15 documented cases of vulvar BCC treated with Mohs surgery, none have recurred, and the procedure is associated with better cosmetic and functional outcomes.[49,51]

PAGET DISEASE OF THE VULVA

Epidemiology

Vulvar extramammary Paget disease (EMPD) is an extremely rare gynecologic malignancy that represents only 1%-2% of vulvar malignancies.[52] Due to its rarity, the true incidence and prevalence remain unknown.[53] Vulvar Paget disease reportedly affects mainly postmenopausal women (of median age 72 years).[54]

Clinical presentation and pathogenesis

The characteristic lesion of vulvar EMPD is a well-demarcated patchy erythematous or eczematous plaque[53,55] with areas of both hypo- and hyperpigmentation; surface changes can include gray scale, crust, exudate, or ulceration (Fig 4).[55] The classic strawberries and cream description of vulvar Paget disease[56,57] is characterized by erythematous plaques with white islands and bridges of hyperkeratosis and cake-icing scale.[53,58] Patients commonly complain of longstanding pruritus and pain, though some remain asymptomatic for years. Lesions are typically multifocal and can occur anywhere on the vulva.[54]

Vulvar EMPD is classified by the origin of the neoplastic cells; primary lesions are malignancies of cutaneous origin within the vulvar epithelium, and secondary lesions result from the spread of a noncutaneous internal malignancy.[54,59] The pathogenesis of primary disease has not been completely elucidated. One hypothesis is that Paget cells originate from mammary-like glands in the interlabial sulci (between the labia majora and minora), perineum, or perianal area.[60] Another theory is that Toker cells (cytokeratin 7−positive clear cells)[61] are the precursors to both mammary and extramammary Paget disease.[62]

Prognosis and management

Paget disease of the vulva often follows an unpredictable clinical course, and intraepithelial lesions can be indolent or slow growing for many years. However, once dermal invasion occurs, it can rapidly and aggressively spread via lymphatic or hematogenous routes.[53] Because lesions can mimic a wide variety of conditions, misdiagnosis and substantial delay in diagnosis (average 2 years) is common.[53,55,63]

Management remains notoriously challenging. Diagnosis is confirmed by the histopathologic presence of Paget cells, although this does not distinguish between primary and secondary vulvar EMPD.[64] Immunohistochemical stains for cytokeratin 7 and 20, carcinoembryonic antigen, gross cystic disease fluid protein 15, and uroplakin III are needed to differentiate between the 2 subtypes.[64]

Associations with adenocarcinomas have also been reported; in a study of 100 patients with vulvar EMPD, 20% had primary nonvulvar malignancies (breast, pancreas, endometrium, bladder, stomach, and rectum), 4% had concurrent vulvar adenocarcinoma, and 12% had invasive vulvar Paget disease.[65] Long-term follow-up is indicated for vulvar EMPD patients given the high risk of recurrence and noncontiguous carcinomas. Besides yearly inspection of the vulva, management should include screening and surveillance for other malignancies, especially genitourinary, gastrointestinal, and breast cancers[66]; anorectal and urothelial adenocarcinomas are the 2 most common causes of secondary vulvar EMPD.[59]

Appropriate treatment differs between primary and secondary vulvar EMPD. Surgical excision is the standard treatment for primary disease, although reported recurrence rates range 12%-58%, regardless of margin status.[58,63,65] Importance of surgical margin status is controversial because there is a lack of concordance between gross and microscopic extent of the disease.[52,65] CO_2 laser ablation has been used successfully but might be associated with significant postoperative pain and a high recurrence rate.[63,67] Topical 5% imiquimod cream has been reported by multiple studies to induce complete response in vulvar EMPD.[68,69] Targeted therapy with trastuzumab plus paclitaxel has also been reported as successful with good long-term response, given the overexpression of human epidermal growth factor receptor 2 and neu in ~30% of vulvar EMPD cases.[70,71] Other treatments for primary disease, including adjunctive radiotherapy, photodynamic therapy, bleomycin, 5-fluorouracil, and combination treatments (eg, surgery followed by imiquimod or laser ablation) have had varying success.[72] As such, no one treatment protocol is universally efficacious.

In contrast, treatment for secondary vulvar EMPD involves a 2-pronged approach: treating the EMPD with superficial excision or ablation (as vulvar involvement is generally limited to the epidermis) and addressing the primary neoplasm.[59]

CONCLUSION

Vulvar malignancies have been increasing in frequency, especially HPV-associated vSCC in younger women. Many vulvar malignancies are initially misdiagnosed as inflammatory conditions, delaying their diagnosis and worsening their prognosis. It is important for dermatologists to be familiar with vulvar malignancies (Table I),[73-110] and consider them during skin examinations and when patients present with nonspecific vulvar symptoms. This is especially important when lesions do not respond to treatment as expected. Dermatologists should aim to minimize further delay in making the correct diagnosis, as early treatment and intervention generally leads to more favorable prognosis. Understanding the epidemiologic, clinical, and prognostic characteristics of each clinical entity can facilitate appropriate diagnostic and management decisions.

Table I. Malignant neoplasms of the vulva

Type[73,74]	% Reported vulvar cancers (no. cases)	Typical location	Age range, decade	Clinical presentation
Epithelial tumors				
Keratinocytic tumors				
Basal cell carcinoma[42-44,49,50]	2-4	Labia majora	7th	Solitary pink or flesh-colored papule or plaque; can also be pigmented, bilateral, or multifocal; might have ulceration or hemorrhage
Squamous cell carcinoma[8,9,12,13]	90	Labia majora	6th-7th	Raised, flat ulcerated, plaque-like, polypoid, or warty mass that can be skin-colored, white, erythematous, or pigmented; might have hemorrhage with invasive disease
Glandular tumors				
Paget disease (EMPD)[53-58]	1-2	Anywhere on vulva	7th	Strawberries and cream appearance: patchy, erythematous, or eczematous well-demarcated plaque with hypo- and hyperpigmentation and scale, crust, exudate, or ulceration; typically multifocal
Bartholin gland carcinoma[75,76]	2-7	Posterior half of the vulva	5th-6th	Painless mass in the posterior half of the vulva and deep in the labia; less frequently has bleeding, burning, or pruritus; can be mistaken for Bartholin gland abscess or cyst
Adenocarcinoma, mammary gland type[77,78]	<1 (30-40)	Labia majora	4th-8th	Erythematous and tender nodule, frequently with ulceration; 60% have regional lymph node metastasis at time of presentation
Adenocarcinoma, Skene gland origin[79-81]	<1	Periurethral region	4th-7th	Large (>2 cm) solitary mass with areas of hemorrhage and necrosis, confined to the periurethral region; one-third of patients have palpable lymph nodes, and >90% are metastatic at diagnosis
Adenocarcinoma, intestinal type[82-84]	<1 (12)	Vulvar vestibule	4th-7th	Exophytic, indurated, reddish nodule with pruritus
Adenocarcinoma, sweat gland type[85,86]	<1	Labia majora	5th-7th	Painless slow-growing papule or nodule in the vulvar skin; might have pruritus or erythema
Sebaceous carcinoma[77,87,88]	<1 (12)	Labia majora	3rd-8th	Yellow-tan firm ulcerated nodules; can be found in the setting of Muir-Torre syndrome or overlying Bowen disease
Phyllodes tumor, malignant[89-91]	<1 (5)	Labia majora	3rd-6th	Exophytic rapidly growing nodule with ulcerated surface and necrosis; might be pedunculated

Neuroendocrine tumors				
High-grade neuroendocrine carcinoma[92-94]	<1 (1-2)	Labia majora	7th-8th	Erythematous mass with superficial erosion; might have pruritus or pain; typically small cell carcinoma subtype
Merkel cell tumor[95]	<1 (17)	Labia majora	3rd-7th	Rapidly growing, firm mobile mass (average 7.5 cm); might have pain, erythema, pruritus, edema, or ulceration
Melanocytic tumors				
Melanoma[24,25,29]	5-10	Glabrous skin or hairy-glabrous junction	5th-7th	Macule, papule, or nodule >6 mm with irregular borders and coloration; might have ulceration or bleeding
Neuroectodermal tumors				
Ewing sarcoma[96,97]	<1 (19)	Labia majora or labia minora	1st-4th	Painful, firm, rapidly enlarging mass (average 5.8 cm) with smooth, well-defined contours
Soft tissue tumors				
Sarcomas[98-100]	1-3	Labia majora, although can involve the clitoris or Bartholin glands, depending on sarcoma subtype	2nd-6th	Asymptomatic vulvar mass; might have nonspecific local discomfort; if longstanding or in advanced stages, might have pruritus, pain, bleeding, or ulceration
Germ cell tumors				
Yolk sac tumor[101,102]	<1 (16)	Right labium majus	Birth-3rd	Painless firm labial mass (average 4.2 cm); preference for the right labium majus, although can occur on the left
Lymphoid and myeloid tumors				
Lymphomas[103-106]	<1 (30-40)	Labia majora or labia minora	4th-7th	Enlarging vulvar mass; sometimes confined to the clitoris or Bartholin gland; widespread destruction of vulvar or perineal areas might occur if left untreated; primarily non-Hodgkin lymphoma
Myeloid neoplasms[107]	<1 (8)	Labia majora	1st-7th	Rapidly enlarging, firm, nontender vulvar mass; might be isolated or precede, coincide with, or represent a relapse in acute myeloid leukemia
Secondary tumors				
Metastases from other primary malignancies[108-110]	5-8	Labia majora	3rd-7th	Progressively enlarging, singular or multiple nodules or masses in the setting of primary cancer at nonvulvar sites (ie, breast, cervix, ovary, endometrium, kidney, colon); might have ulceration, pain, swelling, bleeding, or discomfort

EMPD, Extramammary Paget disease.

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