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Journal of Skin and Sexually Transmitted Diseases

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Vulvar premalignancies – A dermatologist's perspective

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Received: 15 April 2021
Accepted: 21 July 2021
EPub Ahead of Print: 30 April 2022
Published: 14 October 2022

DOI
10.25259/JSSTD_32_2021

Quick Response Code:

ABSTRACT

Vulvar malignancies are rarely encountered in dermatology, yet it is imperative to develop a thorough clinical and diagnostic acumen, as early detection and appropriate treatment can improve quality of life or even prevent fatal outcome. The common premalignant vulvar lesions are vulvar intraepithelial neoplasia (VIN), vulvar Paget's disease, and melanoma *in situ*. These are notable since they are associated with a high post-treatment recurrence rate. The incidence of VIN is increasing in younger women. Early diagnosis and tailoring the management on individual basis may help to reduce the long-term morbidity. This review describes etiology, clinical features, management, and prognosis of vulvar premalignancies.

Keywords: Vulva, Vulvar intraepithelial neoplasia, Human papilloma virus, Vulvar Paget's disease

INTRODUCTION

Premalignant lesions of the vulva are seen in pre- as well as post-menopausal adult women. These lesions lack a typical clinical presentation and often remain undiagnosed till advanced invasive stages. A careful clinical examination and biopsy of suspicious lesions are imperative for accurate diagnosis. Psychological and psychosexual counseling should be an integral part of management. Herein, we discuss the etiopathogenesis, clinical features, and management of common vulvar premalignancies, namely, vulvar intraepithelial neoplasia (VIN), Paget's disease, and melanoma *in situ* (MIS).

VIN

VIN is a non-invasive precursor of squamous cell carcinoma (SCC). The term was first introduced in 1982. The International Society for the Study of Vulvovaginal Diseases (ISSVD) subclassified VIN into VIN 1, 2, and 3, respectively, showing mild, moderate, and severe atypia/carcinoma *in situ*. A modification proposed in 2004 included two types of VIN: "VIN, usual type, (uVIN) human papilloma virus (HPV) related," and "VIN, differentiated type, (dVIN) HPV unrelated." VIN, usual type comprised three histopathological types – warty, basaloid, and mixed (both warty and basaloid).[1]

A further modification was put forth by ISSVD in 2015 to classify vulvar squamous intraepithelial lesions (SILs).[1]

- Low-grade SIL (LSIL) of the vulva (vulvar LSIL, flat condyloma, or human papilloma virus effect)
- High-grade SIL of the vulva (vulvar HSIL, uVIN)
- dVIN

It was further recommended by the ISSVD executive council that the previous terminologies of VIN may be replaced by the 2015 modification, but this has not been widely accepted, and to date, the terminology VIN is in use.[1] uVIN is associated with HPV whereas dVIN is associated with inflammatory vulvar pathology such as lichen sclerosus (LS) and lichen planus (LP). Although less common (only up to 5% of total), dVIN is more likely to progress to invasive SCC, if left untreated.

Epidemiology

uVIN is more common at younger age, while dVIN occurs in older women. Incidence of HPV-associated VIN is on the rise, with the highest frequency in women of 20–35 years.[2]

Risk factors

The purported risk factors include multiple sexual partners, cigarette smoking, and immunocompromised individuals such as organ transplant recipients and those with human immunodeficiency virus infection.

Etiopathogenesis

The association between HPV and vulvar neoplasia was reported for the first time by Charlewood and Shippel in 1953. Further reports have since then established the malignant transformation of vulvar condyloma acuminata.[3] The prevalence of HPV in VIN ranges from 72% to 100% and is strongly associated with uVIN.[4] HPV 16 is the most common type (77.2%) followed by HPV 33 (10.6%) and HPV 18 (2.6%).[5] HPV deoxyribonucleic acid (DNA) is more commonly associated with multifocal VIN and VIN coexisting with other multicentric intraepithelial lower genital tract lesions. HPV viral DNA integrates into host cells, resulting in the production of oncoproteins E6 and E7 which interfere with normal cellular function.[6]

dVIN shows *de novo* tumor suppressor protein (p53) genetic alterations unrelated to HPV. Mutations in p53, phosphatase, and tensin homologue tumor suppressor gene and microsatellite instability are demonstrated in HPV independent carcinogenesis.[7] Loss of expression of the tumor suppressor GATA-binding protein 3 (GATA3) is seen in all SCC associated with uVIN and in 81% of those associated with dVIN.[8] GATA3 immunohistochemistry along with p53 may be a useful tool in accurate diagnosis of VIN.

Vulvar carcinogenesis and severity thereof are associated with DNA methylation, emphasizing the potential of DNA methylation biomarkers in the diagnostic workup of VIN.[9]

Clinical features

uVIN is seen on hair bearing areas of labia majora and appears as a raised, well-demarcated asymmetrical whitish to erythematous plaque [Figure 1]. It may be asymptomatic or may present with pruritus, pain, burning, and dysuria.

dVIN presents as a unifocal, rough surfaced, gray-white discoloration, or an erythematous lesion with or without ulceration; occasionally, it can present as ill-defined whitish plaques. It is often associated with LS and LP. Early detection and proactive management of LS may reduce the risk of VIN.

Differences between uVIN and dVIN are given in Table 1.

Differential diagnoses to be considered include condyloma acuminata, condyloma lata, lichen simplex chronicus, LS, LP, vulvovaginal candidiasis (VVC), and Paget's disease of vulva.

Investigations

Colposcopy

Colposcopy is indicated in subclinical lesions with persistent pruritus and pain. It helps to identify additional lesions in lower genital tract and perineal area in patients with VIN.[10]

Dermoscopy

Dermoscopy helps to differentiate infective and inflammatory conditions of the vulva and aids in avoiding unnecessary biopsies. The recognition of specific dermoscopic patterns may improve the diagnostic accuracy in vulvar diseases, especially in early phases.

Table 1: Differences between uVIN and dVIN.

Characteristics	uVIN	dVIN
Age	Young women	Older women
Distribution	Multifocal	Unifocal
Etiology	Related to human papilloma virus, mainly 16, 18, 33	Not related to human papilloma virus. Associated with lichen sclerosus and lichen planus
Risk of malignancy	20% changes to invasive cancer	80% changes to invasive cancer
Histopathology	Atypia involving two-thirds to full thickness of the epidermis of the vulva	Atypia confined to the basal layer of epidermis
Immunohistochemistry	p53 negative p16 positive	p53 positive p16 negative

uVIN: Usual vulvar intraepithelial neoplasia, dVIN: Differentiated vulvar intraepithelial neoplasia

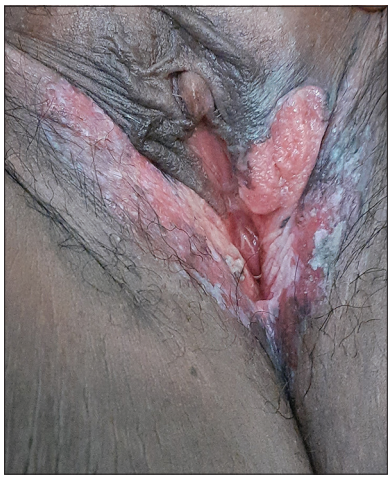

Figure 1: Usual vulvar intraepithelial neoplasia (high-grade squamous intraepithelial lesion) showing, indurated plaque involving the left labia and whitish plaques near the fourchette and labial commissure.

In uVIN, dermoscopy shows numerous white dots surrounded by glomerular vessels with irregular patchy distribution. Focal structureless, bluish-brown areas, and peripheral gray-blue/brownish dots arranged in a linear fashion are seen.[11]

Dermoscopy of dVIN shows pink to red, structureless, background with red areas due to superficial erosions and vascular structures (consisting of curvy, short, serpentine, and dotted vessels).[12]

Histopathology

Indications for biopsy include:

- Any vulvar lesion not responding to empiric therapy
- Rapid change in color, size, and border
- Suspected condyloma which is resistant to topical therapy
- Post-menopausal women with apparent genital warts.

Multiple lesions may need multiple biopsies.

uVIN shows epidermal hyperkeratosis and parakeratosis. There is loss of cell maturation with nuclear hyperchromasia, high nuclear-to-cytoplasmic ratio, pleomorphism, and numerous mitotic figures at all levels of the epidermis. Warty type shows papillomatous projections with wide and deep rete ridges.[13] Basaloid type has flat surface with diffuse proliferation of small, undifferentiated, basaloid cells. Mitotic figures are numerous, but koilocytes are less than the same in warty type. If the same histopathology specimen has manifestations of both basaloid and warty patterns, it is reported as mixed VIN.

Histopathology findings in dVIN are epidermal hyperplasia with parakeratosis and atypical keratinocytes restricted to basal and parabasal layers. Nuclear pleomorphism, hyperchromatism, and mitoses are seen. Macronuclei and angulated nuclei are most specific for dVIN and useful to differentiate it from the reactive nuclear enlargement seen in LS and non-neoplastic epithelial disorders. Staining with MIB1 and p53 is helpful to differentiate dVIN from normal epithelium.[14]

Immunohistochemistry

dVIN is p53 positive and p16 negative while uVIN is p53 negative and p16 positive. In a study by Takacs *et al.*, all VIN and vulvar cancers were sec62/ki67 and p16/ki67 dual stain positive whereas normal cells and LSILs stained negative.[15]

Treatment

The ideal treatment for VIN aims at complete destruction of the lesion while preserving the vulvar architecture and function. Treatment modality depends on the type, size, number, location, extent of the disease, and risk of invasive malignancy.

Treatment options in uVIN include wide local excision, vulvectomy, laser ablation, topical treatment, photodynamic therapy (PDT), and therapeutic HPV vaccination.

Surgical excision is the treatment of choice in dVIN.

Wide excision including 1 cm normal margin is indicated in raised, ulcerated lesions with irregular borders. Positive epithelial margins are a risk factor for recurrence.[16] Removal up to underlying dermis helps to prevent early invasive disease.

Skinning vulvectomy

Skinning vulvectomy may help when topical treatments, laser ablation, and smaller excisions fail. It is also the treatment option in multifocal, large VIN lesions with extensive involvement. Here, vulvar skin is removed along a relatively avascular plane beneath the epidermis, preserving the subcutaneous tissue.[17]

Extensive surgery can diminish the quality of life and sexual function leading to significant somatic and psychosexual morbidity. If clitoris, urethra, or anus are involved, excision may impair the functions.

Laser ablation

Laser ablation is preferred in non-hair bearing areas and is attempted for single as well as multiple or confluent lesions. Recurrence rates are comparatively higher. Taking multiple biopsies are a safe method to exclude invasive disease before the procedure.

Carbon dioxide (CO2) laser surgery permits outpatient treatment under local anesthesia with excellent cosmetic and

functional results.[18] Argon beam coagulation has also been tried in uVIN.[19]

Topical treatment

The major advantage of topical treatment is the preservation of vulvar anatomy and function.

Imiquimod

Imiquimod acts by binding to toll-like receptors on the cell surface of dendritic cells and inducing secretion of pro-inflammatory cytokines. It has antiviral and antitumor properties. Local irritation, erythema, and erosions may occur. Hence, gradual escalation in doses is advised (once a week for 2 weeks, twice weekly for 2 weeks, followed by thrice a week). Minimum 16 weeks of treatment is recommended. Complete response rates range from 5% to 88%.[20] Recurrence rate is 27%.[21] Imiquimod appears to be an effective therapy for uVIN, but further studies are needed.

Topical 5-Fluorouracil (5-FU)

5-FU is useful in uVIN and has up to 74% success rate.[22] It causes burning, pain, edema, and ulceration, and is poorly tolerated.

Cidofovir

Cidofovir is a nucleoside analog with antiviral properties. The RT3VIN trial in 180 VIN patients found cidofovir and imiquimod as active, safe, and feasible options for VIN and recommended a Phase 3 trial.[23]

PDT

PDT is beneficial in treating multifocal disease without tissue loss. Advantages are short healing time, minimal tissue destruction, preservation of vulvar anatomy and excellent cosmetic outcome.[24]

Combined therapy

Combined treatment with superficial shaving and 5-amino levulinic acid-PDT may be a safe and effective option in women with VIN who want to preserve their vulvar architecture; especially in those with large, multifocal, high grade lesions and in repeated recurrences.[25]

HPV vaccination

Prophylactic HPV vaccines reduce premalignancies and malignancies. Bivalent vaccine targets high-risk HPV types 16 and 18, but has not been studied for prevention of VIN. Quadrivalent vaccine targets 16, 18, 6, and 11 and is found to decrease the risk of VIN. Newer recombinant nanovalent vaccine targets HPV serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58. Systematic review of randomized controlled trials indicates that available HPV vaccines are safe and effective for the prevention of infection. Post-vaccination, HPV clearance ranges from 8% to 74%.[26] However, evidence for efficacy of HPV vaccine in the treatment of VIN is insufficient and is of low quality.

Prognosis

If left untreated, VIN may persist, progress, or resolve. In a study including 88 VIN patients, 9% progressed to invasive carcinoma during a period of 1–8 years.[27] Risk factors for invasive SCC are smoking, older age group, multifocality, larger size, raised lesions, positive surgical margins, and basaloid type uVIN.[4] dVIN has a high risk of progressing to SCC (33% as compared to 5.7% for uVIN).[28]

Recurrence

Follow-up of 784 patients treated for high-grade VIN for 89 months revealed a recurrence rate of 26.3%. About 8.2% of patients progressed to invasive cancer.[29] Risk factors for recurrence were age >50 years, tobacco smoking, and immunosuppression.

Long-term surveillance is mandatory in cases of VIN.

Terminologies like Bowen's disease of vulva are no longer used to subclassify *in situ* SCC.[30]

BOWENOID PAPULOSIS (BP) OF THE VULVA

BP represents a form of *in situ* SCC and is associated with oncogenic HPV types 16, 18, 31, and 33. BP commonly occurs between the third to fifth decades of life with a mean age of 31 years in sexually active women.[31]

Clinical features

BP appears as well-demarcated, solitary to multiple, reddish-brown to violaceous papules with flat, smooth or verrucous surface over labia majora, minora, clitoris, inguinal folds, and inside the vagina and perianal area. Lesions are usually asymptomatic, but may be pruritic or sore**.** BP clinically resembles genital warts, but is histologically similar to Bowen's disease.

Differential diagnosis

Genital warts, psoriasis, LP, condyloma acuminata, seborrheic keratosis, and pigmented Bowen's disease are to be differentiated. Histopathology aids in confirming the diagnosis.

Dermoscopy

Brown and gray dots with linear arrangement and glomerular and dotted vascular structures are the common findings.[32] Other signs reported are whitish-red, exophytic papillary structures.

Histopathology

Histopathology features are hyperkeratosis, acanthosis, and cellular atypia of the full thickness of epidermis with crowding and windblown arrangement of nuclei. Scattered dyskeratotic and pleomorphic multinucleate keratinocytes are seen. Basement membrane integrity is preserved.

The differentiating features from uVIN (previously Bowen's disease) are multiple circumscribed papules and plaques, and histology showing less dyskeratosis and atypia and dilated dermal vessels.[31] Immunostaining with p16 protein has high sensitivity and specificity in detecting BP.[33]

Treatment

Topical treatment with 5-FU, imiquimod, podophyllin, cidofovir, and interferon beta gives good success rates.[33] Electrocautery, cryosurgery, CO2 laser vaporization, and 5-aminolevulinic acid-PDT are equally efficacious. Topical and systemic retinoids are also tried.

If left untreated, lesions may either spontaneously regress or persist for years. Evolution to SCC occurs mostly in immunocompromised patients.

PAGET'S DISEASE OF THE VULVA

Extramammary Paget's disease (EMPD) is a rare, premalignant, intraepithelial adenocarcinoma. Vulva is the most common site affected. The WHO defines vulvar Paget's disease (VPD) as "An intraepithelial neoplasm of epithelial origin expressing apocrine or eccrine gland-like features and characterized by distinctive large cells with prominent cytoplasm referred to as Paget's cells." VPD can be primary or secondary. Primary disease arises on the vulva and secondary VPD arises from a malignancy of gastrointestinal tract or urogenital tract. VPD is seen between the sixth and eighth decades of life with a mean age of 65 years.

Wilkinson and Brown classification of VPD is given in Table 2.[34]

Table 2: Classification of VPD by Wilkinson and Brown.

Primary (cutaneous) VPD	
Type 1a	Cutaneous vulvar non-invasive disease
Type 1b	Invasive disease with dermal invasion
Type 1c	Cutaneous vulvar disease as a manifestation of underlying vulvar adenocarcinoma
Secondary VPD	
Type 2	Originates from rectal or anal adenocarcinoma
Type 3	Originates from urogenital neoplasia

VPD: Vulvar Paget's disease

Clinical features

VPD is multifocal and asymmetrical. VPD often affects labia majora and may extend to inguinal folds and perianal area. Labia minora, introitus, and vagina are rarely involved. The lesions may be asymptomatic or may show pruritus, burning, pain, and edema.[35] The primary lesion can be an erythematous, scaly plaque or weepy, crusty erosions, and ulcerations.[36] Hypo or hyperpigmentation, infiltrating nodules, and vegetative lesions with lymphadenopathy may also occur. Scattered areas of erosion and white scale give rise to "strawberries and cream" appearance. Paget's disease starting in the groins and spreading peripherally to areas covered by underwear is a distinct clinical feature of EMPD known as "underpants-pattern erythema." It has an ominous prognosis with rapidly fatal distant metastases.[37]

Differential diagnosis

VVC, psoriasis, lichen simplex chronicus, LS, eczematous dermatitis, VIN, SCC, and melanoma are to be differentiated.

Investigations

Dermoscopy

Although heterogeneous patterns mimicking other conditions like inflammatory dermatoses and melanoma are seen, presence of thick polymorphic vessels diffusely arranged throughout a pinkish-red background with milky red areas, and presence of dotted glomerular vessels improve the diagnostic accuracy of Paget's disease.[38-40]

Histopathology

The histopathology findings are epidermal acanthosis, parakeratosis, and hyperkeratosis. Paget's cell is the pathognomonic cell found in the epidermis, mostly near the basement membrane zone, and is a large, round cell with abundant, pale staining basophilic cytoplasm with a large, central nucleus and a prominent nucleolus.[41] Ulceration, pigmentation, and chronic inflammatory dermal infiltrate may be seen. Clear cells of Toker are intraepithelial cells with clear to pale staining cytoplasm associated with apocrine glands, and are considered as precursors of primary EMPD.[42]

Immunohistochemistry

Immunohistochemistry can differentiate primary and secondary forms of EMPD as well as assess the invasiveness. Primary EMPD is positive for cytokeratin (CK)7 and gross cystic disease fluid protein-15 (GCDFP-15) and negative for CK20. Secondary EMPD is CK20 positive and negative for both CK7 and GCDFP-15.[36] CK19 fragment 21-1 (CYFRA 21-1) is used to assess disease progression and treatment efficacy in EMPD.[43]

Screening for genitourinary, gastrointestinal, and breast diseases is warranted in VPD. Cervicovaginal smears, colposcopy, cystoscopy, colonoscopy, abdominal ultrasound, computed tomography scan, and mammography are done to rule out internal malignancies. Serum carcinoembryonic antigen (CEA) is assessed in invasive EMPD.[36]

Treatment

Mainstay is surgical procedures such as local excision, simple or radical vulvectomy, and Mohs micrographic surgery. Conservative approach with CO2 and neodymium-doped yttrium aluminum garnet lasers is useful in EMPD.[44] PDT alone or in combination with other modalities is tried. Topical 5% imiquimod cream, 5-FU, and bleomycin are also tried. Radiation therapy and chemotherapy are other options. Targeted therapy with trastuzumab is a new treatment for VPD showing overexpression of human epidermal growth factor receptor-2.[45]

Prognosis: Presence of dermal invasion, elevated CEA levels, presence of nodules in the primary lesion, and bilateral lymph node metastases are bad prognostic factors.[46]

MELANOMA IN SITU

MIS is rare on the vulva, but has a definite risk of progression to invasive melanoma.[47] Hence, all doubtful pigmented lesions of the vulva should be biopsied. If melanoma is suspected, excisional biopsy with 5 mm clinically normal margin of skin is recommended, as it can be curative too.[48]

CONCLUSION

The incidence of vulvar premalignancies, especially VIN, is increasing; so dermatologists should approach any atypical vulvar lesion with suspicion. Early diagnosis is of utmost importance to prevent invasive malignancy. Treatment is best accomplished by an interdisciplinary approach. Lifelong surveillance is essential as recurrences are common in all vulvar premalignancies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Kavitha A, Deeksha P. Vulvar premalignancies – A dermatologist's perspective. J Skin Sex Transm Dis 2022;4:180-7.