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Review Article

A scope of histomorphology of vulval lesions: A review

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Abstract

Frequencies and incidence rates of vulval tumours and other pathological lesions are reported regularly in different studies but are mostly limited by histological examination. The vulval lesion may be benign, premalignant or malignant. The vulval abnormalities have variability in presentation. Because multiple diagnoses may have similar gross characteristics, histological evaluation is very important in establishing an accurate diagnosis. The aim of this review is to describe the spectrum of vulval lesions. Results: Different studies reported a wide range of vulval lesions, benign lesions like psoriasis, eczema, allergic dermatitis, epidermal inclusion cyst, condyloma aluminium, vestibular papilloma, fibroepithelial polyp, seborrheic, inverted follicular keratosis and keratoacanthoma. Premalignant lesions are VIN VIN2/3 or H-SIL, and malignant lesion nonkeratinizing squamous cell carcinoma HPV-depended and VIN (d-VIN, VAAD & DEVIL) and malignant lesions keratinizing squamous cell cancer HPV-independent. The vulval includes a spectrum of benign, premalignant, malignant and unusual lesions with different clinicopathological features. The histological examination requires further confirmation and categorization.

Keywords: Benign tumours, Malignant, Vulva lesions, Premalignant, Squamous cell carcinoma.

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1. Introduction

Based on histomorphology, there is a scope/spectrum of vulval lesions as benign, premalignant and malignant. The vulval pathology had variability in presentation. Because multiple diagnoses may have similar gross characteristics, histological evaluation is very important in establishing an accurate diagnosis. Histological classification is based on the tissue of origin, etiological factor and morphology of vulvar lesions. Platz and Benda (1995) studied female genital cancers in the United States and observed that squamous cell carcinoma was the most common invasive malignancy of the cervix (77.1%), vulva (74.4%), and vagina (70.8%).[1] The vulva is formed by the labia majora, labia minora, clitoris, mons pubis and the associated structures of the vestibule, including the urethral meatus. Tumours of the vulva are generally classified into squamous, glandular, melanocytic, and mesenchymal neoplasms.[2] Benign tumours of the vulva include condyloma aluminium, vestibular papilloma, and fibroepithelial polyp.[3] Vulvar squamous cell carcinoma is the fourth most common type of gynaecological cancer and affects the external female genitalia.[4] It accounts for approximately 3–5% of all gynaecological malignancies, with an incidence rate of 1–2/100 000.[4] Primary squamous cell carcinoma of the vulva occurs most frequently in the older age group. The incidence rates are 1:100000 in younger women and 20:100000 in elderly women.[5] Persistent infection with the non-oncogenic, so-called low-risk, human papillomavirus types (mainly types 6 and 11) may cause genital warts (condylomata acuminata).[6] The clinical features of benign tumours may overlap with malignant neoplasms. Therefore, a biopsy/histopathological examination is often necessary to make a definitive diagnosis and classification.

The aim of this study is to describe the histomorphological spectrum of vulval lesions in an educational approach.

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1.1. The types of vulval lesions

Broadly vulval lesions are divided into three types 1) Benign lesions, 2) premalignant lesions and 3) Malignant lesions on the basis of histomorphology.

1.1.1. Benign lesions of vulva

Clinically benign lesions are mostly asymptomatic; patients are usually noted in advanced conditions. Various skin lesions like psoriasis, eczema, and allergic dermatitis can be involved in the vulva also. Vulva is regularly exposed to secretions and wetness because it gets infected frequently. Different studies described benign lesions of the vulva as uncommon to 76%.[7,8] Benign lesions and tumours of the vulva include nonspecific vulvitis (in immunocompromised patients), benign exophytic lesions, epidermal inclusion cyst, condyloma aluminium, vestibular papilloma, fibroepithelial polyp, seborrheic and inverted follicular keratosis and keratoacanthoma.[3] Ullah et al. reported Lichen sclerosis (45%) and squamous papilloma (40%) as the most frequent benign conditions.[8] Pathak et al. reported vulvar lesions as vulvar dermatoses (62.85%), pruritis vulvae (36.19%) and vulvodynia (0.95%) based on clinical presentation.[9] Maldonado et al. reported common benign lesions of the vulva as Bartholin gland cysts or abscesses, epidermoid inclusion cysts, and angiomas.[10] Few studies reported some syndromes of benign lesions such as Reiter's syndrome and autoimmune blistering diseases of the vulva.[11,12]

1.1.2. Premalignant lesions of vulva

Pre-malignant lesions are defined as the precourse of cancer. Pre-malignant lesions of the vulva include VIN (vulval intraepithelial neoplasm), and Paget's disease. Bamberger et al. reported that benign and pre-malignant vulvar lesions be broadly divided into non-neoplastic epithelial disorders of the vulva (NNEDV), vulvar intraepithelial neoplasia (VIN) and Paget's disease of the vulva (PDV).[13] NNEDV lesions include lichen sclerosis (LS), lichen simplex chronicus (LSC) and squamous hyperplasia (SH).[13] Pre-malignant lesions of the vulva clinically present pruritis in most cases. Léonard et al. reported that 50% patients of VIN lesions were asymptomatic.[14] Wallbillich et al. reported pruritus as the most common presenting symptom of VIN.[15] Premalignant lesions are basically clinically present as warty, which arises from VIN.[16]

1.1.3. Malignant lesions of vulva

Malignant lesions of the vulva are uncommon, representing only 3% of all female genital tract malignancies.[16] Malignant lesions of the vulva in more than 75% of women described an average of 60 years.[16] Few studies reported that the usual age of vulval carcinoma at presentation is 60–74 years in the literature.[5,17] Narula et al. also described that malignant lesions of the vulva were associated with a higher age group than benign lesions.[9] Vulvar carcinoma occurs infrequently in younger women and adolescents.[18] The most common malignant tumour of the vulva was keratinizing squamous cell carcinoma.[8,19] Squamous carcinoma is further divided into keratinizing and non-keratinising types based on cytoplasmic keratinization. Narula et al. reported that most of the squamous cell carcinoma of the vulva were large cell non-keratinizing type, and only 2.9% of squamous cell carcinoma were large cell keratinizing type.[9]

1.2. Aetiology factors for vulval lesions

Benign lesions of the vulva are mostly associated with acute and chronic inflammatory aetiology like Bartholin cytes due to infection in the Bartholin gland, various dermatoses (psoriasis, chronic dermatitis) and Condyloma acuminatum due to infection of low-grade HPV (human papillomavirus) type 6 and 11 infections.[16]

Pre-malignant lesions of the vulva like VIN, wary lesions, Bowen disease, Paget's disease and basaloid carcinoma. Carcinoma in situ/VIN/ Bowen disease associated with reproductive age groups and HPV infections of type 16 in women who have early-age sexual activity, sex with multiple partners and sex with males who has multiple sexual partners.[16,20] Cigarette smoking is an established risk factor for VIN 2/3 incidence.[21,22]

SCC (squamous cell cancer) of keratinizing type arises from lichen sclerosis or squamous hyperplasia for a prolonged duration.[16,21] In contrast to many studies stating that keratinizing-type invasive carcinomas have no association with HPV, Demiralay et al. reported a strong p16 positivity in 3 ISCCs (invasive squamous cell carcinoma) which were morphologically keratinizing type.[21-23] WHO 2020 is the latest classification of the female genital tract is classified as a vulval tumour based on aetiology. The vulval tumours are classified as HPV-associated and HPV-independent.[24] HPV-associated vulval neoplasms included VIN-1 low grad and VIN-2 &3 as high grades retained in WHO 2020 classification as such.[24]

HPV-independent VIN has three different morphology 1-d-VIN (differentiated), 2-DEVIN (exophytic differentiated) and 3-VAAD (altered differentiation).[25] Persistent infections with oncogenic, so-called high-risk, human papillomavirus types (mainly types 16, 18, 31 and 45) may cause premalignant and malignant lesions of the uterine cervix, the vagina and vulva in women[26] Spencer et al. reported a persistent vulvar ulcer as the presenting complaint in 11 (13.8%) of 80 women with squamous cell disease.[27] The p53 mutation/ alteration is associated mostly with HPV-independent pre-cancers/ cancer lesions.[28]

1.3. Pathogenesis of vulval lesions

Based on clinicopathological features, vulval SCC presented 40% in 40-60 years, 50-60% in 50-70 years and 20% in 60-70 years of age.[25] Precursor lesions for HPV depended are VIN2/3 or H-SIL and for HPV independent VIN (d-VIN, VAAD & DEVIL).[29] Etiological factors high-risk HPV

infections for HPV-depended lesions and mutation in p53 or few rare mutations (NOTCH-1/HRAS/PIK3CA) for HPV-independent cancer/lesions.[28]

1.4. Histomorphology of vulval lesions

Histomorphology of benign lesions of the vulva is shown in Figure 1a. Lichen sclerosis has thinning of the epidermis, loss of rete ridges, sclerosis in the upper dermis and a band of chronic inflammation in the lower dermis.[16] Squamous cell hyperplasia (lichen simplex chronicus) showed marked hyperkeratosis and thickening of the epidermis due to the elongation of rete ridges. Condyloma acuminatum consists of exophytic growth with papillary architecture and mild nuclear atypia with koilocytic changes.[16]

Pre-malignant changes, mostly VIN (1, 2 &3), have intra-epithelial dysplasia, either lower 1/3 epithelium, 2/3 of epithelium or full thickness in the lesions of HPV-depended. HPV-independent (d-VIN with horizontal spread, DEVIL-differentiated exophytic growth, and VAAD-vulval acanthosis with altered differentiation).[29] Pre-malignant lesions are shown in Figure 1b.

Squamous cell cancer is the most common malignancy of the vulva, with two types keratinizing and nonkeratinizing. The WHO 2020 classified as HPV-depended and HPV-independent.[24] HPV-dependent cancers most commonly present in VIN (usual VIN; u-VIN) forms and nonkeratinizing types, HPV-SCC show a plump pattern of invasion and has block positivity for p16 and wild-type P53 expression, whereas HPV-independent type SCC shows variable morphological patterns VIN includes (d-VIN, DEVIL and VAAD) and keratinizing SCC with a netlike pattern of invasion, negative for p16 and aberrant p53 expression.[24]

1.4.1. Galendular neoplastic lesion of vulva

Modified apocrine sweat glands similar to the breast are also present in the vulva. The tumour that arises from them is papillary hidradenoma, extramammary Paget disease and phyllodes tumour.[16] Papillary hidradenoma mostly arises from labia majora and has a papillary projection which lines two-layer outer columnar and inner flattened myoepithelial cells.[16]

Paget disease of the vulva was reported, similar to breast and clinically present as a red maplike crusted lesion with pruritis. Morphologically, Paget disease has intraepidermal large malignant pagetoid cell proliferation. [16]

Salivary gland types of tumours also arise from the vulva, like adenoid cystic carcinoma.[30] Some mesenchymal tumours, like aggressive angiomyxoma, angiomyofibroblastoma and angiofibroma.[31] Unusual tumours like phyllodes tumours, lactating adenoma, lymphoepithelial lesions and lymphomas are also reported in the literature.[32-34]

Malignant lesions of the vulva are shown in **Figure 1**c, and rare lesions are shown in **Figure 2**.

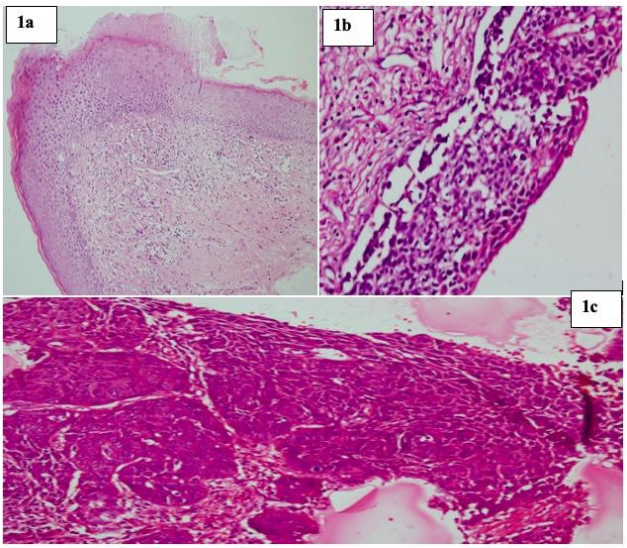

Figure 1: a: Benign lesion of vulva- Lichen sclerosis; shows lined by epidermis and dermis having mild to moderate infiltration of chronic inflammation cells along with pigment incontinence and collagenisation (H&E,400X); **b:** Premalignant lesion- VIN III- section shows stratified squamous epithelium with full thickness dysplasia and underlying chronic inflammation & fibrosis (H&E,400X); **c:** Malignant lesion- Squamous cell carcinoma(H&E,400X).

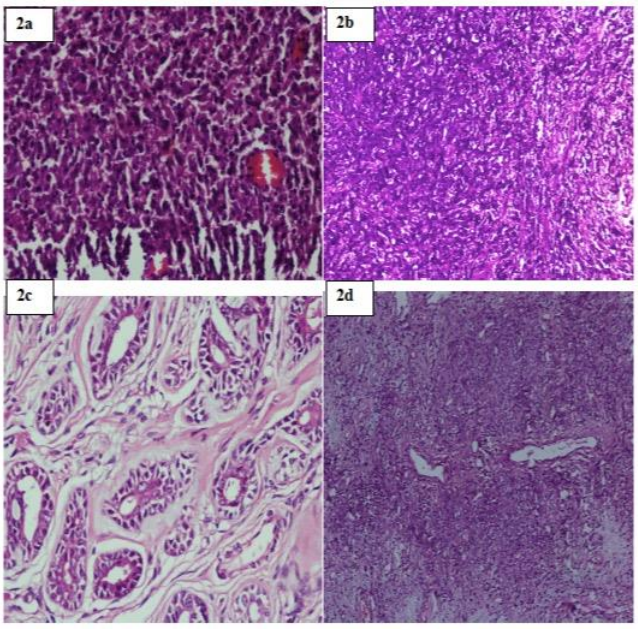

Figure 2: A panel of rare vulvar tumours; **a:** Non-Hodgkin's lymphoma (H&E, 400X); **b:** Rhabdomyosarcoma (H&E,400X); **c:** Adenoid cystic carcinoma (H&E,400X); **d:** Aggressive angiomyxoma, is having hypocellular with abundant oedematous to a myxoid matrix with clusters of vasculatures of various calibres, including medium to large arterials, (H&E,100X).

1.5. Role of biopsy in diagnosis of vulval lesions

The clinical features of benign tumours may overlap with malignant neoplasms, and therefore, a biopsy is often necessary to make a definitive diagnosis.[3] Tyagi et al. reported that duration of symptoms of more than 6 months, hyperkeratosis, asymmetrical distribution of the lesion, surface elevation on naked eye or colposcopy, induration on palpation and positive toluidine blue stain retention of the lesion were significantly associated with a malignant or premalignant lesion.[35] So, for confirmation and further categorization, biopsy/histological examination must be for vulval lesions.

2. Conclusion

The squamous cell carcinoma of keratinizing type was the most frequent malignant tumour of the vulva. There were high discrepancies between clinical diagnosis and histological diagnosis. So, biopsy/histology is a must for accurate diagnosis. Epidemiological studies may provide more definite information regarding risk factors of the vulva and histological subtypes of both malignant and benign diseases.

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4. Conflict of Interest

None.

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