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Original article

Paget's disease of the vulva: a case of delayed diagnosis due to clinical mimicry and review of the literature

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Abstract

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma that primarily affects the epidermis, with the vulva being the most common site of involvement. Its clinical presentation is variable, often presenting with non-specific symptoms and mimicking common dermatological conditions, including eczema, lichen sclerosus, or intertrigo, leading to frequent misdiagnoses and significant delays in diagnosis. This case report presents a 70-year-old postmenopausal female with a longstanding vulvar pruritus who was ultimately diagnosed with Paget's disease of the vulva, over one year

Key words: Paget's disease, Paget's disease of the vulva, extramammary Paget's disease, vulva, genitals

Introduction

Paget's disease of the vulva is a rare entity, constituting only 1-2% of vulval malignancies, 0.06-0.08% of all female genital tract malignancies, and 0.02% of all female cancers[1,2]. EMPD affects approximately 1 in a million people, predominantly involving the vulva (65-83%), followed by the perianal region (more in males), scrotum, penis, and axilla[3,4].

The disease typically appears as persistent erythematous, itchy, scaly, or velvety patches, often leading to delayed diagnosis and mismanagement[5]. Early identification and timely surgical intervention are essential to prevent disease progression and recurrence of vulval Paget's disease.

Case presentation

A 70-year-old previously healthy postmenopausal female presented with a history of recurrent pruritus vulvae for over 1-year duration. Her symptoms had partially responded to topical steroids and combinations of steroid and antifungal treatments prescribed by several general practitioners.

Examination revealed an ill-defined, erythematous area on the vulva with a moist surface and adherent white scales, involving the labia majora bilaterally but asymmetrically, with the condition being more pronounced on the right side, (Figure 1). The per vaginal examination was unremarkable showing pale and atrophic vaginal mucosa without induration. There was no inguinal lymphadenopathy noted. Basic investigations and metabolic profiles were normal.

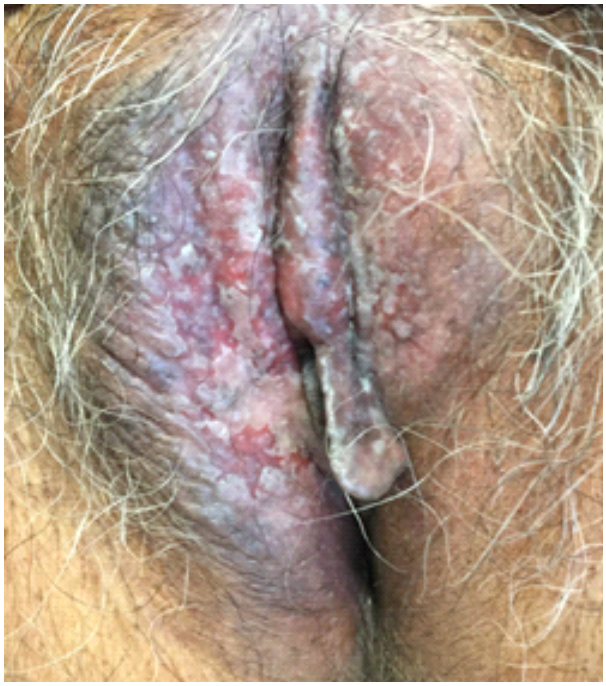

Figure 1. *Paget's disease of the vulva.*

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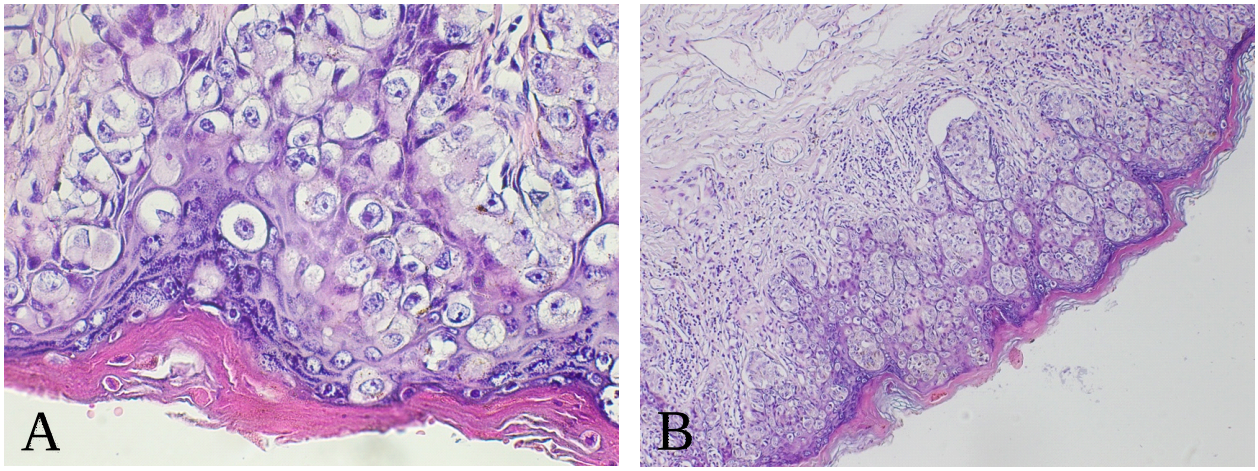

Figure 2. ***(A)*** *EMPD. Paget cells are typically found in clusters within the epidermis, characterized by their large size, round shape, oval vesicular nuclei, and abundant pale-staining cytoplasm at 400x magnification* ***(B)*** *Lymphocytic infiltrate within the dermis at 100x magnification.*

Due to the partial response to treatment and the occurrence in an elderly patient, a biopsy was performed to exclude Paget's disease of the vulva. Histopathology revealed the presence of large pale staining cells with granular cytoplasm and central ovoid nuclei bearing nucleoli with mitotic figures within the epidermis and hair follicles, accompanied by a moderate lymphocytic infiltrate in the dermis (Figures 2A and 2B). The tumor cells were identified at the biopsy margins.

The patient subsequently underwent a skinning vulvectomy, preserving the subcutaneous tissues (Figure 3) and had an uncomplicated postoperative recovery.

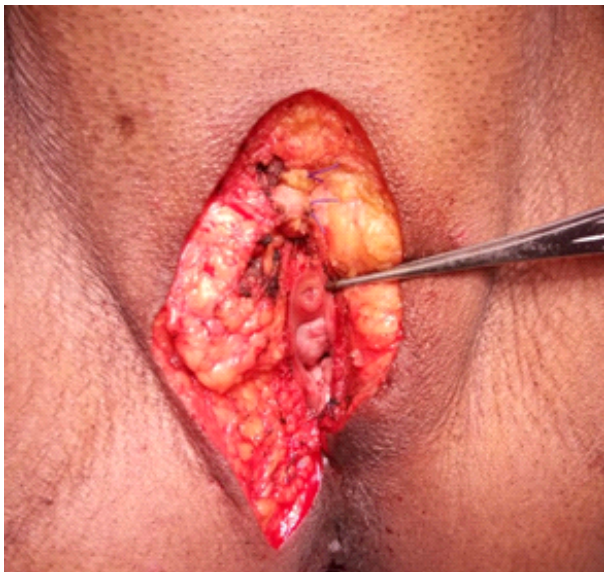

Figure 3. *Skinning vulvectomy.*

Discussion

Paget's disease of the breast was first described by Sir James Paget in 1874[6]. Later in 1899, Radcliffe Crocker identified Extramammary Paget's Disease (EMPD) in a patient with urinary bladder carcinoma who presented with an eczematous lesion on the penis and scrotum[4]. EMPD is an intraepithelial adenocarcinoma arising on apocrine gland-bearing skin, predominantly affecting individuals aged 50-80 years, with a higher prevalence among Caucasians and females[4]. EMPD often affects the vulvar, perianal, scrotal, and penile regions. It was in 1901 that French dermatologist W. Dubreuilh reported the first case of Paget's disease of the vulva[7].

Paget's disease of the vulva commonly presents as vulvar pruritus (affecting between 76.6 and 86% of patients) and pain (reported in about 59%), along with erythema, burning, and bleeding[1,3]. In the studied patients, it was significant pruritus that prompted them to seek medical attention[5,16-23]. Clinically, EMPD presents as an eczematous, well-demarcated, erythematous plaque, with crusting, ulcerations, and exudate[1,3-4,7]. However, Hillmann et al. described a patient with extensive acetowhite areas rather than eczematous lesions, which were difficult to notice without application of toluidine blue. This patient subsequently required a radical vulvectomy[17].

EMPD of the vulva can resemble both benign and malignant dermatological conditions. The benign

dermatoses include eczema, contact dermatitis, seborrheic dermatitis, intertrigo, candidiasis, reverse psoriasis, lichen sclerosus, and vulvovaginitis[3,9-10]. For instance, Feldmeyer *et al*. initially misdiagnosed EMPD as genital seborrheic dermatitis[23]. Malignant conditions that mimic EMPD include melanoma, high-grade HPV-induced intraepithelial vulvar lesions, mycosis fungoides, cutaneous T-cell lymphoma, and Pagetoid basal cell carcinoma[3,10].

EMPD's nonspecific clinical presentation often results in delayed diagnosis, as reported in the literature, a time lag ranging from 1.5 – 4 years[5,10,16-23]. This delay in diagnosis highlights the importance of maintaining a low threshold for suspicion of Paget's disease and other malignant lesions, particularly in post-menopausal women with persistent, treatment-resistant vulvar lesions. While EMPD is known for its non-specific clinical presentation, it does have some distinctive features. In 1901, Dubreuilh described the characteristic erythematous skin changes with white islands and bridges of hyperkeratotic epithelium, referring to this appearance as a "cake-icing" effect, which is pathognomonic for Paget's disease of the vulva[1-2]. Cases in the literature also demonstrate white scaling, ulceration, and erosions on the plaque[5,16-23].

With regards to histopathology, EMPD is identified by mucinous neoplastic cells known as Paget cells[1,3]. These are oval or polyhedral intraepithelial cells with pale cytoplasm and a large centrally located nucleus containing prominent round or oval nucleoli[11]. Over 90% of EMPD cells contain mucin, which can be stained using mucicarmine and periodic acid-Schiff reagent, Alcian blue, and zirconyl hematoxylin[1,12]. Tomar *et al*. reported a patient initially misdiagnosed as lichen planus per the incisional biopsy report, emphasizing the necessity of persistent investigation for non-resolving lesions and the importance of immunohistochemistry markers[22]. The depth of invasion, additionally, is a significant prognostic factor, with a 5-year mortality of approximately 40% in documented invasive disease; hence, multiple biopsy sites of the affected and spared areas should be taken[16].

Treatment typically involves surgical intervention. Most of the cases opted for surgical intervention, either local or wide surgical excision, and in instances with regional lymphadenopathy, radical vulvectomy with inguinal lymph node dissection may be necessary. Despite Paget cells originating locally, they can move both horizontally and vertically within the epidermis, accounting for their multifocal and subclinical skin involvement. Migration of cells can account for the high local recurrence rate (about 40%) of vulvar intra-epidermal EMPD[2]. This high recurrence rate presents significant challenges in treatment and could lead to persistent positive surgical margins despite standard surgical resection. For patients with primary EMPD, recurrence rates are 15% for radical vulvectomy treatments and 43% for wide local excision treatments[1]. Two patients had positive surgical margins and had to undergo several other management modalities, including wide local excision, total vulvectomy, radiotherapy, and imiquimod 5% cream[16,19]. As a result, Mohs micrographic surgery, which allows for intraoperative margin control, is preferred over standard surgical methods due to its lower recurrence rates[16,18].

However, to conserve the aesthetic and functional sequelae, other treatment approaches include radiotherapy, photodynamic therapy, CO_2 laser, and topical treatment such as imiquimod cream and 5% fluorouracil[4]. Imiquimod has shown strong response rates (71% of complete response) and remains a suitable option in patients who decline surgery and in situations with involved surgical margins, given that the patient is willing to tolerate reported local side effects such as residual hypopigmentation, pain, irritation, erythema, erosion[16,21]. Feldmeyer *et al*. published a case report and literature review that identified imiquimod as a safe and effective treatment for cutaneous Paget disease, in 17 patients with primarily non-invasive disease[23]. A summary of the literature on case reports of EMPD of the vulva is given in Table 1.

Despite rigorous treatment, it is essential to continue regular follow-up of the patient, given the subclinical extension of the disease beyond its visible margins. There needs to be ongoing research regarding other alternative and appropriate treatments for Paget's disease as well.

Table 1. Summary of similar case reports in the literature

Study	Age (years)	Demo-graphic	Duration (years)	Clinical Presen-tation	Treatment	Post-treatment
Bouceiro-Mendes R *et al.* 2019[16]	72	Previously healthy Postmenopausal	2	Erythematous plaque in the perianal area, covered by thin and whitish scales, with some areas of erosion	Local surgical excision of the vulva with positive lateral surgical margins	• 9 months – recurrence, WSE with involved surgical margins • Total vulvectomy with fasciocutaneous flap reconstruction • 4 years – recurrence, external radiotherapy • Imiquimod 5% cream
Hillmann BR *et al.* 2016 [17]	48	Smoker – 35 years DM Premenopausal	2	Acetowhite areas in left minora and perineal and anterior perianal regions	Radical vulvectomy and bilateral majora labia, lympha-denectomy	Uncomplicated recovery inguinal
Yadav S *et al.* 2017[5]	55	Postmenopausal	3	Well-defined erythematous plaque with multiple erosions	Advised for excisional surgery but refused	Lost to follow-up
Gavriilidis P *et al.* 2013[18]	75	Postmenopausal	1.5	Eczematoid and erythematous lesion	Radical vulvectomy with bilateral inguinal lymph node dissection	Uncomplicated recovery – regular follow-up
Barmon D *et al.* 2012[19]	65	HTN	4	Erythematous plaque with ulceration on the right labial fold	Right-sided radical vulvectomy with wide surgical margin, along with bilateral groin node dissection	Adjuvant radiotherapy due to positive margin Regular follow-up
Bencherifi Y *et al.* 2023[20]	39	Previously healthy	Not men-tioned	Erythematous vulvar lesions	Right hemi vulvectomy and excision of the left labia minora	Uncomplicated recovery

(Continued)

Study	Age (years)	Demo-graphic	Duration (years)	Clinical Presen-tation	Treatment	Post-treatment
Mota F *et al.* 2017[21]	78	Previously healthy	3	Erythematous, well-demarcated plaque with scaling and ulceration	Simple vulvectomy	Uncomplicated recovery
Tomar TS *et al.* 2016[22]	64	Previously healthy	2	Well-defined pigmented papular plaque	Wide excision of the lesion with a 2-cm gross margin, which amounted to en bloc removal of the bilateral labia majora, minora, and clitoris right labial defect – closed primarily Left labial defect – fasciocutaneous transposition flap reconstruction	Uncomplicated recovery with margins of resection free
Feldmeyer L *et al.* 2011[23]	59	Previously healthy	Several months	Poorly delimited erythematous to squamous patch	Imiquimod 5% cream was applied to the vulvar lesion, including a 1-2 cm circumferential margin of normal-appearing skin three times a week, for 18 weeks.	Clinical and histological remission after one year of treatment

Conclusion

This case highlights the necessity of maintaining a high vigilance for rare diseases and performing early biopsies in patients with persistent and recurrent vulvar lesions, even when symptoms are nonspecific, to prevent diagnostic delays.

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Patient consent

The patient has consented to the publication of the report and all accompanying images.

Conflicts of interest statement

The authors declare that they have no conflict no interest regarding the publication of this case report.

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