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Case Report

Invasive Vulvar Paget's Disease

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Abstract

Vulvar Paget's Disease (VPD) is an intraepithelial adenocarcinoma, with or without underlying invasive adenocarcinoma. It can be primary (cutaneous and/or adnexal) or secondary, originating from the recto-colic or urothelial epithelium. First described by Dubreuilh in 1901, VPD is not always a purely intraepithelial proliferation; it may present as an invasive form. The reported frequency of invasion varies between 10% and 47%, based on small case series. Three levels of invasion have been described: (1) in situ within the epidermis, (2) microinvasion of the papillary dermis, and (3) deep invasion into the reticular dermis and hypodermis. VPD is a rare cutaneous malignancy, predominantly observed in postmenopausal Caucasian women. The underlying etiology remains poorly understood. VPD is rarely associated with an underlying urogenital, gastrointestinal, or vulvar carcinoma. In approximately 25% of cases, VPD is invasive, which is associated with a worse prognosis compared to non-invasive cases. The recurrence rate of invasive VPD is high, reaching 33% in cases with clear surgical margins and even higher when margins are not clear, regardless of invasion status. Historically, surgical excision has been the treatment of choice.

In this article, we report the case of a 67-year-old postmenopausal woman diagnosed with invasive extramammary vulvar Paget's disease, with deep invasion into the underlying dermis and hypodermis, as well as ipsilateral inguinal lymph node involvement. Through this case report and a review of the literature, we discuss the clinical and histopathological diagnosis, treatment, and prognosis of this rare malignancy.

Keywords: Extramammary Paget's Disease (EMPD); Invasive Vulvar Paget's Disease (VPD).

Introduction

Paget's disease is a rare malignancy affecting the superficial layers of the skin. It commonly occurs in the breast, the genital region, or, less frequently, other cutaneous sites. After the breast, the vulva is the second most frequently affected area [11].

The pathogenesis of Paget's disease remains poorly understood. It primarily affects women over the age of 60. Diagnosis is confirmed through biopsy. In rare cases, the disease is associated with another malignancy of the urogenital or anal region, necessitating further investigations such as CT scan, ultrasound, or endoscopy. The choice of treatment depends on the lesion size, symptom severity, and the patient's overall health status. Regardless of the treatment approach, recurrence rates are high, underscoring the importance of regular follow-up [11].

Vulvar Paget's disease accounts for 1% to 2% of vulvar cancers. It is characterized by a classic histological pattern involving a proliferation of large atypical cells within the epidermis. The recurrence of the disease has been found to be independent of histological factors, such as surgical margin status, involvement of hair follicles or adnexal glands, and even dermal microinvasion. Among 32 patients treated surgically, 17 experienced recurrence within a period ranging from 2 to 144 months. An associated malignancy was identified

in 29% of cases, and observed fatalities were primarily attributed to these concomitant neoplasms.

Paget's disease is an adenocarcinomatous proliferation originating in areas of the skin containing apocrine sweat glands. It typically remains intraepithelial [12]. Clinically, it often presents with pruritus and burning sensations but remains asymptomatic in 10% of cases.

The lesion is usually solitary, presenting as a slightly raised plaque with well-defined, asymmetric borders. It appears as a bright red area interspersed with white punctate spots and eroded regions. The disease most commonly begins on the labia majora, potentially extending to the labia minora and clitoris [12].

Case Study

The patient, G.M., is a 67-year-old woman with blood type A Rh-positive (A+), gravida 9, para 6 (G9P6), who experienced menopause at the age of 50. Her medical history includes type 2 diabetes mellitus, hypertension, hypercholesterolemia, and hyperthyroidism. There is no family history of malignancy.

The onset of symptoms dates back three months, with the appearance of a pruritic vulvar lesion prompting medical consultation. A biopsy revealed a dermo-epidermal epithelial neoplastic process.

Immunohistochemical analysis (CK7+, CK20−) supported the diagnosis of invasive extramammary Paget's disease.

Imaging findings

- Pelvic MRI:
  - A vulvar mass arising from the left labia majora, well-encapsulated, with no invasion of perilesional fat, preservation of the midline septum, and no involvement of adjacent structures.
- Lymph Nodes:
  - Bilateral inguinal lymphadenopathy.
- Uterine Findings:
  - Two small intramural myomas.
  - No Ascites was detected.

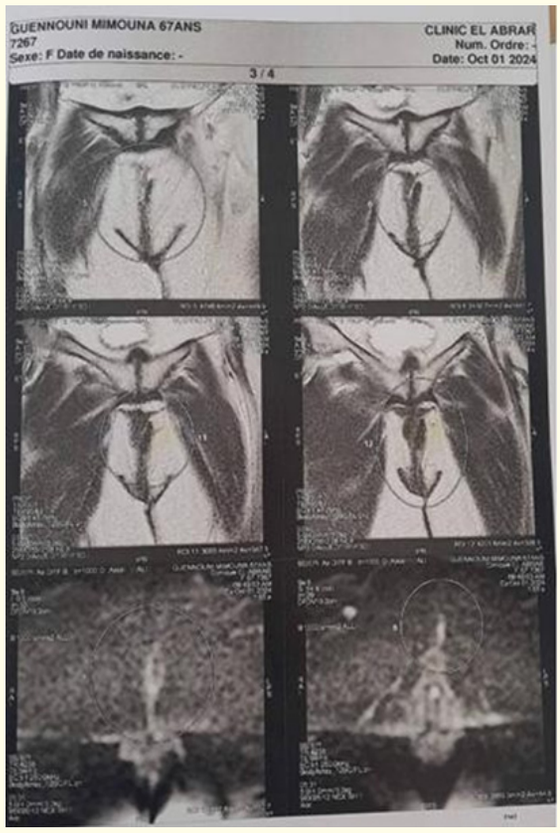

Figure 1: MRI scan of the pelvis centered on the vulva.

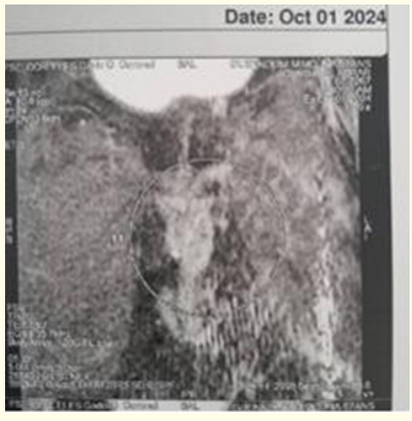

Figure 2: Radiological image of a vulvar tumor located on the left labium.

On clinical examination:

- Functional Signs:
  - Vulvar pain with associated pruritus
- Gynecological Examination:
  - Vulvar inspection: Tumefied, red, firm, ulcerated lesion measuring 1.5 cm × 2 cm (Figure 3).
- Speculum Examination:
  - Easy insertion
  - Macroscopically healthy cervix
  - Macroscopically healthy vaginal walls
  - No intrauterine bleeding
- Vaginal Examination (Combined with Abdominal Palpation):
  - Posterior cervix, long to palpation
  - Clean examining glove
  - Free cul-de-sac
- Breast Examination:
  - No abnormalities detected

Our patient underwent surgical treatment: total vulvectomy with bilateral inguinal lymph node dissection (inguinofemoral lymphadenectomy) (see Figure 3) [14].

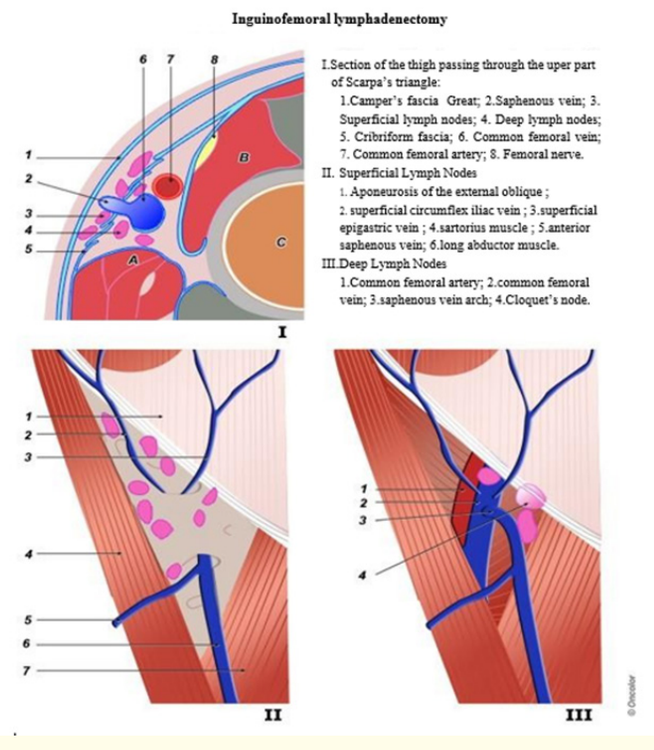

Figure 3: Explicit diagram of inguinofemoral lymphadenectomy.

Total vulvectomy

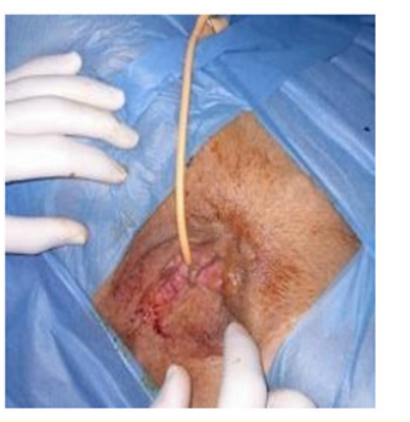

Figure 4: Image showing the patient in the lithotomy position during surgery.

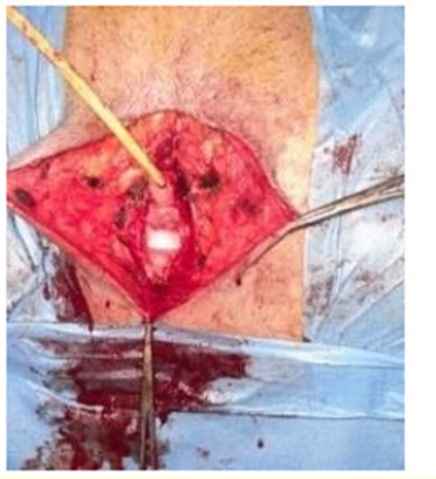

Figure 5: Total vulvectomy with the urinary meatus superiorly and the vagina inferiorly, as indicated by the arrows.

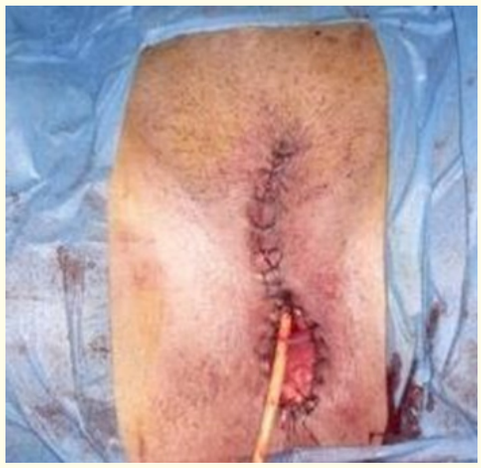

Figure 6: Perineal closure.

Bilateral inguinofemoral lymphadenectomy

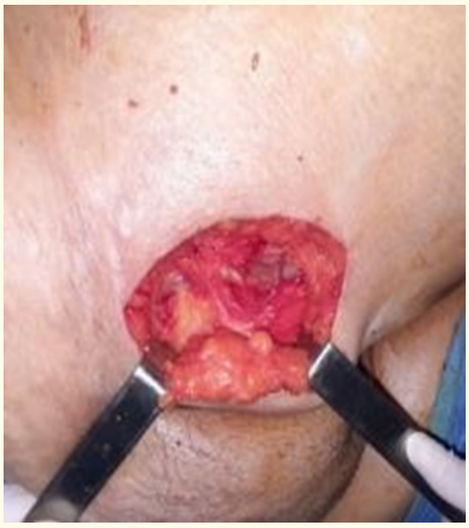

Figure 7: Incision of the left thigh for inguinofemoral lymphadenectomy, approximately 6 cm in length.

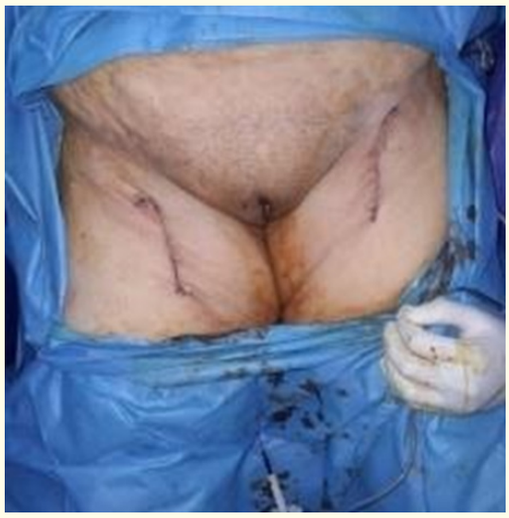

Figure 8: Closure of the incisions made on the right and left thighs after inguinofemoral lymphadenectomy; the specimen is sent for histopathological examination to confirm the diagnosis.

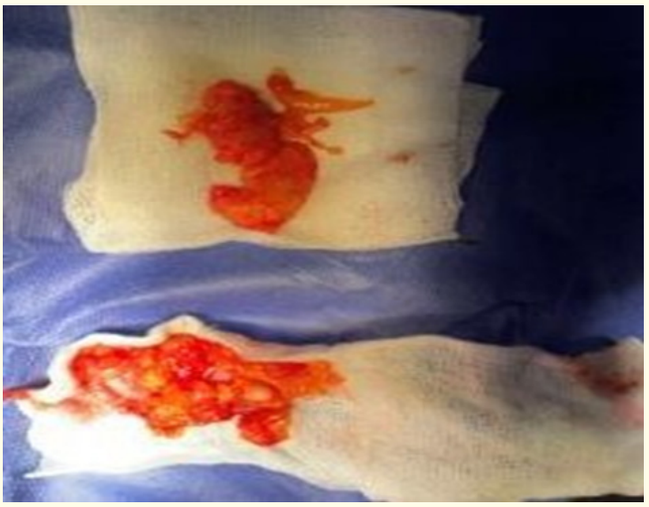

Figure 9: The surgical specimen from the right and left inguinofemoral lymphadenectomy.

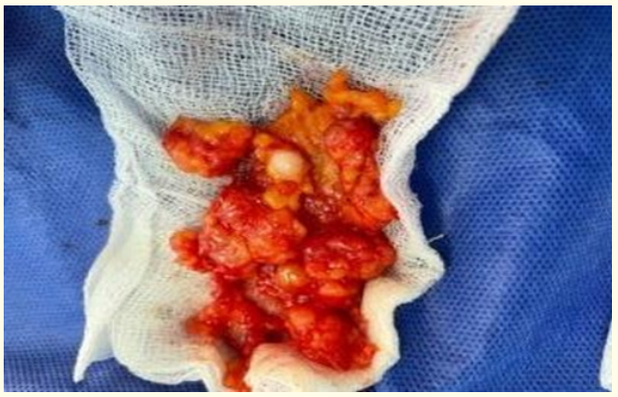

Figure 10: The surgical specimen from the left inguinofemoral lymphadenectomy.

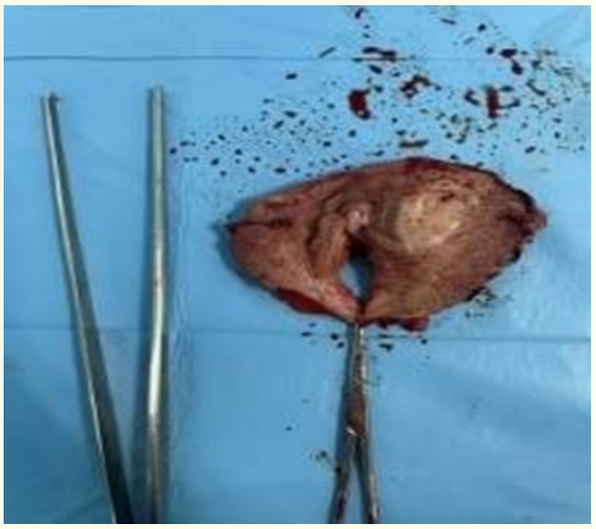

Figure 11: The surgical specimen from the vulvectomy.

Histopathology report (Anapath Report)

The histopathological examination reveals a carcinomatous process of the vulva with lymph node metastases (03N+/10N), classified as pT1bN2c, with clear lateral and deep resection margins. Microscopically, the examination shows a cutaneous epithelium affected by a neoplastic proliferation of epithelial origin, originating from the epidermis and infiltrating down to the hypodermis. The epidermis contains large clear cells with irregular nuclei, corresponding to Paget cells, which are arranged in clusters, glandular structures, and isolated elements. These neoplastic cells infiltrate the underlying dermis and hypodermis. The stroma is fibrous and desmoplastic, with the presence of perineural invasion and vascular emboli. A manual immunohistochemical study was performed using CK7, CK20, CK5/6, S100, HER2, PR (Progesterone Receptor), and ER (Estrogen Receptor) markers.

Results

- A diffuse positivity of tumor cells for CK7 and CK5/6.
- A nuclear positivity for estrogen receptors.
- A negativity of tumor cells for CK20, PS100, and progesterone receptors.
- HER2 score 1 (negative).
- Colonization of the entire thickness of the epidermis by large cells with an eccentric nucleus.
- The cytoplasm contains acidic mucins stained by Alcian blue.

Conclusion

The histopathological and immunohistochemical findings are consistent with invasive vulvar Paget's disease.

- **Figure A1:** Acanthotic epidermis containing isolated atypical Paget cells with dermal infiltration.
- **Figure A2:** Epidermal upward migration of large round cells with abundant clear cytoplasm and variably atypical nuclei.
- **Figure A3:** Paget cells arranged in glandular structures and clusters.

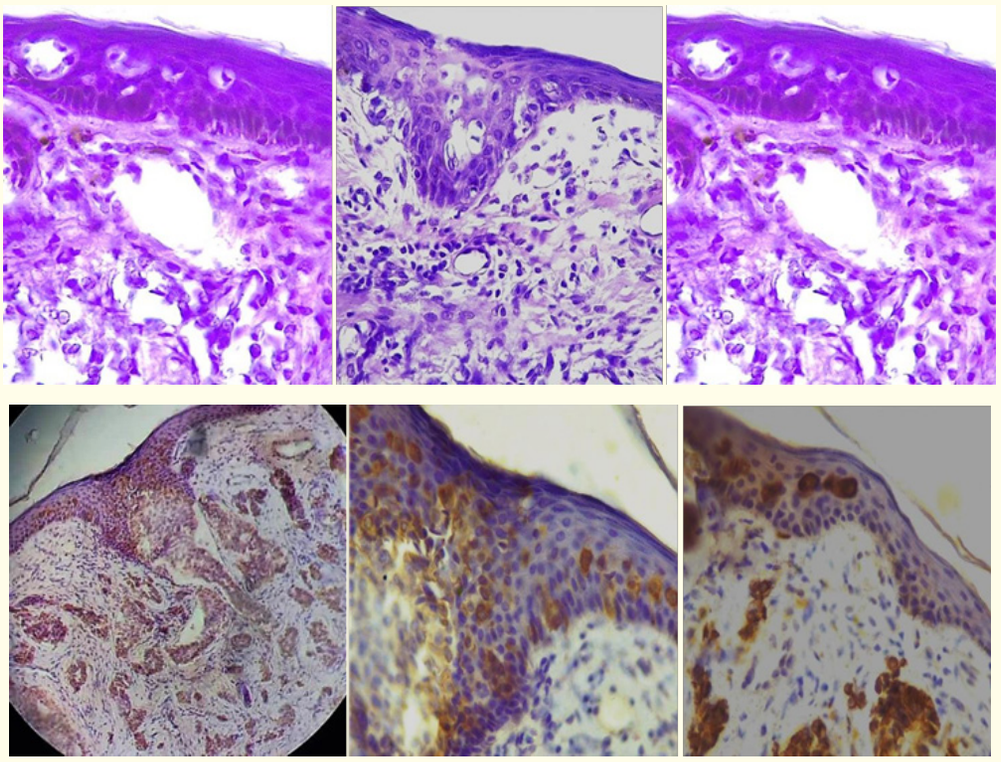

Figure A: CK7 expression highlights intraepidermal Paget cells along with epidermal infiltration.

A thoraco-abdomino-pelvic CT scan (TAP) was performed as part of the investigation to detect secondary localizations. The findings revealed small and micronodular bilateral pulmonary lesions of nonspecific nature. Two hepatic cystic formations were identified, compatible with hydatid cysts, requiring correlation with hydatid serology. There is also a suspected endoluminal cystic formation in the cecum. The postoperative evolution was favorable, and the patient was discharged on day 10 (J10). Good healing observed on postoperative day 21 (J21); see Figures 12 and 13.

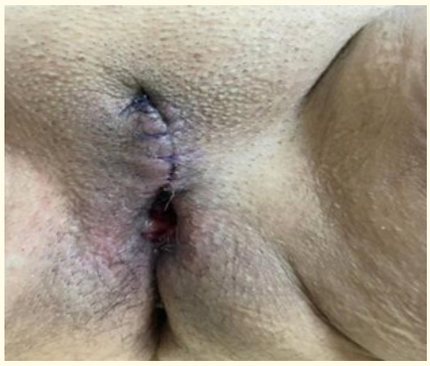

Figure 12: Image of the perineum in the process of healing.

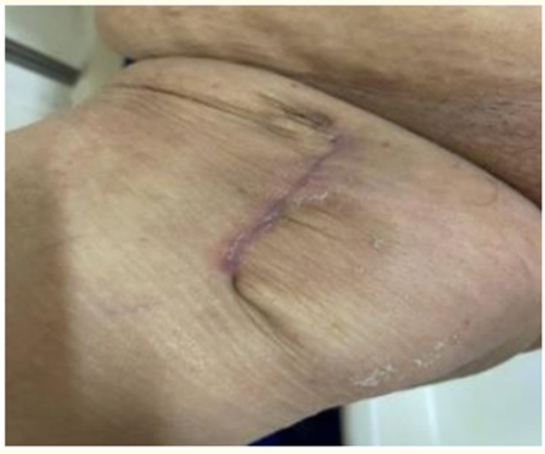

Figure 13: Healing of the lymphadenectomy site.

Discussion

The histological diagnosis in our case is relatively straightforward. The epidermal lining is acanthotic and infiltrated by Paget cells, which are large, round cells with abundant clear or vacuolated cytoplasm, variably atypical vesicular nuclei, and a prominent nucleolus (Figure A1). These cells appear either isolated or grouped in clusters and ascend within the mucous body (Figure A2), with possible glandular differentiation (Figure A3). Histochemically, Paget cells stain positive with PAS, mucicarmine, and Alcian blue. The most reliable immunohistochemical marker for Paget's disease is CK7. Paget cells have an epithelial origin, as indicated by their positivity for pancytokeratins (AE1/AE3, CAM5.2), EMA, and CEA, and negativity for melanocytic markers PS100 and HMB45. Hormone receptor positivity (PR, ER) and ERBB2 (HER2) expression are rare. Immunohistochemistry is crucial for differentiating primary from secondary Paget's disease (colorectal or urothelial origin), where CK7 positivity and CK20 negativity favor primary extramammary Paget's disease. It also helps rule out differential diagnoses such as melanoma, which is positive for PS100 and HMB45, and intramucosal squamous cell carcinoma (Bowen's disease), where cells are positive for P40, p63, and CK5/6 but negative for CK7.

Two important concepts should be noted:

- The diagnosis of primary vulvar Paget's disease (type 1) is based on morphology and immunohistochemistry, characterized by a CK7+/CK20– profile, which helps exclude a primary colorectal lesion, and a PS100– marker, ruling out melanoma.
- It is crucial to assess the presence of invasion or microinvasion to avoid underestimating the potential metastatic risk [2].
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- Depending on its origin, vulvar Paget's disease has recently been subdivided into three subtypes [4]:

- Type 1 Vulvar Paget's Disease, accounting for 90–95% of cases [4,5], involves primary vulvar lesions. Its cellular origin remains controversial, with hypotheses suggesting it arises from the intraepidermal portion of apocrine glands or from totipotent keratinocytes. Recent studies support a glandular apocrine origin [3]. This type is further subdivided into Paget's disease without (1a) or with (1b) invasion, classifying this intraepithelial neoplasia as potentially invasive. Type 1c refers to Paget's disease associated with primary vulvar adenocarcinoma, such as Bartholin's gland adenocarcinoma or squamous cell carcinoma of the vulva [4]. Studies indicate that 10–20% of women with vulvar Paget's disease present with an invasive component or an associated adnexal adenocarcinoma [1]. Estrogen and progesterone receptors are typically negative in vulvar lesions, which are characterized by CK7+, CK20– (3), and ACE+ (1) markers. Additionally, cerbB2 overexpression is observed in approximately half of the cases.
- Type 2 Vulvar Paget's Disease, accounting for 5–10% of cases [4,5], involves adenocarcinomatous proliferations associated with non-cutaneous primary malignancies, such as *in situ* or invasive rectal carcinoma or cervical adenocarcinoma [4,6]. Paget's disease associated with colorectal carcinoma is characterized by Paget cells that express CK20+ [7].

- Type 3 refers to intraepithelial pagetoid urothelial carcinomas (pseudo-Paget disease) [4]. In this distinct form, diagnosis can be supported by immunohistochemistry [8], particularly uroplakin expression, but is primarily guided by clinical presentation and the nature of the initial symptoms. In this context, Paget's disease represents a manifestation of an underlying urothelial neoplasia [4].

In our case, the diagnosis corresponds to type 1b. The treatment of Paget's disease depends on its subtype, and for type 1, it involves extensive vulvar surgery, including clitoral excision, due to the local aggressiveness of these lesions. Clinically clear margins of 2 cm are necessary, as the lesion boundaries are often poorly defined and difficult to assess preoperatively. In our case, the deep and lateral margins were free of disease: 0.9 cm from the superior border, 2.5 cm from the inferior border, 1.8 cm from the external edge of the labia majora, and 0.5 cm from the deep plane. In cases of invasion, an inguinofemoral lymphadenectomy is performed, with the sentinel lymph node technique currently under evaluation. Lymphatic spread is the predominant route of metastasis in vulvar cancers, extending to the ipsilateral inguinofemoral lymph nodes for small, strictly unilateral lesions, particularly those in the mid and lower parts of the labia majora, while contralateral lymph node involvement is possible but rarely occurs in isolation without ipsilateral inguinal involvement. Lesions in the anterior vulva, frenulum, clitoral hood, and central perineum often have bilateral drainage, while clitoral lesions may drain directly into the pelvic lymph nodes [13]. In our case, the left ipsilateral lymphadenectomy retrieved eight lymph nodes, of which three were metastatic and five were reactive, while the right contralateral lymphadenectomy retrieved two reactive lymph nodes.

All surgical excision procedures can be complicated by wound dehiscence, delayed healing, and infections, including pubic osteitis. The resulting functional difficulties may impact not only sexual function but also urinary and anal continence, leading to pain or disability. Inguinal lymphadenectomy is particularly poorly tolerated, often causing massive and prolonged lymphorrhea, frequent and sometimes superinfected lymphoceles, and, most concerningly, the risk of lower limb lymphedema, which can result in severe disability. In our case, postoperative recovery was favorable, with complete wound healing achieved within 20 days (see Figures 12 and 13), and no infections or lymphoceles were observed. Adjuvant treatment with radiotherapy or chemotherapy must be considered on a case-by- case basis, and our patient underwent radiotherapy. However, vulvoperineal radiotherapy is also poorly tolerated, often causing burns and localized edema, with long-term sequelae such as fibrosis, atrophy, telangiectasia, and even necrosis, which can lead to chronic pain. Inguinal irradiation, although less frequently responsible for lower limb edema than surgery, remains a potential source of complications [13].

In the literature, cases of vulvar Paget's disease with an invasive component exceeding 1 mm almost systematically present metastatic lymph node involvement, with a 70% mortality rate at three years [5] and a 30% recurrence rate [2]. Minimal invasion, less than 1 mm, does not typically recur and rarely leads to metastases [5,7]. Recurrences may occur locally (25%) at the scar site [4,6], perineum, anal margin, or the skin bridge between the vulva and inguinal regions, and may even involve adjacent bone structures; in the inguinal lymph nodes (10%); or, less commonly, as distant metastases (3%) affecting the lungs, liver, brain, or bones. In our patient, vulvar Paget's disease has a risk of recurrence and/or distant metastasis, given its invasive nature (extending into the hypodermis) with ipsilateral lymph node involvement, despite clear surgical margins. Therefore, rigorous follow-up must be established, including perineal examination, pelvic exams, and lymph node palpation every four months for the first year, then every six months for the next two years; inguinal ultrasound monitoring with or without cytology every 4–6 months during the first two years; and thoraco-abdominopelvic CT scans as needed, depending on the initial stage and risk factors [13].

When Paget's disease is more extensive, alternatives to surgery can be considered, including imiquimod cream, which stimulates the body's immune response against the disease but may cause significant irritation, and laser therapy or photodynamic therapy, both of which aim to superficially destroy the affected area [1].

Conclusion

Extramammary vulvar Paget's disease is characterized by a high tendency for recurrence following surgical resection. Surgical management can be challenging due to the high rate of residual tumor presence within the surgical margins [15].

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