Conservative Management of Extramammary Paget Disease With Imiquimod

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■ **Abstract**

Objective. Extramammary Paget disease is a rare cutaneous neoplasm that most frequently affects the vulva. Surgery remains the preferred treatment, despite its association with high recurrence rates. Few reports have described conservative treatments for vulvar Paget disease. Our aim was to evaluate the efficacy of conservative treatment with imiquimod.

Materials and Methods. We performed a retrospective analysis of 4 patients who were treated with topical imiquimod 5% cream.

Results. One patient underwent vulvectomy after imiquimod therapy, and 3 patients experienced extensive recurrent disease that was unsuitable for surgical resection and were treated successfully with imiquimod.

Conclusions. Imiquimod is an effective therapeutic agent for the conservative treatment of vulvar Paget disease. ■

Key Words: imiquimod, extramammary Paget disease, treatment outcome

Extramammary Paget disease (EMPD) is a rare cutaneous neoplasm that frequently manifests as an intraepithelial adenocarcinoma in situ that originates from intraepidermal apocrine glands or pluripotent keratinocyte stem cells [1]. It develops most commonly in the vulva but constitutes only 1% to 2% of vulvar malignancies [2, 3]. An underlying malignancy has been reported in 20% to 30% of EMPD [4, 5], and the prevalence of invasive Paget disease or vulvar adenocarcinoma is 4% to 17% [5, 6]. Surgery remains the preferred treatment, despite the high recurrence rates [5, 6]. Conservative management of EMPD with photodynamic therapy (PDT) has been reported with response rates that range from 50% to 78% [7]. Nevertheless, few reports evaluated EMPD treatment with imiquimod, but with promising results. We report 4 cases of vulvar EMPD that was treated clinically with imiquimod.

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The authors declare that there are no conflicts of interest.

MATERIALS AND METHODS

This retrospective analysis included 4 patients with EMPD who were admitted to the Department of Gynecologic Oncology, AC Camargo Cancer Hospital, from May 2005 to July 2009. All patients had vulvar Paget disease and were treated with topical imiquimod 5% cream. All pathology slides were reviewed. The institutional research board has approved the study.

RESULTS

The mean age at first diagnosis was 62.2 years (range = 56–80 y). Three women were white, and 1 was Asian. All patients presented with a red, pruritic lesion and were initially treated topically with an antifungal and/or steroid cream without success. One patient had

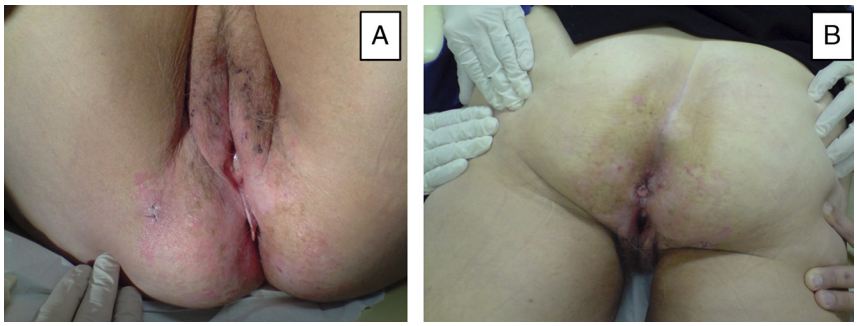

Figure 1. Patient who had persistent disease after PDT and was unsuitable for surgical resection. Physical examination revealed an erythematous plaque that began over the vulva and affected the perineal and perianal (A) and gluteus and sacral regions (B).

an untreated lesion, another patient underwent 5 sessions of methyl aminolevulinate PDT but did not generate a partial response, and the remaining 2 patients had recurrent disease after surgical treatment (simple vulvectomy and wide vulvar resection) with a disease-free interval of 57 and 60 months, respectively.

Only 1 patient had an untreated Paget disease that was limited to the vulva. Surgical excision was proposed, but the patient declined this option. The patient who had persistent disease after PDT and those who experienced recurrence after surgical treatment had extensive Paget disease that was unsuitable for surgical resection. The surgical option would have entailed an extensive surgical procedure that included vulvectomy and wide skin and abdominoperineal resections because the physical examination revealed an extensive erythematous plaque (1 patient also presented with areas of superficial erosions) that began over the vulva and affected the perineal, perianal, and gluteus regions. In 1 patient, the plaque extended to the sacral region (see Figure 1).

An underlying mammary, genitourinary, and gastrointestinal malignancy was excluded in all patients who underwent mammography, echography, colonoscopy, and endoscopy. Even the patient who was virgin had a gynecologic evaluation.

In all cases, a skin biopsy showed large cells with pale-stained cytoplasms and pleomorphic nuclei, distributed singly and in groups throughout the epidermis (see Figure 2A). Positivity for CK7 and carcinoembryonic antigen and negativity for S-100 by immunohistochemical staining confirmed the diagnosis of EMPD.

Topical therapy with imiquimod 5% was proposed. The cream was administered by the patient onto the lesion and its surroundings before going to bed. All patients reported varying degrees of local irritation and tenderness during the treatment.

The patient with EMPD that was limited to the vulva began treatment every other day for 4 weeks and experienced an apparent partial regression, but a biopsy showed persistence of the disease. She underwent a simple vulvectomy with macroscopic margins of 3 cm, but despite a negative frozen section, a cranial margin was considered to be positive. After 21 months of follow-up, the patient showed no signs of disease.

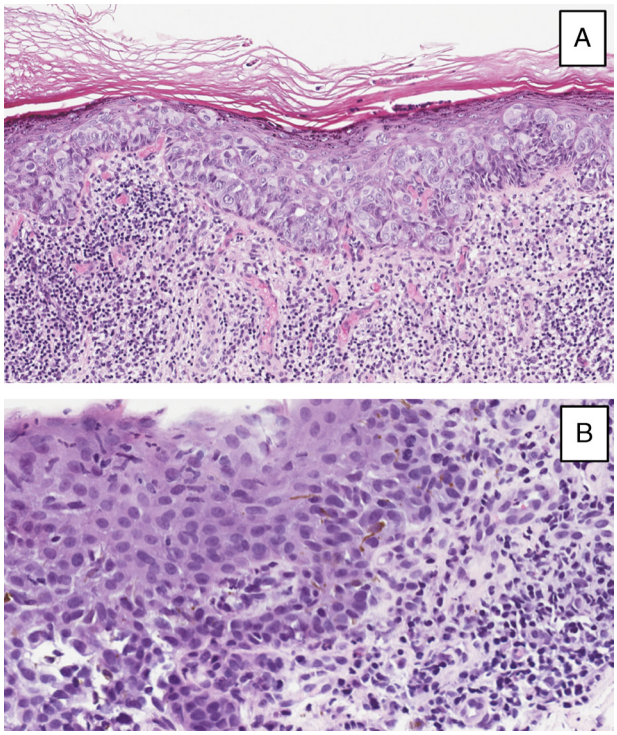

Figure 2. A, Vulvar Paget disease: Clusters of large, pale Paget cells with atypical nuclei are present within the epidermis (hematoxylin and eosin, ×20). B, Vulvar biopsy after treatment: Epidermis with hyperplasia and keratinocytes with reactive changes. There are inflammatory cells and fibrosis, and no viable neoplastic cells are found.

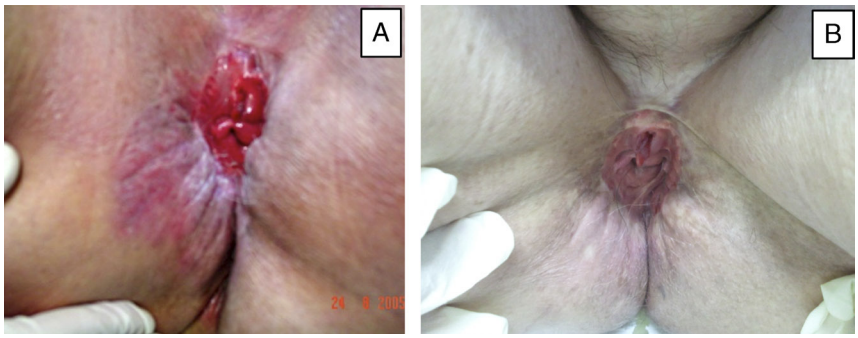

Figure 3. A, Patient who experienced another local recurrence of Paget disease after vulvectomy and imiquimod. B, Complete clinical response after 20 weeks of treatment with imiquimod.

The 3 patients with extensive disease also began topical imiquimod 5% every other day, 3 times per week. One patient failed to tolerate this schedule and decreased the dosage to twice weekly after 2 weeks. Another patient halted the therapy for 4 weeks after 16 weeks of treatment because of intense local irritation.

One patient had a complete response after 32 weeks of treatment, which was confirmed by skin biopsy. After 17 weeks of follow-up, this patient experienced another local recurrence, which was retreated with topical imiquimod, after which the patient had another complete clinical and pathologic response after 20 weeks of treatment (see Figures 2B and 3). After 40 months of follow-up, there was no evidence of the disease.

The patient who received imiquimod twice weekly had a good but partial response (60% clearance) after 20 weeks of treatment. Because of significant local pain and dizziness, treatment with imiquimod was suspended. After 3 months, the treatment was restarted. She continues to receive treatment, and the lesions are decreasing after 4 additional months of treatment.

After 20 weeks of treatment, the last patient had a nearly complete response (75% clearance) but reported vaginal bleeding (see Figure 4). Because she developed vaginal introitus stenosis due to previous treatments and due to her virginity, she underwent physical examination under anesthesia, which demonstrated an infiltrative and superficial ulcerative lesion in the lower anterior third of the vagina. Using magnetic resonance imaging of the pelvis, we noted an enlarged left inguinal lymph node and enlargement of the vaginal anterior wall. Vaginal and inguinal biopsies confirmed invasive Paget disease of the vagina. The patient received conformational external beam radiation therapy (54 Gy), and a complete response was achieved for the vaginal invasive Paget disease, inguinal lymph node, and residual EMPD (see Figures 4 and 5).

DISCUSSION

Extramammary Paget disease is a rare condition that poses many difficulties in its management. The ideal

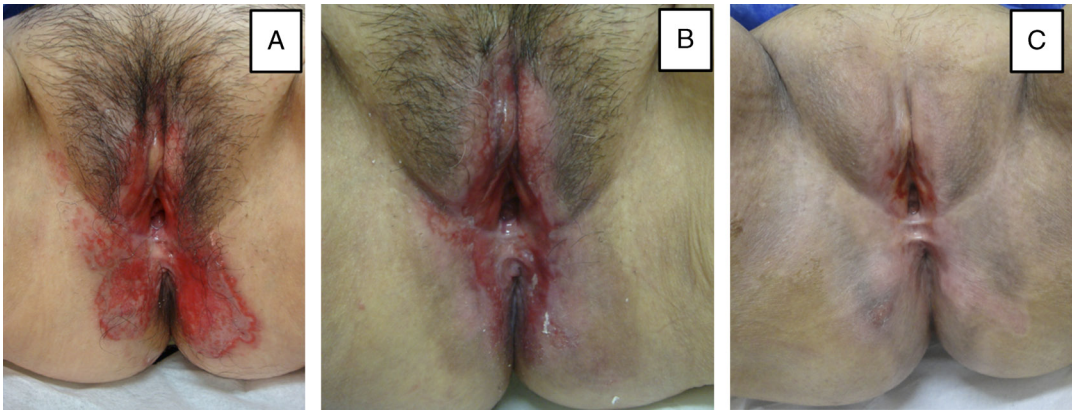

Figure 4. A, Patient who had recurrent disease after wide vulvar resection. Physical examination revealed an extensive erythematous plaque with areas of superficial erosions that began over the vulva and affected the perineal, perianal, and gluteus regions. B, After 20 weeks of treatment, a nearly complete response was achieved (75% clearance). C, Complete response aspect for the vaginal invasive and vulvar Paget disease after completion of external beam radiation therapy.

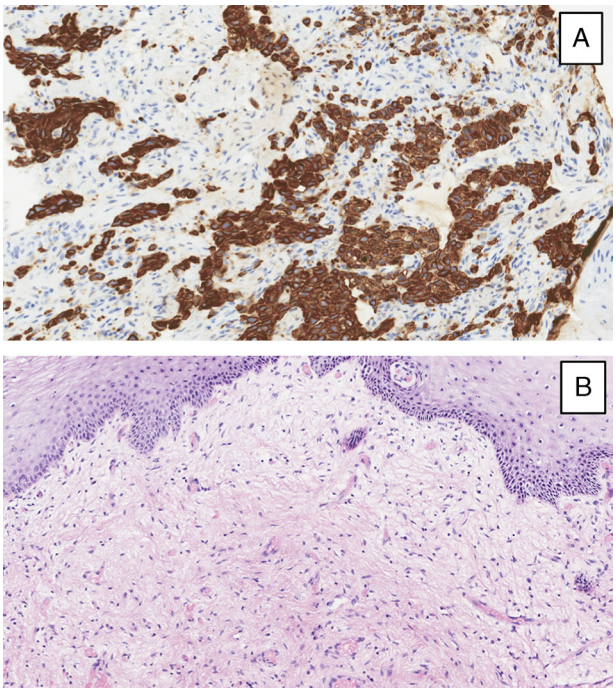

Figure 5. A, Invasive vulvar Paget disease: Clusters of large, round cell with a large nucleus and prominent nucleolus are present in the dermis with immunohistochemical expression of CK7 (×20). B, Vulvar biopsy after treatment of invasive Paget disease: Epidermis showing irregular acanthosis, fibrosis, and vascular congestion in the dermis. There are no viable neoplastic cells (hematoxylin and eosin, ×8).

treatment should affect low recurrence rates and minimal sequelae. Surgery is generally accepted as the standard treatment modality, but it is associated with high local recurrence rates (21%–61%) [5–6], even Mohs micrographic surgery (16%) [8]. Consequently, there has been a shift to a more conservative approach in the management of EMPD.

Imiquimod is an immune response-modifying compound that stimulates the production of a wide range of cytokines, including interferon α and tumor necrosis factor α. It elicits the combined activation of natural, local innate immunity and T_H1 immune responses and inhibits T_H2 cytokines that are overexpressed in skin cancer. Imiquimod might also enhance Langerhans cell migration, induce apoptosis, and inhibit tumor-associated angiogenesis [9].

In recent reports, topical treatment with imiquimod 5% cream has been demonstrated to be a safe and effective option for vulvar Paget disease. However, published reports comprised few patients (n = 10) [1, 9–15] with recurrent or untreated vulvar or perineal Paget disease using various schedules (Table 1).

In contrast to other reports, 3 of our patients had extensive Paget disease that was unsuitable for surgical resection, because it might have resulted in positive margins, despite extensive skin and anal resection. We achieved a complete response twice in a patient after a long follow-up and partial responses—but greater than 75%—for the others. The patient with disease that was limited to the vulva received the current standard treatment with vulvectomy after just 1 month of treatment with imiquimod. If the topical treatment was administered for a longer period, a better result or complete response might have been observed.

In vulvar Paget disease, the coexistence with invasive lesions is an important issue. In patients with extensive

Table 1. Clinical Data and Outcome of the 10 Patients With Vulvar or Perineal Paget Disease Treated With Imiquimod

Author	Age, y	Disease	Schedule	Treatment duration, wk	Follow-up	Outcome
Wang et al. [10]	75	Recurrent	Every day for 6 d Twice a week for 1 wk 3 times a week for 5 wk	7	2 wk	CR/PathR
Geisler and Manahan [11]	80	Recurrent			12 mo	CR/PathR
Hatch and Davis [12]	68	Recurrent	Every other day Every day for 4 wk	24	4 mo	CR/PathR
	60	Recurrent	Twice a day for 2 wk Every day for 5 wk	20	7 mo	CR/PathR
Bertozzi et al. [14]	71	Recurrent		8		CR
Sendagorta et al. [9]	66	Primary	Every day for 3 wk Every other day for 3 wk	6	26 mo	CR/PathR
	58	Primary	Every day for 3 wk Every other day for 3 wk	6	22 mo	CR/PathR
	82	Primary	Every day for 3 wk	6	20 mo	CR/PathR
Cecchi et al. [15]	74	Primary	3 times a week	16	NA	CR
Tonguc et al. [1]	65	Recurrent	Every day for 3 wk Every other day for 3 wk	8	24 mo	CR/PathR

CR indicates complete remission; NA, not available; PathR, pathologic remission.

lesions, we suggest that an incisional biopsy of the worse area should be done before any conservative treatment.

Imiquimod is a potential treatment option for EMPD. The appropriate therapeutic schedule, its safety, and how this novel compound should be tested (frontline, recurrent, or neoadjuvant setting) have not been determined. Two other limitations should be recognized. Because EMPD spreads in a highly irregular manner throughout the skin, long-term follow-up is imperative in averting local recurrence. Conversely, negative skin biopsies might be attributed to sampling errors [16].

Our results corroborate those of other reports and suggest that topical imiquimod should be considered as an effective therapeutic agent in the conservative treatment of EMPD. For patients with extensive lesions that are unsuitable for surgical resection with free margins, imiquimod can be used in a neoadjuvant setting. Nevertheless, these promising results require validation in clinical trials.

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