Failure of Extensive Extramammary Paget Disease of the Inguinal Area to Clear With Imiquimod Cream, 5%

Possible Progression to Invasive Disease During Therapy

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**Background:** Surgical approaches are the standard treatment for extramammary Paget disease (EMPD), but nonsurgical modalities may be preferred and more appropriate for some patients. Topical administration of imiquimod cream, 5%, has improved or resolved in situ EMPD (n=21), but treatment failures (n=6) have also been reported.

**Observations:** We treated an elderly patient with initial biopsy-proved in situ genital EMPD with daily topical imiquimod, 5%, for 14 weeks. Midtreatment mapping biopsy specimens demonstrated invasive disease, with minimal clinical improvement. The patient subsequently underwent surgical excision.

**Conclusions:** Of the 27 published cases that describe imiquimod treatment of EMPD, 6 report treatment failure (22%), but factors that may contribute to treatment failure are not well understood. In the present patient, treatment with imiquimod may have been complicated by variable lesion thickness, which inhibited uniform penetration of imiquimod, or the presence of invasive disease not detected on initial biopsy. The efficacy of imiquimod to treat extensive invasive EMPD has not been demonstrated, and surgical approaches remain the most appropriate treatment for invasive disease. Variable responses to topical imiquimod use among patients suggest that other factors may be important in determining response to therapy.

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SURGICAL MANAGEMENT OF EXTRANAMMARY Paget disease (EMPD) remains a therapeutic mainstay, but alternative treatments for primary limited cutaneous EMPD in the anogenital area that avoid cosmetic and functional defects after extensive tissue removal are under investigation. Local recurrence of EMPD can be significant,1 highlighting the insidious nature of EMPD and the need to identify more effective treatments. The topical immunomodulator imiquimod, 5%, has been reported to induce clinical and histologic resolution of superficial EMPD,2-12 but several cases of imiquimod failure have also been described.13-17 Herein, we present a case of genital EMPD considered to be limited to in situ disease at the beginning of treatment with topical imiquimod that proved refractory, with demonstration of invasive disease during treatment. We also review the current literature (articles published in English and obtained through PubMed, Ovid, and GoogleScholar searches conducted between July 1, 2009, and August 31, 2010) regarding successes (n=21) and failures (n=6) of imiquimod therapy for EMPD and present characteristics that could portend treatment failure.

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**REPORT OF A CASE**

An 82-year-old man presented with a 1-year history of a pruritic lesion in the left inguinal area. Physical examination revealed a 9 × 5-cm velvety pink patch with a central, slightly elevated, verrucous plaque involving the suprapubic area, scrotum, and base of the penis (Figure 1A). Invasive disease was clinically suspected given the central plaque. Six 3-mm mapping punch biopsy specimens were collected peripherally and centrally and demonstrated only in situ EMPD (Figure 1B and C). Findings from lymph node and full-body skin examination, colonoscopy, and cystoscopy were unremarkable. After a urology consultation and discussion of treatment options, the patient chose a nonsurgical approach and applied imiquimod cream, 5%, to the lesion once daily for 14 weeks for a total of 98 applications. During treatment, tolerable mild lesional tenderness and erythema developed. Eleven weeks after the start of treatment, clinical improvement was limited to...
the periphery of the lesion (Figure 2A). Four 3-mm mapping punch biopsy specimens detected residual in situ EMPD peripherally but an invasive component at the center of the lesion. The patient then underwent excision of the lesion. Histopathologic analysis revealed invasive EMPD to a depth of 7.5 mm (Figure 2B). Peripheral margins were free of tumor; however, 1 tumor nest was identified 0.2 mm from the deep margin. The patient elected close observation.

COMMENT

Extramammary Paget disease is a relatively rare neoplasm classically involving skin-bearing apocrine glands in locations other than the nipple or areola of the breast. For unclear reasons, EMPD can be associated with underlying adnexal adenocarcinoma or other internal malignant neoplasms. Most commonly, EMPD involves vulvar skin in women, but it may present in the inguinal, scrotal, and penile areas in men and in the perineal and perianal regions in both sexes. Clinically, EMPD has an insidious onset, with patients reporting symptoms of itching, burning, and pain in affected areas even before visible lesions appear. Lesions of EMPD are described as erythematous or white, well-demarcated plaques with variable amounts of crust, ulceration, and scale. Histopathologic analysis reveals large round cells with abundant pale cytoplasm at all levels of the epithelium. Generally, patients with in situ EMPD have a good prognosis, but the presence of dermal invasion or metastasis seems to significantly increase morbidity and mortality. Similarly, EMPD associated with an underlying visceral malignancy carries a worse prognosis.

Historically, EMPD has been treated with wide surgical excision despite high recurrence rates (31%-61%). More recently, EMPD has been treated with Mohs micro-
bleomycin, 28 various systemic chemotherapeutic regimens, 3, 5, 9, 10, 40, 41 perineum, 2, 5, 11, 42 thigh, 43 and bilateral chest. 17

day; tx, treatment.

Treatment of EMPD of the vulva, 4, 6-8, 12, 40 groin and scrotum has emerged as a potential treatment for superficial EMPD. Recently, topical imiquimod, 5%, has been reported in 27 patients, with treatment success documented in 21 patients (78%).

Of the 21 patients with treatment success, 13 had primary EMPD, 5, 9, 10, 11, 12, 40, 43 and 7 had recurrent EMPD, 3, 8, 10, 41 and 1 had residual EMPD (Table 1). 42 Imiquimod cream, 5%, was applied with a frequency ranging from twice weekly for 16 weeks 7 to daily for 12 weeks. 42 Recurrent and residual cases of EMPD had been treated previously with surgical excision and vulvectomy, 6-8, 42 Mohs micrographic surgery, 3, 10, 41 electrodessication and curettage, 3 and photodynamic therapy. 3, 51 Of the 21

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<td>None</td>
<td>1: Negative immediately after tx cessation</td>
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Abbreviations: bx, biopsy; ED&C, electrodessication and curettage; EMPD, extramammary Paget disease; MMS, Mohs micrographic surgery; qod, every other day; tx, treatment.

Additional data about treatment were not included in original reports.
reported cases of treatment success, 18 were characterized as in situ EMPD on pretreatment biopsy; 1 contained dermal microinvasion, and 2 were not clarified.10,40 Posttreatment biopsy specimens were negative for EMPD in 18 patients and were not obtained in 3 patients.11,40 Follow-up was a relatively brief 10.8 months for the 18 patients for whom such details were provided (Table 1). In 5 of these patients, follow-up was 6 months or less, and in 4 patients, follow-up was recorded for 4 months or less.

To date, there are 6 cases (6 of 27 [22% of cases reported]) of topically initiated failure in the treatment of EMPD in the literature (Table 2).13-17 Among these, 3 cases of in situ EMPD were noted on pretreatment biopsy,13,15,17 but pretreatment biopsy findings were not reported for the remaining 3 cases (Table 2). One case was documented to be recurrent in situ EMPD,13 for which the patient had previously undergone surgical excision. The treatment regimen in these patients ranged from application of imiquimod cream, 1%, daily for 12 weeks15 to application of 5% cream every other day for 24 weeks and then every 3 days for 12 additional weeks.17 Posttreatment biopsy specimens revealed residual EMPD in all 5 patients for which such information was provided (Table 2). Length of follow-up was noted only for 1 case, in which recurrence was noted clinically 11 weeks after the cessation of treatment, with no posttreatment biopsies performed.17

Herein, we report apparent resistance to imiquimod therapy in an elderly patient with genital EMPD with either missed invasive disease at initial presentation or progression from in situ to invasive disease during treatment. In this case, only in situ EMPD was initially detected on mapping biopsies, including biopsies of the thicker and more hyperkeratotic portion of the lesion. Given these pathology results, our impression was that the biopsy specimens of the thick central portion of the lesion represented pronounced in situ disease. Therefore, we proceeded with imiquimod therapy. Several important points should be considered. Mapping biopsy specimens are typically collected from multiple representative areas of a lesion in an attempt to predict the general histopathologic condition of the lesion as a whole, but they do not allow the pathologist to examine the entire lesion. They are merely a “sampling” of a lesion’s histopathologic appearance. Therefore, in the present patient, invasive disease may have been missed from the outset by the initial mapping biopsy specimens. The efficacy of topical imiquimod use in extensive invasive EMPD has not been documented,9 and surgical excision in these cases may be more appropriate. Another point to consider is that therapeutic responses may be related to the depth of penetration of imiquimod such that thicker portions of an in situ lesion or tumor with extensive adnexal involvement or invasive disease may exhibit incomplete responses. In addition, variable responses to imiquimod in patients with presumed in situ EMPD suggests that additional, as yet unknown, factors may be important in predicting response to treatment. Furthermore, although topical imiquimod application may be effective in cases of in situ EMPD, refractory cases of presumed in situ EMPD may require further evaluation for an invasive component or other contributing factors.

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REFERENCES


