Perianal Extramammary Paget Disease Treated With Topical Imiquimod and Oral Cimetidine

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RESIDENT **PEARLS**

- Topical imiquimod cream 5% and oral cimetidine can be a potential alternative treatment regimen for poor surgical candidates with perianal extramammary Paget disease (EMPD).
- Its antineoplastic and immunomodulatory properties may suggest a role for oral cimetidine as an adjuvant therapy in the treatment of perianal EMPD.

Extramammary Paget disease (EMPD) is a rare intraepithelial adenocarcinoma. The current mainstay of treatment is wide local excision. We present the case of a 56-year-old woman with perianal EMPD that recurred 4 years after initial treatment with wide local excision with Mohs micrographic surgery tissue processing of marginal tissue. Upon recurrence with anal canal involvement, the patient was treated with a 16-week combination course of topical imiquimod and oral cimetidine. There is growing evidence to support both the use of topical imiquimod for the treatment of EMPD as well as the antioncogenic effects of oral cimetidine. We present this case of primary perianal EMPD to highlight an alternative treatment regimen for poor surgical candidates.

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Case Report

A 56-year-old woman with well-controlled hypertension, hyperlipidemia, and gastroesophageal reflux disease initially presented with itching and a rash in the perianal region of 1 year's duration. She had been treated intermittently by her primary care physician over the past year for presumed hemorrhoids and a perianal fungal infection without improvement. Physical examination at the time of intitial presentation revealed a single, well-demarcated, scaly, pink plaque on the perianal area on the right buttock extending toward the anal canal (Figure 1). Histologic sections of a punch biopsy of the lesion showed a proliferation of cells with atypical nuclei and clear cytoplasm located throughout the epidermis (Figure 2A). Immunohistochemistry was positive for cytokeratin 7 (Figure 2B) and cytokeratin 20 (Figure 2C) and negative for melanoma antigen and

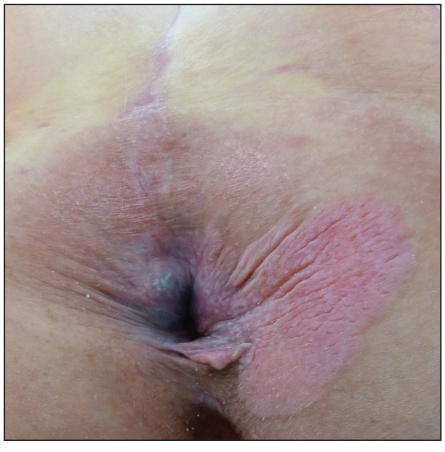

FIGURE 1. Perianal extramammary Paget disease presenting as a well-demarcated, scaly, pink plaque on the perianal region of the right buttock extending toward the anal canal.

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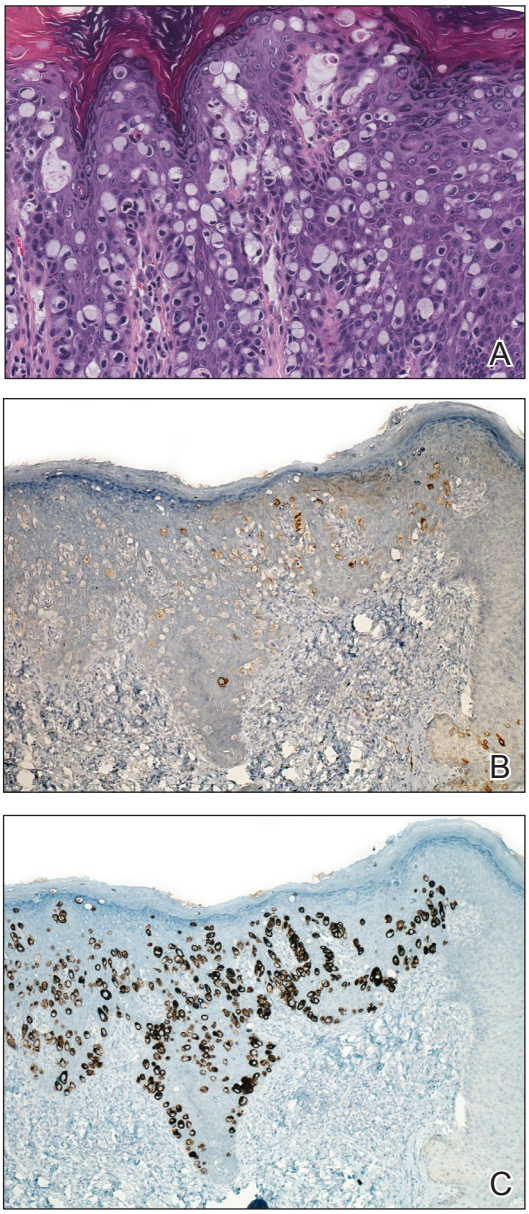

FIGURE 2. Histologic sections of a punch biopsy of the lesion in a patient with perianal extramammary Paget disease showed a proliferation of cells with atypical nuclei and clear cytoplasm located throughout the epidermis (A)(H&E, original magnification ×40). Pagetoid cells stained focally positive for cytokeratin 7 (B) and diffusely positive for cytokeratin 20 (C)(original magnification ×20).

human melanoma black 45. Following a negative workup for internal malignancy, which included basic laboratory testing (including serum carcinoembryonic antigen and cancer antigen 125 levels), computed tomography of the abdomen and pelvis, positron-emission tomography, Papanicolaou test, mammography, and colonoscopy, a diagnosis of primary extramammary Paget disease (EMPD) was made. The patient underwent wide local excision (Figure 3A) of the lesion with Mohs micrographic surgery tissue processing of marginal tissue (Figure 3B) with clear margins and reconstruction of the perianal region.

Four years later, the patient returned with new symptoms of bleeding when wiping the perianal region, pruritus, and fecal urgency of 3 to 4 months' duration. Physical examination revealed scaly patches on the anus that were suspicious for recurrence of EMPD. Biopsies from the anal margin and anal canal confirmed recurrent EMPD involving the anal canal. Repeat evaluation for internal malignancy was negative.

Given the involvement of the anal canal, repeat wide local excision would have required anal resection and would therefore have been functionally impairing. The patient refused further surgical intervention as well as radiotherapy. Rather, a novel 16-week immunomodulatory regimen involving imiquimod cream 5% cream and low-dose oral cimetidine was started. To address the anal involvement, the patient was instructed to lubricate glycerin suppositories with the imiquimod cream and insert intra-anally once weekly. Dosing was adjusted based on the patient's inflammatory response and tolerability, as she did initially report some flulike symptoms with the first few weeks of treatment. For most of the 16-week course, she applied 250 mg of imiquimod cream 5% to the perianal area 3 times weekly and 250 mg into the anal canal once weekly. Oral cimetidine initially was dosed at 800 mg twice daily as tolerated, but due to stomach irritation, the patient self-reduced her intake to 800 mg 3 times weekly.

To determine treatment response, scouting biopsies of the anal margin and anal canal were obtained 4 weeks after treatment cessation and demonstrated no evidence of residual disease. The patient resumed topical imiquimod applied once weekly into the anal canal and around the anus for a planned prolonged course of at least 1 year. To reduce the risk of recurrence, the patient continued taking oral cimetidine 800 mg 3 times weekly. Recommended follow-up included annual anoscopy or colonoscopy, serum carcinoembryonic antigen evaluation, and regular clinical monitoring by the dermatology and colorectal surgery teams.

Six months after completing the combination therapy, she was seen by the dermatology department and remained clinically free of disease (Figure 4). Anoscopy examination by the colorectal surgery department 4 months later showed no clinical evidence of malignancy.

Comment

Extramammary Paget disease is a rare intraepithelial adenocarcinoma with a predilection for white females and an average age of onset of 50 to 80 years.[1-3] The vulva, perianal region, scrotum, penis, and perineum are the most commonly affected sites.[1-3] Clinically, EMPD presents as a chronic, well-demarcated, scaly, and often expanding plaque. The incidence of EMPD is unknown, as there are only a few hundred cases reported in the literature.[2]

Extramammary Paget disease can occur primarily, arising in the epidermis at the sweat-gland level or from primitive epidermal basal cells, or secondarily due to pagetoid spread of malignant cells from an adjacent or contiguous underlying adnexal adenocarcinoma or visceral malignancy.[2] While primary EMPD is not associated with an underlying adenocarcinoma, it may become invasive, infiltrate the dermis, or metastasize via the lymphatics.[2] Secondary EMPD is associated with underlying malignancy most often originating in the gastrointestinal or genitourinary tracts.[1,2]

Currently, treatment of primary EMPD typically is surgical with wide local excision or Mohs micrographic surgery.[1,2] However, margins often are positive, and the local recurrence rate is high (ie, 33%–66%).[2,3] There are a variety of other therapies that have been reported in the literature, including radiation, topical chemotherapeutics (eg, imiquimod, 5-fluorouracil, bleomycin), photodynamic therapy, and CO_2 laser ablation.[1,3] To our knowledge, there are no randomized controlled trials that compare surgery with other treatment options for EMPD.

Despite recurrence of EMPD with involvement of the anal canal, our patient refused further surgical intervention, as it would have required anal resection and radiotherapy due to the potentially negative impact on sphincter function. While investigating minimally invasive treatment options, we found several citations in the literature highlighting positive response with imiquimod cream 5% in patients with vulvar and periscrotal EMPD.[4,5] A large, systematic review that analyzed 63 cases of vulvar EMPD—nearly half of which were recurrences of a prior malignancy—reported a response rate of 52% to 80% following treatment with imiquimod.[5] Almost 70% of patients achieved complete clearance while applying imiquimod 3 to 4 times weekly for a median of 4 months; however, little has been written about the effectiveness of topical imiquimod in EMPD. Knight et al[6] reported the case of a 40-year-old woman with perianal EMPD who was treated with imiquimod 3 times weekly for 16 weeks. At the end of treatment, the patient was completely clear of disease both clinically and histologically on random biopsies of the perianal skin; however, the EMPD later recurred with lymph node metastasis 18 months after stopping treatment.[6]

Given the growing evidence demonstrating disease control of EMPD with topical imiquimod, we elected to utilize this agent in combination with oral cimetidine in our patient. Cimetidine, an H_2 receptor antagonist, has been shown to have antineoplastic properties in a broad range of preclinical and clinical studies for a number of different malignancies.[7] Four distinct mechanisms of action have been shown. Cimetidine, which blocks the histamine pathway, has been shown to have a direct

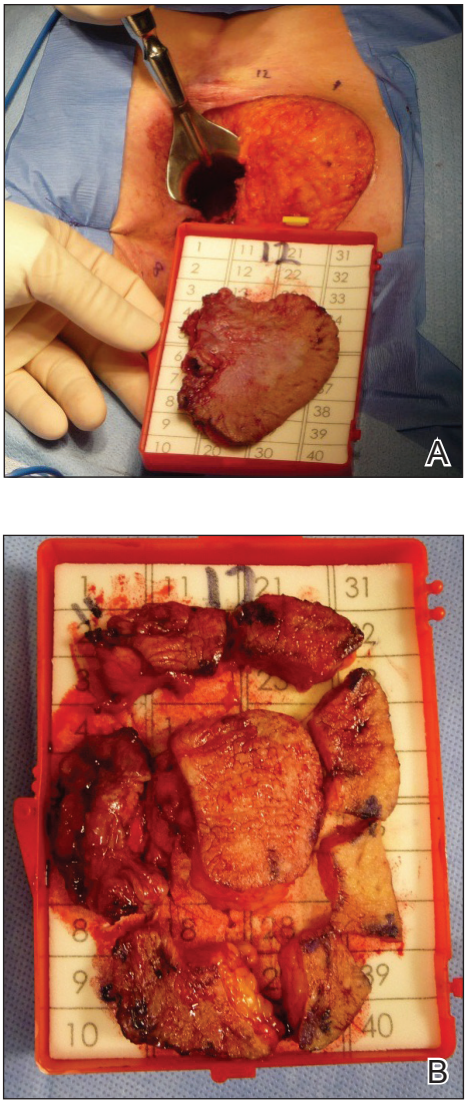

FIGURE 3. Wide local excision (A) with Mohs micrographic surgery tissue processing of marginal tissue (B) in a patient diagnosed with extramammary Paget disease.

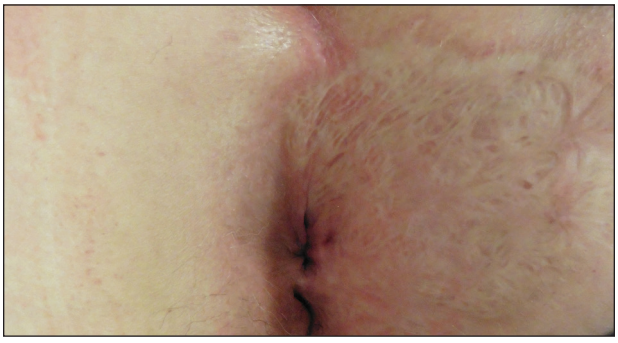

FIGURE 4. Six months after treatment with local excision with Mohs micrographic surgery tissue processing of marginal tissue for extramammary Paget disease, a well-healed scar is seen with no clinical evidence of recurrence.

antiproliferative action on cancer cells.[7] Histamine has been associated with increased regulatory T-cell activity, decreased antigen-presenting activity of dendritic cells, reduced natural killer cell activity, and increased myeloid-derived suppressor cell activity, which create an immunosuppressive tumor microenvironment in the setting of cancer. By blocking histamine and thus reversing this immunosuppressive environment, cimetidine demonstrates immunomodulatory effects.[7] Cimetidine also has demonstrated an inhibitory effect on cancer cell adhesion to endothelial cells, which is noted to be independent of histamine-blocking activity.[7] Finally, an antiangiogenic action is attributed to blocking of the upregulation of vascular endothelial growth factor that is normally induced by histamine.[7]

Cimetidine's antineoplastic properties, specifically in the setting of colorectal cancer,[8] were particularly compelling given our patient's EMPD involvement of the anal canal. The most impressive clinical trial data showed a dramatically increased survival rate for colorectal cancer patients treated with oral cimetidine (800 mg once daily) and oral 5-fluorouracil (200 mg once daily) for 1 year following curative resection. The cimetidine-treated group had a 10-year survival rate of 84.6% versus 49.8% for the 5-fluorouracil–only group.[8]

Conclusion

We present this case of recurrent perianal and anal EMPD treated successfully with imiquimod cream 5% and oral cimetidine to highlight a potential alternative treatment regimen for poor surgical candidates with EMPD.

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