A case of genital pyoderma gangrenosum successfully treated with cyclosporine without relapse of established follicular lymphoma

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Management of pyoderma gangrenosum in established malignancy is challenging. When vital structures are at risk from ulceration, aggressive management is required; however, immunosuppressive therapy may compromise the prognosis for an underlying malignancy. The optimal management of pyoderma gangrenosum in this setting is unclear. We report on a 64-year-old woman with follicular lymphoma in partial remission, who had severe genital pyoderma gangrenosum. After multidisciplinary evaluation, she was treated with corticosteroids and cyclosporine and healed fully with scarring over 7 weeks. She has required low-dose cyclosporine for 3 years to maintain remission of her genital ulceration; however, she remains well with no relapse of her lymphoma on serial imaging. (J Am Acad Dermatol 2018;4:474-6.)

Pyoderma gangrenosum (PG) is an ulcerating neutrophilic dermatosis associated with inflammatory bowel disease, rheumatologic diseases, hematologic disorders and malignancy. PG most commonly affects the lower limbs, may affect peristomal skin, and rarely involves mucosal and internal sites. Genital PG is rare.

A 64-year-old woman with stage IV follicular B-cell lymphoma in stable partial remission after 8 cycles of chemotherapy (including rituximab), had painful vulvo-vaginal and perianal erosions. These rapidly progressed to frank ulceration with extensive destruction of vulvar architecture. She had severe vulvar pain without additional systemic or gastrointestinal symptoms and raised inflammatory markers. Empirical treatment for candidal, bacterial, and herpetic infection had no benefit. Repeated cultures of swabs and skin biopsies were negative for viral, bacterial, mycobacterial, and fungal causes of ulceration; syphilis serology was negative. Computed tomography found stable lymphoma in partial remission, intact anal sphincter with no fistula formation, and no new malignancy. Examination under anaesthesia confirmed rectal and urethral integrity despite extensive deep ulceration of the vulva and perianal skin (Fig 1). The differential diagnosis at this point was wide but included aphthous ulceration, autoimmune blistering disease (especially in the setting of hematologic malignancy), and PG. Skin biopsies found nonspecific epidermal ulceration with abscess formation but without evidence of vasculitis, malignancy, or lymphoma. An inflammatory infiltrate extended into the subcutaneous adipose tissue comprising neutrophils, lymphocytes, histiocytes,

Abbreviation used:

PG: pyoderma gangrenosum

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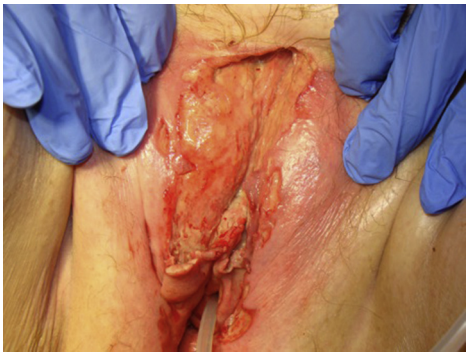

Fig 1. Extensive deep ulceration of the vulva.

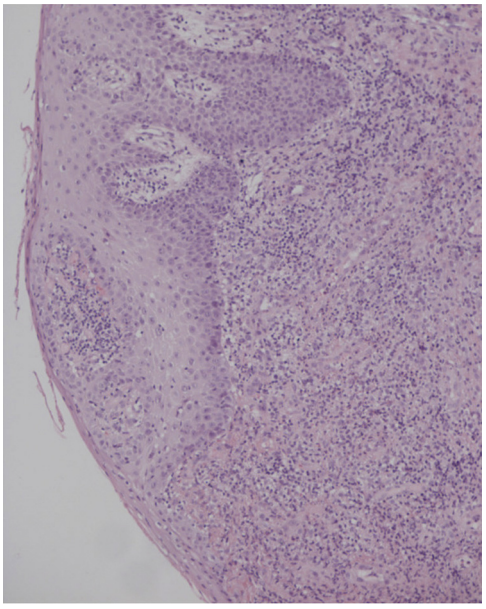

Fig 2. Nonspecific ulceration. (Hematoxylin-eosin stain; original magnification: ×10.)

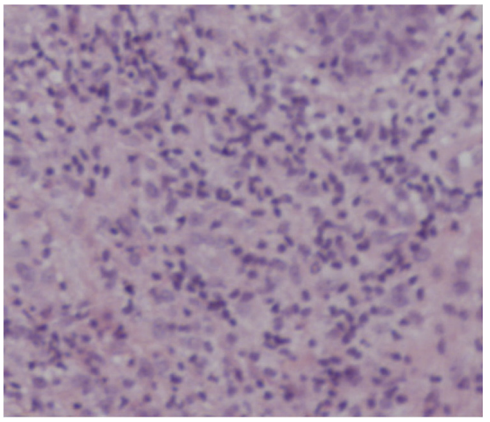

Fig 3. An inflammatory infiltrate comprising neutrophils, lymphocytes, histiocytes, and eosinophils. (Hematoxylin-eosin stain; original magnification: ×20.)

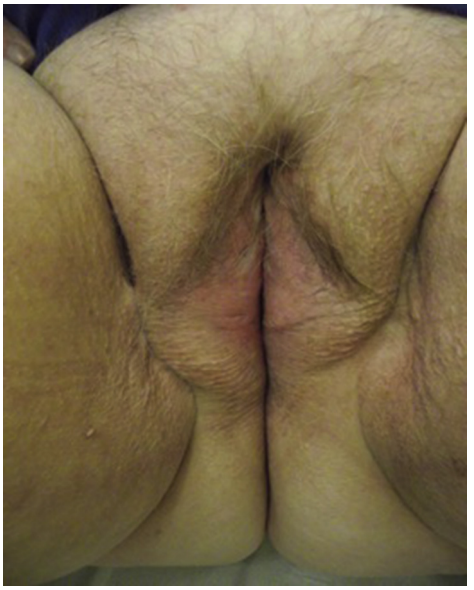

Fig 4. Improvement after treatment for 7 weeks.

and few eosinophils (Figs 2 and 3). The adjacent epidermis showed prominent irregular acanthosis with spongiosis and acute inflammation, but papillary dermal edema was not seen. There was no granuloma formation. Viral cytopathic changes or fungal elements were not seen, and a PAS stain was negative for fungi. Deeper levels found no additional features. There was no evidence of malignancy, polarizable foreign material was not seen, there was no evidence of koilocytosis, and special stains for micro-organisms were all negative. Immunohistochemistry findings for herpes simplex virus 1 and 2 were also negative. The case was further discussed at the dermatopathology multidisciplinary meeting, and it was felt that the most likely diagnosis, given the clinical picture, histology, microbiology, and immunohistochemistry was PG. Genital PG was diagnosed, assumed secondary to her lymphoma. After discussion with hematology colleagues, it was established that her lymphoma would require hematopoietic stem cell transplantation to effect cure and would carry significant risk. Anti–tumor necrosis factor therapy for her PG was considered; however, because of uncertainty regarding potential effect on tumor biology, consensus opinion was that a better risk/benefit profile would be obtained by treating her PG with cyclosporine and corticosteroids and monitoring her lymphoma for relapse. Our patient responded rapidly to therapy with prednisolone, 0.6 mg/kg/d, cyclosporine, 3 mg/kg/d, and minocycline, 100 mg/d. By week 7 she was fully healed with scarring (Fig 4). Prednisolone was successfully tapered to 7.5 mg/d over 18 weeks. However, subsequent attempts at tapering

cyclosporine to less than 1 mg/kg/d resulted in relapses, characterized by copious nonoffensive sterile discharge and superficial erosions, which responded each time to increased cyclosporine dose. Her lymphoma remains stable on serial imaging over 30 months with no further recurrence of PG on relatively low-maintenance-dose cyclosporine (1 mg/kg/d). Complications during therapy included mild adrenal suppression, pulmonary embolism, and mild (stable) renal impairment. The long-term impact of cyclosporine on her lymphoma prognosis is uncertain, and she is undergoing close follow-up by the hematology service. With close clinical surveillance, radiologically and serologically, she has remained well and symptom free without progression of her follicular lymphoma.

DISCUSSION

Genital PG is rare, but reported cases in the literature highlight the importance of including it in the differential diagnosis for recalcitrant genital ulceration, especially in cases of underlying systemic disease. In most cases, ineffective treatment is initially instituted[1] and broad ranging investigations are needed to rule out other potential causes.[2,3] PG affecting various sites is reported in several cases of hematologic malignancy.[4,5] In addition, it has been suggested that rituximab treatment itself may be a cause of PG in the treatment of B-cell non-Hodgkin lymphoma.[5,6] However, only one case of hematologic malignancy—related genital PG is reported to our knowledge,[2] which responded quickly to prednisolone and minocycline only. Busick et al[7] describe a case of PG responding to cyclosporine without adverse effects in a patient with lymphomatoid papulosis, with an improvement in plantar foot ulceration over 4 months, and no evidence of cutaneous T-cell lymphoma during a follow-up of 6 years.[7] The risk of cyclosporine-associated lymphoma after solid organ transplant is a well-established concept, and several case reports of non—transplant-associated hematologic malignancies in patients on cyclosporine have been published, which may raise concern. Suzuki et al[8] describe lymphoproliferative disorders after immunosuppressive therapy with a case of diffuse large B-cell lymphoma developing after cyclosporine treatment for aplastic anemia and notes that, although rare, it should be a consideration in all patients treated with this drug. Gattu et al[9] report a case of a solid B cell lymphoma occurring in a patient treated with cyclosporine even at psoriatic dosing. Behnam et al[10] in 2005 concluded "The recently published 5-year cohort study is the most rigorous data to date on the long-term safety of cyclosporine and shows no increased risk of lymphoma or internal malignancies." The study, however, illustrates increased risk of nonmelanoma skin cancers, especially squamous cell carcinoma.[10] It has been suggested that because cyclosporine has no direct genotoxic effect, tumor promotion is likely to be dose dependent; therefore, by reducing dosage and by avoiding combination therapy with other immunosuppressants, this risk may be diminished.[11] Treatment of PG is challenging in cases with established malignancy, and there is little published data to suggest optimum management.[12] Currently, the use of cyclosporine in hematologic malignancy remains controversial.[13] Therefore, multidisciplinary evaluation is crucial in defining the optimal risk benefit for patients with PG and malignancy and may not necessarily preclude cyclosporine therapy.

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