Pyoderma gangrenosum associated with alitretinoin therapy

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INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon ulcerative cutaneous condition, the etiology of which is poorly understood but is thought to be related to improper neutrophil function and chemotaxis. PG is a clinical diagnosis that requires exclusion of other ulcerative and inflammatory cutaneous disorders. A rare side effect of isotretinoin is the development of PG. We report the first case, to our knowledge, of PG associated with alitretinoin therapy (Appendix).

CASE REPORT

A 45-year-old woman with a long-standing history of presumed bilateral hand and foot eczema was treated with alitretinoin after not responding to topical super potent corticosteroid therapy. She was started on alitretinoin (30 mg daily), and the dermatitis significantly improved. However, 5 months after initiation of therapy, a painful ulcer developed on her left shin. Treatment with multiple courses of intravenous antibiotics was not effective. The patient was then referred to our dermatology clinic while still taking alitretinoin.

Physical examination found 2 discrete ulcers with violaceous, undermined borders on her left lower leg (Fig 1). The histopathologic features seen in the punch biopsy section taken from the left shin were mild and nonspecific (Figs 2 and 3). The epidermis was mildly acanthotic with the area of ulceration missing in the sampling. Mildly increased vascularity was noted in the papillary dermis, suggesting mild stasis-induced changes at this site. Dense neutrophilic infiltrate, granulomatous inflammation, and vasculitis were not noted. Periodic acid–Schiff stain was negative for fungal elements. Sterile superficial and deep skin cultures were negative for bacteria, fungi, and mycobacteria. Other investigations including complete blood count, serum protein electrophoresis, liver enzymes, and urinalysis were within normal limits, and hepatitis B surface antigen, antibody to hepatitis C, and HIV results were negative. Her medical history is relevant for eczema, type 2 diabetes mellitus, gastroesophageal reflux disease, and hypercholesterolemia. The patient had no systemic symptoms, including arthralgias or gastrointestinal symptoms, and did not suffer from any of the conditions noted to be associated with PG. PG was clinically diagnosed, and alitretinoin was withdrawn, as it was suspected to be the cause of the PG. The patient was treated with tacrolimus, 0.1% ointment twice daily, and intralesional corticosteroids. The ulcers did not heal completely, but after treatment with prednisone, 20 mg orally once daily, the ulcers healed within 2 months with cribriform scarring.

At the patient's request, and informed consent of an understanding of the risks, she was restarted on alitretinoin because of worsening hand dermatitis. A painful nodule developed at the same site on the leg 5 weeks after reinitiation. After prompt discontinuation, the lesions resolved in 3 weeks and never

Abbreviation used:

PG: pyoderma gangrenosum

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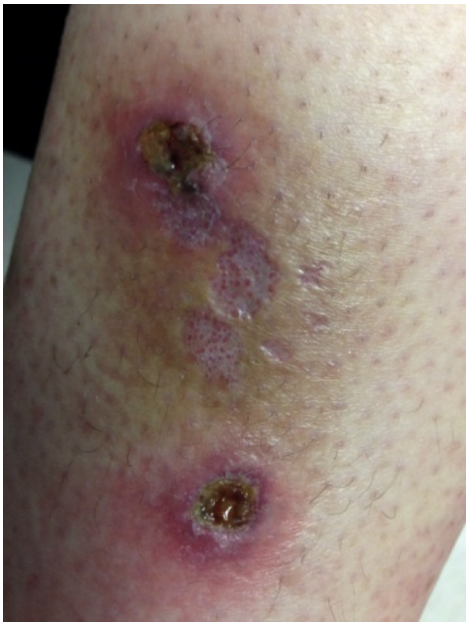

Fig 1. Pyoderma gangrenosum of the left lower extremity. Two necrolytic cutaneous ulcers with irregular, violaceous, and undermined borders. Cribriform scarring is present at sites treated with intralesional corticosteroids.

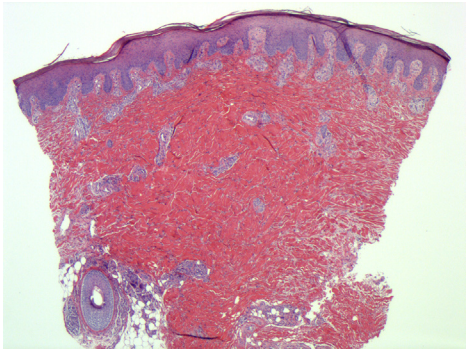

Fig 2. Pyoderma gangrenosum. Low-power examination shows mild nonspecific changes. Ulceration is not seen in this biopsy. (Hematoxylin-eosin stain; original magnification: ×25.)

recurred. Subsequent biopsy of the hand dermatitis was consistent with psoriasis. Given the new diagnosis, the patient was then treated with narrow-band ultraviolet B phototherapy with a moderate response. She later started ustekinumab (45 mg subcutaneously at weeks 0 and 4 and then every 12 weeks) and her hands cleared. After the PG, she did not have inflammatory bowel disease, arthritis, or any hematologic disorder.

DISCUSSION

PG is an uncommon neutrophilic dermatosis that presents as an inflammatory and ulcerative disorder

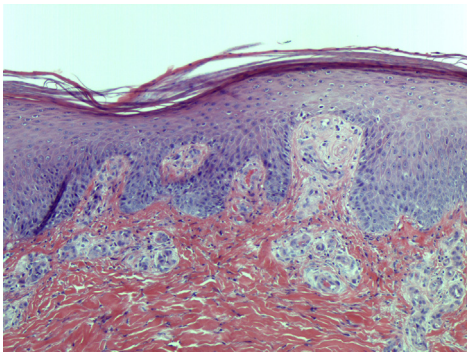

Fig 3. Pyoderma gangrenosum. High-power examination shows mildly increased vascularity in the papillary dermis. Dense neutrophilic infiltrate is not seen. (Hematoxylin-eosin stain; original magnification: ×100.)

of the skin. To our knowledge, this is the first reported case of PG in association with treatment with alitretinoin. Five cases of PG associated with isotretinoin therapy have been reported,[1-5] but PG associated with alitretinoin or any of the other retinoids has never been reported. The mechanism of PG resulting from retinoid use is unknown, but it is suggested that it is related to altered neutrophil chemotaxis,[5] increased skin fragility, or vascular proliferation.[1,6]

The biopsy result in this case showed nonspecific changes, and features diagnostic for PG were not seen. Two possibilities may account for this: the biopsy was taken from an area peripheral to the lesion, thus, missing the main findings or the lesion was partially treated or resolved at the time of biopsy, and only chronic nonspecific histopathologic changes remained. The location of the ulcers, presence of pain, undermining and cribriform scarring, negative tissue cultures, and rapid response to systemic steroid therapy are in keeping with a diagnosis of PG despite the lack of confirmatory histologic findings, which are not required for diagnosis.[7]

PG is associated with several autoinflammatory syndromes, but given our patient's lack of acne, hidradenitis suppurativa, arthritis, and systemic symptoms, her findings are not consistent with pyogenic arthritis, PG, and acne (PAPA) syndrome; PG, acne, and suppurative hidradenitis (PASH) syndrome[8]; or pyogenic arthritis, PG, acne, and hidradenitis suppurativa syndrome.[9] Other autoinflammatory conditions, such as deficiency of the interleukin-1 receptor antagonist; deficiency of the interleukin-36 receptor antagonist; and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome, may present with palmoplantar pustulosis[8] but also have osteoarticular and other findings that are notably absent in this case.

A small case series that showed the effectiveness of alitretinoin in treating palmoplantar psoriasis indicated that alitretinoin altered the number of innate inflammatory cells, including neutrophils, in skin sections.[10] Paradoxically, isotretinoin was reported to be efficacious in the treatment of PG in 2 cases[11,12] and in the treatment of PAPA syndrome in a third case.[13] Isotretinoin's paradoxical benefit in the treatment of PG is postulated to be owing to its inhibitory effects on neutrophil function.[11] Clinicians should consider the possibility of alitretinoin as the etiologic factor of PG.

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APPENDIX

We state in the manuscript that this is the first reported case of pyoderma gangrenosum associated with treatment with alitretinoin. Using the search criteria *pyoderma gangrenosum AND alitretinoin* OR *Toctino*, we searched both Ovid MEDLINE(R) and PubMed. The Ovid MEDLINE(R) database was queried from 1946 to the present, with no limitations on the published language. This search yielded zero articles. The PubMed database was queried using the same search criteria, and the results yielded just 1 article (Scheinfeld N. Dissecting cellulitis (Perifolliculitis Capitis Abscedens et Suffodiens): a comprehensive review focusing on new treatments and findings of the last decade with commentary comparing the therapies and causes of dissecting cellulitis to hidradenitis suppurativa. *Dermatol Online J*. 2014;20(5):22692); however, this article is not relevant to the case we are reporting. The Toctino drug monograph states the following dermatologic side effects:

1. Common side effects: dryness of the skin, especially of the lips and face, inflamed skin, hair loss.
2. Uncommon side effects: hair loss, skin peeling, rash, dry skin eczema.

There are no rare dermatologic side effects listed. Ulcers, and specifically pyoderma gangrenosum, are not listed as one of the side effects of the medication. Given this review of the literature and product monograph, we can confidently state that there are no previous reported cases of our findings in the published literature.