Intractable pyoderma gangrenosum in a Crohn's disease patient on vedolizumab

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INTRODUCTION

Pyoderma gangrenosum (PG) is a rare infiltrative neutrophilic dermatosis that characteristically presents with painful ulcers with violaceous, undermined borders on the lower extremities and less commonly presents with tender nodules or pustules.[1] Along with erythema nodosum, PG is one of the most frequent extraintestinal manifestations of inflammatory bowel disease (IBD). Although it is a common extraintestinal manifestation of IBD, PG does not always resolve when a patient's IBD is in remission, suggesting that PG may not be related to the activity of IBD.[2] We report the first case, to our knowledge, of intractable PG in a patient whose gastrointestinal Crohn's disease is well controlled on vedolizumab.

Abbreviations used:

IBD:	inflammatory bowel disease
PG:	pyoderma gangrenosum
TNF-α:	tumor necrosis factor alpha

CASE REPORT

A 32-year-old woman with history of Crohn's disease complicated by fistulas and PG, presented to our wound healing center for evaluation and management of rapidly expanding ulcers on both lower extremities. She had Crohn's disease diagnosed approximately 10 years before presentation. Initial treatment for her Crohn's disease included mercaptopurine, azathioprine, and methotrexate, all of which failed to adequately control her gastrointestinal symptoms. Approximately 1 year after diagnosis of Crohn's disease, lower extremity ulcers developed that were clinically diagnosed as PG. These ulcers were managed with high-dose prednisone, up to 100 mg daily, resulting in complete resolution of her wounds and improvement in her Crohn's disease. In an attempt to wean her from oral corticosteroids, she was started on the tumor necrosis factor alpha (TNF-α) antagonist, infliximab, but anaphylaxis developed after infusion of this medication. She was switched to another TNF-α antagonist, adalimumab, and was able to discontinue oral corticosteroids without flaring of her Crohn's disease or PG for approximately 5 years. Six months before presenting to our wound healing center, worsening gastrointestinal symptoms developed consistent with active Crohn's disease. Adalimumab was discontinued and she was started on the $\alpha4\beta7$ integrin antagonist, vedolizumab, with resolution of her gastrointestinal symptoms. Within 1 month of initiating vedolizumab, multiple rapidly expanding ulcers developed on her bilateral shins. Prednisone was started at 100 mg daily, with healing of her ulcers. However, the ulcers recurred once oral corticosteroids were tapered to doses less than 40 mg daily prompting referral to our wound healing center.

Physical examination was notable for a violaceous plaque with overlying ulceration on her right lateral tibia and an edematous violaceous plaque with scattered ulcerations in a cribriform pattern on her left medial foot (Fig 1, *A*). Laboratory values were notable for elevated white blood cell count with neutrophil predominance. Results of other investigations, including complete metabolic panel, were within normal limits. The patient had no systemic symptoms such as fever, malaise, arthralgia, or

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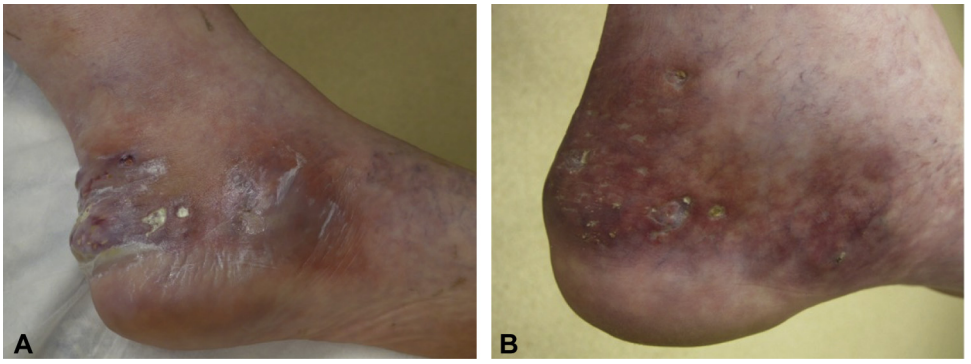

Fig 1. Clinical images of pyoderma gangrenosum. **A**, Necrolytic ulcer with irregular, violaceous, undermined borders on the left medial foot at initial presentation. **B**, Residual tender, violaceous erythema and cribriform scarring after 4.5 months of local and systemic treatments for pyoderma gangrenosum.

myalgia. Her lower extremities had minimal edema and no signs of chronic venous stasis. Pedal arterial pulses were normal intensity and equal bilaterally. Based on her presentation and history, she was given a clinical diagnosis of classic, ulcerative PG. A skin biopsy for histopathology was not performed, but she otherwise met major and minor diagnostic criteria for PG including rapid progression of painful, necrolytic cutaneous ulcers with violaceous and undermined borders; cribriform scarring; systemic disease associated with PG (IBD); and rapid response to treatment with systemic corticosteroids.[3] She was initially treated with intralesional triamcinolone (40 mg/mL) and maintained on 40 mg of prednisone daily. Topical therapy was started with cromolyn 4% drops and clobetasol ointment twice daily. Her prednisone was decreased to 35 mg daily, and dapsone, 100 mg daily, and cyclosporine, 5 mg/kg, daily were added to her treatment regimen. Despite this combination of multiple topical and systemic immunosuppressive treatments, her PG shows minimal clinical response (Fig 1, *B*). Meanwhile, her gastrointestinal Crohn's symptoms including abdominal pain and diarrhea have been well controlled on vedolizumab.

DISCUSSION

Vedolizumab is a humanized monoclonal antibody antagonist of $\alpha 4\beta 7$ integrin that was approved in 2014 for the treatment of moderately to severely active IBD in patients who have not responded to at least 1 conventional therapy including TNF-α antagonists. By binding to the $\alpha 4\beta 7$ integrin subunit and blocking its interaction with mucosal addressin cell adhesion molecule-1, vedolizumab inhibits leukocyte adhesion and migration.[4,5] Because IBD is largely driven by lymphocyte trafficking to sites of inflammation, and mucosal addressin cell adhesion molecule-1 is specifically expressed by blood vessels in the gastrointestinal tract, vedolizumab is unique in its gut selectivity and more targeted immunosuppression. Such selectivity is thought to carry a better safety profile, with fewer serious infections compared with those of anti−TNF-α agents. Vedolizumab also represents an improvement on its parent molecule, natalizumab, which targets $\alpha 4$ integrin in both gut and brain lymphocytes and thus has been associated with progressive multifocal leukoencephalopathy from reactivation of John Cunningham (JC) polyomavirus.[5]

Although some extraintestinal manifestations of IBD, such as erythema nodosum, parallel disease activity and respond to treatment of the underlying bowel disease, the association between PG and IBD activity is less clear.[6] The fact that this patient's PG worsened while her gastrointestinal symptoms remained in remission on vedolizumab raises questions about the potential differences in molecular drivers of gastrointestinal versus extraintestinal manifestations of IBD and differences in the pathogenesis of various cutaneous manifestations of IBD. Although one possibility is that her protracted treatment with multiple therapies contributed to more refractory disease, another explanation is that different manifestations of Crohn's disease are driven by distinct molecular mechanisms. Because of its gut selectivity, vedolizumab should not affect inflammatory pathways thought to be important in neutrophilic dermatoses, and thus initiation of the agent has the potential for flaring of PG. Because vedolizumab has been found to be a safe and effective treatment option for patients with moderate-to-severe Crohn's disease,[7] a more thorough understanding of the interplay between vedolizumab and PG would help guide future management of extraintestinal IBD and may uncover insights for developing

targeted therapies for specific extraintestinal complications.

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