

# Pyoderma gangrenosum induced by secukinumab in a patient with psoriasis successfully treated with ustekinumab



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## INTRODUCTION

Pyoderma gangrenosum is an inflammatory condition characterized by the presence of painful and necrotic ulcerations with a neutrophil-rich infiltrate. Although its pathogenesis is not completely understood, pyoderma gangrenosum has been associated with autoimmune disorders, such as inflammatory bowel disease. Drug-induced pyoderma gangrenosum has also been reported in the literature, particularly in relation to new targeted therapies including infliximab, adalimumab, and rituximab.<sup>1</sup> Herein, we present a novel case of pyoderma gangrenosum induced by secukinumab, an anti-interleukin (IL) 17A antibody in a patient with psoriasis.

## CASE REPORT

A black woman in her 50s presented with a 10-month history of plaque psoriasis and palmoplantar pustulosis. Initial, ineffective treatments included acitretin 17.5 mg daily and adalimumab 40 mg every other week, each tried for 3 months. Secukinumab 300 mg weekly was started for a total of 3 doses, which initially improved her psoriasis. The patient presented urgently because of rapidly evolving ulcerations on the bilateral aspect of her lower legs. Examination showed ulcers with elevated, edematous borders and central necrotic debris (Fig 1, A). The diagnosis was consistent with pyoderma gangrenosum, using the criteria by Maverakis et al<sup>2</sup> as follows: 1 major criterion with the histology of ulcer edge demonstrating a neutrophilic infiltrate plus 5 of 8 additional minor criteria, including negative results for bacterial, fungal, and mycobacterial cultures, thereby excluding infection;

### Abbreviation used:

IL: interleukin

history of pustule ulcerating; peripheral erythema, undermining border, and tenderness at the ulceration site; multiple ulcerations; and cribriform scars at healed ulcer sites (Fig 1, B).<sup>2</sup> Therefore, an evaluation for possible causes of pyoderma gangrenosum was performed.

Laboratory evaluation included normal results for complete blood cell count with differential, complete metabolic panel, urinalysis, and serum and urine electrophoresis, as well as negative results for antinuclear antibody, rheumatoid factor, antiphospholipid, and antineutrophil cytoplasmic antibodies. Screening results for inflammatory bowel disease, with esophagogastroduodenoscopy and colonoscopy, as well as screening results for malignancy, with age-appropriate surveillance and computed tomography of the chest, abdomen, and pelvis, were unrevealing. Secukinumab was discontinued because of concerns about drug-induced pyoderma gangrenosum. Treatment with cyclosporine 150 mg twice daily (dosed at 3 mg/kg/d) was initiated. Because of refractory pyoderma gangrenosum lesions (Fig 1, C) despite 4 months of cyclosporine, intravenous infliximab 5 mg/kg was added. The patient developed biopsy-proven leukocytoclastic vasculitis after 2 infliximab doses (weeks 0 and 2), so infliximab was stopped. Prednisone 80 mg daily was added to cyclosporine. The leukocytoclastic vasculitis did not recur after termination of infliximab.

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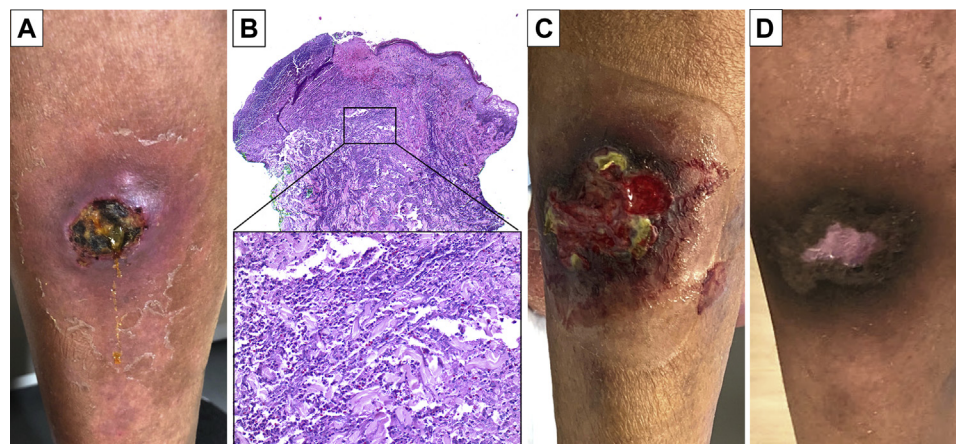
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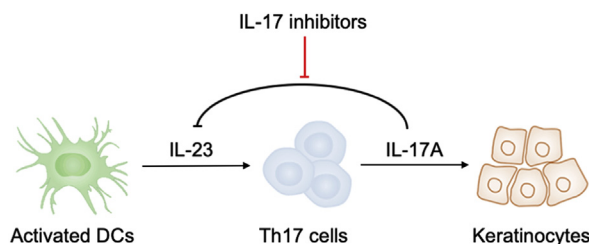
**Fig 1.** Gross and histologic examinations of the patient's pyoderma gangrenosum lesion. **A**, Physical examination revealed an ulceration with raised, gray and edematous borders and central necrotic debris on the posterior aspect of the right calf after 3 doses of secukinumab 300 mg once per week. **B**, Histologic examination of the biopsy at ulcer edge revealed an acute inflammatory infiltrate primarily consisting of neutrophils within the dermis and subcutaneous tissue, leading to epidermal necrosis, ulceration, and deep abscess formation. **C**, Physical examination showed an ulceration with gray, erythematous border and excessive drainage and fibrinous debris on the posterior aspect of the right calf after 4 months of cyclosporine 150 mg twice daily (dosed at 3 mg/kg/d). **D**, Physical examination showed an ulceration with a macular, hyperpigmented border and pink, re-epithelialized granulation tissue on the posterior aspect of the right calf after 2 doses of ustekinumab 90 mg at weeks 0 and 4, and then every 8 weeks. (**B**, Hematoxylin-eosin stain; original magnifications:  $\times 4$  and  $\times 20$ .)

To taper prednisone and cyclosporine, ustekinumab 90 mg on weeks 0 and 4 and then every 8 weeks was started. This resulted in significant improvement of the pyoderma gangrenosum, with the largest lesion on the right posterior aspect of the lower leg mostly re-epithelialized after only 2 doses of ustekinumab (Fig 1, D). The patient's psoriasis also improved. Cyclosporine and prednisone were successfully tapered 2 months after initiation of ustekinumab, and the patient continued to heal well.

## DISCUSSION

Secukinumab, a recombinant human IgG1 monoclonal antibody against IL-17A, is approved for the treatment of moderate to severe psoriasis and psoriatic arthritis in adults. Common adverse effects of secukinumab include nasopharyngitis and candidiasis.<sup>3</sup> Although development of pyoderma gangrenosum has been reported for the use of tumor necrosis factor  $\alpha$  inhibitors in patients with psoriasis,<sup>4</sup> pyoderma gangrenosum has never been linked to IL-17 antagonists in the United States. To our knowledge, this represents the first reported case of pyoderma gangrenosum induced by IL-17 inhibition in a psoriasis patient successfully treated with an IL-12/23 antagonist.

Upregulation of IL-23 has been observed in pyoderma gangrenosum lesions, and targeted



**Fig 2.** Proposed schematic of the interleukin 23/17 pathway implicated in the development of pyoderma gangrenosum after interleukin 17 inhibition. DC, Dendritic cells; IL, interleukin; Th17, T helper type 17.

treatments with ustekinumab, an IL-12/23 antibody, have yielded favorable clinical improvement.<sup>4,5</sup> Mechanistically, IL-23–induced activation of plasmacytoid dendritic cells and dermal dendritic cells triggers the release of IL-17A from T helper type 17 cells, which then act on epidermal keratinocytes to create a feed-forward inflammatory response (Fig 2).<sup>1</sup> However, inhibition of IL-17A may also paradoxically increase IL-23 production, triggering the development of pyoderma gangrenosum as observed in our patient and 2 similar cases reported in Japan and Germany.<sup>6,7</sup> All cases were found in patients with psoriasis, suggesting a possible association between pyoderma gangrenosum and IL-17A

inhibition in this patient population. Our patient's pyoderma gangrenosum lesions improved significantly after she received ustekinumab, further demonstrating that paradoxical IL-23 upregulation may be driving the development of pyoderma gangrenosum in patients treated with IL-17A-targeting biologics. Further clinical and laboratory studies are warranted to better define the role of IL-17A inhibitors in the treatment of psoriasis and development of pyoderma gangrenosum.

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