

Pyoderma gangrenosum in pregnancy successfully treated with infliximab and prednisone



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INTRODUCTION

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis with an important inflammatory component that usually presents as a nonhealing ulcer.¹ This cutaneous disorder has been associated with several systemic conditions including inflammatory bowel disease.² Treatment options for PG in pregnancy are limited. We present a case of pyoderma gangrenosum in a gravid patient treated successfully with infliximab and prednisone.

CASE REPORT

A 21-year-old woman (gravida 2, para 1), at 21 weeks of gestation, presented to a surgical clinic with an indurated lesion 4.5 cm in diameter with purulent drainage in her left pretibial region. The lesion initially developed days after trauma to her leg and subsequently failed to improve with empiric antibiotic therapy. Medical history was significant for ulcerative colitis under moderate control with mesalamine and pre-eclampsia in her previous pregnancy that necessitated an emergency cesarean delivery. Physical examination found no ascending cellulitis or adenopathy. Serologic findings for HIV, hepatitis B, and hepatitis C were negative. Serum protein electrophoresis result was normal. Antiphospholipid antibodies, antinuclear antibodies, and rheumatoid factor were negative. A bacterial infection was initially clinically suspected, and she underwent multiple surgical debridements.

The dermatology department was consulted because the pretibial ulcer continued to increase in

Abbreviations used:

PG: pyoderma gangrenosum
 TNF: tumor necrosis factor

size, developing a dark violaceous hue of the wound borders and increased purulence through the ulcer base (Fig 1, A). A biopsy found an ulcer with an underlying infiltrate consisting of predominantly neutrophils mixed with eosinophils, lymphocytes, and histiocytes in the dermis along with areas of dermal abscess formation. Special stains and cultures for bacteria, atypical mycobacteria, and fungus were negative. Based on the clinical presentation, histopathology, and negative tissue cultures, a diagnosis of pyoderma gangrenosum was made.

Prednisone (40 mg/d) was used to help control progression of the expanding ulcer. Infliximab (5 mg/kg) was concomitantly added as a steroid-sparing agent with an induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen every 8 weeks. Complete healing was observed at week 36, after receiving 4 infliximab treatments over 14 weeks. The prednisone dosage was also tapered over 16 weeks to 10 mg/d at the time of her delivery with no recurrence of the PG observed. The patient delivered a healthy full-term (38 weeks' gestation) baby by elective cesarean delivery with no recurrence of pre-eclampsia and no postpartum complications. In the early postpartum period, the patient was monitored by her local dermatologist who did not see any signs of wound infection or recurrence.

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Fig 1. Ulcer on the left pretibial region. **A**, Pretreatment with infliximab. **B**, Posttreatment with infliximab (4 months postpartum).

At her 4-month postpartum follow-up visit to our facility, the patient had discontinued prednisone with no recurrence or new areas of involvement (Fig 1, B). She is currently taking only infliximab for her ulcerative colitis and receives infusions every 8 weeks. The total duration of infliximab treatment has been 10 months.

DISCUSSION

PG is a rare, inflammatory neutrophilic dermatosis that is classically described as a painful ulcer with violaceous borders and a predilection for the lower legs. The phenomenon of pathergy, the provocation of new lesions by trauma, has been described in roughly 30% of patients with PG³ and was present in this case. The diagnosis of PG is challenging and requires the exclusion of other causes of nonhealing ulcers, particularly infections and neoplasms. PG is often associated with systemic conditions such as inflammatory bowel disease, hematologic malignancies, and rheumatologic conditions.¹

The pathogenesis of PG is unclear. It is thought to be an immune-mediated process involving neutrophil dysfunction, abnormal inflammatory cytokines, and abnormal production of tumor necrosis factor (TNF)- α , a powerful proinflammatory cytokine.^{4,5} Systemic therapies have included corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, infliximab, methotrexate, and intravenous immunoglobulin.^{3,6}

PG during pregnancy is quite uncommon.⁷⁻¹⁰ In a recent literature review by Steele et al⁷ of 26 published cases, 22 of the patients had PG between

the second trimester and postpartum. Steele et al⁷ hypothesized that the physiologic changes of pregnancy, which include elevations in granulocyte macrophage colony-stimulating factor,¹¹ a known attractant of neutrophilic inflammation, and increased band neutrophils may create conditions that mimic other inflammatory disorders, amplifying the risk of neutrophil-driven PG in response to local trauma. Supporting evidence included 11 cases likely involving pathergy in which PG developed at the site of cesarean incisions. The patients' treatment courses varied, although most women received systemic corticosteroids and half received adjuvant therapy with cyclosporine, dapsone, intravenous immunoglobulin, or other drugs. Notably, they found no report of TNF- α inhibitors being used to treat PG in a pregnant patient.

Treatment of PG in pregnancy can be challenging because of the possible adverse effects of medication on the fetus. In a recent review, corticosteroids and cyclosporine were the systemic therapies most commonly used to treat PG in pregnancy⁷; however, steroid use can impact fetal health, and cyclosporine can cause hypertension and renal toxicity, adverse effects that were concerning given our patient's history of pre-eclampsia. Intravenous immunoglobulin is another relatively safe option that has had reported success with PG in pregnancy.¹² To avoid complications associated with the continued use of high-dose systemic steroids and considering her history of ulcerative colitis, infliximab was chosen in consult with her gastroenterologist as the preferred steroid-sparing agent.

When steroids and steroid-sparing agents are started concomitantly, it can be challenging to distinguish the impact of each drug. In this case, systemic steroids played a major role, particularly initially, in controlling inflammation. It is possible that ulcer healing may have been caused by prednisone alone. It is also possible that infliximab prevented formation of a new ulcer at the cesarean incision site or relapse of the original ulcer, as prednisone dosage had been tapered at the time of delivery.

TNF- α inhibitors have been used successfully to treat PG in nonpregnant patients and, unlike many systemic treatments, are category B (US Food and Drug Administration classification) for pregnancy.⁴ Infliximab is a chimeric IgG1 monoclonal antibody that binds both soluble and membrane-bound TNF- α and induces apoptosis of TNF-expressing cells.¹ It is currently approved for the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis. Although the exact mechanisms of inflammation in PG are not clear, abnormal production of cytokines,

including TNF- α , a powerful proinflammatory cytokine, have been implicated.

Of the TNF- α inhibitors, infliximab has the most data supporting its use in the treatment of PG (including a randomized controlled trial¹³) and has been considered first-line treatment for PG associated with inflammatory bowel disease, with an 80% favorable response rate in corticosteroid-resistant PG.^{1,6} Use of anti-TNF- α biologics is associated with a slightly increased risk of serious infections and malignancies, although the most common adverse effects are infusion reactions and upper respiratory infections.¹ Our patient did not report any adverse effects.

Some researchers hesitate to consider the use of infliximab after 30 weeks of gestation, as infliximab crosses the placenta in the late second and third trimesters and is detectable in infant's serum for several months after birth.¹⁴ However, based on data from more than 300 pregnancy outcomes, infants born with detectable levels of infliximab do not appear to have an increased risk of infection in the first year of life and have no reported risk of long-term immunologic compromise. The infants show normal responses to nonlive vaccines; however, vaccination with live viruses should be avoided for at least 6 months.¹⁴

PG in pregnancy is a rare condition without consensus treatment guidelines. Infliximab was found to be an effective treatment for PG in this pregnant patient with comorbid ulcerative colitis. Further investigation is needed to compare the outcomes of infliximab and alternate steroid-sparing systemic agents for the treatment of PG in pregnancy.

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