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# Fellows' Corner

by Archit Garg

## CASE PRESENTATION

The patient, a 46-year-old woman, came to the emergency room with three blisters on her right leg, which had appeared a week prior and were getting bigger. No recent trauma, bites, or contact with seawater were noted. Never before had she encountered such lesions.

Previous medical issues: ulcerative colitis (diagnosed eight years ago), type 2 diabetes, and recurring iliopsoas abscesses due to uncontrolled diabetes, which needed several surgical drainages. She currently takes insulin, mirikizumab, mesalamine enemas, and budesonide, but she stopped taking budesonide two weeks ago.

On presentation, she was febrile (103°F) and tachycardic (HR 104 bpm). The physical examination is illustrated in Figure 1. There was no soft tissue gas detected on the lower extremity CT scan. During hospitalization, the bullae ruptured, leaving ulcers (Figure 2). Cultures taken from the ulcer remain negative. A biopsy was performed, which is shown in Figure 3.

### Question 1:

Which of the following is the treatment choice for the above condition?

- A) High-dose systemic corticosteroids
- B) Broad-spectrum intravenous antibiotics
- C) Surgical debridement and drainage
- D) Intensive insulin therapy and glycemic control
- E) Total colectomy

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Figure 1.

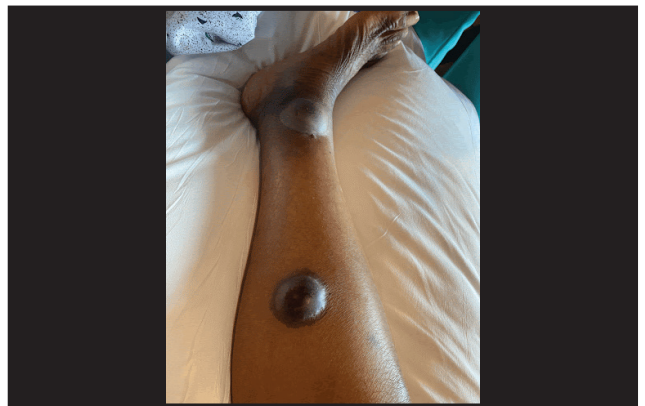
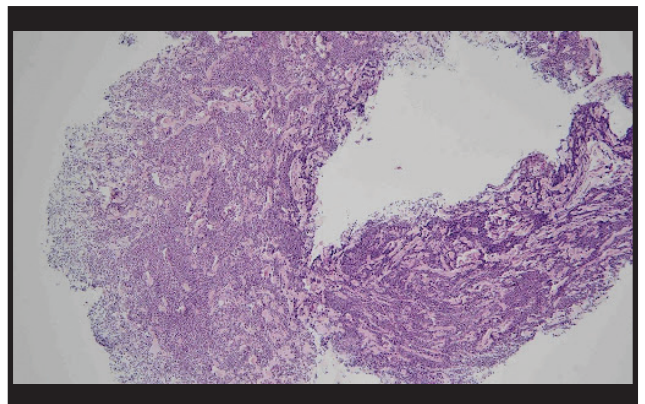


Figure 2.



Figure 3.



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### Correct Answer: A

#### Explanation

Pyoderma gangrenosum (PG) is the condition described above. The patient has a history of ulcerative colitis and painful purple blisters (Figure 1) that turned into ulcers (Figure 2), with purple, eroded edges, a dead base, and surrounding redness. The biopsy of the skin lesion shows an abundant neutrophilic infiltrate with leukocytoclasia and necrosis, strongly suggesting PG (Figure 3).

The first-line treatment for acute, severe PG is corticosteroids. Corticosteroids are potent anti-inflammatory and immunosuppressive agents that cause the sequestration of CD4+ T-lymphocytes and inhibit the transcription of cytokines. The usual dose is 0.5-1.5mg/kg per day of oral prednisone or its equivalent. Pulse therapy with 1 g methylprednisolone for 1-5 days may be considered for aggressive disease. The patient's recent cessation of budesonide may have contributed to this flare, making re-initiation of a high-dose steroid imperative. The response to steroids is usually rapid, and studies have shown complete healing after 6 months in about half of the patients.<sup>1,2</sup>

#### Option B:

While the ulcer may appear infected, in a setting of febrile presentation with immunosuppression, antibiotics are often initiated. However, the negative cultures, lack of evidence of primary infection (no gas on CT scan and bacteremia) indicate an autoimmune process, and antibiotics are ineffective in treating PG.

#### Option C:

Surgical debridement is contraindicated in the management of PG. In fact, surgery can provoke pathergy (trauma to the skin causing new, large ulcer formation). Debridement should be absolutely avoided in the initial phase of presentation.<sup>3</sup> In rare circumstances, once active disease is controlled and the ulcers are in the healing phase, careful removal of dead necrotic tissue can be considered.

#### Option D:

Optimizing glycemic control is essential for the

supportive management of diabetic patients. Ecthyma gangrenosum is a pseudomonas skin infection that typically manifests in individuals with uncontrolled diabetes. However, the absence of a typical clinical presentation (hemorrhagic bulla or pustule followed by necrotic ulcer) and bacteremia rules out ecthyma gangrenosum.

#### Option E:

Total colectomy was once considered a treatment option for PG, specifically in the context of peristomal PG associated with active IBD.<sup>4</sup> However, current recommendations are medical immunosuppression, given the significant morbidity and mortality associated with surgical interventions.

### Question 2: What is the pathogenesis of pyoderma gangrenosum?

PG is classified as a neutrophilic dermatosis. It arises from a complex dysregulation of innate and adaptive immunity. It involves dysregulated immune responses, with neutrophil recruitment and activation mediated by cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-17. [5] Th17/Th1 skewing and a neutrophil-driven inflammatory cascade marked by elevated cytokines (e.g., TNF- $\alpha$ , IL-1 $\beta$ , IL-17, IL-23, IL-36) are caused by antigenic priming in genetically predisposed individuals. IL-1 $\beta$  release is further amplified by genetic variants that impact the inflammasome pathways (PSTPIP1, MEFV, NLRP3, NLRP12, and NOD2). In addition to complement (C5a), NETosis, T-cell imbalance, and other triggers, such as trauma (pathergy), cause keratinocytes to release cytokines that contribute to the pathogenesis.<sup>6</sup>

### Question 3: What is the prognosis of pyoderma gangrenosum?

Nearly 50% of patients who receive treatment for PG achieve complete wound healing within one year. New lesions can develop during or after healing of other lesions, and relapses can occur after the disease has remained quiescent for months to years. The triggers for relapse can be minimal trauma, surgery, or, in some cases, no apparent trauma. PG is a lethal disease with reported mortality as high as 30%. Male sex, old

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age of onset, and bullous PG in the presence of hematological malignancies or disorders are some poor prognostic factors.<sup>6</sup> Death may occur due to underlying associated disorders (e.g., malignancy), sepsis from superimposed infection from the ulcers themselves, or from immunosuppressive therapy. The overall prognosis of pyoderma gangrenosum without underlying disease is good, particularly in those patients who readily respond to treatment, but considerable scarring and disfigurement may eventually result. The overall prognosis for PG in patients without underlying conditions is generally favorable, especially among those who exhibit a prompt response to treatment. However, significant scarring and disfigurement may ultimately occur.<sup>7</sup>

#### Question 4: How do immunomodulators compare to corticosteroids in the treatment approach for pyoderma gangrenosum?

The first-line treatment choice for PG remains corticosteroids. This is because of their rapid onset of action in controlling acute inflammation. However, long-term use of steroids is limited due to associated adverse effects. Steroid-sparing agents like immunomodulators, including cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, and biologics such as anti-TNF agents (e.g., infliximab, adalimumab) or IL-12/23 inhibitors (e.g., ustekinumab), play a crucial role as steroid-sparing agents and as primary therapy in severe, refractory cases. Biologics are often initiated along with steroids in patients with underlying autoimmune conditions associated with PG, for example, IBD, rheumatoid arthritis, etc. Hence, while steroids/cyclosporine remain the initial treatment of choice for rapid control, immunomodulators are essential for long-term disease management, relapse prevention, and minimizing steroid-related toxicity.<sup>6,8,9</sup>

#### Question 5: Is pyoderma gangrenosum specific to ulcerative colitis?

No, PG is not specific to ulcerative colitis. Although PG is recognized as a well-known extraintestinal manifestation of IBD (both Crohn's disease and ulcerative colitis), it can occur independently of IBD. It is associated with rheumatoid arthritis, seronegative arthritis, hematologic disorders

(such as leukemia, monoclonal gammopathy, myelodysplastic syndromes), and other autoimmune disorders.<sup>10</sup> Moreover, in up to one-third of the cases, the cause of PG is unidentifiable without any associated systemic disease.<sup>10</sup>

#### CONCLUSION

Pyoderma gangrenosum is a severe inflammatory skin condition strongly associated with ulcerative colitis. The first-line treatment is high-dose corticosteroids or cyclosporine. In severe cases, biologic therapy/ immunomodulators, such as infliximab, adalimumab, or mycophenolate, may be added. Surgical intervention is contraindicated due to the risk of worsening skin lesions through pathergy. The entity was first described by Brocq and Simon in 1908 as "*phagédénisme géométrique*" and subsequently renamed by Brunsting et al. in 1930. (5) ■

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