Rapidly Enlarging Bullous Plaque

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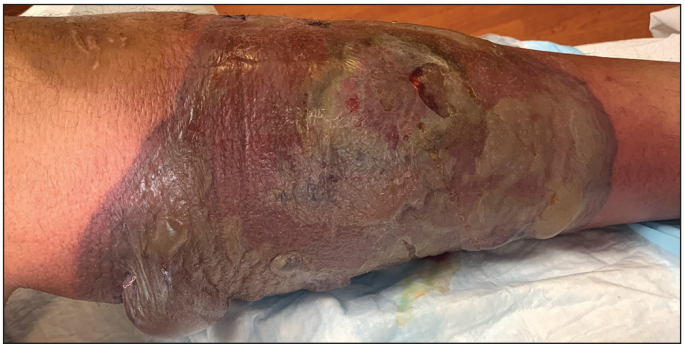

A 26-year-old previously healthy man presented to the emergency department with a new asymptomatic enlarging lesion on the lower leg that had appeared 4 days prior as a self-described "pimple" and rapidly evolved. The patient also reported chills, fatigue, and decreased appetite during that time. Physical examination revealed a red to violaceous, well-demarcated, bullous plaque involving much of the left lower leg. Laboratory studies demonstrated a hemoglobin level of 8.1 g/dL (reference range, 14.0–17.5 g/dL), hematocrit level of 23.7% (reference range, 41%–50%), platelet count of $26\times10^3/\mu L$ (reference range, $150–350\times10^3/\mu L$), and a population of circulating blast cells and metamyelocytes.

WHAT'S YOUR **DIAGNOSIS?**

a. brown recluse spider bite
b. bullous fixed drug eruption
c. bullous pyoderma gangrenosum
d. necrotizing fasciitis
e. Sweet syndrome

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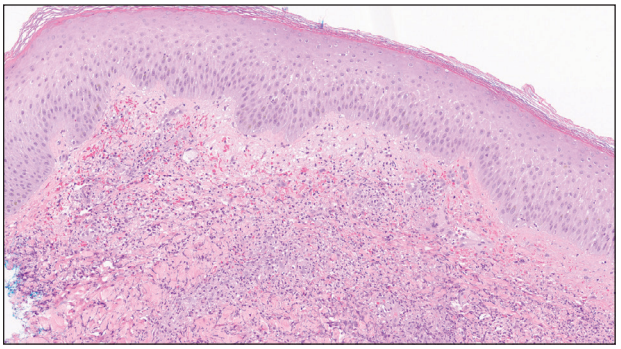
THE **DIAGNOSIS:** Bullous Pyoderma Gangrenosum

A bone marrow biopsy revealed 60% myeloblasts, leading to a diagnosis of acute myeloid leukemia (AML). A biopsy obtained from the edge of the bullous plaque demonstrated a dense dermal neutrophilic infiltrate with extravasated erythrocytes (Figure). Fite, Gram, and Grocott-Gomori methenamine-silver staining failed to reveal infectious organisms. Tissue and blood cultures were negative. Given the pathologic findings, clinical presentation including recent diagnosis of AML, and exclusion of other underlying disease processes including infection, the diagnosis of bullous pyoderma gangrenosum (PG) was made. The lesion improved with systemic steroids and treatment of the underlying AML with fludarabine and venetoclax chemotherapy.



Medium-power view demonstrated a dermal neutrophilic infiltrate with extravasated erythrocytes (H&E, original magnification ×20).

First recognized in 1916 by French dermatologist Louis Brocq, MD, PG is a sterile neutrophilic dermatosis that predominantly affects women older than 50 years.[1,2] This disorder can develop idiopathically; secondary to trauma; or in association with systemic diseases such as inflammatory bowel disease, rheumatoid arthritis, and hematologic malignancies. The pathogenesis of PG remains unclear; however, overexpression of inflammatory cytokines may mediate its development by stimulating T cells and promoting neutrophilic chemotaxis.[3]

Pyoderma gangrenosum classically presents as a rapidly enlarging ulcer with cribriform scarring but manifests variably. Four variants of the disorder exist: classic ulcerative, pustular, bullous, and vegetative PG. Ulcerative PG is the most common variant. Bullous PG is associated with hematologic malignancies such as primary myelofibrosis, myelodysplastic disease, and AML. In these patients, hematologic malignancy often exists prior to the development of PG and portends a poorer prognosis. This association underscores the importance of timely diagnosis and thorough hematologic evaluation by obtaining a complete blood cell count with differential, peripheral smear, serum protein electrophoresis with immunofixation, and quantitative immunoglobulins (IgA, IgG, IgM). If any of the results are positive, prompt referral to a hematologist and bone marrow biopsy are paramount.[3]

The diagnosis of PG remains elusive, as no validated clinical or pathological criteria exist. Histopathologic evaluation may be nonspecific and variable depending on the subtype. Biopsy results for classic ulcerative PG may reveal a neutrophilic infiltrate with leukocytoclasia. Bullous PG may include subepidermal hemorrhagic bullae. Notably, bullous PG appears histologically similar to the superficial bullous variant of Sweet syndrome.

Sweet syndrome (also known as acute febrile neutrophilic dermatosis) is a type of neutrophilic dermatosis characterized by fever, neutrophilia, and the sudden onset of tender erythematous lesions. Variations include idiopathic, subcutaneous, and bullous Sweet syndrome, which present as plaques, nodules, or bullae, respectively.[4] Similar to PG, Sweet syndrome can manifest in patients with hematologic malignancies. Both PG and Sweet syndrome are thought to exist along a continuum and can be considered intersecting diagnoses in the setting of leukemia or other hematologic malignancies.[5] There have been reports of the coexistence of distinct PG and Sweet syndrome lesions on a single patient, further supporting the belief that these entities share a common pathologic mechanism.[6] Sweet syndrome also commonly can be associated with upper respiratory infections; pregnancy; and medications, with culprits including granulocyte colony-stimulating factor, azathioprine, vemurafenib, and isotretinoin.[7]

Other differential diagnoses include brown recluse spider bite, bullous fixed drug eruption (FDE), and necrotizing fasciitis (NF). Venom from the brown recluse spider (*Loxosceles reclusa*) can trigger toxin-mediated hemolysis, complement-mediated erythrocyte destruction, and basement membrane zone degradation due to the synergistic effects of the toxin's sphingomyelinase D and protease content.[8] The inciting bite is painless. After 8 hours, the site becomes painful and pruritic and presents with peripheral erythema and central pallor. After 24 hours, the lesion blisters. The blister ruptures within 3 to 4 days, resulting in eschar formation with the subsequent development of an indurated blue ulcer with a stellate center. Ulcers can take months to heal.[9] Based on the clinical findings in our patient, this diagnosis was less likely.

Fixed drug eruption is a localized cutaneous reaction that manifests in fixed locations minutes to days after exposure to medications such as trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory drugs, salicylates, and oral contraceptives. Commonly affected areas include the hands, legs, genitals, and trunk. Lesions

initially present as well-demarcated, erythematous to violaceous, round plaques. A rarer variant manifesting as bullae also has been described. Careful consideration of the patient's history and physical examination findings is sufficient for establishing this diagnosis; however, a punch biopsy can provide clarity. Histopathology reveals a lichenoid tissue reaction with dyskeratosis, broad epidermal necrosis, and damage to the stratum basalis. A lymphocytic perivascular infiltrate also may appear in the dermis.[10] Both the clinical findings and histopathology of our case were not characteristic of FDE.

Necrotizing fasciitis is a fulminant, life-threatening, soft-tissue infection precipitated by polymicrobial flora. Early recognition of NF is difficult, as in its early stages it can mimic cellulitis. As the infection takes its course, necrosis can extend from the skin and into the subcutaneous tissue. Patients also develop fever, leukocytosis, and signs of sepsis. Histopathology demonstrates neutrophilic infiltration with bacterial invasion as well as necrosis of the superficial fascia and subepidermal edema.[11] Pyoderma gangrenosum previously has been reported to mimic NF; however, lack of responsiveness to antibiotic therapy would favor a diagnosis of PG over NF.[12]

Treatment of PG is driven by the extent of cutaneous involvement. In mild cases, wound care and topical therapy with corticosteroids and tacrolimus may suffice. Severe cases necessitate systemic therapy with oral corticosteroids or cyclosporine; biologic therapy also may play a role in treatment.[4] In patients with hematologic malignancy, chemotherapy alone may partially or completely resolve the lesion; however, systemic corticosteroids commonly are included in management.[3]

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