Violaceous-rimmed ulcers

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A 40-year-old man presented with a violaceous-rimmed ulceration on his inner thigh. He complained of crusting and drainage, but the lesion was otherwise asymptomatic. It began as a pimple, expanded into a small erosion, and then progressed to an ulceration (*Figure*). Medications at the time of presentation included prednisone and delayed-release mesalamine.

What is the diagnosis? What are the therapy options?

Figure. Violaceous-rimmed ulceration on the inner thigh.

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DIAGNOSIS: Pyoderma gangrenosum (PG) associated with Crohn's disease.

DISCUSSION

PG is an idiopathic neutrophilic dermatosis, which is associated with an underlying systemic disease in over 50% of cases (1, 2) (Table). Clinically, PG begins as follicocentric pustules with inflammatory halos that subsequently expand peripherally and form ulcers with sharply circumscribed violaceous raised edges in which necrotic pustules may be seen (1). Patients may have one or numerous lesions. The incidence of PG is uncertain, but it has been reported as 3 cases per million per year (4). While PG can occur at any age, patients are most commonly women aged 30 to 50 years. Lesions have a predilection for the lower extremities and trunk (5), and PG may occur at sites of trauma, a phenomenon called pathergy (6). Oftentimes, surgical debridement of PG leads to larger lesions and is therefore contraindicated (7). Fever, malaise, myalgias, and arthralgias frequently accompany rapidly progressing lesions (8).

Although the pathogenesis of PG is incompletely understood, the condition appears to be immune mediated (9). Numerous infectious agents have also been implicated in the pathogenesis of PG; however, no specific bacterium, fungus, or virus has been consistently identified (9). The concept of an altered immunologic reactivity is supported by the observation that PG is associated with inflammatory bowel disease, rheumatoid arthritis, non-Hodgkin's lymphoma, and myeloproliferative disorders (10).

Clinical variants of pyoderma gangrenosum

There are four clinical variants of PG: *ulcerative*, *pustular*, *bullous*, and *vegetative*. The *ulcerative* form occurs primarily in the extremities or lower trunk (2, 11); however, it has been reported in the vulva, the penis, the breasts, and the head and neck region (12–14). The lower limbs are involved in >70% of patients, and the lesions may arise either by themselves or in response to minor trauma, insect bites, or surgical procedures (11). *Pustular* PG typically occurs in the setting of ulcerative colitis and presents as painful pustules on the extensor aspects of extremities. Not all pustules evolve into ulcers, and these slowly resolving lesions may persist for unpredictable periods (11). The lesions may progress to, or coexist with, the ulcerative form in patients with inflammatory bowel disease (15–17). *Bullous* PG is a superficial blistering dermatosis, which may be associated with a concomitant leukemia (18). The lesions consist of bullae a few centimeters in size, resembling bullous impetigo, and often break down rapidly (1). *Vegetative* PG is a superficial form that generally remains confined to the skin and has no association with systemic disease (19). Lesions typically occur on the trunk

Table. Disorders associated with pyoderma gangrenosum*

Category	Disorders
Inflammatory bowel disease (15%)	Ulcerative colitis Crohn's disease
Arthritis (37%)	Seronegative, monoarticular arthritis, affecting large joints Symmetrical polyarthritis Psoriatic arthritis
Hematologic diseases	Acute and chronic myeloid leukemia Monoclonal gammopathy in up to 15% of patients (usually IgA) Large granular lymphocytic leukemia Hairy cell leukemia Myelofibrosis Waldenström's macroglobulinemia Polycythemia vera Hodgkin's, non-Hodgkin's, and cutaneous T-cell lymphoma
Humoral immune abnormalities	Congenital and acquired hypogammaglobulinemia Streaking leukocyte factor
Cell-mediated immune abnormalities	Defective neutrophil function Abnormal monocyte function Congenital deficiency in leukocyte-adherence glycoproteins Immune deficiency/immunosuppression
Solid tumors associated with PG	Colon, bladder, prostate, breast, bronchus, ovary, adrenocortical carcinoma
Other disorders	Chronic active hepatitis, cryoglobulinemia and hepatitis C, thyroid disease, chronic obstructive pulmonary disease, hidradenitis suppurativa, acne conglobata, sarcoidosis, atrophic gastritis, diabetes mellitus, lupus erythematosus, Takayasu's arteritis, dermatomyositis, HIV, Wegener's granulomatosis, sensorineural deafness, paroxysmal nocturnal hemoglobinuria, peripheral ulcerative keratitis, lung injury, Behçet's disease, diverticulitis, regional enteritis

*Based on reference 20; see also references 1 and 2.

and without the violaceous undermining border and pustular base that is characteristic of the ulcerative variant (1).

Evaluation and diagnosis

A thorough history and physical examination are mandatory. A skin biopsy should be sent for routine histologic examination. Additionally, tissue should be sent for special stains and cultures to evaluate for bacterial, fungal, mycobacterial, or viral organisms. To exclude other entities, physicians may order a variety of laboratory tests: complete blood count; chemistry tests (including liver and renal function tests); tests for antinuclear antibodies, antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies; serum protein electrophoresis; immunofixation electrophoresis; and urinalysis. Additionally, chest radiographs and a gastrointestinal tract evaluation are appropriate.

PG is a diagnosis of exclusion based on clinicopathologic correlation. Histologically, lesions are characterized by an accumulation of neutrophils throughout the dermis and epidermis (20).

Special stains and cultures for fungal, bacterial, or mycobacterial organisms are all negative (1). Ulcers develop as necrosis of the epidermis ensues after the inflammatory process spreads within the dermis (8). Of note, there is no associated vasculitis.

The clinical differential diagnoses for PG include folliculitis, furuncle, necrotizing vasculitis, cutaneous lymphomas, and insect bites (9). Other conditions to consider are venous, thrombotic, atherosclerotic, vasculitic, or neuropathic ulcers; squamous cell carcinoma; basal cell carcinoma; postoperative gangrene; ecthyma gangrenosum; atypical mycobacterial and clostridial infections; deep mycoses; amebiasis; tropical ulcers; bromoderma; North American blastomycosis and pemphigus vegetans; brown recluse spider bite; and sporotrichosis (9, 21–25).

The histologic differential diagnosis for PG includes Sweet's syndrome, which is another neutrophilic dermatosis without associated vasculitis (10). Clinically, patients with Sweet's syndrome present with symmetrical, red, sharply demarcated papules and plaques associated with fever, malaise, and an elevated peripheral white blood cell count (10, 26).

Treatment and prognosis

Treatment of PG should always start with finding and treating any associated underlying disorder (1). Thereafter, the aim of therapy is to halt the progression of ulcers, promote re-epithelialization, minimize pain, and limit scarring. Local (hydrocolloid dressing and intralesional corticosteroids) and systemic therapies may be required for adequate disease control (27–29). Traditionally, the cornerstone of therapy has been treatment with corticosteroids and cyclosporine (30). Sulfa drugs such as dapsone, sulfapyridine, and sulfasalazine have also shown some utility (11). Steroid-refractory cases may require combinations of corticosteroids and cytotoxic drugs such as azathioprine, cyclophosphamide, or chlorambucil (18).

Exciting novel therapeutic options include treatment with infliximab, etanercept, and intravenous immunoglobulin. Several case reports have documented the successful use of infliximab in PG associated with inflammatory bowel disease. Sapienza et al reported rapid resolution of PG in 4 female patients with fistulizing Crohn's disease treated with infliximab (32). Lopez San Roman et al described a patient whose PG could not be controlled with steroids and azathioprine (33). A single dose of infliximab 5 mg/kg was given, and the patient achieved an impressive response of the skin lesions followed by complete healing 3 months later. Additionally, McGowan et al reported a case in which a patient with widespread PG unresponsive to systemic corticosteroids had a rapid clinical remission with etanercept therapy (34).

Several case reports have also described successful use of intravenous immunoglobulin, usually in conjunction with corticosteroids (35, 36). Hagman et al described a patient who was successfully treated with intravenous immunoglobulin 400 mg/kg per day for 5 consecutive days (35). Of note, after 1 week there was an arrest in the evolution of the ulcers and a marked decline in pain, followed by clinical improvement of the ulcers 2 weeks later.

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