

# Pyoderma Gangrenosum

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## Abstract

Pyoderma gangrenosum (PG) is an idiopathic, painful and destructive condition that usually presents as an ulceration on the pretibial region of the legs. It primarily affects patients with inflammatory bowel disease, arthritis, myeloproliferative disorders and chronic hepatitis, and occasionally affects patients with other conditions, but it may also occur without any associated illness. Since there are no specific serologic or histologic markers for PG, it must be diagnosed clinically. Treatment usually involves immunosuppressant therapy as well as treatment of the underlying disease. The course of PG is unpredictable, and prognosis depends on the extent of the skin lesions at the time of diagnosis, underscoring the need for early and aggressive management.

**Key Words:** Pyoderma gangrenosum, inflammatory bowel disease, neutrophilic dermatoses, chemokines, cyclosporine, tacrolimus, corticosteroids.

PYODERMA GANGRENOSUM (PG) is an uncommon inflammatory skin disease that typically presents as a painful, destructive ulceration on the anterior surface of the legs. It was originally described by Brocq in 1916 (quoted in Bennett) (1) and later by Brunsting et al. in 1930 (2). A number of contributions to the study of PG have come from the Mount Sinai School of Medicine. Greenstein et al. studied the extra-intestinal manifestations of inflammatory bowel disease (IBD) in a large series of patients and provided data on the prevalence of PG in this group of disorders (3). Regional enteritis or Crohn's disease, a disease frequently associated with PG, was first described at Mount Sinai (4), and the occurrence of PG in this condition was reviewed by Libin et al., also from this institution (5). Talansky et al. studied the effect of intestinal resection on the course of PG (6) and Keltz et al. reviewed peristomal pyoderma gangrenosum (7). Freedman et al. described PG associated with anticardiolipin antibodies in a pregnant patient (8) and Klein et al. described three patients with diverticulitis, arthritis and PG (9). Hecker and Lebwohl (10) reported the efficacy of thalidomide in the treatment of recalcitrant PG.

The characteristic PG ulcer expands centrifugally and has a necrotic center filled with

blood, pus and granulation tissue (Fig. 1). The necrosis may be superficial or deep, involving skin, subcutaneous tissue, fascia, and rarely muscle. The boggy, raised border is characteristically deep red, purple or dusky blue with an undermined, ragged, overhanging edge (2). The advancing border is surrounded by an erythematous halo and may sometimes be studded with pustules (Fig. 2). On palpation, a purulent exudate can be expressed from sinus tracts at the base of the lesion and from under the violaceous border. About 40% of the cases of PG follow minor trauma, a phenomenon referred to as pathergy (11–13). In Brunsting's original paper, the condition was described as usually beginning with single or multiple pustules that ulcerated — but the primary lesion can also be a papule, erythema nodosum-like nodule or plaque (Fig. 3). The ulcer frequently expands



**Fig. 1.** Large ulceration involving pretibial area of leg. Note central blood and pus with region of deep necrosis.

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**Fig. 2.** Pyoderma gangrenosum: Advancing erythematous border with pustulation.



**Fig. 3.** Pyoderma gangrenosum: Early lesion beginning as erythematous plaque with a few pustules.

rapidly, resulting in massive tissue destruction, or it may extend slowly over weeks to months.

Lesions of PG are usually situated on the anterior aspect of the legs, but lesions can occur anywhere on the body, including the head and neck, abdomen and genitals (14, 15). There may be involvement in a peristomal distribution (Fig. 4) in patients with Crohn's disease or ulcerative colitis who have undergone ileostomy (7). This is possibly the result of a pathergic response to stomal appliances or fecal irritation. In addition to being uncomfortable, PG interferes with appliance adhesion. Involvement of the vulva, penis or perineal area can result in severe mutilation.

Ulcerations may be single or multiple. Adjacent PG lesions often become confluent, to form a single large ulcer with a polycyclic, scalloped border. The resulting lesion varies in size from a few centimeters to almost total limb involvement. Typically, severe pain and tenderness are associated with PG. Before complete healing has occurred, pus may be expressed from open-



**Fig. 4.** Peristomal pyoderma gangrenosum in a patient with ulcerative colitis. There is early re-epithelialization at the borders following perilesional corticosteroid injection.

ings in the re-epithelialized skin. PG ultimately heals with an atrophic, cribriform scar.

### Etiology

The etiology of PG is currently unknown. Brunsting, who considered PG to be an infectious process, referred to it as a pyoderma or ecthyma (1). Although cultures of early lesions are usually sterile, ulcers of longer duration may yield positive cultures for staphylococci and streptococci as a result of colonization and wound superinfection. Although removal of these colonies may aid wound healing, they are thought not to be involved in pathogenesis (16). Bacteria may, however, promote further tissue destruction, cellulitis and sepsis. The clinical spectrum of PG has been expanded to include atypical lesions, and there have been cases that occurred simultaneously with acute febrile neutrophilic dermatosis (Sweet's syndrome). Whether typical and atypical PG are precisely the same disease process remains to be determined.

The association of PG with immunologic disorders such as inflammatory bowel disease, paraproteinemia and rheumatoid arthritis, and its clinical response to immunomodulating agents such as corticosteroids and cyclosporine suggest an immune etiology. While several immunological abnormalities have been described in patients with PG (17–19), these findings must be interpreted cautiously, owing to the small number of cases studied. How a variety of diverse conditions with distinct immune abnormalities can lead to the final common pathway of neutrophilic infiltration and tissue destruction is not understood.

Immune defects that have been described include cell-mediated, humoral and complement

abnormalities, immune complex deposition, and the possible existence of circulating factors influencing lymphocyte function. It is important to note that no immune defect common to all, or to a majority of cases, has been delineated. While altered, delayed-type hypersensitivity has been noted in several patients, many patients have had normal function (20). In one case, altered type III hypersensitivity was associated with a circulating serum factor that inhibited *in vitro* immunologic responses of the patient's lymphocytes and those of normal controls (20).

An association of PG with benign monoclonal gammopathy, especially of the immunoglobulin A (IgA) type, has been described in some patients. Abnormalities of neutrophil and monocyte chemotaxis and phagocytosis have also been described (21). Mast cell activation has been implicated in the etiology of PG in one report (17). Interestingly, decreased neutrophil chemotaxis has been associated with elevated IgA levels in psoriasis, PG and Sweet's syndrome (22). This is thought possibly to be of significance in other dermatoses with neutrophilic infiltration, such as dermatitis herpetiformis, IgA pemphigus and Henoch Schonlein purpura. Moreover, neutrophils may undergo chemoattractant-induced upregulation of IgA receptors and concomitant IgA-induced increases in superoxide production *in vitro* (23).

The presence of pus as a clinical hallmark of PG and the large neutrophilic infiltrate on biopsy suggest that tissue destruction is mediated by the polymorphonuclear leukocyte. In disease states characterized by neutrophilic destruction of tissue, an oxidizing environment is created by neutrophil oxidants, such as hypochlorous acid (HOCl), which facilitates unregulated expression of neutrophil proteases such as elastase, collagenase or gelatinase (24).

At the same time, biopsy of the advancing edge of PG lesions demonstrates a lymphohistiocytic infiltrate, and more recently these lesions have been noted to contain activated mast cells (17). Snyder (25) has suggested that the mononuclear infiltrate on the advancing margin may initiate the chemotaxis of neutrophils. There have been conflicting reports regarding the deposition of immune reactants in PG. Dantzig (26) found no deposition of IgG, IgA, IgM, IgE or C3 in two patients with PG, whereas Su et al. (27) found deposition of C3 and IgM in the papillary and reticular dermis and proposed a lymphocytic vasculitis. Immune deposits have been reported by others

(28, 29). Although these immune deposits may play a role in the development of PG, it is possible that they are an epiphenomenon of the inflammatory process.

Recent work suggests that when inflammation occurs in the skin, inflammatory cell infiltration follows the upregulation of adhesion molecules on endothelial cells of post-capillary venules (30). In certain neutrophilic processes, endothelial cell activation by interleukin-1 (IL-1) produced by resident macrophages and tumor necrosis factor alpha (TNF $\alpha$ ) produced by macrophages and lymphocytes acting on some stimulus, lead to the expression of E-selectin and intercellular adhesion molecule-1 (ICAM-1) on the endothelial cell surface. This promotes adhesion and subsequent rolling of neutrophils on the endothelial surface. Chemotactic cytokines (chemokines) such as IL-8, ENA78, GRO $\alpha$ , GRO $\beta$  and GRO $\gamma$  are generated by macrophages, fibroblasts, endothelial cells and epithelial cells in response to TNF $\alpha$  or IL-1 in areas of inflammation (31). These chemokines cause directed extravasation of neutrophils. Mast cells, as have been identified in PG, may play a role in the expression of P-selectin (CD62P) on endothelial cell surfaces (15). Extravasated neutrophils can induce additional neutrophil recruitment as a result of their ability to produce IL-8, platelet activating factor (PAF) and leukotriene B<sub>4</sub> (LTB<sub>4</sub>). This scenario has not as yet been demonstrated in PG, but a positive feedback loop for neutrophilic infiltration has been suggested in psoriasis, another dermatosis in which neutrophils are prominent (32).

The rapid improvement of PG with cyclosporine therapy suggests the involvement of T-lymphocytes in the pathogenesis of PG. The predominant mechanism of action of cyclosporine is inhibition of T-lymphocyte activation, with profound reduction of IL-2 production. The target of immunosuppressive drugs such as cyclosporine and tacrolimus is held to be nuclear factor of activated T cells (NF-AT). This cyclosporine-sensitive transcription factor is expressed in T cells, B cells, natural killer (NK) cells, mast cells, monocytes and macrophages, but is not found in neutrophils (33). On the other hand, since cyclosporine may also inhibit monocyte and neutrophil phagocytosis and neutrophil superoxide production, its effects are not entirely limited to lymphocytes (34, 35). One research group has called the neutrophil an "obeying cell" driven by other cells of the immune system (36).

Although there have been no systematic studies of the pathergy reaction in PG, such studies have been performed on another neutrophilic dermatosis, Behçet's disease. One such study (37) reported subcorneal pustule formation and a variable, dense mononuclear infiltrate of T-lymphocytes and monocytes around vessels and skin appendages extending into the deep dermis. Endothelial cells expressed E-selectin and ICAM-1, but not vascular cell adhesion molecule-1 (VCAM-1). The authors suggested that the pathergy reaction might result from an antigen-independent, delayed-type, hypersensitivity-like reaction. This would differ from the normal response to trauma by a disproportionate release of inflammatory cytokines from injured keratinocytes, that might later be amplified by infiltrating activated lymphocytes.

Another possibility is that an unidentified autoantigen might be present in the skin of patients with PG. Das et al. (38) identified an epithelial autoantigen in ulcerative colitis that was present in colon, skin and biliary epithelium and suggested this might be a link in the pathogenesis of ulcerative colitis, pyoderma gangrenosum and sclerosing cholangitis.

PG commonly occurs in patients with other disorders such as inflammatory bowel disease, arthritis (39), chronic hepatitis (40, 41) or myeloproliferative disease (1, 2, 16, 42–44) (Table 1). Although it has been reported with a multitude of other conditions, including two cases with HIV infection, some of these associations are undoubtedly coincidental. IBD is the most commonly reported co-morbid condition; it has been noted in 30–60% of cases. Although 50% of PG cases were linked with ulcerative colitis in early reports, more recent series have suggested that this association is less common (1, 17, 45–47). Greenstein et al. (3), at this institution, found that five percent of patients with ulcerative colitis developed PG. In various studies, from 0.15% to 1.5% of patients with Crohn's disease have developed PG (46, 48, 49). In Greenstein's series, 1.4% of patients with Crohn's disease developed PG. Up to 50% of cases are idiopathic.

Visceral involvement by PG has been reported rarely, including pulmonary, bone, liver and spleen involvement (50). Kasuga et al. (51) described a patient with multiple aseptic pulmonary nodules that on biopsy showed chronic, nonspecific, inflammatory changes with neutrophils and lymphocytes.

PG is a relatively rare condition. It can affect any age group, but is most common in the third,

**TABLE 1***Diseases Associated with Pyoderma Gangrenosum***Common Associations**

- Inflammatory bowel disease
  - Chronic ulcerative colitis
  - Regional enteritis, granulomatous colitis (Crohn's disease)
- Arthritis
  - Seronegative with inflammatory bowel disease
  - Seronegative without inflammatory bowel disease
  - Rheumatoid arthritis
  - Spondylitis
  - Osteoarthritis
- Hematologic diseases
  - Myelocytic leukemias
  - Hairy cell leukemia
  - Myelofibrosis, agnogenic myeloid metaplasia
  - Monoclonal gammopathy (IgA)

**Rarely Reported Associations**

- Chronic active hepatitis
- Myeloma
- Polycythemia rubra vera
- Paroxysmal nocturnal hemoglobinuria
- Takayasu's arteritis
- Primary biliary cirrhosis
- Systemic lupus erythematosus
- Wegener's granulomatosis
- Hidradenitis suppurativa
- Acne conglobata
- Malignancy
- Thyroid disease
- Pulmonary disease
- Sarcoidosis
- Diabetes mellitus

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fourth and fifth decades of life. Children are affected less commonly, but have disease associations similar to those of adults, including IBD, arthritis and leukemia. Some cases in children have been reported in association with hypogammaglobulinemia (52). Rarely, PG in children may be complicated by chronic, recurrent, multifocal osteomyelitis (53). According to some authors, females and males are equally affected, but other investigators have noted a female predilection for the disease (54). PG has been reported rarely to develop after treatment with granulocyte colony-stimulating factor (G-CSF) and isotretinoin (55, 56).

Powell et al. (54) distinguish four variants within the clinical spectrum of PG: ulcerative, pustular, bullous, and vegetative forms. According to this schema, the ulcerative variant is typically associated with arthritis and IBD, the pustular variant with acute IBD, and the bullous

variant with myeloproliferative disorders (57). The vegetative form has no specific association. Although this schema is useful, there is often overlap between the different forms.

A recent retrospective study of 86 patients with PG treated at two medical centers compared the clinical findings in patients with typical PG and patients with atypical PG (1). Patients who presented with hemorrhagic bullae that ulcerated and who had more superficial findings on skin biopsy were considered to have atypical PG (APG). Among patients with typical PG, three out of four had involvement of the legs. Only one of 64 patients (1.5%) had head and neck involvement. Among patients with APG, 77% had upper extremity involvement, frequently on the dorsal aspect of the hands. Of the 22 patients with APG, 10 (46%) were associated with an underlying condition usually considered a PG-associated disease. Hematologic malignancy or disease was also associated with APG in six patients (27.3%) as compared to 10.9% of typical PG cases.

Patients acutely ill with ulcerative colitis may develop fever and a sterile pustular eruption reminiscent of the skin lesions of gonococemia (58). The pustules usually heal without scarring, but on occasion progress to typical PG ulcerations that heal with atrophic scars.

### Diagnosis

Since there are no specific serologic or histologic markers for PG, diagnosis is based on the clinical presentation (16, 54). When painful, destructive ulcers with purple-red overhanging borders occur on the legs in the context of IBD, the diagnosis is usually straightforward. Ulcers in other areas, such as those appearing on the face, scalp or neck, may be more problematic. Head and neck involvement, when it occurs, is usually accompanied by lesions involving more characteristic sites (e.g., the anterior legs), but in some cases involvement is limited to the face, scalp and/or neck (59, 60). Although activity of PG may parallel that of active ulcerative colitis and has in fact been used as indication for colectomy, there is evidence that PG can occur during periods of remission, even by as much as 12 years after colectomy (61). Talansky et al. (6) studied 9 patients with PG who underwent intestinal resection for IBD. Two patterns of postoperative PG healing were noted: (a) prompt healing in 5 patients with moderate or severe IBD and (b) persistent disease requiring immunosuppressive treatment in

patients with mild IBD prior to surgery or persistent bowel disease postoperatively. In the series studied by Levitt et al. (62), of 13 patients who underwent 15 resection procedures, PG healed quickly in 6 cases, only with additional therapy in 4 cases, and belatedly or not at all in 5 cases. PG has been reported to begin years after total proctocolectomy for IBD (63).

### Differential Diagnosis

Many conditions have been confused with PG, resulting in delayed diagnosis, inappropriate treatment and unnecessary surgery. The differential diagnosis depends on the stage and site of disease and whether an atypical form of PG is present (Table 2). Early lesions of classical PG may present as an inflammatory pustule or nodule and might suggest folliculitis, gonococemia, furunculosis, inflamed epidermal cyst, erythema nodosum, erythema induratum, vasculitis or thrombophlebitis. When an inflammatory ulcer is present, the differential diagnosis includes a variety of infections, vascular ulcers, neoplasms and reactions to ingested or external agents. Infections that may be confused

TABLE 2

*Differential Diagnoses of Pyoderma Gangrenosum*

#### Early Nonulcerated Pyoderma Gangrenosum

- Folliculitis
- Furuncles
- Arthropod bites
- Streptococcal gangrene
- Erythema multiforme
- Necrotizing vasculitis

#### Late Ulcerated Pyoderma Gangrenosum

- Atypical mycobacteria
- Behçet's disease
- Brown recluse spider bite
- Circulatory insufficiency
- Cryptococcosis
- Cutaneous amebiasis
- Factitial
- Halogenoderma
- Meleney's ulcers
- North American blastomycosis
- Pyoderma vegetans
- Sporotrichosis
- Syphilitic gumma
- Systematic lupus erythematosus
- Thrombophlebitis with gangrene
- Ulcerative necrobiosis lipoidica diabetorum
- Wegener's granulomatosis
- Wound infection

Adapted in part from Keltz M, Lebwohl M, Bishop S. Peristomal pyoderma gangrenosum. *J Am Acad Dermatol* 1992; 27:360–364 (7) (with permission).



**Fig. 5.** Chronic ulcerative herpes simplex infection on the chin of a patient with AIDS.

with PG include chronic ulcers of herpes simplex virus as seen with HIV infection (Fig. 5), bacterial pyodermas, blastomycosis-like pyoderma (Fig. 6), ecthyma gangrenosum, syphilitic gummas, cutaneous tuberculosis, atypical mycobacterial infections, deep fungal infections, leishmaniasis (Fig. 7) and cutaneous amebiasis.

Chronic vascular ulcers on the lower legs, common in older age groups, are exceptional in younger adults at risk for PG. Stigmata of venous insufficiency include varicosities, stasis dermatitis, pigmentary changes and chronic edema. Venous ulcerations usually occur near the medial malleolus and are rarely confused with PG. Arterial insufficiency generally produces ulcers that are painful on elevation. The extremity may be cool with shiny, hairless skin and decreased pulses. Vasculitic conditions such as polyarteritis nodosa, rheumatoid arthri-



**Fig. 6.** Blastomycosis-like pyoderma (pyoderma vegetans) caused by *Pseudomonas aeruginosa*. Lesion healed completely with antibiotic therapy.



**Fig. 7.** Cutaneous leishmaniasis in a child who had visited Ecuador.



**Fig. 8.** Ulceration from rheumatoid vasculitis mimicking PG.

tis (Fig. 8), Wegener's granulomatosis, and Churg-Strauss syndrome can cause ulceration that could be confused with PG. Neuropathic ulcers occur in association with diabetes on weight-bearing surfaces.

Certain drugs have been implicated as causes of PG and non-PG ulcerations. Isotretinoin and granulocyte-macrophage colony stimulating factor (GM-CSF) have been reported to cause PG, and ingestion of bromides or iodides may produce halogenoderma, a rare ulcerative condition resembling PG. Warfarin anticoagulants may induce painful necrotic lesions (Coumadin necrosis) in predisposed individuals, usually within the first five days of treatment (64).

We recently encountered an elderly woman with chronic lymphocytic leukemia who developed nonhealing, inflammatory ulceration of the legs several months after beginning hydroxyurea. There was no response to high-dose corticosteroids; in fact, she developed cellulitis after the initiation of cyclosporine. Such painful leg ulcerations have been described in

the literature in patients receiving hydroxyurea for myeloproliferative disorders (65–73). It is thought that the selective cytotoxicity of hydroxyurea for cells that divide most actively (such as those of the skin) might cause these ulcerations by impairing normal wound healing in areas of trauma, especially if there is concomitant arterial or venous disease (65, 66). The impaired circulation of megaloblastic erythrocytes may also be of importance (68, 69).

Other rare conditions to be considered are brown recluse spider bite, syphilitic gumma, cutaneous blastomycosis, leishmaniasis and trigeminal trophic syndrome (74–78). Jemec and Konradsen (79) describe a case in which PG was mistaken for necrotizing fasciitis.

Once PG is suspected, certain laboratory studies should be obtained based on the clinical findings. These should include complete blood count, rheumatoid factor serology, antinuclear antibodies and an activated partial thromboplastin time (APPT). An elevated APPT might suggest the antiphospholipid antibody syndrome, which can cause cutaneous ulceration (80). Under certain circumstances, bone marrow examination, gastrointestinal studies, or HIV testing may be indicated. Because PG may occur prior to the onset of an associated disease, patients with PG should be re-evaluated periodically.

The role of biopsy in the work-up of patients with PG is controversial, because pathologic changes are not diagnostic and there is risk of a superimposed pathergic response and extension of the ulcer. However, it may be necessary to accept the added risk to exclude infection or vasculitis.

The histopathology of PG is nonspecific and varies according to stage, variant, and biopsy location (81, 82). Necrotizing, suppurative neutrophilic infiltration is prominent along with ulceration, and there may be evidence of leukocytoclasia. Frank vasculitis is rarely reported in areas of maximal tissue destruction, but the underlying process is probably not primarily a neutrophilic vasculitis (81, 82). In some cases, a necrotizing, pustular, neutrophilic, follicular reaction may be the central nidus of the lesion. PG is considered one of the neutrophilic dermatoses, which include leukocytoclastic vasculitis, Sweet's syndrome, Behçet's disease, erythema elevatum diutinum, rheumatoid neutrophilic dermatitis, and skin lesions of bowel bypass syndrome. Biopsy of the erythematous leading border may show a mononuclear infiltrate of lymphocytes, macrophages, plasma

cells and mast cells (17). To aid in cases where an infectious etiology is suspected, culture and sensitivity of the biopsy specimens is advisable for bacteria, tuberculosis, atypical mycobacteria, and fungi.

### Treatment

The treatment of PG depends on the extent, severity and chronicity of the lesions, previous treatment, underlying conditions and pertinent coexisting medical disease. Currently, there is no one definitive treatment regimen for PG. Local therapy alone is sometimes adequate to arrest smaller, early lesions, but systemic treatment is required for more severe disease (7, 54). We favor aggressive treatment to halt progression, decrease pain and prevent extensive scarring. Because PG is extremely painful, treatment should include adequate analgesia. Opiates are often necessary.

Local therapy includes topical wound care and sometimes topical and intralesional corticosteroids (19). Daily cleansing, antiseptic compresses and dressing changes are useful in avoiding wound superinfection. Triamcinolone acetonide 10–40 mg/mL injected into the base and borders of the lesion is sometimes helpful but should not be used in infected lesions (16, 83). Injections are painful and often not well tolerated. Topical anesthetics are of some value in decreasing the pain of injection, but to prevent excessive absorption and toxicity, they should be used cautiously on large wounds. Surgical debridement should be avoided, since it may cause extension of the ulcer and further tissue damage.

Aggressive, rapidly progressing lesions and/or lesions unresponsive to local measures require systemic therapy, usually with glucocorticoids (16, 83). In the last few years, cyclosporine has been found to be highly effective and is considered by some to be the treatment of choice for PG. Prior to the initiation of immunosuppressant therapy, infection should be excluded. If corticosteroids are used, large doses of prednisone, up to 120 mg daily, may be required to halt the rapid progression of the ulceration. Once the ulcer ceases to expand and the peripheral erythema fades, corticosteroids can be tapered slowly over a three-month period. Rapid withdrawal of prednisone may precipitate reactivation of PG and should be avoided. Corticosteroid pulse therapy using suprapharmacologic doses of corticosteroids has been reported to be effective in patients

with severe PG (84, 85). Patients must be carefully monitored for cardiac arrhythmias and electrolyte abnormalities (86). Recently, in a recalcitrant case, pulse methylprednisolone was used in combination with cyclosporine (60).

Dapsone, a sulfone used for a variety of infectious and inflammatory diseases, is reported to be helpful in the treatment of PG. Its main advantage is that it allows reduction in corticosteroid dosage. Although dapsone is used safely worldwide with minimal toxicity for the treatment of leprosy, there are some well-established toxic effects. Blood dyscrasias, including hemolysis, methemoglobinemia, leukopenia and rarely agranulocytosis, have been reported (87). Most patients on dapsone will develop some hemolysis and mild anemia, but in patients with a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD), the anemia may be more profound and life threatening. This is especially relevant in patients with underlying cardiovascular disease. Pretreatment measurement of this enzyme is recommended in high-risk groups. Agranulocytosis, though rare, is life threatening. Along with low white blood cell count, it presents with sore throat, fever and sometimes a morbilliform eruption. Other adverse effects of dapsone include toxic hepatitis, renal disease, drug hypersensitivity syndrome and neuropathy, as well as gastrointestinal side effects.

Cyclosporine, a highly potent immunosuppressant agent used in transplantation patients, has recently been found to be effective in the treatment of refractory and severe cases of PG (88–92). The drug prolongs allograft survival by suppressing T-lymphocytes and lymphokines (89). An advantage of cyclosporine over other immunosuppressants is the absence of bone marrow suppression (83). Most PG patients respond to low doses of cyclosporine, ranging from 3–6 mg/kg per 24 hours (83, 88–90). Patients receiving cyclosporine should be carefully monitored for blood pressure elevation and deterioration of renal function. In addition, liver functions and triglycerides should be evaluated periodically. Other side effects associated with high doses of cyclosporine include anaphylaxis, hyperkalemia, and hyperuricemia. Cyclosporine should only be administered by physicians experienced in its use.

Mycophenolate mofetil has been used to improve the efficacy of cyclosporine in particularly recalcitrant cases of PG (93, 94). It is usually administered in doses of 1 g twice daily. Reported side effects include abdominal cramps, nausea, vomiting, diarrhea, mild-to-

moderate leukopenia, and anemia and liver function abnormalities. As with any immunosuppression, patients should be advised of the potential for the development of lymphoma, although the incidence of this complication is not known.

Systemic tacrolimus (FK-506) and tacrolimus ointment alone or in combination with systemic tacrolimus or cyclosporine have been effective in treating PG (95–97).

Thalidomide has been used successfully in the treatment of PG (10, 98, 99). Because of severe teratogenicity, it should not be administered to women who might become pregnant. Side effects of thalidomide include a sensory peripheral neuropathy, drowsiness and constipation (100). Other treatments that have been reported anecdotally to benefit patients with PG are transdermal nicotine, subcutaneous and perilesional GM-CSF, minocycline, clofazimine and chlorambucil (101–105). A recent case report of PG associated with ulcerative colitis and arthritis was attributed to margination of neutrophils from increased adherence of neutrophils to vascular endothelium (106); the patient had a rapid response to intravenous heparin.

If an associated systemic disease is present, it should be treated aggressively. Occasionally, successful chemotherapy of leukemia and other myeloproliferative disease may cure PG (107). In some patients with ulcerative colitis, resection of the affected colon was followed by healing of the skin lesions. However, the correlation between associated disease activity and skin disease progression is variable, and colectomy usually is not indicated merely for treatment of PG.

The prognosis of PG is variable. Depending on the initial severity of the ulcer and choice of treatment, healing occurs in weeks to months and, in some cases, may take up to a year (6). PG may recur upon withdrawal of steroids or immunosuppressive agents. Chronic treatment may sometimes be necessary.

### Summary

PG is an uncommon clinical condition whose pathophysiology remains poorly understood. It is often painful, and because of rapid spread and extensive tissue destruction, requires immediate, aggressive treatment. The presence of PG is frequently an indication of concomitant serious medical illness, most commonly IBD. These illnesses should be treated by the appropriate medical specialist.

The differential diagnosis of PG must include cutaneous infections, vascular disorders and malignancy. Clues to the diagnosis of PG include a violaceous overhanging edge with tender surrounding erythema, a granular purulent base and the ability to express pus. Because the treatment of PG often requires immunosuppressive agents that can exacerbate infection, it is essential to make a correct diagnosis prior to initiating therapy. Infection should be ruled out, or if present, treated aggressively with antibiotics. Appropriate medication should be given to alleviate pain. Patients should be monitored carefully to avoid adverse effects of treatment and drug interactions.

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