## Answer to Dermacase *continued from* ***page 377***

### 4. Pyoderma gangrenosum

Pyoderma gangrenosum (PG) is one of a group of diseases known as *neutrophilic dermatoses*. It is a rare, ulcerative condition characterized by the presence of irregular, boggy ulcers with blue or red to violaceous borders surrounding a purulent and necrotic base.[1] Brunsting et al first described the condition in 1930 and originally hypothesized that it had an infectious pathogenesis. However, several repeated cultures failed to grow any organisms.[2] Although the pathogenesis of PG remains unknown, recent studies have suggested it is an overactive response to traumatic, inflammatory, or neoplastic processes in a susceptible patient.[3]

Approximately 50% of cases are associated with underlying systemic diseases, most commonly inflammatory bowel disease (IBD), rheumatoid arthritis, hematologic disease, and malignancy. Although approximately one-third of cases of PG occur in association with IBD, only 2% of patients with IBD will develop PG.[4] The severity of IBD does not correlate with the development of PG; the condition can present before the bowel disease and can also occur after the disease is in remission or after colectomy. All age groups can be affected by PG; however, there is a peak incidence between the ages of 40 and 60 years and a slight predominance in women.[1]

Several varieties of PG exist, but in the classical form, PG is a painful ulcer that most commonly appears on the lower extremities, although any part of the body might be involved. The ulcer usually begins as a small violaceous or red papule or pustule or group of papules, and rapidly progresses to a crater in 24 to 48 hours. The lesion often undergoes necrosis to form a single ulcer. The lesion has a well-defined border, usually with a blue or violaceous appearance, and the surrounding skin is erythematous and indurated.[5] Between 25% and 50% of lesions exhibit pathergy, in which minor trauma to the skin, surgical incision, or prick tests can initiate new lesions.[6] Pyoderma gangrenosum is usually very painful, and in the acute setting the patient might develop systemic symptoms such as fever and malaise.

Other variants of PG include pustular, bullous, vegetative, and site-specific (such as peristomal PG) forms (**Table 1**).[5,7-10]

**Table 1. Variants of PG**

| VARIANT | DESCRIPTION |
|---|---|
| Pustular | • Process stops at pustular stage (ie, does not coalesce and ulcerate)<br>• Pustule might last up to several months; seems to be limited to patients with IBD; and tends to occur on trunk and extensor limb surfaces[7] |
| Bullous | • Bullous areas spread rapidly in a concentric pattern[5]<br>• Areas break down to form superficial ulcers; are often associated with hematologic malignancies; and affect upper limbs and face most commonly[8] |
| Vegetative | • Typically presents as a solitary furunculoid purple abscess, nodule, or plaque most commonly located on the trunk<br>• Lesions are often not painful and tend to enlarge slowly<br>• Lesions respond well to topical therapy and are usually not associated with systemic disease[9] |
| Peristomal (site-specific) | • Ulcers occur close to abdominal stomas; have a similar morphology to classic PG; and often interfere with adherence of stoma bag to abdominal wall[10] |

IBD—inflammatory bowel disease, PG—pyoderma gangrenosum.

## Diagnosis

Pyoderma gangrenosum is a diagnosis of exclusion and is based mainly on clinical findings, as there are no specific diagnostic features on biopsy or with bloodwork. It is important to distinguish PG from other ulcerating skin conditions, as early diagnosis is essential to preventing disfigurement and scarring.

A thorough history should be taken from all patients to identify potential underlying systemic diseases associated with PG. In certain cases if symptoms are present, an abdominal examination, upper gastrointestinal series, and barium enema might be appropriate.[11] Although bloodwork is not diagnostic for PG, it is helpful to rule out other causes of ulcerating skin conditions. Complete blood count, liver function tests, inflammatory marker tests, and peripheral blood smear evaluation should be ordered. Patients with PG often exhibit neutrophilia and an elevated erythrocyte sedimentation rate. Serum protein electrophoresis and bone marrow aspiration can be performed in patients with suspected hematologic malignancy or monoclonal gammopathy.[11] In addition, tissue from a biopsy of the ulcer should be cultured to rule out infection caused by bacteria, fungus, or atypical mycobacterium. Finally, a biopsy of the skin surrounding the ulcer should be conducted to rule out other diseases, despite the possibility of extending the ulcer.[12]

There are many differential diagnoses for PG, including vascular occlusive or venous disease, vasculitis, infectious diseases, malignancies, exogenous tissue injury, and drug reactions. Specific differential diagnoses in each of these categories are listed in **Table 2**.[13]

## Treatment

Given the rare occurrence of PG and its unknown pathogenesis, few controlled trials have investigated

**Table 2. Differential diagnoses**

| DISEASE CATEGORY | SPECIFIC DIFFERENTIAL DIAGNOSIS |
|---|---|
| Vascular occlusive or venous disease | Calciphylaxis |
| Vasculitis | Wegener granulomatosis, antiphospholipid-antibody syndrome |
| Malignancy | Primary or secondary lesions might present as suppurative ulcers |
| Infectious disease | Sporotrichosis, ecthyma, ecthyma gangrenosum, deep mycosis, atypical mycobacterium infection, *Clostridium* spp infection |
| Exogenous tissue injury | Factitious panniculitis, insect bites |
| Drug reactions | Pustular drug reactions |

Adapted from Weenig et al.[13]

its treatment. Thus, there is no uniformly effective treatment—it should be tailored to the patient and the severity of the lesion. Therapeutic options include wound care, topical treatment, systemic immunosuppressants, immunomodulating agents, blood products, and, occasionally, surgical treatment.

***Wound care.*** We recommend using moist wound healing principles for treatment of PG. Dressings should be changed according to drainage.

***Topical treatments.*** In mild cases and in the absence of systemic disease, topical treatments might be sufficient to induce remission of the skin lesion and are effective at reducing pain and preventing infection. Potent topical corticosteroids like clobetasol dipropionate can be used. Tacrolimus (0.1% or 0.03%) has also shown some benefit.[14] Triamcinolone (10 to 20 mg/mL) injected at the ulcer edge has been shown to be effective both as monotherapy and in combination with other systemic therapies.[15]

***Systemic immunosuppressants.***

*Steroids:* In many cases, topical treatment is insufficient and systemic treatment with high-dose oral prednisone (initial dose of 0.5 to 2 mg/kg) is administered. This is the current mainstay of treatment of PG. The dose of the drug should be tapered once the lesion is well controlled to prevent recurrence and reduce the risks associated with long-term systemic steroid use.[16] In severe disease, pulse therapy with methylprednisolone, 1 g for 3 to 5 days, has been shown to control the disease.[17] Small case series have shown some efficacy of minocycline, dapsone, clofazimine, or sulfasalazine in combination with systemic steroids.[5,15,18-24] Minocycline is administered in doses of 100 mg twice a day, and the total daily dose can be increased up to 300 mg.[18] Dapsone dosages have ranged from 100 to 400 mg a day.[25]

*Cyclosporine:* Cyclosporine is often used as a steroid-sparing agent and is also used for lesions that are refractory to oral steroids. Low doses of 3 to 5 mg/kg a day should be initiated to limit the occurrence of serious side effects such as hypertension and nephrotoxicity.[26]

*Other immunosuppressants:* Other immunosuppressant drugs that have been reported to be effective in some patients include methotrexate, azathioprine, and systemic tacrolimus.[16,27] In addition, the use of dapsone or mycophenolate mofetil in combination with other systemic therapies has been shown to be successful in some cases.[21-24,28-31]

***Immunomodulating agents.***

*Infliximab:* Pyoderma gangrenosum has been reported to respond to infliximab, a monoclonal antibody to tumour necrosis factor–α that is useful for patients whose lesions failed to respond to corticosteroids and cyclosporine. In addition, infliximab has been shown to help both PG and IBD, and it is now considered the best treatment of refractory PG with underlying IBD (especially Crohn disease). In a randomized controlled trial of 30 patients, infliximab (5 mg/kg) was shown to be superior to placebo. The response rate of the 2 groups differed by 40% at week 2, producing a number needed to treat of 2.5.[32]

*Etanercept:* More recently, PG has been shown to respond to etanercept, a recombinant protein that acts as a tumour necrosis factor–α inhibitor. A retrospective study of 7 patients whose ulcers did not respond to topical treatment or immunosuppressive and immunomodulating drugs was conducted. Each patient was treated with subcutaneous injections of etanercept (25 to 50 mg twice a week) and their ulcers either completely healed or were markedly reduced in size within 8 to 18 weeks. The drug was well tolerated, and no serious side effects were reported.[33]

***Other novel medical treatments.*** A number of new medical treatments, including intravenous immunoglobulin and granulocyte apheresis, have been reported to be effective in the treatment of PG.[34,35] However, the success of these therapies is mostly anecdotal and they are not commonly used other than in severely refractory cases.

***Surgical treatment.*** Surgical treatment of PG is rare, as it can often worsen the lesion, but it is occasionally warranted. Surgery should only be considered as an adjuvant therapy to systemic medications and should only be conducted during a period of disease quiescence.[36]

## Conclusion

Pyoderma gangrenosum is a rapidly evolving, chronic, and severely debilitating skin disease. It is an important differential diagnosis in patients with painful, fast-growing ulcers on any part of the body. A multidisciplinary and stepwise approach to treatment is essential in the management of this condition. Although there is no known cure for PG, early diagnosis followed by aggressive therapy is essential for good outcomes and to prevent serious disfigurement and scarring.

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**Competing interests**
None declared

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