Management of pyoderma gangrenosum – An update

Ramesh M. Bhat
Department of Dermatology, Venereology and Leprosy, Fr. Muller Medical College, Mangalore, India.

Address for correspondence: Dr. Ramesh Bhat, Professor, Department of Dermatology, Venereology and Leprosy, Fr. Muller Medical College, Kankanady, Mangalore - 575002, India. E-mail: rameshderma@yahoo.com

ABSTRACT

Pyoderma gangrenosum is a neutrophilic dermatosis with distinctive clinical manifestations. It is frequently associated with systemic diseases like inflammatory bowel disease, rheumatoid arthritis and myeloproliferative diseases. The etiopathogenesis of pyoderma gangrenosum is still not well understood. Clinically it is classified into ulcerative, pustular, bullous and vegetative types. The diagnosis mainly depends on the recognition of evolving clinical features as there are no specific investigations for the diagnosis. It is essential to exclude other infectious diseases before therapy is initiated as corticosteroids and immunosuppressant therapy are the mainstays in the treatment of this disease. Recently, drugs like tacrolimus, mycophenolate mofetil and infliximab have shown promising results in this condition. Recent concepts regarding the various types of pyoderma gangrenosum and its management are reviewed.

Key Words: Pyoderma gangrenosum, Therapy, Corticosteroids

INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon ulcerative cutaneous condition with distinctive clinical characteristics and a frequent association with systemic disease.1 It is also known as phagedena geometrica, dermatitis gangrenosa and phagedenic pyoderma.2 PG was first described and named by Brunsting, Goeckerman and O’Leary in 1930.3 They believed that streptococcal infection was a significant component leading to secondary cutaneous gangrene and named it as pyoderma gangrenosum. Hence, the term pyoderma gangrenosum is a misnomer.

ETIOLOGY AND PATHOGENESIS

The exact causative mechanism of PG is unknown. Even though it is frequently associated with autoimmune diseases, their exact role in producing the lesions of PG is not known.4,5 Several studies have shown disordered immune responses in patients with PG, mainly defective cell-mediated immunity but also impaired phagocytosis by neutrophils.6 Thus it may be considered that the predisposed patient experiences an inciting event such as minor trauma, and instead of a normal response that recognizes and removes the damaged tissue, the patient’s abnormal response results in lesions of PG.5 Recently, Chlamydia pneumoniae, which is an obligate intracellular parasite that can infect endothelial, monocytes and smooth muscle cells and is associated with cardiopulmonary disease, has been considered as a potentially contributing factor to the development and chronicity of PG.7 Neutrophil mediated diseases like Sweet’s syndrome and PG have

also been reported after treatment with granulocyte colony stimulating factor (G-CSF).\(^8\)

**CLINICAL FEATURES**

PG is a rare disease. Its annual incidence in southern Germany has been reported to be 2 cases per year per 10\(^6\) population.\(^9\) The disease develops in most patients between 25 and 45 years of age.\(^10\) Approximately 4% of patients are infants and children. Around 50 cases of PG have been reported in children, the youngest being a 3 week old infant.\(^11,12\) We have also reported a case of PG in a 3½ year old child.\(^13\) PG affects men and women equally.\(^14\)

Clinically, PG is classified into the following four varieties:

1. **Ulcerative type:** This is the classic form of PG described by Brunsting et al.\(^3,15\)
2. **Pustular type:** This is considered as a forme fruste of ulcerative PG in which pustules do not evolve into ulcers.\(^10\) It may be associated with exacerbations of inflammatory bowel disease, fever or arthralgias.\(^16\) However, in one of the reports, 2 patients with quiescent inflammatory bowel disease developed pustular PG.\(^17\)
3. **Bullous type:** In this type, reported in patients who have myeloproliferative diseases like leukemia,\(^18\) a superficial painful bulla evolves into erosion and superficial ulceration.\(^10\) Because of their clinical appearance, some authors believe that bullous PG and atypical Sweet’s syndrome represent different points in the same spectrum of reactive skin conditions in patients with myeloproliferative diseases.\(^19\)
4. **Vegetative type:** The lesions are chronic and limited. Many patients with this type do not have an associated systemic disease. This type of PG was recently termed as superficial granulomatous pyoderma,\(^20\) and is considered as a non-aggressive variant of PG.\(^21\)

**ASSOCIATED DISEASES**

Approximately 50% of the patients have an associated systemic disease.\(^22\) PG is associated with diseases like inflammatory bowel disease (which may precede or follow it, or occur simultaneously), arthritis, monoclonal gammopathy, myeloproliferative disorders, acne conglobata, malignancies and a host of other conditions like hidradenitis suppurativa, sarcoidosis and Takayasu’s arteritis.\(^10,12,23-25\) Ocular involvement in the form of scleritis and periorbital tissue involvement has also been reported.\(^26,27\)

PG has also been reported in HIV patients, both children and adults.\(^28-30\) In the HIV-infected, the perineum is the most common site of affection. The lesions are often secondarily infected with bacteria.\(^29\)

PG may be associated with another neutrophilic dermatosis like subcorneal pustular dermatosis, Sweet’s syndrome, erythema elevatum diutinum or Behçet’s disease.\(^10,19\)

**DIAGNOSIS**

The diagnosis depends mainly on recognition of the evolving clinical features because the histopathological changes are not specific. The histopathological distinction of PG from other ulcerative processes with dermal neutrophilia is challenging and at times impossible.\(^31\) Massive neutrophilic infiltration in the absence of vasculitis and granuloma formation is considered as suggestive of PG.\(^22\) However, recently it has been shown that PG lesions when associated with Crohn’s disease may contain granulomatous foci as compared to the histopathology of lesions in patients of PG without inflammatory bowel disease.\(^23\)

**TREATMENT**

It is essential to exclude other diagnoses such as infectious diseases before therapy is initiated as corticosteroid and immunosuppressant therapy is the mainstay in the treatment of PG.\(^34\) The treatment of the underlying disease may aid in healing the ulcer.\(^35\) In patients without an identifiable associated disease, it is still possible for it to appear later; hence evaluation is indicated even after the skin lesions have healed.\(^34\)

**LOCAL THERAPY**

Local therapy is an important adjunct to systemic
therapy and may provide relief from symptoms. Gentle debridement of the ulcer can be done with Burrow’s solution, silver nitrate or potassium permanganate baths. Aggressive surgical debridement or skin grafting is discouraged because of the risk of a pathergic response. However, skin grafting may be successful if systemic steroid cover is given during the procedure and until both the graft and donor sites have healing. Cultured keratinocyte autografts and allografts have also been reported to be useful in some cases. These skin substitute cell culture grafts offer the possibility of providing a temporary ulcer cover in patients in whom the inflammatory element of the disease is controlled but where re-epithelialization is slow to progress.

Various agents that have been used for local therapy include topical and intralesional corticosteroids, topical 5-aminosalicylic acid, benzoyl peroxide, topical sodium cromoglycate, intrallesional cyclosporine and topical nitrogen mustard. For early and localized lesions, intralesional corticosteroid injections with triamcinolone acetonide may halt progression and induce healing. Caution must be exercised to avoid introducing infection and interfering with healing through overly aggressive injections.

Topical 10% 5-aminosalicylic acid cream application daily to a PG lesion in a patient with Crohn’s disease helped in regression of the ulcer in 5 weeks, although bowel symptoms persisted. Suppression of leukocyte motility and cytotoxicity, rather than the effects on arachidonic acid metabolites, may have been the mode of action. Topical application of 2.5% of benzyl peroxide presumably acts by increasing the oxygenation of wound tissue. Sodium cromoglycate used topically as a 2% solution three times daily induced healing of ulcers in 3 weeks. It works through its effect on the stabilization of mast cells and modulation of the inflammatory process.

In one patient intrallesional cyclosporine at a dose of 35 mg in isotonic saline was injected twice in one week. Improvement was seen in 2 weeks and complete healing was observed in 3 months. Improvement in lesions of PG was also reported with daily applications of an aqueous solution (20%) of nitrogen mustard. Topical tacrolimus (0.5% solution) can be used as an add-on and follow-up medication in the treatment of PG. Topical tacrolimus exerts significant local immunosuppression and is capable of inhibiting the destructive skin inflammation characterizing PG. It has the advantage in that when used topically it is absorbed through the skin. Perilesional use of granulocyte macrophage colony stimulating factor has also been reported to be effective in a patient but caution should be exercised in the use of this agent, as there have been cases of PG in which the initiation of lesions was linked to the use of this agent.

**SYSTEMIC THERAPY**

Systemic corticosteroids are considered as the drug of choice for the treatment of PG and are particularly effective in treating the acute, rapidly progressive form of this disease. Initial doses of prednisolone in the range of 40-80 mg/day or higher are usually required initially whereas maintenance requirements vary considerably. A steroid-sparing agent such as a sulfa drug may be added as the steroid is withdrawn to maintain the improvement.

In some cases pulse steroid therapy has produced rapid improvement of lesions that were previously unresponsive to oral corticosteroids. In one study, 9 of 11 patients healed after 5½ months of 1 g methylprednisolone pulse therapy. Dexamethasone pulse therapy has also been used in the management of PG. In one Indian study, three patients of PG improved after 4, 6 and 6 pulses of dexamethasone. There was no recurrence in any of the cases during a follow-up period of 1.5 years. However, the potential for sudden electrolyte shifts with subsequent cardiac arrhythmias indicates that pulse therapy should be used only in selected patients whose disease is resistant to other forms of therapy.

Sulfasalazine, sulfapyridine and sulfamethoxypyridazine have been successfully used in the management of PG. Sulfasalazine was the first drug tried for the treatment of PG. It was beneficial in 9 of
12 patients at dosages of 1-4 g daily. Sulfapyridine, a metabolite of sulfasalazine, was used with success even in patients who didn’t respond to sulfasalazine.\textsuperscript{34} Dapsone has also been shown to be effective in the treatment of PG. Dapsone in a dose of 100-200 mg/day healed the lesions of PG completely in one study.\textsuperscript{50} However, when PG is aggressive, dapsone may not be sufficient and additional corticosteroids may be needed. The mechanism of action of sulfonamides and sulfones in controlling PG is not fully understood but appears to be because of their ability to inhibit neutrophil chemotaxis.\textsuperscript{51}

Clofazimine, an imino phenazine dye mainly used in the treatment of leprosy and other mycobacterial diseases, is reported to be effective in the treatment of PG.\textsuperscript{52} Its mode of action is thought to relate to its antiinflammatory effect rather than its anti-bacterial activity.\textsuperscript{10} Many studies have reported that treatment with clofazimine 200-400 mg/day results in the healing of the lesions of PG within weeks to months.\textsuperscript{34} Although side effects are rare, these include intestinal obstruction in Crohn’s disease, splenic infarction and discoloration of the skin.\textsuperscript{10,52}

Minocycline is another antimicrobial agent with possible beneficial effects in PG. It is used in a dosage of 200-300 mg/day and the response was noted in weeks, regardless of disease severity or underlying disease.\textsuperscript{53} The efficacy of minocycline in PG is possibly related to the anti-inflammatory effect of the tetracyclines such as diminishing the chemotactic responsiveness of neutrophils and the inhibition or binding of neutrophilic chemotactic factors.\textsuperscript{34}

Immunosuppressive agents like azathioprine, mercaptopurine, cyclophosphamide, arabinoside, chlorambucil, colchicine and daunorubicin have been used as an adjunctive or alternative therapy to systemic corticosteroids with varying success in PG.\textsuperscript{10,34,54,55} They probably correct the immunological defects present in PG. Azathioprine, a purine analogue, impairs DNA synthesis in lymphoid cells and thus inhibits T cell function, cell-mediated immunity and, to a lesser extent, B cell function. It was effective in some patients when used in a dose of 100-150 mg/day or in combination with steroids. Mercaptopurine, the active metabolite of azathioprine, has been used with some success in refractory PG in a dose of 75 mg/day.\textsuperscript{34} Cyclophosphamide 100-150 mg/day was effective in the treatment of 5 cases of PG.\textsuperscript{54} Recently, it has been reported to effect lasting remission when administered as intermittent high dose "pulses" (500 mg/m\textsuperscript{2}).\textsuperscript{55} Although cyclophosphamide was reported to be well tolerated it has been associated with serious side effects like myelosuppression, hemorrhagic cystitis and immunosuppression.\textsuperscript{34}

Chlorambucil is a less toxic but more slow-acting alkylating agent than cyclophosphamide. The experience with cytosine arabinoside and daunorubicin in PG is limited to one patient who received both drugs to treat underlying acute myeloblastic leukemia.\textsuperscript{34} Results with methotrexate therapy in PG have been poor.\textsuperscript{10} Since there is a risk of severe adverse effects, especially bone marrow suppression, these drugs should be reserved for severe or resistant cases.

Cyclosporine, which does not cause significant myelosuppression, is one of the most promising immunosuppressants for the treatment of PG.\textsuperscript{34,56,57} In one study seven patients with PG unresponsive to conventional therapies responded well to treatment with cyclosporine.\textsuperscript{56} The dose required to achieve remission is between 5 and 10 mg/kg daily. Potential side effects may be significant and include hypertension, hirsutism, tremor, hepatotoxicity, abnormalities of the central nervous system, nephrotoxicity and a potential for lymphoma development.\textsuperscript{10,56} Tacrolimus, a novel macrolide antibiotic with immunosuppressive properties, has recently been used as a steroid-sparing or replacing agent in the treatment of PG. Tacrolimus 0.15 mg/kg twice daily resulted in complete healing in eight of nine patients with PG.\textsuperscript{58} Mycophenolate mofetil has been found useful as a relatively well tolerated immunosuppressive agent in various immune-mediated inflammatory dermatological diseases including PG.\textsuperscript{59} It selectively inhibits inosine monophosphate dehydrogenase and induces apoptosis of activated T cells, decreases the recruitment of T lymphocytes and induces immune
tolerance. It is used in a dosage of 1 g twice daily. Nausea, cramps, gastrointestinal side effects and mild to moderate leucopenia have been reported.\textsuperscript{40}

Recently, infliximab has shown promising results in the treatment of PG, with complete healing of skin lesions reported in a series of 13 cases. Three patients had a complete response to induction infliximab therapy whereas ten patients required maintenance infusions every 4-12 weeks. The only treatment-related adverse events were sunburn in one patient and infusion reaction in another.\textsuperscript{61} Tripterygium wilfordii multiglycoside (TWG), a Chinese medicine extracted from a Chinese medicinal herb, has potent anti-inflammatory and immunosuppressive effects. It has shown improvement in two patients with PG. It can be used as an alternative in the treatment of steroid-resistant, steroid-dependent or steroid-contraindicated PG patients.\textsuperscript{62}

Plasma exchange, intravenous immunoglobulin, hyperbaric oxygen therapy, thalidomide, nicotine, and potassium iodide have also been used with varying success in the management of PG.\textsuperscript{34,63-66} Seven out of the ten patients who underwent plasma exchange showed clearance. However, rationale for the use of plasma exchange is unclear as no abnormal plasma constituent has been consistently demonstrated.\textsuperscript{34} Intravenous immunoglobulin 0.4 g/kg per day for 5 days initially and 1 g/day for 2 days once in 2 weeks resulted in improvement in one patient with PG.\textsuperscript{63} The principal disadvantages of this treatment are high cost, adverse effects (headache, chills, fever) and the potential for the transmission of the disease with pooled sera.\textsuperscript{34} Hyperbaric oxygen therapy is thought to benefit PG by elevating oxygen tension in the ulcers either through the greater arterial oxygen supplied to the capillary bed or through the local delivery of oxygen to the ulcer surface.\textsuperscript{34}

Thalidomide 400 mg/day in a patient with Behçet’s disease and PG has been reported to have shown a dramatic response.\textsuperscript{64} The anti-inflammatory effects of thalidomide include inhibition of both macrophage phagocytosis and neutrophil chemotaxis which help in the healing of PG lesions.\textsuperscript{34}

Nicotine gum 6 mg/day was reported to be effective in clearing the skin lesions of one patient with intractable PG within 3 weeks.\textsuperscript{65} Potassium iodide suppresses the production of inflammatory oxygen intermediates from activated neutrophils.\textsuperscript{66} Paradoxically, it can also exacerbate PG.\textsuperscript{3}

**CONCLUSION**

PG, although clinically characteristic, remains an enigma with regard to its etiology and pathogenesis. Its rapidly progressive course makes it at times a medical emergency. Dermatologists thus should be prepared to diagnose this disease and manage it proactively by appropriate topical and systemic therapy.

**REFERENCES**

Bhat RM: Management of pyoderma gangrenosum


