Pyoderma Gangrenosum


Abstract

Pyoderma gangrenosum (PG) is an idiopathic, ulcerative, noninfective chronic inflammatory skin disorder of unknown etiology. It is associated with systemic medical illness in 50% of cases like inflammatory bowel disease, systemic arthritis, haematological diseases and malignancies. Characteristic lesions begin as pustule or vesiculopustule and progresses to an ulcer or deep erosion with violaceous overhanging or undermined borders. Diagnosis of pyoderma gangrenosum is clinical and depends on exclusion of other causes of cutaneous ulceration. The management of PG is treatment of underlying systemic medical illness and judicious use of immunosuppressants. Association of PG with these medical illneses and treatment with immunosuppressants make the clinical utility for internists, gastroenterologists, haematologists and rheumatologists.

Introduction

Pyoderma gangrenosum (PG) was first described in 1930 by Brusting and colleagues. PG is an idiopathic, ulcerative, chronic inflammatory skin disease of uncertain etiology. PG is more frequent in adults but children may be affected on rare occasion. Cutaneous lesions are characteristic as PG begin as pustule or vesiculopustule and progresses to an ulcer or deep erosion with violaceous overhanging or undermined borders. Lesions are most commonly found on the lower legs, but they may occur on the abdomen, thighs, buttocks, chest, head, neck, and anywhere on the skin.

“Pyoderma gangrenosum” term was given because of characteristic appearance of the lesion. The cutaneous lesion most commonly presents typically as a tender pustule of essentially non-infectious aetiology that evolves to an enlarging necrotic suppurative ulcer after gangrenous changes into the overlying skin. The lesions tend to endure, lasting months to years, and heal with cribiform scarring.

Diagnosis is clinical and depends on the exclusion of other causes of cutaneous ulceration. No specific pathologic or laboratory findings exist. Concurrent systemic disease occurs in 50% of affected patients (Table 1). Remaining cases are thought to be idiopathic or autoimmune. The management of this disorder begins with treatment of underlying disease and local or systemic glucocorticoids and immunomodulators.

Actually PG is generally associated with other medical illnesses like rheumatoid arthritis, inflammatory bowel disease, leukaemia etc. Therefore, early diagnosis of PG is mandatory because this condition is usually misdiagnosed and underdiagnosed by physicians as well as surgeons as these cases are also referred to them as non-healing ulcers.

Moreover, surgical intervention may lead to deterioration of natural history of PG because of pathergy reaction. Cases of PG are erroneously referred to surgeons but surgical intervention leads to more harm due to pathergy phenomenon and this entity should be treated by immunosuppressants.

Pathophysiology

The pathophysiology of PG is poorly understood, but dysregulation of immune system, especially altered neutrophil chemotaxis is the primary process. The complete connection between neutrophil and tumor necrosis factor (TNF) has yet to be established, however, evidence of enhanced neutrophil activation due to TNF-α has been uncovered. TNF-α increases neutrophil infiltration by-

i. Upregulating expression of adhesion molecules namely intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin.

ii. Increasing levels of interleukin-8.

iii. Increases synthesis of granulocyte colony stimulating factor.

Pathergy phenomenon i.e. development of skin lesion at the site of injury, is a common feature of PG and occurs in 30% of patients.

Clinical Variants: To aid understanding of clinical variants of PG, lesions have been classified into 4 categories:

A. Ulcerative
B. Pustular

Table 1: Associated systemic diseases

<table>
<thead>
<tr>
<th>No.</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inflammatory bowel disease 15%</td>
</tr>
<tr>
<td>2</td>
<td>Rheumatoid arthritis and systemic lupus erythematosus (37%)</td>
</tr>
<tr>
<td>3</td>
<td>Immune abnormalities:</td>
</tr>
<tr>
<td></td>
<td>- Humoral-</td>
</tr>
<tr>
<td></td>
<td>- Congenital and acquired hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>- Selective and complete hyperimmunoglobulin E syndrome</td>
</tr>
<tr>
<td></td>
<td>- Cell Mediated-</td>
</tr>
<tr>
<td></td>
<td>- Immune deficient/ Immunosuppressed</td>
</tr>
<tr>
<td></td>
<td>- Congenital deficiency in leukocyte adherence glycoprotein</td>
</tr>
<tr>
<td></td>
<td>- Defective neutrophil function</td>
</tr>
<tr>
<td>4</td>
<td>Hematologic Diseases-</td>
</tr>
<tr>
<td></td>
<td>- Acute and chronic myeloid leukaemia</td>
</tr>
<tr>
<td></td>
<td>- Multiple myeloma</td>
</tr>
<tr>
<td></td>
<td>- Monoclonal gammopathy</td>
</tr>
<tr>
<td></td>
<td>- Waldenstrom's macroglobulinemia</td>
</tr>
<tr>
<td></td>
<td>- Lymphoma-Hodgkin's lymphoma, non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td></td>
<td>- Polycythemia Vera</td>
</tr>
<tr>
<td></td>
<td>- Large granular Lymphocytic leukaemia</td>
</tr>
<tr>
<td></td>
<td>- Myelofibrosis</td>
</tr>
<tr>
<td>5</td>
<td>Liver Diseases:</td>
</tr>
<tr>
<td></td>
<td>- Chronic active hepatitis</td>
</tr>
<tr>
<td></td>
<td>- Cryoglobulin in hepatitis C</td>
</tr>
<tr>
<td></td>
<td>- Primary biliary cirrhosis</td>
</tr>
<tr>
<td>6</td>
<td>Solid tumours like colon, bladder, prostate, breast, bronchus, ovary,</td>
</tr>
<tr>
<td></td>
<td>- adenocortical carcinoma</td>
</tr>
<tr>
<td>7</td>
<td>Drugs = Alpha 2-b Interferon</td>
</tr>
<tr>
<td>8</td>
<td>Miscellaneous –Thyroid diseases, sarcoid, diabetes mellitus, HIV, COPD</td>
</tr>
</tbody>
</table>

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Received: 16.01.2009; Revised: 18.06.2009; Accepted: 20.06.2009
C. Bullous

D. Vegetative

A. Ulcerative (Typical or Classic) PG

This is the typical form of PG. Lesions are most commonly located on lower limbs but may occur anywhere. Lesions often begin as pustules, but can also be pathergic in etiology. A large ulcer with a well defined, undermined border (Fig. 1) surrounded by a halo of erythema is usually formed within a few days at the site of minor trauma. There is associated pain often severe and out of proportion to size of lesion. Ulcerative PG is often associated with arthritis, inflammatory bowel disease and monoclonal gammopathies. It has been suggested that the ulcerations in patients who have classic PG associated with arthritis are more refractory to treatment than in patients who have PG without associated arthritis.

B. Pustular PG

Pustular lesions are initiating feature of ulcerative PG as discussed above. Although not all pustules progress to ulceration and in some patients multiple painful eruptive inflammatory cutaneous pustules develop without subsequent ulceration. This distinctive eruption has been reported almost exclusively in the setting of acute IBD, which often clear with control of bowel disease. Pyostomatitis vegetans, a 2-3mm pustule which may ulcerate is found on oral mucosa, is a pustular variant of PG. Oedematous mucosa makes deep folds called “snail track” appearance.

C. Bullous (Atypical) PG

Characteristic feature of atypical PG is that they begin as bullae and are superficial. Patients with this type of PG develop painful rapidly enlarging bullous lesion which becomes superficially erosive and then ulcerative, especially on the dorsum of the hands (Fig. 2). This variant is also termed as “Neutrophilic dermatoses of dorsal hands”. It is associated with hematological diseases especially myelogenous leukemia, myelodysplastic disorders, refractory anemia and IgA paraproteinemia. The presence of lesions is an indicator that the patient with leukemia has a poor prognosis. This condition may be confused with sweet’s disease, acute febrile neutrophilic dermatoses. It has been proposed that atypical PG and sweet’s disease are points on a continuum.

D. Vegetative PG

Vegetative PG, also known as superficial granulomatous pyoderma, presents as chronic, nonprogressive, superficial ulcer that is not painful and often lacks a violaceous undermined border. It is often a solitary lesion, especially on trunk, that is uncommonly associated with systemic diseases. Histologically histiocytes are prominent within the neutrophilic infiltrates. This variant has a good prognosis. It responds to simple modes of treatment.

E. Other variants

Peristomal PG

This variant characterized by ulcerations resembling classic PG in a peristomal (ileostomy or colostomy) location. It occurs most often in patients who have IBD particularly
Systemic diseases associated with PG

1. Rapid treatment response (rapid response to systemic glucocorticoid therapy)
2. Histopathologic findings (sterile dermal neutrophilia ± mixed inflammation ± lymphocytic vasculitis)
3. Blood tests – CBC, ESR
4. Ulcer cultures
5. Skin biopsy (histology with stain for organisms + culture)
6. Extracutaneous Disease
7. Malignancies
8. Thrombophilic states
9. Venous insufficiency
10. Ext. of underlying IBD
11. Factitious
12. Insect bite
13. Drugs
14. Post surgical PG (PSPG): Generally responds to a dosage of 1 to 2 mg/kg/d, with a 50% decrease in ulcer size within 1 month; a 50% increase in ulcer size within 1 month; bTypically preceded by a papule, pustule, or bulla; cUlcer development at sites of minor cutaneous injury; dInflammatory bowel disease, polyarthritis, myelocytic leukemia, or preleukemia; eGenerally responds to a dosage of 1 to 2 mg/kg/d, with a 50% decrease in size within 1 month

Table 3: Criteria (including clinical characteristics) for diagnosis of Pyoderma Gangrenosum

Major criteria
1. Rapid progression of a painful necrotic cutaneous ulcer with an irregular, violaceous, and undermined border
2. Exclusion of other causes of cutaneous ulceration
Minor criteria
1. History suggestive of pathergy or clinical finding of cribiform scarring
2. Systemic diseases associated with PG
3. Histopathologic findings (sterile dermal neutrophilia ± mixed inflammation ± lymphocytic vasculitis)
4. Treatment response (rapid response to systemic glucocorticoid treatment)

Table 4: Evaluation of Possible PG

1. Detailed history including drugs, trauma, insect bite, detailed systemic review
2. General physical examination
3. PG lesion – location, type, size, outline, depth
4. Blood tests – CBC, ESR
5. Serum urine and protein electrophoresis, cryoglobulins
6. Urine analysis
7. Bone marrow aspiration and biopsy
8. Angiographic or Doppler studies

Timing and Course with Associated Diseases

Cases associated with an internal malignancy do not demonstrate unique histopathologic findings compared with other cases of pyoderma gangrenosum. Treatment of an associated malignancy may or may not lead to improvement of pyoderma gangrenosum. There are no reliable clinical features to predict which cases have a paraneoplastic association.

The mean duration of chronic ulcerative colitis before the appearance of PG is 10 years. The lesions generally appear during the course of active bowel disease, but they also occur in inactive colitis or less severe disease and may not appear until after colectomy. Pyoderma resolved without intestinal resection in two thirds of patients. Healing after intestinal resection is unpredictable regarding both timing and extent of resection.

Differential Diagnosis

The diagnosis of PG involves the exclusion of other diseases that cause erosive or ulcerative skin lesions. Differential diagnosis of PG includes: (Table 2)

Evaluation of Possible PG

The diagnosis of PG is established by consideration of clinical features, review of histopathologic findings and with the benefit of negative culture results and other investigations (Table 4), undertaken as appropriate in the individual patients. Blood and other investigations are carried out as indicated by the history and examination. Investigations are done to diagnose or exclude the presence of an associated systemic disease.

As described above, the diagnosis of PG is clinical and depends on exclusion of other causes of cutaneous ulcerations. Various diagnostic criteria have been proposed for PG, one of them given by Su WPD, Davis MD et al is shown in Table 3. It includes characteristic clinical features of pyoderma gangrenosum, helpful in diagnosis. It has been recommended to help guide clinical evaluation and avoid misdiagnosis.

Table 4 shows systematic workup of a patient that comes...

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**Table 2: Differential diagnosis of PG**

1. Infections
   - Herpes simplex, impetigo, ecthyma gangrenosum, cutaneous tuberculosis, deep fungal infections
2. Vasculitis
   - Polyarteritis nodosa, Wegener’s granulomatosis, mixed cryoglobulinemia
3. Thrombophilic states
   - Livedoid vasculitis, antiphospholipid syndrome, factor V Leiden mutation
4. Venous insufficiency
5. Malignancies
   - Squamous cell carcinoma, cutaneous lymphoma, metastatic carcinoma
6. Ext. of underlying IBD
7. Factitious
8. Insect bite
9. Drugs
   - Isotretinoin, granulocyte colony stimulating factor, iodine and bromide overdosage, alpha 2b-interferon

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  2. Exclusion of other causes of cutaneous ulceration
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  1. History suggestive of pathergy or clinical finding of cribiform scarring
  2. Systemic diseases associated with PG
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  4. Treatment response (rapid response to systemic glucocorticoid treatment)

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Table 5: Multistep approach to therapy for pyoderma gangrenosum

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Initial therapy</th>
<th>Incomplete response to corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>I. First choice</td>
<td>Corticosteroids + cyclosporine A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroids + azathioprine</td>
<td></td>
</tr>
<tr>
<td>II. Second choice</td>
<td>Mycofenolate mofetil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td></td>
</tr>
<tr>
<td>III. For recalcitrant PG</td>
<td>Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Systemic therapeutic options for pyoderma gangrenosum

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose schedule</th>
<th>Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral steroids</td>
<td>Prednisone 0.5-1 mg/kg/d</td>
<td>Agent of choice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High doses until lesion is healed, followed by low-dose maintenance along with steroid sparing agents to prevent recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term risk for infections, insulin resistance, HTN, glaucoma, and adrenal suppression</td>
</tr>
<tr>
<td>Intravenous pulsed steroids</td>
<td>Methyl prednisone 1 g daily in 5% dextrose for 1-5 days</td>
<td>Fewer side effects than oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can cause cardiac arrhythmias, sudden death and anaphylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Refractory cases only</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4–5 mg/kg/d</td>
<td>Most effective steroid sparing agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of Hypertension, renal toxicity, hypertriglyceridemia, hypertrichosis</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1-2 mg/kg/d (50-200 mg)</td>
<td>Check thiopurine methyltransferase levels to prevent toxicity in patients lacking the enzyme</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slow onset of action, Bone marrow suppression</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1.5–3.0 mg/kg/d (oral)</td>
<td>Hemorrhagic cystitis(Good hydration before and during therapy), azoospermia</td>
</tr>
<tr>
<td></td>
<td>IV Pulse-500 mg /2 wks or 1000 mg/month</td>
<td>Slow onset of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of methemoglobinemia, anemia, neuropathy</td>
</tr>
<tr>
<td>Dapsone</td>
<td>50-200 mg/d</td>
<td>Risk of hepatotoxicity, bone marrow suppression</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10-30 mg/wk</td>
<td>Steroid sparing agent, slow onset of action</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>2-3 g/d</td>
<td>Steroid sparing agent. Used in penile PG.</td>
</tr>
<tr>
<td></td>
<td>50-200 mg/d</td>
<td>Risk of birth defects, neuropathy, coagulopathy</td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
<td>Soluble p75 TNF receptor fusion protein (sTNFR-lg). Inhibits TNF binding to cell surface receptors</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50-100 mg SC qwk</td>
<td>Risk of pathergy reaction, infections at injection site pain, rare cases of lupus like symptoms and heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For recalcitrant PG</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 mg/kg IV infusion</td>
<td>For recalcitrant PG</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg SC q wk</td>
<td>For recalcitrant PG</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.15 mg/kg twice daily</td>
<td>Macrolide antibiotic with immunosuppressant property</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxicity- Nephrotoxic, Diabetes Mellitus &amp; Neurotoxicity</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td></td>
<td>Effective in isolated cases, used alone or in combination with other modalities</td>
</tr>
<tr>
<td>IVIG, hyperbaric O2, radiation, electron beam irradiation</td>
<td></td>
<td>Effective in isolated cases</td>
</tr>
</tbody>
</table>

with cutaneous ulceration having characteristic features of PG. After detailed history, general physical examination and local examination, a biopsy of the affected area (Elliptical incisional biopsy preferable to punch biopsy) for routine processing and special stains for microorganisms should be performed in almost all patients. Laboratory evaluation should include a complete blood count, chemistry profile, hepatitis panel and urinalysis.

Patients who have peristomal PG should be evaluated carefully for active bowel disease or malignancy if there is a previous history of gastrointestinal malignancy. Serum and/or urine protein electrophoresis, peripheral smear, and bone marrow aspiration should be performed if indicated to evaluate for hematologic malignancies. Colonoscopy or other tests to exclude associated inflammatory bowel disease or ulcerative colitis may be useful in patients with symptoms. The evaluation of patients with pyoderma gangrenosum and no symptoms of...
bowel disease is still uncertain.

**Histological Findings**

Histopathological findings in PG are not specific. However a biopsy is suggested in all instances to exclude other diseases. Biopsy should not be deferred because of concerns of pathergy. Microscopic features include extensive sterile dermal neutrophilia. In early cases mixed cell infiltrations may be present. Although vascular inflammation in lesions of PG is not uncommon, the histology is not that of true vasculitis (leukocytoclastic vasculitis). Granuloma formation is generally believed to be incompatible with the diagnosis of PG.

**Management**

Management of PG is divided into local wound care, topical therapy and systemic therapy.18,19

**Local Wound Care**

Local care includes moist dressings (such as hydrocolloid, allograft, Vaseline gauze) to relieve pain, promote re-epithelialization and prevent trauma. Bioengineered skin dressings may be beneficial in covering ulcers and preventing the need for skin grafts.20

**Topical Therapy**

Topical therapy is helpful in some cases and successful use of cromolyn sodium, potent topical glucocorticoids, tacrolimus, pimecrolimus, nicotine or hyperbaric oxygen has been used in individual patients. Intraleisional injections of glucocorticoids, cyclosporine or tacrolimus are alternative local therapies, although most useful in early ulcers or there are small isolated ulcers.

**Systemic Therapy**

Systemic treatment may be required for more severe cases or those refractory to local treatment (Tables 5, 6). Systemic therapies for PG have include glucocorticoids, azathioprine, cyclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil, methotrexate, thalidomide, and dapsone, minocycline or sulfapyridine.

Among these systemic modalities, high dose corticosteroids are usually first line therapy. Steroid sparing agents should be considered early in the course of PG, because of various toxicities (Table 6). Cyclosporine is considered as most effective steroid sparing agent. In steroid resistant cases of PG, combination of corticosteroids with cyclosporine or azathioprine are considered as first choice therapy on the basis of clinical experiences though there are currently no general recommendations for the management of PG. Another alternatives are mycophenolate mofetil, dapsone, sulfasalazine, cyclophosphamide and biologics. Pulse methylprednisolone, pulse cyclophosphamide and intravenous immunoglobulin have shown benefits in some patients. Doses and salient features of these therapies are explained in Table 6.

**Biologics**

TNF-α inhibitors (infliximab, adalimumab and etanercept) are showing promise in the treatment of PG.31-35 Infliximab is preferred TNF-α inhibitor because of risk of pathergy along with subcutaneous injection of etanercept and adalimumab.

Infliximab is administered as 3-5 mg/kg iv infusion every 1-3 weekly. Important considerations and side effects regarding infliximab therapy are reaction of latent tuberculosis and other infections, demyelinating diseases, lymphomas, congestive heart failure and lupus like illness. The pain and swelling decreased within first 4-5 days and complete healing was achieved within 1-3 months.

**Surgical Intervention**

Surgical intervention may be harmful because there is risk of pathergy. When extensive necrosis of the skin is present or vital tissues, such as tendons and ligaments, are exposed at the ulcer bed, debridement and skin grafting may be necessary. In such cases, concomitant systemic therapy with steroids is required to halt the inflammatory process. Cultured keratinocyte autografts are shown to be effective.

**Course & Prognosis**

The prognosis of PG for most patients is good. Many patients who have PG develop a single episode i.e. uniphasic resolves with a short course of therapy. Patients having chronic or relapsing form of PG often require long term therapy and are associated with chronic diseases. They may require combination therapy and regular follow up for close monitoring for toxicities from therapy. A recent series of 41 patients demonstrated that 50% of patients required long-term therapy to avoid recurrence.4 Some patients demonstrate reactivity, and, in such instances, protection of skin from trauma may prevent a recurrence. Patients who present with atypical PG need regular follow-up to evaluate for the development of myeloproliferative disorders.

**References**


