Pyoderma Gangrenosum

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18.1 Introduction

Pyoderma gangrenosum (PG) is a rare, non-infectious, inflammatory disease of unknown etiology, characterized by sterile neutrophilic infiltration of the skin. It is commonly associated with underlying systemic disease [1–4].

18.2 History and Nomenclature

Pyoderma gangrenosum was first described by Brocq in 1916 [5] and later in 1930 by Brunsting et al. [1]. Brunsting, Goeckerman, and O'Leary coined the term "pyoderma gangrenosum" in 1930. The prevalence of PG in inflammatory bowel disease was discussed by Greenstein et al. in 1976 [6]. Several clinical variants of PG have been described, and PG at unusual sites or with specific triggers, such as pathergy, has been reviewed [7]. There is some evidence that the pustular type of PG may be mainly associated with inflammatory bowel disease (IBD) and the bullous type with hematological malignancies (Table 18.1). Peristomal pattern is mainly, but not exclusively, associated with IBD, and the vegetative type of PG is not associated with underlying disease [2, 8]. Although the above-mentioned associations have been described, none of the morphologies is consistently or exclusively associated with any specific cause. Although the vegetative pattern of PG is not accompanied by other lesions. Different morphologies may coexist with each other or with other neutrophilic dermatosis or pustular vasculitis or may evolve from one form to another [9]. 50–70 % of patients with PG will have an underlying disease, equally

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Table 18.1 Different associated diseases reported with pyoderma gangrenosum

Category of disorders	Examples
Gastrointestinal	Ulcerative colitis, Crohn's disease, collagenous colitis, gastritis, gastroduodenal ulcers, intestinal polyps
Hematological	Leukemia (myelogenous, hairy cell), myelofibrosis, myelodysplastic syndromes, paraproteinemia, Waldenstrom macroglobulinemia, paroxysmal nocturnal hemoglobinuria
Hepatic	Chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis
Collagen vascular disorders	Wegener's granulomatosis, Takayasu's arteritis, Behcet's disease, systemic lupus erythematosus, systemic sclerosis
Acne and related disorders	Acne conglobata, acne fulminans, hidradenitis suppurativa, PAPA
Autoimmune	Thyroid disease, diabetes mellitus
Drugs	Colony-stimulating factors, gefitinib, interferon, propylthiouracil, isotretinoin
Solid organ tumors	Colon, pancreas, breast, bronchus, carcinoid
Miscellaneous	Sarcoidosis, HIV infection

divided between inflammatory bowel disease, arthritides and hematological disorders (IgA monoclonal gammopathy, acute myelogenous leukemia, myelodysplasia); but clinical course of PG is usually unrelated to their severity or activity [10].

18.3 Epidemiology

Pyoderma gangrenosum occurs worldwide. Accurate epidemiological data on PG are missing. The peak of incidence occurs between the ages of 20 and 50 years with women being more often affected than men [11]. Cases in infants and adolescents account for only 4 % of PG. PG in elderly people has occasionally been reported [12]. The general incidence has been estimated to be between 3 and 10 per million per year [10].

18.4 Etiology and Pathogenesis

The etiology of PG is unknown and its pathogenesis is poorly understood. Currently an immune-mediated process is thought to play an important role. Both humoral and cell-mediated abnormalities have been reported with PG, but none of these findings have been demonstrated consistently and it is not clear whether they are of primary importance or represent an epiphenomenon [2].

Pathergy phenomenon is reported to occur in 20–30 % of patients with PG. This refers to heavy neutrophilic infiltrates or pustular reaction that develops at the site of nonspecific trauma [13]. Pathergy phenomenon is elicited by injecting 0.1 ml of normal saline obliquely to the depth of 5 mm with a 20–22-gauge needle [13]. An erythematous papule of more than 2 mm at the prick site develops within 48 h.

Humoral defects described in PG include autoantibodies against skin and bowel, a dermo-necrotic factor and a serum factor [14, 15]. Some studies have suggested the mechanism to be consistent with Arthus and Shwartzman reaction [14–17], in which circulating immune complexes are deposited in blood vessels leading to activation of complement pathways.

Cross-reactivity between cutaneous and bacterial antigens, especially *Escherichia coli*, has been suspected. A recent support for this possibility was documented in a study [18]. Appearance of PG-like lesions in these patients represents an abnormal reaction to bacteria rather than a form of pathergy and suggests a local failure to terminate IL8 production resulting in marked neutrophilic infiltration. However, the role of bacterial antigens warrants further study. Cell-mediated defects described in PG include cutaneous anergy to candida, streptokinase and purified protein derivative, as well as altered production of macrophage inhibition factor by lymphocytes [19]. Oligoclonal T-cell response due to antigenic stimulus and trafficking between the skin and other organs occurs in PG [20]. Decreased neutrophil chemotaxis and impaired monocyte phagocytosis have been reported in association with PG [21]. The leukocyte abnormalities may contribute to the pathergy phenomenon [11, 22, 23]. Elevated levels of IL8 in the blood have been documented in PG [24], and high IL8 levels have been demonstrated in fibroblasts from PG lesions [25]. Cytokines like IL1 or TNF-α stimulate production of IL8.

Although ulcerative colitis is more commonly associated with PG than Crohn's disease, the latter became increasingly recognized as having association with PG; both classic and peristomal PG have been reported with ulcerative colitis, Crohn's disease, and collagenous colitis. Smoking is a significant factor favoring the development of extraintestinal manifestations of ulcerative colitis including PG and erythema nodosum [26].

PG is not associated with vasculitis, but cases with positive tests for c-ANCA or p-ANCA have been reported specially drug-induced PG (thiouracil). Recently a patient with PG and c-ANCA specific for h-lamp-2 has been reported [27]. Several families with inherited PG have been described [28, 29]. There is predisposition to PG in patients with mutation in caspase recruitment domain 15 leading to autosomal dominant autoinflammatory syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne; the mutations affect CD2-binding protein 1 [30, 31].

18.5 Clinical Features (Figs. 18.1 and 18.2)

Pyoderma gangrenosum can have a variety of clinical presentations. The lesions can be classified morphologically as (a) classic ulcerative, (b) bullous, (c) pustular, (d) vegetative (superficial granulomatous), and (e) pyostomatitis vegetans. These clinical variants of PG differ in their clinical presentation, location, and associated diseases.

Patients with PG complain of severe pain that is out of proportion to the clinical appearance of lesions. Pathergy occurs in 20–30 % of patients; it is defined as the development of lesions at sites of cutaneous trauma (needle stick, venesection,

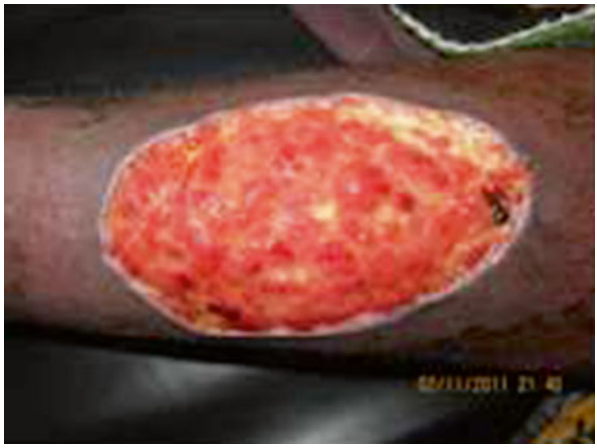

Fig. 18.1 An ulcer of pyoderma gangrenosum on the leg

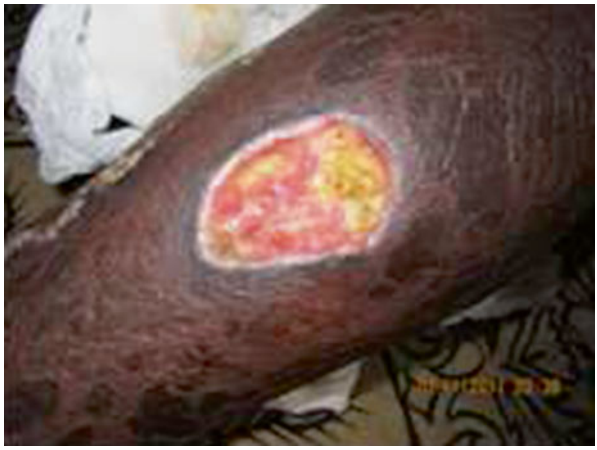

Fig. 18.2 Close-up view of a lesion of pyoderma gangrenosum on the leg showing a well-defined ulcer with violaceous undermined edges, granulation tissue, and purulent exudate at the base

insect bite, scalds, varicella, or surgical procedures, especially breast surgery, may act as trigger).

Cutaneous lesions most frequently develop on lower extremities especially on pretibial areas but can occur anywhere including mucous membranes. Sterile neutrophilic abscesses of internal organs (lungs, bones, joints, central nervous system, cardiovascular system, eye, intra-abdominal viscera) can occur with or precede cutaneous PG.

Skin lesions begin as tender papulopustule with surrounding erythematous or violaceous induration, or erythematous nodule or bulla on violaceous base. Necrosis occurs forming a central ulcer; a fully developed ulcer has purulent base with irregular undermined and overhanging, gunmetal color border which extends centrifugally. Re-epithelialization from margins occurs and lesions heal with atrophic cribriform pigmented scarring. Ulcers may be single or multiple and are rapidly progressive, but some may be less inflammatory and expand slowly.

PG-associated hematological disorders or drug-induced PG presents with acute onset hemorrhagic or purulent bullous lesions with widespread distribution and

rapid progression. Fever and signs of toxicity are present. PG associated with inflammatory disorders is usually a chronic slowly enlarging ulcer with increased granulation tissue at base, and it sometimes regresses spontaneously. PG in children is clinically similar to adults, but the lesions occur more frequently on head and anogenital areas.

18.6 Clinical Variants

18.6.1 Classic or Ulcerative PG

It is the commonest clinical variant. It presents with small tender red-blue papule, pustule, or plaque that erodes into painful ulcers with violaceous undermined edges, and the base shows granulation tissue, necrosis, or purulent exudate (Figs. 18.1 and 18.2). Most common site is lower extremities (70 %) but it may occur at other sites. Healing occurs with atrophic cribriform scar. Constitutional symptoms are present. Genital and mucosal involvement can occur. Seventy percent of the patients have associated disorders. Peristomal and postoperative PG present as ulcerative PG.

18.6.2 Pustular PG

It usually occurs during acute exacerbation of inflammatory bowel disease and presents as discrete painful sterile pustules with surrounding erythema on normal skin usually on extensor aspects of limbs. Lesions often resolve with control of inflammatory bowel disease (in some cases using treatment appropriate for both PG and IBD), but some may evolve into ulcerated classic PG [31].

18.6.3 Bullous PG

Superficial hemorrhagic bullae are present on the face, dorsum of hands, and upper extremities. Clinical and histopathological findings may be similar to superficial bullous variant of Sweet's syndrome, but bullous PG typically ulcerates and heals with scarring [31]. It is commonly associated with myeloproliferative disorders and can also occur with acute flare of inflammatory bowel disease.

18.6.4 Superficial Vegetative PG or Superficial Granulomatous Pyoderma

It presents as furunculoid nodule, abscess, plaque, or superficial ulcer most commonly on the trunk. It has non-purulent base and lacks the violaceous, undermined border [2, 32, 33]. Lesion is usually solitary, slowly progressing, and relatively painless. It is not associated with any systemic disease and resolves with less aggressive treatment [34, 35].

18.6.5 Peristomal PG

It is an ulcerative PG, accounting for about 15 % of cases. It may coexist with pustular vasculitis or PG at other sites. It is almost always associated with inflammatory bowel disease. Other associations include diverticular disease, bowel carcinoma, perforated bowel, neurogenic bladder, collagenous colitis, and systemic sclerosis.

18.6.6 Pyostomatitis Vegetans

It is characterized by oral mucosal thickening with multiple pustules and snail track ulcers on an erythematous base. It is strongly linked with inflammatory bowel disease (active ulcerative colitis). Skin lesions (pyodermatitis vegetans) have flexural distribution and are clinically similar to pemphigus vegetans. Based on evidence it is best to view it as inflammatory bowel disease-associated eruption and not a form of PG [31].

18.7 Histopathology

The histopathological findings of PG are variable and nonspecific but are useful in excluding other possible etiologies. The findings depend on clinical variant, type of lesion, site of lesion, site within the lesion, stage of evolution of lesion, and the treatment taken by the patient [2]. Site of biopsy is important because biopsy taken from the center of established ulcerative, bullous, or pustular PG lesions usually shows marked neutrophilic infiltration with abscess formation in mid and deep dermis extending to the panniculus, whereas those taken from peripheral areas (ulcer edge or inflammatory zone of erythema) show mixed or predominantly lymphocytic inflammatory infiltrate.

Typical findings are central necrosis and ulceration of the epidermis and dermis, surrounded by acute inflammatory cell infiltrate with peripheral mixed or chronic inflammatory cells.

Each clinical variant has additional more specific features which are as follows:

(a) Ulcerative: dermal-epidermal neutrophilic infiltrate extending to panniculitis with abscess formation.
(b) Pustular: perifollicular neutrophilic dense dermal infiltrate with intraepidermal vesicle.
(c) Vegetative: granulomatous reaction with palisading histiocytes and giant cells in the setting of focal dermal neutrophilic abscess and pseudoepitheliomatous hyperplasia is seen.
(d) Bullous: subepidermal or intraepidermal necrosis and marked upper dermal edema with prominence of neutrophils.

In most patients with typical PG, chronic ulcers have inflammation at the edge of ulcer bed. Presence of vasculitis in PG is debatable. True vasculitides and infective causes should be excluded if vasculitis is evident. Lymphocytes may be seen to infiltrate vessel wall with intramural or intravascular fibrin deposition (lymphocytic vasculitis). Culture and staining of biopsy tissue for bacteria, fungi, and

mycobacteria should be done if granuloma is present in absence of inflammatory bowel disease.

18.8 Evaluation of a Patient with PG

Clinical presentation of PG may be diverse, and there is neither a diagnostic laboratory test nor pathognomic histopathological findings; therefore, it is a diagnosis of exclusion. Most important considerations are exclusion of infection, vascular disease (stasis, occlusion, and vasculitis), and malignancy. Thorough history should be taken to rule out systemic involvement due to associated disorders, malignancy-related symptoms, and exposure to drugs (iodides, bromides, hydroxyurea), and physical examination should be done.

Skin biopsy and tissue culture should be done to rule out other causes. The best site for skin biopsy (incisional) is from the edge of the lesion (reducing potentially misleading features that may occur in any chronic ulcer) [2]. The patient should be investigated to rule out associated disorders (arthritis, inflammatory bowel disease, and hematological malignancies). Serological evaluation may also be performed (antinuclear antibodies, antiphospholipid antibodies, serum protein electrophoresis, ANCA).

18.9 Diagnosis

There is no confirmatory diagnostic test for pyoderma gangrenosum. The following diagnostic criteria have been proposed for cutaneous lesions of classic ulcerative PG [36]. Diagnosis requires both of the major criteria and at least two minor criteria (Table 18.2).

Table 18.2 Proposed diagnostic criteria for classic ulcerative pyoderma gangrenosum [36]

Major criteria
1. Rapid[a] progression of a painful[b], necrolytic cutaneous ulcer[c] with an irregular, violaceous and undermined border
2. Other causes of cutaneous ulceration have been excluded[d]
Minor criteria
1. History suggestive of pathergy[e] or clinical finding of cribriform scarring
2. Systemic diseases associated with pyoderma gangrenosum[f]
3. Histopathologic findings (sterile dermal neutrophilia,+/−mixed inflammation,+/− lymphocytic vasculitis)
4. Treatment response (rapid response to systemic corticosteroids)[g]

[a]Characteristic margin expansion of 1–2 cm per day or a 50 % increase in ulcer size within 1 month
[b]Pain is usually out of proportion to the size of ulceration
[c]Typically preceded by a papule, pustule or bulla
[d]Usually necessitates skin biopsy and additional evaluation to exclude other causes
[e]Ulcer development at sites of minor cutaneous trauma
[f]Inflammatory bowel disease, arthritis, IgA gammopathy, or underlying malignancy
[g]Generally responds to prednisone (1–2 mg/kg/day) or another corticosteroid at an equivalent dosage, with 50 % decrease in size within 1 month

18.10 Differential Diagnosis

18.10.1 Early Inflammatory Non-ulcerative Stage (Papules, Pustules, Plaques, or Nodules)

- Follicular infections (folliculitis, furuncle, carbuncle of bacterial, fungal, or viral origin)
- Cellulitis or cellulitis-like lesion (bacterial, mycobacterial, or fungal origin)
- Insect bite reaction
- Cutaneous T- and B-cell lymphomas
- Halogenoderma (iododerma or bromoderma)
- Panniculitides (inflammatory, infectious, metabolic, neoplastic)
- Cutaneous polyarteritis nodosa
- Sweet's syndrome
- Behçet's disease
- Bowel-associated dermatosis–arthritis syndrome

18.10.2 Later Ulcerative or Vegetative Stage

- Infections – streptococcal synergistic gangrene, botryomycosis, ecthyma gangrenosum, gummatous treponemal ulcers, cutaneous lesions of the deep mycoses (e.g. blastomycosis, coccidioidomycosis, paracoccidioidomycosis, chromomycosis), and atypical and typical mycobacterial infections
- Parasitic infections – leishmaniasis, amebiasis, and schistosomiasis
- Vascular diseases – ulcerations due to venous hypertension, arterial insufficiency, non-septic emboli, hemoglobinopathies, and thrombosis (secondary to hypercoagulability)
- Vasculitis – cutaneous polyarteritis nodosa, microscopic polyangiitis, granulomatous vasculitides (Wegener's granulomatosis, Churg–Strauss syndrome, temporal arteritis), autoimmune connective tissue disease (systemic lupus erythematosus, rheumatoid arthritis), and Behçet's disease
- Malignancy – squamous cell carcinoma, basal cell carcinoma, and cutaneous T- and B-cell lymphomas
- Miscellaneous – brown recluse spider bite, ulcerative necrobiosis lipoidica, pemphigus vegetans of the Hallopeau or Neumann type, blastomycosis-like pyoderma, nonhealing surgical wound, factitious ulcers, ulcers in patients with Chédiak–Higashi syndrome, and leukocyte adhesion deficiency

18.11 Treatment

There is neither specific nor uniformly effective therapy for PG. The nature and intensity of the therapeutic approach depend on the number, size and depth of the lesions, the rate of expansion and appearance of new lesions, the associated

disorder, the medical status of the patient, and the risk and patient tolerance of prolonged therapy. The therapeutic thrust is to reduce the inflammatory process of the wound in order to promote healing and reduce pain and to control the contributing underlying disease (especially leukemias and inflammatory bowel disease) with least adverse effects. The treatment of PG consists of (a) general measures, (b) wound care, and (c) specific therapy (topical, intralesional, systemic). The specific treatment of PG is local or combined local and systemic corticosteroid therapy with or without adjunctive systemic therapy.

18.11.1 General Measures

Adequate bed rest, efficient pain relief, correction of anemia, and appropriate therapy of associated disease should be started. If surgery is anticipated, appropriate measures (use of subcuticular sutures and systemic steroid cover) should be adopted to avoid precipitating new postoperative PG lesions. Patient should be given realistic expectations of the speed of recovery in the disease.

18.11.2 Wound Care

The cutaneous lesions of PG are usually extremely tender so cleansing should be carried out with tepid sterile saline or a mild antiseptic solution. Potassium permanganate solution diluted 1:2,000 is helpful if there is marked exudation; it also inhibits bacterial growth. Nonadhesive dressing should be applied over lesion with a crepe elasticized bandage. Hydrocolloid dressings can be used for superficial lesions. Patient should be instructed to avoid use of irritants such as chemical desloughing agents, caustics, gauze impregnated with soft paraffin or antibacterial agents, or pressure dressings.

A variety of bacteria may be cultured from the wound, but they usually represent contaminants and antibiotics are not required unless there are signs of incipient cellulitis around the wound.

18.11.3 Specific Therapy (Table 18.3)

Key to evidence-based support: (1) prospective controlled trial, (2) retrospective study or large case series and (3) small case series or individual case reports.

Systemic corticosteroids have generally been the most predictable and effective medication when delivered in adequate dosage. Unfortunately, more resistant lesions require more protracted therapy (>3 months) at a higher than desirable dosage, thus inviting adverse side effects. Such patients should be closely monitored and should receive supplemental calcium (1500 mg/day) and vitamin D (800 IU/day). Bisphosphonates may be used when required. Cyclosporine is an alternative first-line therapy of PG [38, 39] or may be used in combination with systemic

Table 18.3 Therapeutic ladder for the treatment of pyoderma gangrenosum [37]

Drugs	Dosage	Level of evidence
Inflammatory disease		
(a) Mild disease		
Intralesional corticosteroids		2
Topical tacrolimus		2
Clofazimine	100–400 mg PO daily	2
Superpotent topical corticosteroids		3
Oral antibiotics (sulfonamides, minocycline)		3
Colchicine	0.6 mg PO thrice daily	3
Dapsone	50–150 mg PO daily	3
Combination colchicine/dapsone		3
Others (oral potassium iodide, intralesional cyclosporine, topical cromolyn sodium, nicotine patch or cream)		3
(b) More severe disease		
TNF-α inhibitors[a]: infliximab	5 mg/kg IV at weeks 0, 2, 6	1
Adalimumab	80 mg sc as initial dose then 40 mg sc weekly or every other week	3
Etanercept	50–100 mg sc weekly	3
Prednisone	60–120 mg PO daily	2
Cyclosporine	2.5–5 mg/kg PO daily	2
Thalidomide[b]	50–150 mg PO nightly	2
Methotrexate[c]	2.5–25 mg PO or IM weekly	
Azathioprine[c]	50–100 mg PO twice daily	3
Mycophenolate mofetil[c]	1–1.5 g PO twice daily	3
Methylprednisolone[d]	1 g daily for 3–5 days (IV pulse)	3
Tacrolimus	0.1–0.2 mg/kg PO daily	3
Cyclophosphamide	50–100 g daily	3
Chlorambucil	4–6 mg PO daily	3
IV Ig	2–3 g/kg IV monthly (given over 2–5 consecutive days)	3
Granulocyte apheresis, plasmapheresis		3
Total colectomy (severe chronic ulcerative colitis)		3
Non-inflammatory disease		
Bio-occlusive dressings compression, limb elevation		

[a]Especially in patients with inflammatory bowel disease
[b]Especially in patients with Behcet's disease
[c]Often used in combination with other agents or maintenance therapy
[d]Followed by daily oral prednisone

corticosteroids to achieve rapid control of disease. Tacrolimus [39–42] and mycophenolate mofetil have been used successfully in the treatment of PG either as monotherapies or in combination with systemic corticosteroids or cyclosporine [43]. Pulsed intravenous corticosteroid therapy has been reported to be effective in some cases refractory to oral corticosteroids, and it has been recommended in PG refractory to other forms of treatment. Methotrexate and TNF-α inhibitors like infliximab, adalimumab, and etanercept are being used especially where there is associated inflammatory bowel disease or inflammatory arthritis. Thalidomide has been effective as well, especially in those who have Behçet's disease. For treating PG of PAPA syndrome, anakinra (IL1 receptor antagonist) and infliximab have found to be effective [44–51].

Other treatment modalities found to be effective in small studies include plasmapheresis, leukocytapheresis or granulocytapheresis IVIG, and low-dose colchicines [52–57]. Evidence for benefit from minocycline, dapsone, and clofazimine is anecdotal. Surgical procedures, if required, should be carefully performed in patients with PG because pathergy phenomenon can take place [56–58]. Aggressive surgical debridement is contraindicated, but split-skin grafts and cultured keratinocyte autografting have been successfully performed while using prolonged courses of immunosuppressants to minimize the pathergy phenomenon [59–61].

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