

PYODERMA GANGRENOSUM: A MINI-REVIEW

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ABSTRACT

Pyoderma gangrenosum (PG) is a rare, chronic neutrophilic dermatosis of unknown aetiology that usually presents with necrotising ulcers, although the evolution of the disease can be variable and is not always progressive. Its pathogenesis is poorly understood but an underlying immunological abnormality seems to be implicated in the genesis of the lesions. This hypothesis is supported by its frequent association with inflammatory bowel disease, malignancies, and rheumatological disorders. The diagnosis is challenging even for dermatologists as there are no specific tests or histological features. There are no clinical trials evaluating the efficacy of the different drugs used to treat the disease due to its rarity, and therefore there is no 'gold standard' therapy. In this mini-review we describe the main clinical aspects of PG, its pathophysiology, association with underlying diseases, diagnosis, treatment options, and prognosis.

Keywords: Pyoderma gangrenosum (PG), neutrophilic dermatoses (NDs), ulcer, treatments.

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, chronic, recurrent, ulcerative dermatosis that is now included within the spectrum of the neutrophilic diseases. PG lesions are characterised by prominent neutrophilic infiltration of the skin in the absence of infectious cause or vasculitis, although they can show evidence of leukocytoclastic vasculitis.^{1,2} The condition is potentially lethal and causes considerable morbidity. It goes unrecognised or is misdiagnosed in up to 30% of cases and can occur at any age, with a peak of incidence between 20–50 years of age. Women are slightly more susceptible to the disease than men.^{3,4} Paediatric PG represents 4% of all cases.⁵ It usually presents as a papule or pustule that develops into one or more painful ulcers with violaceous and undermined borders.^{6,7} Several variants are recognised. Since there are no accepted consensus diagnostic criteria and the diagnosis is one of exclusion, identification of PG is often delayed and challenging. This is made more difficult by there being no clinical trials that have evaluated the efficacy of the different drugs used in the treatment of PG due to the rarity of the disease; therefore there is no 'gold standard' therapy.

PATHOGENESIS

Both the aetiology and pathogenesis of PG are not yet completely understood. An abnormal immunological response to undefined triggers and factors may combine and be responsible for the clinical manifestations. The pathergy phenomenon, an aberrant exaggerated inflammatory response, is characteristically observed in up to 30% of PG cases.³

PG is frequently associated with inflammatory bowel disease (IBD). This supports the hypothesis of possible cross-reactivity between intestinal and cutaneous antigens.⁸ Dysregulation of the normal T cell response also appears to be implicated. This is supported by the observation that PG lesions heal when treated with immunosuppressive drugs and tumour necrosis factor (TNF) inhibitors. Nevertheless, lesions may appear during treatment with etanercept or infliximab, although this is rare.⁹⁻¹¹

PG is considered to be within the spectrum of the neutrophilic dermatoses (NDs). This group comprises a number of heterogeneous disorders characterised by inflammatory skin lesions that, observed histologically, show an intense

inflammatory infiltrate composed primarily of neutrophils, with no evidence of infection.^{1,2} These entities probably share a common pathophysiological mechanism that involves an abnormal recruitment or haemostasis of polymorphonuclear neutrophils. An elevation of the cutaneous and/or circulating levels of pro-inflammatory cytokines and potent attracting chemokines, namely interleukin (IL)-6, chemokine (C-X-C motif) ligand (CXCL) 8, and CXCL1-3, are observed in PG ulcers.^{12,13} An overexpression of matrix metalloproteinases (MMPs), namely MMP-2, 9, and 10, is also observed in PG and Sweet's syndrome (SS) lesions. An increase in the neutrophil elastase inhibitor, elafin, as well as an intensification of the Fas/FasL system are contributing factors for ulcer formation and abnormal wound healing.¹²⁻¹⁴ Some authors have suggested that PG during pregnancy and puerperium may be a consequence of high granulocyte-colony stimulating factor (G-CSF) levels and pathergy.¹⁵ Levels of IL-17, IL-23, and Th17 cells have been found to be increased in PG cutaneous lesions.¹⁶⁻¹⁹

An abnormal genetic background is thought to play a role in the pathogenesis of PG. This is supported by the presence of PG lesions in patients with: PAPA syndrome (pyogenic sterile arthritis, PG, and acne); PAPASH syndrome (pyogenic sterile arthritis, PG, acne, and hidradenitis suppurativa); and PASH syndrome (PG, acne, and hidradenitis suppurativa). In these patients, several mutations, namely in the *PSTPIP1* gene on chromosome 15q25, result in an aberrant production of IL-1.^{13,20,21} On the other hand, PG associated with IBD may show abnormalities in *IL8RA*, *TIMP3*, and *TRAF3IP2* genes.²¹ Due to recently acquired knowledge regarding its pathophysiology, it is now accepted that PG is a systemic immune-mediated inflammatory disease rather than a purely cutaneous disease.

ASSOCIATED DISEASES

PG can be idiopathic, but most cases are associated with other diseases (50-80%): IBD (up to 41%), rheumatoid arthritis, seronegative arthritis, haematological malignancies, paraproteinaemia, and, rarely, solid tumours (single reports or small case series) (Table 1).^{6-8,22} A recent study indicates that new-onset PG can herald a recurrence of a previously diagnosed solid organ malignancy, and recurrent PG can be associated with new-onset

solid organ malignancy.²³ Furthermore, PG has been associated with hepatitis C virus infection, HIV infection, and other NDs, such as SS, subcorneal pustular dermatosis, aseptic abscesses syndrome, Behçet's disease, and Sjögren's syndrome. It may also be drug-induced (interferon alpha 2b, G-CSF, gefitinib, pazopanib, sunitinib, imatinib, infliximab, rituximab, etanercept, and propylthiouracil).^{2,9,11,24,25} Familial forms have been reported in the context of the PAPA, PAPASH, and PASH syndromes. Recently, a case of PG associated with common variable immunodeficiency has been reported.²⁶

CLINICAL FEATURES

Four major clinical variants of PG have been described: ulcerative (classic), pustular, bullous, and vegetative (superficial). In most cases only one form is seen, but more than one subtype can be observed simultaneously in the same patient. In addition, PG may present overlapping features of other NDs.^{5,27} PG most commonly presents on the lower limbs, namely the pretibial area, but other skin areas (head, neck, breasts, genitalia, and upper extremities) can be involved.^{5,28} Clinically, the classical form (ulcerative) is characterised by rapidly progressing, painful ulcers with well-defined, violaceous, undermined borders (Figure 1A). The base of the ulcers is usually granulation tissue, and is sometimes necrotic and covered with purulent exudates. There is also inflammation of the perilesional skin.^{6,29}

The pustular type presents as multiple sterile pustules with a surrounding erythematous halo on the extensor surface of the extremities and upper trunk, and is commonly associated with IBD (Figure 1B).³⁰ It usually remits with the control of the digestive disease.^{3,7}

Bullous PG is associated with haematological malignancies and has features that overlap with bullous SS (Figure 2A and 2B). In this type of PG, grouped vesicles typically coalesce to form large bullae that ultimately ulcerate. The dorsal aspect of the hands, extensor surface of the arms, and the face are the most common locations. The presence of PG in these patients is suggestive of a poor outcome.^{31,32}

The vegetative (superficial) type is the most uncommon, most localised, and least aggressive variant of PG. It presents as a unique, erythematous, ulcerated plaque without the

characteristic undermined border. It is usually localised on the trunk and less associated with underlying disorders.^{33,34} The pathergy phenomenon is observed in these cases, and therefore surgical procedures, such as breast surgery or caesarean section, may worsen or trigger the lesions. Peristomal PG (15% of PG) is a pathergy phenomenon and may be observed after any stomal creation, with most of the cases occurring in patients who underwent ileostomy or colostomy for the treatment of IBD (namely, Crohn's disease).^{4,7} An average of 17.1 postoperative days has been reported for the development of the lesions.³⁵

PG can be associated with systemic symptoms (due to IL-1 β elevation) and, rarely, with extracutaneous neutrophilic infiltrates, namely in the lungs, heart, bones, and central nervous system. Eyes, oral mucosa, pharynx, larynx, and vulva may be affected in the form of aphthous lesions.^{2,36} During the healing process, new epithelial growth connecting the ulcer bed to the surrounding normal skin is observed and referred to as 'Gulliver's sign'.³⁷ The final stage of the process usually results in cribriform ('cigarette paper-like') scars. Adult and childhood PG have a similar clinical appearance, but in the latter the condition tends to involve the head, genital, and perianal areas.^{2,7,11}

Table 1: Diagnostic criteria and systemic diseases associated with pyoderma gangrenosum.²⁹

Diagnosis of classic ulcerative pyoderma gangrenosum requires two major and at least two minor criteria.	
Major criteria	
<ul style="list-style-type: none"> ✓ Rapid progression of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous, and undermined border ✓ Exclusion of other causes of cutaneous ulceration 	
Minor criteria	
<ul style="list-style-type: none"> ✓ History suggestive of pathergy ✓ Clinical finding of cribriform scarring ✓ Systemic diseases associated with pyoderma gangrenosum ✓ Histopathological findings (sterile dermal neutrophilic infiltration \pm mixed inflammation \pm lymphocytic vasculitis) ✓ Treatment response (rapid response to systemic steroid treatment) 	
Systemic diseases associated with pyoderma gangrenosum	
Inflammatory bowel diseases	Ulcerative colitis, Crohn's disease
Arthritis	Seronegative arthritis, ankylosing spondylitis, rheumatoid arthritis, PAPA and PAPASH syndromes
Hepatic disease	Autoimmune hepatitis
Infections	HIV, HCV
Malignancies	Myelodysplasia, acute myeloid leukaemia, Hodgkin disease, monoclonal gammopathy Colon, prostate, and bladder carcinoma, glioblastoma multiforme
Drugs	Propylthiouracil, antipsychotic drugs, isotretinoin, pegfilgrastim, TNF inhibitors, gefitinib, pazopanib, rituximab, infliximab, G-CSF, interferon
Others	Hidradenitis suppurativa, PASH syndrome Systemic lupus erythematosus, Behçet's disease, sarcoidosis Takayasu's arteritis Autoimmune thyroid disease Gastric and duodenal ulcer Diabetes mellitus Pregnancy CVI

PAPA: pyogenic sterile arthritis, pyoderma gangrenosum, and acne; PAPASH: pyogenic sterile arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa; HIV: human immunodeficiency virus; HCV: hepatitis C virus; G-CSF: granulocyte-colony stimulating factor; PASH: pyoderma gangrenosum, acne, and hidradenitis suppurativa; CVI: common variable immunodeficiency; TNF: tumour necrosis factor.



Figure 1: Pyoderma gangrenosum with well-defined, violaceous, undermined borders (A). Cribriform inflammatory pyoderma gangrenosum ulcer in a patient with inflammatory bowel disease (B).

DIAGNOSIS

There are no specific, accepted tests or consensus diagnostic criteria for PG. Su et al.²⁹ proposed that diagnosis of PG could be made if two major and at least two minor criteria were present (Table 1). However, the diagnosis relies on clinical suspicion and requires exclusion of other causes of skin ulceration, namely: infections (ecthyma gangrenosum, deep mycoses, and infection with atypical mycobacteria), vascular diseases (venous or arterial insufficiency), vasculitis, factitia, other NDs, and neoplasms (Table 2).^{6,38} Histopathology is useful to rule out other causes of ulcerations, and the histological findings vary depending on PG variant, the site, and the timing of the skin biopsy. Biopsy should include the ulcer's border and the adjacent skin, and a specimen should be sent for culture. In recent, actively expanding lesions, a dense neutrophilic dermal infiltrate with micro-abscesses, occasional vasculitis, and leukocytoclasia is observed. In older, fully developed

lesions, tissue necrosis along with a surrounding mononuclear cell infiltrate is usually seen.³ Analyses should include: a complete blood cell count, chemistry and liver function tests, erythrocyte sedimentation rate, C-reactive protein level, serum and urine protein electrophoresis, and anti-nuclear and anti-neutrophil cytoplasmic antibodies. Colonoscopy should also be performed to exclude IBD.

TREATMENT

Prospective, randomised case-control studies that evaluate and compare treatment regimens are lacking in the literature due to the rarity of PG. Indeed, no randomised controlled trials have been performed. Therefore, there is no 'gold standard' therapy or therapeutic guidelines.^{38,39} The treatment approach is mostly empirical or based upon expert recommendations, and tries to target the different immunological mediators that seem to be involved in its pathogenesis.

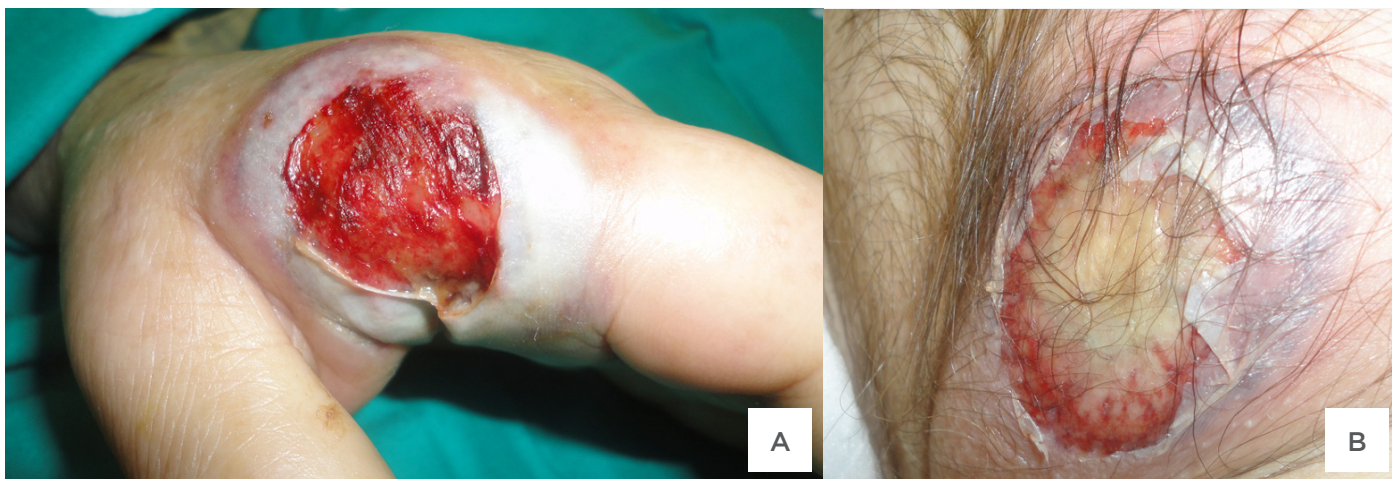


Figure 2: Bullous pyoderma gangrenosum on the dorsal aspect of the hand (A) and genital area (B) of a patient with a myelodysplastic syndrome.

Table 2: Differential diagnoses of pyoderma gangrenosum.⁶

Vascular diseases	Arterial or venous insufficiency Vascular occlusive diseases - livedoid vasculopathy, Dowling–Degos disease, ulcers of sickle cell disease, antiphospholipid antibody syndrome
Malignancies	Basal cell carcinoma Squamous cell carcinoma Cutaneous T cell lymphoma Leukaemia cutis
Infections	<i>Bacterial</i> Impetigo, ecthyma, necrotising fasciitis, anthrax, tuberculosis, atypical mycobacteria, Buruli ulcer, syphilitic gumma <i>Viral</i> Chronic herpes simplex, cytomegalovirus <i>Protozoal</i> Leishmaniasis, amoebiasis cutis <i>Fungal</i> Blastomycosis, histoplasmosis, sporotrichosis, cryptococcosis, aspergillosis, penicilliosis, zygomycosis
Exogenous tissue injury	Arthropod bite Factitial ulcers Drug-induced tissue injury Halogenodermas (iododerma/bromoderma) Calciphylaxis
Neutrophilic dermatoses	Sweet's syndrome Subcorneal pustular dermatosis Bullous lupus erythematosus
Vasculitis	Behçet's disease Polyarteritis ANCA-associated vasculitides Cryoglobulinemic vasculitis
Others	Cutaneous Crohn's disease

ANCA: anti-neutrophil cytoplasmic antibody.

Therapeutic choice is influenced by several factors: associated disease, extension, number and depth of the lesions, patient's performance status, and long-term side effects of the drugs.^{3,7} Treatment of the

underlying disease should be performed. PG may heal spontaneously, but most cases require local and systemic treatment.

TOPICAL TREATMENT

A good response to topical treatments may occur in mild lesions, namely in the vegetative type.^{7,11} Topical modalities include: dressings, topical agents, and intralesional injections. Topical corticosteroids (Class III and IV) or tacrolimus are the most frequently used. Topical sodium cromoglicate, 5-aminosalicylic acid, nitrogen mustards, benzoyl peroxide, and nicotine have been used with success.^{7,40-42} Topical tacrolimus 0.3% seems to be more effective than clobetasol propionate 0.05% in the treatment of peristomal PG, namely in lesions larger than 2 cm.⁴³ Recently, two cases have been successfully treated with autologous platelet-rich plasma gel.⁴⁴ Collagenase ointment and timolol gel have also been used to treat idiopathic PG.⁴⁵ Infliximab gel has been used to improve refractory lesions in a patient with ulcerative colitis,⁴⁶ and crushed dapsone has been used in the treatment of peristomal PG.⁴⁷ Intralesional corticosteroids or cyclosporine administered on the edges may also control the disease. Recently, the use of a dermal injection of activated protein C has been described.⁴⁸ Ulcer debridement or stoma relocation is not recommended, as it can aggravate the lesions. The use of adequate wound dressing is important, namely for managing heavy exudates. It is important to note that topical treatments alone are usually inefficient.

SYSTEMIC THERAPY

Systemic treatment is required in severe disease or rapidly progressive lesions. Corticosteroids and cyclosporine are widely accepted as first-line therapies, but Ormerod et al.⁴⁹ only recently published the first randomised controlled trial that compared prednisolone (0.75 mg/kg/day) and cyclosporine (4 mg/kg/day) in PG treatment. They concluded that both have comparable effectiveness, with ulcers healing in 47% of the patients after 6 months of treatment. It appears that starting with high doses (ranging from 0.5–2.0 mg/kg/day) of oral prednisone is an effective strategy. Disease stabilisation usually occurs within 24 hours. Tapering or discontinuation of the drug should only be recommended when the inflammatory component is absent or when the ulcer is healed, respectively.^{28,40} The sulpha drugs, such as dapsone (50–200 mg/day), may be beneficial, but not all patients will have a favourable response. Sulfasalazine (4–6 g/day) is the most effective sulpha drug, especially in

patients with associated ulcerative colitis and idiopathic forms of PG.^{3,7} Other systemic drugs have been reported to successfully treat PG, or have been used as effective corticosteroid-sparing agents, namely: azathioprine (100–150 mg/day), clofazimine (200–400 mg/day), mycophenolate mofetil (2–4 g/day), thalidomide (400 mg/day), methotrexate, minocycline, cyclophosphamide, and intravenous immunoglobulin.^{34,50-52} New therapeutics have emerged due to recently acquired knowledge regarding PG pathophysiology suggesting that PG represents the cutaneous manifestation of a generalised inflammation. Anti-TNF agents, adalimumab, etanercept, and infliximab seem to be effective, especially if there is associated IBD. Only one prospective, double-blind, placebo-controlled study has been performed in the treatment of PG with biologics (infliximab 5 mg/kg) to date.³⁹ Another alternative treatment is the human monoclonal antibody ustekinumab (anti-IL-12/IL-23).⁵³

The literature shows that PG lesions associated with auto-inflammatory syndromes have successfully been treated with the recombinant human IL-1 β receptor antagonist anakinra and the human monoclonal IL-1 β antagonist canakinumab.^{54,55} There have only been single case reports on the treatment of PG with the chimeric monoclonal anti-CD20 antibody rituximab.⁵⁶ Certolizumab pegol, a recombinant antigen-binding fragment of a humanised monoclonal antibody that selectively neutralises TNF may be an alternative therapy for the treatment of PG in cases of intolerance or ineffectiveness of other anti-TNF agents.⁵⁷ Multidrug regimens may be considered for refractory disease, namely systemic steroids in combination with cyclosporine. Other valid combinations include: methotrexate and infliximab; and cyclosporine, mycophenolate mofetil, and prednisone.¹¹

ADJUVANT THERAPY

Patients should receive local antimicrobial treatment if superinfection is clinically suspected. Pain management should be considered. Therefore, addition of osmotically active agents, such as macrogol, should be avoided. Morphine-containing hydrogel formulations can be used,⁵⁸ and oral narcotics may be required in severe cases.²

PROGNOSIS

Some ulcers may heal spontaneously with cribriform scars, but PG usually has a chronic relapsing course (up to 70%).⁵⁹ PG patients have a risk of death that is three-times higher than the

general population.⁶⁰ Proper management of any underlying systemic disease prevents rebound flares. Ulcerative and bullous variants have a worse prognosis. A rapid response to treatment suggests a good course for the disease.

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