Pyoderma gangrenosum

Introduction

Pyoderma gangrenosum is a rare ulcerating skin disorder which often occurs in association with systemic diseases. It was first described in 1930 and is characterized by rapidly progressive destructive skin ulcers, which are typically exquisitely painful. It can occur at any age, most frequently between the 3rd and 5th decades (Teagle and Hargest, 2014). The rarity of pyoderma gangrenosum limits accurate epidemiological data, but its incidence is estimated at 3–10 per million per year (Langan et al, 2012).

Approximately 50% of cases of pyoderma gangrenosum are associated with systemic disease, predominantly inflammatory bowel disease, rheumatoid arthritis, paraproteinaemias and haematological malignancies (Powell et al, 1996). A wide range of rarer causes is recognized, including primary biliary cirrhosis, hepatitis, spondyloarthropathies and systemic lupus erythematosus.

Although it is an uncommon presentation pyoderma gangrenosum results in significant morbidity as a result of pain, poor wound healing, skin destruction and unpleasant cribriform scarring. Mortality in patients with pyoderma gangrenosum is three times greater than that in the general population, with an increased mortality in cases associated with inflammatory bowel disease (Saracino et al, 2011). A poorer prognosis is associated with arthritis with slower healing and longer treatment duration (Charles et al, 2004).

Pathophysiology

The exact pathogenesis of pyoderma gangrenosum is unknown but it is commonly described as a reactive inflammatory neutrophilic dermatosis. It was first described in 1930 and initially thought to be an infectious dissemination from a distant source of infection (Miller et al, 2010). However, theories changed in the 1950s after the development of cortisone for treatment of rheumatoid arthritis resulted in unexpected healing in those patients with co-existent pyoderma gangrenosum ulcers.

An immune-mediated mechanism is now widely accepted, supported by clinical response to immunosuppressive therapy and association with immunological disorders such as inflammatory bowel disease and rheumatoid arthritis. Various atypical immune processes have been described, including complement defects, lymphocyte dysfunction, and abnormal monocyte and neutrophil chemotaxis (Adachi et al, 1998; Oka, 2007; Kawakami et al, 2009; Weizman et al, 2014). Protein deposition in the vasculature of affected sites suggests immune complex formation, further supporting an immunological pathogenesis.

Increasing evidence suggests a role of neutrophil trafficking abnormalities and alterations in cell surface integrins CR3 and CR4 (Adachi et al, 1998). Immunohistochemistry from pyoderma gangrenosum specimens shows high expression of myeloperoxidase (a neutrophil marker), and of IL-6 (recruits neutrophils to sites of infection). Raised serum levels of interleukin (IL)-8, IL-6 and granulocyte colony-stimulating factor have been reported in active pyoderma gangrenosum, all suggesting association with neutrophil proliferation (Oka, 2007; Kawakami et al, 2009). Pyoderma gangrenosum has also been induced by prophylactic granulocyte colony-stimulating factor in patients receiving chemotherapy (Miall et al, 2006). IL-23 has been implicated in Crohn's disease and may also play a role: treatment with ustekinumab (an anti-IL-23 monoclonal antibody) resulted in complete healing of pyoderma gangrenosum (Guenova et al, 2011).

Genetic factors may also play an important role. PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, acne) is a rare autosomal dominant autoinflammatory syndrome (Smith et al, 2010). This occurs as a result of a gene mutation in PSTP1P1 (proline-serine-threonine phosphatase-interacting protein 1), which encodes a cytoskeletal adaptor protein inflammasome involved in IL-1beta production (Yeon et al, 2000). Hyperphosphorylation of the protein occurs with overproduction of IL-1beta. A new syndrome PASH (pyoderma gangrenosum, acne, hidradenitis) has been documented without the arthritis component (Braun-Falco et al, 2012). Genetic factors have also been identified in inflammatory bowel disease-specific cases (Weizman et al, 2014).

There are also reports of pyoderma gangrenosum induced by various drugs, including propylthiouracil, isotretinoin, sulpiride and sunitinib (Teagle and Hargest, 2014).

Examination

Pyoderma gangrenosum is characterized by rapid progression of painful deep necrotic ulcers. Typically these occur in the lower extremities and on the pre-tibial region but can affect any area of the body; cases have been described on the head, trunk, neck, upper limb and genitals. It often occurs in a peristomal distribution in patients with inflammatory bowel disease and accounts for 50% of chronic parastomal ulcers (Brooklyn et al, 2006).

Pyoderma gangrenosum ulcers start as a nodule or sterile pustule which progresses to a necrotic exquisitely painful mucopurlent ulcer. Ulcers often develop rapidly, typically within 24–48 hours.

On examination, ulcers typically have well-defined, irregular, raised, undermined, serpiginous purple borders (*Figure 1*). The skin surrounding the ulcer is erythematous and indurated. The ulcer base is necrotic and filled with purulent exudate, blood and granulation tissue. Ulceration involves the skin, subcutaneous tissue and muscle layers.

Around 25% of cases have a history of skin trauma, scars or burns demonstrating pathergy phenomenon (Su et al, 2004). Older lesions heal with a characteristic thin cribriform scar with a criss-cross pattern. Associated systemic symptoms can occur including fevers, malaise, arthralgia and myalgia. Extracutaneous manifestations have also been documented, including

Dr SH Mehrtens *is Core Medical Trainee 2 and* **Dr JM Crawley** *is Consultant Dermatologist in the Department of Dermatology, University College London Hospital, London NW1 2BU*

Correspondence to: Dr SH Mehrtens (smehrtens@doctors.org.uk)

ulceration of the oropharynx, upper airway, eye and genitals. Other reports document neutrophilic myositis and sterile infiltrates in the liver, spleen, lungs and bone.

Variants of pyoderma gangrenosum include classic ulcerative, pustular (predominantly superficial ulceration associated with inflammatory bowel disease), bullous and vegetative (indolent course).

Although pyoderma gangrenosum has a characteristic appearance as described, other ulcerating conditions may have a similar appearance and there may be diagnostic error. In a study of 157 patients diagnosed with pyoderma gangrenosum, 15 patients were found to have been misdiagnosed (Weenig et al, 2002).

Su et al (2004) suggested diagnostic criteria to assist diagnosis including two major and four minor criteria. To make a diagnosis both major and at least two minor criteria need to be fulfilled (*Table 1*).

As 50% of cases of pyoderma gangrenosum are associated with systemic diseases, the examination should include signs of associated disease:

1. Inflammatory bowel disease: stomas, clubbing, arthropathy, laparotomy scars, anaemia
2. Myeloproliferative disorders: hepatosplenomegaly, lymphadenopathy
3. Chronic active hepatitis: signs of chronic liver disease
4. Primary biliary cirrhosis: pruritic scratch marks, xanthelasma
5. Arthropathies: rheumatoid arthritis, ankylosing spondylitis, psoriatic changes
6. Polycythaemia rubra vera: splenomegaly, plethoric facies, dusky cyanosis
7. Sarcoidosis: lupus pernio, erythema nodosum, interstitial lung disease.

Disease associations

About 50–70% of cases of pyoderma gangrenosum are associated with systemic disease. The most common associations are inflammatory bowel disease, rheumatoid arthritis and haematological malignancies (Binus et al, 2011). Other important causes include multiple myeloma, IgA paraproteinaemia and hepatitis. There is also a large group of rarer associated diseases (*Table 2*).

Differential diagnosis

The differential diagnoses of pyoderma gangrenosum include other conditions which cause skin ulceration (*Table 3*). It is crucial to exclude other ulcerating conditions, particular infectious and vascular causes.

Investigation and management

Pyoderma gangrenosum is a clinical diagnosis. There are no specific serological tests or investigations to confirm the diagnosis. It must be considered in any patient with non-healing ulceration, particularly in the context of associated systemic diseases as discussed.

Pyoderma gangrenosum is a challenging diagnosis and if delayed can lead to significant morbidity (Brooklyn et al, 2006; Langan et al, 2012). If suspected an urgent dermatology referral is advised. Missed diagnosis may result in extensive tissue damage with scarring and/or harmful inappropriate therapy.

Blood tests are important to screen for associated diseases and exclude differentials which may present similarly. Important serological requests include full blood count, blood film, liver/kidney function tests, erythrocyte sedimentation rate, protein electrophoresis, anti-neutrophil cytoplasmic antibody and cryoglobulins. Also consider chest radiograph, colonoscopy and vascular studies to assess venous and arterial function.

A skin biopsy is necessary mainly to exclude other causes of ulceration, importantly vasculitic conditions and malignancy. Histopathology is non-specific. Early lesions often show deep folliculitis, neutrophil infiltration, epidermal necrosis and pus (Powell et al, 1996). There may be lymphocytic infiltration at the ulcer edge with fibrinoid necrosis of blood vessels. Microscopic features of later ulcers include haemorrhage, infarction, necrosis and fibrosis.

Figure 1. Pyoderma gangrenosum ulcers showing characteristic features.

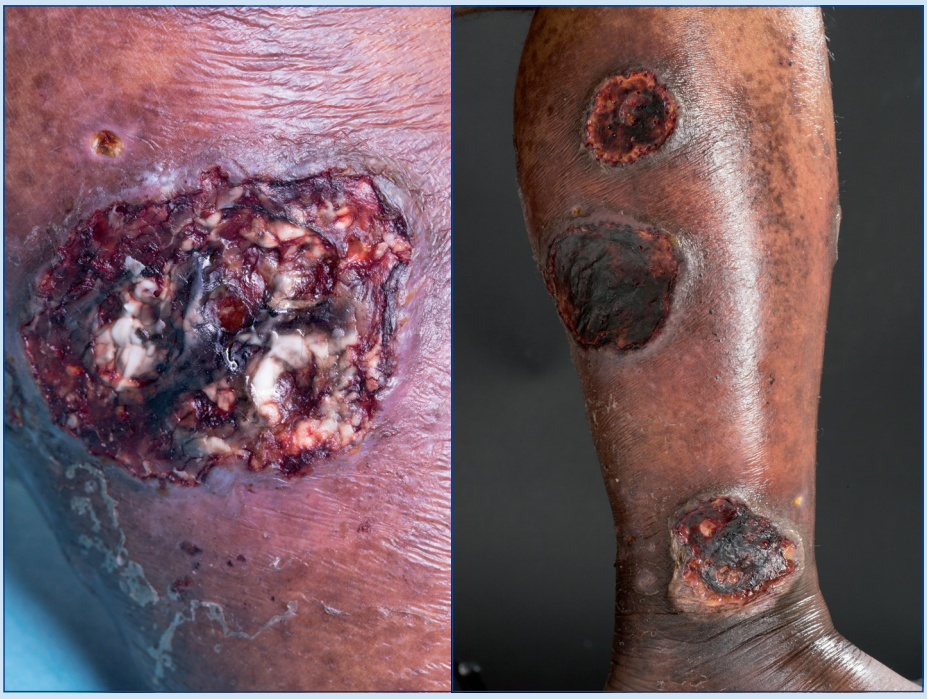

Table 1. Diagnostic criteria for pyoderma gangrenosum

Major criteria	A painful rapidly progressive necrotic cutaneous ulcer with irregular, violaceous and undermined border. Characteristic margin expansion 1–2 cm per day, or 50% increase in ulcer size within 1 month
	Exclusion of other causes of ulceration
Minor criteria	History suggestive of pathergy or clinical finding of cribriform scarring
	Presence of systemic diseases associated with pyoderma gangrenosum
	Characteristic histopathological findings: sterile dermal neutrophilia, mixed inflammation, lymphocytic vasculitis
	Response to treatment with systemic steroids and/or immunosuppression

From Su et al (2004)

Successful management of pyoderma gangrenosum requires a multidisciplinary approach involving dermatologists, plastic surgeons, gastroenterologists and immunologists. Pyoderma gangrenosum can be unpredictable in its response to treatment and there is currently no gold standard of treatment or protocol for therapy. There is a lack of targeted, universally successful therapies, mainly because of the lack of high quality data available. Literature is limited by rarity of presentation and studies are often inconclusive as a result of the small sample sizes. Treatment combines local wound care and systemic treatment alongside treatment of the underlying disease (*Table 4*). Surgical debridement is contraindicated because of pathergy.

Systemic options include high dose corticosteroids, immunosuppressive agents and ciclosporin (Miller et al, 2010). Ciclosporin is the most widely used first-line alternative to systemic steroids; ulcer healing is often seen within 3 months and a maintenance dose may be required. Unfortunately ciclosporin has many side effects including CNS effects, nephrotoxicity, hypertension, development of lymphoma and myopathy. Dapsone and sulfasalazine are often used as adjuncts and are particularly beneficial in patients with colitis. Immunosuppressants (azathioprine, 6-mercaptopurine, metho-trexate, cyclophosphamide, chlorambucil) are also used as steroid-sparers and first-line adjuncts; however, therapeutic effect is less predictable and there may be significant associated cytotoxicity. Newer treatment options include immune modulators such as interferon-alpha and thalidomide. Patients have also been successfully treated with intravenous immunoglobulin and leukocyte apheresis. Infliximab (anti-tumour necrosis factor monoclonal antibody) is becoming increasingly popular, particularly in the treatment of pyoderma gangrenosum associated with systemic disease. Etanercept and adalimumab are also used. Biologics have shown promising response in several small trials and case reports, but variability in assessment and outcomes makes it difficult to accurately compare treatments.

Table 2. Common and rare disease associations of pyoderma gangrenosum

Common	Gastrointestinal	Ulcerative colitis	In 15–35% of cases
		Crohn's disease	
	Haematological	Leukaemia (most frequently acute myeloid)	20% of cases
		Monoclonal gammopathy (mostly IgA)	Pyoderma gangrenosum often atypical
		Hairy cell leukaemia	
	Arthritides	Rheumatoid arthritis	20–33% of cases – most commonly seronegative
		Seropositive symmetrical polyarthritis	Unrelated to arthritis activity
Rare	Gastrointestinal	Chronic active hepatitis	
		Primary biliary cirrhosis	
	Haematological	Myelofibrosis	
		Myeloma	
		Polycythaemia rubra vera	
		Lymphoma	
		Paroxysmal nocturnal haemoglobinuria	
	Arthritides	Ankylosing spondylitis	
		Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome	
		Psoriatic arthritis	
		Juvenile idiopathic arthritis	
	Immunological	Systemic lupus erythematosus	
		Sarcoidosis	
		Immunodeficiency	

Table 3. Differential diagnoses of pyoderma gangrenosum

Vascular	Vascular occlusive disease	Antiphospholipid syndrome
		Livedoid vasculopathy
		Sickle cell disease
	Arterial insufficiency ulcers	
	Venous insufficiency stasis ulcers	
	Vasculitis	ANCA vasculitides
		Behçet's disease
		Cryoglobulinaemic vasculitis
Infective	Bacterial	Necrotizing fasciitis
		Syphilis
		Atypical mycobacteria
		Erysipelas
	Viral	Chronic herpes simplex
	Fungal	Histoplasmosis
		Aspergillosis
		Sporotrichoses
		Cryptococcosis
	Parasitic	Amoebiasis cutis
		Leishmaniasis
Malignancy	Basal cell carcinoma	
	Squamous cell carcinoma	
	Cutaneous T-cell lymphoma	
	Leukaemia cutis	
Exogenous	Drug reaction	
	Tissue injury	
	Factitious ulcers or dermatitis artefacta	
	Calciphylaxis	
Neutrophilic dermatoses	Sweet syndrome	
	Bullous lupus erythematosus	
Inflammatory	Cutaneous Crohn's disease	
	Ulcerative necrobiosis lipoidica	

ANCA = anti-neutrophil cytoplasmic antibody

Antibody-mediated infusion reactions do occur and tumour necrosis factor-alpha inhibition may worsen bacterial infections while masking the signs. A case of death from septic shock of a patient with pyoderma gangrenosum receiving infliximab highlighted the risks of biological treatments (Wolbing et al, 2009).

Table 4. Management of pyoderma gangrenosum

Topical	Wound management	Elevation
		Regular lavage
		Compression and dressing
	Topical agents	Antibiotics
		Analgesics
		Corticosteroids
		Tacrolimus
		Mesalazine
		Benzoyl peroxide
	Surgical	Skin grafts (debridement contraindicated)
Systemic	Corticosteroids	High dose oral prednisolone
		Pulsed methylprednisolone if extensive ulceration
	Antimicrobials or anti-inflammatories	Dapsone
		Sulfasalazine
		Adjuncts
	Ciclosporin	First line steroid alternative
	Biological immune modulators	Anti-tumour necrosis factor monoclonal antibodies
		Intravenous immunoglobulin
		Interferon-alpha
	Immunosuppressants	Steroid-sparers
		Methotrexate
		Azathioprine
		Cyclophosphamide
		Mycophenolate mofetil

Conclusions

Pyoderma gangrenosum is a severe ulcerating skin disease associated with significant morbidity and mortality. It is often related to an underlying systemic disease and it is therefore critical that physicians from all specialties recognize the key clinical features. This will ensure prompt diagnosis and treatment, which will help to optimize management and minimize skin destruction and scarring disfigurement. It is also essential that assessment of the patient with pyoderma gangrenosum includes thorough screening for associated conditions. BJHM

Conflict of interest: none.

Adachi Y, Kindzelskii AL, Cookingham G et al (1998) Aberrant neutrophil trafficking and metabolic oscillations in severe pyoderma gangrenosum. *J Invest Dermatol* **111**: 259–68 (doi: 10.1046/j.1523-1747.1998.00311.x)

Binus AM, Qureshi AA, Li VW et al (2011) Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br J Dermatol* **165**: 1244–50 (doi: 10.1111/j.1365-2133.2011.10565.x)

Braun-Falco M, Kovnerystyy O, Lohse P, Ruzicka T (2012) Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) – a new autoinflammatory syndrome distinct from PAPA syndrome. *J Am Acad Dermatol* **66**: 409–15 (doi: 10.1016/j.jaad.2010.12.025)

Brooklyn T, Dunnill G, Probert C (2006) Diagnosis and treatment of pyoderma gangrenosum. *BMJ* **333**: 181–4 (doi: 10.1136/bmj.333.7560.181)

Charles CA, Bialy TL, Falabella AF, Eaglstein WH, Kerdel FA, Kirsner RS (2004) Poor prognosis of arthritis associated pyoderma gangrenosum. *Arch Dermatol* **140**: 861–4 (doi: 10.1001/archderm.140.7.861)

Guenova E, Teske A, Fehrenbacher B et al (2011) Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. *Arch Dermatol* **147**: 1203–5 (doi: 10.1001/archdermatol.2011.168)

Kawakami T, Yamazaki M, Soma Y (2009) Reduction of interleukin-6, interleukin-8, and anti-phosphatidylserine- prothrombin complex antibody by granulocyte and monocyte adsorption apheresis in a patient with pyoderma gangrenosum and ulcerative colitis. *Am J Gastroenterol* **104**: 2363–4 (doi: 10.1038/ajg.2009.271)

Langan M, Groves RW, Card TR, Gulliford MC (2012) Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. *J Investig Dermatol* **132**: 2166–70 (doi: 10.1038/jid.2012.130)

Miall FM, Harman K, Kennedy B, Dyer MJ (2006) Pyoderma gangrenosum complicating pegylated granulocyte colony-stimulating factor in Hodgkin lymphoma. *Br J Haematol* **132**: 115–16 (doi: 10.1111/j.1365-2141.2005.05839.x)

Miller JM, Yentzer BA, Clark A et al (2010) Pyoderma gangrenosum: A review and update on new therapies. *J Am Acad Dermatol* **62**(4): 646–54 (doi: 10.1016/j.jaad.2009.05.030)

Oka M (2007) Pyoderma gangrenosum and interleukin-8. *Br J Dermatol* **157**: 1279–81 (doi: 10.1111/j.1365-2133.2007.08202.x)

Powell FC, Su WPD, Perry HO (1996) Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* **34**: 395–409 (doi: S0190-9622(96)90428-4)

Saracino A, Kelly R, Liew D et al (2011) Pyoderma gangrenosum requiring inpatient management: a report of 26 cases with follow up. *Aust J Dermatol* **52**: 218–21 (doi: 10.1111/j.1440-0960.2011.00750.x)

Smith EJ, Allantaz F, Bennett L et al (2010) Clinical, molecular, and genetic characteristics of PAPA syndrome: a review. *Curr Genomics* **11**: 519–27 (doi: 10.2174/138920210793175921)

Su WPD, Davis MDP, Wenig RH, Powell FC, Perry HO (2004) Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol* **43**: 790–800 (doi: 10.1111/j.1365-4632.2004.02128.x)

Teagle A, Hargest R (2014) Management of pyoderma gangrenosum. *J R Soc Med* **107**: 228 (doi: 10.1177/0141076814534407)

Weenig RH, Davis MD, Dahl PR et al (2002) Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med* **347**: 1412–18 (doi: 10.1056/NEJMoa013383)

Weizman A, Huang B, Berel D et al (2014) Clinical, serologic, and genetic factors associated with pyoderma gangrenosum and erythema nodosum in inflammatory bowel disease patients. *Inflamm Bowel Dis* **20**: 525–33 (doi: 10.1097/01.MIB.0000442011.60285.68)

Wolbing F, Fierlbeck G, Hotzenecker W, Schaller M, Rocken M (2009) Septic shock after treatment of pyoderma gangrenosum with infliximab. *Acta Derm Venereol* **89**: 93–4 (doi: 10.2340/00015555-0540)

Yeon HB, Lindor NM, Seidman JG, Seidman CE (2000) Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome maps to chromosome 15q. *Am J Hum Genet* **66**: 1443–8 (doi: 10.1086/302866)

KEY POINTS

- Pyoderma gangrenosum is a rare neutrophilic dermatosis characterized by rapidly progressive necrotic skin ulcers.
- Pyoderma gangrenosum is associated with systemic disease in 50–70% of cases, most commonly rheumatoid arthritis, inflammatory bowel disease and haematological malignancies.
- Ulcers characteristically resemble deep necrotic ulcers with an irregular purple overhanging edge surrounded by erythematous indurated skin.
- Pyoderma gangrenosum is a clinical diagnosis of exclusion; skin biopsy is essential to exclude other causes of skin ulcers.
- Successful management requires control of the underlying condition and a combination of local wound care with systemic treatment.