

# Pyoderma gangrenosum: a diagnosis not to be missed

Pyoderma gangrenosum (PG) is a rare, painful, non-infectious, ulcerative, inflammatory skin condition. Clinicians need to be aware of PG because if the condition is incorrectly managed, it can lead to extensive tissue damage. Diagnosis is made largely on clinical appearance, from the patient history and from the exclusion of other possible diagnoses. Management requires a multidisciplinary approach as systemic therapies are often required to avoid the spread of the disease and to achieve wound healing. PG is often associated with underlying systemic disease, but can also be found in isolation, as the case study in this article highlights.

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## KEY WORDS

Pyoderma gangrenosum  
Atypical skin ulceration  
Inflammatory ulcer  
Systemic co-factors

Pyoderma gangrenosum (PG) is a rare, painful, non-infectious, ulcerative, inflammatory skin condition that was first described by Brocq in 1916 but more completely studied in 1930 by Brunstring et al. It occurs typically in adults between 40 and 60 years of age and is commonly associated with underlying systemic diseases.

### Aetiology

The aetiology of PG is not fully understood but it is believed to be an immune-mediated process (Weedon, 2002). Both humoral and cell-mediated abnormalities have been associated with PG. Where humoral abnormalities are suspected, antibodies against skin and bowel have been discovered along with the production of dermonecrotic factors.

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When isolated, these have been found to initiate tissue necrosis when injected into the subject's own skin (Samitz, 1966; Ebringer et al, 1969).

Cell-mediated defects have been found to include altered production of macrophage inhibition by lymphocytes, decreased neutrophil chemotaxis, and impaired monocyte phagocytosis (Nerella et al, 1985).

Von den Driesch (1997) reports that 50% of all sufferers also have co-existing systemic disease present. These are categorised into four main groups (Schwaegerle et al, 1988):

- ▶ Inflammatory bowel conditions (including ulcerative colitis and Crohn's disease)
- ▶ Haematological disorders (including lymphoid and myeloid leukaemias and myeloma)
- ▶ Rheumatoid conditions (including rheumatoid arthritis, and systemic lupus erythematosus)
- ▶ Hepatopathies (Callen, 1989) (including chronic active hepatitis, primary biliary cirrhosis and sclerosing cholangitis).

In 50% of cases, the disease follows acute trauma or injury to the area (including surgery), in a process known as pathergy (Cairns et al, 1994; Esnault et al, 1995). It is felt that cell-mediated defects are responsible for this form of PG presentation.

It is believed that Interleukin-8 may play a key role in the development of PG. It has been identified that in sufferers, there is an over-expression of this pro-inflammatory cytokine in the skin.

On histological examination, tissue with PG shows necrosis of the superficial dermis and epidermis. The centre of the lesion exhibits necrotising suppurative inflammation which subsequently leads to ulceration. The advancing edge of the lesion shows a lymphocytic vascular reaction (Magro et al, 1997). This tissue shows a high number of invading neutrophils.

There is marked oedema in the tissues with superficial vascular damage. In some cases, the central point of the lesion originates from a pustular necrosis of the hair follicle, with granulomatous inflammation.

### Presentation

Generally PG is most common on the lower extremities and the trunk. Although predominantly a condition seen in adult life, occasionally it can be seen in childhood and may be seen on the buttocks, perineum, and the head and neck (Graham et al, 1994). As already described, PG may initially present following trauma including surgery. There are a number of clinical presentations of PG described in the texts, these being known as ulcerative,

pustular, bullous, and vegetative. The clinical signs of PG vary with each type (Barham et al, 2004).

#### Ulcerative PG

The ulcerative form of PG is the easiest to recognise and is the one most commonly associated with this diagnosis. Painful ulcers evolve from one or more tender papules or pustules, frequently around hair follicles. These characteristically have well demarcated purple (sometimes described as violaceous) undermined borders and surrounding erythema. Ulcers may be singular or multiple and occur anywhere on the body (although most commonly on the trunk and lower limbs) (Powell and Su, 1996).

#### Pustular PG

Pustular PG develops as small painful pustules on otherwise healthy skin during acute exacerbations of inflammatory bowel disorders (Powell and Su, 1996).

#### Bullous PG

Bullous PG arises from rapidly developing haemorrhagic blisters mainly located on the arms (Bennett et al, 2000) in patients with myeloproliferative disorders (Powell and Su, 1996).

#### Vegetative PG

The vegetative form of the condition is the least typical. This presents as a non-painful superficial ulcer generally without the classic purple edge. It is often solitary and progresses slowly. It is not usually associated with any systemic conditions (Powell and Su, 1996).

Healing, when it does eventually occur, often leaves a characteristic cruciform (star or cross-like) scar. It is thought this is due to anomalies in fibrin deposition caused by the abnormal inflammatory response.

#### Diagnosis/differential diagnosis

No single test is diagnostic of PG, but the diagnosis is normally made from the clinical presentation. However, a battery of tests are normally undertaken to exclude other causes of ulceration.

Differential diagnoses include:

- ▶ Sweet's syndrome (although this rarely presents with peri-follicular inflammation and there is no destruction of the capillary bed)
- ▶ Behçet's disease
- ▶ Rheumatoid vasculitis
- ▶ Hepatic folliculitis (Magro et al, 1997)
- ▶ Necrotising cutaneous infections such as necrotising fasciitis
- ▶ Cutaneous anthrax
- ▶ Pustular drug reactions.

As the condition may be found in association with a number of other systemic disease processes it may be necessary to undertake a wide variety of tests including blood chemistry, renal and hepatic function, colonoscopy, radiography, and bone marrow biopsy (Trent and Kirsner, 2001).

#### Treatment

There have been a number of treatment regimes indicated for the management of PG. The choice of therapy depends on the severity of the presenting symptoms and the presence or absence of underlying systemic disease. Where the condition is found in association with systemic disease, the first priority should be the control of this condition (Barham et al, 2004).

Where lesions are mild and there is an absence of systemic disease it may be possible to control the condition with topical preparations such as topical corticosteroids and local dressings (Callen, 1989). Topical tacrolimus, a drug licensed for the management of atopic eczema, has recently been shown to be effective in the management of early PG lesions (Petering et al, 2001).

Where the condition is more widespread or aggressive in nature, a systemic approach is favoured. High-dose oral corticosteroids have been the mainstay of treatment for a number of years (Barnham et al, 2004). Sulphonides and other antileptotics and antimicrobials have also been found to be useful. It is believed that these drugs act predominantly as anti-inflammatory mediators,

while additionally altering neutrophil function (Chow and Ho, 1996). Systemic immunosuppressant drugs such as cyclosporin have been used, however, these are not without risk. Secondary infection can occur and the immuno-compromised individual may be at risk of catastrophic sepsis. The recent development of biological TNF- $\alpha$  inhibitors such as infliximab and etanercept normally used in the management of severe rheumatoid disease and psoriatic arthritis does offer new options for PG sufferers who fail to respond to other therapies.

There appears to be a lack of consensus on the topical management of pyoderma lesions. Samuel and Williams (1996) found in their review of the condition a variety of topical strategies employed from alginate dressings, hydrogels, topical corticosteroids, antimicrobials and hydrocolloids. In some cases, debridement has been suggested, however, in view of the potential role of pathergy in the development and acceleration of this condition, this option does not appear appropriate.

Barham et al (2004) suggested a therapeutic ladder for the management of PG. This progresses from relatively simple topical steroid therapy to high-cost, high-risk systemic interventions. While these guidelines are of use, they leave the clinician with little advice on how to manage the cutaneous manifestations of the condition.

#### Future developments

The future management of PG will rely heavily on our increased understanding of the disease process. The diversity of its presentation and the failure of clinicians to diagnose the condition early, along with the failure to develop a reliable diagnostic tool, make systematic research into the condition difficult to achieve. Newer systemic therapies designed for moderating the immune response appear to be the main thrust of research. Topical wound management is designed at managing the symptoms of pain, exudate management and,

**Table 1**

**Therapeutic ladder for pyoderma gangrenosum**

Drug	Action
Topical or intralesional corticosteroids	Local anti-inflammatory
Topical cromolyn sodium	Anti-inflammatory
Topical tacrolimus	Local immunosuppressant
Minocycline	Antimicrobial
Clofazimine	Antileprotic
Dapsone	Antileprotic
Sulfasalazine	Aminosalicylates
Thalidomide	Antileprotic
Methotrexate: weekly pulse	Anti-metabolite
Prednisolone	Anti-inflammatory
Cyclosporin	Immunosuppressant
Azathioprine	Immunosuppressant
Cyclophosphamide	Alkylating chemotherapy
Mycophenolate mofetil	Immunosuppressant
Intravenous gammaglobulin	Immunoglobulin
Etanercept	TNF- $\alpha$ inhibitor
Infliximab	TNF- $\alpha$ inhibitor

(Barham et al, 2004)

following the successful implementation of corrective medical treatment, healing.

**A case study**

Jim Penworthy (pseudonym) is a 58-year-old farmer in the south-west of England. He owns a large prize-winning dairy herd. During the past few years his work has been influenced first by concerns over BSE and by the UK outbreak of foot and mouth disease. Although in both cases his livestock were not directly affected, this has increased the amount of work required of him while reducing his income from the herd. Despite this, apart from mild hypertension, he enjoys good health and is looking forward to passing the farm on to his son in the next few years.

While bathing, Jim noticed two small lesions on his skin. One was on his left inner thigh, the other on his right inner calf. Both of these areas appeared as small dark purple spots. He could not recall injuring himself, but because of

the physical nature of his work, thought he must have scratched his skin while working with the cattle. Over the next few days these lesions rapidly grew in size and ulcerated. They were intensely painful, and thinking they were abscesses, he decided to visit his GP.

On examination, his GP noted that the two areas had extended very rapidly from approximately 1 cm to approximately 25cm each within three days. Fearing a serious destructive infection, he administered an intravenous bolus injection of Augmentin 1.2g and made arrangements for Jim to be seen urgently by the surgeons at the district general hospital.

On admission, Jim's medical history was taken and measurements taken of the lesions. Jim was found to have a mild pyrexia of 37.7°C. Surrounding each lesion was an area of distinct erythema. It was decided to admit Jim to facilitate further administration of

intravenous antibiotics. Wound swabs were taken of the lesions to identify the probable cause of the infection and to ensure the administration of the most appropriate antibiotic. The diagnosis of necrotising fasciitis was considered but was thought to be unlikely as the pyrexia was of low level (Barker et al, 1987). Instead it was thought that the causative organism was more likely to be related to his work with cattle. Cross-species bacterial transfer is a potential risk and can be of major significance. Many species of bacteria harmless to one species can be pathogenic in others.

Jim was moved to a side room and barrier-nursed in order to prevent the spread of organisms to other patients on the ward. Meanwhile his antibiotic regimen was supplemented with metronidazole to provide cover against gram-negative organisms.

Following three days of intravenous antibiotic therapy, there had been no improvement in Jim's condition. He still exhibited a low pyrexia and the areas of tissue damage had extended to approximately 10x10cm at the calf area and 15x15cm on the thigh wound. Blood culture had failed to reveal any septicaemia and wound swabs had only grown *Staphylococcus aureus* and skin flora. The area remained intensely painful with a distinct area of peri-wound cellulitis. The surgeons considered that further investigations were required urgently to exclude more unusual infections. Specifically, the potential for a diagnosis of cutaneous anthrax needed to be considered.

Jim was becoming increasingly worried. He found the social isolation imposed on him, due to barrier nursing, intolerable. Although not a very sociable man, he was used to spending most of his days with his animals and walking in the fields. He was very worried about the speed at which his wounds had deteriorated and was worried that the surgeons had been unable to find the cause of the infection. If anthrax was the cause, not only would this be



**Figures 1 and 2.** The florid red-purple edge of the lesions is clearly visible in these views. The central area of the lesions show ulceration to the dermal layers.

medically serious for him but would be disastrous for his herd. The Ministry of Food and Fisheries would have to be informed and his herd would be isolated and possibly destroyed.

Due to the deterioration in his wounds, the surgeons booked him in for excision of the areas under general anaesthetic in theatre. However, before this procedure it was decided to refer him to the dermatologists and the nursing staff of the skin and wound care service. A joint visit was arranged with the tissue viability nurse and the on-call dermatologist.

On examination, Jim was found to have two clearly defined regular shaped ulcers to his legs (*Figures 1 and 2*) Both lesions appeared to extend into the lower levels of the dermis with extensive destruction of the tissues. The edges of the ulcers were clearly defined with a purple haemorrhagic border. Jim explained that this colour had been present throughout the infection and had been the issue that had prompted him to go to his GP. Physical examination failed to reveal

any other features of note. Jim's past medical history was also unremarkable. Importantly he denied any rheumatoid disease or bowel condition.

Both the dermatologist and the TVCNS had seen similar lesions and agreed that this was an inflammatory ulcer, most probably PG.

#### Treatment

Jim appeared to present with the classic ulcerative variant of PG but with no obvious underlying disease and so his planned surgery was cancelled (further pathergic stimuli could intensify the ulceration and lead to an escalation of the condition) and was prescribed high dose oral corticosteroids (prednisolone 60mg daily). The aim of this treatment was to reduce the abnormal inflammatory response Jim was experiencing.

In the absence of any atypical bacterial colonisation, it was decided to discontinue barrier nursing. Jim was finding segregation increasingly difficult to manage and welcomed this change in treatment.

Meanwhile the care team was faced with the dilemma of managing his ulcers. Both ulcers were leaking moderate to high amounts of exudate. The wound beds were covered in a fine layer of necrotic slough, however, they remained exquisitely painful. Samuel and Williams (1996) found the association of pain, inflammation, and exudate common in many case studies of this condition. Wound management in Jim's case was based around the need for good symptom control and the need to reduce inflammation until such time that the systemic corticosteroids took effect. There was also a need to minimise the risk of secondary infection. High dose systemic corticosteroids reduce the inflammatory response and so can mask the signs of infection. Although the antibiotic therapy initiated earlier provided cover, reducing bacterial colonisation of the skin reduces the potential pool of pathogenic bacteria.

It was decided to control Jim's skin flora with the regular application of Dermal 500® (Dermal Laboratories, Hitchin) as a skin and peri-wound





**Figures 3 and 4.** The purple margins of the lesion have now resolved. Despite some superficial slough, granulation tissue is clearly visible and there are early signs of islands of re-epithelialisation.

emollient. Dermal lotion is an effective emollient that is composed of liquid paraffin, with benzalkonium chloride, isopropyl myristate, and chlorhexidine hydrochloride (British National Formulary, 2004) making it effective in reducing normal skin pathogens.

Both ulcers were dressed with a hydrofibre dressing (Aquacel®). (ConvaTec Ltd, Uxbridge). This product has a highly hydrophilic action that enables it to absorb significant fluid levels. In so doing, the product changes to a gel. This prevents the product adhering to the wound bed, minimising wound bed trauma and inflammation, and so reducing pain at dressing change. This dressing was initially retained with a simple wound pad held in place with an elasticated tubular bandage (Tubifast®) (SSL International plc, Manchester) as it was essential to monitor the progress of the wound closely. These were changed daily.

Within a few days, the ulcers noticeably changed. The purple wound edges began to fade in colour and

the surrounding erythema resolved. Further extension of the ulcers into the surrounding skin ceased. Exudate levels subsided and Jim stated that the pain was noticeably reduced.

Despite the reduction in exudate it was decided to continue with Aquacel as a primary dressing for both ulcers. This could now be left on for up to three days before saturation of the hydrofibre was achieved. As frequent observation of the wound was less imperative, an adhesive foam dressing was utilised as a secondary dressing (Biatain adhesive) (Coloplast Ltd, Peterborough). This in turn permitted less frequent dressing changes.

Following 14 days of steroid therapy it was decided that Jim should be discharged. Plans were put in place for him to return twice weekly to the clinic as an outpatient. This would enable ongoing management of his ulcers and would allow the nursing staff to monitor for side effects of the corticosteroids. Blood glucose levels were monitored to check for steroid-induced diabetes.

After three weeks of treatment (Figures 3 and 4), Jim's PG appeared under control and so he was commenced on a decreasing steroid regimen. High-dose corticosteroids administered for three weeks or more need to be reduced gradually to prevent adrenal insufficiency (British National Formulary, 2004). Initially his prednisolone was reduced to 50mg daily, and then it was reduced by 10mg a day in weekly decrements until he was taking 10mg daily. At this point his dose was reduced by 2mg per day at weekly intervals.

Long-term use of corticosteroids can have a detrimental effect on wound healing. Although Jim was making good progress, it was felt he had a significant risk of developing chronic ulceration. It was therefore decided to discontinue Aquacel dressings (exudate levels had now reduced considerably) and commence the use of a matrix metalloproteinase (MMP) inhibiting therapy. Promogran® dressings (Johnson and Johnson Medical, Ascot) were used on both

ulcers as the primary wound contact layer from week three of steroid therapy. This product consists of a mixture of collagen and cellulose that is able to bind to excess MMPs in the wound bed and exudate. Excess MMPs are believed to be one of the major causes of chronicity in wound healing. In line with local protocol, Promogran® was used in conjunction with a topical antimicrobial (Inadine®). (Johnson and Johnson, Peterborough, UK) In our experience, failure to do so increases the risk of critical colonisation and local wound infection.

#### Outcome

Jim went on to heal completely, and he has now stopped his systemic therapy. Although he does have a risk of recurrence of the PG, to date he has had no signs of its reactivation. Once stable Jim had extensive investigations to find the underlying cause of the problem including gastroscopy and colonoscopy. No abnormalities were found.

It is recognised in patients with PG that on healing, many demonstrate cruciform scarring (Barham et al, 2004). Jim has been advised to massage the scarred area with a simple emollient daily to maintain tissue health and keep the scar tissue flexible. Jim is now back working full time on the farm.

#### Conclusion

PG is an uncommon skin condition but one that clinicians need to be aware of. Although linked to other autoimmune conditions it can, as in this case, be found in isolation. In such cases confirmation of the diagnosis can be difficult. However, failure to identify and treat it promptly can lead to significant areas of tissue loss, or worse still, surgical intervention which can lead to significant escalation of the disease process. **WUK**

### Key Points

- ▶▶ Pyoderma gangrenosum is a rare, but potentially debilitating condition which can cause considerable skin damage.
- ▶▶ In the absence of a reliable diagnostic test for PG, it is necessary to rely on clinical presentation and elimination of other possible conditions when arriving at a formal diagnosis of this condition.
- ▶▶ The different forms of the condition can make diagnosis even more difficult for the clinician.
- ▶▶ Treatment is targeted at moderating the immune response and supportively managing associated wound problems.

### References

- Barham KL, Jorizzo JL, Grattan B, Cox NH (2004) Vasculitis and neutrophilic vascular reactions. 49.38 In: Burns T, Breathnach S, Cox N, Griffiths C, eds. *Rook's Textbook of Dermatology*. Blackwell Science, Oxford
- Barker FG, Leppard BJ, Seal DV (1987) Streptococcal necrotizing fasciitis. Comparison between histological and clinical features. *J Clin Pathol* **40**: 335–41
- Bennett ML, Jackson JM, Jorizzo JL, et al (2000) Pyoderma gangrenosum: a comparison of typical and atypical forms with an emphasis on time to remission. *Medicine* **79**: 37–46
- British National Formulary (2004) British Medical Association and Royal Pharmaceutical Society of Great Britain, Oxford
- Brocq L (1916) Nouvelle contribution à l'étude du phagedenisme geometrique. *Ann Dermatol Syphiligr* **6**: 1–39
- Brunstring LA, Goeckerman WH, O'Leary PA (1930) Pyoderma gangrenosum: clinical and experimental observations in five cases occurring in adults. *Arch Dermatol* **22**: 655–80
- Cairns BA, Herbst CA, Sartor BR et al (1994) Peristomal pyoderma gangrenosum and inflammatory bowel disease. *Arch Surgery* **129**: 769
- Callen JP (1989) Pyoderma gangrenosum and related disorders. *Med Clin North Am* **73**: 1247
- Chow RKP, Ho VC (1996) Treatment of pyoderma gangrenosum. *J Am Acad Dermatol* **34**: 1047–60
- Ebringer A, Doyles AE, Harris GS (1969) Dermonecrotic factor I: nature and properties of a dermonecrotic factor to guinea pig skin found in human serum. *Br J Exp Pathol* **50**: 559–65
- Esnault P, Dompartin A, Moreau A, Caraes B, Leroy D (1995) Recurring postoperative pyoderma gangrenosum. *Int J Dermatol* **34**: 647–50
- Graham JA, Hansen KK, Rabinowitz LG, Esterly NB (1994) Pyoderma gangrenosum in infants and children. *Ped Dermatol* **11**: 10
- Magro C, Crowson AN, Mihm M (1997) Cutaneous manifestations of nutritional deficiency states and gastrointestinal disease. In: Elder et al, eds. *Lever's Histopathology of the Skin*. 8th edn. Lippincott-Raven Publishers, Philadelphia: 357–9
- Nerella P, Daniela A, Guido M, et al (1985) Leukocyte chemotaxis and pyoderma gangrenosum. *Int J Dermatol* **24**: 45–7
- Petering H, Kiehl P, Breuer C et al (2001) Pyoderma gangrenosum: successful topical therapy with Tacrolimus. *Hautarzt* **52**: 47–50
- Powell FC, Su WPD (1996) Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* **34**: 395–409
- Samitz MH (1966) Cutaneous vasculitis in association with ulcerative colitis. *Cutis* **2**: 383–7
- Samuel J, Williams C (1996) Pyoderma gangrenosum: an inflammatory ulcer. *J Wound Care* **5(7)**: 314–8
- Schwaegerle SM, Bergfeld WF, Senitzer D et al (1988) Pyoderma gangrenosum: a review. *J Am Acad Dermatol* **18**: 559
- Trent JT, Kirsner RS (2001) Diagnosing pyoderma gangrenosum. *Adv Skin Wound Care* **14(3)**: 151
- Von den Driesch P (1997) Pyoderma gangrenosum: a report of 44 cases with follow-ups. *Br J Dermatol* **137**: 1000–5
- Weedon D (2002) The vasculopathic reaction pattern: pyoderma gangrenosum. In: *Skin Pathology* (2nd Edn). Churchill Livingstone, London: 251–2