Pyoderma gangrenosum: guideline for wound practitioners

Pyoderma gangrenosum (PG) is an atypical ulceration of the skin with unknown aetiology, usually associated with autoimmune systemic illnesses and haematological malignancies. Diagnosis is based on clinical suspicion and exclusion of other conditions. Treatment options vary greatly, ranging from conservative local and systemic immunosuppression to surgical measures, including amputation, but none is shown to be universally effective. Currently no guideline regarding escalation of treatment exists. Based on a review of the current literature and three illustrative cases of PG, a working treatment guideline is presented for wound practitioners.

Pyoderma gangrenosum; ulceration; pathergy; autoimmune; corticosteroid

Pyoderma gangrenosum (PG), first described in 1930, is a condition characterised by ulcerative cutaneous lesions of an unknown aetiology. It is classified as a non-infectious reactive neutrophilic dermatosis, initially beginning with simple pustules that become painful ulcers which vary in size and depth, with classical undermined violaceous borders. Diagnosis is made by exclusion of other potential causes of the ulceration, such as infection, malignancy, diabetes and trauma. The exact aetiology of PG is unclear; the underlying disease is thought to be associated with alterations of humoral and cellular immunity, potentially involving intrinsic defects of neutrophils with alterations of chemotaxis and phagocytosis. When analysed, neutrophils show abnormal neutrophil trafficking and metabolic oscillation. In addition, interleukin-8 (IL-8) and -16 (IL-16), leucocyte chemoattractant agents, are overexpressed in PG ulcers.

Studies in mice have shown similar neutrophil dysfunction to that of humans with PG can be caused by a genetic abnormality, with a spontaneous autosomal mutation causing similar features to neutrophilic dermatoses, including PG. These mice also displayed high serum levels of immunoglobulins and autoantibodies, cytokines and acute-phase proteins, indicating there was potential for further inflammatory dysfunction to occur. This likely genetic aspect of PG suggests that certain patients are predisposed to the disease and, when experiencing minor trauma, the normal self-limiting inflammatory response does not occur, but rather a heightened and ongoing response takes place, resulting in the initial blistering and later deep ulceration that is pathognomonic of PG.

When trauma precipitates the formation of PG, as described above, the process is termed pathergy. Pathergy is considered to be a characteristic feature of PG, occurring in 20–40% of those with the disease. There are essentially two variants of PG. The classic ulcerative form usually occurs on the lower limbs, while atypical PG occurs on the upper limbs, consisting of three subtypes: Pustular, Bullous and Vegetative.

Approximately 50% of patients afflicted with PG have an underlying systemic illness, such as inflammatory bowel disease, or rheumatoid arthritis. Extracutaneous manifestations are rare, but present as sterile neutrophilic abscesses throughout particular parts of the body with no obvious pattern; the most common site of involvement is the lungs. The prognosis of PG is good if diagnosed in a timely manner, but refractive cases and recurrences are still common, occurring in 46% of patients, independent of the treatment options used. The obscure presentation of PG initially often leads to delayed diagnosis. Most common treatment options involve adequate dressing with topical and systemic immunosuppressive agents, coupled with appropriate
dressing. If these fail, surgical treatments of debridement, skin grafts and eventual amputation, used simultaneously with immunosuppressive measures, may provide relief from this illness.

Method

A literature review was conducted using MedLine and Google Scholar to access relevant articles. The search terms used were as follows: ‘pyoderma gangrenosum’, ‘ulceration’, ‘autoimmune’, ‘haematological malignancy’, ‘pathergy’ and ‘immunosuppression’. Searches were not limited to a time period; however, most articles selected were published recently.

The case studies included were selected by the coauthor of this paper (SS), from patients presenting to the wound clinic at the Royal Hobart Hospital in Australia. The three patients with the diagnoses of PG were chosen to illustrate that different treatments may be required to induce remission of the disease.

Literature review

Clinical features

PG presents classically as one or more painful skin ulcers with undermined violaceous borders, preceded by folliculocentric pustules or fluctuant nodules. There are two overall variants of PG, classic and atypical, with three minor variants, which fall into the atypical category, as mentioned earlier.

- Ulcerative pyoderma gangrenosum
  Ulcerative PG occurs mainly on the lower limbs and trunk. The illness can arise as either new ulcers or as a pathergic response to trauma. These ulcers exhibit a peripheral inflammatory halo and, while most commonly occurring on the lower extremities or trunk, can appear on the vulva, penis, head and neck and breast.

- Pustular pyoderma gangrenosum
  Pustular PG is most often associated with patients who have coexisting inflammatory bowel disease. Clinically it presents as painful pustules that occur on the extensor aspects of the limbs, with an associated fever and arthralgia. It may progress to the more severe ulcerative form, which often overlaps with the group of sterile neutrophilic dermatoses, including aphthous stomatitis, erythema nodosum and Sweet’s syndrome, which are seen in patients with inflammatory bowel disease and patients who have had intestinal procedures performed in the spectrum of bariatric surgery. These conditions each present with their own distinct features, but the overlap exists in their aetiologies of altered immunologic reactivity.

In cases of pustular PG, it is seen that the ulcerative lesions of PG resolve in line with the resolution of the active mucosal disease of the gut. However, overall only approximately 50% of patients who have pustular PG are found to have an underlying systemic disease.

- Bullous pyoderma gangrenosum
  First described in 1972, this variant of PG is often associated with myeloid malignancies. In appearance, the ulcers present as a painful, superficial blistering with eroded dermatosis, often found in patients with leukaemia or myelofibrosis. The ulcer can be deep with violaceous erythema in the surrounding area.

<table>
<thead>
<tr>
<th>Differential diagnoses</th>
<th>Authors</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>Malignancy</td>
<td>Squamous cell carcinoma, verrucous carcinoma, cutaneous lymphoma</td>
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<tr>
<td>Infection</td>
<td>Fungal, mycobacterial, herpetic folliculitis</td>
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<td>Diabetes</td>
<td>Neuropathic ulceration</td>
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<td>Trauma</td>
<td>Blunt, insect bites</td>
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<tr>
<td>Autoimmune conditions</td>
<td>Vasculitis, inflammatory bowel disease, Behçet’s disease, rheumatoid vasculitis, Wegener’s granulomatosis</td>
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<tr>
<td>Drug induced</td>
<td>Granulocyte colony stimulating factor</td>
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Fig 1. A step-wise approach to treating pyoderma gangrenosum

- **Initial clinical suspicion**
  - Wound swab
  - ± Biopsy (to exclude malignancy)

- **Systemic therapy**
  - Corticosteroids
  - Methotrexate
  - Cyclosporine
  - Infliximab
  - Intravenous immunoglobulins

- **Dressing and/or topical therapy**
  - Corticosteroids
  - Tacrolimus
  - Cyclosporine
  - ± Hyperbaric oxygen therapy
As a link exists between PG and malignancy, it is beneficial to investigate for underlying haematological malignancy, if clinically indicated. In the instance where PG occurs in association with haematological malignancy, treatment of the haematological malignancy and its subsequent resolution can also result in a simultaneous resolution of the associated PG.

**Vegetative pyoderma gangrenosum** Confined to the skin and with no associated systemic disease, vegetative PG ulcerations occur on the trunk, without a violaceous border, pustular base or undermining. The lesions present as a raised, verrucous, well-defined plaques, which are studded with small pustules.

**Diagnosis**

The diagnosis of PG is based on the clinical findings described above. Classic PG is characterised clinically by a rapidly enlarging, painful ulcer with a violaceous border, undermined edges and a necrotic haemorrhagic base; however, the other variants of PG are more difficult to diagnose due to such wide range in features at presentation.

While the histology gained from a biopsy of PG is non-specific and, at times, impossible to differentiate from other inflammatory diseases, its benefit is to rule out suspicion of malignancy. Biopsy of the lesion must be performed only if clinical suspicion of malignancy exists, due to risk of pathology.

In cases where an autoimmune condition is suspected, further laboratory testing can be employed to support a diagnosis. For example, in Wegener’s granulomatosis, rheumatoid vasculitis or Behçet’s disease, laboratory testing, involving antibody analysis of antineutrophilic cytoplasmic antibodies (ANCA), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody, or inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and complement component C9, can be used to aid diagnosis.

There are no such specific serologic markers available to support diagnosis of PG. However, wound swabs are beneficial as they can exclude fungal or mycobacterial infection, prior to the initiation of immunosuppressive treatment. Table 1 provides some of the conditions that should be considered in a case of chronic ulcer with clinical suspicion of PG.

**Management**

Careful physical examination and early detection of ulcers is vital, as early treatment reduces risk of complications, such as scarring. Given that the pathology of PG is thought to be immune mediated, local and systemic immune modulatory agents are utilised. Refractory cases may necessitate surgical intervention.

**Local therapy** The range of local therapy reported varies from normal saline to various moisture-retentive dressings, with the objective of maintaining optimum moisture balance in the lesion. Topical medications commonly used are corticosteroids, tacrolimus, sodium cromoglicate and intralesional injections of cyclosporine and phenytoin. Injection of any drug as local therapy is generally not recommended, due to the further risk of infection to the affected area and risk of pathergic response expanding the affected region.

These local therapies are mainly beneficial for early lesions and are also used as an adjuvant with systemic therapies.

**Systemic therapy** Systemic corticosteroids are considered to be the gold standard treatment for PG, although these cannot guarantee resolution of the ulceration. Other systemic immunosuppressive agents, such as cyclosporine and methotrexate, have shown to be effective in some cases, with reported instances of antibiotics as complementary therapy.

When the PG is considered intractable, intravenous immunoglobulins have been used with some success; however, these are expensive and only indicated if all other conventional treatments have failed. In addition to these, infliximab therapy has also performed promisingly, in some instances.

**Surgical therapy** Patients with intractable PG can also be treated using surgical measures, such as split-thickness skin grafting (STSG), in conjunction with hyperbaric oxygen (HBO) therapy and finally amputation. Again, the potential for pathergic response causing PG through traumatic nature of surgical intervention should be noted. In addition, to further complicate the process, postoperative PG can be difficult to differentiate from wound infection, causing difficulty in early diagnosis and treatment. However, cases of successful amputation have been reported, refuting the risk of pathology.

Successful outcomes in certain patients have been published following operative measures, with improved quality of life and absence of recurrence of PG.

Surgical therapy should be viewed as a last resort in PG, to be used simultaneously with topical and systemic immunosuppressive agents. The risk of pathergic response needs to be considered, but in refractory cases of PG, once inflammation has been controlled with topical therapy, ulceration can be treated with either STSG and simultaneous immunosuppression, or amputation if necessary.

The treatment of PG has been summarised in the form of a step-wise diagram, which we hope would be useful to the busy wound-care clinician in managing a suspected case of PG (Fig 1).

### Case reports

#### Case 1

Mrs LB, a 60-year-old Caucasian woman, initially presented to the wound clinic in 2002 with a small recalcitrant ulcer on the dorsum of her left foot (Fig 2a).
The ulcer was precipitated by minor trauma and did not heal following multiple dressings prescribed by her general practitioner (GP), over several months.

She had a complex medical history, including rheumatoid arthritis, chronic pain syndrome of the lower back and chronic fatigue syndrome, for which she was being treated by a senior rheumatologist. She had no history of diabetes mellitus or smoking.

Initial examination showed no signs of peripheral vascular disease, but did indicate mild, bilateral lower limb oedema. Duplex scans confirmed no evidence of thrombus, venous obstruction or arterial or venous insufficiency. Punch biopsy taken at the clinic demonstrated interstitial inflammatory cells, including neutrophils, lymphocytes and histiocytes, dermal oedema, and, deep to this, fibrosis and a thick walled blood vessel: a non-specific picture.

The ulcer was mechanically debrided and dressed. Ciprofloxacin 500mg twice daily was commenced empirically initially. The wound swabs sent at this stage later revealed a group G streptococcal infection, and hence ciprofloxacin was continued for 6 weeks. She was treated with 45 HBO dives over the following 5 months, with no noted improvement.

During this time, the ulcer enlarged and became increasingly painful, culminating in an admission for pain control; her pain scores on a visual analogue scale (VAS) during this time were 8–9 out of 10 in severity. The ulcers were debrided, followed by negative pressure wound therapy (NPWT) dressings. This achieved complete healing for a brief period with subsequent relapse after 2 months. At the same time, a second larger ulcer arose in the pretibial region of her right leg (Fig 2b).

Both ulcers continued to grow in size, and were ‘very painful’ (VAS 10) for the patient, requiring significant opioid analgesia of methadone (phosphate 50mg/day) over a period of a further 4 months. During this time, the patient regularly attended the clinic for ongoing review, debridement and dressing.

Further biopsy sections were taken from the right leg ulcer at the end of 4 months and, at the same time, further specialist opinion was sought from her rheumatologist and a plastic surgeon. A diagnosis of PG was made and she was started on a course of cyclosporine. Surgical options such as skin grafting and amputation were not considered at this stage due to fear of worsening of ulceration from pathergy.

Her ulcers failed to make any progress toward healing, despite multiple medical therapies, including prednisolone, cyclosporine, cyclophosphamide, topical tacrolimus, potassium permanganate washes, mycophenolate and multiple courses of antibiotics (oral and intravenous [IV]) for superinfection with *Pseudomonas aeruginosa*. Infliximab therapy was instituted but, although showing remarkable improvement for a limited period, still did not induce complete resolution of the ulceration.

Subsequently, a debridement and application of STSG was performed to cover both left and right ulcers. The patient received a course of HBO dives immediately following the skin graft. This resulted in complete healing of the ulcers with significant reduction in pain for the patient (Fig 2c).

Recurrence occurred 3 months postoperatively, when the graft became infected; the infection was managed with IV antibiotics, debridement and further STSG. Following this, there was relapse of the PG and several courses of infliximab failed to achieve healing. Her pain became unbearable, for which she was treated with epidural analgesia as an inpatient.

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19 Harris, A.J., Regan, P., Burge, S. Early diagnosis of pyoderma gangrenosum is important to prevent disfigurement. BMJ. 1998; 316: 7124, 52–53.
Unfortunately she developed an epidural abscess. At this stage it was felt that all options of local and systemic therapy had been exhausted and bilateral above-knee amputations were discussed with the patient, who finally accepted this option. She underwent drainage of her epidural abscess and bilateral below-knee amputations, 6 years after her initial presentation to wound clinic with a small recalcitrant ulcer. Following this, she had an uncomplicated recovery with primary healing of the amputation stumps. She is being followed up by the rheumatologist at periodic intervals due to her ongoing rheumatoid arthritis and has had no further relapse of PG for the past 4 years.

There was no ulceration at any of the donor sites for the skin graft. Despite eventual relapse of skin grafting, finally culminating in bilateral above-knee amputations, a long, pain-free remission in a patient otherwise refractory to all prior medical interventions was achieved.

**Case 2**

Mrs BG, an 87-year-old woman, initially presented to the wound clinic in 2007, with an atypical ulcer on the right flank above the hip region (Fig 3a). Punch biopsies showed extensive dermal inflammation, with features of a suppurative granulomatous process. On the specimens, the process appeared to be infective; however, Gram, periodic acid-Schiff (PAS) and Grocott stains were found to be negative, with no identifiable micro-organisms. Swabs and biopsy should only be considered in order to exclude tuberculous, fungal and malignant causes. Wound swabs and biopsy were taken and the ulcer was treated with topical kenacomb dressing (Inadine; Systagenix) and alginate dressings, successfully with a non-adherent, povidone-iodine dressing (Inadine; Systagenix) and alginate dressings, before relapsing after a period of 11 months. Subsequently, the ulcer was treated with topical kenacomb and alginate dressing with no evidence of recurrence (Fig 4b). Mr CS is reviewed regularly by the stoma therapy nurses and was last seen in October 2012.

**Conclusion**

A review of the literature on PG confirms many atypical presentations of this disease, and each of the cases presented were treated with different therapies with successful resolution. Early diagnosis of PG can be made with a high level of suspicion (case 3). Wound swabs and biopsy should only be considered in order to exclude tuberculous, fungal and malignant causes. In our opinion, local therapy of topical corticosteroids and appropriate dressings should be used initially (case 3), followed by systemic immunosuppressive agents, monoclonal antibodies, such as infliximab (case 2) and intravenous immunoglobulins. If the PG is refractory surgical therapies can be instituted, such as STSG and finally amputation (case 1).
Erratum in:
In the editorial, King’s College Hospital is incorrectly listed as a partner of the National Centre for Innovation in Wound Prevention and Treatment. This is not correct. The editorial should have stated that King’s College London is a partner.

Erratum in:
The reference list was incorrectly numbered from reference 21 onwards. The corrected reference list is included below.

The Journal of Wound Care and the authors would like to apologise for these errors.