The challenges of managing patients with pyoderma gangrenosum: three case reports

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ABSTRACT

Pyoderma gangrenosum (PG), although first described nearly 100 years ago, remains challenging for clinicians. The aetiology of PG remains a mystery. There are no specific guidelines for the diagnosis and treatment of PG. Other ulcerating wounds can mimic PG, leading to misdiagnosis, which can have detrimental effects for the patient. The aim of this paper is to provide an overview of the challenges faced by the clinician in diagnosing and managing patients with PG. Three case studies demonstrate the complexity of diagnosing and treating patients with PG.

Keywords: Pyoderma gangrenosum; ulcers; venous disease.

OVERVIEW

Pyoderma gangrenosum (PG) is an atypical neutrophilic dermatosis that appears as an inflammatory and ulcerative condition of the skin[1]. First described by Brocq in 1916, as *phagedenisme geometrique,* a rare neutrophilic dermatosis[2]. Brunstig, Goeckerman and O'Leary in 1930 named it pyoderma gangrenosum. This was based on a series of five case reports of patients with ulceration of the skin[3]. Initially they believed that the condition was related to streptococcal infection, leading to cutaneous gangrene. Four of the patients had chronic ulcerative colitis, hence the initial association with inflammatory bowel disease. Brunstig *et al.* describe the ulcers as enlarging, painful, necrotic with bluish edges and circumferential erythema. Contrary to its name, it is neither infectious or a gangrenous disorder. Although first described almost 100 years ago, the aetiology remains a mystery[4].

EPIDEMIOLOGY

Epidemiology data for the condition is based predominantly on case reports, case series and cohort studies, mostly in patients with inflammatory bowel disease[2,5-10]. A rare condition, the incidence is estimated at three to 10 cases per million per year[2,4]. Based on a large population-based cohort study the incidence in the UK is estimated at six per million per year[8]. PG generally affects people between the ages of 20 and 50 years[4]; it has also been reported in approximately 4% of children[1,2,11-13]. Data regarding gender is contradictory. According to some there is a higher incidence in females[2,4,8,9,14], although others have reported no gender preference[2,5].

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PATHOGENESIS

PG is classified as a neutrophilic dermatoses, with neutrophil predominant infiltrates of the skin, without evidence of primary vasculitis[15]. The physiological process that leads to PG remains ambiguous. Early hypotheses included occult bacterial infection, circulating antibodies, or the Shwartzman reaction (an immune response to bacterial endotoxins leading to tissue necrosis). However, there is a lack of evidence to support these theories[1]. Current postulations regarding the pathogenesis of PG include neutrophil dysfunction, genetic factors and dysregulation of the innate immune system.

In pathology specimens there is the presence of neutrophilic infiltrates; this combined with the clinical response to anti-neutrophil agents, such as colchicine and dapsone, which disrupts chemotaxis and phagocytosis, suggests that neutrophilic dysfunction plays a role in the pathophysiology of PG[16,17]. One study suggests that there are abnormalities in neutrophil trafficking and signalling, related to intracellular metabolic oscillations in patients with PG[18].

Genetic features that have been reported include familial cases of PG and also PG related to pyogenic sterile arthritis syndrome (PAPA) and acne[19-24]. There is also a growing body of evidence to suggest that dysregulation of the innate immune system is associated with PG[25,26]. This builds on the evidence of neutrophil dysfunction.

Table 1: Diseases associated with pyoderma gangrenosum[29]

More frequent associations	**Inflammatory bowel disease, including:**
	Crohn's disease
	Diverticulitis
	Ulcerative colitis
	Myeloproliferative disease, including:
	Aplastic anaemia
	Essential thrombocytopenia
	Hodgkin's disease
	Leukaemia (different types)
	Monoclonal gammopathy
	Myelofibrosis
	Myeloma
	Non-Hodgkin's lymphoma
	Polycythemia vera
	Rheumatologic disease, including:
	Osteoarthritis
	Psoriatic arthritis
	Relapsing polychondritis
	Rheumatoid arthritis
	Seronegative arthritis
	Spondylitis (different types)
	Sterile chronic multifocal osteomyelitis
	Systemic lupus erythematosus
	Takayasu syndrome
Less frequent associations	Acne conglobate
	Chronic active hepatitis
	Complement deficiency
	Diabetes mellitus
	Erythema elevated diutinum
	Fanconi's anaemia
	Haemoglobinaemia
	Hepatitis C
	Hidradenitis suppurative
	HIV
	Kartagener's syndrome
	Lung cysts
	Necrotising sclerokeratitis
	PAPA (pyogenic arthritis, pyoderma gangrenosum and acne)
	Paroxysmal nocturnal haemoglobinuria
	Phospholipid syndrome
	Primary biliary cirrhosis
	Sarcoidosis
	Vaquez disease
	Wegner's granulomatosis

Wollina U. Clinical management of pyoderma gangrenosum. Am J Clin Dermatol 2002;3(3):149–58.

CLINICAL PRESENTATION

The lesions commonly occur on the lower legs, classically the pre-tibial region, but can occur on any anatomical location including: trunk, head, neck, breasts, upper limbs, genitalia, mucous membranes and peristomal distribution[1,2,27-29]. Lesions have been reported to occur concurrently on different anatomical locations[2]. Characteristically, the lesions begin as a small nodule or sterile pustule[30] which enlarge into well-demarcated ulcers, which can extend to the fascia with violaceous margins (red-blue) undermined border, surrounding erythema and induration. Typically the lesions have necrosis at the base, friable granulation tissue with a purulent or haemoserous exudate[2]. The ulcers are often described as "necrolytic", a process whereby as the tissue is destroyed, the liquefactive necrosis reveals a red-blue undermined wound edge[30]. Invariably the lesions are extremely painful. Atrophic cribriform pigmented scarring can occur as the lesions heal, particularly with delayed diagnosis and treatment[2,4]. PG has also been described in association with pathergy, a process that occurs as a result of trauma. This has been reported in wounds ranging from minor trauma to surgical incision sites[10,31]. In surgical wounds, PG has been erroneously diagnosed as infection leading to wound debridement, which has triggered pathergy, resulting in aggravation of the disease and on occasion leading to amputation[32,33]. In a retrospective review of 103 patients, pathergy was documented in 31% of patients[14].

CLINICAL VARIANTS

According to Powell *et al.* there are four clinical subtypes: ulcerative or 'classic'; bullous (atypical); pustular; and vegetative, all sharing similar characteristics[6]. Peristomal PG, genital PG, extracutaneous PG and infantile PG have also been described in the literature[1,2,4].

Ulcerative: Most common variant. Starts as a tender papule or vesicle that rapidly ulcerates, has a purulent base, with undermined, inflamed, violaceous borders. Painful lesions associated with systemic disease, requiring immunosuppressive treatment[6,29].

Bullous: Less common variant, associated in patients with haematological malignancy, an indicator of a poor prognosis. It is characterised by painful bullae, usually located on the upper limbs and face. The bullae may spread and progress to superficial lesions and ulcers. Systemic immunosuppression is required[2,4,6].

Pustular: This variant of PG is most often associated with inflammatory bowel disease (IBD) and may occur during exacerbations of bowel inflammation. Small painful pustules, with surrounding erythema, that usually improve with the treatment of IBD[4,6].

Vegetative: Also known as superficial granulomatous pyoderma, the least painful and aggressive of all the variants of PG. It is a superficial nodule, plague or ulcer that progresses slowly without undermined edges or a purulent wound bed. Responds well to less aggressive forms of treatment[4,6].

Peristomal: Development of lesions in the peristomal area following formation of an ileostomy or colostomy in patients with ulcerative colitis or Crohn's disease. Possibly as a result of pathergy from the surgical procedure, leakage of faeces on to the skin, or irritation from adhesive stomal appliances[2,4,28,34].

Genital: Lesions occurring on the vulva, penis or scrotum. Behçet's disease should be excluded[4].

Extracutaneous: Rare form of PG, sterile neutrophilic infiltrates occurring in sites such as the lungs, spleen, central nervous system, gastrointestinal tract, intestine, liver, cornea, heart, and lymph nodes[4].

Associated disorders (Table 1[29])

It has been estimated that approximately 40–50% cases of PG are associated with a systemic disease and the remainder are idiopathic[2,4]. PG is the most common skin disorder associated in patients with IBD (Crohn's disease and ulcerative colitis) and has been reported in approximately 2–12% of patients with IBD[35]. Other common disorders include arthritis[9], haematological malignancy[14], PAPA syndrome[2], hidradenitis suppurativa, and HIV[1].

DIAGNOSIS

Histopathology and laboratory findings in PG are non-specific; therefore, the diagnosis is based on clinical history, physical examination and confirmed through a process of elimination. There should be a high index of suspicion in patients with non-healing ulcers, especially in the presence of systemic diseases[2]. The clinician must, however, err on the side of caution as many of the associated diseases may not be overtly obvious[4]. There are several differential diagnoses, and ulcerative cutaneous lesions that mimic PG (Table 2[1]) including: malignancy, infectious disease, antiphospholipid antibody-associated occlusive disease, vasculitis, and drug reactions[2,4].

Laboratory investigations are not diagnostic for PG; patients often have neutrophil leukocytosis[30,36]. The inflammatory process is reflected with elevated erythrocyte, C-reactive protein, and protein electrophoresis[29]. It is important to target laboratory investigations for associated diseases, such as IBD or arthritis, and to exclude other ulcerating conditions; for example, other autoimmune connective tissue diseases, or anticardiolipin syndrome[29,30]. Tissue biopsy for histopathology should be performed to exclude other conditions such as malignancy or vasculitis. A biopsy can also be performed for microbiology, culture and sensitivity (MC&S), particularly looking for atypical mycobacteria, fungi and parasites. Although performing a tissue biopsy can cause pathergy, the procedure should be performed, as this will assist in ruling out other aetiologies[1,2,4].

Table 2: Differential diagnosis of pyoderma gangrenosum[1]

Vascular/neuropathic	Vascular occlusive disease Livedoid vasculopathy Dowlin-Degos disease Ulcers of sickle cell disease Antiphospholipid antibody syndrome Arterial disease Venous insufficiency Diabetic/trophic ulcer
Cancer	Basel cell carcinoma Squamous cell carcinoma Cutaneous T-cell lymphoma Leukaemia cutis
Exogenous tissue injury	Arthropod bite Factitial ulcers Drug-induced tissue injury Halogenodermas Calciphylaxis
Systemic vasculitis	Behcet disease Polyarteritis Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides Cryoplobulinemic vasculitis
Skin manifestations of autoimmune or connective tissue disorders	Cutaneous Crohn disease
Neutrophilic dermatoses	Sweet syndrome Subcorneal pustular dermatosis Bullous lupus erythematosus
Bacterial	Impetigo Ecthyma Necrotising fasciitis Anthrax Tuberculosis Atypical mycobacteria Buruli ulcer Syphilitic gumma
Viral	Chronic herpes simplex virus
Protozoal	Leishmaniasis Amebiasis cutis
Fungal	Blastomycosis Histoplasmosis Sporotrichosis Cryptococcosis Aspergillosis Penicilliosis Zygomycosis

Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. Am J Clin Dermatol 2012;13(3):191–211.

Table 3: Topical and systemic treatment of pyoderma gangrenosum[4]

Corticosteroids	Topical Intralesional Systemic
Antimicrobial agents	Benzoyl peroxide Clofazimine Diaminodiphenysulfone (dapsone) Rifampicin Sulfapyridine Minocycline Vancomycin Mezlocillin
Steroid-sparing immunosuppressive agents	5-aminosalicylic acid (topical) 6-mercaptopurine Azathioprine Cyclophosphamide Cyclosporine (topical, systemic) Methotrexate Chlorambucil Mycophenolate mofeteil Tacrolimus (topical, systemic)
Immune modulation	Infliximab Alefacept Interferon-α Intravenous immunoglobulin Plasmapheresis Thalidomide Colchine Heparin Nicotine (topical) Disodium cromoglycate (topical) Hyperbaric oxygen

Rucco E, Sangiuliano AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: an updated review. J Eur Dermatol Venerol 2009;23(9):1008–17.

The important factor to take into consideration is that PG mimics many other conditions, leading to misdiagnosis[1,30,37]. Delay in treatment can lead to extensive tissue loss, undue pain for the patient and potentially inappropriate therapies[2]. Early referral to a physician or dermatologist is recommended if PG is suspected[30]. Su *et al.* proposed a diagnostic criterion for classic ulcerative PG, to consider the essential features for diagnosing PG. Both of the major criteria must be met and two from the minor criteria[30].

Major criteria

1. *Rapid progression of a painful, necrolytic cutaneous ulcer with an irregular, violaceous, and undermined border*
2. *Other causes of cutaneous ulceration have been excluded*

Minor criteria

1. *History suggestive of pathergy or clinical finding of cribriform scarring*
2. *Systemic diseases associated with PG*
3. *Histopathologic findings (sterile neutrophilia, +/– mixed inflammation, +/– lymphocytic vasculitis)*
4. *Treatment response (rapid response to systemic steroid treatment)*

TREATMENT

There is a paucity of guidelines for the treatment of PG. This is due to a lack of clinical controlled trials. The disease process in poorly understood and treatment is based predominately on clinical experience[4]. Approach to treatment should be multidisciplinary, including dermatology, rheumatology, wound care specialists, pain specialists and pathologists[36]. Treatment aim is to reduce the inflammation, minimise pain, promote wound healing, and control underlying disorders[1,2,4]. If the patient has any underlying systemic disease, control of this often results in the control of skin lesions[2]. As there are numerous approaches to treatment a comprehensive review is outside the scope of this article. The authors have provided a summary of treatment options. Response to treatment is considered one of the minor diagnostic criteria, as suggested by Su *et al.*

WOUND CARE

At each presentation the lesions should have a comprehensive assessment of the wound bed and the wound border, paying attention in particular to the type of tissue at the wound bed, amount and type of exudate, evidence of violaceous wound margins and the level of pain the patient is experiencing. The wound(s) should be measured, including length, width, depth, and, if possible, clinical photography of the wound as this allows for accurate ongoing wound assessment[38]. The TIME principle should be used as a guide for selecting the appropriate wound dressing[39,40]. Dressing selection will depend on the wound assessment; however, the dressing should be non-adherent to the wound bed and removed easily to minimise pain and trauma. Dressings that adhere to the wound bed may increase pain on removal and trigger pathergy[1]. Although PG is not infectious, having an open wound may increase the risk of infection; therefore, the wound and peri-wound must be monitored for clinical signs of infection such as: erythema, warmth, increased pain, increased exudate, lymphangitis and malodour[1]. In the presence of infection appropriate treatment should be commenced, including antibiotics and topical antimicrobial dressings[40].

TOPICAL AGENTS

For small lesions, such as superficial pustules or shallow ulcers, treatment can include local application of high-potency corticosteroid lotion, ointment, cream or intralesional injections[1,21,29,38]. Topical agents can also be used in conjunction with systemic therapy for patients with severe PG[38]. Topical corticosteroids are more effective in patients with peristomal PG. Local injections of triamcinolone are preferred for non-peristomal PG[29]. Tacrolimus (FK-506), cyclosporine solution and intralesional injection of cyclosporine have also been used on PG lesions[1,29,38]. However, there is the need for larger clinical studies to prove their efficacy in the management of PG[38]. These must be applied with caution due to the risk of systemic absorption[38]. Other topical agents described in the literature include: topical application of 5-Aminosalicyclic acid[1], recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF)[41]. There are also reports of the application of nicotine transdermal delivery on the ulcers and use of nicotine gum[42,43].

SYSTEMIC TREATMENT

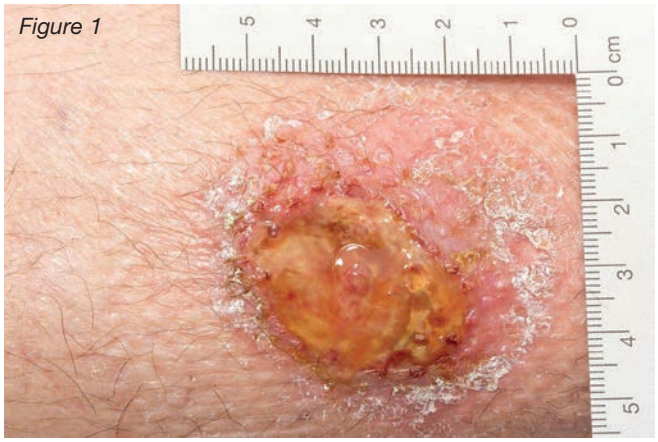
Systemic therapy is required in patients with all but superficial lesions[2]. Topical agents also do not address systemic disease and as the disease progresses a combination of topical and systemic agents may be required (Table 3[4]). Systemic treatments have many side effects and can dampen the patients' immune response, leaving them more susceptible to infections. Systemic high-dose corticosteroids, such as prednisolone, are often used initially with a rapid response; however, there are well-documented adverse effects with long-term use[1,38]. Another first-line treatment is cyclosporine; however, side-effects include renal toxicity, myelosuppression, hepatotoxicity and increased risk of infection[1,38]. Patients with underlying IBD have gone into remission with the use of cyclosporine[44]. Other modes of immunosuppression include mycophenolate, mofetil, methotrexate and azathioprine. These agents are considered more effective as adjunct therapy[1]. Immune modulators such as thalidomide are an emergent treatment option. These suppress neutrophil chemotaxis and tumour necrosis factor alpha (TNF-α)[2]. Thalidomide and methotrexate are considered more effective as adjunctive therapy[38]. In patients with less severe forms of PG sulphur drugs are considered a second choice. Dapsone alone or in combination with corticosteroids is a common treatment. Neutrophil function and the production of reactive oxygen species is inhibited with dapsone[29]. Patients must have normal levels of glucose-6-phosphate dehydrogenese for this line of therapy[29,38]. Other immune modulation agents include infliximab and interferon-α[1,2,4,36].

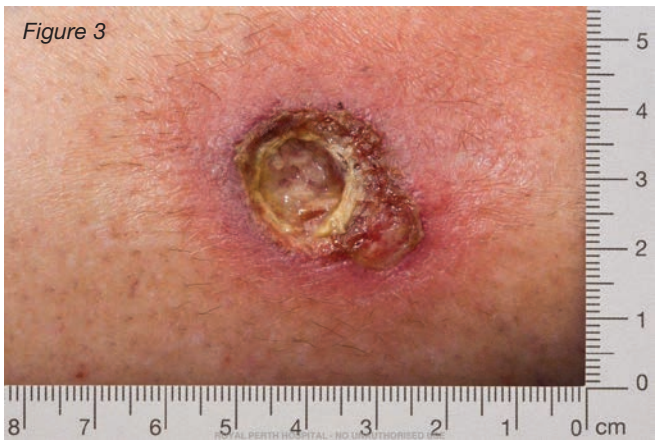
SURGICAL INTERVENTION

Surgery is not generally recommended due to the risk of pathergy[1,45]; as a result the ulcers could potentially worsen following surgery[1]. However, there are a few reports in the literature of success following surgical intervention. There is one report of success with a free flap to cover a large lesion[46], and the use of split-skin grafts and keratinocyte autografts[47]. Split-skin grafting has also been shown to reduce the patients' pain[45]. There is also a case report of debridement, vacuum-assisted closure (VAC®) and hyperbaric oxygen therapy to promote wound healing[48]. According to Teagle and Hargest[2], hyperbaric oxygen therapy can be helpful, even in recalcitrant cases. In general, surgery should be based on individual assessment of the patient and their wounds, weighing up the risk of pathergy.

PAIN MANAGEMENT

Pain associated with PG can be distressing for the patient. Patients report the pain as "stabbing" in nature. There are reports of severe pain leading to amputation of the affected limb[38] The source of pain associated with PG is multifactorial and is attributed to the inflammatory process in the dermis and subsequent ulceration[38]. Pain levels should be monitored and

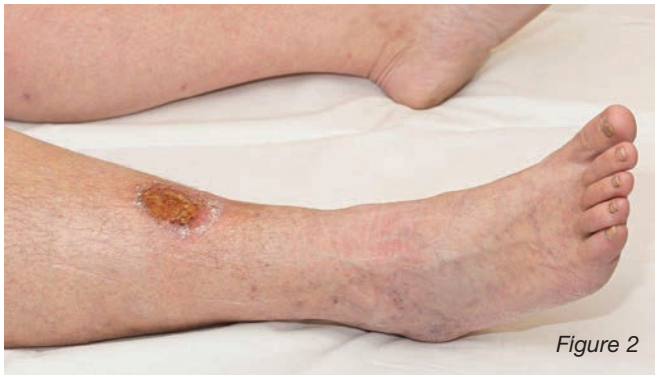




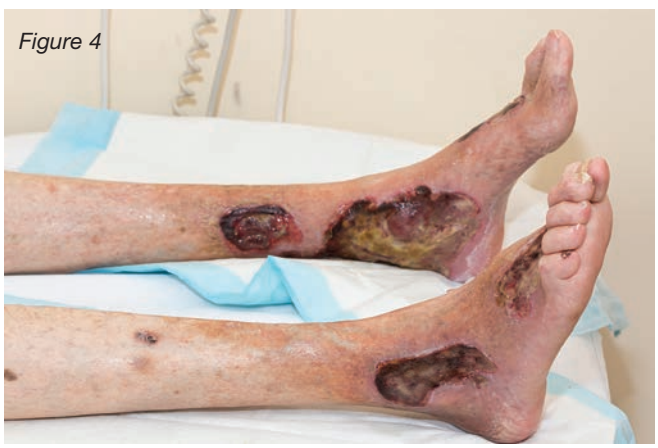
as the ulcer improves pain levels should decrease. Although dressing changes are fundamental they may also be a source of pain; this must be considered when selecting a dressing and during dressing changes. Pain relief may be required and administered before dressing changes and during the procedure. Due to the chronicity of the wounds, narcotics should be avoided or limited to breakthrough pain[38]. A multidisciplinary approach may be required for pain management[1]

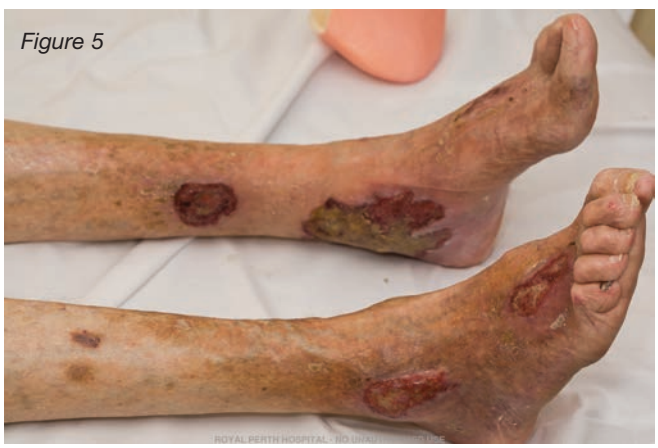
CASE ONE

A 37-year-old female was referred to the wound clinic with a non-healing leg ulcer to the anterior aspect of her right lower leg, which was sustained four months earlier after knocking it on a wooden crate at work. Regular wound management



was being performed by community nurses with a variety of dressings. On examination, the wound was 2.2 cm x 1.7 cm, had a sloughy base, and was extremely painful (Figures 1 and 2). Her only medical history was a right recurrent deep vein thrombosis (DVT) and a pulmonary embolus. A previous venous duplex scan revealed non-occlusive thrombus throughout much of the deep venous system of her right leg. Her only medication usage was warfarin. Ankle brachial indices were on the right: 0.9: left: 0.97. In view of her history of previous DVTs, a repeat venous duplex scan was ordered which revealed deep and superficial incompetence. Bacterial culture grew *Pseudomonas aeruginosa* and *Staphylococcus aureus* sensitive to ciprofloxacin. Based on the venous duplex scan and patient's history, the wound was diagnosed as a venous leg ulcer and was initially treated with an appropriate primary dressing and compression bandaging 30–40 mmHg. Despite this, the wound increased in size, developed a violaceous margin, and became extremely painful (Figure 3). The patient was referred to a dermatologist, where a tissue biopsy was performed. This demonstrated non-specific ulceration; cultures for atypical mycobacteria and fungus were negative. Based on the clinical picture the patient was diagnosed with PG and commenced on a reducing dose of prednisolone starting at 50 mg per day along with a course of ciprofloxacin. Investigations were performed to rule out associated underlying medical conditions, such as IBD, autoimmune and haematological disease, all of which were negative. It was therefore deemed that the PG developed as a result of pathergy as a result of trauma rather than an associated medical condition. As the wound continued to display no signs of response to treatment





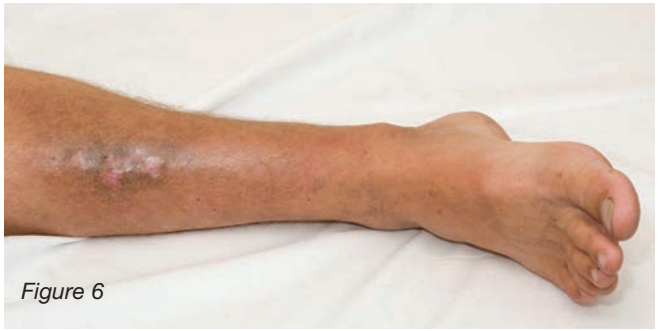


Figure 6

a referral was made to the infectious diseases team who have requested another tissue biopsy to retest for atypical mycobacterial infection. The dermatology team were managing the patient at the time this paper was prepared.

CASE TWO

A 79-year-old gentleman presented with a two-month history of non-healing leg ulcers bilaterally. His past medical history included chronic venous insufficiency, gastro-oesophageal reflux disease (GORD), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), and left total hip replacement. Initially the wounds measured 4 cm x 1 cm on the right lateral lower leg, and 2 cm x 2 cm, on the left medial lower leg. There was evidence of haemosiderin staining, pedal pulses were palpable, and the ulcers were painless. Originally the wounds were managed with local wound care and compression bandaging. However, over time, they gradually

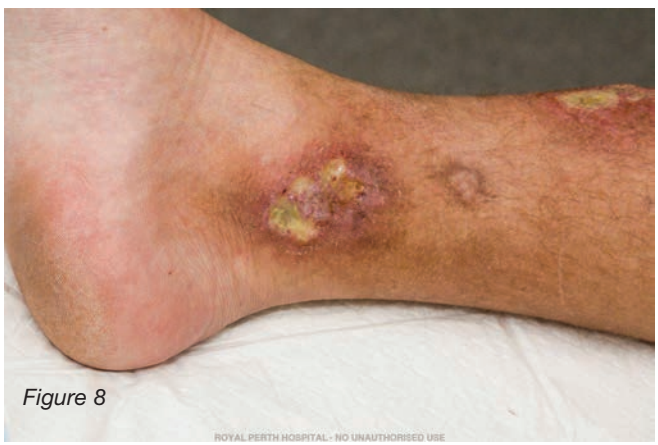


Figure 8

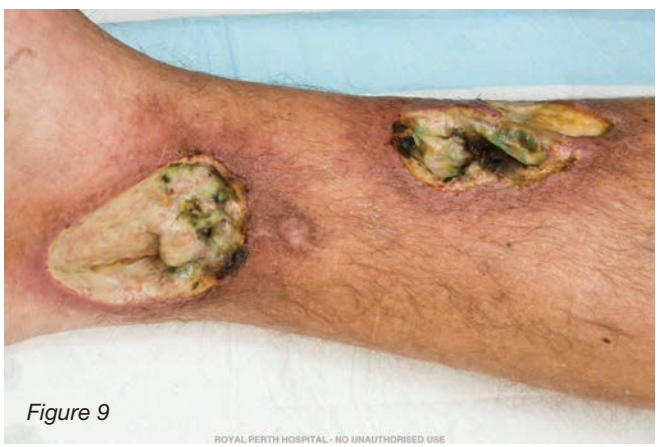


Figure 9

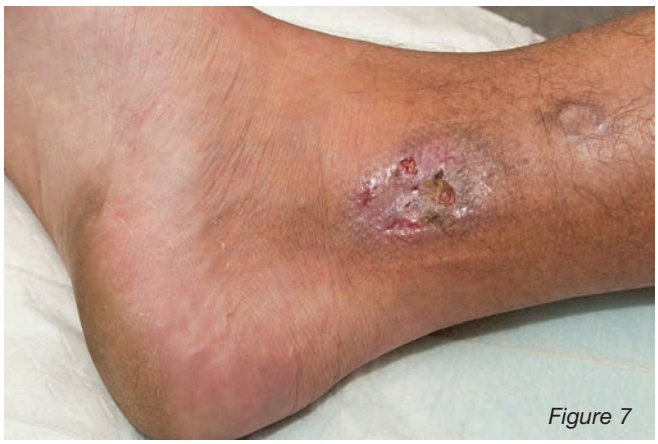


Figure 7

increased in size, and became infected and painful. The patient was admitted to hospital for intravenous antibiotics. During this admission the patient had a venous duplex scan, which demonstrated deep venous incompetence of the left leg, lesser saphenous vein, and incompetence of the saphenopopliteal junctions. He had varicose veins in the left calf draining into the lesser saphenous vein. The right lower leg demonstrated a competent deep system; varicose veins were identified draining into both greater and lesser saphenous veins with incompetent valves. Venous ablation was performed on the left short saphenous vein, and stenting of the left common iliac and left external iliac veins. The patient was discharged home and monitored as an outpatient with the support of community nurses for wound care. The wounds continued to deteriorate and the patient was admitted three months later with cellulitis. During this admission the patient underwent diagnostic angiogram and tibial peroneal trunk angioplasty and stent. Over time the ulcers continued to worsen (Figure 4). The patient was admitted for surgical debridement of his wounds. However, on the same day the dermatologists were consulted to review the patient. They diagnosed PG, and advised against any form of debridement due to the risk of pathergy. The patient was commenced on prednisolone 40 mg daily, methotrexate 30 mg weekly, and an increase in analgesic agents. The wounds were cleansed with Prontosan® solution and dressed with PolyMem® silver. The wounds responded well to wound care and systemic corticosteroids (Figure 5).

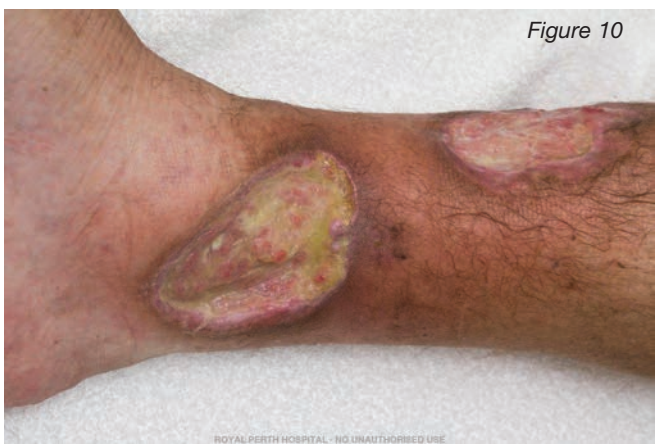


Figure 10

CASE THREE

A 30-year-old gentleman was referred to the wound clinic for management of a venous leg ulcer. He had a past medical history of ulcerative colitis (currently in remission) and GORD, reoccurring ulcers to the right lower leg for three to four years, and he had recently undergone venous ablation. On examination, there was evidence of a healed ulcer over the anterior aspect of the right lower leg, haemosiderin staining (Figure 6), and an ulcer over the medial aspect of the same leg, small satellite ulcers, and there was also evidence of atrophic cribriform scarring proximal to this lesion (Figure 7). The patient was a fly-in, fly-out worker, five weeks on and five weeks off; therefore, it was difficult to have consistency with wound care. Initially the patient was managed with a silicone foam dressing and compression hosiery 30–40 mmHg, with the patient attending to his own wound care. At his next review the wounds had increased in size, demonstrated violaceous margins and were extremely painful (Figure 8.) An urgent referral was made to see a dermatologist. Biopsy was performed, which demonstrated ulceration associated with inflammation and vascular proliferation with associated small vessel neutrophilic vasculitis and small vessel micro-thrombi. Despite this, based on the clinical appearance of the wounds and the patient's history of ulcerative colitis, a diagnosis of PG was made and he was commenced on prednisolone 50 mg daily. Over the coming month the wounds did not respond to the immunosuppression agent and the pain increased. A trial of prednisolone 1 mg crushed and applied topically to the wounds was initiated. However, the wounds increased significantly in size (Figure 9). The patient was then commenced on cyclosporine 200 mg and prednisolone 75 mg daily. During this period of time the patient had several admissions for wound infection and pain control. As there was very little response from the immunosuppressive agents, the patient was commenced on weekly infusions of Infliximab; an MRI was also performed to exclude osteomyelitis. There was gradual improvement in the wounds (Figure 10). As would be expected, pain has been an issue; this was managed in collaboration with the acute pain service, at our facility. Unfortunately, during the course of the treatment the patient lost his job.

DISCUSSION

These three case studies illustrate the complexity of diagnosing PG. Two of the cases responded poorly to treatment. This is consistent with the literature where, despite appropriate therapy for PG, there can be a failure for the wounds to progress[27]. Underlying conditions should be treated; however, PG can also occur when the underlying condition is in remission[27], as was the situation with case three. The second case did have underlying RA; however, he responded well to systemic treatment for PG.

When treating patients with suspected PG, one must always be open to the possibility of misdiagnosis. Indeed, many other ulcerating wounds can mimic PG[30,37]. Weenig *et al.* reported that out of 157 patients being treated for PG, 10% (n=15) were found not to have PG[37]. The consequences of misdiagnosis can be disastrous; particularly taking into account that the immunosuppressive agents used to treat PG may be contraindicated in other conditions[37]. Systemic immunosuppression can also make the patient vulnerable to infection, as was the case with patient three who had several admissions to hospital with wound infection. In a study conducted by Weenig *et al.*, they identified six broad disease categories that can mimic PG: vascular occlusive or venous disease; vasculitis; malignancy; exogenous tissue injury; infection; and other inflammatory disorders[37]. All three of the patients had underlying venous disease and were managed according to best practice[49], with appropriate wound care, compression bandaging or compression hosiery and, where clinically indicated, surgical intervention. Treating the ulcer as venous in origin possibly delayed the diagnosis of PG.

The accurate diagnosis of PG is challenging. The proposed diagnostic criteria by Su *et al.* aids the clinician with the diagnosis of PG[30]; this should not be used in isolation but as a guide. Independently, Von den Driesch had previously developed a diagnostic criteria for PG[50]. The criteria are virtually the same as the one developed by Su *et al.* von den Driesch studied 44 patients with PG, where each patient was diagnosed using a standardised diagnostic criteria. There was long-term follow-up in 42 of the patients in the study cohort. Adopting a diagnostic criterion into clinical practice could potentially reduce the number of cases misdiagnosed with PG.

Treatment of PG remains challenging to the clinician. Treatment is typically based on the individual requirements of the patient, underlying medical conditions, the presence of diseases associated with PG, and the extent of the ulceration[2]. The main goal of therapy is to reduce inflammation, control pain and promote healing[1]. Recommended first-line treatment is appropriate wound care, with topical and/or systemic corticosteroids[1,2]. In the three cases, patient two responded well to a combination of prednisolone, methotrexate, and simple wound care. However, the other two cases proved to be challenging.

CONCLUSION

Despite first being described almost a century ago, the diagnosis and management for patients with PG remains complex. Although three cases were presented, each of them proved challenging in diagnosis and treatment. Indeed, at the time of writing this paper two of the patients were still proving to be difficult to manage. Endless pain affects patients' quality of life. Unfortunately one of the patients lost his job due to repeated hospital admissions, which put strain on his marriage and his ability to pay his mortgage.

Misdiagnosis of PG can have devastating consequences, using the diagnostic criteria proposed by Su *et al.* should aid the clinician with diagnosis of PG. As there is a lack of specific guidelines for the treatment of PG, we recommend referral to a dermatologist or physician. A multidisciplinary approach is essential in managing this complex condition.

CONFLICTS OF INTEREST

The authors do not have a conflict of interest to declare.

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