Understanding pyoderma gangrenosum

KEY WORDS
- Immunosuppression
- Pathergy
- Pyoderma gangrenosum

Pyoderma gangrenosum (PG) is a rare immune-related chronic ulcerating skin condition with a predilection for the lower limbs. It is more common in females, with the average age of onset between 20 and 50 years. There are two stages of the disease process: an ulcerative phase and a healing phase. The latter occurs once the heightened and ongoing inflammatory response has subsided, although the exact pathophysiology of PG has yet to be elucidated. Half of the cases of PG are associated with other comorbidities, such as inflammatory bowel disease, arthritis or haematological malignancies. The skin condition pathergy can be a stimulus for the onset of the disease and is due to incidental or healthcare-related trauma. There is no definitive test to diagnose PG and the diagnosis is one of exclusion. The aim of the treatment is to reduce the inflammation and therefore immunosuppression is the basis of any therapy. Nevertheless, the disease can recur following completion of the healing phase.

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PG is a chronic ulcerating skin condition that appears to be immune-mediated. It is characterised by deep skin ulcers with undermined edges that occur most often on the lower limbs but may affect any skin surface (Brooklyn et al, 2006a).

It is an overactive inflammatory response to traumatic, inflammatory or neoplastic process and is therefore classified as a systemic auto-inflammatory disease (Ratnagobal and Sinha, 2013; Adışen et al, 2016).

HISTORY

Brocq, a French dermatologist, first described PG in 1908 as Phagedenisme Geometrique (Gameiro et al, 2015). In 1931 Brunsting renamed it Pyoderma gangrenosum, believing it to be a disseminated streptococcal infection causing cutaneous gangrene (Teagle and Hargest, 2014). In the 1930s, patients with Rheumatoid Arthritis were treated with cortisone and it was noted their co-existent PG ulcers started to heal: the theory of PG migrated from infective to autoimmune (Mehrtens and Crawley, 2015). The bullous variant of PG was first described in 1972 (Ratnsglobal and Sinha, 2013).

INCIDENCE OF PG

Patel et al (2015) report incidence of PG as 3–10 patients per million worldwide. In Europe, incidence is thought to be six million per year, with children accounting for 4% of that number (Teagle and Hargest, 2014).

There is a reported female predominance for PG (Laun et al, 2016; Sasor et al, 2018) and the condition is most common among 20–50 year olds (Adusen et al, 2016). There is significant morbidity due to pain and poor wound healing, and the mortality rate is three times higher in people with PG than the general population — higher still when the patient also has inflammatory bowel disease (IBD) (Mehrtens and Crawley, 2015).

PATHOPHYSIOLOGY

In the general population, there is a self-limiting inflammatory response, however, patients with PG have a heightened and ongoing inflammatory response. The duration of this abnormal inflammatory response may last weeks to many years (Ratnagobal and Sinha, 2013). There are two stages of the disease: the active, ulcerative stage and the wound healing stage (Gameiro et al, 2015).

Box 1. Proposed diagnostic criteria (Su et al, 2004)

Major criteria:

- a painful rapidly progressing ulcer
- exclusion of other causes of ulceration

Minor criteria:

- the presence of systemic diseases associated with PG
- history suggestive of pathergy
- characteristic histopathological findings
- response to systemic steroids or immunosuppression

Box 2. Differential diagnosis

- Skin infection, skin malignancy, vascular ulceration, systemic conditions — systemic lupus erythematosus, rheumatoid arthritis, Behcet's disease, Wegener's granulomatosis, and Sweet's syndrome (Brooklyn et al, 2006)
- Drug reaction, insect bite, factitious disorder, dermatitis artefacta (Teagle and Hargest, 2014; Schotanus et al, 2014; Montero et al, 2016).
- Necrotising fasciitis as can occur in the vulva, groin and penis (Tay et al, 2014; Bhaskaran et al, 2016).
- Allergic contact dermatitis in peristomal PG (Afifi et al, 20180)

Unfortunately, the cause and exact pathophysiology of PG is not well understood. However, there is thought to be an abnormal functioning of the neutrophils (Teagle and Hargest, 2014; Patel et al 2015; Abtahi-naeini et al, 2016; Laun et al, 2016), which is affected by alterations in chemotaxis and phagocytosis (Ratnaglobal and Sinah, 2013).

Genetic factors and mutations have been identified in patients with PG, as demonstrated in PAPA syndrome (pyogenic arthritis, PG, acne) and PASH syndrome (PG, acne, suppurative hidradenitis) (Mehrtens and Crawley, 2015; Braswell et al, 2015; Shavit et al, 2017).

ONSET

The onset of PG is variable: some patients present with one or two slowly growing ulcers, others experience the sudden appearance of multiple rapidly enlarging ulcers (Patel et al, 2015). In a retrospective study of 27 patients, the disease duration spanned between 15 and 14,600 days (Adisen et al, 2016).

Around 50% of cases of PG are associated with another underlying condition, the remaining 50% are idiopathic, having no known cause (Teagle and Hargest, 2014).

PG can also occur in patients with HIV, solid tumours and during pregnancy (Gameiro et al, 2015; Shavit et al, 2017) and can be drug-induced, with Isotretinoin reported as a causative agent (Teagle and Hargest, 2014).

DIAGNOSIS

In the absence of a definitive test (serologic or histological), PG is diagnosed by exclusion of other diseases (Patel et al, 2015; Wallace, 2017). Nevertheless, a biopsy will be taken from the ulcer bed and the adjacent skin and sent for histological examination (Patel et al, 2015). A typical biopsy result will identify a neutrophil and other inflammatory cell infiltration into the dermis (Brooklyn et al, 2006b; Schotanus et al, 2014, Teagle and Hargest, 2014). If the PG inflammation is minimal, the biopsy result will identify non-specific histopathology (Shavit et al, 2017).

In PG, the generic systemic inflammatory markers will be raised, e.g. C-reactive protein, and more so in the active ulcerative stage of the disease (Tay et al, 2014).

The individual will present with pain that is often thought to be out of proportion to the size of the ulcer bed (Schotanus et al, 2014; Tay et al, 2014) and should be screened for the underlying associated diseases (Ratnagobal and Sinha, 2013).

In 2004, Su et al proposed a framework to aid the diagnosis of PG *(Box 1)*. A positive diagnosis is made if the individual has two major and at least two minor diagnostic characteristics.

As is evident in *Box 2*, PG is often confused with other skin conditions/diseases (Sasor et al, 2018). Furthermore, inability to distinguish between sub-types of PG can delay diagnosis and have serious clinical consequences (Brooklyn et al, 2006a), including delayed treatment and negative effects on quality of life.

PATHERGY

Pathergy is defined as a pathological hyper-reactivity to normal stimuli (Teagle and Hargest, 2014). In PG, 25% of cases are triggered by pathergy due to incidental or healthcare-related trauma (Ormerod et al, 2015). Examples of pathergy-induced PG include wound infection and surgical procedures, e.g. caesarean section, breast reduction and central line insertion (Braswell et al, 2015; Patel et al, 2015, Abtahi-naeini et al, 2016, Pichler et al, 2016). Stoma formation can induce PG along with accompanying excoriation from bowel contents and skin stripping during removal of containment device (Wallace, 2017).

Litvinov and Sasseville (2014) report a case of PG hastened by red tattoo dye, which caused an allergic contact dermatitis — the pathergy trigger.

TYPES OF PG

There are five subtypes of PG and an individual can suffer from more than one subtype at any one time (Gameiro et al, 2015) *(Box 3)*.

Classic PG is associated with IBD, arthritis and haematological malignancies, with 25–50% associated with pathergy (Brooklyn et al, 2006b; Teagle and Hargest, 2014).

The clinical presentation is of a deep ulcer that can extend into the subcutaneous fat and fascia, with a purulent or haemorrhagic discharge (Schotanus et al, 2014). The ulcer has a well-defined undermined violaceous border accompanied by erythema of the surrounding

Box 3. Five subtypes of pyoderma gangrenosum

- Classic pyoderma gangrenosum
- Peristomal pyoderma gangrenosum
- Pustular pyoderma gangrenosum
- Bullous pyoderma gangrenosum
- Vegitative/superficial pyoderma gangrenosum

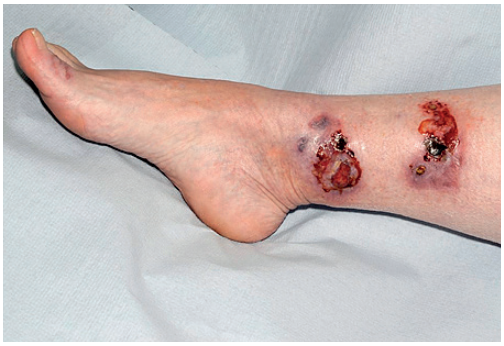

Figure 1. Classic PG

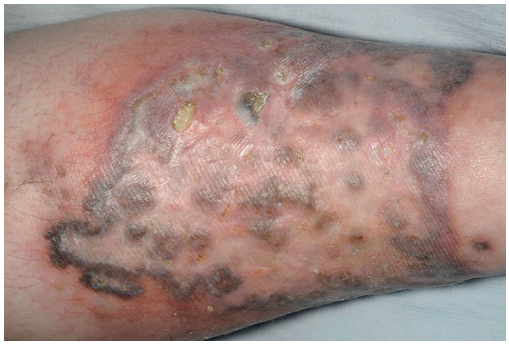

Figure 2. Healed PG

skin *(Figure 1)*. It often starts as a small papule or collection of papules that break down to form small ulcers that coalesce and form a wound with a necrotic centre. The individual is systematically unwell with symptoms such as fever, malaise, arthralgia and myalgia. The ulcers, commonly found on the legs, are excruciatingly painful and form unsightly, cribriform scarring.

Peristomal PG is associated with IBD and occurs close to abdominal stomas, comprising about 15% of all cases of PG. The clinical presentation is like classic PG with painful, rapidly progressing ulcers with an undermined violaceous border (Afifi et al, 2018). Gulliver's sign, which consists of string-like growths of epithelial tissue that straddle the border between the ulcer and the surrounding skin, are present in the wound healing stage of the disease (Tay et al, 2014, Gameiro et al, 2015) and may affect stoma bag fixation (Brooklyn et al, 2006a). Peristomal PG is particularly difficult to manage due to proximity to the stoma (Wallace, 2017).

Pustular PG is a rare superficial form of PG associated with IBD (Teagle and Gargest, 2014; Shavit et al, 2017) and can evolve into classic PG. It presents with a pustule (0.5cm–2cm) or group of pustules that coalesce to form lesions; however, they do not go on to ulcerate (Schotanus et al, 2014). The pustules and lesions are found on the trunk and extensor surfaces of limbs (Brooklyn et al, 2006a). They are painful and may be present for months yet usually heal without scarring *(Figure 2)*.

Bullous PG is a superficial type of PG associated with haematological conditions; prognosis is often poor (Brooklyn et al, 2006a; Teagle and Hargest, 2014).

The clinical presentation is rapidly evolving painful concentric bullae and vesicles that spread swiftly in a concentric pattern with a violaceous flare that can develop into superficial ulcers (Ratnaglobal and Sinha, 2013; Schotanus et al, 2014).

It affects the upper limbs and face and dorsum of the hands (Shavit et al, 2017).

Vegetative/superficial granulomatous PG is a rare superficial type of PG that is indolent and thus less aggressive than other types (Mehrtens and Crawley, 2015; Shavit et al, 2017).

The clinical presentation is of a single localised slow growing lesion or well-defined plaque that may be studded with small pustules and does not have a violacious flare (Ratnaglobal and Sinha, 2013; Schotanus et al, 2014; Teagle and Hargest; 2014). There is no systemic illness associated with this type of PG (Brooklyn et al, 2006a) and it responds well to topical treatment alone.

TREATMENT

Due to the rarity of PG, scientific research into treatment options is limited and there are no standardised treatment guidelines (Adisen et al, 2016; Wallace 2017). PG will require interventions from a range of medical teams including dermatologists, plastic surgeons, gastroenterologists, immunologists, haematologists and rheumatologists (Mehrtens and Crawley, 2015).

The treatment plan will depend on the severity and extent of the ulceration and associated disease, alongside specific patient factors (Teagle and Hargest, 2014) *(Figure 3)*.

Treatment goals include reduction of inflammation and pain, promotion of healing,

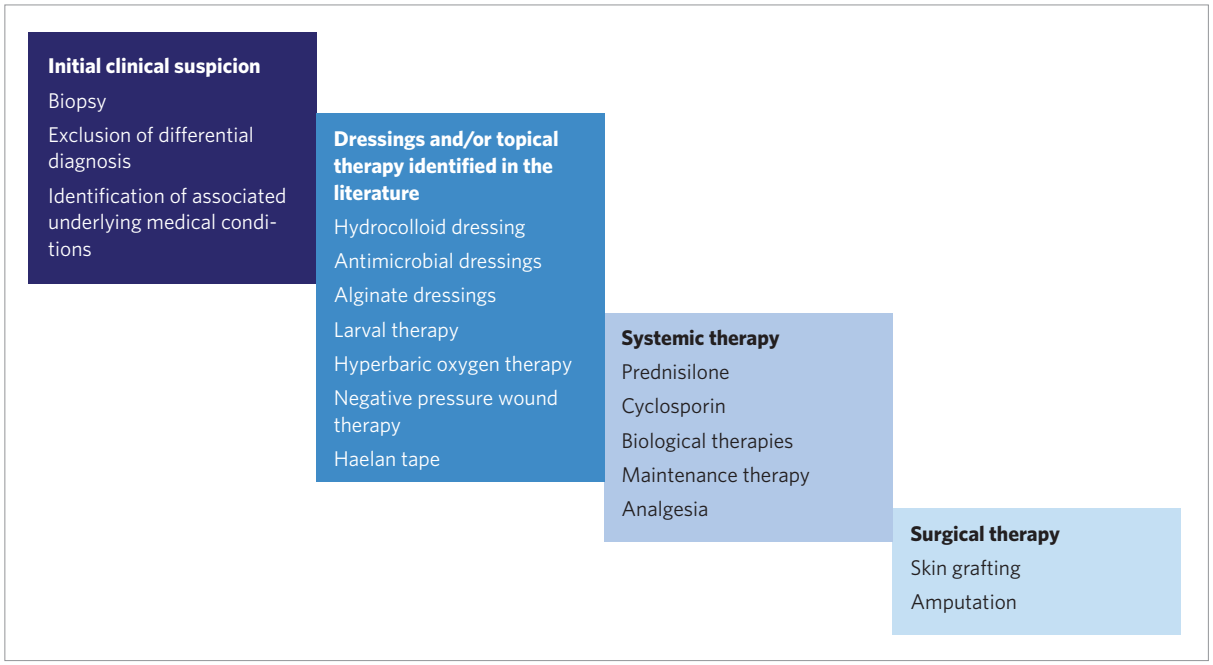

Figure 3. A step-wise approach to treating PG

diagnosis and control of systemic disease and minimising adverse drug events (Teagle and Hargest, 2014).

The mainstay of treatment is immunosuppression (Brooklyn et al, 2006b). The first line of delivery is via systemic corticosteroids or cyclosporin. However, PG has an unpredictable response to systemic and topical treatment (Mehrtens and Crawley, 2015). Furthermore, the drugs used to treat PG are highly potent and have significant and potentially life-threatening side effects (Teagle and Hargest, 2014). Tapering the levels of systemic therapy may decrease the risk of side effects while obtaining maximum clinical benefits. Some advocate a stepwise approach to topical and systemic treatments (Brooklyn et al, 2006a), while others recommend synergistic drug combinations rather than switching from one immunosuppressant to another (Patel et al, 2015). This latter approach aims to maintain remission with a less toxic regimen as long-term maintenance therapy is often necessary to prevent relapses.

A single randomised controlled trial was undertaken to compare cyclosporin to prednisolone. The trial of 112 patients demonstrated similar efficacy between the treatment arms. Contrary to the anecdotal belief that these drugs are efficacious in PG, the study found fewer than half the ulcers healed after prolonged treatment, and the speed of onset of response did not differ (Ormerod et al, 2015). Wilkes et al (2016) reviewed trial data that indicated an early treatment response at six weeks appeared to be a good indicator of healing.

There is reported success in treating intractable PG or disease that has not responded to conventional treatment with the newer targeted biological therapies, although again there are risks associated with long-term use (Ratnaglobal and Sinha, 2013; Shavit et al, 2017).

Topical therapy can be used as first-line treatment of superficial PG or as an adjunct alongside systemic immunosuppression in the more severe cases of the disease.

In cases of peristomal PG, barrier preparations and adhesive removers help to prevent pathergy. Positive clinical outcomes such as reduction in pain have been reported when using the topical preparation of Haelan tape that provides a regulated dose of fludroxycortide (Wallace, 2017).

Treatment effectiveness that demonstrates that the inflammation is under control is recognised clinically when the ulcer edges become more even with surrounding skin. However, even after the pathogenic inflammation has resolved, PG lesions

may take weeks, months or years to heal with only 50% of patients achieving remission after 6 months of immunosuppression. In patients who respond well to treatment, relapses occur in 30–60% of cases (Mehrtens and Crawley, 2015; Pichler et al, 2016).

WOUND SPECIFIC TREATMENTS

Various advanced wound dressings have been examined for the topical treatment of PG; hydrocolloid, antimicrobial dressings, alginates. Additional treatments included larval therapy and hyperbaric oxygen and negative pressure wound therapy (Schuppe, 1998; Ratnaglobal and Sinha, 2013; Teagle and Hargest, 2014; Laun et al, 2016; Pichler et al, 2016).

A main area of contention is the use of debridement for PG ulceration. Surgical and sharp debridement have the potential to cause pathergy (Afifi et al, 2018). Conversely, debridement, amputation and skin grafting has been reported to be successful once the inflammation has been controlled (Ratnaglobal and Sinha, 2013; Laun et al, 2016; Pichler et al, 2016)

CONCLUSION

PG is a rare ulcerating skin disease that can have a profound effect on an individual's quality of life. It is often associated with underlying diseases namely IBD, arthritis and haematological malignancy. The pathophysiology of PG is poorly understood, yet the abnormal inflammatory profile of the disease is known to be neutrophil-driven, resulting in an absence of a self-limiting immune response.

There is no equivocal diagnostic test and consequently, PG can lay undetected. Prognosis and disease limitation is subject to early diagnosis and immediate treatment. The cornerstone of treatment is systemic corticosteroids with the newer biological therapies successfully emerging for the more complex cases of PG. Unfortunately, PG is a cyclical disease consisting of periods of ulceration, healing and recurrence.

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