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REVIEW ARTICLE

Pyoderma gangrenosum - An update and literature review

Pioderma gangrenoso - Uma atualização e revisão da literatura

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Abstract

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis, often associated with systemic diseases, including inflammatory bowel disease, rheumatoid arthritis, and hematological disorders. Its etiopathogenesis is complex, including neutrophil dysfunction, immunological dysregulation, and genetic alterations. PG lesions can be single or multiple, with varying sizes and morphologies, affecting different anatomical areas. The most common clinical variant is the ulcerative/classic, but bullous, pustular, vegetative, peristomal, and post-surgical variants are also described. Indeed, the diagnosis of PG is challenging due to the heterogeneous clinical presentation and the absence of specific analytical and histopathological findings. Moreover, its lesions can mimic cutaneous ulcers of other etiologies. A wide array of complementary tests may be required not only to rule out alternative diagnoses but also to investigate underlying systemic diseases and extracutaneous manifestations. PG has a significant impact on the quality of life. Its treatment relies on a multimodal approach aimed to reduce disease activity, optimize wound healing, manage pain, and treat associated comorbidities. Topical and systemic immunomodulatory drugs, analgesics, and appropriate wound care are the available therapeutic options. Therefore, this review provides a narrative synthesis of the published literature, contributing to a better understanding of the disease and an optimized approach to these patients.

Keywords: Pyoderma gangrenosum. Neutrophilic dermatosis. Autoinflammation. Autoimmunity. Immunosuppression.

Resumo

O pioderma gangrenoso é uma dermatose neutrofílica frequentemente associada a doenças sistémicas, nomeadamente doença inflamatória intestinal, artrite reumatóide e distúrbios hematológicos. A sua etiopatogenia é complexa, incluindo disfunção dos neutrófilos, desregulação imunológica e alterações genéticas. As lesões do pioderma gangrenoso podem ser únicas ou múltiplas, com tamanhos e morfologias variadas, afetando diferentes áreas anatómicas. A variante clínica mais comum é a ulcerativa/clássica, mas as variantes bolhosa, pustulosa, vegetativa, periestomal e pós-cirúrgica estão também descritas. De facto, o diagnóstico de pioderma gangrenoso é desafiante devido à apresentação clínica heterogénea e à ausência de alterações laboratoriais e histopatológicas específicas. Além disso, as suas lesões podem mimetizar úlceras cutâneas de inúmeras etiologias. Um vasto conjunto de exames complementares pode ser necessário não só para excluir diagnósticos alternativos, mas também para investigar doenças sistémicas subjacentes e manifestações extracutâneas. O pioderma gangrenoso tem um impacto significativo na qualidade de vida. O seu tratamento baseia-se numa abordagem

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multimodal com o objetivo de reduzir a atividade da doença, otimizar a cicatrização das feridas, controlar a dor e tratar comorbilidades associadas. Imunomoduladores tópicos e sistémicos, analgésicos e cuidados de penso adequados são as opções terapêuticas disponíveis. Assim, esta revisão oferece uma síntese narrativa da literatura publicada, contribuindo para uma melhor compreensão da doença e uma abordagem otimizada aos pacientes.

Palavras-chave: Pioderma gangrenoso. Dermatose neutrofílica. Autoinflamação. Autoimunidade. Imunossupressão.

Introduction

Pyoderma gangrenosum (PG) is included in the group of neutrophilic dermatoses[1-4], along with Sweet' syndrome and Behçet' disease[4-8], which share a histopathological substrate rich in neutrophils[4-9]. The diagnosis of PG is challenging due to its rarity, variable clinical presentation, and the absence of specific markers[2,9-15]. Although it has been recognized for over a century, its etiopathogenesis remains poorly understood, and there is no consensual treatment[2,8]. Thus, the approach to a patient with PG is complex, requiring a better understanding of the physiopathology and the development of new therapeutic targets.

Therefore, we performed a review of the published literature on PG to provide the medical community a better understanding and management for this disease. PubMed was the primary database consulted. The revised articles are predominantly < 10 years old, with a higher prevalence of articles from the last 5 years. There were no restrictions regarding language or study type; however, most of the chosen articles are narrative reviews, systematic reviews, and case reports.

Epidemiology

The global annual incidence of PG is estimated at 3-10 cases per million individuals[8,11,13,15-18]. The prevalence is approximately 5.8 patients per 100,000 individuals[14,16,19], with PG affecting predominantly those over 50 years of age[10]. Women are slightly more affected than men[15-17] and pediatric patients account for only 4%[8,15,16].

Etiopathogenesis

The etiopathogenesis of PG is complex and remains poorly understood, but genetics, neutrophil dysfunction, and immunological dysregulation are main contributing factors[2,8,9,20-23]. The pilosebaceous unit may be the initial target of the inflammatory process, due to the absence of lesions in body areas without follicular adnexal structures[24,25].

Defects in neutrophil chemotaxis, phagocytosis and metabolism[1,20,23,26], along with oligoclonal expansion of T cells observed in skin biopsies highlights the potential role of these cells[1,19,21,23], also supported by the overexpression of cytokines and chemokine, namely, interleukin (IL)-8, IL-17, Tumor necrosis factor-α (TNF-α) and CXCL-1/2/3/16, and matrix metalloproteinases 2 and 9[1,2,19,20,23,27,28]. Elevated levels of IL-1β suggests an autoinflammatory process induced by the activation of the inflammasome[21,23,27,29]. This may also explain the association with other diseases with mutations in the *PSTPIP-1* gene that regulates the inflammasome, namely, the PAPA, PASH, and PAPASH syndrome which includes apart from PG, acne, pyogenic arthritis and hidradenitis suppurativa[1,8,23,27,29]. Furthermore, pathergy can be explained by an inflammatory reaction to trauma.

Furthermore, specific genetic loci associated with a higher susceptibility to inflammatory bowel disease (IBD) are commonly found in PG patients, suggesting a common genetic background[1,23,26].

Various medications appear to induce PG lesions, including some used in the treatment of comorbidities and even in the treatment of PG, such as TNF-α antagonists, rituximab, and gefitinib[1,9,14,20].

Clinical presentation

The clinical presentation of PG is heterogeneous. Solitary or multiple lesions, differing in size, depth, and morphology may occur[9,26]. The pre-tibial area is the most common site[9,30], but any skin area can be affected[15,26,30,31]. Typically, cutaneous lesions are extremely painful[16] and are not associated with lymphangitis or lymphadenopathy[6].

The most recognized clinical variants include ulcerative/classic, bullous, pustular, vegetative, peristomal, and post-surgical PG[1,6,19,22]. Transformation from one variant to another can occur[27] and usually each subtype is related to different systemic diseases[1,6,19].

Extracutaneous manifestations can occur, such as scleritis, corneal ulcers, aseptic pulmonary nodules, pleural effusions, sterile hepatic and splenic abscesses,

neutrophilic myositis, sterile osteomyelitis, and aortitis[1,16,19,22,32]. Consequently, a patient with PG may experience multiple symptoms including fever, malaise, abdominal pain, myalgia, arthralgia, respiratory, and visual changes[6,9,16,31].

Ulcerative/classic PG

Ulcerative PG is the most common variant, representing about 85% of cases. It predominantly affects the legs, possibly due to greater exposure to trauma[10,12,19,26,27], and includes two stages: ulcerative and cicatricial[1].

The ulcerative phase presents with a painful papule, pustule, or nodule that evolves, within 1-2 days, into an expansive ulcer with well-defined borders. The edges are raised, with an erythematous, violaceous, or purpuric hue, sometimes with pustules and epidermal detachment (Figs. 1 and 2). The ulcer base is covered by a non-specific necrotic tissue[1,19], typically associated with a hematopurulent exudate[30]. It may be limited to the superficial dermis or extend through the subcutaneous tissue to the muscular fascia[26]. Pain is usually severe and disproportionate to the physical examination, especially if the progression is fast[1,10,12,26]. When multiple ulcers are present, they may gradually merge, sparing delicate strips of normal epidermis[11].

In the cicatricial phase, the wound margin develops epithelial extensions projecting into the ulcer, known as Gulliver's sign, creating a distinct cribriform or "cigarette paper" appearance (Fig. 3)[1,12,18,19].

Systemic diseases most frequently associated with the classic variant are IBD, hematological malignancies, rheumatoid arthritis (RA), seronegative arthritis, and monoclonal gammopathies[6,10,11].

Bullous PG

In bullous PG, the initial presentation is a painful vesicle in an erythematous base that evolves into blue-gray blisters. These blisters may coalesce and upon erosion, they form a shallow, superficial ulcer with a necrotic base[11,26,27,33]. Bullous PG typically appears in unusual locations such as the face, dorsum of the hands or extensor surfaces of the arms. This variant is significantly associated with myeloproliferative disorders, especially acute myeloid leukemia (AML)[1,4,10,11,34].

Pustular PG

Pustular PG is a rare clinical variant often observed in association with other types of PG[8]. This subtype features painful sterile pustules surrounded by an erythematous halo, symmetrically distributed on the trunk and extensor surfaces of the limbs[1]. There are reports of scalp and penis involvement, in association with other types of PG[8]. Pyostomatitis vegetans, a pustular intraoral eruption strongly associated with IBD, may represent a mucosal form of pustular PG[11,19]. This clinical variant is often described in IBD exacerbations, improving with treatment of the enteropathy, but can also occur in quiescent IBD[11,26].

Vegetative PG

Vegetative PG, also known as superficial granulomatous pyoderma, is considered the rarest and the mildest variant of PG. Its clinical presentation ranges from vegetative lesions to superficial ulcers, lacking the violaceous undermined edge and the hematopurulent exudate seen in the classic variant. It typically presents as a single, minimally symptomatic lesion on the trunk. These lesions are more likely to resolve spontaneously without scarring and show a fast response to topical therapies. The vegetative PG is not strongly associated with systemic diseases[1,8,10,11].

Peristomal PG

Peristomal PG can affect approximately 0.6% of patients with stomas annually. It is characterized by classic ulcers surrounding the stoma and it is believed to represent a pathergy response to trauma. It can develop shortly after surgery or later, possibly due to skin irritation caused by feces/urine, adhesives, or stoma devices[8,11,26,27,35].

Post-surgical PG

Post-surgical PG manifests as an erythematous patch followed by an ulcer, localized in the surgical wound and mimicking its dehiscence (Fig. 4)[6]. This variant mostly develops within the first 2 weeks after any surgical procedure[26]. Surgical interventions most frequently associated with post-surgical PG include mammoplasties, laparotomies, and skin grafts[30]. When the breast is involved, the nipple is generally spared. Only one in six patients with this variant has a personal history of PG[1].

Associated diseases

PG is the second most common cutaneous manifestation of IBD[36], particularly ulcerative colitis[1,36].

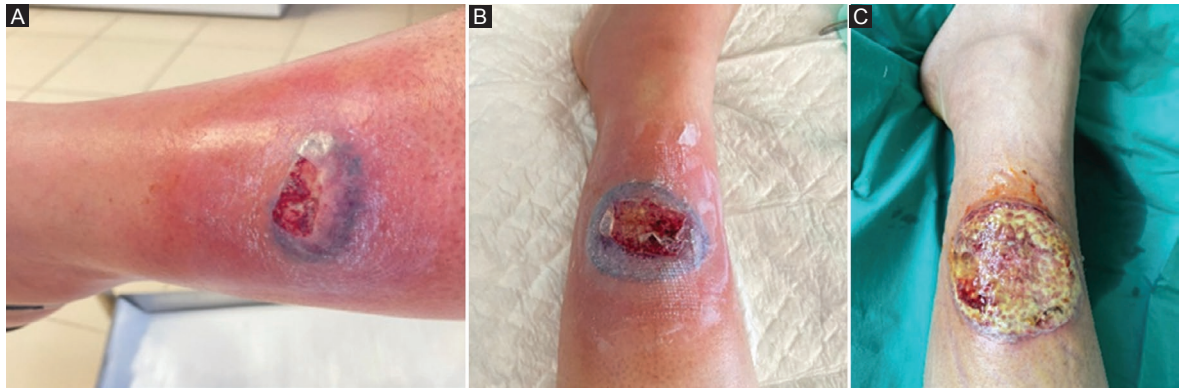

Figure 1. A-C: evolution of an ulcerative pyoderma gangrenosum lesion on the leg over 4 days.

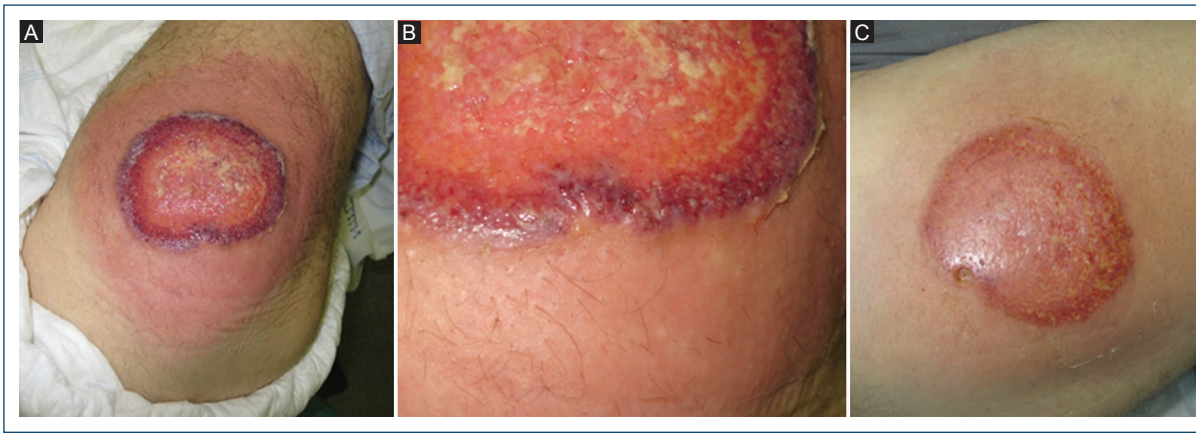

Figure 2. A: ulcerative pyoderma gangrenosum lesion surrounded by an erythematous halo, **B:** with raised violaceous edges, and pustules causing superficial detachment. **C:** the same lesion after 4 days of oral corticosteroid therapy.

The activity of IBD does not directly correlate with PG[14], as PG can precede the onset of IBD or even persist after surgical intervention[26]. However, PG usually appears after the diagnosis of IBD[19,37]. The classic, peristomal, and pustular variants are commonly observed, with the latter being more related with disease activity[11].

Inflammatory arthropathies, such as RA and some seronegative arthritis, are frequently associated with PG, especially its classic variant[6,19].

Hematological disorders are also associated with PG, especially myelodysplastic syndrome (MDS), AML, and monoclonal gammopathy of undetermined significance, predominantly of the immunoglobulin A type. In most cases, the diagnosis of a hematological malignancy precedes the development of PG that often presents with multifocal lesions[5] and in AML in atypical locations and mostly as the bullous. Legs are frequently involved, except in B-cell Non-Hodgkin lymphoma, where lesions predominantly affect the genital area[1,5,10,11].

Diagnosis

The diagnosis of PG is a challenge due to its variable clinical presentation and the absence of specific laboratory and histological findings[1,3,4,6,9-14]. It is considered a diagnosis of exclusion, but some well-defined diagnostic criteria have been developed (Table 1)[3,4,6].

The skin biopsy cannot provide a definitive diagnosis of PG, as histological features are nonspecific and vary depending on the biopsy location, stage, and clinical subtype, but histopathology is useful for excluding alternative diagnoses, particularly malignancies and infections[9-12,16,27].

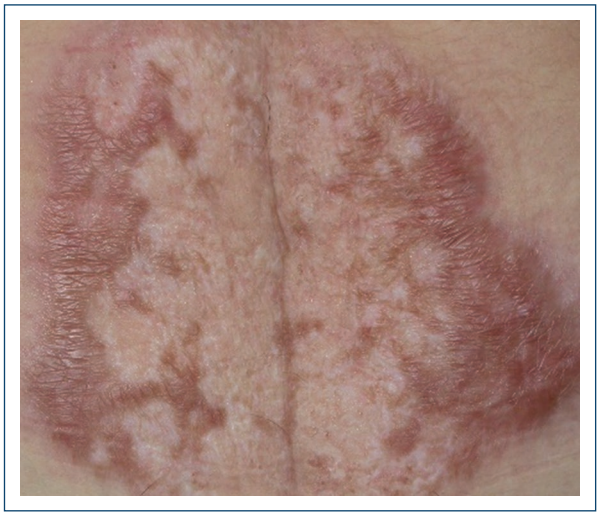

Figure 3. Cribiform or "cigarette paper" scar of the pyoderma gangrenosum lesion.

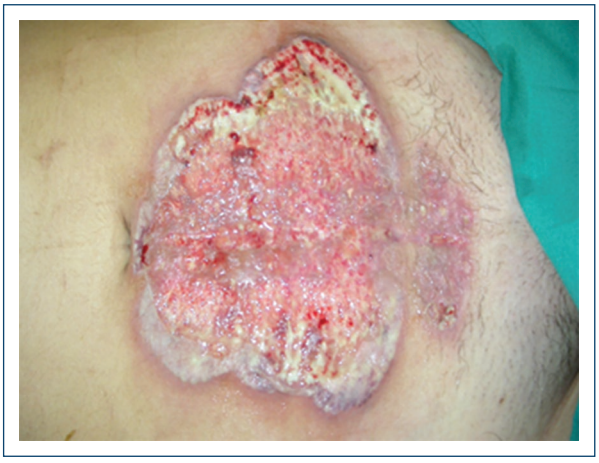

Figure 4. Ulcerative pyoderma gangrenosum with the typical undermined edge and pustules that emerged on a surgical wound of a cesarean section, with centrifugal growth.

The need for an accurate diagnosis before beginning appropriate treatment must overlap the risk of exacerbating PG due to biopsy-induced pathergy[12,26].

In classic PG, there is a significant infiltration of neutrophils in the dermis and subcutaneous tissue, which leads to necrosis of pilosebaceous units and epidermis[9,10,16,27]. The bullous variant of PG presents with subcorneal, subepidermal, and intraepidermal blisters, along with a dermal neutrophilic infiltrate and microabscesses. In the pustular form, there is an accumulation of neutrophils under the stratum corneum and in the dermis, associated with subepidermal edema. The infiltrate tends to be concentrated around the hair follicles, and the infundibulum often shows signs of rupture or perforation. Vegetative PG is characterized by a palisaded granulomatous reaction, neutrophilic abscesses with sinus tracts, and pseudoepitheliomatous hyperplasia[9-11,16,33].

A broad range of additional tests may be required, not only to rule out alternative diagnoses but also to investigate associated systemic diseases and extracutaneous manifestations of PG[6,9,12].

A complete blood count, along with erythrocyte sedimentation rate and C-reactive protein, as well as kidney and liver function, should be assessed along with urine analysis to search for Bence Jones protein, serum protein electrophoresis, and immunofixation to exclude monoclonal gammopathy, autoantibody tests to rule out connective tissue diseases, RA, antiphospholipid syndrome (APS), granulomatosis with polyangiitis (GPA), and other vasculitis, and coagulation studies to exclude thrombotic causes of ulceration. Lower limb echo Doppler should be performed to evaluate for venous insufficiency and peripheral arterial disease. Fecal calprotectin analysis and colonoscopy should be conducted if IBD is suspected. Serological tests for Hepatitis B virus, Hepatitis C virus, human immunodeficiency virus, and an interferon-gamma release assay for *Mycobacterium tuberculosis* should be performed to exclude underlying infections before starting immunosuppressive therapy. A chest X-ray and computed tomography scan should be considered if extracutaneous manifestations are suspected[4,10-12,27,38].

Differential diagnosis

The differential diagnosis of classic PG includes venous insufficiency ulcers, cutaneous infections, APS, GPA and other vasculitis, factitious ulcers, vascular occlusive disorders, and malignancies[12]. Bullous PG should be differentiated from autoimmune blistering dermatoses, erythema multiforme and the superficial bullous variant of Sweet' syndrome[5,6,8,11,13,27,34]. Pustular PG should be distinguished from bacterial pyodermas, pustular psoriasis, Sneddon-Wilkinson disease and drug reactions[6]. Peristomal PG must be differentiated from bacterial and fungal skin infections, chemical dermatitis and irritative or allergic eczema[35].

Treatment

Treatment can be challenging, with several factors to consider when choosing the best therapeutic

Table 1. Comparison of suggested diagnostic criteria for pyoderma gangrenosum[3,7,10,19,75]

Criteria	Daniel Su et al. (2004)*	Delphi Consensus (2018)†	ParaceIsus (2019)‡
Major criteria	Rapid progression of a painful, necrotic cutaneous ulcer with an irregular, violaceous, and undermined border	Biopsy with a neutrophilic infiltrate	Progressive disease (3 points)
	Exclusion of other causes of cutaneous ulceration		Absence of relevant differential diagnoses (3 points)
			Reddish-violaceous wound border (3 points)
Minor criteria	Clinical history suggestive of pathergy or clinical finding of cribriform scarring	Exclusion of infection on histopathology/ microbiological assessment	Improvement with immunosuppressive treatment (2 points)
	Systemic diseases associated with pyoderma gangrenosum	Pathergy	Typical irregular ulcer shape (2 points)
	Histopathologic findings (sterile dermal neutrophilic infiltrate ± mixed inflammatory infiltrate ± lymphocytic vasculitis)	Personal history of inflammatory bowel disease or inflammatory arthritis	Severe pain - > 4/10 on visual analogue scale (2 points)
	Treatment response (rapid response to systemic steroids)	Papule, pustule or vesicle that rapidly ulcerates	Lesion at site of previous trauma (2 points)
		Peripheral erythema, undermining border, and tenderness at the site of ulceration	Suppurative inflammation in histopathology (1 point)
		Multiple ulcers (at least one on the anterior surface of the leg)	Undermined wound border (1 point)
		Cribriform or wrinkled paper scars at healed ulcer sites	Associated systemic disease (1 point)
		Reduction in ulcer size after immunosuppressive treatment	

*Diagnosis requires both major criteria and at least two minor criteria.
†Diagnosis requires confirmation of the major criteria and at least 4 of the 8 minor criteria.
‡Score ≥ 10: pyoderma gangrenosum highly probable. Score < 10: pyoderma gangrenosum unlikely.

option. These include the site, depth, size, and number of the lesions, extracutaneous involvement, comorbidities, side effects, and costs[1,14]. Treatment goals are disease activity reduction, wound healing optimization, pain control, and prevention/treatment of secondary infections[1,12,26,34].

Although there are no guidelines, PG treatment is based on the use of topical and systemic immunomodulatory drugs, analgesia, and wound care[1,11,12,25,39,40]. Their use is based on expert opinions and data from case reports, small case studies, and a limited number of randomized clinical trials[1,25].

Topical treatment

Topical treatment is mostly used as an adjunct to systemic therapy[14]. However, a subset of patients with a reduced number of small ulcers without involvement of deep structures may be treated only with topical therapy, mostly high-potency corticosteroids and calcineurin inhibitors tacrolimus and pimecrolimus[11,31]. When used as monotherapy, both have the same level of evidence for mild or unilesional disease. The most common adverse effect of topical calcineurin inhibitors is a burning sensation, which can be reduced if refrigerated before use[14,25,26,41,42]. Regarding corticosteroids, they are generally used as creams or ointments or intralesional injections and, in peristomal PG, as lotions, foams, mixtures with adhesive agents, through inhalers or impregnated tapes. In addition, new ostomy bases are being developed to prevent skin complications around the stoma[14,42-44]. Topical corticosteroids can lead to cutaneous atrophy and delay in wound healing, but a low rate of significant side effects is reported[14].

Other topical therapies have also been described, including 0.5% nicotine cream, platelet-derived growth

factor, nitrogen mustard, coagulation factor XIII, gels with cyclosporine, dapsone, sodium cromoglycate, phenytoin solution, benzoyl peroxide, 5-aminosalicylic acid, and becaplermin[1,14,26,31,42,45]. Topical timolol appears to be effective in promoting reepithelialization in the scarring phase of wounds[46].

Systemic treatment

Systemic treatment is indicated in severe or multilesional PG and, in milder cases if there is no improvement after 2-4 weeks of topical therapy. A large multicenter retrospective cohort study and an expert survey showed that patients with PG receive, on average, two different systemic agents, emphasizing the importance of drug combination in clinical practice[14,25,38,47].

Systemic corticosteroids are the first-line therapy. Oral prednisolone (0.5-1 mg/kg/day) induces a clinical response in about 40-50% of cases, with heterogeneous rates of complete response depending on the severity of PG and associated systemic diseases. The therapeutic response can be observed in 2-3 days[1,14,25,47,48] with reduction of pain, exudate, edema, and erythema[11]. Once healing is achieved, the dose of oral corticosteroid can be gradually tapered. Adverse effects such as osteopenia, weight gain, glaucoma, cataracts, hyperglycemia, diabetes, Cushing's syndrome, immunosuppression, adrenal insufficiency, and psychosis should be monitored[1,14,25,42].

Cyclosporine has the same level of evidence as systemic corticosteroids. In fact, a randomized clinical trial involving 112 patients with PG compared cyclosporine (4 mg/kg/day) with prednisolone (0.75 mg/kg/day), found equivalent clinical outcomes in healing time, inflammation reduction, reported pain, and incidence of adverse reactions[2,14,25,26,41,49]. Thus, cyclosporine is a solid alternative, especially in patients with limitations to corticosteroid use but it is contraindicated in patients with renal insufficiency and high blood pressure. Combining systemic corticosteroids with cyclosporine is also a possible option, especially if ulcers are in sensitive areas such as the face, neck, and genitals, or associated with extracutaneous manifestations. In these situations, intravenous pulses of methylprednisolone 1000 mg for 3-5 consecutive days is also an effective alternative, with a faster outcome[1,14,25].

Other systemic therapies, including methotrexate, azathioprine, mycophenolate mofetil, dapsone, thalidomide, colchicine, intravenous immunoglobulin, sulfasalazine, and granulocyte and monocyte adsorption apheresis have been reported in controlling disease activity, however, controlled trials supporting the effectiveness of these therapies is scarce[1,11,14,15,25,26,50,51]. After cyclosporine, dapsone, and mycophenolate mofetil are the non-biological corticosteroid-sparing agents with more scientific evidence for PG treatment[14].

Biological agents are a promising therapeutic approach in PG, including TNF-α, IL-1β, IL-17, IL-23, and C5a inhibitors[1,11,14,25,52,53]. Among TNF-α inhibitors, adalimumab and infliximab have higher response rates[14,25]. However, infliximab remains the only anti-TNF-α agent with demonstrated efficacy in classical PG, based on a double-blind, randomized controlled trial[54]. Moreover, it is also treating synchronous diseases, such as IBD[1,11,14,38]. IL-1β inhibitors, namely, anakinra, canakinumab, and gevokizumab, are of particular interest in patients with autosomal dominant autoinflammatory syndromes, such as PAPA[14,25,53,55]. Spesolimab is an IL-36 receptor blocker recently approved for generalized pustular psoriasis that has also shown excellent results in the treatment of PG, particularly in refractory cases, with very rapid clinical responses according to some reports[56,57].

The appropriate time for discontinuation of systemic therapy remains a therapeutic challenge. The primary purpose of systemic therapy lies in modulating the inflammatory activity of the disease, with pain reduction and regression of the livid wound margin. In the absence of overt signs of persistent inflammation, tapering of systemic therapy is mandatory, until the complete healing of skin lesions[11,14].

Wound care

In addition to topical and systemic therapies, appropriate wound care is essential for wound healing[34,40]. Moreover, it reduces local pain and the risk of superinfection[40].

Wound cleansing should be performed with caution, namely, with sterile water especially when using silver-based dressings, as the chloride ions present in saline inhibit silver cations action[34]. Due to pathergy, surgical debridement is not recommended[11,14,34], especially during the inflammatory phase and in the absence of systemic immunosuppression[14], and more conservative debridement is more convenient, including autolytic and enzymatic methods[1,14,25].

The choice of dressings must be individualized, depending on the disease phase, wound nature, and pain level[25,34]. In the inflammatory phase with active

ulceration with erythematous edges, antimicrobial and hyper absorbent dressings are preferable, whereas in the healing phase, foam dressings such as polyurethane and silicone foam, are more suitable[25,40]. Dressings containing antimicrobials, such as polyhexanide or silver, decrease the microbiological load in the wound, are more useful in the active phase[14,58], but prophylactic topical antibiotic therapy is not advised due to the risk of bacterial resistance and contact dermatitis[34]. For exudative lesions, absorbent dressings, particularly alginate or hydrofiber dressings, are recommended[11,25,34,40] and for hemorrhagic ulcers, priority should be given to the use of alginates due to their hemostatic properties[25].

Surgical treatment of PG lesions in the active phase is not recommended. However, partial-thickness skin grafts have shown promising results, especially when applied with negative pressure therapy, and under systemic immunosuppression[25,34,39,59]. This approach appears to accelerate healing and promote early wound closure[39,59,60]. Considering that corticosteroids and other immunosuppressants delay wound healing, combining medical therapy with these surgical interventions may be advantageous once therapeutic success can be achieved with a lower burden of systemic therapy[39].

Hyperbaric oxygen therapy seems to be a promising alternative, given its influence on neovascularization, edema reduction, inflammation control, collagen synthesis by fibroblasts, and bacterial load attenuation[61]. As a rescue therapy, it has been successful in achieving partial improvement or even complete healing in cases of PG refractory to conventional treatments, with a satisfactory safety profile[62-65].

In addition, compression therapy is beneficial in most ulcers located on the lower extremities[34,66]. as it reduces edema associated with inflammation and appears to promote wound healing[1,14,34,40]. However, it is important to exclude peripheral arterial disease[1] and consider that excessive compression may induce pathergy, especially if disease inflammation is not controlled[11].

Analgesia

PG is a highly painful dermatological condition[26]. The depth of the ulcer and associated nerve damage may contribute to the higher pain intensity reported by patients. In addition, with nerve fiber regeneration, hypersensitivity may arise in the previous wound area, requiring an adequate approach to pain[67]. Thus, simple analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) may be insufficient, with opioids, antidepressants, and anticonvulsants being required for an adequate pain control[26,67]. Topical lidocaine can also be useful[25], and the topical application of cannabis is a promising alternative[68]. The use of NSAIDs is not recommended in the presence of an underlying IBD, as they are associated with gastrointestinal exacerbations[26].

Finally, the importance of analgesia transcends the imperative need to comfort by enabling an easier wound care and the proper application of compression therapy[1,34].

Other considerations

Various clinical conditions may coexist with PG and its treatment is important, as it can have a positive impact on disease activity. These treatments include drugs with anti-inflammatory and immunomodulatory properties that are effective in PG and underlying diseases, such as anakinra, in the context of PAPA syndrome[14,25,53,55], ustekinumab, infliximab, and other TNF-α inhibitors, in the context of IBD[1,11,14,26,38], and methotrexate, frequently used in RA[25,50]. In addition, interventions such as colectomy (in individuals with ulcerative colitis), cytapheresis (in patients with leukemia or potentially IBD), and administration of thalidomide (in cases of MDSs) may also be used[15,31,51,69-73].

In a malignant scenario, the administration of immunosuppressants must be carefully managed, limited to appropriate minimum doses, or less immunosuppressive drugs, such as methotrexate[25,31].

When there is superinfection, corroborated by positive blood cultures and increased levels of C-reactive protein in blood analysis, antibiotics have to be added and immunosuppression should be maintained, except in cases of sepsis[31].

Prognosis and impact on quality of life

PG is a chronic disease, with lesions tending to heal slowly, over several months. In addition, it can have an unpredictable clinical course[9,26,31], recurring in more than 25% of cases[37], even after a rapid and complete clinical response to initial treatment[31]. High disease severity, ulcerative and bullous variants, advanced age, associated diseases refractory to treatment, and secondary infection are associated with a poor prognosis[31], as well as the male sex, given the higher prevalence of neoplasia and hematological disorders[5,9]. The risk of

death in patients with PG is 3 times higher than in the general population[26].

PG is a debilitating condition with a very significant biopsicossocial impact that clearly compromises patients' quality of life. Painful ulcers may limit mobility and lead to difficulties in daily activities. The odor and visual impact of the lesions contribute to an overwhelming social stigma, leading to the construction of a negative body image and decreased self-esteem. States of anxiety and depression can emerge and cause changes in eating and sleeping patterns. Comorbidities amplify clinical complexity and furthers worsens quality of life. In addition, frequent medical consultations and treatments are both costly and time-consuming[1,14,26,31,74].

Conclusion

PG is a rare neutrophilic dermatosis with a challenging diagnosis and treatment. A detailed anamnesis and thorough physical examination are mandatory, including searching for signs of pathergy, extracutaneous involvement, or underlying comorbidities.

Pathergy should not exclude performing a biopsy as, despite the absence of specific histological markers, histopathology reveals a typical neutrophilic infiltrate and allows exclusion of neoplasms and infections. Other complementary tests should be considered for differential diagnosis and to search for extracutaneous involvement and systemic diseases, including IBD, RA, hematologic disorders, and neoplasms.

PG treatment is based on a multimodal approach whose main objectives are to reduce inflammation and disease activity, optimize wound healing, control pain, prevent or/treat secondary infections, and control associated comorbidities. In solitary, small, and shallow lesions, topical treatment with corticosteroids or calcineurin inhibitors, complemented by appropriate wound dressing, is usually sufficient. In multiple, larger, and deeper lesions, systemic therapy is mandatory. Corticosteroids and cyclosporine are first-line treatments, in combination in severe disease. Infliximab has the same level of evidence as the previous drugs but is usually reserved for refractory disease or in the presence of concomitant IBD. Other pharmacological agents have shown benefit but lack strong scientific evidence. Surgical treatment of PG lesions in the active phase is not advised. However, partial-thickness skin grafts have shown promising results, especially when applied after negative pressure therapy and under systemic immunosuppressants. In addition, a rehabilitation plan can optimize patients' mobility and improve their independence in activities of daily living. Patient education is also crucial, including physical activity, smoking cessation, and trauma avoidance. PG is not just a dermatological condition as it transcends the biological domain, permeating the emotional and social aspects of patients' health. Thus, psychological support could also be offered.

Finally, despite the recent advances in the therapeutic armamentarium, PG remains a potentially debilitating disease, with a threefold risk of death compared to the general population. Therefore, a more specific and effective therapeutic approach is mandatory, requiring a deeper understanding of the pathophysiological mechanisms.

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Conflicts of interest

None.

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Protection of people and animals. The authors declare that no experiments involving humans and/or animals were conducted for this research.

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