PYODERMA GANGLEROSUM – AN INTERDISCIPLINARY APPROACH TO THE DISEASE

ALEKSANDRA KAPUŚNIAK A–F
ALEKSANDRA CZACHOR C–F
GRAŻYNA WĄSIK C–F

ABSTRACT
Pyoderma gangrenosum is a rare dermatosis of unknown etiology. It is classified as being a neutrophilic dermatosis, in which there is inflammatory infiltration consisting primarily of mature polymuclear leukocytes. Its pathogenesis is multifactorial and is thought to involve neutrophilic dysfunction, inflammatory mediators in combination with a genetic predisposition for the disease. Neutrophilic infiltration is observed in new lesions, while necrosis associated with fibrosis and granulomas are seen in chronic lesions, however these findings are not pathognomonic. Pyoderma gangrenosum can occur at any age. However, it most commonly develops in young and middle-aged adults predominantly women between the second and fifth decades of life. Grossly, pyoderma gangrenosum is characterized by skin lesions in the form of rapidly spreading ulcers, with cylindrical edges and necrotic bottoms. These ulcers are painful and crusted but have undermined borders. Pyoderma gangrenosum commonly presents with the rapid development of one or more purulent ulcers with undermined borders on sites of normal or traumatized skin. Pyoderma gangrenosum is often associated with other systemic diseases such as ulcerative colitis, Crohn's disease, monoclonal gammopathies, IgG or IgA myelomas and tumors of internal organs and hematopoietic system diseases, which supports the immunological mechanisms involved in the pathogenesis of the disease. Of note, neutrophilic infiltration associated with other extracutaneous manifestations and different systemic disorders can co-exist with pyoderma gangrenosum. Despite the recent development of immune modulating drugs in the treatment of skin conditions, steroid therapy still plays a pivotal role. For patients with mild pyoderma gangrenosum, the local application of topical corticosteroids or calcineurin inhibitors can be sufficient. Systemic therapy is necessary in patients with more extensive disease. The role of surgery is controversial, as it is associated with the induction of pathergy. The clinical, histopathologic and laboratory findings in pyoderma gangrenosum are non-specific, and a diagnosis can only be made once other diagnoses have been excluded.

KEYWORDS: pyoderma gangrenosum, ulcers, neutrophilic dermatosis

BACKGROUND
Pyoderma gangrenosum is a rare disease with an incidence of 1/100,000 per year in Western European countries [1]. The disease is observed in all age groups with a peak incidence between the ages of 40 and 60, with a slight female predominance [2,3]. It is rarely found in children and infants (about 4%), in which symptoms more frequently affect the scalp and anogenital region [4,5]. The exact etiology of pyoderma gangrenosum is unknown, but it is thought to be due to immune system dysfunction. Pyoderma gangrenosum is classified as a neutrophilic dermatosis due to the presence of extensive neutrophilic infiltrations within the skin, which subsequently leads to secondary vascular injury. Although neutrophilic infiltrations are found in the tissues affected by pyoderma gangrenosum, bacterial infection does not play a direct role in pathogenesis. Bacterial cultures from the skin lesions and blood are always negative and antibiotic therapy does not affect the course of the disease [6].

The aim of our article is to illustrate the ambiguous clinical picture and diagnostic difficulties associated
with the disease, and the multidisciplinary approach required to treat patients with pyoderma gangrenosum.

Co-existing diseases

Pyoderma gangrenosum occurs spontaneously, either as the idiopathic or primary form or as secondary to another systemic disease. In cases where pyoderma gangrenosum occurs with another disease, it may precede, parallel or follow the disease. Patients with pyoderma gangrenosum often attend multidisciplinary clinics. As pyoderma gangrenosum is a diagnosis of exclusion, before a diagnosis is made patients often have been treated with the suspicion of another disease process. Pyoderma gangrenosum often accompanies:

- Inflammatory bowel diseases such as Crohn's disease, ulcerative colitis, diverticulosis, solid tumors of the large intestine, carcinomas and peptic ulcer disease (14–30%).
- Hematological disorders such as IgA Gammopathy, Multiple myeloma, myeloid leukemia, real dysentery, malignant granuloma and lymphomas (15–28%).
- Rheumatic diseases such as rheumatoid arthritis and ankylosing spondylitis (10–20%).
- Other systemic diseases such as diabetes, hepatitis, cirrhosis, Takayasus's disease, Wegener's granulomatosis, systemic lupus erythematosus, autoimmune thyroid disease, Sweet's syndrome and Sarcoidosis [1–3,7,8].

Pyoderma gangrenosum also occurs more frequently in immunocompromised patients. With the more frequent use of immunosuppressive drugs, as well as the increase in the incidence of HIV, the incidence of pyoderma gangrenosum has also increased [7].

Pyoderma gangrenosum may occur as one of the manifestations of monogenic autoinflammatory syndromes such as: PAPA (purulent arthritis, pyoderma gangrenosum and acne syndrome), SAPHO (synovitis, acne, pustulosis, hyperostosis and osteoarthritis) or PASH (pyoderma gangrenosum, acne, acne inverted acne) [9].

Clinical picture

Pyoderma gangrenosum initially takes the form of a small lesion imitating a boil, pimple or blister, but can rapidly develop into a larger area of ulceration associated with necrosis. The lesion spreads rapidly peripherally, thus producing a large but relatively superficial area of ulceration with a swollen necrotic bottom and elevated dark red edges. These edges are usually submerged, blue or violet in color, irregular, or can be elevated in cases where fistulas are present. The bottom of the ulceration is filled with hemorrhagic secretion, partially covered by necrotic scabs, with or without granulation. Pimples are present both in the active edge and at the bottom of the ulceration [1,2]. The ulcers are sometimes preceded by inflammatory infiltration or a blistering reaction [3]. Skin lesions disappear leaving scars, these scars which result from the healing of lesions are referred to as 'sieve-like' scars as they are associated with numerous small recesses and holes [1,2]. Skin lesions are painful, often appearing on the lower limbs, mainly on the anterior surface of the lower thighs. However, they may occur on any part of the skin or mucous membranes [4]. Patients with facial lesions can often visit beauty parlors prior to seeking medical attention, therefore it is important that cosmetologists are aware of this condition and the phenomenon of pathergy. Mesotherapy and cosmetic procedures aimed at treating the skin are contraindicated, as they may intensify the disease process. According to reports, pyoderma gangrenosum can also affect organs outside of the skin and mucous membranes, and there can be associated neutrophilic infiltration of the bone, lungs, liver, pancreas, spleen, kidneys and central nervous system [10].

The course of the disease may be rapid and in untreated cases may lead to the involvement of deeper tissues, such as the muscles, vessels, nerves, fascia and bones.

The main symptom of pyoderma gangrenosum is pathergy. This altered skin reaction involves the appearance of skin lesions at the sites of minor injury. Pathergy occurs in 25% of patients with pyoderma gangrenosum. It is one of the criteria used for the diagnosis of the disease [1,2,9]. If the disease is not properly diagnosed and incorrectly treated by surgical debridement, it can lead to further peripheral disease progression [11]. Therefore, where pyoderma gangrenosum is suspected, any procedures are contraindicated, as they may adversely affect the course of the disease.

Diagnostic criteria

Larger:

- Rapidly growing, painful ulceration with features of necrosis with an irregular, violet-colored and submerged edge.
- Exclusion of other potential diagnoses.

Smaller:

- History suggesting pathergy or the presence of reticular scars.
- The presence of a disease associated with pyoderma gangrenosum.
- A rapid response to conventional treatments such as systemic steroid therapy.
- Typical histopathological picture such as neutrophilic infiltration and perivascular lymphocytic infiltration.

Recognition

2 larger criteria and 2 smaller criteria
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Clinical forms
- Blistering dysentery,
- Malignant pyoderma,
- Pyostomatitis vegetans,
- Periapical pyoderma gangrenosum,
- Postoperative skin gangrenosum,
- Genital pyoderma,
- Superficial granulomatous pyoderma,
- Pyoderma vegetans,
- Pustular pyoderma [1–3,7,8].

In pyoderma gangrenosum, patients may also report general symptoms such as; fever, malaise and joint pain. Of note, the ulcers are invariably painful [1].

Diagnostic tests
There is no clear diagnostic test to confirm a diagnosis of pyoderma gangrenosum. Neither histopathological examination nor specific laboratory tests can confirm a diagnosis, it is primarily diagnosed clinically [1]. However, the majority of authors recommend the collection of a skin segment for histopathological examination to exclude other causes of ulcers. For histopathological examination, it is recommended to take a cuticle from the edge and bottom of the ulceration [9]. In some cases, neutrophil and fiber deposits are found in superficial vessels in biopsy from the edge of the lesion. Neutrophilic inflammation with abscess formation and necrosis is often present [2]. There are no serological or hematological markers for this disease [7]. Laboratory tests performed in patients diagnosed pyoderma gangrenosum are important only in the search for possible coexisting systemic diseases.

Pyoderma gangrenosum is a chronic disease. In the idiopathic form, the course of the disease is chronic, with periods of exacerbation and remission. In the case of pyoderma gangrenosum coexisting with other diseases, its course depends on the prognosis of the underlying illness. If the underlying disease is curable, the prognosis is good, if not, the curability of the disease is much less likely.

Differential diagnostics
Differential diagnoses include; bacterial infection, gangrenous atypical mycosis, systemic mycoses, arthritic conditions, subcutaneous tissue inflammation, pemphigus erythematosus, self-inflicted injuries, Sweet’s syndrome, Behcet’s disease, Churg-Strauss syndrome, inverted acne, leukoclastic vasculitis, Wegener’s syndrome, insect bites, leishmaniasis, amoebiasis and cancer [12].

Patient with pyoderma gangrenosum should be adequately cared for and the examinations necessary for differential diagnostics should be performed. The diagnosis of pyoderma gangrenosum often requires dermatologist expertise, however, doctors of various specialties are often involved in the search for possible coexisting diseases.

Treatment of Pyoderma Gangrenosum
Treatment of skin lesions may be topical or systemic, depending on the severity of pyoderma gangrenosum that is the extent and depth of skin lesions, the rate of appearance of new lesions and the general condition of the patient [4]. It is often necessary to use both forms of treatment simultaneously. Corticosteroids or cyclosporine are used as first choice drugs in systemic treatment. If steroids and cyclosporine are ineffective, biological drugs are used such as; infliximab, adalimumab, etanercept, alefacept and ustekinumab. Additional drugs that may be used include; sulfones, sulfasalazine, antibiotics, mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, chlorambucil, thalidomide, intravenous immunoglobulins, as well as NSAIDs and opioids for pain [1,2,13–15]. In terms of local treatment, patients require careful wound management and dressing by specialist nurses. Surgical interventions should be discontinued, as both the surgical treatment of wounds and the location of skin grafts may result in failure or even deterioration due to the process of pathergy [1]. According to some authors, pyoderma gangrenosum patients who take immunosuppressive medications should not develop pathergy during surgical wound cleaning [16]. Topical treatments include; corticosteroids, calcineurine derivatives, hydrogel dressings, antiseptics and hyperbaric oxygen therapy [1–3,13,15,17–19].

Conclusions
Pyoderma gangrenosum remains a challenge for modern medicine due to its poorly understood etiology and pathogenesis, its variable clinical picture and a lack of useful diagnostic tests. A strong understanding of this condition, an awareness of the phenomenon of pathergy and a knowledge of potential treatment modalities is key to optimizing care in patients with pyoderma gangrenosum. An interdisciplinary approach will result in the avoidance of errors, appropriate wound management and better outcomes for patients with the disease.

References: