

Pyoderma gangrenosum – one of the causes of lower limb ulcers

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Abstract Pyoderma gangrenosum (PG) is a skin disorder with formation of ulcers which develop spontaneously as a result of even a minor trauma. The lesions are usually located within the lower limbs, especially the legs. The aetiopathogenesis has not been clarified but excessive activation of neutrophils is known to play the key role in the pathomechanism of development of the lesions. Pyoderma gangrenosum is often associated with other diseases such as inflammatory bowel disease, rheumatoid arthritis or haematological malignancies. Thus, PG is an important marker of systemic diseases and allows early diagnosis and initiation of causative treatment. The particularity of PG ulcers is their good therapeutic responsiveness to corticosteroids.

Key words leg ulcers • pyoderma gangrenosum

Introduction

Pyoderma gangrenosum (PG) is a rare skin disorder the aetiology of which has not been fully explained. Ulcers which develop suddenly, as a result of the pathergy phenomenon (pathological lesion development at the site of a trauma), are characteristic for the course of PG. This disease was described for the first time by Brunsting et al., in 1930 [5]. Although its name may erroneously suggest a correlation with a bacterial infection, it is still used today. Numerous reports describe the ever wider spectrum of systemic diseases coexisting with pyoderma gangrenosum (Table 1) [2, 3, 6, 9, 18–20, 27, 28]. In view of the predominating role of neutrophils in the pathomechanism of disease lesions, pyoderma gangrenosum was included in the class of neutrophil dermatoses [12].

Pyoderma gangrenosum is a disease which affects mainly adults. It has equal incidence in women and men, most commonly between the fourth and sixth decades of life [9]. According to most authors, in approximately 50% of patients the underlying disease can be found [3, 12, 22]. Often the first symptom is pyoderma gangrenosum, which allows early diagnosis and thus implementation of causative treatment, targeted on the underlying disease.

Table 1. Diseases coexisting with pyoderma gangrenosum (according to Sobjanek et al. [27]).

Inflammatory bowel diseases and gastrointestinal tract diseases	Crohn's disease Ulcerative colitis Diverticulitis Solid tumours of colon Carcinoid syndrome Peptic ulcers
Rheumatologic diseases	Rheumatoid arthritis Psoriatic arthritis Seronegative arthritis Spondylitis Systemic lupus erythematosus Complement deficiency
Haematologic diseases	Aplastic anaemia Monoclonal gammopathy (IgA, IgG) Myeloma Polycythaemia vera Hodgkin's disease Myelofibrosis Paroxysmal nocturnal haemoglobinuria Leukaemia Lymphoma Fanconi's anaemia
Others	Solid tumours of adrenals, bladder, ovaries, lung, breast Acne inversa Acne conglobata PAPA syndrome Hepatitis C Primary biliary cirrhosis Sarcoidosis Hyperthyreosis Erythema elevatum et diutinum Haemoglobinaemia HIV infections Antiphospholipid-antibody syndrome Sweet's syndrome Wegener's granulomatosis Katagener's syndrome Behçet's syndrome Diabetes mellitus

Aetiopathogenesis

Despite numerous studies, the aetiology of pyoderma gangrenosum has not been fully explained. Yet, its frequent coexistence with diseases with documented immunological causes (ulcerative colitis, Crohn's disease, gammopathy or rheumatoid arthritis) may suggest an immunological background. The predominating view of many authors assumes the leading role of immune system dysfunction in the pathomechanism of pyoderma gangrenosum [9, 12]. Particular importance is attributed to abnormal cellular response. It is manifested by defective chemotaxis and hyper-reactivity of neutrophils and monocytes [12, 27]. Focal neutrophil activation – spontaneous or in the pathergy mechanism – results in damaging of the infiltrated tissue [12]. In patients with pyoderma

gangrenosum, hyper secretion of tumour necrosis factor (TNF α) has been found, similarly as in patients with ulcerative colitis [24], which may suggest pathogenetic similarity of both disorders. In some patients with pyoderma gangrenosum, anergy to bacterial and/or fungal antigens has been detected. Cases of coexistence of pyoderma gangrenosum with hyperimmunoglobulinaemia E have been described [9]. The wide spectrum of immune disorders suggests that these are symptoms developing in the course of the disease and not directly related to it (*epiphenomena*) [3].

Clinical picture

Skin lesions appear as deep, rapidly enlarging ulcers with a necrotic bed and elevated undermined edges. Blue-red coloration of the edges is preceded by the inflammatory reaction manifested as an erythematic halo at the periphery of the lesion. The ulcer always develops from the primary eruption, i.e. from a pustule or inflammatory nodule. Evolution of lesions is very rapid, and the time passing between the appearance of the first symptoms and development of the characteristic clinical picture ranges from several days to around two weeks. The course of the disease may be fulminant and in untreated cases muscles, fascias, and even bones may be exposed [3]. Necrosis does not progress in accordance with a specific anatomical pattern but follows the developing thrombotic lesions in the rich network of arterial and venous capillaries of the skin and subcutaneous tissue [3, 19]. Several clinical variants of pyoderma gangrenosum are known (Table 2).

Table 2. Clinical and histopathological variants of pyoderma gangrenosum (classification after Crowson et al. [9]).

Variant	Clinical features	Histopathological findings	Coexisting diseases
Ulcerative (classic)	Usually affects lower limbs. Extensive ulcers with a purple inflammatory halo	Tissue destruction with neutrophil infiltrations. Undermined ulcers	Inflammatory bowel disease (IBD) more often than haematological malignancies
Proliferating	Chronic painless ulcers without the presence of an inflammatory halo, slow evolution	Marked tissue neutrophilia with epidermal undermining	Usually without coexisting diseases
Pustular	Numerous 2–5 mm pustules on the trunk and extremities, often symmetrical	Marked tissue neutrophilia with less undermining	Inflammatory bowel disease, mucosal infections
Bullous	Frequent location on shoulders and face. Clinically similar to Sweet's syndrome. Very rapid evolution of the lesions associated with haematological malignancies.	Epidermal necrosis. Undermined ulcers. Tissue destruction with neutrophil infiltrations	Haematological malignancies more often than inflammatory bowel disease (IBD)

Vesiculo-pustular	Coexisting or overlapping vesicular or pustular eruptions. On the trunk and extremities	Epidermal necrosis with sub-epidermal blisters. Tissue destruction with neutrophil infiltrations	Autoimmune hepatic diseases, infectious hepatitis, inflammatory bowel disease
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Pathological lesions may appear in any area of the body, but the most classic location is lower limbs, where as much as 60% of the cases are located on the legs [27]. In children often buttocks, head and neck are affected [9]. Head and neck lesions in some patients are typical of the malignant form of pyoderma gangrenosum, with a severe and frequently fatal course [3, 9].

The lesions may develop de novo within the apparently healthy skin, without participation of any initiating factors, although their development after a trauma is most characteristic. Skin ulcers are sometimes provoked by a surgical procedure such as, for example, pacemaker implantation [13] or caesarean section [1].

Lower limbs are the main location of the ulcerative variant of pyoderma gangrenosum [16, 22]. The age range of typical patients with this variant is between 25 and 50 years. The patients often report to vascular surgeons with a single extensive leg ulcer with blue-purple edges (Fig. 1A). Differential diagnostics include infections (tuberculosis, deep mycosis, syphilis, and skin amoebiasis), various forms of vasculitis, and ulcers with underlying venous insufficiency. Pathological lesions may cover extensive areas, they appear within healthy skin, are very painful, with wound secretion initially sterile in cultures, and secondarily bloody-purulent or serious-purulent (Fig. 2). The pustular variant of pyoderma gangrenosum may be associated with fever, arthralgia and often with inflammatory bowel disease [17].

Sometimes, in patients with venous insufficiency symptoms, the lesions resemble varicose ulcers, which makes the diagnosis difficult for less experienced physicians. Such lesions are also occasionally mistreated with numerous surgical interventions, repeated surgical cleaning of the wound surface and many months of antibiotic therapy targeted at the bacteria cultivated in the material from the ulcers. Upon initiation of corticosteroids, the ulcer healing process commences. The treatment takes months. As a result of proper treatment, ulcers heal, most often leaving atrophic scars (Fig. 1B-C).

Physical examination of patients often does not detect any abnormalities in internal organs. Usually, the overall clinical condition of the patients is good, and the only sign is severe pain from the ulcers. In approximately 40% of the cases, vasculitis symptoms develop (Fig. 3). In these patients, serum antineutrophil antibodies p-ANCA and c-ANCA are detected [3].

The pathergy symptom is typical of this dermatosis and is a very valuable marker helpful in posing the diagnosis. It is worth emphasising that no specific markers of pyoderma gangrenosum exist. The diagnosis of this dermatosis is mainly based on the clinical picture, typical history and, to a lower extent, on the histopathological examination which excludes other causes of pathological lesions. The lesions may be associated with pain of often large joints (elbows, knees) and asthenia [3]. In some patients pyoderma gangrenosum may coexist with or precede the appearance of acute or chronic myeloid leukaemia, myeloma, mainly of the IgA type, but also of the IgG and IgM types, and other haematological disorders as well as malignancies of abdominal organs [2, 3, 7, 9, 20, 27].

Pyoderma gangrenosum appears also secondarily to a congenital or acquired immunity disorder – congenital hypogammaglobulinaemia, infections due to HIV or HTLV-III [26],

and also as an iatrogenic disorder – in patients receiving interferon α -2b, thymosine kinase inhibitors or macrophage colony-stimulating factor (M-CSF) [9, 25].

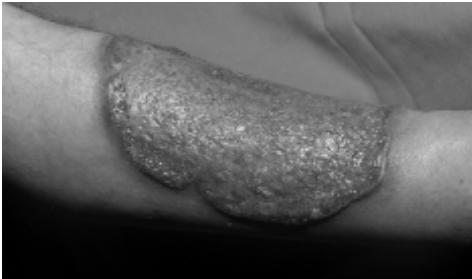


Fig. 1A. Extensive ulcer with an undermined edge typical of pyoderma gangrenosum.

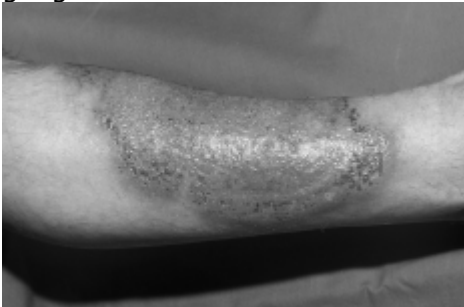


Fig. 1B. Ulcer in the same patient (Fig. 1A) after initiation of corticosteroids; epithelialisation in the central part is visible.

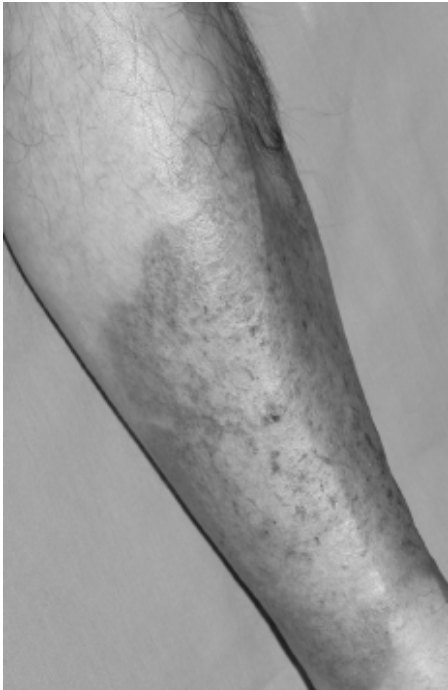


Fig. 1C. Healed ulcer; visible characteristic, filter paper-thin scar and blood vessels, showing through the trophically changed epidermis.



Fig. 2. Pyoderma gangrenosum; erosions

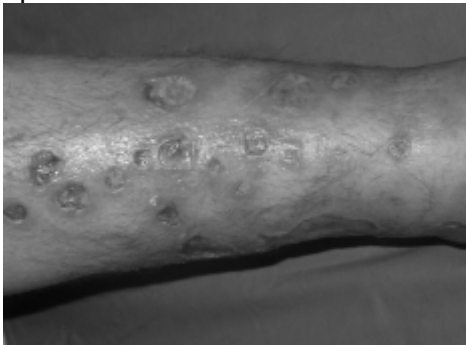


Fig. 3. Pyoderma gangrenosum; numerous

and ulcers on the inflammatory bed, with ulcers with vasculitis signs. blue-purple shade, and skin oedema.

Histopathological picture

Regardless of the clinical variant of the disease, the histopathological examination of skin biopsy shows central necrosis with inflammation. Vascular reaction resembling the Sweet's syndrome is noticeable at the periphery of the lesion. In both cases, perivascular and intraparietal lymphocytic infiltrations with marked neutrophil component at the periphery are visible (Fig. 4) [9]. In the initial phases of the disease process, features of oedema of the papillary layer of the dermis and lymphocytic infiltrations at the border between the epidermis and dermis resembling the picture seen in herpetic inflammation of the skin are sometimes found [9]. Variations of the clinical picture correlate with specific histopathological features. In the bullous variant, marked epidermal necrosis is seen, while superficial granulomatous pyoderma gangrenosum is a manifestation of intense pseudoepitheliomatous proliferation with the presence of neutrophil granulomas and plasmacytes in the epidermis and dermis. In the latter variant, another characteristic feature is also tissue eosinophilia [9].

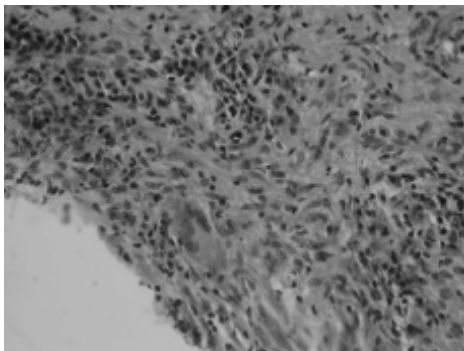


Fig. 4. Histopathological picture of pyoderma gangrenosum. Visible profuse neutrophil infiltration. Magnification 100x.

Treatment

The drugs of choice in pyoderma gangrenosum are systemic glucocorticosteroids. A particular indication for their use is in cases with fulminant course. Therapy is initiated from the dose of 0.5-1.0 mg/kg body weight of prednisone daily. The initial dose must be used until remission is obtained, and then it is gradually lowered. Another method of treatment is administration of methylprednisolone pulses (1.0 g of methylprednisolone in 150 ml 5% dextrose in intravenous infusions, within 3-5 subsequent days). The therapeutic effect of corticosteroids in pyoderma gangrenosum is associated with their immunosuppressant and anti-inflammatory actions. In prolonging therapy of a patient, all side effects of corticosteroid use should be considered. Furthermore, combinations of corticosteroids with other drugs, such as sulphones, sulfasalazine, clofazimine or immunosuppressants are used in therapy. In the class of sulphonamides, sulfasalazine, sulfapyridine and sulfamethoxypyridazine are most often used. They have been found useful in the treatment of pyoderma gangrenosum cases complicated by inflammatory bowel disease. Sulfasalazine doses start from 1-4 g daily, with the maintenance dose of 0.5-1 g daily. The mechanism of action of sulphonamides and sulphones in pyoderma gangrenosum seems to be independent from their antibacterial effect. Much less frequently clofazimine, an anti-leprotic anti-inflammatory drug is used. Clofazimine increases phagocytosis of neutrophils and macrophage function but the mechanism of its action in pyoderma gangrenosum also has not been fully investigated. Treatment with clofazimine is associated with a marked risk of side effects, the most important of which are hyperpigmentation of the skin and significant skin dryness [2, 3, 8, 11]

Beneficial therapeutic effects are also attributed to minocycline, and among other antibacterial agents – rifampicin, vancomycin and mezlocillin. These drugs may be of importance in modulating chemotactic factors for neutrophils but their mechanism of action is also unclear [8].

Among immunosuppressants, azathioprine, cyclosporine, cyclophosphamide, tacrolimus [8] and, especially in the cases resistant to corticosteroids, intravenous immunoglobulin infusions [21, 29] are used. From other drugs, Thalidomid® (used more often in Behçet`s syndrome) and potassium iodide have been used. Some centres recommend the use of hyperbaric chambers [8].

The most recent treatment includes the use of monoclonal antibodies active against TNF (infliximab) and other biological drugs, such as adalimumab, in the treatment of neutrophil diseases, including idiopathic pyoderma gangrenosum or pyoderma gangrenosum coexisting with gastrointestinal disorders [4, 10, 14, 24].

External treatment is of adjunctive importance, but appropriate care of the ulcers, with disinfection and topical application of corticosteroids, plays an important role. Some reports have been published on effective treatment of pyoderma gangrenosum with calcineurin inhibitors (tacrolimus) in ointment [3, 8, 23].

Summary

In summary, the importance of the idiopathic neutrophil dermatosis which is pyoderma gangrenosum should be emphasised. This rare disorder may cause leg ulcers and often raises diagnostic doubts, and the name itself, which is rather outdated, is sometimes erroneously associated with bacterial diseases. The diagnosis of pyoderma gangrenosum is determined by the clinical progression and histopathological picture which allows exclusion of other pathologies (infectious or proliferative). In every other case this nosological entity is associated with various systemic disorders which interfere with make treatment difficult. The most common of these disorders are arthritis, bowel inflammation, haematological malignancies, monoclonal gammopathy and paraproteinemia, usually IgA. In uncomplicated cases, corticosteroids constitute reference treatment. The authors are of opinion that multidisciplinary treatment should be used in pyoderma gangrenosum.

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