Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.52.008288

# Pain, Chronic Wounds and Pyoderma Gangrenosum – Case Report and Review

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**ARTICLE INFO**

**Received:** August 28, 2023

**Published:** September 05, 2023

**Citation:** Tímea Hevér. Pain, Chronic Wounds and Pyoderma Gangrenosum – Case Report and Review. Biomed J Sci & Tech Res 52(4)-2023. BJSTR. MS.ID.008288.

**ABSTRACT**

Pyoderma gangrenosum (PG) is a rare, non-infectious, autoinflammatory neutrophilic, rapidly progressive, ulcerative skin disease that is not easily diagnosed. The article presents one case and summarizes the knowledge about pyoderma gangrenosum. A 66-year-old man with lower extremity ulcers had many comorbidities, e.g. hip wear requiring opiate analgesics. For a year, his leg ulcers, which were judged to be caused by atherosclerosis, were treated by the local dermatologist. Improvement was visible, but new ulcers appeared, that's why he turned to us. After a thorough examination, we recommended nutrients, physical vascular therapy, and changes of dressings. The patient and his wife were educated, we recommended dressing changes at home. One month later the expected improvement did not start. Therefore, we continued the treatment with weekly dressing changes performed by professional staff. After some improvement, the condition of the wounds worsened. The possibility of pyoderma gangrenosum was raised. Histology confirmed the assumption, but due to the increase in complaints, we started steroid treatment at the same time as the sampling. The treatment proved effective, and the extent of the wounds gradually decreased. In summary, if the wound progresses despite the optimized treatment conditions or does not show a healing tendency, it is necessary to think about what other reasons could be behind it. An ulcer formed from newly appearing blisters raises the possibility of pyoderma gangrenosum.

**Keywords:** Chronic Wounds; Pyoderma Gangrenosum; Complex Treatment; Newly Appearing Bullae; Histology; Steroid; Cyclosporine

**Abbreviations:** PG: Pyoderma Gangrenosum; IBD: Inflammatory Bowel Disease; PA: Pyogenic Arthristis; MMF: Mycophenolate Mofetil; TNF: Tumour Necrosis Factor; IL: Interleukin

**Key Messages:** The circumstances of the development of non-healing, suddenly progressive wounds can help in finding the diseases. This paper presents a case and summarizes the knowledge about pyoderma gangrenosum.

## Introduction

Pyoderma gangrenosum (PG) is a rare, non-infectious inflammatory skin disease classified within the group of neutrophilic dermatoses and clinically characterized by painful, rapidly evolving cutaneous ulcers with undermined, irregular, erythematous-violaceous edges [1-3]. Early detection and appropriate treatment of the disease is a serious challenge.

## Case Report

The history of the 66-year-old man includes several diseases, such as tonsillectomy, appendectomy, skull surgery, left hip surgery, surgery for right shoulder arthrosis, varicose vein surgery on both lower limbs, right knee prosthesis surgery, diabetes, atrial fibrillation, coronary angiography, left tibial anterior percutaneous transluminal angioplasty. He was awaiting prosthesis implantation due to left hip wear. Because of the pain he required opiate painkillers. The operation prerequisited defocalization. A year earlier on both lower limb ulcers developed, which were judged to be caused by atherosclerosis. Ulcers were treated by the local dermatologist. Based on the wife's photo documentation, an improving trend was visible, but blisters and new ulcers appeared on her legs, that's why he turned to us.

During a thorough physical examination of the patient, both femoral arteries and the right tibial anterior artery were palpable, the other peripheral vessels were not palpable. Both legs were tight, edematous, and hyperpigmented Doppler index was 0.8 at the right anterior tibial artery, 0.9 at the right posterior tibial artery, 1.0 at the left anterior tibial artery, 0.9 at the left posterior tibial artery. On the front surface of the middle-lower third of the right leg, a 4x3x0.5 cm partly plaque-like, partly granulating ulcer was with a straight edge. On the dorsal part of the left foot, there was a 9x4x0.2cm ulcer with an irregular shape, a concave edge, and covered with a yellow plaque. Under the left outer leg, there was a 2.5x2.5x0.2cm ulcer with an irregular shape, a concave edge, and covered with a yellow plaque. There was a 2.5x1.5x0.2cm plaque-based, macerated wound with a threaded edge at the border of the dorsal middle-lower third of the left leg. Finally, numerous plaque-based wounds scattered medially were visible on the left leg. On both legs, traces of purple dye remained in places after the dermatological treatments.

We performed a thorough debridement (as much as the pain allowed) and cleaning of the wounds area on both legs. We applied after wound disinfection and the use of hemoglobin spray and care of the wound area, an antimicrobial gelling fiber dressing, a hydrofiber bandage and a compression bandage. We recommended for the patient nutrients, physical vascular therapy six times per day, and changes of dressings. Due to the distance of several hours between the patient's home and the hospital, we trained the patient and his wife to bandage at home. However, at the one-month follow-up, the expected improvement based on the therapy did not start. Therefore, in consultation with the patient, we continued the treatment on a weekly basis, with a dressing change performed by a specialist.

One month later, Pseudomonas infection developed on the ulcer on the dorsal part of the foot, which disappeared with the application of a silver-containing bandage and boric acid powder. During that month, the depth and outer size of the wounds gradually decreased, but new blisters and growing wounds with reddish wound border appeared on the left leg. At that time, it came up that we should also conduct tests in the direction of another disease, pyoderma gangraenosum. Histology confirmed the assumption, but due to the increase in pain, we started steroid treatment (metilprednisolon 1 mg/kg/day) at the same time as the sample was taken. The treatment proved to be effective already one week after the beginning of the treatment. In the coming month, the size of the wounds gradually decreased in diameter and depth. Granulation and desquamation of the wounds have started. However, the patient's pre-existing stomach problem worsened while taking the stomach acid-reducing medication. Gastroscopy confirmed Helicobacter pylori infection.

Due to further deterioration and difficulty swallowing, he was referred to internal medicine. Here, inflammation affecting the lower third of the esophagus and multiple stomach ulcers were confirmed. The steroid treatment was stopped immediately, afterwards the condition of the already partially exfoliated wounds deteriorated rapidly, and the size of the wounds increased again. The patient died suddenly 10 days after hospitalization.

## Discussion

Complex and customized treatment must be used in the treatment of chronic wounds. Important factor is to get supplement of trace elements and protein with different types of nutrients, to use physical vascular therapy six times per day, and use special dressings and the treatment of the underlying disease. At this patient we used Granudacyn® disinfectant, Granulox® spray, Exufiber AG® and Aquacel AG Foam® dressings. We found that the condition of the wounds did not improve, and even new wounds appeared. There was no suspicion of a tumor, but there was the possibility of pyoderma gangraenosum, which was also confirmed by histology.

The annual incidence of PG is low, approximately 0.63 per 100.000. [4] PG usually affects middle-aged adults, and literature data is divided in terms of gender prevalence. At the same time, Xu et al. found a double female dominance among the cases they examined. [5] Its development is based on a genetic predisposition and, most often, an abnormal immune response with or without previous trauma (injury or surgery, a phenomenon known as 'pathergy'). [2] In 50–80% of cases, PG is associated with a systemic underlying disease, most commonly inflammatory bowel disease (IBD), hematologic disorders, solid organ malignancy, and inflammatory arthritis. [6] Autoimmune diseases and medications prescribed as treatments, such as propylthiouracil, tyrosine kinase inhibitors, TNFα inhibitors, and granulocyte-colony-stimulating factor, are common triggers. [7] We know PG associated syndromes as PG with cystic acne and hidradenitis suppurativa (PASH), [8] PG with pyogenic arthritis and acne (PAPA), [9] and PG with pyogenic arthritis, acne and hidradenitis suppurativa (PAPASH) [10].

Its histological picture is not characteristic. Early lesions show dermal neutrophilia, and severe skin lesions show tissue necrosis and surrounding mononuclear infiltration. The pathophysiology of PG is unclear however Braun-Falco M. et al. and Flora A. et al. found that neutrophils play a key role in the disease process [8,11]. Upregulation of a number of key proinflammatory and neutrophil chemotactic factors within lesional skin have been identified and these include IL-1β, IL-17, TNFα, IL-8, IL-6, IL-17 and IL-23. These factors result neutrophil-mediated autoinflammation [12].

PG is not well understood and not recognized during routine clinical practice. Symptoms of PG are very painful skin ulcers mostly on the lower extremities. We know different types of PG, like the classic ulcerative type (approximately 85%), bullous, vegetative, pustular, peristomal, superficial granulomatous variants and as rarity the malignant [13] pyoderma. The initial stage of classical PG presents with erythematous papules or pustules that rapidly develop into painful skin ulcers or multiple ulcers with gray borders and violaceous ery-

thema. Entering the chronic stage, large wounds may appear without characteristic signs, which makes the diagnosis even more challenging [1].

Three diagnostic criteria have been proposed: the Su and Delphi consensus, and the PARACELSUS score but the PARACELSUS score has shown the highest sensitivity among comparative studies. [14,15] At our patient according to PARACELSUS criteria we found progressive course of disease, absence of relevant differential diagnoses, reddish-violaceous wound border as three major criteria, amelioration due to immunosuppressant, extreme pain >4 (visual analog scale for pain, at our patient 8-9) as two minor criteria and more than the expected one additional criteria, as suppurative inflammation in histopathology and associated systemic disease.

Gold standard treatment is not available because of the disease's systemic characteristic and the unpredictability of the clinical course. Local or intralesional immunosuppressants can be used to treat small PG ulcers (≤4 $cm^2$) that do not affect deep structures (e.g. muscle/tendon). Most commonly corticosteroids (e.g. clobetasol) and calcineurin antagonists (tacrolimus available as an ointment and pimecrolimus as a cream) are used locally. As intra-lesional steroid injection (mostly in peristomal PG) triamcinolone is recommended because it is relatively insoluble. At the first time around the edge of the ulcer 1 ml of 40 mg/ml triamcinolone recommended, then every 4 weeks 2 ml of 10 mg/ml.

The addition of systemic treatment should be considered if progress is lacking after 2–4 weeks of therapy. Corticosteroid is one of the systemic immunsupressants, which recommended dosage is 0.5–1 mg/kg/day and its dose can be tapered usually within 6 months. [16] Pulse therapy with 1 g of intravenous methylprednisolone for 3-5 days may be considered in refractory cases [17]. Cyclosporine is the other one systemic immunsupressants, which recommended dosage is 4 mg/kg/day. The use of prednisolone is recommended in the presence of kidney failure, malignancy and hypertension, while the use of ciclosporin is recommended in patients with obesity, diabetes, osteoporosis, peptic ulcer disease or mental illness. [18] Another immunosuppressive drug is mycophenolate mofetil (MMF).

Classical immunomodulation drugs are dapson and intravenous immunoglobulin (0.5-2.0 g/kg). Biologic treatment includes Tumour Necrosis Factor (TNF)-α Inhibitors (e.g. infliximab, adalimumab), Interleukin (IL)-23 Inhibitor (ustekinumab), IL-1 Inhibitors (anakinra, canakinumab), IL-17 Inhibitors (secukinumab, brodalumab, ixekizumab), Complement Factor C5a Inhibitor (vilobelimab, recommended dose is 2400 mg intravenous biweekly). However, IL-17 Inhibitors were observed to induce PG, possibly due to paradoxical upregulation of IL-23 [16].

Special attention should be paid to the wound management of PG. Surgical debridement may not be performed. An atraumatic alternative is maggot therapy, either autolytic (eg hydrogel) or enzymatic (eg collagenase) therapy. [19] Due to systemic immunosuppression, the use of antimicrobial dressings (wound preparations containing polyhexanide or silver) is recommended [20]. The bandage should be non-adhesive and hyperabsorbent. [21] On the lower extremity applied low resting pressure (20 Hgmm) compression bandage reduces edema, thereby increasing the anti-inflammatory activity. [22] Due to the pain, PG significantly limits the quality of life, [23] mental health and work ability of patients, [24] so it is important to start adequate pain relief and targeted treatment as soon as possible.

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**ISSN: 2574-1241**

DOI: 10.26717/BJSTR.2023.52.008288

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