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Pyoderma gangrenosum — the long road from diagnosis to treatment

ABSTRACT

Pyoderma gangrenosum is a rare inflammatory skin disease. It is a type of neutrophilic dermatosis characterised by painful, rapidly enlarging ulcerations. Its frequent co-occurrence with diseases such as inflammatory bowel disease or rheumatic disorders, including psoriatic arthritis, is noteworthy. Using the patient's case and the available literature, we show that the diagnosis and treatment of pyoderma gangrenosum are complex and require a multi-specialist approach due to its rarity and systemic comorbidities. New diagnostic criteria and developed treatment algorithms may facilitate diagnosis and shorten the time to introduce effective treatment, including biological therapy, and current research on PG appears promising.

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KEY WORDS: pyoderma gangrenosum; inflammatory arthritis; psoriatic arthritis

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare inflammatory skin disease. It is a type of neutrophilic dermatosis characterised by painful, rapidly enlarging ulcerations with irregular shapes and a bluish-purple, undermined rim. The disease manifests initially as small pustules or blisters, which may develop due to trauma (pathergy).

Despite the name indicating bacterial aetiology, microbial infections are sometimes only secondary, and the disease has an immunological basis [1]. The pathogenesis of PG is complex and involves profound dysregulation of innate and acquired immunity components in genetically predisposed individuals. The inflammatory response of T helper cells and exaggerated inflammasome activation lead to a dysregulated environment with neutrophil dominance and high levels of tumour necrosis factor alpha (TNF-α) and interleukins (IL): IL-1β, IL-1α, IL-8, IL-12, IL-15, IL-17, IL-23, and IL-36 [2].

PG may be idiopathic, but it is noteworthy that it frequently co-occurs with diseases such as inflammatory bowel disease (most common), rheumatic disorders, haematological malignancies or as a component of autoinflammatory diseases: PAPA (pyogenic arthritis, pyoderma gangrenosum and acne); PASH (pyoderma gangrenosum, acne and hidradenitis suppurativa), PAPASH (pyogenic arthritis, acne, pyoderma gangrenosum and hidradenitis suppurativa) and, in a small proportion, also SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis). Isolated cases of drug-induced PG have been described.

There are four subtypes of PG: ulcerative, otherwise known as classic, which is the most common, as well as bullous, pustular and vegetative [1]. The lesions are usually single, rarely multiple. They most commonly develop on the lower extremities, but other less common sites are also possible. After successful treatment of the ulceration, the lesions resolve, leaving an atrophic cribriform scar [3].

The diagnostic criteria for classic ulcerative PG were confirmed by a consensus of international experts at Delphi in 2018 and aimed to standardise the diagnostic process (Fig. 1).

The treatment of PG is complex and combines topical wound care, immunosuppressive and immunomodulatory drugs, and biolog-

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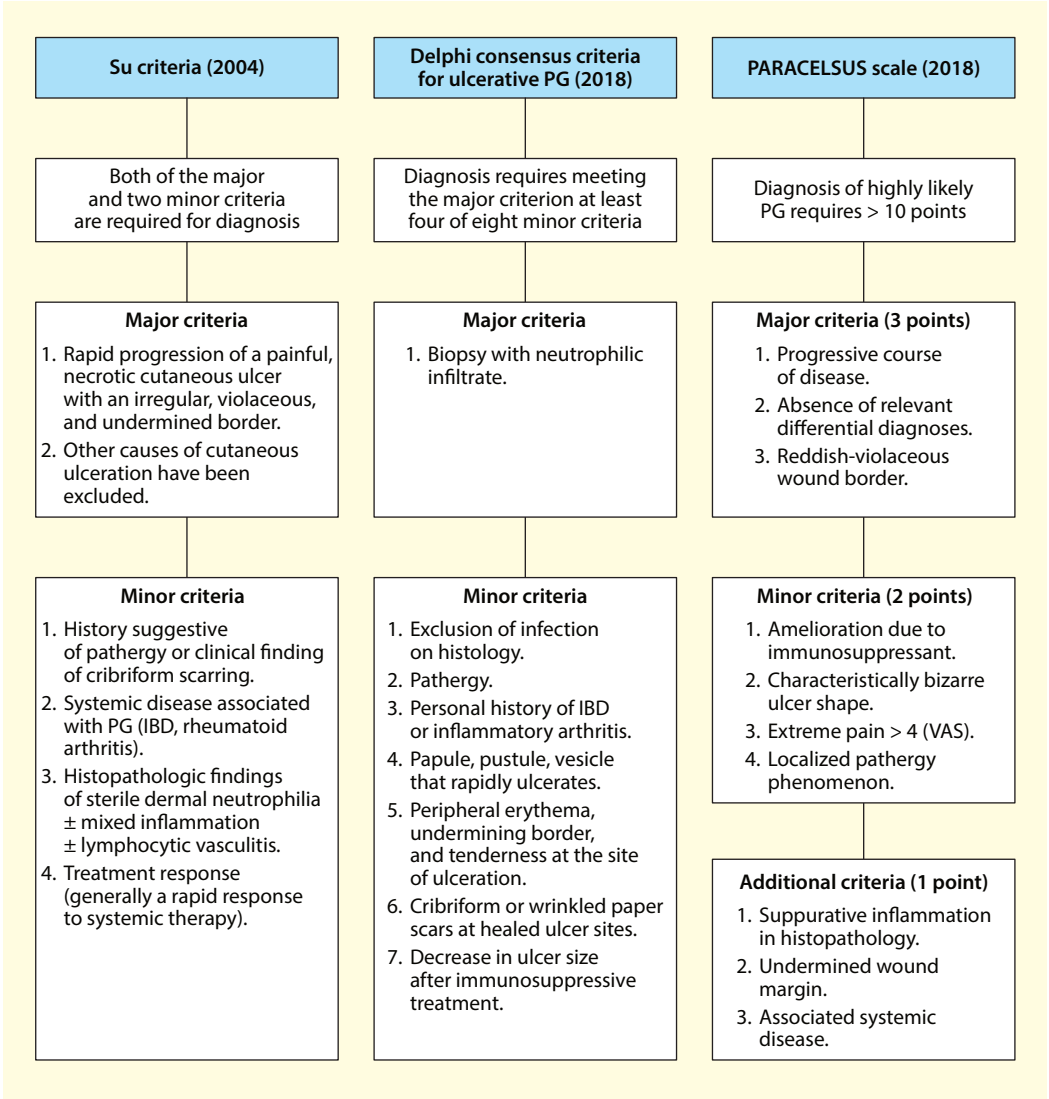

Figure 1. Comparison of three diagnostic criteria for pyoderma gangrenosum (PG). Adapted from [18] with mofifications. IBD — inflammatory bowel disease; VAS — visual analogue scale

ics. Due to pathergy, debridement should be avoided. The prognosis also depends on the proper treatment of comorbidities.

CASE REPORT

The patient, now 39, reported pain and swelling in her peripheral joints since 2007. She was initially treated with intra-articular injections and nonsteroidal anti-inflammatory drugs (NSAIDs), and after the diagnosis of psoriatic arthritis (PsA) was established in 2012, methotrexate (MTX) was included.

One year after diagnosis, the patient reported gastrointestinal complaints: abdominal pain, diarrhoea, and gastrointestinal bleeding leading to anaemia requiring blood transfusions. A colonoscopy revealed drug-induced lesions in the form of flat erosions and mucosal scarring; inflammatory bowel disease was not confirmed.

In 2014, the first skin lesions developed on the lower extremities. The patient described them as small pustules that quickly progressed to ulcers but responded well to topical treatment.

Two years later, the patient was admitted to the rheumatology department with exacerbated PsA. Due to advanced joint changes and lack of improvement despite MTX, leflunomide and steroids, cyclosporine was started, and the patient was initially qualified for biological therapy after oral treatment (advanced caries).

Over the next year, there was a significant progression of skin lesions. In 2017, a histopathological examination was performed on an ulceration of the left ankle joint area in

the dermatology department. Profilative necrotising inflammatory lesions were found, which could be related to venous insufficiency, but the picture did not exclude PG either. Initially, high doses of prednisone (40 mg/day) were initiated, cyclosporine was discontinued, and MTX was continued. Due to the persistence of hard-to-heal wounds, the diagnosis was reviewed, and topical treatment, as in venous insufficiency, was applied in the surgical outpatient clinic, gradually reducing immunosuppressive treatment. She suffered a recurrence of abdominal pain and diarrhoea, which was accompanied by persistently active arthritis secondary to PsA. Outpatient sulphasalazine therapy was initiated.

In 2019, the patient was again hospitalised in the rheumatology department, where she was admitted with fever, arthritis hindering mobility and high inflammatory parameters [C-reactive protein (CRP) — 262 mg/L; erythrocyte sedimentation rate (ESR) — 118 mm) with normal procalcitonin (PCT — 0.22 ng/mL), iron-deficiency anaemia [haemoglobin (Hb) — 7.2 g/dL], thrombocytosis (684 G/L). The patient required strong analgesics (buprenorphine) and was in a wheelchair. After a dermatological consultation, ulcers on the medial ankle and dorsum of the left foot were identified as the source of infection (*P.mirabilis* and *P.aeruginosa* cultures). Ceftazidime was started, resulting in a significant clinical improvement in the patient and a decrease in inflammatory parameters (CRP — 23 mg/L). However, the picture of the skin lesions and their course suggested an autoimmune background and a secondary bacterial infection. Therefore, it was decided to reintroduce cyclosporine and biological treatment immediately after completion of the hyperbaric oxygen therapy, which the patient did not undertake.

During the following year, the patient was hospitalised several times for latent gastrointestinal bleeding and required blood transfusions. Colonoscopy revealed features of eosinophilic colitis, which required differentiation from drug-induced damage or an autoimmune process of unspecified aetiology. Sulphasalazine and high doses of prednisolone (30 mg/day) were reintroduced.

In 2020, new ulceration developed on the right extremity, which healed after topical treatment and antibiotic therapy administered during several stays in the dermatology department. The ulcers on the left lower extremity were persistent and very painful. The patient was taking morphine.

During these years, PsA remission was not achieved. The patient developed ankylosis in the left ankle joint and both wrist joints; she also developed contractures in both elbow joints and recurrent swelling of the small joints of the hands.

In November 2021, the patient was re-qualified for biological therapy for PsA, and cyclosporine 4.6 mg/kg (300 mg/day) was again administered as the primary drug. For administrative reasons, the treatment was redirected to another centre, where, after completing the investigations necessary for the drug programme, it was decided to start infliximab therapy in June 2022.

DISCUSSION

Making a diagnosis of PG is difficult and requires a multi-specialist approach. It is often diagnosed by exclusion.

In the patient described, the diagnosis has presented many difficulties over the years due to the inconclusive histopathological findings and doubts about the vascular aetiology of the lesions. According to the new Delphi criteria, neutrophilic inflammatory infiltration on histopathological examination of a specimen from the ulcer margin is necessary to diagnose the disease. The above criteria have a sensitivity of 86% and a specificity of 90% [4]. In the patient described here, another biopsy was not attempted due to pathergy occurring in PG with a frequency of approximately 31%, which is associated with ulcer enlargement after trauma as well as surgical interventions.

The patient also did not meet the required two major criteria according to Su of 2004 (Fig. 1), where, in addition to the characteristic painful and rapidly enlarging ulceration, exclusion of other causes, such as vascular causes, is needed.

In the patient in question, the criteria proposed by a German team called the PARACELSUS score, which is designed to differentiate PG from venous insufficiency, helped establish a definitive diagnosis (Fig. 1).

The PARACELSUS score is a novel, easy-to-implement, effective and sensitive diagnostic tool for PG. The study retrospectively analysed the cases of 60 patients with previously confirmed PG in the lower extremity and a control cohort of 50 patients with venous leg ulcers, which were evaluated

by expert panels at two dermatology centres specialising in wound management. The newly developed diagnostic scoring system consists of ten criteria [5].

The three major diagnostic criteria are rapidly progressive disease, lack of a corresponding differential diagnosis and a reddish-violaceous wound margin (found in 98.3% of PG patients). Minor criteria (found in 61–95% of PG cases) include amelioration (alleviation) after immunosuppressive medication, characteristically irregular ulcer shape, extreme pain > 4/10 on the visual analogue scale and location of the lesion at the site of trauma. Three additional criteria (observed in up to 60% of PG patients) include suppurative inflammation in histopathology, undermined wound borders and concomitant systemic disease. A total score of 10 or more indicates a high probability of PG and differentiates it from venous leg ulcers. The first letters of the above criteria in the English-language version form the acronym PARACELSUS [5].

In 2021, a systematic review of papers on PG with associated inflammatory arthritis was published in Clinical Rheumatology. A total of 1,399 articles were analysed, and 129 patients with inflammatory arthritis and PG were included in the review. The most common types of arthritis were rheumatoid arthritis (RA) (50.4%), inflammatory bowel disease (IBD)-associated arthritis (10.9%) and psoriatic arthritis (PsA) (8.5%). More than two-thirds of PG cases associated with arthritis presented on the lower extremities (67.4%). In the vast majority of cases, joint symptoms preceded PG by an average of 10 years. RA and other arthritis did not differ significantly in treatment success or healing time [6].

A smaller proportion of patients experienced reduced inflammatory arthritis with the onset of PG. This is consistent with the observation indicating that PG activity is unrelated to the severity of arthritis and that the clinical course of PG does not reflect the clinical course of the associated inflammatory disease [7, 8]. Similar observations were noted in the presented case.

PG treatment can be challenging. In addition to medical therapy, wound care with appropriate dressings depending on the inflammatory and non-inflammatory phase is crucial in managing PG cases [9].

To date, most published studies on PG treatment have a low level of clinical evidence (level 3–5), i.e. retrospective case series and single case reports, with only a few controlled clinical trials. In addition, there is an unmet need for studies evaluating the treatment of refractory or recurrent PG and the optimal duration of therapy to achieve recovery. In addition, the lack of standardised outcomes hinders the comparability of clinical trials dedicated to PG [2]. Patients with PG receive an average of two systemic drugs, highlighting the importance of combination treatment regimens in real-world clinical practice [10, 11].

In 2022, the American Journal of Clinical Dermatology published an updated literature review of established and emerging pharmacological treatments for PG (Tab. 1). A therapeutic algorithm was also presented (Fig. 2) [2].

Analysing the presented patient's case and the therapies used over many years, the patient did not respond to first-line systemic PG treatment, i.e. neither cyclosporine nor prednisolone, despite well-adjusted doses.

The STOP GAP multicentre randomised controlled trial was conducted to compare prednisolone and cyclosporine. Patients received oral prednisolone at a dose of 0.75 mg/kg/day or cyclosporine at a dose of 4 mg/kg/day. The study's limitations included the possibility of misdiagnosis of PG, as the diagnostic framework for PG was not used, and the inclusion of mainly mild cases of PG. There was no difference between the two therapies regarding speed of healing at six weeks, time to healing, response to treatment, resolution of inflammation, pain, quality of life, treatment failure, and time to recurrence. It is noteworthy that almost half of the included patients receiving systemic corticosteroids or cyclosporine did not achieve healing of their PG ulcers after six months, and nearly one-third of patients in both treated groups relapsed, with a median time to relapse of 582 days in both groups. In addition, approximately two-thirds of patients in each group experienced adverse reactions [12].

In severe cases, combining systemic corticosteroids with immunosuppressive/immunomodulatory adjuvants is recommended, with cyclosporine being the most commonly used drug [13]. Such combination therapy was not performed in the patient described here, and the combination with other drugs, including MTX, was of no benefit in healing the ulceration or achieving remission of PsA.

The evidence on the use of MTX in the treatment of PG is mainly limited to isolated reports. Interestingly, a case has been

Table 1. Posology, mechanism of action, and current level of evidence for the main treatment options discussed for pyoderma gangrenosum. Reproduced without modification from: [2] available under Creative Commons Attribution-Non-Commercial 4.0 International License, http://creativecommons.org/licenses/by-nc/4.0/.

Drug	Dosage, main routes of administration and schedule[a]	Target/mechanism of action	Current level of evidence
Classical immunosuppressive and immunomodulating agents			
Corticosteroids	0.5–2 mg/kg/day *p.o.* or *i.v.*	Bind glucocorticoid-responsive elements, thereby altering transcription, with NF-κB inhibition and broad anti-inflammatory and immunosuppressant effects	1B
Cyclosporine	3–5 mg/kg/day *p.o.*	Inhibits calcineurin-NFAT pathway, thereby reducing IL-2 production and blocking lymphocyte activation	1B
Methotrexate	15–25 mg/kg/week *s.c.*	Inhibits ATIC, leading to increased adenosine release, which has immunomodulatory effects; inhibits DHFR, leading to nitric oxide synthase uncoupling and increased sensitivity of T cells to apoptosis; increases the expression of lincrNa-p21, which broadly regulates immune responses	4
Mycophenolate mofetil	2 g/day *p.o.*	Inhibits inosine monophosphate dehydrogenase, thereby blocking lymphocyte proliferation	2B
Azathioprine	1.5–2 mg/kg/day *p.o.*	Inhibits GPAT, halting purine synthesis; inhibits RAC1 and/or BCL-XL, increasing proneness to apoptosis of activated T and mononuclear cells	4
Tacrolimus	2 mg/day *p.o.*	Binds to FK506 binding protein, then inhibits calcineurin-NFAT pathway, thereby reducing IL-2 production and blocking lymphocyte activation	4
Dapsone	1.5–2 mg/kg/day *p.o.*	Inhibits the myeloperoxidase-peroxide halide-mediated cytotoxic system, dampening neutrophil respiratory burst; inhibits neutrophil migration and adhesion	2B
Colchicine	2 mg/day *p.o.*	Disrupts microtubule polymerization, thereby perturbing intracellular trafficking, inflammasome assembly, proinflammatory chemokine/cytokine secretion, cell (e.g., neutrophil) migration and division	4
Thalidomide	100–400 mg/kg/day *p.o.*	Binds cereblon, inhibiting TNF-α release and exerting complex immunomodulatory and antiangiogenic effects	4
Intravenous immunoglobulin	0.4–2 g/kg/day *i.v.*, 2–5 consecutive days infusions every month	Inhibits immune complex-mediated activation of Fc Rs; disrupts auto-reactive T-cells/APC interactions; antagonizes proinflammatory cytokines; down-regulates antibody production; reduces half-life of circulating antibodies through neonatal Fc receptor binding; blocks complement activation	3A
Granulocyte and monocyte adsorption apheresis	10 or more sessions at 5-day or 7-day intervals	Reduces circulating leukocytes	4

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Table 1. Posology, mechanism of action, and current level of evidence for the main treatment options discussed for pyoderma gangrenosum

Drug	Dosage, main routes of administration and schedule[a]	Target/mechanism of action	Current level of evidence
Biologics			
Infliximab	5–10 mg/kg/day *i.v.* on week 0, 2, 6 then every 8 weeks	TNF-α	1B
Adalimumab	80 mg/week *s.c.*, then taper to 40 mg/week and then to 40 mg every other week	TNF-α	2B
Etanercept	25–50 mg *s.c.* twice a week	TNF-α	3A
Certolizumab pegol	400 mg *s.c.* on week 0, 2, 4, then 200–400 mg *s.c.* every 2–4 weeks	TNF-α	4
Golimumab	200 mg *s.c.* on week 0, then 100 mg *s.c.* on week 2 then every 4 weeks	TNF-α	4
Anakinra	1–8 mg/kg/day *s.c.*	IL-1β	3A
Canakinumab	150–600 mg *s.c.* on week 0, (1, 2), then every 4–8 weeks	IL-1β	2B
Gevokizumab	NA	IL-1β	5
Secukinumab	300 mg *s.c.* on week 0, 1, 2, 3, 4 then every 4 weeks	IL-17A	2B
Brodalumab	210 mg *s.c.* on week 0, 1, 2 then every 2 weeks	IL-17RA	4
Ixekizumab	160 mg *s.c.* on week 0, then 80 mg *s.c.* on week 2, 4, 6, 8, 10, 12 then every 4 weeks	IL-17A/F	4
Ustekinumab	45–90 mg *s.c.* on week 0, 4 then every 8–12 weeks	Common p40 subunit of IL-12 and IL-23	3A
Guselkumab	100 mg *s.c.* on week 0, 4 then every 8 weeks	p19 subunit of IL-23	4
Risankizumab	150 mg *s.c.* on week 0, 4 then every 12 weeks	p19 subunit of IL-23	4
Vilobelimab	NA	C5a	2B
Tocilizumab	162 mg/week *s.c.*	IL-6R	4

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Table 1. Posology, mechanism of action, and current level of evidence for the main treatment options discussed for pyoderma gangrenosum

Drug	Dosage, main routes of administration and schedule[a]	Target/mechanism of action	Current level of evidence
Visilizumab	NA	CD3	4
Rituximab	1 g *i.v.* on week 0, 2	CD20	4
Vedolizumab	300 mg *i.v.* on week 0, 2, 6 then every 8 weeks	Targets $\alpha 4\beta 7$ integrin, thereby blocking lymphocyte homing	4
Small molecules			
Apremilast	30 mg twice a day	PDE4	4
Tofacitinib	10–11 mg/day	JAK1/3	4
Ruxolitinib	10 mg twice a day	JAK1/2	4
Baricitinib	4 mg/day	JAK1/2	4

APC — antigen-presenting cell; ATIC — aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase; BCL-XL — B-cell lymphoma-extra large; DHFR — dihydrofolate reductase; GPAT — glutamine-phosphoribosyl pyrophosphate amidotransferase; IL-1 — interleukin 1; IL-6R — interleukin 6 receptor; IL-12 — interleukin 12; IL-17 — interleukin 17; IL-17RA — subunit A of the IL-17 receptor; IL-23 — interleukin 23; *i.v.* — intravenous; JAK — Janus kinase; lincrNa-p21 — long intergenic non-coding rNa p21; NA — not applicable; NFAT — nuclear factor of activated T cells; NF-κB — nuclear factor kappa-light-chain-enhancer of activated B cells; PDE4 — phosphodiesterase 4; RAC1 — RAS-related C3 botulinum toxin substrate 1; *s.c.* — subcutaneous; TNF-α — tumor necrosis factor-alpha. [a]Whether in monotherapy or combined, consider tapering 2–6 months after healing is achieved

reported in which, despite the lack of response after oral MTX with systemic corticosteroids, switching to intralesional MTX injected weekly along the ulcer border led to a dramatic improvement in a patient with classic ulcerative PG, with almost complete healing by the seventh week of therapy [14].

Growing evidence supports TNF-α inhibitors as first-line drugs, especially infliximab and adalimumab [15]. They represent the best option in cases refractory to systemic corticosteroids, cyclosporine or combination therapy with both [16]. To date, infliximab remains the only anti-TNF-α drug with proven efficacy in classic PG, as demonstrated in a randomised, double-blind controlled trial [17]. Anti-TNF-α drugs can also be used as adjuvant treatment to avoid the long-term side effects of corticosteroids and/or cyclosporine [2].

The use of infliximab in the presented patient is expected to have the expected therapeutic effect, whether in relation to skin, joint, or intestinal lesions.

CONCLUSIONS

Using the presented patient's case and the available literature, it can be said that the diagnosis and treatment of PG are complex and require a multi-specialist approach due to its rarity and systemic comorbidities. New diagnostic criteria and developed treatment algorithms may facilitate diagnosis and shorten the time to introduce effective treatment, including biological therapy, and current research on PG appears promising.

ETHICS STATEMENT

This case report does not disclose the patient's personal information. The accompanying photographs protect the patient's anonymity and prevent identification.

AUTHOR CONTRIBUTIONS

K.K. — conceptualisation, assumptions, data analysis, writing the manuscript; D.S.F. — conceptualisation, assumptions.

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CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this case report.

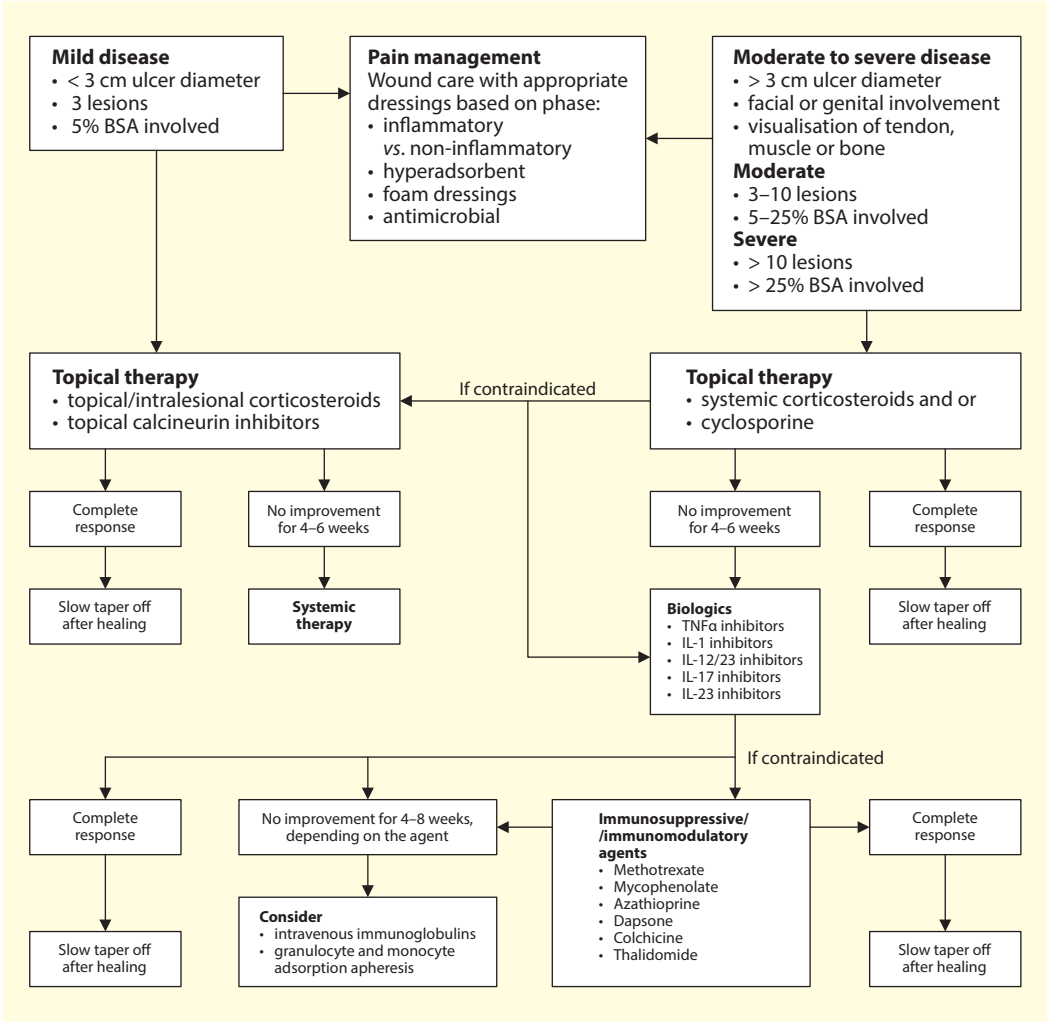

Figure 2. Proposed algorithm for the treatment of classic ulcerative pyoderma gangrenosum. Reproduced without modification from: [2] available under Creative Commons Attribution-Non-Commercial 4.0 International License, http://creativecommons.org/licenses/by-nc/4.0/. TNF-α — tumour necrosis factor alpha; IL — interleukin

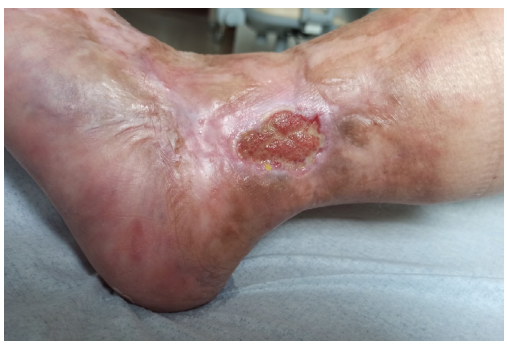

Figure 3. Ulceration of the lateral ankle region of the left ankle joint

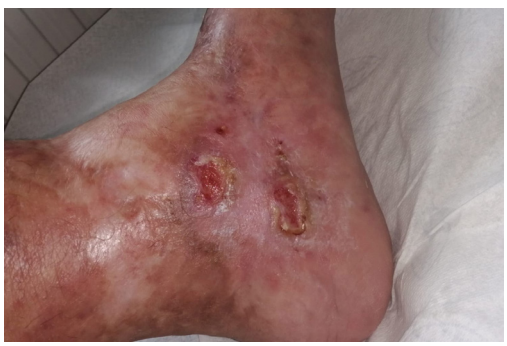

Figure 4. Ulceration of the medial ankle area of the left ankle joint

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