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Pyoderma Gangrenosum and inflammatory bowel disease: a combined medical and surgical approach – case report and literature review

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Abstract. – OBJECTIVE: Pyoderma Gangrenosum (PG) is an immune-mediated neutrophilic dermatosis, characterized by large painful ulcers occurring in various body segments. It can be associated to Inflammatory Bowel Disease (IBD) including both Ulcerative Colitis and Crohn Disease. Prompt and effective management is fundamental, due to its high morbidity and mortality rates. By presenting our clinical experience, we aimed at showing the efficacy of a combined therapeutic approach, in which the best of every specialty cooperates managing this hazardous disease.

PATIENTS AND METHODS: We report on two patients attending our outpatient clinic with ulcerative skin lesions at the level of the back. Patient 1 suffered from Crohn disease and Patient 2 presented a positive history of abdominal pain, diarrhea with mucus and blood in the stool. Histological exam was performed with final diagnosis of PG associated with IBD. A Literature review was carried out in order to highlight the role of combined clinical-surgical management of PG in adult patients with IBD.

RESULTS: Complete resolution of the lesions was achieved in 4 months and 3 months for each patient respectively without relapse. PubMed was searched from 2000 to 2020 with the following keywords: (Pyoderma) AND/OR (Pyoderma Gangrenosum) AND (Inflammatory Bowel Disease) AND/OR (Ulcerative Colitis) AND/OR (Crohn Disease) AND (Management). Seven papers were included (4 case reports, 2 case series, 1 comprehensive review) and reviewed using a descriptive checklist.

CONCLUSIONS: PG should be treated by dedicated multidisciplinary teams, in which every specialist plays a crucial role from the diagnosis to the treatment and up to the long-term follow-up.

Key Words:
Pyoderma gangrenosum, Ulcerative colitis, Crohn disease.

Introduction

As reported in Literature, in 1916, Brocq first described the "phagedenisme geometrique", a pathology that was named Pyoderma Gangrenosum (PG) by Brunsting in 1930[1]. PG is an immune-mediated neutrophilic dermatosis, characterized by large painful ulcers occurring in various body segments. The incidence is estimated to be as 2-3 cases per million inhabitants per year. Both adults and children may be affected, but it tends to occur in individuals between 30- and 50-years-old, with a slightly major prevalence among women[2,3]. Four main clinical variants of PG have been described: ulcerative, bullous, vegetative, and pustular, with

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the ulcerative form being the most common. Less common presentations include peristomal PG (PPG) and postsurgical PG (PSPG)[2]. Lower limbs are more frequently involved, although other body areas including genitals, mucous membranes as oral mucosa, and internal organs can be affected[4].

Alike the Erythema Nodosum, PG can be associated to Inflammatory Bowel Disease (IBD), representing up to 1-3% of its extraintestinal dermatological manifestations. PG may occur with both Ulcerative Colitis (UC) and Crohn Disease (CD), with similar prevalence[5,6]. Correlation between IBD activity and PG is still controversial: even if PG onset may anticipate the IBD by years, the two conditions seem to progress independently according to some studies[2,7].

Pathogenesis of PG is poorly defined, still. It is considered an auto-inflammatory disease, being characterized by a dysregulation of the innate immune system, with abnormal Th1-weighted overexpression of Interleukin (IL)-1β, IL-1α, Tumor Necrosis Factor- α (TNF α), IL-6 and IL-8[8,9].

No pathognomonic histologic feature distinguishes PG skin samples, which show sterile massive neutrophilic infiltration of the dermis. Necrosis of the epidermis without gangrenous process is generally reported[3,8].

To date, PG's diagnostic and therapeutic management indications derive from case reports/series; there is a literature lack in prospective studies and randomized controlled trials with large numbers of patients. In clinical practice, the most used diagnostic criteria are the Daniel Su criteria[10], that allow PG diagnosis in presence of one major and at least two minor criteria. According to a recent consensus[11], the histological finding of neutrophilic infiltrate at the edge of an ulcer should be considered as the single major criteria for PG diagnosis.

For what concerns treatment, several options are at disposal, from topical medications to immunosuppressants and immunomodulators[12]. Surgical intervention's benefit is debated, due to possible pathergy phenomenon[13]. Negative pressure wound therapy (NPWT) may be applied in cases of ulcers[14,15] and split-thickness or full-thickness skin grafts can be used for definitive coverage[16].

In the current paper we present our experience with the management of two selected cases of PG associated with IBD; patients were managed with a combined medical and surgical therapeutic approach, in which the best of every specialty cooperates managing this hazardous disease. Moreover, a thorough literature review was carried out focusing on PG clinical and surgical management options at disposal to date.

Patients and Methods

Case Report 1

A 37-year-old male with a 10-year history of intermittent ileo-colonic inflammatory CD presented to our unit showing round erythematous infiltrated and painful skin lesions on the back, that appeared in the previous two weeks (Figure 1). The patient was in treatment with mesalazine. In the past years, he had performed only three cycles of treatment with budesonide at a dosage of 9 mg/day and mesalazine at a dosage of 3 g/day.

The patient reported abdominal pain with 6 evacuations/day of liquid stool, and he was admitted in the Gastroenterology Department. Blood test, colonoscopy with ileoscopy and biopsy sampling, Magnetic Resonance Enterography and skin biopsy were performed. The tests confirmed the diagnosis of CD with moderate activity according to 10 sec. Harvey Bradshaw Index[17]. PG diagnosis was put in accordance with the clinical and histological Daniel Su criteria[10]. The patient received Prednisone (1 mg/kg every 24 h), Tigecycline (50 mg every 12 h), Ciprofloxacin (400

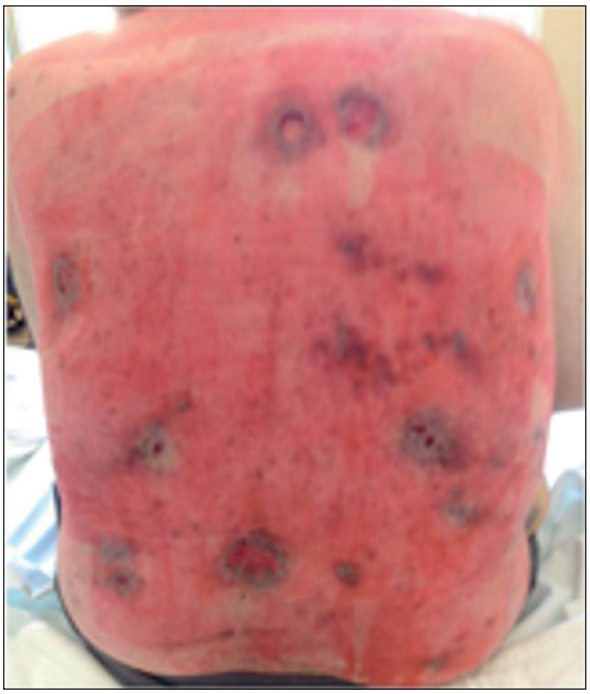

Figure 1. First presentation of case 1 patient with round erythematous infiltrated and painful skin lesions on the back.

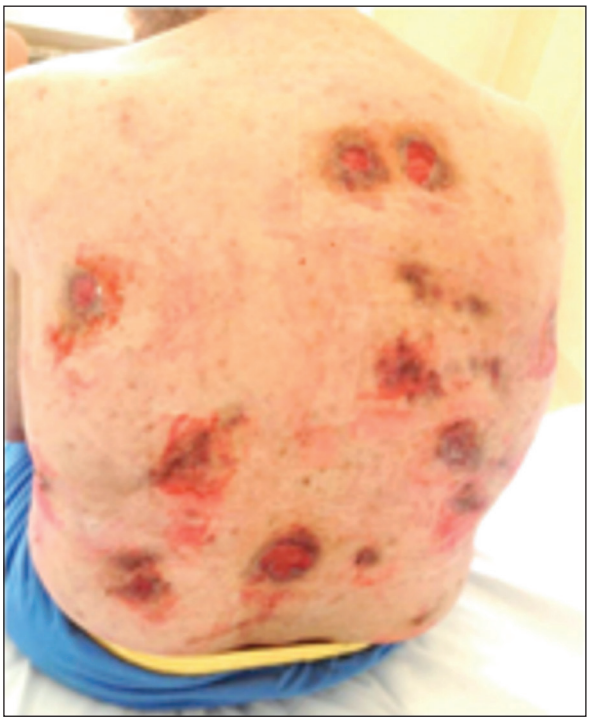

Figure 2. Case 1 patient: lesions after therapy with prednisone (1 mg/kg every 24 h), Tigecycline (50 mg every 12h), Ciprofloxacin (400 mg/8h) and Voriconazole (400 mg/12h).

mg/8 h) and Voriconazole (400 mg/12 h), achieving some clinical improvement (Figure 2).

After a voluntary discharge and 2 months of steroid taper treatment, the patient came back to the hospital for relapse of the gastrointestinal symptoms and a severe worsening of the skin ulcers (Figure 3). Anti-TNF-α (Infliximab) 5 mg/kg therapy was administered, according to following dosing schedule: at time 0, after 2 and 6 weeks and every 8 weeks following. At the 2-weeks check-up, the patient reported improvement of intestinal symptoms, but only partial benefits were observed on skin lesions. Therefore, plastic surgery evaluation was required and advanced wound dressings with carboxymethyl cellulose (AQUACEL Ag+ ™, ConvaTec Inc.), alginate gauze, antiseptic soft paraffin dressing (BACTIGRAS*, Smith+Nephew) and topical antibiotics were set up. Complete remission and re-epithelialization of the back lesions were achieved after 8 weeks of combined treatment with advanced wound dressings and Infliximab (Figure 4).

Case Report 2

A 60-year-old male came to our observation for a consistent substance loss in the right scapular region, associated with severe sleep disturbances due to nocturnal pain (Figure 5). The patient reported Diabetes Mellitus type II and arterial hypertension. He was in treatment with Metformin and Bisoprolol. For the last 6 months, before our visit, he had been suffering abdominal pain with 7-8 evacuations/day of liquid stool with mucus and blood. The patient was hospitalized in the Plastic Surgery Department. Blood test, colonoscopy, ileoscopy with biopsy sampling and skin biopsy were performed. The diagnosis of UC was carried out involving the whole colon with moderate activity (Mayo Score: 10)[18] (Figure 5). Moreover, PG diagnosis was put in accordance with the Daniel Su criteria[10].

Given the considerable size of the skin lesion (18 x 25 cm), a pedicled Latissimus dorsi muscle flap was performed to fill the gap after debridement; meshed split-thickness skin graft was applied as final coverage. Simultaneously, the patient started a treatment with Golimumab for UC, after gastroenterology consultation. The following dosing was scheduled: 200 mg at time 0, 100 mg after 2 weeks and finally 100 mg every 4

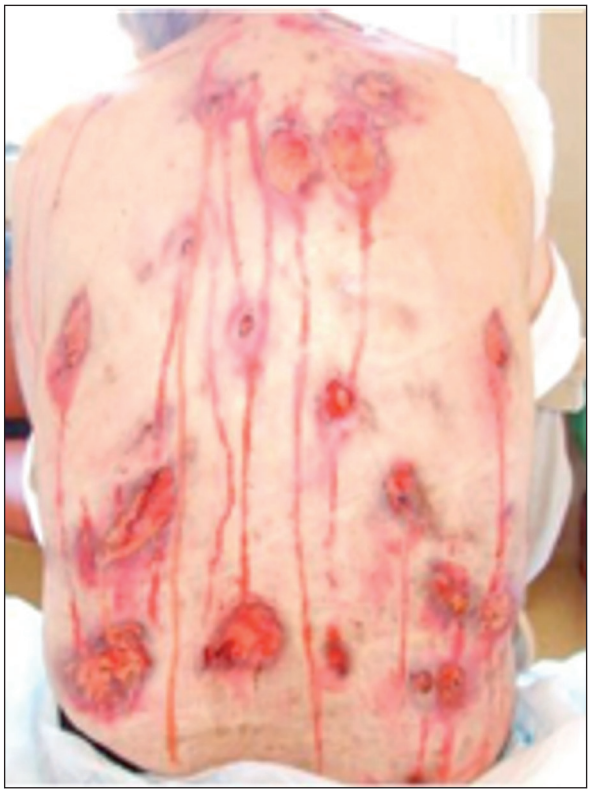

Figure 3. Severe worsening of the case 1 patient skin ulcers after 2 months of taper steroid therapy.

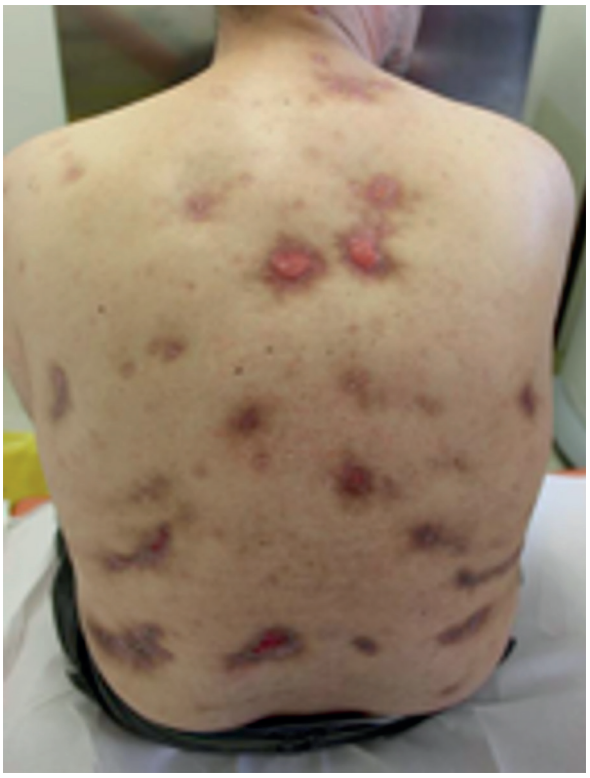

Figure 4. Complete remission and re-epithelialization of the case 1 patient back lesions was achieved after 8 weeks of combined treatment with advanced wound dressings and Infliximab.

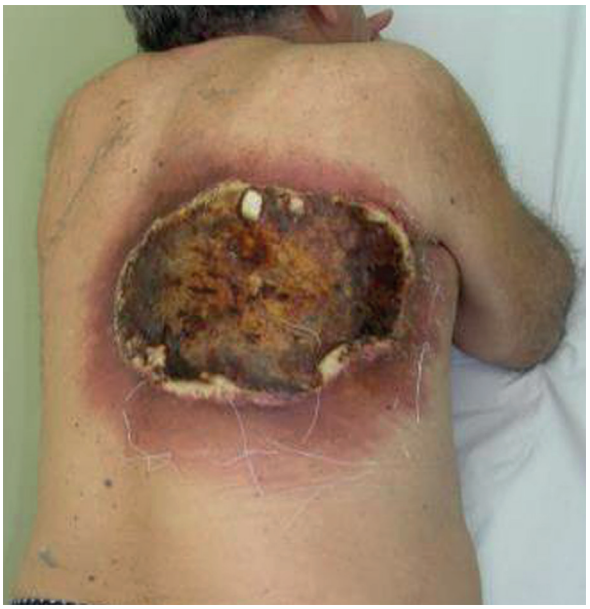

Figure 5. First presentation of case 2 patient with consistent substance loss in the right scapular region.

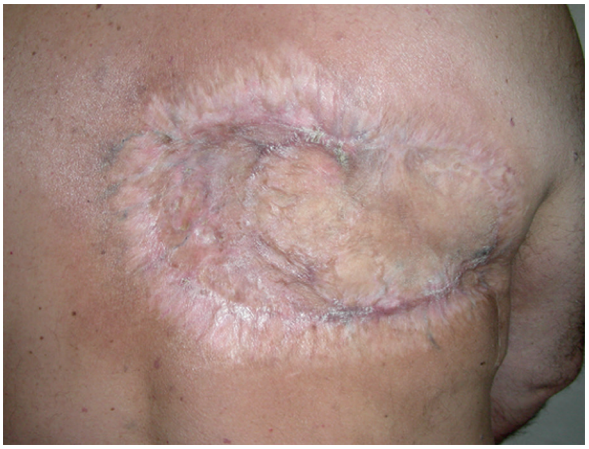

Figure 6. Complete healing of the substance loss gained after 3 months of multidisciplinary treatment with Golimumab and surgical management with debridement, reconstruction with latissimus dorsi and skin graft pedicled Latissimus dorsi muscle flap was used to fill the gap after debridement and meshed split-thickness skin graft was applied as final coverage.

weeks. After 3 months of therapy, significant improvement in intestinal symptoms was registered and complete healing of the cutaneous lesion was achieved (Figure 6).

Literature Review

A literature review from 2000 to 2020, was carried out in order to highlight the role of combined clinical-surgical management of PG in adult patients with IBD.

A search on PubMed (National Library of Medicine, NLM) database was performed with the aim of finding similar cases in the literature, focusing on clinical and surgical management options at disposal to date. We used the following PubMed keywords: (Pyoderma) AND/OR (Pyoderma Gangrenosum) AND (Inflammatory Bowel Disease) AND/OR (Ulcerative Colitis) AND/OR (Crohn Disease) AND (Management). The searches were conducted with no date or language limits. The databases were searched the inception to date forward. The reference lists of the selected papers were subsequently reviewed for additional papers. Full-text papers were retrieved according to the selected abstracts, then read and screened by the authors. Studies with pediatric, non-IBD and oncologic patients were excluded.

Results

Multidisciplinary medical and surgical approach was offered to both patients. Complete

resolution of the lesions was achieved in 4 months and 3 months for each patient respectively without relapse. PubMed was searched from 2000 to 2020 and seven papers matching our criteria were considered in this study (4 case reports[32,34-36], 2 case series[16,33] and 1 comprehensive review[37]). The included reports were reviewed using a descriptive checklist including first author, title, journal and year of publication, study design, patient characteristic, IBD, comorbidity, PG location, systemic therapy, type of surgeries and outcomes (Table I).

Discussion

Due to the rarity of PG and the poor information at disposal concerning its etiology and diagnosis, there is no validated consensus on its treatment[19]. On the other side, prompt and effective management is fundamental, as the disease is associated to high morbidity and mortality rates, being the incidence of adverse events 3 times higher than in general population[20].

In the last 20 years, the most effective therapeutic PG management has been proven to be based on immunosuppressive – immunomodulatory drugs, as steroids and calcineurin inhibitors (Cyclosporine or Tacrolimus). Either systemic or topical administration showed efficacy. Aside to these conventional treatments, anti-TNF-α efficacy has been described in IBD patients with moderate-severe PG, with low rate of adverse events[21,22]. Indeed, in 2003, a retrospective study[23] gave the major evidence to date, proving the anti-TNF-α utility in treating 13 patients with IBD and PG. Three of them underwent one Infliximab administration, the other 10 continued the medication every 4-12 weeks, according to the remission maintenance schedule. Research on anti-TNF- α kept moving forward and, in 2006, Brooklyn et al[24] published the first randomized placebo-controlled trial. In a group of 30 patients, 46% of the patients treated with Infliximab[13] at a dosage of 5 mg/kg reported remission of PG at week 2, against the 6% of the subjects treated with placebo[17].

Besides Infliximab, other monoclonal antibodies such as Golimumab[4], Adalimumab[25], Anakinra (IL-1 receptor inhibitor)[26], Ixekizumab (IL-17 inhibitor)[27], Ustekinumab (IL-12/23 inhibitor)[28], and IL-23 antibodies alone showed good clinical responses and low incidence of side effects. Besides systemic drugs, local therapy plays a crucial role in relieving PG symptoms. Advanced wound dressings with wet compresses and saline alginate dressings demonstrated their utility[29]. On the other side, some patients may present with advanced and large lesions requiring prompt and reliable coverage[30]. In such cases, surgery would apparently represent an attractive solution. Nevertheless, up to 30% of PG patients suffer from pathergy phenomenon consequent to micro-traumas, eventually[31]. For this precise reason, surgical management of PG, with debridement or skin grafts or flaps has been discouraged, with exceptions in severe cases, only when combined to adequate immunosuppressive treatment.

In the current paper, we present our experience with the management of two selected cases of PG in patients suffering from IBD. A combined clinical and surgical treatment allowed us to achieve successful outcomes in both patients, with complete PG wound healing and intestinal symptoms remission achievement. A literature review from 2000 to 2020 was carried out, in order to highlight the role of combined clinical-surgical management of PG in adult patients with IBD. Studies with pediatric, non-IBD and oncologic patients were excluded. Seven papers[16,32-36] were included in our review: there were 4 case reports[32,34-36], 2 case series[16,33] with 15 patients, and 1 comprehensive review[37] with 161 cases described. In 2008, Chia et al[32] stated that the non-simultaneous use of immunosuppressive therapy with autologous skin-graft appears to fail in PG treatment. In their case, the addition of Prednisolone (60 mg/kg/day) led to rapid lesion's improvement. In 2011, Saracino et al[33] described 16 surgeries (debridement, toe amputation, and skin grafts) performed in their series of 26 patients. All surgical procedures were performed in combination with adjuvant immunosuppressive drugs and no pathergy or flare of the disease were observed. Six months after discharge, 80% of patients showed complete healing of the lesions.

In the same year, Bisarya et al[34] pointed out the importance of proper diagnosis, in order to choose the most effective surgical treatment. In their case report, a 33-years-old patient was diagnosed with UC and suspected necrotizing fasciitis. First, he underwent surgical debridement that appeared to worsen the lesion. Only after the correct diagnosis of PG, the patient received steroid therapy and split-thickness skin graft with complete healing of the lesion, alike our case report number 2.

Few years later, Andrisani et al[35] described a case of PG ulcer complete healing in a patient

Table I. Literature review on medical and surgical management of Pyoderma Gangrenosum.

Title, authors, year of publication	Study design	Patients	IBD	Comorbidity	PG location	Systemic Therapy	Surgery	Outcomes
Pustular PG: An uncommon variant which is easily misdiagnosed. Chia et al[32]	Case Report	44-yo male	UC	ND	Left Ankle	Antibiotics; Prednisolone	Split-thickness skin graft	Rapid improvement of the lesion only after adding steroid therapy
PG requiring inpatient management: A report of 26 cases with follow up. Saracino et al[33]	Case Series	26 (17 female)	2 (7.7%) UC; 2 (7.7%) CD	ND	85% on lower limbs	all but one patient corticosteroid and/or systemic immunosuppressive 3 IBD patients IFX	13 surgical debridements, one toe amputation, one pinch graft and one split skin graft) were performed on 10 patients	Improvement of the lesion in 90 % at 1 month post discharge
Necrotizing Fasciitis Versus PG: Securing the Correct Diagnosis! A Case Report and Literature Review. Bisarya et al[34]	Case Report	33-yo male	UC	ND	Leg	Antibiotics; prednisolone (after diagnosis of PG)	Split-thickness skin graft	Rapid improvement of the lesion, after correct diagnosis
A case of PG with UC treated with combined approach: Infliximab and surgery. Andrisani et al[35]	Case report	76-yo male	UC	Arterial Hypertension; Diabetes Mellitus type 2	Left breast	Infliximab	Split thickness skin graft.	Skin lesion and intestinal symptoms significantly improved after infliximab induction; Complete healing after 6 months.
PG as a first presentation of inflammatory bowel disease. Shadid et al[36]	Case Report	22-yo female	CD	ND	Axilla and back	Antibiotics, Steroids; Azathioprine	Regular moist wound dressings	Good response with daily wound care and topical steroids Subsequently azathioprine for Crohn's disease.
Surgical treatment of PG with NPWT and STSG under adequate immunosuppression is a valuable treatment option: Case series of 15 patients. Pichler et al[16]	Case series	15 (66% female)	ND	Monoclonal gammopathy (5), Cancer (1), SLE (1), Hypertension (9), Obesity/ IGT/Diabetes (6)	Legs 15; Occipital 1	CS (15), Dapsone (8), IFX (4), MTX (2), Ptxphyll (3), Iloprost (2), IVIG (2), MMF (1), HQ (1)	Split thickness skin graft (STSG)with negative pressure wound therapy (NPWT)	NPWT followed by STSG secured by NPWT induced complete healing within 1 month after grafting in 67% (10/15) of cases; improvement of more than 90% in 4 (27%)
Surgical Treatment of PG with NPWT and STSG, Including Xenografts: Personal Experience and Comprehensive Review on 161 Cases. Eisendle et al[37]	Case series and literature review	161	ND	ND	ND	ND	Various surgical approaches: Split thickness skin graft (STSG) secured by Negative Pressure Wound Therapy (NPWT); also, xenografts (2 porcine xenodressings)	Successful treatment in 86% of cases, including xenotransplants; 10% improved; failures mainly reported without immunosuppression

Abbreviations: CD - Crohn's Disease; CS - corticosteroids; HQ - Hydroxychloroquine; IGT - Impaired glucose tolerance; IVIG - IntraVenous Immunoglobulin; MMF - Mychophenolate Mofetil; MTX - Methotrexate; ND - Not Detectable; PG - Pyoderma Gangrenosum; Ptxphyll - Pentoxyphylline; SLE - Systemic Lupus Erythematosus; UC - Ulcerative Colitis.

with UC, thanks to a combination of split-thickness skin-graft coverage and pharmacological therapy with Infliximab 5 mg/kg given at time 0, at week 2 and 6 and 8 weeks after.

In 2014, Shadid et al[36] reported a case consistent with our case report number 1. In their case, a 22-year-old patient suffering from PG and CD was treated with oral and topical steroids associated to regular moist wound dressings.

More recently, a case series by Pichler et al[16] and a comprehensive review of 161 cases by Eisendle et al[37] showed how NPWT alone and subsequent STSG secured with NPWT can lead to successful PG healing, when associated to adequate immunosuppression. The reports described above, appear consistent with our experience and previous protocols in the management of complicated chronic wounds[38-40].

PG is a rare pathology, and its natural history has not yet been fully understood. Optimal timing and procedure choices are still debated for what concerns surgical treatment. Differential diagnosis with necrotizing fasciitis, septic abscesses, pyoderma and malignant lesions is fundamental to guarantee prompt and correct management[41]. The ability to recognize PG properly, avoids unnecessary manipulations such as surgical debridement, which could worsen the pathergy phenomenon[31]. Furthermore, a correct diagnosis allows to start the immunomodulation therapy, which determines lesions' healing in an important percentage of cases[29].

PG treatment should involve topical therapy, wound care, surgery and systemic therapy, all combined together. A multidisciplinary approach is mandatory, as well as an accurate wound care is essential as it has to be tailored to the specific wound characteristics[42-44]. In PG patients, a moist wound environment is favored, as it may promote healing[45]. In cases of massive substance loss, wound healing by secondary intention can be too slow and patients may risk complications as superinfections and unsatisfactory aesthetic results. In such cases, reconstructive surgery represents an excellent solution[46,47]. As evidenced in the present literature review, split-thickness skin grafts are the method of choice, in association with systemic immunomodulatory/immunosuppressive therapy.

Further randomized controlled trials are required to better define the right immunomodulatory treatment with new biological drugs in association with surgical treatment, searching for the optimal PG management.

Conclusions

To date, PG patients' management indications are poorly defined and are based on few case reports and case series. Several therapeutic options are at disposal, including topical medications and systemic immunosuppressive drugs. To date, surgical intervention's benefits are debated. By presenting our clinical experience, we show the efficacy of a combined therapeutic approach, in which the best of every specialty cooperates managing this hazardous disease. Complex pathologies such as PG should be evaluated and treated by dedicated multidisciplinary teams, in which every specialist plays a crucial role in facing every stage of the disease.

Conflicts of Interest

The authors declare no conflicts of interest.

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Informed Consent

Obtained.

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