Dermatology Practical & Conceptual

Pyoderma Gangrenosum: A Retrospective Case Series of 44 Patients

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ABSTRACT

Introduction: Pyoderma gangrenosum (PG) poses a significant dermatological challenge due to its rapidly evolving painful necrotic ulcerations. Understanding its multifaceted pathogenesis and diverse clinical presentation is crucial for effective management.

Objectives: We aimed to analyze demographic characteristics, clinical manifestations, lesion distributions, systemic disease associations, therapeutic interventions, and patient outcomes in PG cases.

Methods: Medical records from 2017 to 2023 of PG patients at IRCCS Sant'Orsola Malpighi Hospital, Bologna, Italy, were retrospectively analyzed. Inclusion criteria encompassed persistent ulcers with clinical and histological evidence of PG, excluding cases with alternative diagnoses or inadequate follow-up. Clinical evaluations, including pain assessment and lesion measurements, were conducted at diagnosis and follow-up visits.

Results: A total of 44 patients were evaluated. Pain was a universal symptom, and tissue pathergy was documented in 28.6% of patients. Ulcerative PG was the most common subtype (88.1%). Associations with inflammatory bowel diseases (25%), rheumatoid arthritis (9.1%), and hematological diseases (17.2%) were noted. Lower limbs were frequently affected (63.6%). Treatment approaches included wound management, topical and systemic corticosteroids, and immunosuppressive therapy, with varying response rates.

Conclusion: Advanced dressing and steroid therapy were pivotal in mild PG cases, while moderate-to-severe cases often associated with systemic diseases showed incomplete healing despite treatment, especially in patients with inflammatory bowel diseases and hematological disorders. This study contributes to the understanding of PG's complexities, suggesting the use of biological therapy as first line in moderate-to-severe PG.

Introduction

Pyoderma gangrenosum (PG) is recognized as a complex dermatological challenge, manifesting as rapidly evolving painful necrotic ulcerations. Despite its misleading nomenclature, PG is acknowledged as a non-infectious neutrophilic dermatosis, with predominant skin involvement but frequently associated with systemic inflammatory conditions [1]. The pathogenesis of PG is multifaceted, implicating immune dysregulation, genetic susceptibilities, and environmental factors. The clinical manifestation of PG is diverse, often mimicking other dermatological conditions, thereby necessitating a heightened diagnostic vigilance [2-4]. The management of PG requires a collaborative approach, integrating expertise from dermatology, rheumatology, gastroenterology and often surgery [5].

Objectives

This retrospective investigation collected the demographic characteristics, clinical manifestations, lesion distributions, systemic disease associations, and therapeutic interventions of patients diagnosed with PG attending our department from 2017 to 2023. The study further aimed to assess the efficacy of treatments and patient outcomes, contributing valuable insights into the management and prognosis of PG.

Methods

Study Design

We adopted a retrospective study design, meticulously analyzing medical records from the "Ambulatorio Lesioni Aperte" at IRCCS Sant'Orsola Malpighi Hospital, Bologna, Italy, over a 6-year span. Clinical records of PG patients were reviewed by three independent researchers, ensuring the exclusion of differential diagnoses through comprehensive histological evaluations. Our inclusion criteria were persistent ulcers exceeding three months, corroborated by clinical and histological evidence of PG, and the absence of pathogenic organisms in cultures. We excluded cases lacking histopathological confirmation or those with inadequate treatment initiation or follow-up.

All patients were evaluated at diagnosis and at every follow-up visit through clinical photography. The change in lesion size was measured by taking a cast on transparent graph paper at each follow-up visit. We considered the lesions healed when there was no longer need of sequential dressing.

Our approach to comorbidities tended to exclude common ailments like diabetes, hypertension, hypercholesterolemia, and peripheral vascular disease, which are prevalent in the older population.

Data Analysis

Data are presented as mean for continuous distributed variables and as number and % for categorical variables. All the data were collected using Microsoft Excel ® (version 2403).

Results

Patient Demographics

A total of 44 patients affected by PG were evaluated. Data analysis showed the prevalence of females (54.5%, n: 24). Mean age at the time of diagnosis was 57 years (range 15-91). For males, the mean age at the onset was 56.3 years (range 16-84) and for females it was 55.3 years (range 15-91). The percentage of White/Caucasian individuals in our study was 97.6%, followed by Black/African Americans (4.8%) and Asian and Hispanics (2.4%). We examined the histopathological records to rule out other possible diagnoses such as vasculitis, infection, and malignancy. The mean follow-up duration was 24 months (range 6-78); six patients were lost to follow-up after 6 months.

Clinical Presentation and Associated Diseases

Pain was a universal symptom and was explicitly recorded for all the patients. Pain was evaluated with a Visual Analogue Scale (VAS) at the time of diagnosis with a mean pain of around 7.6 points (range 3-9). Tissue pathergy, reported as worsening or development of new lesions after minor trauma, was documented in 28.6% (n: 12) of patients within the period of follow-up. The majority of the patients presented ulcerative PG (88.1%, n: 37) (Figure 1). Lower incidences were reported for bullous PG (4.8%, n: 2) (Figure 2), vegetative PG (4.8%, n: 2) (Figure 3), and pustular PG subtypes (2.4%, n: 1) (Figure 4).

We looked at associated major comorbidities in our cohort of study: 25% (n: 11) of the patients presented inflammatory

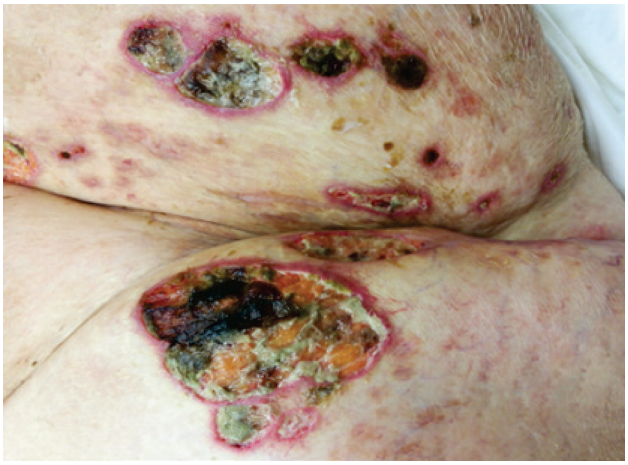

Figure 1. Ulcerative pyoderma gangrenosum.

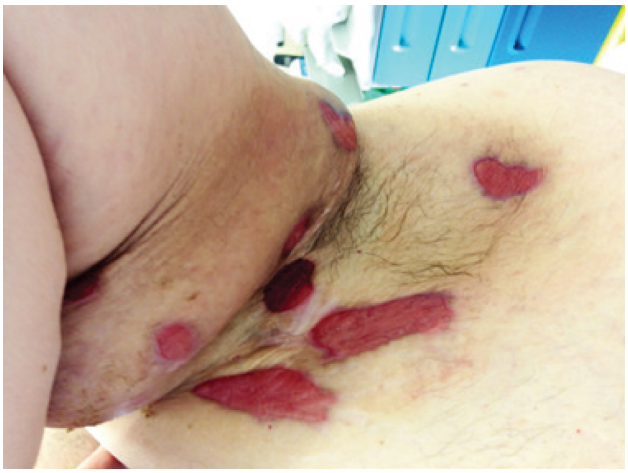

Figure 2. Vegetative pyoderma gangrenosum.

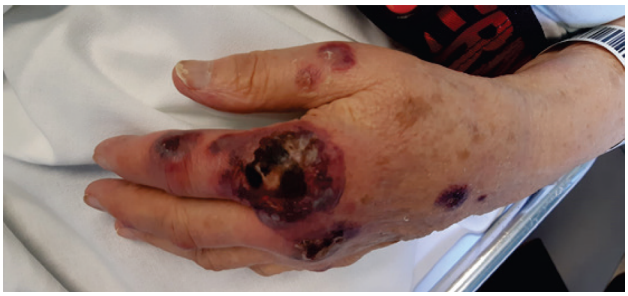

Figure 3. Bullous pyoderma gangrenosum.

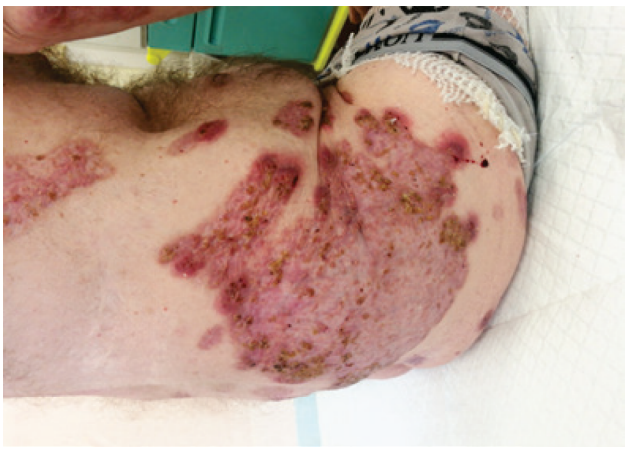

Figure 4. Pustular pyoderma gangrenosum.

bowel diseases (IBD), five patients had Chron's disease, six had ulcerative colitis, 9.1% of patients (n: 4) had rheumatoid arthritis. An important association was also found with hematological diseases: 11.4% (n: 5) of the patients were affected with an MGUS and 6.8% (n: 3) presented hematological malignancies such as follicular lymphoma, acute myeloid leukemia, and chronic myeloid leukemia (one patient each). Psoriasis was diagnosed in 9.1% (n: 4) of the patients in the analysis, of whom two also presented psoriatic arthritis. Obesity was the most common comorbidity among our patients; a total of 17 (38.6%) patients presented various grades of obesity (Table 1).

In analyzing the location of the ulcers, we noticed that 29.5% of the patients (n: 13) developed a single lesion, while the other 31 patients developed multiple lesions or simultaneous involvement of different body areas. Lower limbs were the most frequent site for PG in our cohort, with a total of 28 patients (63.6%) with lower limb involvement. The second most affected region was the abdomen, with a total of nine cases (20.5%), of which four were peristomal involvement. Less frequent were the involvement of the upper limbs (six patients), mammary region (three patients), back (three patients), and hands (one patient).

The temporal analysis showed no increase in diagnoses after March 2020, coinciding with the outbreak of COVID-19 pandemic. Twenty-four cases of PG (54.55%) were diagnosed before March 2020 and 20 after that date. Seventeen out of 20 patients diagnosed after the onset of the COVID-19 pandemic reported Sars-Cov2 infection or vaccination during the six months preceding the emergence of PG.

Treatment

In all patients, wound management was guaranteed in our Outpatient Clinic every 2-6 weeks. In this setting, they also underwent a gentle sharp debridement of nonviable tissue, performed by a wound care specialist. Among the follow-up visits, our medication was repeated by a wound specialist nurse 2-3 times per week.

Following the therapeutic algorithm by Maronese et al., we differentiated mild disease (ulcer diameter ≤3 cm, ≤3 lesions, ≤5% body surface area involved) from moderate-to-severe (ulcer diameter >3 cm, visualization of tendon, muscle, or bone) [5]. Mild disease was treated with super-potent topical corticosteroids as first-line therapy. If there was no improvement in 4-6 weeks, we added systemic therapy. In the four (9.1%) cases of peristomal PG (PPG), we dressed the wound with crushed prednisolone and hydrocolloid powder, as already proven by Wendy et al. [6]. For moderate-to-severe disease, we started directly with systemic and topical therapy. Systemic corticosteroids was by far the most frequent treatment used as first-line systemic therapy. Twenty out of 44 patients received 0.5-1 mg/kg of oral prednisone (or equivalent steroid dose) for a duration of 8-42 weeks.

Eighteen patients (41%) were steroid-resistant and needed other immunosuppressive therapy. Steroid-sparing drugs such as cyclosporine, methotrexate and dapsone were used. Seven patients (15.9%) were treated with cyclosporine (200 mg/day) for a duration of 8–30 weeks, and three patients obtained clinical improvement. Methotrexate was used in three patients without any significant improvement of the disease. Two patients were treated with dapsone, of whom one obtained a good clinical response. Twenty-two (50%)

Table 1. Demographics and Comorbidities of Pyoderma Gangrenosum Patients.

Comorbidities	Males	Females	Total
Ulcerative colitis	1 (2.3%)	5 (11.4%)	6 (13.6%)
Chron	3 (6.9%)	3 (6.9%)	6 (13.6%)
MGUS	1 (2.3%)	4 (9.1%)	5 (11.4%)
Hematological malignancies	2 (4.6%)	1 (2.3%)	3 (6.9%)
Rheumatoid arthritis	1 (2.3%)	2 (4.6%)	3 (6.9%)
Psoriasis	1 (2.3%)	3 (6.9%)	4 (9.1%)
Obesity (BMI ≥30)	3 (6.9%)	5 (11.4%)	8 (18.2%)

Abbreviations: BMI: body mass index; MGUS= monoclonal gammopathy of undetermined significance.

patients completely healed. Eleven (25%) patients recovered thanks to high-potency topical steroid and advanced dressing, six (13.6%) with both topical and oral steroids. Five patients (11.4%) recovered with non-steroid immunosuppressants, one of whom also receiving one cycle of rituximab (1 g at day 0 and 1 g at day 15).

A total of six patients presented no clinical improvement or worsening of the disease and had to shift to biologic agents to control their PG. Adalimumab was used as first-line biological therapy in five patients, administered at an initial dose of 80 mg, followed by 40 mg every 2 weeks (if body weight was over 90 kg, the dose was doubled). One patient with a positive Quantiferon test was treated with secukinumab administered at an initial dose of 600 mg, followed by 300 mg every two weeks. The biological treatment is ongoing for these six patients, with partial improvement of the PG lesions.

Discussion

Our retrospective case series of 44 patients with PG offers a nuanced perspective on the demographics, clinical manifestations, treatment responses, and associated comorbidities of this troublesome dermatological condition. In line with the existing literature, we found a slight female predominance, without a significant difference between sexes [7-9]. This result, aligning with previous reports, raises intriguing questions about the potential role of hormonal, genetic, or immunological factors that might predispose females to PG. This underscores the need for a deeper exploration into the underlying mechanisms, including potential biases in diagnosis or referral patterns that might contribute to this observation.

Our study confirms that PG occurs in most cases in older individuals [9]. Our data also reinforce the strong link between PG and IBD, such as Crohn's disease and ulcerative colitis, which is consistent with the literature, which that reports a 20%-30% prevalence. This association underscores the systemic nature of PG and its potential pathophysiological overlap with other inflammatory conditions. The comparable prevalence of hematologic malignancies and monoclonal gammopathy of undetermined significance (MGUS) in our cohort aligns with previous findings, further emphasizing the need for a comprehensive systemic evaluation in patients presenting with PG [10-12].

Advanced dressing and use of high-potency topical steroids play a fundamental role in the management of PG, often leading to the resolution in mild forms. We observed that patients without systemic associations responded positively to first-line treatments. Conversely, as Agarwal et al. also observed, patients with IBD and hematologic comorbidities required biologic agents to control their lesions [13].

The associated disease can precede, coexist, or follow PG [4,10,14]. Systemic disorders started, for most of our patients, within one year before and one year after PG was diagnosed. Based on our findings and on the existing literature, conducting a thorough investigation for IBD and hematologic conditions in patients diagnosed with PG is recommended. Indeed, we suggest extending the observation period to at least two years post-diagnosis, although there is a lack of consensus regarding the criteria for the duration and frequency of follow-up [15].

We noticed that obesity reduced the therapeutic response, as in other inflammatory dermatosis such as psoriasis. In our opinion, this may be due to the higher levels of proinflammatory cytokines in obese patients. Instead, we saw no increase in PG diagnoses following the onset of the COVID-19 pandemic, consistent with previous findings [16].

The anatomical predilection for lower extremity involvement in PG, observed in our study, is consistent with prior reports and suggests potential contributing factors such as trauma, vascular insufficiency, or localized immune dysregulation, which warrant further investigation [17, 18]. Furthermore, five of the six patients treated with biological therapy presented PG localized to lower extremities. We hypothesize that, as in other inflammatory skin conditions, there is a heightened concentration of resident T lymphocytes and memory T cells in the legs. This can be one of the causes for a lower response to the first-line therapies [19].

Our findings on PPG show that pain and burning were the most common symptoms. In our cohort, PPG was predominantly associated with IBD, suggesting that PPG can be triggered by proinflammatory cytokines from active IBD [20]. As recently stated by Afifi et al., pathergy is recurrent in PPG because of ostomy leakages and frequent dressing changes [21].

The diagnostic utility of biopsy in our series was primarily to exclude other conditions, reflecting the ongoing challenge in PG diagnosis. Histopathological findings often support the diagnosis by exclusion rather than confirmation; this underscores the importance of a thorough and multifaceted diagnostic approach in suspected cases of PG [22].

Limitations

Our study provides a comprehensive overview of PG in a well-defined cohort and is, to our knowledge, one of the largest in the current literature [3,11,15]. In our experience, we used biological therapy in moderate-to-severe PG, notably when systemic steroids or other immunosuppressants achieved no improvement. Given the promising results and the current accessibility to biosimilar drugs, we suggest considering biological therapy as the first line in moderate-to-severe PG. At the same time, we acknowledge the limitations inherent in retrospective analyses, including potential selection biases and the influence of referral patterns on comorbidity profiles. Our findings underscore the complex and systemic nature of PG, necessitating a multimodal, multidisciplinary approach to management.

Conclusion

In our experience, the renewal of advanced dressing together with steroid therapy played a key role in the healing process. Moreover, we encourage the use of biological therapy in patients affected with moderate-to-severe form of PG.

In summary, our study enriches the understanding of PG, reaffirming its association with systemic diseases and underscoring the challenges in diagnosis and management. Further prospective studies are essential to unravel the complexities of PG, optimize treatment strategies, and ultimately improve patient outcomes in this challenging condition.

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