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Clinical, epidemiological, and therapeutic hallmarks of pyoderma gangrenosum: a case series of 35 patients

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Abstract

Background Over the past few decades, advances in medical research and diagnostic tools have shed light on some aspects of pyoderma gangrenosum (PG). Nevertheless, the multifactorial etiology, pathogenesis, and optimal management strategies for PG need to be further investigated.To address these knowledge gaps and contribute to a better understanding of this complex dermatological disorder, we collected epidemiological, clinical, and therapeutic aspects of a case series of PG patients occurring in our department over the past 10 years.

Methods We performed a single-centered, retrospective, observational study analyzing all cases with a diagnosis of PG observed at the Dermatology clinic of the Fondazione Policlinico A. Gemelli IRCCS Catholic University from January 1, 2013, to January 1, 2023. For each case, we retrieved demographic data, the presence of other skin and systemic conditions, and the histopathological and clinical characteristics of PG, such as clinical variant, number of lesions, disease localization, previous therapy, response to treatment, and occurrence of relapse.

Results We included 35 patients, 22 females and 13 males with a mean age of 40.0 years. Twenty patients (57.1%) had multiple localizations of disease, and the most commonly involved site was the lower limbs (85.7%). The lesions were mainly associated with inflammatory bowel diseases (51.4%) and hidradenitis suppurativa (37.1%). Clinical resolution with complete re-epithelialization was achieved in 25 patients (71.4%) with an average time of 20.8 months. On average, patients who underwent therapy with biological drugs had better outcomes.

Conclusions PG is a severe, rare, and pleomorphic disease associated with a broad spectrum of conditions. Corticosteroids remain the primary first-line approach for severe forms, but using biological immunosuppressants is promising.

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Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis, in its ulcerative variant, characterized by rapidly developing, painful, and irregularly shaped skin ulcers (single or multiple) with undermined violaceous borders.[1] PG lesions are typically located on the lower extremities but can also affect the trunk, head, neck, and even mucosal surfaces.[2] The incidence is estimated to be around 10 cases per 1 million people annually, with a slightly higher prevalence in females and a typical onset between the third and sixth decade.[3]

Up to 70% of PG cases are associated with other conditions, primarily systemic immune-mediated diseases such as chronic inflammatory bowel diseases (IBD), connective tissue disorders, and arthritis. Additionally, neoplasms, especially hematological malignancies, have been associated with PG.[4,5] Moreover, PG contributes to defining neutrophilic syndromic conditions, such asPAPA (pyogenic arthritis, PG, and acne), SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis), PASH (PG, acne, and hidradenitis suppurativa [HS]), and PsAPASH syndrome.[6–9] PG exhibits a histological pattern of neutrophilic infiltration without any discernible signs of infection or vasculitis. The genesis of this neutrophilic infiltration remains obscure; however, various evidence, along with a better understanding of syndromic forms, suggest a complex autoinflammatory mechanism involving the dysregulation of innate and adaptive immunity.[10–12]

Over the past few decades, advances in medical research and diagnostic tools have shed light on multiple aspects of PG. Nevertheless, the multifactorial etiology, pathogenesis, and optimal management strategies for PG need to be further investigated.[13,14] To address these knowledge gaps and contribute to a better understanding of this complex dermatological disorder, we collected epidemiological, clinical, and therapeutic aspects of a case series of PG patients occurring in our department over the past 10 years.

Materials and methods

We performed a single-centered retrospective observational study analyzing all cases with the diagnosis of PG observed at the Dermatology clinic of the Fondazione Policlinico A. Gemelli IRCCS Catholic University from January 1, 2013, to January 1, 2023. We included patients with a score ≥10 according to the PARACELSUS criteria[15] for diagnosing PG (Table 1). For each case, we retrieved clinical and demographic data, including age, gender, age at PG onset, presence of other skin and systemic conditions (comorbidities), and related therapies. Additionally, we collected data on the histopathological and clinical characteristics of PG, such as the clinical variant (ulcerative, vegetative, pustular, peristomal, bullous form), number of lesions, disease localization, previous therapy, response to treatment, and occurrence of relapse. Only cases with complete, available data were considered suitable for inclusion in the study.

For the analysis of continuous variables, we used mean or median, standard deviation, or interquartile range (IQR), depending on the statistical analyses performed. A dedicated electronic database was created to collect data on the clinical and demographic characteristics of patients who were undergoing treatment.

Institutional review board approval was not required for this study because the procedures did not deviate from routine clinical practice. All patients signed a hospital-based informed consent. The study was performed following the principles of the Declaration of Helsinki.

Results

Our study included 35 patients, 22 (62.2) females and 13 (37.8%) males, with a median age of 41.0 years (IQR = 20.5). The mean age at PG diagnosis was 40.0 years (SD: 14.2) (Table 2).

Twenty patients (57.1%) had multiple localizations of disease, most commonly involving the lower limbs (30 patients, 85.7%); among these patients, exclusive involvement of the lower limbs was observed in 27 cases (77.1%). Other anatomic locations included the trunk (5 cases, 14.3%), the face (2 cases, 5.7%),

Table 1 PARACELSUS score for the diagnosis of pyoderma gangrenosum

Three major criteria (3 points)	**1** Rapidly progressing disease
	2 Assessment of relevant differential diagnoses
	3 Reddish-violaceous wound border
Four minor criteria (2 points)	**1** Amelioration by immunosuppressant drugs
	2 Irregular shape of ulceration
	3 Extreme pain >4/10 on a visual analog scale
	4 Localization of lesion at the site of the trauma
Three additional criteria (1 point)	**1** Suppurative inflammation in histopathology
	2 Undermined wound borders
	3 Association with systemic disease

A cumulative score of 10 points or more has been validated as a strong predictor of PG.[14]

Table 2 Demographic and clinical characteristics of patients

Age at diagnosis (years), mean (SD)	40.0 (14.2)
Gender, *n* (%)	
F	22 (62.8)
M	13 (37.1)
Number of lesions, *n* (%)	
Single	15 (42.9)
Multiple	20 (57.1)
Variant, *n* (%)	
Ulcerative	26 (74.3)
Vegetative	5 (14.2)
Pustular	2 (5.7)
Peristomal	1 (2.7)
Associated disorders *n* (%)	
CD	10 (28.6)
UC	8 (22.9)
HS	13 (34.3)
Trauma	3 (8.5)
Non-Hodgkin's lymphoma	1 (2.8)
None	3 (8.6)
Time interval between diagnosis of associated disorder and onset of PG and PG (years), mean (SD)	7.4 (6.5)

CD, Crohn's disease; F, female; HS, hidradenitis suppurativa; M, male; UC, ulcerative colitis.

the upper limbs (2 patients, 5.7%), and the breast region (1 case, 2.3%).

As for clinical variants of PG, 27 (77.1%) had an ulcerative form, 5 (14.2%) had a vegetative subtype, 2 (5.7%) had a pustular subtype, and 1 (2.7%) had a peristomal variant.

Thirty-two patients (91.4%) had a condition commonly associated with PG, while in only 3 cases (8.6%), PG was considered to be idiopathic. The most frequently associated conditions were IBD, found in 18 out of 35 patients (51.4%). Among these, 10 patients (28.5% of the total sample) had Crohn's disease (CD), and 8 (22.9% of the full sample) had ulcerative colitis (UC). Four patients with IBD (22%) had a previous history of extra-intestinal joint manifestations. One patient with CD-like IBD had an associated X-linked inhibitor of apoptosis-deficient (XIAP) syndrome (Figure 1).

Moreover, in the clinical history of a 24-year-old patient, PG was part of a broader cluster of multiple immune-mediated disorders, including UC, bullous pemphigoid, primary sclerosing cholangitis, and autoimmune hepatitis (Figure 2). HS was present in 13 patients (37.1%). Three patients had both IBD and HS. In one patient, HS was part of a SAPHO syndrome. In three cases (8.6%), PG was associated with previous trauma or surgical wounds. These included two cases of PG in the mammary region following total mastectomy after breast cancer (one of them developed after subsequent trauma in the same area) (Figure 3) and one case that developed after a facial injury in a car accident. In one patient with CD, a peristomal variant of PG was observed. In another case, PG was associated with non-Hodgkin lymphoma. The mean time interval between the diagnosis of the associated condition and the onset of PG was

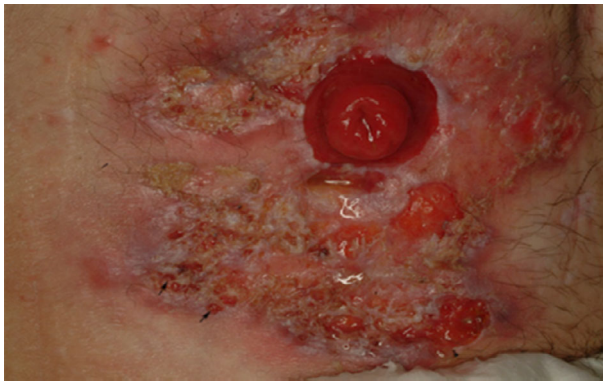

Figure 1 Peristomal PG in a 36-year-old patient affected by XLP2

7.4 years (SD: 6.5). Notably, in one patient (with concomitant CD), PG preceded the onset of aplastic anemia by a few months.

Moreover, 11 patients (31.4%) had concurrent skin comorbidities (genital condyloma, folliculitis, fungal intertrigo, psoriasis, bullous pemphigoid), and 12 (34.3%) had other various systemic comorbidities (thyroid nodules, hypertension, diabetes mellitus, scoliosis, polycystic ovary syndrome, kidney stones). Two patients had a history of erythema nodosum (EN), which in one case was an extra-intestinal manifestation of the underlying CD. In contrast, in the other case, it was associated with HS.

Regarding treatment, topical therapies were administered in all patients, with the majority receiving topical corticosteroids; in six patients (17.1%), they were used as monotherapy, while in the remaining patients, topical therapy was combined with systemic drugs. Topical tacrolimus was also used, with benefit, in 8 (22.9%) patients, associated with topic corticosteroids (two patients) or with other systemic drugs (6 patients). Systemic therapies with classical immunosuppressants were required in 17 (48.6%) patients. Among these, 13 (37.1%) received systemic corticosteroids, one patient (2.3%) received methotrexate, and two patients (5.7%) received cyclosporine. One patient was treated with systemic corticosteroids and cyclosporine concomitantly. Twenty patients (57.1%) underwent biologic drugs during the clinical course of the disease alone (in 12 patients) or in association with other systemic drugs. It is important to note that many of these patients had complex medical histories with numerous comorbidities, many of which required immunosuppressive therapies and/or biologic drugs. At the time of diagnosis of PG, 19 patients were already on treatment with immunosuppressants for the underlying condition, and changes in drugs or dosages were adopted to manage PG. In detail, 12 patients received adalimumab, 6 received infliximab, and 2 received ustekinumab, while golimumab and secukinumab were used in one patient each. The therapeutic approaches, with remission and relapse rates, can be found in Table 3.

The mean follow-up was 44.3 months. At the time of the study, clinical resolution with complete skin re-epithelialization was

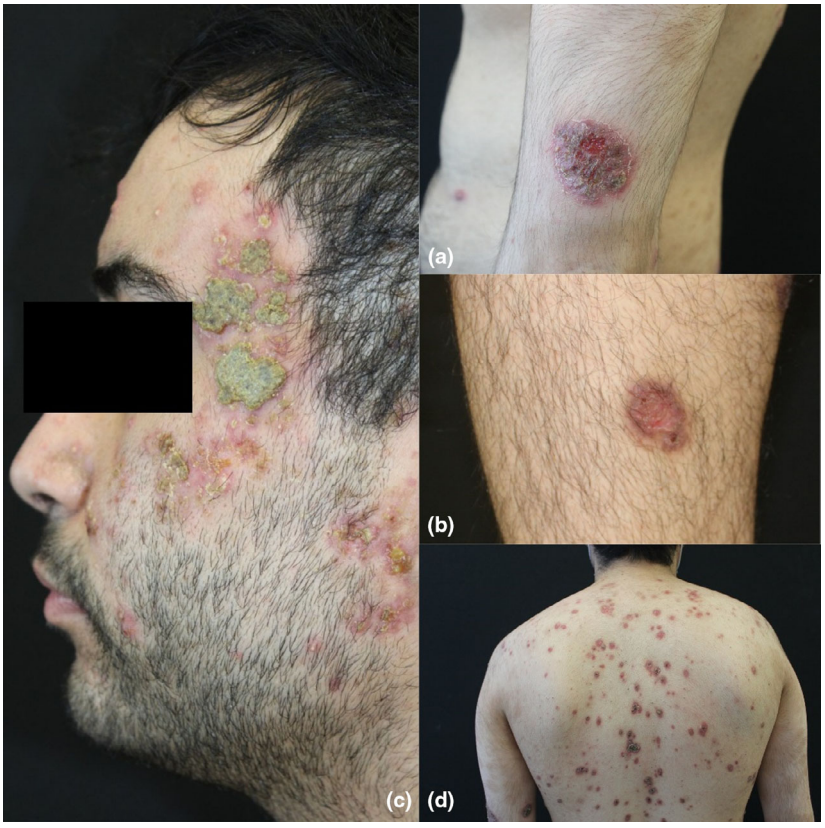

Figure 2 PG of the left arm (a) and the right thigh (b) in a 24-year-old patient with concomitant suppurative folliculitis (c,d). He also had a complex history of multiple concomitant autoimmune and immunomediated conditions, including UC complicated by primary sclerosing cholangitis (PSC) and spondyloarthritis, as well as a previous history of bullous pemphigoid and autoimmune hepatitis

achieved in 25 patients (71.4%) within a variable range of 4 to 90 months since the onset of PG, with an average time of 20.8 months (SD: 23.0) and a median of 12.2 months (IQR = 13.2). A recurrence of PG was observed in six patients (17.1%).

On average, patients who underwent therapy with biological drugs had better outcomes, with complete re-epithelialization observed in 18 out of 22 patients. Specifically, infliximab was the drug associated with more rapid improvements, inducing clinical remission, on average, within 5.3 months of therapy.

The proportion of complete clinical remission was lower in patients with the vegetative subtype: only one out of five had achieved complete remission at the time of the study. During the considered period, 1 patient with lymphoma out of the 35 recruited died due to complications related to the neoplasm.

Discussion

Our study confirms that PG is a complex condition characterized by comprehensive clinical heterogeneity and significant therapeutic challenges. In our setting, we observed a female-to-male ratio of approximately 2:1, confirming the higher prevalence of PG in females. Similar ratios can be found in various other case series and meta-analyses that consistently describe a gender difference in this condition[16] and other neutrophilic dermatoses (Table 3). Moreover, according to recent studies, in patients with IBD, the female gender appears to be a predictive factor for the development of extra-intestinal manifestations such as EN and, specifically, PG.[17,18] Although there is vast evidence of a proinflammatory environment in the skin of female patients, much remains to be understood about the mechanisms underlying the more significant tendency toward dysregulation of innate and adaptive immunity in the female gender. This is likely the result of a complex interplay of factors, including chromosomal makeup, epigenetic expression, hormonal factors, and environmental influences.[19,20]

Regarding the localization of PG, the results of our study showed that the most frequent site is the lower limbs, affected in 85.7% of cases in our series. This finding aligns with one previous multicenter study involving 103 patients with PG, which found that the lower limbs were affected in 78.0% of cases.[21] As observed by Riyaz et al.,[22] atypical localizations (other than the lower limbs) may be a risk factor for multiple ulcers. This is in line with the data from our study, as 7 out of 8 patients (87.5%) with atypical presentations exhibited multiple ulcerations. In comparison, the same was true for only 13 out of 27 patients (48.1%) with localization of the lesions on the lower

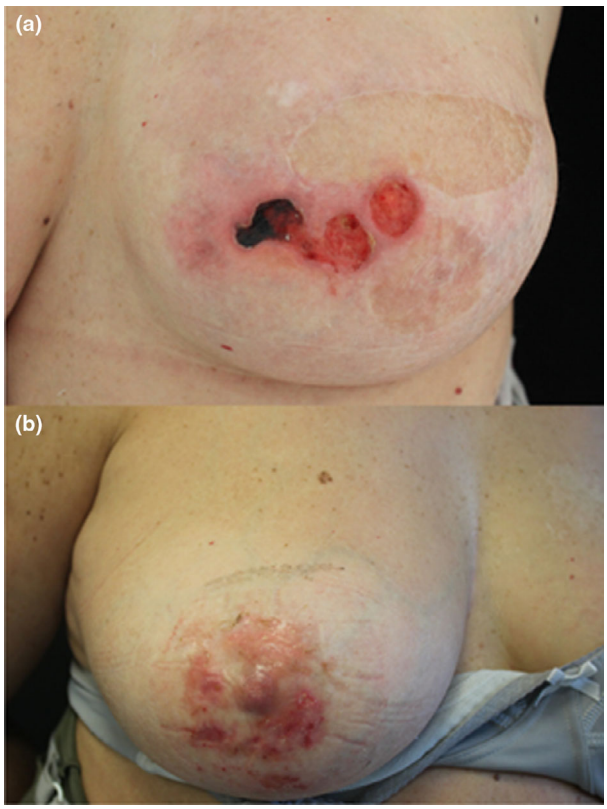

Figure 3 Recalcitrant postoperative and pathergy-related PG in a 49-year-old patient. In panel a, PG emerged at the site of a prior left total mastectomy, due to breast carcinoma. Four years after surgery, and a few weeks after a major accidental trauma in the same region, the patient developed multiple ulcerations at the surgical site which resolved after treatment with infliximab. Three years later, PG recurred, with localization on the other breast (panel b). After several treatment failures, clinical remission was obtained with secukinumab treatment

limbs. In our study, the ulcerative form was the most frequent variant of PG. No patient had the bullous variant of PG, probably due to the rarity of this presentation and its close association with hematological disorders (under-represented in our population). The peristomal variant was present in one case (2.7%), thus emphasizing the rarity of this condition (representing less than 14% of all PG cases associated with IBD[22]).

We found that 91.4% of patients had a comorbidity classically associated with PG. This prevalence is higher than that found in similar studies, where association rates have been reported to vary from 19 to 86%[16] (Table 4). However, this discrepancy is likely attributable to our institution's specific setting, a tertiary referral center for IBD therapy. Nevertheless, our study further highlights the close relationship between PG and IBD, which was a concomitant disease in 51.4% of patients, supporting the hypothesis that PG can be considered an extra-intestinal manifestation of IBD. In this regard, the presence of a patient with PG and CD in our study who reported a previous episode of EN anecdotally sustains the hypothesis that prior cutaneous extra-intestinal manifestations of IBD may be a risk factor for the development of additional cutaneous manifestations.[17]

Confirming their effectiveness in inducing clinical remission, our study supports the use of systemic corticosteroids as the primary first-line approach for severe forms of PG; nevertheless, our findings add further evidence to the existing literature supporting the potential benefit of anti-TNF medications in the management of PG. Infliximab showed favorable outcomes in our study, with clinical benefit observed in all six patients who received it. This finding is consistent with other studies in the literature, particularly with the only randomized clinical trial conducted on this condition[23] in which infliximab at a dose of 5 mg/kg demonstrated clinical benefit compared to placebo. Additional studies, including a survey with six patients[24] and a study with 13 patients,[25] as well as various case reports,

Table 3 Description of therapeutic approaches, with remission rates, mean time between the commencement of therapy to the achievement of full cutaneous re-epithelialization

Therapy	Treated patients (*n*)	Patients achieving remission, *n* (%)	Mean time to achieve remission (months)	Recurrence
Topical clobetasol (0.05% ointment)	4	2[a] (50)	15.6	0
Topical tacrolimus 0.1%	2	0	12	2
Systemic corticosteroids	9	4 (44.4)	10.25	0
Cyclosporine	2	1 (50)	6	0
Cyclosporine + systemic Corticosteroids	1	0	–	0
Golimumab (100 mg every 4 weeks)	1	1 (100)	12	0
Infliximab (5 mg/kg every 2 weeks)	6	6 (100)	5.3	1
Ustekinumab (45 mg every 12 weeks)	2	2 (100)	11	1
Adalimumab (80 mg every 2 weeks)	7	5 (71)	8.4	1
Adalimumab (80 mg every 2 weeks) + systemic corticosteroids	4	3 (75)	14.3	0
Adalimumab (80 mg every 2 weeks) + methotrexate	1	0	–	0
Risankizumab (150 mg every 12 weeks)	1	1 (100)	6	0

[a]One patient died of concomitant non-Hodgkin lymphoma.

Table 4 Demographic characteristics and main associated conditions in the case series of PG in the literature

Study	Year	No. involved centers	Site	No. of patients	Age at onset (mean)	Female patients (%)	Comorbidities (%)	UC (%)	CD (%)	Hematological disorders (%)	Solid malignancy (%)	Rheumatoid arthritis (%)	Pathergy (%)
Powell et al.[27]	1985	1	USA	86	NR (7–71)	50.0	77.9	19.8	16.3	12.8	5.8	32.6	26.7
Von Den Driesch et al.[28]	1997	1	Germany	44	50.3	68.2	77.3	6.8	6.8	9.1	11.4	NR	38.6
Bennett et al.[29]	2000	2	USA	86	48.4	55.8	50.0	11.6	9.3	9.3	NR	18.6	0
Milka et al.[30]	2002	1	Tunisia	21	41.8	47.6	52.4	19.0	4.8	14.3	0	4.8	0
Vidal et al.[31]	2004	1	Spain	26	45 (17–72)	69.2	84.6	26.9	15.4	23.1	11.5	NR	7.7
Hasselmann et al.[32]	2007	1	Germany	18	53.1	77.8	38.9	5.6	5.6	11.1	0	11.1	0
Binus et al.[21]	2011	2	USA	103	51.6	75.7	78.6	17.5	16.5	10.7	0	29.1	31.1
Marzano et al.[33]	2011	1	Italy	21	45 (13–80)	52.4	42.9	4.8	0	9.5	4.8	NR	0
Suarez-Perez et al.[24]	2011	1	Spain	15	49.2	46.7	60.0	26.7	6.7	0	0	NR	20.0
Langan et al.[5]	2012	PB	UK	313	59	59.0	32.9	20.2	NR	3.8	NR	NR	NR
Al Ghazal et al.[34]	2012	1	Germany	49	59.7	59.2	36.7	4.1	2.0	10.2	12.2	6	32.6
AlGhazal et al.[35]	2013	20	Germany	259	57.3	54.8	41.3	6.6	2.7	3.9	12.4	15.8	42.9
Saracino et al.[36]	2013	1	Australia	26	58.4	65.4	57.7	7.7	NR	7.7	15.4	23.1	61.5
Pereira et al.[37]	2014	1	Portugal	24	58.3	79.2	75.0	16.7	4.2	25.0	8.3	NR	8.3
Ye et al.[38]	2014	1	Australia	23	62.8	69.6	47.8	4.3	4.3	4.3	17.4	NR	26.1
Cabalag et al.[39]	2015	1	Australia	29	71(38–92)	58.6	86.2	3.4	10.3	17.2	20.7	24.1	10.3
Adısen et al.[40]	2016	1	Turkey	27	48.6	63.0	29.6	7.4	NR	3.7	11.1	NR	14.8
Jockenhofer et al.[16]	2016	PB	Germany	1227	NR	60.3	19.0	4.2	4.5	4.0	NR	NR	NR
Jockenhofer et al.[41]	2016	3	Germany	121	59.8	66.9	44.6	5.8	4.1	6.6	14.0	14.0	38.8
Inoue et al.[42]	2017	9	Japan	62	50.2	53.2	74.2	32.3	1.6	16.1	4.8	11.3	0
Vacas et al.[43]	2017	1	Argentina	31	57.0	58.0	74.2	32.3	NR	22.6	0	16.1	51.6
Kikuchi et al.[44]	2018	1	Japan	41	54.8 (15–89)	58.5	NR	21.0	NR	9.7	NR	NR	9.7
Ashchyan et al.[45]	2018	3	USA	356	51.6	75.0	66.3	15.4	25.8	4.8	6.5	8.4	28.1
Schøsler et al.[46]	2018	1	Denmark	63	63.4 (18–88)	61.6	73.4	28.1	NR	7.8	20.4	12.5	35.9
Zhao et al.[47]	2023	1	USA	95	54.0	73.6	NR	20	NR	3.2	15.7	NR	NR
Our data	2023	1	Italy	35	40.0 (18–80)	62.8	91.4	28.6	22.9	2.8	NR	NR	8.5

CD, Crohn's disease; NR, not reported; UC, ulcerative colitis.

suggest the effectiveness of this drug in PG, especially as a therapy for forms associated with IBD (given the proven efficacy of infliximab in Crohn's disease and UC) and as a second-line treatment for refractory forms.[26]

The relatively small sample size represents the main limitation of this study due to the rarity and clinical-diagnostic challenges of PG. The potential selection bias due to the clinical setting is also worth noting: many patients were referred from other departments, leading to an overrepresentation of complex medical histories and specific pathological associations (such as IBD). Furthermore, difficulties in standardizing the patients' clinical course should be highlighted because of the complexity of their medical histories, the concomitance of numerous comorbidities and related therapies, and the absence of objective disease assessment scales for PG.

In conclusion, PG remains a rare and pleomorphic condition. Considerable progress has been made in recent decades in understanding the underlying molecular mechanisms and potential therapeutic approaches. However, our knowledge remains limited and burdened by significant gaps. The data collected at our department confirm that PG is a difficult-to-treat disease with a tendency for a chronic-recurrent course, closely associated with a variety of immune-mediated and hematological disorders.

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Data availability statement

Enquiries related to the data generated or analyzed during this study can be directed to the corresponding author.

References

1 Weiss EH, Ko CJ, Leung TH, Micheletti RG, Mostaghimi A, Ramachandran SM, et al. Neutrophilic dermatoses: a clinical update. *Curr Dermatol Rep*. 2022;**11**(2):89–102. https://doi.org/10.1007/s13671-022-00355-8
2 Marzano AV, Borghi A, Wallach D, Cugno M. A comprehensive review of neutrophilic diseases. *Clin Rev Allergy Immunol*. 2018;**54**:114–30.
3 Maronese CA, Pimentel MA, Li MM, Genovese G, Ortega-Loayza AG, Marzano AV. Pyoderma gangrenosum: an updated literature review on established and emerging pharmacological treatments. *Am J Clin Dermatol*. 2022;**23**(5):615–34. https://doi.org/10.1007/s40257-022-00699-8
4 Ashchyan HJ, Nelson CA, Stephen S, James WD, Micheletti RG, Rosenbach M. Neutrophilic dermatoses: pyoderma gangrenosum and other bowel- and arthritis-associated neutrophilic dermatoses. *J Am Acad Dermatol*. 2018;**79**(6):1009–22. https://doi.org/10.1016/j.jaad.2017.11.063
5 Langan SM, Groves RW, Card TR, Gulliford MC. Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. *J Invest Dermatol*. 2012;**132**(9):2166–70. https://doi.org/10.1038/jid.2012.130
6 Marzano AV, Borghi A, Meroni PL, Cugno M. Pyoderma gangrenosum and its syndromic forms: evidence for a link with autoinflammation. *Br J Dermatol*. 2016;**175**(5):882–91. https://doi.org/10.1111/bjd.14691
7 Saraceno R, Babino G, Chiricozzi A, Zangrilli A, Chimenti S. PsAPASH: a new syndrome associated with hidradenitis suppurativa with response to tumor necrosis factor inhibition. *J Am Acad Dermatol*. 2015;**72**(1):e42–4. https://doi.org/10.1016/j.jaad.2014.10.002
8 Cugno M, Borghi A, Marzano AV. PAPA, PASH and PAPASH syndromes: pathophysiology, presentation and treatment. *Am J Clin Dermatol*. 2017;**18**(4):555–62. https://doi.org/10.1007/s40257-017-0265-1
9 Ma M, Wu X, Cao Y, Liu Y, Liu S, Li C. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome associated with pyoderma gangrenosum: report of two patients. *Int J Dermatol*. 2023;**62**(3):e186–9. https://doi.org/10.1111/ijd.16492
10 Marzano AV, Ortega-Loayza AG, Heath M, Morse D, Genovese G, Cugno M. Mechanisms of inflammation in neutrophil-mediated skin diseases. *Front Immunol*. 2019;**10**:1059. https://doi.org/10.3389/fimmu.2019.01059
11 Marzano AV, Damiani G, Genovese G, Gattorno M. A dermatologic perspective on autoinflammatory diseases. *Clin Exp Rheumatol*. 2018;**36 Suppl 110**(1):32–8.
12 Moura RR, Brandão L, Moltrasio C, Agrelli A, Tricarico PM, Maronese CA, et al. Different molecular pathways are disrupted in Pyoderma gangrenosum patients and are associated with the severity of the disease. *Sci Rep*. 2023;**13**(1):4919. https://doi.org/10.1038/s41598-023-31914-z
13 Patel F, Fitzmaurice S, Duong C, He Y, Fergus J, Raychaudhuri SP, et al. Effective strategies for the management of pyoderma gangrenosum: a comprehensive review. *Acta Derm Venereol*. 2015;**95**(5):525–31. https://doi.org/10.2340/00015555-2008
14 Garcovich S, De Simone C, Berti E, Marzano AV. Drug management of neutrophilic dermatoses. *Expert Rev Clin Pharmacol*. 2017;**10**(10):1119–28. https://doi.org/10.1080/17512433.2017.1356719
15 Jockenhöfer F, Wollina U, Salva KA, Benson S, Dissemond J. The PARACELSUS score: a novel diagnostic tool for pyoderma gangrenosum. *Br J Dermatol*. 2019;**180**:615–20. https://doi.org/10.1111/bjd.16401
16 Jockenhöfer F, Klode J, Kröger K, Roesch A, Al Ghazal P, Dissemond J. Patients with pyoderma gangrenosum - analyses of the German DRG data from 2012. *Int Wound J*. 2016;**13**(5):951–6. https://doi.org/10.1111/iwj.12463
17 Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol*. 2001;**96**(4):1116–22. https://doi.org/10.1111/j.1572-0241.2001.03756.x
18 Ampuero J, Rojas-Feria M, Castro-Fernández M, Cano C, Romero-Gómez M. Predictive factors for erythema nodosum and pyoderma gangrenosum in inflammatory bowel disease. *J Gastroenterol Hepatol*. 2014;**29**(2):291–5. https://doi.org/10.1111/jgh.12352
19 Moulton VR. Sex hormones in acquired immunity and autoimmune disease. *Front Immunol*. 2018;**9**:2279. https://doi.org/10.3389/fimmu.2018.02279
20 Kronzer VL, Bridges SL Jr, Davis JM 3rd. Why women have more autoimmune diseases than men: an evolutionary perspective. *Evol Appl*. 2020;**14**(3):629–33. https://doi.org/10.1111/eva.13167
21 Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br J Dermatol*. 2011;**165**(6):1244–50. https://doi.org/10.1111/j.1365-2133.2011.10565.x

22 Riyaz N, Mary V, Sasidharanpillai S, Roshin RA, Snigdha O, Latheef EN, et al. Pyoderma gangrenosum: a clinico-epidemiological study. *Indian J Dermatol Venereol Leprol*. 2017;**83**(1):33–9. https://doi.org/10.4103/0378-6323.188654

23 Brooklyn TN, Dunnill MG, Shetty A, Bowden JJ, Williams JD, Griffiths CE, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomized, double blind, placebo-controlled trial. *Gut*. 2006;**55**(4):505–9. https://doi.org/10.1136/gut.2005.074815

24 Mooij JE, van Rappard DC, Mekkes JR. Six patients with pyoderma gangrenosum successfully treated with infliximab. *Int J Dermatol*. 2013;**52**(11):1418–20. https://doi.org/10.1111/j.1365-4632.2011.05201.x

25 De la Morena F, Martin L, Gisbert JP, Fernandez Herrera J, Goiriz R. Refractory and infected pyoderma gangrenosum in a patient with ulcerative colitis: response to infliximab. *Inflamm Bowel Dis*. 2007;**13**:509–10.

26 Kouklakis G, Moschos J, Leontiadis GI, Kadis S, Mpoumponaris A, Molyvas E, et al. Infliximab for treatment of pyoderma gangrenosum associated with clinically inactive Crohn's disease. A case report. *Rom J Gastroenterol*. 2005;**14**:401–3.

27 Powell FC, Schroeter AL, Su WP, Perry HO. Pyoderma gangrenosum: a review of 86 patients. *Q J Med*. 1985;**55**(217):173–86.

28 von den Driesch P. Pyoderma gangrenosum: a report of 44 cases with follow-up. *Br J Dermatol*. 1997;**137**(6):1000–5.

29 Bennett ML, Jackson JM, Jorizzo JL, Fleischer AB Jr, White WL, Callen JP. Pyoderma gangrenosum: a comparison of typical and atypical forms with an emphasis on time to remission. Case review of 86 patients from 2 institutions. *Medicine (Baltimore)*. 2000;**79**:37–46.

30 Mlika RB, Riahi I, Fenniche S, Mokni M, Raouf Dhaoui M, Dess N, et al. Pyoderma gangrenosum: a report of 21 cases. *Int J Dermatol*. 2002;**41**:65–8.

31 Vidal D, Puig L, Gilaberte M, Alomar A. Review of 26 cases of classical pyoderma gangrenosum: clinical and therapeutic features. *J Dermatolog Treat*. 2004;**15**:146–52.

32 Marzano AV, Trevisan V, Lazzari R, Crosti C. Pyoderma gangrenosum: study of 21 patients and proposal of a "clinicotherapeutic" classification. *J Dermatolog Treat*. 2011;**22**:254–60.

33 Hasselmann DO, Bens G, Tilgen W, Reichrath J. Pyoderma gangrenosum: clinical presentation and outcome in 18 cases and review of the literature. *J Dtsch Dermatol Ges*. 2007;**5**:560–4.

34 Al Ghazal P, Körber A, Klode J, Dissemond J. Investigation of new co-factors in 49 patients with pyoderma gangrenosum. *Dtsch Dermatol Ges*. 2012;**10**:251–7.

35 Al Ghazal P, Herberger K, Schaller J, Strölin A, Hoff N-P, Goerge T, et al. Associated factors and comorbidities in patients with pyoderma gangrenosum in Germany: a retrospective multicentric analysis in 259 patients. *Orphanet J Rare Dis*. 2013;**8**:136.

36 Saracino A, Kelly R, Liew D, Chong A. Pyoderma gangrenosum requiring inpatient management: a report of 26 cases with follow up. *Australas J Dermatol*. 2011;**52**:218–21.

37 Pereira N, Brites MM, Goncalo M, Tellechea O, Figueiredo A. Pyoderma gangrenosum: a review of 24 cases observed over 10 years. *Int J Dermatol*. 2013;**52**:938–45.

38 Ye MJ, Ye JM. Pyoderma gangrenosum: a review of clinical features and outcomes of 23 cases requiring inpatient management. *Dermatol Res Pract*. 2014;**2014**:461467.

39 Cabalag MS, Wasiak J, Lim SW, Raiola FB. Inpatient management of pyoderma gangrenosum: treatments, outcomes, and clinical implications. *Ann Plast Surg*. 2015;**74**:354–60.

40 Adışen E, Erduran F, Gürer MA. Pyoderma gangrenosum: a report of 27 patients. *Int J Low Extrem Wounds*. 2016;**15**(2):148–54. https://doi.org/10.1177/1534734616639172

41 Jockenhofer F, Herberger K, Schaller J, Hohaus KC, StoffelsWeindorf M, Ghazal PA, et al. Tricenter analysis of cofactors and comorbidity in patients with pyoderma gangrenosum. *J Dtsch Dermatol Ges*. 2016;**14**:1023–30.

42 Inoue S, Furuta JI, Fujisawa Y, Onizawa S, Ito S, Sakiyama M, et al. Pyoderma gangrenosum and underlying diseases in Japanese patients: a regional long-term study. *J Dermatol*. 2017;**44**:1281–4.

43 Vacas AS, Torre AC, Bollea-Garlatti ML, Warley F, Galimberti RL. Pyoderma gangrenosum: clinical characteristics, associated diseases, and responses to treatment in a retrospective cohort study of 31 patients. *Int J Dermatol*. 2017;**56**:386–91.

44 Kikuchi N, Yamamoto T. Clinical analysis of pyoderma gangrenosum: 41 Japanese cases over 15 years. *Eur J Dermatol*. 2018;**28**(2):230–2. https://doi.org/10.1684/ejd.2017.3204

45 Ashchyan HJ, Butler DC, Nelson CA, Noe MH, Tsiaras WG, Lockwood SJ, et al. The association of age with clinical presentation and comorbidities of pyoderma gangrenosum. *JAMA Dermatol*. 2018;**154**(4):409–13. https://doi.org/10.1001/jamadermatol.2017.5978

46 Schøsler L, Fogh K, Bech R. Pyoderma gangrenosum: a retrospective study of clinical charac-teristics, comorbidities, response to treatment and mortality related to prednisone dose. *Acta Derm Venereol*. 2021;**101**(4):adv00431. https://doi.org/10.2340/00015555-3776

47 Zhao H, Mostaghimi A, Sisley JM, Ortega-Loayza AG. Multilesional pyoderma gangrenosum is associated with longer healing times and higher rates of underlying comorbidities: a single-center prospective registry study. *JAAD Int*. 2023;**12**:133–5. https://doi.org/10.1016/j.jdin.2023.05.009