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ORIGINAL ARTICLE

Epidemiology of pyoderma gangrenosum: Results from an Italian prospective multicentre study

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Pyoderma gangrenosum (PG) is a neutrophilic dermatosis characterised by painful, necrotic ulcerations. PG is described as a rare disease: the world-wide incidence is estimated to be around 3 to 10 cases per million population per year. These estimations are based mostly on case reports and retrospective case series; there are no prospective, multicentre studies on the matter. The apparent rarity of PG is in contrast with our clinical perception as dermatologists: in our opinion, PG is not so uncommon. Therefore, we decide to investigate the epidemiology of PG in the Italian population and confirm our clinical suspicions that it is not an orphan disease. We enrolled all patients diagnosed with PG in 8 Italian Dermatological Departments from 1st October 2014 to 1st November 2015, and we recorded their features. Our data, collected from 64 patients, are in accordance with those of the published literature regarding the epidemiology and features of PG. In an Italian population of roughly 8 million inhabitants of 7 provinces, we found an incidence of 5.17 new cases per million population per year. Unlike our predictions before the study, we confirmed the world-wide incidence of PG. To our knowledge, this is the first observational, multicentre study on PG. We hope that it provides a stimulus for further researches on PG and for the creation of an Italian register.

KEYWORDS
epidemiology, pyoderma gangrenosum

1 | INTRODUCTION

Pyoderma gangrenosum (PG) was first described by Brocq[1] and named by Brunsting et al.[2] This ulcerating skin disease was called PG because they believed that streptococcal infection was a significant component leading to secondary cutaneous gangrene.[2] Subsequently, it was recognised as a neutrophilic dermatosis, primarily typified by aseptic neutrophilic infiltration and systemic inflammation.[3] Current research suggests that neutrophil dysfunction, a clonal T expansion, elevated levels of inflammatory mediators (IL 17, IL 23), and genetic predisposition plays a role in PG progression.[4] There are currently 4 widely recognised subtypes of PG: classic (ulcerative), bullous, pustular, and vegetative.[5] Three more variants have been reported but are generally not regarded as distinct subtypes: drug-induced PG,[6] peristomal PG (PPG),[7] and post-surgical PG (PSPG).[8] A classic PG lesion starts with a small discrete pustule that rapidly evolves in a sharply marginated ulcer with undermined, violaceous borders and a surrounding zone of erythema. Cribiform or "sieve-like" atrophic scars often appear as the lesion heals. These ulcerations are characteristically

extremely painful and commonly occur on the lower extremities. Pathergy is present in 30% of cases and characterises PPG and PSPG subtypes. PG is associated with other conditions in 50% to 75% of patients; these conditions may occur prior to, concurrently with, or following the diagnosis of PG. The most frequent association is with inflammatory bowel disease (IBD) and less frequently with arthritis and haematological disorders.[4,9,10] In a retrospective multicentre study, a significant association between PG and metabolic/endocrinological diseases[11] is also described. Furthermore, PG is a clinical manifestation of syndromes described recently, including PAPA (pyogenic arthritis, PG, and acne),[12–14] PASH (PG, acne, and suppurative hidradenitis),[15–17] PASS (PG, acne, suppurative hidradenitis, and ankylosing spondylitis),[18] PAPASH (pyogenic arthritis, PG, acne, and suppurative hidradenitis)[19] and PsAPASH (psoriatic arthritis, PG, acne, and suppurative hidradenitis) syndromes.[20] PG is considered a "diagnosis of exclusion" because of the lack of definitive laboratory or histopathological diagnostic criteria[4] and is thus frequently misdiagnosed as vascular disease (arterial ischaemia or venous insufficiency), vasculitis, malignancies, infections, drug-induced or exogenous tissue injury, and manifestations of other autoimmune diseases.[21] Misdiagnosis can lead to serious morbidity and ultimately to death; the prognosis of PG is characterised by a mortality of 16% to 27%.[22–24] There is no gold standard for treatment of PG; it varies from patient to patient and even varies at different times for the individual patient. Optimal management may include: recognition and avoidance of triggers; appropriate wound care; adequate pain management; treatment of underlying conditions; discontinuation of the suspected drug in case of drug-induced PG; and topical, systemic, and targeted immunomodulatory therapies.[4,6]

The world-wide incidence of PG is estimated to be around 3 to 10 cases per million population per year, usually affecting patients aged 25 to 54 years without a clear gender predilection. Children represent approximately 4% of cases.[5,9,10] These estimations are based mostly on case reports and retrospective case series. To the best of our knowledge, there is only 1 population-based study that assesses the epidemiology of PG[24] and 1 prospective single-centre study that does not give hints about the incidence of PG.[25] The apparent rarity of PG is in contrast with our clinical perception as dermatologists: in our opinion, PG is not so uncommon. Therefore, we decided to investigate the epidemiology of PG in an Italian population and confirm our clinical suspicions that it is not an orphan disease. Here, we describe the first observational multicentre study on PG, performed for 1 year, in 8 Italian Dermatological Departments all around Italy.

Key Messages

- pyoderma gangrenosum (PG) is described as a rare disease, but there are no prospective multicentre studies on the issue
- the aim of this study was to investigate the epidemiology of PG in Italian population; we enrolled all the patients receiving a diagnosis of PG in 8 Italian Dermatological Departments during a 13-month study
- we found an incidence of 5.17 new cases per million population per year, confirming the world-wide epidemiology of PG; to our knowledge, this is the first observational, multicentre study on PG

2 | MATERIALS AND METHODS

In our prospective multicentre study, we enrolled all patients diagnosed with PG in 8 Italian Dermatological Departments (Spedali Civili di Brescia, Ospedale di Circolo e Fondazione Macchi di Varese, Azienda Ospedaliera Sant'Orsola-Malpighi di Bologna, Seconda Università degli Studi di Napoli, Ospedale di Sassuolo, Ospedale "F. Tappeiner" di Merano, Ospedale "Maggiore" di Trieste, Policlinico di Modena) from 1st October 2014 to 1st November 2015.

Diagnosis of PG was performed using the set of criteria proposed by Su et al.,[26] requiring the fulfilment of 2 major criteria: (1) rapid progression of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous, and undermined border and (2) exclusion of other causes of cutaneous ulceration; and at least 2 minor criteria, including: (1) history suggestive of pathergy or clinical finding of cribiform scarring, (2) systemic diseases associated with PG, (3) histopathological findings (sterile dermal neutrophilia, ±mixed inflammation, ±lymphocytic vasculitis), and (4) treatment response (rapid response to systemic corticosteroid treatment).

For each case, we investigated: age and gender of the patient, who referred him or her to the dermatology department (general practitioner, other dermatologist, other specialist), if the manifestation was the first event or was a relapse of the disease, if a skin biopsy was performed, the clinical subtypes of PG (classic/ulcerative, bullous, pustular, vegetative, post-surgical), the affected areas (trunk, superior limb, inferior limb, face, other location, or multifocal), associated conditions (none, haematological, gastrointestinal, autoimmune, others), the topical therapy applied (none, topical calcineurin inhibitors [TCI], steroids, topical antibiotics, antiseptic agents, advanced dressings, other topical products), and systemic therapy (none, steroids, cyclosporine, dapsone, biological drugs, other drugs).

Statistical analysis was performed using Microsoft Excel 2016 (Microsoft Corp, Redmond, Washington).

3 | RESULTS

During the 13-month enrolment period, 64 patients were collected. The mean age was 58.3 years (range 20-93), with equal gender distribution (32 males and 32 female). All our patients were adults, and 40 of them (62.5%) were referred to our clinics for the first manifestation of PG, while the other 24 (37.5%) were evaluated for a relapse of PG. A total of 30 patients (46.8%) were sent to the dermatological division by their general practitioner, 23 (36%) by another specialist, and 11 (17.2%) by another dermatologist. A skin biopsy was performed in 70.3% of patients, while in the remaining 29.7%, diagnosis was based only on clinical manifestations (Table 1).

The classic presentation of a deep skin ulcer with a well-defined violaceous border was the most common clinical finding of PG (68.8%). Other skin manifestations of PG in our series were the vegetative (14.1%) and the pustular variant (9.3%); rarer was the bullous type (3.1%). In 4.7% of cases, PG was post-surgical. We did not report any case of PPG. Concerning the affected areas, the lower extremities were the most frequently affected site (75%), followed by the upper extremities (7.8%) and the trunk (6.2%). Any other areas of the body accounted for the remaining 7.8%, while only 2 patients (3.1%) were affected in more than 1 site (Table 2).

PG was associated with 1 or more systemic diseases in 59.4% of patients: IBD (25%), autoimmune disease (14.1%), haematological disorder (6.2%), and others (17.2%) (Table 3).

The choice of therapy was very similar in the different hospitals: 53 patients (82.8%) were treated with systemic therapy, while 11 (17.2%) used topical therapy alone. Generally, patients underwent topical monotherapy (62.5% of cases), and the application of steroids was performed in more than half of the subjects (54.7%). Advanced dressings have been used in 23 patients (35.9%), antiseptic agents in 16 (25%), topical antibiotics and other topical products in 15 (23.4%), and only 3 patients (4.7%) were treated with TCI (Table 4).

About systemic therapy, 57.8% of the patients has been treated with 1 drug, while 25% required the combination of 2 treatments. The systemic drugs of choice were steroids (29.7%), followed by cyclosporine (15.6%) and dapsone (14.1%); 10 patients (15.6%) were treated with an anti-TNFα biological drug (Table 5).

TABLE 1 General features

	No. of patients (%)
Males	32 (50%)
Females	32 (50%)
First manifestation	40 (62.5%)
Relapse	24 (37.5%)
Sent by general practitioner	30 (46.8%)
Sent by another specialist	23 (36%)
Sent by another dermatologist	11 (17.2%)
Clinical diagnosis	19 (29.7%)
Clinical/histological diagnosis	45 (70.3%)

TABLE 2 Clinical features

	No. of patients (%)
Classic (ulcerative)	44 (68.8%)
Bullous	2 (3.1%)
Pustular	6 (9.3%)
Vegetative	9 (14.1%)
Post-surgical	3 (4.7%)
Lower extremities	48 (75%)
Upper extremities	5 (7.8%)
Trunk	4 (6.2%)
Other area	5 (7.8%)
Multifocal	2 (3.1%)

4 | DISCUSSION

PG is described as an orphan disease: the world-wide incidence is estimated to be around 3 to 10 cases per million population per year, usually affecting patients aged 25 to 54 years without a clear gender predilection.[5,9,10] These estimations are mostly based on case reports and retrospective case series. Langan e al. analysed the incidence, mortality, and disease associations in the United Kingdom, reporting an incidence of between 6.9 and 9.1 cases per million population per year.[24] Jockenhöfer et al., looking at the Diagnosis-Related Group (DRG) introduced in Germany in 2005, reported 1227 patients with PG as the primary diagnosis and 985 patients with PG as secondary diagnosis in 2012.[27] Sadly, the main limitation of the DRG analysis is that it cannot permit the calculation of a real incident of PG. Inoue et al. recently investigated the epidemiology and characteristics of PG in the Japanese population of 9 regional hospitals mainly in Ibaraki Prefecture between 1982 and 2014, recruiting only 62 patients.[28] In their prospective study, Riyaz et al. diagnosed PG in 61 patients in a single department of dermatology in India during the 10-years study period.[25]

In our observational multicentre study, we collected a total of 64 cases, of which 40 were new cases, in a 13-month

TABLE 3 Underlying diseases

	No. of patients (%)
Total	38 (59.4%)
IBD	16 (25%)
Autoimmune	9 (14.1%)
Haematological	4 (6.2%)
Others	11 (17.2%)

Some patients had more than 1 underlying disease.

TABLE 4 Topical therapy

	No. of patients (%)
Monotherapy	40/64
Polytherapy	21/64
None	3/64
Steroids	35 (54.7%)
Advanced dressings	23 (35.9%)
Antiseptic agents	16 (25%)
Topical antibiotics	15 (23.4%)
TCI	3 (4.7%)
Other topical products	15 (23.4%)

TCI, topical calcineurin inhibitors.

TABLE 5 Systemic therapy

	No. of patients (%)
Monotherapy	37/64
Polytherapy	16/64
None	11/64
Steroids	19 (29.7%)
Cyclosporine	10 (15.6%)
Dapsone	9 (14.1%)
Anti-TNFα	10 (15.6%)
Other drugs	11 (17.2%)

period, with a mean age of 58.3 years and equal gender distribution. This being a prospective study, our data on PG are based on clinical diagnosis and not the analysis of retrospective data or DRG. If we consider that the population in the 8 provinces is comprised of nearly 7 729 611 individuals (end of October 2015, data from demoistat.it), we found an incidence of 5.17 new cases per million per year. Thus, unlike our predictions before the study, we confirm the world-wide incidence of PG. However, we think that the real epidemiology of PG could be still underestimated. First, the hospitals participating in the study are not the only dermatological centres of their province. For example, the Spedali Civili of Brescia is only 1 of 5 different dermatological divisions in the province of Brescia. So, it is possible that the incidence would be higher if every centre participated and, ultimately, if there was an Italian register of PG. Secondly, patients affected by skin ulcers may be evaluated by different specialists, such as a general practitioner, general surgeon, plastic surgeon, orthopaedics, etc. In our study, while most of our patients (46.8%) were sent to the dermatologist by the general practitioner and 17.2% of them by other dermatologist, 36% of them were referred to us after being evaluated by other specialists. PG is considered a "diagnosis of exclusion" and is thus frequently misdiagnosed, with grievous consequences in terms of morbidity and mortality. The dispersion of patients affected by PG among different specialists can only facilitate misdiagnosis. Weenig et al. calculated that as many as 10% of PG cases are misdiagnosed. Actual diagnoses, delayed on average by 10 months, included vascular disease (occlusive or venous insufficiency), vasculitis, malignancies, infections, drug-induced or exogenous tissue injury, and manifestations of other autoimmune diseases.[21] In the DRG investigated by Jockenhöfer et al., 985 patients had a secondary diagnosis of PG, while the first was chronic leg ulcers in 75% of cases.[27] The need to rule out an alternative disease should override the fear of exacerbating the condition (because of pathergy) by performing a biopsy.[21] We agree with this paradigm: in 70.3% of our cases, the diagnosis of PG was confirmed on histological features that excluded other causes of skin ulceration.

Clinical findings are similar to those found in the literature[9,10,25,28]: ulcerative PG was the most frequent subtype (68.8% of cases), and the lower extremities were the site of predilection for the arising ulcers, interestingly, in 4.7% of cases with PSPG.

PG is associated with underlying conditions in 50% to 75% of patients, and the most frequent association is with IBD (34%-65.2%) and less frequently with arthritis (16.1%-37%) and haematological disorders (6.5%-20%).[4,9,10,24,25,27,28] In accordance with these data, we found an associated disease in 59.4% of cases, with IBD being the most common, affecting up to 16 patients (25%), even if less frequently than in literature. Secondly, there were autoimmune diseases (like rheumatoid arthritis or diabetes mellitus type I) in 14.1% of patients. Thirdly, 4 subjects (6.2%) had a haematological condition, and 11 (17.2%) had other underlying diseases, usually not described as associated with PG, such as arterial hypertension or diabetes mellitus type II. Nevertheless, in the retrospective multicentre study of Al Ghazal et al., a description is given about a significant association between PG and metabolic/endocrinological diseases,[11] confirmed subsequently by the work on DRG data by Jockenhöfer et al., who report a prevalence of diabetes mellitus type II in 25% of patients affected by PG (>20% respect to normal adult German population).[27]

There is no gold standard in the therapy of PG, but our findings mostly adapt to the indications of other authors.[4,9,10,29] First, we underline the importance of using topical and/or intralesional corticosteroids (used in 54.7% of cases in our study): acting on the pathophysiology of the ulcer, they are particularly effective in treating the indolent, localised, and smaller forms of PG or, in association with systemic therapy, the progressive and malignant cases. In contrast with other reports, TCI have been used in only 3 patients. With regard to systemic drugs, steroids were the mainstay of treatment; second choices were cyclosporine and dapsone. Following the recent expansion on the use of biological drugs, 15.6% of patients have been treated with anti-TNFα with good results, but further studies and trials must be performed before considering these drugs (included IL-1 antagonist and IL-12/23)[30,31] the first choice

in treating PG. Finally, Japanese authors report the use of granulocyte and monocyte adsorption apheresis (GCAP) to treat steroid-resistant PG,[28] but we have no experience with such therapies.

5 | CONCLUSION

In our study, we investigated the epidemiology and the characteristics of PG in an Italian population of roughly 8 million inhabitants of 7 provinces. The data we gathered of 64 patients during the 13-month study period are in accordance with those described in the literature: the incidence of PG was of 5.17 new cases per million population per year. To our knowledge, this is the first observational multicentre study on the matter. Prospective multicentre studies are the only reliable way to collect a critical number of patients to better understand the real epidemiology of PG and its features, being a disease still underestimated and frequently misdiagnosed. In conclusion, we hope that our study provides a stimulus for further research on PG and for the creation of an Italian register.

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