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Predilection sites of pyoderma gangrenosum: Retrospective study of 170 clearly diagnosed patients

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Abstract

Pyoderma gangrenosum (PG) is a non-infectious, neutrophilic dermatosis that was difficult to diagnose in clinical practice. Today, the PARACELSUS score is a validated tool for diagnostics. Based on this score, patients with clearly diagnosed PG were examined with regard to predilection sites. In this retrospective study, the data of patients from the University Hospitals of Essen and Erlangen were analysed in whom the diagnosis of PG could be clearly confirmed using the PARACELSUS score. A total of 170 patients, 49 men (29%) and 121 women (71%) with an average age at first manifestation of 55.5 years, could be included in the analysis. The predilection sites were identified as the lower legs in 80.6% of the patients and the extensor sides in 75.2%. Other localisations of PG were the thighs in 14.1%, mammae and abdomen in 10.0% each, back and gluteal in 7.1% each, feet in 5.9%, arms in 4.7%, genital in 3.5% and head in 2.9%. This retrospective study is the first to identify a collective of PG patients with the highest data quality using the PARACELSUS score. It could be shown that PG can basically occur on the entire integument. However, the predilection sites of PG, which have now been reliably identified for the first time, are the lower legs and in particular the extensor sides.

KEYWORDS

chronic wounds, leg ulcer, PARACELSUS score, predilection sites, pyoderma gangrenosum

Key Messages

- PARACELSUS score is a new, validated diagnostic tool for PG
- This is the first retrospective study using the PARACELSUS score to identify a collective of PG patients with the highest data quality
- PG can occur on the entire integument, but especially the extensor sides of the lower legs are the predilection sites

1 | INTRODUCTION

Pyoderma gangrenosum (PG) is a non-infectious, neutrophilic dermatosis that belongs to the orphan diseases with an estimated incidence of 0.3–1 per 100 000.[1,2] Although initial manifestation of the disease is possible at any age, the risk increases with age, with a peak described as occurring between 75 and 79 years of age.[3] Women are reported to be affected approximately 2–3 times more frequently than men.[3,4] Numerous associated comorbidities have been reported in the literature. Here, inflammatory bowel disease (IBD), diabetes mellitus and rheumatoid arthritis have been described most frequently. In addition, PG is considered a potentially paraneoplastic disease.[3–8]

The underlying pathophysiological processes of PG remain insufficiently understood. A central role seems to be played by autoinflammatory mechanisms with dysfunction of neutrophil granulocytes as well as abnormal T-cell functions.[1,5,7] Here, the important role of IL(interleukin)−1β, −1α, −6, −8, −17, −23, −36α, CXCL1/2/3, RANTES, Fas ligands, JAK (Janus kinases), STAT (Signal Transducers and Activators of Transcription) proteins and TNF (tumour necrosis factor)-α has been particularly pointed out.[7,9–11] In the acute inflammatory phase of PG, systemic glucocorticoids are still the first-line therapy. Increasingly, biologics are also being successfully used to therapeutically target the above-mentioned pathophysiological processes.[1,7]

Sterile pustules or papules that rapidly ulcerate are described as a typical initial symptom. Patients often report suspected insect bites or other traumata as triggers. In principle, PG can develop at any location on the body with hair follicles.[12] Nevertheless, there were repeated reports of predilection sites, which were most frequently described on the lower legs and represent a high relevance, especially under differential diagnostic aspects of leg ulcers as well as the rarity of PG.[7,8,13–16] However, a further differentiated description has not yet been made.

For a long time, PG was considered a diagnosis of exclusion. In the meantime, the diagnosis can be reliably made on the basis of clinical parameters using the PARACELSUS score, so that this score is also recommended, for example, by the current German AWMF guidelines.[1,17]

Due to the difficulty and inconsistency of diagnosis, there are considerable doubts regarding the reliability of the data collected to date.[18] Thus, our intention in this retrospective study was to review patient cases with a coded diagnosis of PG, to re-evaluate them using the PARACELSUS score, and to create a data set with clearly confirmed PG patients. This quality-focused data set should serve as the basis for evaluating predilection sites to make more reliable conclusions about patients with PG.

2 | PATIENTS AND METHODS

2.1 | Inclusion and exclusion criteria

All patients with an ICD-10-coded diagnosis of PG were included in this retrospective study. The observation period was set to documented cases from 2002 to 2021. Patients were treated in the departments of dermatology in the University Hospitals of Essen or Erlangen. Only patients with a PARACELSUS score of ≥10 points were then included in the core data set. All patients with a PARACELSUS score of <10 points were excluded. If individual points could not be clearly traced in patients, they were included as "not present" and thus without a score.

2.2 | Data acquisition

Data acquisition of patients coded as PG was performed exclusively from digital or digitized patient information. In the second step, patients were selected regarding the re-evaluation of the clinical diagnosis. For this purpose, the PARACELSUS score was applied to each patient (Table 1). If the PARACELSUS score was ≥10 points, the diagnosis of PG was considered highly probable, and the corresponding patients were included in the core data set for further statistical analysis. The following items were recorded: Age at initial manifestation, sex, duration to initial diagnosis in months, localisations on the integument (feet, lower legs, thigh, genital, gluteal, abdomen, mammae, back, upper extremities, head), localisation specifically on the lower leg (ventral, medial, lateral, dorsal), number of ulcerations, and recurrences in the same or different localisation.

2.3 | PARACELSUS score

To validate the diagnosis and ensure good data quality, the PARACELSUS score was applied to each of the patients analysed here in the study. The score, published for the first time in 2019, is an acronym of the relevant diagnostic criteria, which are subdivided into major, minor and additional criteria. The three major criteria (three points each) in this score are a progressing disease, assessment of relevant differential diagnoses, and a reddish-violaceous wound border. The four secondary criteria (two points each) include amelioration by immunosuppressant drugs, a characteristically irregular (bizarre) ulcer shape, extreme pain of >4/10 on the visual analogue scale (VAS), and a localisation of lesion at site of trauma (pathergy phenomenon). The three additional criteria (one point each) are suppurative inflammation in

TABLE 1 Second column: PARACELSUS score with points to be awarded, if ≥10 points a PG is considered very likely.

PARACELSUS score		
Major criteria	Points	%
Progressing disease	3	98%
Assessment of differential diagnoses	3	92%
Reddish-violaceous wound border	3	95%
Minor criteria		
Amelioration by immunosuppressant drugs	2	86%
Characteristically irregular (bizarre) ulcer shape	2	63%
Extreme pain >4/10 on visual analogue scale	2	84%
Localisation of lesion at site of trauma	2	42%
Additional criteria		
Suppurative inflammation in histopathology	1	47%
Undermined wound border	1	38%
Systemic disease associated	1	44%

Note: Third column: Percentage evaluation in how many patients the respective criterion applied.

histopathology, undermined wound border and association of relevant systemic disease. With an additive score of ≥10, the presence of PG is considered highly probable (Table 1).

2.4 | Statistics

Statistics were performed using MS Excel tools (version 16.56, Microsoft®). For each of the points recorded during data collection, the sum and percentage, as well as the average and median, were calculated when mathematically appropriate. In addition, statistical comparisons were made within subgroups such as by gender or localisations on the lower leg.

3 | RESULTS

3.1 | Patient cohort

A total of 450 patients were included in whom the diagnosis of PG was coded at the University Hospital of Essen or Erlangen in the period 2002–2021. In a total of 170 patients, the diagnosis was clearly confirmed by a PARACELSUS score of ≥10 points each, whereas in the remaining half of the patients, much information was missing to confirm the diagnosis, and in the other half, a different diagnosis was found in the further course of

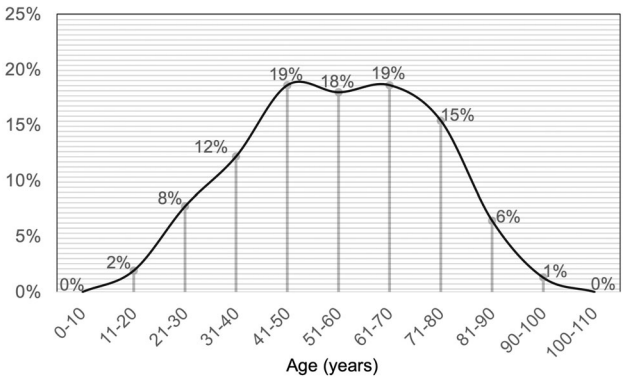

FIGURE 1 Average age of patients at first manifestation of PG.

treatment. This core data set included 49 men (29%) and 121 women (71%). In 164 of the 170 patients, age at first manifestation could be evaluated and calculated. The mean age at first manifestation was 55.5 years and the median was 56.0 years, with the youngest patient being 15 years old and the oldest patient being 95 years old. More than half of the patients (56%) had an age range of 41–70 years. Only 2% of patients were younger than 20 years and 1% of patients were older than 90 years (Figure 1). Arterial hypertension was found in 46% of all patients, type II diabetes mellitus in 29%, chronic venous insufficiency (CVI) in 17% and peripheral arterial disease (PAD) in 11%.

3.2 | Number of wounds

The number of wounds caused by a PG ranged from a single wound to 30 wounds per patient. On average, 45.9% of patients had only one wound and 54.1% of patients had two or more wounds. On average, the number of wounds was 3.2 and the median was two wounds. Looking exclusively at patients with two or more wounds, the median in this subgroup increases to three wounds per patient. Eleven patients (6.5%) had between 10 and 30 wounds.

3.3 | Anatomical localisations

In all 170 patients, the localisations of the PG could be clearly traced, and in some cases several localisations per patient were possible (Figure 2). In 80.6% of the total 170 patients, the lower legs were shown to be most frequently affected by the PG. In this study, where PG was localized to the lower legs, it occurred on the ventral lower leg in 75.2% of patients, the lateral lower leg in 44.5%, the medial lower leg in 38.0% and the dorsal lower

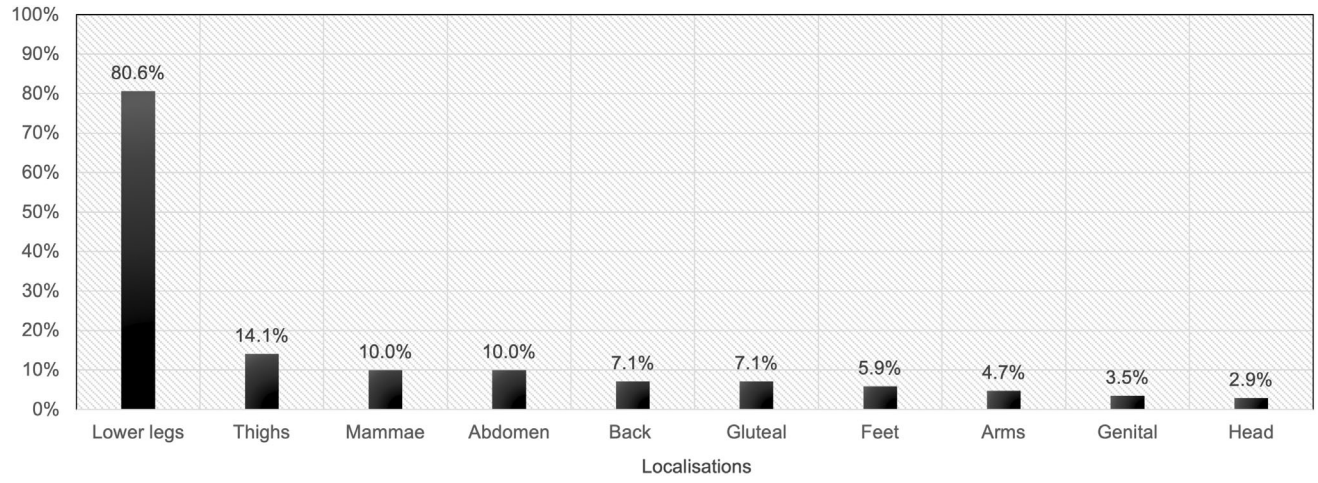

FIGURE 2 Localisation of PG on the integument. Partially with multiple PG localisations per patient.

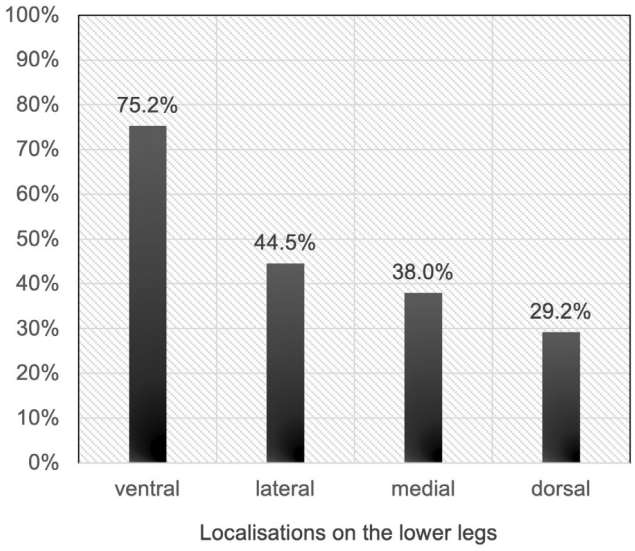

FIGURE 3 Anatomic localisation of PG on the lower legs.

leg in 29.2% (Figure 3). In 44 (32.1%) of these patients, the PG was localized only on the left lower leg and in 46 (33.6%) only on the right lower leg. A total of 47 (34.3%) patients showed PG on both lower legs. Thus, we could not detect a relevant difference with regard to manifestation on the right or left lower leg.

In 14.1% of patients, the PG showed localized on the thighs, in 10.0% each on the mammae and abdomen, in 7.1% each on the back and gluteal, in 5.9% on the feet, in 4.7% on the arms, in 3.5% on the genital and in 2.9% on the head (Figure 2).

3.4 | PARACELSUS score

The PARACELSUS score was recorded and evaluated in all 170 patients. In the major criteria, 98% of these patients showed a (rapidly) progressive disease course, 92% had exclusion of relevant differential diagnoses and 95% had a reddish-violaceous wound border. In the secondary criteria category, 86% of patients responded to immunosuppressant therapy, 63% showed a characteristically irregular (bizarre) ulcer shape, 84% reported extreme pain of >4/10 on the visual analogue scale (VAS) and 42% had a local pathergy phenomenon. For the additional criteria, histopathologic examination of a biopsy revealed suppurative histopathologic inflammation in 47%, undermined wound borders in 38% and 44% had associated systemic diseases (Figure 1). The mean PARACELSUS score in the patients we evaluated was 15 points (minimum 10, maximum 20 points).

4 | DISCUSSION

For our study, we used for the first time a data set on PG in which the diagnosis was based on the validated PARACELSUS score. Thus, these data are different from all previous studies on PG in terms of quality. Data quality is very important in studies of PG because misdiagnosis is otherwise common, especially in this disease entity, which has long been considered a diagnosis of exclusion.[18,19] A retrospective study of 240 patients with a documented diagnosis of PG showed that at least in 95 patients, another diagnosis turned out to be the cause of the wounds in the further course of the disease history. In this study, of the 95 patients with a clinically established suspected diagnosis of PG, a total of 64 patients were treated with immunosuppressants over a mean period of 10 months. Among the initiated systemic immunosuppressive therapies, only 23% of the patients showed transient improvement of symptoms due to

TABLE 2 Examples of clinical differential diagnoses of PG with their respective predilection sites.

Differential diagnosis	Predilection sites
Artificial wounds	Thigh, breast, face
Buruli ulcer	Extremities
Erythema induratum Bazin	Lower leg
Calciphylaxis	Lower extremities
Cutaneous lymphoma	Entire integument
Leishmaniasis	Extremities, face
Livedo vasculopathy	Distal lower leg, dorsum of foot
Lues maligna	Entire integument
Necrobiosis lipoidica	Distal lower leg, dorsum of foot
Arterial leg ulcer	Malleolus lateralis, pretibial
Venous leg ulcer	Malleolus medialis
Hypertensive leg ulcer (Martorell)	Dorsolateral distal lower leg
Cutaneous leukocytoclastic vasculitis	Distal lower leg

vasculitis, antiphospholipid antibody syndrome, or lymphoma as the actual underlying disease and cause of the wound. A total of 36% of the patients showed no improvement in symptoms and 12% of the patients showed a progression of symptoms due to infections caused by the medically unnecessary immunosuppressive therapy or due to progression of the underlying disease.[18] This study impressively shows the frequency of misdiagnosed patients with PG and the resulting consequences. In our analysis, we were also very often unable to confirm the coded diagnosis of PG. In about half of these patients, this was due to incompletely comprehensible diagnostics, as not all patient information could be retrieved over a period of up to 20 years, and in the other half of the patients, there were clear misdiagnoses. In these cases, patients usually presented to the clinic for the first time with a suspected PG and were initially coded correspondingly, although a different diagnosis emerged in the further course of treatment and was treated accordingly. Clinically, there are many differential diagnoses that must be considered and ruled out when PG is suspected (Table 2). For these differential diagnoses, the therapeutic approach is sometimes completely different. Of particular importance are systemic therapies, which should be performed, for example, with immunosuppressants, rheologics or antibiotics.[18] In addition, initial wound treatment often includes surgical debridement, which can lead to a further progression of the symptoms, at least in the inflammatory phase of the PG as a pathergy phenomenon.[17] Here, in view of the pathergy phenomenon, a non-inflammatory time point should be waited for if possible or non-traumatizing alternatives such as biosurgery or proteolytic enzymes should be resorted to.[20,21] Thus, it is clear that all studies published to date on PG must be critically questioned with regard to the safety and reliability of the diagnoses made.

Considering the points listed so far, the importance of a reliable diagnosis of a PG is emphasized both for clinical routine and scientific analyses. Therefore, it is very important that with the PARACELSUS score an easy to collect and reliable diagnostic tool is now available. Alternatively, the so-called Su criteria and the validated Delphi consensus exist as diagnostic scores. In both approaches, different main and secondary criteria are used to establish the diagnosis. In a retrospective study comparing the three established diagnostic instruments, a total of 76 patients diagnosed with PG were included. Of these, the diagnosis of PG was confirmed by experts in 47 patients. Direct comparison of the three diagnostic tools showed that the PARACELSUS score identified 89% (42 of 47) of patients as PG. The Delphi and Su criteria showed only 74% agreement (35 of 47 patients), indicating inferiority in direct comparison with the PARACELSUS score.[22]

With the help of the PARACELSUS score, a validated score for the diagnosis of PG is now available, which is recommended among others by the German guideline and thus ensures a significantly higher as well as more comparable data quality compared with the previously available diagnostic options.[1,22,23]

4.1 | Predilection sites

In some of the clinical studies published on PG, information on the sites of manifestation can also be found. However, due to the rarity of PG, there are few larger and thus representative studies on this diagnosis. Without further differentiation, the lower extremities are reported with a frequency of 57.8%[8] and 79.2%,[14] respectively, especially the lower leg with 71.9%.[24] A differentiated evaluation regarding the exact localisation on the lower leg has not been published in the literature so far. In our study, the lower leg could also be objectified as a predilection site with 80.6%. Thereby, the extensor sides of the lower leg were most frequently affected with 75.2%. The description of the typical morphology and the predilection sites (Table 2) helps in the initial classification of a suspected diagnosis, which then needs to be further clarified by additional, targeted examinations.[25–28] The mean age of 55.5 years was only slightly lower than in

comparable studies, in which the mean age was 63.4,[8] 58.3[14] and 59.8 years.[24]

The pathergy phenomenon can be discussed as a possible reason for the frequent presence of PG on the extensor sides of the lower leg. The pathergy phenomenon refers to the occurrence of a disease-specific lesion due to a non-specific stimulus.[17,29,30] The extensor sides of the lower leg provide a typical anatomic location for minor trauma. Trauma has previously been shown to cause the release of cytokines and other second messengers. For example, there is a release of IL-36 from keratinocytes, leading to activation of the immune response.[31] Among other cytokines, IL-36 has an important role in the pathophysiology of PG, where it contributes to neutrophil granulocyte dysfunction and abnormal T-cell functions through these autoinflammatory mechanisms.[7,9,10,32] In addition, it has been shown that even minor trauma to the skin can also lead to increased expression of the IL-8 gene, which also has an important pathophysiologic role in the development of PG.[33] Thus, there is some evidence that there is a pathophysiologically explainable connection between the often described traumas and the resulting, more frequent occurrence of PG, especially on the extensor sides of the lower legs.

Furthermore, comorbidities were described as often associated factors in patients with PG. Overall, in the analysed patients with PG, arterial hypertension was known in 46% of patients, type II diabetes mellitus in 29%, chronic venous insufficiency (CVI) in 17% and peripheral arterial disease (PAD) in 11%. It must be discussed that in a prospective design of the study, these results would have been found more frequently, because not all patients had a complete vascular, diabetic or blood pressure diagnostic and also the documentation was partly based on the information given by the patients or on the medication taken. These comorbidities could also be demonstrated accordingly in other larger studies.[3–5,15,24]

PG occurs much less frequently on the mammae and abdomen than on the lower legs. In our study, 10.0% of patients showed manifestation of PG in each of these two localisations. These localisations are also particularly related to the pathergy phenomenon, as PG is frequently described here after breast or stoma surgery. As a postoperative complication, PG occupies a particularly difficult and complicated position.[34,35] Nevertheless, both the various scores and the current German guideline on PG recommend performing a biopsy, although this can potentially trigger a pathergy phenomenon. Although histopathological results are often not conclusive in PG, they are helpful, especially for the exclusion of differential diagnoses.[1]

4.2 | Comorbidities

The other comorbidities, especially the systemic diseases associated with PG, can be divided mainly into two categories. First, neoplasms such as solid or haematologic neoplastic diseases, and second, inflammatory disease patterns, also referred to as TRECID (TNF-α related chronic inflammatory diseases).[36] These so-called TNFα-associated diseases are, for example, inflammatory bowel diseases, acne inversa, psoriasis, rheumatoid arthritis and uveitis. The underlying pathophysiology of these syndromes is often similar, so it has been discussed whether the comorbidities are different manifestations of a systemic inflammatory immune response rather than diseases that should be considered separately. Thus, some of these comorbidities may then be treated together, with one strategy. In addition to the TNFα inhibitors originally described, there are now several other biologics or small molecules like janus kinase (JAK) inhibitors that can be successfully used both in the systemic therapy of PG and in the associated comorbidities.[36–38]

4.3 | Limitations

Initially, 450 cases were identified in which the diagnosis of PG had been coded in the last 20 years. In approximately one fourth of the cases, a different diagnosis was identified in the subsequent medical history, as the initial PG diagnosis was refuted. In the remaining patients, data quality was sometimes insufficient to fully collect the PARACELSUS score. For example, objectified information on pain was more often missing. Therefore, it can be assumed that significantly more patients were still treated with a PG in the clinics but were not included in the core data set due to data quality. Depending on this data quality, the scores in the PARACELSUS score could have been higher for some patients. In this way, a smaller data set was finally accepted, which was upgraded with an even higher data quality and data density.

The PARACELSUS score is currently the best diagnostic score for PG evaluation. Nevertheless, even this score does not provide 100% certainty, because false positive and false negative diagnoses must still be considered in patients with PG.

5 | CONCLUSION

Validated PARACELSUS score now offers the possibility to identify a collective with PG patients and a high data quality. Thus, we were able to objectify very reliable data on this rare clinical entity in this retrospective study. In principle, PG can occur on the entire integument.

However, the first reliably identified predilection sites of PG are the lower legs, especially the extensor sides.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest in the context with this study.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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