

Pyoderma gangrenosum: a report of 44 cases with follow-up

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Summary

Results of a study of 44 patients with pyoderma gangrenosum (PG) are presented. Each patient was diagnosed using standardized diagnostic criteria and followed up systematically. Thirty patients were women and 14 men. Their mean age was 50 years (range 11–80). Twenty patients had idiopathic and 14 parainflammatory occurrences (e.g. ulcerative colitis, Crohn's disease), whereas in 10 patients an associated haemoproliferative disease or neoplasia was noted. Whereas idiopathic and parainflammatory PG was found predominantly in women, the association with haemoproliferative diseases occurred more often in men. The lower legs and feet represented the typical predilection sites. Fifty-two per cent of patients had one lesion, 37% had up to five, and 11% had more than five lesions. Histologically, lymphocytic and/or leucocytoclastic vasculitis was present in 73% of the biopsy specimens obtained from the borders of the lesions. Long-term follow-up ($n = 42$, median follow-up 26.5 months) revealed that eight patients had died, in six cases due to the PG and/or the underlying diseases. Of the remaining 34 patients, 44% are in complete remission without further treatment, whereas continuing therapy is needed in 56%. No difference between idiopathic and parainflammatory PG was demonstrable in the follow-up and in no patient with idiopathic PG was a possibly related disease diagnosed in the follow-up. These data suggest that PG should be considered to be an independent disease and not a purely cutaneous complication in most patients.

Pyoderma gangrenosum (PG), first described by Brunsting *et al.* in 1930, is characterized by the occurrence of one or a few chronic ulcerations with typical violaceous and undermined borders.¹ Rare cases with acute onset of multiple ulcerating² or chronic vegetating and granulomatous^{3,4} lesions, as well as bullous PG in association with leukaemia⁵ have been described. PG is associated with systemic disease in more than 50% of patients.^{6,7} To date, more than 500 cases have been published, but there is only one study on more than 40 patients seen at a single centre.^{8,9} In particular, the long-term behaviour of the disease is completely unknown. In 1985, a multiparameter study was started to collect data based on a larger number of patients, especially focused on their long-term follow-up.

Patients and methods

Since 1985, 44 cases of PG following standardized diagnostic criteria (Table 1) were included in the study. These criteria included clinical appearance, and histological examination of at least two biopsies from the border of a typical lesion including direct immunofluorescence staining with antisera against IgG, IgM, IgA and complement factor C3. Histological diagnosis of

a vasculitis was made if at least five of the following six histological criteria were fulfilled: endothelial swelling, fibrinoid necrosis of the vessel walls, erythrocyte extravasation, migration of leucocytes through vessel walls, perivascular infiltrates of neutrophils with leucocytoclasia, and dense perivascular infiltrates of lymphocytes.

Laboratory investigations included the following: full blood cell count with differential, platelet count, serum electrolytes, chemistry studies with a serum analyser, multiple day profiles of blood sugar, haemoglobin A₁ determination, electrophoresis and immunofixation electrophoresis, quantitative serum IgA, IgM and IgG levels, titres of antinuclear antibodies, determination of complement factor C3 and C4, and complete urinalysis including determination of Bence Jones proteinuria. Cytoplasmic immunofluorescent pattern antineutrophilic cytoplasmic antibodies (cANCA) and perinuclear immunofluorescent pattern antineutrophilic cytoplasmic antibodies (pANCA) were determined by immunofluorescence and ELISA in 12 more recently diagnosed patients. The evaluation programme additionally included tests for blood in the stools (Haemocult), chest X-ray, abdominal sonography, and rectoscopy. Gastroscopy, colonoscopy, computed tomographic scans and bone marrow biopsies were performed if any

pathological finding was obtained by clinical or laboratory tests. To exclude diseases relevant for differential diagnosis, all patients suffering from lesions on their legs were subjected to a detailed analysis of the function of their arterial and venous vessels by bidirectional Doppler or colour-coded duplex sonography. Arteriographies and venographies were performed if any pathological findings were obtained.

After establishing the diagnosis, each patient was treated individually. As soon as the initial treatment response could be evaluated, all patients were included in a systematic follow-up programme. Clinical investigations and, if necessary, histological and immunohistological investigations were performed when recurrence was suspected. All data were collected in an SPSS databank and subjected to statistical analysis.

Results

Demography

Forty-four patients were diagnosed between January 1985 and December 1996 as having PG. Between one and six cases were observed each year. Comparison of 3-year intervals (1985–87, 1988–90, 1991–93 and 1994–96), however, revealed a constant frequency of 11 new cases in each of these time intervals. There were 30 women and 14 men (female/male ratio 2:1). The mean age was 50.3 years (range 11–80) for all, 51 years (range 12–78) for men and 50 years (range 11–80) for women. The peak incidence was between the ages of 51 and 60 years.

Clinical and histological data

Ulcerated lesions were the characteristic finding in patients with PG. Fifty-two per cent of patients suffered from one lesion, 37% had up to five lesions and 11% had more than five lesions. Thirty-nine cases represented the classical type with chronic enlarging ulcerated lesions with violaceous undermined borders (Figs 1 and 2). One woman had the acute disseminated form, and another had a prolonged history of a non-healing ulceration on her upper right leg, which histologically showed the superficial granulomatous form of PG initially described by Wilson Jones and Winkelmann.³ In another patient, vegetating ulcerations were present in association with a follicular occlusion syndrome (hidradenitis suppurativa). After 8 years of continuous slow growth, despite intermittent

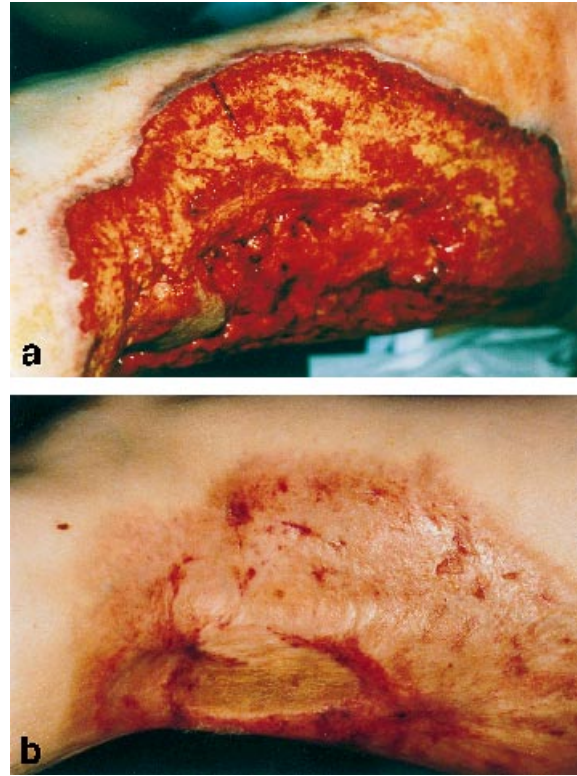


Figure 1. Classical pyoderma gangrenosum associated with osteomyeloclerosis in a 73-year-old woman. (a) Progression was in part due to unsuccessful topical surgical treatments. (b) Healing with scarring after 6 months of therapy with cyclosporin A (5 mg/kg per day) and corticosteroids. Follow-up (40 months) revealed a continuing need for therapy.

therapy of the hair occlusion syndrome with orally administered 13-*cis*-retinoic acid as well as local excisions, ulcerations rapidly resolved after systemic treatment with corticosteroids.

This case belonged to the vegetating form of PG. Two patients suffered from rapidly progressive bullous PG in association with a malignant haemoproliferative disease. A local trauma as the initial event was reported by 17 of the 44 patients; in eight patients, lesions were enlarged by unsuccessful local surgical treatments (Fig. 1) before the correct diagnosis was made. A classical pathergy phenomenon after injection of 1 mL sterile 0.9% NaCl solution was noted in three patients only. Chronic venous or arterial ulcers as well as local bacterial infections were the most frequent false diagnoses.

Eighty per cent of our patients had lesions on their lower legs and feet. The trunk was affected in 36%, the upper legs in 16%, the arms in 14%, and the head and neck regions in 5% of patients. In the biopsy specimens from the borders, a vasculitis, in almost all cases



Figure 2. Classical pyoderma gangrenosum in a 35-year-old woman. (a) Multiple lesions persisted for more than 10 years. No associated disease could be diagnosed. (b) Remission after 4 months of therapy with cyclosporin A (5 mg/kg per day) and corticosteroids. There was a need for continuing therapy (follow-up 20 months).

affecting deep dermal and subcutaneous venules, was found by histopathological examination in 73% of the cases. Of these, 68% were leucocytoclastic and 32% predominantly lymphocytic. Direct immunofluorescence staining of cryopreserved biopsy specimens

revealed positive staining of vessels with antisera against complement factor C3 in 83%, against IgM in 78%, against IgA in 17%, and against IgG in 11% of cases.

Microbiological examination of swabs from the ulcers revealed sterility in 50% of the patients. In the other 22 patients, the presence of *Staphylococcus aureus* was found in nine, *Pseudomonas aeruginosa* in eight, enterococci in five, streptococci and klebsiellae in three, and *Escherichia coli* and *Candida albicans* in one instance(s).

Standard laboratory results revealed no consistent findings typical for PG. The erythrocyte sedimentation rate, for example, was found to be < 15 mm in the first hour (Westergren) in 24% of the patients, and leucocytosis ($> 10 \times 10^9/L$) was present in 32%. The search for the presence of cANCA and pANCA yielded negative results in all 12 patients tested.

Associated diseases

An associated disease was presumed to be relevant for the occurrence of the PG in 24 (55%) of our 44 patients (Table 2). The idiopathic group consisted of 16 women and four men (45%); their mean age was 44 years. Parainflammatory occurrence was noted in 14 (32%) patients, 10 women and four men. Their mean age was 46 years. Rheumatoid polyarthritis ($n = 5$), Crohn's disease ($n = 3$) and ulcerative colitis ($n = 3$) were the most frequent associations. A haematological disease or abnormality in the serum (e.g. paraproteinaemia or cryoglobulinaemia) was present in nine (20%) patients, six men and three women. The mean age of the group was 65 years. A glioblastoma of the brain was associated in another patient, a 57-year-old woman.

Table 1. Diagnostic criteria for pyoderma gangrenosum used in this study

I	Major criteria
1	Occurrence of (a) primary sterile, chronic ulceration(s), typically with violaceous undermined borders
2	Exclusion of relevant differential diagnoses (e.g. pyoderma, ulcerations based on arterial or venous vessel diseases, and ulcerations based on a classical leucocytoclastic vasculitis)
II	Minor criteria
1	Histology from the border of the ulceration: neutrophile-rich infiltration of the dermis with signs for vasculitis and deposits of immunoglobulins and/or complement factors on the vessels
2	Presence of a relevant associated disease (e.g. chronic autoimmune bowel disease, chronic autoimmune arthritis, paraproteinaemia, or haemoproliferative disease)
3	Response to treatment with systemic immunosuppressive therapy, little or no response to conventional external ulcer therapy

Patients fulfilling both major and at least two minor criteria were included in the study.

Table 2. Occurrence of pyoderma gangrenosum and associated diseases ($n = 44$)

Associated condition	Disease	Mean age (years)	Sex	<i>n</i>
Idiopathic		44 (11–75)	16 F, 4 M	20
	Parainflammatory	46 (19–78)	10 F, 4 M	14
	Rheumatoid arthritis			5
	Crohn's disease			3
	Ulcerative colitis			3
	Hair occlusion syndrome			1
	Amoebiasis			1
	Chronic tonsillitis			1
Haematological disease/neoplasm		65 (51–80)	4 F, 6 M	10
	Benign paraproteinaemia			3
	Cryoglobulinaemia			1
	Osteomyelosclerosis			1
	Plasmocytoma			1
	Chronic lymphatic leukaemia			1
	Chronic myelogenous leukaemia			1
	Mycosis fungoides			1
	Glioblastoma of the brain			1

Therapy and follow-up

A comparative study on the effect of different treatments was not the primary aim of our study. Decisions on the type of therapy were instead dependent on the individual medical situation of each patient as well as on the availability of new drugs. The treatment options chosen in our patients were: monotherapy with corticosteroids in 50%, a combination of steroids and azathioprine in 23%, of steroids and cyclosporin A in 16%, of steroids and dapsone in 7% and of steroids and clofazimine in 4%. None of these treatments was found to be ineffective. In one case, a combination of corticosteroids and dapsone was used without sufficient success and a good response was achieved with a combination of corticosteroids and cyclosporin A. One patient with widespread PG did not respond to a local application of cyclosporin A followed by a monotherapy with cyclosporin A performed prior to admission to hospital, but showed good remission with a combination of cyclosporin A and corticosteroids (Fig. 2). The median duration of the initial therapy was 4 months.

Long-term observation ($n = 42$, median follow-up 26.5 months) showed that within the idiopathic group ($n = 18$), 10 patients experienced recurrences of their lesions and needed continuing therapy. One patient died from causes unrelated to his PG. In no case in this group could a possible underlying disease be diagnosed during the follow-up. In the parainflammatory group ($n = 14$), a 78-year-old woman suffered from

a rapidly progressive PG and subsequently died from sepsis. An ulcerative colitis had been diagnosed between the ages of 23 and 56, but she had been in complete remission for 20 years before the PG occurred. Of the remaining 13 patients, continuing therapy was necessary in seven to control their disease. Three of four patients with PG associated with haematological neoplasms died in consequence of their underlying disease. In two of them, a rapidly progressive, bullous PG almost resistant to therapy was present at the time of death. Another patient suffering from associated cryoglobulinaemia died 13 months after the diagnosis of PG had been made. No information about the cause of his death is available. All three patients with benign paraproteinaemias are alive (mean follow-up, 33 months), in two cases without continuing need for therapy.

Discussion

Forty-four patients were found to have PG over a 12-year period, diagnosed using standardized criteria (Table 1). These have proven useful and might be a basis for further studies on PG. The study showed no evidence for an increasing frequency of the diagnosis of PG. From these data, the annual incidence of PG in southern Germany can be estimated to be at least two cases/year per 10^6 population.

Systematic studies including large numbers of patients have rarely been performed so far. The present

knowledge on PG is mostly based on a series of 86 patients studied at the Mayo Clinic in Rochester, NY, U.S.A. between 1971 and 1980 and published in 1985 by Powell *et al.*⁸ With respect to many aspects including the clinical findings as well as the frequency and types of associated diseases, the results of the present study are in good agreement with this classical study. One major difference is the sex distribution of the patients. The present study, in agreement with others,^{9–12} found female preponderance for PG. This is perhaps not surprising, as other reactive neutrophilic dermatoses are also known preferentially to affect females.¹³ In a more detailed analysis the cases were subdivided into the three major forms of PG: idiopathic, parainflammatory and associated with haematological diseases. In the first two groups women are affected much more often than men and the patients are younger. No significant differences with respect to the clinical picture and prognosis were revealed between the idiopathic and the parainflammatory group, suggesting that these two forms of PG are closely related. It is interesting that the patients with idiopathic PG represent a stable subgroup with, in the majority of patients, long-lasting PG lacking an obvious cause. These data support the concept that PG represents a disease on its own and is not a purely secondary manifestation or complication of a systemic disease. Furthermore, the relation between the disease activity of underlying (auto)immune-mediated inflammatory conditions such as rheumatoid arthritis, Crohn's disease or ulcerative colitis, and occurrence of PG was loose, because in most cases these diseases were stable or in clinical remission when the PG occurred. This is in agreement with the view that PG even in this group represents an additional disease and not a cutaneous complication. This is supported by the fact that after stoma revision in patients suffering from ulcerative colitis and Crohn's disease, PG may persist with unchanged activity.^{10,11,14–16}

Men were more often affected by PG associated with haematological diseases and had a worse prognosis, whereas idiopathic PG in men below 50 years of age was rare. The clinical findings in our patients confirm what is already known about PG. Most cases exhibited the classical clinical picture, but the rarer subtypes described in the literature were also found. Histologically, a vasculitis was found in the majority of the biopsies. Both types of vasculitis, predominantly leucocytoclastic and lymphocytic, could be found. The data from our direct immunofluorescence studies are in good agreement with previous results of Ullmann *et al.*,¹⁷

Powell *et al.*¹⁸ and Su *et al.*¹⁹ They further support the view that immunocomplex-mediated vasculitis plays a more fundamental role in the pathogenesis of PG than in other reactive neutrophilic dermatoses such as Sweet's syndrome.¹³

Compared with Powell *et al.* who found only one patient with leukaemia, the frequency of patients with PG and associated malignant haemoproliferative diseases was higher in our study. Many case reports, however, support the view that chronic haemoproliferative diseases including leukaemias and lymphomas play a substantial role in the occurrence of PG. The relation between haemoproliferative diseases and PG is much closer than that between parainflammatory PG and its associated diseases. Not surprisingly, association of PG with haematological diseases and malignancy is associated with a poor prognosis. Six of eight of our patients known to have died since the diagnosis of PG was made belong to this group. The median survival time in these six patients was 12 months.

One of the main aims of our study was to elucidate the long-term behaviour of PG. For both the idiopathic and the parainflammatory group, the results were quite similar: more than 50% of the patients require long-term therapy to avoid recurrences. No evidence for a better prognosis was found in the idiopathic group, again suggesting that PG represents a disease of its own and not a secondary cutaneous complication. The close relationship between idiopathic PG and auto-immune inflammation-associated PG with respect to the affected patients and the long-term clinical outcome leads furthermore to the hypothesis that PG in both groups represents an independent autoimmune disease. Autoimmune phenomena have been suggested to be the cause of PG in myelodysplastic syndromes.²⁰ No experimental studies (e.g. characterization of autoreactive T cells) have so far addressed this issue in detail.

The need for a long treatment in many patients should be included in the treatment plan. Combination therapies such as corticosteroids and cyclosporin A or azathioprine were effective and well tolerated by the patients in this study. No comparative therapeutic trials have yet been published for PG²¹ and it should be kept in mind that any decision on treatments is based on empirical data only.

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References

- 1 Brunsting LA, Goeckermann WH, O'Leary PA. Pyoderma (echthyma) gangrenosum—clinical and experimental observations in five cases occurring in adults. *Arch Dermatol* 1930; **22**: 655–80.
- 2 Callen JP, Woo TY. Vesiculopustular eruption in a patient with ulcerative colitis. *Pyoderma gangrenosum*. *Arch Dermatol* 1985; **121**: 399–402.
- 3 Wilson Jones E, Winkelmann RK. Superficial granulomatous pyoderma: a localized vegetative form of pyoderma gangrenosum. *J Am Acad Dermatol* 1988; **18**: 511–21.
- 4 Schnetter D, Haneke E. Pyoderma gangrenosum vegetans. An overview of chronic pyoderma vegetans and pyoderma gangrenosum. *Hautarzt* 1994; **45**: 635–8.
- 5 Perry HO, Winkelmann RK. Bullous pyoderma gangrenosum and leukemia. *Arch Dermatol* 1972; **106**: 901–5.
- 6 Powell FC, Su WPD, Perry HO. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.
- 7 Hüner A, Hornstein OP, von den Driesch P. Pyoderma gangrenosum—Klinik, assoziierte Erkrankungen und Therapiemöglichkeiten. *Dtsch Arztebl* 1995; **92**: A1998–2002.
- 8 Powell FC, Schroeter AL, Su WP, Perry HO. Pyoderma gangrenosum: a review of 86 patients. *Q J Med* 1985; **55**: 173–86.
- 9 Odeh F. Pathogenesis and prognosis of pyoderma gangrenosum (dermatitis ulcerosa). *Z Hautkr* 1981; **56**: 1572–7.
- 10 Cairns BA, Herbst CA, Sartor BR, Briggaman RA *et al*. Peristomal pyoderma gangrenosum and inflammatory bowel disease. *Arch Surg* 1994; **129**: 769–72.
- 11 Tjandra JJ, Hughes LE. Parastomal pyoderma gangrenosum in inflammatory bowel disease. *Dis Colon Rectum* 1994; **37**: 938–42.
- 12 Ko CB, Walton S, Wyatt EH. Pyoderma gangrenosum: associations revisited. *Int J Dermatol* 1992; **31**: 574–7.
- 13 von den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol* 1994; **31**: 535–56.
- 14 Talansky AL, Meyers S, Greenstein AJ, Janowitz HD. Does intestinal resection heal the pyoderma gangrenosum of inflammatory bowel disease? *J Clin Gastroenterol* 1983; **5**: 207–10.
- 15 Mir Madjlessi SH, Taylor JS, Farmer RG. Clinical course and evolution of erythema nodosum and pyoderma gangrenosum in chronic ulcerative colitis: a study of 42 patients. *Am J Gastroenterol* 1985; **80**: 615–20.
- 16 Levitt MD, Ritchie JK, Lennard Jones JE, Phillips RK. Pyoderma gangrenosum in inflammatory bowel disease. *Br J Surg* 1991; **78**: 676–8.
- 17 Ullman S, Halberg P, Howitz J. Deposits of complement and immunoglobulins in vessel walls in pyoderma gangrenosum. *Acta Derm Venereol (Stockh)* 1982; **62**: 340–1.
- 18 Powell FC, Schroeter AL, Perry HO, Su WP. Direct immunofluorescence in pyoderma gangrenosum. *Br J Dermatol* 1983; **108**: 287–93.
- 19 Su WP, Schroeter AL, Perry HO, Powell FC. Histopathologic and immunopathologic study of pyoderma gangrenosum. *J Cutan Pathol* 1986; **13**: 323–30.
- 20 Enright H, Jacob HS, Vercellotti Howe R *et al*. Paraneoplastic autoimmune phenomena in patients with myelodysplastic syndromes: response to immunosuppressive therapy. *Br J Haematol* 1995; **91**: 403–8.
- 21 Chow RK, Ho VC. Treatment of pyoderma gangrenosum. *J Am Acad Dermatol* 1996; **34**: 1047–60.