Pyoderma gangraenosum associated with autoimmune thyreopathy and hyperandrogenic syndrome

M. Nečas, V. Semrádová and V. Vaškù

SUMMARY

An unusual clinical appearance and course of pyoderma gangraenosum (PG) in a 35-year-old woman is presented. Signs of both the ulcerative and vegetative forms of PG were expressed. The association of two systemic diseases, the autoimmune thyreopathy and the hyperandrogenic syndrome were observed in a female. The recommended conventional therapy for PG: corticosteroids, antibiotics, cyclosporine and cyclophosphamide yielded a poor response, whereas after thyroidectomy and reaching an euthyroid state the symptoms receded. This close association of PG and autoimmune thyreopathy supports the autoimmune concept of PG.

KEY WORDS

pyoderma gangraenosum, autoimmune thyreopathy, management

Introduction

Pyoderma gangraenosum (PG) is a rare, destructive, inflammatory skin disease in which a painful nodule or pustule breaks down to form a progressively enlarging ulcer with raised, tender, undermined borders (1). Lesions may be solitary or multiple and present either as a purely cutaneous manifestation or be associated with a systemic disease (in 50-80% of cases): with ulcerative colitis and Crohns disease in about 33%, with polyarthritis in 33% , with IgA-gammopathy in about 10%, with malignancies in 7%, and also with further conditions like chronic active hepatitis and Behçet syndrome. There are anecdotal reports of other concomitant rather than associated diseases like chronic active hepatitis, atrophic gastritis, sarcoidosis, systemic lupus erythematosus, Wegener granulomatosis, acne conglobata, hidradenitis suppurativa and thyreopathy (1-3). The etiology of this disorder is still unknown.

As for the clinical manifestations of PG we can distinguish 4 main variants of PG: ulcerative, pustular, bullous and vegetative (3-5). A superficial granulomatous form of PG described by Lachapelle et al. is closest to the vegetative form of PG (6). An overlap between the different forms is possible (7). The exact etiology of PG is still not known.

When Brunsting et al. described PG in 1930, they implicated streptococci as causative agents. Today PG is no longer supposed to be triggered by either bacteria or by other infectious agents. The concept of pathergy is probable as new lesions may follow trivial trauma suggesting that an over-expressed or deviated immunity could be responsible for the development of PG. No consistent pattern of an immunologic hyperreactivity has, however, emerged so far (1,8).

The disorder shares certain characteristics with autoimmune diseases (4,7). Some authors consider PG a T lymphocyte mediated disorder with subsequent activation of macrophages which produce IL-8, attracting neutrophils, which play the central pathogenetic role in PG (7,8). The responsible antigen activating the T lymphocytes is so far unknown, and it could be an antigenically modified tissue component appearing in a patient with altered immune reactivity (3). Intrinsic defects have been observed in neutrophils and macrophages, with impaired chemotaxis and abnormal phagocytosis (3,10).

PG affects predominantly adults, and both men and women alike (5). The age of onset is mostly between 25 and 54 years (5). There are no specific serologic or histological markers for PG, so the diagnosis is established on clinical and histopathologic criteria (1, 4, 5,10).

Many conditions have been confused with PG: ulcus cruris, pyoderma, bacterial synergistic gangrene, atypical mycobacterioses, cutaneous tuberculosis, deep fungal infections, amebiasis, leishmaniasis, wound infections, tertiary syphilis, Wegener's granulomatosis, Behçet disease, antiphospholipid syndrome, bromoderma, neoplasmas and artefacts (1,4,5,7,8,10).

Topical treatment alone is rarely efficient so systemic treatment must be used in most cases of PG. Application of corticosteroids (CS) is mostly considered to be the best treatment (the so-called golden standard) (11,12). The CS-sparing drugs like azathioprine or cyclophosphamide (5,12) are additional therapeutic options. In the last few years cyclosporine has been found to be effective and is considered by some authors to be the treatment of choice (7,9).

Further therapeutic options are sulfasalazine, dapsone, clofazimine, antibacterial agents, chlorambucil, thalidomide and tacrolimus (12). Anecdotal treatment options are plasmapheresis, interferon alpha 2A, GM-CSF and mycophenolate mophetil (4,10,12)

Case report

In February 1997 a 35-year-old woman with a history of hirsutism and thyreopathy developed a small ulcer over the inner ankle of her left leg, followed by a similar lesion in the left hypogastrium. Initially she was diagnosed as pyoderma vegetans and treated with antibiotics (cefuroxim, ampiciline, etc.) in combination with prednisone. Consequently the diagnosis was modified into pyoderma gangraenosum and the patient was treated with cyclosporine (up to 400 mg daily). All the above mentioned therapeutical strategies had only a temporary effect and did not stay the subsequent progression of the disease.

In January 1999 the patient was referred to our clinic, where she presented with an extensive (30 x 20 cm) serpiginous vegetating, proliferating and partially cicatricial lesion on her left calf (Figure 1) and a small oval hyper-pigmented and slightly scarred lesion in the left hypogastrium (Figure 2).

She had also papulonecrotic acne on her back, hirsutism and a palpable struma, and in addition she was trembling and cachectic. The lesions and skin caused her considerable discomfort.

On admission the laboratory tests revealed an elevated sedimentation rate, leucocytosis, an elevated CRP test and a slightly elevated testosterone level of 3,47 nmol/l (normal values 0.25-3.5 nmol/l). She also had extremely elevated levels of thyroid hormones: T4 over 309 pmol/l (normal values 10-25 pmol/l), and T3 7.48 nmol/l (1.23-3.2 nmol/l), as well as positive antibodies against the microsomes of the thyroid gland: 283 IU/ml. The results were interpreted by the endocrinologist as an exacerbation of her chronic thyreotoxicosis. The patient confessed that since six months she had discontinued the therapy with the thyreostatic agent carbimazole (Carbimazol, Slovakofarma), and the drug was reintroduced.

Staphylococcus aureus, Streptococcus pyogenes and *Proteus mirabilis* were found in the lesions.

Tuberculosis, tertiary syphilis, deep fungal infection and malignancy were excluded. The histopathology revealed pseudoepitheliomatous hyperplasia of the epidermis, granulation tissue with newly formed vessels and a chronic inflammatory infiltrate with numerous small abscesses filled with neutrophils and eosinophils, supporting the diagnosis of pyoderma vegetans. The patient was treated with cefuroxime in a long-term regimen. The treatment led to central healing of the lesions, but a peripheral spreading of the ulcer in the patient's left calf was observed. In July 1999 the lesion on the patient's left calf healed but left a scar.

In October 1999 several new lesions developed at various sites: on the right thigh (Figure 3), on the right leg, above the right hip, and later on the right shin. Elevated levels of thyroid hormones and antithyroid autoantibodies reappeared. The patient had again discontinued her therapy with carbimazole.

Due to the rapid progression and to the presence of *Proteus mirabilis* and *Streptococcus beta haemolyticus*, a diagnosis of bacterial synergistic gangrene was also considered and treatment with procain penicillin G and ciprofloxacine was instituted.

Evaluation of a biopsy from the fresh lesions was consistent with the diagnosis of PG. Prednisolone in an initial dose of 30 mg daily was added together with the antibiotics azithromycine and clarithromycine simultaneously. This treatment led to partial healing.

Finally a combined treatment with cyclophosphamide (at an initial dose of 50 mg daily) and prednisone, beginning in August 2000, led to the stabilization of the disease.

After thyroidectomy the histopathology confirmed the diagnosis of struma parenchymatosa Basedow in April 2001, and a slow healing of the lesions on the lower ex-

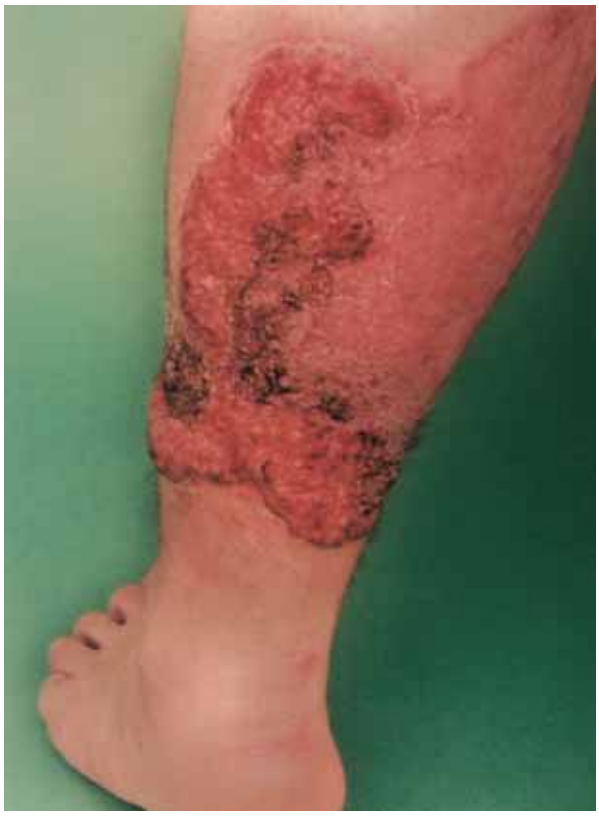

Figure 1. Initial lesion of PG on the left calf.

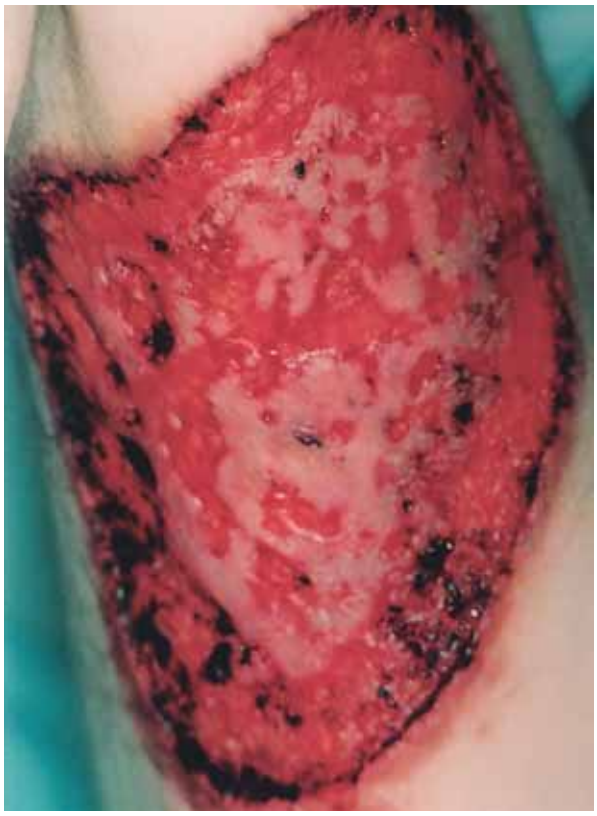

Figure 3. New lesions of PG on the patient's right thigh.

tremities has set in. Since July 2003 all lesions have completely healed with hyperpigmented scars (Figure 4).

The patient has a maintenance therapy with prednisone 5 mg every second day and cyclophosphamide 50 mg 5 times a week, and she also has substitution therapy due to the thyroidectomy as well as cyproterone acetate.

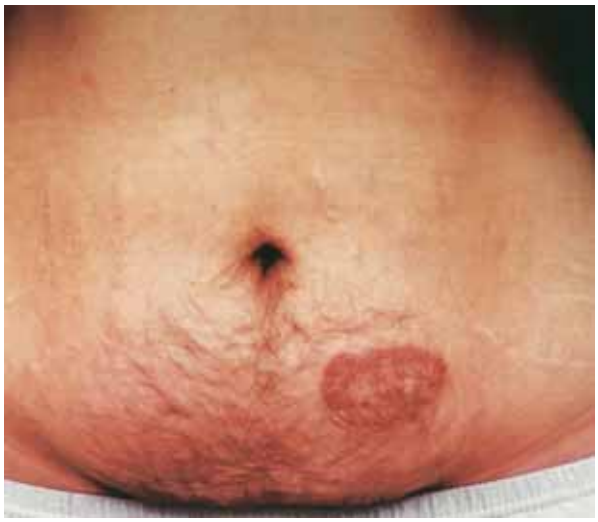

Figure 2. Initial lesion of PG in the left hypogastrium.

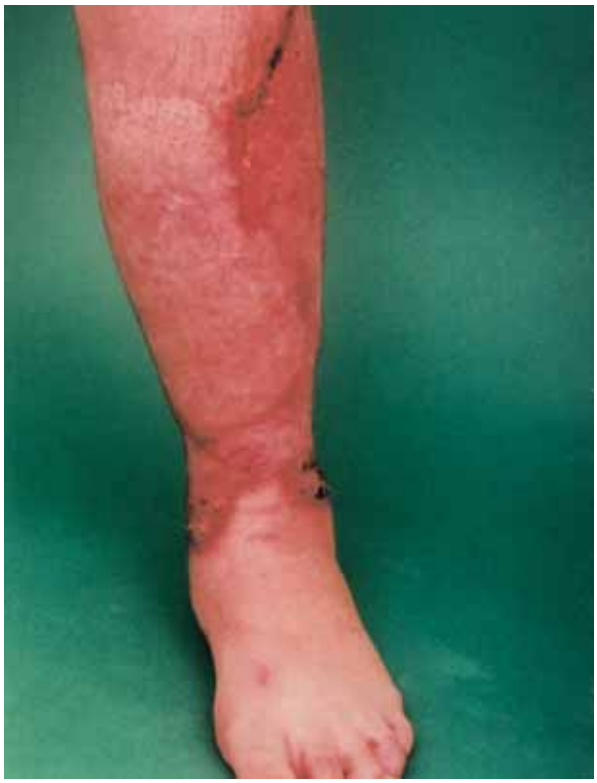

Figure 4. Healed lesions on the left calf.

Discussion

The diagnosis of PG was based on the character of lesions, the histopathology, some laboratory tests, the course, and also on the exclusion of other conditions that may provoke similar ulcerations. Bacterial synergistic gangrene was considered, and the suspicion of pyoderma vegetans was supported by the presence of mixed bacterial flora in the ulcers. The effect of antibiotic treatment alone was insufficient. By analyzing all the available data a diagnosis of pyoderma gangraenosum was accepted, although some lesions were not entirely typical.

Considering the main clinical variants of PG we attributed the majority of the lesions to the vegetative form of PG. On the lower extremities some lesions could be attributed to the ulcerative form: the ulcers were slowly spreading in a serpiginous pattern. The base was exophytic, while the borders were not undermined, but very painful.

The effect of antibiotics was relatively positive but short-lived.

Corticosteroids and immunosuppressive agents which are widely used for the treatment of PG produced only a limited success: prednisone alone acted only on the more superficial and more acute lesions with the exception of those on the lower extremities; cyclosporine had a good effect only in the early stage of the disease, but later its effect was controversial. The combination of prednisone and cyclophosphamide proved to be efficient and accelerated the healing.

The most interesting aspect of this case is the striking correlation between the course of pyoderma gangraenosum and the activity of thyreopathy. As soon as the thyroidectomy was performed and the euthyroid state was reached, the lesions started to heal rapidly.

The association of PG with some internal diseases is well known.

We have, however, not found such a close association of PG with autoimmune thyreopathy in medical literature as we observed in our case, where exacerbations of PG manifested themselves immediately after the decompensation of the autoimmune thyreotoxicosis.

A second endocrine disorder in our patient, hyperandrogenic syndrome, had no influence on the course of PG.

Conclusion

This case shows that PG is sometimes difficult to diagnose, and sometimes even more difficult to treat, and that it is always necessary to look for and treat any associated disorder.

The association of PG with the autoimmune thyreopathy supports the autoimmune etiopathogenesis of PG, at least in this case.

REFERENCES

1. Fitzpatrick TB, Eisen AZ, Wolff K, et al. Pyoderma gangraenosum. Dermatology in General Medicine. McGraw-Hill; 1987. p. 1328–36.

2. Kashefsky H, Callahan E, Ruder UC, et al. Pyoderma Gangraenosum Involving the Foot. J Am Podiatr Med Assoc. 1999; 89(3): 137–40.

3. Kilian J, Pizinger K. Pyoderma gangraenosum. Čs Derm 1997, 72 (5): 198–201.

4. Müller M, Vaškù V, Semrádová V. Pyoderma gangraenosum in a patient with a chronic lymphatic leukemia and prostatic carcinoma. Čs Derm 1999; 74(6): 249–52.

5. Powel FC, Su WPD, Perry HO. Pyoderma gangraenosum: Classification and management. JAAD 1996; 34: 395–409.

6. Lachapelle JM, Marot L, Jablonska S. Superficial granulomatous pyoderma gangraenosum of the face, successfully treated by cyclosporine: A long-term follow-up. Dermatology 2001; 202: 155–7.

7. Blitz NM, Rudikoff D. Pyoderma gangraenosum. Mt Sinai J Med 2001 Sep-Oct; 68 (4-5): 287–97.

8. Weiss SJ. Tissue destruction by neutrophils. N Engl J Med 1989; 320: 365–76.

9. Jarčušková D, Benečová K, Ficová M, et al. Pyoderma gangraenosum-clinical aspects, management. Čs Derm 2002; 77(2): 80–3.

10. Huish SB, De la Paz EM, Ellis PR, et al. Pyoderma Gangraenosum of the Hand: A Case Series and Review of the Literature. J Hand Surg 2001; 26(4): 679–85.

11. Masarovičová A. Current possibilities of local and systemic treatment of pyoderma gangraenosum. Čs Derm 1996; 71(2): 72-4.

12. Mokni M, Philips T. Management of pyoderma gangraenosum. Hosp Pract (Off Ed). 2001 Apr 15; 36(4): 40–4.

AUTHORS' ADDRESSES

Miroslav Nečas MD, Dept. of Dermatovenereology, St. Ann's Faculty Hospital, Pekarská 53, 656 91 Brno, Czech Republic
Vera Semrádová MD, PhD, Professor and Chairlady, same address
Vladimír Vaškù MD, PhD, Ass. Professor, same address