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CASE REPORT

Symmetrical, painful ulceration of the lower limbs in a vascular surgery ward: a diagnostic challenge
Pyoderma gangrenosum associated with IgG-κ paraproteinaemia

S. Simsek[1*], R.F.F. van den Haak[2], A.E. Voskuyl[3], J.A. Rauwerda[2], R.J.M. Strack van Schijndel[4]

Departments of [1]Endocrinology/Diabetes Centre, [2]Surgery, [3]Rheumatology and [4]Internal Medicine, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, the Netherlands, tel.: +31 (0)20-444 43 07, fax: +31 (0)20-444 43 13, e-mail: Simsek@vumc.nl, * corresponding author

ABSTRACT

We describe a 61-year-old patient who had been suffering from chronic ulcers of both legs for 18 months. Initially, his condition was diagnosed as ischaemic because of an ankle-brachial index of 0.6, as confirmed by additional angiography.

A successful femoro-infragenual bypass procedure was performed, but the ulcers increased in size and number. He was then extensively analysed for a possible (macro)vascular origin of his symptoms. Angiographic analysis of both legs showed no arterial stenosis or occlusion. Despite the extensive experience of the vascular surgeons with leg ulcers, consultations by internal medicine, vascular medicine and dermatology, and tissue examination by our pathologists, pyoderma gangrenosum was not recognised. During a multidisciplinary meeting one of the specialists, to whom the lesions were shown, immediately considered the diagnosis on clinical grounds. The additional finding of IgG-κ paraproteinaemia and improvement of the ulcers on treatment with corticosteroids were consistent with the diagnosis. Although the majority of patients on the vascular surgery ward have ulcers caused by ischaemia or a combined arterial/venous origin, another (rare) cause, namely pyoderma gangrenosum in association with IgG-κ paraproteinaemia without the presence of multiple myeloma, should be taken into account.

INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon, idiopathic, chronic ulcerative inflammatory skin disease.[1-5] Four types of PG have been recognised: the ulcerative, pustular, bullous and vegetative types.[4] The first type is characterised by a severely painful ulceration surrounded by an erythematous halo. In the majority of the affected patients there is an underlying condition, usually inflammatory bowel diseases (such as ulcerative colitis, Crohn's disease and diverticular disease), arthritis (such as rheumatoid arthritis, spondylarthropathy), chronic hepatitis and haematological malignancy (including acute and chronic myeloid leukaemia, myelofibrosis, lymphoma) and solid tumours of the colon, bladder, prostate, breast, bronchus, ovary, and adrenocortical carcinoma. This type is commonly located on the lower limb, but location on the trunk, penis, head and neck, breast, and ocular sites have also been reported. The ulcerative form of PG typically affects people in the age range 25 to 55 years. The second type is also painful with pustules again surrounded by an erythematous halo. This condition is usually associated with inflammatory bowel disease (ulcerative colitis) and rarely with polycythaemia rubra vera, hepatobiliary disease and pyostomatitis vegetans. The third type (also designated as atypical PG) is characterised by painful vesicles, with a tendency to enlarge rapidly in waves with central necrosis and erosion with an erythema as a surrounding halo. This type is usually present in

combination with haematological dyscrasias. Confusion with Sweet's disease (acute febrile neutrophilic dermatosis) can easily occur. Sweet's disease is very uncommon and characterised by uncomfortable chronic erythematous plaques with sinus discharge. Other disorders associated with PG include HIV, hepatitis C, thyroid disease, diabetes mellitus, cryoglobulinaemia, lupus erythematosus, dermatomyositis, sarcoidosis, vasculitis (Wegener's granulomatosis, Takayashu's arteritis, Behçet's disease) and paroxysmal nocturnal haemoglobinuria (*table 1*).
The association of the ulcerative type of PG with benign monoclonal gammopathy, especially of immunoglobulin A (IgA), has also been described.[6-9] We report a patient suffering from the ulcerative type of PG of both legs, which was found to be associated with IgG-κ paraproteinaemia.

CASE REPORT

A 61-year-old patient was admitted to the department of vascular surgery because of chronic ulcers of both legs (for 18 months). These ulcers were initially identified as ischaemic lesions (an ankle-brachial index of 0.6) and femoro-infragenual bypass surgery was performed. Soon after this operation, he developed more painful ulcers, despite normalisation of the ankle-brachial index. Moreover, subsequent angiographic analysis of the arteries of the legs showed an open bypass without any indication for (macro)vascular stenosis/occlusion. Duplex examination did not show venous occlusion either. The patient had been treated with several antibiotics, without any improvement in the clinical situation. Then he was send to our university hospital. Cardiovascular risk factors, including hypertension and dyslipidaemia, were adequately controlled. He was not complaining of headache, fever or changes in bowel movement. Further medical history was unremarkable. Physical examination revealed a normal blood pressure, normal temperature, lack of tenderness of the temporal arteries, and large ulcerations involving the pretibial area of both legs, with blood and pus in the centre and a region of deep necrosis (*figure 1A*). Laboratory data disclosed an elevated erythrocyte sedimentation rate (100 mm/h), Hb 6.2 mmol/l, MCV 82 fl, leucocytosis 11.9 x 10^9/l with 90% neutrophils, normal platelet count, slightly elevated creatinine level 152 μmol/l, and a normal calcium. Thyroid function was normal. Tests for hepatitis B, C and lues were negative. Antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies and antiphospholipid antibodies were absent. A chest radiogram and a computer tomography of the abdomen revealed no abnormalities. A skin biopsy revealed lymphocytic as well as neutrophilic inflammation. Moreover, the biopsy showed plasma cells, necrosis and re-epithelialisation. Vasculitis was absent in the biopsy.

Table 1
Diseases associated with pyoderma gangrenosum

INFLAMMATORY BOWEL DISEASE	
(Chronic) ulcerative colitis	
Crohn's disease	
Diverticular disease	
Regional enteritis	
ARTHRITIS	
Seronegative with inflammatory bowel disease	
Seronegative without inflammatory bowel disease	
Rheumatoid arthritis	
Spondylarthropathy	
HAEMATOLOGICAL DISEASE	
(Acute and chronic) myelocytic leukaemia	
Monoclonal gammopathy (IgA)	
Hairy cell leukaemia	
Myelofibrosis	
Polycythaemia rubra vera	
Lymphoma: Hodgkin's disease, non-Hodgkin's disease, cutaneous T cell	
IMMUNE ABNORMALITIES	
Humoral	Congenital and acquired hypogammaglobulinaemia
	Selective, complete and hyperimmunoglobulin E syndrome
	Streaking leucocyte factor
Cell-mediated	Defective neutrophil function: reduced chemotaxis and impaired phagocytosis and oxygen uptake, aberrant neutrophil trafficking
	Abnormal monocyte function
	Abnormal response to skin antigens
	Congenital deficiency in leucocyte-adherence glycoproteins
	Immunodeficiency/immunosuppression
SOLID TUMOURS ASSOCIATED WITH PG	
Colon, bladder, prostate, breast, bronchus, ovary, adenocortical carcinoma	
DRUGS TRIGGERING PG	
Alpha 2b-interferon	
OTHERS	
Chronic active hepatitis, cryoglobulinaemia and hepatitis C, thyroid disease, pulmonary disease, hidradenitis suppurativa, acne conglobata, sarcoidosis, atrophic gastritis, diabetes mellitus, systemic lupus erythematosus, Takayasu's arteritis, dermatomyositis, HIV, Wegener's granulomatosis, sensorineuronal deafness, paroxysmal nocturnal haemoglobinuria, peripheral ulcerative keratitis, lung injury, primary biliary cirrhosis	

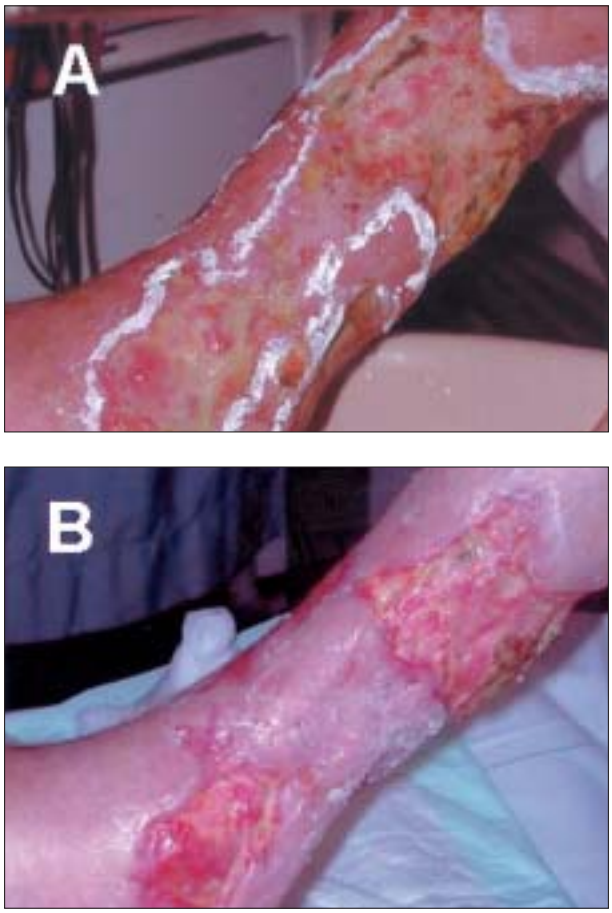

Figure 1
Ulcerative pyoderma gangrenosum before (A) and after (B) treatment with steroids

Initially a definitive diagnosis could not be made. During a multidisciplinary meeting, however, one of the specialists, to whom the lesions were shown, immediately considered the diagnosis pyoderma gangrenosum on clinical grounds. Further laboratory analysis, i.e. serum protein electrophoresis, showed an IgG-κ paraproteinaemia. To see whether there was a systemic skeletal involvement additional radiograms were performed, without signs of multiple myeloma. Moreover, neither cytology nor histology of the bone marrow showed a localisation for multiple myeloma. The ulcers of both legs started to heal within a week after treatment with prednisolone 1 mg/kg was initiated (*figure 1B*). Altogether, the presence of the monoclonal gammopathy and the improvement of the lesions after treatment were consistent with PG.

DISCUSSION

Pyoderma gangrenosum in association with IgG-κ paraproteinaemia is uncommon.[10-12] Although the association with monoclonal IgA gammopathy is well recognised, multiple myeloma is rarely found. Also in our patient, we could not find signs of systemic skeletal involvement. The conditions that may mimic ulcerative PG are systemic vasculitis, dermatitis artefacta, infection (mycobacterial, atypical mycobacterial, amebiasis, syphilis, herpes simplex, deep fungal infection), drug reactions (hydroxyurea), insect bite (spider), synergistic gangrene, antiphospholipid syndrome and cutaneous neoplasma (*table 2*). PG is a diagnosis of exclusion, so the above-mentioned conditions should be ruled out before the diagnosis of PG is made. Weenig *et al*. have described that substantial misdiagnosis of skin ulcers as PG can occur (approximately 10%).[10] Misdiagnosis of PG can expose patients to risks associated

Table 2
Differential diagnosis of pyoderma gangrenosum

ULCERATIVE PG
Systemic vasculitis
Dermatitis artefacta
Infection: (atypical) mycobacterial, amebiasis, syphilis, herpes simplex (especially in HIV patients), deep fungal infections
Drug reactions (hydroxyurea)
Insect bite (spider)
Synergistic gangrene
Antiphospholipid syndrome
Cutaneous neoplasms
PUSTULAR PG
Infection: bacterial, viral, fungal
Gonococcal septicaemia
Folliculitis
Pustular vasculitis
Pustular drug eruptions
Bowel bypass syndrome
Pyostomatitis vegetans
BULLOUS PG
Atypical Sweet's syndrome
Insect/arthropod bite
Viral infection (in immunocompromised patients)
Acute cellulitis
Bullous mycosis fungoides
Bullous dermatoses (erythema multiforme, etc.)
VEGETATIVE PG
Pyoderma vegetans
Blastomycosis-like pyoderma
Deep fungal infection
(Atypical) mycobacterial infection
Dermatitis artefacta
Cutaneous neoplasm

with its treatment. In that study, 95 patients appeared to have skin ulcers caused by other diseases, although initially PG was suspected. These causative diseases were vascular occlusive or venous disease (such as antiphospholipid syndrome, venous stasis ulceration and type I cryoglobulinaemia), vasculitis (among them Wegener's granulomatosis, polyarteritis nodosa and cryoglobulinaemic (mixed) vasculitis), cutaneous involvement of malignant process (usually lymphoma), primary cutaneous infection (such as deep fungal infection, herpes simplex virus type 2, cutaneous tuberculosis), drug-induced or exogenous tissue injury (among them Münchausen's syndrome/factitial disorder, hydroxyurea-induced ulceration). The authors thus stress the need to follow a thorough diagnostic evaluation, including collecting careful medical historical data, being aware of characteristic features on physical examination, performing a skin biopsy for not only histopathological purposes but also for tissue culture, and ordering laboratory investigations with the aim of ruling out diagnoses that mimic PG (such as erythrocyte sedimentation rate, complete blood count, blood chemistry, protein electrophoresis, chest radiography, antiphospholipid, antinuclear, and antineutrophil cytoplasmic antibodies). When PG is eventually established as the diagnosis, the patient should be evaluated thoroughly to rule out other diagnoses after long-term follow-up.

However, in our patient, the opposite of what Weenig *et al.* described in their study population happened. Namely, it took rather a long time before a definitive diagnosis of PG was made, due to the other possible causes of the ulceration. Skin biopsies in all forms of PG are characterised by a central necrosis accompanied by a massive peripheral neutrophilic infiltration and perivascular and intramural lymphocytic infiltrates.[13] A possible pathogenetic mechanism underlying the association between PG and monoclonal gammopathy could be the defective monocyte function, as was suggested by Norris *et al.*[14] and Jones *et al.*[12] Other possible mechanisms include abnormality of neutrophil and monocyte chemotaxis, phagocytosis (including defective leucocyte adhesion glycoproteins), mast cell activation, hypogammaglobulinaemia or association with hyperimmunoglobulinaemia E.[5,13] Crowson *et al*. mention in their review article that the pathogenetic mechanism and the initial trigger are dependent on the associated/underlying systemic disease, eventually leading to the endpoint of a neutrophilic dermopathy with diverse destruction of the epidermis and the adnex.[13]

In conclusion, we report a patient with chronic ulcers of both legs with a history of peripheral bypass surgery and (cardio)vascular risk factors. Despite an extensive search for an ischaemic aetiology, a rare diagnosis, pyoderma gangrenosum associated with IgG-κ paraproteinaemia, was found to be the cause of the lesions. This case illustrates that the diagnosis of pyoderma gangrenosum is not easy: many specialists were involved before one of them coined the possibility of a PG. Since the disease is rare, recognition is difficult. Suspicion of PG should be raised when ulcers are present on the lower legs that are painful and symmetrical and for which there is no other obvious explanation. A thorough diagnostic effort must be made to reveal underlying disease when PG is diagnosed.

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