

Fatal Bullous Pyoderma Gangrenosum in a Patient with Klinefelter's Syndrome

Angelo V. Marzano, Valentina Trevisan, Chiara Galloni and Elvio Alessi*

Institute of Dermatological Sciences, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via Pace 9, IT-20122 Milano, Italy. *E-mail: francesca.alessi@unimi.it
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Sir,

Pyoderma gangrenosum (PG) is an idiopathic neutrophilic dermatosis may occur in association with a wide variety of disorders, including inflammatory bowel disease, haematological and rheumatological conditions, and states of perturbed immune function. In addition to the classical ulcerative form of PG, less common variants exist. Among these, bullous PG was first described in 1972 as a painful superficial blistering and eroded dermatosis in patients with leukaemia (1). Because of their clinical similarity, some authors believe that bullous PG and atypical Sweet's syndrome represent points on a continuum of diseases that have in common dermal neutrophilia (2).

We describe here a male patient with Klinefelter's syndrome who developed bullous PG resistant to various immunosuppressive regimens and died following the occurrence of septicæmia.

CASE REPORT

A 60-year-old man presented to our department with an ulcerative skin lesion that had appeared as a nodule on the right leg approximately 10 days previously. The lesion was painful and accompanied by fever that was unresponsive to systemic antibiotic therapy. The patient was divorced and had no children. No significant clinical precedents were present. Physical examination revealed a 6×10 cm, superficial ulcerative lesion with

hemorrhagic blistering edges on the right leg (Fig. 1a). In addition, an erythematous violaceous nodule, with a central pustule, was present on the left leg. In the following 72 h both lesions underwent a dramatic evolution, the first rapidly extending to involve almost the entire leg (Fig. 1b) and the second also becoming ulcerative. Laboratory examination disclosed increased erythrocyte sedimentation rate (100 mm/h; normal 1–20) and macrocytic anaemia (Hb 9.6 g/dl; normal 12.0–16.0). Immunological investigations showed positive antinuclear antibodies at a titre of 1:160 with a fine speckled pattern and anticardiolipin antibodies (11.7 IgM phospholipid units and 26.6 IgG phospholipid units; normal limits <10). Results of a wide coagulation screening, including, among others, partial thromboplastin time, factor V Leiden, prothrombin mutation, homocysteine, factor VIII: C, plasminogen activator inhibitor-1, protein S and protein C and lupus anticoagulant, were within normal limits. Serology for various viruses, notably Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus, were negative or consistent with previous infections. Microbiological cultures for bacteria, mycobacteria and fungi, both from lesional skin and blood, yielded negative results. Instrumental analyses, notably total body computerized axial tomography and recto-colonoscopy, failed to reveal any abnormalities. Bone marrow aspiration and biopsy also showed no changes. As the patient had mild gynaecomastia and small firm testes, karyotyping was performed, both from bone marrow specimens



Fig. 1. (a) Ulcerative skin lesion with haemorrhagic bullous edges on the right leg on admission to our department. (b) Rapid spreading of the lesion 72 h after admission.

and blood, by quinacrine fluorescence (QFQ) banding technique, disclosing a 47 XXY karyotype, which is diagnostic for Klinefelter's syndrome. We also determined the serum levels of testosterone (1.6 nmol/l; normal 10–35), follicle stimulating hormone (12.0 U/l; normal 1.0–10.5) and luteinizing hormone (13.9 U/l; normal 1.0–8.4), suggesting hypergonadotrophic hypogonadism. Thus, androgen replacement therapy with a monthly 250 mg i.m. injection of testosterone enanthate was started. Biopsy specimens taken from the edges of the ulcerative lesion were consistent with PG. Intravenous methylprednisolone 80 mg daily was given, achieving resolution of the fever and halting the progression of the disease within one week. To obtain more rapid clinical improvement, oral cyclosporine (300 mg daily) and pentoxifylline (1200 mg daily) were added, but with poor response. Cyclosporine was then substituted by the tumour necrosis factor- α blocking agent infliximab, 5 mg/kg of body weight intravenously, on a schedule consisting of 3 infusions at time 0 and after 2 and 6 weeks, respectively. However, after the second infliximab infusion, fever (41°C) recurred and cultures led to isolation of methicillin-resistant *Staphylococcus aureus* (MRSA) from both lesional skin and blood. In spite of various intravenous antibiotics, the fever and septicaemia did not resolve and the patient died about 3 months after onset of the disease. Autopsy was refused by the patient's family.

DISCUSSION

Klinefelter's syndrome is the most frequent major abnormality of sexual differentiation in men, with a prevalence of 1 in 500 male births (3). Among clinical manifestations of dermatological interest, leg ulcers occur in 13% of cases of Klinefelter's syndrome (4). Platelet hyper-aggregability, abnormalities in fibrinolysis, and elevation of plasminogen activator inhibitor-1 activity were implicated as possible pathogenetic factors in these patients. Also, immunological abnormalities resulting in coagulation dysfunction, such as positive antinuclear factor and antiphospholipid

antibodies, are thought to influence the formation of leg ulcers in Klinefelter's syndrome (5). Moreover, a higher incidence of immune-mediated diseases in men with Klinefelter's syndrome than in healthy men was observed, possibly related to the low levels of testosterone (5). We report here the first case to our knowledge of Klinefelter's syndrome occurring in association with PG and antiphospholipid antibodies. We realize that PG-like lesions as a cutaneous manifestation of the so-called antiphospholipid antibody syndrome (APS) might be considered for the present case, particularly based on the resistance to therapy (6). However, criteria for the diagnosis of APS, as recently established (7), could not be fulfilled in our patient. Finally, we speculate that both immunological changes and Klinefelter's syndrome in itself may have contributed to the pathophysiology of PG in the present case and determined its aggressive clinical behaviour, as for PG seen in the setting of myeloproliferative disorders.

Conflict of interest: None to declare.

REFERENCES

1. Perry HO, Winkelmann RK. Bullous pyoderma gangrenosum and leukemia. *Arch Dermatol* 1972; 106: 901–905.
2. Caughman W, Stern R, Haynes H. Neutrophilic dermatosis of myeloproliferative disorders. Atypical forms of pyoderma gangrenosum and Sweet's syndrome associated with myeloproliferative disorders. *J Am Acad Dermatol* 1983; 9: 751–758.
3. Klinefelter HF, Reifenstein EC, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without Leydigism, increased excretion of follicle stimulating hormone. *J Clin Endocrinol* 1942; 2: 615–627.
4. Campbell WA, Newton MS, Price WH. Hypostatic leg ulceration and Klinefelter's syndrome. *J Ment Defic Res* 1980; 24: 115–117.
5. Igawa K, Nishioka K. Leg ulcer in Klinefelter's syndrome. *J Eur Acad Dermatol Venereol* 2003; 17: 62–64.
6. Schlesinger IH, Farber GA. Cutaneous ulceration resembling pyoderma gangrenosum in the primary antiphospholipid syndrome: a report of two additional cases and review of the literature. *J La State Med Soc* 1995; 147: 357–361.
7. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002; 346: 752–763.