Leg Ulcers Associated with Positive Lupus Anticoagulant in Two Cases of Klinefelter's Syndrome

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Klinefelter's syndrome (KS) is caused by the presence of an extra X-chromosome. Leg ulcers occur in 6–13% of patients with KS (1). The occurrence of leg ulcers is related to a variety of factors, including chronic venous insufficiency (2), platelet hyperaggregability (3, 4) and elevated levels of plasminogen activator inhibitor-1 (PAI-1) (5, 6). We report here 2 KS patients with positive lupus anticoagulant who had leg ulcers, suggesting that immunological abnormalities may be associated with the development of leg ulcers in KS.

CASE REPORTS

Case 1. A 56-year-old Japanese man visited our hospital with painful ulcers on both legs. He had been treated with oral prednisolone at a dose of 5 mg/day for rheumatoid arthritis for the past 24 years. Necrotic ulcers were found in the malleolar and pretibial regions of both legs, along with dense brown pigmentation (Fig. 1a). Laboratory studies revealed a red blood cell count of 3.49×10^6/μl, white blood cell count of 7.07×10^3/μl and platelet count of 2.44×10^5/μl. There were no abnormalities in the prothrombin time, partial thromboplastin time or plasminogen level. Spontaneous aggregation of platelets was not observed, and the PAI-1 activity was normal. A nuclear pattern of antinuclear antibody was detected at 1:80 (normal range, < 1:40) without antibodies to single-stranded DNA, double-stranded DNA, Sm, SS-A/Ro or SS-B/La. Rheumatoid factor level was within the upper limit of normal (10 IU/ml; normal range, 0–10 IU/ml). Lupus anticoagulant was positive by both kaolin clotting time and platelet neutralization procedure, whereas anti-cardiolipin antibody, β2 glycoprotein 1 antibodies, and cryoglobulin were negative. Hormonal examinations showed a low serum testosterone level (0.21 ng/ml; normal range for adult males, 2.01–7.00 ng/ml), and high follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels (26.1 mIU/ml and 7.2 mIU/ml, respectively; normal ranges for adult males, 2.00–8.30 mIU/ml and 0.79–5.72 mIU/ml, respectively). Chromosomal analysis revealed a 47,XXY/46,XY mosaic karyotype. A diagnosis of KS was made, associated with positive lupus anticoagulant. In addition to 5 mg of prednisolone, he was treated with warfarin, limaprost alfadex and low-dose aspirin for 4 years, but his ulcers became worse. We administered testosterone enanthate at a dose of 250 mg/month for 3 months. This treatment alleviated his ulcers, and lupus anticoagulant became negative. In addition to administration of testosterone, his leg ulcers were healed completely by skin graft (Fig. 1b). No recurrence on his legs was observed during 3 months of follow-up.

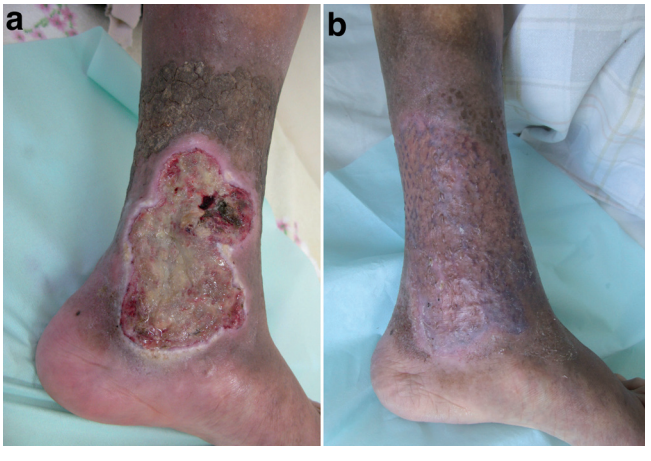

Fig. 1. (a) A large necrotic ulcer on the left lower leg of case 1. (b) Healed leg ulcer after therapy.

Case 2. A 50-year-old Japanese man was diagnosed with systemic lupus erythematosus (SLE) with a 4-year history of malar rash and increased titres of anti-nuclear antibody (1:10,240) and anti-double-stranded DNA antibody (36.2 IU/ml; normal range, < 12 IU/ml). Histopathological features of the malar rash were compatible with SLE. His condition responded to oral prednisolone at 20 mg/day, which was tapered and maintained at a lower dose of 5 mg/day. Five years later, he suffered from a refractory painful ulcer on his left leg (Fig. 2). Laboratory examinations showed mildly increased IgG anti-cardiolipin antibody (12 U/ml; normal range, < 10 U/ml), and lupus anticoagulant was detected by kaolin clotting time. Laboratory examinations, including PAI-1, were normal. Hormonal examinations revealed low serum testosterone level (0.06 ng/ml) with high levels of FSH (38.0 mIU/ml) and LH (9.9 mIU/ml). Chromosomal analysis revealed a 47,XXY/46,XY mosaic karyotype. A diagnosis of KS was made, associated with positive lupus anticoagulant. The patient rejected our suggestion to try testosterone administration. He was treated with warfarin, cilostazol and low-dose aspirin, but his ulcers were refractory to anticoagulant therapy.

DISCUSSION

Leg ulcers occasionally occur in patients with KS. The pathogenesis is unclear, but recent reports suggested that some abnormalities in coagulation/fibrinolysis pathways, such as high levels of PAI-1 activity (5, 6) and platelet hyperaggregability (3, 4), have been implicated as causes of ulcer formation. In particular, increased PAI-1 activity is a likely pathogenic factor of leg ulcers in KS, because testosterone was reported not only to improve the leg ulcers, but also to normalize PAI-1 activity in KS (7). This effect of testosterone is consistent with the inverse relationship between testosterone and PAI-1 activity (8).

However, our two cases showed normal PAI-1 activity. Instead, positive lupus anticoagulant associated with autoimmune diseases (rheumatoid arthritis and SLE) suggests that immunological abnormalities are probably related to the development of the leg ulcers in these cases. Igawa & Nishioka (9) also reported a case of leg ulcer in KS syndrome that showed immunological abnormalities, such as the presence of antiphospholipid

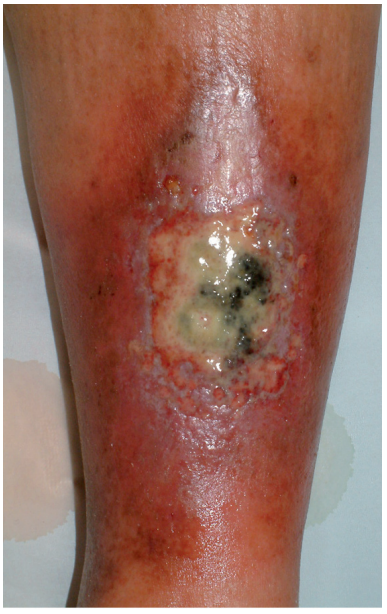

Fig. 2. An ulcer on the left lower leg of case 2.

antibodies. Testosterone administration improved the leg ulcer in their case, similar to our case 1. KS is occasionally associated with autoimmune diseases, such as SLE and Sjögren's syndrome (10), and these autoimmune diseases were also improved by testosterone administration (11). Therefore, the formation of the leg ulcers in KS is attributed not only to the abnormalities of PAI-1 activity and platelet hyperaggregability, but also to immunological defects due to androgen deficiency.

The authors declare no conflicts of interest.

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