Venous Leg Ulcers in a Patient with Klinefelter's Syndrome and Increased Activity of Plasminogen Activator Inhibitor-1

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Sir,

Klinefelter's syndrome, originally described by Klinefelter et al. in 1942 (1), is the most frequent major abnormality of sexual differentiation in men with two or more X-chromosomes. Its prevalence has been estimated at one male birth in 500. The prevalence of leg ulcers as a result of a venous insufficiency in patients with Klinefelter's syndrome is about 13% (2). The pathogenesis of this venous insufficiency is still unknown.

CASE REPORT

A 65-year-old Caucasian male with a history of recurrent deep vein thrombosis of both legs since puberty had suffered from ulcers on both legs for about 40 years. The patient was married but had no children. Our patient shows the typical features of Klinefelter's syndrome, with eunuchoid body proportions, obesity (height 188 cm, weight 93 kg), scanty facial and body hair, gynaecomastia and small, firm, 2 ml volume-containing testes (Fig. 1).

Ulcers were found in the malleolar and pretibial regions of both legs along with oedema, atrophie blanche and purpura jaune d'ocre caused by severe post-thrombotic syndrome. A chromosome analysis revealed a 47 XXY karyotype. Routine laboratory investigations including prothrombin time, partial thromboplastin time, fibrinogen level and plasminogen level were within normal limits. In a subsequent analysis, we found increased activity of plasminogen activator inhibitor-1 (PAI-1) in the plasma. The patient refused any further hormone diagnostics and further therapy apart from ulcer treatment. He was treated with an initial surgical debridement followed by a conservative phase-adapted, wound-healing strategy and then compression therapy, until complete recovery (Fig. 2). As a life-long prophylaxis for thrombosis, oral anticoagulation therapy with a coumarin derivative that had been taken for 5 years was continued.

DISCUSSION

Leg ulcerations in patients with Klinefelter's syndrome are often attributed to venous insufficiency

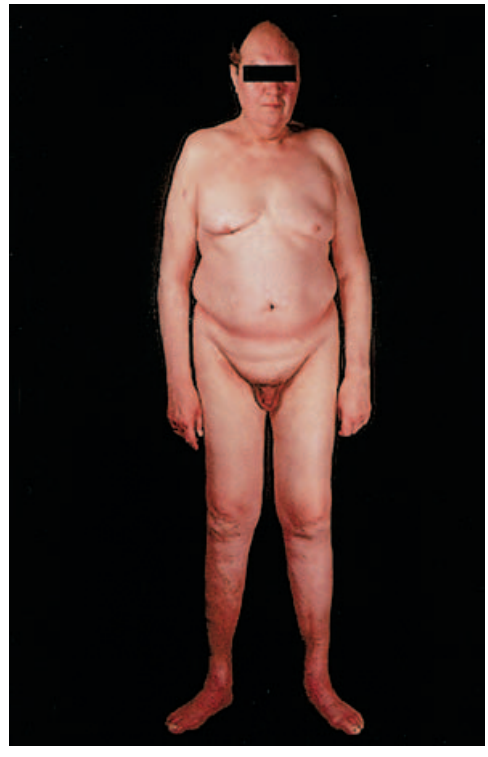

Fig. 1. A 65-year-old patient with Klinefelter's syndrome and recurrent venous leg ulcers. Note eunuchoid body proportions, obesity, scanty facial and body hair, gynaecomastia, and small testes.

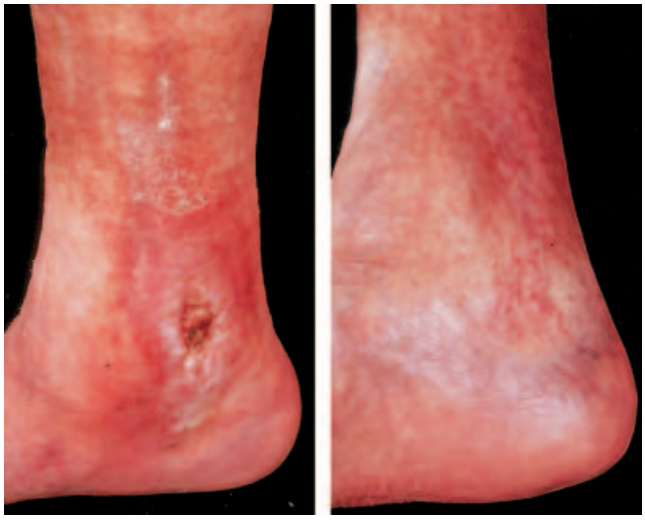

Fig. 2. Before phase-adapted wound therapy, both of the lower legs showed fibrinous and necrotic ulceration (left) which is not seen after therapy (right).

and complicated by thromboembolic processes. Some investigators have found an association between Klinefelter's syndrome and thrombophlebitis (3, 4), or evidence of platelet hyperaggregability (5). Local impairment of fibrinolysis leading to the development of microthrombi may be another important factor in these thromboembolic processes (6). Fibrinolysis is partly regulated by a group of plasminogen activator inhibitors (PAI). Two different PAI have recently been identified. PAI-1 is the primary inhibitor of the tissue plasminogen activator (t-PA) as well as of the urokinase plasminogen activator (u-PA). PAI-1 can be found, for example, in plasma, platelets, or endothelial cells (7, 8). A causal relationship between venous leg ulcers and elevated levels of PAI-1 activity in Klinefelter's syndrome has been discussed (6, 9). Increased activity of PAI-1 may indicate diminished fibrinolysis in Klinefelter's syndrome, known to be associated with relative androgen deficiency. It has been demonstrated that there is an inverse relationship between testosterone and PAI-1 levels (10). Furthermore, since a bilateral orchidectomy in rats has been shown to induce an increase in the activity of PAI-1, and administration of testosterone results in venous ulcer healing and stimulates fibrinolysis, the underlying problem may be associated with androgen deficiency (11–14). Therefore supplemental androgen therapy may be a satisfactory strategy in the long-term treatment of PAI-1-related venous ulcers in Klinefelter's syndrome.

Dermatologists should be aware that recurrent phlebothromboses in young patients with subsequent severe post-thrombotic syndrome and chronic venous leg ulcers may be a manifestation of a congenital syndrome.

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