

CLINICAL REPORT

Association Between Venous Leg Ulcers and Sex Chromosome Anomalies in Men

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We report here two cases of men, aged 46 and 23 years, with refractory chronic venous leg ulcers in association with sex chromosome aberrations: one with a 47,XXY/48,XXXY karyotype (Klinefelter syndrome) and the other with a 47,XXY karyotype (Jacob syndrome). In both patients, the occurrence of leg ulcers was the reason for seeking medical care; their medical history was otherwise unremarkable. Chromosomal analyses were performed due to the unusually young age for development of venous leg ulcers. The pathophysiology behind the occurrence of venous leg ulcers in patients with numerical aberrations of the sex chromosomes is incompletely understood. Involvement of elevated plasminogen activator inhibitor-1 levels in the pathogenesis of venous leg ulcers has been reported in patients with Klinefelter syndrome. Notably, our patient with 47,XXY/48,XXXY presented with androgen deficiency but normal plasminogen activator inhibitor-1 activity. Key words: Klinefelter syndrome; Jacob syndrome; sex chromosomes; chronic venous insufficiency; plasminogen activator inhibitor-1.

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Chronic leg ulceration affects between 1.5 and 3.0 per 1000 people. The prevalence in western countries increases with age, to approximately 20/1000 in people over 80 years of age (1). In 57–80% of patients, chronic venous insufficiency (CVI) is the underlying problem for non-spontaneously healing ulcers. Active or healed venous leg ulcers occur in approximately 1% of the general population western countries (2). Risk factors for chronic insufficiency include family history of CVI, age, female sex, obesity, pregnancy, prolonged standing, greater height, and cigarette smoking in men (3). Given its strong dependence on age (4), the occurrence of venous leg ulcers in young patients should prompt the consideration of additional rare risk factors, such as hereditary coagulation defects or other genetic disorders/diseases.

Klinefelter syndrome (XXY syndrome) affects approximately 1–2 per 1000 male newborns worldwide (5).

However, up to 80% of current patients are undiagnosed. Multiple clinical features and coexisting disorders are associated with Klinefelter syndrome. Among those, venous leg ulcers due to recurrent phlebothromboses and subsequent post-thrombotic syndrome (PTS) occur in approximately 13% of all patients with XXY syndrome (6). Jacob syndrome (47,XXY syndrome) has an incidence of approximately 1.5 per 1000 live male births, and/but may as well also be underdiagnosed. It has also been reported to predispose to chronic leg ulcers (7).

Since patients with undiagnosed sex chromosome anomalies are often seen for their leg ulcers by a dermatologist, increasing awareness of this association is of crucial importance to enable earlier diagnosis and management of the underlying genetic disorder (genetic counselling, etc.).

CASE REPORTS

Case 1

A 46-year-old unmarried male was admitted to our department with non-healing bilateral leg ulcers of approximately 2 years' duration (Fig. 1a). He worked as a baker with prolonged periods of standing. Physical examination revealed marked obesity (body mass index (BMI) 41) as a risk factor for venous insufficiency. Additionally, he presented with eunuchoidal bodily proportions (Fig. 1b), sparse body hair and small testes (Fig. 1c). In his lower legs, both the *dorsalis pedis* and *posterior tibial* pulses were palpable bilaterally and no varicose veins were obvious. Chromosomal analysis revealed a 47,XXY/48,XXXY mosaic karyotype (Klinefelter syndrome). Routine laboratory examinations, including erythrocyte sedimentation rate, haemoglobin concentrations, numbers of platelets, blood sugar, liver and renal functions were all within normal limits. Hormonal examinations revealed a low serum testosterone level (1.3 ng/ml, normal range for adult males 3.0–9.0 ng/ml), elevated luteinizing hormone level (20.9 mU/l, normal range 1.5–9.3 mU/l) and follicle-stimulating hormone level (30.5 mU/ml, normal range for adult males 1.4–18.1 mU/ml). Extensive coagulation analyses showed no abnormalities in prothrombin time, partial thrombin time, fibrinogen, anti-thrombin III, protein C/protein S anticoagulant pathway, plasmino-



Fig. 1. Case 1. (a) Venous leg ulcer on the right lower leg (*left*) and the left lower leg (*right*) in a patient with Klinefelter syndrome (47,XXY/48,XXXY karyotype). (b) The patient also has central obesity and gynecomastia, and (c) feminine fat distribution and testicular atrophy.

gen activator inhibitor-1 (PAI-1) activity. Immunological laboratory examinations showed negative anti-nuclear antibodies, anti-phospholipid antibodies and cryoglobulins. A diagnostic work-up was performed and revealed bilateral great saphenous vein insufficiency by Duplex ultrasound and osteoporosis by bone densitometry. The patient was treated with continued consistent compression therapy in combination with androgen replacement for a 3-month period, but this did not significantly improve ulcer healing. Removal of segments of insufficient veins by bilateral cross-section resulted in rapid and complete ulcer healing without recurrence for more than 6 months (end of follow-up period).

Case 2

A 23-year-old unmarried man presented with a lower leg ulcer above the left inner ankle, which he had had for approximately 13 months (Fig. 2a). The patient's BMI was 22 (Fig. 2b). He worked in the catering and hotel industry with periods of prolonged standing. His

medical history revealed 3 deep venous thromboses in his left leg 3 subsequent years. Six months prior to admission he had undergone valvular reconstruction of the proximal great saphenous vein due to chronic venous disease caused by obstruction of the deep venous system with PTS. The patient's medical history was otherwise unremarkable. Routine laboratory examinations, examinations, coagulation and immunological analyses were also within normal ranges, except for a mildly elevated homocysteine level (16.5 $\mu\text{mol/l}$; normal range $< 12.0 \mu\text{mol/l}$). Apart from cigarette smoking and being of unusually tall stature no other risk factors for CVI were identified. Chromosome analysis was performed because of the patient's young age for developing venous leg ulcers, and revealed a 47,XYY karyotype (Jacob syndrome). After conservative management with compression therapy and consequent bed-rest/horizontal body position, which failed to facilitate ulcer healing, meshed skin grafting was performed. Skin grafting resulted in rapid and complete ulcer healing without any/with no recurrence for a period of 7 months (end of follow-up period).



Fig. 2. Case 2. (a) Venous leg ulcer on the left inner ankle in a patient with Jacob syndrome (47,XYY karyotype). (b) The patient has a tall thin body, with thin chest and shoulders, many superficial blood vessels, and sparse body hair.

DISCUSSION

The overall prevalence (for the adult population in the age range 18–79 years) of venous leg ulcers in western countries is estimated to be approximately 0.6% for healed and 0.1% for non-healed ulcers. Notably, the prevalence of venous leg ulcers is strongly dependent on age, with 0.2% occurring between 30 and 39 years of age and 2.4% occurring between 70 and 79 years of age for healed ulcers (8). Recurrent venous thromboses in young patients with subsequent severe PTS and chronic venous leg ulcers are commonly caused by underlying hereditary haemostasis disorders, or may occur in the context of other congenital syndromes. The most common hereditary disorders of haemostasis so far appear to be deficiencies of anti-thrombin III, protein C, and protein S, and activated protein C resistance. Less frequently, dysfibrinogenemia, increased plasminogen activator inhibitor levels, as well as deficiencies of tissue plasminogen activator or heparin cofactor II may be found (9). Klinefelter (XXY) syndrome and hyperhomocysteinaemia are prime examples of rare congenital disorders indirectly associated with an elevated risk of thrombosis in young individuals.

In most cases, XXY syndrome is not diagnosed until adulthood. In addition, approximately 75% of adult males with XXY are estimated to be undiagnosed. Since it affects one in 500–1000 males, a substantial number of venous leg ulcers in young male patients may be attributable to Klinefelter syndrome.

Leg ulcers in Klinefelter syndrome have been proposed to be caused by CVI and complicated by recurrent phlebothromboses. The predisposition for venous ulceration has been partly explained by common risk factors for primary venous disease, since men with venous stasis are known to be significantly taller and more obese than age-matched control subjects, and patients with XXY tend to be tall and obese. Furthermore, the underlying problem may be associated with androgen deficiency, as men with CVI have been generally shown to be less fertile. Some clinical reports have suggested a causal relationship with abnormalities in the fibrinolytic pathway, such as platelet hyper-aggregability, factor V Leiden mutation, decreased anti-thrombin III level, elevated factor VIII activity and particularly elevated levels of PAI-1 activity (10, 11). The serine protease inhibitor PAI-1 is the primary physiological inhibitor of tissue plasminogen activator and urokinase, the activators of plasminogen and hence fibrinolysis. Abnormalities in concentration of PAI-1 are frequently associated with vascular disease. For example, it is elevated in a variety of thrombotic conditions, including myocardial infarction and deep venous thrombosis. Interestingly, the major sources for PAI-1 are adipocytes. In this regard, the key role of the adipose tissue is emphasized by the fact that, in obesity, expression of PAI-1 is dramatically

up-regulated (12). The correlation between PAI-1 activity and BMI appears to be independent of age or sex. In one study of 13 XXY patients the authors concluded that PAI-1 activity is not elevated in Klinefelter syndrome in general. In these patients, PAI-1 activity was highly significantly elevated in the subgroup with leg ulcerations when compared with the subgroup without ulcerations and elevation of PAI-1 activity was found to be unrelated to other PAI-1 influencing parameters (e.g. age, testosterone level, BMI, diabetes) (13). The clinical relevance of a causal relationship between elevated PAI-1 levels and androgen deficiency in XXY syndrome has been demonstrated by the observation that androgen therapy: (i) normalizes both the low testosterone level and its associated high PAI-1 level; and (ii) facilitates ulcer healing (14). Increased PAI-1 activity thus appears to indicate diminished fibrinolysis in Klinefelter syndrome and this inverse relationship supports the beneficial role of androgen therapy in XXY patients with venous leg ulcers.

Jacob syndrome (47,XXY syndrome) has an incidence of approximately 0.5–1.5 per 1000 live male births, but may well also be underdiagnosed. Affected individuals are often tall, some exceptionally so. Gonadal development and testicular size are usually normal, but some patients have small testes and subfertility. It has been suggested that the prevalence of venous ulceration is increased in males with XYY syndrome (7). However, clear evidence of a disease-specific (hormonal) pathogenesis is lacking, and the occurrence might thus be related to the greater height of these patients.

The PAI-1 levels were normal in our two patients. In the first patient, obesity and a prolonged standing at work were identified as risk factors for primary CVI. The second patient presented with a history of cigarette smoking, an occupation with several hours standing per day and hyperhomocysteinaemia. No other contributing factors (e.g. diabetes mellitus, peripheral arterial disease) were identified in either patient. Although the patient with XXY syndrome showed androgen deficiency, but normal PAI-1 activity, we did not observe a definitive therapeutic effect of androgen replacement therapy. Notably, both patients also presented with a characteristic syndrome-related morphology (obesity, taller size). Thus, they were also predisposed to develop primary venous disease for which a higher incidence has been reported in patients with sex chromosome anomalies (15).

Treatment of venous leg ulcers in patients with sex chromosomal anomalies involves the same medical and surgical methods as in other patients (i.e. diet and lifestyle, diuretics, compression, herbal supplements, sclerotherapy, surgical removal of insufficient veins/laser therapy, and skin grafting of ulcers). Furthermore, androgen replacement therapy may be a promising approach in the long-term treatment of PAI-1 related venous leg ulcers in XXY patients.

Some complications of Klinefelter syndrome, such as osteoporosis in our patient, can be prevented or treated with testosterone therapy. Dermatologists should be aware that recurrent phlebothromboses in young males with subsequent severe post-thrombotic syndrome and chronic venous leg ulcers may be attributable to a congenital syndrome. Early diagnosis of these disorders will enable timely treatment and counselling of patients and their family members.

The authors declare no conflicts of interest.

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