

Improvement of venous leg ulcers with androgen replacement therapy in a patient with undiagnosed klinefelter syndrome

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Abbreviations: KS, klinefelter syndrome; BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; hCG, human chorionic gonadotropin; PAI, plasminogen activator inhibitor; PA, plasminogen activator

Klinefelter syndrome (KS) is the most common genetic form of male hypogonadism. The majority (80–90%) of patients have 47, XXY karyotype while mosaicism is seen in only 10–20% of patients. Leg ulcers may be a presenting symptom of KS with a prevalence of 6–13%. Treatment with testosterone has been reported to improve the ulcers.

Introduction

Klinefelter syndrome (KS) is characterized by hypergonadotropic hypogonadism. Patients usually present with symptoms of low testosterone such as erectile dysfunction, poor libido and infertility. Men with mosaicism are less affected and often are not diagnosed. Leg ulcers may be a presenting symptom of KS. Here, we report a case of undiagnosed mosaic KS presenting with non-healing bilateral leg ulcers.

Case Report

A 58-year-old man was referred to our endocrine clinic for evaluation of long standing erectile dysfunction which had not been previously investigated. His medical history was significant for bilateral leg ulcers with no improvement despite compression wound care therapy for 5 years. He denied tobacco abuse. Physical examination revealed marked obesity (BMI 33), sparse hair on the face and body, bilateral gynecomastia (Fig. 1), gynecoid habitus, micropenis, small testes, chronic venous ulcers (Fig. 2) and hyperpigmentation on both lower extremities. Routine laboratory examination did not show any evidence of diabetes. Hormonal evaluation revealed a testosterone level of 12 (350–890 ng/dl), follicle stimulating hormone (FSH) of 40 (1.2–19.26 mIU/mL), luteinizing hormone (LH) of 24 (1.2–8.62 mIU/mL), prolactin of 7.5 (2.6–13) ng/mL and estradiol of <10 pg/mL. Testing for hypercoagulable disorder was negative for any abnormalities in protein C, protein S, antithrombin III, lupus anticoagulant, anticardiolipin antibody, Factor V Leiden mutation and prothrombin gene mutation. Doppler ultrasound of the legs did not show any evidence of deep venous



Figure 1. Gynecomastia.

thrombosis. Chromosomal analysis revealed a 47, XXY/46, XY/48, XXXY/46, XX karyotype which was diagnostic for mosaic Klinefelter syndrome (KS). He was begun on androgen replacement therapy and his repeat total testosterone was 591 ng/dl, FSH was 10.6 mIU/mL and LH was 16.6 mIU/mL. The

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Figure 2. Leg ulcer prior to initiation of androgen therapy.



Figure 3. Healing leg ulcer after androgen therapy.

plasminogen activator inhibitor (PAI-1) was low, however this was measured after treatment. The patient noted healing of his leg ulcers within 6 months of treatment with androgen therapy (Fig. 3).

Discussion

KS is characterized by hypergonadotropic hypogonadism. Leg ulcers may be a presenting symptom of KS with a prevalence of 6–13%. Men with mosaicism often remain undiagnosed, as was our patient. Elevation of plasminogen activator inhibitor-1 (PAI-1) may play a role in the pathogenesis of leg ulcers since it inhibits plasminogen activator (PA) and urokinase which activate breakdown of fibrin.

Leg ulceration in KS results from a combination of reduced testosterone levels, obesity and chronic venous insufficiency.

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Treatment with testosterone has been reported to improve the ulcers by reducing PAI-1 levels.

We think that it is important for the dermatologists to recognize the association between venous leg ulcers and Klinefelter syndrome as these patients are likely to present to them with complaints of skin ulcers. KS should be considered in the differential diagnosis of non-healing venous ulcers in male patients with eunuchoid body habitus and erectile dysfunction in whom the cause of the ulcers cannot be otherwise explained, as androgen replacement therapy promotes better healing of ulcers in these patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.