Leg ulcers associated with Klinefelter’s syndrome: a case report and review of the literature

Victoria K Shanmugam, Katina C Tsagaris, Christopher E Attinger


ABSTRACT
We present the case of a young man with type II diabetes, stage III chronic kidney disease, hypertension, obstructive sleep apnea and diabetes who presented to the Georgetown University Hospital Center for Wound Healing with refractory lower extremity ulcers. Autoimmune work-up was negative. However, chromosome analysis showed a genetic variant of Klinefelter’s syndrome (48 XXYY). Lower extremity ulceration is a recognised complication of Klinefelter’s syndrome. The pathogenesis of ulcers in this endocrinopathy is unclear, but associations with abnormalities of fibrinolysis and prothrombotic states are reported. This case emphasises the importance of considering Klinefelter’s syndrome in the differential diagnosis of a sterile male patient with non healing lower extremity ulcers.

Key words: Fibrinolysis • Klinefelter’s syndrome • Leg ulcer • Prothrombotic

CASE
A 38-year-old male was evaluated at the Georgetown University Center for Wound Healing for bilateral lower extremity ulcers that had been present for 4 years. Three years prior to presentation he had been diagnosed with type II diabetes, but his disease was well controlled with a haemoglobin A1c of 5.9% (normal less than 7%). He also had a history of stage III chronic kidney disease, hypertension, obstructive sleep apnea and obesity consistent with a diagnosis of metabolic syndrome. The patient attributed the wound development to obesity, lower extremity oedema and immobility. At the time of presentation, he had circumferential ulcers on both legs below the knees. He experienced constant pain from the ulcers rated at 8 out of 10, which was present both at rest and with ambulation. He did not have a typical history of intermittent claudication, and he denied prior thromboembolic disease. Treatment with local wound care, including silver sulfadiazine cream and compression therapy, had been ineffective.

The patient was single, lived with his mother and had a 30-pack-year smoking history. He had previously worked as a cashier and at the time of evaluation was not working because of disability. He experienced learning difficulties during childhood and young adulthood. He also reported progressing through puberty without erections and without increased testicular size. He had never fathered a child.

Key Points
- a 38-year-old male was evaluated at the Georgetown University Center for Wound Healing for bilateral lower extremity ulcers that had been present for 4 years
- three years prior to presentation he had been diagnosed with type II diabetes, but his disease was well controlled
- the patient attributed the wound development to obesity, lower extremity oedema and immobility
- at the time of presentation, he had circumferential ulcers on both legs below the knees
- he experienced constant pain from the ulcers rated at 8 out of 10, which was present both at rest and with ambulation
- treatment with local wound care, including silver sulfadiazine cream and compression therapy, had been ineffective
- he also reported progressing through puberty without erections and without increased testicular size
PHYSICAL EXAMINATION
On examination, the patient was 192-cm tall, 194 kg and his body mass index was 49.4. Cardiovascular, pulmonary and abdominal exams were unremarkable. However, he was noted to have gynaecomastia and bilateral small testes, approximately 10 ml each (normal 12–25 ml). Joint examination did not show any active synovitis; however, there was soft tissue overgrowth. Evaluation of the lower extremities showed bilateral multiple draining ulcers with a fibrogranular base on anterior and medial lower legs (Figure 1). The periwound skin was erythematous and infiltrated consistent with chronic obesity lymphedematous mucinosis although biopsy was not performed. There were no varicosities, but the patient had 2+ pitting oedema bilaterally. Dorsalis pedis pulses were palpable bilaterally.

LABORATORY DATA
Laboratory evaluation showed normal complete blood count. Fasting serum glucose was 85 mg/dl, and haemoglobin A1c was 5.9% (normal less than 7%). Serum creatinine was elevated at 2.7 mg/dl (normal 0.76–1.27 mg/dl). His chronic renal insufficiency was attributed to longstanding hypertension and use of non steroidal anti-inflammatory drugs.

Consistent with our protocol for patients with non healing leg ulcers, this patient was evaluated by rheumatology and haematology. Autoimmune screen showed negative antinuclear antibody, negative double-stranded DNA antibodies and negative extractable nuclear antigen antibodies. Complement levels were within normal limits. C-reactive protein was elevated at 15.8 mg/l (normal 0–4.9 mg/l) and erythrocyte sedimentation rate was 56 mm/hour (normal 0–15 mg/l). Prothrombotic evaluation showed negative prothrombin gene, methytetrahydrofolate reductase mutation and factor V Leiden mutation. Proteins C, S and antithrombin III activities were normal. However, the patient was heterozygous for the 4G/5G plasminogen activator inhibitor (PAI)-1 mutation.

In view of the testicular atrophy, gynaecomastia, and history of infertility, a chromosomal analysis was performed and showed 48, XXY karyotype consistent with a diagnosis of variant Klinefelter’s syndrome. Endocrine evaluation showed a low testosterone of 141 ng/dl (normal 241–827 ng/dl), elevated follicle-stimulating hormone at 40.9 mIU/ml (normal 1.4–18.1 mIU/ml) and luteinising hormone (LH) at 32.8 mIU/ml (normal 1.5–9.3 mIU/ml). Thyroid-stimulating hormone, prolactin and insulin-like growth factor 1 were normal. These values suggest hypergonadotrophic hypogonadism consistent with Klinefelter’s syndrome. Testicular ultrasound showed bilateral atrophic testes. Androgen replacement therapy was initiated with topical testosterone gel 50 mg applied to non lesional skin daily. This therapy resulted in 75% reduction in ulcer size (Figure 2).

DISCUSSION
The differential diagnosis of non healing lower extremity ulcers is well documented elsewhere, including venous stasis, peripheral vascular disease, diabetes, autoimmune disease and prothrombotic states (1). Patients with
ulcers should be referred when they fail to respond to local wound care therapy, are of non venous origin, show rapid deterioration, involve an ischemic foot or have an atypical distribution (2).

This patient was young and had failed to respond to conventional treatment. He had no varicose veins and arterial supply was intact based on normal capillary refill and palpable arterial pulses. The appearance of his lower extremities was consistent with chronic obesity lymphedematous mucinosis, which is often seen in the metabolic syndrome. However, while this patient suffered from diabetes, his disease was well controlled with oral hypoglycaemic medications and he had a normal serum glucose and haemoglobin A1c. We postulate that his endocrinopathy could have predisposed him to these changes. Autoimmune work-up including evaluation by a rheumatologist and autoimmune laboratory evaluation was negative. Prothrombotic work-up was remarkable only for the PAI-1 mutation.

Klinefelter’s syndrome, first described in 1942 by Harry F. Klinefelter, is the most common congenital abnormality causing primary hypogonadism, occurring in 1 in 500 to 1 in 1000 live births (3). Patients with this syndrome are phenotypically male, but have at least one extra X chromosome, resulting from the non disjunction of the sex chromosomes of either parent during meiotic division. Hormonally, patients have testosterone levels of approximately 50% of normal because of seminiferous tubule dysgenesis. Gonadal consequences of the syndrome include scant facial and body hair, small, firm testes, reduced sperm count and infertility (4).

Metabolic syndrome, which was present in the reported case, is a known complication of Klinefelter’s syndrome, occurring in up to 40% of Klinefelter patients (5). Development of metabolic syndrome in these patients is thought to be secondary to the hypogonadal state leading to truncal fat distribution, decrease in muscle mass and inactivity, as was reported by our patient. Other reported extragonadal manifestations of Klinefelter’s syndrome include long bone abnormalities resulting in increased length of legs and there are some reports of psychosocial abnormalities leading to difficult social interactions. In addition, associations with varicose veins, thromboembolic disease, breast cancer and autoimmune diseases including systemic lupus erythematosus have been reported (6).

Leg ulceration is a recognized complication of Klinefelter’s syndrome (7). In a series of Klinefelter’s patients observed for up to a 20-year period, the prevalence of leg ulcers was 6–13% (8). Furthermore, the genotypic variant seen in our patient, 48 XXXY, has been found in several studies to have an even stronger association with cutaneous changes (9). Some authors have suggested that because of these findings and the increased risk of cognitive abnormalities associated with the 48 XXXY karyotype, this particular karyotype should be identified as a separate entity (10–12).

The aetiology of lower extremity ulcers in Klinefelter’s patients is believed to be multifactorial with chronic venous insufficiency, obesity, arterial dysplasia in legs and decrease in fibrinolysis because of elevated levels of PAI-1 all reported (13). The role PAI-1 plays in Klinefelter’s syndrome, and its contribution to leg ulceration in this case, is unclear. PAI-1 is produced by endothelium and adipose tissue and inhibits tissue plasminogen activator and urokinase plasminogen activator, thus inhibiting fibrinolysis and promoting thrombosis. The 4G/5G polymorphism is a common polymorphism in the promoter region of the gene, with the 4G variant exhibiting higher transcription and thereby increased plasma PAI-activity relative to the 5G/5G variant. Low levels of testosterone are associated with elevated levels of PAI-1, and increased activity of PAI-1 is implicated in the pathogenesis of ulceration (14). Zollner et al. (13) compared Klinefelter’s syndrome patients with and without lower extremity ulcers and found a higher PAI-1 activity in the group with ulcers. It has been hypothesised that the increase in PAI-1 can lead to impairment of fibrinolysis causing development of microthrombi that contribute to skin ulceration.
Leg Ulcers Associated with Klinefelter’s Syndrome

The positive outcome with testosterone administration in this case was consistent with that seen in other cases of Klinefelter’s syndrome associated leg ulcers (7). In our case, we selected the transdermal method of administration of testosterone because it is known to produce normal serum testosterone concentrations (15). However, both the association of leg ulcers with Klinefelter’s syndrome and the positive response to testosterone therapy are contradictory to animal data suggesting that testosterone is detrimental to wound healing and that inhibiting testosterone activity improves wound healing (16–18). This case illustrates the importance of considering Klinefelter’s syndrome in a young infertile man presenting with lower extremity ulcers.

ACKNOWLEDGEMENT
Dr. Shanmugam is funded by award numbers KL2RR031974 and UL1RR031975 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not represent the official views of the National Center for Research Resources or the National Institutes of Health.

REFERENCES