Acne in Klinefelter Syndrome-46XY/47XXY Mosaicism?

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Introduction
This syndrome is characterized by a male phenotype but have an extra X chromosome due to nondisjunction of the sex chromosomes of either parent during meiotic division. Testosterone levels are decreased to about half of the normal levels. The deficiency of testosterone is thought to be the reason for the absence of acne in classical Klinefelter’s syndrome (KFS). Low levels of testosterone are associated with elevated levels of plasminogen activator inhibitor (PAI)-1.1 Lower limb ulcers are frequently observed and the etiology is thought to be multifactorial including chronic venous insufficiency, obesity, and elevated levels of PAI-1 that may cause impaired fibrinolysis and development of microthrombi with resultant skin ulceration. A case of KFS with post acne scars and leg ulcers is presented, who responded well to testosterone replacement therapy with complete healing of the leg ulcers. The rarity of acne in this syndrome is explained by the phenomenon of mosaicism.

Case Report
A 27-year-old male presented with 6 months history of non-healing ulcers over the both lower limbs and acne scars over the face [Figures 1 and 2]. He was tall and thin with sparse body hairs and gave history of frequent nocturnal emissions. Physical examination revealed bilateral gynecomastia and small testes [Figure 3] and a female escutcheon. Considering the possibility of KFS, he was investigated. Semen analysis showed azoospermia. Serum gonadotrophins were elevated with FSH 31.54 MIU/ML (<10 MIU/ML NORMAL), LH 23.9MIU/ML (<6 MIU/ML NORMAL). Serum testosterone was 0.9 ng/ml (2.6–13.5 ng/ml normal). Buccal smear stained with Giemsa stain showed 1 Barr body [Figure 4]. Chromosomal analysis revealed a 47 XXY karyotype diagnostic of KFS [Figure 5]. Ultrasound Doppler scan of the right lower limb showed superficial varicosities. He was started on androgen replacement therapy (injection testosterone 100 mg I/M stat) at monthly interval for
18 months along with a short course of antibiotics and compression with crepe bandage. There was complete healing with scarring after 18 months. He subsequently stopped all treatment on his own as he complained of breathlessness and palpitations following injections and remains lesion free 2 months later [Figure 6].

**Discussion**

The presence of acne is driven by the male hormone testosterone along with other factors. It is extremely rare to encounter acne in individuals with hypergonadotropic hypogonadism typical of KFS as in our case. Some individuals have the extra chromosome in only few cells and are described as mosaic KFS. Mosaicism results in clinical variations in KFS as some of the cells have normal karyotype. The degree of mosaicism helps to explain variable clinical presentations and response to therapy.

A multifactorial etiology has been proposed for the development of lower limb ulcers in KFS, including chronic venous insufficiency, obesity, arterial dysplasia in legs and decreased fibrinolysis due to elevated levels of PAI-1. PAI-1 is produced by endothelium produced by endothelium and adipose tissue and inhibits tissue plasminogen activator and urokinase plasminogen activator, thus inhibiting fibrinolysis and promoting thrombosis. 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.

Karyotyping from lymphocyte culture of peripheral smear is the standard diagnostic technique to identify chromosomal anomalies but it does not pick up low degrees of mosaicism. Interphase fluorescent in situ
hybridization (FISH) technique is more sensitive to detect mosaicism.[4]

Mosaic KFS would have populations of normal and abnormal number of chromosomes in their cells. Like KFS, mosaic 46, XY/47, XXY is also not inherited. It occurs as a random event during cell division early in fetal development. As a result, some of the body’s cells have one X chromosome and one Y chromosome (46, XY), and other cells have an extra copy of the X chromosome (47, XXY). Such individuals would manifest acne and also would be able to father children following successful sperm retrieval.[1] Treatment with androgens reduces gynecomastia and evidence of male hypogonadism and increases strength and libido in all variants. In a few, sperm obtained from the testes have successfully fertilized oocytes in vitro.

Other rarer chromosomal complements resulting in mosaic KFS include 48, XXXY, 48, XXXY, 49, XXXXY, 49, XXXXY. These types of mosaic KFS are also associated with intellectual disability. The 49, XXXXY type is characterized by fusion of the forearm bones and other skeletal anomalies, underdevelopment of the penis and scrotum, undescended testes and severe intellectual impairment. Although about 40% of men affected by KFS have a normal XY pattern, others possess a chromosome variant known as XX syndrome, in which Y chromosome material is transferred to an X chromosome or a non-sex chromosome (autosome). Men with XX syndrome have a male phenotype but have changes typical of KFS.

**Conclusion**

A hidden mosaicism should be identified in all cases of KFS as mosaic Klinefelter is less severe than the classical one. The effects of testosterone as evidenced by acne scars, nocturnal emissions, would point to the presence of mosaicism in our patient and is can help in predicting prognosis and the ability to father children. When sophisticated techniques like FISH are not available for confirmation of mosaicism, the presence of acne may serve as a clue to underlying mosaicism.

**References**