

## A rare case of Klinefelter syndrome diagnosed at Satara city, Maharashtra state, India.

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**Abstract:** Klinefelter syndrome is a common genetic disorder in which there is at least one extra X chromosome (XXY), giving them a total of 47 instead of the normal 46 chromosomes associated with phenotypically males. Sex chromosome numerical abnormalities are more frequently associated with male infertility. A patient attended to our Satara based hospital with loss of secondary sexual characteristics and male infertility. Physical examination revealed thin built, gynaecomastia, hypogonadism and absence of beard / pubic hairs. Semen analysis, karyotype and relevant biochemical analysis were performed to detect chromosomal abnormality as well as hormonal level to confirm the diagnosis of Klinefelter syndrome. Chromosomal analysis of the peripheral blood lymphocytes demonstrated the constitutional karyotype of 47, XXY. Using karyotype the presence of extra X chromosome was confirmed, supporting the cytogenetic finding. The 47, XXY syndrome is relatively uncommon and can be missed clinically because of its variable clinical presentations, shyness of patients. Accurate diagnosis of this constitutional karyotype provides a valuable aid in the counselling and early management of the patients who undertake fertility evaluation.

**Keywords:** Klinefelter syndrome, Semen analysis, 47XXY

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### I. Introduction

Klinefelter syndrome (KS) is the result of two or more X chromosomes in a phenotypic male. The clinical phenotype of KS was first described in 1959 in males with tall stature, small testes, gynaecomastia, and azoospermia with the genetic etiology of supernumerary X chromosomes. Extra X-chromosomes lead to testicular hyalinization, fibrosis leading to testicular firmness and testicular hypofunction which may result in genital abnormalities, that is usually hypogonadism and infertility.<sup>[1-2]</sup>

Neurocognitive differences related with KS began to be recognized through the middle part of the 20th century. Behavioral difficulties including immaturity, insecurity, shyness, poor judgment, and the formation of meaningful close relationships may be affected. Often, androgen replacement and neuropsychological / adaptive therapies are beneficial in its treatment. However, deficits in clinical care do exist as there are gaps in diagnosis, lack of standardization of care and access to treatments are not always available / affordable in India.<sup>[3-4]</sup> We report such an infertility case which is rarely diagnosed in clinical practice at Satara district of Maharashtra state, India.

### II. Case Report

A 28-year-old gentleman visited our chief gynaecologist with his wife for inability to conceive since their marriage of three years. He visited many gynaecologists since two years before arriving at us. His healthy wife had normal physical and per-vaginal examinations. Her menses were regular, monthly cycles. So the male patient was focused upon.

On physical examination, this male had a height of 150 cm, weight of 63kg with gynaecomastia, and wide gap in toes. He had a normal gait. Both testes were small and secondary sexual hairs were absent. He was not anaemic and without any gastrointestinal complaints. He was neither on any medications nor did he have history of diabetes/ hypertension. He complained of stressful lifestyle/ work.

These findings were suggestive of androgen deficiency syndrome with male infertility. There was no family history of same. This patient was referred for semen analysis, karyotype and relevant biochemical tests to confirm the diagnosis and know the cause of this infertility syndrome.

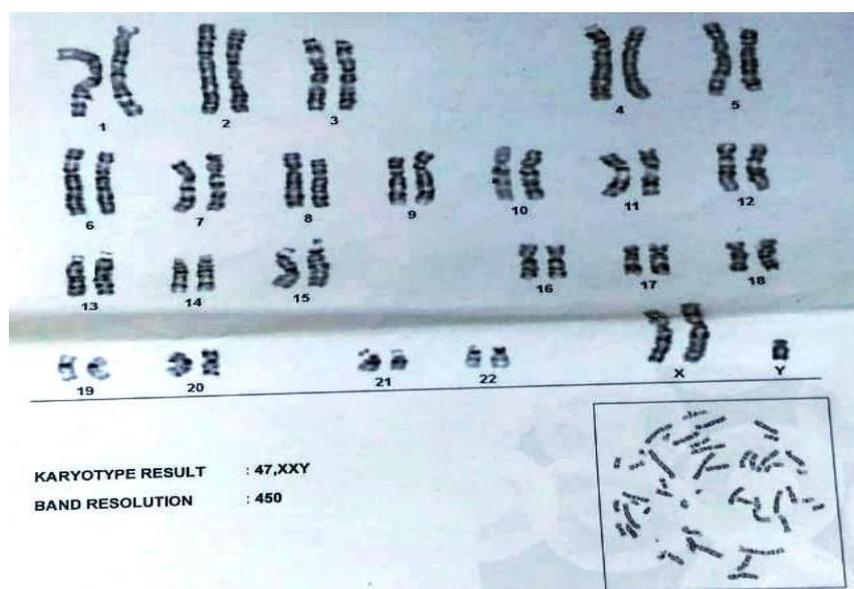
There was shyness/ problem with semen ejaculation via masturbation in reclusive room by the patient. Semen liquefaction time was delayed and was two hours. The manual sperm count was much below the set normal lower limit prescribed by WHO (2010 based Semen analysis), which was 3 millions /cu mm of seminal fluid in this case. Seminal analyses done by pathologists' revealed severe oligoasthenoeratozoospermia (OAT), which is low sperm count, poor Grade 4/ 3 sperm motility, dead sperms.

Follicular stimulating (FSH) hormone was highly raised [FSH: 39.96 mIU/mL] (Reference range for adult: 0.95-11.95 mIU/mL). Luteinizing (LH) hormone was higher limit of normal range [LH: 9.03 mIU/mL] (Reference range for adult: 0.57-12.07 mIU/mL).

Because hyperprolactinemia in males may be associated with impotence, decreased libido, infertility, gynecomastia, serum prolactin levels (PRL) were done. PRL was 5.83 ng/ mL (Reference range in males: 3.46-19.4 ng/mL).

Serum testosterone levels were very low [26.82 ng/dL] (Reference range for adult males more than 19 years of age: 240-950 ng/dL). Serum ultra-sensitive TSH levels were 0.85  $\mu$ IU/mL (Reference range: 0.40-4.00  $\mu$ IU/mL).

Karyotyping study of peripheral blood by G-banding was done which revealed karyotype result as 47, XXY with 44 autosomes and presence of one extra sex chromosome in all the metaphases analysed (Figure 1). This karyotype was consistent with Klinefelter syndrome which became the final diagnosis for male infertility in this case after proper work-up. The couple was advised genetic counselling thereafter with androgen replacement and neuropsychological / adaptive therapies.



**Figure 1:** Metaphase spread and karyotype showing 47, XXY chromosome.

### III. Discussion

Sex chromosome abnormalities are the most frequent chromosome related cause of infertility. KS is the most common form of aneuploidy, which occurs when an individual has an abnormal number of chromosomes in a cell. KS has an estimated prevalence of between 1:500 to 1:1000 males.<sup>[1,5,6]</sup> Extra X-chromosome material is responsible for testicular hyalinization and fibrosis leading to primary gonadal failure that often evolves through adolescence and young adulthood. If there is early dysfunction, the affected newborn manifests micropallus/ micropenis, hypospadias, cryptorchidism, and unusually small testes. Later, evolving hypogonadism leads to incomplete puberty and gynecomastia. Long-term hypogonadism and infertility are typical, like in our case. The additional gene dosage of the *SHOX* gene in the pseudo-autosomal region of the X chromosome leads to tall stature, long limbs, and reduced upper/lower segment ratio. The pathophysiology of neuropsychological differences observed in KS is not well-understood.<sup>[4-6]</sup>

KS is not always recognized prior to adulthood and may be diagnosed later. KS may occur more often in the setting of increasing parental age, environmentally-derived errors in meiosis I, or decreased elective termination for prenatally-diagnosed cases. Under-diagnosis is also likely due to variable phenotype with many cases having only subtle findings. It is estimated that approximately a quarter of individuals with KS have no discernable diagnostic features by history or exam.<sup>[4-6]</sup>

On testicular biopsy, the seminiferous tubules demonstrate hyalinization and fibrosis in the setting of gonadotropin excess leading to firm, often undersized testes. Limited studies of testicular biopsies from patients

with KS demonstrate reduced germ cell number across the lifespan with a progressive deficit, especially following puberty and only infrequent pockets of spermatogonia in adulthood.<sup>[5-6]</sup>

Cytogenetic analysis using GTG-banding technique revealed the karyotype 47, XXY. Karyotyping is a 'gold standard' in diagnosis of Klinefelter syndrome; however, the test is expensive, labour-intensive. The information obtained by such techniques provides a basis for deciding the necessary clinical management and genetic counselling of patients. With the increased use of non-invasive prenatal testing/screening (NIPT) wherein after pregnancy, the maternal blood is used for testing without harming the fetus, the frequency of prenatal diagnosis of KS is expected to increase worldwide, resulting in early diagnosis and management.<sup>[3-6]</sup>

Some authors who had investigated chromosomal anomalies, specifically among patients with severe oligospermia and azoospermia, have shown higher figures such as 20.86%<sup>[7]</sup> and 21.1%<sup>[8]</sup> respectively. The frequency of abnormal karyotypes in various studies showed a wide range from 2.2% to 15.7% (from 1995 to 2009) in infertile men<sup>[9-11]</sup>.

Advanced reproductive technology such as testicular sperm extraction (micro-TESE) has been successful in allowing up to half of the men with KS deemed "infertile" to have an opportunity to have a biologic child. This is deemed possible because the male having cells with the XXY chromosome, may also have cells with the normal XY chromosome count. Individuals with 47, XXY have variable fertility, depending on the karyotype present and if the individual displays mosaicism (the property or state of being composed of cells of two genetically different types).<sup>[12-13]</sup> In this advanced reproductive technique, small pockets of gonadal tissue producing sperm cells with the normal XY chromosome count may be identified, extracted and then injected by intracytoplasmic sperm injection into an ovum for fertilization.<sup>[5,6]</sup>

#### IV. Conclusion

Long-term, men with KS are more likely to develop disorders related to insulin resistance such as type-2 diabetes, dyslipidemia, fatty liver disease, poor bone mineral density as well as peripheral vascular disease, thromboembolic disease. Various cancers like breast, NHL, extragonadal germ cell tumors can occur on follow-up. This signifies the importance of diagnosing KS early in life and following-up of such patients to avoid above conditions. Karyotyping is a 'gold standard' for diagnosing KS apart from corroborative evidence from clinical presentation, relevant serum based biochemical tests and semen analysis.

In this study, we found that the infertile male had 47, XXY karyotype. For mosaicism, he was advised FISH/ chromosomal microarray/ molecular studies but he did not do the same due to high costs. Based on our karyotype report on peripheral blood, this person may or may not be able to produce 'normal' children. However even now if this couple decide to continue with any future precious pregnancy, non-invasive prenatal testing/diagnosis (NIPT) can help to detect KS in the unborn baby.

- **Conflict of interest statement:** We declare that we have no conflict of interest.
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