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Klinefelter syndrome and its association with male infertility

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ABSTRACT

Klinefelter's syndrome is the most common genetic disorder in which there is at least one extra X chromosome. Males normally have an X chromosome and a Y chromosome (XY). But males who have Klinefelter syndrome have an extra X chromosome (XXY), giving them a total of 47 instead of the normal 46 chromosomes. Sex chromosome abnormalities are more frequently associated with male infertility. The prevalence of XXYs has risen from 1.09 to 1.72 per 1 000 male births. A patient attended to fertility and genetic clinic, during the clinical diagnosis we found the following complaints of loss of secondary sexual characteristics and infertility. Physical examination revealed breast development, thin built, small size testes, and absence of beard and pubic hairs. Karyotype and biochemical analysis were performed to detect chromosomal abnormality as well as hormonal level to confirm the diagnosis of Klinefelter's 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. Accurate diagnosis of this constitutional karyotype provides a valuable aid in the counselling and early management of the patients who undertake fertility evaluation.

1. Introduction

Klinefelter's syndrome (KS) is the most common genetic cause of hypogonadism and male infertility with an incidence of 1 in 500 males. This case has one or more extra X chromosomes. The most common form of Klinefelter syndrome is due to a 47, XXY karyotype and is found in about 80% of cases, but can also be due to variant karyotypes, such as 48, XXXY, 48, XXYY, 49, XXXXY, and 47, XXY/46, XY mosaicism^[1]. The syndrome is usually detected during the development of secondary sexual characteristics. In adulthood, small soft testes and symptoms of androgen deficiency associated with azoospermia, tall

stature, and bilateral Gynaecomastia characterize it^[2]. Nowadays Karyotype is the definite test for the syndrome to identify various types of chromosomal abnormalities in both germline and cancer cells. This case of Klinefelter syndrome is being reported considering its importance in the diagnosis and management of male infertility.

2. Case report

A 33-year-old married male visited our outpatient clinic with complaint of loss of infertility. Physical examination revealed a normal male with a height of 159 cm and a weight of 60 kg and general body texture. Both testes were small and secondary sexual hairs were absent (Figure 1–3). These findings were suggestive of androgen deficiency syndrome complaining of infertility. There was no family history of similarly affected members and the patient was

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referred for karyotype and biochemical tests to confirm the diagnosis. Follicular stimulating (FSH) and luteinizing (LH) hormones level were increased. [FSH: 46.81 mIU/mL (Reference range: 1.0–15.0 mIU/mL), LH 12.31 mIU/mL (Reference range: 0.7–7.4 mIU/mL), PRL 10.91 ng/mL (Reference range: 1.8–17 ng/mL) respectively] and a very low level of testosterone (0.75 ng/mL). (Reference range: 3.84–34.17 pg/mL). Seminal analyses revealed severe azoospermia (no motile and immotile sperm). Karyotype result showed 47, XXY chromosome complement (Figure 4) in all screened metaphase spreads.



Figure 1. A patient with Klinefelter syndrome showing breast development.



Figure 2. A patient with Klinefelter syndrome showing narrower shoulders.



Figure 3. A patient with Klinefelter syndrome showing wide gap in the toes.

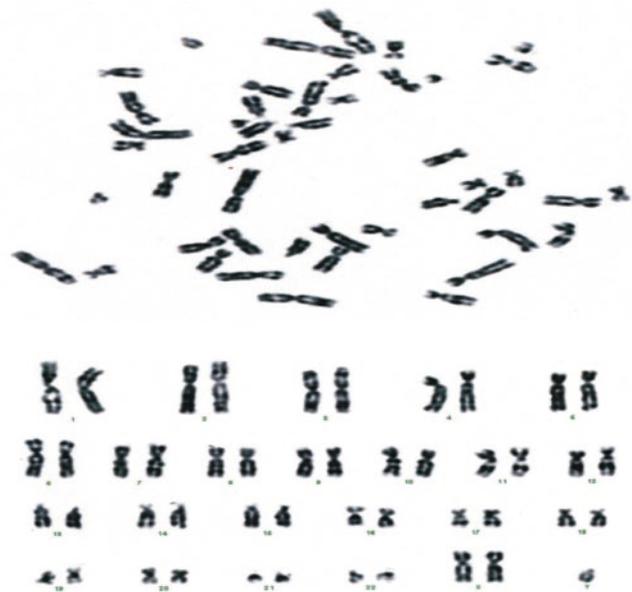


Figure 4. Metaphase spread and karyotype showing 47, XXY chromosome.

3. Discussion

Klinefelter syndrome (47, XXY) has greatly impaired spermatogenesis, with severe oligozoospermia or azoospermia. Sex chromosome abnormalities are the most frequent chromosome related cause of infertility. Studies on sperm chromosomes from men with Klinefelter syndrome have also demonstrated that the extra sex chromosome appears to be eliminated during spermatogenesis.

Chromosomal abnormalities are one of the possible causes of male infertility. 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 [5–7]. Azoospermia is a common feature of Klinefelter's syndrome, although severe

oligozoospermia and fertility have been reported [8]. Some authors who had investigated chromosomal anomalies, specifically among patients with severe oligospermia and azoospermia, have shown higher figures such as 20.86% [9] and 21.1%[10]. In this study, we found that the person having 47, XXY karyotype has a relatively frequent cause of male infertility and there is a no mosaicism in the case, so that the person cannot produce children and confirmed with the chromosome count. This abnormality is associated with severe spermatogenic failure causing a marked reduction in testicular size and azoospermia resulting in infertility[11].

As we know in general, male with Klinefelter syndrome have infertility. In a very small number of cases, males with Klinefelter syndrome have been able to produce children through assisted reproductive techniques because the person having cells with the XXY chromosome, these males 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[12–13].

Cytogenetic analysis using GTG–banding technique revealed the karyotype 47, XXY. Karyotyping is a gold standard in Klinefelter syndrome diagnosis; however, the test is expensive, labor intensive. The information obtained by such techniques provides a basis for deciding the necessary clinical management and genetic counseling of patients.

Conflict of interest statement

We declare that we have no conflict of interest.

References

- [1] Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* 2004; **364**: 273–283.
- [2] Kamischke A, Baumgardt A, Horst J, Nieschlag E. Clinical and diagnostic features of Patients with suspected Klinefelter syndrome. *J Androl* 2003; **24**: 41–47.
- [3] Fenech M, Morley AA. Measurement of micronuclei in lymphocytes. *Mutat Res* 1985; **147**: 29–36.
- [4] ISCN. *An international system for human cytogenetic nomenclature*. F Mitelman (ed.). Basel: Karger; 1985.
- [5] Yoshida A, Tamayama T, Nagao K. A cytogenetic survey of 1007 infertile males. *Contracept Fertil Sex* 1995; **23**: 103.
- [6] Nakamura Y, Kitamura M, Nishimura K. Chromosomal variants among 1790 infertile men. *Int J Urol* 2001; **8**: 49–52.
- [7] Akgul M, Ozkinay F, Ercal D. Cytogenetic abnormalities in 179 cases with male infertility in Western Region of Turkey: Report and review. *J Assist Reprod Genet* 2009; **26**: 119–122.
- [8] Tournaye H, Camus M, Liebaers I. Testicular sperm recovery in nine 47, XXY Klinefelter patients. *Hum Reprod* 1996; **11**: 1644–1649.
- [9] Zhou H, Zhu JW, Li HG, Tang YP. Genetic defect in Chinese azoospermic patients and their relationship with reproductive hormones. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2009; **26**: 427–430.
- [10] Ng PP, Tang MH, Lau ET, Ng LK, Ng EH. Chromosomal anomalies and Y–microdeletions among Chinese subfertile men in Hong Kong. *Hong Kong Med J* 2009; **15**: 31–38.
- [11] Pandiyan N, Jequier AM. Mitotic chromosomal anomalies among 1210 infertile men. *Hum Reprod* 1996; **11**: 2604–2608.
- [12] Denschlag D, Tempfer C, Kunze M, Wolff G, Keck C. Assisted reproductive techniques in patients with Klinefelter syndrome: a critical review. *Fertil & Steril* 2004; **82**: 775–779.
- [13] Linden MC, Bender BC, Robinson A. Intrauterine diagnosis of sex chromosome aneuploidy. *Obstet Gynecol* 1996; **87**: 468–475.