Case Report ISSN 2639-9342

Gynecology & Reproductive Health

Mosaic 47,XYY/45,X Presenting With Male Infertility: A Rare Case Report

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Received: 01 November 2021; **Accepted:** 16 December 2021

Citation: Zamri WNWM, Zin NMZM, Nawi NAM, et al. Mosaic 47,XYY/45,X Presenting With Male Infertility: A Rare Case Report. Gynecol Reprod Health. 2021; 5(5): 1-4.

ABSTRACT

Sex chromosome aneuploidies are the most common chromosome abnormalities associated with infertility in adult men. 47, XYY syndrome also known as Jacob Syndrome (JS) is one sex chromosome aneuploidy. Majority of 47, XYY men show normal spermatogenesis while minority may have varying degrees of impairment in spermatogenesis. This case report discusses about a 32 year old Malay gentleman who was diagnosed to have azoospermia for which cytogenetic analysis revealed an abnormal mosaic 47,XYY/45,X karyotype pattern as the underlying genetic cause. Abnormal mosaic 47,XYY/45,X karyotype associated with infertility is extremely rare in human population and hence reported for its rarity.

Keywords

Male infertility, Chromosome analysis, Mosaic karyotype.

Introduction

Infertility, the inability of a couple to conceive after one year of unprotected intercourse, is a global issue of concern although it is not life threatening. According to World Health Organization, infertility is a medical condition that needs early attention as soon as possible as it will affect the country's reproduction rate and in future, population number. It has been reported to affect around 15% of reproductive age couple worldwide [1,2]. The decline in fertility rate is a solid proof of rising number of infertility cases globally. In Malaysia, it was reported that fertility rate has declined from 2.2 in 2011 to 1.8 in 2019 [3]. According to the American Urological Association and American Society for Reproductive Medicine, male factor is a primary or contributory cause of infertility in almost 30%-50% of infertile couple and around 10% to 20% are of unexplained cases. In addition to the effect of environmental toxins (such as pesticides, glycol ethers and heavy metals), excessive oxidative stress, improper lifestyle habits, systemic disorders (like hypothalamic-pituitary disease, testicular cancers and germ cells aplasia), genetic factors including chromosomal aneuploidies and single gene mutations are also involved as pathogenic mechanism underlying male infertility [4,5]. In up to 20% of infertile men with semen defects, constitutional chromosome abnormalities are the most frequent cause [6,7] of which 47, XXY karyotype that characterizes Klinefelter syndrome is the most frequent one [8]. Other sex chromosomal aneuploidy such as 47, XYY in full or mosaic form are also encountered in infertile men rarely. Here, we report one such rare case of mosaic aneuploid 47, XYY/ 45, X in a young male.

Case Presentation

A 32 years old Malay gentleman was referred to Human Genome Centre, Universiti Sains Malaysia, Malaysia for conventional cytogenetic analysis to rule out any constitutional abnormality. He is the only child of non-consanguineous marriage. This patient was initially presented to infertility clinic due to failure of conceiving a child after married to a normal healthy woman for 4 years. On physical examination, he was a medium built gentleman with normal intelligence. He was non-smoker.

Laboratory investigation

Seminal fluid analysis was done and showed he was azoospermic. Laboratory studies revealed increased level of leutinizing hormone (LH 12.38 IU/L) and follicular stimulating hormone (FSH 17.56 IU/L) by one-fold and normal values of testosterone hormone (9.8 nmol/L), thyroid function test (1.06 mIU/L) and liver function test.

Cytogenetic analysis was carried out using peripheral blood lymphocyte culture, and chromosome preparations were made as per standard cytogenetic procedures. Chromosome abnormalities were identified and reported following ISCN (2016) guidelines. Karyotype analysis carried out in 36 GTG banding metaphases revealed 47,XYY [21] /45,X [15] karyotype pattern (Figure 1). Abnormal mosaic male karyotype with one cell line showing 47 chromosomes with an extra chromosome Y (47,XYY) in 58.3% of cells examined and the other second cell line showing 45 chromosomes with loss of Y chromosome (45,X) in 41.7% of cells examined. The karyotype result was in favour of 47, XYY/45, X syndrome, which is very rare in human population.

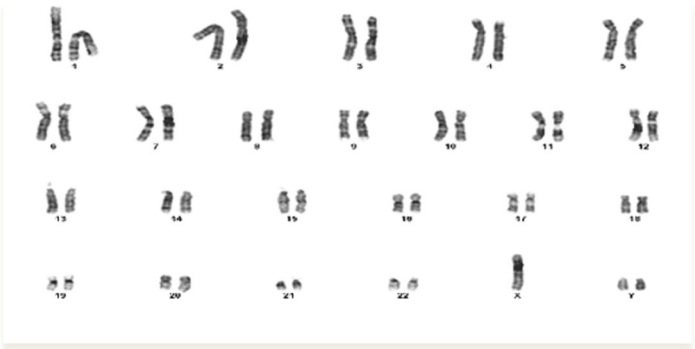

Figure 1: 47, XYY.

Discussion

Cytogenetic abnormalities, especially involving the sex chromosomes are responsible for 2% to 16% of male infertility [9]. Nevertheless, mosaic chromosomal constitution 47, XYY/45, X with an incidence of 1.7/10,000 pregnancies, is fairly uncommon and rarely been reported. This is the first report from Malaysia. Individuals with this chromosome anomaly may remain undiagnosed throughout their lifespan due to subtlety of the phenotype and lack of associated health problem [10]. Most of the men with 47, XYY karyotype, phenotypically will appear as normal adult male however having varying degrees of spermatogenesis impairment, ranging from normal spermatogenesis to severe form of azoospermia. Although 47, XYY is common after Klinefelter syndrome in male with sex chromosome abnormalities [11], mosaic 47, XYY/45, X is rare in population. Mosaic 47, XYY/45, X karyotype is a mosaic aneuploid pattern of the sex chromosomes in which a human male receives an extra Y chromosome, producing a 47, XYY chromosome complement in some of the cells and remaining cells show absence of Y chromosome, producing a 45,X chromosome complement. Chromosomal translocations and robertsonian translocation are also sources of chromosomal aneuploidies which contribute to male infertility, higher than normal male populations [6].

This mosaic aneuploid occurs due to parental nondisjunction at meiosis II resulting in an extra Y chromosome, producing a 47,XYY karyotype in the affected offspring [12,13]. Due to non-disjunction there is a possibility that a particular pair of chromosomes is inherited to a gamete or it may be lost. There can be error in the gametogenesis due to the accumulation of mutations which might have taken place during the life span of an individual [14]. In 47,XYY men, it has been reported that germ cells with an extra Y chromosome show abnormal meiotic pairing which results in disrupted meiosis, eventual sperm apoptosis and subsequent oligospermia and infertility [15].

The anatomy and gonadal histology of 47,XYY/45,X individuals has been reported to be more complex than previously thought. The majority of 47,XYY males are fertile and contribute to produce chromosomally normal children [16]. However, some patients may present with gonadal dysgenesis or azoospermia in spite of phenotypically present as normal male. This was postulated due to persistence of the extra Y chromosome during meiosis in XYY oligozoospermic males, responsible for spermatogenesis impairment and the probable elimination, via apoptosis, of most XYY germ cells, during and after meiosis [17].

This theory has also been in support of the findings by Wong *et.al* (2008) and Rives *et al*. [18,19].

This reported patient with gonosomal aneuploidy is azoospermic. This report is in agreement with other researches in male with infertility where gonosomal abnormalities are most commonly seen in azoospermic cases while autosomal abnormalities especially reciprocal translocations are commonly associated with non-azoospermia [6,20]. Aside of chromosomal aneuploidy, non-chromosomal alteration involving Y chromosome also plays a part in male infertility. Most of the time, majority of male infertility cases reported showed involvement of Y chromosome microdeletion of either complete or partial deletion of AZF regions [21,22]. In some cases, cystic fibrosis patients who have CFTR gene mutation were reported to have obstructive azoospermia with prevalence of 60-70% of cases. Other gene mutations involved in male infertility are androgen receptor (AR) gene and INSL3-LGR8 mutations where the former usually interfere with spermatogenesis while the later commonly is associated with cryptorchidism [8].

In this patient, the levels of endocrine hormones such as testosterone and thyroid hormone together with liver function test are in normal range. However, this patient showed high level of follicular stimulating hormone (FSH) and leutinizing hormone (LH). This finding is in agreement with El- Dahtory, *et al* [23], who reported four 47, XYY patients with very high FSH and LH and low testosterone levels. Zhao *et al* [24] also reported that high gonadotrophin levels (FSH >10IU/L and/or LH >12IU/L) and low testosterone level are significantly associated with risk

of chromosomal abnormality. Further test such as microdeletion of AZF region of Y chromosome needs to be done as some cases show normal seminal analysis and do not necessarily cause infertility. Histopathological examination of testes tissue also should be done to quantify the percentage of tissue mosaicism and the morphology of testes. A study by Rives *et al* [25] found that chromosome abnormalities in the spermatozoa of XYY males were probably the result of segregation errors at the first and second meiotic division in XY germ cells, rather than survival of XYY germ cells in the testis. If the mosaicism is more toward 47, XYY karyotype, in vitro fertilization will be favourable for the couple who desire to have a child [26].

The patient was counselled to explain the genetic risk of transmitting this anomaly to offspring and risk of patient's health because this syndrome is associated with shorter lifespan compared to normal male population as well as higher chances of developing cancer, pulmonary, neurological and other diseases. Infertile males with spermatogenetic defects need to be evaluated for gonosomal mosaicism after peripheral blood conventional cytogenetic analysis in order to get better assessment for estimating the outcome of assisted reproduction techniques. Although gonosomal abnormalities are higher in azoospermic men with increased gonadotrophin levels, the occurrence of mosaic 47, XYY/ 45, X karyotype is extremely rare. Hence, this case is reported because of its rarity and being the first report from Malaysia.

Acknowledgement

Special thanks to Cytogenetic staff, Human Genome Centre, Universiti Sains Malaysia, patient and his family for all the cooperation.

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