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Case Report

48 / XXYY MALE CASE WITH PRIMARY INFERTILITY

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Abstract: *Klinefelter syndrome is a sex chromosomal aneuploidies with at least one extra X chromosome than normal male karyotype. The classic form of the 47 / XXY karyotype, the incidence of this syndrome is one in 500-1000 live male births. The incidence of 48 / XXYY male individuals with many phenotypic features of Klinefelter syndrome is extremely rare and occurs in 1: 18000 -1: 100.000 men. However, they differ from Klinefelter syndrome with serious behavioral problems, mental retardation and susceptibility to psychiatric diseases [1]. A 38-year-old man referred to our Medical Biology and Genetics laboratory for karyotype analysis with primary infertility. He had undergone varicocele surgery and had high levels of FSH, low levels of testosterone and high levels of LH. Semen analysis demonstrated azoospermia In the psychiatric examination of the patient, whose IQ level was 90, language, learning and behavior disorder were diagnosed. The patient with deep vein thrombosis was recommended angiography because of right heart failure. Karyotype analysis revealed with 48, XXYY. This rare case shows the importance of karyotype analysis in diagnosis. In this study, the clinical and laboratory findings of the case are presented with the literature.*

Keywords: *Male infertility, 48/XXYY, azoospermia, Klinefelter syndrome*

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1. Introduction

Klinefelter syndrome is the most common chromosomal abnormality observed in the presence of azoospermia in severe male infertility (%10-30) [2]. 11% of azoospermic men and 3% of infertile men have Klinefelter syndrome [3-4]. 48 / XXYY men also have more serious reproductive disorders. These men have a progressive testicular malfunction that causes atrophic testists that cannot produce sufficient testosterone. Androgen insufficiency, gynecomastia, and azoospermia are also common [5]. Most infertile men are diagnosed with infertility during adulthood. Only 10% of males with Klinefelter syndrome are diagnosed earlier than age 14 years. Clinical symptoms in Klinefelter syndrome may be due to hypogonadism caused by the disease or may also be a directly chromosomal abnormality. It can be manifested with learning disability and behavioral disorders in school-age and infertility in

adulthood. It is difficult to detect Klinefelter syndrome in patients with mild signs and symptoms. Clinical features of patients with classic Klinefelter syndrome begin to become apparent during adolescence. The most striking feature in adolescence is that the testicular volume does not increase. Testis becomes hard with the loss of germ cells and fibrosis of seminiferous tubules [6]. 48, XXYY male individuals have many phenotypic features of Klinefelter syndrome, but they are separated from Klinefelter syndrome with the accompany of common psychotic reactions, aggression and mental retardation [7]. The presence of one or more X chromosomes in male individuals results in the presence of testicular dysgenesis and hypergonadotropic hypogonadism [6]. While mental retardation is rare in Klinefelter syndrome, in 48, XXYY syndrome, 26% of the patients have mental retardation and learning disabilities in almost all of them. The IQ levels of 48, XXYY syndrome men ranged from 70 to 80 [1]. It was shown that in each additional X chromosome IQ decreased by an average of 15-16 points and there was no relationship between the extra Y chromosome and the severity of the disease [8]. Also, aggressive behaviors coincide with the psychiatric findings previously described in this syndrome [9].

2. Materials and methods

2.1. Case

A 38 year-old-male whose parents were consanguineous referred to our Medical Biology and Genetics laboratory for karyotype analysis because of primary infertility. According to the information of his family, he had three sisters and three brothers. The family history of infertility was negative. He was married for 7 years and had no children. His 36 year-old-wife had no apparent fertility problem. The couple had one unsuccessful IVF trial. On the physical examination, he was found to be 182 cm tall, weighing 82 kg. The faces of 48, XXYY individuals are generally thin. Hooded eyelids, hypertelorism, epicanthal folds, fifth digit clinodactyly, pes planus and prominent elbows with cubitus varus are other phenotypic features observed [10]. He had a high broad forehead, sloping palpebral fissures, hypertelorism, peculiar nose shape, abnormally shaped maxilla, and mandible, characterized by 'Pugilistic' facial appearance. His physical examination revealed hypertelorism, increased thickness of the neck, acne, sparse body hair, triangular pubic hair distribution, fifth digit clinodactyly, small testicles and penis, and gynecoid pelvis. The result of our patient's brain MRI was observed that the brain volume decreased, the lateral ventricles expanded and gray matter decreased in the temporal lobes. The MRI result is compatible with the literature [11].

In laboratory tests, his spermiogram was azoospermic; on scrotal ultrasonography (USG), the right testicle was atrophic (26 x 10 x 19 mm). Parenchyma was heterogeneous and hypoechoic. Diffuse thickening and heterogeneity increase in the right epididymis. The right testicular volume was measured as 3.5 ccs. The left testicle was atrophic. (23 x 10 x 17 mm). The left epididymis had a normal appearance. There was no bilateral hydrocele. Pampiniform plexuses were normal width. The reflux flow was not detected. He had the following laboratory work-up that included hormone testing: follicle-stimulating hormone: 68.01 mlU / ml (reference 1.5-12.4 mIU/ml), luteinizing hormone: 32.69 mlU / ml (reference 1.7-8.6 mIU/ml) levels and low testosterone levels 1.05 ng /mL (reference 2.18-9.05 mIU/ml). Semen analysis demonstrated normal volume azoospermia. The growth hormone level was low and insulin level was normal. The patient had never received hormone therapy. The results were suggestive for hypergonadotropic hypogonadism and KS was the most possible diagnosis. His Y chromosome microdeletion test was positive.

In the psychological examination of our patient, the Kent Egy test was applied. IQ level was measured as 90 intelligence age 13 and it was at a dull normal level. He started walking at the age of 2 and talking at the age of 3. At the psychiatric examination, language, learning, and mood disorders were noticed. Autistic behavior was not observed.

Figure 1. Facial features in 48, XXYY, syndromes Pugilistic facial appearance. Fifth-digit clinodactyly (and nail-biting), prominent elbows with hyperextensibility.

2.2. Cytogenetic analysis

Chromosomal analysis was performed on phytohemagglutinin-stimulated peripheral blood cultures using standard cytogenetic methods [2]. In the karyotype analysis of the patient with the GTG banding technique, 48, XXYY chromosome establishment was detected.

2.3. Ethical procedures:

This study is approved by Dicle University Research Ethics Committee. Approval number and date: 08/2019; 05.12.2019.

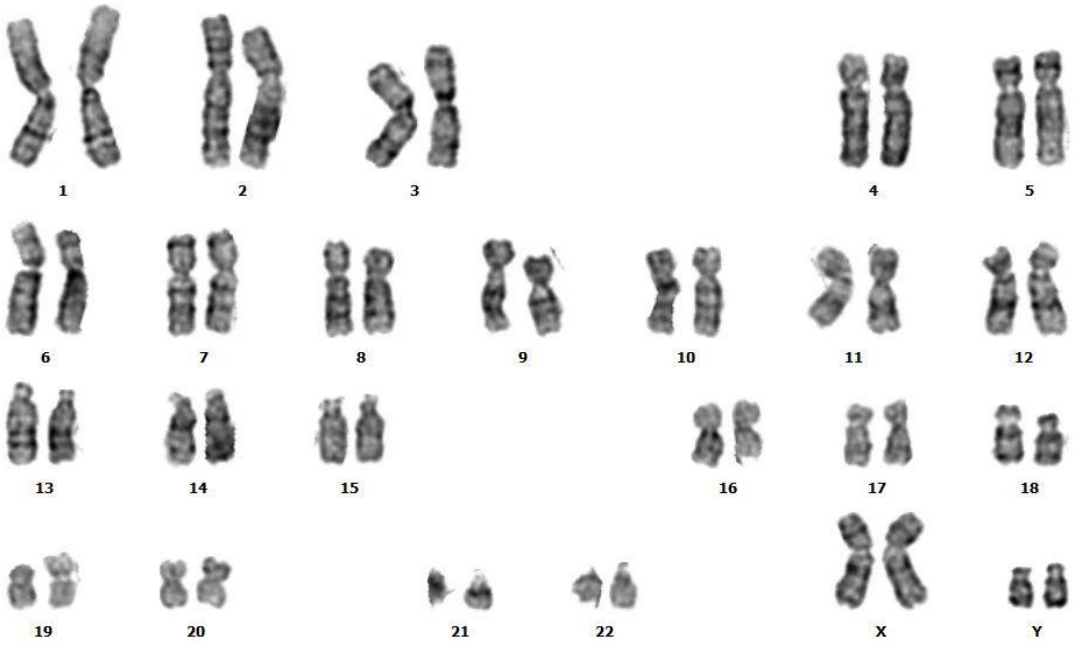

Figure 2. Klinefelter karyotype analysis [48, XXYY]

3. Discussion

The first or second maternal meiotic division may result from the chromosome not being separated or from a mitotoic defect after fertilization. It may also occur as a result of the formation of XY spermiums as a result of the first paternal meiotic division [5]. The extra X chromosome that causes the syndrome is maternal in 54% and paternal in 46% [13]. The majority of cases with maternal origin are due to errors in meiosis I. The remaining ones are mosaic cases originating from meiosis II and postzygotic mitotic errors [14].

48, XXYY individuals have low communication skills. They display an easily angered, impatient and anxious attitude [11]. In the psychological examination of our patient is compatible with the literature, IQ level was measured as 90 intelligence age 13 and it was at a dull normal level. At the psychiatric examination of our patient, language, learning and mood disorders were noticed.

48, XXYY syndrome is a form of hypergonadotropic hypogonadism characterized by long height, aggressive behavior, mental retardation and circulatory disorder [15-16]. 48, XXYY individuals develop increasing tremors with age. Our 38-year-old patient also had increased tremors at night.

Our patient had an adult height of 182 cm. The reason for the tall stature in Klinefelter syndrome is the decrease and delay in testosterone levels [17]. The patient was examined in the cardiology outpatient clinic due to dyspnea problem. Echocardiography showed enlargement in the right heart cavities. CT angiography was recommended with the possibility of a pulmonary venous return anomaly. Men affected by 48, XXYY syndrome are at risk of developing what is seen in the leg, known as deep vein thrombosis (DVD). In our case, skin ulcer formation was observed due to peripheral vein thrombosis. Enlargement and reflux flow were observed in the main, superficial and deep femoral veins.

The important topic of treatment is the treatment of hypogonadism. Especially in patients with low testosterone levels, testosterone replacement is required. It is important to diagnose the patients in the pubertal period as early as possible and start the treatment. Testosterone therapy improves muscle

mass, strength, and endurance, hair growth, bone mineral density, and libido. The patient's mood and self-confidence are significantly improved. Patients who remained untreated have a marked increase in irritability and aggressiveness, as well as weakness, unwillingness. Therefore, we started the treatment of testosterone replacement for our patients. Testosterone replacement therapy eliminates all the negative effects associated with androgen deficiency but does not affect fertility [18]. Testosterone replacement does not provide spermatogenesis. Most Klinefelter syndromes have germ cells with chromosomal abnormalities. Therefore, it is necessary to accurately predict the frequency of abnormal cells when referring to assisted reproductive techniques.

Our case was admitted due to infertile. There is no treatment to cure for spermatogenesis in Klinefelter syndrome. In vitro fertilization (IVF) with intracytoplasmic injection (ICSI) is an option for patients with mosaic Klinefelter syndrome and severe oligozoospermia [19]. In the literature, the probability of sperm extraction by testicular sperm extraction (TESE) method is reported to be between 40-50% and the probability of pregnancy after sperm injection (ISCI) is reported to be 20-25% in patients with Klinefelter syndrome [19]. Unfortunately, our patient could not benefit from assisted reproductive techniques because there was no sign of spermatogenesis.

Gynecomastia is seen in 30% of patients. Therefore, the risk of breast cancer in patients with Klinefelter syndrome increased by twenty percent. Testosterone treatment does not affect gynecomastia [20]. Aesthetic surgery and breast tissue resection should be performed in the required patients. In an adult male who referred to suffering infertility should be considered the possibility of Klinefelter syndrome. Gynecomastia is seen in 30% of patients. Therefore, the risk of breast cancer in patients with Klinefelter syndrome increased by twenty percent. Testosterone treatment does not affect gynecomastia [20]. In our patient, gynecomastia is seen as compatible with the literature.

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Ethical procedures: This study is approved by Dicle University Research Ethics Committee. Approval number and date: 08/2019; 05.12.2019

Information about the volunteer informed/consent form: In this study, the consent forms have been signed by volunteers.

The compliance to the Research and Publication Ethics: This study was carried out in acoordence with the rules of research and publication ethics.

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