Case Report – Andrology

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A Rare Cause of Infertility: 48XXYY Syndrome

İnfertilitenin Nadir Görülen Bir Nedeni: 48XXYY Sendromu

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Abstract

In the evaluation of a 32-year-old male patient who was referred to our clinic with the complaint of gynecomastia and primary infertility, ennuchoid structure, hypergonadotropic hypogonadism, and azoospermia were detected. Based on these findings, the genetic evaluation revealed the presence of 48XXYY syndrome. In this case report, we aimed to report the diagnostic algorithm and management of 48 XXYY syndrome. It should be noted that fertility should not be expected in patients with 48XXYY syndrome.

Keywords: male infertility, azoospermia, Y-chromosome deletions, Klinefelter syndrome

Öz

Otuziki yaşında jinekomasti ve primer infertilite şikâyeti nedeni ile kliniğimize yönlendirilen erkek hastanın yapılan değerlendirilmesinde ennuchoid yapı, hipergonadotropik hipogonadizm, azospermi saptanmıştır. Bu bulgulara dayanarak yapılan genetik incelemede 48XXYY sendromu tespit edilmiştir. Bu olgu sunumunda 48XXYY sendromunun tanı algoritmasını ve hastalık yönetimini sunmayı amaçladık. 48XXYY sendromlu hastalarda doğurganlığın beklenmemesi gerektiği unutulmamalıdır.

Anahtar kelimeler: erkek infertilitesi, azospermi, Y-kromozom delesyonları, Klinefelter sendromu

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Introduction

The incidence of infertility, which is the inability to achieve conception at the end of one year despite regular attempts at unprotected sexual intercourse, ranges from 7% to 15% [1]. Infertility is an important problem that causes loss of self-confidence, mental disorders, sexual dysfunction and social withdrawal in couples. Male factor infertility is present in approximately half of all infertile couples [2]. In the etiology of male infertility, several congenital or acquired factors such as urogenital abnormalities, varicocele, undescended testis, infections of the genital tract, metabolic and endocrine disorders, testicular failure, immunologic problems, cancer, drugs, radiotherapy, altered lifestyle, and genetic factors have been reported [3].

Apparently, genetic factors, especially in oligozoospermic and azoospermic patients, have been increasingly investigated in recent years. Genetic examination in infertility is important in terms of revealing the etiological factor and predicting the pregnancy potential, and the need for future counseling. Klinefelter syndrome (KS), known as 47XXY, can be seen in up to 10% of the cases with nonobstructive azoospermia and in one in 500-1000 live births [4]. Various variants of Klinefelter syndrome have been reported. Here, a case with a genetic diagnosis of 48XXYY, which is a very rare variant of Klinefelter syndrome, will be presented.

Case

A 32-year-old male patient, who was followed up in the endocrinology clinic due to gynecomastia, was referred to our clinic for fertility evaluation. Informed consent form was obtained from the patient. It was understood from his past medical history that he had been born with a normal spontaneous vaginal delivery at term and a normal birth weight. The patient's penile erection was normal, but he was never married and had no sexual partner. We noted that the patient had learning difficulties. In addition, tremor was observed in the hands of the patient during the physical examination. The patient was 192 cm tall, and weighed 90 kg with a body mass index (BMI) of 24.45 kg/m^2, and blood pressure of 125/80 mmHg. In addition, physical examination revealed eunuchoid appearance, reduced muscle mass, long arms and legs. Routine hematologic and biochemical parameteres such as complete blood count, results of hepatic and renal function tests were within normal ranges.

In the hormonal evaluation of the patient, levels of testosterone (1.74 ng/mL: 1.93-8.36 ng/mL), FSH (60.61 mIU/mL: 0.7-11.1 mIU/mL), and LH (35.82 mIU/mL: 0.8-7.6 mIU/mL) were as indicated. Other serum hormone levels were within normal limits. No pathological finding was detected in the pituitary parenchyma or sellar cavity in the MRI examination of the case. In scrotal ultrasonography, the dimensions of the left, and right testes were measured as 13x10x19 mm, and 11x18x10 mm, respectively. Millimetric calcification was observed in the upper pole of the right testis. Upon detection of azoospermia in the requested semen analysis, genetic analysis was performed. Genetic evaluation revealed the presence of a 48XXYY syndrome (**Figure 1**). Based on these findings, the patient was told that he had no fertility potential.

Discussion

Knowing the genetic causes in the etiology of infertility is important for obtaining correct information and applying the optimal treatment approach to the patients. While the risk of chromosomal anomaly is up to 4% in those with sperm counts less than 5 million compared to the general population, the risk increases even more in cases with nonobstructive azoospermia [5]. Genetic disorders manifest themselves as sex chromosomal anomalies or autosomal chromosomal anomalies. Sex chromosome aneuploidies are the most frequently occurring chromosomal abnormalities with an incidence of 1 in 400 births [6]. The most common sex chromosomal anomalies are KS and its variants. Patients with KS have 47XXY in 80-90%, and 48,XXXY, 48,XXYY, 49,XXXXY or 46,XY/47,XXY mosaicism or other structurally abnormal sex chromosomes in 10-20% of the cases [7].

The 48XXYY variant, which is seen in 2.3% of KS cases, was first reported by Muldal and Ockey in 1960 [8]. The 48,XXYY syndrome affects 1 in 18,000 to 50,000 male births. This syndrome is hypothesized to result from double nondisjunction during meiosis in spermatogenesis. In this syndrome, patients usually present to clinics with abdominal obesity, small testicles, learning difficulties, behavioral disorders, skeletal deformities, or delayed puberty [6,7]. The patient in this case report was sent to our clinic for infertility evaluation. In a study of 95 patients, the diagnosis of 48,XXYY syndrome had been made between the ages of 1-5 in 37%, between the ages of 6-10 in 25%, and at the age of ≥ 11 years in 27% of the cases [8]. Although the diagnosis is usually made in adolescence according to the findings mentioned above, prenatally diagnosed cases have been also reported [9,10]. It has been reported that only 30% of the cases are diagnosed based on the symptoms secondary to an endocrinological disorder [10,11].

The additional X and Y chromosomes lead to disorders of testicular dysgenesis and hypergonadotropic hypogonadism. Accordingly, this syndrome is characterized as azoospermia and small testicles as in our case. In the literature, testicular volumes between 1-4 mL have been detected in cases with this

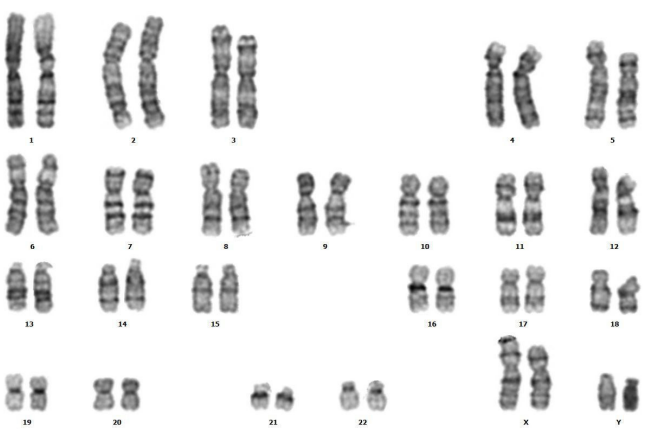

Figure 1. Analysis showing the 48,XXYY karyotype of the patient. GTG, G-banded karyotypes

syndrome [11]. In these cases, testosterone insufficiency may cause gynecomastia and decrease in muscle mass. Our patient had gynecomastia. In one study, the incidence of gynecomastia was reported to be 25% in adolescents and 41% in adults [12]. Another remarkable finding in these cases is related to their body structures. In a clinical study, Borgaonkar et al., reviewed the reported data of 53 patients and concluded that 48,XXYY cases are taller starting from an earlier age, compared to the growth parameters of the general population as in our case [13]. In addition, cardiac, cerebral and pulmonary defects, recurrent respiratory tract infections, strabismus, neurological symptoms, or diabetes mellitus may occur [11,14]. According to these findings, 48,XXYY syndrome has been defined as a different clinical and genetic disorder by some researchers. In the literature, achievement of in vitro fertility has been reported in only one case with 48XXYY syndrome [15].

The 48XXYY syndrome is an extremely rare genetic disorder and should always be considered in the etiology of male infertility when evaluating azoospermic cases. When 48XXYY syndrome is detected, guidelines strictly recommend informing the patient and in case of need his relatives in detail regarding impossibility of spontaneous fertility.

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