Translocation Y;21 in an Infertile Male Patient Having 45, X Karyotype: Case Report

45, X Karyotipe Sahip İnfertil Erkek Hastada Y;21 Translokasyonu

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ABSTRACT A 30-year-old male patient referred to our clinic for unraveling the underlying etiology of the azoospermia. He had no unusual medical history. At physical examination, obesity, short neck and gynecomastia were noted. All hormone levels were normal except estradiol which was 2-fold higher than the upper limit. Having azoospermia in the spermiogram, scrotal ultrasonography was normal. Cytogenetic analysis and fluorescence in situ hybridization were performed subsequently, 45,X,add(21)(p10) and 45,X,add(21)(p10).ish der(Y;21) (q12;p10) were found, respectively. On C-banding, dicentric staining of translocated chromosome was observed. NOR banding was negative. Molecular genetics studies using multiplex polymerase chain reaction revealed the presence of Y chromosome sequences at SRY, AZFa, AZFb, AZFc regions.

Key Words: Azoospermia; translocation, genetic; infertility

ÖZET Otuz yaşındaki erkek hasta altta yatan azoospermi etiyolojisini aydınlatmak için kliniğimize başvurdu. Olağan dışı bir tıbbi özgeçmişi yoktu. Fiziksel muayenede obezite, kısa boyun ve jinekomasti görüldü. Üst sınıra göre iki kat yüksek olan östradiol haricindeki tüm hormon düzeyleri normaldi. Spermiogramda azoospermi varken skrotal ultrasonorafi normaldi. Daha sonra sitogenetik analiz ve floresan in situ hibridizasyon yapıldı ve sırası ile 45,X,add(21)(p10) ve 45,X,add(21)(p10).ish der(Y;21) (q12;p10) bulundu. C bantlama üzerinde transloke olan kromozomun disentrik boyanması gözlendi. NOR bantlaması negatifti. Multipleks polimeriz zincir reaksiyonu kullanan moleküler genetik çalışmalar SRY, AZFa, AZFb, AZFc bölgelerinde Y kromozom dizilerinin varlığını açığa çıkardı.

Anahtar Kelimeler: Azospermi; translokasyon, genetik; kısırlık

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Male factor problems are observed in about 25-40% of the infertile couples in the population. The etiology of infertility is unknown in 30% of infertile males. Genetic causes of male infertility include numerical or constitutional chromosomal aberrations (inversion or translocation), microdeletions of Y chromosome, mitochondrial DNA mutations, monogenic diseases and multifactorial diseases. Chromosomal abnormalities are detected in 5.1% of all infertile men, 13.7% of azoospermic and 4.6% of oligospermic patients. Sex chromosome aneuplodies account for approximately 70% of chromosomal abnormalities seen in infertile males.[1-5] Other cytogenetic abnormalities include translocations between autosomes or Y chromosome and acrocentric chromosomes. The most com-

mon translocation between Y chromosome and acrocentric chromosomes is between heterochromatic region of Y chromosome and short arm of one of the acrocentric chromosomes (usually chromosome 15).[6]

CASE REPORT

A 30-year-old male patient referred to our center due to primary infertility. His brother died in an accident, and he has unrelated parents. He had been married for 3 years. On physical examination, his weight was 96 kg, and height 162 cm. He had a short stature and central obesity, short neck and gynecomastia. His body hair was android type and quite dense. Laboratory investigation revealed azoospermia and elevated E2 levels [86.31 pg/mL (7.63-42.6)]. Total testosterone, FSH, LH, prolactin and TSH values were within the normal limits. Scrotal Doppler ultrasonography showed normal testis volume and appearance.

CYTOGENETIC, FLUORESCENCE IN SITU HYBRIDIZATION (FISH) AND MOLECULAR ANALYSIS

Chromosome analysis was performed on lymphocyte metaphases using GTG banding. A 45,X karyotype was found in 50 metaphases. Moreover, an additional segment was observed on the short arm of chromosome 21 without stalks and satellites (Figure 1). C banding showed that the translocated chromosome was dicentric and did not have a heterochromatic region (Figure 2). NOR banding was negative (Figure 1C). The patient's parent's chromosomes were also analyzed. His father's karyotype was normal but his mother's chromosome analysis was not available. To explain the additional segment on 21p, FISH was performed using Chromosome X&Y alfa- satellite combination

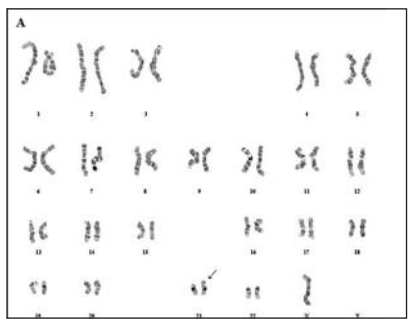

FIGURE 1A: Karyotype of the patient (GTG banding). Note the additional material on the chromosome 21p (arrow).

FIGURE 1B: C Banding. The dicentric chromosome without a heterochromatic region (arrow).

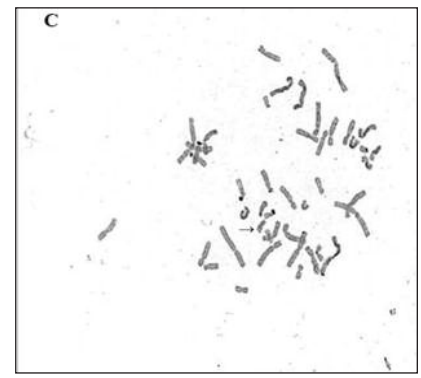

FIGURE 1C: NOR Banding showed no stalk or satellite (arrow).

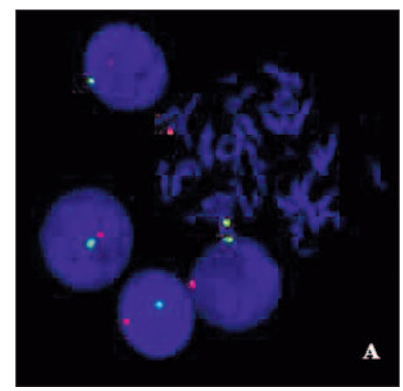

FIGURE 2A: Fluorescence in situ hybridization with X centromeric and Y centromeric probes (X cen green, Y cen red). Note that one green signal indicates the centromere of X chromosome and one red signal indicates the centromere of Y chromosome on the interphase nucleus and the metaphase chromosome. (See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

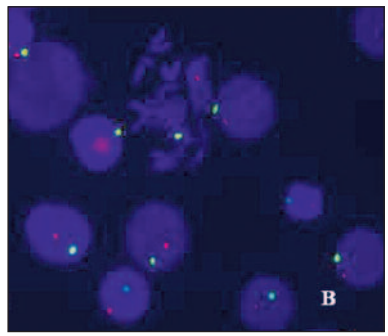

FIGURE 2B: Fluorescence in situ hybridization with X and SRY probes shows one X chromosome and the presence of SRY region (X cen green, SRY red).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

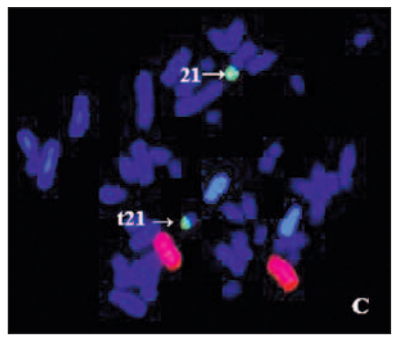

FIGURE 2C: Fluorescence in situ hybridization with the whole 8., 12., 21. chromosomes painting probe (chromosome 8 red, chromosome 12 blue, chromosome 21 green). Note that one green signal represents the normal chromosome 21 and the other green signal not spread into the long arm, indicates translocated chromosome 21 (arrow).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

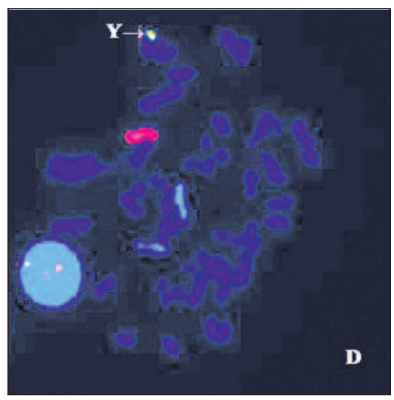

FIGURE 2D: Fluorescence in situ hybridization with the whole X, Y and 6th chromosomes painting probes (Chromosome 6 blue, Chromosome X red, chromosome Y green). Green signal revealed the rearranged chromosome Y (arrow).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

probe (Kreatech) (Figure 2A) and LSI SRY/CEP X (Vysis) probe (Figure 2B) Chromoprobe Multiprobe-System OctoChrome (Cytocell) (Figure 2C, D). The results of FISH analysis revealed that this additional chromosome segment was originated from chromosome Yq and Yp including SRY region. Thus, the karyotype of our patient was ascertained as 45,X,add(21)(p10).ish der (Y;21)(q12;p10) (wcp21+, wcpY+, DYZ3+, DXZ1+, SRY+). Molecular study was also performed to detect Y chromosome. The following primers set was used: SRY (SY14, SY81), AZFa (SY86, SY84), AZFb (ST182, SY121, SYPR3, SY124, SY127, SY128, SY130, SY133, SY134, SY145, SY152), AZFc (SY242, SY208, SY254, SY255, SY157, SY145, SY152), control primers (SMCX, ZFX/ ZFY) (Data not indicated). Molecular result showed that the amplicons regarding SRY, AZFa, AZFb and AZFc regions were positive.

DISCUSSION

The Y chromosome can be translocated onto an autosome, especially an acrocentric chromosome, due to close relationship between sex vesicle and nucleolus during meiosis.[7] The phenotype of the patients who have Y; autosome translocation is variable according to the amount of autosomal deletion and the presence of Y-euchromatic region. Chen et al. reported a patient with 45, X,der(Y;18)(q11.2;p11.2) and reviewed the literature.[8] There were 31 patients who had Y;autosome translocation with 45,X karyotype. Mental retardation and multiple congenital abnormalities are more common if the translocation is with a non-acrocentric chromosome.[8-24] The patients with Y; acrosentric chromosome translocation usually suffer from infertility due to azoospermia or oligozoospermia.[25-29] In our patient, there is a dicentric chromosome with an unbalanced translocation between q12 region of Y chromosome and p10 region of chromosome 21 which results in loss of heterochromatic region of Y chromosome. On physical examination, gynecomastia and short stature were observed. Elevated estradiol (E2) levels and azoospermia were also detected. There are few published reports about translocation between chromosomes Y and 21. Nataf et al. reported a case with prenataly diagnosed 45,X karyotype and male phenotype.[30] The

patient had a translocation between chromosomes Yp and 21p.[30] After delivery, he had male external genitalia with normally located testicles and a normal-sized penis. The translocation involved distal part of Yp and the short arm of chromosome 21. The SRY gene was present but the genes in the AZFa, AZFb and AZFc regions were missing. The authors suggested that the patient would have a risk of azoospermia. Davalos et. al. reported a 31-year-old patient having a monocentric chromosome with translocation between p10 region of Y chromosome and q10 region of chromosome 21.[28] In that particular patient, testicular volume was assessed as 12 ml and bilateral varicoceles were observed. His laboratory findings revealed normal hormone levels, however there was azoospermia in spermiogram.

Infertility due to translocations between Y chromosome and autosomal chromosomes depends on the occurrence of breakage within AZF locus located in the euchromatic region of Y chromosome (Yq11), however it has also been reported that breakages more distal to this locus (Yq12) have caused infertility.[29,31] The presence of AZF region has been shown by molecular techniques in our patient. Dicentric chromosomes are unstable during cell division.[7] We consider that the dicentric chromosome might block meiosis and therefore might cause azoospermia in our patient. Moreover, PRM1, PRM2 and AR gene mutations have been reported in infertile males causing azoospermia and oligospermia.[32,33] Analysis of PRM1, PRM2 and AR gene mutations may enlighten the etiology of azoospermia in our patients.

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