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An Azoospermic Male with mos 46, XY/45, X, psu dic (Y) Karyotype: A Case Report

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Abstract

Infertility is one of the important problems in reproductive age. Y chromosome anomalies appear as one of the reasons in men with azoospermia. Chromosomal changes in regions that are effective in spermatogenesis can seriously affect sperm production.

In the case of azoospermia presented here, microdeletion was not detected in the Y chromosome analysis. mos 46, XY/45, X, psu dic (Y) karyotype was detected by using conventional cytogenetic analysis and confirmed by FISH analysis. There was no deletion in the SRY region.

In our case, the X-Y matching is disrupted due to the change in the PAR1 region on the Y chromosome. As a result, spermatid formation is affected.

Keywords: Azoospermia; Pseudodicentric isochromosome; Mosaicism

Introduction

Infertility is a serious problem for 15% of couples of reproductive age. Recent research has shown that approximately 30-40% of infertility cases are due to male factor infertility, which affects about 5-7% of the male population [1]. The most common genetic causes of male infertility include sex chromosome aneuploidies, translocations involving the sex chromosomes, Y chromosome microdeletions, gene mutations, gene polymorphisms, and congenital absence of the vas deferens [2].

Besides to determining development of the indifferent gonad to the male sex, the Y chromosome plays an important role in spermatogenesis [3]. Essential genes on the long arm of the Y chromosome are known to be necessary for normal spermatogenesis. The AZF (azoospermia factor) gene is one of the most researched Y chromosome genes related to infertility. It consists of 3 subregions: AZFa, AZFb, and AZFc. Approximately 10% of patients with idiopathic infertility exhibit complete or partial deletion of the AZF region [4].

The SRY (sex-determining region on Y/testis-determining factor) gene located on the short arm of the Y chromosome is responsible for regulating early differentiation of the gonad [3]. The SRY gene has been mapped to band Yp11.31 [5].

The pseudoautosomal regions (PAR1 and PAR2) are short regions of homology between the X and Y chromosomes, and genes in this region are inherited autosomally rather than in a strictly sex-linked pattern. PAR1 in humans includes 2.6 Mb of the short arm tips of both the X and Y chromosomes and is necessary for pairing of the X and Y chromosomes during male meiosis. PAR2 is located in the long arm tips and is a much shorter region, spanning only 320 kb. PAR2 exhibits a much lower frequency of pairing and recombination than PAR1 and is not necessary for fertility [6].

Balanced or unbalanced translocations can occur between the Y chromosome and autosomal chromosomes. Males with balanced autosomal-Yq translocation may exhibit arrest during meiosis or spermatid formation. The breakpoint in these males is generally in the Yq11 region, where genes associated with spermatogenesis are located. In addition, incorrect pairing and separation of chromosomes during mitosis and meiosis may result in slightly reduced spermatogenesis [3].

Here, we discuss the causative mechanisms of the genetic analysis results in a case of non-obstructive azoospermia.

Case Presentation

A 29-year-old man with non-obstructive azoospermia was referred from the urology department. Informed consent was obtained from the patient to use his data in this publication. The methods

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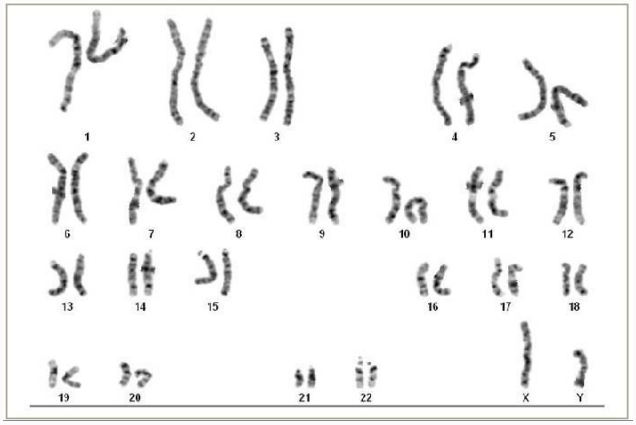

Figure 1: Karyotype from a peripheral blood metaphase of the patient showing 46, X, psu dic (Y) (qter→p11 32::p11.2→qter).

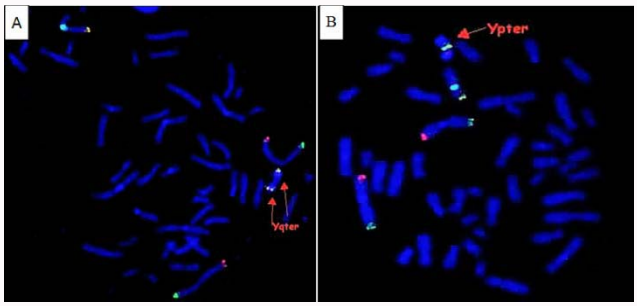

Figure 2: A). Two Yq(ter) (spectrum green+ spectrum orange) signals were seen that suggest duplication of Y(q) arm in subtelomeric FISH (Fluorescence in situ hybridization) analysis and B) One singal is seen belong to Yp(ter) (spectrum green+ spectrum orange).

used to establish the diagnosis are presented below.

Chromosome analysis: After culturing the patient's peripheral blood lymphocytes, metaphase chromosome smears were stained using the Giemsa-trypsin banding technique. Microscopic examination was done with an Olympus BX51 microscope (Olympus, Tokyo, Japan) and analyzed using Cytovision 3.0 image analysis software (Leica Biosystems, Oberkochen, Germany). Analysis results were reported according to the International System for Human Cytogenetic Nomenclature (ISCN) 2013.

Y chromosome microdeletion analysis: The AZFa, AZFb, and AZFc regions of the Y chromosome were amplified by PCR (polymerase chain reaction) using appropriate primers. PCR products belonging to 25 gene loci were evaluated by 2% agarose gel electrophoresis.Subtelomere FISH analysis: The Vysis ToTelvysion FISH (fluorescence in situ hybridization) probe kit was used. Probes were specific to the 1pter (S. Green), 1qter (S. Orange), Xpter (S. Green + S. Orange), Xp11.1-q11.1 (CEP X) (S. Aqua), Xqter (S. Green + S. Orange), Ypter (S. Green + S. Orange), and Yqter (S. Green + S. Orange) regions (Abbott Molecular, Illinois, USA).

SRY FISH analysis: A Cytocell-SRY Probe kit was used for Yp11.31 (SRY) (S. Orange), Yq12 (DYZ1) (Green), and Xp11.1-q11.1 (DXZ1) (Blue) (Cytocell, Cambridge, UK).

In the chromosome analysis (Giemsa staining) performed using the conventional cytogenetic method, 20 metaphases were examined and the karyotype was identified as 46, X, psu dic (Y) (qter→ p11 32::p11.2→qter) (Figure 1).

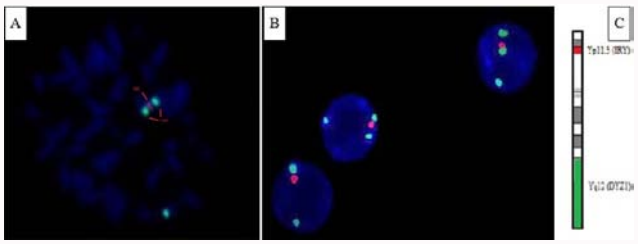

Figure 3: A) SRY FISH (Fluorescence *in situ* hybridization) probes for Yp11.31 (SRY) (S.Orange), Yq12 (DYZ1) (Green) and for Xp11.1-q11.1 (DXZ1) (centromeric X) (Blue) were used. One SRY signal was seen. Two Yq12 signals were seen that point out psu dic (Y), B) One green signal and one red signal in a cell support normal Y chromosome, while two green signals and one red signal indicate Y(q) duplication and C) Targeted areas that belong to SRY FISH probe.

In Y chromosome microdeletion analysis, no deletion was detected in the 25 gene loci (sY14 [SRY], sY81, sY82, sY83, sY84, sY86, sY88, sY182 [AZFa]; sY121, sY124, sY127, sY128, sY130, sY133, sY134, sY135, sY143 [AZFb]; sY145, sY152, sY157, sY158, sY254, sY255 [AZFc], and sY160 Y het).

This was followed by two separate FISH analyses. First, a single signal pertaining to the Ypter region and two signals pertaining to the Yqter region were detected by subtelomere FISH analysis. The two signals pertaining to the Y chromosome long arm demonstrated duplication of the long arm of the Y chromosome. The single Ypter region signal suggested translocation to this region. This confirmed the 46, X, psu dic (Y) (qter→p11 32::p11.2→qter) karyotype (Figure 2A and 2B). Secondly, Xp11.1-q11.1 (Centromeric X) (blue), Yq12 (DYZ1) (Green), and Yp11.3 (SRY) (Red) probes were used for SRY gene region analysis. Of 100 cells analyzed, detection of 2 green, 1 red, and 1 blue signal in 32% confirmed the presence of 2 long arms of the Y chromosome. In 68% of the cells, 1 green, 1 red, and 1 blue signal were detected, indicating a normal chromosome configuration (Figure 3A, 3B and 3C).

Discussion/Conclusion

In general, two mechanisms are proposed to explain male infertility. The first is deletion or alteration of the AZF gene, which is located in the Yq11 region and responsible for spermatogenesis, secondary to translocation. The second mechanism is meiotic arrest and impaired spermatogenesis caused by impaired X-Y pairing [5]. An example of these are deletions in gene regions important for spermatogenesis in the AZF regions of patients with an idic (Yp) chromosome caused by a break in the long arm of the Y chromosome [6-8]. However, in our azoospermic patient, 25 gene loci were examined through Y chromosome microdeletion analysis and no deletion was detected in the AZF regions.

Chromosome analysis revealed a dicentric isochromosome Y(q). Sister chromatid separation and recombination is the most common mechanism in the formation of dicentric isochromosomes [9]. The dicentric Y chromosome appears as either dic Y(p) due to a break on the long arm or as dic Y(q) due to a break on the short arm. In dic Y(q), the breakpoint is often in PAR1, while in dic Y(p) it is more commonly found in the Yq11 region, where the euchromatin region begins. Dicentric isochromosomes are formed during spermatogenesis or in the postzygotic stage [8].

In our patient, 20 metaphases were analyzed in karyotype analysis and his karyotype was identified as 46, X, psu dic (Y) (qter→p11 32::p11.2→qter). The SRY region was identified by SRY FISH analysis. This confirmed the breakpoint of Yp11.32 that we had identified by karyotype analysis. This point is located in the PAR1 region, outside of the SRY gene region. The detection of two signals pertaining to the long arm of the Y chromosome in subtelomere FISH analysis indicates duplication of the long arm of the Y chromosome. The single signal corresponding to the Ypter region suggests translocation to this region. This confirms the 46, X, psu dic (Y) (qter→p11 32::p11.2→qter) karyotype.

The presence of two long arms of the Y chromosome in 32% of the cells analyzed in SRY FISH analysis confirms the psu dic (Y) formation detected in chromosome analysis. In the other 68% of the cells, the two separate signals belonging to the Yq12 (DYZ1) and Yp11.3 (SRY) regions suggest a normal Y chromosome structure. This indicates the presence of mosaicism. The patient has no deletion in the SRY gene region.

We believe that the formation of the isodicentric chromosome in our patient was postzygotic because the presence of mosaicism suggests a defect in postzygotic division. In our patient, a break in Y chromosome chromatids first occurred in the same region (Yp11.32). Then, there was a second break in the Yp11.2 region during the translocation of one of the chromatids containing the long arm to the other chromatid.

In patients with idic (Y) (p11.3), loss of the PAR1 region in the distal Yp can cause sperm maturation to cease. Cases of azoospermia associated with defects in the PAR1 region have been presented in the literature. Mis-pairing of the homologous regions of the X and Y chromosomes during meiotic division disrupts spermatid formation. Therefore, chromosomal translocations that cause changes in PAR regions and deletions in this region impact sperm formation [10].

In conclusion, we believe that in this case, the PAR1 gene region on the short arm of the Y chromosome was affected due to the pseudodicentric isochromosome, with the resulting disruption in X-Y pairing affecting spermatid formation. In addition, we attribute the mosaicism in our patient to defective postzygotic division.

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