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ANDROLOGY

Case Report

Male infertility associated with *de novo* pericentric inversion of chromosome 1

Kromozom 1'in de novo perisentrik inversiyonu ile ilişkili erkek infertilitesi

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ABSTRACT

Inversion occurs after two breaks in a chromosome have happened and the segment rotates 180° before reinserting. Inversion carriers have produced abnormal gametes if there is an odd number crossing- over between the inverted and the normal homologous chromosomes causing a duplication or deletion. Reproductive risks such as infertility, abortion, stillbirth and birth of malformed child would be expected in that case. A 54-year- old male patient was consulted to our clinic for primary infertility. The routine chromosome study were applied using peripheral blood lymphocyte cultures and analyzed by giemsa-trypsin-giemsa (GTG) banding, and centromer banding (C-banding) stains. Y chromosome microdeletions in the azoospermia factor (AZF) regions were analyzed with polymerase chain reaction. Additional test such as fluorescence in situ hybridization (FISH) was used to detect the sex-determining region of the Y chromosome (SRY). Semen analysis showed azoospermia. A large pericentric inversion of chromosome 1 46,XY, inv(1) (p22q32) was found in routine chromosome analysis. No microdeletions were seen in AZF regions. In our patient the presence of SRY region was observed by using FISH technique with SRY-specific probe. Men who have pericentric inversion of chromosome 1, appear to be at risk for infertility brought about by spermatogenic breakdown. The etiopathogenic relationship between azoospermia and pericentric inversion of chromosome 1 is discussed.

Keywords: Azoospermia; chromosome 1; male infertility; pericentric inversion.

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ÖZ

Kromozom üzerinde iki kırık meydana gelmesi ve aradaki parçanın tekrar yapışmadan önce 180° dönmesi ile inversiyonlar oluşur. Eğer normal ve inversiyonlu homolog kromozomlar arasında tek sayıda krosing over olursa, inversiyon taşıyıcılarında duplikasyon ve delesyona neden olarak anormal gamet üretimine neden olurlar. Bu durumda malformasyonlu çocuk, ölü doğum, düşük ve kısırlık gibi üreme sorunları beklenir. Kliniğimize primer infertilite şikayetiyle 54 yaşındaki erkek hasta refere edildi. Periferik kandan lenfosit kültürü yapılarak rutin kromozom çalışması yapıldı ve giemsa-tripsin-giemsa (GTG) bantlama ve sentromer bantlama (C bantlama) ile analiz edildi. Azoospermi faktör (AZF) bölgelerindeki Y kromozom mikrodelesyonları polimeraz zincir reaksiyonu ile incelendi. Ek test olarak Y kromozomundaki cinsiyet belirleyici bölgenin (SRY) tespiti için floresan in situ hibridizasyon (FISH) uygulandı. Semen analizinde azoospermi görüldü. Kromozom 1'in geniş perisentrik inversiyonu, 46,XY, inv(1) (p22q32) karyotipi rutin kromozom analizinde bulundu. AZF bölgelerinde mikrodelesyon görülmedi. Hastamızdaki SRY bölgesinin varlığı SRY-spesifik problar ile FISH tekniği kullanılarak gösterildi. Kromozom 1'in perisentrik inversiyonuna sahip erkekler spermatogenik bozulmanın getirdiği infertilite açısından riskli görünmektedir. Kromozom 1'in perisentrik inversiyonu ve azospermi arasındaki etyopatojenik ilişki tartışılmıştır.

Anahtar Kelimeler: Azospermi; kromozom 1; erkek infertilitesi; perisentrik inversiyon.

Introduction

Infertility is the inability to conceive a child despite for one year of unprotected sex. It affects an almost 15% of all couples. Infertility arises from female disorders in approximately 30-40%, a male disorder in 30%, and disorders in both partners in 30% of the cases. In the remaining cases no abnormalities are found. Approximately half of the cases, male-related factors are commonly associated with decreasing sperm counts. Relative to the normal population, the incidence of chromosomal anomalies have been found to be high among

infertile males.[1] Structural chromosomal aberrations are observed in approximately 5% of all men who have severely low sperm counts. Pericentric inversions are structural chromosomal aberrations occuring in a segment of chromosomal pieces that are reversed in orientation relative to a reference karyotype. In pericentric inversions rotating segment contains the centromere. Individuals with a pericentric inversion have not any phenotypic characteristic unless genetic dysfunction or chromosomal damage is present Usually inversion carriers had normal fertility potential. Pericentric inversions are mostly identified incidentally, and infrequently associated with infertility. If a crucial region on chromosome is broken, adverse phenotypic changes will occur.[2] As the size of the inverted chromosomal segment decreases, the risk of unbalanced gametes will increase. Besides, some inversion carriers may have reproductive problems because of the presence of aberrant meiotic events that cause chromosomally unbalanced gametes. Reproductive risks such as infertility, abortion, stillbirth and birth of malformed child will be expected in that case. The frequency of pericentric inversions in azoospermic and oligozoospermic men who were asking for *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) varies from 0% to 0.3%.[3] Here, a case with pericentric inversion of chromosome 1 associated with azoospermia was reported and also the etiopathogenic reasons was discussed.

Case presentation

A 54-year-old man was applied to our clinic for primary infertility. Written informed consent was obtained from the patient who participated in this case. Physical examination revealed the presence of normal-sized testicles with intact vas deferenses, normal external male genital organs without any sign of gynaecomastia. Semen examination was performed according to World Health Organization's (WHO) criteria which demonstrated the presence of azoospermia. His routine hematological, biochemical test results and hormon levels [FSH 3.1 mIU/mL (1.5-12.4 mIU/mL), LH 2.4 mIU/mL (1.7-8.6 mIU/mL), PRL 10.4 mIU/mL (2.1-17.7 ng/mL), total testosterone 6.19 ng/dL (2.8-8 ng/dL) and free testosterone 24.0 pg/mL (12-30 pg/mL)] were within normal ranges. Conventional cytogenetic analyses were performed using currently accepted cytogenetic processing methods, and chromosomes were analyzed following staining with giemsa-trypsin-giemsa (GTG) banding and C-banding dyes (Figure 1, 2). A large pericentric inversion of chromosome 1 46,XY, inv(1)(p22q32) was detected. The proband's parents were investigated and his parent's karyotypes were found normal. His inversion was evaluated as *de novo*. There were no family history of any abnormal pregnancies and infertility. Sex-determining region of the Y chromosome (SRY) was present as detected using FISH technique with SRY-specific probe (SRY/X) (Vysis). Y chromosome microdeletions in the Azoospermia factor (AZF) regions (AZFa, AZFb, AZFc and AZFd) were analyzed with polymerase

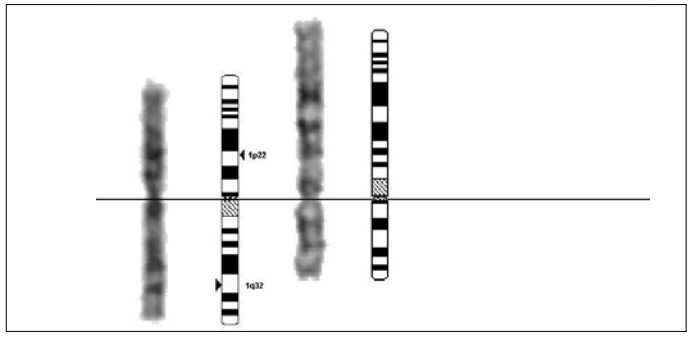

Figure 1. GTG-banded normal and inverted chromosome 1 with idiogram
GTG: giemsa-trypsin-giemsa

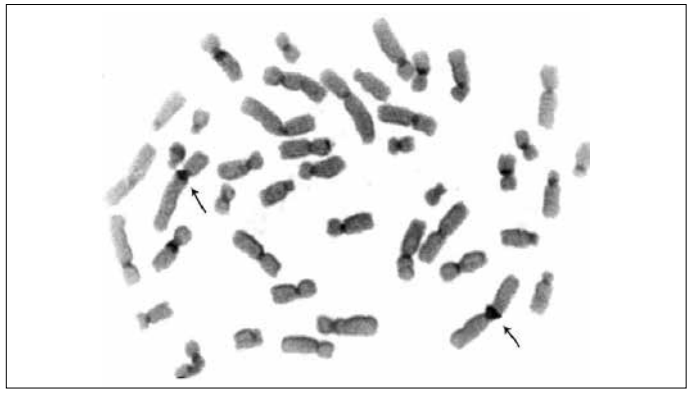

Figure 2. C-banded metaphase, inverted (left side) and normal chromosome 1 (right side) indicated with arrows

chain reaction using markers (sY254, sY84, sY86, sY141, sY160, sY158, sY142, sY152, sY233, sY147) and any microdeletions at AZF loci were not seen.

Discussion

In pericentric inversion carriers, crossing-over does not usually occur within the inversion loop because of incomplete pairing between the homologous chromosomes. Any odd number of crossing- overs occurring within the inversion loop involving the same chromatids can lead to the production of duplicated and deficient chromosome segments. Large pericentric inversions are more likely to result in the production of viable recombinant offsprings than small inversions, because the unbalanced segments in the recombinant progeny are smaller than those seen in case of small inversions. In general, individuals with a pericentric inversion have 1%-10% risk of having a live birth with an unbalanced chromosomal karyotype.[4] The clinical significance of the inversion is related to the consequences of each chromosomal reorganization. The main issues of ascertainment in the literature are recombination, aneusomy, malformations, abortions, and sterility or infertility, with different frequencies

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for each recurrent type.[5] In about 12% of the individuals with pericentric inversion male-factor infertility is observed.[6] Pericentric inversion of chromosome 1 (p13q25) was found in three infertile male siblings, and familial azoospermia has been reported in the literature.[7] These cases, like our patient, have large inversions, azoospermia with normal physical examination findings. There are several opinions on the relationship between the pericentric inversion and azoospermia.

The first explanation was related to disturbed chromosome pairing and synapsis. Between the homologous chromosomes pairing, synapsis, and recombination processes occur during the prophase of meiosis I where accurate allocation of genetic material to each gamete takes place. If these processes are impaired by chromosomal aberrations such as inversion and translocation, accurate pairing and synapsis will not happen. Mistaken pairing and synapsis induces the meiotic pachytene checkpoint that initiates the meiotic arrest and subsequent apoptosis. Heterosynapsis, asynaptic region and decreased recombination were observed on the inversion carrier. Compliance with synapsis is critical for proper progression through spermatogenesis as unpaired chromosomes are caught by meiotic checkpoints leading to spermatogenic arrest, azoospermia or reduced sperm concentration.[8] Also recombination is reduced within the pairing loop which leads to breakdown of spermatogenesis.[9]

The last issue is related to the interferences with the function of the gene or genes at breakpoints. Deficiency of any gene which plays a role in spermatogenesis exerts its function close to breakpoints can cause infertility as observed in individuals with pericentric inversion. In infertile men, increased number of breakpoints of chromosome 1 were demonstrated so this mechanism might be responsible for our patient's infertility.[10] This argument cannot be verified, unless the breakpoint regions of inversion were sequenced. Any obvious evidence of azoospermia or proof suggesting that pericentric inversion might be accounted for impaired spermatogenesis could not be demonstrated in our patient.

In this paper we briefly mentioned about the possible causes which will help to clarify the etiopathogenic etiology of infertility by applying molecular techniques. We propose that some large inversions, like this of the current case might disrupt spermatogenesis in male carriers. Cytogenetic analysis should be performed for men with azoospermia.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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