

Case Report on Xq Deletion - As a Cause for Primary Infertility in Male

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Abstract

Male infertility is often described in terms of role played by Y chromosome and Yq microdeletions. But studies have shown that X chromosome, being enriched for testis specific genes plays a significant role in formation of mature spermatozoa. The couple under study had undergone treatments for infertility including 7 Intrauterine inseminations (IUI) and 6 *Invitro* Fertilization (IVF) cycles but without any success. On cytogenetic analysis chromosomal aberrations were observed in both male and female partners. But male had more aberrations with major clonal aberrations in the form of Xq deletions. The genes *CPXCR1*, *ARPT1*, *GLUD-2*, *SAGE-1* and *USP26* are located on Xq21, Xq25 and Xq26 regions. These genes show testis specific expression pattern and play an important role in spermatogenesis. Therefore Xq deletions could be a cause for primary infertility in male.

Keywords: Cytogenetic aberrations, deletions, male infertility.

1. Introduction

Infertility is the inability of a sexually active couple who is not making use of any contraceptive measure to achieve pregnancy in one year. Worldwide 48.5 million couples suffer from infertility. Though infertility affects men and women equally, males alone are responsible for 20 to 30% of cases of infertility and overall they contribute to 50% of infertility cases [1]. One of the chief reasons of male infertility is absence of/poor quality of sperm (spermatozoa). Male infertility is often described in terms of role played by Y chromosome and Yq microdeletions. But studies have shown that X chromosome, being enriched for testis specific genes also plays a significant role in formation of mature spermatozoa [2]. Thereby any aberration in X chromosome may also result in male infertility. A case of infertile couple is discussed here in which male partner has Xq deletions along with various other structural aberrations which could be a probable cause of primary infertility.

2. Case Report

A couple Mr A (Age 39 years) and Mrs B (Age 37 years) consulted the doctors at Genesis Fertility and Surgical Center, Jalandhar with the complaint of non conception even after having active sexual life and non use of contraceptives. They had been married for 16 years. The couple did not have a positive family history of infertility in their respective

families and had no consanguinity. They were physically healthy and followed an apparently healthy lifestyle. They were residents of urban area and did not report a consistent exposure to any specific pollutants. The male partner (Mr A) had low sperm count. The couple had undergone treatments for infertility including 7 IUI and 6 IVF cycles but without any success; even after using healthy donor eggs conception had failed. At this juncture cytogenetic analysis for both Mr A and Mrs B was done. Microscopic and automated karyotyping analysis for the couple was performed by using chromosomes isolated from the cultured peripheral lymphocytes using Giemsa banding (GTG) to identify chromosome abnormalities. 50 metaphases each were examined in both the cases. Occurrence of chromosomal aberrations in Mr A was 60% whereas in case of Mrs B it was 40%.

The cytogenetic aberrations observed in both Mr A and Mrs B are represented in Table 1. Cytogenetic investigations of Mr A revealed the presence of distinctively clear deletions in Xq21, Xq25 and Xq26 in 7 metaphases (fig.1). The deletion of Xq was observed even in a polyploid metaphase with 82 chromosomes. This mosaicism was found along with other structural aberrations like formation of ring by chromosome 3, chromatid break in 1q12 region. Telomeric associations (tas) were observed in more than 10 metaphases involving both autosomes and gonosomes. A

single translocation in 6p24 and 12p13.2 was observed. In cytogenetic investigation of Mrs B, 44% structural and 24% numerical aberrations were seen. Robertsonian translocation (rob) in chromosome 13, 14 and 15 was seen (fig 2). Telomeric associations were observed in chromosome numbers 6, 8, 9, 13, 14, 15, 21 and 22. Chromosome 14 and

21 were found to be involved more in telomeric associations. Both the subjects appeared to have more chromosomal losses. Loss of chromosome 2, 5, 6, 10, 13, 16, 17, 21 and 22 in female and loss of 2, 5, 4, 8, 10, 11, 14, 18 & 21 in male was observed. Gain of chromosome 8 while loss of chromosome 2, 5 and 10 was observed in both male and female.

Fig.1: Karyotype showing del(X) in male 46,Y,del(X)(q21.3)

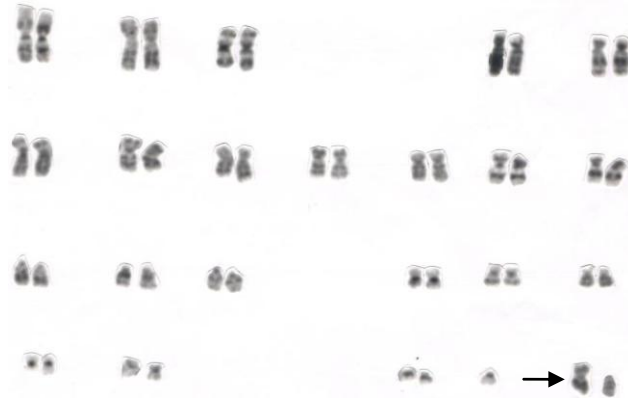
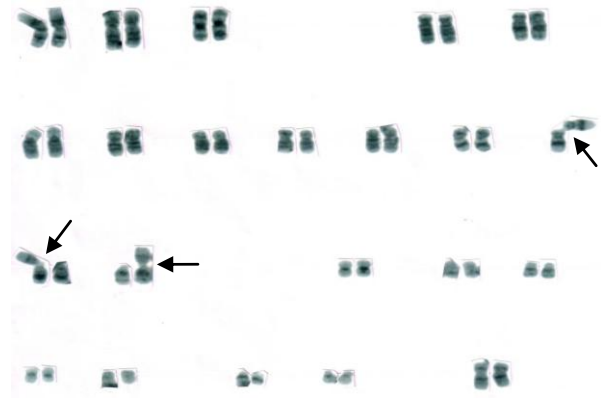


Fig.2: Karyotype showing rob and tas in female 46,XX,tas(12p;12p),tas(13p;15p),rob(14;15)(p13;p13)



3. Discussion

The cytogenetic analysis of the couple revealed various structural and numerical aberrations in both autosomes and sex chromosomes. In case of infertile male clear deletions in Xq21.3, Xq25, Xq26 regions of chromosome X were observed in a mosaic form. It was a constitutional anomaly that could be a cause of infertility [3-6]. Xq deletion along with other structural and numerical aberrations was the probable cause of male infertility. This also correlated with the low sperm count and low sperm motility found in Mr A. Both X and Y chromosomes have been reported as key players in spermatogenesis [2,7-10].

The genes *CPXCRI*, *ARPT1*, *GLUD-2*, *SAGE-1* and *USP26* are located on Xq21.3, Xq25 and Xq26 regions. These genes show testis specific expression pattern and play an important role in spermatogenesis [3]. *USP26* gene, located on Xq26.2 region is expressed throughout the testes in the preliminary stages of spermatogenesis [11]. Any mutation in this gene results in the severe impairment of spermatogenesis [12]. Another gene *DIAPH2* located at Xq22 region which affects spermatogenesis is disrupted due to deletion at Xq21.3. In females with premature ovarian failure *POF1*, *XPNPEP2* genes located at Xq25 region are found to be disrupted [13].

Table 1: Representative Karyotype of the couple

Category	Mr A	Mrs B
Clonal Aberration	45,Y,del(X)(pter→q26:),tas(1;18)(1qter→1pter→18qter→18qter),-5 46,Y,del(X)(pter→q26:),tas(6;22)(6qter→6pter→22qter→22pter) 45,Y,del(X)(pter→q26:),tas(14;14;15)(14qter→14pter→15pter→15qter),-18 45,Y,del(X)(pter→q26:),-21 46,Y,del(X)(pter→q25:),tas(8;21)(8qter→8pter→21pter→21qter) 46,Y,del(X) pter→(q25:),del(13)(p11.2) 46,Y,del(X)(pter→q21.1:) 45,XY,-10 44,XY,-4,-10	43,XX,-2,-16,-22 42,XX,-2,-6,-10,-13
Non Clonal Anomalies	44,XY,-2,-11 46,XY,r(3) 45,XY,t(6;12)(p24;p13.2) 45,XY,-8 45,XY,-14	45,XX,-5 47,XX,+8 44,XX,rob(13;15)(p10;p10),rob(14;15)(p10;p10) 45,XX,rob(14;22)(p13;p13) 45,XX,-17 45,XX,-21
Telomeric Associations	46,X,tas(Y;22)(Yqter→Ypter→22pter→22qter),chr(1)(q12) 46,XY,tas(2;9)(2qter→2pter→9qter→9qter) 46,XY,tas(4;13)(4qter→4pter→13pter→13qter) 46,XY,tas(11;19)(11qter→11pter→19pter→19qter) 46,XY,tas(13;14)(13qter→13pter→14pter→14qter) 46,XY,tas(13;15)(13qter→13pter→15pter→15qter) 46,XY,tas(14;22)(14qter→14pter→22pter→22qter) 46,XY,tas(15;21)(15qter→15pter→21pter→21qter),tas(15;21)(15qter→15pter→21pter→21qter) 46,XY,tas(21;21)(21qter→21pter→21pter→21qter) 46,XY,tas(18;21)(18qter→18qter→21pter→21qter)	46,XX,tas(6;8)(6pter→6qter→8qter→8qter) 46,XX,tas(9;21)(9qter→9pter→21pter→21qter) 46,XX,tas(13;14)(13qter→13pter→14pter→14qter), tas(17;18)(17qter→17pter→18pter→18qter) 46,XX,tas(13;15)(13qter→13pter→15pter→15qter) 46,XX,tas(13p;21p)(13qter→13pter→21pter→21qter) 46,XX,tas(14;15)(14qter→14pter→15pter→15qter) 46XX,tas(14;22)(14qter→14pter→22pter→22qter) 46,XX,tas(21;22)(21pter→21qter→22pter→22qter)
Normal	46,XY[27]	46,XX[31]

In male partner acrocentric chromosomes were seen associated with Y chromosomes and other autosomes like 1, 6, 8 and 18. The involvement of sex chromosomes has been reported to disturb the reproductive fitness¹⁴. Translocation was observed between chromosome 6 and 12. In the breakpoints involved in the translocation at region 6p24, *DSP* gene is located which is responsible for cell-cell adhesion whereas at 12p13.3 region *KCNA1* gene is located which plays role in repolarisation of membranes. The genes might be disrupted because of translocation which might have an effect on the efficiency at which sperm cell first interacts with egg cell. The ring of chromosome 3 observed in one metaphase has been previously associated with spermatogenic impairment [15-17]. Close associations in acrocentric chromosomes 13, 14, 15, 21 and 22 were seen in 26% of metaphases in male. Telomeric associations were seen in autosomal chromosomes 2, 9, 11 and 19. Translocations in acrocentric chromosomes and increased frequency of telomeric associations indicate genomic instability that could be a cause of male infertility [18].

In female partner increased genetic instability was observed. Although there were no clonal aberrations but similar chromosomes (6, 8, 13, 14, 15, 17, 21 and 22) were found involved in different aberrations. In previous reports, the chromosomes from D, G and E groups (16, 21, 22) have been observed most frequently in aneuploid oocytes whereas in males chromosome 21 and 22 show significantly elevated level of aneuploidies. Hence increased frequency of aberrations in sperm and oocyte contribute to high burden of infertility¹⁹. In both male and female, chromosomes presented a distinct increased stickiness as the frequency of telomeric associations was high.

This study suggests that Xq deletion along with other structural and numerical aberrations might be one of the probable causes of primary male infertility. In case of infertile patients having repeated ART failures genetic instability in both male and female may be the reason. Further studies of this type are needed to substantiate this claim.

4. Conclusion

Deletion in Xq regions may cause the disruption of genes resulting in production of low quality as well as low quantity sperms which in turn prohibits the production of healthy embryo. Though in present case the female partner had certain aberrations but male partner had more clonal aberrations. ART failures thus were attributed more to male partner as conception did not take place even when healthy donor eggs were used. Further, the importance of cytogenetic analysis before going in for ARTs has also been highlighted in this case report as proper karyotyping of patients will lead to appropriate genetic counseling to the infertile couples. This will avoid unnecessary treatment overburden and mental agony among infertile patients. The couple could consider

going in for sperm donation/embryo donation/pre-implantation genetic diagnosis or adoption for fulfilling their desire to have a baby.

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