A Rare Case: Non-Syndromic 46,XX Testicular DSD with Derivative Autosome

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46,XX testicular disorder of sex development (DSD) is a known cause of male infertility. Derivative chromosomes formed by complex rearrangements and translocations between two or more autosomes are also found to play role in male and female infertility in different studies. Combinations of sex chromosomal DSD and derivative autosomes are rare and unique. We report a case of 46,XX testicular DSD with a derivative autosome formed by rearrangement between chromosomes 2 and 3. The person was phenotypically normal (non-syndromic) with only complaint of infertility.

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Key words: 46, XX testicular DSD, derivative chromosome, infertility

Introduction

Disorder of sex development (DSD) is a congenital condition where there is a disagreement between chromosomal, gonadal and phenotypic sex.[1] The discrepancies among these three determinants are highly variable and depend on patients' cytogenetic and molecular abnormalities.[2] The Chicago Consensus Nomenclature (2005) divides DSD into three broad categories: sex chromosomal DSD, 46,XY DSD and 46,XX DSD. Each of these has subclassifications with defined characteristics. Non-syndromic 46XX testicular DSD is a subclass of 46,XX DSD in which the person is phenotypically male and possesses testes.[3] These individuals, though are deficient of a Y chromosome, have SRY (sex-determining region on Y) gene in one of the X chromosomes. This SRY gene induces development of testes that are, however, often smaller in size with impairment of spermatogenesis of varying degrees. As a result the persons are infertile though otherwise normal.[4] The mechanisms underlying SRY-positive 46,XX testicular DSD are understood by multiple studies.[5,6]

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A derivative chromosome (der) is a structurally rearranged chromosome generated either by a rearrangement involving two or more chromosomes, or by multiple aberrations within a single chromosome. The term always refers to the chromosome that has an intact centromere.[7] The structural changes involving autosomes, in different studies, are also seen to be associated with male and female infertility.[8-11]

We report a case of male infertility with a combination of 46,XX testicular DSD and a derivative autosome formed by rearrangement between chromosomes 2 and 3. To our knowledge, no report has been published so far with this unique combination.

Case Report

A 30 year old male person and his 26 year old wife attended the Gynaecology Outdoor, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka with the complaint of infertility. On query, they revealed that they had been married for four years and had not been using any contraceptive. Their past and present medical history, family history and drug history were non-contributory. The wife was examined physically in the Gynaecology Outdoor and no abnormality was detected. She was advised an ultrasonography of pelvic organs, thyroid function tests, and assay of sex hormones (oestrogen, progesterone) and their trophic hormones (follicle stimulating hormone and luteinizing hormone). The husband was advised semen analysis, ultrasonography of the testes, serum levels of testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH).

The reports of investigations of the wife were normal. Those of the husband revealed azoospermia, small-sized testes with heterogenous echotexture on ultrasonography, low serum level of testosterone and high LH. His thyroid function tests, however, were normal. The couple was next advised karyotyping to find out chromosomal abnormality if any. They were referred to the department of Pathology, BSMMU.

The wife's karyotype was found normal with normal autosomes and sex chromosomes (46,XX). The husband was found having abnormalities in both autosomes and sex chromosomes. His karyotype showed two X chromosomes and a large derivative chromosome which appeared a long chromosome 2 with attached extra portion to its long arm. The extra portion was recognized as the long arm of chromosome 3. The karyogram also showed single normal second and single normal third chromosome. The other chromosome 3 was clearly deficient of its long arm and consisted only of the short arm. We reported the karyotype as 46, XX + der(2)t(2;3) (qter;q). The man was advised a FISH (fluorescence in situ hybridization) to study the breakpoints of the involved chromosomes; however, he did not come for a follow-up and we could not get further information.

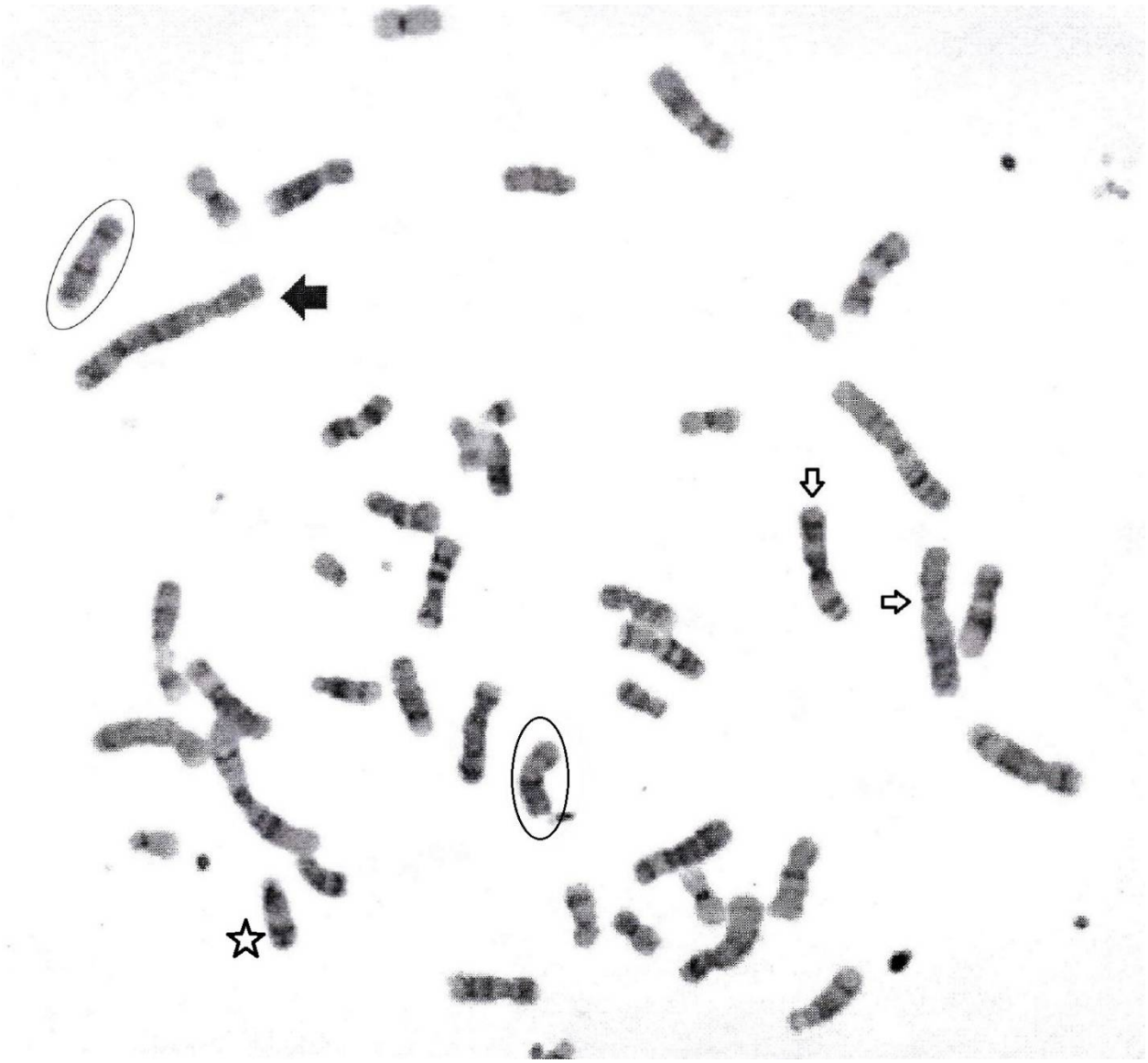

Figure 1**.** Photomicrograph of a chromosome spread showing a derivative autosome formed of chromosomes 2 and 3 (black arrow), one normal chromosome 2 and one normal chromosome 3 (white arrows). The spread also shows two X chromosomes (in ellipses) and short arm of the other chromosome 3 (star).

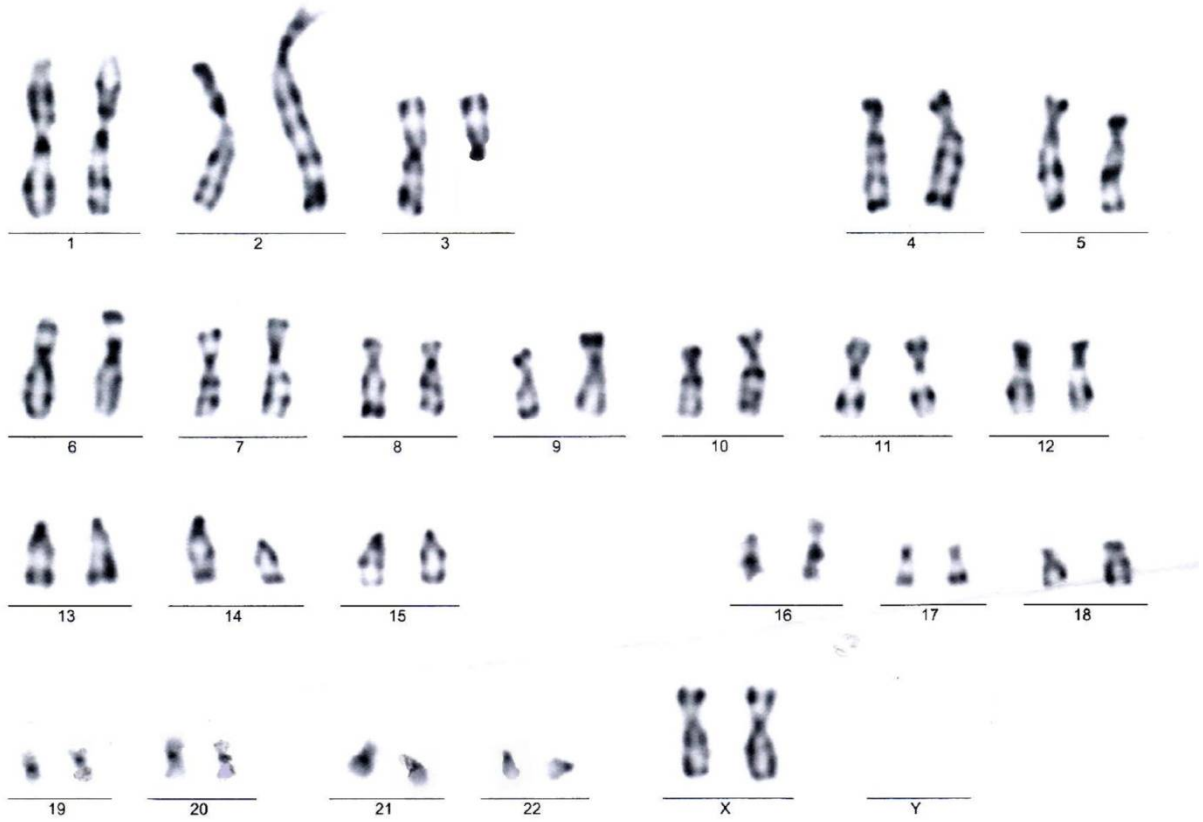

Figure 2**.** Karyogram of the study case: 46, XX, der(2)t(2;3) (qter;q).

Discussion

Male infertily can result from a variety of genetic, chromosomal, developmental, hormonal and other causes like infections. There are a number of genetic and chromosomal aberrations related to male infertility. Disorders of sex development (DSD) are a group of sex chromosomal aberrations commonly associated with male and female infertility. Though the DSD categories usually show varying degrees of genital and other phenotypic abnormalities, the 46,XX testicular DSD subgroup males are sometimes phenotypically normal with mere complaints of infertility.[4,5] On examination, however, these persons often show small testes and different levels of cryptorchidism. Impairment of spermatogenesis ranges from oligo-, through astheno- and teratozoospermia to complete azoospermia.[5] The testicular development in these Y-deficient individuals is instructed by the SRY (sex-determining region on Y) gene present in the paternally derived X chromosome. The SRY gene which is normally located in Y chromosome, is generally misplaced on to the X chromosome in the affected person's father during formation of sperm cells. This occurs in a random fashion by an abnormal exchange of genetic material between the chromosomes (translocation).[4,6]

Among the structural chromosomal abnormalities, complex rearrangements involving sex chromosomes and/or autosomes in various combinations are seen. Derivative chromosomes formed by reciprocal translocations between autosomes are found

associated with both male and female infertility.[7,8] These are, however, rare in humans. Relatively commoner are rearrangements within Y chromosome (deletions, inversions, insertions) in males and within chromosome 9 in both males and females.[9]

Other reported patterns are very rare and appear unique events. Lauricella SA, et al (2016) found an infertile mosaic woman with a karyotype 45,XX,der(18)t(18;21)(p11;q21)-21/46,XX,t(18;21)(p11;q21). 86% of her cell lines showed 45,XX-21 pattern and only 14% showed 46,XX pattern containing the derivative (18 & 21) chromosome. This is explained by the marked instability of the derivative chromosomes which can be reduced in size or disappear during karyotype evolution. The authors also explained the patient's infertility despite having two X chromosomes by the possibility of formation of a high risk offspring affected by an unbalanced chromosomal disorder (deletion or duplication of chromosomes 18 and 21) that might had been eliminated every time of attempted conception.

The patient of the present report is already an XX male; however, the unbalanced derivative (2 & 3) chromosome he possesses can be explained similarly in having a role in his infertility. Song SH, et al (2011) found impaired spermatogenesis ranging from oligo-, astheno-, teratozoospermia to complete azoospermia in their male subjects with complex chromosomal rearrangements (CCRs) of various combinations. Among their 10 cases, there were inversions within chromosome 3, complex translocations between chromosomes 2, 7 and 4, and between chromosomes 2, 19 and 22, and also other patterns. All these cases, however, possessed normal male sex chromosomes, that is 46, XY.

Other similar studies on autosomal rearrangements producing derivative autosomes also showed association with male infertility.[10,11]

Conclusion

Cases of male and female infertility are best investigated through a multidisciplinary approach involving cytogenetic, molecular, hormonal, histopathological and imaging studies. With cytogenetic study, rare sex chromosomal and autosomal rearrangements forming derivative chromosomes should be kept in mind for proper evaluation.

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