Balanced X-Autosome Translocation in Infertile Woman: Report of Two Cases

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Individuals with apparently balanced translocations, often, show no clinical findings. X-chromosomal translocations involving different autosomes have been reported. The phenotypic manifestations of these translocations depend on several factors. X-autosome translocations can also affect fertility where chromosomal changes result in inactivation of genes governing reproduction. This report is described two cases of phenotypically normal Bangladeshi women with the complaint of primary infertility associated with secondary amenorrhea and streak ovaries. Chromosomal analysis revealed an apparently balanced reciprocal translocation involving the long arm of the X chromosome (q2) with the short arm of chromosome 1(p3) and the long arm of chromosome 19(q13) in all the cells with the karyotype 46,X,t(X:1)(q22:p32) and 46,X,t(X:19)(q22:q13.1). Studies examining X-chromosome deletions have predicted that Xq aberrations within the Xq13–Xq27 region can result in gonadal failure. Reciprocal translocations between autosomes and gonosomes contribute significantly to primary infertility.

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Introduction

X-autosome translocations are rare and associated with different phenotypes. There are balanced and unbalanced X-autosome translocation. Balanced type is usually associated with normal phenotype whereas the unbalanced one is with various congenital anomalies. Phenotypic effects of balanced X-autosome translocations in females: a retrospective survey of 104 cases reported from UK laboratories by Water JJ et al.[1] Their cases were: multiple congenital abnormalities and/or developmental delay (MCA/DD): 26 (42%); gonadal dysfunction: 22 (35%); phenotypically normal with or without recurrent miscarriage (NRM): 9 (15%); recognized X-linked syndrome: 5 (8%). X chromosome translocations are frequently associated with primary or secondary amenorrhea. In this report, the clinical, biochemical and cytogenetic aspects of two healthy infertile women with balanced X-autosome translocation between chromosome X and two different autosomes: chromosome 1 and 19 were presented.

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Case Presentation

Case 1

A 27 year-old female with the complaint of primary infertility, was referred to the department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh for cytogenetic evaluation. She was born to a nonconsanguineous parent and her mother had no menstrual problem. Her siblings were healthy. Her menarche was at 13 years of age but she had irregular menstruation with 4-8 months interval. She was married for 7 years. Her husband lived abroad. Her physical examination revealed normal height and weight and showed normal intelligence. On per vaginal examination small uterus was found with no abnormality of the external genitalia. Her luteinizing hormone and TSH level were normal but follicle stimulating hormone and anti-Mullerian hormone were at postmenopausal level. Ultrasound examination of the pelvis revealed normal uterus and streak ovaries.

Cytogenetic analysis of the peripheral blood lymphocytes was carried out according to the standard karyotyping technique. Peripheral blood lymphocytes were stimulated with phytohemagglutinin and harvested at 72 hours with colchicine. Hypotonic treatment was given to the cells and then they were fixed with Carnoy's fixative. Standard GTG banding was done.[2] Karyotype analysis of 100 metaphases revealed a pattern of 46, X, t(X;1)(q22; p32), suggestive of a balanced sex autosome translocation involving the long arm of chromosome X and short arm of chromosome 1 (Figure 1). ISCN guidelines for the chromosomal nomenclature (2016) were followed for the karyotype analysis and analysed by using Leica DM6000 B Motorized microscope and Leica Cytovision software.[3] Parental and siblings karyotypes were not done.

Case 2

A 32 year-old female was referred with the complaint of primary infertility. She had two sisters and they had children. She had delayed puberty with menarche at the age of 15 years. After then menstruation occurred only after taking pills. She was married for 16 years. Her height was 5 feet 3 inch and weight was 60 kg. She was graduated and was a health worker. She had complaint of decrease libido. On per vaginal examination small uterus was found with no abnormality of the external genitalia. Her luteinizing hormone, thyroid stimulating hormone, prolactin and testosterone level were normal but follicle stimulating hormone was at postmenopausal level. Ultrasound examination of the pelvis revealed hypoplastic uterus and streak ovaries.

Cytogenetic analysis of the peripheral blood lymphocytes was carried out and standard GTG banding was done.[2] Karyotype analysis of 100 metaphases revealed 46, X, t(X;19)(q22; p13.1), suggestive of a balanced sex autosome translocation involving the long arm of chromosome X and long arm of chromosome 19 (Figure 2).

Table I: Previously reported cases of balanced X; 1 and X; 19 translocations

Symptoms	Karyotypes	Data by
Developmental delay	46, X, t (X; 1)(p22.1;p31) *de novo*	Waters JJ et al[1] (2001)
Recurrent miscarriages	46, X, t (X; 1)(p22.1;p32) *de novo*	
Learning difficulties	46, X, t (X; 1)(p11.4;p36.3) *de novo*	
Mother: abnormal scan	46, X, t (X; 1)(q26;p22) *de novo*	
Multiple congenital anomalies/developmental delay	46, X, t (X; 1)(q26;p22) *mat*	
Primary amenorrhea	46X: t (X; 1) (q21;p32) de novo	Venkateshwari A et al[9] (2015)
Primary amenorrhea	46,X,t(X; 1)(q22;p13)	Razavi Z and Momtaz HE[10] (2017)
Primary amenorrhea	46,X,t(X;19)(q28;p13.1)	Shetty DL et al[11] (2014)

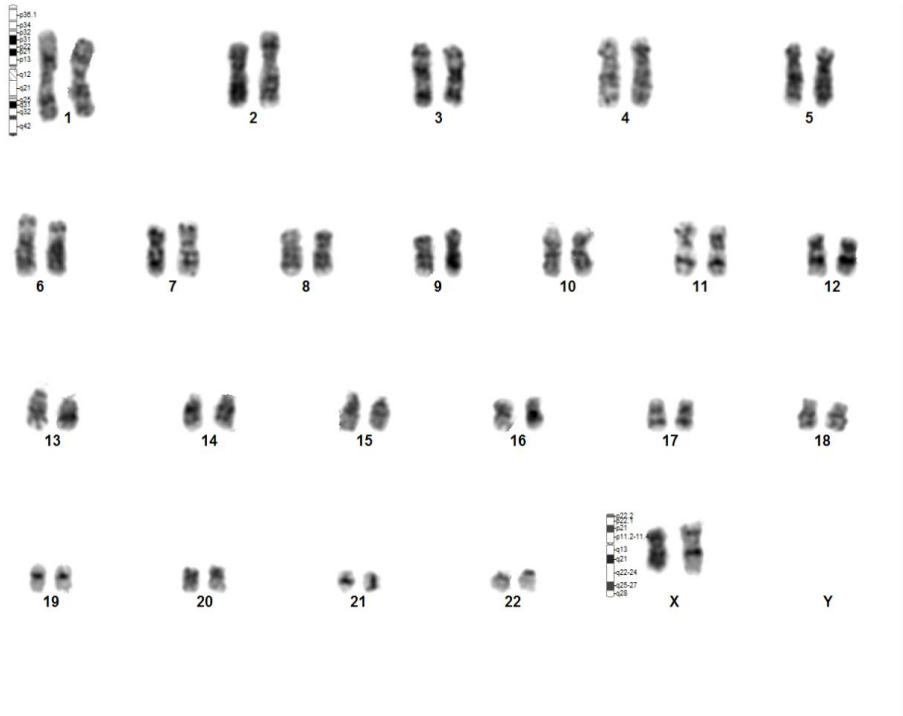

Figure 1. Photomicrograph of a karyotype showing translocation between chromosome X and chromosome 1 [46, X, t(X; 1) (q22; p32)] (Giemsa stain).

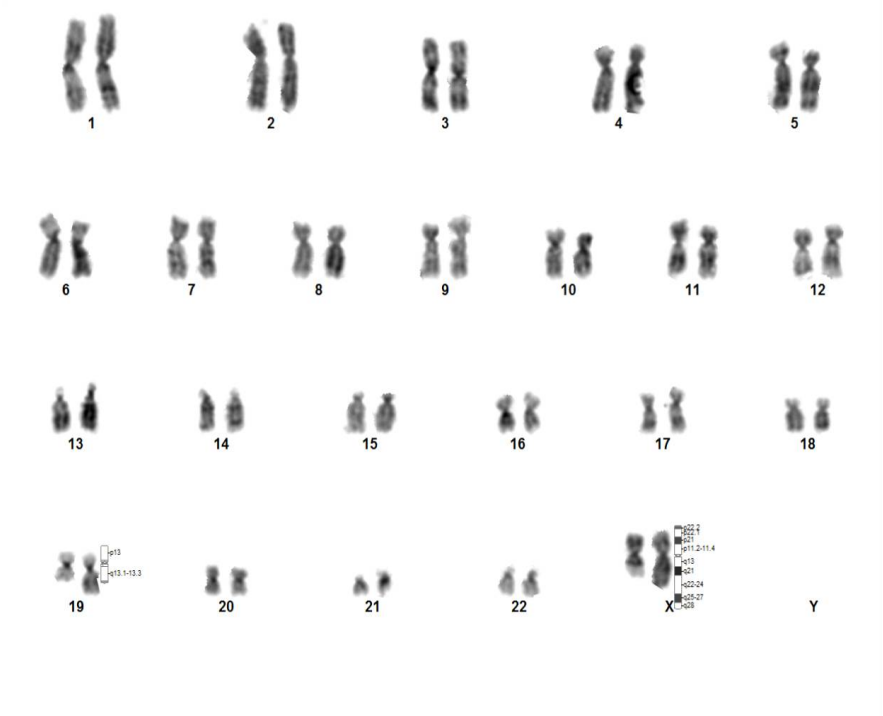

Figure 2. Photomicrograph of a karyotype showing translocation between chromosome X and chromosome 19 [46, X, t(X; 19) (q22; p13.1)] (Giemsa stain).

Discussion

Chromosomal conditions involving the sex chromosomes often affect sex determination (whether a person has the sexual characteristics of a male or a female), sexual development, and the ability to have children (fertility). The signs and symptoms of these conditions vary widely and range from mild to severe. They can be caused by missing or extra copies of the sex chromosomes or by structural changes in the chromosomes.

X-autosome translocations are rare, being estimated to occur in about 1/30,000 live births.[4] In cases of balanced X-autosome translocation in female carriers, the normal X chromosome is usually inactivated, leaving the derivative X chromosome in the active state. The present cases revealed sex autosome translocation in phenotypically normal female with secondary amenorrhea. Cytogenetic analysis revealed 46, X, t (X; 1) (q22; p32) and 46, X, t(X; 19) (q22; p13.1) karyotype indicating its possible association with irregular menstruation and abnormal hormone level. Most carriers of an X-autosome translocation are phenotypically normal.[5,6,1] In female carriers, gonadal dysgenesis may occur, and ~9% may have multiple anomalies and/or mental retardation.[7] Since the 2 copies of the X chromosome are necessary for ovarian development and integrity, the gonadal dysgenesis with infertility in our patient can be attributed to the partial loss of Xq, which contains various genes necessary for a normal ovarian reproductive function. MG Mattei et al concluded that in X-autosome translocation 50% women will be sterile.[8] There are reported cases of balanced X; 1 and X;19 translocations with different clinical manifestations including infertility showed in Table I.

Balanced X-autosome translocations show exchange between long arm segments of an X

chromosome to an autosome with larger number of breakpoints. Infertility because of gonadal dysgenesis is common among those women in whom the breakpoint in the derivative X-chromosome involves the critical region Xq13–q26.[1,5,6] X-autosome translocation causing gonadal dysgenesis with bilateral streak gonads as well as aberrant ovarian and sex development has been demonstrated by numerous studies.[12, 13] Translocations involving the long arms of the X-chromosome and several autosomes (1–4, 6–9, 11, 12, 14, 15, 17, 19, 21, and 22), resulting in various degrees of gonad dysfunction, have also been reported.[14]

X-autosomal translocations are generally of maternal in origin or may arise in *de novo*.[6] Fertility effects of a balanced X-autosome translocation vary depending on the sex of the carrier, the position of the translocation breakpoints and the pattern of X-inactivation.[5,6,7] In the reported cases X autosome translocation may be de novo as their siblings had no menstrual abnormality. To conclude that balanced X-autosome translocation can be a cause secondary amenorrhea associated with infertility and should be investigated by cytogenetic analysis followed by genetic counseling.

References

1. Waters JJ, Campbell PL, Crocker AJ, Campbell CM. Phenotypic effects of balanced X-autosome translocations in females: a retrospective survey of 104 cases reported from UK laboratories. Hum Genet 2001; 108 (4): 318– 27.
2. Verma RS and Babu A. Human chromosome: manual of basic techniques.1st ed. New York, USA. 1989: pp 4-44, 152-165.
3. ISCN: an international system for human cytogenomic nomenclature .In Jean McGowan-Jordan, Annet Simons, Michael Schmid eds. Cytogenetic and Genome Research. New York, Karger. 2016: Vol. 149, No. 1-2.
4. Sharp AJ, Spotswood HT, Robinson DO, Turner BM, Jacobs PA. Molecular and cytogenetic analysis of the spreading of X inactivation in X;autosome translocations. Hum Mol Genet. 2002; 11 (25): 3145– 56.
5. Madan, K. Balanced structural changes involving the human X: effect on sexual phenotype. Hum. Genet. 1983; 63: 216–221.
6. Kalz-Füller B, Sleegers E, Schwanitz G, Schubert R. Characterisation, phenotypic manifestations and X-inactivation pattern in 14 patients with X-autosome translocations. Clin. Genet. 1999; 55: 362–366.
7. Schmidt, M. and Du Sart, D.) Functional disomies of the X chromosome influence the cell selection and hence the X inactivation pattern in females with balanced X-autosome translocations: a review of 122 cases. Am. J. Med. Genet1992; 42: 161–169.
8. Mattei MG, Mattei JF, Ayme S Giraud F. X-Autosome translocation: cytogenetic characteristics and their consequences. Hum Genet 1982; 61:295-309.
9. Venkateshwari A, Srilekha A, Veena K, Sujatha M, Jyothy A. A Rare De Novo Balanced 1X; 1 Translocation in an Indian Female with Primary Amenorrhea. J Reprod Infertil. 2015; 16: 171–3.
10. Razavi Z and Momtaz HE. Balanced Reciprocal Translocation t(X; 1) in a Girl with Tall Stature and Primary Amenorrhea Iran J Med Sci. 2017 Mar; 42(2): 210–214.
11. Shetty DL, Kadam AP, Koppaka NT, Dalvi RC, Chavan DS, Das BR, Mandava S. X-autosome translocations in amenorrhoea: a report of a three way translocation from Indian Population. Gynecol Endocrinol, 2014 Early Online: 1–5.

12. Mohandas T, Geller RL, Gerald P, Yen H. Cytogenetic and molecular studies on a recombinant human X chromosome: implications for the spreading of X chromosome inactivation. In Proceedings of the National Academy of Sciences of the United States of America, 1987;84(14):4954–4958.
13. Carpenter NJ, Say B, Browning D. Gonadal dysgenesis in a patient with an X; 3 translocation: case report and review. Journal of Medical Genetics, 1980; 17(3): 216–221.
14. Madan KP, Hompes GA, Schoemaker J, Ford CE. X-autosome translocation with a breakpoint in Xq22 in a fertile woman and her 47, XXX infertile daughter. Human Genetics, 1981; 59(4):290–296.