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Balanced X; 22 Translocation in a Patient with Premature Ovarian Failure

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Abstract. A case of balanced X; autosome translocation 46, X, t (X; 22) (q 24; q 13) in a 25-year-old female with secondary amenorrhea and premature ovarian failure (POF) is described. The relationship between balanced X; autosome translocation [t (X; A)] and varied phenotypic expression observed in these women is discussed. This case highlights the importance of early recognition of these women in order to give them the best chance of conception in their oligohypomenorrhic phase before complete loss of gonadal function.

Key words: Ovarian failure, Premature; X- chromosome; Translocation – Genetic; Chromosome-Human pair – 22

INTRODUCTION

POF is seen in approximately 1% of females below 40 years of age [1]. Balanced t (X; A) as a cause of gonadal dysgenesis and thus POF is infrequently reported in the literature [3, 5, 6]. It has been proposed that there is a "critical region" on the long arm of the X chromosome from X q13-q26 which is responsible for normal ovarian function [3]. Any break in this region would lead to gonadal failure. Patients with t (X; A) may be phenotypically normal or may have only slight variation from normal in the form of slightly underdeveloped breasts or external or internal genitalia. Therefore, these patients may pass off as normal on clinical examination. We report a case of balanced t (X; A), 46, X, t (X; 22) (q24; q13) in a patient with secondary amenorrhea and primary infertility. Identifying these patients early would save them from extensive investigations, and from the frustration of failure of infertility treatment, once secondary amenorrhea sets in.

CASE REPORT

A 25-year-old female presented with complaints of primary infertility of seven years and secondary amenorrhea of six year duration. She attained menarche at the age of 13 years and was having oligomenorrhea since then. Her periods used to last for 1-2 days and come every 2-3 months. She had been prescribed oral contraceptive pills to regularise her cycles by a private practitioner which she took till the age of 19 years. After one year of marriage, she was advised to stop oral contraceptive pills as she desired pregnancy. After stopping pills, she became amenorrhic. Withdrawal bleeding to Medroxy – progesterone acetate (MPA) was present. Patient was put on Clomiphene citrate for seven cycles, but without success. Finally, the patient was referred to us for management of amenorrhea and infertility. On examination, she was a normal looking female, weighing 52 kgs, whose height was 5 feet 5 inches. Her phenotype was normal except that she had sparse axillary and pubic hair and breasts were Tanner III. Her external genitalia were normal. She had normal vagina, cervix was nulliparous and uterus was slightly smaller in size than normal. Her routine investigations were within normal limits. Her FSH was 34 IU/L, LH 44 IU/L, and prolactin 12 ng/l. Cytogenic study revealed balanced t (X; A), 46, X, t (X; 22) (q24; q13).

DISCUSSION

Balanced translocations usually do not lead to change in phenotype of an individual as there is no loss of genetic material. However, t (X; A) is an exception to this rule. Women with t (X; A) present with variable phenotype. They may have normal phenotype with: normal ovarian function or may have slight variations from normal with loss of gonadal function [3, 5, 6] leading to sparse axillary and pubic hair, small breasts and underdeveloped external and internal genitalia. This is explained by the altered pattern of X chromosome inactivation in balanced t (X; A) [5]. According to Lyon's hypothesis, there is a random inactivation of one of the X chromosomes of the female embryo. However, in cases with balanced t (X; A), there is a preferential inactivation of the normal X chromosome [5]. Though the active chromosome is not intact, there is no loss of genetic material and theoretically there should not be any functional impairment, but this is not always the case. The hypotheses proposed to explain these observations are:

1) There is a "critical region", now recognised to be on the long arm of the X chromosome from Xq13-q26 for normal ovarian function and any break in this region would lead to phenotypic abnormality [4, 5].
2) Inactivation of the same chromosome in all the cells causes amenorrhea because of effective homozygosity of a recessive gene on the active X chromosome [5].
3) There is a direct effect on the oocyte by t (X; A) leading to meiotic arrest [2].

The present case can be explained on the basis of position effect of translocation involving Xq24 to 22q13 which may lead to a greater rate of oocyte atresia and finally POF.

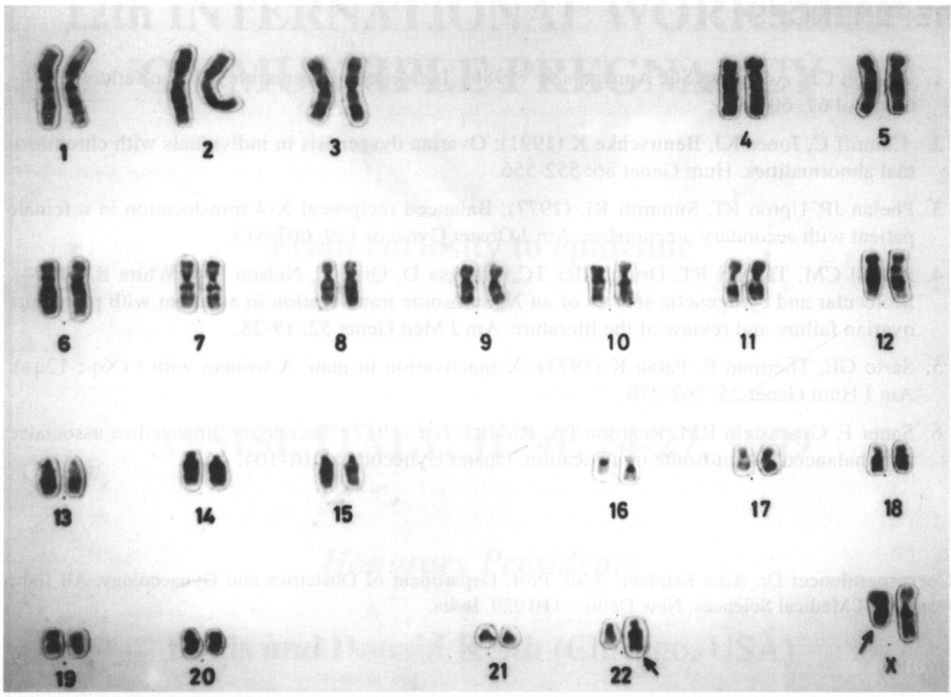

Fig. 1 - A karyotype showing 46, X, t (X; 22) (q24; q13) translocation. Arrows indicate der (22) and der (X) chromosomes.

As these patients with oligomenorrhea or amenorrhea have near normal phenotype, the treating physician should have a high index of suspicion for gonadal dysgenesis while treating such patients. Drugs for ovulation induction are commonly prescribed in patients who present with oligomenorrhea and infertility without considering the diagnosis of gonadal dysgenesis; this is particularly true for women with normal phenotype. This line of management inevitably leads to treatment failure, resulting in frustration for the patient and physician alike. The experience of our patient highlights another error that physicians may make when confronted with these patients. She was prescribed oral contraceptive pills during her oligomenorrhic phase in order to regularise her cycles; this was the only time she could have conceived, if the correct diagnosis had been considered.

Once the diagnosis of gonadal dysgenesis is made, hormone replacement therapy should be instituted in order to prevent estrogen deficiency and its attendant complications.

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