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Premature Ovarian Insufficiency in Balanced X-autosome Translocation: A Case Report

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Abstract

Premature ovarian insufficiency is a condition of hypergonadotropic hypoestrogenism with innumerable etiologies. Women with balanced translocations between the long arm of the X chromosome (Xq) and an autosome frequently suffer from premature ovarian failure (POF). The condition affects women physically and psychologically. It has profound impact on women's reproductive system and subfertility is the most devastating consequences of POI. The presentation of POI is widely variable, and diagnosis is often delayed. Patient with POI may present with primary amenorrhoea, oligomenorrhoea or secondary amenorrhoea, subfertility and with features of hypoestrogenism. Here we present a case of a 24-year-old married woman presenting with secondary amenorrhoea and subfertility. Clinical and laboratory assessment, imaging study, karyotyping and cytogenetic analysis confirmed her as a case of POI with balanced X-autosomal translocation. Tender counselling was done and HRT was given to alleviate her vasomotor symptoms and to minimize long term health complications. Early diagnosis and appropriate intervention is vital for fertility treatment and for cryopreservation of ovarian cortical tissue, oocyte and embryo. So, high index of suspicion, identification of the women at risk, anticipating iatrogenic POI is crucial for fertility preservation.

Keywords: Premature ovarian insufficiency, Amenorrhoea, Subfertility, Translocation

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Introduction

Premature ovarian failure (POF) or updated nomenclature Premature ovarian insufficiency (POI) is a condition characterized by amenorrhoea and elevated serum gonadotropin level before the age of 40 year.[1] More precisely, Premature ovarian insuffiency is defined as the occurrence of primary amenorrhoea or secondary amenorrhoea for at least 4 months before the age of 40 years, serum FSH level greater than 40mIU/ml, and presence of hypoestrogenism.[2] The condition results from early depletion of the follicle or due to unresponsive ovaries to endogenous and exogenous FSH. POI is found in 0.01 percent of women under the age of 20, 0.1 percent of women under the age of 30, and about 1-2% of women under the age of 40 years.[3,4]

The known causes of POF are genetic aberrations, such as single gene mutation and chromosome imbalances involving X chromosome or autosomes; autoimmune diseases with anti-ovarian antibodies causing ovarian damage; iatrogenic factors following pelvic surgery, chemotherapy or radiotherapy. There are some environmental factors like viruses, tuberculosis, mumps, malaria causing infectious oophoritis; some environmental toxins and pollutants-smoking, recreational drugs, pesticides, phthalates, bisphenol A and so on. Some metabolic causes (galactosemia, 17 OH deficiency, etc.) may play role in this condition. More than 50% of the cases of premature ovarian failure remain idiopathic. POF may be familial (4-33%) or sporadic.[3-6]

Patients with POI may present with absent pubertal development and primary amenorrhoea, or post-pubertal onset of the menstrual cycle, irregular menstruation. It also may present with secondary amenorrhoea, and subfertility, or menopausal symptoms such as hot flushes, night sweats, vaginal dryness, and osteoporosis.[4]

Case Presentation

A 24-year-old young married woman presented with irregular menstruation followed by secondary amenorrhoea for the last 10 months and primary infertility for 2 years. Her menarche was at 13 years of age. The first 2-3 years menstrual period was irregular, then she developed regular menstrual cycle with average bleeding. At 18 years of age, she again developed irregular menstruation. But she was

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not so much concerned about the problem and did not consult with any doctor. At 21 years of age, she experienced amenorrhoea for 6 months. She also noticed significant weight gain in the meantime.Then she consulted with a doctor and was diagnosed as a case of hypothyroidism. She was treated with levothyroxine and progesterone hormone cyclically. She got married at 22 years of age. After menstruating irregularly for few months with very scanty bleeding, she again developed amenorrhoea for 10months. She also complaints that she is experiencing hot flushes, night sweats, and mood swings for the last couple of months. She has no history of any pelvic surgery or chemo-radiation, TB, or Mumps.She has no family history of premature ovarian insufficiency in her first- and second-degree relatives. She has two younger sisters with regular menstrual cycles since menarche and well-developed secondary sexual characteristics. She has been trying to conceive since her marriage but failed. For infertility problem she consulted with us.

On Examination

She was anxious, height -1.55m, weight-52kg. The thyroid gland was not enlarged. Her secondary sexual characteristic was well developed.

Investigation

TVS was done at her initial visit, uterus was found smaller in size and anteverted, myometrium homogenous and endometrium was thin, both ovaries were indistinguishable. On evaluation, S.FSH-86 mIU/ml, S.LH-55mIU/ml, S. Estradiol -12pg/ml, AMH <0.001ng/ml S.TSH-2.60µIU/ml, S. FT4-1.29ng/dl, AntiTPO antibody-negative, S. Prolactin-21ng/ml, S. vitamin D-12.80 ng/ml. Bone mineral density test was given. Repeated test for ovarian reserve after 4 weeks also revealed POI. Karyotype and cytogenetic analysis revealed karyotype 46,x,t(x;9)(q22.1;q21.2~21.33), a female karyotype with a balanced X-autosome translocation between chromosome X and 9, with breakpoints approximately at Xq22.1 and 9q21.2~21.33 respectively.

Fig. 1: TVS showing small uterus with thin endometrium

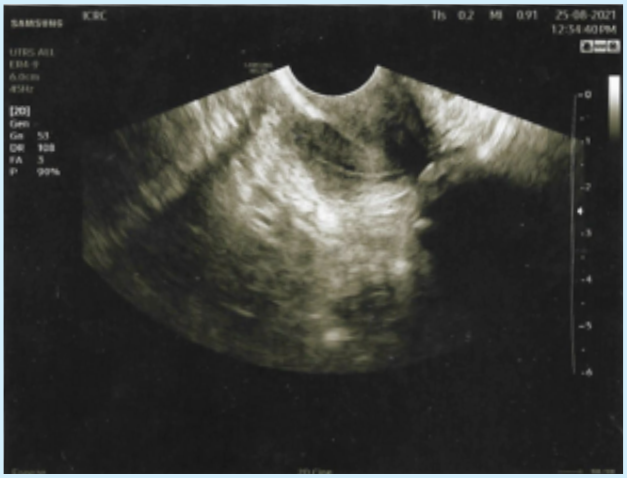
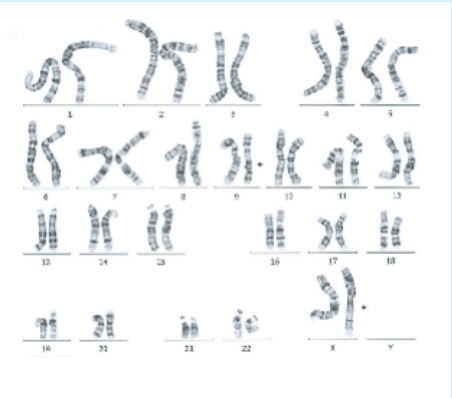


Fig. 2: karyotype 46,x,t(x;9)(q22.1;q21.2~21.33), a female karyotype with a balanced X-autosome translocation between chromosome X and 9, with breakpoints approximately at Xq22.1 and 9q21.2~21.33 respectively.



Management

POF has a wide-ranging health impact on general, psychological, sexual, and reproductive quality of life. It has also long-term bone, cardiovascular, and cognitive health effects. So the patient was counseled and advised to take a balanced diet including calcium and vitamin D-rich foods, maintenance of normal body weight, regular weight-bearing exercise, avoidance of smoking and alcohol. Hormone replacement therapy (HRT) was given orally by conjugated equine estrogen (0.625mg) and norethisterone 5 mg cyclically. She was advised to continue the HRT until the average age of menopause. Vitamin D3 (1000IU/day) and calcium (1000mg/day) were advised in addition to food supplementation. Thyroxin was given accordingly as she was suffering from hypothyroidism. The gonadotropin level was very high and ovaries were almost atrophied. So, regarding fertility prospects, she was advised for the option of donor oocytes and IVF or adoption. POF has a long-term consequence, so she was advised to continue her treatment under a multi-disciplinary team and periodic follow-up.

Discussion

Among the genetic causes, X chromosome numerical and structural alterations like X chromosome aneuploidy (monosomy or trisomy) and chromosome rearrangement such as partial deletion, inversion, isochromosome, balanced X-autosome translocation are associated with POI.[3]

POI is caused by X chromosomal abnormalities in about 12% of cases. Approximately 50% of X chromosome translocation carriers suffer from POF regardless of which autosome is involved in the rearrangement. From cytogenetic analysis, a 'critical region' is identified on the long arm of the X chromosome (q) for normal ovarian function. This critical region extends from Xq13.3-q27, divided into two portions, Xq13-Xq21, and Xq23-q27, known as POI 1 and POI 2 region respectively. Balanced X; autosome translocation often occur at Xq13-21 region and breakpoints at Xq23-27 commonly results in deletions.[1,2] In our patient balanced X; autosome translocation occurred between chromosome X and autosome 9, with breakpoints approximately at Xq22.1 and 9q21.2~21.33 respectively.

Translocation causes POI by disrupting the expression of certain X-linked genes that are required for normal ovarian function, or by chromosomal effects like meiotic error or incomplete meiotic pairing, apoptosis at meiosis checkpoint, altered X inactivation, and /or position effect.[7,8] Over the last few years, several genes have been identified as candidate genes for POI. Mutations of these genes like BMP15, FMR1, NR5A1, NOBOX, FOXL2, FIGLA, GDF9 and so on, located on X chromosome and different autosome may cause POI.[3]

According to some research, many X-linked genes on both X chromosomes were related to POI. Whereas other studies found that X; autosome translocation frequently causes no gene disruption.

Davison et al. 2000 proposed that a group of genes at the critical region that is involved in normal ovarian function may lead to gonadal dysgenesis or POI due to X-autosome translocation. But Mumm et al. 2001 found that breakpoints in the X-autosome translocation occur where there were no genes.[3]

Recently the position effect of the X breakpoints on autosomal genes has been proposed as a possible explanation for genetic mechanisms.[9]

Rizzoli et el. mapped 23 novels X-autosome balanced translocations between Xq and different autosomal regions by FISH. Among them, twenty-one were found with POF and two women were fertile. The majority corresponded to a gene-poor region in Xq21, implying that POF is caused by the position effect of the breakpoints on adjacent genes and suggested that X-linked gene disruption is not so common in POF patients.[1]

With the abnormality about half of the women experienced primary amenorrhea, whereas the majority of the others developed secondary amenorrhea after a few years of irregular cycles. Severe infertility was present in all POF patients.[1]

If a POI patient can be diagnosed at an earlier stage, one ovary can be cryopreserved for future infertility treatment and IVA treatment can be done. Cryopreservation of ovarian cortical tissues and oocyte allows for the preservation of fertility in unmarried POI patients.[10]

Conclusion

Premature ovarian insufficiency is a multifactorial origin disorder that affects women's quality of life. Infertility can be a significant issue, for which POI women suffer psychologically and socially. Early detection and timely intervention are critical for preserving the residual reproductive potential of POI women.

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