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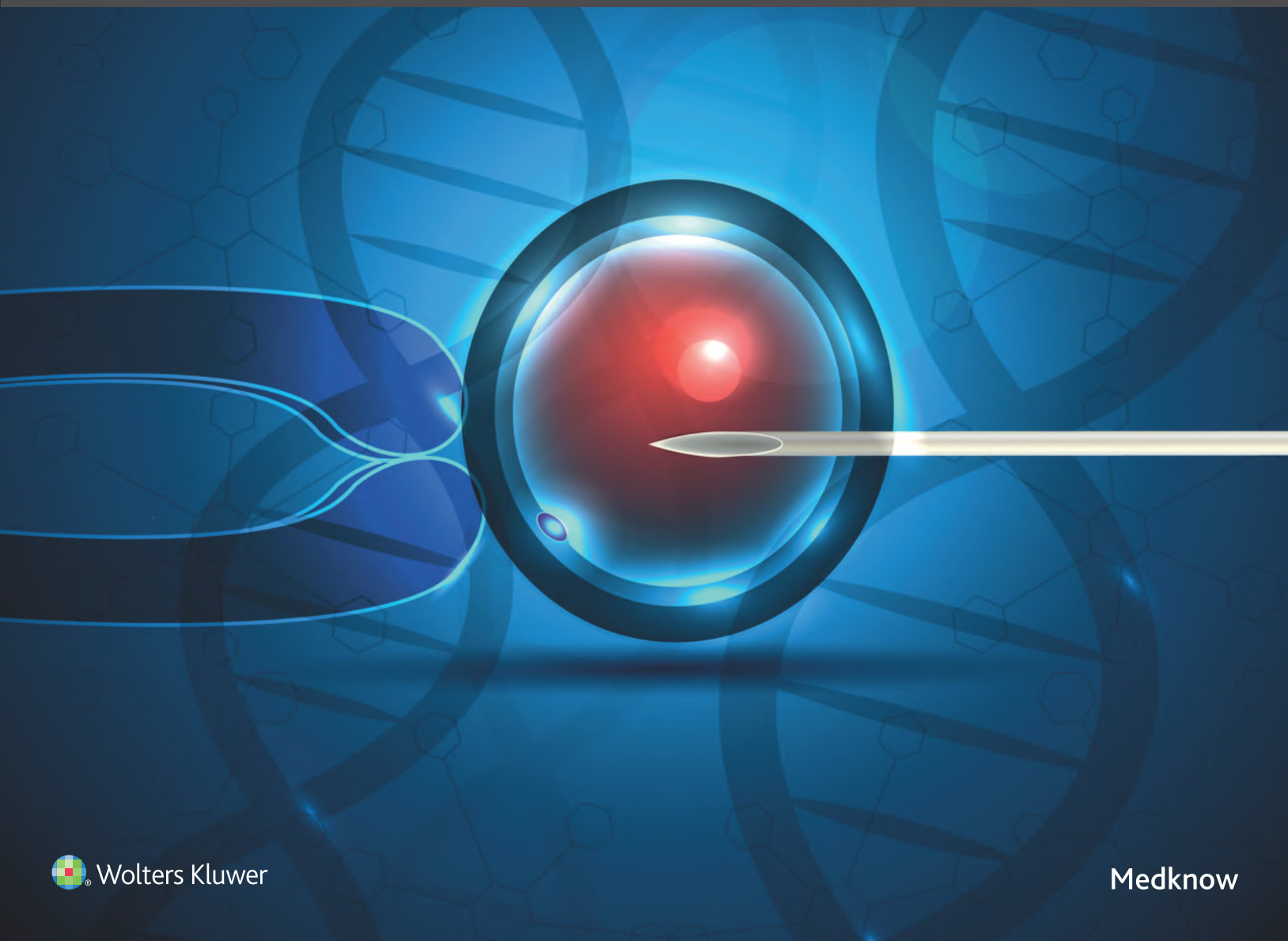

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A Rare Case of 46XX,t(X;11)(q24;q23.3) with Premature Ovarian Insufficiency

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Abstract

Here, we report a rare case of chromosomal abnormality with translocation between bands Xq24 and 11q23.3 leading to premature ovarian insufficiency (POI). POI can occur due to various causes. Studies have shown that 10%–12% of women with POI have chromosomal abnormalities. This patient presented to us with secondary amenorrhea for the past 3 years. She had attained menarche at 13 years and had regular menstrual cycles for 9 years before suffering from secondary amenorrhea. She had no family history of POI. Her karyotype revealed 46XX,t(X;11)(q24;q23.3). Other investigations showed hypoestrogenism, raised follicle-stimulating hormone, low volume ovaries, small sized uterus, and cholelithiasis. Laparoscopic cholecystectomy was done along with pelvic laparoscopy and hysteroscopy. Sequential estrogen and progesterone was given to the patient for 3 months. Following that, *in vitro* fertilization with oocyte donation was done which resulted into positive beta-human chorionic gonadotropin.

Keywords: Oocyte donation, premature ovarian insufficiency, reciprocal translocation, secondary amenorrhea

Introduction

Premature ovarian insufficiency (POI) is defined as amenorrhea due to loss of ovarian function before the age of 40 years resulting in hypergonadotropic hypogonadism.[1,2] As per ESHRE guidelines, the diagnosis of POI is based on menstrual disturbance, i.e., oligomenorrhea/amenorrhea for at least 4 months and biochemical confirmation with an elevated follicle-stimulating hormone (FSH) level >25 IU/L on two occasions >4 weeks apart.[3] Approximately 1% of women develop POI before 40 years of age and 0.1% before the age of 30 years.[1,2,4] Important causes of POI are chromosomal and genetic defects, autoimmune processes, chemotherapy, radiation, infections, surgery, and idiopathic.[1,3] Studies show that 10%–12% of women with POI have chromosomal abnormalities out of which the majority (94%) are X chromosomal abnormalities.[3]

Here, we present a case of secondary amenorrhea with infertility, the cause being structural chromosomal abnormality.

Case Report

A 27-year-old female, married for the past 4 years, presented to us with a history of primary infertility. She had attained menarche at the age of 13 years and was having regular menses at the interval of 25 days with moderate flow lasting for 3–5 days. However, for the past 3 years, she had withdrawal bleeding only after taking progesterone tablet. There was no other significant medical history, and she had not undergone any surgery in the past. Her family history was also not significant, and there was no history of POI in the family [Figure 1].

On examination, her height was 5 feet 5 inches and she had well-developed secondary sexual characters (breast - Tanner Stage 4 and pubarche - Tanner Stage 5). On per vaginal examination, the uterus was anteverted, mobile, nontender, and small and adnexae were free. All the other parameters were normal. Her previous investigations showed serum FSH - 42.77 mIU/ml, estradiol (E2) - 5 pg/ml, and anti-Müllerian hormone - 0.03 ng/ml. Transvaginal sonography showed

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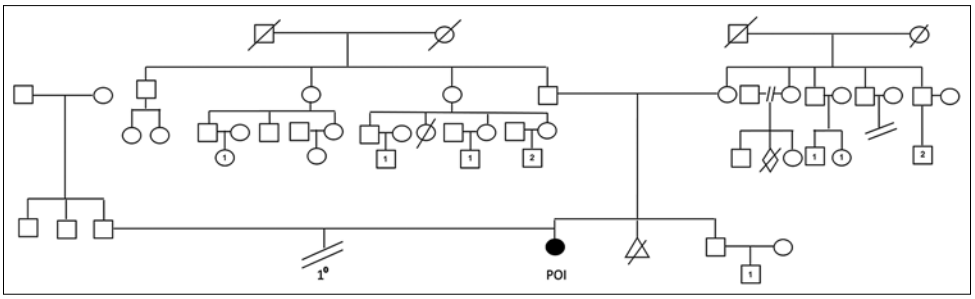

Figure 1: Pedigree chart

bilateral resting, low volume ovaries (right - 1.6cc and left - 1.1 cc), and uterus measured 46 mm × 26 mm × 34 mm. Her repeat FSH done at the interval of 5 weeks showed a value of 44.76 mIU/ml.

On further investigation, husband's semen analysis report was normal. Patient's hysterosalpingography report was normal and her sonography showed low volume ovaries, small sized uterus, and cholelithiasis. Patient's karyotype report was − 46XX,t(X;11)(q24;q23.3), i.e., translocation had occurred at bands Xq24 and 11q23.3. The segments distal to these bands had been exchanged [Figure 2]. Considering the patient's history and her karyotype report, decision of *in vitro* fertilization with oocyte donation was taken after consultation with the patient. In lieu of cholelithiasis, we first decided to do a cholecystectomy. At the time of laparoscopy, uterus and ovaries were assessed and bilateral streak ovaries were seen [Figures 3 and 4].

After the surgery, we started sequential estrogen and progesterone therapy for the patient and reviewed her every month. After 3 months, uterus measured 68 mm × 45 mm × 34 mm in ultrasonography (USG). The endometrial preparation of the patient was done by giving E2 valerate tablet (2 mg) thrice daily from day 2 of her menses. Repeat USG was done on day 12, and it showed a triple line endometrium of 8 mm. Injection progesterone 100 mg IM daily was started, and on the 6th day, two grade A blastocysts were transferred. Beta-human chorionic gonadotropin 10 days after transfer was 163 mIU/ml. Regular antenatal checkup was done and intrauterine pregnancy was confirmed. The patient is now carrying 12 weeks of pregnancy.

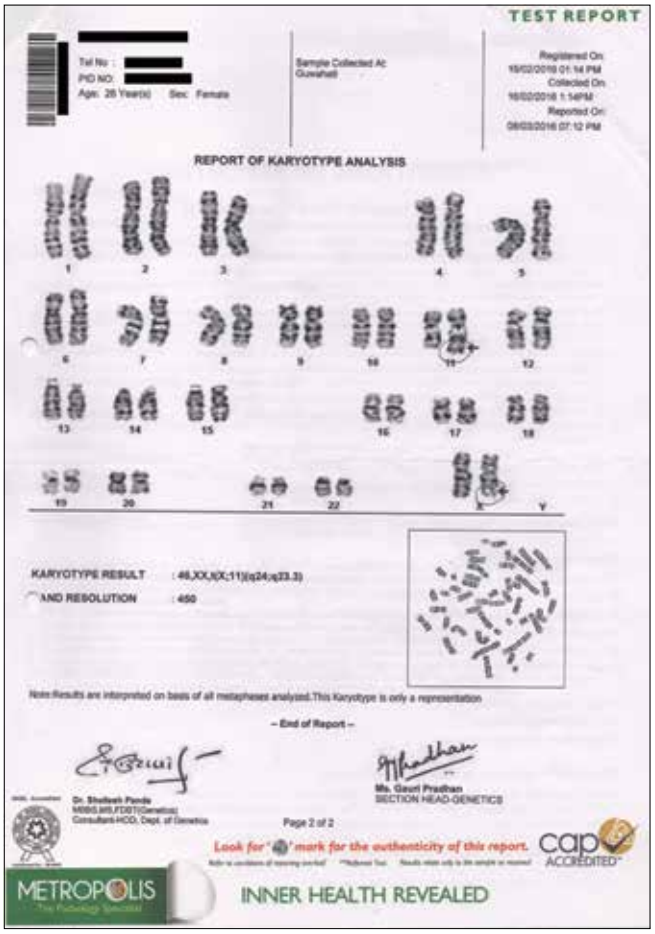

Figure 2: Karyotype

Discussion

In this patient, balanced translocation at bands Xq24 and 11q23.3 is most likely the cause of POI.

Chromosomal abnormalities are an established cause of POI.[5] The genetic basis is supported by the fact that there is 44%–65% heritability of menopausal age between mother–daughter pair, and a first-degree relative is affected in approximately 10%–30% of idiopathic cases.[2,6] Chromosomal abnormalities which can cause POI are numerical defects such as monosomy X, X chromosomal mosaicism, X-deletions and rearrangements, X-autosome translocations, and X-isochromosomes.[5] Carriers of balanced reciprocal translocations have an increased risk of generating chromosomally unbalanced offspring due to partial microduplication or microdeletion of chromosomal segments. Important genes may be disrupted at the points where the breaks occurred in the chromosomes and thus impair its function. Nonspecific defective meiotic pairing or a position effect on contiguous genes may also lead to POI.[5]

The long arm of the X chromosome contains genes which are crucial for normal ovarian function.[1] Multiple genes responsible for POI have been identified on the X chromosome.[5] A few of them have been illustrated in Table 1. A critical region has been identified extending from

Xq13-Xq21 (POI2) to Xq23-q27 (POI1), which is associated with POI.[5] The gene for progesterone receptor membrane component 1 (PGRMC1) is located on Xq22-q24.[5] This protein is expressed in various tissues and is involved in the signaling of progesterone in the reproductive system.[7,8] Mutation or reduction in the levels of PGRMC1 may cause POI by impairing the activation of the microsomal cytochrome P450 and increasing the apoptosis of ovarian cells.[5]

POI can manifest as primary amenorrhea with onset before menarche or secondary amenorrhea. Women who have POI suffer from symptoms similar to natural menopause and also experience an early loss of fertility.[2] Mechanisms that play a role in loss of fertility are depletion of the follicular pool or an inability of the remaining follicles to respond to ovulatory signals or a combination of both.[2] Although ovarian activity may occur spontaneously in up to 5% of women, oocyte donation is considered as the most successful treatment for women with POI desiring pregnancy.[3] Successful pregnancy with oocyte donation in POI patient was first reported in 1984, and it is now done routinely for this group of patients.[9]

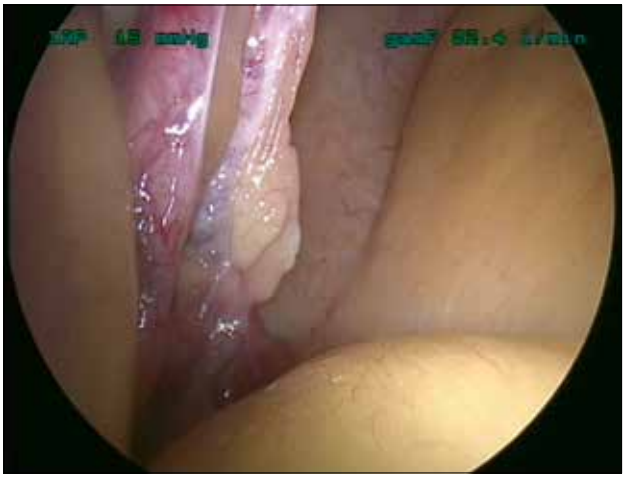

Figure 3: Left ovary

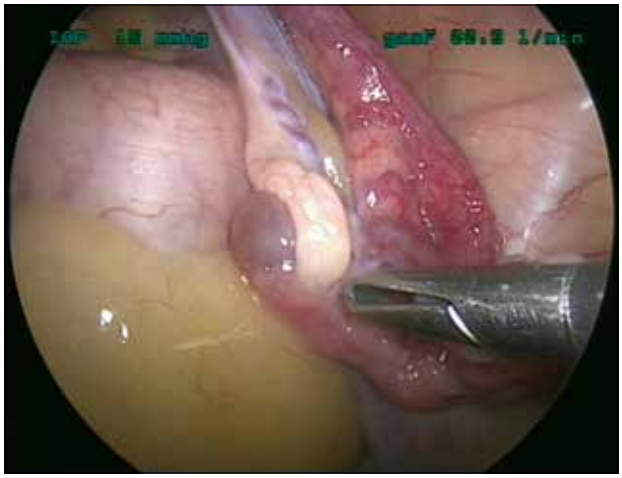

Figure 4: Right ovary

Table 1: List of genetic defects associated with premature ovarian insufficiency

	Frequency in POI	Principal references
X chromosome defects		
Turner's syndrome and related defects	4%-5%	Zinn and Ross (1998)
Fragile X syndrome (*FMR1* premutation)	3%-15%	Marozzi *et al*. (2000) and Wittenberger *et al*. (2007)
DIAPH 2 disruption (translocation)	Unknown	Bione *et al*. (1998)
BMP15 variants	1.5%-12%	Di Pasquale *et al*. (2004), Dixit *et al*. (2006a), Laissue *et al*. (2006), Rossetti *et al*. (2009), Wang *et al*. (2010) and Tiotiu *et al*. (2010)
PGRMC1 variants	1.5%	Mansouri *et al*. (2008)
Autosomal defects		
Complex diseases		
Galactosemia *GALT*, BPES (*FOXL2*), APECED (*AIRE*), mitochondrial (*POLG*), Demirhan syndrome (*BMPR1B*), PHP1a (*GNAS*), ovarian leukodystrophy (*EIF2B*), ataxia telangiectasia (*ATM*)	Rare	Sedgwick and Boder (1991), Perheentupa (1996), Weinstein *et al*. (2004), Fogli *et al*. (2003, 2004), Beysen *et al*. (2009), Luoma *et al*. (2004), Demirhan *et al*. (2005), Pagnamenta *et al*. (2006) and Calderon *et al*. (2007)
Isolated diseases		
FSH/LH resistance (*FSHR* and *LHR*)	<1%	Aittomaki *et al*. (1995), Latronico *et al*. (1996), Beau *et al*. (1998) and Touraine *et al*. (1999)
INHA variants	Unknown	Shelling *et al*. (2000), Marozzi *et al*. (2002), Dixit *et al*. (2004, 2006b) and Corre *et al*. (2009)
GDF9 variants	1.4%	Dixit *et al*. (2005), Laissue *et al*. (2006), Kovanci *et al*. (2007) and Zhao *et al*. (2007)
NOBOX variants	0% in Asiatics; 1% in North Americans	Zhao *et al*. (2005) and Qin *et al*. (2007, 2009)
NR5A1 variants	8% in 25 Europeans	Lourenço *et al*. (2009)
Meiotic gene variants	Rare	Mandon-Pépin *et al*. (2008)
FIGLA mutations	2% (in 100 Chinese)	Zhao *et al*. (2008a, b)

POI: Premature ovarian insufficiency

Till date, only a small proportion of genes influencing idiopathic POI have been identified. Many more genes and molecular pathways influencing idiopathic POI are yet to be determined. Future studies with next generation sequencing and whole-genome association study in large cohorts of well-defined, unrelated, and idiopathic premature ovarian failure patients might provide an opportunity to identify the missing links of inheritance of idiopathic POI.[2]

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Conflicts of interest

There are no conflicts of interest.

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