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Case Report

A 16-year-old patient with 46,X,ider(X)(q28)i(X)(q10) chromosomal abnormalities diagnosed with premature ovarian insufficiency

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Background: Premature ovarian insufficiency (POI) is defined as the onset of a menopausal state prior to 40 years of age. Of the various causes of POI, genetic abnormalities account for 10.8% of all cases, which can be categorized into either chromosomal or gene anomalies. Chromosomal abnormalities of the isochromosome Xq [i(Xq)] type have been recognized as common causes of POI. *Cases*: A 16-year-old female presented with secondary amenorrhea that had persisted for one year. Her physical examination was unremarkable, including a height of 158 cm and the presence of secondary sexual characteristics. Her serum level of follicle-stimulating hormone was elevated (66 mIU/mL), whereas her estradiol and anti-Müllerian hormone levels were decreased (<10 pg/mL and 0.02 pg/mL, respectively). Conventional cytogenetic analyses of a peripheral blood sample showed the karyotype of 46,X,ider(X)(q28)i(X)(q10). *Conclusions*: We describe a novel chromosomal structural abnormality of the i(Xq) type that is associated with a diagnosis of POI.

Keywords

Chromosomal abnormality; Isochromosome Xq; Premature ovarian insufficiency; Secondary amenorrhea; Turner syndrome

1. Background

Premature ovarian insufficiency (POI) is defined as an amenorrheic state occurring before the age of 40 years that is accompanied by hypergonadotropism and hypoestrogenism [1]. The prevalence of spontaneous POI is 0.4% for women under 35 years of age and 1% for women under 40 years of age [2]. Between 10 and 28% of primary amenorrhea and between 4 and 18% of secondary amenorrhea are caused by POI [3]. While the etiology of POI is heterogeneous, the cause of POI in most patients is unknown but can include genetic abnormalities, metabolic disorders, autoimmunity, iatrogenic infection, and environmental factors. Among these causes, genetic abnormalities account for 10.8%, which can be divided into either chromosomal or gene anomalies [4]. Turner syndrome is a representative chromosomal disorder, and a premutation in the fragile X mental retardation (*FMR1*) gene is a representative gene abnormality.

Chromosomal abnormalities have long been recognized as a common cause of amenorrhea and POI. Approximately 20 to 40% of patients with primary amenorrhea are also diagnosed with chromosomal abnormalities. Among the causes of POI due to structural abnormalities of the chromosomes, the most common causes are related to the X chromosome such as the terminal deletion of Xp or Xq, an isochromosome, a ring X chromosome, and an inverted X chromosome [5]. Isochromosome Xq [i(Xq)] is a chromosomal abnormality defined as having only two long arms of the X chromosome. It is caused by either abnormal division of the centromeres during cell division or the breakage and reunion of sister chromatids in proximal Xp; the latter is more common in humans [6]. Approximately 7% of people with Turner syndrome have an i(Xq) abnormality [7]. Unlike individuals in whom the syndrome is caused by monosomy X (45, X), most physical manifestations of Turner syndrome, such as a webbed neck, broad chest, and cubitus valgus, are mild or absent in people with i(Xq). However, a small stature remains a common manifestation in these patients.

Herein, we describe a patient diagnosed with POI who had a novel X chromosomal abnormality of the i(Xq) type, which exhibited a duplicated distal portion of the long arm and translocated to the long arm of the X chromosome.

2. Case report

A 16-year-old female presented with secondary amenorrhea that had persisted for 1 year. Spontaneous menarche occurred at 13 years of age, which was followed by irregular cycles over the next 2 years. There was no family history of genetic abnormalities, and the patient had no siblings. She was delivered at 38 weeks by cesarean section because of placental previa. On examination, the patient was 158 cm tall (in the 25–50th percentile of the population of 16-year-old Korean girls) and weighed 48 kg (10–25th percentile). She exhibited no physical manifestations related to Turner syndrome, such as a webbed neck, lowered hair line, or cubitus valgus.

Her external genitalia appeared normal. Her secondary sexual characteristics were rated as Tanner stage 3 with regard to breast development and Tanner stage 2 with regard to pubic hair. She had normal neurocognitive status and psychomotor and social skills.

The patient's initial laboratory evaluation showed an elevated follicle-stimulating hormone (FSH) level of 66 mIU/mL (postmenopausal state: 26.72–133.41 mIU/mL) and a low estradiol level of less than 10 pg/mL (postmenopausal state: <28 pg/mL). After 4 weeks, the results were 87.76 mIU/mL for FSH and 0.02 ng/mL for anti-Müllerian hormone. Both prolactin and thyroid-stimulating hormone levels were within normal limits (10.58 ng/mL and 0.575 ng/mL, respectively). Pelvic ultrasonography revealed a small uterus (2.74 × 1.54 × 1.39 cm) with an endometrial thickness of 2.3 mm and a mixed echoic appearance as well as small ovaries (right ovary: 1.67 × 0.74 cm, left ovary: 1.14 × 0.63 cm). Small follicles were visible in only the right ovary. Magnetic resonance imaging was performed to look for abnormal findings as a result of the chromosomal abnormalities. No other anomalies were observed. Echocardiography and renal ultrasonography showed no abnormal findings, and shortening of the metacarpals was not visible on X-ray examination.

A peripheral blood sample was obtained for chromosomal analyses, and conventional cytogenetic karyotyping using GTG banding was performed. The karyotype showed a translocation and duplication between the distal portion of Xq and i(Xq) (Fig. 1). Chromosomal microarray and fluorescence *in situ* hybridization studies using a probe specific for chromosome X confirmed these results (Fig. 2). The final karyotype was designated 46,X,ider(X)(q28)i(X)(q10). Testing for fragile X-associated POI using the *FMR1* gene premutation test was negative. To investigate the effects of the patient's genetic background, her parents were encouraged to undergo chromosomal analyses. These tests were not performed because parental consent was not obtained.

3. Discussion

In this study, we describe a female patient with the 46,X,ider(X)(q28)i(X)(q10) karyotype, which is a novel chromosomal aberration involving i(Xq). Although many cases of chromosomal abnormalities associated with POI have been previously reported, none of the abnormalities found in our patient have been previously reported.

Although various genes and pathophysiological mechanisms are reportedly involved in POI, most genetic causes have been associated with X chromosomes. Several mechanisms associated with the X chromosome appear to be involved in the development of POI. First, normal gonadal development requires the zinc finger protein X-linked gene, which is located on the short arm of the X chromosome. One normal X chromosome is required for oocyte development, but two normal X chromosomes are required for oocyte maintenance. Haploinsufficiency of this gene results in gonadal dysgenesis, as is observed in patients with Turner syndrome caused by X monosomy, i(Xq), or short-arm deletion of the X chromosome. Second, two critical regions on the long arm of the X chromosome have been associated with ovarian failure: The Xq13-21 [premature ovarian failure (POF-2)] region, which is the breakpoint of most balanced translocations, and the Xq23-27 (POF-1) region, which has been associated with interstitial deletions. Deletion of the POF-1 region plays a more important role than the POF-2 region in the POI phenotype, which can be affected by the size of the segment deleted from or duplicated in the X chromosome. However, the pathophysiological mechanism causing POI in our patient is thought to differ from those mechanisms previously described.

Two patients with 47,XX,i(Xq) were previously reported. The first patient was a 14-year-old female whose evaluation was unremarkable except for a short stature and hypothyroidism [8]. After thyroid replacement therapy, she attained a height of 157.7 cm and underwent normal pubertal development. She had two spontaneous pregnancies, resulting in the births of two normal infants. Therefore, the short stature of this patient was due to hypothyroidism and not her chromosomal abnormality. The other patient was a 25-year-old female with secondary amenorrhea [9]. She had normal pubertal development and regular menstruation until 21 years of age. After that time, her menstrual cycles became irregular and were later followed by amenorrhea. Her height was 155 cm, but she had no specific abnormal findings on the physical and gynecologic examinations. Because the pathophysiological mechanism of POI in patients with two normal X chromosomes and i(Xq), such as in the latter case above and in our patient, is not fully understood, additional cytogenetic research is necessary.

In addition to POI, a short stature is a characteristic finding in patients with i(Xq) and is caused by haploinsufficiency of the short stature homeobox-containing (*SHOX*) gene located on the short arm of the X chromosome. *SHOX* encodes a transcription factor involved in skeletal development. Consequently, a short stature manifests in patients with X chromosome monosomy (45,X), deletion of Xp, and deletion of i(Xq). The clinical phenotype of our patient differed from those previously reported in patients with i(Xq) and Turner syndrome. Our patient had the i(Xq) chromosomal abnormality, but because of the presence of two short arms of the X chromosome, she did not exhibit a short stature unlike patients with either other i(Xq) chromosomal abnormalities or monosomy X.

Abnormal division of centromeres and U-type strand exchange are suggested mechanisms for the formation of an isochromosome. Abnormal division of centromeres occurs during chromatid separation when the centromeres are transversely divided, forming an isochromosome. Since more than 90% of i(Xq) contains proximal Xp sequences, this mechanism is not a common mechanism for i(Xq) formation [6]. U-sharp strand exchange occurs primarily during early

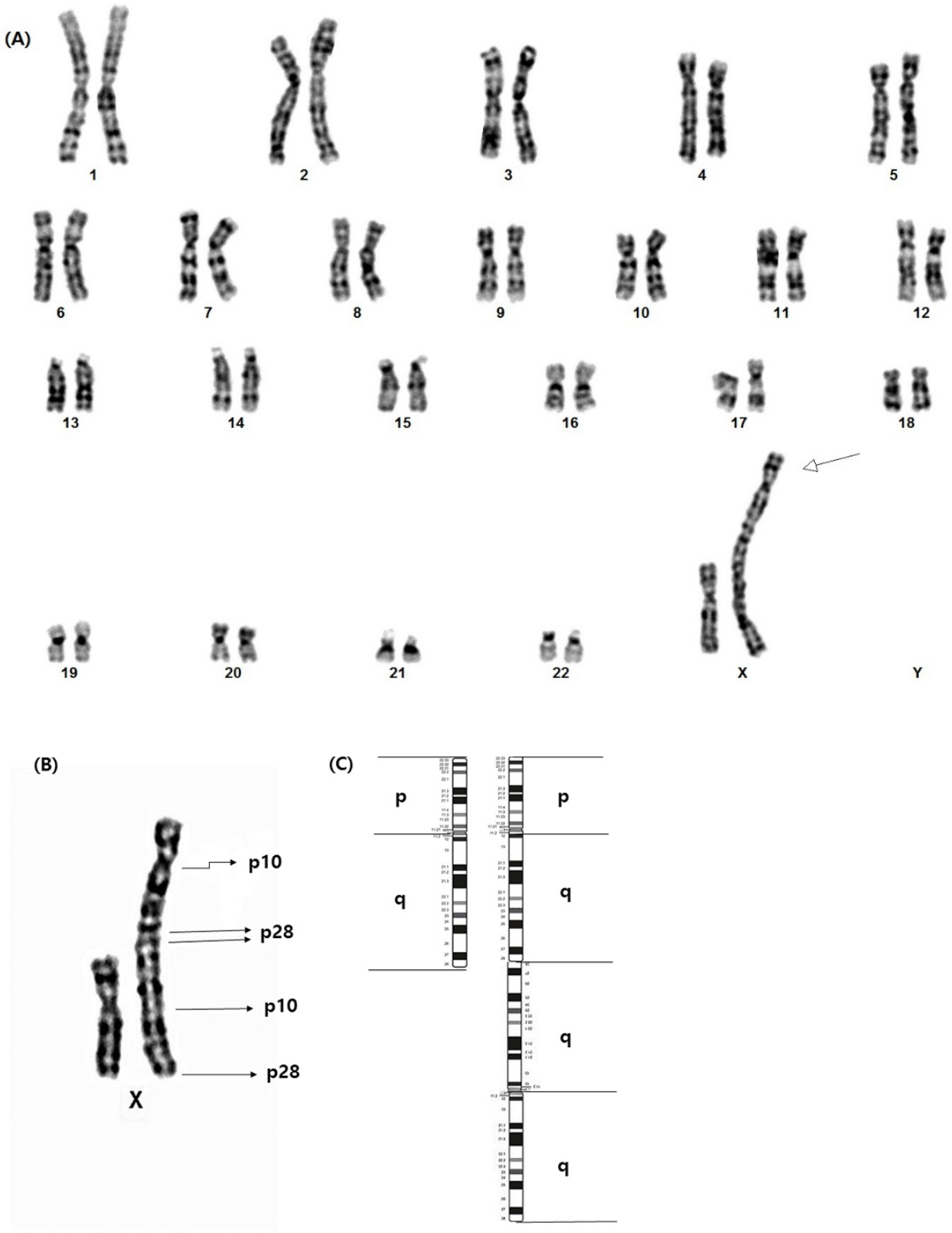

Fig. 1. G-band Karyotype of the patient: 46,X,ider(X)(q28)i(X)(q10). (A) The arrow indicated an abnormal X chromosome. (B) Structure of the abnormal X chromosome shows a translocation and duplication between the distal portion of the Xq and i(Xq). (C) X chromosome ideogram, according to the International System for Cytogenetic Nomenclature (ISCN 2009).

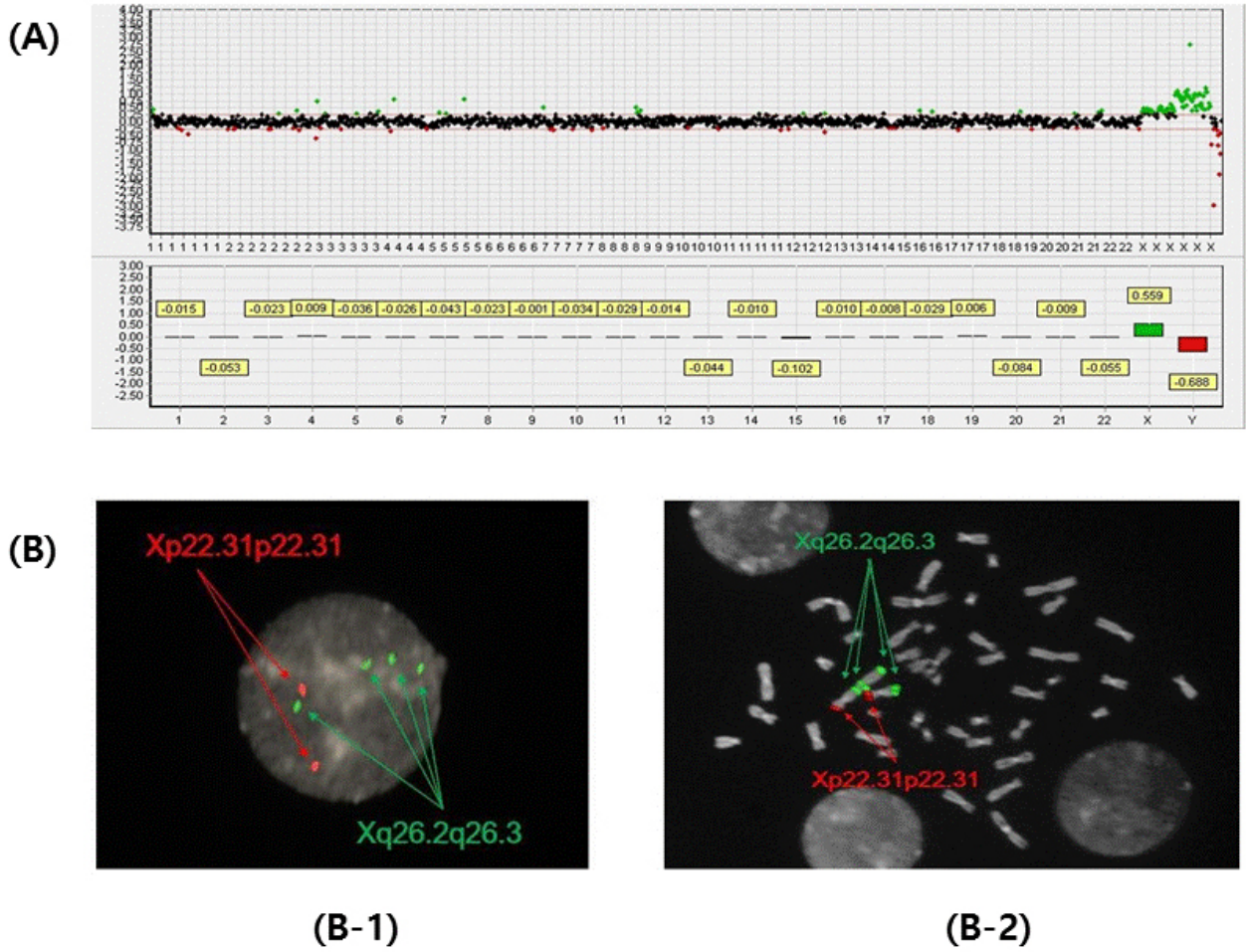

Fig. 2. Chromosomal microarray analysis and Fluorescence *in situ* hybridization finidngs in patient showing 46,X,ider(X).ish i(X)(q26.2q26.3)(PHF6X4). (A) Comparative genomic hybridization-array-based chromosomal microarray analysis profiles of a peripheral blood sample. Green colored dots indicated the long arm of X chromosome. The result of test depicting a gain in copy number of clones corresponding to the Xq of the X chromosome. The *x*-axis shows the spots of bacterial artificial chromosome clones ordered from chromosomes 1–22, X, and Y. The *y*-axis shows the fluorescence ratio of differently labeled samples to control DNA. (B) Fluorescence *in situ* hybridization with both the q26.2q26.3 (green)-specific long arm of the X chromosome and the p22.31 (red)-specific short arm of the X chromosome. (B-1) Interphase, showing duplication of the long arm of the X chromosome (four green color) and normal of the short arm of the chromosome (two red color). (B-2) Metaphase cell showing the long arm (including the q26.2q26.3 region of the X chromosome) formed an isochromosome Xq that was duplicated and translocated at the end of normal X chromosome.

anaphase during meiosis or mitosis. Sister chromatids form a U-sharped structure via breakage and fusion and then create an isodicentric chromosome. Dicentric and heterozygote, monocentric and homozygote, and dicentric and homozygote isochromosomes can be formed via this mechanism [10]. We assumed that our patient had a dicentric and homozygote isochromosome, which likely formed by U-type joining after breakage in the p arm of the X chromosome during mitosis.

Because approximately 15% of cases of POI occur in families, it is assumed that there is a genetic predisposition for POI. Determining parental karyotypes for children with chromosomal abnormalities is recommended to help predict recurrence or inheritance in the family. Unfortunately, we could not perform cytogenetic analyses or molecular genetic studies to identify inheritance patterns in our case because the parents did not agree to undergo testing and the patient had no siblings.

It is important to both prevent adverse outcomes caused by estrogen deficiency and provide emotional support during the treatment of patients with POI. Hormone replacement therapy (HRT) is recommended for the relief of menopausal symptoms such as vasomotor instability and for the prevention of osteoporosis and cardiovascular diseases. Transdermal estradiol, which has a low risk of thromboembolism and few effects on hemostatic factors, is used more commonly than oral estrogen for these purposes. However, the benefits of a specific regimen, type, and dose of HRT are unclear in patients with POI [11]. It is thus recommended that the patient's preferred method of HRT administration be considered. Our patient preferred to be treated with an oral rout of

HRT. We subsequently prescribed 2 mg estradiol valerate per day and 100 mg micronized progesterone for 12 days every 4 weeks.

We presented a novel chromosomal abnormality and clinical features in female patient diagnosed with POI. the described case and our review will expand the current knowledge about the clinical manifestations of patients with i(Xq) genotype.

Abbreviations

FMR1, fragile X mental retardation; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; i(Xq), isochromosome Xq; POI, premature ovarian insufficiency; *SHOX*, short stature homeobox-containing.

Author contributions

SML and IAC performed experiments and data collection. JCB and HCJ worte most of the paper and JEP drafted the figures. All authors contributed to manuscript revisions. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures carried out in this study involving human participants in need of ethical approval were in accordance with the Declaration of Helsinki in 1964 and subsequently amended or similar ethical standards. This case-report was approved the Institutional Review Board of Gyeongsang National University Changwon Hospital (GNUCH 2021-01-010). All methods were performed in accordance with the relevant guidelines and regulations of institution. Patient's consent for the publication of this case was obtatined from the patient and her mother.

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Conflict of interest

The authors declare no conflict of interest.

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