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Case Report

Delayed puberty and premature ovarian failure in a seventeen-year-old girl with 46,XX,del(q24)

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Abstract: Premature ovarian failure (POF) is a rare medical condition in adolescents. Its common cause is gonadal dysgenesis and an abnormal karyotype. Herein we report a rare case of POF resulting from a deletion in the terminal portion of Xq, 46,XX,del(q24). A 17-year-old girl was referred to our hospital for amenorrhea. Menarche had occurred at age 16 years; since then, irregular menstruation and amenorrhea appeared. She was of normal height, but her bone age was delayed compared to her chronologic age. While her breast development was normal, she had scant pubic hair. Her serum levels of luteinizing hormone and follicle stimulating hormone were 26.83 mIU/mL and 99.36 mIU/mL, respectively. A pelvic ultrasound examination revealed a small uterus and ovaries. Following the initiation of hormone replacement therapy, her menstrual cycle returned. In addition to this case report, we provide a brief review of the X chromosome regions involved in ovarian function.

Keywords: Xq24 deletion, premature ovarian failure, delayed puberty, Turner syndrome

Introduction

Premature ovarian failure (POF), also referred to as primary ovarian insufficiency (POI), which is defined as amenorrhea for >6 months that occurs before the age of 40 and is accompanied by an elevated serum level of FSH (>40 mIU/mL) [1, 2]. POI can be induced by viral infection or autoimmune disease, metabolic disorders, environmental toxins, pelvic surgery, radiation, or chemotherapy [3]. In addition, abnormalities of the X chromosome have been reported in patients with POF. For example, women with fragile X syndrome or Turner syndrome (TS) are at higher risk for POF. Defects in the long arm of the X chromosome, particularly Xq13-q21 [4] and Xq26-q27 [5], may be associated with POF. However, the relationship between POF and X chromosome abnormalities is unclear. Here, we report the case of a patient with a deletion in the long arm of the X chromosome, POF, and persistent growth in height. Relevant studies linking POF and X chromosome abnormalities are briefly reviewed.

Case report

A 17-year-old girl visited the gynecology clinic at our hospital due to amenorrhea of a duration of 10 months. Her menarche occurred at the age of 16 years, but with an irregular menstrual cycle for 6 months and no menstruation thereafter. She was a non-smoker and had no history of drug use or other diseases, including mental disorders. Her initial laboratory findings included an LH level of 26.83 mIU/mL, an FSH level of 99.36 mIU/mL, an estradiol (E2) level of <5.0 pg/mL, and an anti-Mullerian hormone (AMH) level of 0.02 ng/mL. Thyroid function tests revealed an euthyroid state. Her anti-thyroglobulin (TG) antibody level was 436.20 IU/mL (reference range: 0-115 IU/mL). Cytogenetic analyses revealed a 46,XX,del(q24) karyotype, with no evidence of mosaicism (**Figure 1**). A gynecological ultrasound examination revealed a small uterus (endometrial thickness 2.8 mm) and ovaries (**Figure 2**). There were few follicles in the ovaries. The gynecological diagnosis was TS and premature ovarian failure.

She was referred to our pediatric endocrinology clinic for management of TS. On presentation to our clinic, she was 160 cm tall and weighed 50 kg. Her breast development was Tanner stage V, but her pubic hair development was Tanner stage III. She had no dysmorphic features indicative of TS, as determined by a physical examination. In radiological images, the metacarpals

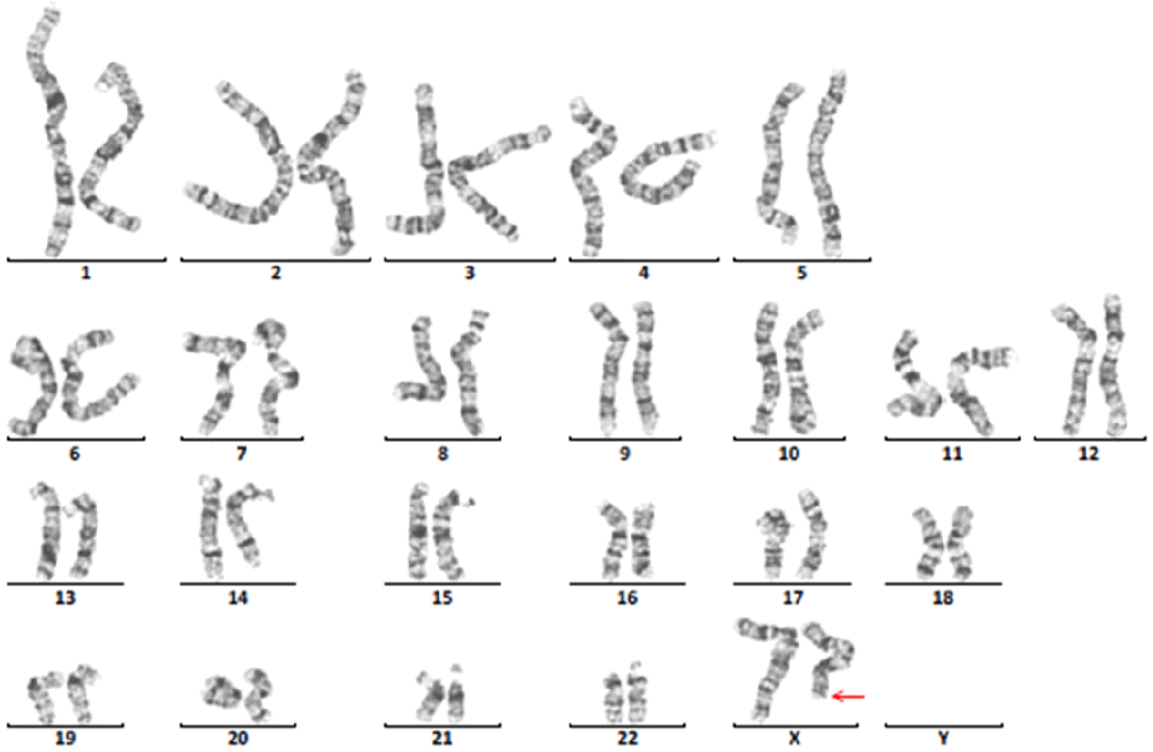

Figure 1. Chromosomal analyses revealed a karyotype of 46,XX,del(q24).

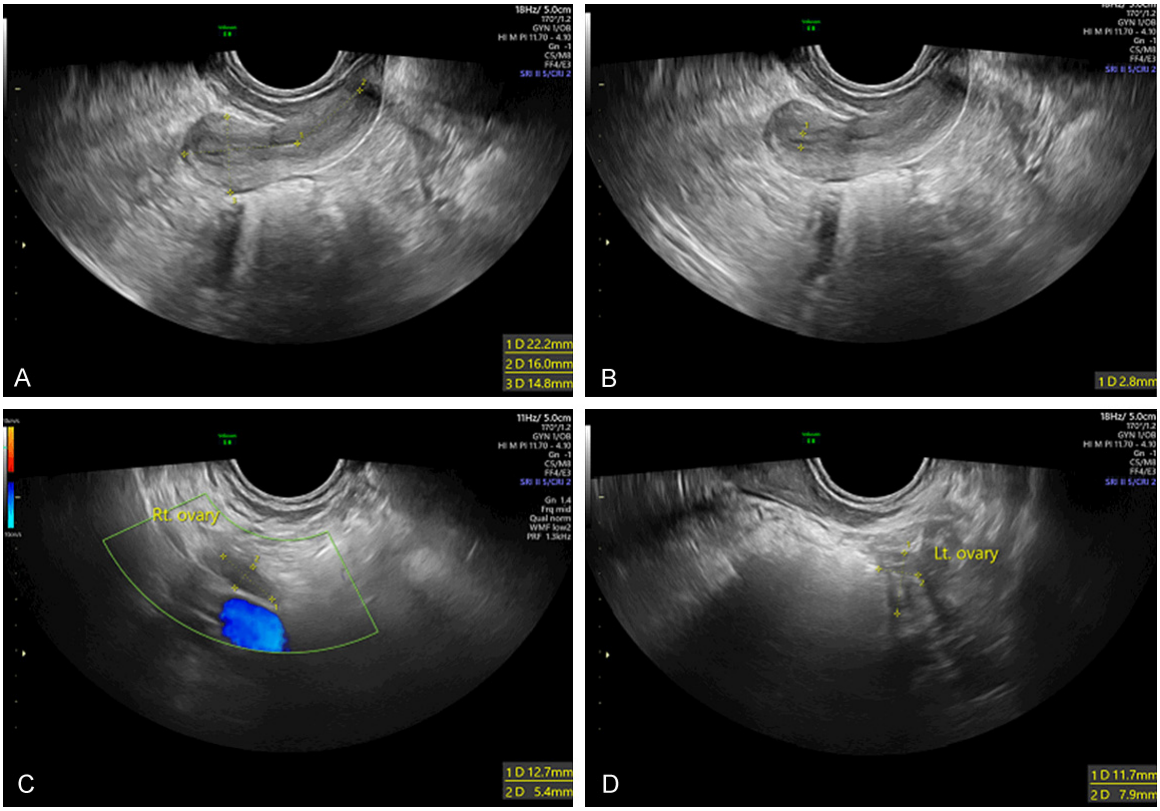

Figure 2. Gynecologic ultrasound images of our patient with 46,XX,del(q24). A. (upper left) Uterus diameter 22.2 mm, thickness 16.0 mm. B. (upper right) Endometrial thickness: 2.8 mm. C. (lower left) Right ovary. D. (lower right) Left ovary.

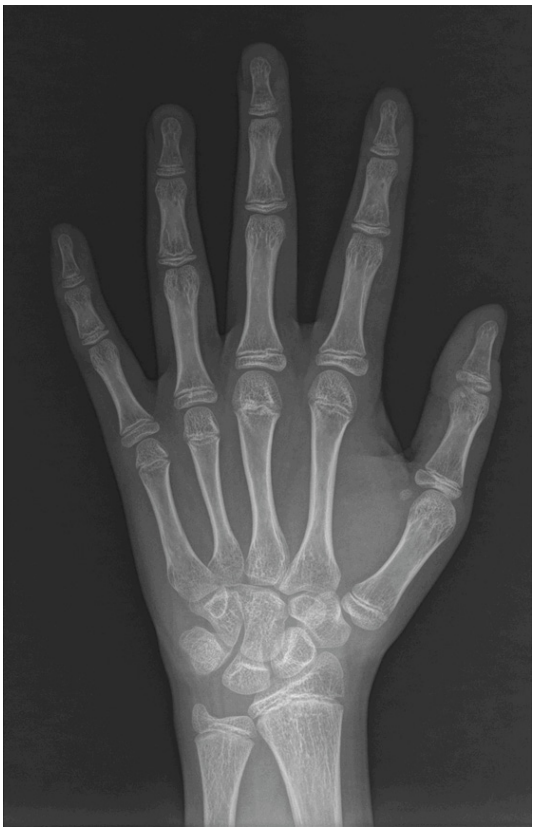

Figure 3. Delayed bone age in a 17-year-old girl with a 46,XX,del(q24) karyotype.

were not shortened and her bone age was ~13 years, assessed using the Greulich-Pyle method (**Figure 3**). There was no familial history of POF. Her systolic blood pressure was 138 mmHg, and her diastolic blood pressure was 86 mmHg. No abnormalities were seen in echocardiography. The patient wanted to have a normal menstrual cycle, but because she was a senior in high school and preparing for her college entrance exams, her parents were worried about her ability to cope and preferred postponing restoration of her menstrual cycle until she became a college student. About 1 year later, she entered college and visited our hospital again. She was still suffering from amenorrhea. She was 162.1 cm tall and weighed 54 kg. Laboratory tests showed LH, FSH, and E2 levels of 27.40 mIU/mL, 123.0 mIU/mL, and <5.0 pg/mL, respectively. Thyroid function tests again revealed an euthyroid state, with a TG antibody level of 45.08 IU/mL. Her bone age was still around 13 years. She was started on hormone replacement therapy (HRT) with oral estradiol valerate (1 mg once daily). After 3 months, breakthrough bleeding occurred, and progestin was added to the HRT regimen. She is currently under cyclic estrogen-progestin substitution therapy.

Discussion

A deletion of distal Xq24 results in the development of POF, including primary or secondary amenorrhea [6]. Our patient had a structural abnormality of the X chromosome, 46,XX,del(q24), and showed signs of delayed puberty. Compared to the average menarche age of Korean girls (12.7 years) [7], she had menarche at age of 16 years, and since then secondary amenorrhea had appeared. Eventually, she was diagnosed with POF. In addition to incomplete sexual maturity, the growth plate of the long bones did not close, resulting in continuous height growth but within the normal range.

Delayed puberty and POF, as occurred in our patient, are among the characteristics of TS. In fact, she was diagnosed with TS at the gynecology clinic of our hospital. However, our patient had a normal height and did not have characteristic phenotypes of TS, including facial abnormalities, heart defects, and renal anomalies. Updated clinical practice guidelines from the 2016 Cincinnati International Turner Syndrome Meeting for the care of girls with TS recommends against a diagnosis of TS in females with one X chromosome and a deletion distal to Xq24 on the other, as the quality of evidence is classified as low [8]. Nonetheless, it is necessary to refer to the results of research on TS to predict the clinical symptoms and prognosis of the Xq24 deletion.

Turner syndrome is one of the most common sex chromosomal disorders and is mainly caused by the partial or complete loss of the X chromosome [9]. Short stature and ovarian insufficiency occur in >90% of TS patients [10, 11]. The typical deletions in TS are Xp or Xq [12, 13]. Xp deletions in TS patients also cause significant ovarian insufficiency and gonadal dysgenesis [14]. In particular, the Xp11.2-p22.1 segment of the X chromosome carries a TS-critical region responsible for ovarian failure, short stature, and autoimmune thyroid disease [15]. The gene encoding bone morphogenetic protein 15 (*BMP15*), located at Xp11.2, is important for ovarian function [16], and the ubiquitin specific protease 9 (*USP9X*), located at Xp11.4, has been implicated in ovarian dysgenesis [17].

Genes affecting POF are located not only in the short arm of the X chromosome but also in the long arm. Two critical regions for POF are located on the long arm of the X chromosome: Xq13.3-q22 and Xq26-q28 [4, 18, 19]. Trunca *et al*. reported three patients with a distal Xq deletion whose symptoms included no or irregular menstruation and secondary or primary amenorrhea. They reported that the chromosomal breaks in these patients were within the critical Xq13-q27 region [20]. Although the symptoms of POF differ depending on the site of the deletion in the long arm of the X chromosome, most Xq deletion patients have oligomenorrhea, followed by secondary amenorrhea or premature menopause [21, 22]. Goldman *et al*. [23] reported that functioning ovarian tissue is more frequently present in patients with a short-arm rather than a long-arm X chromosome deletion. They suggested that ovarian failure in patients with a long arm deletion in the X chromosome generally ensues if the critical region Xq13-q26 is involved [23]. Our patient had a deletion in the long arm of the X chromosome (Xq24-), which is located in a critical region associated with amenorrhea and irregular menstruation, and showed delayed puberty, secondary amenorrhea, and POF.

Kaiser *et al*. [24] found that most patients with Xq deletion had small stature and ovarian insufficiency, but they found no evidence of a direct dependency between individual symptoms and/or their expression and the position of the missing segment in patients with a long-arm deletion in the X chromosome. They suggested that the loss of a tiny terminal segment distal to q26 may not affect body growth and may result in only minor gonadal dysfunction. Additionally, previous research suggested that most genetic factors influencing stature are located on the short arm of the X chromosome, but some determinants may be located on the long arm, close to the centromere [23]. Thus, it may be that the height of the patient will depend on the site of the deletion in the long arm of the X chromosome. Because the height of patients with these deletions is often within the normal range, the short arm of the X chromosome is more likely to determine a normal stature.

Several genes located on the short arm of the X chromosome have been implicated in somatic development. These genes escape X inactivation and are expressed from both the active and inactive X chromosomes. An example is the short stature homeobox-containing gene (*SHOX*, located at Xp22.33 and Yp11.3), which encodes a transcription factor involved in skeletal growth and development [25, 26]. Haploinsufficiency of the *SHOX* gene is responsible for the short stature and skeletal abnormalities in TS [27]. Our patient had an intact short arm of the X chromosome and normal height. Also, she did not show a TS phenotype except POF. This is consistent with a previous study result [22].

Molecular investigations of X chromosome abnormalities, including TS, have led to the identification of a number of candidate genes for POF, but the function of most remains unknown. However, current evidence suggests that two intact X chromosomes are essential for normal ovarian development and function. The karyotype of our patient was 46,XX,del(q24). She showed delayed puberty, secondary amenorrhea, POF, and persistent height growth. Reproductive function in our patient remains unclear as does whether it might have been improved by an earlier assessment of her abnormal ovarian function and delayed puberty.

Our findings may be helpful in the genetic counseling of patients with POF attributed to Xq deletion and in future investigations aimed at the molecular identification of POF genes. The availability of additional patients should improve mapping of the location of the Xq genes associated with ovarian development and function, in addition to providing insights into whether the symptoms are manifestations of haploinsufficiency in a single gene or a gene cluster. Mutational analyses of karyotypically normal individuals with POF may reveal the culprit genes and allow for optimized treatment for the preservation of reproductive function.

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Disclosure of conflict of interest

None.

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