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CLINICAL REPORT

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Incidence, puberty, and fertility in 45,X/47,XXX mosaicism: Report of a patient and a literature review

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Turner syndrome (TS), characterized by short stature and premature ovarian failure, is caused by chromosomal aberrations with total or partial loss of one of the two X chromosomes. Spontaneous puberty, menarche, and pregnancy occur in some patients depending on the abnormality of the X. Moreover, spontaneous pregnancy is uncommon (<0.5%) for TS with 45,X monosomy. Among TS patients, 45,X/47,XXX karyotype is extremely rare. Previous reports have demonstrated that TS with 45,X/47,XXX is less severe than common TS due to higher occurrence of puberty (83%), menarche (57–67%), and fertility (14%) and lower occurrence of congenital anomalies (<5%). However, TS mosaicism may not reduce the frequency of short stature. We diagnosed a 10-year-girl with TS with 45,X/47,XXX mosaicism who presented with short stature. She showed mild TS phenotype including short stature but had spontaneous puberty. Based on our case and previous reports, we expect that girls with 45,X/47,XXX mosaicism may progress through puberty normally, without estrogen therapy. Therefore, it is necessary to consider specific guidelines for clinical decisions surrounding pubertal development and fertility in TS with 45,X/47,XXX karyotype.

KEYWORDS
fertility, mosaicism, puberty, Turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is a common chromosomal disorder affecting approximately 1:2,500 live female births and is characterized by the partial or complete absence of one X chromosome (Stochholm et al., 2006). About 45–50% of TS patients have 45,X monosomy and the remainder have structural chromosome abnormality or mosaicism (Wolff, Van Dyke, & Powell, 2010). Twenty percent of TS patients are diagnosed at birth on the basis of typical stigmata or somatic abnormalities such as aortic coarctation, bicuspid aortic valve, horseshoe kidney, and webbed neck, which are often related to 45,X monosomy. Other TS patients are diagnosed during childhood or later due to short stature, delayed puberty, or primary or secondary amenorrhea (Gicquel, Gaston, Cabrol, & Le Bouc, 1998; Gonzalez & Witchel, 2012). Individuals with 45,X monosomy tend to have more clinical features than those with typical cell line (45,X/46,XX), and phenotypic variability is based on parental origin of X, cell line mosaicism, imprinting, and X-linked mutations (Gonzalez & Witchel, 2012).

In particular, the gonadal dysgenesis associated with early ovarian failure is the most important issue in treating adolescents and young adults with TS. Several studies have reported the possibility that spontaneous pubertal development and menarche, and unassisted pregnancy in TS with mosaicism are greater than in those with monosomy X (Birkebaek, Cruger, Hansen, Nielsen, & Bruun-Petersen, 2002; Bryman et al., 2011).

Trisomy X (47,XXX) is a sex chromosome aneuploidy condition in which patients have an extra X chromosome; population prevalence makes this a rare condition at 0.03–0.09% (Witek, Skalba, & Zieba, 2001). The common clinical features of girls with trisomy X include tall stature, motor and speech delay, learning disability, and psychological issues. However, pubertal onset and sexual development are usually normal in trisomy X (Tartaglia, Howell, Sutherland, Wilson, & Wilson, 2010; Wallerstein et al., 2004). This is quite different from TS, yet in a study of 146 subjects with clinically suspected TS who had short stature and primary amenorrhea, trisomy X accounted for 2.7% (Moka, Sreelakshmi, Gopinath, & Satyamoorthy, 2013).

45,X/47,XXX is a very rare genotype in TS. Moreover, the incidence and clinical manifestations of TS with 45,X/47,XXX mosaicism remain uncertain. Here, we describe the case of a 10-year-old girl with 45,X/47,XXX TS mosaicism who had spontaneous puberty. The issues

TABLE 1 Incidence of cytogenetic manifestation in Turner syndrome

	Kleczkowska et al. (1990) (*n* = 478)	Laundon et al. (1996) (*n* = 17)	Jacobs et al. (1997) (*n* = 211)	Catovic (2005) (*n* = 30)	Moka et al. (2013) (*n* = 54)	Al et al. (2014) (*n* = 52)	Total (*N* = 842) *n* (%)
45,X	249	14	97	19	19	16	414 (49.2)
45,X/46,XX	52	1	9	2	11	7	82 (9.7)
45,X/47,XXX	8	1	4	0	0	0	13 (1.5)
45,X/46,XX/47,XXX	12	0	1	0	1	0	14 (1.7)
Isochromosome X	77	1	38	5	8	16	145 (17.2)
Ring chromosome X	21	0	33	1	2	3	60 (7.1)
Others	59	0	29	3	13	10	114 (13.5)

of incidence and prognostic counseling for spontaneous puberty, menarche, and fertility are discussed in relation to this case and the current literature.

2 | CLINICAL REPORT

A 10-year-old girl was referred to our clinic on the basis of short stature and breast budding. She was the first child of a 38-year-old mother and a 38-year-old father. The parents appeared healthy, and both had normal height and weight. There was no familial history of inherited or congenital diseases. The patient's birth weight was 3.3 kg and she was born via nonsurgical vaginal delivery at full term. She had no significant medical history and had achieved normal developmental milestones. On physical examination, her height was 128 cm (−1.7 of standard deviation score [SDS]), and her weight was 37 kg (0.4 of SDS). She showed slightly webbed and short neck, normal posterior hairline, and mild shield chest with wide distance between nipples. However, her external genitalia appeared normal and her hands and feet were nonedematous. Her Tanner stage was breast II, pubic hair I, and axillary hair I. Her breast budding was found 1 month prior. She had no cardiac murmur. Her serum laboratory tests were 1.00 ng/dl of free thyroxine (*n*: 0.8–1.8), 4.83 uIU/ml of thyroid stimulation hormone (*n*: 0.5–5.0), 0.93 mIU/ml of luteinizing hormone (pubertal range of 9–13 yr; <0.15–7.2), 3.28 mIU/ml of follicular stimulation hormone (pubertal range of 9–13 yr: 1.1–9.0), 18 pg/ml of estradiol (pubertal range of 9–13 yr: <10–55), and 217.37 ng/ml of insulin like growth factor-1 (*n*: 85–363). Her bone age was 11 years old. Her mean parental height was 161 cm (0.0 of SDS), and predicted adult height was 141 cm (−4.3 of SDS). Sonographic findings showed normal kidney shape, and small but normal uterus contours and ovaries. Echocardiography revealed normal aorta and aortic valve. Ophthalmologic examination and audiogram showed normal findings. Cytogenetic analysis of blood lymphocytes revealed a karyotype of TS mosaicism with 45,X (32 cells)/47,XXX (8 cells). She was treated with growth hormone for final adult height. Her spontaneous pubertal development is continuously progressing.

3 | DISCUSSION

45,X/47,XXX in TS is extremely rare, and this is the first reported case of 45,X/47,XXX TS mosaicism in Korea. Kaneko et al. (1990) reported that the frequency of mosaic TS with 47,XXX cell line is 3–4%, and that patients with 45,X/47,XXX make up 1.7% of TS. A large population study of TS by Kleczkowska, Dmoch, Kubien, Fryns, and Van den Berghe (1990) revealed a frequency of 45,X/47,XXX of about 2% of TS. We reanalyzed these values using additional data in Table 1 (Al Alwan et al., 2014; Catovic, 2005; Jacobs et al., 1997; Kleczkowska et al., 1990; Laundon, Spencer, Macri, Anderson, & Buchanan, 1996; Moka et al., 2013). In this study, 49.2% of TS was monosomy X, 12.9% was mosaicism without structural abnormalities

TABLE 2 Comparison of pubertal development and fertility in Turner syndrome according to karyotypes

	45,X/47,XXX Mosaicism		45,X Monosomy	All Turner syndrome
	Blair et al. (2001) (*N* = 7)	Sybert (2002) (*N* = 11)	Pasquino et al. (1997) (*N* = 272)	Pasquino et al. (1997) (*N* = 522)
Age, mean (range)	14.3 (6.1–20.4)	20.7 (5.0–54.0)	>12	>12
Prepubertal state, *n*	1	4	0	0
Spontaneous puberty	5/6 (83%)	NA	61/272 (22.4%)	175/522 (33.5%)
Spontaneous menarche	4/6 (67%)	4/7 (57%)	25/272 (9.2%)	84/522 (16.1%)
Spontaneous pregnancy	NA	1/7 (14%)	1[a]/200 (<0.5%)	3/84 (3.6%)

NA, not accessed.
[a]The data from Birkebaek et al. (2002).

(45,X/46,XX, 45,X/46,XX/47,XXX, and 45,X/47,XXX), and only 1.5% was 45,X/47,XXX. However, a more accurate incidence of 45,X/47,XXX among patients with TS may be slightly higher than 1.5% for two reasons. First, the standard cytogenetic analysis of peripheral blood lymphocytes cannot exclude the possibility of undetected very low-level mosaic aneuploidy such as 46,X,del(Xq), 47,XXX, 46,XY, and 47,XYY (Bisat, May, Litwer, & Broecker, 1993; Hook & Warburton, 2014; Nazarenko, Timoshevsky, & Sukhanova, 1999). In addition, several studies have revealed a tissue-specific mosaicism, different from blood lymphocyte, in patients with 45,X cell line (Bisat et al., 1993; Nazarenko et al., 1999).

Although somatic growth and sexual development are dependent on numerous X chromosome genes, and over 95% of those with TS have short stature and primary amenorrhea (Moka et al., 2013), most TS patients with monosomy/trisomy-derivate cell lines have less severe clinical features than 45,X monosomy or other mosaic TS (Akbas et al., 2009; Sahinturk et al., 2015). Interestingly, the frequency of short stature as height <3 centile and the median height SDS in 45,X/47,XXX do not differ significantly from those in other girls with TS (Blair, Tolmie, Hollman, & Donaldson, 2001; Sybert, 2002). However, TS patients with 45,X/47,XXX have fewer cardiovascular and renal anomalies (<5%) (Tauchmanova et al., 2001) as well as fewer skeletal anomalies (<4%) (Tauchmanova et al., 2001) compared with common TS patients. Our patient also showed mild TS morphology with short stature (−1.7 of height SDS), spontaneous puberty, and no structural anomalies.

Sexual development is one of the most important clinical issues for adolescents with TS. Gonadal dysgenesis and infertility occur in 95–98% of TS patients (Abir et al., 2001), caused by oocyte loss that results in streak ovaries containing no ova or few follicular derivatives. However, a minority, mostly mosaic TS patients, have ovaries with a relatively low number of follicles, so that there is spontaneous puberty (Abir et al., 2001). Furthermore, the presence of an XXX cells can carry with a greater likelihood of residual ovarian function. Descriptions of ovarian development in TS with 45,X/47,XXX range from normal to completely absent with streak gonad (Bouchlariotou et al., 2011). We have summarized these pubertal features of TS in Table 2.

Spontaneous puberty occurs in 20–33.5% of TS cases (Bouchlariotou et al., 2011; Pasquino, Passeri, Pucarelli, Segni, & Municchi, 1997), spontaneous menarche in 5–16.1% (Hovatta, 1999; Pasquino et al., 1997; Sybert, 2002), and spontaneous pregnancy is 2–5% (Birkebaek et al., 2002; Hovatta, 1999; Pasqualini-Adamo, 1988; Pasquino et al., 1997). Pasquino et al. (1997) also found that the incidence of spontaneous puberty and menarche in TS with 45,X monosomy was 22.4% and 9.2%, respectively. Moreover, spontaneous pregnancy is uncommon (<0.5%) for TS patients with 45,X monosomy (Birkebaek et al., 2002).

It is worth noting that karyotype impacts pubertal development and that most pregnancies in TS patients occur for woman with mosaicism (Bryman et al., 2011). Pubertal development and fertility are more prominent in TS with the presence of either a 46,XX or 47,XXX cell line or both, compared with X monosomy (Bouchlariotou et al., 2011). Previous studies have reported that the frequency of spontaneous puberty, menarche, and pregnancy in TS with 45,X/47,XXX was 83%, 57–67%, and 14%, respectively (Blair et al., 2001; Sybert, 2002). Blair et al. (2001) suggested that estrogen therapy might not be required for pubertal development in TS with 45,X/47,XXX compared with those with typical TS who should be counseled on this therapy at the age of normal puberty.

Our patient showed spontaneous breast development as in TS with 45,X/47,XXX but had not yet achieved menarche. However, we expect that she will successfully achieve spontaneous menarche without estrogen therapy due to her normal uterus and ovaries, and based on previously reported evidence.

Pregnancy in TS is known to carry risks of miscarriage, stillbirth, fetal malformations, and chromosomal disorders compared with the general population (Kaneko et al., 1990). However, Tarani et al. (1998) reported that the frequency of heathy infants in TS with 45,X/47,XXX who had spontaneous pregnancy were higher than those in whole TS group (16/20 [80%] vs. 62/160 [38%]). Interestingly, the presence of maternal mosaicism, even the 47,XXX cell line, may not reduce the risk of congenital malformations and chromosomal defects in their offspring due to the higher frequency of chromosomal transmission aberrations (Birkebaek et al., 2002; Tarani et al., 1998).

In summary, our patient was a 10-year-girl diagnosed with 45,X/47,XXX TS mosaicism following evaluation for short stature. However, she did not show abnormal pubertal development. Because 45,X/47,XXX TS mosaicism is very rare, we investigated the 45,X/47,XXX TS mosaicism through our case and previous reports to determine the specific clinical features. From our case and review of the existing literature, we expect that girls with 45,X/47,XXX mosaicism may develop normally through puberty without estrogen therapy. Therefore, we believe that this case may contribute to better consultation to TS with 45,X/47,XXX karyotype in pubertal development and fertility. And further study adding cases with a 45,X/46,XX/47,XXX karyotype will be needed to determine the phenotype of TS with a 47,XXX cell line.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest and no financial relationships relevant to this article to disclose.

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