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45,X mosaicism with Y chromosome presenting female phenotype

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ABSTRACT

Prophylactic gonadectomy is recommended in patients with 45,X mosaicism with the Y chromosome and presenting a female phenotype because of the risk of gonadoblastoma development. The characteristics of this disorder remain unclear because of its low incidence. We report 4 patients with 45,X mosaicism with the Y chromosome and presenting complete female external genitalia. We analyzed the characteristics and the macroscopic and histopathological findings of their gonads and performed hormonal assays of the 4 patients. All 4 patients were referred to us with short stature as the chief complaint. Chromosomal studies revealed 45,X/47,XYY in 1, and the others had a 45,X/46,XY karyotype. Three patients (6 gonads) underwent laparoscopic bilateral gonadectomy. The macroscopic appearance of gonads of 1 patient was similar to an ovary, whereas gonads of the rest appeared as streak gonads. The histopathological findings revealed bilateral gonadoblastoma in 1 patient, although the macroscopic findings did not show tumor characteristics. It is impossible to distinguish the histopathological findings of gonads according to their macroscopic appearance among patients with 45,X mosaicism with the Y chromosome and presenting a female phenotype.

Sex chromosome mosaicism may cause disorders of sex development. Turner syndrome is the most frequent case with sex chromosomal mosaicism and presenting a female phenotype. Approximately 5% of Turner syndrome patients presenting a female phenotype are known to have karyotypes containing the Y chromosome [1]. Prophylactic bilateral gonadectomy is recommended in patients with 45,X mosaicism containing the Y chromosome and presenting a female phenotype because of the risk of gonadoblastoma development. The reported incidences of gonadoblastoma vary and the estimated risk of developing it ranges from 7% [2] to more than 30% [3].

The characteristics of this disorder remain unclear because of its low incidence. The aim of this report was to describe 4 patients with 45,X mosaicism with the Y chromosome and presenting complete female external genitalia.

1. Materials and methods

Among the patients with Turner syndrome treated at the Aichi Children's Health and Medical Center between January 2006 and August 2012, we experienced 4 patients with 45,X mosaicism with the Y chromosome and presenting complete female external genitalia. We retrospectively analyzed the chief complaint, chromosomal studies, associated anomalies, and hormonal assays of the 4 patients, as well as the macroscopic and histopathological findings of the gonads of each patient.

The present retrospective study was approved by the institutional review board.

2. Results

Twenty-nine patients with Turner syndrome were treated at the Aichi Children's Health and Medical Center during the period. Four of 29 patients (13.8%) had the Y chromosome. Blood karyotypes were 45,X/47,XYY in 1 patient, 45,X/46,XY in 2 and 46,XY in 1. The patient with the 46,XY blood karyotype was identified as 45,X/46,XY by fluorescence *in situ* hybridization (FISH) of buccal mucosal cells. These 4 patients were delivered at a mean gestational age of 37.5 weeks (36–38 weeks) with a mean birth weight of 2476 g (2140–2645 g). All 4 patients were referred to us for further evaluation of short stature (−2.0 to −3.3 SD) at the mean age of 65 months (48 to 81 months). Short stature was defined as −2.0 SD or shorter compared with the normal growth chart for a Japanese girl. The sex-determining region Y gene was positive on the Y chromosome, as determined by FISH analysis in all patients. The characteristics of Turner syndrome are listed in Table 1. A high-arched palate was seen in 3 patients, cubitus valgus in 2, and webbed neck in 2. There was no cardiovascular anomaly. Horseshoe kidney was detected in 1 patient. All 4 patients showed the presence of complete female external genitalia and 1 had vaginal atresia. The uterus was not detected on MRI in any of the patients.

The hormonal assays are listed in Table 2. Overreaction of plasma follicle-stimulating hormone (FSH) and normal reaction of plasma luteinizing hormone (LH) after LH-RH administration were observed in all the patients.

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Table 1
The characteristics of the patients.

	Patient 1	Patient 2	Patient 3	Patient 4
karyotype (relative mosaicism percentage)	45,X/47,XYY (13:87%)	45,X/46,XY (25:75%)	45X/46,XY (80:20%)	45,X/46,XY (10:90%)
features of Turner synd.	high-arch palate cubitus valgus	high-arch palate webbed neck cubitus valgus	webbed neck	high-arch palate
associated anomaly	cardio-vascular (−)	cardio-vascular (−)	cardio-vascular (−)	cardio-vascular (−) horse-shoe kidney
external genitalia	complete female	complete female	complete female	complete female vaginal atresia
vagina	normal depth	normal depth	normal depth	unknown yet
uterus	hypoplastic	hypoplastic	hypoplastic	not detected on MRI

Three of 4 patients underwent laparoscopic prophylactic bilateral gonadectomy at the mean age of 79 months (71–98 months) at our hospital. The remaining 1 patient has not undergone bilateral gonadectomy yet. Her bilateral gonads still show no abnormalities according to the most recent imaging tests and she is scheduled to undergo laparoscopic bilateral prophylactic gonadectomy around 11 years of age based on the parents' wishes.

Macroscopic appearances revealed that all 3 patients had a hypoplastic uterus. Patient 1 (45,X/47,XYY karyotype) had a streak gonad on the right side and an ovary-like gonad with a smooth surface on the left side. Patients 2 and 3 had bilateral streak gonads (Fig. 1). Histopathological findings revealed that Patient 1 had ovarian stroma with nests of gonadoblastoma in both gonads. In Patient 2, both streak gonads had ovarian stroma. Patient 3 had 46,XY blood karyotype, which revealed Sertoli cell-like components corresponding to 45,X/46,XY in buccal mucosa cells (Fig. 2). The postoperative course was uneventful in all patients.

3. Discussion

The spectrum of phenotypes associated with the 45,X mosaicism with the Y chromosome ranges from female, to ambiguous, to almost normal male. Approximately 95% of all 45,X mosaicism with the Y chromosome patients diagnosed prenatally will have normal male genitalia [4], and they may live as normal males. However, some patients may remain undiagnosed. The remaining 5% may present various phenotypes of external genitalia.

Approximately 5 % of all diagnosed women with Turner syndrome are known to have karyotypes containing a Y chromosome on cytogenetic examination [1]. The presence of the Y chromosome is associated with the development of gonadoblastoma, and the estimated risk of developing it is from 7% to more than 30% [2,3,5]. According to the consensus statement on the management of disorders of sex development [6], 45,X mosaicism with the Y chromosome and presenting a female phenotype is classified in the intermediate-risk category of gonadoblastoma development: thus, bilateral prophylactic gonadectomy is recommended. In this disorder, the gonad characteristics are unclear because of its low incidence. We have described 4 new patients of 45,X mosaicism with the Y chromosome and presenting complete female external genitalia.

In our series, 4 of 29 patients with Turner syndrome who were referred to our hospital for further evaluation of short stature were identified as presenting the Y chromosome. On conventional cytogenetic analysis with 20 to 30 cells, 3 of 4 patients were found to be positive for the Y chromosome. The remaining patient was found to be positive for the Y chromosome only after evaluating a larger number of cells (100 cells) by buccal smear chromosome analysis and FISH. Sallai et al. [7] stated that a routine molecular real-time polymerase chain reaction (PCR) screening to detect hidden Y chromosome sequences is strongly recommended for the patients with Turner syndrome who are negative for the Y chromosome on conventional cytogenetic analysis, because of the increased risk of developing gonadoblastoma in the future. Conversely, Gravholt et al. [2] stated that none of the patients with only PCR-detected Y chromosome developed gonadoblastoma, and the incidence of gonadoblastoma among patients with Turner syndrome with the Y chromosome was low. Thus, the management of 45,X mosaicism with the Y chromosome and presenting a female phenotype remains controversial.

Prophylactic bilateral gonadectomy was performed in 3 patients and remaining 1 is scheduled to perform prophylactic bilateral gonadectomy in our series. A variety of histopathological components, including ovarian stroma, were observed among the patient gonads. Sertoli cell-like components and ovarian stroma with gonadoblastoma nests were found although the macroscopic appearances corresponded to streak gonads and ovary-like gonads with smooth surfaces (left gonad of Patient 1). One of the patients was histopathologically diagnosed with bilateral gonadoblastoma, although no clinical symptoms were evident (Figs. 1, 2).

With regard to the macroscopic appearances of gonads of patients with 46,XY disorders, Wünsch et al. [8] reported that 1of 4 patients with complete gonadal dysgenesis and histologically detected gonadoblastoma presented a macroscopically evident tumor in the gonad with an irregular surface. The remaining 3 patients had no macroscopic anomalies in gonads. With regard to Turner syndrome with Y chromosome, Brant et al. [9] reported that, although they could also evaluate only a small number of patients, atypical diagnosis such as gonadoblastoma could not be identified in 7 patients who underwent bilateral laparoscopic gonadectomy according to the macroscopic appearance of the gonads. Thus, their findings were in accordance with our results and it is difficult, if not impossible to distinguish the histopathological components of gonads according to the macroscopic appearance.

In general, according to the hormonal assays, both LH and FSH showed hormonal reaction to some extent to LH-RH administration in patients with Turner syndrome. In our series, as listed in Table 2, overreaction of plasma FSH and normal reaction of plasma LH after LH-RH administration were observed in all the patients, and there seemed to be no relationship between hormonal reactions to LH-RH administration and the possibility of the development of gonadoblastoma.

Although some epidemiological studies have questioned the postulated high incidence of gonadoblastoma in Turner syndrome with the Y chromosome [10,11] and the prophylactic bilateral gonadectomy remains controversial, Olsen et al. [12] recommended the removal of the gonads in all females with Y mosaicism because infertility and ovarian failure were major characteristics of this disorder and multiple sections of the streak gonad are required to demonstrate a microscopic gonadoblastoma. Cools et al. [13] also stated that bilateral gonadectomy may be the most reasonable option because of the nonfunctioning streak gonads.

Table 2
The hormonal assays of the four patients.

	Patient 1	Patient 2	Patient 3	Patient 4
LH/FSH (mIU/mL)	0.2/10.9	0.5/32.4	0.2/10.9	<0.1/5.9
LH/FSH after LHRH	9.0/50.2	14.4/27.6	3.7/38.9	7.1/50.3
testosterone (ng/dL)	6.9	14.4	3.7	7.1
testosterone after hCG	3.6	35	16.9	7.7
E2 (pg/mL)	5.8	<5.0	<5.0	<5.0
IGF-1(ng/mL)	169	62.4	146.6	153.0

LH: Lutenizing Hormone, FSH: Follicle Stimulating Hormone, E2: Estradiol, IGF: Insulin-like growth factor.