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Mosaicism ratios of 45,X to 46,X idicY can explain a phenotype in a case with mixed gonadal dysgenesis.

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Take-home message

The sclerotic lesions (streak gonad and coarctation of the aorta, characteristics of Turner's syndrome) in a mixed gonadal dysplasia patient with 45,X/46X,idicY are attributable to higher proportions of 45,X cells.

Background

1. Mixed gonadal dysgenesis (MGD) is cytogenetically defined by 45,X/46,XY, while Tuner's syndrome is typically characterised by 45,X.

2. MGD patients sometimes have overlapping features of Tuner's syndrome; however their incidence remains unknown. Only 8 MGD patients associated with coarctation of the aorta have been reported (1-5). The most plausible explanation for the overlapping features is a higher proportion of cells with a 45,X karyotype in the affected organs.

3. The developmental pathology of Tuner's syndrome
(1) The ovary is histopathologically normal until the mid-gestation and then undergoes apoptosis, resulting in streak gonad.
(2) The aortic arch is hypoplastic in the mid-gestation and the narrowing part becomes restricted, leading to coarctation of the aorta.
These observations indicate that the majority of 45,X cells might undergo apoptosis and differentiate into stromal cells, leading to sclerotic tissues (streak gonad and coarctation of the aorta) later in the fetal period (6).

Hypothesis

We hypothesised that MGD could have the same pathological change as Tuner's syndrome due to higher proportions of cells with 45,X compared to those with 46,XY.

Case Study

- Born at 38 weeks of gestation with normal delivery.
- Physical examination (day 5)

Ambiguous genitalia
Hypospadias severe, Bifid scrotum, penis with a length of 25 mm
Bilateral cryptorchidism (Right, palpable in the inguinal canal; Left, not palpable)
Bilateral inguinal herniation
No stigmata of Turner's syndrome such as low hair line, webbed neck and high arched palate.

- Endocrine examination (Table 1) :
Primary hypogonadism pattern

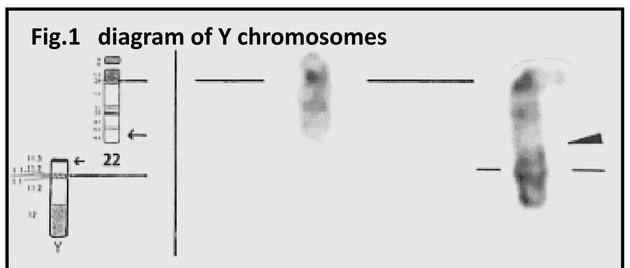
- Chromosomal analysis (Fig1) :
45,X dic (Y;22)(p11.3;q13.3) [23]/45,X [7]
ish dic (Y;22)(SRY+,DYZ3+,DAZ+,DYZ1+)

Table1

LHRH test 100μg/㎡
hCG test 4,000IU/㎡

4 months	hCG test	T	0.1	→ 3.8	ng/ml
1y11m	LHRH test	LH	<0.5	→ 15.9	mIU/ml
		FSH	8.2	→ 64.7	mIU/ml
	hCG test	T	<0.1	→ 2.9	ng/ml

Fig.1 diagram of Y chromosomes



- At the age of 1 year, cystoscopy, right orchiopexy and left gonadectomy were performed. The removed gonad histopathologically showed a streak gonad with mixed Müllerian and Wolffian ducts derivatives (Fig.3 a-f).

- At the age of 10 years, coarctation of the aorta was accidentally noted and surgical repair was carried out for the condition (Fig.4 a-d). The removed aortic tissue showed an increased collagenous tissue in the media of the aorta.

- At the age of 13 years
Pubic hair Tanner 3, Right testis 3 ml
Bone Age 13 years, LH 6.8 mIU/ml, FSH 49.8 mIU/ml, Testosterone 2.3 ng/ml

Methods

Fluorescence in situ hybridization (FISH) and/or chromogenic in situ hybridization (CISH) was performed for the gonadectomy and aorta specimens to determine the proportion of cells with 45,X to those with 46,XY.

A normal testis with a 46,XY karyotype (1 year old) and an ovary Tuner's syndrome were also similarly examined as controls.

Each subject gave their informed consent and patient anonymity was preserved.

Results

The distribution and proportion of the 45,X cells in the gonads, aortic tissue and the control testicular tissues are summarised in Table 2.

There was a marked difference in the mosaicism for cells with 45,X and 46,X idicY between the sclerotic lesions (streak gonad and stricture of the aortic tissue) and non-sclerotic tissues (peripheral blood and Müllerian duct), supporting that the higher proportion of 45,X cells is associated with the sclerotic lesions that are commonly seen in Turner's syndrome.

Table 2 The proportion and distribution of 45,X cells in the aortic, gonadal and Müllerian duct tissues

%45,X cells	Patient		Control	
			45,X	46,XY
Peripheral lymphocyte	**23.3%** (7/30)		100%	0%
Gonadal tissue	Streak gonad	**98.7%** (224/227)	100% (100/100)	19.3% (132/683)
	Müllerian duct	**51.7%** (75/145)		
Aortic tissue	**87.6%** (149/170)		NA	NA

NA, not available

Fig.3 Gonadal tissue

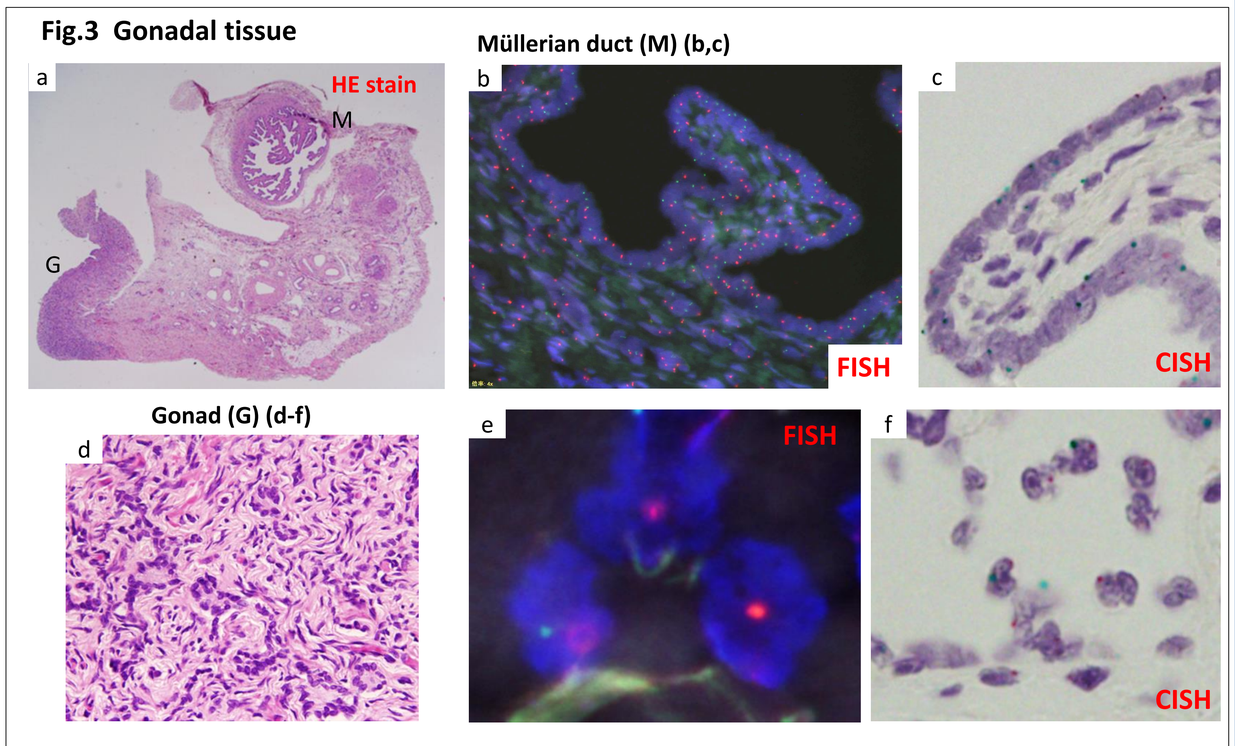
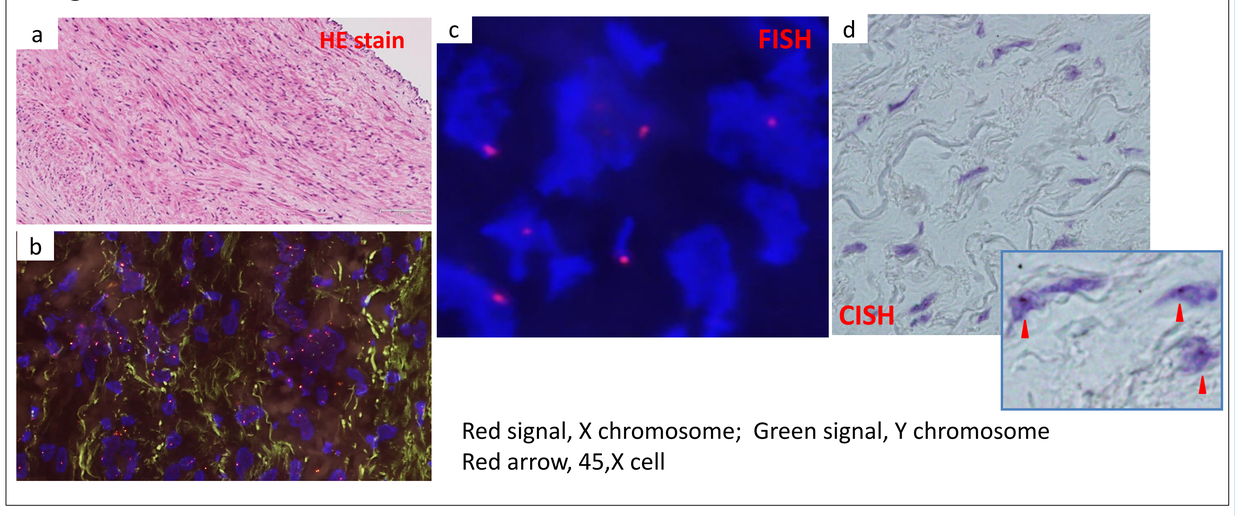


Fig.4 Aortic tissue



Red signal, X chromosome; Green signal, Y chromosome
Red arrow, 45,X cell

Discussion

1) Higher proportions of 45,X cells might cause a regressive change (apoptosis and stromagenesis), leading to sclerotic lesions such as streak gonad and coarctation of the aorta in MGD.

2) Since MGD is sometimes associated with cardiovascular anomalies, all patients with 45,X cell lines should be proposed for both endocrine and cardiologic follow-up as is performed for Turner syndrome.

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