Case Report

Mosaic Turner Variant Adult Female Presenting with XO/XY Karyotype

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Abstract

Turner syndrome (TS) is the most frequently detected chromosomal abnormality in females caused by the partial or complete absence of second X chromosome. Due to varied phenotypical presentation, the diagnosis of TS can create a spectrum of clinical concerns related to morbidity and mortality. At least 10% of Turner females exhibit the presence of Y chromosome or Y-derived sequences. Patients with 45,X/46,XY mosaicism may have a phenotypic variation of the external genitalia and exhibit features ranging from normal male to ambiguous to female genitalia with features of TS. Turner mosaic variants with Y chromosome components have increased risk for gonadoblastoma. Although the risk is not exactly quantifiable, according to the 2016 Cincinnati International TS Meeting Clinical Practice guidelines, bilateral prophylactic gonadectomy is mandatory if Y chromosomal component is identified in mosaic Turner. We describe a rare case of an adult female patient detected as mosaic Turner variant with the presence of Y chromosome and reconfirmed by an aneuploidy FISH probe.

Keywords: *46X/46XY, adult female, mosaic, turner variants, Y chromosome*

Introduction

Turner syndrome (TS) is characterised cytogenetically by X chromosomal monosomy, the occurrence of an abnormal X chromosome or mosaicism of a 45,X cell line with another cell line in an apparently phenotypic female. The clinical severity is usually related to the type of chromosomal anomalies, the timing of chromosomal nondisjunction and the proportion of affected cells. TS occurs approximately 1 in 2500 live-birth females.[1] Ninety-nine percentage of 45,X karyotype conceptuses spontaneously abort by 28 weeks of gestation. Fifty percentage of the TS present with classical 45,X karyotype, the remainder exhibit mosaicism and or structural abnormalities of X chromosome, of which only 6%–9% of Turner mosaic exhibit the presence of Y chromosome or Y-derived sequences. In approximately 75% of Turner cases, the X chromosome is maternal in origin.[2] Due to the complexity in phenotypic and clinical presentations, the diagnosis is most commonly suspected during adolescence. Classic clinical presentation features of TS include short stature and primary ovarian insufficiency.[3] The prognosis in adults is mostly related to various cardiovascular diseases, such as congenital cardiac anomalies, hypertension, aortic dilatation and increased risk for aortic dissection. TS can affect multiple organs through various life stages, requiring support involving multidisciplinary approach. Therefore, in 2016 in Cincinnati International TS Meeting Clinical practice guidelines were formulated for the care of females with TS.[4]

In this case report, we describe the clinical, laboratory and cytogenomic findings and treatment approach in a rare case of an adult mosaic TS female who presented with Y chromosomal component.

Case Report

An 18-year-old unmarried female presented with complaints of short stature, primary amenorrhoea and no breast development. She is the second child of a

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non-consanguineous couple and her elder brother did not have any medical problems. She had a normal birth history and did not have any other significant past history. She did not have a family history of pre-mature ovarian failure. The mother gave a history of the girl growing slower than her friends of the same age group since birth. She was studying in school and had not demonstrated gross motor or intellectual or neurocognitive impairment. On physical examination, the patient was 144 cm in height and weighing 43 kg. Her vital signs were normal. On vulval inspection, she had a normal vagina and hymenal opening. She had no signs of hirsutism or clitoromegaly but had Tanner stage 1 growth of pubic hair and Tanner stage 2 of breast development. She had no scoliosis, webbed neck, high-arched palate, hearing loss or deformities of the extremities. Her intellectual development was normal for her age.

Laboratory studies showed features suggestive of hypergonadotropic amenorrhoea with raised levels of follicular-stimulating hormone and luteinising hormone. Estradiol (E2), testosterone and prolactin levels were within the normal range [Table 1]. Thyroid function tests, liver function tests and renal function tests were within normal limits. Ultrasonography imaging of the abdomen and pelvis showed a hypoplastic uterus measuring 2.4 cm × 1.2 cm × 0.5 cm with hypoplastic ovaries. Magnetic resonance imaging pelvis (plain) showed hypoplastic uterus with non-visualisation of the upper 2/3rd of the vagina. Conventional karyotyping was performed on the peripheral blood samples using standard cytogenetic protocols. For each sample, 50 GTG banded (G banding with trypsin using Giemsa stain) metaphases were analysed. An automated karyotyping system (MetaSystems, GmbH, Altlussheim, Germany) was used for analysis. Cytogenetic analysis of fifty metaphases from phytohaemagglutinin-stimulated cultures using peripheral blood samples showed a mosaic karyotype with two cell lines. One cell line showed 45 chromosomes due to monosomy X in the 30 metaphases analysed. The other cell line showed 46 chromosomes due to the presence of a Y chromosome in 20 metaphases. This was confirmed on FISH with 45,X chromosomal constitution in 60% and 46,XY chromosomal constitution in 40% of interphase cell nuclei out of 500 cells studied [Figure 1]. The karyotypes of the parents were normal.

Bearing in mind the increased risk of gonadoblastoma in TS with a mosaic Y chromosomal component, the patient and her parents were counselled for bilateral prophylactic gonadectomy. However, as they were not willing for surgical management even after proper counselling, the patient is now undergoing regular close follow-ups.

Discussion

The mosaic 45,X/46,XY genotype can present a wide range of phenotypic variation from a male with normal testis to a TS female.[5] Virilisation in a female may be present based on the availability of functional testicular tissue. TS guidelines mentioned that aged women (≥50 years) and low levels of mosaicism (<5%) for monosomy X should not be labelled as having TS.[6] Our case is one of the instances where a Turner female with X/XY mosaicism presented without virilisation.

The American College of Medical Genetics (ACMG) guideline recommended karyotyping to be performed on a minimum of 30 cells for diagnosis of TS. Whenever there is a suspicion of the presence of a Y chromosome, the guideline recommends 200 cell FISH analysis with the X and Y centromeric probes when there is ambiguity with a nonmosaic 45,X karyotype.[7] In the reporting pattern, we have followed the ACMG guideline incorporating the International System of Cytogenomic Nomenclature, 2020.[8]

In phenotypic females with 45,X/46,XY mosaicism, there is an increased risk of gonadoblastoma (12%–60%) due to intra-abdominal gonad location hence it is always recommended to have a mandatory prophylactic gonadectomy and hormone replacement therapy (HRT) as per the 2016 international TS meeting guidelines.[4] A gonadoblastoma is a neoplasm composed of germ cell and sex cord–stromal derivatives and has an excellent prognostic outcome if identified early. However, gonadoblastomas can progress to dysgerminomas with possible metastasis later. The proposed neoplasm susceptibility locus does not correlate with the SRY gene but with pericentromeric region of the Y chromosome.[9] In this case, the patient has not yet developed any evidence of gonadoblastoma, but following the international guideline, the patient and her parents were counselled for the requirement of bilateral prophylactic gonadectomy.

TS is sporadic in nature. Paternal nondisjunction was responsible for 70% of 45,X liveborn cases.[10] In this case, the parental karyotype was normal.

Our study is highlighting the recommendation of performing cytogenomic evaluation of all cases of phenotypic TS so that we should not miss out the diagnosis of rare causes of sex chromosomal aneuploidies having prognostic significance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and

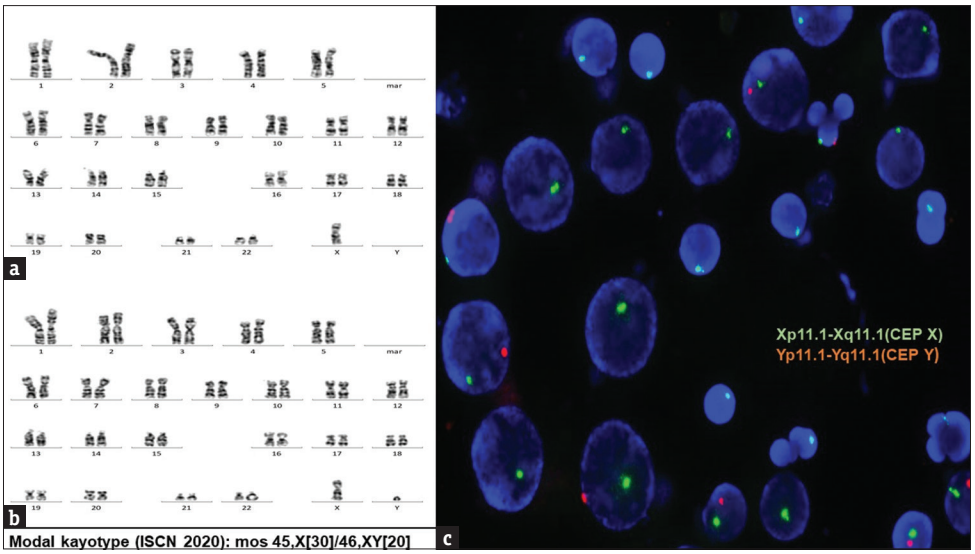

Figure 1: (a) Karyotype showing 45 chromosomes due to monosomy X (b) Karyotype showing 46 chromosomes due to the presence of Y chromosome (c) FISH analysis with centromeric XY probe on interphase cells showing the presence of mosaicism with some cells exhibiting a single hybridization green signal for the X chromosome admixed with some cells exhibiting one green hybridization signal for the X chromosome and one orange hybridization signal for the Y chromosome

Table 1: Relevant clinical and laboratory parameters

Parameter	Results
Height (cm)	144
Weight (kg)	43
BMI	20.7
Hb (%)	12.1 (g/dL)
FSH (RR: 3.08–8.08 IU/L)	105.87
LH (RR: 1.04–15.0 IU/L)	49.13
Prolactin (RR: 4.07–24.4 ng/mL)	8.17
E2 (RR: Premenopausal 30–400 pg/mL)	93
Free testosterone (RR: 12–18 years female 0.00–2.24 pg/mL)	0.58
Total testosterone (RR: 0.38–1.97 nmol/L)	0.66
Total T3 (RR: 60–181 ng/dL)	69.15
Total T4 (RR: 4.5–12.6 µg/dL)	8.24
TSH (RR: 0.3–5.5 uIU/mL)	1.66
HCG (RR: Cyclic women: 0.00–4.0 mIU/mL)	<2.00
CA 125 (RR: 0–35 µ/mL)	<4.00
AFP (RR: <10 IU/mL)	2.34
Chest X-ray (PA view)	NAD

FSH=Follicle-stimulating hormone, LH=Luteinising hormone, RR= Reference range, T3=Triiodothyronine, T4=Thyroxine, TSH=Thyroid-stimulating hormone, HCG=Human chorionic gonadotropin, AFP=Alpha-fetoprotein, CA 125=Cancer antigen 125, BMI=Body mass index, Hb=Haemoglobin, E2=Estradiol, PA=Postero-anterior

other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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