CASE REPORT

Mosaic Variant of Turner Syndrome with XY Cell Lines

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Abstract

Aim: The aim of this study was to assess the outcome of Turner mosaic variant with multidisciplinary management.

Background: Turner syndrome is a complex developmental disorder in individuals with short stature associated with 45X genotype. A mixture of genotypes are also present in approximately 50% of all cases. Individuals with a mosaic 45 X/46XY genotype have a variety of phenotypic presentations, which are not correlated with the percentage of mosaicism.

Case description: A case of an 18-year-old girl evaluated for primary amenorrhea who looked phenotypically normal female. Turner mosaic was suspected. Karyotyping and fluorescent *in situ* hybridization (FISH) of sex chromosomes revealed 46X/46 XY mosaic variant. During chromosomal analysis along with karyotyping, a detailed FISH analysis for sex chromosomes is required in order not to miss out presence of Y chromosome.

Conclusion: Turner mosaic with XY variant is a rare condition and management requires multidisciplinary approach. Prophylactic gonadectomy has to be done to prevent gonadoblastoma.

Clinical significance: This case is presented to emphasize the importance of proper genetic analysis in order not to miss out the presence of Y chromosome in Turner mosaics.

Keywords: Case report, Fluorescent *in situ* hybridization, Karyotyping, Multidisciplinary approach, Prophylactic gonadectomy, Turner mosaic XO/XY variant.

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Introduction

Henry Turner described Turner syndrome in 1938 before chromosome analysis came in vogue. Affected females have short stature, sexual infantilism, webbed neck, and cubitus valgus.[1] Diagnosis of Turner syndrome depends on characteristic features combined with genotype of one normal X chromosome and a complete or partial absence of other X chromosome.[2] Turner syndrome is a sporadic condition, which has no association with advanced maternal age. Since the single X chromosome is maternally derived in 80%, the genesis of the 45X karyotype is due to instability of Y chromosome leading to its loss during meiosis. The missing X chromosome is paternal in origin for approximately 75% of live born who are 45X, which has been found using many different methods like Xg blood grouping, restriction-fragment length polymorphism, and single-nucleotide polymorphism in parents.[3] Patients with a normal female phenotype without evidence of masculinization may also have a 46,XY cell line. Those patients should be closely monitored due to the risk of any germ cell tumor, especially gonadoblastoma.[4]

Case Description

An 18-year-old female came with complaints of primary amenorrhea. She attained menarche at the age of 13. She had only one episode of spotting per vaginam as withdrawal bleeding after two cycles of combined oral contraceptive pills. Nil significant family history such as menstrual irregularities, infertility, or primary ovarian insufficiency.

On examination, she was 154 cm tall and weighed 44.5 kg with body mass index (BMI) of 18.72 kg/m^2. She presented with normal female secondary sex characteristics with Tanner second stage breast development and pubic hair growth. No mass palpable in the inguinal region suggestive of undescended testes. Tone and reflexes appeared normal.

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Follicle-stimulating hormone and luteinizing hormone levels were elevated.

Liver and thyroid functions were normal. Ultrasonogram showed a hypoplastic uterus measuring 2.8 × 1 × 1.5 cm with endometrial thickness of 2 mm. Both ovaries were not seen. The magnetic resonance imaging (MRI) pelvis reported hypoplastic uterus with thin endometrial cavity and hypoplastic left ovary and absent right ovary.

Karyotyping reported as 45 XO(15)/46, X, dup (Y) (p.11.2q11.23), del (Y) (q11.23), del (Y) (q11.23) (15)/46, XY (10)—Turner mosaic variant 37.5% of metaphase show monosomy X, 25% normal XY, 37.5% duplication of bands between Yp11.2 and Yq11.23, and deletion of terminal heterochromatin on q12 of chromosome Y. In fluorescent *in situ* hybridization (FISH) analysis, 30% of cells showed

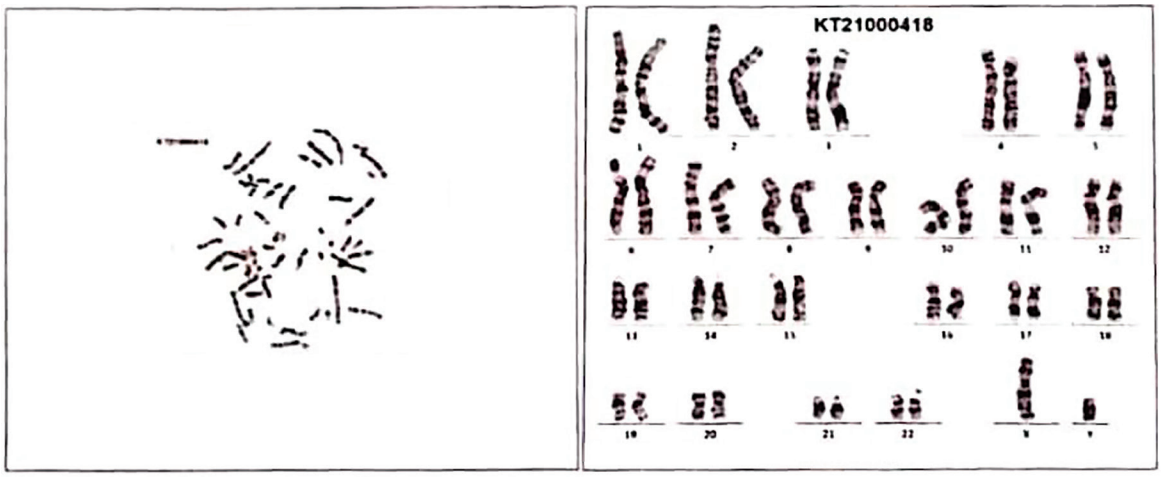

Fig. 1: Karyotyping images showing Turner mosaic variant

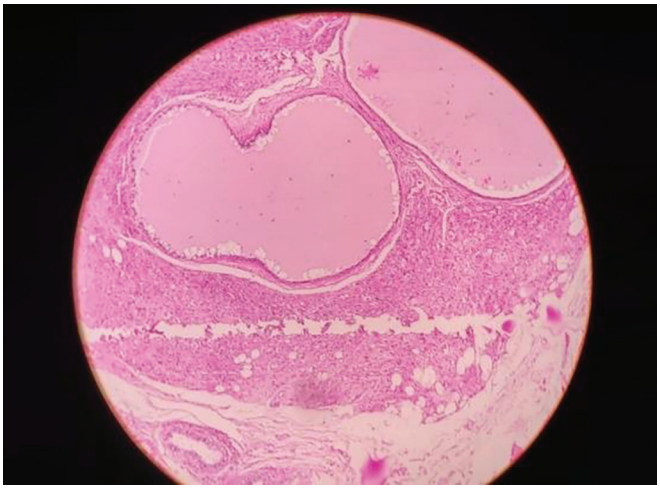

Fig. 2: Dilated tubules lined by cuboidal epithelium, filled with eosinophilic secretion surrounded by Leydig-like cells

one signal for chromosome X, 35% of cells showed one signal for chromosome X and one signal for chromosome Y, and 35% of cells showed one signal for chromosome X and two signals for chromosome Y (Fig. 1). Echocardiography showed normal cardiac function.

The patient was counseled about the risk of gonadoblastoma and necessity for prophylactic gonadectomy. Intraoperative findings on laparoscopy hypoplastic uterus seen with underdeveloped round ligaments. Both fallopian tubes appeared normal. Streak gonads were seen bilaterally, and proceeded with laparoscopic bilateral prophylactic gonadectomy and bilateral salpingectomy. Histopathology reported ovarian parenchyma with absence of ovarian follicles, fallopian tubes, and few dilated tubules (likely Leydig cells) (Fig. 2).

Postoperatively, patient was advised hormone replacement therapy till her natural age of menopause.

Discussion

Turner syndrome is associated with multiple abnormal genotype abnormalities including 45 X, and Turner mosaics 45X/46XX, 45X/47XXX, and 45X/46XY. The 45X/46XY mosaic variant genotype accounts for approximately 10–12% of cases of Turner syndrome.[2] Low level mosaic variant of Turner syndrome with 45X/46XY cell lines may be missed by conventional karyotype method. In such cases, FISH analysis is necessary for the diagnosis.

In a literature search by Cool et al.,[5] overall prevalence of germ cell tumors in 45X/46XY patients was 15%. In Gravholt et al.'s study, the cumulative risk of gonadoblastoma is 7.9% (95% CI: 3.1–19.0).[2] Although Turner syndrome of mosaic variant have varying risks of gonadoblastoma, current evidence suggested approximate risk of 10%.[6] At the time of diagnosis for patients with Turner syndrome and Y chromosome material such as 45, X/46, XY mosaicism, women require additional prophylactic bilateral gonadectomy.[3]

When any genotype of Turner syndrome is observed, they should undergo a multidisciplinary approach and management.[3] In order to prevent early bone loss, induced puberty, and maintain secondary sexual characteristics, hormonal replacement therapy is indicated till menopause. In one third of girls with Turner syndrome, spontaneous thelarche occurs, mostly in girls with mosaic variant. Almost 6% of girls with mosaic variant have regular menstrual cycles.

Our case had menstruation only after estrogen progesterone challenge. After gonadectomy, patient is now on estrogen supplementation. Future fertility is also possible by oocyte donation and *in vitro* fertilization, if the uterus attains normal size after hormone stimulation.

Conclusion

Turner syndrome is a complex reproductive developmental disorder. Most cases of Turner syndrome diagnosed by the first trimester screening are pure 45XO. Most living cases of Turner syndrome are mosaics. The most common mosaic pattern is 45XO/XX. However, 45XO/XY mosaic variant may also be present, which may be missed by conventional karyotyping. The use of XY interphase FISH as a complement to karyotyping is necessary in all cases of Turner syndrome or suspected Turner mosaic to have a complete picture of the chromosomal pattern in order not to miss out Y chromosome. Apart from hormone replacement as a part of management, these individuals require additional gonadectomy in view of future risk of developing gonadoblastoma.

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