Rare mosaic isochromosome of Turner syndrome: A case report

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Abstract

Turner syndrome with isochromosome mosaicism is a very rare condition, especially in Saudi Arabia. Here we are presenting a case of a 13 year old female with a karyotype of 45, X/46,X,i(X)(q10) having Isochromosome Mosaic Turner Syndrome (IMTS). This is an uncommon variant of TS. Our patient was complaining of short stature, and upon physical and chemical evaluation, she was reported to have late sexual development (primary), hypothyroidism, hypogonadism. Later an ultrasound examination showed no ovary in the right side and a small sized ovary on the left side. Bone aging was that of a 11 year old female with non-fusion of epiphyseal plates. She received conjugated estrogenic and progesterone hormone therapy that patterned the hormonal changes and positively affected amenorrhea. This is a representation case to report a rare condition of IMTS, to indicate related symptoms and to add to the knowledge base of presented cases to help with early screening for the sake of early detection. Early screening especially in Saudi Arabia is imperative due to the rarity.

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Introduction

Turner syndrome is a genetic condition named after Dr. Henry Turner in the 1938. On average, for every 2500 female births worldwide, one of them has turner syndrome (Shankar Kikkeri and Nagalli, 2022). Turner syndrome is not an inherited disorder, TS is not age-associated or caused by any known environmental factors. Usually, it happens at random, and is caused by defective mitosis that usually results in missing X chromosome in the resulting gametes, this leads to a genotype of 45 X after fertilization. This is the classic monosomy picture of Turner syndrome. However, other genotypes do exist that result in the final picture of Turner syndrome. Our case here is a prime example of a variant, a genotype of 46, X, i(X)(q10), this type of isochromosome has been previously estimated internationally to be in the order of 8-9% of the cases of Turner syndrome.

Turner syndrome results in many clinical symptoms and illnesses, this includes, short stature, webbed neck, wide carrying angle, ovarian failure, puberty delays and amenorrhea, infertility, osteoporosis, heart disease, kidney disease, thyroid disorders, and learning challenges, Intelligence however is not affected. Turner syndrome symptoms and complications can be improved with symptomatic treatment to reduce the burden of the disease and reduce the incidence of complication.

Patient History

A 13 years-old Saudi female was admitted in the pediatric clinic because of short stature then after investigation in her second visit, it was found that she has hypothyroidism, osteoporosis, and celiac disease. After that chromosome analysis was ordered, the result of it showed abnormal

karyotyping compatible with isochromosome Turner syndrome. Also, the result of hormone investigation showed hypogonadism in addition to primary ovarian failure. When we saw the report of radiology during her first visit September 2018 the X-ray was showed there a decrease in bone marrow age of around 2.4 units below the standard deviation of normal individuals of same age.

Prior to her second visit in October 2019 the patient had completed a course of growth hormone therapy (GHT). This intervention appear to have enabled her attain normal bone marrow age. During her third visit in September 2020 the patient showed a decrease of 4.1 points below standard deviation of normal for individuals of her age. She was at 14 years old of age, but her bone age was that of an 11 year old. This decrease in bone maturity was the outcome of stopping the GHT mid-course without finishing it. The fourth visit was in June 2021. The patient showed no ovary in the right side and a small sized ovary of a 1 x 0.5 cm on the left side.

Laboratory tests of thyroid function analysis revealed that the thyroid- stimulating hormone (TSH) level was 1.77 mIU/L (normal range: 0.5 to 5.0 mIU/L), and the free T4 22.66 pmol/L (normal range: 12 to 30 pmol/L), the free T3 level 3.5 pmol/L (normal range: 2.0 to 7.0 pmol/L). The Follicle-stimulating hormone was 33.41 IU/L (normal range 1.5 to 12.4 IU/L). Luteinizing hormone was 21.56 (normal range follicular phase of menstrual cycle: 1.37 to 9 IU/L). Women midcycle peak 6.17 to 17.2 IU/L) this indicates infertility or problem in ovary function. Her IGF-1 was 294 ng/mL (normal range: 95 to 380 ng/mL). And the level of IGFBP3 was 7460 (normal range between 2444 and 6184 mcg/l). Parathyroid hormone level was 6.63 pg/mL (normal range 6 to 55 pg/mL). The patient has a high level of Alkaline phosphatase was 231IU/L (normal range 44 to 147 UI/L). TTG-IgA level was 6.7 ug/u (normal range 0 to 100 ug/u).

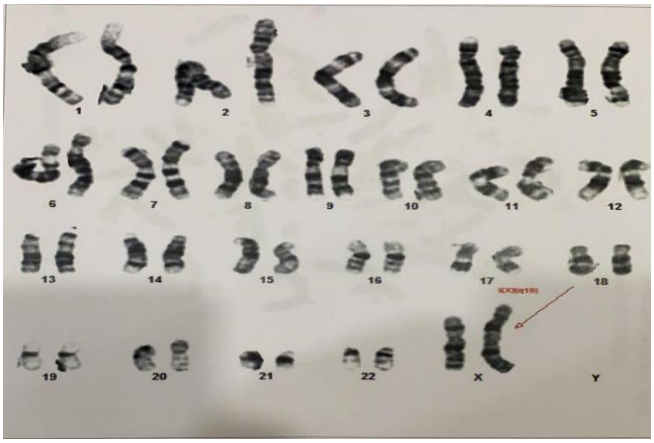
Results

Non-fusion of epiphyseal plates with bone aging for a female of 13 years old by Greulich and Pyle standards. Cytogenetic study of peripheral blood through G-banding technique revealed three cell lines present. As shown in (Table 1). This is consistent with the diagnosis of IMTS variant (Figure 1).

Table 1: Cytogenetic results showing the different cell lines found.

Cell Lines	n (%)	Karyotype	Karyotype classification
Cell Line 1	77%	47, XXX	Trisomy X
Cell Line 2	16%	46,X,i(X)(q10)	Isochromosome X
Cell Line 3	6.3%	45,X	Monosomy X

Fig 1: The cell line with an isochromosome of the long arm of X chromosome



FISH technique was performed to confirm the different cell lines. Based on 220 interphase nuclei analyzed using LSI SRY spectrum Orange /CEP X spectrum Green DNA probe manufactured by (Abbott Molecular, USA). Three different cell lines were found (Chart 1).

Chart.1:Three different cell lines were found

- 77.7 % of the cells showed three copies of Xp11.1-q11.1
- 16% of the cells showed two copies of Xp11.1-q11.1
- 6.3% of the cells showed one copy of Xp11.1-q11.1

No SRY gene was found in all of the cells.

The results of FISH are as follows:

Ish Yp11.3/Xp11.1-q11.1
(SRYx0;DXZ1x3)[171/220]
(SRYx0;DXZ1x2)[35/220]
(SRYx0;DXZ1x1)[14/220]

Table 1: Levels of free T4 hormone for period 2018-2022

Date	FT4
06\09\2018	≈ 22
26\09\2018	≈ 30
14\01\2019	≈ 13
18\02\2019	≈ 15
04\04\2019	≈ 14
22\07\2019	≈ 13
21\10\2019	≈ 18
20\09\2020	≈ 16
01\02\2021	≈ 15
15\06\2021	≈ 14
07\09\2021	≈ 15
30\11\2021	≈ 20
21\03\2022	≈ 16
18\07\2022	≈ 15

Table 3: The levels of thyroid stimulating hormone for period 2018-2022

Date	TSH
06\09\2018	≈ 12
26\09\2018	≈ 0
14\01\2019	≈ 35
18\02\2019	≈ 20
04\04\2019	≈ 19
22\07\2019	≈ 20
21\10\2019	≈ 0
20\09\2020	≈ 0
06\01\2021	≈ 0
01\02\2021	≈ 0
15\06\2021	≈ 3
07\09\2021	≈ 1
30\11\2021	≈ 1

Discussion

Turner syndrome or monosomy X is a chromosomal abnormality impacting the X chromosome in which a female is missing one of the sexual chromosomes resulting in the classical and most common form of TS 45, X karyotype. However other karyotypes are possible. Including deletion of short or long arm in chromosome X (Xp) (Xq), ring chromosome formation (rX), isochromosome (iX) that is a structural abnormality where two short arms or two long arms are found, or mosaicism, which is when different variations of X chromosome abnormalities are found in cell lines (Shankar Kikkeri and Nagalli, 2022).

Table 4: The levels of IGF-1 for period 2018-2022

Date	IGF-1
06\09\2018	≤ 0
22\07\2019	≈ 200
21\10\2019	≈ 400
20\09\2020	≈ 240
06\01\2021	≈ 190
01\02\2021	≈ 490
15\06\2021	≈ 450
05\07\2021	≈ 400
30\11\2021	≈ 250
21\03\2022	≈ 220
18\07\2022	≈ 200

Table 5: The levels of estradiol period 2019-2022

Date	Estradiol hormone
22\07\2019	≈ 40
06\11\2019	≈ 70
20\09\2020	≈ 40
01\02\2021	≈ 40
15\06\2021	≈ 50
30\11\2021	≈ 0
21\03\2022	≈ 160
18\07\2022	≈ 120

Table 2: The levels of follicle stimulating hormone for period 2019-2022.

Date	FSH
22\07\2019	**≈ 60**
06\11\2019	**≈ 70**
20\09\2020	**≈ 80**
15\06\2021	**≈ 70**
30\11\2021	**≈ 35**
21\03\2022	**≈ 50**
18\07\2022	**≈ 20**

Table 7: showing the levels of Luteinizing Hormone from the period of 2019 to 2022.

Date	LH
22\07\2019	≈ 30
20\09\2020	≈ 33
15\06\2021	≈ 26
30\11\2021	≈ 21
21\03\2022	≈ 35
18\07\2022	≈ 5

In the present case, the patient was diagnosed with IMTS as she showed mosaic and isochromosome variation cell lines. Where 77.7% cells had a karyotype of 47, X and an extra copy of X chromosome was found, in addition to 16% of 46,X,i(x) where the long arm of the x chromosome was duplicated and 6.3% cells with monosomy x 45,X.

Treatment and management were aimed at growth enhancement, including sexual characteristics, and health. Fertility counselling and regular follow-ups after screening for medical complications was performed.

The patient showed short stature but responded to the growth hormone therapy when taken regularly as prescribed. Her hypogonadism and hypothyroidism were ameliorated with hormonal replacement therapy alongside multi supplements to help with amenorrhea as well. Some women with TS show difficulties in intellectual performances however our patient showed little to no cognitive impairment.

If the patient is planning for pregnancy as it is very rare in women with TS. Pregnancy mostly could result in abortions, fetal malformations, or chromosomal abnormalities. Where permissible donor oocyte in addition to in vitro fertilization can be applied, however fetal fatality may still occur (Gomez-Lobo et al., 2016).

In the long-term plan, it is greatly advised to have the primary sexual characteristic development monitored. As well as the hormonal replacements, physical examination, and blood analyses on annual visits. Heart ultrasound and bone densitometry and audiogram must also be checked every 3-5 years (Llanes and Uyking-Naranjo, 2019).

In the present case, it took approximately 12 years before the underlying cause of the patient's maladies were suspected as a condition related to chromosomal abnormality and to consider cytogenetic analysis. Patient's growth and live quality were strongly negatively impacted by the exceeding long time taken to diagnose the condition and to commence treatment. This incident underscores the crucial need for early referral and detection so that such cases could be treated early to avoid as many complications as possible and to prevent severe disadvantages of poor quality of life precipitated by such a condition.

Conclusion

We report a case of isochromosome mosaic Turner syndrome to document the unique symptoms manifested and to demonstrate the diversity in presentation of patients with Turner syndrome. It is anticipated this report will enhance the literature on possible diversity in presentation of such cases. There is a need ensure suspected cases of TS are referred to relevant clinics for early screening to prevent complications of late diagnosis. Late diagnosis appears endemic in Saudi Arabia where many cases probably go reported.

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