A Variant of Turner’s Syndrome Presenting with Secondary Amenorrhea

Hallert C. Ramos M.D. 1 and Frances Lina Lantion-Ang M.D. 2

Abstract

Turner syndrome with isochromosome, karyotype 46X,i (X) (q10) is rare and presents with atypical clinical features that should be thoroughly investigated because of potential complications.

A 29 year old female was referred to the Endocrinology clinic because of cessation of menstruation at age 20 after her menarche at age 15. She was not pregnant on initial evaluation and progesterone challenge induced breakthrough bleeding. Her height is 135 cm and weighed 41 kg. Mental function was normal. There were multiple pigmented nevi on her face and body. She had high arched palate he neck was short with no webbing. She had shield-like chest and normal cardiac findings. The upper extremities were in cubitus valgus. Secondary sexual development was immature.

Her karyotype showed one normal X chromosome and an isochromosome on the long arm of one X chromosome. Hormonal evaluation revealed normal prolactin levels, subclinical hypothyroidism and post menopausal level of gonadotropins and estradiol.

Work up for coexisting illness revealed osteoporosis, severe mixed hearing loss on the right and mild sensorineural hearing loss on the left and bilateral horse shoe kidneys. She had infantile uterus and immature ovaries on pelvic imaging. Echocardiogram, hematology and renal function tests were normal. The above case is a rare variant of Turner syndrome, the patient needs supportive medical and psychological management.

Keywords: Turner’s syndrome, secondary amenorrhea

Introduction

Turner syndrome (Ulrich-Turner syndrome) first described in 1938 is a common sex chromosome abnormality in females. It is caused by complete or partial X monosomy in some or all cells. The most frequent karyotype is 45,X and mosaicism. In some instances it can be due to structural changes in one X chromosome (isochromosome). 45,X karyotype is more frequently associated with profound congenital defect such as cystic hygroma, renal and cardiac anomaly. The mosaic and isochromosome types present with a wide range of mild somatic features and are diagnosed later. 1 TS is a special variant of hypergonadotrophic hypergonadism and is a common cause of infertility. Its incidence is one in every 2500 live births. 2 The aim of this report is to present a rare variant of TS and its work up.

The Case

A 29 year old female, single consulted the out patient department, endocrinology clinic for secondary amenorrhea. She had her menarche at age 15. Subsequent menstruation was five years later. Thereafter she became amenorrheic. At the endocrinology clinic the other complaints were short stature and delayed development of her secondary sexual characteristics (age 20).

Physical Findings

Her height was 135 cm and her weight was 41.5 kg. Her blood pressure was 110/70 mmHg. She had decreased hearing acuity. High arched palate and short neck. She had a shield like chest with the breast fat mound and areola lacked contour separation. No lymph node was palpable and hepatosplenomegaly was absent. Pubic and axillary hairs were absent. She had multiple pigmented nevi and were seen at the face and trunk. Upper extremities were in cubitus valgus.

Figure 1. Patient featuring short stature, rounded face with multiple nevi cubitus valgus, shield like chest, immature secondary sexual characteristics.
Investigation

Initial work up showed a negative pregnancy test. She had withdrawal bleeding after progesterone challenge. Cytogenetic study of peripheral blood showed one normal X chromosome and an isochromosome of the long arm of one X chromosome. This was confirmed by gross G bonding. Closely resembled the standard for an 18 year old female. The bone mineral density was consistent with osteoporosis (Z score -3.6, T score -3.6).

Discussion

Turner syndrome with the chromosome 45,X commonly present with primary amenorrhea. The 45,X chromosome constitution is a consequence of non-disjunction or chromosome loss during gametogenesis in either parent. This results in a sperm or ovum which lacks one sex chromosome. Since the two copies of the X chromosomes are necessary for ovarian development and integrity, girls with classic TS have ovarian dysgenesis. In about 10 percent of TS patients, secondary amenorrhea is said to occur, two to five percent of the patients may achieve spontaneous pregnancy. Sex chromosome mosaicism or structural abnormality of an X chromosome may modify the typical features of the syndrome.

The most common and consistently seen features of the syndrome are dysmorphic features, short stature and streak gonads. In one third of females with the karyotype 45,X they present at birth with lymphedema or cardiac anomaly hence they are invariably diagnosed earlier than the variants mosaic or isochromosome. The average age of diagnosis of TS isochromosome variant is 14 years. Our case had no overt physical abnormality during childhood and had good functional status hence the delay in seeking medical attention.

Absent pubertal development is one of the most common features of TS. This is because 90% of TS have gonadal failure; however, up to 30% of girls will undergo spontaneous pubertal development.

The hypergonadotrophic hypogonadism puts these patients at risk for osteoporosis. At this young age our patient already has osteoporosis o screening hence the need to start treatment to prevent fracture.

Short stature is the most readily recognizable feature of TS. The deficit I height is caused by the haploinsufficiency of the short stature homeo-box containing gene (SHOX) located within the Xp terminal, pseudoautosomal region of the X chromosome. It affects virtually all individuals with TS. The typical growth pattern in TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of childhood component of growth and absence of pubertal growth spurt. A disproportionate growth causes girls to appear stocky, with wide body and relatively large hands and feet. The girls are at higher risk for scoliosis and kyphosis than the general population. The development abnormalities of the bones result I short neck, cubitus valgus, genu valgum and short fourth metacarpals. Our patient is 21 cm short of her target height, had short neck and cubitus valgus.

Our patient had multiple pigmented nevi a common skin lesion of TS. The risk for melanoma does not appear to be increased in TS. High arched palate short neck, reduced posterior cranial base length, retrognastic face

<table>
<thead>
<tr>
<th>TEST</th>
<th>Result</th>
<th>Normal value</th>
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<tbody>
<tr>
<td>Prolactine</td>
<td>375.9 mIU/L</td>
<td>90-200 mIU/L</td>
</tr>
<tr>
<td>Free T4</td>
<td>14.0 pmol/L</td>
<td>11.24 pmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>7.5 mIU/L</td>
<td>0.3-3.8 mIU/L</td>
</tr>
<tr>
<td>Testosterone</td>
<td>1.5 nmol/L</td>
<td>0.9-4.5 nmol/L</td>
</tr>
<tr>
<td>FSH</td>
<td>84.7 mIU/L</td>
<td>Ovulatory peak 4-13.5</td>
</tr>
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<td></td>
<td></td>
<td>Pre/post ovulatory 0.8-9.5</td>
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<td></td>
<td></td>
<td>Post menopausal 30-135</td>
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<tr>
<td>LH</td>
<td>32.9 mIU/L</td>
<td>Ovulatory peak 25-94</td>
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<tr>
<td></td>
<td></td>
<td>Pre/post ovulatory 0.7-9.0</td>
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<tr>
<td></td>
<td></td>
<td>Post menopausal 13-80</td>
</tr>
<tr>
<td>Estradiol</td>
<td>51.5 pg/mL</td>
<td>Ovulatory peak 97-227</td>
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<tr>
<td></td>
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<td>Pre/post ovulatory 127-476</td>
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<td></td>
<td></td>
<td>Middle luteal 77-277</td>
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<tr>
<td></td>
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<td>Post menopausal &lt;82</td>
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and wide mandible are the distinct craniofacial feature of TS. Malocclusion and abnormal tooth development can lead to loss of teeth.

Hearing problems and ear malformation are common in TS. Due to abnormal anatomical relationship of Eustachian tube, middle ear and cranial base recurrent otitis media is common and result in conductive hearing loss. The more significant hearing impairment is due to progressive sensorineural hearing loss which may present as early as six years of age. Surveillance and early use of hearing aid in childhood prevent worsening of developmental delay.\(^1\)\(^,\)\(^6\) Our patient was referred to audiologist and otorhinolaryngologist for management.

Urinary system malformation is present in 30-40% of patients with TS. The most common phenotype is collecting system malformation (20%) followed by horse-shoe kidneys (10%), malrotation and other positional abnormalities (5%). Most reported genitourinary abnormalities are clinically insignificant but patients may develop hypertension and urinary tract infection.\(^6\)

Aside from abnormalities of the gonadal axis and osteoporosis, the other important endocrinologic feature of TS is thyroid dysfunction, which is present in our case. TS are at increased risk for autoimmune thyroiditis hence it is recommended that they be screened with TSH and T4 annually from four years onwards.\(^1\)

Other features that can be present in TS but were not found in our case are congenital cardiovascular disease, atherosclerosis, dyslipidemia, ocular malformation, color blindness and visual impairment.\(^1\)\(^,\)\(^3\)\(^,\)\(^4\)

Conclusion

Our case was an isochromosome variant of TS who presented with secondary amenorrhea. Further screening for congenital and endocrinologic abnormalities showed hearing impairment, osteoporosis, horsehoe kidneys, hypogonadotrophic hypogonadism and subclinical hypothyroidism. This case emphasizes the importance of thorough screening of a patient with TS to prevent complications.

References