A Rare Case of an Isochromosome Mosaic Turner Syndrome

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Turner syndrome is characterized by a complete or partial absence of one X chromosome. The most common karyotype is 45,X0. A variant of Turner syndrome is Isochromosome Mosaic Turner syndrome which presents with an abnormality of the chromosome structure. This is a case of a 22 year old female who presented with short neck, widely spaced nipples, low posterior hairline, absence of nose bridge, minimal axillary hair and underdeveloped breasts. Ultrasound examination showed an infantile uterus with small ovaries. Her karyotype showed an isochromosome of the long arm of the X chromosome and the remaining eight cells showed a loss of one X chromosome, resulting in monosomy X (ISCN: 46,X,i(X)(q10)[42]/45,X[8]). Hormonal evaluation showed a hypergonadotropic and hypogonadism state. Test results for auditory, ophthalmologic, cardiac and renal functions were all within normal limits. The patient was diagnosed with isochromosome mosaic Turner syndrome and started on hormonal therapy.

Key words: Turner syndrome, isochromosome mosaic Turner syndrome

Introduction

Turner syndrome (or Ullrich-Turner syndrome) was first described by Ullrich in 1930 and by Turner in 1938. In 1959, Ford was able to identify the chromosomal cause of the syndrome. It is a variant of hypergonadotropic hypogonadism and classified as category I (absent breast development; uterus present) in the classification based on the presence or absence of secondary sexual characteristics (breasts) and female internal genitalia (uterus) (Table 1).[1]

Turner syndrome is characterized by short stature, developmental delays, webbed neck, low posterior hairline, broad chest with widely spaced nipples, amenorrhea, gonadal dysgenesis, absence of secondary sexual characteristics and anomalies of skeletal, auditory, ophthalmologic, cardiac, renal and endocrine origin.[2,3] The syndrome is caused by complete or partial absence of the second X chromosome from all or some cell lines, affecting approximately 1 in 2000-4000 live births.[4] In a 2016 local report released by the Institute of Human Genetics, National Institute of Health (IHGNIH), University of the Philippines (UP) Manila, a total of 414 cases of Turner syndrome were seen at the cytogenetics laboratory from 1991 to 2015 (153 cases of 45,X and 261 cases of Turner syndrome variants).[5]

The most common karyotype in Turner syndrome is 45,X(50%) and the rest of the patients have structural abnormalities of mosaicism involving 45,X/46,XX (20%); 46,X,i(Xq)(15%); 46,X,r(X) or 46,X,del(X)(10%); 45,X/46,X,i(Xq) (8%); 45,X/46,X,+ring (6%); 45,X/46,X,+mar (1%); 45,X/46,XY or 46,X,Yvar/Ydel (7%); 45,X/46,XX/47,XXX (3%); 46,X,Xp (short-arm deletions) (2%); 46,X,Xq (interstitial long-arm deletions) (2%); and others (6%).[6] Most living Turner syndrome patients are mosaics while about 97% of the 45,X monosomy are spontaneously aborted.[7] The case to be presented has a mosaic karyotype of 45,X/46,X,i(Xq).

Table 1. Classification of disorders with primary amenorrhea and normal female external genitalia.

I. Absent breast development; uterus present
   A. Gonadal failure
      1. 45,X (Turner's syndrome)
      2. 46,X, abnormal X (e.g., short- or long-arm deletion)
      3. Mosaicism (e.g., X/XX, X/XX,XXX)
      4. 46,XX or 46,XY pure gonadal dysgenesis
      5. 17α-hydroxylase deficiency with 46,XXs

   B. Hypothalamic failure secondary to inadequate GnRH release
      1. Insufficient GnRH secretion due to neurotransmitter defect
      2. Inadequate GnRH synthesis (Kallman's syndrome)
      3. Congenital anatomic defect in central nervous system
      4. CNS neoplasm (craniopharyngioma)

   C. Pituitary failure
      1. Isolated gonadotrophin insufficiency (thalassemia major, retinitis pigmentosa)
      2. Pituitary neoplasia (chromophobe adenoma)
      3. Mumps, encephalitis
      4. Newborn kernicterus
      5. Prepubertal hypothyroidism

II. Breast development; uterus absent
   A. Androgen resistance (testicular feminization)
   B. Congenital absence of uterus (uterovaginal agenesis)

III. Absent breast development; uterus absent
   A. 17,20-desmolase deficiency
   B. Agonadism
   C. 17α-hydroxylase deficiency with 46,XY karyotype

IV. Breast development; uterus present
   A. Hypothalamic etiology
   B. Pituitary etiology
   C. Ovarian etiology
   D. Uterine etiology

CNS, Central Nervous System; GnRH, Gonadotropin Releasing Hormone
Reference: Lobo R, Gershenson D, Lentz G, and Valea F: Comprehensive Gynecology, 7th ed. USA: Elsevier Mosby, 2017.p 833

The Case

The patient is a 22-year old female who consulted for evaluation of primary amenorrhea. She is the youngest child in a family of three girls and one boy with healthy unrelated parents. Her brother was diagnosed with autism. She was born term to a 39 year old mother via cesarean section secondary to malpresentation (breech presentation) after an uneventful pregnancy. Her mother noted slow growth of the patient during infancy and childhood. The mother had not received any antenatal hormonal therapy or had been exposed to radiation during pregnancy. Past medical history was unremarkable. There was no history of congenital anomalies or heredofamilial diseases in the family. She graduated with a degree in education and is presently taking classes for Master's degree in education. The patient had history of one episode of vaginal bleeding when she was 17 years old lasting for 3 days, using approximately 2 moderately soaked pads per day with no associated dysmenorrhea. She denies any sexual contact. Two years prior to consult, the patient started to experience significant hair loss (alopecia). She initially consulted a dermatologist and was given topical medications for hair growth. Her symptom persisted despite the medications. One year prior to consult, she started to notice significant hair growth on the sides of her face and inner thighs. Hair on her legs and arms had also become thicker.

On physical examination, the patient had stable vital signs with a normal BMI of 22. Her height was 57 inches. She has a short neck, widely spaced nipples, low posterior hairline and absence of nose bridge. She has minimal axillary hair and undeveloped breasts (Tanner stage I) (Figure 1). The patient was noted to have normal female external genitalia and Tanner stage II for pubic hair distribution (Figure 2). Modified Ferriman Gallwey Score was 8 indicating moderate hirsutism. (Figure 3). Ludwig scoring for alopecia revealed mild to moderate hair loss (Figure 4). The patient did not consent to be photographed.

A transrectal ultrasound was requested revealing an infantile uterus measuring 2.3cm x 2.2cm x 0.7cm with small ovaries.

Initial impression was Turner syndrome. Further diagnostic evaluations were requested to confirm the diagnosis.

Karyotyping revealed ISCN result of 46,X,i(X)(q10)[42]/45, X[8]; Abnormal karyotype: Mosaic

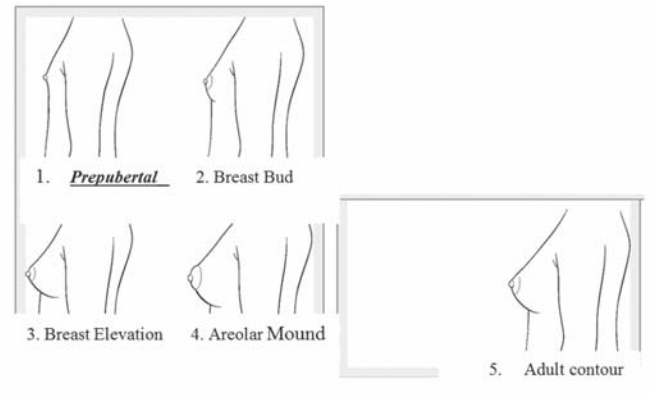

Figure 1. Tanner staging for breast development
(Clinical Gynecologic Endocrinology& Infertility, 7th Edition by Speroff p.378)

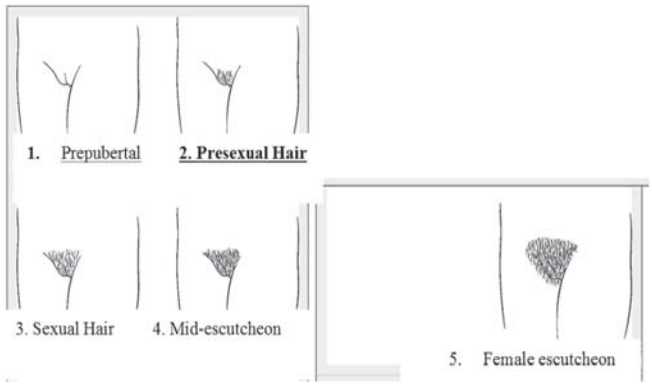

Figure 2. Tanner staging for pubic hair distribution
(Clinical GynecologicEndocrinology & Infertility, 7th Edition by Speroff p.379)

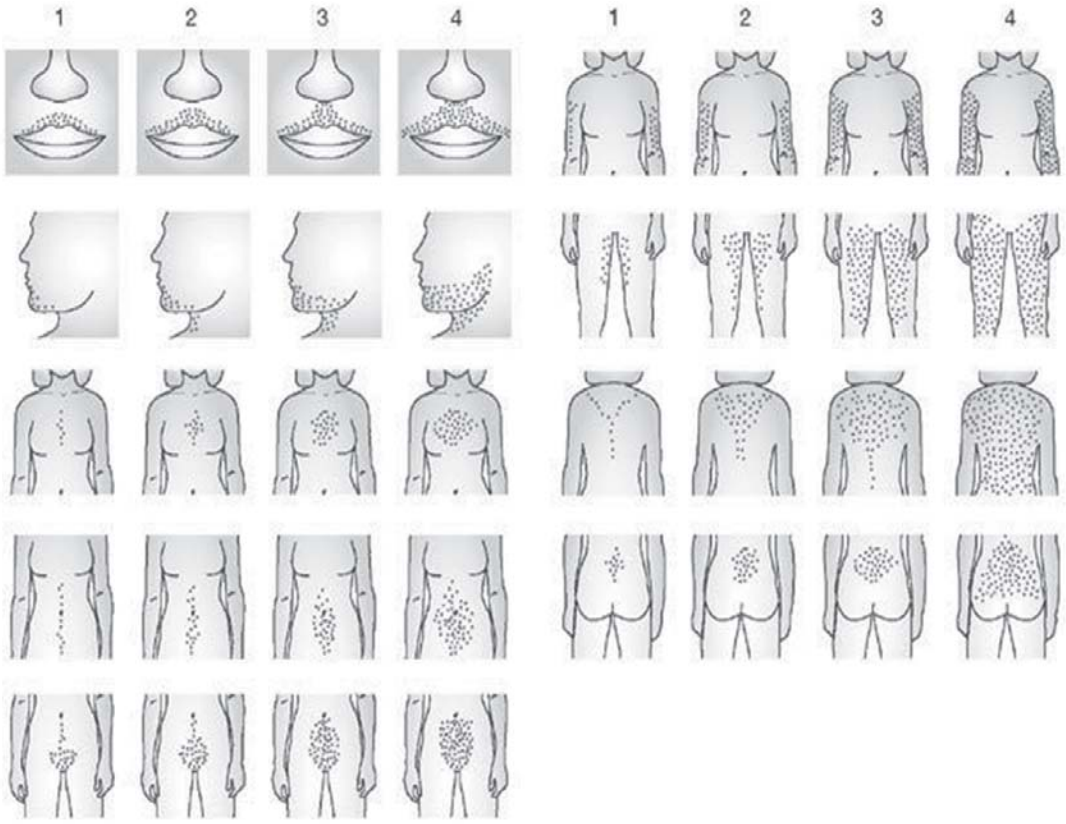

Figure 3. The modified Ferriman-Gallwey scoring system for hirsutism.
Each of the nine body areas is rated from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth) and the numbers in each area are added to obtain the total score. A score 6-8 generally defines hirsutism.

Reference: Azziz R et al. (2006) Androgen Excess Disorders in Women: Polycystic Ovary Syndrome and Other Disorders, edn 2. Totowa, NJ: Human Press. Assessment, diagnosis and treatment of a patient with hirsutism. Bulent O Yildiz Nature Clinical Practice Endocrinology & Metabolism (2008)

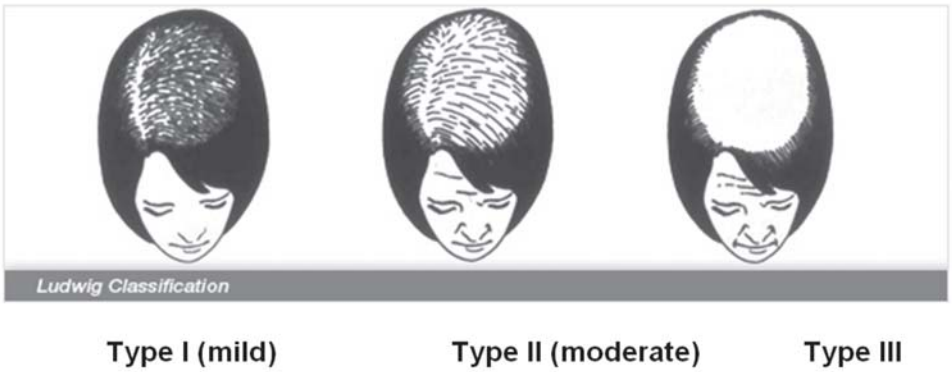

Figure 4. Ludwig scale for alopecia

Type I. In this stage, hair loss is considered to be mild. Most women may have difficulty noticing that hair loss has occurred, as the frontal hairline remains relatively unaffected. Hair loss may occur on the top and front of the scalp, however. Such hair loss may be noticeable when the hair is parted down the center of the scalp, as more and more scalp will become visible over time.
Type II. Type II hair loss is considered moderate. In this stage, women may notice each of the following: Thinning, shedding, general decrease in volume, and a center part that continues to widen over time. Depending on the severity, a hair transplant procedure may be a viable option for women who exhibit a Type II classification.
Type III. Type III is the final and most extreme classification of female hair loss. In this stage, hair is so thin that it has difficulty camouflaging the scalp, rendering it visible to the naked eye. This may be worsened by a number of factors, including hair miniaturization, progressive thinning, and extensive loss.

Reference: J Cutan Aesthet Surg 2016 Jan-Mar; 9(1): 3-12

monosomy X with an isochromosome of the long arm of chromosome X. The chromosome analysis showed two abnormal cell line consistent with the diagnosis of variant Turner syndrome. The first cell line, seen in 42 cells, showed an isochromosome of the long arm of the X chromosome. The remaining 8 cells showed a loss of one X chromosome, resulting in monosomy X. (Figure 5)

Hormonal evaluation revealed a hypergonadotropic (markedly high serum follicle stimulating hormone and elevated luteinizing hormone) and hypogonadism state (low serum estrogen). Serum prolactin, thyroid function tests, antithyroglobulin antibody and androgens were within normal limits. Second hour 75 grams oral glucose tolerance test was elevated indicating insulin resistance (Table 2).

Auditory, ophthalmologic, cardiac, and renal evaluations revealed normal results. The patient was started on metformin and cyclic antiandrogenic combined oral contraceptives. Lifestyle modification and counselling was also advised. For the past 7 months, she has reported cyclic withdrawal bleeding with the hormonal therapy. Two months within the therapy, breast mound was noted. Five months after starting hormonal therapy, she reported decrease in alopecia and hair growth.

Final diagnosis is Isochromosome Mosaic Turner Syndrome.

Discussion

The classic 45,X karyotype of turner syndrome is the most common type. The 45,X chromosome constitution is a consequence of meiotic non-disjunction or chromosome loss during gametogenesis in either parent. This results in a

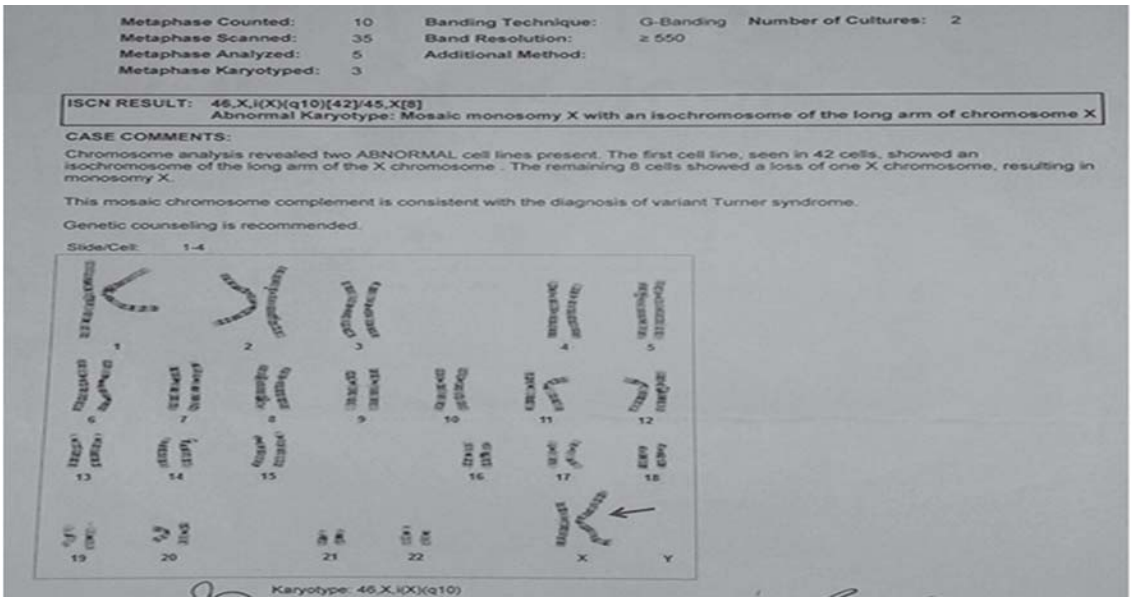

Figure 5. Chromosomal analysis of the patient.

Table 2. Laboratory results of the patient.

Examination	Result	Normal Range
Follicle Stimulating Hormone	101 mIU/ml	Menopausal: 17.0-95.0 mIU/ml
Luteinizing Hormone	20.8 mIU/ml	Menopausal: 8.0-33.0 mIU/ml
Serum prolactin	1.8 ng/dL	1.3 - 25ng/dL
Estradiol	10 pg/ml	Postmenopausal: Non-detected- 14 pg/ml
Serum androgens		
DHEAS	4.2umol/L	3.92-10.66 umol/L
Testosterone	0.23ng/ml	0.1-0.9 ng/ml
17OHP	0.37 ng/ml	Pre/postmenopausal<2ng/ml
Thyroid Function Tests		
Thyroid Stimulating Hormone	1.8 IU/ml	0.25-5.0 IU/ml
Free T4	1.24 pmol/L	9-20 pmol/L
Free T3	5.03 pmol/L	4.0-8.3 pmol/L
75gm OGTT		
FBS	5.27 mmol/L	3.89-5.5 mmol/L
1 hour	9.7 mmol/L	<10.8mmol/L
2 hour	9.39 mmol/L	<8.0 mmol/L
Lipid Profile		
Total Cholesterol	4.8mmol/L	<5.2mmol/L
Triglycerides	1.2mmol/L	<2.26mmol/L
HDL	1.2mmol/L	≥0.9mmol/L
LDL	2.2 mmol/L	≤3.36mmol/L
Renal Profile		
Creatinine	63 µmol/L	62-133µmol/L
BUN	6.2 mmol/L	2.5-7.1mmol/L
Liver Profile		
AST	12 U/L	14-59 U/L
ALT	16 U/L	9-72 U/L

sperm or ovum which lacks one sex chromosome. Since the single X chromosome is maternally derived in 80% of the cases, the genesis of the 45,X karyotype in turner syndrome is due to instability of the Y chromosome leading to its loss during meiosis.[6,7]

Mosaicism is defined as the presence of 2 or more cell lines with different chromosomal constitutions. The cell lines are derived mostly from postzygotic mitotic non-disjunction. Cases of mosaicism are classified according to whether the second cell line contains a whole or part of a sex chromosome. An isochromosome (i) is a structurally abnormal chromosome consisting of 2 short (referred to as Xp) or 2 long (referred to as Xq) arms. The index patient had a chromosomal analysis of 46,X,i(X)(q10)[42]/45,X[8] indicating an isochromosome of the long arm of chromosome X in the first line and monosomy X in the second cell line. Isochromosome Mosaic Turner Syndrome (IMTS) is a variant of Turner syndrome characterized by cytogenetic profile of 1 or more additional cell lineages aside from 45,X, and the presence of a structurally abnormal X chromosome consisting of either two short or two long arms. IMTS is rare, with only 8-10% prevalence among women with Turner syndrome based on international studies.[6] Individuals with i(Xq), as in the patient, show characteristics similar to individuals with the classical 45,X Turner syndrome. In the absence of Y chromosome, hirsutism is not commonly seen in patients with Turner syndrome. If such a complaint is present in nonmosaic 45, X karyotype, a Y cell line must be excluded using fluorescence in situ hybridization (FISH) analysis. Extensive literature search revealed one case of a 20 year old with isochromosome mosaic Turner syndrome who also presented with alopecia, which was resolved with hormonal therapy.[8] Discussion with the cytogenetic laboratory and normal serum androgen levels established hyperandrogenism in the absence of Y chromosome and any adrenal source thus making this a more interesting case.

Other variants such as those with a deletion of Xp have short stature and congenital malformations, and those with a deletion of Xq often display only gonadal dysgenesis.

Diagnosis is based on clinical presentation. Short stature is the most common clinical feature and the only consistent phenotypic finding. It is present in at least 95% of individuals with Turner syndrome with nearly all patients being less than 5 feet in stature. This characteristic depends on the deletion of the short stature Homeobox (SHOX) gene on chromosome X[2]. The typical growth pattern in Turner syndrome is characterized by mild intrauterine growth restriction, slow growth during infancy, delayed onset of childhood growth and absence of pubertal growth spurt. There is a higher risk for scoliosis and kyphosis than the general population. The development abnormalities of the bones result in short neck, cubitus valgus, and short fourth metacarpal.[9] The patient was noted to have slow growth during infancy and childhood. She has short stature and short neck.

Another common feature is the absence of pubertal development. Patients with classic Turner syndrome have ovarian dysgenesis and streak gonads. Absence of estrogen from the gonads leads to failure of development of secondary sexual characteristics and the patients also often present with primary amenorrhea. Mosaic and isochromosome Turner syndrome patients are more likely to develop normal pubertal development, regular menstrual cycles and to conceive spontaneously compared to those with 45,X. Up to 30% of patients with Turner syndrome will undergo spontaneous pubertal development, 5-10% will menstruate regularly and 2-5% can conceive spontaneously.[10,11] The index patient clearly experienced menarche at the age of 17 but this was not followed by subsequent menstrual cycles. Although it may be more likely that patients with Turner mosaicism have ovarian function, that does not necessarily indicate persistent ovarian function. In Turner mosaics who experience spontaneous ovarian function, premature ovarian failure is a frequent occurrence with the mean age of menopause reported to be at 29.3 years.[11]

Women with Turner syndrome should not routinely be assumed to be infertile. Those individuals who undergo spontaneous puberty and who menstruate may have the potential to achieve spontaneous pregnancy, although most women with Turner syndrome will suffer from primary

infertility and would require infertility treatment by oocyte or embryo donation in order to conceive. Pregnancies resulting from spontaneous ovulation and fertilization in Turner syndrome patients occurs in patients with mosaic karyotype containing 46XX cell line or in patients with structural abnormalities of chromosome X in which the genes thought to control ovarian function are spared. The retained fertility among women with variant Turner syndrome is presumably due to partial synapsis occurring at meiosis in 46,X, abnormal X oocytes, resulting in equal frequencies of gametes carrying either normal X or abnormal X chromosome under 1:1 segregation.[9] Spontaneous pregnancy, although extremely rare, can occur and carries risks for the fetus and the woman concerned. Turner syndrome is a relative contraindication to pregnancy. When patients with Turner syndrome conceive spontaneously, there is an increased risk of spontaneous abortion, stillborn, congenital anomalies, and aneuploidy. Only about 30% of pregnancies may have a normal outcome. The risk of Down syndrome is 5% and the recurrence risk of a 45,X fetus is about 10%.[7] In addition, women with Turner syndrome have increased risk for cardiovascular morbidity and mortality (particularly related to aortic dissection) during pregnancy with the risk of death being estimated as 100 times the normal risk. This can occur in natural pregnancies or those resulting from oocyte donation. Women who are considering a pregnancy require preconceptual advice and genetic counselling, as well as full medical evaluation. The index patient is young, had spontaneous menarche and responds to hormonal therapy. The chances of spontaneous conception as well as the risks it entails has been discussed with the patient and her family. Although fertility is an important issue in the management of women with Turner syndrome, there are also some, including the patient, who may require contraceptive advice. Sexual function is normal in patients with Turner syndrome since there are no structurally abnormalities of the vagina; although lubrication might be a problem. As with any other young woman, the patient was advised regarding safe sex, prevention of sexually transmitted infections and the need for cervical cytology.

Intellectual development in patients with Turner syndrome is usually normal; except in patients with a ring X chromosome, who have a greater risk of showing a variable intellectual deficit.

Women with Turner syndrome have greater morbidity and mortality, caused mainly by cardiovascular lesions. Bicuspid aortic valve (13-34%) and coarctation of the aorta (4-14%) are the most common abnormalities. Patients with Turner syndrome also have an increased risk of other conditions such as hypertension, hypothyroidism, diabetes and dyslipidemia. Patients with the isochromosome karyotype are at a higher risk for hypothyroidism and mild mental retardation[6]; both of which were not present in the index patient.

The hypergonadotrophic hypogonadism puts these patients at risk for osteoporosis. Decreased estradiol secretion causes lower bone mineral density (BMD). Hormone replacement therapy (HRT) is a crucial treatment to prevent decrease in BMD, to induce maximum bone mass peak in young women and for subsequent maintenance of adequate bone mass. Natural pregnancies have been reported in amenorrhoeic women with Turner syndrome who were receiving HRT. In those whom the degree of infertility has not been established there may be a need for contraceptive advice. Combined oral contraceptives would seem a reasonable choice for these patients who are at risk for osteoporosis; however, the risk of hypertension and cardiac disease in these patients may be a relative contraindication to hormonal therapy. The index patient was screened for cardiovascular disease prior to initiation of hormonal therapy.

Proper timing of treatment with growth hormone can improve lean body mass and can help achieve normal adult height. Growth hormone therapy should be initiated early around 4-6 years of age and before 12-13 years old.[4] At 22 years of age, growth hormone is no longer recommended for the patient.

Further recommendations made by latest 2016 clinical practice guidelines for the care of girls and women with Turner syndrome from the Cincinnati International Turner Syndrome Meeting were discussed with the patient and include the

following: 1) formal audiometric evaluation every 5 years; 2)cardiac surveillance studies every 5 years in children, every 10 years in adults or prior to anticipated pregnancy; 3) annual assessment of blood pressure; 4) annual screening for hypothyroidism; 5) annual evaluation of HbA1C and lipid profile; 6) clinical evaluation of scoliosis every 6 months while on growth hormone therapy; 7) dual energy x-ray absorptiometry after hormone replacement therapy has been started; 8) comprehensive ophthalmological evaluation; 9) annual liver function tests and 10) renal ultrasound at the time of diagnosis.[4]

Individuals with Turner syndrome may experience psychosocial difficulties such as increased risk of social isolation, disorders related to anxiety and difficulty for couple relationships. They may experinece delayed exit from parental home and late start of sexual life.[12] However, most women with Turner syndrome get a good education and find paid jobs, as noted in the patient.

Conclusion

Early recognition of Turner syndrome and timely investigations should help in improving the quality of life of these individuals by improving adult height, and psychosocial health. Also, early detection and management of co-existing illnesses may be life-saving for these patients.

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