The Link Between the Missing Menses and a Missing Long Arm: A Case of a Variant Turner Syndrome*

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Primary amenorrhea in a 20 year old becomes alarming especially when the woman desires to conceive a child. This paper reports a case of a 20 year old nulligravid with a chief complaint of absence of menses since puberty. Timely diagnosis with thorough clinical history, physical examination and appropriate ancillary procedures like karyotyping led to the diagnosis of sexual chromosomal anomaly. The initial and repeat transvaginal ultrasound reported ovarian hyperthecosis and infantile uterus, respectively. Karyotyping test revealed 46X with terminal deletion of long arm of Chromosome X with break at band Xq21 while serum follicle stimulating hormone (FSH) revealed an elevated result. Primary amenorrhea along with development of secondary sexual characteristics and abnormal karyotyping test, the patient fulfills the criteria of a rare case of variant Turner syndrome. This case discusses the valuable collaboration between the Obstetrician-Gynecologist, Reproductive Endocrinologist, Geneticist and patient for proper evaluation, diagnosis, and management.

Key words: chromosome x long arm deletion, infantile uterus, primary amenorrhea, variant Turner syndrome

Introduction

It was Henry Turner in 1938 who first described seven cases of rather uniform appearance of women with sexual infantilism, primary amenorrhea, webbing of neck, and cubitus valgus. He named this condition as "Turner Syndrome."[1] This syndrome was eventually discovered as the presence of only one normal functioning X chromosome while the other sex chromosome can be missing or can be abnormal.[2]

The presenting clinical features of patients affected with Turner syndrome can vary widely, such as presence of short stature and gonadal dysgenesis that are almost universal in this condition. Many other organ systems are also affected to varying degrees and at different stages of life.[3] Almost all women with Turner syndrome are infertile, although some conceive with assisted reproduction.[4]

On the other hand, primary amenorrhea is the failure of menses to occur by the age of 16, in the presence or absence of normal growth and secondary sexual characteristics. If by the age of 13, menses has not started yet, and onset of puberty, such as breast development, is absent, a workup for primary amenorrhea should be started. However, in any woman of reproductive age presenting with amenorrhea, the first etiology that should be ruled out is pregnancy, and then followed up with investigation for other possible causes of primary amenorrhea.

The psychosocial impact of Turner syndrome may be substantial for affected women of reproductive age. These effects may be caused by infertility, physical abnormality like short stature

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and impaired development of sexual characteristics. Physicians should elicit specific concerns from patients, addressing them individually, and should offer a comprehensive physical and psychoeducational assessment.[6]

The Case

This is a case of G.D.C, a 20 year old nulligravid, Filipino, with live-in partner for 1 year, who consulted at the outpatient clinic of our institution with a chief complaint of primary amenorrhea. The patient did not have any menstrual periods since she noted her breast development at age 14 and growth of pubic hair at the age of 12. There were no associated signs and symptoms noted such as hypogastric mass nor cyclic hypogastric pain. Patient had not consulted previously due to financial constraints, however, her desire to get pregnant prompted her to seek medical help.

The past medical history and family history were unremarkable. Her mother's prenatal course was likewise unremarkable. Her mother claimed to have regular prenatal check-ups and denies history of infections, exposure to teratogenic chemicals or history of trauma. The patient had unremarkable course of birth. Patient had no noted developmental delays in the gross motor, fine motor, language, and personal and social spheres. Patient was at par with age. Pubarche was at 12 years of age, while thelarche was at 14 years of age.

By age 20, patient did not have her menarche. She had her first coitus at 20 years old while in a monogamous relationship. She denied history of dyspareunia. Patient had no history of use of oral contraceptive pills. She had no Pap smear done. She was a non-smoker and non-alcoholic beverage drinker. She denied use of any illicit drugs.

On physical examination, patient was conscious, coherent, and ambulatory, with stable vital signs. She had normal built and stature, with Body Mass Index (BMI) of 20.8 (Figure 1). There was no webbing of the neck nor axillary hair noted (Figure 2). Breasts were symmetrical, both form small mounds, with small area of surrounding glandular tissue, slightly elevated, extending slightly beyond the borders of the areola, which were small and narrow (Figure 3), noted to be Tanner Stage 2-3. The external genitalia was grossly normal. Pubic hair was coarse and curly and slightly extended laterally from the labia (Figure 4), with presence of hymenal ring (Figure 5). On speculum exam vaginal wall was smooth, cervix was pinkish and smooth, with no masses, lesions, erosions, nor bleeding noted. On internal examination, cervix was atrophic, approximately 1cm x 0.5 cm, firm and closed, uterus was non-palpable. No adnexal mass nor tenderness noted.

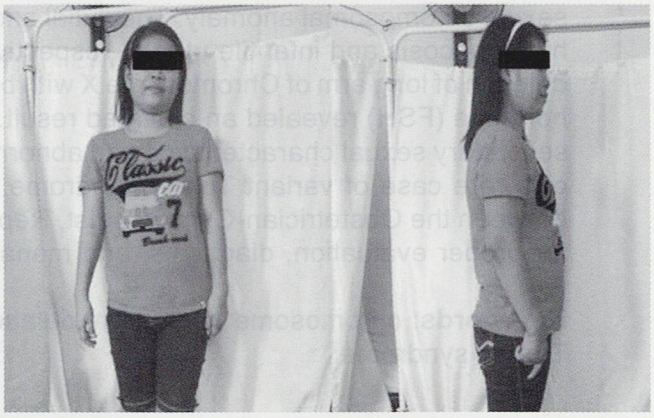


Figure 1. The patient, showing normal built and normal stature, with average height (1.54 meters) and weight (49 kgs) with Body Mass Index (BMI) of 20.8.

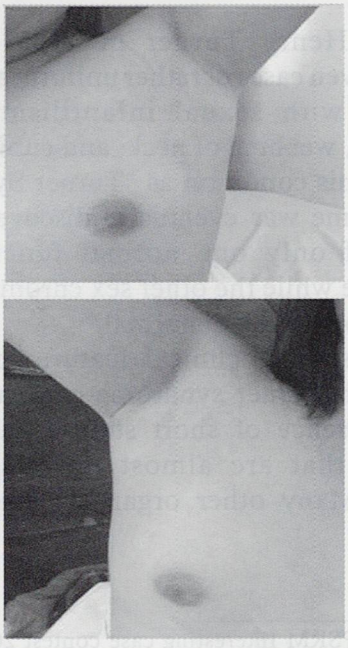


Figure 2. Absence of axillary hair

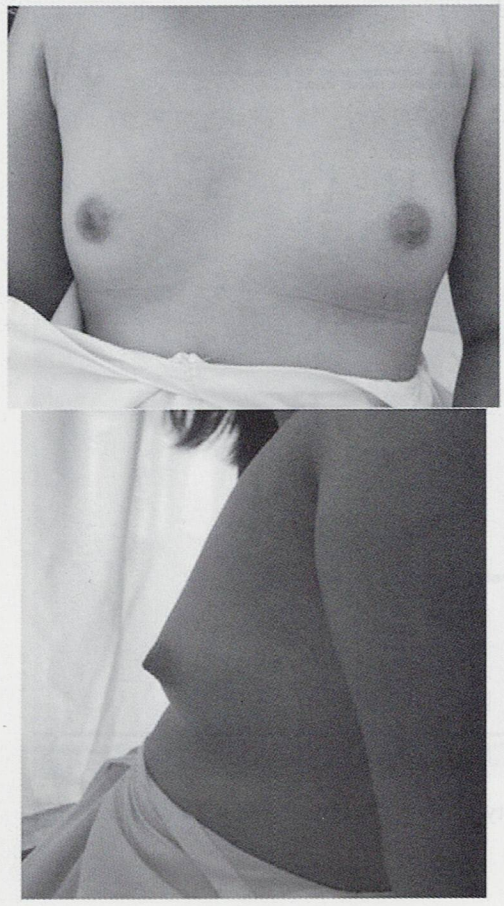


Figure 3. Patient's breasts forming small mounds, with small area of surrounding glandular tissue, slightly elevated, extending slightly beyond the borders of the small areola (Tanner Stage III).

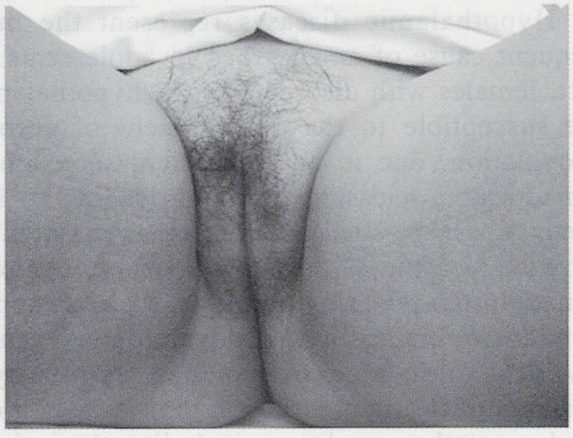


Figure 4. Pubic hair coarse and curly and slightly extends laterally from the labia (Pubic Hair Tanner Stage III).

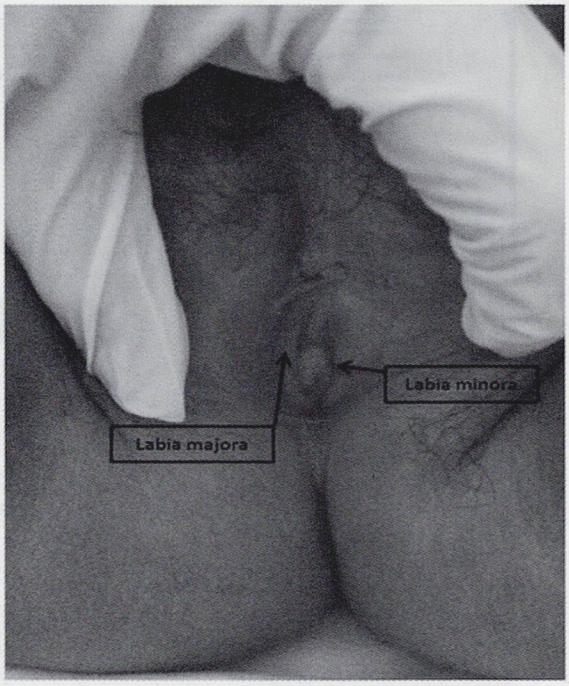


Figure 5. External genitalia grossly normal. Hymenal ring present.

Patient presented a previous ultrasound result which revealed ovarian hyperthecosis. She was referred to Reproductive Endocrinology and Infertility (REI) service. A repeat ultrasound revealed an infantile uterus. Serum FSH assay was noted to be high at 67.8 mIU/ml and karyotyping revealed a chromosome analysis of 46,X, del(X)(q21) (Figure 6). The assessment was Primary Amenorrhea secondary to Turner syndrome - Variant type, Primary Infertility for 1 year, Nulligravid. Patient was advised to start on low dose oral contraceptive pills (OCP) in the form of Gestodene 0.075 mg + Ethinylestradiol 0.02 mg (Meliane) for 2 cycles then was advised to come back for follow up. Patient was also advised to undergo blood chemistry test, bone densitometry scan, 2D-Echocardiography (2D Echo) and to consult a cardiologist for co-management.

Discussion

In the general population, the first menstrual cycle takes place between 12 and 13 years of age,

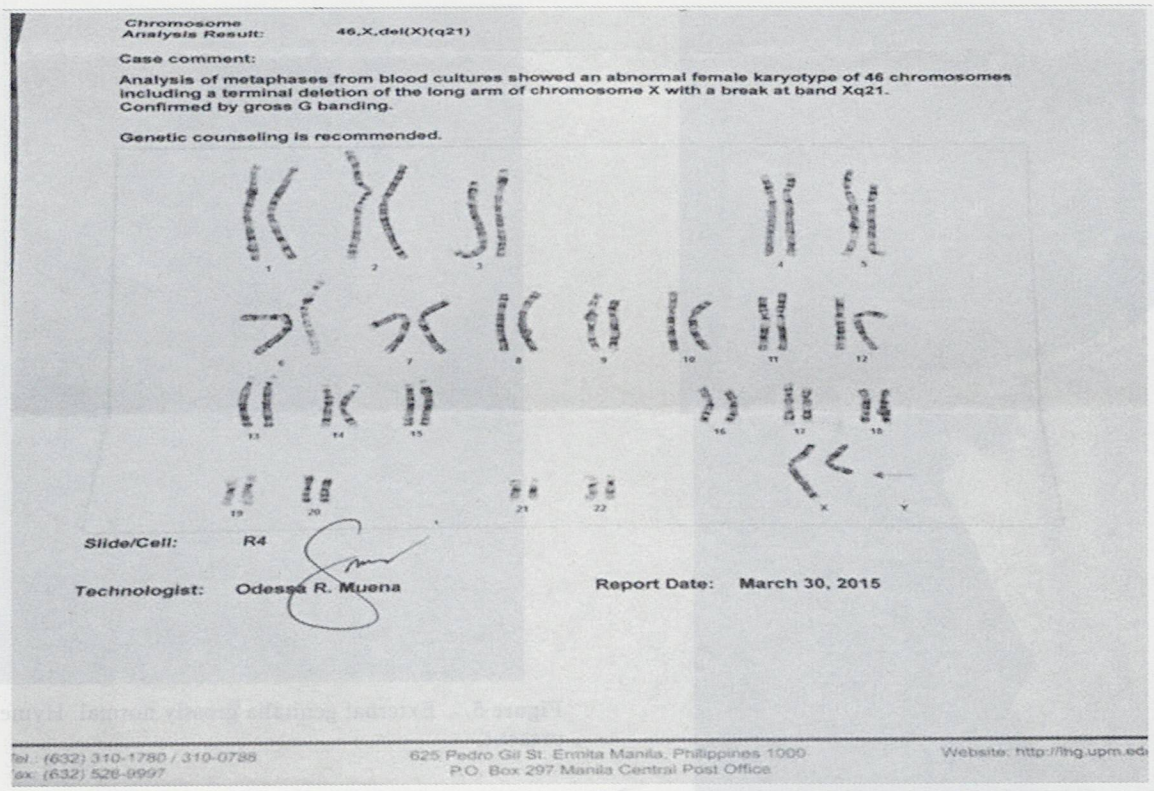


Figure 6. Karyotyping test result an abnormal female karyotype of 46 Chromosomes with deletion long arm of Chromosome X with a break at band Xq21.

but a majority have their menarche by 15 years of age. This stage is called puberty, and begins between 8 and 14 years of age in girls.[7] Adrenarche and gonadarche are the two processes that contribute to the physical manifestations of puberty. Normally, girls begin puberty with breast buds and skeletal growth, followed by the appearance of pubic hair, axillary hair and menarche, as described by Tanner staging (Figure 7).

Amenorrhea is defined as primary when menarche does not occur by the age of 16 years in a female with complete secondary sexual development, or by the age of 14 years in a female without secondary sexual development. On the other hand, it is secondary when menstrual cycles disappear for 6 consecutive months in a female with irregular menses or for 3 consecutive months in a female with regular menses.[8]

Primary amenorrhea can be caused by genetic or anatomic abnormality. It includes hypergonadotropic hypogonadism (48.5% of cases), hypogonadotropic hypogonadism (27.8%), and eugonadism (pubertal delay with normal gonadotropins; 23.7%). Hence, complete history taking and physical examination are necessary in order to achieve proper assessment and management.[8,9]

Hypothalamic diseases represent the most frequent cause of amenorrhea in adolescents. In fact, females with disorders of the hypothalamus are susceptible to the development of chronic anovulation, due to an insufficient secretion of gonadotropin-releasing hormone leading to low levels of basal plasma gonadotropins and estradiol. However, after stimulation with exogenous gonadotropin-releasing hormone, the secretion of gonadotropins is in the physiological range. Hypothalamic amenorrhea has frequently a dysfunctional origin, although in rare cases it can be due to other conditions including the isolated deficit of gonadotropins, chronic diseases, infections, and tumors.[9,10]

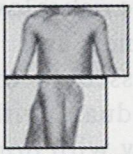
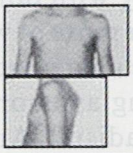
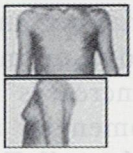
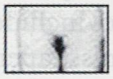
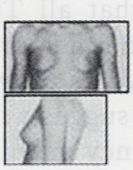
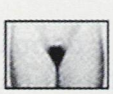
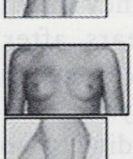
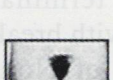
Tanner stage	Breasts*	Standard	Pubic hair*	Standard	Growth	Other
1	Prepubertal, elevation of papilla only		Prepubertal, villus hair only	—	Basal: about 5.0 to 6.0 cm (2.0 to 2.4 in) per year	AdrenarcheOvarian growth
2	Breast bud appears under enlarged areola (11.2 years)		Sparse growth of slightly pigmented hair along the labia (11.9 years)		Accelerated: about 7.0 to 8.0 cm (2.8 to 3.2 in) per year	Clitoral enlargementLabia pigmentationUterus enlargement
3	Breast tissue grows beyond areola without contour separation (12.4 years)		Hair is coarser, curled and pigmented; spreads across the pubes (12.7 years)		Peak velocity: about 8.0 cm (3.2 in) per year (12.5 years)	Axillary hair (13.1 years)Acne (13.2 years)
4	Projection of areola and papilla forms a secondary mound (13.1 years)		Adult-type hair but no spread to medial thigh (13.4 years)		Deceleration: < 7.0 cm (2.8 in) per year	Menarche (13.3 years)Regular menses (13.9 years)
5	Adult breast contour with projection of papilla only (14.5 years)		Adult-type hair with spread to medial thigh but not up linea alba (14.6 years)		Cessation at about 16 years	Adult genitalia

Figure 7. The Tanner stages 7of puberty in girls are based on breast size and shape and pubic hair distribution. Mean age of milestone attainment is shown in parentheses for the reference population of Marshall and Tanner. Actual age at milestone attainment may vary among individuals and among different study populations.

Hypergonadotropic hypogonadism can be due to several conditions including gonadal agenesis or dysgenesis, premature ovarian insufficiency and enzymatic deficiency.[10]

In cases presenting with amenorrhea, pregnancy should always be ruled out first. After pregnancy is excluded, a thorough history, physical and pelvic examination should be done. Ultrasound is done to confirm presence of uterus and to document any anatomic abnormality. If no anatomic abnormality is noted, laboratory examinations such as Thyroid Stimulating Hormone, serum Estradiol, Prolactin, Luteinizing Hormone, and Follicle Stimulating Hormone may rule out other endocrine causes of amenorrhea. For our index case, serum FSH was elevated. which points to an impression of Primary Ovarian Insufficiency. In such case, a variety of disorders such as X-chromosome abnormality, Turner syndrome, FSH receptor deficiency, and autoimmune gonadal destruction may be considered. The patient also presented with an ultrasound result of an infantile uterus, hence an anatomic abnormality was likewise present. To further evaluate what specific condition this case is, karyotyping was requested.

Among the different sex chromosome abnormalities, Turner syndrome is the most common, accounting for 80.1% of the cases, and 38.9% of these cases are the classic type of Turner syndrome.

Turner syndrome or Bonnevie-Ulrich syndrome is a chromosomal disorder presenting with gonadal dysgenesis characterized by sexual infantilism, short stature and somatic anomalies. It occurs in approximately 1 in every 2,500 to

3,000 live female births. The diagnosis of Turner syndrome is performed on the basis of typical phenotypic characteristics in females having partial or total absence of one X chromosome, with or without mosaicism. In approximately 50% of cases it is associated with complete or partial absence of an X chromosome (45X karyotype). Other forms include mosaics, which are a combination of 45X and abnormal 45XX cell line, as well as several other karyotype variations, as in the case being presented. In addition to delayed puberty and primary amenorrhea, other clinical features include short stature, webbed neck, low hairline, misshapen ears, widely spaced nipples, broad chest, cubitus valgus, cardiac anomalies like coarctation of the aorta, and a horseshoe kidney.[11,12]

For the index case, the findings of a normal female phenotype, absence of growth retardation, presence of secondary sexual characteristics and karyotyping test result of 46X with terminal deletion of long arm of chromosome X with break at band Xq21, confirm the diagnosis of Non-typical or Variant case of Turner syndrome.[13]
Most patients with deletion of one long arm of chromosome X (q13 or 21 and greater) have milder or no Turner stigmata and primary amenorrhea. Oligomenorrhea with or without secondary amenorrhea occurs in a minority of patients. Final height is mostly between 1.50 to 1.65 meters; thus the characteristic short stature tends to be absent or milder than those in patients with 45X Turner syndrome.

Furthermore, one of the most frequent characteristics of Turner's syndrome is the lack of pubertal development. In fact, although the ovaries develop normally, they degenerate during intrauterine life and infancy. Among the cases of Turner's syndrome, more than 90% of females will present with gonadal failure. However, approximately 30% of these patients will present with natural pubertal development, and menses will occur in 2 to 5% of girls having 46XX / 45X mosaicism due to a normal oocyte amount ,and in some populations about 5% of girls with Turner syndrome will present with spontaneous pregnancy.[13,14]

Turner syndrome is a lifelong condition. Most live long and healthy lives, but some are susceptible to numerous chronic conditions. Turner syndrome is not an inherited disorder, and the recurrence risk is low. Because of primary ovarian insufficiency and infertility, the syndrome is rarely passed to offsprings.[14] Although almost all individuals with this disorder are infertile, pregnancy with donor embryos is possible. Five percent or more of women with Turner syndrome may have abbreviated menstrual function before developing amenorrhea and hypergonadotropic hypogonadism. An estimated 1 to 2% of all patients may become pregnant. Pregnancy, either spontaneous or more commonly from donor oocyte, increases maternal mortality rate for these women by an estimated ≥100 fold. It appears that all Turner women are at risk of rupture; neither prior spontaneous menses nor age >30 years provides protection. In addition, literature suggests that the physiological changes of pregnancy may increase the risk of rupture in future years after delivery for those Turner women who seemingly made it safely through pregnancy.[14]

According to world literature, only two women with Turner syndrome, hypergonadotropic amenorrhea, and streak ovaries have ever become pregnant spontaneously after their diagnosis. It would be unfair to such women with Turner syndrome to give them the same hope for pregnancy as we do for women with 46XX POI. Nonetheless, amenorrheic women with Turner syndrome truly have ovarian failure.[14,15]

With our inex case, it is most important to have honest, thorough, and compassionate counselling. The management of Turner is usually multidisciplinary and each case is treated on its own merit. Available treatment options include sex hormonal replacement for hypogonadism, and prevention of osteoporosis. The patient did not need growth hormone replacement, because she did not present with short stature. It was, however, important to prevent osteoporotic complications early. Adequate daily intake of calcium (1.0-1.5 g) and vitamin D (at least 400 IU) was taken.

Patients with Turner syndrome should seek consult with a cardiologist. Patients with systemic hypertension or aortic valve anomalies are at higher

risk for aortic dissection. Patients found to have significant anomalies should have long-term follow-up care and possibly Sub-acute Bacterial Endocarditis (SBE) prophylaxis. Due to the risks of aortic root dilatation and mortality due to aortic dissection, cardiac evaluation, including echocardiography, is recommended every 5 years, even in patients with normal findings on initial cardiovascular examination. Patients contemplating pregnancy should have a complete cardiovascular evaluation prior to attempting assisted reproduction or conception. Patients with a bicuspid aortic valve, coarctation of the aorta, or dilation of the aorta have a higher risk of dissecting aortic aneurysm or rupture.[14,15]

Almost a third of patients have renal anomalies that may require evaluation and follow-up care by a nephrologist. At a minimum, such patients should have a yearly urine culture and an annual measurement of BUN and creatinine levels. Patients with horseshoe kidneys have an increased risk for Wilm's tumor, and are therefore advised to undergo renal ultrasound every 4 to 6 months until the age 8 years and every 6-12 months thereafter.[15]

Patients are also well advised to avoid obesity because it increases risk of hypertension and insulin resistance. Physical activity should be encouraged as prevention for obesity and osteoporosis. Eligibility for competitive sports should be established by a cardiologist after a comprehensive evaluation including 2D echocardiography.[16]

At present, it is recommended that adolescent women with Turner syndrome should receive cyclical estrogen and progestin hormonal replacement. The type and dose should be individualized, using the symptoms, physical findings and bone density studies. Sufficient estrogen should be prescribed to prevent the signs, symptoms and sequelae of estrogen deficiency. Proper counselling on issues of sexuality and fertility should also be rendered as part of healthcare program of patients with Turner syndrome. Consideration of referral to other medical specialty like endocrinologists, geneticists and psychotherapist should likewise be done.[17]

Summary

Amenorrhea occurs in Turner syndrome due to an anatomic abnormality in the reproductive system. Turner syndrome is a chromosomal disorder presenting with gonadal dysgenesis characterized by sexual infantilism, short stature and somatic disorders. Variant Turner syndrome is very rare. It presents with no growth retardation and well-developed secondary sexual characteristics, but with undeveloped ovaries, just like in the patient presented in this case. Overall prognosis for patients with Turner syndrome is good. Life expectancy is slightly shorter than average but may be improved by attention to associated chronic illnesses, such as obesity and hypertension. Almost all individuals are infertile, but pregnancy with donor embryos is possible. With such patients, good counselling is of primary importance.

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