Mayer Rokitansky Kuster Hauser Syndrome with Concomitant Turner Syndrome Presented with Primary Amenorrhea in an 18 Year Old Woman: A Case Report

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Primary amenorrhea is a symptom caused by different rare pathologic conditions. It is commonly seen during adolescence due to the absence of menses during this period. Presented here is a rare case of primary amenorrhea in an 18 year old girl with delayed pubertal growth and short stature which on series of investigations revealed hypergonadotropic hypogonadism, absence of the uterus and non-visualized bilateral ovaries on MRI. Karyotyping showed 45,X0. The coexistence of MRKH and gonadal dysgenesis was considered in this case and has been reported in only a few studies up to this date. Its association is uncommon, hence, a multidisciplinary approach is warranted for the management of her case. Further implications on menses and future fertility options are the main considerations, affecting the quality of life.

Key words: Primary amenorrhea, Turner syndrome, Mayer Rokitansky-Kuster-Hauser (MRKH) syndrome

Introduction

Puberty is a defining moment in an adolescent's life. It is a transitional period between childhood and adulthood during which a growth spurt occurs, secondary sexual characteristics appear, fertility is achieved, and profound psychological changes take place.

Amenorrhea is defined as the absence of menses. It has 2 types: primary and secondary amenorrhea. Primary amenorrhea is defined as the absence of menses by 14 years of age in the absence of growth or development of secondary sexual characteristics or absence of menses by 16 years of age regardless of the presence of normal growth and development including secondary sexual characteristics.[1] On the other hand, secondary amenorrhea is the cessation of previously regular menses in a woman who had experienced menstrual bleeding for 3 normal cycles or for more than 6 months.[1,2]

The two most common causes of primary amenorrhea are Mayer-Rokitansky-Küster-Hauser (MRKHS) syndrome and Turner syndrome.

Turner syndrome which occurs in about 1 in 2,500 newborn girls worldwide, is a chromosomal disorder wherein there is partial or complete absence of the X chromosome in females.[3]

MRKH has an incidence rate of 1 in 4000 to 5000 births of female sex children.[1] It is defined as the congenital agenesis of the upper two-thirds of vagina and uterus in women with normal secondary sexual characteristics and female karyotype (46, XX).[4]

This paper presents a rare case of primary amenorrhea in an 18 year old girl with delayed pubertal growth and short stature, which on series of investigations, revealed hypergonadotropic hypogonadism, absence of uterus and non-visualized bilateral ovaries on MRI, and a karyotype of 45,X0. Management of this case

as well as a review of related literature shall be discussed.

The Case

This is a case of T.G., an 18-year-old female, single, born and raised in Sta. Cruz, Manila. T.G. consulted at this institution due to primary amenorrhea, absence of secondary sexual characteristics, and short stature.

She had no history of childhood illnesses, such as measles, mumps, chickenpox. Patient has no known allergies to food and drugs. She denied any history of accidents, trauma, or major illnesses such as hypertension, diabetes mellitus, or asthma. She has no history of exposure to radiation and toxic chemicals. Patient had been admitted on three occasions (2002, 2005, 2019) due to anemia with an initial impression of Iron Deficiency versus Thalassemia.

The patient has no family history of congenital anomalies, cancer, arthritis, blood disorders, tuberculosis, kidney disease, heart disease, epilepsy, mental disorders, hypertension, allergies and asthma.

Patient's height for age is severely stunted as plotted in the World Health Organization's z-score chart.

Other developmental aspects is at par with age with no noted delays in the gross motor, fine motor, language, personal, social and mental spheres.

Patient is a high school undergraduate and is currently an online seller. Patient is neither an alcoholic beverage drinker nor a smoker, and denied use of any illicit drugs.

Patient was amenorrheic since puberty. There was also absence of breast development and pubic hair. Patient denied any sexual intercourse.

On physical examination, patient was ambulatory, weighed 28 kg and stood at 123 cm with a BMI of 18.5 kg/m^2.

On examination, her vital signs were as follows: BP 110/80 mmHg, CR 71 bpm. RR 20bpm and afebrile at 36.5°C. CNS, pulmonary, cardiovascular and abdominal examinations were unremarkable. Abdomen was flabby soft, non-tender, with no masses appreciated. On pelvic examination, she had normal looking external genitalia, Tanner stage 1 both for pubic hair distribution and breast development (Figure 1). No axillary hair was noted. Internal examination revealed a a short vaginal canal of <1cm ending in a blind pouch upon inserting the smallest finger, to which the patient and the mother consented. Rectal examination revealed good sphincteric tone, no palpable masses.

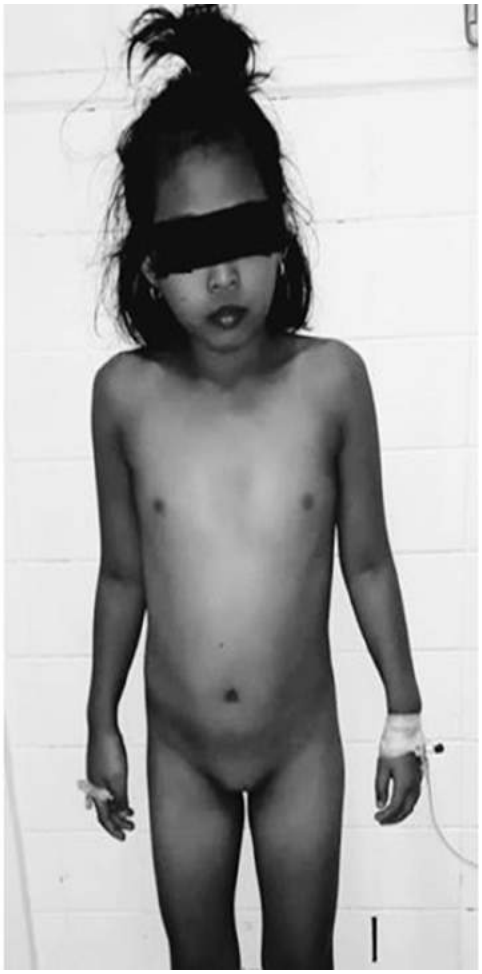

Figure 1. Absence of breast development and pubic hair (Tanner Stage 1).

On laboratory investigations, complete blood count revealed anemia with hemoglobin of 85g/dl, hematocrit of 0.33, white blood cells of 8.5x10^{12}/L, platelet count of 400x10^{12}/L, erythrocyte sedimentation rate of 15 mm/hr. Peripheral blood smear (Table 1) showed red blood cells with severe hypochromia with marked anisocytosis and moderate poikolocytosis, which may be seen in variety of disorders such as iron

deficiency and thalassemia. White blood cells and platelets were normal. Total iron binding capacity and ferritin were within normal range while the iron level was elevated at 48.2 umol/L probably because iron supplementation was already started (Table 2). Hemoglobin electrophoresis showed a band in the A position (97.4%) and the A2 position (2.6%) which does not support the diagnosis of thalassemia. Lipid profile, liver function and kidney functions tests were all within normal values. Hormonal profile (Table 3) showed normal serum human growth hormone and cortisol assay, hypergonadotropic hypogadism with elevated luteinizing hormone (16.52mIU/mL) and follicle stimulating hormone (71.88 mIU/mL) and decreased estradiol (< 5 pg/mL) and progesterone levels (<0.050 ng/mL). Her prolactin level and thyroid function tests were within normal levels.

Table 1. Peripheral blood smear result.

Red Blood Cell	Severe Hypochromia with marked anisocytosis and moderate poikilocytosis. Nucleated cells are not present.
White Blood Cell	Blast cells are not seen. Other immature cells are not present. Estimated smear count is within the normal limits. Adequate in number.
Platelet	Adequate in number. Morphology is normal.

Table 2. Anemia work- up.

	Result	Reference
Reticulocyte count	0.5	0.5-1.5
Total Iron Binding Capacity (TIBC)	53.57 umol/L	47.4-89 umol/L
Ferritin	15.3 ng/mL	6.24-137 ng/mL
Iron	48.2 umol/L	6.6-30.4 umol/L
Hemoglobin electrophoresis		
Hb A	97.4%	96.8-97.8%
Hb A2	2.6%	2.2- 3.2%

Table 3. Hormonal profile.

	Result	Reference
LH	16.52 mIU/mL	Post menopause: 11.2-39.8
FSH	71.88 mIU/mL	Post menopause: 25.8- 134.8
Prolactin	299.4 mIU/mL	40-530
Estrogen/Estradiol	<5.00 pg/mL	Post menopause:<5-54.7
Testosterone	<2.50 ng/dL	Ovulation: 0-80 Post menopausal: 0- 62
Progesterone	<0.050 ng/mL	Follicular phase: 0.20-1.5 Ovulation phase: 0.8-3.0 Luteal phase: 1.7-27 Postmenopause: 0.1-0.8 Male: 0.2-1.40
Cortisol	11.40 ug/dL	Serum Collected: Before 10 am: 3.7- 19.4 After 5pm: 2.9-17.3
Serum Growth Hormone	0.20 ng/mL	0,03- 5.22
Thyroid Stimulating Hormone (TSH)	0.6 Uiu/mL	0.48- 4.17
Free triiodothyonine (FT3)	1.5 ng/dL	01.3- 4.2
Free thyroxine (Free T4)	2.0 ng/dL	0.8- 2.0

Transrectal ultrasound showed a non-visualized uterus and cervix and probable small-sized ovaries. An MRI of the lower abdomen was requested and confirmed that there was agenesis of the uterus and both ovaries (Figure 2). Agenesis of vagina was also noted. Ultrasonography of the whole abdomen also showed absence of uterus and both ovaries (Figure 3). With a high suspicion of Turner syndrome, karyotyping was done which revealed 45 X0, mosaic monosomy X, with cell line with ring chromosome of unknown origin which is consistent with the diagnosis of variant Turner syndrome (Figure 4). A skeletal survey was done as a part of workup for Turner syndrome, which revealed symmetrical appearance of phalanges, metacarpal and carpal bones. Bone age was estimated radiologically to be 16-17 years old. A 2D echo was done to look for any cardiac defect, which turned out to be negative.

At that time, the impression was Turner syndrome with concomitant Mayer Rokintansy Kuster Hauser syndrome, Chronic anemia secondary to iron deficiency anemia. She was admitted in the institution for blood transfusion by the pediatric service and started her on ferrous sulfate bid. Counseling regarding her condition was done. Multidisciplinary team consisted of pediatrician, pediatric endocrinologist, reproductive endocrinologist and psychiatrist. Estrogen replacement therapy was offered which could trigger the development of secondary sexual characteristics and promote bone growth.

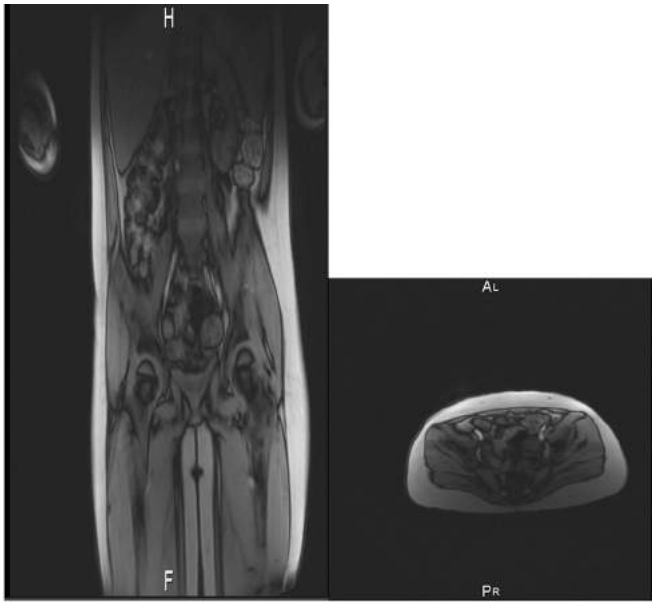

Figure 2. MRI showing the absence of uterus, ovaries and vagina.

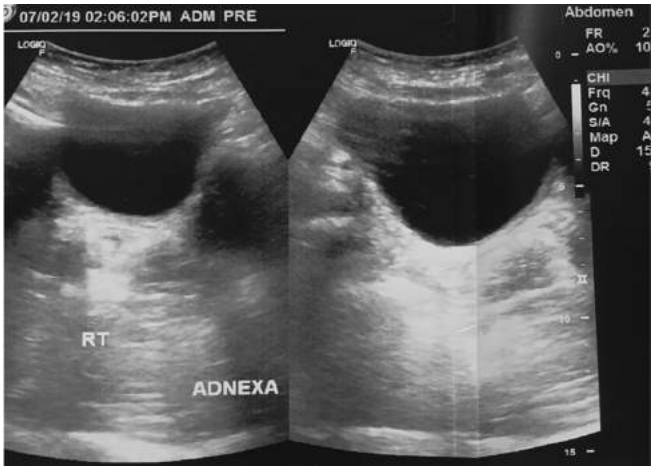

Figure 3. Abdominal ultrasound revealing non-visualization of the uterus and both ovaries

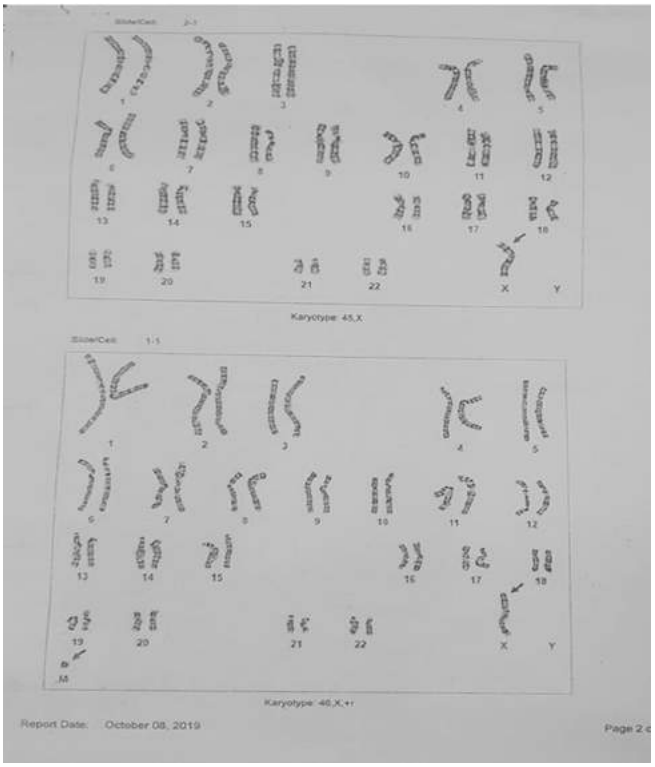

Figure 4. Chromosomal analysis revealing 45, X[98]/46,X,+r[2] Abnormal karyotype: Mosaic monosomy X with cell line ring chromosome of unknown origin.

Discussion

The authors report a patient who presented with delayed puberty and absence of menarche hence the diagnosis of primary amenorrhea. With all the investigations done to this patient, a diagnosis of Turner syndrome with co-existence of MRKH was the reason of her primary amenorrhea.

Turner syndrome also known as congenital ovarian hypoplasia syndrome is a condition in women that is associated with either complete or partial loss of one X chromosome.[3] It is the most common cause of primary amenorrhea and absence of secondary sexual characteristics.[4] Although this is the only monomer that humans can survive, Turner syndrome is associated with several conditions such as short stature, delayed puberty, ovarian dysgenesis, hypergonadotropic hypogonadism, infertility, congenital malformations of the heart, complications such as endocrine disorders such as type 1 and type 2 diabetes mellitus, osteoporosis and autoimmune disorders.[3] Phenotypic features usually include webbed neck, low set ears, shield-like chest, broadly placed nipples, cubitus valgus, lymphoedema of hands and feet, nail dysplasia and genu valgum.[5] Pathogenesis is unclear.[6] The association with any established risk factors, maternal age or familial inheritance pattern is still unclear.[5] Karyotype analysis is the gold standard for diagnosis. Manifestations of patients with Turner syndrome should be monitored through the entire developmental process. Treatment for Turner syndrome includes growth hormone therapy which can increase their final adult height, estrogen replacement therapy to develop their secondary sexual characteristics and uterus.[3] Reproduction in the form of in vitro fertilization using donor oocytes has been successfully employed with good pregnancy outcomes.[5]

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome on the other hand, is caused by embryonic underdevelopment of the Mullerian duct, which results in the agenesis or atresia of the upper two thirds of the vagina, uterus and fallopian tubes with normal appearing ovaries.[9] However, the lower third of the vagina is always present due to its different embryonic origin.[7] The vaginal canal is markedly shortened. Patients with MRKH have a normal female genotype, 46, XX. Its occurrence is sporadic. The first clinical feature is generally primary amenorrhea.[8] Clinical examination usually reveals a normal female phenotype with breast development, presence of axillary and pubic hair and normal looking external genitalia. Patients with MRKH are usually identified when they are investigated with primary amenorrhea with otherwise at par growth and pubertal development.[7] Up to 53% of patients with MRKH have concomitant congenital malformation, especially of the urinary tract and the skeleton, thus, further evaluation is essential. In MRKH patients who want to have a normal sexual life, the appropriate first line of approach is primary vaginal elongation by dilation because it is safer, patient-controlled, and more cost effective than surgery.[9]

MRKH features with absence of bilateral ovaries should raise the suspicion of associated Turner syndrome.[6] The incidence of Turner syndrome associated with Mullerian agenesis is not known as only very few cases have been reported.[5,6,10,11]

Proper timing of treatment with growth hormone can improve lean body mass and can help achieve normal adult height.[2] Growth hormone therapy should begin as soon as height falls below the 5th percentile for age, usually between 2 and 5 years of age.[2]

Since the index patient consulted when she was already 18 years old, growth hormone was less likely to be an effective treatment.

Hormone replacement therapy remains the only therapeutic option.[10] Breast development and bone growth can be achieved through estrogen therapy but induction of menstruation is very rare.[10] Low dose estrogen (such as micronized estradiol of 0.25-0.5 mg) may be given and increased gradually thereafter at 3-6 month intervals up to 2mg micronized estradiol.[10] There was no need to add progestin since she has no uterus.

Future options of having children which includes adoption and gestational surrogacy should be discussed with the patient because the co-existence of Turner syndrome and MRKH leads to a very poor or no chance of conception.[5,6,10,11]

If the patient is ready for sexual intercourse, the primary goal of treatment in women with Mullerian agenesis is a creation neovagina either by

progressive vaginal dilation or by surgical creation of neovagina.[9]

Assisted Reproductive Techniques (ART) may not be helpful for the patient since no follicles can be produced. Adoption, on the other hand, is her one option. Family and friends as a source of social support are very important. Patients carry the burden of social discrimination and low self-esteem because of the absence of ovaries and uterus and inability to conceive. Psychiatric referral is necessary as part of a multidisciplinary approach to the management of the patient. The index patient and her family were advised counseling.

Conclusion

The coexistence of Turner syndrome and MRKH is a double blow to the patient, with very poor chances of conception. Prompt diagnosis will help in the early induction of hormone replacement therapy which can improve bone health during adult life and provide a better quality of life. The case of the patient was thoroughly discussed to her and her parents.

Since there is no chance of conception in such cases, future options for having children should be addressed.

A multidisciplinary approach is needed in the management of patients with this condition. Psychiatric and social support is important in all patients who have a congenital anomaly because they are at risk of experiencing social discrimination and low self-esteem. They may experience anxiety and depression and may question their female identity and be greatly saddened by their infertility.

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