Double Burden: A Rare Case of Turner's Syndrome with Concomitant Mayer-Rokitanski-Kuster-Hauser Syndrome*

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ABSTRACT

Amenorrhea is one of the most taxing cases in the field of gynecologic endocrinology. Turner's and Mayer-Rokitansky-Kuster-Hauser Syndromes are the two most common separate causes of primary amenorrhea worldwide. Presented here is a rare case of an 18-year old female with Turner's Syndrome and concomitant Mayer-Rokitansky-Kuster-Hauser Syndrome. The worldwide incidence of both syndromes occurring simultaneously in an individual is 1 in 15,000,000 livebirths. The index patient presents with primary amenorrhea and chromosomal analysis revealed 45,X. Transrectal ultrasound noted absence of both the uterus and the ovaries. Early detection of this rare case is important for the initiation of hormone replacement therapy. Adoption is the only option to have a child since Assisted Reproductive Technique (ART) by means of in-vitro fertilization is not applicable for patients with both of these syndromes. Parents and children must be educated regarding the limitations of current knowledge about the management of both Turner's and Mayer-Rokitansky-Kuster-Hauser Syndromes and must be given realistic expectations with respect to sexual function and social acceptance.

Keywords: Primary amenorrhea, Turner's Syndrome, Mayer-Rokitansky-Kuster-Hauser Syndrome

INTRODUCTION

It is indeed challenging for a physician to identify the etiology of amenorrhea when presented with such a patient. Amenorrhea is one of the most taxing cases in the field of gynecologic endocrinology.

Primary amenorrhea is defined as the absence of menses in a woman aged 14 without growth or development of secondary sexual characteristics or a woman who has never menstruated by the age 16 but with presence of secondary sexual characteristics.[1] The incidence of primary amenorrhea is less than 0.1%.[2] On the other hand, secondary amenorrhea is defined as the absence of menses for an arbitrary time period, usually longer than 6 to 12 months. Its incidence is reported to be 0.7%.[2]

Anxiety is a major contributing factor why primary amenorrheic patients and their parents consult at clinics, therefore they deserve considerate evaluation.

What is more challenging and interesting in this case report is that the patient presents with two different syndromes as the cause of primary amenorrhea. Hence this paper aims to present a rare case of Turner's Syndrome with concomitant Mayer-Rokitansky-Kuster-Hauser Syndrome and specifically to discuss the pathophysiology, clinical manifestations, diagnosis with appropriate evaluation and management of both syndromes.

CASE REPORT

An 18-year old female consulted for evaluation of primary amenorrhea. No associated symptom of cyclic pelvic pain was noted. Patient's past medical and family history as well as personal and social history were unremarkable. She denies any sexual intercourse. Vital signs were normal. On physical examination (Figure 1), the index patient has short stature (50 inches), webbed neck, broad chest, undeveloped breasts (Tanner stage 1), wide-spaced nipples and cubitus valgus. Patient has female external genitalia with Tanner stage 1 for pubic hair distribution (Figure 2). Patient had a previous consult with an obstetrics and gynecologist wherein transrectal ultrasound revealed absence of uterus and ovaries.

DISCUSSION

It has been found most clinically useful to group patients presenting with primary amenorrhea on the basis of whether secondary sexual characteristics (breasts) and female internal genitalia (uterus) are present or absent (Table 1).[1] The index patient presented with absence of breast development, this would classify the patient under categories I (absent breast development; uterus present) and III (absent breast development; uterus absent). A transrectal ultrasound previously done revealed absence of uterus and ovaries, classifying the index patient under categories II (breast development; uterus absent) and III (absent breast development; uterus absent). To further

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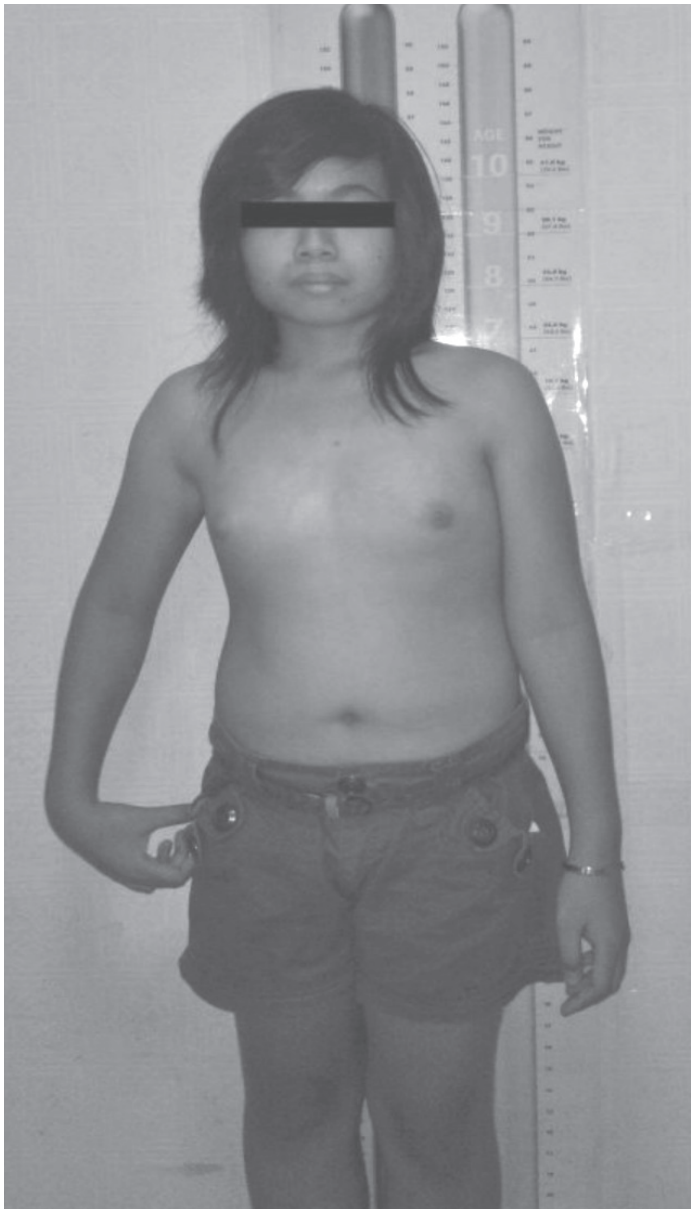

Figure 1. Physical Characteristics of Index Patient

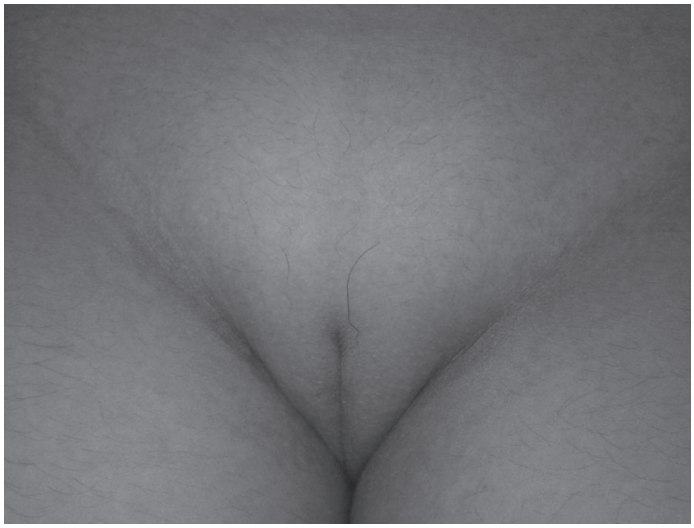

Figure 2. Female External Genitalia with Tanner Stage 1 Pubic Hair Distribution

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 (utero-vaginal agenesis) or Mayer-Rokitansky-Kuster-Hauser Syndrome

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, Lentz G, Gershenson D and Katz V: Comprehensive Gynecology, 6th ed. USA: Elsevier Mosby, 2012. *p.818*

narrow down the differentials, a karyotype was requested. A repeat transrectal ultrasound revealed the absence of uterus and ovaries (Figure 3). A perineal ultrasound showed the presence of a 3.3 cm vaginal canal. Magnetic resonance imaging was requested to confirm the absence

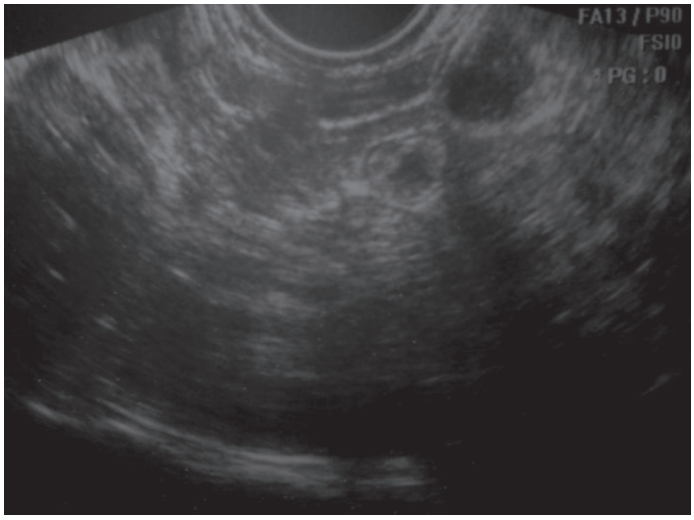

Figure 3. Transrectal ultrasound of the index patient revealing the absence of uterus and ovaries

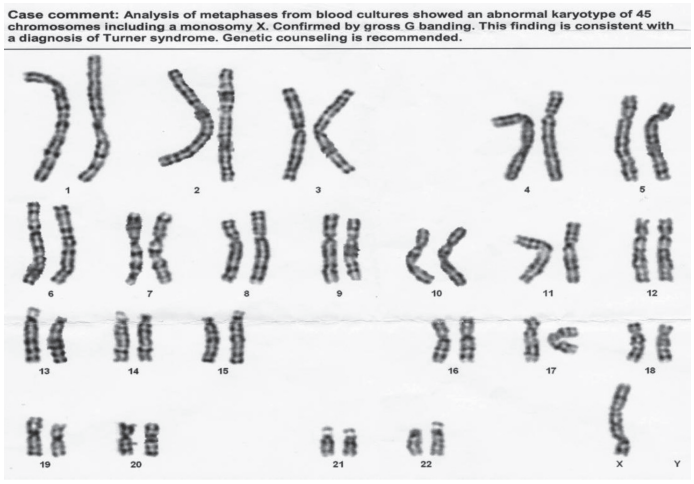

Figure 4. Chromosomal analysis revealing 45,X

of internal genitalia but due to its prohibitive cost, it was not done. Patients presenting under category III or the absence of breast development and uterus in one disease entity would usually present with ambiguous genitalia and male karyotype (XY). Chromosomal analysis of the index patient revealed a 45,X karyotype (Figure 4). The presence of a female karyotype and normal female external genitalia ruled out category III as the cause of primary amenorrhea on this patient. This further narrowed down the diagnosis to categories I and II. Physical examination supports the diagnosis of Turner's Syndrome (Category IA) because of the absence of breast development, short stature, presence of webbed neck, broad chest, wide-spaced nipples and cubitus valgus. This is further supported by the 45,X chromosomal analysis of the index patient and by the absence of ovaries on transrectal ultrasound. Serum gonadotrophins and estradiol were requested and revealed results in the menopausal range (Table 2), consistent with Turner's syndrome. Patients with Turner's syndrome have

Table 2. Laboratory results of the patient

Examination	Results	Normal Range
Follicle Stimulating Hormone	78 mIU/ml	Menopausal: 17.0-95.0 mIU/ml
Luteinizing Hormone	19 mIU/ml	Menopausal: 8.0-33.0 mIU/ml
Estradiol	10 pg/ml	Postmenopausal: Non-detected- 14 pg/ml
Thyroid Function Tests		
Thyroid Stimulating Hormone	1.5 IU/ml	0.25-5.0 IU/ml
Free T4	12 pmol/L	9-20 pmol/L
Free T3	5.2 pmol/L	4.0-8.3 pmol/L
FBS	5.2 mmol/L	4.1-5.9 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

normal uterine development, and the absence of uterus on transrectal ultrasound of the index patient led to a consideration of catergory II as another cause of primary amenorrhea. Androgen resistance and Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS) are the two disease entities under category II. Since androgen resistance has male karyotype and with normally functioning male gonads, Mayer-Rokitansky-Kuster-Hauser Syndrome was strongly considered to occur simultaneously with Turner's syndrome in the case of the index patient.

Turner's syndrome occurs in 1 in 2500 to 1 in 3000 live-born females3, while Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS) occurs in 1 out of 5000 women.[4] The probability of having both abnormalities in an individual is 1 in 15,000,000.[5] This is the 2nd reported case in the Philippines of gonadal and mullerian agenesis occurring simultaneously in an individual.[5] This is the 7th reported case worldwide of the co-existence of gonadal dysgenesis presenting with abnormal karyotype and mullerian agenesis (Table 3).[5,6,7,8,9,10]

Turner's syndrome is a condition involving the absence of all or part of a normal second X chromosome in

Table 3. Internationally Reported Cases of Gonadal Dysgenesis Revealing Abnormal Karyotype Co-existing with Mullerian Agenesis

Authors, Year Published	Patients Karyotype	Clinical Presentation
De Leon, et al., 1984	46,X,i(Xq)	Short stature, subtle features of Turner's Syndrome Absent Uterus
Guitron-Cantu A, et al., 1999	45,X/46,Xdic(X)	No breast development, no pubic and axillary hair Absent Uterus
Ting TC, Chang SP, 2002	45,X/46,X,del(X)(p22.2)	Absent breast development, no axillary hair, no pubic hair, with scoliosis Absent Uterus
Aydos S, Tukun A, Bokesoy I, 2003	46,x,del(X)(pter>q22)	No secondary sexual features Absent Uterus
Guven A, et al., 2008	45,X/46,X,del(X)(p11.21)	Undeveloped breast (Tanner stage I), pubic hair (Tanner stage II), absent axillary hair, short stature, hypertrophy of both 2nd toes, downslanting palpebral features, webbed neck, low posterior hairline, cubitus valgus, short 4th metacarpals, grade 1 systolic murmur Absent Uterus
Marcial SG, Oblepias EG, 2008	45,X[6](46,X,i(X)(q10)[9]	Undeveloped breasts (Tanner stage II), Pubic hair (Tanner stage I), short stature, broad shield-like chest Absent Uterus

females. Monosomy of the X chromosome (45,X) accounts for half of women with Turner's Syndrome. The index patient belongs to this variant. It occurs through paternal nondisjunction unlike autosomal trisomies in which majority are maternally derived. It is not associated with advanced maternal or paternal age, and there is no increased recurrence for 45,X variant. It was noted that 30% to 40% of individuals with Turner's Syndrome are mosaic for the 45,X cell line and another cell line (usually 46,XX) because of postzygotic nondisjunction during mitosis.[2] The proportion of normal 46,XX cell lines influence the clinical appearance of these women. They are generally taller and have fewer anatomic abnormalities than individuals with a 45,X karyotype. Nevertheless, females with a 45,X/46,XY karyotype are at an increased risk for gonadoblastoma. Hence, chromosomal analysis was requested in this patient not only for the diagnosis of Turner's syndrome, but for exclusion of mosaicism for a 46,XY cell line. The remaining 10% to 20% of individuals with Turner's syndrome have a structural abnormality of the X chromosome. Which chromosomal regions and genes account for the physical characteristics of Turner's syndrome remains uncertain. A band of fibrous tissue or gonadal streak is present in place of the ovary. There is absence of ovarian follicles therefore synthesis of ovarian steroids and inhibin does not occur. Due to very low level of circulating estrogen, breasts are undeveloped as seen in the index patient. Since estrogen is not necessary for mullerian duct development or wolffian duct regression, the internal and external genitalia are phenotypically normal female.

In terms of diagnosis, one fifth to one third of girls with Turner's Syndrome are detected during neonatal period because of presence of puffy hands and feet or redundant nuchal skin due to residual effect of cystic hygromas in utero. Approximately one third of these patients are diagnosed during midchildhood on investigation of short stature deviated from their normal familial stature. In most other patients with Turner's syndrome, the condition is diagnosed during adolescence when they fail to enter puberty. As for the case of the index patient, being the eldest child, it was noted that her height of 50 inches was far beyond her tall male siblings who are both basketball players with height of 68 inches and 70 inches.

There have been reported cases of congenital heart disease, hypertension, mitral valve prolapse, hypothyroidism, insulin resistance, and silent hydronephrosis

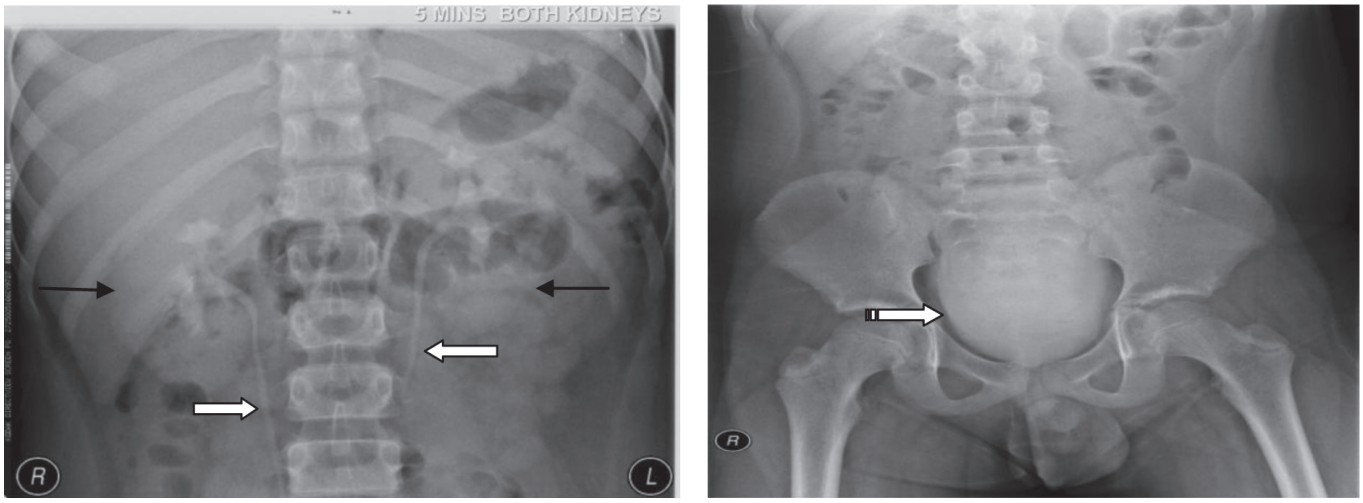

Figure 5. Right and left kidneys and ureters, and bladder showing normal intravenous pyeolography results (➔ kidneys ⇨ ureters ⇨ bladder)

in patients with Turner's Syndrome. Two-dimensional echocardiogram, lipid profile, thyroid function test, fasting blood sugar (Table 2), and kidneys and urinary bladder intravenous pyelography (KUB-IVP) (Figure 5) were requested and revealed normal results.

Turner's syndrome should be suspected in any newborn girl with edema or hypoplastic left heart or coarctation of the aorta, since the frequency of both conditions is increased among children with Turner's syndrome. The prevalence of congenital heart disease among patients with Turner's syndrome ranges from 17 to 45 percent.[3] Most common of these are coarctation of the aorta and bicuspid aortic valve followed by other left-sided defects.

Fifteen to thirty percent of women with Turner's syndrome were reported to have hypothyroidism. The mean age at onset is in the third decade, though 5 to 10 percent of cases occur before adolescence. Screening of thyroid function, including measurement of thyrotropin levels, should begin at about 10 years of age in asymptomatic patients.[3] The index patient is asymptomatic and consulted on her 2nd decade of life.

There may be increased prevalence of insulin resistance and Type 2 Diabetes in patients with Turner's syndrome and majority of them have adult-onset diabetes, and are overweight.

Structural renal malformations, including horseshoe kidney and duplication of the collecting system, are found in up to 40 percent of patients with Turner's syndrome[3]. Silent hydronephrosis resulting from obstruction of a duplicated collecting system may occur therefore screening renal ultrasonography is necessary for all patients with Turner's syndrome.

Skeletal dysplasia, with short stature and mild epiphyseal dysplasia may occur in patients with Turner's syndrome. Dislocation of the patellae and chronic knee pain are common. Cubitus valgus or increased carrying angle of the arm may occur due to malformation of the ulnar head causing limited range of motion. The index patient presents with cubitus valgus but no skeletal pain is noted. No studies have been done to support whether the reduced bone mass is a nonprogressive feature of a general skeletal dysplasia or is analogous to the accelerated bone loss seen in postmenopausal women primarily as a result of estrogen deficiency.[3]

On the other hand, the cause of Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS) is unknown. It is hypothesized that either an unknown toxic substance or a genetically induced event interferes with the development of the Mullerian (paramesonephric) duct, the Wolffian (mesonephric) duct, with its ureteral bud, the metanephros, and the mesoderm, that gives rise to the dorsal spine.

MRKHS is most probably associated with an arrest of development between 8th-12th gestational weeks. The uterus, cervix, and upper three-fourths of the vagina originated from the fusion of caudal ends of the Mullerian (paramesonephric) ducts. The paired fallopian tubes are formed by the unfused upper ends.

When the mesonephric ducts emerge and connect with the cloaca, development of the urinary system occurs. At about fourth to fifth weeks, two ureteric buds develop from the mesonephric (Wolffian) ducts and begin to grow cephalad toward the mesonephros. As each bud lengthens, it induces differentiation of the metanephros, which will become the kidney. The close association between the mullerian and mesonephric ducts has clinical relevance. Damage to either duct system is often associated with anomalies that involve the uterine horn, kidney, and ureter. In approximately one third of cases, there are associated renal abnormalities such as renal agenesis, malrotations, or ectopic kidneys. It is recommended to do renal collecting duct imaging in all patients with mullerian

anomalies. In the case of the index patient, kidneys and urinary bladder intravenous pyelography (KUB-IVP) revealed the presence of normal bladder, renal and collecting duct systems.

The skeleton may also be affected in Mayer-Rokitansky-Kuster-Hauser Syndrome because like the mesonephros, it is derived from the mesoderm. At about the same stage of development when the embryonic defect in genitourinary tract occurs, the vertebra develop from adjacent mesodermal cell concentrations and thus may also be damaged. Two-thirds of the skeletal anomalies involve the spine. The index patient does not complain of back or joint pains.

Parents and children must be educated regarding the limitations of current knowledge about the management of both Turner's Syndrome and Mayer-Rokitansky-Kuster-Hauser Syndrome, and must be given realistic expectations with respect to sexual function and social acceptance.

Proper timing of treatment with growth hormone can improve lean body mass and can help achieve normal adult height. Growth hormone therapy should begin as soon as height falls below the 5th percentile for age, usually between 2 and 5 years of age.[1] Since the index patient consulted in her 2nd decade of life, growth hormone is less likely effective. Ideally estrogen therapy should begin no later than age 15 and not before age 12 when growth is a priority, unless height has already been maximized. Low dose estrogen (0.25-0.5 mg micronized estradiol or its equivalent) must initially be given and increase gradually

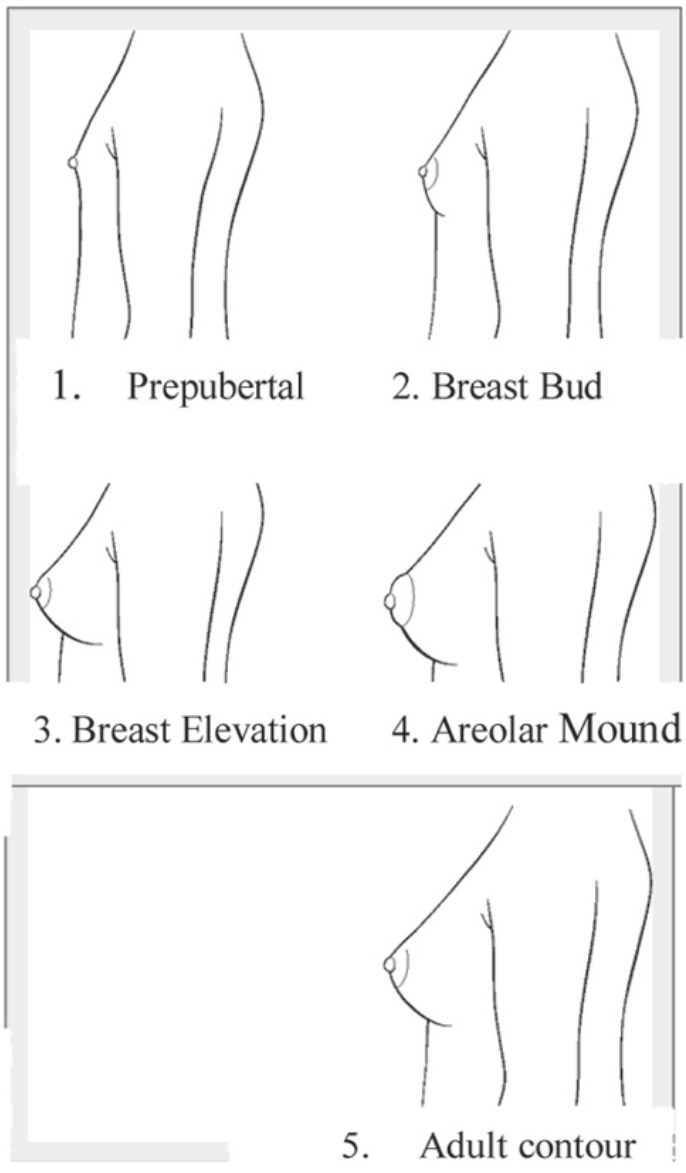

Figure 6. Tanner Staging for Breast Development
(Clinical Gynecologic Endocrinology& Infertility, 7th Edition by Speroff p.378)

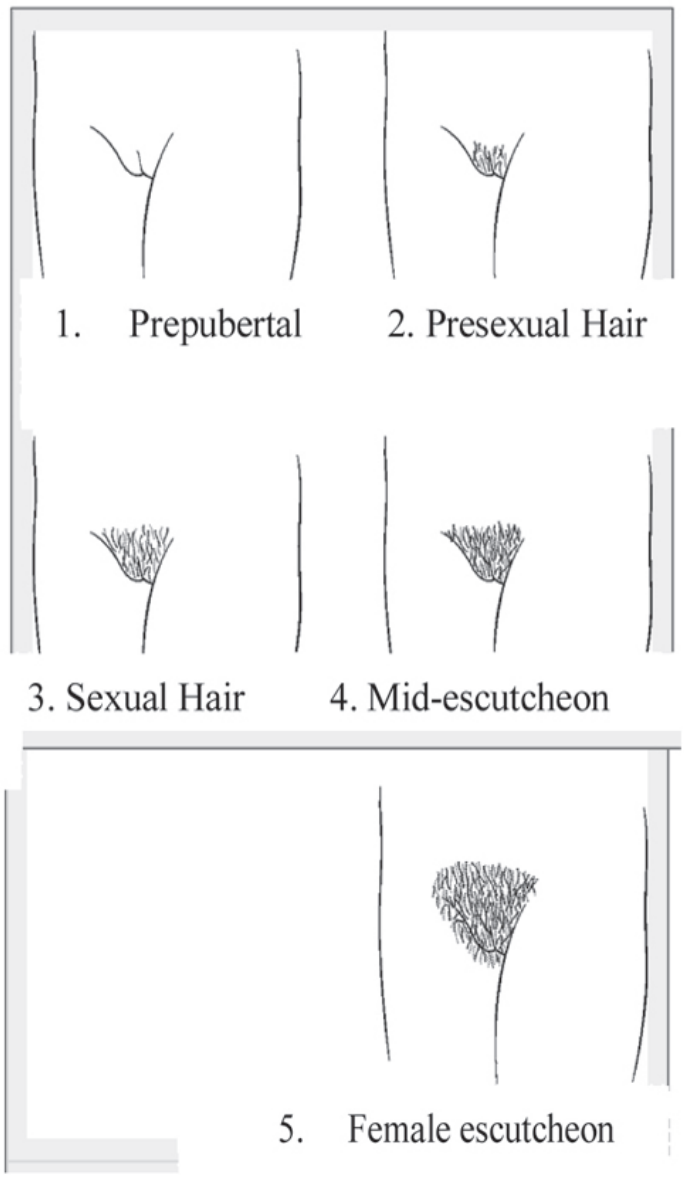

Figure 7. Tanner Staging for Pubic Hair Distribution
(Clinical GynecologicEndocrinology& Infertility, 7th Edition by Speroff p.379)

at 3-6 months intervals upto 2mg micronized estradiol. Ideally, combined treatment with cyclic progestin is given to prevent the stimulating effect of estrogen in the uterus. However absence of uterus in the index patient excludes its administration. At present the index patient is taking 0.625 mg of conjugated equine estrogen daily.

The primary goal of treatment in women with mullerian agenesis is a creation of a functional vagina either by progressive vaginal dilation or by surgical creation of neovagina.[5] The index patient has a 3.3 cm vaginal canal as noted by perineal ultrasound. At present, no intervention for sexual function is contemplated since the index patient is not sexually active. She has been advised that she may seek consult once sexual activity is contemplated.

The advent of Assisted Reproductive Techniques (ART) help patients with MRKHS achieve genetic offspring by in vitro fertilization (IVF) using oocytes retrieved from their own normal ovaries. However since the index patient has gonadal dysgenesis, no mature follicles can be produced hence IVF is not possible. In this case, the index patient's best option is adoption.

Psychiatric and social support is extremely important in every patient with a congenital anomaly. 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 counselling, however they refused. They readily accepted the patient's condition and promised to seek psychiatric consult if the need arises.

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