Case Report

Mayer-Rokitansky-Kuster-Hauser syndrome – An unusual case of primary amenorrhea

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ABSTRACT

The onset of menstruation is a significant milestone of sexual maturation in a girl child. Although there are numerous causes of primary amenorrhea, Mayer-Rokitansky-Küster-Hauser syndrome, also known as Müllerian aplasia, is one of the extremely rare causes of primary amenorrhea which is usually picked up by suitable imaging techniques like magnetic resonance imaging. Affected females have a normal female hormonal function and a normal karyotype but non-functional vagina and uterus which make it an interesting entity. Although specific treatment is not known for this entity except for vaginoplasty and creation of a neovagina for sexual gratification, the clinical and diagnostic workup of these patients has evolved in recent years and infertility treatment and child-bearing through *in vitro* fertilization have become a part of the long-term treatment plan for these females.

Key words: Mayer-Rokitansky-Küster-Hauser, Mullerian aplasia, Neovagina, Vaginal agenesis

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS), also called Müllerian aplasia or Mullerian agenesis, is a rare congenital disorder resulting from the failure of urogenital development with an estimated incidence of 1/4500 live female births [1]. Embryologically, the uterus is formed by the Mullerian ducts that are paired tubes abutting the urogenital ridge giving rise to the upper portion of the female reproductive tract. Failure of proper development of the upper female urogenital tract results in a wide spectrum of anatomical abnormalities of the genitourinary system. MRKHS is characterized by the absence or aplasia of the uterus, cervix, and/or upper vagina without or with associated urological and other organ system involvement (MRKHS type I vs. type II, respectively) [2]. Depending on the particular structures affected and the severity of involvement, such abnormalities may be detected at birth or may go clinically unnoticed until there is an absence of menarche or complaints of dyspareunia/sexual dysfunction with attempted sexual activity [3]. Vaginal agenesis during embryological development often leads to a complete absence of the vagina if not the remnant of a small vaginal dimple in adults [3].

Here, we report a case of MRKHS in an otherwise healthy, unmarried, sexually inactive girl who presented at age 16 with primary amenorrhea and was found to have an aplastic uterus, absent endometrium, and absent cervix along with a blind lower vagina with well-developed secondary sexual characters. Informed consent was obtained from the patient to use her medical information for this case report.

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CASE REPORT

A 16-year-old female child belonging to Ghaziabad, Uttar Pradesh, presented with her mother with a chief complaint of never having a menstrual period. There was no history of tubercular contact in the patient. Other family history was unremarkable. The female was not sexually active. There was no other relevant history. There was no relevant drug history or history of any substance abuse.

On examination, her vital signs were within normal limits and her body mass index was 25.51. The child had mild pallor with no signs of icterus, lymphadenopathy, organomegaly, or thyromegaly. Breasts were well-developed with no masses, tenderness, or discharge. Sexual Maturity Staging or Tanner Staging suggested Stage V. Rest systemic examination was normal. No cardiac or spinal abnormalities were detected. There was no evidence of webbed neck, broad chest, widely spaced nipples or cubitus valgus, nail dysplasia, low hairline, narrow, high-arched palate, or short fourth metacarpals or metatarsals. The child was evaluated for primary amenorrhea based on the history. She had never

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been previously evaluated by a gynecologist. Gynecological examination showed no lesions and normal adult female pubic hair pattern, Tanner Stage V. The cervix was not palpable or visualized. The uterus was not palpable and no adnexal masses were appreciated. Per vaginal examination revealed a blind vagina measuring 1.5 cm in diameter, no bleeding, or discharge. The urethra was normal in appearance.

The child had undergone biochemical evaluation previously at local clinics which revealed hemoglobin – 12 gm%, total leukocyte count – 8200, differentials leukocyte count polymorphs – 58%, lymphocytes – 34%, eosinophils – 6%, and monocytes – 2%. The erythrocyte sedimentation rate was 25 mm/hr, red blood cells were 4.53 million/cubic meter, platelet count was 2.86 lac/cumm, and the blood sugar was 87.6 mg/dl. Mantoux test revealed a highly positive result with induration of 35 × 40 mm after 48 h with 5 TU, chest X-ray suggestive of the left lower zone heterogeneous infiltrates. The human immunodeficiency virus serology was negative and hepatitis B and C markers were also negative.

In light of the patient's presentation, transabdominal ultrasound was performed, which revealed bilateral uteri non-visualization, and only a streak of mass tissue measuring 39 mm × 9 mm was seen with no endometrium appreciated. The cervix was not imaged. Follicle containing ovaries were imaged transabdominally and were normal in size and appearance bilaterally, definitively excluding the presence of testes, and effectively ruling out congenital androgen insensitivity syndrome. The right ovary showing multiple follicles with the largest follicle measuring 15 × 5 mm and a simple cyst of size, 35 × 30 mm. No fluid was appreciated in the cul-de-sac. Non-contrast computed tomography abdomen revealed non-visualization of the uterus, only streaky soft tissue in the region of the uterus with normal-sized ovaries along with the normal follicular appearance and mild mesenteric lymphadenopathy in ileocecal mesentery largest measuring 1.3 × 1.1 cm. Magnetic resonance imaging (MRI) pelvis revealed uterine aplasia with bilateral ovaries with normal morphology. The upper one-third of the vagina was absent, while the lower two-thirds were present.

Together, the findings of primary amenorrhea, normal ovaries, female secondary sexual characteristics, and aplasia of the uterus with an absence of the cervix and upper one-third of the vagina were consistent with a diagnosis of MRKHS. A subsequent biochemical analysis was performed to further support the diagnosis of MRKHS. Levels of estriol, follicle-stimulating hormone, luteinizing hormone, and total testosterone were all within normal limits, again consistent with the diagnosis of MRKHS (Table 1). Karyotyping was done and revealed normal karyotype (46 XX).

Because of the well-known association between MRKHS and anatomical abnormalities of the urological system [2], a renal ultrasound was performed, which demonstrated normal bilateral kidneys, no evidence of hydronephrosis, and no evidence of contour deforming mass. The right kidney shows a calculus of size 4.1 mm seen in the upper pole.

Table 1: Biochemical evidence of female phenotype

Serum marker	Patient value	Reference range
Estriol (ng/mL)	194	43.8–211.0 (luteal phase)
Follicle-stimulating hormone (mIU/mL)	5.2	1.5–9.1 (luteal phase)
Luteinizing hormone (mIU/mL)	15.28	0.5–16.9 (luteal phase)
Prolactin (ng/mL)	17.87	5–25 (female)
Total testosterone (ng/dL)	32.97	14–76 (female)
Thyroid-stimulating hormone (microIU/mL)	2.830	0.25–6.00
Free T3 (pg/mL)	3.53	1.5–4.1
Free T4 (ng/mL)	1.18	0.8–1.9

Thus, our patient displayed characteristics of MRKHS type 1. On hearing the diagnosis, our patient was anxious, especially with regard to future reproductive prospects. However, she was counseled with her parents present regarding the implications of the diagnosis and reproductive options such as the use of a surrogate to carry a pregnancy for her. She expressed gratitude at the end of the encounter for the information and services provided and was offered follow-up as needed.

DISCUSSION

MRKH syndrome represents a spectrum of urogenital anomalies arising from the failure of the upper female reproductive tract (Mullerian duct derivatives) to properly form during embryogenesis. In cases of MRKHS type I, the patient exhibits varying degrees of congenital aplasia of the uterus and upper vagina, without extra-gynecological involvement and with normal secondary sexual characteristics [3]. The typical presentation in this condition is primary amenorrhea. Some women may present with cyclical abdominal pain, and gynecological examination may reveal an absent or rudimentary vagina [3].

MRKHS, a form of Mullerian abnormality also known as Mullerian aplasia, is caused by embryonic growth failure resulting in agenesis or underdevelopment of the vagina, uterus, or both [4]. The ovaries are of a different embryologic origin and they are normal in structure and function; thus, patients with this syndrome usually appear normal on physical examination, with normal height and secondary sexual characteristics. The labia majora, labia minora, clitoris, hymen, and a distal portion of the vagina are usually present because this portion is of a different embryonic origin. Cases of MRKHS type 2 involve renal, vertebral, auditory, and/or cardiac defects in addition to the aforementioned gynecological anomalies. There are two subtypes of MRKHS: The typical and the atypical forms [5]. The typical form is characterized by laparoscopic/laparotomy findings of Mullerian remnants and normal fallopian tubes. The atypical form shows asymmetric hypoplasia of one or two buds, possible dysplasia of the fallopian tubes with one or more of the anomalies, such as unilateral or bilateral renal agenesis, ectopic kidneys, or horseshoe kidneys

in 40–60% of cases. Other abnormalities include cervicothoracic (asymmetric, fused, or wedged vertebrae, scoliosis, and Klippel–Feil anomaly), hearing defects, and varying degrees of digital anomalies. The most severe form of the atypical form is referred to as Mullerian renal cervical somite association [5,6].

The diagnosis is confirmed mainly with imaging modalities of ultrasonography and MRI. These help to definitively characterize the anatomy. The preferred ultrasonography is the three-dimensional mode. Laparoscopy is considered when the earlier mentioned modalities have not yielded adequate information or in the treatment of rudimentary uterine horns [7]. Karyotyping is also needed in establishing the diagnosis of MRKHS as it helps in differentiating it from the other clinical conditions that appear similar in appearances such as androgen insensitivity syndrome and 17α-hydroxylase syndrome [8]. However, the absence of hypoplastic thumbs and a short neck strengthened the diagnosis of MRKHS [5].

While the most cases of MRKHS are sporadic, a subgroup of patients has been shown to harbor mutations in wingless-related integration sign (WNT) family genes [9]. Given the well-established role of WNT signaling in cellular proliferation, dysregulation of this pathway in our patient may have contributed to her phenotype, although this remains unknown at present.

The management of this condition involves the exclusion of other clinical malformations that will hinder the well-being of this patient. The treatment is multidisciplinary and involves surgical and non-surgical treatment options including the creation of a neovagina to have a normal sex life. Non-surgical techniques are considered the first-line approach with the help of vaginal dilators. Vestiges of the uterus can be removed to avoid the development of endometriosis [10]. The timing of the surgical or non-surgical creation of the neovagina should be planned, when the woman is emotionally mature and expresses the desire for correction. Surgery aims to create a vaginal canal in the correct axis of adequate size and secretory capacity to allow intercourse. A procedure commonly done involves dissection of space between the rectum and the bladder, placement of a mold into the space covered with a split-thickness skin graft. After healing, serial dilation is done to prevent skin graft contracture. A neovagina can also be created laparoscopically. Other forms of grafts that can be used include buccal mucosa, bowel mucosa, and amnion [8]. The patient should be equipped with appropriate knowledge of their condition, especially aspects of fertility and sexual function. Frank discussion regarding physical aspects of sexual intercourse should be initiated early and not kept to be "just before marriage" [11]. Despite the clinical management options available, the distress of having such a condition is better managed with support from psychologists, counselors, and a strong social and family support group.

CONCLUSION

MRKH syndrome is a rare anomaly of the Mullerian duct. The absence of sexual and reproductive health education combined with the cultural shame of discussing issues relating to genitals and sexuality results in a lack of communication and delayed diagnosis. An absence of or "missing" education on this diagnosis and "missing" education for health professionals' results in poor communication and often humiliating and negative experiences for the young women. The cultural pressures to bear children impact their capacity to have romantic relationships and marriage. Public awareness of this condition is necessary through mass media. Education regarding this condition needs to be included in the medical undergraduate and postgraduate curriculums.

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