Case Report

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Unusual Coexistence of Mullerian and Ovarian Agenesis with Premature Ovarian Insufficiency, Report of Two Cases, 2025

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ABSTRACT

The occurrence of Müllerian anomalies with concomitant gonadal abnormalities is very rare. The most common cause of primary amenorrhea is gonadal dysgenesis and Mullerian agenesis. Here we report two young females who presented with primary amenorrhea, poorly developed secondary sexual characteristics and short stature. In both cases, breasts weren't developed yet with absent pubic hair and normal appearing female external genitalia. The hormone analysis revealed elevated level of follicle-stimulating hormone and luteinizing hormone which pelvis MRI indicated uterine and vaginal dysplasia with absent ovaries in both cases. Karyotyping may help in differentiating the diagnosis. Treatment options and breaking the bad news was difficult in both cases as surrogacy or assisted fertility wasn't convincing in these cases.

Keywords

Primary amenorrhea, Mullerian agenesis, Gonadal dysgenesis, Premature ovarian insufficiency.

Introduction

Mayer-Rokitansky-Kuster-Hauser syndrome (MRKHS) is characterized by female phenotype, primary amenorrhea, normal secondary sexual characteristics, absent vagina, absent or rudimentary uterus and normally developed ovaries [1]. The syndrome is of two types: Typical – Isolated uterovaginal agenesis, and atypical – Mullerian agenesis along with malformations of kidneys or ovaries [2]. While MRKH Syndrome physical examination reveals normal height, body hair distribution, secondary sexual characteristics, and external genitalia, the patient will often have an absent vagina or shortened blind pouch without a cervix. The atypical form represents 21% of MRKH syndrome patients and is defined as malformations of the ovary or renal systems [3].

The causes of primary amenorrhea include outflow tract abnormalities, resistant endometrium, primary ovarian insufficiency, and disorders of the hypothalamus, pituitary, or other endocrine glands [4]. The most common cause of primary amenorrhea is gonadal dysgenesis, followed by mullerian duct agenesis [5]. Mullerian agenesis is the most common cause of primary amenorrhea with well-developed secondary sexual characteristics [4]. While in gonadal dysgenesis, the secondary sexual characteristics are not well developed owing to a lack of estrogen production by dysgenetic (streak) ovaries, mullerian duct abnormalities with outflow tract obstruction should be suspected in females with otherwise well-developed secondary sexual characteristics [6].

Although karyotype is normal in typical MRKH syndrome, rarely cases have been reported of association if MRKHS with different types of gonadal dysgenesis. In a recent case report of MRKH syndrome and Turner syndrome, the authors reviewed the literature and their case was the 26th ever reported case of association of MRKH and Turner syndrome [7]. Evaluation of a patient with primary amenorrhea should include a vaginal exam, uterine assessment, serum β-HCG, follicle-stimulating hormone, luteinizing hormone, prolactin, and thyroid-stimulating hormone levels and Karyotype analysis [3].

This case indicates a rare congenital anomaly of bilateral ovarian agenesis leading to early diagnosis and profound phenotypical characteristics of absent pubertal development, delayed bone maturation, and primary ovarian insufficiency [8]. Coexistence of MRKH syndrome with other conditions is rare, especially when MRKH was found in a young woman presenting with ovarian malignancy [9]. Here we report two cases with unusual existence of Mullerian and ovarian agenesis and premature ovarian insufficiency.

Case Report

The first case was a 16-year-old female presented with primary amenorrhea, poorly developed breasts and had never seen her menses yet. She had no abdominal pain/distention, and she has no family history of similar congenital anomalies. She had no history of exposure to radiation, specific medications, or infection in her mother during pregnancy. Her medical, surgical, and social history was unremarkable. On physical examination, she was short with a height of 140cm, and her vital signs were within normal range. The breasts weren't developed and had mild sparse pubic hair, with normal appearing female external genitalia without palpable inguinal mass.

She was investigated with trans-abdominal ultrasound, hormone analysis and MRI of the pelvis. The hormone analysis revealed elevated level of follicle-stimulating hormone (FSH), luteinizing hormone (LH) with low level of Estradiol and progesterone (Table 1). MRI of the pelvis without IV contrast indicated non visualization of the uterus and ovaries with abnormal configuration of the vagina. And normal size, shape and contour of the urinary bladder with no intra-vesical filling defect with no evidence of pathological pelvic lymph nodes, with final impression of uterine agenesis with absent ovaries and vaginal dysplasia. The diagnosis of ovarian and uterine agenesis with premature ovarian insufficiency was made and she was counseled and informed her medical problem with further follow-up for her condition.

The second case was a 23-year-old patient with primary amenorrhea since adulthood. She had not developed secondary sexual characteristics yet with short stature. She had no similar problem in the family and had no abdominal pain or distention. She had never been sexually active. Physical examination revealed short girl with height of 130cm and breasts wasn't developed with absent pubic hair and normal appearing female external genitalia.

The hormone analysis revealed elevated level of FSH and LH with low level of Estradiol and progesterone (Table 1). MRI of pelvis without contrast revealed very small uterus and vagina with non-visualized ovaries. And no abnormal pelvic mass or collection without any pathological lymph node with normal shape and contour of urinary bladder, with final diagnosis of uterine and vaginal dysplasia with absent ovaries. She was counseled about the possible options of treatment and had follow up to the outpatient department for further counseling and management.

Table 1: Hormone analysis and MRI result of the two cases.

No.	Hormone analysis	Case 1	Case 2
1.	Estradiol	<5.0 (pg/mL)	<5.0 (pg/mL)
2.	FSH	121.8 (mIU/mL)	133.1 (mIU/mL)
3.	LH	29.9 (IU/L)	27.5 (IU/L)
4.	Progesterone	0.18 (ng/mL)	<0.05 (ng/mL)
5.	Prolactin	8.36 (ng/mL)	9.29 (ng/mL)
6.	Testosterone	<2.5 (ng/dL)	<2.5 (ng/dL)
MRI finding of both cases			
7.	MRI (without contrast)	Uterine agenesis with vaginal dysplasia	Uterine and vaginal dysplasia
		Absent ovaries	Absent ovaries

Discussion

The occurrence of concomitant ovarian and uterine agenesis is extremely rare. The differential diagnosis of primary amenorrhea with normal FSH, LH and external genitalia pointing to an obstructive etiology. But both cases had high level of FSH, LH and poorly developed external sexual characteristics. This was consistent with other literatures that, the association of Mullerian agenesis and gonadal dysgenesis, though reported, is exceedingly rare [9-11]. Besides, approximately 17% of cases of ovarian agenesis had concomitant uterine anomalies and two instances of MRKH with 46, XX karyotype and bilateral ovarian absence were observed [12]. Thus, this could be among the few reported cases in medical literature.

Both cases had primary amenorrhea, short stature and absent sexual external characteristics. It was difficult to classify to specific category due to the combination of abnormalities. This was consistent to other case report that clinical features did not fit into any one disorder as patient had features of Turner syndrome, MRKHS and androgen insensitivity syndrome [2]. Even though they had no clinical features of Turner syndrome, karyotyping may confirm further the diagnosis and guiding management. These patients had primary amenorrhea without abdominal pain/distention, and bluish discoloration of the vulva. Literatures reported that the most common cause of primary amenorrhea is gonadal dysgenesis, followed by mullerian duct agenesis [4,5]. These scenarios exclude the obstructive causes of primary amenorrhea and revealed early insult of ovaries with premature ovarian insufficiency as the secondary sexual characteristics weren't developed in both cases.

Both cases were short with ovarian agenesis and underdeveloped secondary sexual characteristics but had no clinical features of Turner syndrome. Similarly, other report indicated that Turner syndrome or gonadal dysgenesis in females is characterized by complete or partial absence of second sex chromosome with absent or insufficient development of ovaries and may present with lack of development of secondary sexual characteristics, primary amenorrhea and/or specific Turner stigmata [7]. Karyotype testing in these atypical cases is the most important and crucial investigation before clinching the final diagnosis to differentiate

it from androgen insensitivity syndrome or if patient has clinical findings not fitting into diagnosis of MRKH syndrome [2].

The concomitant occurrence of clinical features, MRI finding and hormone analysis of premature ovarian insufficiency were consistent with the diagnosis of ovarian and Mullerian agenesis. Literatures reported that exact reason for unusual association of Mullerian agenesis and gonadal dysgenesis is not clear and needs further exploring the genetic basis of these rare combinations [2]. A small minority of cases reported bilateral ovarian absence, typically presenting as primary amenorrhea [13]. And, other study described patient with primary amenorrhea, hyper gonadotropic hypogonadism, bilateral gonadal absence, rudimentary uterus with a normal vagina and kidneys [14,15].

MRI is recommended in these patients to show the presence of the uterus or remnants, gonads (ovary) and the location of the gonads. Karyotype helps to differentiate androgen insensitivity syndrome (AIS), (46, XY) from those with MRKH (46, XX). Assessment of serum levels of FSH, LH, and testosterone further helps in confirming AIS, where in the testosterone levels will resemble those of a male individual. Absence of karyotyping in low-income countries like Eritrea further complicates the patients' condition and management options. Karyotyping of these patients may reveal the diagnosis, offering patients the accurate diagnosis for proper psychological counseling of patients. This extremely rare occurrence of cases needs further analysis to reach the specific diagnosis. These cases had no signs of AIS as elevated level of testosterone, but karyotyping may help in confirming this condition, excluded Turner syndrome and AIS.

Breaking the bad news and further fertility treatment options was very difficult. Psychological counseling was done, and the treatment alternatives could be medical as continuous combined estrogen–progesterone pills or progesterone-only pills and surgical options as vaginal reconstructive surgery. But future fertility options as gestational surrogacy or egg donation and pregnancy by *in vitro* fertilization can't be offered for both cases. Thus, they were advised about the possible options of adoption and further medical evaluation for concomitant medical complications.

Conclusion

The occurrence of concomitant ovarian and uterine agenesis is extremely rare. The history of primary amenorrhea with absent thelarche, hormone analysis and MRI findings were suggestive. Breaking the bad news and counseling was difficult, which can be solved by karyotyping. Health professionals awareness about these rare occurrence is crucial for proper diagnosis, management and counseling.

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