Co-Existence of Müllerian Agenesis and Gonadal Dysgenesis in a 46, XX Female: A Case Report

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Abstract

Primary amenorrhea is a common clinical presentation with a wide differential, ranging from hormonal to structural etiologies. The co-existence of Müllerian agenesis and gonadal dysgenesis in a phenotypically normal female with a 46, XX karyotype is exceptionally rare and presents a diagnostic challenge. We report a 24-year-old unmarried woman who presented with primary amenorrhea and delayed pubertal development. She had no signs of hyperandrogenism or relevant family history.Physical examination revealed Tanner stage 3 breast development and scanty axillary and pubic hair. Laboratory investigations demonstrated hypergonadotropic hypogonadism with a normal 46, XX karyotype. Imaging revealed absent ovaries and a hypoplastic uterus. The patient was initiated on hormone therapy. This case highlights a rare dual pathology underlying primary amenorrhea in a phenotypically female patient. Clinicians should maintain a high index of suspicion for overlapping structural and gonadal anomalies when evaluating primary amenorrhea.

Keywords: Menorrhea; Gonadal Dysgenesis; Müllerian Agenesis; Hypergonadotropic Hypogonadism; Karyotyping.

Introduction

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a congenital condition characterized by the hypoplastic uterus and the upper two-thirds of the vagina in phenotypically and karyotypically normal females. Women with MRKHS typically have normal ovaries and secondary sexual characteristics. About 1 in 4,500 women is affected by MRKHS and it is considered as the second most common cause of primary amenorrhea.[1] On the other hand, gonadal dysgenesis is characterized by absent or underdeveloped ovaries, leading to hypergonadotropic hypogonadism. It is a very rare condition affecting 1 in 10,000 women and usually associated with a variety of karyotypes, including 46, XX, 45, XO, mosaicism, or partial deletions of the X chromosome.[2] In contrast to MRKHS, women with gonadal dysgenesis present with primary amenorrhea and under-developed secondary sexual characteristic.[2] Data suggests that the coexistence of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome and gonadal dysgenesis is extremely rare.[3,4] The coexistence of the two conditions is associated with varying anatomical presentations. Kisu et al. reported one case of a patient with a rudimentary uterus, with normal fallopian tubes and streak ovaries (3), while another case described a woman with the absence of identifiable internal genitalia.[4] The karyotyping was 46, XX in both cases. Treatment typically involves hormonal replacement therapy to develop secondary sexual characteristics and prevent osteoporosis.[3] In the current case, we presented a 24-year-old woman with primary amenorrhea. Investigations revealed a coexistence of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome and gonadal dysgenesis, which will add to the rare existing literature.

Case Report

A 24-year-old unmarried woman presented to the clinic with a history of primary amenorrhea. She denied any symptoms of acne, hirsutism, constipation, or cold intolerance. There was no history of galactorrhea, headache, cyclical pelvic pain, hot flushes, or mood swings. The patient reported delayed breast development and appearance of secondary sexual characteristics at the age of 19 years. There were no clinical features suggestive of Cushing's syndrome, such as proximal myopathy, purplish striae, facial plethora, or easy bruising. Her family history was unremarkable; her sister had attained menarche at the age of 12 years, and there was no known family history of reproductive or autoimmune disorders. The patient had no history of pelvic trauma or surgery, radiation or chemotherapy, and was not taking any medications. She had also not previously sought medical attention for her condition. On examination, there was no acne or hirsutism. Breast development was consistent with Tanner stage 3, and axillary and pubic hair were scanty. Her blood pressure was 112/56 mmHg, pulse 94 beats per minute, weight 150.4 kg, height 170 cm, and her body mass index was 52 kg/m². Thyroid and abdominal examinations were unremarkable. Laboratory investigations revealed hypergonadotropic hypogonadism, with normal karyotyping (46, XX) as shown in Table 1. Pelvic ultrasound did not visualize the uterus or ovaries [Figure 1], and pelvic MRI revealed a very small uterus with absent ovaries [Figure 2]. Bone densitometry demonstrated osteopenia, with a lumbar spine Z-score of –1.7 and a left femoral neck Z-score of 1.2. Based on the clinical presentation, physical examination, hormonal profile, and imaging findings, the patient was diagnosed with the co-existence of Müllerian agenesis and gonadal dysgenesis, which is a rare clinical entity with only a few cases reported in the literature. .The patient was started on cyclical hormone replacement therapy with Progyluton, containing estradiol valerate and norgestrel, aimed at inducing endometrial proliferation and maintaining secondary sexual characteristics. The follow up treatment plan spans 6–12 months, with periodic reassessment of clinical response, bone health, and metabolic profile. Counseling was provided by the attending physician at the time of diagnosis to help the patient understand her condition and its implications, particularly regarding fertility and long-term hormonal management.

Table 1: Laboratory investigation results.

Lab test	Result	Reference Range
Hemoglobin	11.7 g/dL	11.0-14.5
Estradiol	<0.02 nmol/L	0.09–1.4
Follicle Stimulating Hormone (FSH)	39.3 IU/L	3.5–12.5
Luteinizing Hormone (LH)	20.0 IU/L	2.4–12.6
Testosterone	<0.1 nmol/L	0.3-1.7
Thyroid Stimulating Hormone	4.0 mIU/L	0.27-4.2
Prolactin	126 mIU/L	102-496
Estimated Glomerular Filtration Rate (EGFR)	>90 ml/min/1.73 m2	>90 ml/min/1.73 m2
Karyotyping	46, XX	Normal Female

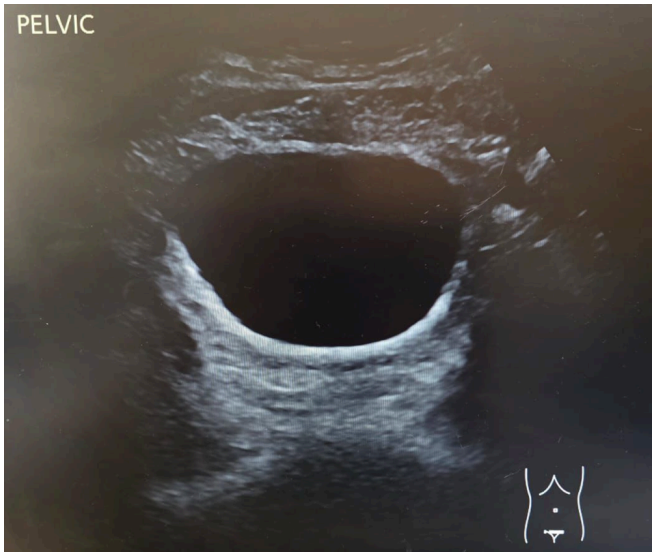

Figure 1: Ultrasound pelvis of a 24-year-old female showing absent uterus and both ovaries

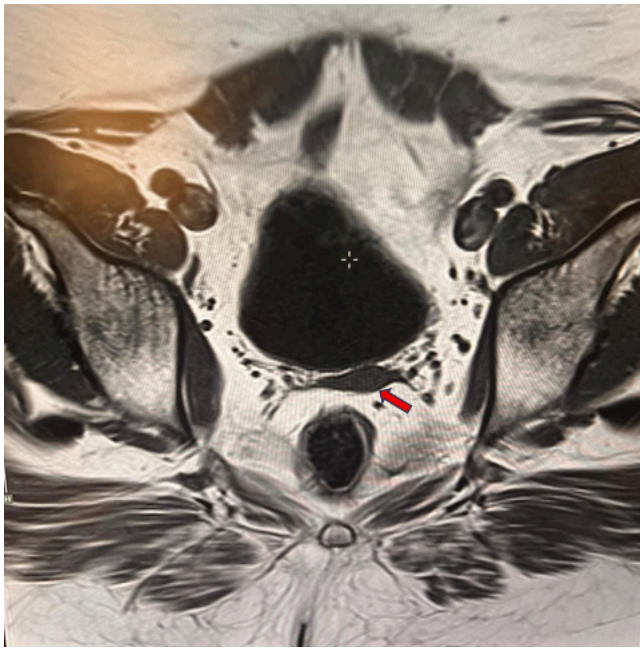

Figure 2. MRI pelvis of a 24-year-old female showing hypoplastic uterus (arrow) with absent both ovaries

Discussion

The coexistence of Müllerian agenesis with gonadal dysgenesis with normal karyotype is extremely rare. Few case reports exist in the literature, posing diagnostic and therapeutic challenges in clinical practice. While both conditions have similar presentation of primary amenorrhea, the presence of under-developed ovaries and hypergonadotrophic hypogonadism should challenge the diagnosis of isolated MRKH. The clinical and diagnostic ambiguity lies in the rarity of both conditions. A systematic approach to such rare cases – including history, physical examination, hormonal studies, karyotyping and radiological imaging – will help in differentiating between isolated or coexisting conditions.

Although the patient had class III obesity (BMI 52 kg/m²), the pattern of hypergonadotropic hypogonadism and delayed secondary sexual development, along with imaging-confirmed absence of ovaries, supports a primary gonadal failure rather than obesity-induced functional hypogonadism. Furthermore, peripheral aromatization in obesity typically increases circulating estrogens, yet our patient exhibited low estradiol levels. While obesity may reduce ultrasound sensitivity, pelvic MRI corroborated Müllerian agenesis and gonadal dysgenesis. Therefore, obesity likely did not contribute significantly to the underlying pathophysiology in this case.[5]

Importantly, the patient's delayed breast development, beginning at 19 years, is a hallmark of disrupted pubertal progression and prompted a broad differential diagnosis. Causes of primary amenorrhea with delayed secondary sexual development include central (hypothalamic or pituitary) causes such as functional hypothalamic amenorrhea and Kallmann syndrome, as well as primary gonadal failure seen in Turner syndrome, its mosaic variants, and 46,XX gonadal dysgenesis. Functional hypothalamic amenorrhea is typically associated with low or normal gonadotropins, in contrast to the marked hypergonadotropic profile observed in our patient. Turner syndrome and its variants were excluded by the patient's normal stature, absence of phenotypic stigmata, and a confirmed 46,XX karyotype. The absence of uterine and ovarian structures on imaging, combined with elevated gonadotropins and low estradiol, favored the rare diagnosis of concurrent Müllerian agenesis and 46,XX gonadal dysgenesis.[6]

Jha et al. (2019) presented a case of a young woman who exhibited the clinical features of both gonadal dysgenesis and Müllerian agenesis in terms of primary amenorrhea and absent secondary sexual characteristics.[4] Her karyotyping was 46, XX. Another case, reported by Opdecam et al, emphasized the importance of a systematic approach in such cases, to avoid misdiagnosing women with isolated MRKH based on the absence of Müllerian structures on imaging, when in fact they have a coexistence of both conditions.[7] The authors substantiated the psychological impact of such a condition on the women affected, mainly driven by challenges in infertility and body image.[7] Additionally, Manne et al. (2016), John et al. (2022) and Dede et al. (2008) reported a young woman with normal karyotype (46, XX), who presented with primary amenorrhea, absent Müllerian structures and streak gonads, indicative of the coexistence of MRKH syndrome and gonadal dysgenesis.[2,8,9] Importantly, variability in anatomical presentation in such cases is evident in the published case reports. For instance, Kisu et al. presented a case of the coexistence of MRKH and gonadal dysgenesis with normal karyotype (46, XX).[3] In their case, the patient had a hypoplastic uterine cervix and a normal vagina, features that are atypical for classical MRKH syndrome.[3] Also, variability in karyotyping is evident in a rare case of an 18-year-old woman with Turner syndrome (45.XO) and concurrent Müllerian agenesis.[10] Renal and skeletal anomalies may occur in women with MRKH. About 35% and 24% of women with MRKH were observed to have unilateral horseshoe shaped kidney and skeletal anomalies, like scoliosis and spina bifida, respectively.[2,11,12]

Supplementary table 1 depicts further details of the cases.

Unlike prior reports, our patient had markedly delayed puberty, confirmed absence of both ovaries and a hypoplastic uterus on MRI, and an exceptionally high BMI (52 kg/m²), which complicated diagnostic imaging and hormonal interpretation. The combination of these findings, along with the late presentation at age 24 without prior evaluation, underscores the diagnostic complexity and clinical uniqueness of this case within the limited literature on dual pathology in 46,XX females.

The coexistence raises questions about shared embryological pathways and possible genetic links between the two conditions. Manne et al. proposed that this overlap might be due to disruptions in genes that regulate both gonadal and Müllerian development.[2] Shah et al. proposed three possible mechanisms for the coexistence: a shared genetic mutation or deletion, microdeletions in the X chromosome disrupting critical developmental proteins, or the influence of environmental endocrine disruptors,[13]

Clinically, this coexistence presents unique challenges in management, particularly regarding fertility preservation and hormonal replacement therapy. While assisted reproductive technologies offer hope for some patients with isolated Müllerian agenesis, those with gonadal dysgenesis often lack functional gametes, making adoption the only viable option. Hormonal replacement therapy is essential for patients with gonadal dysgenesis to maintain secondary sexual characteristics and bone health. Multidisciplinary care teams comprising endocrinologists, gynecologists, geneticists, and psychologists are critical in providing comprehensive care.

Conclusion

The rare coexistence of Müllerian agenesis and gonadal dysgenesis in 46, XX individuals is a complex clinical entity that necessitates a thorough and integrative diagnostic approach. The coexistence of MRKH with gonadal dysgenesis underscores the importance of early diagnosis, multidisciplinary management, and ongoing research to unravel the genetic and developmental underpinnings of this intriguing anomaly. The overlap between these conditions not only complicates clinical care, but also highlights the intricate interplay of the genetic and embryological factors that govern human development.

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Supplementary Table 1: Details of Previously Reported Cases in Literature.

Case number	Author & Year	Age at presentation	Karyotype	Biochemical results	Ultrasound or MRI pelvis findings	Additional anomalies	Treatment
Case 1	(Jha et al., 2019).	24 years	46, XX	Hypergonadotrophic hypogonadism FSH (55.4 IU/L), LH (11.4 IU/L), Estradiol ((<5 pg/ml),	The uterus and both ovaries were not visualized; the vagina was normal but ended blindly superiorly, and both kidneys appeared normal.	Nil	Estrogen (ethinyl Estradiol Valate)
Case 2	(Manne et al., 2016).	20 years	46, XX	Hypergonadotrophic hypogonadism FSH (77 IU/L) LH (37 IU/L) with low estradiol (<5 pg/ml) levels.	US abdomen: single horseshoe shaped kidney and absence of uterus and ovaries. MRI abdomen and pelvis: bladder and rectum without interposition of uterus. Bilateral ovaries are also not seen in the adnexa	Gibbus in the lumbar region with short fourth metatarsal in the left foot. Fusion of L1 and L2 vertebrae and scoliosis of dorsal spine. Dilated aorta and bicuspid aortic valve. Single horseshoe shaped kidney	Ethinyl estradiol 10 µg/day
Case 3	Kisu et al., 2019	17 years	46, XX	Hypergonadotrophic hypogonadism (LH: 17 IU/L, FSH: 63 IU/L, estradiol:<5	Internal genitalia could not be identified on transrectal ultrasound and (MRI), except for the uterine cervix, CT lack of internal genitalia, Laparoscopy revealed a rudimentary uterus with a cervix and round ligaments, normal fallopian tubes and bilateral streak ovaries	Nil	Hormonal therapy with estradiol.
Case 4	**Shah et al., 2013**	21 years	46, XX	Hypergonadotrophic hypogonadism, FSH: 100 IU/L, LH: 32 IU/L, estradiol: <0.5	Ultrasound of pelvis did not show uterus or ovaries. Laparoscopy revealed absence of uterus, normal fallopian tubes and streak ovaries.	Her computed tomography scan of the brain revealed bilateral periventricular and corona radiata hypointensity with undulation of both lateral ventricles suggestive of ischemic insult, rest of brain parenchyma and	Ethinyl estradiol 10 µg/day daily

						pituitary were normal	
Case 5	John et al., 2022	18 years	46, XX	Hypergonadotrophic hypogonadism, LH: 15miu/ml, FSH: 40miu/ml, estradiol was low: 25.2pg/ml	MRI pelvis revealed: absent uterus, ovaries and the fallopian tubes.		Hormonal Replacement Therapy
Case 6	Dede et al., 2008	18 years	46XX	FSH: 85 IU/L, LH:40 IU/L, and estradiol: 14 pg/dL	Diagnostic laparoscopy: rudimentary uterus without ovaries and normal bilateral fallopian tubes.		Oral contraceptives