CASE REPORT

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Mayer-Rokitansky-Küster-Hauser syndrome in a girl with a history of acute lymphoblastic leukemia – COVID-19 pandemic a reason for delayed diagnosis

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Abstract

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is characterized by uterus and vagina aplasia with normal ovary function. The first symptom is primary amenorrhea. It is necessary to exclude potential causes, among which MRKH syndrome takes second place. A 15-year-old patient was first admitted to the gynaecology clinic due to the primary amenorrhea and abdominal pain. The girl had received ALL chemotherapy at the ages of seven and eight. Hormonal tests showed no ovarian dysfunction. In the transrectal USG performed by a paediatric gynecologist a 2.5cm long vaginal fragment was visualized, MRI confirmed a rudimentary uterus. The girl was offered vaginal correction by dilators. Intercourse attempts were still painful despite the treatment, hence the patient agreed to surgery. The diagnosis of MRKH syndrome in paediatric patients can be complicated by the coexistence of other conditions presenting with primary amenorrhea, especially among patients after chemotherapy.

Key words

MRKH syndrome, disorders of sex development, amenorrhea, Mullerian aplasia

INTRODUCTION

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital disease characterized by Müllerian duct aplasia, occurring in approximately 1 in 4,500–5,000 live female births [1]. It is characterized by the aplasia or agenesis of the uterus and upper part of the vagina in individuals with a normal female karyotype (46,XX). The etiology of the disease is not fully recognized, but both genetic and environmental factors affecting embryonic development are suspected [1, 2]. Although most cases are sporadic, familial occurrences have been reported [1]. MRKH syndrome is classified into two types: type I (44%), which presents with isolated müllerian anomalies, and type II (56%), which involves associated renal and skeletal malformations [1–3]. Typically, ovarian function and normal steroid hormone production in MRKH syndrome is preserved. That is why most patients develop normal secondary sexual characteristics with standard signs of thelarche and pubarche; however, they present with primary amenorrhea due to the absence of a functional uterus [1, 2].

The gold standard for diagnosing MRKH syndrome is through pelvic magnetic resonance imaging (MRI) [1]. The diagnosis is most frequently made in adolescent girls who present with primary amenorrhea, which is defined as the lack of menses at the age of 15. The MRKH syndrome is the second most common cause of primary amenorrhea [2, 4]. Diagnosis may be complicated by coexisting comorbidities affecting the endocrine system. Reported associations include Turner syndrome, gonadal dysgenesis, and prolactinoma [5–9]. A rare case is presented of the MRKH syndrome in an adolescent childhood cancer survivor previously treated for acute lymphoblastic leukemia (ALL), who reported to the Department of Paediatric and Adolescent Gynaecology at the Medical University in Lublin, eastern Poland, with primary amenorrhea at the age of 14 years and 11 months.

CASE REPORT

The patient was admitted to the Gynaecological Outpatient Clinic for the first time in October 2020, during the COVID-19 pandemic, at the age of 15 years and 11 months due to primary amenorrhea. She had a history of chemotherapy for ALL at ages 7 and 8 years. The patient's caregiver did not report any other serious or chronic diseases or surgeries in medical history. A gynaecological examination was performed, but was limited to inspection of the external genitalia as the patient had no history of sexual intercourse. The patient's vaginal introitus was visualized with normally appearing hymen, labia majora and minora and the clitoris. Due to patient distress, pelvic

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examination and vaginal patency probing were deferred. The normal-looking vaginal opening was not suspected for genital anomaly. At the initial visit, laboratory evaluation, including HOMA-IR, free androgen index (FAI) and anti-müllerian hormone (AMH) were ordered. There was no indication of ovarian dysfunction or other pathologies. Ultrasonography of the reproductive organs was ordered and performed in the Radiology Department. A transabdominal ultrasound revealed the small uterus with the diameters of the uterine corpus – 30 x 9 mm. The endometrium was described as 'not indistinguishable', and both normally appearing ovaries were present, with no pathological features. Description of the vagina was not included in the examination, which is common in the pelvic ultrasound reports.

After the examination, due to COVID-19-related delays, the patient was not provided with correct interpretation of the test results for almost four months, and subsequently the patient was lost to follow-up for nearly two years. In December 2022, she presented again due to continued primary amenorrhea, acne, periodical abdominal pain, and unsuccessful attempts at intercourse.

On physical examination, the patient presented full maturity according to the Tanner scale (M5 P5), with excess hair extending to cover the perineal and gluteal area as well as the thighs. The gynaecology examination revealed vulvar area within the norm: a normally appearing clitoris, labia majora and minora, as well as hymen and vaginal introitus. The pelvic examination was attempted after patient consent, as she reported to be sexually active. On the bimanual vaginal examination the abnormal vaginal anatomy was revealed with a 3 cm long vaginal pouch and no cervix palpable. On transrectal examination the uterus and ovaries could not be palpated and no abnormal masses were detected. Palpation did not cause any pain or discomfort.

During that visit, a transrectal ultrasound was performed by a gynaecologist, who was not able to visualize a normally appearing uterus. A segment of the vagina measuring 2.5 cm was detected (Fig. 1). Both ovaries with normal follicular

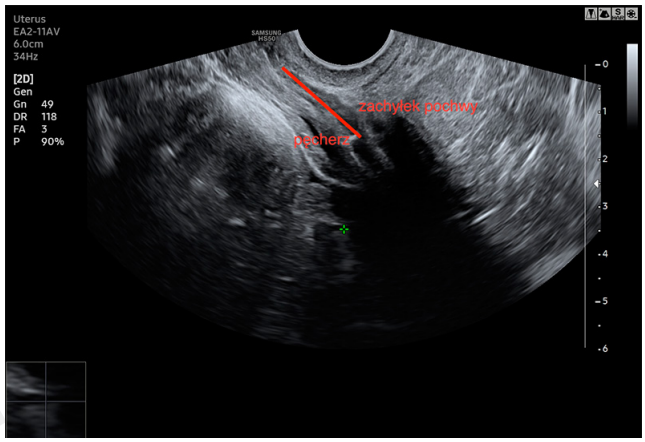

Figure 1. Transrectal ultrasound image depicting a vaginal recess

appearance were visualized (right ovary – 7 ml, left – 9.5 ml) and did not show any pathological features (Fig. 2 and 3). At that point, MRKH syndrome was suspected. As the patient was presenting with periodical lower abdominal pain, it was necessary to exclude the presence of a rudimentary uterine horn. Therefore, the patient was referred for MRI. Additionally, karyotyping and laboratory tests were recommended.

At the next visit, the patient reported aggravated acne – laboratory test results revealed several abnormalities: testosterone concentration at the upper limit of normal (68 µg/dl), elevated dehydroepiandrosterone sulfate (DHEA-S) levels (489 µg/dl), and a lower level of AMH compared to the previous examination from 2020 (2022 – 2.65 ng/ml, 2020 – 3.6 ng/ml). In order to relieve patient's symptoms (abdominal pain and acne) she was prescribed contraceptive pills containing ethinyl estradiol and dienogest. Hyperandrogenism revealed in the laboratory tests with symptoms of acne and abdominal pain could have potentially indicated the presence of polycystic ovarian syndrome (PCOS). However, such a diagnosis could not

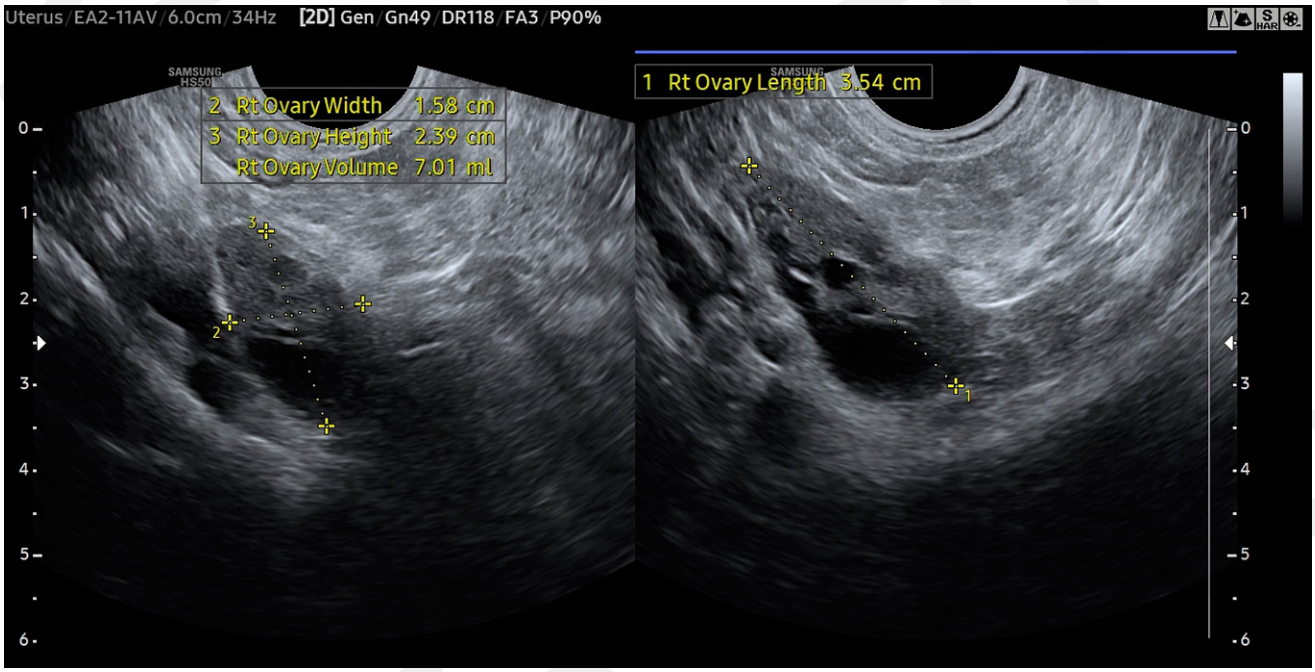

Figure 2. The transrectal ultrasound image depicts the right ovary

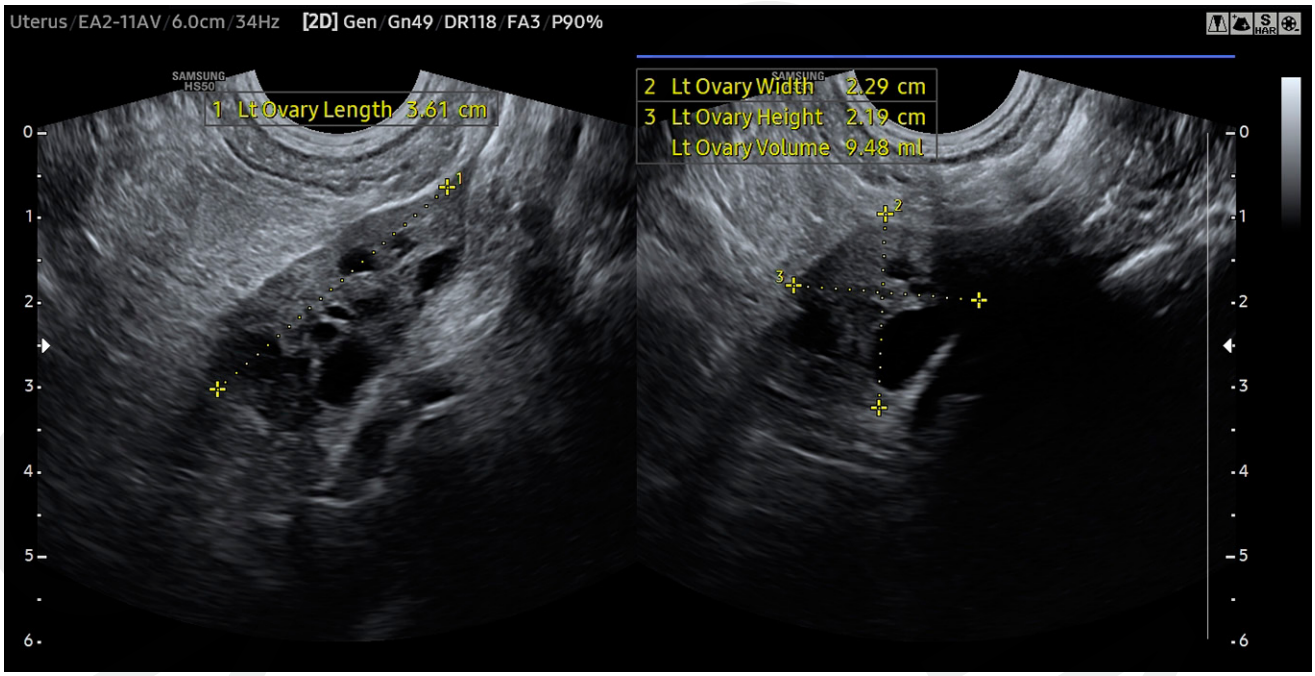

Figure 3. The transrectal ultrasound image depicts the right the left ovary

be unequivocally established because due to the lack of uterus and vagina, bleeding pattern could not have been assessed. Moreover, the patient's hyperandrogenism could be explained by MRKH syndrome itself, which is the reason for the diagnosis of PCOS not being taken up again.

In February 2023, the patient returned to the clinic for the results of the previously ordered tests. The MRI results suggested the presence of a rudimentary uterus, with a length of approximately 4 cm, without visible endometrium, both ovaries present, without pathological features. Genetic testing confirmed a 46, XX karyotype. The patient reported improvement in acne after starting therapy with ethinylestradiol and dienogest, as well as relief from abdominal pain. During the visit, the nature of the condition was explained to the patient and her mother, and the therapeutic management was proposed with the possibility of either the surgical approach (removal of the rudimentary horn) or dilation therapy. Consultation with a reproductive endocrinology specialist was also recommended due to the risk of premature ovarian insufficiency (POI) after ALL treatment. At that point, both the patient and the caregiver (the mother) decided to begin with dilatation therapy combined with oral contraception, and to consider the surgery as a future option. The patient was carefully instructed on the dilation method and explained that the method required patience and could be combined with intercourse attempts to improve outcome. She was able to comply with the method for only a few weeks. Her adherence was poor and neither anatomical improvement nor complications of the dilation therapy were noted on physical examination. Compliance with that treatment modality was difficult for the patient, as she complained about persistent dyspareunia, and therefore she decided to undergo the reconstructive surgery. Consultation with the gynaecology reconstructive surgeon was scheduled to discuss the procedure.

In September 2023, the patient returned to the clinic with the results of the laboratory tests. Due to the declining level of AMH over the past 3 years (12.2020 – 3.6 ng/ml, 02.2022 – 2.65 ng/ml, 05.2023 – 2.91 ng/ml, 09.2023 – 1.39 ng/ml), indicating the progression of ovarian dysfunction, the patient was offered the option of oocyte cryopreservation, but no decision was made in this regard at that time. The patient was recommended to continue with contraceptive pills therapy and return for regular follow-up consultations. Since the patient had reached adulthood in November 2023, she has not returned to the paediatric gynecology clinic. However, a phone conversation revealed that the patient was awaiting a surgical consultation and continued taking hormonal contraception.

DISCUSSION

In the cases of primary amenorrhea, it is important to apply comprehensive diagnostics to differentiate between the most common causes, including: congenital malformations of the reproductive tract (e.g., Müllerian duct agenesis), gonadal dysfunction (Turner syndrome, enzymatic disorders, Primary Ovarian Insufficiency), hypothalamic or pituitary causes, disorders of other endocrine glands, or multifactorial disorders, such as PCOS [10].

Premature ovarian insufficiency may be associated with many different risk factors. A study by Giri Rinky et al. included genetic factors contributing to the development of POI, low birth weight, poor childhood growth and cognitive function, early menarche, obesity [11]. POI is also encountered in many cases of childhood cancer survivors. Ovarian damage that can disrupt fertility often occurs in solid tumours and haematologic malignancies survivors, due to the use of combined chemotherapy with alkylating agents [12].

The diagnostic methods used for the diagnosis of POI are serial measurements of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), as well as the concentration of AMH. In the current case, the patient sought medical

advice due to primary amenorrhea. At the age of 7–8, the girl underwent chemotherapy due to ALL. The initial laboratory results did not indicate ovarian dysfunction. However, during subsequent visits, persistently decreasing levels of AMH were noticed, which could indicate premature ovarian insufficiency caused by the chemotherapy received in childhood.

The diagnosis of MRKH syndrome in paediatric patients can also be complicated by the coexistence of other conditions presenting with primary amenorrhea. Mohammad Moin Shahid described the case of a 16-year-old girl presented with complaints of absent menarche and stunted growth. Further investigations confirmed Turner syndrome with associated Müllerian agenesis, horseshoe kidneys, and gross hydronephrosis [5]. In the current case, karyotype analysis was recommended to rule out genetic causes. Genetic testing confirmed a 46, XX karyotype, which excluded Turner's syndrome as a cause of primary amenorrhea. No urinary tract abnormalities were noted.

The coexistence of MRKH syndrome alongside gonadal dysgenesis, marked by ovarian absence or impaired development, is a rare occurrence. Dickson Hezekiah John reported the case of an 18-year-old Nigerian woman with primary amenorrhea, incomplete breast development, without history of cyclical abdominal pain or attempts at penetrative vaginal intercourse. Additional tests showed significantly elevated serum gonadotropins, decreased levels of serum estradiol and progesterone, and elevated testosterone levels. Imaging studies confirmed the absence of uterus, ovaries, and fallopian tubes. Karyotyping revealed a 46, XX karyotype. The diagnosis of Mullerian agenesis with coexisting gonadal dysgenesis and poorly developed secondary sexual characteristics was made [6].

In the current study, hormonal findings showed abnormalities consistent with the diagnosis of PCOS; however, due the lack of menses, the menstruation pattern which is a hallmark of PCOS diagnosis in adolescent patients, could not be assessed; therefore the diagnosis of PCOS could only be provisional.

When diagnosing the underlying cause of primary amenorrhea, it is crucial to consider disorders affecting the endocrine system, including hypothalamic or pituitary causes and disorders of other endocrine glands. The literature review indicates that, there are cases of co-occurring MRKH syndrome with macro or microprolactinoma [8, 9]. Jarial Kush Dev Singh and Nur Aisyah Zainordin described cases of 17-year-old girls with complaints of not attaining first menarche. Laboratory test results revealed low levels of LH and FSH, along with elevated serum prolactin levels. MRI revealed the presence of pituitary tumours. In the current case, an MRI of the head was not ordered due to the lack of indications and correct hormonal test results (prolactin, LH and FSH levels were within the range of reference standards).

Imaging is crucial for the diagnosis of MRKH. Transabdominal ultrasound is the first line of investigation, but abdomino-pelvic MRI provides more precise and clear information about the patient's condition [13]. In the current case, both ovaries were normal and visualized by ultrasonography. MRI is most commonly used, however, as an additional method of detection. In literature, ovaries are often described as being within the norm, although MRKH syndrome may be accompanied by atrophic inguinal ovaries [14], ectopic ovaries [15], or malignant ovarian teratoma [16].

The primary concern for women with MRKH syndrome is limited fertility. Monitoring of FSH and estradiol levels is recommended for assessing ovarian function, and in certain cases, AMH levels may also serve as an additional indicator. Regarding fertility options, patients with MRKH may be offered surrogacy with embryo transfer, and in some countries, uterine transplantation is also available as a potential solution [2]. It is also important to underline that the appearance of the vaginal vestibule and the introitus may vary and there is a broad spectrum of vaginal abnormalities encountered in MRKH syndrome. There may be no vaginal pouch, a small pouch that accommodates only the tip of a swab, or, as in the presented case, a larger pouch that in paediatric patients can be mistaken for a normally developed vagina, potentially delaying diagnosis. This contributes to another challenge for patients with MRKH syndrome: dyspareunia and difficulty engaging in sexual activity. According to ACOG recommendations, the primary treatment for this condition involves the use of vaginal dilators to achieve gradual expansion of the vaginal walls. However, vaginal dilation in adolescent patients can be challenging, as it requires significant patience, persistence, and time. In such cases, alternative approaches, including surgical reconstruction, may need to be considered and discussed with the patient [2]. For persistent pain, pharmacological interventions may also be employed to suppress menstruation.

Many studies have increasingly focused on the genetic background of MRKH syndrome, although its etiology remains complex and multifactorial. Most cases of the occurrence of the disease are sporadic, but multiple familial cases have been reported, supporting the hypothesis of autosomal dominant inheritance with variable expressivity and incomplete penetrance [17]. Regarding specific genes that may contribute to impaired development of the Mullerian ducts, studies indicate links with a number of candidate genes, such as GREB1L, WNT4, LHX1, PAX8, TBX6 or HNF1B [18]. In addition, chromosomal microdeletions and duplications detected in regions 1q21.1, 16p11.2, and 17q12 have been implicated in contributing to the phenotypic diversity of MRKH syndrome [2].

CONCLUSIONS

MRKH syndrome is a rare cause of primary amenorrhea, which requires careful evaluation with pelvic MRI as the diagnostic gold standard. Coexisting hormonal abnormalities, such as hyperandrogenism in the course of PCOS, may complicate this diagnosis due to the absence of menstruation. Additionally, previous cancer treatment and declining AMH levels in a young patient highlight the risk of POI. The 3 conditions require long-term gonadal monitoring in terms of future endocrine well-being. Multidisciplinary care, including early fertility counselling, psychological support and regular hormone assessment, is essential to optimize long-term outcomes in patients with MRKH syndrome. Moreover, treatment in adolescents can be particularly difficult, since maintaining compliance with vaginal dilation is often problematic and may ultimately necessitate surgical intervention.

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