Received: 2 February 2024 | Revised: 24 June 2024 | Accepted: 29 July 2024

DOI: 10.1002/ccr3.9318

CASE REPORT

Clinical Case Reports Open Access WILEY

Rare case of complete gonadal dysgenesis in a female patient with primary amenorrhea and a 46XY karyotype

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Key Clinical Message

A comprehensive diagnostic approach is crucial for patients with primary amenorrhea and short stature. Karyotyping and imaging studies help to detect hidden chromosomal abnormalities and anatomical differences, emphasizing their value in this context.

Abstract

A 16-year-old girl with absent menstruation and short stature. Further examination revealed constitutional stunting and primary amenorrhea. Karyotyping revealed a 46, XY chromosomal abnormality, whereas pelvic ultrasonography showed uterine hypoplasia and a unicornuate uterus with a rudimentary horn. After 11 months of therapy, she experienced menarche and improved secondary sexual characteristics.

KEYWORDS

gonadal dysgenesis, karyotype 46, XY, primary amenorrhea, Swyer syndrome, uterine hypoplasia

1 | INTRODUCTION

Irregularities in fetal development can lead to health issues, such as disorders of sex development (DSD), which affect the formation of ovaries, testicles, sex chromosomes, and genital development in both males and females. Swyer syndrome or complete gonadal dysgenesis, which is characterized by the absence of menstruation, a normal or underdeveloped uterus, and the presence of gonadal streaks, was identified by Swyer in 1955.[1] This condition affects females with primary amenorrhea and a 46XY karyotype and is caused by mutations or deletions in the SRY gene located on the Y chromosome. It occurs in approximately one in 80,000–100,000 births.[2–5]

The cause of 46, XY complete gonadal dysgenesis is thought to be deletion of the short arm of the Y chromosome, which affects the SRY gene responsible for testicular development. Alternatively, it could be caused by mutations in other genes that hinder the function of SRY, or mutations in the SRY gene itself.[6] The primary transcription factors involved in testicular differentiation are SRY, SOX9, AMH, DAX1, SF1, WT1, GATA4, DHH, PTC, WNT4, and WNT7a.[7] Disabling SRY results in abnormal gonad formation. However, only approximately 10%–15% of females with a 46, XY karyotype have an SRY mutation.[8]

Females with Swyer syndrome are at higher risk of developing neoplastic transformation in their dysgenetic

gonads.[9] Approximately 30% of cases involve gonadal tumors, with gonadoblastoma being the most common type. While bilateral gonadectomy is recommended, timely surgical intervention is vital to prevent the growth of malignant neoplasms. In a study by Jiang et al., 67 patients with congenital gonadal dysgenesis were analyzed, and 15 patients (22.4%) had tumors including gonadoblastoma, seminoma, dysgerminoma, and choriocarcinoma.[10] It is essential to note that gonadoblastoma, although initially benign, can progress to a malignant dysgerminoma.[11]

Identifying rare genetic disorders is a global priority, and research on sex-differentiation mechanisms is crucial. Although treatment options for sexual development disorders have improved, further research is needed. Conducting thorough investigations and providing comprehensive accounts of each case are essential to determine the frequency and characteristics of clinical variations in complete gonadal dysgenesis in the Kyrgyz Republic. This article describes a unique case of complete gonadal dysgenesis in a patient with a 46XY karyotype and female phenotype.

2 | CASE PRESENTATION

A 16-year-old girl accompanied by her mother visited our medical center with concerns about absent menstruation and short stature. The patient was a single girl born to her mother and took birth through normal delivery with no reported complications.

2.1 | Past and family history

During birth, the newborn weighed 3000 g, measured 46 cm in length, and had an Apgar score of 8/9. The patient experienced delayed growth since infancy and her family history was unremarkable, with all close relatives having normal growth. The patient's mother reported that her menarche began at the age of 17. The heights of the patient's father and mother were 170 cm and 171 cm, respectively.

2.2 | Physical examination

The patient's arm length was 145 cm and the height percentile was 97. Their height was 147.4 cm, with a standard deviation of −2.38. Her BMI was 19 kg/m^2, with a standard deviation of +0.43. Her blood pressure was 120/70 mmHg and their heart rate was 72 beats per minute. However, their body composition is disproportionate and masculine. On examination, the thyroid gland appeared normal in size, texture, and elasticity. Furthermore, the individual exhibited typical patterns of female sexual development and hair thinning at the forehead area.

2.3 | Investigations

After endocrinological and gynecological examinations, the structure of the external genitalia according to the female type was observed, and constitutional stunting and primary amenorrhea were diagnosed. Laboratory test results showed normal levels for common blood and urine tests as well as for glucose, liver enzymes, iron, electrolytes, creatinine, and thyroid hormones. The hormone levels were as follows: luteinizing hormone at 35.0 mMU/ml, follicle-stimulating hormone at 86.6 mMU/ml, estradiol at 5.0 pmol/L, testosterone at 0.19 nmol/L, dehydroepiandrosterone at 2.7 mmol/L, prolactin at 12.9 ng/mL, somatotropic hormone at 0.17 nmol/L, and 17-OH-progesterone at 0.79 ng/mL.

2.4 | Karyotyping

The karyotype revealed sex inversion with a 46, XY chromosomal abnormality (Figure 1).

2.5 | Pelvic ultrasonography

Pelvic ultrasonography revealed that the uterus was prepubertal and in an anteflexion position, while its contours were clear and smooth. The uterus measured 6.4 cm

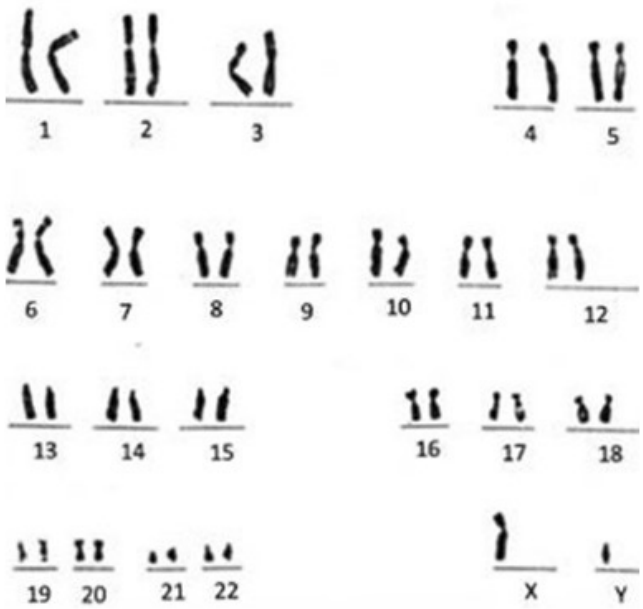

FIGURE 1 46XY karyotype of the patient.

×10 cm ×13 cm, and the endometrium was 1 mm thick. The cervix was 18 mm long and the uterine cavity 2.5 mm expanded due to liquid contents. Ultrasound failed to identify the right and left ovaries but revealed uterine hypoplasia and a unicornuate uterus with a rudimentary horn (Figure 2).

2.6 | Differential diagnosis

Turner syndrome was suspected, and genetic consultation and cytogenetic study were recommended.

Ultrasound imaging of the mammary glands revealed a well-developed ductal system with a hypoechoic stromal zone and fibrosis surrounding the ducts, with no signs of nodular or cystic formations. Abdominal and pelvic ultrasounds showed normal echo parameters, and magnetic resonance imaging of the chiasmal-cellular region did not reveal any pathological changes or focal pituitary lesions. Radiography of the hands and wrist joints indicated that the bone age was consistent at 13.5 years.

2.7 | Pelvic magnetic resonance imaging

Findings from pelvic magnetic resonance imaging demonstrated the absence of both the uterus and its associated adnexa, along with a concomitant blind vagina (Figure 3). The bladder was well filled and the bladder wall remained unchanged. The contents were homogeneous, and the urethra was typically expressed. Distal parts of the ureters were visible without any signs of expansion or local constriction.

2.8 | Treatment

Based on the examination results, the patient was advised to undergo laparoscopic removal of the gonads on both sides, followed by hormone replacement therapy with estrogen and progesterone to initiate a menstrual-like reaction.

2.9 | Outcome and follow-up

Eleven months after initiating hormone replacement therapy, the patient experienced menarche and noticeable improvement in her secondary sexual characteristics. Breast development progressed to Tanner stage II.

3 | DISCUSSION

DSD are conditions in which chromosomal, gonadal, and anatomical sex development are atypical.[12] Swyer syndrome is a group of clinical conditions that involve abnormal gonad development in the fetus, including partial and complete forms. Partial forms are characterized by partially developed Wolffian ducts and varying degrees of testicular development and function.[13,14] Complete forms involve fully or partially developed structures derived from Mullerian ducts and dysgenetic or strip-shaped gonads.[12]

Primary amenorrhea is characterized by the absence of menstruation at age 15 or 3 years after the onset of menarche, while secondary amenorrhea is defined as the absence of menstruation for at least 3 months in a woman with regular menstrual cycles or for at least 6 months in any woman who had previously experienced spontaneous menstruation.[15]

Swyer syndrome, characterized by underdeveloped testicles, feminine external genitalia, a potential uterus, and a 46 XY genetic makeup, can be caused by mutations in SRY.[16] However, other genetic abnormalities may present with similar symptoms. Mutations in WT1, SF1, SOX9, and ATRX can lead to Fraser syndrome, Denis-Drash syndrome, campomelic dysplasia, and various other conditions, respectively.[16] In this case, the patient

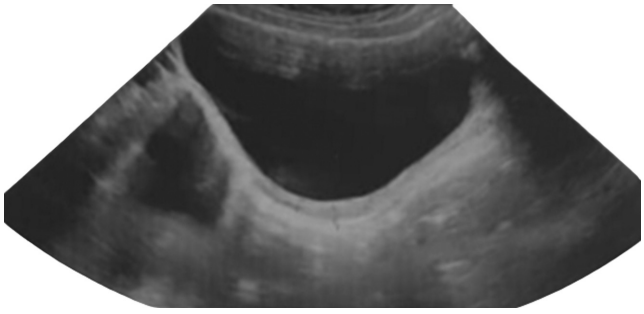

FIGURE 2 Ultrasound findings revealed uterine hypoplasia and unicornuate uterus with a rudimentary horn.

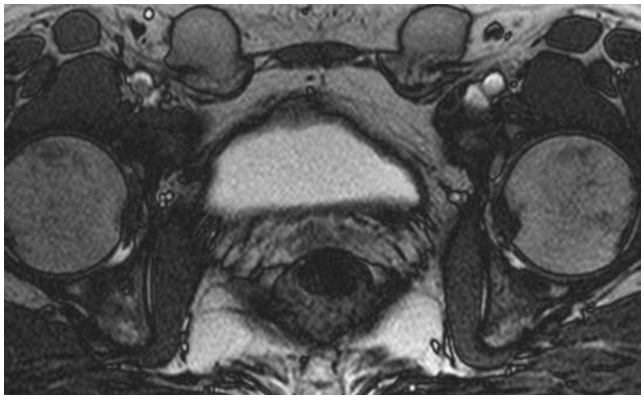

FIGURE 3 Pelvic magnetic resonance imaging showed the absence of the uterus and adnexa as well as a blind vagina.

did not exhibit any physical abnormalities associated with these disorders. As the genetic testing results would not affect treatment strategies and were not relevant to the adolescent or his family, we decided to omit the molecular genetic verification of these diseases at this time.

Despite advancements in identifying genetic disorders at the molecular level, the underlying cause remains unknown in about half of the cases. However, mutations and deletions in SRY have been found in 10%–20% of patients with Swyer syndrome.[17] Molecular diagnosis allowed for the determination of the patient's genetic makeup and provided an accurate prognosis.

The treatment for Swyer syndrome varies based on the age at diagnosis due to the risk of developing gonadal neoplasia. The risk of developing neoplasms increases with age: 5.5% at 15 years, 27.5% at 30 years, and almost 50% at 40 years.[18,19] Consequently, the patient underwent prophylactic gonadectomy at an early age.

All individuals with XY chromosomes, regardless of age or sex, require ongoing hormone therapy after gonadectomy to prevent malignant neoplasms, promote menarche, prevent osteoporosis and cardiovascular disease, and support the development of secondary sexual characteristics.[20]

Therefore, in cases where female physical appearance is caused by congenital or structural ovarian insufficiency, the primary causes of amenorrhea include Mayer-Rokitansky-Küster-Hauser syndrome, Turner's syndrome, and androgen insensitivity syndromes.[21]

Women with complete gonadal dysgenesis often struggle with infertility, but they have the option of improving their chances of having a child using assisted reproductive technologies, such as donor oocytes.[22,23] Although successful pregnancies can result from this method, cesarean sections are often necessary because of twin pregnancies or failed induction.[22,23]

It is important to provide therapy for sexuality and gender issues, genetic counseling, and psychiatric therapy. Psychosexual development involves three components: gender identity, gender role, and sexual orientation. In this case, the patient underwent psychological evaluation to address these concerns.

The patient was diagnosed with Swyer syndrome based on primary amenorrhea, stunted growth, and 46XY karyotype. Elevated gonadotropin levels, an underdeveloped uterus, and gonadal agenesis were confirmed by ultrasound and magnetic resonance imaging. Surgical intervention and hormone replacement therapy are recommended.

4 | CONCLUSIONS

Swyer syndrome is a rare genetic condition that increases the risk of malignant tumors and necessitates prompt surgery and hormone replacement therapy. Assisted reproductive technologies can enhance the reproductive outcomes. A thorough evaluation, including hormone profiling and pelvic ultrasonography, is essential to assess the absence of menarche beyond the age of 16 years.

AUTHOR CONTRIBUTIONS

Nurbek Monolov: Conceptualization; data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Ulbolsun Nurbekova:** Conceptualization; data curation; formal analysis; investigation; writing – original draft; writing – review and editing. **Elmira Mamytova:** Data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Abdurashid Unusov:** Data curation; investigation; methodology; writing – original draft. **Meerim Osmonova:** Data curation; investigation; methodology; resources. **Meerim Makambaeva:** Conceptualization; data curation; methodology; writing – original draft; writing – review and editing. **Yethindra Vityala:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Tugolbai Tagaev:** Data curation; formal analysis; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

Published with written consent of the patient.

FUNDING INFORMATION

No financial support was received for the study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Monolov N, Nurbekova U, Mamytova E, et al. Rare case of complete gonadal dysgenesis in a female patient with primary amenorrhea and a 46XY karyotype. *Clin Case Rep*. 2024;12:e9318. doi:10.1002/ccr3.9318