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Complete androgen insensitivity syndrome in twins with discordant phenotypes: a case report and review of the literature

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Abstract

Background Complete androgen insensitivity syndrome is caused by inactivated mutations in the androgen receptor gene, which results in complete androgen resistance and a female phenotype with a 46,XY karyotype. This condition is rare in twins.

Case presentation We report on a Han Chinese twin girl, aged 18 years, with the presence of a vagina and breasts but no uterus and ovaries and chromosomal karyotype analysis showing 46, XY, who was diagnosed with complete androgen insensitivity syndrome. The patient underwent bilateral gonadectomy and hormone replacement therapy, and pathological diagnosis showed immature testicular tissue development.

Conclusion In addition to rebuilding the external genitalia and preventing the emergence of gonadal tumors, continuing hormone replacement therapy after surgery is critical for the treatment of complete androgen insensitivity syndrome, and patients' psychological difficulties should be addressed.

Keywords Complete androgen insensitivity syndrome (CAIS), 46, XY, Twins, Hormone replacement therapy (HRT), Case report

Introduction

Androgen insensitivity syndrome (AIS) is a significant contributor to abnormalities in sexual development. Clinically, it is classified into three distinct types: complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome [1]. The characteristic of CAIS is the presence of female external genitalia in 46,XY individuals, which can secrete androgens in cryptorchidism, but the cells are completely unresponsive to androgens, and estrogen plays a major role. Therefore, patients with CAIS exhibit female appearance and female external genitalia. The prevalence of CAIS among individuals with a 46,XY phenotype is exceedingly rare [2], which constrains the available data regarding age and clinical presentation for the diagnosis of AIS. A nationwide study conducted in Denmark assessed all known women with 46,XY karyotypes since 1960 through medical records, revealing an incidence rate of 6.4 cases per 100,000 live births. The overall incidence of AIS was determined to be 4.1 cases per 100,000 live births [3]. Furthermore, the estimated incidence of CAIS, as confirmed by molecular diagnostics in genetically male individuals, ranges from 1 in 20,400 to 1 in 99,100 [4]; however, the determining factors of gender selection in CAIS and the standard

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treatment methods are unclear. Currently, there is limited literature on CAIS in twins; therefore, we report on this specific twin with CAIS.

Case description

The patient, an 18-year-old Han Chinese girl (social gender), has no sexual or menstrual history. In March 2024, the patient came to our hospital for "primary amenorrhea" treatment. Hormonal analysis showed estradiol testosterone levels of 6.870 ng/ml and free testosterone index of 55.98% (refer to Table 1). Chromosome analysis indicated a karyotype of 46,XY (Fig. 1). On physical examination, she exhibited female secondary sexual characteristics, with no evidence of an Adam's apple, and normal breast development that was small and symmetrical. A gynecological examination revealed normal-sized labia minora with sparse pubic hair; the hymen was intact, and a cotton swab could be inserted approximately 4 cm into the vagina.

An ultrasound examination revealed the absence of a normal uterine echo within the pelvic cavity. Instead, a tortuous and dilated tubular structure was observed posterior to the bladder, exhibiting visible blood flow signals. The bilateral ovaries were not distinctly visualized, and solid hypoechoic areas were noted in both inguinal regions, measuring approximately 2.7 cm × 1.4 cm on the left and 3.0 cm × 1.4 cm on the right, characterized by uneven internal echoes and detectable blood flow signals (Fig. 2A). Both breasts demonstrated well-defined glandular structures characterized by alternating regions of high echogenicity and honeycomb-like low echogenicity (Fig. 2B).

Both plain and enhanced pelvic magnetic resonance imaging (MRI) scans revealed no ovaries or uterus, along with two elliptical signal anomalies in the lower abdomen on either side close to the groin. The left and right anomalous dimensions were roughly 2.6 cm × 1.4 cm × 2.0 cm and 2.0 cm × 1.1 cm × 2.0 cm, respectively. However, signal shadows were observed in the vaginal area. In addition, no obvious enlarged lymph nodes were found in the pelvic cavity (Fig. 3).

The patient underwent a small incision non-pneumoperitoneum laparoscopic bilateral tumor resection. Upon laparoscopic examination, the vaginal cavity showed closed sheath-like protrusions on both sides but no uterus or ovaries. There were two distinct masses on either side of the extraperitoneal abdominal wall, each measuring about 2.5 cm by 2.0 cm. Then, we made a joint incision in the pubic area and a 2 cm incision in the right inguinal area. After carefully dissecting the surrounding tissues layer by layer, we used tissue forceps to clamp the tumor and visually inspected its appearance. It was not an ovary or a normal testicle, we removed the mass. Resection of the left mass using a similar surgical method was performed, followed by bandaging and suturing of the incision. Postoperative pathological examination showed immature testicular tissue under a microscope, accompanied by peripheral fibrosis, vascular dilation, congestion, bleeding, and focal proliferation of interstitial cells (Fig. 4). After a month of outpatient follow-up, the

Table 1 Seven items of sex hormones

Inspection item	Results		Units	Reference values
	Preoperative	Postoperative		
Follicle-stimulating hormone (FSH)	14.30	119.00	mIU/mL	Male: 1.5–12.4 Female: follicular phase 3.5–12.5
Luteinizing hormone (LH)	58.60	74.00	mIU/mL	Male: 1.7–8.6 Female: follicular phase 2.4–12.6
Estradiol (E2)	22.10	< 5	pg/ml	Male: 11.3~43.2 Female: follicular phase 30.9~90.4
Prolactin (PRL)	31.00	15.80	ng/ml	Male: 4.04–15.2 Female: nonpregnant period 4.79–23.3
Testosterone (TESTO)	6.870	0.025	ng/ml	Male: 7–18 years old T1 < 0.025; T2 < 0.025–4.32; T3 0.649–7.78; T4 1.80–7.63 Female: 7–18 years old T1 < 0.025–0.061; T2 < 0.025–0.104; T3 < 0.025–0.237; T4 < 0.025–0.268; T5 0.046–0.383
Progesterone (PROG)	0.304	0.056	ng/ml	Male: < 0.149 Female: follicular phase 0.05–0.193
Sex hormone binding protein (SHBG)	4.05	3.03	mg/L	Male: 20–49 years old 1.57–5.31 Female: 20–49 years old 2.34–11.59
Free testosterone index (FAI)	55.98	0.27	%	Male: 20–49 years old 35–92.6 Female: 20–49 years old 0.297–5.62

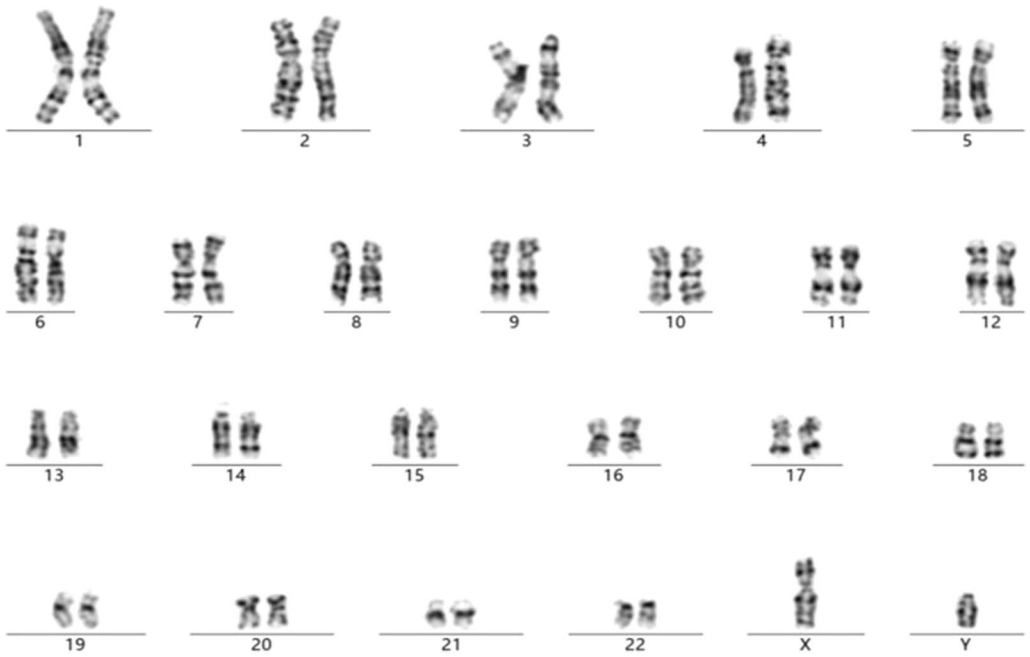

Fig. 1 Chromosome karyotype

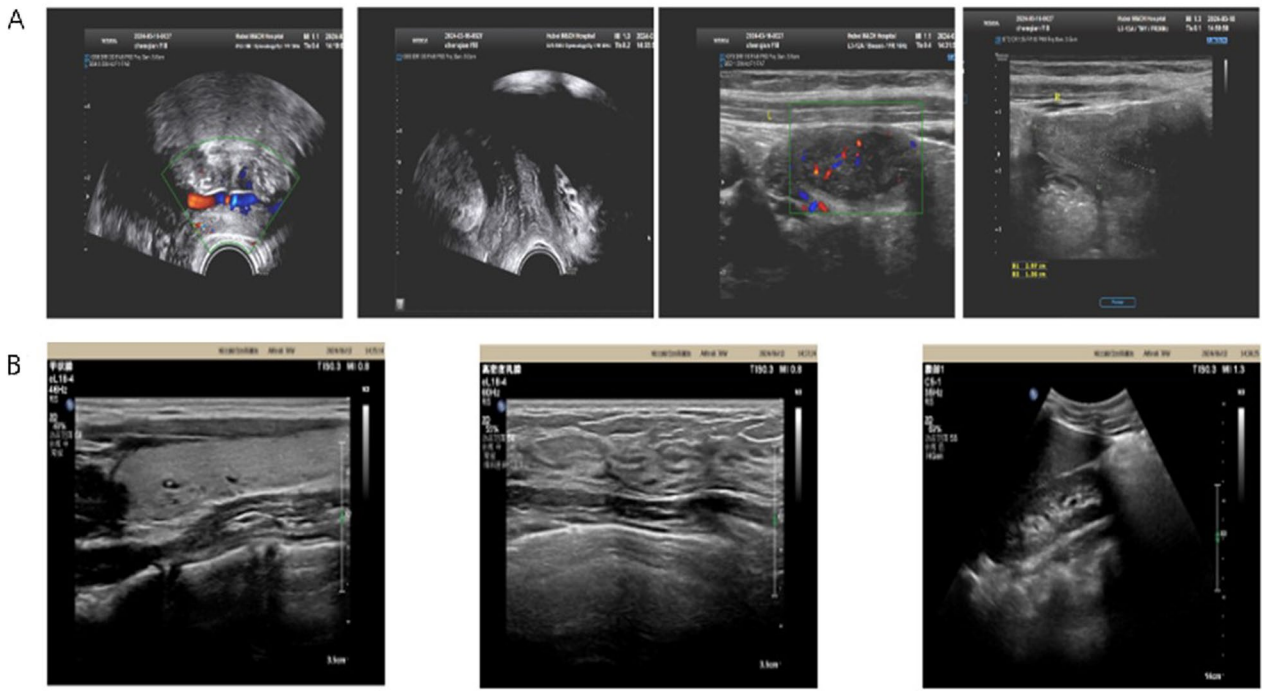

Fig. 2 Ultrasound results of the patient's gynecology (**A**); Thyroid, liver, pancreas, kidney, bilateral breast and drainage area lymph nodes (**B**)

patient's wound returned to normal, and she continued to receive hormone replacement therapy (HRT).

The patient's twin brother is a boy. We conducted some examinations on the patient's twin brother, and the physical assessment showed male facial features, prominent Adam's apple, normal development of penis and scrotum, and palpable testicles on both sides; peripheral blood chromosome karyotyping analysis showed a

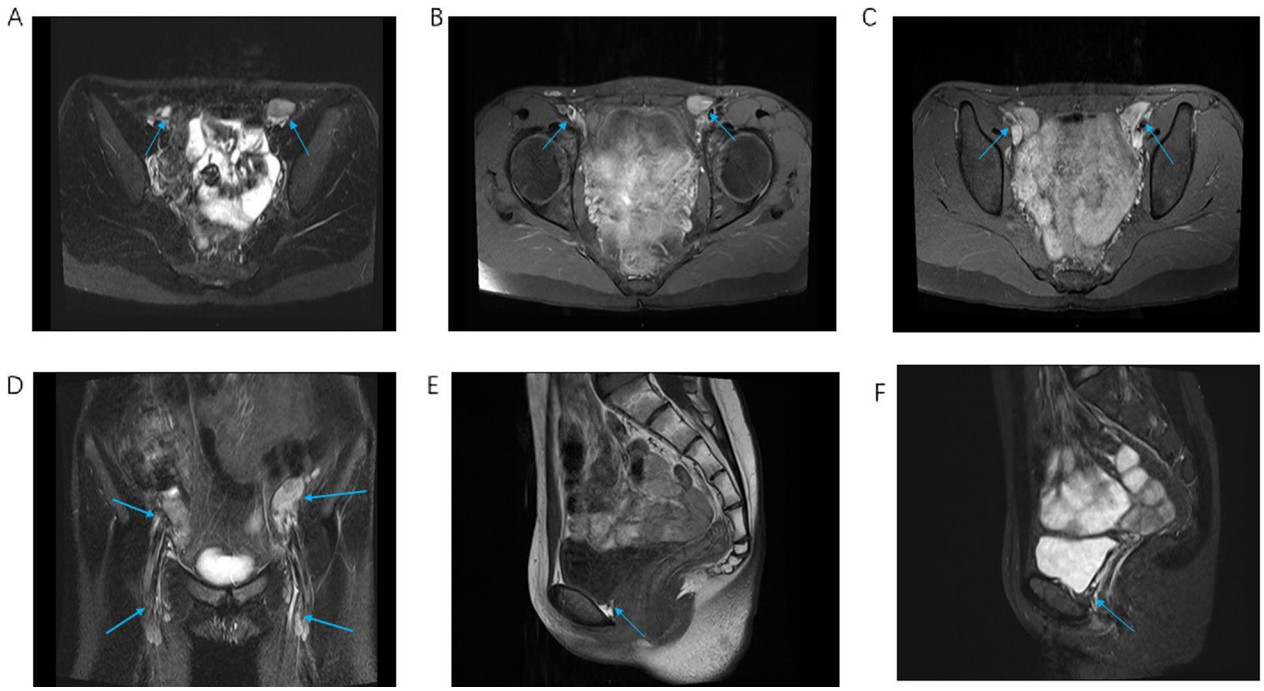

Fig. 3 Location and size of cryptorchidism in the inguinal region (**A**–**D**) No uterus or ovaries; (**E**, **F**)visible residual vaginal shadow. The arrows in (**A**, **B**, **C**) indicate the position and size of the patient's bilateral cryptorchidism on the MRI plane. (**D**) The arrows in the middle indicate the location and size of bilateral cryptorchidism on the coronal plane of MRI. The arrows in (**E**, **F**) represent the vaginal stump in the sagittal plane of MRI

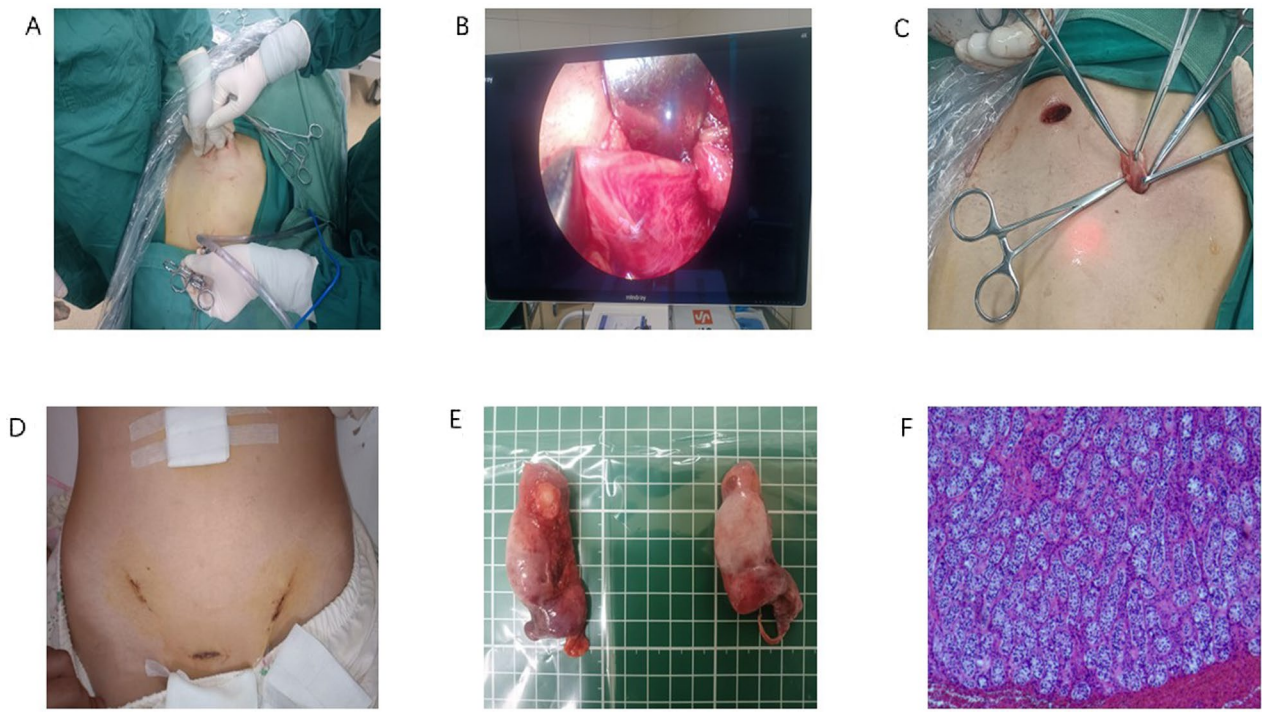

Fig. 4 Surgical procedures and intraoperative observations (**A**–**C**) Postoperative wound healing status of patient (**D**); undescended testis specimens (**E**); and pathological results (**F**)

composition of 46,XY; ultrasound examination revealed normal morphology and size of the testes and groin; semen routine analysis showed low sperm concentration and total count.

Discussion

The pathogenesis of CAIS is caused by mutations in the androgen receptor (AR) gene located in the Xq11–12 region [5], with mutations in the N-terminal domain (NTD) of the AR gene being more common in patients with CAIS [6]. Unfortunately, AR gene testing and detailed family assessments have not yet been conducted on patients and their families. Individuals with CAIS typically have a chromosome karyotype of 46,XY, and the testes function as gonads; however, their bodies are completely insensitive to androgens. This insensitivity leads to a completely female phenotype, characterized by the presence of female external genitalia but without menarche. The androgens produced by the testes can be converted into estrogen in the body, allowing for the natural progression of puberty and the development of breast tissue [7]. Because breast development mainly relies on androgens, patients with CAIS may exhibit breast dysplasia. Under the action of androgens, the patient exhibits a feminine appearance and small, symmetrical breasts. During fetal development, the presence of anti-Müllerian hormone secreted by the testes results in the absence of female internal genitalia, which prevents the formation of the fallopian tubes, uterus, and the upper portion of the vagina [8]. The lower third of the vagina originates from the urogenital ridge. Imaging studies have shown that the patient does not have a uterus or ovaries, but a curved and dilated tubular structure is observed in the posterior part of the bladder. A short blind-end vagina with a hymen was also found during physical examination.

Throughout the treatment process, comprehensive explanations were provided to both the patient and her family regarding the surgical intervention for complete androgen insensitivity syndrome (CAIS), including the associated benefits and drawbacks of selecting different gender identities. The patient was raised as a girl by her parents since childhood and has adapted to living as a woman. She and her family hope to undergo surgery to remove both cryptorchidic testes and the patient hopes to continue to maintain her female identity. According to a research report, the incidence of testicular germ cell tumors in individuals with CAIS increases with age; specifically, the risk for pre-adolescent patients is estimated to be between 0.8% and 2%, rising to approximately 3.6% by age 25, and reaching 33% by age 50 [9]. Given the lower incidence of malignant tumors in the gonads during and before puberty, alongside the advantages associated with gonadal preservation, the majority of experts advocate for the timely execution of gonadectomy and HRT following puberty [1, 10]. In this particular case, the patient, who has no sexual history and retains a hymen, underwent a small incision non-pneumoperitoneum laparoscopic procedure to address masses in both inguinal regions, thereby mitigating the risk of malignant transformation. The surgical approach involved the use of tissue forceps to enhance visibility and avoid the use of pneumoperitoneum. The use of pneumoperitoneum has been associated with elevated plasma catecholamine levels, increased plasma renin activity, and diminished chest and lung compliance, all of which can lead to heightened heart rate, elevated blood pressure, and reduced cardiac output during surgical procedures [11]. Conversely, patients undergoing laparoscopic surgery without pneumoperitoneum tend to experience improved recovery outcomes and a reduction in adverse effects typically associated with pneumoperitoneum, such as inflammation, acidosis, reactive oxygen species production, and the development of adhesions [12].

The postoperative pathological analysis revealed the presence of immature testicular tissue upon microscopic examination, with no evidence of malignancy. Subsequently, 1 week after surgery, we reexamined seven levels of sex hormones and found that follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels increased, while estradiol, prolactin, testosterone, progesterone, sex hormone binding globulin, and free testosterone index levels decreased (see Table 1). The surgical removal of the testes leads to a reduction in androgen secretion, which consequently results in a decrease in estrogen levels derived from androgens. The observed increase in FSH levels, alongside normal or slightly elevated LH levels, can be attributed to negative feedback mechanisms within the hypothalamic–pituitary axis [1]. Consequently, HRT is essential for patients with complete androgen insensitivity syndrome (CAIS) who have undergone gonadectomy. The primary objectives of HRT are to preserve secondary sexual characteristics, mitigate bone density loss, and promote cardiovascular and mental well-being. It is recommended that HRT be maintained until the average age of natural menopause in unaffected women. Currently, transdermal estradiol formulations are advised, as they offer several advantages over oral estrogen preparations in adult women, including a more physiological delivery method, diminished first-pass metabolism effects, reduced variability in liver metabolic markers, lower correlation with insulin-like growth factor 1 (IGF-1) levels, and a decreased risk of thromboembolic events [13]. Regular postoperative monitoring of sex hormone levels enables endocrinologists to make timely adjustments to hormone supplementation

on the basis of individual patient circumstances. To supplement estrogen, we advise patients to wipe the head and neck with estradiol gel 24 mg/once a day. We also advise patients to periodically check the bone density and sex hormone levels so that the dosage of the hormone supplement can be promptly adjusted.

The patient did not receive vaginal dilation or reconstruction surgery, because she has a hymen. Should the patient encounter insufficient vaginal length during subsequent sexual activity, secondary interventions such as vaginal dilation or vaginoplasty may be considered to accommodate the sexual needs of both the patient and their partner. It is important to note that the patient lacks a uterus and bilateral appendages, rendering conception through pregnancy impossible. The inability to conceive may lead to significant psychological challenges in the patient's future life. It is essential for family members to exhibit understanding and support and to seek psychological intervention if necessary.

On the basis of the results of the physical examination, color ultrasound, semen routine, and peripheral blood chromosome analysis it was determined that the patient's twin brother is male. However, certain parameters in semen analysis, such as sperm concentration and total sperm count, were determined to be below the normal range, which may indicate potential concerns about his sexual function development. Unfortunately, there is a lack of further and more in-depth examinations.

Conclusion

Complete androgen insensitivity syndrome (CAIS) is an uncommon sexual developmental disorder characterized by nonspecific clinical presentations. The diagnosis can be substantiated through a combination of clinical data, hormone level assessments, ultrasound examination, magnetic resonance imaging (MRI), and chromosomal karyotyping. MRI is particularly significant in the diagnostic process for CAIS, as it exhibits distinctive imaging characteristics. By evaluating the morphology and signal characteristics of the gonads, clinicians can ascertain the potential association of these structures with tumor development, which is a critical component of preoperative assessment for CAIS. In addition to reconstructing the external genitalia and mitigating the risk of gonadal tumors, ongoing HRT post-surgery is essential for the management of CAIS. Furthermore, it is imperative to address the psychological support needs of patients throughout their treatment.

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Author contributions
Kangji Liao was the main writer of the case report, contributing to all of the sections of the report. Ying Wang and Xianlin Yi helped to write part of the case report and edited it. Ying Wang provided direct patient care while the patient arrived for the treatment. All authors read and approved the final manuscript.

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Availability of data and materials
Datasets used and/or analyzed during the current study are available by request to the first and corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

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