Sexual Medicine, 2024, **12**, qfae026
https://doi.org/10.1093/sexmed/qfae026
Case Report

Ovotesticular disorder of sexual development manifested as hematospermia: a case report and literature review

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Abstract

Background: Ovotesticular disorder of sexual development (OT-DSD) is a rare sexual development disorder defined by the simultaneous existence of testicular and ovarian tissues (including follicular) in the same- or opposite-sex glands of an individual, with an incidence rate of about 1 in 100 000.
Aim: This report aims to supplement the clinical presentation, pathology, diagnosis, and treatment of OT-DSD and to improve the diagnostic ability of clinicians for modified disease.
Methods: This article is a retrospective analysis of a case of OT-DSD at our institution. Additionally, a comprehensive search of the PubMed database with the keywords "ovotesticular disorder of sexual development" or "true hermaphroditism" was conducted between 1956 and 2024, resulting in approximately 250 cases, and the results of the search are summarized.
Results: The patient, a 44-year-old male, sought treatment at our hospital on February 6, 2023, primarily due to "intermittent hematospermia for over a month." He stated that it was discovered during infancy that his right scrotum was empty and lacking a testicle. Due to the low local medical services and the low-income family's economic conditions, he did not seek further diagnosis and treatment. After admission, the patient underwent computed tomography and magnetic resonance imaging and decided to undergo robot-assisted pelvic mass resection, which was pathologically confirmed as OT-DSD.
Outcomes: The patient's definitive diagnosis was provided by postoperative pathology, and although the patient ultimately had a favorable outcome, diagnosis and treatment were delayed due to his atypical clinical presentation.
Strengths and Limitations: This is a single case report; however, uncommon clinical presentations of rare diseases were identified, and a literature review was conducted. Unfortunately, there are some important missing data in the patient's medical history, including hormone assessment (testosterone, luteinizing hormone, follicle-stimulating hormone), tumor marker examination, semen analysis, scrotal ultrasound, and chromosomal analysis.
Conclusion: Patients with OT-DSD have diverse types of gonads, chromosomal karyotypes, and phenotypes of external genitalia, and further exploration and research are needed for early diagnosis and treatment. In addition, cases of OT-DSD with fertility and no ambiguous genitalia are even rarer. This case guides us for adult patients with no ambiguous genitalia: if there is an inability to palpate 1 or both gonads and there is intermittent hematospermia, the possibility of OT-DSD should be suspected.

Keywords: sexual development disorder; chromosome abnormality; ovotesticular disorders of sex development; gonadal development.

Introduction

Ovotesticular disorder of sexual development (OT-DSD) is a rare sexual development disorder, defined by the simultaneous existence of testicular and ovarian tissues (including follicular) in the same- or opposite-sex glands of an individual, with an incidence rate of about 1 in 100 000.[1] Its etiology and pathogenesis are not yet fully understood, but it is currently believed to be related to genetic mutations or endocrine disorders. OT-DSD can present with a variety of clinical symptoms and chromosomal karyotypes. Due to its rarity, there are no standard guidelines for early diagnosis of OT-DSD. Different combinations of the 2 types of gonads can be divided into 3 types according to Hinman's method:

Bilateral: Both sides are ovotesticular mixed glands (ie, ovotestis).
Unilateral: One side is a simple testicle or ovary, and the other side is an ovotestis.
Lateral: One side is an ovary, and the other side is a testicle.[2]

Patient information

The patient, a 44-year-old male, sought treatment at our hospital on February 6, 2023, primarily due to "intermittent hematospermia for over a month." He stated that it was discovered during infancy that his right scrotum was empty and lacking a testicle. Due to the low local medical services and the low-income family's economic conditions, he did not seek further diagnosis and treatment. After he entered puberty, his secondary sexual characteristics developed normally.

Physical examination

The patient's height was 168 cm; weight, 70 kg; and body mass index, 24.80 kg/m^2. The patient had a masculine facial appearance, a visible beard, and an Adam's apple, with no

Received: January 15, 2024. **Revised:** March 24, 2024. **Accepted:** May 8, 2024
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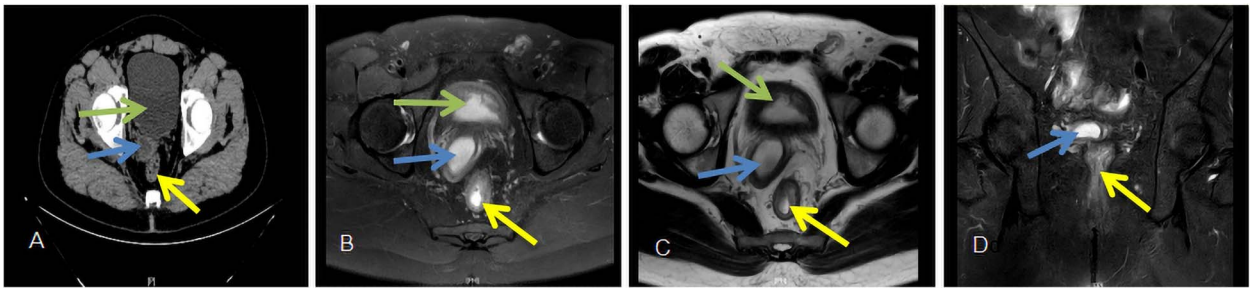

Figure 1. Computed tomography scan image and magnetic resonance imaging results: topmost arrows, bladder; middle arrows, the location of the uterus; bottom arrows, rectum. (A) Patient's pelvic computed tomography scan. (B) T2 sequence image of magnetic resonance imaging. (C) T1 sequence image of magnetic resonance imaging. (D) Coronal image of magnetic resonance (The arrow above, the location of the uterus; the arrow below, rectum).

unusual breast development. His penis was not abnormally small under static conditions but exhibited a downward curvature when erect. The foreskin was normal; the right scrotum was empty; no masses were palpated in the right inguinal region; and the left scrotum showed no abnormalities. The patient reported no daily difference between himself and other typical males, and he had considered himself male since childhood.

Marital and childbirth history

The patient got married at 27 years old and had 1 son and 1 daughter after marriage, both of whom did not have similar diseases. The son was 15 years old and the daughter 13 years old, and both were developing normally. The daughter had not yet started menstruating, while the son's scrotum was full with palpable testicles on both sides. The patient and his family gave oral consent for this case report. Also, individual case reports do not require approval from the institutional review board. Publishing case reports involving <3 patients without involving the review of medical records is not considered human subject research and does not require committee review and approval.

Diagnostic assessment

Testicular and epididymal palpation

The right scrotum was empty, and no testis or epididymis was palpable. The left scrotum was full, and a testis approximately $4 \times 2 \times 3$ cm in size could be palpated, with firm texture and no tenderness. The epididymis was of normal size with a regular contour and soft texture, and no tenderness or nodules were felt.

Vas deferens palpation

The right vas deferens was not palpable, while the left vas deferens was palpable as a cord-like structure without thickening, nodules, or tenderness.

Digital rectal examination

The rectal mucosa was smooth without any abnormal masses. The anal sphincter tone was moderate, and the reflex was normal. The prostate was of normal size with a soft texture and smooth surface, without palpable nodules or hard masses. Computed tomography scan showed a strip of soft tissue density in the pelvic region, with a cystic low-density shadow at its upper end, approximately 2.0×2.8 cm, and another cystic low-density shadow at its lower end, approximately 1.9×1.7 cm, closely associated with the prostate. Magnetic resonance imaging showed a mass-like abnormal signal on the right side of the pelvis and a cystic abnormal signal behind the right bladder, which seemed to be continuous on both sides and converge into the urethral area at the far end (Figure 1). Unfortunately, imaging methods could determine the nature of the mass preoperatively.

Therapeutic intervention

The patient underwent a robotic-assisted pelvic mass resection. Intraoperative exploration revealed 2 masses posterior to the right iliac vessels: 1 was connected to the spermatic cord, and 1 was connected to the right vas deferens and right seminal vesicle, with a thick wall. The operation went smoothly; the pelvic mass was removed and sent for pathologic examination.

Histopathologic findings

Tissues for examination included ovaries, fallopian tubes, uterus, seminal vesicle glands, and vas deferens. No tumorous lesions were observed in any of these tissues. The ovaries showed corpora lutea, with occasional cystic follicles observed locally. The uterus exhibited endometrial tissue, a uterine muscle wall, endocervical mucosa, and cervical squamous epithelium. Seminal vesicles and vas deferens were found beneath the squamous epithelium of the cervical wall (Figure 2). The morphologic characteristics of this patient are consistent with OT-DSD: no testicular tissue was found on the right side, which is a rare lateral type. Unfortunately, due to the patient's request/economic reasons, karyotype analysis was not performed. The patient recovered well after surgery and was discharged 7 days later.

Follow-up and outcomes

Follow-ups were conducted at 1- and 3-month periods after the patient was discharged from the hospital. According to the patient's self-report, the disease and surgery did not have an impact on his life (eg, sex life), but it had a psychological effect. Once again, the patient refused to undergo chromosomal karyotyping.

Discussion

OT-DSD is a rare sexual development abnormality, accounting for about 3% to 10% of human sex differentiation abnormalities, and most individuals with it are infertile.[3] The etiology and pathogenesis are not yet fully understood. OT-DSD is believed to be related to genetic mutations or endocrine disorders.[4]

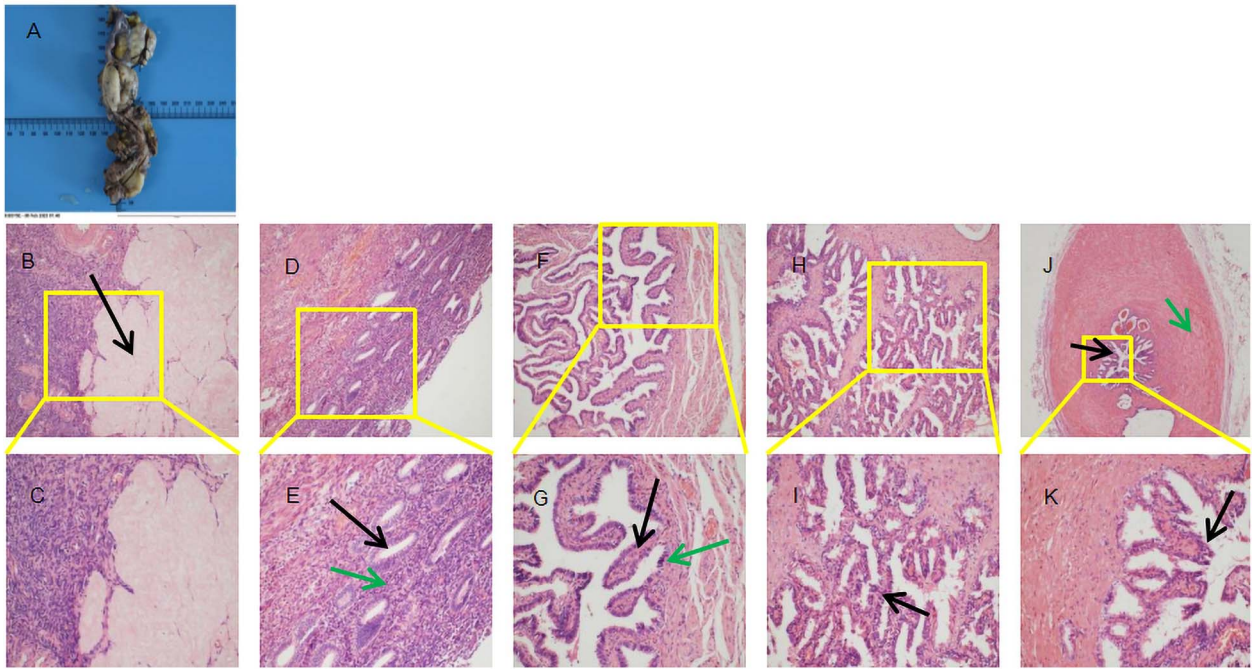

Figure 2. Pathologic specimens and immunohistochemical staining results. (A) Surgical excision specimen. (B, C) Immunohistochemical staining results: ovarian tissue (HE staining 100×, 200×). Arrow, ovarian corpus luteum surrounded by a connective tissue membrane. (D, E) Endometrium (HE staining 100×, 200×). The arrow above, uterine glands; the arrow below, stroma cells. (F, G) Fallopian tube (HE staining 100×, 200×). The arrow above, ciliated cells of the fallopian tube; the arrow below, secretory cells of the fallopian tube. (H, I) Seminal vesicle (HE staining 100×, 200×). Arrow, seminal vesicle mucosa. (J) Vas deferens (HE staining 40×). Left arrow, thin mucosa of the vas deferens; right arrow, smooth muscle layer. (K) Vas deferens (HE staining 200×). Arrow, thin mucosa of the vas deferens. HE, hematoxylin and eosin.

Clinical manifestations of OT-DSD

The clinical manifestations of OT-DSD are diverse, such as primary or secondary amenorrhea, abnormal external genitalia, and male bilateral breast development.[5] There are also some rare clinical presentations in the search literature, such as scrotal urgency, scrotal mass, inguinal hernia, cryptorchidism, vaginal effusion, intermittent hematuria, and inguinal pain. About three-quarters of people with OT-DSD are raised as males, and less than one-fifth of those with OT-DSD have normal male external genitalia.[6] Most individuals with OT-DSD show ambiguous genitalia at birth or during infancy and are diagnosed within months to years. However, this case is rare. Except for intermittent hematospermia and preoperative consideration of "cryptorchidism," the external genital phenotype was generally normal; the secondary sexual characteristics were fully developed; only the reproductive organ was deformed when erect; and the disorder was not diagnosed for 44 years.

Additionally, we raised concerns regarding the patient presenting with "hematospermia." Although the patient's symptom was hematospermia, the possibility of it being endometrial shedding cannot be ruled out. We speculate that the incomplete previous development of the patient's pelvic female reproductive organs, coupled with normal development of the left testicle, resulted in minimal impact on the patient's sexual characteristics and fertility. By the time that the patient started experiencing symptoms, his female reproductive organs had matured vs before, thus acquiring the functionality of female genital organs. However, due to the lack of hormone testing and semen analysis, it is difficult to verify this assumption. Finally, the patient was married and had 1 son and 1 daughter. We reviewed previously reported cases but did not find any patients with offspring and no ambiguous external genitalia or abnormal secondary sexual characteristics.

Diagnosis of OT-DSD

Preoperative diagnosis is mainly made through medical history, physical examination, imaging examinations (ultrasound, magnetic resonance imaging, etc), hormone analysis, and karyotype examination. However, the patient's external genitalia possessed a broad spectrum. For chromosomal karyotype examination, various chromosomal abnormalities have been described in the case of OT-DSD, such as 46,XX, 46,XY, 46,XX/46,XY, 45X/46,XY, and others.[7] Therefore, chromosomal karyotype examination is not essential for the diagnosis of OT-DSD, but its abnormal manifestations can help clinicians consider the possibility of OT-DSD. As such, there is no unified diagnostic clinical, laboratory, or radiologic feature to clearly distinguish it; clear diagnosis still requires pathologic histologic examination.

Treatment of OT-DSD

The treatment of OT-DSD is still controversial. According to expert consensus, sexual development is unpredictable, and treatment decisions should include a discussion with a group of experts, including parents, and should be combined with the specific situation of gonadal differentiation and external genital development. Because the development and function of the gonads cannot be fully evaluated in infants and toddlers, there is controversy over whether to have surgery and the timing of surgery. Experts such as Syryn Hannes advocate that for any child with OT-DSD, early and nonconsensual genital surgery, including gonadectomy (partial or otherwise),

should be absolutely avoided. This claim is mainly based on irreversible surgical treatment, which can cause damage to the patient's future fertility and psychology. It is recommended to wait until puberty for surgical intervention, but this also increases the possibility of malignant tumors in the patient's gonads.[8] Experts in countries such as Japan advocate early treatment.[9,10] They believe that it is difficult for parents to accept the long-term existence of a child's "unknown gender" status and deal with the child's psychological response in the future. Due to societal difficulties in accepting ambiguous genitalia, it has an impact on the patient's psychology.

In conclusion, patients with OT-DSD exhibit diverse gonadal types, chromosomal karyotypes, and external genital phenotypes. The rarity and diversity of clinical manifestations often lead to delayed diagnosis and treatment. This case guides us for adult patients with no ambiguous genitalia: if there is an inability to palpate 1 or both gonads and there is intermittent hematospermia, the possibility of OT-DSD should be suspected.

Author contributions

M.C. and Yuantao W. contributed equally to this work.

Study concept and design: Yuantao W., M.C. Data acquisition: C.S., Yuantao W., M.C. Drafting of manuscript: C.S., Yuxiong W., H.C. Critical revision of the manuscript: Yuxiong W., Yuantao W., G.Z.

Funding

None declared.

Conflicts of interest

The authors declare no conflict of interest.

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