Cureus
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Open Access Case Report

# Ovotesticular Difference of Sex Development Presenting as Episodic Hematuria in a Young Adult

**Review began** 10/09/2026
**Review ended** 11/04/2026
**Published** 11/06/2026

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**DOI:** 10.7759/cureus.119244

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## Abstract

Ovotesticular difference of sex development (OT-DSD) is a rare condition characterized by the presence of both ovarian and testicular tissue in the same individual. Its clinical presentation is highly variable, and diagnosis may occasionally be delayed until adulthood. We describe a 26-year-old individual, reared as male, who presented with episodic hematuria since puberty associated with lower abdominal pain. Examination revealed bilateral gynecomastia, atypical male genitalia with microphallus, proximal hypospadias, and asymmetric gonads. Hormonal evaluation revealed elevated serum luteinizing hormone and low testosterone, suggestive of hypergonadotropic hypogonadism. Pelvic and inguinoscrotal imaging demonstrated left-sided Müllerian structures, a left pelvic gonad, and a right scrotal gonad. Further karyotypic evaluation followed by fluorescence in situ hybridization (FISH) established the 46,XX SRY-negative status, while whole-exome sequencing did not identify any pathogenic or likely pathogenic variants in genes RSPO1, WNT4, WT1, SOX9, SOX3, NR5A1 or NR2F2. Following multidisciplinary evaluation, the patient underwent surgical removal of the Müllerian structures and left gonad. Histopathological study confirmed the presence of ovarian tissue in the excised left gonad and testicular tissue in the right scrotal gonad. Thus, diagnosis of OT-DSD was established. Testosterone replacement therapy was initiated in accordance with the male gender identity. This case highlights the marked phenotypic variability of OT-DSD and the possibility of delayed diagnosis despite significant genital abnormalities. It also emphasizes the importance of a multidisciplinary approach to the management of OT-DSD. The underlying molecular mechanism remained unresolved despite genetic evaluation.

**Categories:** Internal Medicine, Endocrinology/Diabetes/Metabolism
**Keywords:** difference of sex development, episodic hematuria, gynecomastia, ovotestes, sry-negative

## Introduction

Ovotesticular difference of sex development (OT-DSD) is a rare disease with an estimated incidence of one in 100,000 live births [1]. This condition is defined by the presence of male and female gonadal tissue in the same individual. The most common presentation is the unilateral type, in which an ovotestis is found on one side and an ovary or testis is found on the other side, which is seen in 50% of cases. It can also present as bilateral or lateral in 30% and 20% of cases respectively [2]. The 46,XX karyotype is the most common type, being identified in 60% of cases, followed by 46,XX/46,XY in 33% and 46,XY in 7% of cases [3]. Individuals are usually identified at birth due to atypical genitalia, whereas it may present in an adult with episodic hematuria. The phenotypic presentation has wide variation from complete male genitalia to complete female genitalia. If the case is missed in infancy and childhood, it may present as a rare case of episodic hematuria in a phenotypic male. The diagnosis is confirmed by histological demonstration of both ovarian and testicular tissue in separate or a single gonad. Treatment of the condition is mainly individualized, guided by the person's gender identity. Here we report a case of a 26-year-old, reared as male, presenting with episodic hematuria and atypical genitalia.

## Case Presentation

A 26-year-old individual, assigned male sex at birth and reared as male, was referred from the Department of Urology for evaluation of hematuria. The hematuria was first noticed by the patient around puberty and was episodic in nature and irregular, occurring at an interval of one to six months. It was confirmed by the presence of red blood cells in urine on microscopic examination during the episode of hematuria. He was the fourth-order child of a consanguineous marriage and had been delivered prematurely at 34 weeks of gestation. According to the history obtained from the family, asymmetry of the gonads had been noted since childhood, with a palpable gonad within the right-side scrotum and no palpable gonad on the left-side scrotum. There was no history of salt-wasting episodes, lethargy, diarrhea, vomiting, or generalized hyperpigmentation. Patient noticed pubic hair development and gynecomastia at 13 years of age. The patient underwent surgery for gynecomastia at 15 years of age. The gender identity and gender role are male and the patient wishes to continue male gender role.

**How to cite this article**
Ravi Kumar P, Samantaraya K, Dash D K, et al. (November 06, 2026) Ovotesticular Difference of Sex Development Presenting as Episodic Hematuria in a Young Adult. Cureus 18(11): e119244. DOI 10.7759/cureus.119244

On examination, the individual was hemodynamically stable, with a blood pressure of 110/80 mm Hg with no postural drop. Height was 164.4 cm (-1.23 SDS), weight was 74.3 kgs (+1.02 SDS), and BMI was 27.5 kg/m². The upper segment-to-lower segment ratio was 0.93. There was no facial hair, acne or temporal recession of the hairline. Residual gynecomastia with scar marks were noted over the breast region (Figure *1*). Voice was high-pitched and sexual maturity rating revealed the presence of axillary hair and pubic hair with Tanner stage P4. The external genitalia were atypical with microphallus (stretched phallic length 6.5 cm) and penoscrotal hypospadias (Figure *2*). The gonad in the right-side scrotum was approximately 4 cc in volume, soft, and non-tender, whereas the left gonad was not palpable in the scrotum. The external masculinization score was 4.5/12.

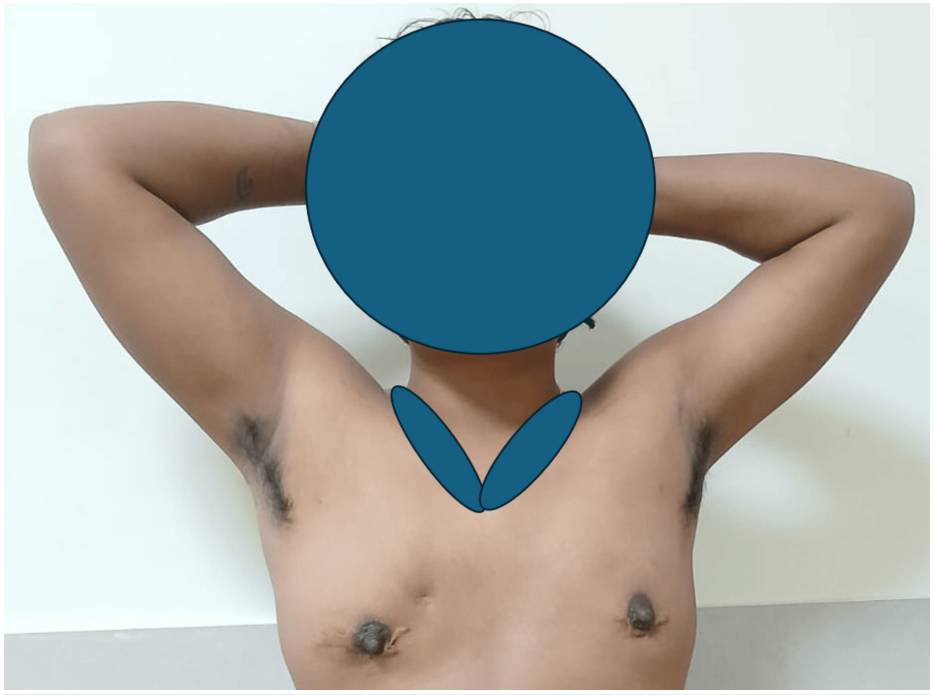


**FIGURE 1: Clinical photograph demonstrating bilateral gynecomastia with scar marks**



**FIGURE 2: External genitals showing penoscrotal hypospadias, with the urethral opening at the penoscrotal junction (arrow)**

Hormonal evaluation, performed between 8-9 AM in fasting state, demonstrated a luteinizing hormone (LH) level of 12.3 IU/L and testosterone of 48.51 ng/dl, suggestive of hypergonadotropic hypogonadism, although follicle-stimulating hormone (FSH) of 16 IU/L was within the normal reference range. The serum estradiol level of 138.9 pg/mL and prolactin of 30.13 ng/ml may be explained by the presence of functional ovarian tissue and estradiol stimulating lactotrophs. The 8 AM serum cortisol was 12.59 µg/dL. Human chorionic gonadotropin (hCG) stimulation test was performed using 1,500 IU administered intramuscularly daily for three consecutive days and serum testosterone, measured 24 hours after the last dose, was 42.58 ng/dL, suggestive of inadequate testicular response (Table *1*) [4]. Other routine hematological, biochemical and thyroid function tests were normal.

| Parameters | Result | Reference range |
|---|---|---|
| LH (IU/L) | 12.3 | 1.5-9.3 |
| FSH (IU/L) | 16.0 | 1.4-18.1 |
| Testosterone (ng/dl) | 48.51 | 197.4-669.5 |
| Estradiol (pg/ml) | 138.9 | 11.6-41.2 |
| 8 AM Cortisol (mcg/dl) | 12.59 | 5.2-22.45 |
| TSH (mIU/L) | 1.52 | 0.27-4.2 |
| T3 (nmol/L) | 3.24 | 1.3-3.1 |
| T4 (nmol/L) | 119.71 | 66-181 |
| Prolactin (ng/ml) | 30.13 | 2.1-17.7 |
| 17-Hydroxyprogesterone (ng/ml) | 1.3 | 0.05-1.60 |
| Three-day hCG stimulation test (day 4 testosterone) | 42.58 ng/dl | Normal response: Increase in serum testosterone to 230-280 ng/dl or higher or by two times the baseline value |

**TABLE 1: Results of Hormonal Tests**

LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone; T3: triiodothyronine; T4: thyroxine; hCG: human chorionic gonadotropin

## Ultrasound findings

Ultrasonography of the abdomen and pelvis demonstrated a left gonad, suspected to be an ovary, of size 3.2×1.8×1.8 cm with a dominant follicle measuring 13 mm. Ultrasonography of the bilateral inguinoscrotal region revealed a right gonad measuring 1.5×1.6×3.8 cm within the right side of the scrotum, with heterogeneous echotexture suggestive of an atrophic testis. The left gonad was not visualized within the left side of the scrotum.

## MRI findings

MRI of the pelvis demonstrated a hemi-uterus measuring 5.5×2.8×2.7 cm in the left side pelvis, with an endometrial thickness of 10 mm and a rudimentary vaginal canal. A left ovarian cyst measuring 3.6×3.5 cm and left hydrosalpinx were also identified (Figure *3*). MRI of the bilateral inguinoscrotal region demonstrated an atrophic right testis within the scrotum and non-visualization of the left gonad in the scrotal sac.

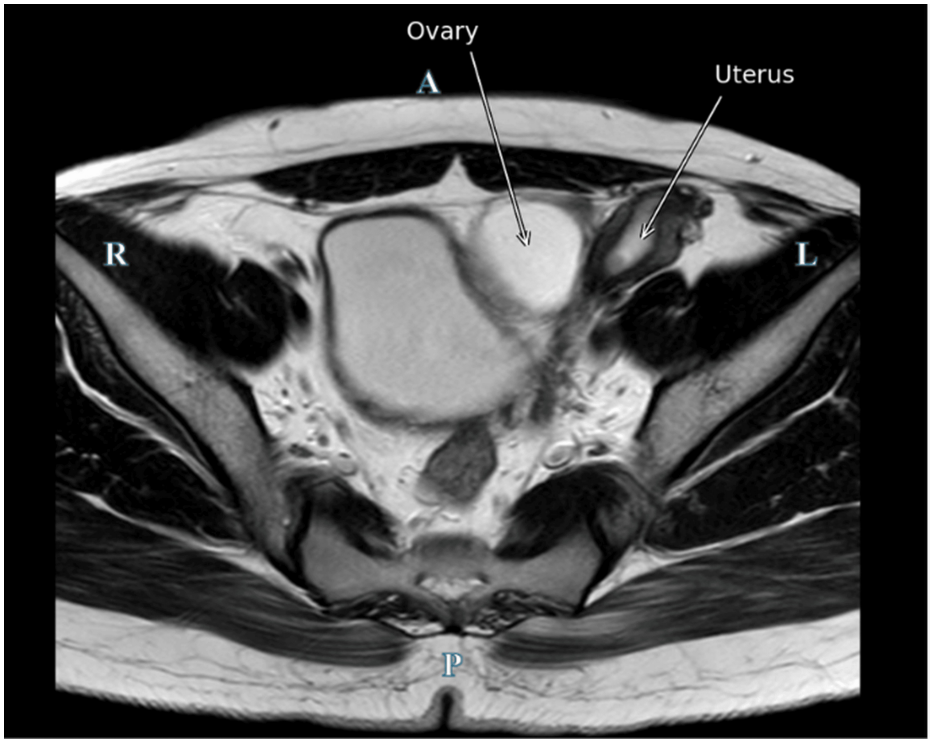



**FIGURE 3: Axial T2-weighted MRI of the pelvis showing a left hemiuterus and left ovary**

A: anterior; P: posterior; R: patient's right; L: patient's left

Biopsy of the right scrotal gonad showed atrophic seminiferous tubules with fibrous stroma and absence of any histological structures suggestive of an ovary (Figure 4). No evidence of malignancy was identified in the sections examined.

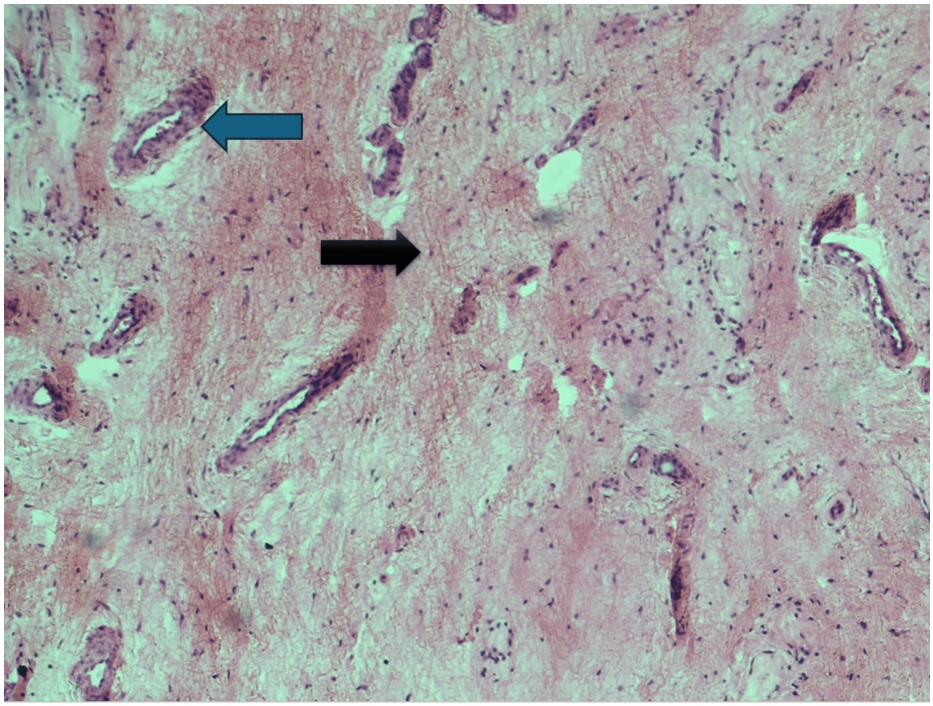


**FIGURE 4: Histopathological study of hematoxylin and eosin-stained image (10x) obtained using light microscopy of the right scrotal gonad**

Blue arrow: Atrophic seminiferous tubule

Black arrow: Fibrous stroma

Karyotyping of the patient was 46,XX (Figure *5A*). Fluorescence in situ hybridization (FISH) analysis of peripheral blood cells demonstrated two X-centromeric (DXZ1) signals, with no detectable SRY (Yp11.31) or Y-chromosome heterochromatin (DYZ1, Yq12) signals. These findings were consistent with an XX signal pattern and absence of detectable SRY in the cells analyzed.

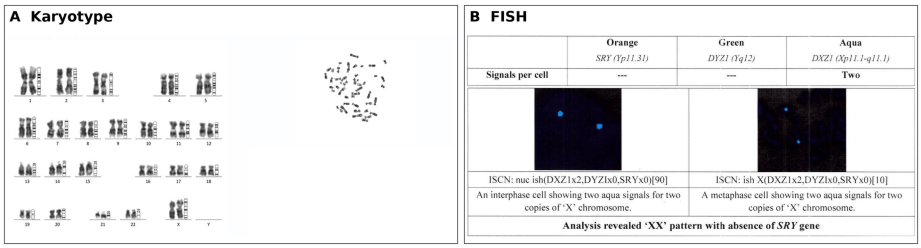



**FIGURE 5: Karyotype and fluorescence in situ hybridization (FISH) findings**

A: Karyotype showing a 46,XX chromosomal complement

B: Fluorescence in situ hybridization showing two aqua signals for the X-chromosome, with no detectable signals for the SRY

To further investigate, whole-exome sequencing (WES) was performed on peripheral blood cells, achieving a mean depth of 145× (97.11% coverage at ⩾20×). No pathogenic or likely pathogenic variants were detected in RSPO1, WNT4, WT1, SOX9, SOX3, NR5A1, or NR2F2. High-depth coverage (⩾20×) was successfully obtained for all coding regions and three flanking intronic nucleotides of these seven genes. Variant interpretation was conducted using American College of Medical Genetics and Genomics (ACMG) based classification criteria [5]. Additionally, copy-number and structural-variant analyses yielded no clinically relevant findings within the detection boundaries of the assay.

Cystourethroscopy followed by genitogram using urografin dye (Figure 6) demonstrated a tubular structure suggestive of the uterocervical canal communicating with the posterior urethra at the level of the verumontanum. This finding supported an inferred uterine origin of the episodic hematuria.

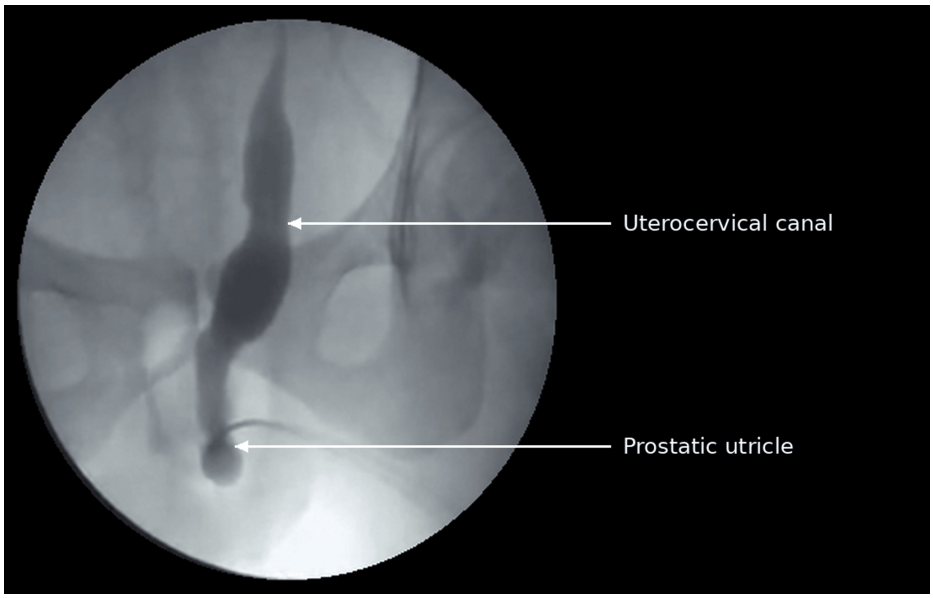



**FIGURE 6: Genitogram with urografin dye (anteroposterior view) showing the uterocervical canal communicating with the posterior urethra.**

Based on imaging, histopathological evaluation, and genetic studies, a provisional diagnosis of lateral OT-DSD was established. Psychiatric evaluation revealed no gender dysphoria; the patient expressed a male gender identity and a strong preference to maintain it.

A multidisciplinary team consisting of specialists in endocrinology, obstetrics and gynecology, urology, plastic surgery, and psychiatry was assembled to oversee patient management. Following detailed counselling regarding diagnosis and therapeutic options, a two-stage surgical plan was formulated to align with the patient's male gender identity and address the primary concern of episodic hematuria. The initial stage comprised the surgical excision of the left gonad, left hemiuterus, and fallopian tube. The planned subsequent stage involves hypospadias repair and bilateral breast liposuction for residual gynecomastia following adequate androgen replacement therapy. Accordingly, the patient underwent diagnostic laparoscopy followed by laparotomy for removal of the left gonad, left hemiuterus and fallopian tube without any postoperative complications. Gross pathology (Figure 7A) identified a hemiuterus (6×3×2 cm), gonad (4.5×3×2 cm), and fallopian tube (1 cm in length, lumen 0.1 cm in diameter). On histopathology, the left gonad demonstrated isolated ovarian tissue characterized by ovarian follicles, stroma, and corpus albicans, devoid of testicular elements. The hemiuterus sections showed endometrial glands and stroma, and the fallopian tube sections revealed epithelial-lined mucosal folds, lamina propria, and smooth muscle (Figure 7B-7D). This confirmed a diagnosis of lateral OT-DSD; the right scrotal gonad was retained.

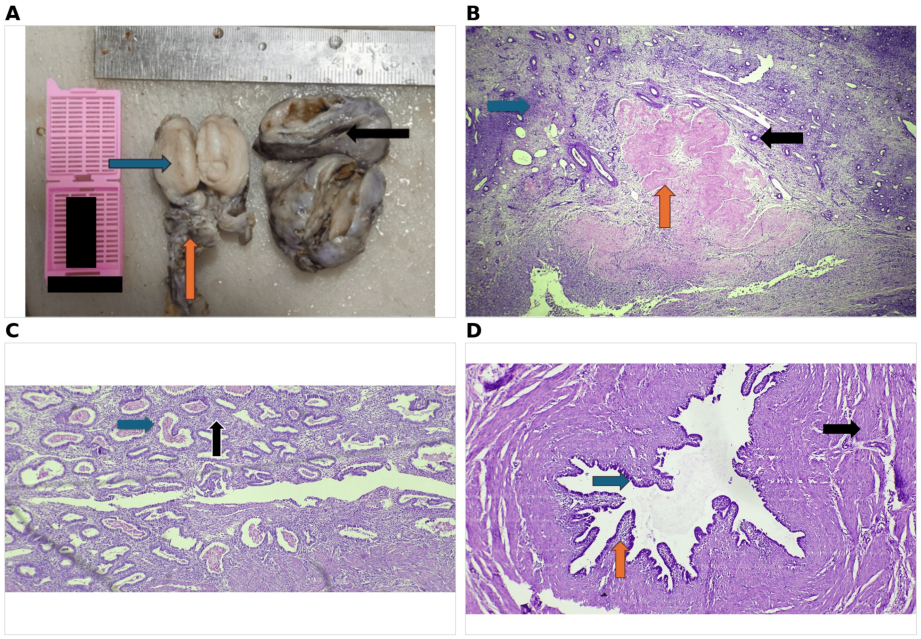



**FIGURE 7: Gross specimen and histopathological study of hematoxylin and eosin-stained images of left ovary, hemiuterus and fallopian tube obtained using light microscopy**

A: Gross specimen showing the left ovary (4.5×3×2 cm, blue arrow), left hemiuterus (6×3×2 cm, black arrow), left fallopian tube (1 cm length, 0.1 cm lumen diameter, orange arrow).

B: Ovarian tissue (10x) showing follicles (black arrow), ovarian stroma (blue arrow), and corpus albicans (orange arrow)

C: Endometrium (10x) showing glands lined by glandular epithelium (blue arrow) and surrounding endometrial stroma (black arrow).

D: Fallopian tube (10x) showing mucosal folds (blue arrow), lamina propria (orange arrow) and smooth muscle layer (black arrow)

For the management of hypogonadism, testosterone enanthate therapy was initiated at a dose of 250 mg intramuscularly every two weeks. The patient was followed up every three months to evaluate clinical response (such as virilization, phallic growth, sexual function, muscle strength, and general well-being), monitor serum testosterone levels, hematocrit, lipid profiles, and potential adverse effects. At the initial three-month post-operative follow-up visit, the patient reported resolution of hematuria, sparse new hair growth over the chin and upper lip, regular nocturnal penile tumescence, increased libido, and improved overall well-being. Mid-cycle serum testosterone, measured between injections, was 300 ng/dL; hematocrit and lipid profiles remained within normal physiological reference ranges. Consequently, testosterone replacement therapy was continued under the same regimen.

Although the risk of gonadal malignancy in patients with 46,XX SRY-negative OT-DSD is substantially low, an individualized surveillance strategy was implemented for the retained right scrotal gonad. This surveillance protocol comprises regular clinical examinations during routine follow-up visits alongside annual scrotal ultrasonography. The patient received comprehensive counselling regarding the importance of regular self-examinations and the necessity of promptly reporting clinical red flags, such as new swelling, palpable masses, or persistent discomfort. Additionally, counselling addressed the highly unfavorable prognosis for biological paternity and the long-term reproductive outcomes associated with ovarian removal. The patient was advised that while testosterone replacement therapy effectively addresses hypogonadism, it does not restore fertility. Alternative pathways to parenthood - specifically donor-sperm assisted reproduction and adoption - were discussed, and a referral for specialist reproductive counselling was provided.

## Discussion

OT-DSD is a rare condition with a wide spectrum of phenotypic variability. The condition is most commonly diagnosed at birth because of atypical genitalia. Our case underscores the possibility of delayed or missed diagnosis of OT-DSD, which may be attributed to limited awareness among primary healthcare providers,

sociocultural barriers, and psychological factors that may restrict timely access to appropriate medical evaluation.

Classification of a patient as OT-DSD requires the presence of both ovarian tissue with follicles and testicular tissue with seminiferous tubules. Based on the frequency of distribution of gonads, the most common pattern observed is unilateral with ovotestes on one side and ovary or testes on the other side, followed by the bilateral type with ovotestes on both sides. The lateral type with ovary on one side and testes on the other side is the least common pattern of distribution. Our patient belongs to the lateral type with testes on the right side and ovary on the left side.

The most common karyotype associated with OT-DSD is 46,XX (60%), followed by 46,XX/46,XY (33%), and the least common karyotype is 46,XY (7%). Testicular differentiation in patients with 46,XX OT-DSD can be attributed to translocation of SRY to the X chromosome or an autosome [6-8]. Molecular studies have revealed that 90% of patients with 46,XX OT-DSD are SRY negative [9]. In SRY-negative 46,XX OT-DSD, testicular differentiation may result from increased activity of pro-testicular genes (SOX9, SOX3) or impaired ovarian-promoting pathways (WNT4, RSPO1, NR2F2) [6,10-12]. Apart from this, DNA methylation with accidental silencing of pro-ovarian genes like WNT4, microRNA (miRNA) prematurely degrading pro-ovarian genes, mutations in the enhancer or promoter region upstream or downstream of SOX9 or cryptic mosaicism of the SRY gene limited to gonads are other proposed mechanisms of testicular differentiation in 46,XX OT-DSD [6,13].

Although WES in this patient failed to identify pathogenic variants within the primary candidate genes (RSPO1, WNT4, WT1, SOX9, SOX3, NR5A1, and NR2F2), a genetic etiology cannot be entirely discounted. The negative result must be interpreted within the limitations of peripheral-blood WES, which possesses restricted sensitivity for certain structural variants and fails to capture distant regulatory disruptions. Additionally, testing peripheral tissue cannot rule out tissue-specific or low-level gonadal mosaicism, nor does it account for unexamined epigenetic or miRNA-driven mechanisms of testicular development. Ultimately, securing a molecular diagnosis in these cases is paramount, as a definitive causative variant provides critical utility for inheritance profiling, family planning counselling, and longitudinal risk management.

## Conclusions

OT-DSD is a rare condition that may present in adulthood with episodic hematuria and gynecomastia. A high index of suspicion for OT-DSD should be maintained in patients presenting with atypical genitalia and asymmetry of gonads. Diagnosis requires histological confirmation of both ovarian and testicular tissue in separate or a single gonad. Management should be individualized through multidisciplinary assessment and shared decision-making. Negative peripheral-blood genetic testing does not exclude OT-DSD or an underlying genetic cause, as regulatory variants and low-level or gonad-limited mosaicism may remain undetected.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Padala Ravi Kumar, Kamalakhya Samantaraya, Deepak K. Dash

**Acquisition, analysis, or interpretation of data:** Padala Ravi Kumar, Kamalakhya Samantaraya, Deepak K. Dash, Debasish Patro, Pradosh K. Sahu, Kapileswar Swain

**Drafting of the manuscript:** Padala Ravi Kumar, Kamalakhya Samantaraya, Debasish Patro, Pradosh K. Sahu, Kapileswar Swain

**Critical review of the manuscript for important intellectual content:** Padala Ravi Kumar, Kamalakhya Samantaraya, Deepak K. Dash, Debasish Patro, Pradosh K. Sahu, Kapileswar Swain

**Supervision:** Padala Ravi Kumar, Deepak K. Dash, Debasish Patro, Pradosh K. Sahu, Kapileswar Swain

### Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have

declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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