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# Ovotesticular Disorders of sexual development (DSD): A rare case of peritoneal carcinomatosis in an elderly DSD male patient

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ABSTRACT

Disorders of sexual development (DSDs) represent a spectrum of conditions characterized by atypical gonadal and/or genital development. The incidence is 1 in 5,000 live births. Patients with DSD may be at increased risk for developing gonadal and reproductive tract tumors. This report summarizes the current knowledge on the risks of gonadal tumors in patients with DSD. Specifically, we focus on ovotesticular DSD (OT-DSD), which accounts for 5% of DSD cases and is defined by the presence of both ovarian and testicular tissues in the same individual. We present a rare case of a phenotypically male XY patient with OT-DSD who was diagnosed with aggressive peritoneal cancer at the age of 71.

## 1. Introduction

Disorders of sexual development (DSDs), previously termed intersex disorders, encompass a spectrum of conditions characterized by incomplete or disordered gonadal and/or genital development, leading to a discordance between genetic, gonadal, and phenotypic sex (Cools et al., 2006). DSDs occur in 1 of every 4,500 to 5,500 births globally (Kathrins and Kolon, 2016). Ovotesticular DSD (OT-DSD), previously known as true hermaphroditism, is one of the rarest variants, accounting for only 5 % of DSD cases (Mahmoudzadeh et al., 2019). It is defined by the presence of both ovarian and testicular tissues in the same individual. Several types of DSD are associated with an increased risk of gonadal tumors (Cools et al., 2006; Kathrins and Kolon, 2016). Given the rarity and spectrum of etiologies in DSD, the guidelines for cancer risk assessment, oncologic management, and surveillance have not been established. We present a rare case of a 71-year-old phenotypically male XY patient with OT-DSD diagnosed with an aggressive peritoneal cancer. We highlight the features of this rare congenital condition and summarize the current knowledge on the risk of gonadal and reproductive tract tumors in patients with DSD.

## 2. Case Presentation

A 71-year-old 46, XY male, born with ambiguous genitalia, was referred to gynecologic oncology with an enlarging ovarian mass discovered on recent imaging (Griggers et al., 2024). The patient was born with both a phallus and a vagina and underwent multiple surgeries as a child to achieve male external genitalia. He reported a history of hypospadias repair, testicular prostheses placement, and possible bilateral orchiectomy. He had received testosterone injections since the age of 18 years and was able to achieve satisfactory erections. His height was 5′2″, and his karyotype was 46, XY with the *SRY* gene present, based on the analysis of 50 cells to exclude mosaicism. A DSD gene panel was offered but not performed.

The patient underwent regular exams with a urologist. At age 68, a computed tomography (CT) scan was performed to assess a renal cyst, and it incidentally revealed a normal-appearing uterus. A follow-up CT scan two years later showed a uterus with endometrial thickening or intracavitary fluid, along with a new 3.5 cm low-attenuating lesion with soft tissue density in the adnexal region. He had bilateral kidneys with 7.6 cm right renal cyst. To further characterize the adnexal mass, a magnetic resonance imaging (MRI) scan was conducted. This revealed

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the upper third of the vagina, uterus, a right ovary with a 2.5 cm cyst containing a small solid nodule along its lateral aspect, an atrophic left ovary with a small cyst, and a normal-size prostate gland. Comparison of MRIs seven months apart indicated right ovarian enlargement of a solid and cystic mass, measuring 5.5 x 3.4 cm (Fig. 1-A, B). Physical examination was notable for a small phallus with testicular prostheses. Laboratory tests including Beta-HCG, LDH, CEA, CA19-9, AFP, and Prostate Specific Antigen were within normal limits, except for an elevated serum CA-125 level of 505 U/mL. Consequently, the patient underwent a diagnostic laparoscopy for the removal of the adnexal mass.

Upon abdominal entry, extensive peritoneal carcinomatosis with a miliary pattern of distribution was observed, involving the omentum, diaphragm, bowel, anterior abdominal wall, and bilateral paracolic gutters. The uterus and bladder were not visualized as the anterior and posterior cul-de-sac were obliterated by the tumor. Ovarian-like tissue tumor was adherent to the anterior abdominal wall (Fig. 1-C). Biopsies were taken of the anterior abdominal wall and the adnexa. A Fagotti score of 10 excluded the patient from qualifying for cytoreductive surgery. Pathologic examination of the biopsy specimens was suspicious for an ovarian malignancy but inconclusive due to extensive necrosis and abundant inflammatory cells. Immunohistochemistry could not be performed. Repeat sampling was suggested. Post-surgery, the patient was diagnosed with acute adjustment disorder with depressed mood. He declined further biopsy and surgery. Chemotherapy was offered, but the patient declined. Instead, he opted for supportive care and passed away eight months later.

## 3. Discussion

DSD is a heterogeneous group of congenital conditions involving abnormal development of chromosomal, gonadal, or phenotypic sex (Cools et al., 2009). Some subgroups of DSD patients have an increased gonadal tumor risk (Table 1) (Cools et al., 2009; Kathrins and Kolon, 2016; Lee et al., 2016; Li et al., 2020). To our knowledge, this is the first reported case of an elderly phenotypically male patient with suspected 46,XY OT-DSD who developed an aggressive cancer, most likely of

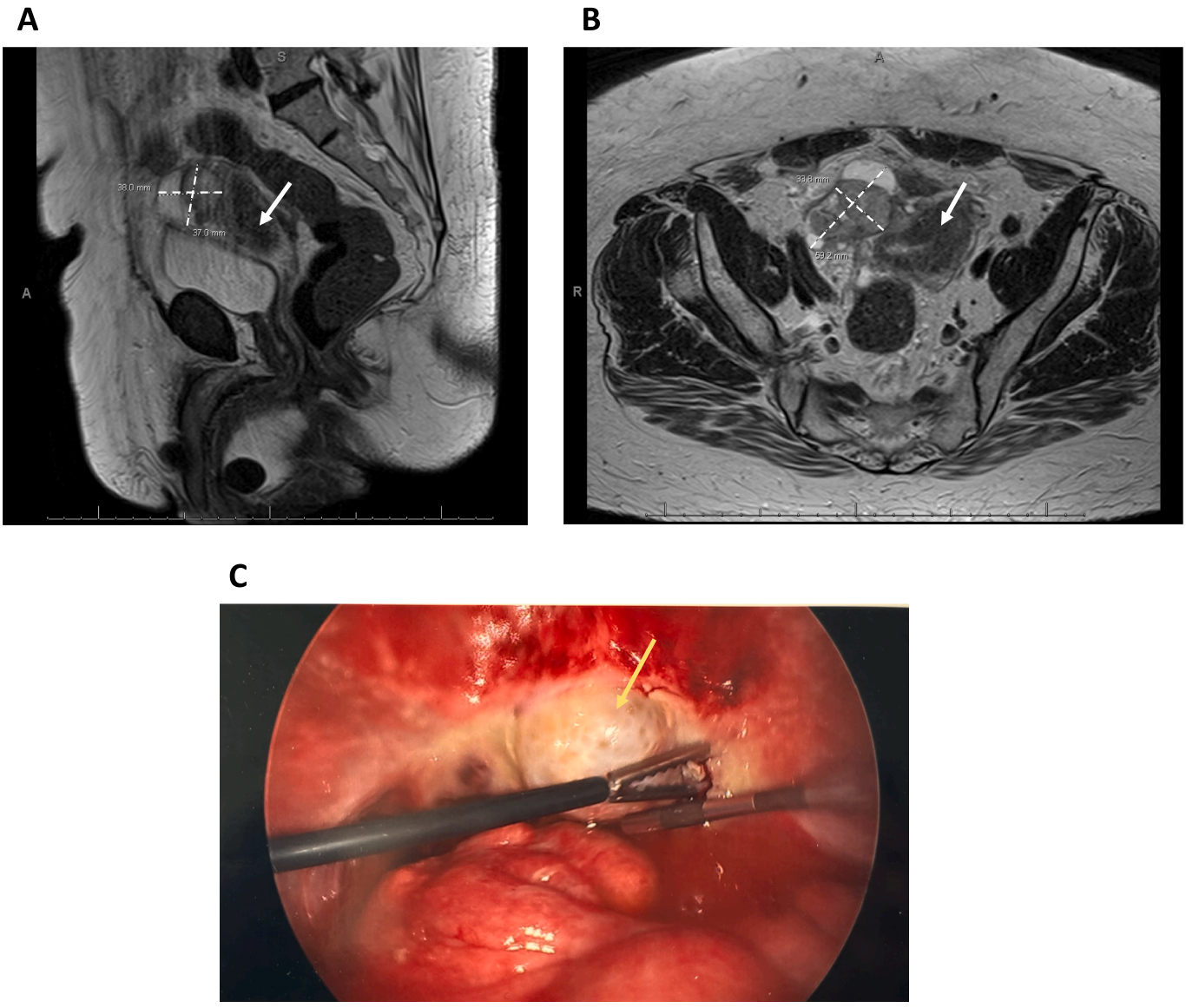


**Fig. 1.** A 71-year-old male with a uterus and a right adnexal mass. Magnetic resonance and intraoperative image. Sagittal (A) and axial (B) T2-weighted images of the pelvis demonstrate a 5.9 cm right adnexal mass with solid and cystic components. White arrows are pointing at the uterus. Intraoperative image of the pelvis (C) one month after MRI shows an ovarian-like tissue tumor (yellow arrow) densely adherent to the anterior abdominal wall, obliterating the anterior and posterior cul-de-sac. The uterus and bladder were not visualized due to dense disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 1**
. Classification of disorders of sexual development (DSDs) and gonadal tumor risk (Cools et al., 2009, 2006; Kathrins and Kolon, 2016; Lee et al., 2016).

| DSD Karyotype | Underlying defect | DSD Types | Reported Gonadal Tumor Risk Examples[a] (%) |
|---|---|---|---|
| 46, XX | Gonadal (ovarian) dysgenesis | 1. Ovotesticular DSD<br>2. Testicular DSD<br>3. GD | – Low risk for GCT (< 3 %) in ovatesticular disorder<br>– Increased risk for gonadal and peritoneal serous tumors with papillary tubal hyperplasia |
| 46, XX | Androgen excess | 1. Congenital adrenal hyperplasia<br>2. Aromatase deficiency<br>3. Maternal androgen excess (exogenous vs tumors) | No increased risk for all |
| 46, XY | Gonadal (testicular) dysgenesis | 1. GD (partial & complete)<br>2. Regression of testes<br>3. Gonadal regression ovotesticular disorder | – High risk for GCT (60 %) in Frasier syndrome (WT1 pathogenic variant) with GD<br>– High risk for GCT (40 %) in Danys-Drash (WT1 pathogenic variant) with GD<br>– Increased risk for GCT with GD: 15–35 % risk with intra-abdominal gonads; unknown risk with scrotal testes<br>– Low risk for GCT (3 %) in ovotesticular disorder<br>– Increased risk for gonadal and peritoneal serous tumors with papillary tubal hyperplasia |
| 46, XY | Defects in androgen biosynthesis | Defective androgen synthesis | Possible increased risk (28 %) for GCT with 17β-hydroxysteroid dehydrogenase (17β-HSD) deficiency |
| 46, XY | Defects in androgen action | 1. Partial AIS<br>2. Complete AIS | – High risk for GCT (15 %) with partial AIS and non-scrotal gonads<br>– Unknown malignancy risk with partial AIS and scrotal gonads<br>– Low risk for GCT (0.8 %) with complete AIS |
| 46, XY | Defective function of AMH or AMH receptor | Persistent Mullerian Duct Syndrome (PMDS) | Increased risk for malignancy (including adenocarcinoma) of Mullerian remnant |
| 45, X (+/- second X mosaicism) | Sex chromosome: numerical | Turner Syndrome and variants | No increased risk |
| 47, XXY | Sex chromosome: numerical | Klinefelter Syndrome and variants | No increased risk |
| 46, XX/46, XY | Sex Chromosome: numerical, chimerism | 1. Complete GD<br>2. Testicular dysgenesis<br>3. Ovatesticular disorder | Increased risk for GCT with GD |
| 45, X/46, XY | Sex Chromosome: numerical | 1. Complete GD<br>2. Testicular dysgenesis<br>3. Ovatesticular disorder<br>4. Undifferentiated dysgenesis | – Intermediate to high risk for GCT (15 %) in Turner (Y + )<br>– Increased risk for GCT with GD |

AIS: androgen insensitivity syndrome; AMH: anti-Mullerian hormone; CIS: carcinoma *in situ*; GCT: Germ cell tumor; DSD: disorders of sexual development; GD: gonadal dysgenesis.

[a] Not a complete list. Tumor Risk (%) describes a tumor incidence or prevalence reported in the literature, often based on a limited number of patients.

ovarian origin, late in life. Based on limited data, patients with 46,XX OT-DSD do not have an increased risk for gonadal tumors. However, the presence of a specific Y-chromosomal material, positive DSD genetic testing, non-scrotal location of the testicular tissue, histopathology notable for undifferentiated gonadal tissue, carcinoma *in situ*, gonadoblastoma, or papillary tubal hyperplasia heighten the risk of gonadal tumors, and patients should be offered risk-reducing surgery.

The synergy of time-sensitive genetic activating and inhibiting mechanisms is essential in normal gonadal differentiation. Minor aberrations in this process can have major consequences on sex development. Several genes (e.g., *WNT4, FOXL2,* and *RSPO1)* have been shown to be essential in gonadal cell decision towards testicular or ovarian differentiation. Some pathogenic variants in genes that are involved in early sex development can explain the phenotype and are diagnostic (Lee et al., 2016). Thus, all patients with suspected DSD should, at minimum, have karyotype testing and a DSD genetic panel.

Ovatesticular disorder (OT-DSD) is a rare type of DSD where both ovarian and testicular tissues are present. Familiarity with gonadal tissue distribution in OT-DSD by gynecologic oncology can assist with risk stratification and surgical planning. OT-DSD can be categorized into three groups: lateral, where one gonad (usually the left) is an ovary and the other is a testis; bilateral, with an ovotestis on each side; and unilateral (most common), with an ovotestis on one side (usually the right) and a normal testis or ovary on the other (Mahmoudzadeh et al., 2019). In the ovatestes gonad, the testicular tissue is central, and ovarian tissue is polar in location (Ceci et al., 2015). Our patient reported undergoing bilateral orchiectomies, which is questionable given that he had both ovary-appearing gonads on imaging. The degree of gonadal descent corresponds to the amount of testicular tissue present. While almost all ovaries are abdominal and 50 % of testes are labioscrotal, ovatestes can be found in the abdomen (50 %), inguinal (25 %), and labioscrotal (25 %) regions. A fallopian tube or a vas deferens is usually present beside an ovatestis. OT-DSD primarily occurs in the setting of a 46,XX karyotype (65–90 %), with 46,XY/XX chimerism and 46,XY being less common (Barseghyan and Vilain, 2014; Mahmoudzadeh et al., 2019). A Y chromosome is frequently observed in cases of lateral ovatestes. Patients with OT-DSD are more likely to be raised as boys and almost always have a uterus.

The diagnosis of OT-DSD is established by histologic evidence of both testicular and ovarian tissues in the same individual. Pathology could reveal various combinations of testicular, ovarian, fibrous, fallopian tube, myometrial, endometrial, epididymal, and tumor tissues within the same gonad (Ceci et al., 2015; McCann-Crosby et al., 2014). Although no definitive tissue diagnosis was made for our patient due to significant necrosis of the biopsied tissue, we conclude that the patient likely had OT-DSD because he had an XY karyotype with *SRY* gene, a virilized external genitalia at birth, low-level testosterone production during puberty, all suggestive of the presence of functional testicular tissue. No adrenal tumors as an alternative source of androgen production were found by MRI or CT. In addition to testosterone-producing testicular tissue, recent imaging, intraoperative findings, and high serum CA-125 were highly suggestive of the presence of ovarian tissue.

A few subgroups of DSD patients are at an increased risk of developing germ cell tumors and other gonadal or reproductive tract malignancies (Table 1) (Cools et al., 2009; Kathrins and Kolon, 2016; Lee et al., 2016). Germ cell tumors are more likely to arise in undifferentiated gonadal tissue. Clinical management guidelines have been proposed to stratify patients with DSD based on their germ cell tumor risk (van der Zwan et al., 2015). Neoplastic changes can also occur in testicular and ovarian tissues in patients with ovatestes. However, the chance of malignancy is reported to be lower than in most DSDs: 3 % in 46,XY OT-DSD and even lower in 46,XX OT-DSD (Ceci et al., 2015; Cools

et al., 2006). Prophylactic removal of the gonads is not indicated. Our XY patient with the *SRY* gene lived into his late 60 s without developing gonadal malignancy.

The invasive germ cell tumors that develop in the ovatestes are - dysgerminoma and seminoma, which are always preceded by gonadoblastoma (originating in the ovary or dysgenetic gonad) or carcinoma *in situ* (CIS, originating in the testes) (Cools et al., 2006; van der Zwan et al., 2015). Sporadically, sex cord-stromal, Sertoli-Leydig, or epithelial tumors, mucinous cystadenoma, and Müllerian cysts can be found in ovatestes. No serum markers for screening and early tumor detection in patients with DSD have been established yet, although several markers are under investigation (Kathrins and Kolon, 2016). Risk factors for gonadal malignancy include undescended gonads, genital and gonadal undifferentiation, and older age (Lee et al., 2016; Li et al., 2020; Şimşek et al., 2016). The gonadoblastoma locus (*GBY*) on the Y chromosome can promote germ cell tumor development in dysgenetic and possibly normally developed testes (van der Zwan et al., 2015). This genetic fragment encodes for a testis-specific protein on the Y chromosome (TSPY), which is suspected to be associated with an increased risk for germ cell tumors.

Patients with persistent Mullerian duct syndrome (PMDS) are at an increased risk for malignancy of Mullerian remnant structures (Kathrins and Kolon, 2016). Histopathologic findings of papillary tubal hyperplasia on gonadal biopsy are associated with an increased risk for gonadal and peritoneal serous tumors in patients with gonadal dysgenesis and OT-DSD (Şimşek et al., 2016). It remains unclear whether Mullerian structures in OT-DSD predispose patients to uterine, endometrial, or fallopian tube cancers. Given the rarity of OT-DSD, no guidelines have been established.

Diagnostic laparoscopy with biopsies is the most sensitive and specific modality for the evaluation of gonadal tissue and Mullerian derivatives, and gonadal cancer risk assessment in patients with suspected DSD (Şimşek et al., 2016). Physical examination, ultrasonography, CT, or MR imaging should be performed prior to surgery to delineate pelvic anatomy and the location of the gonads. In our case, it remains unclear whether the patient underwent diagnostic laparoscopy earlier in life.

Most diagnoses of DSD, especially for patients who present with ambiguous genitalia, are made in early childhood (Lee et al., 2016). Often, multidisciplinary care is implemented rapidly in specialized pediatric services. However, adolescents and adults frequently face challenges in finding access to expert adult care, which ultimately leads to the loss of information and/or cessation of medical follow-up. Our patient's lack of clarity about their DSD diagnosis highlights gaps in long-term follow-up and preventive care. Discovering their uterus and ovaries incidentally at 68 underscores the need for ongoing gynecologic care and cancer risk assessment. While no reliable screening test exists for ovarian cancer, a more comprehensive DSD assessment earlier may have allowed for proactive measures, like surgical removal of at-risk female reproductive organs, potentially averting the development of aggressive peritoneal cancer. If a pathogenic genetic variant of DSD or concerning gonadal biopsy were identified, the patient could have chosen surgery to remove female reproductive organs earlier.

In conclusion, karyotype evaluation, DSD-specific genetic testing, and imaging should be performed early in patients with suspected DSD. In the presence of a Y-chromosome and depending on histopathology and the gonadal location, the gonads might need to be removed to prevent the development of gonadal malignancy. Evaluation of Y-chromosomal material not evident in traditional karyotyping and diagnostic laparoscopy with gonadal tissue biopsy should be considered. Gonads or Mullerian structures with papillary tubal hyperplasia have malignant potential and should be removed. Long-term monitoring of DSD patients is crucial for evaluation, early detection, and treatment, particularly given the variable, albeit heightened, risk for malignancy. Adopting a long-term, multidisciplinary approach can further address potential gaps in early screening and treatment. Further research is needed to better understand cancer risks in this rare condition.

informed consent

Unfortunately, the patient is now deceased, and this case report was written after the patient's death. Thus, informed consent was unable to be obtained. The authors affirm there is no personal identifiable information included in this report, nor are there descriptors that could potentially identify the patient.

## CRediT authorship contribution statement

**Anastasia Navitski:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Sakshi Sehgal:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Kalyani Ballur:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Lawrence C. Layman:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Robert V. Higgins:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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