Ovotesticular Disorder of Sex Development: A Rare Case of Lateral Subtype 45X/46XY kariotype Diagnosed in Adulthood

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A 53-year-old male referred to our centre because of hypergonadotropic hypogonadism detected during urological follow-up for urethral lithiasis. Physical examination showed short stature, micropenis, ambiguous external genitalia, and normal secondary sexual characteristics. Karyotype: 45 × 0/46XY. Abdominal MRI revealed the presence of uterus-like structure, right annex, and left testes without prostate. He underwent laparoscopic removal of dysgenetic tissues; histologic examination confirmed the presence of little uterus, fallopian tubes, little atrophic ovary, and vaginal tract; left testes was atrophic with sclero-jalinosis of seminal tubes and Leydig's cells hyperplasia. Testosterone replacement therapy was started after surgery and prostate became MRI visible after 2 years. UROLOGY 129: 68–70, 2019. © 2019 Elsevier Inc.

Disorders of sex development (DSD) comprise a diverse spectrum of genotypic and phenotypic presentations, with an overall incidence of approximately 1/4.500 live births.[1] Ovotesticular disorder of sex development (OT-DSD, formerly known as "true hermaphroditism") accounts for less than 10% of all DSD, with an overall incidence of 1/100.000 live births.[1] While the distribution of karyotypes in OT-DSD seems to vary by geographic region, mosaicism in this disorder is quite rare.[2] We report a rare case of lateral subtype of OT-DSD (ovary on one side and testis on the contralateral side, without the presence of an ovotestis) with 45X/46XY mosaic karyotype, diagnosed in adulthood. As common practice, patients have been requested to sign an informed consent to the collection of clinical and pathological data.

CASE DESCRIPTION

A 53-year-old man referred to the Urology clinic of our Institution because of recurrent urethral lithiasis, urinary flow disorders, and cyclical abdominal pain.

In childhood surgical procedures to correct scrotal hypospadias, ventral penis deviation, and left undescended testis were performed. At the age of 18, he underwent a urethroplasty.

At physical examination the patient presented with short stature (height: 150 centimeters, weight: 54 kg, BMI 24 kg/m^2), ambiguous external genitalia with micropenis, unpalpable right testes, and prostate. Secondary sexual characteristics were normal and consensual to male development, without gynecomastia.

He described a normal sexual life; he was married without children.

The hormonal evaluation showed hypogonadism (total testosterone 0.8 ng/ml), which prompted an endocrinological evaluation. Hypergonadotropic hypogonadism was detected (Follicle Stimulation Hormone 50.8 mUI/ml, Luteinizing Hormone 15.7 mUI/ml, Sex Hormone Binding Globulin 40.8 mol/l, normal prolactin and estrogenic levels, Prostate-Specific Antigen (PSA) 0 ng/ml). He presented normal corticotroph, thyrotroph and somatotropic axis and bone mineral densitometry showed osteopenia (lumbar T score -1.5, Z score -0.8, SDS Bone Mineral Density (BMD) 1.040 g/cm^2, femoral neck T score -2.8, Z score -1.7, SDS BMD 0.640 g/cm^2) with normal morphometry.

Step by step the following exams were performed:

- Karyotype, that resulted in a mosaicism 45, X0 (44) /46, XY (56);
- Left-hand X-Ray, that showed translucency, carpus pyramidalization and mild Madelung deformity (narrowing of the ulnar portion of the distal radial physis, anterior bowing of the radial shaft, and dorsal subluxation of the ulnar head);

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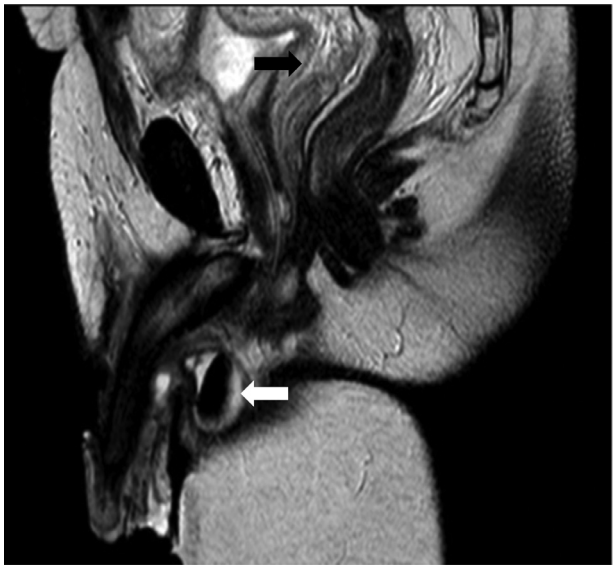

Figure 1. MRI image of the pelvic region (black arrow: uterus; white arrow: left testis).

- Abdominal Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) that suggested the presence of uterus-like structure, with a right annex, correct visualization of the left testes without prostate and without right testes (Fig. 1).

As the diagnosis of OT-DSD was suspected, the patient began a psychological approach, and surgical exploration for prophylactic bilateral gonadectomy was suggested.

Laparoscopic exploration confirmed the presence of the uterus, right fallopian tube, and right ovary with own vascularization on the right side, and deferential duct in the left internal inguinal channel with left testes on the left side. Prostate was not found. Surprisingly uterus was continued with a cavity recovered by epithelium in communication with the urethra, compatible with a draft of the vagina.

The definitive histologic examinations revealed the presence of a little uterus, fallopian tubes, a little atrophic ovary, and a vaginal tract. The left testis was atrophic and presented sclero-jalinosis of seminal tubules and Leydig's cells hyperplasia (Fig. 2).

After surgery, the patient started replacement therapy with testosterone gel with good response on biochemical and clinical parameters. Two years after the beginning of replacement therapy BMD was improved and interestingly PSA was measurable with prostate visualization at MRI. He carries on the phycological path.

DISCUSSION

OT-DSD is a rare disorder of sex development. The diagnosis is based on unequivocal histologic demonstration of both ovarian and testicular tissue in an individual.[1] Pathogenesis remains unclear but paternal meiosis is a critical phase.[3] Clinical manifestations of OT-DSD are variable and based on the extent of functional testicular and ovarian tissue present during the time of sex determination and development. OT-DSD can be classified as lateral if testis is present on one side and ovary on the other (as in our case),

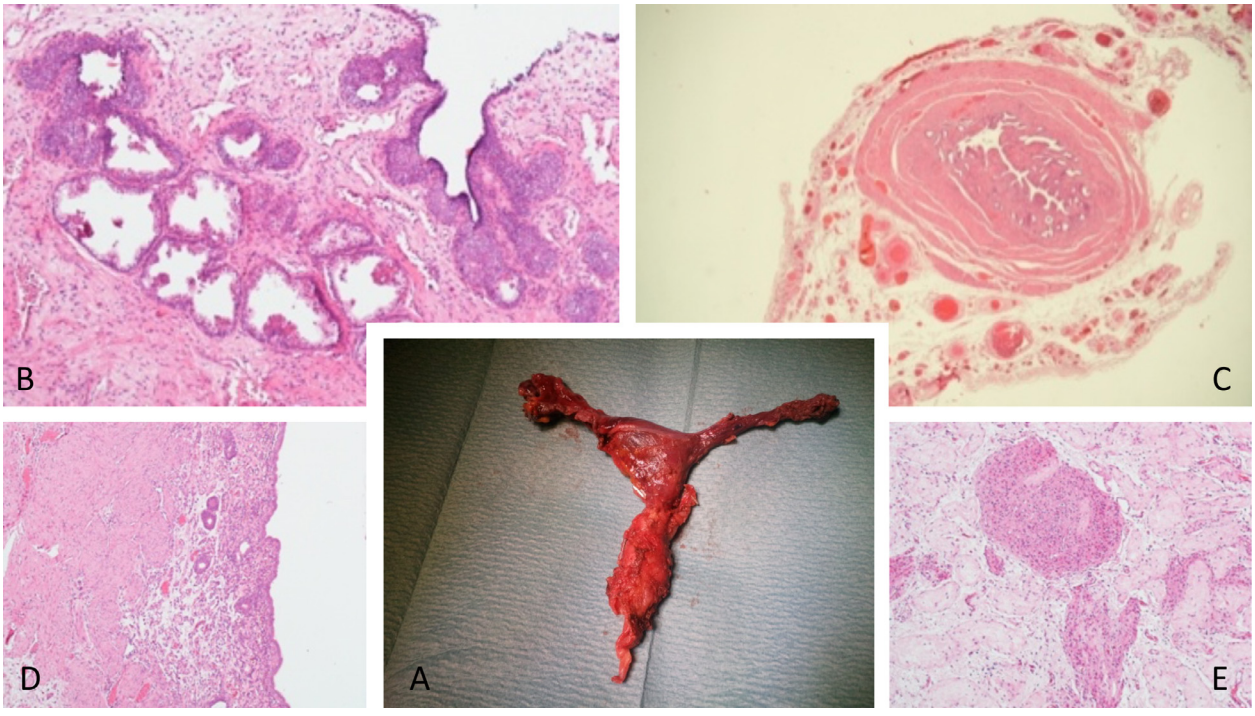

Figure 2. Macroscopic (**A**) and microscopic (**B**–**E**) examination of removed tissue. (**A**) Atrophic uterus, bilateral fallopian tubes, right ovary, and vaginal tract. (**B**) Vaginal portion of the cervix. (**C**) Tubaric tissue. (**D**) Uterus. (**E**) Left testis with sclero-jalinosis of seminal tubes and Leydig's cells hyperplasia. (Color version available online).

unilateral if an ovotestis is present on one side and testis or ovary on the other, or bilateral if there is an ovotestis on both sides.[4]

Cytogenetically, the most common karyotype encountered in OT-DSD is 46XX, followed by 46 XX/XY mosaicism and 46XY. Interestingly, our patient was a mosaicism 45 × 0/46XY. Karyotype typically shows a geographic variation in OT-DSD. Mosaicism is common in Europe and North America, 46XY in Japan, Sri Lanka, and Brazil, whereas 46XX in South and West Africa.[2]

To our knowledge this is one of the very rare cases of 45X/46XY OT-DSD, since only 7 patients were previously reported[5]; moreover, it is the second case of 45X/46XY lateral presentation with testes on one side and ovary on the other side; the other one, described by Becker et al, was a child with ambiguous genitalia who underwent bilateral prophylactic gonadectomy at the age 14 months.[5] Since diagnosis was made in adulthood, we can analyze particular phenotypic features of our patient. First of all, he presented short stature despite hypogonadism, which is probably explained by *SHOX* haploinsufficiency as in Turner syndrome, with accelerating premature epiphyseal fusion. Moreover, *SHOX* haploinsufficiency causes an ovarian estrogen-independent selective reduction in cortical BMD. 45 × 0 karyotype, in fact, is also associated with low BMD in cortical rather than trabecular bones and it would primarily be ascribed to *SHOX* haploinsufficiency. Even, the Madelung deformity and the shortened metacarpals could result from a loss of *SHOX* expression in the distal ulna and radius.[6]

Even if our patient presented a mosaicism karyotype with ambiguous external genitalia, sex assigned at birth was male. In cases of genital ambiguity, sex assignment is largely dependent on the anatomy of the external genitalia, internal genitalia, prospects of sexuality, and fertility. Sociocultural influences play also a crucial role in sex assignment, as observed in studies from India, and Brazil, with predominant male sex.[2,7]

Surgical management includes removal of ovotestis when present and gonads incongruous to the chosen sex, along with reconstructive surgery of the external genitalia. Some centers[2,8] prefer conservative surgical techniques, with preservation of maximal gonadal components. The timing of surgery depends on ethical and sociocultural sentiments, which vary widely. In our case, the delayed diagnosis has influenced therapeutic choices and the possibility of fertility.

The closest differential diagnoses of OT-DSD is mixed gonadal dysgenesis (MGD), especially when the karyotype observed is 45X/46XY, as in our case. This can be resolved only by gonads histopathologic analysis, which shows in MGD a unilateral streak gonad and lack of multiple primordial follicles.[3] It is imperative to distinguish between the 2, as MGD is associated with very high risk of gonadal tumors (15%-40%) as well as with a higher proportion of associated anomalies, such as dental, skeletal, renal, and cardiac.[3] On the other hand, OT-DSD is not associated with any other developmental defect. The frequency of gonadal tumors in patients with OT-DSD has been reported as 2.6%-4.6%, with dysgerminoma being the common subtype.[9]

The differential diagnosis of differences of DSD belongs to the most complex fields in medicine and requires a multidisciplinary team conducting a synoptic and complementary approach consisting of thorough clinical, hormonal, and genetic workups. Reaching a correct diagnosis is important as it may guide patient management in relation to gender choice, assessment of adrenal and gonadal function, gonadal cancer risk, associated morbidity, as well as long-term outcomes. Therefore, a multidisciplinary team (pediatric or adult endocrinology, urology or gynecology, clinical biochemistry, genetics, radiology, pathology, psychology, and psychiatry) should be mandatory for the care of these patients. An individualized plan is needed, especially for the rare cases diagnosed in adulthood. The complex network of the development of the dysgenetic tissue, in fact, cannot be totally explained yet. Interestingly, for instance, in our patient prostate was not found at the laparoscopic examination but PSA was measurable 2 years after starting replacement therapy with prostate visualization at MRI. The prostatic gland will require careful attention during follow-up.

Due to the rarity of these disorders, the majority of DSD literature is based on small retrospective clinical series and case reports. Further studies are needed to guide clinicians in the classification, risk-stratification, and appropriate management of these patients, in particular for the rare cases diagnosed in adulthood.

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