Case Report

Disorder of Sex Development: A Case of Late-Diagnosed Ovotestis and Its Postsurgical Follow-up

Zenilda Vieira Bruno PhD [1,*], Camila Sampaio Nogueira BSc [1], Maria Vieira de Lima Saintrain PhD [2], Nadiejda Mendonça Aguiar Nobre BSc [3], Diane Isabelle Magno Cavalcante MSc [1], Nádia Dantas Gomes MSc [1], Maria Tereza Pinto Medeiros Dias BSc [3]

[1] School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil
[2] Public Health Graduate Program, University of Fortaleza, Fortaleza, Ceará, Brazil
[3] Department of Gynecology and Obstetrics, Assis Chateaubriand Maternity Hospital, Federal University of Ceará, Fortaleza, Ceará, Brazil

A B S T R A C T

Background: True hermaphroditism is characterized by the presence of both testicular and ovarian tissue. This case report aimed to describe a case of ovotestis in adolescents.
Case: A 17-year-old patient presented with undifferentiated genitalia. Thelarche occurred at age 14, menarche occurred at age 15, and menstruation was regular. Physical examination showed female phenotype, Tanner IV breasts, gynecoid hair, enlarged clitoris, and labia majora symphysis with a single orifice. The patient presented high levels of total testosterone. The left gonad contained typical ovarian tissue and the right gonad contained both seminiferous tubules and ovarian tissue (ovotestis). Vaginoscopy revealed a single orifice (urethra and vagina). Right gonadectomy confirmed the presence of ovotestis.
Summary and Conclusion: Knowledge of true hermaphroditism is important for early diagnosis and proper management.
Key Words: Ovotesticular disorder of sex development, Disorders of sex development, Gonadal disorders, Urogenital abnormalities

Introduction

Disorders of sex development (DSD) involve broad aspects regarding sexual orientation, sensitivity, psychosocial and clinical care, and surgical treatment. Physical changes occur primarily in adolescence, a stage of life that is also marked by emotional changes. Therefore, early diagnosis and management of DSD are necessary to minimize mental, social, and physical pain in these patients. Moreover, the various forms of clinical manifestations require different approaches.

Ovotesticular disorder of sex development (OT-DSD), formerly known as true hermaphroditism, is the rarest disorder of sex development in humans and has an approximate incidence of less than 1 in 20,000. It is characterized by the presence of testicular tissue with seminiferous tubules and ovarian tissue with Graafian follicles that may be coexistent in the same gonad (ovotestis) or on opposite sides in individuals with karyotypes 46, XX or 46,XY.[1,2]

The present study describes a case of OT-DSD in a patient who, despite having undifferentiated genitalia since birth, was diagnosed only in adolescence.

Case

A 17-year-old patient from the countryside of the state of Ceará was admitted to the specialized health care center complaining of undifferentiated genitalia (Figure 1). The patient had a female sex assignment. Thelarche occurred at age 14 years and menarche occurred at age 15 years. The patient reported regular menstruation and denied similar family history.

Physical examination showed Tanner IV breasts, gynecoid hair, enlarged clitoris (4 cm long and 2 cm wide), and labia majora symphysis, with a single narrow orifice (urethra and vagina). The patient was 1.55 m tall, weighed 66.5 kg, and had no acne or hirsutism. Laboratory tests showed total testosterone values of 137.7 ng/dL (reference value o[RV], 14-76 ng/dL) and hydroxyprogesterone values of 1.35 ng/mL (RV, 0.2-4.5 ng/ml). Pelvic ultrasound showed a 2-cm^3 uterus (expected volume for nulliparous women is 28-65 cm^3), a 5-mm endometrium, right ovary measuring 4.2 cm^3, and left ovary measuring 3.6 cm^3.

Exposure of the female fetus to androgen excess produced by ovotestis causes virilization of the external genitalia. The physical examination was based on Prader's classification of ambiguous genitalia, which ranges from I to V.[3] The patient in the present study was classified as Prader III, given the presence of an enlarged clitoris and a deep funnel-shaped opening with the urethral opening leading to a vaginal canal like a pseudo urogenital sinus.

These characteristics led us to consider two diagnostic possibilities: nonclassical congenital adrenal hyperplasia inherited from the mother with in utero virilization due to maternal hyperandrogenism; or true hermaphroditism with presence of ovotestis. The patient's mother attended the health care facility and reported no history of adrenal hyperplasia or hyperandrogenism during pregnancy, nor consanguineous marriage.

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

* *Address correspondence to:* Zenilda Vieira Bruno, PhD, Rua Paula Ney, 55, Apto. 902, Aldeota, Fortaleza, Ceará, Brazil CEP 60.140-200; Phone: (85) 99981-1044
E-mail address: zenildavieirabruno@gmail.com (Z.V. Bruno).

1083-3188/$ - see front matter
https://doi.org/10.1016/j.jpag.2020.03.007

Videolaparoscopy and vaginoscopy allowed for histological evaluation of the gonads and a more detailed examination of the single genital orifice. The examinations revealed a normal uterus, left gonad with typical ovarian tissue, and right gonad with a differentiated aspect and mixed texture (Figure 2).

Biopsies of the left gonad and of the area with altered texture in the right gonad were performed. Biopsy of the normal-appearing portion of the right gonad was also performed. Vaginoscopy revealed a slightly distensible tubular vaginal canal of reduced diameter, an orifice in the vaginal fundus with glandular crypts (possibly the cervical canal) that did not allow deep insertion of the hysteroscope and visualization of the uterine cavity, and a urethral opening leading to a vaginal canal.

Biopsy of the left gonad showed ovarian tissue containing developing primordial follicles. Biopsy of the altered portion of the right gonad showed seminiferous tubules containing Leydig cells and Sertoli cells with an absence of spermatogenesis, and biopsy of the normal-appearing portion of the right gonad showed ovarian follicles. Thus, the diagnosis of true hermaphroditism with right ovotestis was confirmed.

Surgical Management

Videolaparoscopic gonadectomy was performed on the right side, and the histopathological findings confirmed the ovotestis. The gonad contained primary follicles and testicular tissue, and the transition zone was clearly visible (Figure 3). The ovarian portion contained primary follicles, corpus luteum, and abundant stroma. The testicular portion was adjacent to the ovarian portion, and it contained several seminiferous tubules with Sertoli cells and some Leydig cells. There was no evidence of neoplastic tissue.

The surgical procedure consisted of a technique of clitoroplasty with creation of labia minora using preputial skin flaps. Clitoral reduction was done through a semicircular incision in the gland with preservation of dorsal and ventral neurovascular pedicles and removal of clitoral bodies. The procedure was performed at the Department of Urology of the Albert Sabin Pediatric Hospital. The left gonad was preserved (ovary confirmed by macroscopy and histopathological examination) and hormone therapy was not required.

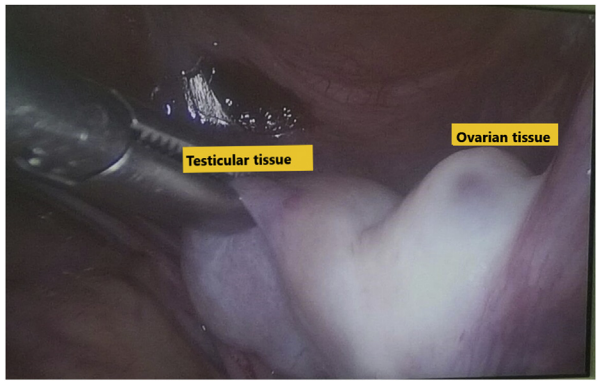

Fig. 2. Videolaparoscopic biopsy of right gonad (ovotestis).

Outpatient Follow-up

Karyotyping results came out during follow-up and showed 46,XX karyotype in 20 metaphases analyzed. One month after gonadectomy in the right hemisphere, the patient was stable, had regular menstrual cycles lasting 5 days, and did not complain of hirsutism or acne. She exhibited normal hormone levels within the female range: 17-hydroxyprogesterone, 3.20 ng/ml; androstenedione, 2.3 ng/mL; and free testosterone, 1.2 ng/dL. Pelvic

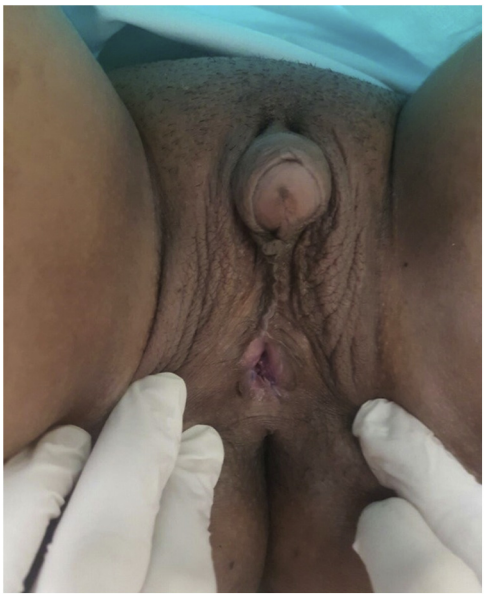

Fig. 1. Undifferentiated genitalia at first consultation.

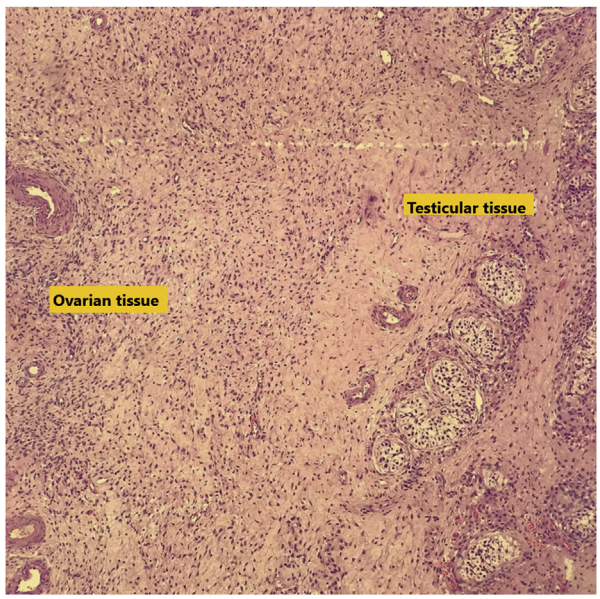

Fig. 3. Histological evaluation of right gonad: Transitional gonadal tissue at 400× magnification. The ovarian portion is represented by primary follicles, corpus luteum, and abundant stroma. The testicular portion was adjacent to the ovarian portion, and it contained several seminiferous tubules with Sertoli cells and some Leydig cells.

ultrasonography showed a uterus with a volume of 39.0 cm^3, an endometrium of 4.9 mm, and a left ovarian volume of 3.53 cm^3.

One year after gonadectomy in the right hemisphere (ovotestis), the hormone test results showed normal levels as follows: free testosterone, 0.7 ng/dL; 17-hydroprogesterone, 3.32 ng/mL; and androstenedione, 1.4 ng/mL.

The vaginal opening remains narrow and there is no possibility of penetration in sexual intercourse. Only digital palpation to a depth of 3 cm is possible. The patient was instructed to use vaginal dilators. However, the patient reported having no interest in sexual intercourse so far, and therefore does not want to use vaginal dilators.

Summary and Conclusion

In people with ovotesticular disorder of sex development, ovarian and testicular tissue are found either in the same gonad, which is termed ovotestis, or on each side of the body. The ovotestes may be in both the scrotal and intraabdominal areas.[2]

The diagnosis of ovotestis requires the presence of seminiferous cords (or tubules) and ovarian follicles with oocytes. The mere existence of a fibrous ovarian-like stroma without follicles is insufficient for the diagnosis.[4] However, the presence of numerous primordial follicles containing primary oocytes, with or without maturing follicles, is considered well-developed ovarian tissue.[5]

In our study, the histopathological findings showed seminiferous tubules and ovarian follicles in the right gonad and normal ovarian tissue in the left gonad.

Ovarian steroids suppress gonadotropins, which results in testicular atrophy. This is the reason why early gender assignment may be considered,[5] with the realization that early assignment may not reflect the patient's gender identity or sexual orientation.

The most common karyotype is 46,XX, as in the case described herein, followed by mosaic 46,XX/XY and 46,XY.[1,6]

Age at diagnosis may vary. In a study of 7 OT-DSD patients, the age at diagnosis ranged from 2 months to 25 years. Although early surgical intervention may be beneficial for some reasons,[7] permanent consequences should be weighed against functional and cancer risks and should consider the patient's gender identity, sexual orientation, and functional consequences. The patient analyzed in our study was diagnosed late, at the age of 17 years. The patient had atypical genitalia and identified as female, which facilitated the medical intervention.

With regard to the clinical presentation, the genital phenotype may vary between male or female; however, most patients with present undifferentiated genitalia,[1,2] as in the patient analyzed in our study.

Biopsy findings have shown that the ovarian tissue of patients with OT-DSD has numerous follicles and remains functional for at least 17 years, thereby allowing spontaneous breast development and cyclical menstruation or hematuria. On the other hand, testicular tissue gradually develops signs of dysgenesis.[8]

In an analysis of cases of OT-DSD, a uterus was noted in 48% (n = 31) of the participants. The karyotype was 46,XX in 29 and 46,XY in 2 of these participants. Additionally, a normal uterus was noted in 31%, a hypoplastic uterus in 16%, and a hemi-uterus in 1% of the participants.[9]

About half of the ovotestes are found in the inguinal region.[2] The patient analyzed in our study had a small uterus, abdominal gonads, and an ovotestis in a normal ovarian position. Despite having testosterone levels above the normal female range and virilization of the external genitalia, the patient has been menstruating regularly since the age of 15 years.

Surgical intervention decision for sex reassignment is multifactorial. Surgery should be conducted as early as possible, and it depends on the functional status of the ovaries, as reassignment to female sex is more feasible.[5,7] This choice must be overseen by a multidisciplinary team. Patients and their parents must evaluate the appearance of the external genitalia, the karyotype, the gonadal functionality, the presence of the Müllerian duct, and social and cultural issues. The patient's gender identity is independent of karyotype.

In many places, social and cultural influences are very strong but may not be beneficial to successful patient outcomes. In Chinese social culture, for example, parents are more willing to have sons. Research conducted in China found that parents insisted on male as final gender even if the multidisciplinary team suggested that female was more appropriate.[5]

Although the association between consanguineous marriage and atypical genitalia is well described in the literature,[1,6] there was no degree of genetic relationship between the parents of the patient analyzed in our study.

The patient in the present study was socially defined and actively participated in the choice of her sexual identity and proposed treatment. The diagnosis of the disorders of sex differentiation should occur as early as possible. The present study described a case of late diagnosis that featured the important participation of the patient throughout the process (diagnosis and treatment), which increased her self-esteem and improved her quality of life. Although controversial, the early diagnosis and decisions, by contrast, are the responsibility of parents who make decisions based on the external genitalia and sociocultural influences. Therefore, DSD cases are multidisciplinary in nature and should always be evaluated individually by the team. The patient presented herein was seen by an obstetrician-gynecologist, an endocrinologist, and a psychologist and is still receiving outpatient follow-up. Furthermore, appropriate genital corrections, such as vaginal dilation or neovagina, will be made according to the patient's progress and desire to initiate sexual activity.

Acknowledgments

The authors acknowledge all colleagues who followed this case and collaborated in the diagnosis and subsequent therapeutic approaches.

References

1. Domenice S, Costa EMF, Mendonça BB: Distúrbios do desenvolvimento sexual. In: Saad MJA, Maciel RMB, editors. Mendonça BB: Endocrinologia: princípios e práticas. Atheneu, Rio de Janeiro, 2017, pp 97–137
2. Lee PA, Houk CP, Ahmed SF, et al: Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Eur Soc Paediatr Pediatrics 2006; 118:488
3. Prader A: Der genitalbefund beim pseudo-hermaphroditismus femininus des kongenitalen adrenogenitalen syndrome. Helv Paediat Acta 1954; 9:231
4. Grispon RP, Rey RA: Disorders of sex development with testicular differentiation in SRY-negative 46,XX individuals: clinical and genetic aspects. Sex Dev 2016; 10:1
5. Mao Y, Chen S, Wang R, et al: Evaluation and treatment for ovotesticular disorder of sex development (OT-DSD))-experience based on a Chinese series. BioMedCenter Urol 2017; 17:21
6. Palo LB, Daniel M, Padma A, et al: True hermaphrodite presenting as primary amenorrhea. Indian J Endocrinol Metabol 2012; 16:640
7. Khadilkar KS, Budyal SR, Kasaliwal R, et al: Ovotesticular disorder of sex development: a single-center experience. Endocr Pract 2015; 21:770
8. Verkauskas G, Jaubert F, Lortat-Jacob S, et al: The long-term follow-up of 33 cases of true hermaphroditism: a 40-year experience with conservative gonadal surgery. J Urol 2007; 177:726
9. Ganie Y, Aldous C, Balakrishna Y, et al: The spectrum of ovotesticular disorders of sex development in South Africa: a single-centre experience. Hormone Res Pediatr 2017; 87:307