Case Report

Ovotesticular Disorders of Sex Development: Improvement in Spermatogonia after Removal of Ovary and Müllerian Structures

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A B S T R A C T

Background: Ovotesticular disorders of sex development is a condition defined as the presence of ovarian tissue containing ovarian follicles and testicular tissue containing seminiferous tubules in the same individual.
Case: We report on a 19-year-old who is phenotypically male, with a 46,XX/46,XY mosaicism karyotype, who presented later in life with cyclical abdominal pain that resembled menstrual cramps and unilateral undescended testes.
Summary and Conclusion: He underwent laparoscopic hysterectomy and right salpingo-oophorectomy, resulting in cessation of his symptoms and improved sperm count.
Key Words: DSD, OTDSD, Disorders of sexual development, Sex differentiation disorders, Ovotestis, True hermaphroditism, Gonads, Azoospermia, 46XX/46XY

Introduction

Ovotesticular disorders of sex development (OTDSD), formerly known as "true hermaphroditism" is a condition defined as the presence of ovarian tissue containing ovarian follicles and testicular tissue containing seminiferous tubules in the same individual.[1] It is one of the rarest diversity of all intersex anomalies accounting for 1:100,000 live births.[2] We report a case of 19-year-old phenotypically male, with 46,XX/46,XY mosaicism karyotype who presented later in life with cyclical abdominal pain that resembled menstrual cramps and unilateral undescended testes. Previous investigation showed him to have had azoospermia. He underwent laparoscopic hysterectomy and right salpingo-oophorectomy, resulting in cessation of his symptoms and improved sperm count.

Case

A 19-year-old, phenotypically male patient was referred to the Gynecology Department from the Urology Department for suspected disorder of sex development. He was seen in the urology unit for right undescended testis, which he said was diagnosed since childhood but he had missed his follow-up visits. He experienced chronic cyclical lower abdominal pain since the age of 15 years. There was no bowel or bladder symptoms. He had a twin brother who had no similar medical issue. He attained adrenarche at age 11 and admitted having a "small" penis but claimed normal erection and could ejaculate semen. On physical examination, it was revealed that he had gynecomastia (breast size of Tanner 3) whereas genital examination revealed he had a female distribution of pubic hair (Fig. 1). His unerect penis, although present, was small measuring only 2.8 cm in length and 0.5 cm in diameter. The urethral meatus was normally located at the glans of the penis. He had an asymmetric scrotum with a small left testis (4 cm^3) whereas his right scrotum was "empty" (devoid of testis). On digital rectal examination, a firm mass was felt anterior to his rectum.

Pelvic ultrasonography showed a "uterus-like" structure filled with hypoechoic fluid, which might denote hematometra; and an elongated hypoechoic mass on the right adnexa measuring 8 × 4 cm, which could represent hematosalpinx. His right ovary was normal and measured 1 × 2 × 3 cm, however, his left adnexa was "empty." Both of his kidneys were present and normal on ultrasound scan. Pelvic magnetic resonance imaging confirmed the presence of a blind-ended uterus (2.8 × 2.5 × 5 cm) with no distinctive cervix and vagina. There was hematosalpinx of the right fallopian tube and the right ovary was normal in size.

He was asked to give his sperm sample, which showed azoospermia and other laboratory blood tests revealed normal follicle-stimulating hormone and luteinizing hormone levels for a male subject. However, his blood testosterone was low (3.17 nmol/L) and estradiol was very high, at 775.5 pmol/L (Table 1). His chromosomal analysis revealed 46,XY (60)/46,XX (10) with the presence of mosaicism.

The patient was counseled and agreed to undergo laparoscopic hysterectomy and salpingo-oophorectomy of the

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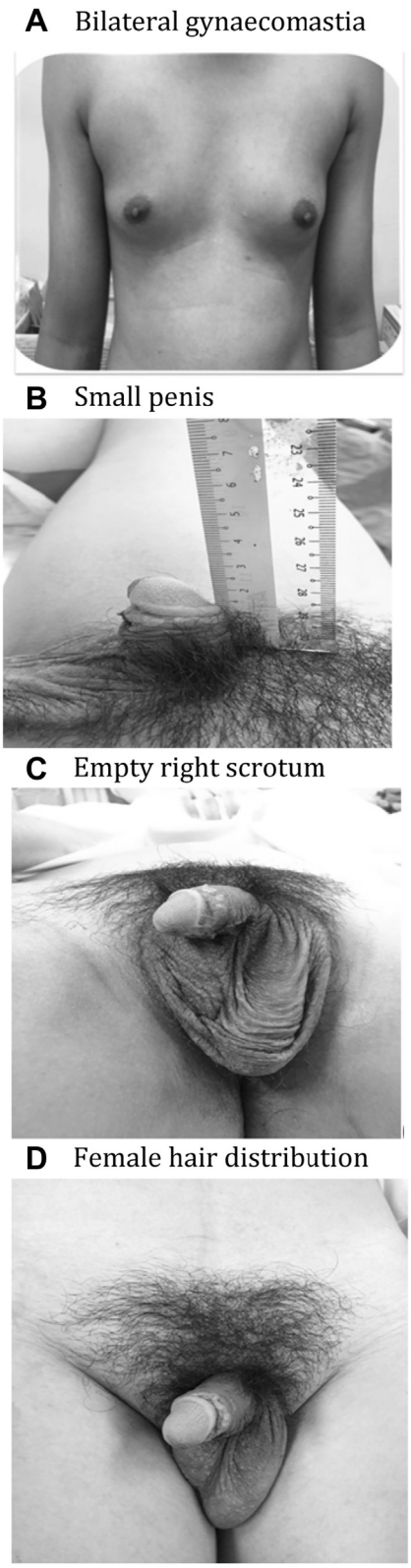

Fig. 1. Physical examination of the patient showed (A) bilateral gynecomastia, (B) small penis, (C) empty right scrotum, and (D) female hair distribution.

right fallopian tube and ovary. Intraoperative findings revealed a small uterus (approximately 3 cm × 5 cm) and devoid of cervix. The right fallopian tube was dilated with hematosalpinx whereas the right ovary was normal in appearance and size. There was no left fallopian tube or ovary seen. Externally, his left scrotum was not explored (Figure 2).

Histopathological examination showed endometrium in a proliferative phase and no significant pathology of the myometrium. The right ovary was purely ovarian tissue without any testicular tissue. Ovarian tissue had an endometriotic cyst with corpus albicans and a follicular cyst whereas the fallopian tube had evidence of chronic salpingitis.

The patient started intramuscular testosterone injections three weekly (125 mg) 2 months after his surgery. He seemed happy when he noticed his voice slowly turned hoarser and was more muscular physically, however, there was no reduction of his gynaecomastia. His serum testosterone had risen from 3.17 nmol/L (before surgery) to 50.40 nmol/L (7 months after testosterone treatment). Unfortunately, no serum testosterone test was repeated after surgery, before the testosterone treatment regimen; therefore, we could not determine whether his serum testosterone level had spontaneously increased with the removal of the ovary. Nonetheless, because his testosterone level was above normal levels after 7 months of treatment, we decided to stop the testosterone injections (Table 1). His follicle-stimulating hormone and luteinizing hormone levels remained normal at 2.41 IU/L and 3.32 IU/L, respectively, after 7 months of testosterone treatment. However, his estradiol level had decreased to 142 pmol/L from 775.5 pmol/L 10 months later, although this level (142 pmol/L) can be considered high for a male patient. There was also reduction of progesterone level from 56.8 nmol/L to 1.1 nmol/L (Table 1). Surprisingly, a repeated semen analysis 7 months after the testosterone injection regimen showed the presence of motile spermatozoa (0.9 million/mL) although normal morphology was only 2% (Table 2). Repeated serum testosterone level tests were normal after 10 months and 14 months (18.55 nmol/L and 17.56 nmol/L, respectively), hence we stopped his testosterone regimen therapy. Furthermore, there was an improvement of sperm count although he was no longer receiving testosterone injections. A repeat of his seminal fluid analysis 10 months after stopping the testosterone injections showed his sperm concentration to be normal (60 million/mL; Table 2).

Discussion

OTDSD has a low incidence of approximately 1 per 100,000 live births.[2] Because of its rarity, the understanding and management of this condition is still controversial. The genotype is predominantly 46,XX (96.9% of cases reported in Africa) and the remainder is 46,XX/46,XY mosaicism, or 46,XY karyotype.[2] Patients with OTDSD are divided into 3 types, on the basis of the location of the gonads and their histology; unilateral, bilateral, and lateral. Most OTDSD are of the unilateral type with ovotestis on one side and normal testicular or ovarian tissue on the other. In the bilateral type (34%), there is presence of testicular and ovarian tissues in each gonad (ie, ovotestis) whereas in those of the lateral

Table 1
Hormonal Parameters before Surgery and Postoperatively with Testosterone Replacement Therapy

Hormonal Parameter	Hormone Level				Normal Range (Adult male)*
	Preoperative	Postoperative (7 months with Testosterone)	Postoperative (10 months without Testosterone)	Postoperative (14 months without Testosterone)	
Serum follicle-stimulating hormone	1.7 IU/L (normal)	2.41 IU/L (normal)	13 IU/L (normal)	19.4 IU/L (high)	1.4-18.1 IU/L
Serum luteinizing hormone	4.8 IU/L (normal)	3.32 IU/L (normal)	6.6 IU/L (normal)	11.1 IU/L (high)	1.5-9.3 IU/L
Serum testosterone	3.17 nmol/L (low)	50.40 nmol/L (high)	18.55 nmol/L (normal)	17.56 nmol/L (normal)	8.4-28.70 nmol/L
Serum estradiol	775.5 pmol/L (high)	142 pmol/L (normal)	143 pmol/L (normal)	124 pmol/L (normal)	<146.1 pmol/L
Serum progesterone	56.8 nmol/L (high)	1.1 nmol/L (normal)	0.7 nmol/L (low)	0.8 nmol/L (low)	0.89-28.70 nmol/L
Serum anti-Müllerian hormone	–	16.1 pmol/L (normal)	–	–	5.5-103.0 pmol/L

* Normal ranges were set by the Department of Pathology, Queen Elizabeth Hospital, Sabah, Malaysia.

type (11%), one gonad is a testis and the other an ovary.[3–5] Our patient was of the lateral variety, whereby his ovary was present intra-abdominally and his testis was in his left scrotum. Although no biopsy was taken from his testis during surgery, the presence of spermatozoa on repeated seminal analysis after 7 months of intramuscular testosterone treatment confirmed the presence of a normal functioning testis.

At birth, OTDSD typically presents with ambiguous genitalia whereas those diagnosed at puberty tend to have a more well differentiated external genital appearance.[6] In addition, depending on the patient's age and sex, other clinical presentations might include inguinal hernia, gynecomastia, cyclical abdominal pain, or primary amenorrhea.[2,7,8] Our patient was not identified at birth and was perceived by his parents then as “normal” and hence was brought up as a boy by his family. Although the patient considered his penis to be “small,” it appeared to be normal on clinical examination, albeit short for a male adult. He was asymptomatic until he had reached puberty, at which time he complained of cyclical pelvic pain, enlargement of the breasts (gynecomastia), and an “empty” right scrotum. It is certain that his cyclical pelvic pain was due to the obstructed menstrual blood flow leading to hematometra with hematosalpinx and endometriosis (evidenced by the histopathological report). He achieved full symptomatic pain relief after the laparoscopic hysterectomy and right salpingo-oophorectomy.

The ovarian tissues in OTDSD cases are commonly functional and are normally preserved in phenotypically female subjects to ensure normal female sexual development and fertility preservation.[9] However, the ovary in our patient was resected because he was phenotypically male with male psychosexual orientation and was reared by his family as a boy. When the ovary was removed, we saw a drastic decrease of his estradiol serum level, confirming that his ovary was the source of endogenous estradiol. Subsequently, this resulted in the loss of estradiol-negative feedback from the ovary thus elevating his serum testosterone level. His testis was also free to normally produce testosterone. We found that it was not necessary to continue the androgen supplementation therapy because his serum testosterone level has reached normal adult male level (Table 1). Nevertheless, he will undergo lifelong hormonal surveillance every 6 months.

Malignant tumor of the gonads is rare in OTDSD, with an incidence estimated to be between 2.6% and 4.6%.[5] Those who tend to develop tumors are of the 46,XX/46,XY subtype,[10] for whom total resection of the testis is indicated. However, we do not see the need to remove the testis of our patient because the incidence of malignancy is low and management of such a condition is still uncertain. His gonad appears to be functional with fertility potential, therefore the risk is lower compared with dysgenetic gonads or intra-abdominal testes. Furthermore, because the testis was in the scrotum, surveillance and biopsy can be easily done in the future to detect tumor.

OTDSD patients are generally infertile but there are case reports to have stated otherwise.[11–13] Sugawara et al reported a successful pregnancy from an OTDSD patient (46,XX/46,XY) using intracytoplasmic sperm injection of frozen thawed testicular spermatozoa.[11]

Unlike in normal young prepubertal male subjects, there are no tests to ascertain the fertility potential of OTDSD patients, although serum anti-Müllerian hormone (AMH) has been used to clinically evaluate the gonad function.[14–17] In our patient, it was shown that his AMH level was normal after surgery but its level was not measured before the surgery, so no comparison could be made. Nonetheless, with his normal AMH level as well as the normalization of other hormonal parameters, he can

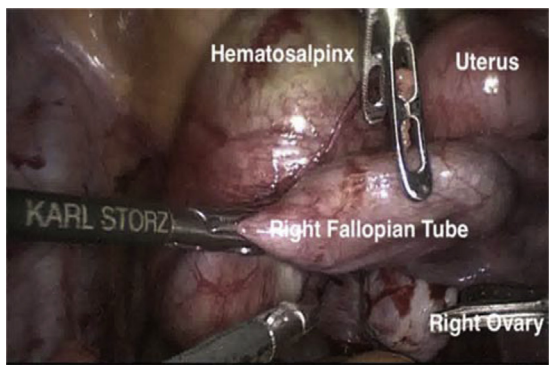

Fig. 2. Intraoperative findings. Laparoscopic finding showed a uterus without cervix or proximal vagina with a single ovary and dilated right fallopian tube.

Table 2
Seminal Fluid Analysis before and after Surgery

Seminal Fluid Parameter	Preoperative	Postoperative (7 months of Testosterone Treatment)	Postoperative (10 months without Testosterone Treatment)
Volume	0.2 mL	0.2 mL	0.5 mL
Concentration	Nil	0.9×10^6/mL	60×10^6/mL
Motility	Nil	33%	67%
Progressive motility	Nil	22%	40%
Normal morphology	Nil	2%	1%
Remark	Azoospermia	Most of the sperms have head and neck defects	Most of the sperms have head and neck defects

rest assured that his fertility is possible. It was also surprising that for his repeated seminal fluid analysis it was reported that motile spermatozoa were found, although low in concentration. This would give him a ray of hope that fathering a child is possible with assisted reproductive therapy. Last, it is important to note that such patient require long-term follow-up to assess gonadal and sexual functions, future malignancy risks, and quality of life.

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