

46 XX Ovotesticular Disorder of Sexual Development with Detected SRY (Sexdetermining Region Y) Gene: A Case Report

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Abstract

Ovotesticular disorder or true hermaphroditism is a condition in which an individual has both ovary and testis. The ovary is usually located on the left side, whereas the testis is on the opposite side. The SRY gene is detected in one third of cases of 46 XX ovotesticular DSD. The most common karyotype of ovotesticular DSD is 46 XX. Here, we report the case of a girl with SRY positive 46 XX karyotype diagnosed as ovotesticular DSD by gonadal biopsy. The patient presented with female phenotype and ambiguous genital since birth. The external genital showed an accessoria penile without OUE with rough right labia majora that looked like scrotum. Testicle was felt on the right side of scrotum. USG revealed no appearance of normal uterus, right testicle was visualized but no visualization of left testicle. Right and left ovaries were not clearly visualized. Karyotyping-46 XX and SRY gene was detected on 472 bp fragment on multiplex PCR of AZF/SRY gene analysis. Diagnostic laparoscopy showed left hemiuterus with fallopian tube and unilateral left side ovary. The shape and size of left fallopian tube was normal. Histopathologic examination report revealed left gonad was ovarium with primary follicle and right gonad was testicle with leydig cell and seminiferous tubules. This patient was decided as a girl. The operation was initiated and divided into 2 phases. The first phase was orchidectomy of the right side testicle and the second phase was genital reconstruction (clitoroplasty and labioplasty).

Keywords: Ovotesticular DSD; Ambiguous genitalia; SRY gene

Introduction

Disorder of sexual development (DSD) is a rare condition with a reported incidence of 1:4500 in newborn and less than 10% of which is ovotesticular disorder [1]. Ovotesticular disorder or true hermaphroditism is a condition in which an individual has both ovary and testis. The ovary is usually located on the left side, whereas the testis is on the opposite side [2]. The SRY gene is detected in one third of cases of 46 XX ovotesticular DSD. The most common karyotype of ovotesticular DSD is 46 XX (61.6% of total 8 cases from year 1991-2008 at Osaka Medical Center Japan) [3].

There are many mechanisms correlated with ovotesticular DSD. They are genetic chimerism, non-disjunction, X-Y gene chromosomal translocation, X gene mutation or hidden mosaic [4]. Genetic chimerism is a fusion of two different zygotes within one embryo. Non disjunction is the failure of chromosomal separation during meiosis. Therefore, the cell has different numbers of chromosome. Mosaic is the existence of two or more cells population with different genotypes of one zygote within one embryo. X-Y gene chromosomal translocation is the movement of short segment of Y chromosome, including SRY gene to short segment of X chromosome. This mechanism contributes to the characteristic of ambiguous genital to individuals with 46 XX or 46 XX male phenotype ovotesticular DSD [5].

A comprehensive management is needed to care for children with ovotesticular DSD. The management is patient-centered, which includes psychological counselling, hormonal and fertility treatment, operation, as well as management of potential malignancy and failure of sexual function. The risk of malignancy was reported to be 20% to 30% on the first to second year of life [6].

This report describes a 13-year-old girl who was diagnosed as a case of SRY-positive 46 XX ovotesticular DSD. The patient presented with female phenotype and ambiguous genital since birth.

Case Report

A 13-year-old girl presented with ambiguous genital. The patient was born at term, of a twin, and of spontaneous delivery. The twin

of the patient was male without ambiguous genital. Her birth weight was 2100 grams and the twin was 2500 grams. There was no parental consanguinity. The patient's father also had a twin with ambiguous genital who died after birth. The patient's body weight was 42 kg and her height was 156 cm. She had a BMI (Body Mass Index) of 17.28 ($-1 < Z \text{ score} < 0$). Her father's height was 164 cm and her mother's height was 150 cm. Vital sign was within normal limit. The face was not dysmorphic. Physical examination of the heart, lungs, abdomen and extremities were normal (Figures 1 and 2).

Physical examination of genital showed an accessoria penile without OUE (Ostium Urethrae Externum) with rough right labia majora that



Figure 1: Pubertal status on the first examination (Tanner stage II).

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looked like a scrotum. The vaginal opening was narrowed and OUE was located near it. It was classified as Prader III-IV. The pubic hair was Tanner stage II and the breast was Tanner stage III. The results of ultrasounds were as follows: no appearance of normal uterus, right testicle was visualized but no visualization of left testicle. Right and left ovaries were not clearly visualized, impression of the ovaria showed no antral follicles. Chromosomal examination showed karyotype 46 XX, female genotype without chromosomal abnormality. The laboratory analyses were as follows: follicle stimulating hormone (FSH), taken on 7th day of menstrual period was 15.01 mIU/mL (pre-ovulation phase) (4.7 mIU/mL to 21.5 mIU/mL) estradiol 15.50 pg/mL (follicular phase) (12.5 mIU/mL to 166 pg/mL) and testosterone level 0.219 ng/mL (Female) (0.06 ng/mL to 0.82 ng/mL). The 17-OH progesterone level was 4.1 nmol.L (0.1 nmol.L to 1 nmol.L). It excluded the possibility of congenital adrenal hyperplasia (CAH). The SRY gene was detected



Figure 2: A testis-like mass was felt on the right scrotum.



Figure 3: Penile without OUE.



Figure 4: External genitalia before surgery.



Figure 5: After reconstruction surgery.

on 472 bp fragment on multiplex PCR of AZF/SRY gene analysis (Figures 3 and 4).

Laparoscopy examination showed the existence of left hemi-uterus with fallopian tube and unilateral left side ovary. The size of hemi-uterus was 63 × 2 cm, piriform shaped. The shape and size of left fallopian tube was normal. There was no right side ovarian intrapelvic. The result of gonadal biopsy was as follows: Left gonad was ovarium with primary follicle. Right gonad was testicle with leydig cell and seminiferous tubules. The estradiol level examination during 12th day of menstrual period showed 127.2 pg/mL (ovulation phase) (85.5 pg/mL to 498 pg/mL) and progesterone level during 21st day of menstrual period was 24.69 ng/mL (luteal phase) (1.7 ng/mL to 27 ng/mL). It is concluded that on the ovulation phase, estradiol level highly rose and the progesterone level showed an ovulation (Figure 5).

Based on patient and family decision, the genotype, phenotype, laboratory, laparoscopy, biopsy result and the possibility of surgery intervention, this patient was decided as a girl. The operation was initiated and divided into 2 phases. The first phase was orchidectomy of the right side testicle and the second phase was genital reconstruction (clitoroplasty and labioplasty).

Discussion

Ovotesticular DSD is an abnormality of gonadal development. Based on location, it is divided into three types: lateral (testis and contralateral ovary-30%) bilateral (testicular and ovarian tissue identified on both sides, usually as ovotestis-50%) and unilateral (ovotestis on one side and testis or ovary on the other side-20%) [7]. Our patient was of lateral variety in which testis was on right side and ovary on left side. The patient had chromosome of 46 XX (female) thus bipotential gonad grew into ovary and Mullerian duct grew into uterus. However, the patient also had SRY gene (determining gene for male), thus the testis grew and produced androgen which caused enlargement of prothallus and rough rugae of right labium majus mimicking a scrotum.

The genotype of patient was 46 XX with ambiguous genital. The patient's father was a normal male without ambiguous genital, but father's twin died afterbirth with clinically ambiguous genital. The genotype of patient's father was 46 XY, and patient's mother was 46 XX. The SRY gene of patient possibly existed because of translocation of father's Y chromosome segment to X chromosome of patient during embryonic development, thus the patient had 46 XX with ambiguous genital.

The patient was decided as a girl based on following reasons: phenotype of patient was female, without Adam's apple, and patient acted as a female on daily activities. Laparoscopy showed there was left hemi-uterus with fallopian tube and ovary. The testosterone level also showed as female (0.219 ng/mL) even though biopsy of right gonad showed a testis with leydig cell and seminiferous tubules. Testosterone hormone is important for sexual function (erection, maturation of sperm, libido) and maturation of sex development. It was difficult to perform reconstruction surgery as male because the patient did not have OUE at the tip of phallus.

Based on hormone, anatomy, and function, patient had complete reproduction organs. However, references showed that pregnancy with hemi-uterus has a risk of ectopic pregnancy (2.7%), abortion on the first trimester (24.3%), second trimester (9.7%), preterm baby (20.1%) and intrauterine fetal death (10.5%). The survival rate of birth with hemi-uterus is 49.9% [8]. During the gender assignment, it is important to exclude the possibility of Congenital Adrenal Hyperplasia (CAH) because of the risk of adrenal crisis when operation or invasive management is needed. The result of 17-OH progesterone did not support diagnosis of CAH.

After orchidectomy and genital reconstruction, further evaluation of pubertal and fertility status was conducted. The follow up of this patient lasted for 18 months. By the end of the follow up, the pubic hair was Tanner stage III and the breast was Tanner stage IV. The height increased by 5 cm and the weight gained 4 kg. Patient also experienced menstruation in the last 5 months of the 18 months follow up period. The fertility status was conducted by estrogen level examination during ovulation phase and progesterone level examination during mid-luteal phase. The estrogen level showed a significant increase compared with follicular phase (15.50 pg/mL to 129 pg/mL) whereas progesterone level was 24.69 or 61 nmol/L on a single examination. Progesterone level that shows an ovulation is 65 nmol/L or 21 ng/mL for the cumulation of three times examination or more than 45 nmol/L on a single examination [9]. It was concluded that patient had an ovulation.

Testosterone level was evaluated after orchidectomy. It showed reduction level from 0.219 ng/mL to 0.161 ng/mL. The examination

was done to evaluate if there was any residual testis after the operation. Testosterone is produced by testis in male, whereas in female, it is also produced at low level by ovary and adrenal gland. Testosterone is needed for growth, bone density, muscle growth and libido during ovulation period.¹⁰ The patient's quality of life was evaluated using Pediatrics Quality of Life (Peds QL) Scoring and showed increased scores of physical, emotional, social and academic functions. It is also proven by better results in school report. She had more confidence, was more communicative and actively involved at school's organization [10].

In conclusion, 46 XX female ovotesticular DSD, who is presented with an ambiguous genitalia in early childhood, should be considered in the differential diagnosis of cases. Comprehensive management is needed to improve the patient's quality of living.

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