Case Report

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Bilateral Incidental Gonadoblastoma in a Woman with Swyer Syndrome Presenting with Primary Amenorrhea

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ABSTRACT

Swyer syndrome is a very rare cause of primary amenorrhea. Affected individuals have an XY karyotype but their external and internal genitalia are of the female type. The gonads are usually replaced by fibrous streaks. Early diagnosis is vital because of the significant risk of germ cell tumor, and bilateral gonadectomy should be performed. Laparoscopy provides a minimally invasive approach for the management of these cases. These patients can have a normal sexual intercourse and they need hormone replacement therapy for development of breast and prevention of osteoporosis. They can conceive through oocyte donation and artificial reproductive techniques.

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Introduction

Swyer syndrome is a condition characterized by the presence of an unambiguously female phenotype and mullerian structures in the presence of a "Y" line (XY karyotype), that was first described by Jim Swyer in 1955 (1).

Affected individuals have an XY karyotype but their external and internal genitalia are of the female type.

The sex-determining region Y (SRY) gene is believed to be critical in initiating male sex determination by triggering undifferentiated gonadal tissue to transform into testes.

In approximately 15-20 percent of patients, Swyer syndrome occurs due to mutations of the SRY gene on the Y chromosome, or deletion of the segment of the Y chromosome containing the SRY gene.

The gonads are usually replaced by fibrous streaks. Patients, usually in adolescence, present primary amenorrhea and lack of

secondary sexual characters. Swyer syndrome is a rare entity with the incidence of 1:30000. The diagnosis and management of patients with Swyer syndrome is complex, and optimal care requires an experienced multidisciplinary team. Early diagnosis is vital because of the significant risk of germ cell tumor, and bilateral gonadectomy should be performed. Furthermore, early sex hormone treatment is necessary to induce and maintain typical pubertal development and to achieve optimal bone mineral accumulation. Pregnancy is possible via oocyte donation, and outcomes are similar to women with 46 XX, who suffer from ovarian failure (2).

Purpose of reporting this case is its rarity and the importance of diagnosis of XY female, as there is high incidence of gonad malignancy in affected person.

Case Report

The patient, first at the age of 18, sought care at the gynecology department of Shariati hospital, Tehran City, Iran for amenorrhea. She reported experiencing an adolescent growth spurt at the age of 11 and thelarche at the age of 16 with no personal history of disease.

On general examination, she was 152 cm tall and weighed 49 kg. There was no evidence of acanthosis nigricans, acne, hirsutism, goiter, cushingoid features of Turner's stigmata like webbed neck and cubitus valgus. Examination of secondary sexual characteristics revealed no breast development (Tanner 1) with hypopigmented areola. Pubic and axillary hairs were sparse.

Examination of external genitalia revealed that they were of female type, and there was no evidence of clitoromegaly. Vaginal opening was seen.

Laboratory investigations showed that CA 125 was 6.50 U/ml (normal range: 0.00 ~ 35.00 U/ml), free testosterone was 33.10 pmol/l (normal range: 0.77 ~ 33.03 pmol/l), FSH was 88.00 mIU/ml, and LH was 16.70 mIU/ml. Sex hormone binding globulin (SHBG) was 15.7 nmol/l (normal range: 18.0 ~ 114.0 nmol/l) and estradiol was less than 5.0 mIU/ml. Serum TSH and serum prolactin were normal.

Ultrasound showed rudimentary uterus and bilaterally ill-defined adnexa, no renal abnormality was detected.

The karyotype study revealed that she had normal 46 XY chromosomes. Meanwhile, the direct sequencing of the SRY gene on peripheral blood DNA from the patient showed that SRY gene is present. Other mutation analysis was not available in our department of clinical genetics.

The patient was subjected to a diagnostic laparoscopy which showed a small uterus and bilateral normal fallopian tubes (Figure 1).

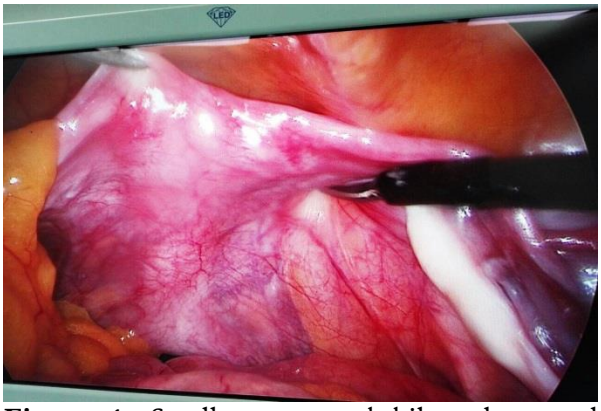

Figure 1. Small uterus and bilateral normal fallopian tubes visualized during laparoscopy

Ovaries could not be visualized; instead, the fibrous bands were seen on either side (Figure 2).

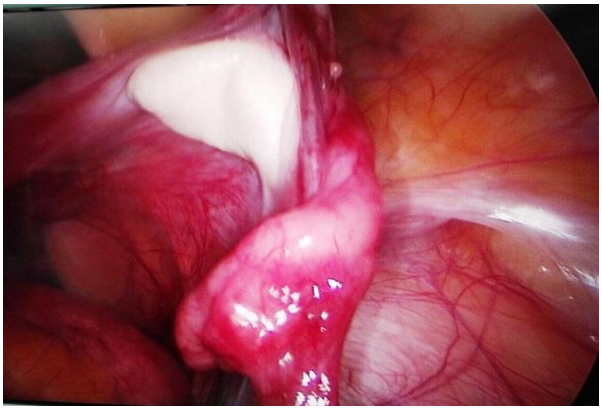

Figure 2. Gonadal streaks in which the ovaries do not develop properly and are replaced by fibrous tissue.

Consequently, laparoscopic bilateral gonadectomy was done; and surprisingly, the pathologic examination of the both resected gonads showed gonadoblastoma.

In view of streak gonads and genotype of XY, the diagnosis of Swyer syndrome was made.

Discussion

Swyer syndrome is a rare form of pure gonadal dysgenesis. In 46 XY gonadal dysgenesis, lack of testis development may be triggered by SRY, NR5A1, DHH or testis-determining gene loss-of-function mutations, DAX1 or WNT4 duplication or MAP3K1 gain-of-function mutations (3).

The first known step of sexual differentiation in a normal XY fetus is the development of testes. The early stages of testicular formation in the second month of gestation requires the action of several genes, the most important gene is SRY gene.

Although mutations of SRY gene accounts for many cases of Swyer syndrome but only 15-20 percent of patients have a mutation in the SRY gene; and the remaining, like our patient, probably have defects involving other genes which can also cause the disorder. These other genes are all suspected to play a role in the development of the testes and ultimately, in the differentiation of an XY fetus into a male (4).

When such a gene is defective, the indifferent gonads fail to differentiate into testes in an XY (genetically male) fetus. Without testes, no testosterone or anti-mullerian hormone (AMH) is produced. Without testosterone, the external genitalia fail to virilize,resulting in normal female genitalia. Without AMH the mullerian duct develops into normal internal female organs, i.e. uterus, fallopian tubes, cervix and vagina.

The baby, who is born, externally is normal in all anatomic aspects except that the child has nonfunctional streak gonads. Because of the inability of the streak gonads to produce sex hormones (both estrogens and androgens), most of the secondary sex characters do not develop. Therefore, there is absence of breast development, widening of the pelvis and hips, and menstrual periods. Adrenal gland is not affected and can produce androgens, and most of these persons will develop pubic hair, though it often remains sparse.

The Swyer syndrome in an XY woman should be differentiated from the other conditions of the XY woman such as testicular feminization, because they have different implications on the current management and future reproductive function (5).

We made a diagnosis of Swyer syndrome because the patient was a normal statured girl with primary amenorrhea and with clinical features of sexual infantilism whose genotype was pure XY, and the gonadal tissues were fibrous band.

The main differential diagnosis of Swyer syndrome is mixed gonadal dysgenesis which is more frequently seen than the former. In this condition, the gonads on histopathology will show testicular differentiation in addition to ovarian differentiation. Besides, the genotype is usually a mosaic pattern.

The incidence of malignant gonadoblastoma in patients with dysgenetic gonads is high (25-35%), and gonadectomy must be done for these patients.

These patients can have a normal sexual intercourse and they need hormone replacement therapy for development of breast and prevention of osteoporosis. They can conceive through oocyte donation and artificial reproductive techniques. Moreover, the patients require long-term follow-up in specialist centers.

Early diagnosis in women presenting with amenorrhea is important. Swyer syndrome is an extremely rare cause of primary amenorrhea. Since there is a high incidence of gonadoblastoma and dysgerminoma, early gonadectomy is a must, and laparoscopy provides a minimally invasive approach for the management of these cases if detected at an appropriate time.

Conflict of Interests

Authors have no conflict of interests.

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