Case Report

Atypical Presentation of Swyer Syndrome

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A B S T R A C T

Background: Swyer syndrome is a rare type of disorder of sex development and typically presents with delayed puberty and primary amenorrhea. We describe an unusual presentation of this condition.
Case: A 17-year-old female patient with typical thelarche and adrenarche presented with primary amenorrhea. Pelvic ultrasound showed normally developed uterus and bilateral ovoid hypoechoic structures suggestive of gonads. Laboratory investigations revealed highly elevated gonadotrophins with estradiol level within a range typical for a female of reproductive age and chromosome analysis showed a 46,XY karyotype. Histopathological examination of the gonadectomy specimens revealed gonadoblastoma and dysgerminoma with no functional ovarian or testicular tissue.
Summary and Conclusion: This report reminds us the possibility of diagnosis of Swyer syndrome in the presence of normal pubertal development and normal sex steroid levels considered to be produced by gonadoblastoma.
Key Words: Swyer syndrome, Puberty, Amenorrhea, Gonadoblastoma

Introduction

A complete 46,XY gonadal dysgenesis (Swyer syndrome) is a rare type of disorder of sex development and characterized by typical appearance of female external genitalia and normal Müllerian structures due to lack of testosterone and anti-Müllerian hormone secretion from streak gonads.[1] The incidence of this condition is estimated at approximately 1 per 80,000 births.[2] The syndrome typically presents during adolescence with the absence of breast development and primary amenorrhea and usually other clinical manifestations of estrogen deficiency such as low bone mineral density in the setting of primary gonadal failure. The condition has a significant risk (estimated at approximately 30%) for development of germ cell neoplasms, especially gonadoblastoma and dysgerminoma.[3] We describe a 17-year-old-girl with Swyer syndrome presented with primary amenorrhea, who have spontaneous breast development of Tanner stage 5 and estradiol level in the typical female range for a breast development in this stage.

Case

A 17-year-old girl presented with primary amenorrhea. She started having breast and pubic hair development at ages 12 and 13, respectively. She denied any history of pubertal induction or hormone replacement therapy. Her medical and surgical history were unremarkable. On physical examination, her weight was 70.2 kg; height was 170.5 cm, and body mass index was 24.2. She had Tanner stage 5 breast and pubic hair development (Fig. 1). Perineal inspection revealed normally developed labia majora, minora, clitoris with normal opening of the urethra, and vagina (Fig. 2). Vaginal mucosa looked estrogenized and vaginal length was measured as 7-8 cm. There was no sign of clinical hyperandrogenism or virilization. Transabdominal ultrasound showed normally developed uterus (54 × 39 × 27 mm) and bilateral ovoid hypoechoic structures (right: 33 × 17 × 22 mm, and left: 28 × 12 × 18) suggestive of gonads. Laboratory investigations revealed normal levels of estradiol (27 pg/mL) and slightly elevated testosterone level (0.97 ng/mL) and, high follicle-stimulating hormone (60 IU/mL) and luteinizing hormone (34 IU/mL) levels. Chromosome analysis was performed because of the diagnosis of hypergonadotropic hypogonadism and showed a 46,XY karyotype and sex-determining region Y gene expression was confirmed using multiplex polymerase chain reaction. The results of a dual-energy x-ray absorptiometry scan showed normal bone mineral density (Z-score 0.5 at the lumbar spine), which was also a clinical finding showing the presence of sex steroids and spontaneous breast development.

Serum tumor markers including α-fetoprotein, β human chorionic gonadotrophin, and lactate dehydrogenase were normal. Laparoscopic bilateral gonadectomy was planned because of the risk of germ cell neoplasms in this condition. During the surgery, normally developed uterus bilateral fallopian tubes and bilateral ovoid shaped gonads were observed (Fig. 3). The postoperative period was uneventful. Histopathologic examination revealed gonadoblastoma with focal malignant dysgerminoma in both dysgenetic

The authors indicate no conflicts of interest.

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1083-3188/$ - see front matter
https://doi.org/10.1016/j.jpag.2019.07.007

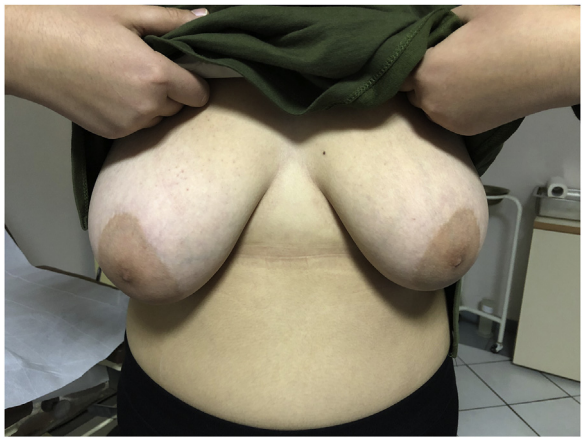

Fig. 1. Tanner stage 5 breast development.

gonads. Microscopically, normal ovarian or testicular tissue were not observed anywhere in the gonads. Her estradiol level was <10 pg/mL at 4 weeks postoperatively. A close clinical follow-up, including magnetic resonance imaging and serum tumor markers (α-fetoprotein, β human chorionic gonadotrophin, and lactate dehydrogenase) every 3 months for the first 2 years, was planned. She also started hormone replacement therapy containing estrogen and progestin.

Summary and Conclusion

Swyer syndrome typically presents with delayed puberty and primary amenorrhea due to absence of hormonal production from dysgenetic gonads. In this condition, the evaluation of the hormone profile is characterized by highly elevated serum concentration of luteinizing hormone and follicle-stimulating hormone with low circulating levels of gonadal steroids (estradiol and testosterone). These patients usually have little or no breast development but normal axillary and pubic hair.[1] Normal female external genitalia, small prepubertal uterus, and bilateral streak gonads are observed with physical examination and pelvic imaging such as pelvic ultrasound and magnetic resonance imaging.[1] In the presence of breast development and menstrual bleeding in this condition, a history of pubertal induction and exogenous hormone use should be primarily excluded with a detailed history. However, spontaneous breast development and even spontaneous menarche characterized by some episodes of menstrual bleeding were reported in only a few cases of Swyer syndrome in the literature.[4–7] It has been suggested that gonadoblastoma, a benign germ cell neoplasm that can develop at a high rate from dysgenetic gonads, can produce gonadal steroids such estrogen and testosterone and leads to pubertal development in these cases. However, unexplained spontaneous breast development was also reported in a patient with Swyer syndrome despite the absence of hormone-producing gonadal neoplasms, low estradiol level, and the presence of other findings of hypoestrogenemia such as osteoporosis.[4]

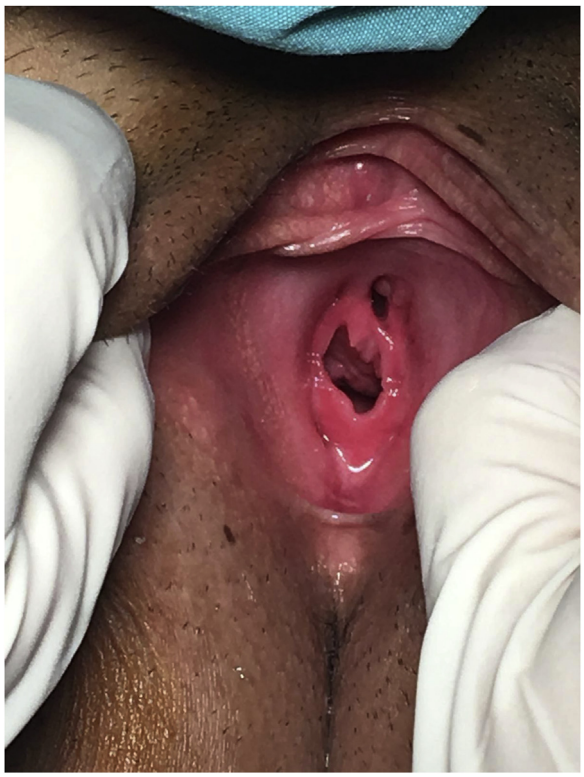

Fig. 2. The appearance of external genitalia.

In the present case, we also suggest that normal estradiol level and spontaneous breast development were associated with the presence of the active hormone secretion from gonadoblastomas. The normal bone mineral density in this patient was also consistent with the long-term presence of sex steroids. Normal estradiol level of the patient was considered to be originated from the tumor cells and/or from the peripheral conversion of testosterone produced from the tumor cells. Inhibin positivity in gonadal stroma and in gonadoblastoma was shown with immunohistochemical analysis of gonadectomy specimens in a patient with Swyer syndrome and was evaluated as a proof of active hormone production from these cells.[5] Hormonally active gonadoblastoma in a patient with complete 46,XY gonadal dysgenesis was also reported as the cause of the peripheral precocious puberty.[8] Gonadoblastomas, rare gonadal tumors, consist of a mixture of germ cells and sex cord stromal derivatives that resemble immature granulosa and Sertoli cells. They almost always arise from dysgenetic gonads with a Y chromosome and their development is probably related to the presence of the testis specific protein Y-encoded.[3] Although gonadoblastoma is considered benign, it is a tumor with high potential for progression to invasive germ cell tumors such as dysgerminoma, embryonal carcinoma, and endodermal sinus tumors. Because of the significant risk for development of these germ cell neoplasms, the current practice is to perform bilateral gonadectomy when the diagnosis of 46,XY gonadal dysgenesis is made.[1]

In conclusion, during the evaluation of patients with primary amenorrhea, elevated luteinizing hormone and follicle-stimulating hormone levels should be an immediate indication for performing karyotype analysis even in the

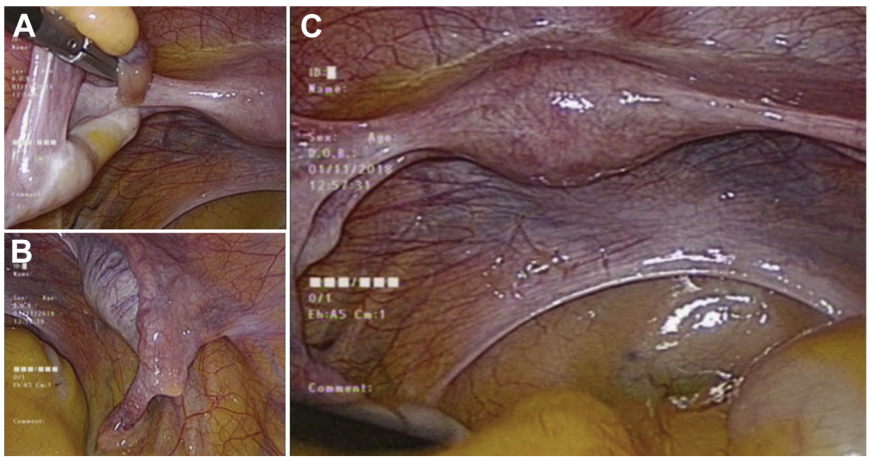

Fig. 3. Laparoscopic view of internal genitalia.

presence of spontaneous pubertal development and estradiol level within a range typical for a female of reproductive age. This rare presentation of Swyer syndrome reminds us of the possibility of diagnosis of this condition in adolescents who have normal pubertal development and present with primary or even with secondary amenorrhea as reported in the literature. This report also suggests that normal or elevated levels of sex steroids in patients with Swyer syndrome can be evaluated as a finding for the presence of a hormonally active tumor. As a result, in the presence of laboratory and clinical findings of gonadal hormone production in a patient with complete 46,XY gonadal dysgenesis, surgical intervention without delay is of great importance in preventing the development or progression of invasive tumors and improving the long-term prognosis of the patient.

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