A Case of Swyer Syndrome Associated with Advanced Gonadal Dysgerminoma Involving Long Survival

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Key Words

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Abstract

Swyer syndrome is caused by abnormal sex differentiation during the embryonic period, resulting in incomplete intrauterine masculinization and undifferentiated gonads. The current case report describes a patient with Swyer syndrome associated with stage 3 gonadal dysgerminoma who has survived for 23 years. At age 18, this patient sought assistance for primary amenorrhea from the Gynecological Services Department of the University of Brasília Hospital. A physical examination revealed that the patient was at Tanner stage 4 with respect to axillary hair, breasts, and pubic hair; she presented with a eutrophic vagina and a small cervix. She was treated with a combination of estrogens and progestogens to induce cycling. Approximately 4 years later, a complex tumor was found and resected; a histopathological analysis revealed that this tumor was a right adnexal dysgerminoma with peritoneal affection. The patient was also subjected to chemotherapy. Her follow-up has continued to the present time, with no signs of tumor recurrence. In conclusion, this report describes an extremely rare case in which Swyer syndrome was associated with ovarian dysgerminoma; relative to similar patients, the described patient has survived for an unusually prolonged time.

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Introduction

Disorders of sex development (DSD) are congenital conditions characterized by atypical chromosomal, gonadal, or anatomical sex development [1]. In 2006, a consensus statement was issued that recommended the use of the DSD classification to replace various terms that are no longer utilized, such as pseudohermaphrodite, intersex, and sex reversal, among others [2]. Complete gonadal dysgenesis is characterized by a female phenotype, nonambiguous genitalia, the presence of Müllerian derivatives, gonadal dysgenesis, and a normal karyotype [3]. One type of gonadal dysgenesis is Swyer syndrome, which is a rare cause of DSD with an incidence of 1:80,000. This syndrome, which was described by Swyer in 1955, is caused by an error in sex determination during the course of embryogenesis. Patients with Swyer syndrome present with an incomplete masculinization due to deficiencies in the production of testosterone and Müllerian-inhibiting factors that result in the failure of gonadal progression [4]. Molecular and genetic abnormalities associated with this condition include mutations in the ARX, ATRX, CBX2, DHH, DMRT1, GATA4, MAMLD1, MAP3K1, NR0B1 (which relates to DAX1 expression and congenital adrenal hypoplasia), NR5A1 (which encodes steroidogenic factor 1), SOX9, WNT4, WT1, WWOX, SRY, and WNT4 genes. The SRY gene is deleted in approximately 10–15% of patients with Swyer syndrome and mutated in an additional 10–15% of Swyer syndrome patients [1, 3]. Most Swyer syndrome patients first seek medical attention in adolescence for primary amenorrhea and/or the absence of secondary sex characteristics [5].

Swyer syndrome patients are normal too, tall in height and present with small or undeveloped breasts, but normal axillary and pubic hair. The external genitalia are typical of females, the upper part of the vagina and tubes are normal or reduced in size, and the uterus is small or rudimentary. The gonads are dysgenetic strips composed of only fibrous tissue; they do not exhibit hormonal function, gametogenesis, or any structure that allows them to be identified as either ovaries or testicles, although their karyotype is 46,XY. The gonads are at high risk for gonadal tumors, which are typically gonadoblastomas and/or dysgerminomas [3, 4]. Dysgerminomas are generally rare, accounting for less than 5% of ovarian tumors, but exhibit a high malignant potential [6]; however, this type of tumor is found in 1 out of every 3 individuals with Swyer syndrome [7]. Dysgerminomas typically present with abdominal pain (70–80%) and a lower abdominal mass [8].

Case Report

The patient first sought care at the Gynecological Services Department of the University of Brasília Hospital at the age of 18 years for amenorrhea. She reported experiencing an adolescent growth spurt at the age of 11 years and thelarche at the age of 16 years, with no personal history of disease. With respect to family history, she reported having a nulliparous aunt with similar complaints who had been subjected to pharmacological treatment to induce menstruation. Upon physical examination, the patient's height was 1.69 m, and her axillary hair, breasts, and pubic hair were consistent with Tanner stage 4. The vagina was eutrophic, with physiological secretions. The cervix was small, although a large area of the cervix was positively stained by the Schiller iodine test; this result indicates hypoestrogenism. Laboratory tests produced the following results: follicle-stimulating hormone (FSH) levels of 50 mIU/ml, luteinizing hormone (LH) levels of 68 mIU/ml, estradiol levels <20.00 ng/ml, triiodothyronine levels of 150.0 ng/dl, thyroxine (T₄) levels of 8.0 ng/dl, thyroid-stimulating hormone levels of 1.4 µIU/ml prolactin levels of 13.0 ng/ml, and a karyotype of

46,XY. The patient was prescribed estrogens in combination with progestogens. A pelvic ultrasound (US) was performed approximately 4 years later. This US revealed a mass with irregular contours, heterogeneous echogenicity, and a largest diameter of 9.5 cm that involved the uterus; this mass was interpreted as a solid pelvic tumor that required further elucidation. The patient was subjected to a total hysterectomy and a bilateral salpingo-oophorectomy. Perioperative observations revealed a rudimentary uterus, a nonadhered and small left tube, a left gonad with a strip-like appearance, and a large irregular mass that included the right adnexa and omentum. A histopathological examination revealed a right adnexal tumor that measured $12 \times 7 \times 5$ cm. This tumor had a shiny, lumpy surface and exhibited an elastic consistency. Upon sectioning, multiple grayish nodules were observed; certain nodules featured cystic cavities with yellowish-gold regions. A portion of the large omentum that measured 18 cm along its longest axis had adhered to the tumor. A sample of peritoneal fluid tested positive for malignancy. The histopathological report indicated that the tumor was a stage 3 right-side adnexal dysgerminoma (fig. 1, fig. 2).

The patient was subsequently subjected to 12 sessions of chemotherapy. In a recent routine visit, at the age of 47 years, the patient had no complaints. She reported that she had been ingesting a daily dose of 0.625 mg of conjugated estrogens for the preceding 25 years and told us that she did not wish to change this treatment because she had become well adapted to it. Bone densitometry tests revealed osteopenia; no abnormalities were detected by pelvic US, mammogram, or tumor marker tests.

Discussion

Individuals with Swyer syndrome exhibit female phenotypes and are typically raised as girls; these individuals are generally diagnosed in adolescence when they seek medical assistance for amenorrhea and the absence of secondary sex characteristics [5]. Her breasts were consistent with the typical breast development among 11- to 15-year-old adolescents. Her breasts were consistent with Tanner stage 4 [9]. Her vagina was normal and her cervix was small; these characteristics are in accordance with the typical traits of Swyer syndrome patients [3].

Patients suspected to suffer from Swyer syndrome are first subjected to laboratory testing for diagnostic confirmation. These tests include measurements of electrolytes and of the hormones FSH, LH, prolactin, thyroid-stimulating hormone, free T_4 , sex hormone-binding globulin, androstenedione, estradiol, and testosterone [1]. In the described case, FSH and LH levels were elevated and estradiol levels were low; these findings are indicative of hypogonadotropic hypogonadism, a condition consistent with descriptions of Swyer syndrome in the extant literature. As a rule, Swyer syndrome patients exhibit low androgen levels and low or undetectable levels of androgen precursors. Cytogenetic analyses of these patients reveal a nonmosaic karyotype of 46,XY. In addition, patients can be tested for levels of anti-Müllerian hormone and inhibin, although these tests are not mandatory [1].

Differential diagnoses of patients with primary amenorrhea should consider various possibilities, including Mayer-Rokitansky-Küster-Hauser syndrome (XX), which is the second most common cause of this condition; this syndrome is characterized by varying degrees of Müllerian duct abnormalities and a rudimentary or absent uterus [10]. In addition, complete androgen insensitivity syndrome should be considered. Patients with this syndrome, which was formerly known as Morris syndrome, are XY individuals with primary amenorrhea and normal breast and vaginal development, but with no uterus [11]. Karyotyping should be performed in any individual with elevated gonadotropins and pubertal delay.

Analyses of urinary steroid profiles are relevant when testosterone or cortisol deficiency is suspected because these profiles allow these conditions to be distinguished from 5-alpha-reductase deficiency. Once gonadal dysgenesis is confirmed, the tumor markers alpha-fetoprotein, beta-human chorionic gonadotropin, lactate dehydrogenase, and alkaline phosphatase should be examined; however, according to certain authors, these markers should only be measured in cases involving gonadal tumors [1]. Transabdominal US is the first-choice diagnostic imaging method for investigating such lesions, with MRI restricted to cases in which US fails to clearly reveal Müllerian structures or urinary tract abnormalities [1, 2]. In the case described in the current report, uterine contours, size, and echogenicity were not clearly defined by the first US; thus, given that MRI was not available at our department at that time, it could not be established whether the case involved myoma or an adnexal tumor. Assessments of the NR5A1 gene are relevant for genetic counseling in cases with a relevant family history [1]. In the present case, the family history was suggestive of Swyer syndrome but did not provide conclusive evidence for this syndrome.

In cases of Swyer syndrome, after surgical treatment, hormone replacement therapy to induce puberty and the development of secondary sex characteristics is indicated [4]. Estrogen therapy should be administered as quickly as possible to ensure adequate bone mass formation and prevent reductions of bone mineral density that lead to osteopenia and osteoporosis. Cyclic estrogen and progesterone replacement is indicated until 50 years of age, when hormonal therapy may be discontinued [1, 2]. In the case described in this report, hormonal treatment commenced relatively late with respect to bone formation; this timing could account for the appearance of osteopenia in the examined patient.

Patients with Swyer syndrome should be subjected to surgery for gonad removal as soon as the diagnosis has been established because of their high risk for tumors such as dysgerminomas, which are the most common type of tumor found among these patients [4]. The objective of this surgery is to concurrently diagnose, stage, and treat the patient. For early-stage patients, the recommended procedure is unilateral salpingo-oophorectomy because this surgery preserves a patient's fertility [8]. Unfortunately, in the case described in this report, gonad removal surgery was performed only after a malignant tumor had progressed to an advanced stage; thus, a hysterectomy was required. This hysterectomy requirement represented a meaningful sacrifice for the patient; although the uterus of Swyer syndrome patients is small [3], these women can become pregnant via egg donation. In fact, several cases of pregnancy among Swyer syndrome patients have been described since 1988; the prognoses for these pregnancies is similar to the prognoses for the pregnancies of 46,XX patients with ovarian failure [12]. Adjuvant chemotherapy is particularly necessary in the most advanced stages of disease. Dysgerminomas are highly sensitive to chemotherapy; thus, the use of chemotherapy has been associated with a remarkable increase in patient survival, particularly following the introduction of platinum-based regimens [8].

The survival rates of patients with XY gonadal dysgenesis and dysgerminoma are similar to the survival rates of XX individuals with malignant ovarian germ cell tumors; in both types of patients, survival rates are largely dependent on tumor stage [13]. In particular, survival rates are lower among patients with more advanced tumors (stages 2–4; 53.9%) than among patients with stage 1 tumors (96.9%) [13]. Reports regarding these patients largely reflect 5 years of follow-up but have seldom examined 10-year survival [14, 15]. The Swyer syndrome patient with advanced dysgerminoma who has been described in this report has exhibited an extremely long survival time of 23 years, with no recurrence of disease.

In summary, the current case report is relevant because it calls attention to the need to subject women with primary amenorrhea to thorough investigation to exclude Swyer syndrome and other chromosomal abnormalities associated with high rates of incidence of ma-

lignant gonadal tumors. The accurate and early diagnosis of these abnormalities would allow for conservative treatment, which can ensure the preservation of fertility, reduce emotional trauma, and improve patient survival [1, 8].

Disclosure Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Fig. 1. The dysgerminoma. Nests of tumor cells with a clear cytoplasm and well-defined membranes were observed; fibrous septae and lymphocytic infiltrate were evident. $\times 100$.

Fig. 2. a, b The dysgerminoma. Upon detailed examination, neoplastic cells with large nuclei, prominent nucleoli and a clear cytoplasm were observed; mature lymphocytes were present amidst the fibrous stroma. $\times 400$.