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Swyer syndrome in a woman with pure 46,XY gonadal dysgenesis: a rare presentation

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Summary

46,XY pure gonadal dysgenesis (Swyer syndrome) is a rare cause of disorder of sexual development. It is a genetic aberration characterized by a 46,XY karyotype which are phenotypical females, with female genitalia at birth, and normal Müllerian structures. The condition usually becomes apparent first in adolescence with delayed puberty and primary amenorrhea. Herein the authors present the case of a 27-year-old woman with primary amenorrhea and undeveloped breasts. The patient had pure 46,XY gonadal dysgenesis with hypoplastic uterus, estrogen treatment for amenorrhea, and no neoplastic changes on the histopathology report. The authors highlight the high risk of neoplastic transformation of the patient with gonadal dysgenesis, and 46, XY karyotype should be referred for bilateral gonadectomy. Once the diagnosis of Swyer syndrome is established, early treatment is crucial to prevent the development of gonadal malignancy and to enable a normal sex life, and even carry a fetus in an immature uterus.

Key words: 46,XY pure gonadal dysgenesis; Dysgerminoma; Primary amenorrhea; Swyer syndrome.

Introduction

Swyer syndrome, present on the 46,XY karyotype, is caused by a defect in the definition of sex during embryogenesis and phenotype with female external genitalia, normal or rudimentary uterus, and streak gonads. Patients are generally diagnosed in adolescence with delayed pubertal development and most often with primary amenorrhea due to the fact that gonads have no hormonal or reproductive potential [1]. Psychosocial and reproductive implications of the condition require multidisciplinary management involving pubertal induction, psychosocial support, and assisted reproductive technologies. Streak gonads are associated with a risk of 30% with the development of gonadoblastoma and 50% to 60% with germ cell malignancies, mainly dysgerminoma [2]. Therefore, prophylactic gonadectomy is recommended once diagnosis is established.

Management of Swyer syndrome is in line with other causes of ovarian failure and involves induction of puberty with estrogen to develop secondary sexual characteristics and long-term combined replacement therapy with estrogen and progesterone [1]. It has been hypothesized that women with Swyer syndrome have a particularly severe degree of estrogen deficiency and according to the definition, they are completely devoid of any gonadal steroid production.

Case Report

A 27-year old, single, Chinese female presenting with a history of primary amenorrhea with pure gonadal dysgenesis was admitted to the hospital. The patient initially had primary amenorrhea, few pubic and axillary hairs, with undeveloped breasts. She was treated with estrogen estradiol valerate and cyproterone acetate at the age of 20 after which menstruation started. When she stopped the medication, menstruation disappeared. Later on, she continued her treatment and had menstruation until now with a regular cycle of five days, with intervals of 27-30 days. She had an average height with undeveloped breasts, normal vagina and cervix, no apparent somatic abnormalities, and no clitoral enlargement or any evidence of virilization.

Sonographic examination was performed which showed hypoplastic uterus with unremarkable ovaries. Karyotype studies were performed to confirm the diagnosis of pure 46,XY gonadal dysgenesis. Hormone tests showed a serum FSH level of 68.05 mIU/ml, LH level of 36.9305 mIU/ml, and T level of 47.88 ng/dl which was within the normal range for women. Laparoscopic gonadectomy was scheduled for the patient. During the operation, a retroverted uterus of about 3×3×2 cm with smooth surface was seen along with fallopian tubes on left and right side holding a piece of tissue (resembling streak gonads) measuring 2×2×1 cm and 4×3×2 cm, respectively. Right side of gonad was covered by dense connective tissue of 1×2×1 cm. Tissues were sent for frozen section which suspected a testis. Based on the agreement with the patient and her family, bilateral gonadectomy and salpingectomy were performed and sent for pathological studies. Histopathology of the left gonad revealed fibrous tissue whereas right gonad revealed the nodular distribution of atypical cells with translucent cytoplasm with fibrous tissue hyperplasia and infiltration of lymphocytes, which is illustrated by Figure 1. Similarly, histopathological study of the right dense connective tissue suspected short spindle cells of ovarian stroma with calcification.

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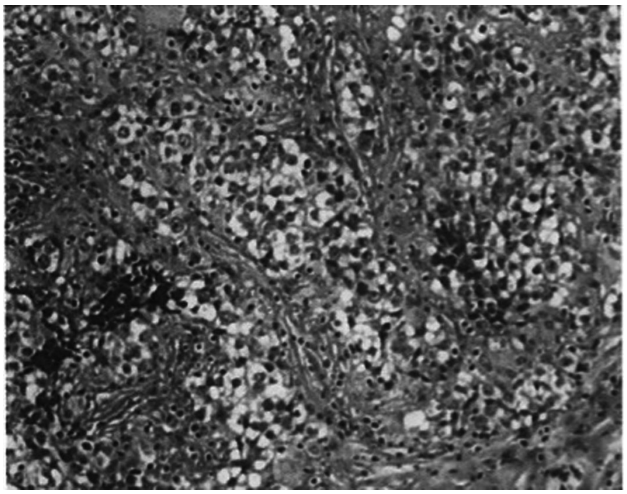

Figure 1. — The nodular distribution of atypical cells with fibrous tissue hyperplasia and infiltration of lymphocytes.

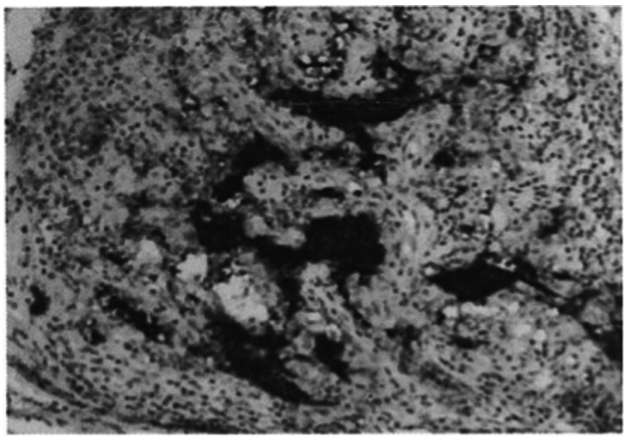

Figure 2. — CD117 (c-Kit) cytoplasmic immunoreactivity.

Immunohistochemical report showed that the tumor cells for CD117 was positive as shown in Figure 2. Similarly, CD99 and P53 were also found positive but negative for PLAP, CK, inhibin, SMA, CD3, CD20, and CD21.

Discussion

The Swyer syndrome, 46,XY gonadal dysgenesis is a rare chromosomal defect seen in females and is a phenotypic rare condition of sexual abnormality [3]. The external genitalia are phenotypically female, the upper part of the vagina and tubes are normal or reduced in size, and uterus is normal but undeveloped with small or undeveloped breasts and normal or few axillary and pubic hairs. 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 [4].

In patients suspected to suffer from Swyer syndrome, first measures should include location of gonads, morphology and functions of gonadal tissue, as well as the hormonal tests to determine risk for developing malignant transformation. Immunohistochemical markers (IHM) may help establish the diagnosis of malignant germ cell tumors (GCT). OCT 3/4, CD117, and Placental alkaline phosphatase (PLAP) are three established markers of germ cell malignancy, and these markers are easily identified with in-situ and invasive GCTs. Previous studies have observed that PLAP showed the highest specificity; however, they are unreliable in detecting the germ cells of neonates in very young children [5].

Early diagnosis is important for several reasons: firstly, because of the high risk of neoplastic transformation in the dysgenetic gonads, secondly, early institution of estrogen therapy for induction of puberty, and thirdly, to allow adequate hormone replacement therapy (HRT) to prevent osteoporosis [6].

The main differential diagnosis of Swyer syndrome is mixed gonadal dysgenesis which is more frequently seen than the former. In mixed gonadal dysgenesis, one gonad is a fibrous streak and the other is testis which is usually rudimentary, whereas in Swyer syndrome, a streak gonad consists of fibrous ovarian stroma without follicles [7].

Gonadal dysgenesis corresponds to impaired formation of the gonads (ovary and testis) that result in a variable ambiguous phenotype, depending on the initial genetic anomalies. Various karyotypes can be observed as 45,X, 46,XX, 46,XY, 45,X/46,XY, and 47,XXY or more complex mosaicisms [8]. The etiology of 46,XY gonadal dysgenesis is believed to be deletion of short arm of Y chromosome involving the sex determining region of Y (SRY) gene, mutation in other genes leading to inhibition of SRY function, or mutation of SRY itself [3].

It had been hypothesized that chromosome Y contains a gonadoblastoma which is responsible for benign tumor, which may also develop bilaterally and coexist with other neoplasms such as dysgerminoma. The patients with gonadal dysgenesis and 46, XY karyotype should be referred for bilateral gonadectomy because of the high risk of neoplastic transformation [1, 8]. Therefore, females with Swyer syndrome require close follow up because of the high risk of neoplastic transformation in the dysgenetic gonads.

In the present case, since the diagnosis was delayed and done at the age of 27 years only, Y chromosome had high propensity towards tumoral development [1, 8]. Moreover, the frozen section of the tissues also suspected a testis. Therefore, bilateral gonadectomy and salpingectomy were carried out. Patient is undergoing additional HRT which will be helpful in order to minimize psychological effect and hypoestrogenemia, and also the effect in cardiovascu-

lar system, osteoporosis, and vaginal epithelium. Thus she has had regular menstruation until now and also intends to become pregnant through ART within several months. Therefore, follow up is required and further studies should be performed to find the exact factors.

Presence of XY genotype and H-Y antigen does not affect the uterine and the endometrial response. Thanks to the presence of a uterus in Swyer syndrome, we can treat this type of sterility with hormonal replacement and donated oocytes. Previously a case study reported a patient with pure gonadal dysgenesis XY, who successfully became pregnant through a donated oocytes programme [9, 10]. It provides evidence that even an individual with male genetic gender can become pregnant and deliver a healthy child if the uterus is not removed due to malignant etiology.

Conclusion

In an adolescent patient with primary amenorrhea, karyotype analysis and investigation of gonads is recommended. Therefore, early diagnosis and treatment could help these patients to have a normal sex life and carry a fetus in an immature uterus using donor oocytes and hormonal replacement.

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