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46, XY pure gonadal dysgenesis with malignant mixed germ cell tumor: a case report and literature review

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Summary

46, XY pure gonadal dysgenesis, which is also known as Swyer syndrome, is a medical condition of gonadal abnormalities. The authors report a case of a 15-year-old phenotypic female who presented with bulky abdominal mass and underwent laparotomy with right cystectomy, as well as left ovary biopsy. Post-operational pathology demonstrated that malignant mixed germ cell tumors in the right ovary. Taking consideration of no menstruation, abnormal hormone levels, and malignant mixed germ cell tumors in the ovary, the patient took the karyotype test and the result was confirmed: 46, XY. Taking into consideration pure gonadal dysgenesis with mixed malignant germ cell tumors, surgical resection of bilateral gonads is primarily recommended. The patient and her families were well consented on sex selection, cancer treatment strategy, reproductive function, and resection of the pelvic mass, together with uterus, it was decided to maintain female phenotype without reproductive function. Post-operational pathology showed ovarian gonadal blastoma and dysgerminoma, with bilateral calcification. The nodule from the excavatio rectouterina was identified as mature teratoma, without immature components. The patient received four cycles of postoperative chemotherapy using bleomycin, etoposide, and cisplatin (BEP) regime. Long-term hormone replacement therapy was recommended. There has been no sign of recurrence since then.

Key words: 46, XY pure gonadal dysgenesis; Malignant mixed germ cell tumor; Immature teratoma; Yolk sac tumor; Gonadal blastoma.

Introduction

Swyer syndrome is associated with 46, XY karyotype, primary amenorrhea as well as the presence of female internal genital tract and bilateral streak gonads in a phenotypic female. The genetic background of this syndrome includes mutations of several genes involved in the testis differentiation cascade. 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 tumour, and bilateral gonadectomy should be performed.

Case Report

A 15-year-old phenotypic female presented to local hospital with acute fever, lower abdominal pain, bulky abdominal mass, and underwent laparotomy on June 29th, 2012. with right cystectomy as well as left ovary biopsy. Perioperatively she had a right ovary with multilocular cystic-solid mass (22×18×16 cm), fibrous tissue in the left ovary, with primordium uterus. Serum tumor marker testing six days postoperatively revealed elevated AFP (5,710 ng / ml) and CA125 (45.6 U/ml) levels. Postoperative pathology demonstrated that fibrous tissue with calcification and ossification was seen in left ovary and immature teratoma (grade II) in the right ovary, with regional tubular or sparse reticular structure. Atypical cell was also recorded and germ cell tumours needed to be determined.

The patient came to the present clinic, and pathological consultation revealed a malignant mixed germ cell tumors [grade II immature teratoma (75%) and yolk sac tumor (25%)] in the right ovary (Figure 1) and clustered calcification was seen in the surface of the left ovary (calcification with immature teratoma and yolk sac tumor were separately oriented). Though no tumour cells were identified, the presence of calcification strongly suggested the possibility of gonadal blastoma (Figure 1). Re-examination of AFP level was 51.30 ng/ml.

The patient was premenarchal and had no medical history. On physical examination, she was 165 cm tall and weighed 47.5 kg. She did not have any secondary sexual characters (flat breasts, small and pale nipples, sparse armpit hair). No palpable inguinal mass was identified bilaterally, female, but sparse pubic hair distribution with female genitals (infantile), and gynecologic examination demonstrated vagina of cervical-like structure, with a diameter of around 1.5 cm, with no uterus or adenexa structure palpated. Blood test of hormone levels were abnormal: estradiol 5.21 pg/mL, FSH 134.4I U/L, testosterone 0.033 ng/ml, and progesterone 0.227 nmol/L. There was no family history of any malignancies or developmental anomalies. Taking into consideration the lack of menstruation, abnormal hormone levels, and malignant mixed germ cell tumors in the ovary, chromosomal abnormalities needed to be determined and karyotype results (from two independent hospitals) was confirmed to be 46, XY.

Taking into consideration pure gonadal dysgenesis with mixed malignant germ cell tumors, surgical resection of bilateral gonads was primarily recommended. The patient and her families were well consented on sex selection, cancer treatment strategy, and reproductive function, and resection of the pelvic mass; together with uterus it was chosen to maintain female phenotype without reproductive function. On January 9th, 2013, the patient under-

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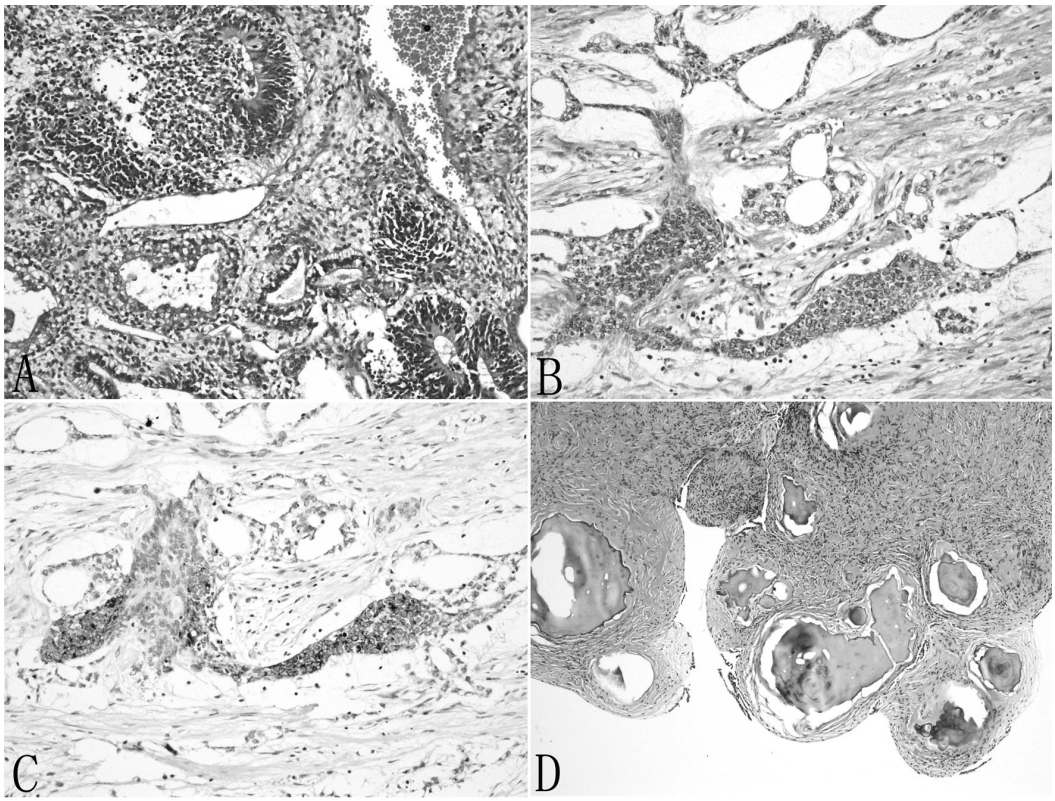

Figure 1. — Immature teratoma tumor (A) and yolk sac tumor (A, B) in the right ovary. Immunohischemistry (IHC) staining for AFP in the yolk sac tumor (C). Calcification is shown in tissue biopsy from the surface of the left ovary (the D). Though no epithelium is seen, calcification of this pattern strongly suggests the existence of gonadal blastoma.

went hysterectomy, resection of bilateral ovarian tube and gonad, together with resection of tumor with general anesthesia. Visual inspection revealed that both ovaries were cord-like, without nodules. Bilateral annex (ovaries and fallopian tubes) were embedded for pathological examination. Microscopic images showed ovarian gonadal blastoma and dysgerminoma, with bilateral calcification (Figure 2). The nodule from the excavatio rectouterina was identified as mature teratoma, without immature components; no other abnormalities were found in bilateral tubal, uterus, endometrial, myometrium or cervix.

Postoperative diagnosis reconfirmed 46, XY pure gonadal dysgenesis, right gonadal immature teratoma (grade II), right gonadal yolk sac tumor, bilateral gonadal blastoma,and bilateral gonadal dysgerminoma. Patients received four cycles of postoperative chemotherapy using bleomycin, etoposide and cisplatin (BEP) regime until May 2013. Follow-up was routinely conducted every three months and long-term hormone replacement therapy was recommended. There has been no sign of recurrence since then.

Discussion

Sexual abnormalities could be categorized due to different mechanisms, including sex chromosome, gonadal, and hormone abnormalities, while gonadal abnormalities would be divided into XX pure gonadal dysgenesis, XY pure gonadal dysgenesis, true hermaphroditism (46, XX or 46, XY), and testicular degeneration. 46, XY pure gonadal dysgenesis, which is also known as Swyer syndrome, is a medical condition of gonadal abnormalities. Normally, testis differentiation begins during the sixth week of the fetal period. The development of a chromosomal karyotype 46 XY into a male requires two conditions: testis-determining factor (TDF) promotes the formation of the testes, and Müllerian inhibiting substance (MIS) secreted from testis and androgen. MIS acts as an inhibitor of the development of fallopian tubes and uterus; meanwhile, dihydrotestosterone, which is transformed from androgen by 5α-reductase promotes male external genitalia. At present, studies suggest that sex-determining region Y gene (sex determining region Y, SRY), located on the Y chromosome should be the male TDF, and work concomitantly with SOX9 (SRY-box 9), which also located on the Y chromosome to encode binding protein, activating MIS1 with the association of targeted DNA[1-2]. About 10-20% of XY pure gonadal dysgenesis patients, whose sex chromosome is 46 XY, have SRY gene mutation [3, 4]. Additionally ZFY, SOX9, SF1, WT1, DYZ1, and DAX1 gene mutations might also be the underlying causes of this disease [5]. Due to the aforementioned reasons, the gonads do not grow during early embryonic development, with no MIS and androgen production, thus failing to suppress the development of the uterus and fallopian tubes, and without male external genitalia, resulting in gonadal abnormalities.

The incidence of 46 XY pure gonadal dysgenesis is very low, approximately 5 / 100,000 [6]. Patients phenotype are female, and usually regarded as “normal” before the development of secondary sexual characteristics, therefore

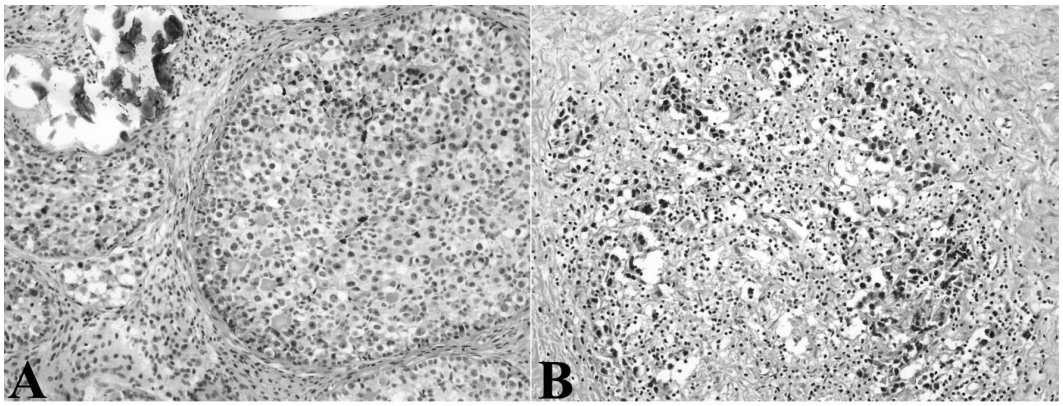

Figure 2. — Surgical specimen demonstrated gonadal blastoma (A) dysgerminoma in bilateral ovaries (B). Calcification is seen in the gonadal blastoma from the annex (A).

difficult for early diagnosis [7]. The most common reasons for visit is primary amenorrhea, which is usually the first diagnosis in adolescence. Due to the limitations of social environment and medical technology, in many countries and regions, numerous patients could not be properly diagnosed and treated, even if the developmental abnormalities and amenorrhea are present. Therefore, the incidence of this disease may be far higher than the current data.

The most common first symptom is primary amenorrhea for 46, XY pure gonadal dysgenesis patients, followed by a pelvic mass and abdominal pain [8, 9]. Patients of 46, XY pure gonadal dysgenesis have immature female external genitalia, vagina, primordial uterus, fallopian tubes, and streak gonads [10]. Since the streak gonads cannot secrete and maintain normal levels of estrogen or androgen, the patient cannot be achieved normal development of secondary sexual characteristics in adolescence, such as: breast dysplasia, no pelvis and hip broadening, and no menstrual onset. Since the adrenal glands can secrete small amount of androgen, some patients might have normal armpits and pubic hair development and distribution. However, hormones, like estrogen and testosterone levels are lower than normal ones, with enhanced FSH levels. Suspected patients can be referred to peripheral blood test, and karyotype 46, XY can confirm the diagnosis. For adolescent female patients with pelvic mass and no menstrual onset, chromosomal abnormalities should be considered and referred to peripheral blood karyotype analysis.

The differential diagnosis of this disease includes androgen insensitivity syndrome [11] and 46, XY 17-α-hydroxylase deficiency. These three patients were all karyotype 46, XY, having female external genitalia, but patients with androgen insensitivity syndrome (total type) have blind-end vagina, no uterus, no artificial cycle withdrawal bleeding, and only with gonadal dysgenesis of the testes. Patients with 46, XY 1-7α hydroxylase deficiency suffer from hypertension and hypokalemia, besides breast dysplasia and blind-end vagina.

Patients with 46, XY pure gonadal dysgenesis are prone to germ cell tumors, and current studies report the incidence of neoplasia in the literature, which is about 30-75% [12]. The most common type of tumors is gonadal blastoma, followed by dysgerminoma. The risk of cancer increases with age [13]. In summary, it is routinely recommended that these patients undergo preventive resection of bilateral gonads to reduce the risk of tumor after diagnosis [6, 14-16].

Doctors are supposed to pay attention to the cognitive and mental disorders for patients with 46, XY pure gonadal dysgenesis. The concept of gender is complicated, including chromosomal sex, genital sex, sex hormones, social gender, and psychological gender. Most patients usually grow up as female before diagnosis, who establish preliminary gender and gender identity after puberty. When informed of their male sex chromosome, either by family members or doctors, patients will confront cognitive problems caused by gender-targeted conflict due to gender orientation. Therefore, as an oncological specialist, in clinical practice, the treatment of Swyer syndrome might involve psychiatrists' contribution, providing professional psychological counseling to patients and their families; on the other hand, medical education, to the patient and family, especially the patients' participation in the choice of further treatment, might be helpful in reducing the risks of mental disorders after treatment [15]. Current data also demonstrated that the majority of patients and their families choose to maintain female gender and their physiological functions after the diagnosis [17], but the rates of marriage and childbirth in patients with 46, XY pure gonadal dysgenesis are much lower than in the normal population [18].

46 XY pure gonadal dysgenesis is a rare disease. The diagnosis and treatment of Swyer syndrome involving gynecologic oncology, endocrinology, psychology, and other related professionals, require multidisciplinary collaborations. The risk of ovarian cancer in patients with this disease is significantly higher than that in the general population, therefore prophylactic resection of the gonads is recommended after the diagnosis. In this case, the 15-year-old patient suffered from ovary gonadal blastoma and dysgerminoma, suggesting the importance of early diag-

nosis and early removal of both gonads. Dysgerminoma is sensitive to chemotherapy, and in some cases chemotherapy instead of resection of bilateral gonads might be considered, but about 75% of patients suffer relapse within one year after the initial treatment [19]. Since the primitive gonad does not have the function of hormone secretion, the conservation of gonad raises the risk of cancer, therefore doctors should pay more attention to communication of tumorogenesis, surgical risks, and postoperative long-term hormone replacement therapy with patients and their families, and be more careful with gonad-retention treatment, and these patients require close follow-up in case of tumor recurrence.

Patients with 46 XY pure gonadal dysgenesis, especially after bilateral gonadal resection, should receive long-term hormone replacement therapy. Application of exogenous hormones can maintain the normal menstrual cycle and reduce the risk of tumors, also prevent the occurrence of osteoporosis and cardiovascular disease [20]. The present study describes a patient with 46 XY pure gonadal dysgenesis undergoing hormone replacement therapy with higher dose than that of the general population after menopause.

The psychological problems of 46, XY pure gonadal dysgenesis patients should not be ignored. Appropriate professional counseling should be provided. Patients and their relatives are encouraged to discuss on sex selection and future life-plan, for emotional support. Before the attempt of sexual activity, consultation on psychological and physiological issues is necessary. Information for patients to join social groups facilitate the adaptation to normal social life.

Currently, China is lacking legal provision on allogeneic egg donor for IVF, however there are many cases reported of foreign patients with 46, XY pure gonadal dysgenesis having a successful pregnancy [21-25]. All cases underwent caesarean section to terminate the pregnancy, with good maternal prognosis. Patients are unable deliver vaginally mainly due to two reasons: firstly, the majority of patients with non-female-type pelvis and abnormalities in bone birth canal cannot guarantee vaginal delivery; secondly, due to lack of hormone receptors, primordial uterus is not sensitive to prostaglandins and oxytocin, resulting with the failure of uterine contractions and cervical dilation. If patients with allogeneic donor egg wish to complete fertility, they should begin hormone replacement therapy earlier before pregnancy to adjust the amount of hormone for uterine suitable for embryo transplantation under the guidance of reproductive experts. Exogenous hormone therapy should be maintained during early pregnancy until 12th week of pregnancy [4].

Conclusions

The incidence of 46 XY pure gonadal dysgenesis is low and its pathogenesis as well as its cause of high incidence of cancer are yet not clear. Current treatment strategies are based on previous case reports and retrospective studies with small samples, lacking evidence-based medicine. The treatment of patients with 46 XY pure gonadal dysgenesis should be comprehensive and individualized. Doctors should take precise consideration of the related physically and psychologically issues, to help understand the medical knowledge and treatment options, in order to achieve successful treatment selection through communication. With the development of medical concept and legal provision, patients with 46 XY pure gonadal dysgenesis patients could benefit from treatment with better efficiency and safety.

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