

Gonadoblastoma in a patient with 46, XY complete gonadal dysgenesis

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46, XY complete gonadal dysgenesis (Swyer syndrome) is a rare cause of 46, XY sexual development disorder. The patient presented to our clinic with absence of breast development and lack of periods at the age of 17 years. Her history and familial history involved no relevant conditions. She had Tanner stage 1 thelarche, and Tanner stage 2 pubic hair development with no axillary hair development. External genital structure appearance was consistent with female phenotype and the patient had no palpable gonad. The patient diagnosed as 46, XY complete gonadal dysgenesis after evaluation of laboratory analyses, radiological methods and karyotype. The Sexual Orientation and Gender Identity Committee concluded that gonadectomy should be performed. Histopathologic analysis demonstrated gonadoblastoma. Gonad structures should be sought laparoscopically and once diagnosed, streak gonads should be removed prophylactically in patients with 46, XY complete gonadal dysgenesis.

Key words: gonadal dysgenesis, gonadoblastoma, sexual differentiation.

Complete gonadal dysgenesis (Swyer syndrome) is a gonadal dysgenesis syndrome in individuals with 46, XY karyotype characterized by female phenotype, infantile uterus and tubes. Two initial cases were reported by Swyer in 1955^{1,2}. It has an incidence of 1/80.000³. The most common clinical presentation includes delayed pubertal findings and primary amenorrhea. The patients have a 30% probability of developing gonadoblastoma from dysgenetic gonads, while there is a 50-60% likelihood of malignant transformation of gonadoblastoma and, frequently, to dysgerminoma⁴.

Patients with complete gonadal dysgenesis are difficult to manage. An experienced specialist and a multidisciplinary approach are required. In terms of prognosis, malignant transformation is the most important aspect of the syndrome¹. Early diagnosis is crucial with respect to the risk of gonadal malignancy, early hormone replacement therapy, psychosocial development and in reaching appropriate bone mass³.

Case Report

A 17-year-old patient raised as a female presented to our clinic with absence of breast development and lack of periods. According to her history, she was born term. Her parents were not relatives. Mother's menarche age was 12 and the familial history involved no other person with similar delayed pubertal findings. Physical examination revealed height 155.8 cm (-1.06 SDS), body weight 49.3 kg (-1.08 SDS), Tanner stage 1 thelarche, Tanner stage 2 pubic hair with no axillary hair development. The patient exhibited a female external genitalia, with normal labia majora and minora and a visible vaginal orifice. No palpable mass was identified in the groin or labia majora. Findings of other system examinations were normal. Laboratory analyses showed: FSH 56.3 mIU/ml (1.4-11.7), LH 22 mIU/ml (0.6-21), E2 13.07 (13-71) pg/ml, total testosterone <10 ng/dl (8-80), cortisol 10.1 µg/dl (8.7-25), ACTH 17.8 pg/ml (0-46), DHEA-SO4 151.48

$\mu\text{g}/\text{dl}$ (65-368), 17-OHP 0.48 ng/ml (0.4-4.2), 1-4 androstenedione 0.65 ng/ml (0.5-4.7), progesterone <0.21 ng/ml, AMH 0.078 ng/ml (1.5-18.5). Patients' karyotype was 46, XY and she was positive for SRY. HCG test was performed and her stimulated testosterone response was inadequate with 17 ng/dl. With pelvic ultrasonographic analysis, uterus was smaller than normal and gonads could not be visualized. Uterus could not be visualized with pelvic MRI. Image potentially from an atrophic gonadal tissue was observed at the right adnexal area and left gonad could not be visualized. Images from patient's pelvic MRI are given in Figures 1 and 2. The patient was diagnosed as 46, XY complete gonadal dysgenesis with these findings. Sexual Orientation and Gender Identity Committee concluded that gonadectomy should be performed. Uterus was minimally small during gonadectomy. Tuba uterine was seen. Streak gonadal tissue at both salpinx ends was excised. Histopathologic analysis demonstrated gonadoblastoma at the right gonad. Ductus structures were observed at bilateral tuba uterina and peripheral tissue. Histopathologic images of patient's gonads are shown in Figure 3.

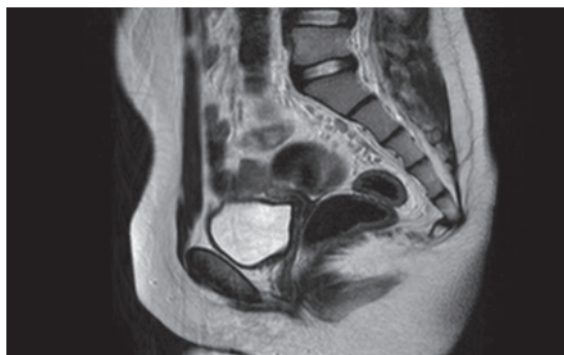


Fig. 1. Rudimentary vagina and uterus in sagittal T2 weighted MRI

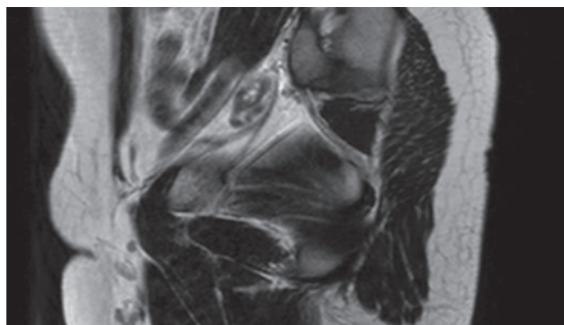


Fig. 2. Right dysgenetic gonad in sagittal T2 weighted MRI

Discussion

Patient with 46, XY complete gonadal dysgenesis are phenotypically female and are born with normal female genitals. Mullerian structures are developed. Patients typically present during puberty with primary amenorrhea and delayed pubertal findings³. Similarly, our patient presented with primary amenorrhea, absence of breast development and was diagnosed at the age of 17 years. Because findings were normal during prepuberty, early diagnosis is only possible when karyotype analysis is performed for another reason or if the patient has a sibling with similar complaints. These patients generally do not have familial history. A study has found affected siblings in only 4% of the cases³. Indeed, our case was diagnosed sporadically and there was no family history.

Of the patients diagnosed with complete gonadal dysgenesis, 10-20% has deletion at the DNA-binding site of the SRY gene. The SRY gene is normal in the remaining 80-90% (5). SRY gene was positive in our patient. Defects in genes including *ARX*, *ATRX*, *CBX2*, *DHH*, *DMRT1*, *GATA4*, *MAMLD1*, *MAP3K1*, *NROB1*, *NR5A1*, *SRY*, *WNT4*, *WT1* and *WWOX* which are effective in testis development, probably caused complete gonadal dysgenesis in our patient and other patients with normal SRY gene³.

Dysgenetic gonads of patients with complete gonadal dysgenesis do not have normal physiological functions and also are at an increased risk of malignancy. The risk of gonadoblastoma is variable but is estimated to be >30%⁶. This risk increases further with

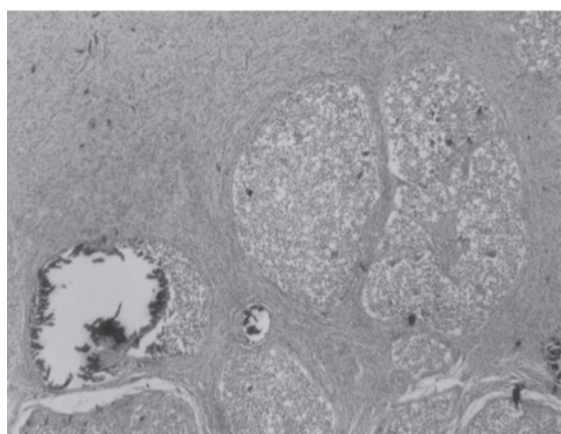


Fig. 3. Tumoral tissue with micronodule formation and calcified areas

age and reaches 50-70% in the third decade and to around 80% in the fifth decade⁵. There are opinions that gonadoblastoma development can be induced by the interaction of abnormal gonads with intra-abdominal environment or by the mutations that cause the disease⁶. Gonadoblastoma development in the right gonad was identified in our patient who was diagnosed and operated at the age of 17. Gonadoblastomas are benign lesions but may be precursors for germ-cell malignancies. Dysgerminoma, teratoma, embryonal carcinoma and endodermal sinus tumors may develop from a gonadoblastoma background. Therefore, prophylactic gonadectomy should be performed in diagnosed patients.

46, XY complete gonadal dysgenesis is a condition that is quite difficult to diagnose and manage. Because the patients are at risk of malignancies and may require pubertal induction, psychosocial support and assisted reproductive techniques, they should be followed-up by an experienced specialist and with a multidisciplinary approach⁴. In cases where gonads could not be shown radiologically as in our patients, gonadal structures should be sought laparoscopically and once diagnosed, streak gonads should be removed prophylactically.

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