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A 45,X/46,XY Male with Orchidopexy Diagnosed with Mixed Germ Cell Tumor After 21-year Follow-up

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ABSTRACT

A case of a 45,X/46,XY boy with gonadal dysgenesis is presented. The patient showed hypospadias and right undescended testis. He underwent underwent repair surgery for hypospadias, right orchidopexy, and bilateral testicular biopsy. Testicular biopsy revealed no malignant finding. He was followed-up annually by scrotum palpation. When the patient grew up to 24 years old, he was diagnosed to have right testicular tumor. High orchiectomy revealed pT1 seminoma. The management of undescended testis in men with gonadal dysgenesis and disordered sexual development is discussed.

Introduction

Karyotype 45,X/46,XY gonadal dysgenesis (GD) results in DSD. Individuals with 45,X/46,XY GD are also known to be at increased risk of developing GCTs.[1] This risk of malignancy has been associated with gender phenotype and gonad location. Patients with a female phenotype or intra-abdominal testes have greater risks of malignancy, and their gonads should thus be removed prophylactically in early childhood. In contrast, 45,X/46,XY GD males with scrotal testes are classified as having a lower risk of malignancy, and the gonads may thus be preserved.[2] However, the precise risk of malignancy in the undescended testis after surgery remains unclear and the standard management of such patients has not been determined. Here we report a case of a 45,X/46,XY GD male in whom early-stage GCT developed in the undescended testis during a 21-year follow-up period after orchidopexy.

Abbreviations: GD, gonadal dysgenesis; DSD, disordered sexual development; GCT, germ cell tumor; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

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Case presentation

A 3-year-old boy had been referred to a previous hospital with hypospadias and right undescended inguinal testis. A chromosome test revealed a 45,X/46,XY mosaicism karyotype. He underwent repair surgery for hypospadias, right orchidopexy, and bilateral testicular biopsy. Testicular biopsy revealed no malignant finding. He was followed-up annually by scrotum palpation.

At 17 years old, the patient was referred to our hospital for further follow-up. His height and weight were 156 cm and 51 kg, respectively. Breast and pubic hair development were consistent with Tanner grade 2. His external genitalia appeared male, with a short penis. His bilateral testes were palpable in his scrotum, with no abnormal masses. The right testis was smaller than the left and had microlithiasis on US.

His FSH level of 12.7 IU/L, LH level of 8.5 IU/L, and testosterone level of 358.3 pg/mL were within the normal ranges. The tumor markers Human Chorionic Gonadotropin-β, Alpha-Fetoprotein, and Lactate Dehydrogenase were all normal. Because he had received a testicular biopsy at age 3, he was scheduled to receive follow-up by periodic scrotal palpation, US, and tumor marker tests every 6 months, without further testicular biopsy.

At 24 years old, a 10 mm testicular mass was identified on US (Fig. 1). The mass was not palpable, but MRI revealed a solitary mass in his right testis (Fig. 2). Abdominal and thoracic CT revealed

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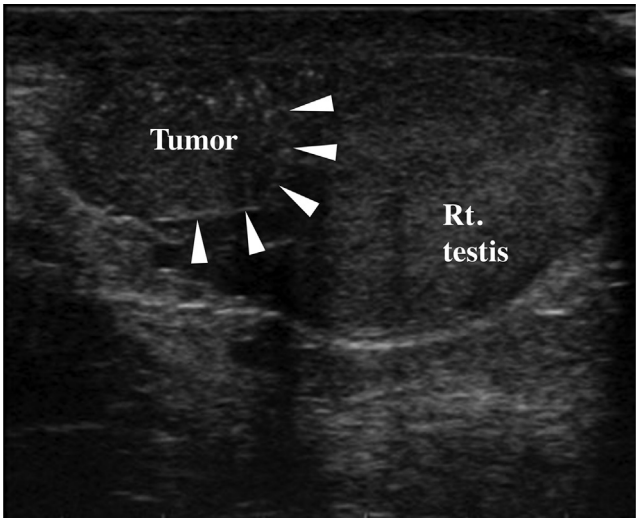

Figure 1. US findings of right testis. Arrows indicate the testicular tumor.

no metastatic lesions. Tumor markers were within the normal ranges. Semen analyses revealed azoospermia. More precise chromosomal study revealed loss of the Y chromosome in the AZF b+c area.

He was diagnosed with a localized right testicular tumor, and underwent right high orchiectomy and left testicular biopsy. Pathological analyses revealed seminoma with mature teratoma (pT1) in the right testis and no malignancy in the left testis (Fig. 3).

His regular follow-up continued for 1 year after surgery, with no evidence of disease recurrence. His FSH, LH, and testosterone levels remained within normal ranges.

Discussion

The incidence of 45,X/46,XY GD is estimated to be <1 in 15,000 live births. The gender phenotypes are distinguished by external genitalia features, and vary among female, male, and ambiguous (significant genitalia anomaly).[2]

The Consensus Statement on Management of Intersex Disorder was published in 2006.[3] This statement classified the various karyotypes of DSDs, including 45,X/46,XY, into high-, intermediate-, and low-risk groups for GCT. The risk of malignancy in 45,X/46,XY GD patients with intra-abdominal testes was 15–35%, which was assigned to the high-risk group, while the risk of malignancy in female gender phenotype 45,X/46,XY was much higher than in male phenotype individuals (22.5–50%). Unilateral or bilateral gonadectomy has been recommended for these patients at high risk of malignancy. In contrast, patients with scrotal testes were assigned to the intermediate-risk group. However, the precise risk of malignancy remains unknown, because male 45,X/46,XY GD patients may remain undiagnosed until adulthood. A previous patient was only diagnosed as 45,X/46,XY GD as an adult after surgery for GCT in the scrotal testis.[4] To the best of our knowledge, the current case provides the first report of the development of GCT in a 45,X/46,XY male patient after 20 years of follow-up from the first diagnosis.

In recent years, a proposed treatment strategy for GD males has involved retaining their gonads in order to maintain their hormonal functions and gender identity.[5] Orchidopexy and biopsy in childhood are recommended in the case of patients with undescended gonads. Palpation and self-examination are easy and US follow-up is efficient in scrotal gonads or after orchidopexy. Repeat biopsy should be considered, depending on the results of the first biopsy, and gonadectomy should be recommended if carcinoma in situ (CIS) or gonadoblastoma is detected on biopsy. In the present case, we decided to preserve the patient's gonads because of his male

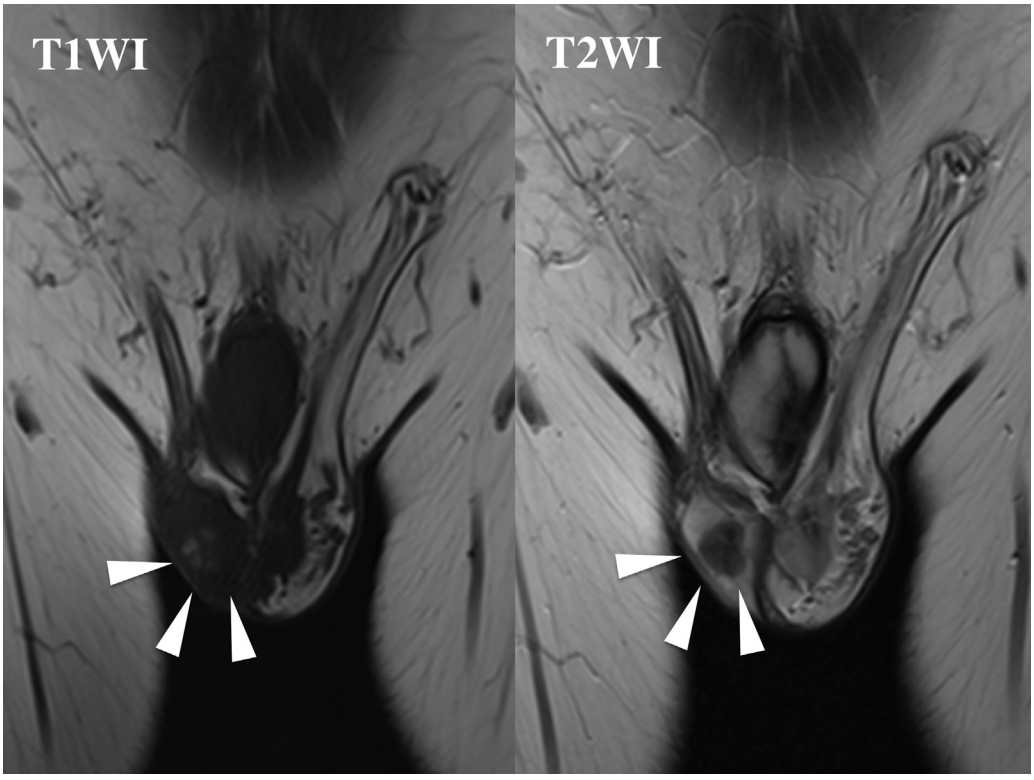

Figure 2. Magnetic resonance imaging findings. Images taken by T1WI (left) and T2WI (right). Arrows indicate the testicular tumor.

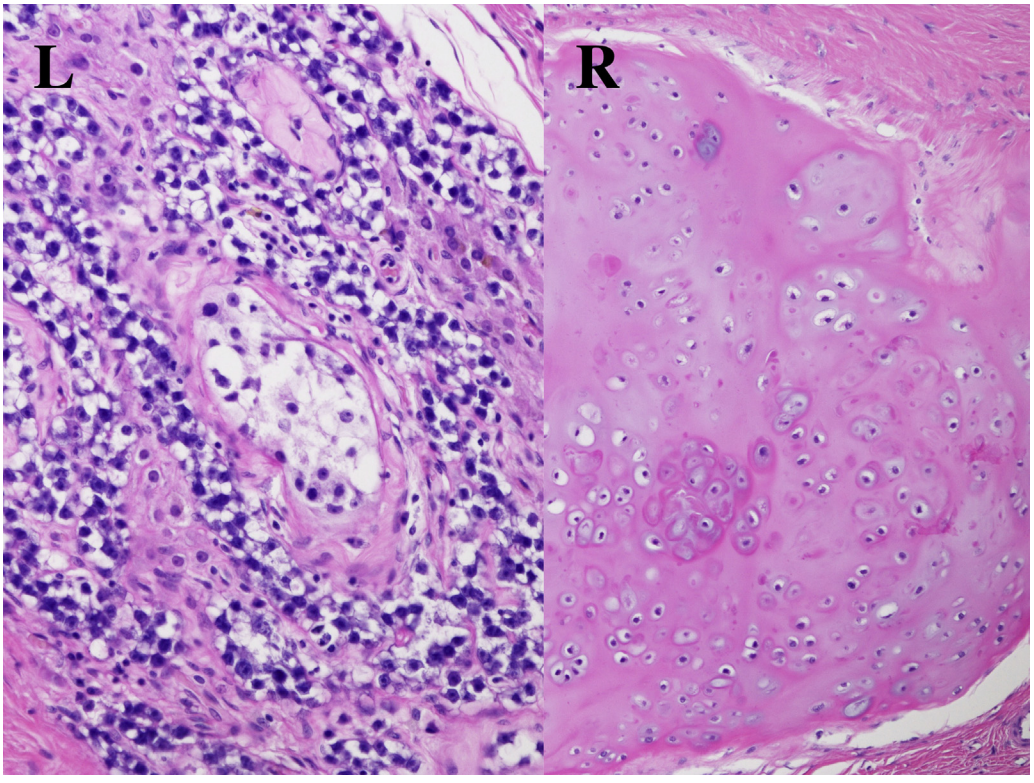

Figure 3. Microscopic findings (Hematoxylin–Eosin staining). Left image, seminoma; right image, teratoma.

phenotype, scrotal testes after orchidopexy, and negative malignancy on biopsy at age 3 years. However, GCT had developed by 24 years old. CIS was previously reported in the testis in five of 13 45,X/46,XY male patients,[2] with four of the CIS patients identified after age 10 years. These results indicated that malignant cells may appear after puberty, even when no CIS is detected on testicular biopsy in early childhood. In our case, the GCT was fortunately detected at an early stage and completely resected, with close follow-up. However, testicular re-biopsy after puberty could be an optional treatment strategy in these patients. More outcome reports of conservative management of gonads in this karyotype are needed to establish a therapeutic policy for GD patients, classified according to their malignancy risk.

Conclusion

Close follow-up of a 45,X/46,XY GD male patient with intact scrotal gonads enabled the detection of a testicular tumor at an early stage. This case suggests that gonads may be preserved in 45,X/46,XY GD males with scrotal testes, though patients with a history of cryptorchidism may be at comparatively high risk of developing GCT. Appropriate risk assessment of each patient is thus needed before deciding to retain the gonads in patients with this karyotype.

Conflict of interest

None.

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