CASE REPORT

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A Boy with 46,XX Karyotype (SRY Double-positive) and a Leydig Cell Tumor

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What is already known on this topic?

Ninety percent of the patients with 46,XX testicular disorder of sex development (DSD) are SRY positive, but double positivity is rare. To date, Leydig cell tumors have been only reported in adult cases with 46,XX, testicular DSD.

What this study adds?

We report the first pediatric case of 46,XX testicular DSD associated with a Leydig cell tumor.

Abstract

Leydig cell tumors are the most common type of testicular sex cord stromal tumors. The presence of the Y chromosome is associated with tumor risk in sex development disorders (DSD), however tumor development without Y chromosome is extremely rare. A 16-year-old boy diagnosed with Leydig cell tumor due to a mass in the right testis was referred after the right orchiectomy. On physical examination, the left testis was 10 mL, and there was a labial residue in penoscrotal region. Bilateral gynecomastia was present. The karyotype was 46,XX and SRY was double-positive on fluorescent *in situ* hybridization analysis. Ifosfamide, carboplatin and etoposide chemotherapy was initiated due to the Leydig cell tumor. Here, we report the first pediatric case having 46,XX testicular DSD with double-positive SRY and a Leydig cell tumor.

Keywords: Leydig cell tumor, sex determining region of Y-chromosome, testicular DSD

Introduction

Disorders of sex development (DSD) are defined as the incompatibility between chromosomal sex and phenotype, and DSD is seen in 1 in every 4,500 births (1). However, 46,XX DSD is usually sporadic and may be classified into three major groups; gonadal development disorders (gonadal dysgenesis, ovotesticular DSD, and testicular DSD), disorders due to androgen excess, and unclassified disorders, such as Mullerian agenesis, labial fusion and vaginal atresia (2). Furthermore, 46,XX testicular DSD is characterized by a male phenotype despite 46,XX karyotype, mainly due to *SRY* translocation, and was first reported by Delachapelle (3) in 1964. These patients usually present with gynecomastia, infertility and hypergonadotropic hypogonadism in the post-pubertal period of life. The presence of Y chromosome in

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DSD patients increases the risk of gonadal tumors. Gonadal tumors are extremely rare in 46,XX testicular DSD without Y chromosome (4). In childhood and adolescence, sex-cord stromal tumors (SCSTs) constitute approximately 5% of all testicular tumors and the remainder is of germ-cell origin (5). SCSTs originating from the supportive tissues of the testis include Leydig, Sertoli and granulosa cell tumors (6). Among these, Leydig cell tumors are the most common testicular SCSTs, and present usually with precocious puberty due to excessive testosterone secretion.

Here, we report the first pediatric case of 46,XX DSD with SRY double-positivity and with a Leydig cell tumor.

Case Report

A 16-year-old boy was admitted to a urology out-patient clinic with a mass in the right testis. The right testis was > 25 mL while the left testis was 10 mL. On initial examination, bilateral gynecomastia was present. Laboratory test results were; prolactin 51.8 µg/L (2.6-13), total testosterone 0.79 µg/L (1.7-7.8), estradiol 12 ng/L (< 15), luteinizing hormone (LH) 3.75 U/L (1.2-8.6), follicle stimulating hormone (FSH) 5.54 U/L (1.2-19.2), α-fetoprotein 2.18 µg/L and beta-hCG < 0.005 U/L. The patient underwent radical right orchiectomy, and a well-circumscribed solid tumoral tissue with a diameter of 1.5 cm was excised. On histopathology, mixed type SCST, consisting of Leydig cell tumor in 99% of the area, and granulosa cell tumor in 1% of area, was present. No other tissue involvement, nor lymphovascular invasion, were detected (Figure 1).

Then, the patient was referred to our pediatric endocrinology out-patient clinic because of gynecomastia and hyperprolactinemia. On physical examination, height was 162.9 cm (3-10 p), weight was 49.5 kg (50-75 p), left testis was 10 mL, penis size was 7.5 cm (6.4 ± 1.1), and pubarche was Tanner stage 5. Severe gynecomastia with glandular tissue of about 6x6 cm in both breasts, and a labial residue in the penoscrotal region were detected (Figure 2). His mental development was normal, and he had no syndromic features. Laboratory results showed that while he was euthyroid, prolactin was 8.2 µg/L, total testosterone was 0.7 µg/L, estradiol was 19 ng/L, LH was 4.67 U/L and FSH was 3.78 U/L. Pituitary magnetic resonance imaging was normal. However, karyotype was 46,XX, and *SRY* was double-positive on fluorescent *in situ* hybridization analysis (Figure 3). Psychiatric evaluation found no gender dysphoria. Subsequently, a chemotherapy regimen consisting of ifosfamide, cisplatin and etoposide was initiated because of the diagnosis of stage 3 Leydig-cell tumor.

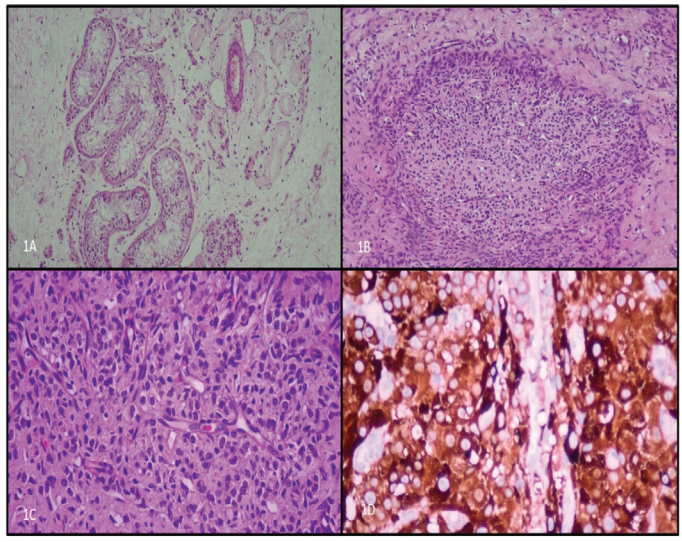

Figure 1. Histological findings of the testicular biopsy specimen. 1A) Testicular tissue containing Leydig cells and seminiferous tubules (hematoxylin-eosin stain x10). 1B) The tumor with nodular growth pattern in fibrotic stroma (hematoxylin-eosin stain x4). 1C) Tumoral tissue (hematoxylin-eosin stain x20). 1D) Strong positive immunohistochemical staining with inhibin in tumoral tissue (x10)

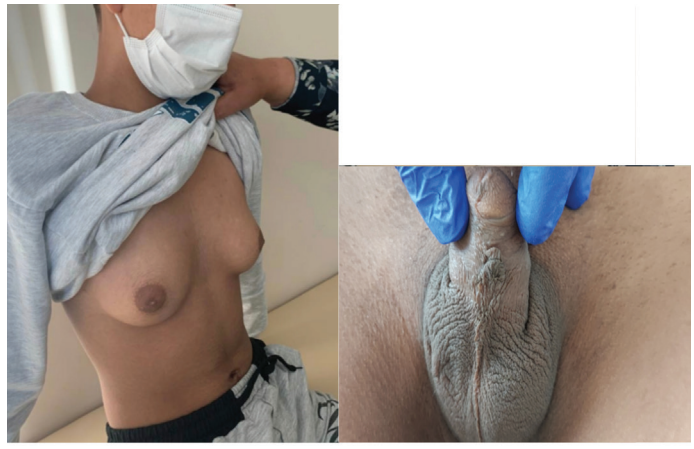

Figure 2. Bilateral gynecomastia and labial residue in penoscrotal region

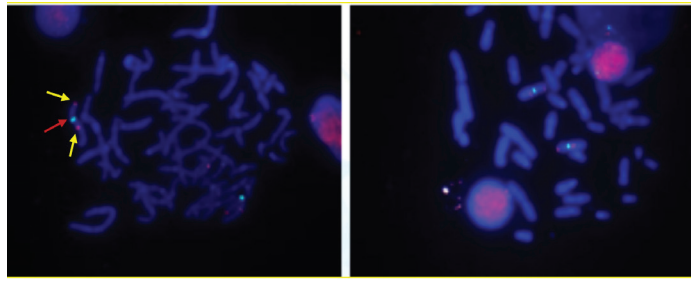

Figure 3. Fluorescent *in situ* hybridization analysis with double-positive SRY (DXZ1x2, DYZ1x0, SRYx2, [200]), in 46,XX karyotype (yellow arrow; SRY and red arrow; X chromosome)

At his last follow-up visit, at 17.6 years of age, the left testis was 5 mL and a glandular tissue of about 3x3 cm in both breasts was present. His blood test results showed euthyroidism, prolactin was 10.1 µg/L, total testosterone was 2.8 µg/L, estradiol was 24 ng/L, LH was 51.8 U/L, and FSH was 110.4 U/L. Subsequently, testosterone enanthate therapy (250 mg, im/monthly) has been initiated due to hypergonadotropic hypogonadism.

Discussion

There are at least three mechanisms for the etiology of 46,XX testicular DSD; occult mosaicism of Y chromosome only present in gonads, translocation of *SRY* gene to the X chromosome or autosomal chromosomes, or X-linked mutation/overexpression in the genes causing testis differentiation or mutation/overexpression in the autosomal genes (7). *SRY* gene at the distal end of the Y chromosome has an important role in male gender differentiation, and is effective in the differentiation of bipotential gonad towards testis. The task of this gene is to synthesize SRY protein that will ensure the formation of testicles. If the *SRY* gene does not synthesize SRY protein, ovary is formed instead of testis (8).

Ninety percent of cases with 46,XX testicular DSD are *SRY* positive. This condition is not usually hereditary, as it results from unbalanced Xp;Yp translocations during paternal meiosis resulting in the presence of *SRY* on the X chromosome. In contrast, *SRY* negative 46,XX testicular DSD originates from the rearrangements or changes in copy number in *SOX9* or *SOX3* genes, and specific heterozygous pathogenic variants in *NR5A1* or *WT1* (1,9).

Nearly, 85% of the individuals with 46,XX testicular DSD present with small testicles, gynecomastia and infertility due to azoospermia after puberty, and they usually have normal genital hair development and normal penile size. Only 15% of the cases present with ambiguous genitalia (9). While testosterone levels are normal at pubertal ages, it declines after puberty due to impaired synthesis. If untreated, osteopenia, low body muscle strength with high fat mass, decreased secondary sex characteristics, erectile dysfunction and impaired libido may occur.

The length of the translocated SRY has a role in variations in the secondary sex characters. If translocated Yp materials are smaller than 100 kb, genitalia is under masculinized due to X-inactivation into *SRY* or compromised *SRY* expression according to change in the *SRY* position relative to chromosomal environments (position effect). On the contrary, if large Yp materials are translocated onto Xp, *SRY* is protected from both the position effect and X-inactivation. Exceptionally, some patients are under masculinized under translocation of large Yp materials, or *vice versa* (10).

In the presented case, karyotype was 46,XX, SRY was double-positive, and he presented with gynecomastia, labial residue in the penoscrotal region, a small normal left testis (the right testis contained tumoral tissue) and low testosterone level for age, while his genital hair development and penile size were normal. The signals from the *SRY* region on each X chromosome indicate that there were two *SRY* genes. Therefore, we speculate that *SRY* double-positivity causes the presence of abundant Yp materials permitting near-normal male phenotype. In addition, because one X chromosome is inactivated, double *SRY* positivity has no dosage affect. Currently, in the literature, there is insufficient data to confidently understand the clinical effect of *SRY* double positivity (11).

In childhood and adolescence, SCSTs constitute approximately 5% of all testicular tumors and the remainder are germ-cell in origin (5). SCSTs originating from the supportive tissues of testis include Leydig, Sertoli and granulosa cell tumors, as well as malignant mesothelioma of tunica vaginalis (6). Among these, Leydig cell tumors are the most common testicular SCSTs, and usually present with painless testicular mass and/or precocious puberty due to excessive testosterone secretion. Although Leydig cell tumors are very rare, they develop at any age of life, but are usually seen between 5 to 10 years of age (12). Unlike in adults, Leydig cell tumors in prepubertal patients do not metastasize and can be treated with radical orchiectomy or testis-sparing surgery (13). Although Leydig cell tumors are generally benign in childhood, in the present case, radical orchiectomy was performed and a chemotherapy regimen has been initiated due to a risk of malignancy in 10% of adult male cases (14).

In ovotesticular or 45,X/46,XY DSD, there is an increased risk of germ cell tumors. Non-germ cell tumors are rarely seen. The first and only case having *SRY* positive 46,XX testicular DSD with Leydig cell tumor was reported by Osaka et al. (2) in 2020. The Leydig cell tumor was detected incidentally in a male patient during tests performed for infertility. This case was an adult patient having unilateral mass with a benign course (2). The presented case is important as he is the first pediatric case with a Leydig cell tumor having *SRY* double-positive, 46,XX testicular DSD.

Conclusion

In conclusion, we presented this first published case of 46,XX testicular DSD with double-positive *SRY*. This case is

even more unusual because it is the first case of 46,XX, *SRY* positive testicular DSD with a Leydig cell tumor.

Ethics

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Doğa Türkkahraman, Sultan Aydın, Merve Güllü, Tangül Pınarcı, Tarkan Kalkan, Concept: Doğa Türkkahraman, Sultan Aydın, Merve Güllü, Design: Doğa Türkkahraman, Sultan Aydın, Merve Güllü, Data Collection or Processing: Doğa Türkkahraman, Sultan Aydın, Merve Güllü, Analysis or Interpretation: Doğa Türkkahraman, Sultan Aydın, Merve Güllü, Tangül Pınarcı, Tarkan Kalkan, Literature Search: Doğa Türkkahraman, Sultan Aydın, Merve Güllü, Writing: Doğa Türkkahraman, Sultan Aydın, Merve Güllü.

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