

Case report

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

Merve GULLU¹, Sultan AYDIN², Tarkan KALKAN³, Tangül PINARCI⁴, Doğa TURKKAHRAMAN¹

¹Department of Pediatric Endocrinology, University of Health Science, Antalya Training and Research Hospital, Antalya, Turkey

²Department of Pediatric Hematology and Oncology, Antalya Training and Research Hospital, Antalya, Turkey

³Bio-Gen Genetic Diseases Evaluation Center, Antalya, Turkey

⁴Department of Pathology, Antalya Training and Research Hospital, Antalya, Turkey

What is already known on this topic?

Ninety percent of the cases with 46 XX testicular DSD are SRY positive but double positivity is rare. Up to now, 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 with Leydig cell tumor.

Abstract

Leydig cell tumors are the most common type of testicular sex cord stromal tumors. Presence of Y chromosome is associated with tumor risk in sex development disorder (DSD), however tumor development without Y chromosome are 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. In physical examination, left testis was 10 ml, and a labium residue in penoscrotal region with bilateral gynecomastia was present. Karyotype was 46,XX, and SRY was double-positive in FISH analysis. Ifosamide, carboplatin and etoposide chemotherapy was initiated due to Leydig cell tumor. Here, we report the first pediatric case having 46,XX, SRY double-positive testicular DSD with Leydig cell tumor.

Keywords: Testicular DSD, SRY, Leydig cell tumor

Prof. Dr. Doga Turkkahraman, University of Health Science, Antalya Training and Research Hospital, Department of Pediatric Endocrinology, Antalya, Turkey

drdoga@hotmail.com

0000-0002-7472-5712

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Introduction

Disorder of sex development (DSD) is defined as the incompatibility between chromosomal sex and phenotype, and seen in 1 in every 4500 births (1). 46, XX DSD is usually sporadic and classified into 3 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). 46, XX testicular DSD is characterized by a male phenotype despite 46, XX karyotype mainly due to SRY translocation, and first reported by de la Chapelle in 1964 (3). These patients are usually presented with gynecomastia, infertility and hypergonadotropic hypogonadism in post-pubertal period of life. The presence of Y chromosome in 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 are germ-cell origin (5). SCSTs originating from the supportive tissues of 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, SRY double-positive testicular DSD with Leydig cell tumor.

Case Report

A 16-year-old boy admitted to a urology out-patient clinic with a mass in the right testis. The right testis was >25 ml, left testis was 10 ml, and bilateral gynecomastia was present in his initial examination. Laboratory test results were as follows; prolactin: 51.8 µg/L (2.6-13), total testosterone: 0.79 µg/L (1.7-7.8), estradiol: 12 ng/L (<15), LH: 3.75 U/L (1.2-8.6), FSH: 5.54 U/L (1.2-19.2), α-fetoprotein (AFP): 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. In histopathology, mixed type sex cord stromal tumor (Leydig cell tumor in 99% of area, and granulosa cell tumor in 1% of area) were present. No over tissue nor lymphovascular invasion were detected (**Figure 1**).

Then, the patient was referred to our pediatric endocrinology out-patient clinic because of gynecomastia and hyperprolactinemia. In 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 a glandular tissue of about 6x6 cm in both breasts, and a labial residue in penoscrotal region were detected (**Figure 2**). His mental development was normal, and he has not any syndromic features. In laboratory, 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 MRI was normal. However, karyotype was 46, XX, and SRY was double-positive in FISH analysis (**Figure 3**). In psychiatric evaluation, there

was no gender dysphoria. Then, a chemotherapy regimen consisting of ifosfamide, cisplatin and etoposide was initiated with the diagnosis of stage 3 Leydig-cell tumor.

In his last control, at 17.6 years of age, left testis was 5 ml and a glandular tissue of about 3x3 cm in both breasts was present. In laboratory, he was euthyroid, 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. Then, 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; the secret mosaicism of Y chromosome only in gonads, translocation of *SRY* gene to X chromosome or autosomal chromosomes, and 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 effective in 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 the 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 X chromosome. On the other hand, 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 presents 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 translocated onto Xp, SRY is protected from position effect and X-inactivation. Exceptionally, some patients are under masculinized under translocation of large Yp materials, or vice versa (10).

In our case, karyotype was 46, XX, SRY was double-positive, and he presented with gynecomastia, labial residue in penoscrotal region, small testis (except right testis with tumoral tissue) and low testosterone level according to his age while his genital hair development and penile size were normal. The signals from SRY region on each X chromosomes indicate that there are 2 SRY genes. Therefore, we can speculate that *SRY* double-positivity causes the presence of abundant Yp materials permitting near-normal male phenotype. Additionally, because of the one of X chromosome is inactivated, double SRY positivity has no dosage affect. Currently, in the literature, there is insufficient data for 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 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 present usually 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, and usually seen between 5 to 10 years of age (12). Unlike adults, Leydig cell tumors do not metastasize in prepubertal patients 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 has been done, and a chemotherapy regimen has been initiated due to a risk of being malignant in some (10%) of the 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 seen rarely. The first and the single case having SRY positive 46, XX testicular DSD with Leydig cell tumor was reported by Osaka et al. in 2020. 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). Our patient is important as he is the first pediatric case with Leydig cell tumor having SRY positive 46, XX testicular DSD.

In conclusion, we presented our case since he is the first case of 46, XX testicular DSD with double-positive SRY. Our patient is also important as he is the first case of 46, XX, SRY positive testicular DSD with Leydig cell tumor.

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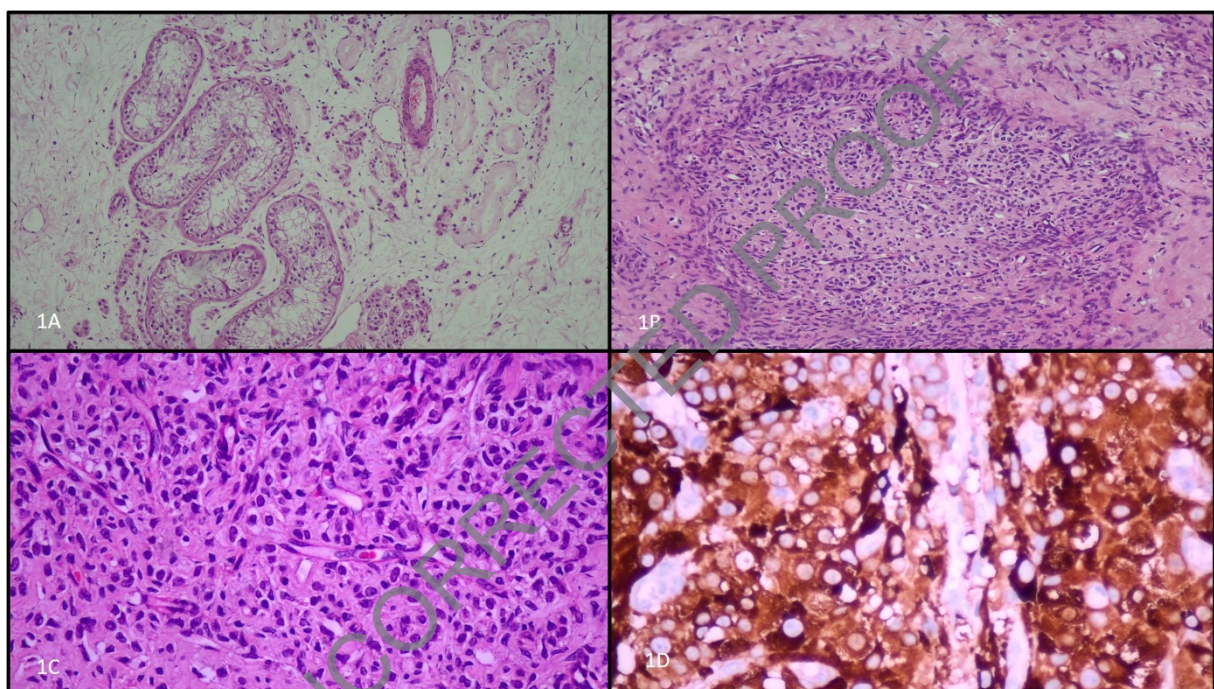


Figure 1. Histological findings of the testicular biopsy specimen. 1A; Testicular tissue containing Leydig cells and seminiferous tubules (hematoxylin-eosin stain x10). 1B; The tumor with nodular growth pattern in fibrotic stroma (hematoxylin-eosin stain x4). 1C; Tumoral tissue (hematoxylin-eosin stain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



Figure 2. Bilateral gynecomastia and labial residue in penoscrotal region.

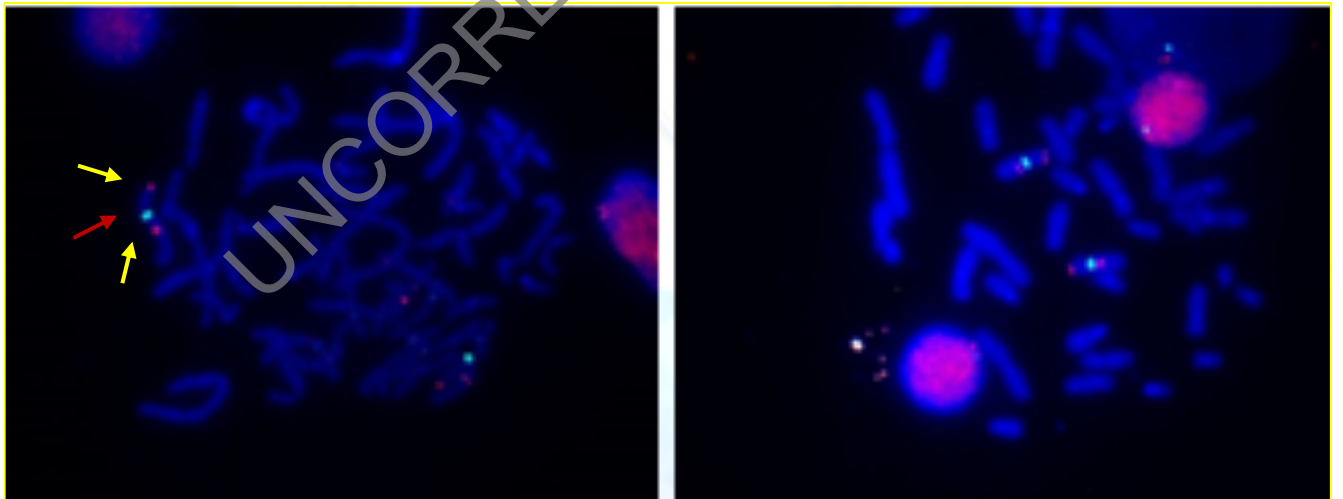


Figure 3. FISH analysis with double-positive SRY (DXZ1x2, DYZ1x0, SRYx2, [200]), in 46, XX karyotype (yellow arrow; SRY and red arrow; X chromosome).