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SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TÜRKİYE

Leydig Cell Tumor Mimicking Testicular Adrenal Rest Tumor in a Child with Congenital Adrenal Hyperplasia

CASE REPORT
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ABSTRACT

Leydig cell tumors (LCT) are usually unilateral and can seldom show malignant behavior. Testicular adrenal rest tumors (TART), which typically present bilaterally, are always benign and associated with congenital adrenal hyperplasia (CAH). Herein, along with a literature review, we aim to present a rare case of CAH associated with bilateral testicular masses, which led to difficulty in differential diagnosis between LCT and TART. An 8-year-old boy with 11β-hydroxylase deficiency was referred to an outpatient clinic because of bilateral testicular masses. From his medical history, it was ascertained that he was under hydrocortisone treatment for 4 years after his first surgical examination, followed by serial ultrasounds with a preliminary diagnosis of TART. However, testicular masses gradually enlarged during follow-up, and magnetic resonance imaging showed characteristic findings for LCT. The patient underwent bilateral testis-sparing surgery, and histopathological examination was reported as benign LCT. The patient has been doing well postoperatively for 6 months. Although emerging bilateral testicular masses in patients with CAH may suggest TART, they may rarely originate from LCT and cause delay in diagnosis or difficulties in differential diagnosis in cases that do not respond to hormonal replacement.

Keywords: Congenital adrenal hyperplasia, Leydig cell tumor, testicular adrenal rest tumor

Introduction

Testicular tumors account for 1%-2% of all pediatric tumors in children.[1] Generally, testicular masses are due to benign pathologies in the prepubertal age group and malignancies in postpubertal males. Management for benign masses is by testis-sparing surgery and by radical orchiectomy for malignant masses.[1]

Leydig cell tumors (LCT) are testicular tumors that are generally benign. Leydig cell tumors accounts for 4% and 1%-3% of testicular tumors in prepubertal children and adults, respectively.[2] In determining malignancy, the only definitive clinical indicator is the presence of distant metastases.[3] Congenital adrenal hyperplasia (CAH) is a group of inherited autosomal recessive disorders characterized by enzymatic deficiencies, which include 21 alpha-hydroxylase (90%-95%), 11 beta-hydroxylase (5%), and 17 alpha-hydroxylase (<1%) in the cortisol synthesis pathways.[4,5] Testicular adrenal rest tumor (TART) is a common complication of CAH in children and is considered an aberrant remnant of intra-testicular adrenal tissue.[5,6] Testicular adrenal rest tumor may occur in children with CAH as young as between the ages of 4 and 7.5 years, and approximately 80% of cases present as bilateral disease.[5] Although TART is a benign tumor, it can affect testosterone production and lead to infertility.[5,7]

To emphasize the importance of the differential diagnosis in CAH-associated testicular masses, we present an unusual case of CAH that was initially misdiagnosed and followed as TART and subsequently diagnosed as LCT, together with a literature review. Written informed consent wase obtained from the patient's parents who agreed to take part in the study.

Case Presentation

The first physical examination was performed when the patient was referred to a pediatric endocrinologist for virilization when he was 2 years old. Adrenocorticotropic hormone (ACTH), 17-OH progesterone, 11-deoxycortisol, and renin levels were 1090 pg/mL (0-46), 12.34 ng/mL (0.07-1.53), 3017 ng/dL (normal level <344), and 0.04 ng/mL/h (0.6-4.3 ng/mL/h), respectively. Total testosterone level was 1.42 ng/mL (2.41-8.27).

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The patient was diagnosed with CAH, and oral hormone replacement therapy with 10 mg/m^2/day hydrocortisone (HC) in 3 divided doses was initiated. After 1 year of treatment, the ACTH, 17-OH progesterone, and total testosterone returned to 20.3 pg/mL, 3.9 ng/mL, and 0.3 ng/mL, respectively. The aldosterone level (4.87 ng/dL) was also within the normal range (2-9 ng/dL). However, the 11-deoxycortisol level (585.7 ng/dL) was still high despite a significant decrease compared to the initial measurement.

In the second year of HC treatment, physical and ultrasound examinations of both testes were normal. To establish the molecular genetic diagnosis, molecular testing of CYP11B1 was performed by Sanger sequencing using a specific primer, confirming the diagnosis of 11βOHD due to CYP11B1 gene mutation [c.1120C>G (p.Arg374Gly) homozygous mutation in exon 6].

Routine testicular ultrasound revealed that the testes were small (right: 2.6 mL, left: 2.5 mL) and a hypoechoic/hypervascularized mass with microcalcifications was present on each side (right: 18 × 9 mm, left: 14 × 9 mm). Then, the patient was referred to the pediatric surgical department for bilateral testicular masses with a preliminary diagnosis of TART. On physical examination, both testes were normally palpable within the scrotum, with no palpable mass. Surgical intervention was not indicated, and conservative follow-up was planned.

After an additional 4 years of follow-up with HC treatment, at the age of 8, the patient re-consulted our department because of palpable bilateral testicular masses. Serial ultrasonographic evaluations performed during the follow-up period revealed a gradual increase in the size of both testes and intraparenchymal lesions. Magnetic resonance imaging (MRI) showed bilateral hypointense masses (right: 32 × 15 mm, left: 30 × 14 mm) with micro-calcifications in T2-weighted images concurrent with LCT. After obtaining written consent from the parents, the patient underwent bilateral inguinal exploration with an intraoperative frozen biopsy, which confirmed the masses as benign lesions on both sides. Bilateral testis-sparing tumor excision was performed (Figures 1 and 2). Histopathological examination revealed the presence of Reinke crystals and strong inhibin positivity (Figures 3 and 4). HC treatment was continued after surgery and has been followed up in our outpatient clinic for 6 months postoperatively without any complications.

Figure 1. Photograph of the excised right testicular mass.

Discussion

Testicular tumors account for 1%-2% of all childhood tumors.[1] The most crucial step in successfully managing testicular masses is choosing the proper surgical technique. There are few small series of LCT reported in the literature up to date. Testis-sparing surgery is an applicable approach for LCT. This study aims to review the literature on the management and outcomes of testis-sparing surgery in children with testicular mass.

In prepubertal age, a scrotal mass may be associated with LCT. However, other tumors or pseudo-tumor processes such as TART, granulosa cell tumors, and germ cell tumors have been reported.[8] According to the related literature, LCT accounts for 4% of prepubertal testis tumors and is mostly benign lesion. The most relevant tumor markers should be investigated preoperatively to evaluate

MAIN POINTS

- Testicular mass is a rare pathology in children; bilateral lesions are even rarer.
- In congenital adrenal hyperplasia (CAH) patients, testicular adrenal rest tumor (TART) is a common benign pathology and usually presents bilaterally.
- Due to the high incidence of TART in CAH patients with testicular mass, other rare diagnoses, such as Leydig cell tumors, can be overlooked, which may cause a delay in treatment.

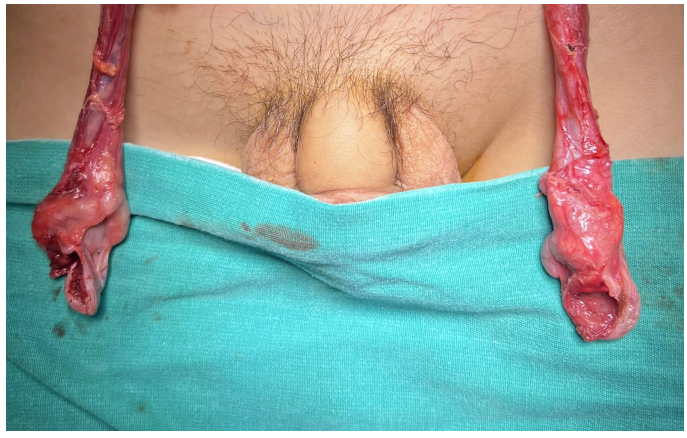

Figure 2. Intraoperative appearance of the right and left testes after performing bilateral testis-sparing surgery.

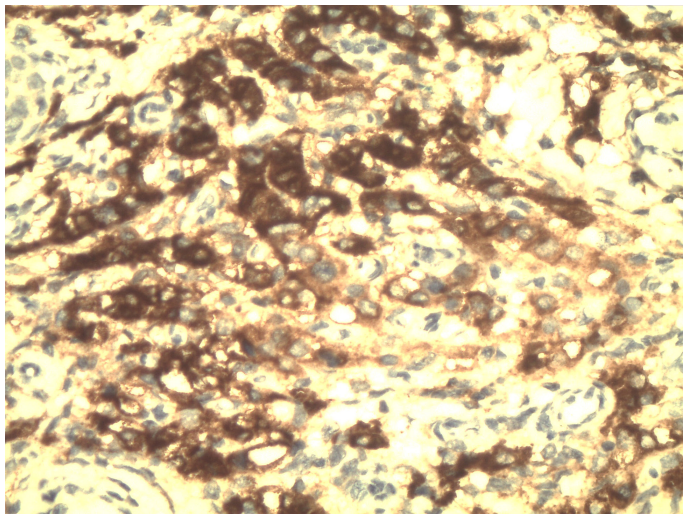

Figure 3. Photomicrograph shows strong inhibin positivity in brown color in the cytoplasm of tumor cells (inhibin ×400).

malignancy, such as alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-hCG).[2]

Testicular adrenal rest tumor, a known complication of CAH, is supposed to be derived from remnant adrenal cells that migrate to the testes during embryogenesis.[5,6] Testicular adrenal rest tumor is seen in 18% of patients with undiagnosed CAH and is commonly diagnosed in adolescents and adults.[6] Literature reports TART prevalence to be 40%-94% for male CAH patients.[5] Generally, TART has a bilateral presentation (more than 80%), while LCT rarely presents bilaterally (3%).[6] The most crucial step of a successful treatment is considering TART in the differential diagnosis of the testicular mass and planning an endocrinological evaluation. After diagnosis, TART can be managed with either a medical or a surgical approach.

Medical treatment may lead to the reduction of tumor size.[9] Therefore, the preferred treatment method of TART in patients with CAH is primarily glucocorticoid and mineralocorticoid therapy.[10] When the medical approach is ineffective in reducing tumor size, surgical treatment should be performed, preferably by a testis-sparing procedure.[9]

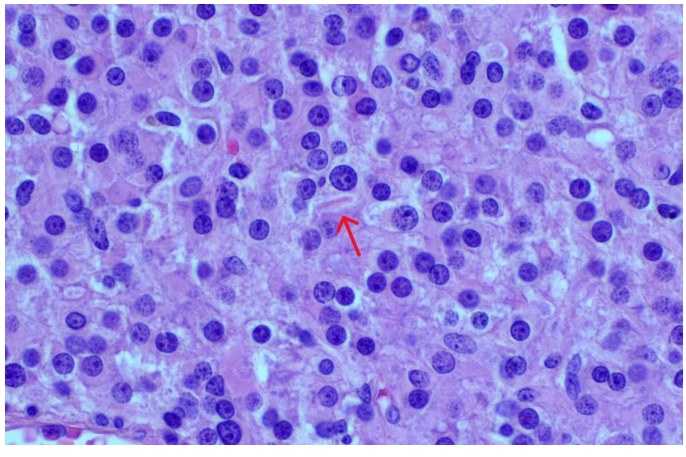

Figure 4. Photomicrograph shows a Reinke crystal marked with a red arrow between polygonal (Leydig) cells with abundant eosinophilic granular cytoplasm, uniform round nuclei, and prominent central nucleoli (HE ×200).

Radiological evaluation is the preferred method for diagnosis in nonpalpable testicular masses in asymptomatic prepubertal boys.[11] Lambropoulos et al[11] showed that the sensitivity and specificity of ultrasound for a testicular mass were 96% and 44%, respectively. Typical ultrasound findings for LCT are isolated hypoechoic lesions with peripheral hypervascularization in adults, but ultrasound signs are vague in children.[8] Characteristic signs of TART in ultrasound are (i) bilateral involvement (77%), (ii) hypoechogenic characteristics (90%-94%), (iii) rich vascularity (76%), and (iv) multilocular pattern which also differentiates TART from LCT.[4,8] Another imaging modality is MRI, which may clarify the diagnosis of testicular masses. Testicular adrenal rest tumor on MRI is isointense in T1 and hyperintense in T2-weighted images.[6] At the same time, LCT on MRI is hypointense in T2-weighted photos.[12] However, the high cost and the need for sedation are significant disadvantages in children.[11]

In this case report, the patient who presented with virilization was diagnosed with CAH and followed up for bilateral testicular masses. Ultrasound showed hypoechoic lesions with hypervascularization in bilateral testes, which supported TART. In serial clinical/ultrasonographic examinations, despite glucocorticoid therapy, the size of testicular tumors did not decrease. Magnetic resonance imaging showed bilateral testicular masses, which were isointense in T1 and hypointense in T2-weighted images as concordant with LCT. In addition, preoperative AFP and β-hCG levels were evaluated and found to be normal, which supported a benign tumoral growth. The patient underwent surgery, and a frozen biopsy confirmed benign lesions in both testes. A transinguinal testis-sparing surgery was performed bilaterally for the testicular masses. Testis-sparing surgery may allow for protection of fertility potential in such cases of CAH complicated with LCT. Even though there is a low risk for malignancy in LCT, testis-sparing surgery combined with frozen biopsy seems to be a reasonable intraoperative strategy to minimize subsequent malignant transformation.

Distinguishing LCT from TART is only sometimes easy from a histopathological perspective. The polygonal cells show positivity for certain immunohistochemical markers known to be shared between LCT and TART, such as inhibin, vimentin, and calretinin. In the presented case, histopathological diagnosis was established by identifying Leydig cells consisting of Reinke crystals, which are structures having an important function in both testosterone production and male reproduction.[13] Although Reinke crystals are pathognomonic for LCT, the crystals are found only in 25%-40% of the patients with LCT. A clinical picture unresponsive to suppressive medical therapy, MRI findings suggesting LCT, and the presence of Reinke crystals together with strong inhibin positivity establish the diagnosis of LCT, as the relevant literature indicate.[14]

This case report highlights the importance of evaluating CAH-associated testicular masses and considering differential diagnoses of these lesions. Due to the high incidence of TART in CAH patients, other rare diagnoses, such as LCT, can be overlooked, which may cause a delay in diagnosis and treatment.

Informed Consent: Written informed consent was obtained from the patient's parents who agreed to take part in the study.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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