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Case report

Leydig Cell Tumor in Children: a Case Report and Literature Review

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HIGHLIGHTS

- Leydig cell tumors (LCTs) are infrequent testicular tumors happening in 1%–3% of all testicular neoplasms.
- Pathological studies, especially Immunohistochemistry (IHC), play a great role in differentiating this tumor from other malignancies.
- Early diagnosis and treatment are necessary to avoid needless radical inguinal orchiectomy is crucial for Leydig cell tumors (LCTs) in children.

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Introduction

Leydig cell tumors (LCTs) are a member of the sex cord-stromal tumor group. It arises from Leydig cells and categorizes as one of the most common non-germ cell tumors (NGCTs) (1, 2). They presented at

ABSTRACT

Introduction

Leydig cell tumors (LCTs) comprising of 1 to 3 percent of testicular cancers in children, one of the single most common symptom in prepubertal patients is painless testicular swelling with or without a sign of precocious puberty. Other symptoms depend on age and the type of tumor. The tumor is usually asymptomatic if secretes androgens can cause precocious puberty in young children. If the tumor secretes estrogens, it can cause rarely gynecomastia in young boys.

Case presentation

Here we are reporting pure LCTs in a ten-year-old boy presented with gynecomastia. His height and weight were in the normal range. Differential diagnosis of large cell calcifying Sertoli cell or Leydig cell tumor, teratomas and revealed the normal size and echogenicity of both epididymis confirmed the Leydig cell tumor.

Conclusions

Due to the extremely variable clinical presentation tumor especially children and the importance of maintaining the fertility in this group and increased incidence of malignancy, especially in adolescence early detection and timely treatment are crucial.

Keywords: Gynecomastia; Precocious Puberty; Testicular Tumor

any age especially in children between 5 and 9 years with precocious pseudopuberty or gynecomastia, and men between 20 and 60 years (1, 2). The main clinical presentation includes unilateral testicular mass in 90%, Isosexual precocious pseudopuberty, a gynecomastia in

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20%, and elevated levels of 17-ketosteroid (3). Radical inguinal orchiectomy is considered as a classical treatment, but young children with tumors tend to follow a benign course due to maintenance of fertility testis-sparing surgery by tumor enucleation suggested as the treatment of choice (4, 5).

Case presentation

The patient is a 10-year old boy who was admitted to the out-patient clinic with a history of left painful scrotum since last month. After signing the informed consent by his parents agreed to report the case and reporting of his case is based on CARE guidelines. Physical examination revealed a testicular asymmetry and trans-illumination test showed a dark shadow in the left testis and gynecomastia but no sign of precocious puberty (Figure 1). Penis size was 2.5cm, and with severe meatus stenosis, pubic and both axillary sites were hairless. First testicular Doppler ultrasound of the bilateral testis identified; left testis with 22×12mm size containing a hypoechoic space-occupying lesion with the size of 8.7×8mm with multiple calcifications, and right side of 19×11mm. The volume of the left and right testicles was 22ml and 19ml respectively. His height and weight were in the normal range of 50th percentage for sex and age. Laboratory evaluation for teratomas tumour markers revealed alpha-fetoprotein (AFP)<2.0 IU /mL with the references of <7.25, and human chorionic gonadotropin (HCG) titration <0.1IU/ mL with the references of up to 2.6 (ECL, Roche).

The patient was under observation for two weeks, then the second testicular color Doppler ultrasonography

(CDUS) of both testes showed right testis with 20×9mm size with normal echogenicity and left testis with the size of 21×10mm which is contained with a well-defined and hypoechoic mass with the size of 8.5×7mm and has internal coarse areas of calcification. This suggested a differential diagnosis of large cell calcifying Sertoli cell or Leydig cell tumor, teratomas and revealed the normal size and echogenicity of both epididymides, no hydroceles in both scrota, and with the normal parenchymal vascularity. The result of the hormonal assessment is shown in (Table 1) and all of them were in the normal range before the operation, after 2 weeks of workup, a left-testis-sparing surgery was performed.



Figure 1. A 10-year-old boy with left testicular swelling and gynecomastia

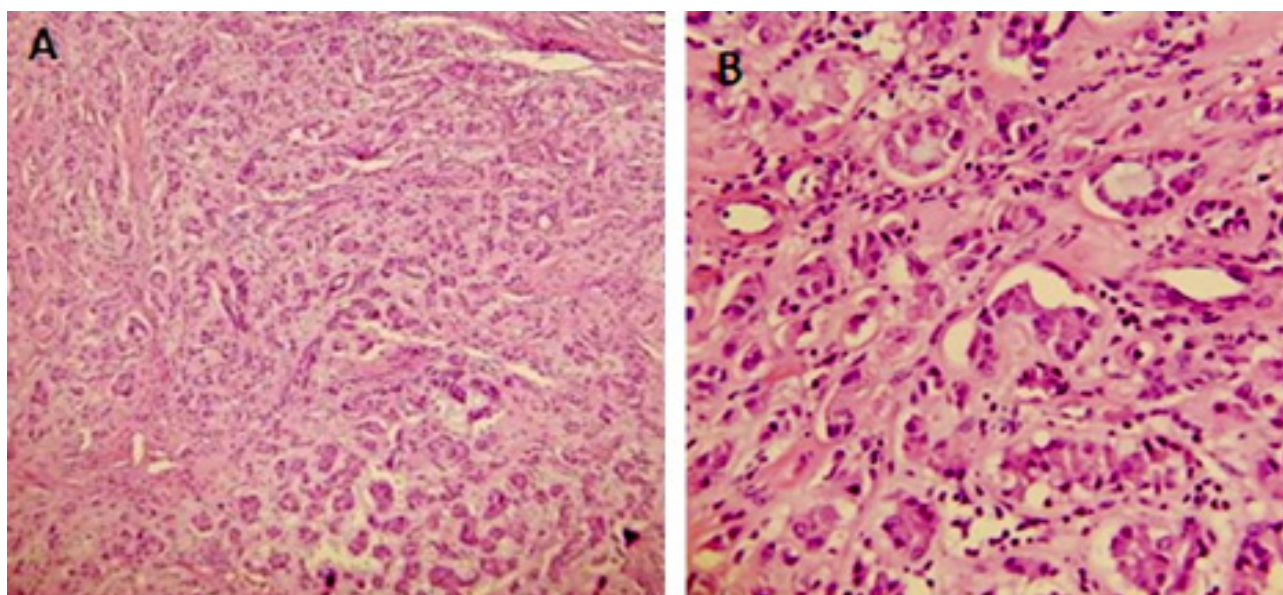


Figure 2. A: Hematoxylin and eosin staining (H&E-4X) in which tumor cells with abundant eosinophilic cytoplasm. B: Neoplastic cell with well-distinguished cell border (H&E-40X)

Initial histologic reports revealed a 1-centimeter mass compatible with Leydig cell tumor with foci of calcification, neoplastic cells with eosinophilic cytoplasm, and large cell calcifying Sertoli cell tumor in its deferential diagnosis but according to immunohistochemistry (IHC) stain, tumoural cells express (inhibin, vimentin, calretinin, and melan-A), and negative for s100 and AFP, and the final diagnosis of Leydig cell tumor was confirmed (Figure 2). Several testing like surgical pathology, immunohistochemistry (IHC), post-operative abdominal, and pelvic Computed Tomography (CT) was performed, which indicated to the negative retroperitoneal adenopathy, small and large bowel and urinary bladder were unremarkable. The result of the hormonal evaluation was performed and shown in Table 1.

Discussion

Leydig cells as interstitial cells that are found between seminiferous tubules. They are responsible for secondary sexual characteristics and the maintenance of spermatogenesis by producing testosterone (6). These tumors are the most common sex cord-stromal tumor but rare in children, they occur especially in boys aged 5 to 10 years (peak incidence around age 5 yrs) in 20 % and adult between the age of 20 to 60 (average 47 yrs) and account for 1 to 3% of all testicular tumors (7). Most of these tumors have benign behavior during this

period and are mostly characterized by the secretion of androgen and sometimes estrogen (8). If it is secreting androgens, the tumor is usually asymptomatic but can cause precocious puberty in pre-pubertal boys. If the tumor secretes estrogens it can cause feminization in young boys. In adults, this causes several problems including gynecomastia, erectile dysfunction, infertility, genital atrophy, and a loss of libido (9) There are not proven reports about malignancy transformation of these tumors in children whereas in up to 10% of cases of adults these tumors appear as become malignant variant (10). Due to high testosterone levels, most children present with signs of precocious puberty such as gynecomastia (11). Besides, our case was referred to the clinic with a palpable mass in the left testicle and gynecomastia, However, his hormonal assessment revealed normal levels of androgen, estradiol, and no evidence of other signs of precocious puberty, such as early development of axillary and pubic hair, penile growth, and accelerated musculoskeletal development, was not seen which could be inferred different presentation of pediatric age LTCs versus adult ones. In all patients with testicular mass and gynecomastia other causes such as teratoma, Granulosa cell, and Sertoli tumors should be considered (12). Changes in tumor size (>5centimeters), tumor hemorrhage, and tumor necrosis may suggest malignant changes especially 5 to 10 percent of prepubertal and

Table 1. Result of serology testing targeted hormonal assessment

| Test | Result | Normal range |
|---------------------------|--------------|--------------------------|
| Beta-hCG | < 0.1 mIU/mL | Up to 2.0 |
| ESTRADIOL (CLIA) | <10pg/mL | (1-10 years); boy<10-27 |
| FSH (CLIA) | 0.9mIU/mL | (6-10 years); 0.1-1.9 |
| LH(CLIA) | 0.1mIU/mL | (6-10 years) ; 0.1-0.4 |
| Free Testosterone (CLIA) | 1.3pg/mL | (<11 years); 0.2-0.9 |
| Testosterone (ECLIA) | 0.040µg/mL | (7-12 years); 0.03-0.68 |
| DHEA Sulfate (CLIA) | 242.4µg/mL | (5-10 years); 24.4-209.7 |
| Cortisol. Morning (CLIA) | 11.7µg/dL | (2- 16 years); 3.0-21 |
| ACTH (CLIA) | 22.8mg/mL | up to 46.0 |
| 17 OH Progesterone (CLIA) | 1.60mg/mL | 0.32—1.97 |
| TSH (CLIA) | 3.1mU /L | 0.55-5.31Mu/L |

Beta-hCG: Beta human Chorionic Gonadotropin; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; DHEA: Dehydroepiandrosterone; ACTH: Adrenocorticotropic Hormone; TSH: Thyroid Stimulating Hormone

adults between the ages of 30 and 60 (8). The common microscopic pathology is characterized by medium to large polygonal cells with round to oval nuclei and prominent nucleoli with rich eosinophilic cytoplasm separated by fibrovascular septa and resembling normal Leydig cells and in 30 to 40 % of cases pale-staining, plump rod-shaped or rhomboid structures in the cytoplasm intranuclear structures (Reinke crystals) can be seen. (13, 14) Immunohistochemistry (IHC) staining shows positivity for inhibin, calretinin, vimentin, and Melan-A and negativity for S100, AFP, and EMA and our IHC stain showed the cells of tumor positive for (inhibin, vimentin, calretinin, and melan-A) but negative for s100 and AFP (8, 15, 16).

Testis-sparing as tumor enucleation seems to be a rationale for LCTs with benign behavior (the mass is less than 2.5 cm and the tumor markers are normal before surgery) and negative intraoperative frozen section for malignancy is mandatory (4) and in children to keep the fertility can be the method of choice and observation is sufficient for this group in long term monitoring. Radical inguinal orchidectomy is known as a classical treatment especially in malignant cases, and it can be accompanied by retroperitoneal lymphadenectomy (RPLND) in metastatic cases, these LCTs rarely respond to chemoradiotherapy (11, 17).

Due to the possibility of Tumor recurrence in the malignant group during the first two years after surgery, so patient monitoring at regular intervals needed. These monitoring should include precise clinical exam, check hormonal profile (luteinizing hormone [LH], follicle-stimulating hormone [FSH], testosterone, estrogen, and estradiol), tumor markers (beta-HCG, LDH, AFP) and follow up imaging (chest and abdominal computed tomography scan) at 4 months during the first year, followed by similar imaging two-yearly during the second year and yearly examinations thereafter (18). Metastases most frequently occur in the retroperitoneal lymph nodes, liver (45%), lung (40%), and bone (25%) (19).

Conclusions

Due to the extremely variable clinical presentation tumor especially children and the importance of maintaining the fertility in this group and increased incidence of malignancy, especially in adolescence early detection and timely treatment are crucial, a testicular ultrasound should be done as an extension of the physical exam for any children with Painless swelling, sudden hydrocele or any symptoms related to the scrotum of the unknown cause even in the absence of signs of precocious puberty and referred all these patients to a pediatric urologist for further work-up.

Authors' contributions

All authors contributed equally. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

All authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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Ethical statement

This manuscript is based on the CARE guidelines and informed consent was signed by the case's parent in this study.

Data availability

Data will be provided by the corresponding author on request.

Abbreviations

| | |
|----------|---|
| ACTH | Adrenocorticotrophic hormone |
| Beta-hCG | Beta human chorionic gonadotropin |
| CLIA | Chemiluminescence immunoassay |
| DHEA | Dehydroepiandrosterone |
| ECLIA | Electrochemiluminescence immunoassay Analyzer |
| ECL | Electro chemi luminescence |
| FSH | Follicle stimulating hormone |
| LH | Luteinizing Hormone |
| TSH | Thyroid Stimulating Hormone |

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