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Hormonally active Leydig cell tumor treated by partial orchiectomy: A case report and review of the literature

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Abstract

A 6-year-old boy was referred to our hospital due to early appearance of pubic hair, face comedones and behavior changes. Testosterone levels, higher for the age, were found in the serum. The ultrasound scan established sharply delineated hypoechoic tumor in the left testicle. Partial orchiectomy, excising the tumor in healthy borders, and preserving the testicle, was performed. The histological and immunohistochemical examinations revealed benign Leydig cell tumor. One year after surgery, the testosterone values and the bone age of the child corresponded to his actual age.

Keywords

isosexual pseudoprecocious puberty; pubarche; testicle; Leydig cell tumor; partial orchiectomy

Introduction

Testicular tumors are rare in children, comprising up to 1% of all neoplasms [1]. Among them, Leydig Cell Tumors (LCTs) are even rarer 1–3% of all testicular neoplasms [2]. These tumors are most commonly met in prepubertal boys, but they can occur at any age. While benign in children, around 10% of LCTs in adults exhibit exclusively aggressive malignant behavior and are characterized by poor outcome [3].

We present a rare case of hormonally active LCT that was successfully treated by testicle-sparing surgery.

Case Presentation

A 6-year-old boy presented to our pediatricians because of the appearance of pubic hear, comedones and skin greasiness around the nose, first noticed by his mother 6 months ago. The mother reported behavior changes of her child, who became extraordinarily emotional and nervous.

At physical examination the boy looked more mature compared to his chronological age. The current weight of the patient was 26.8 kg; height was 131 cm; body mass index 15.8 kg/m^2. His reconstructed growth curve showed that height until 1 year of age was between 75th and 90th persentile. Height at presentation was above 97th persentile, out of the estimated target height range (20th- 90th

persentile). The bone age corresponded to 11-year-old boy.

The skin was well hydrated, with preserved turgor and elasticity, without rashes, but with comedones on the face (nose). The subcutaneous fat tissue was normally expressed, adequately distributed. Pubertal stage evaluation according to the Tanner staging system showed pubarche of II stage and axilarche I stage (Figure 1). Both testicles were in the scrotum; the left testicle volume was around 6 ml; right testicle - around 4 ml.

All routine **laboratory examinations** were within normal ranges.

Hormonal tests were as follows: 17-OH-progesterone 0.92 nmol/ml (r.r. 0.2–1.2); 4-androstendion 5.5 ng/ml (r.r. 0.57-2.63); luteinizing hormone (LH) <0.1mIU/ml (r.r. men 8.4-28.7, children <0.1); follicle-stimulating hormone (FSH) 0.250 mIU/ml (r.r. men 0.7-11.1, children <0.1); testosterone 4.75 nmol/l (r.r. men 8.4-28.7, children <0.7); dihydroepiandrosterone sulphate (DHEA-S) 1.42 μmol/l (r.r. 2.17-15.2).

All these features were consistent with isolated (peripheral, partial) isosexual premature puberty. An attempt to find the source of testosterone was made.

Tumor markers: alpha-fetoprotein (AFP) 2.53 ng/ml (normal <6 ng/ml); beta human chorionic gonadotropin hormone (β-hCG) < 0.01 mIU/ml (normal <0.01).

Abdominal ultrasound (US): Normal US image of all abdominal structures.

Testicular US: Right testicle – normal appearance. Left testicle – a central hypoechoic zone was found, 11.4/7.4 mm in size. The zone was homogeneous, with small calcifications and scarce vascularization, sharply delineated from the surrounding testicular parenchyma (Figure 2).

MRI of brain and pituitary: Normal MRI image.

After urological consultation, the child was referred to the Urological Clinic for surgical treatment. The latter one was approved by the Institutional Review Board. All risks, benefits and therapeutic alternatives were discussed with the parents, and their written informed consent was obtained prior to surgery.

Surgical technique: Under general anesthesia, left inguinal incision was done. The testicle was explored in the surgical field. After opening of *tunica vaginalis* a round tumor mass (≈1/1 cm in size), occupying the lower pole of the testicle, was found. The cordon was temporarily clamped by vascular tourniquet and a partial orchiectomy was performed, with tumor excision in healthy borders (Figure 3). Biopsies were taken from the tumor bed, immediately sent for frozen section analysis (FSA). The results showed normal infantile testicular parenchyma, no spermatogenesis, no Leydig cell hyperplasia, and no evidence of malignancy. *Tunica albuginea* was closed by a running 6-0 polydioxanone suture. The hydatid of Morgagni was excised, and the testicle was returned into the scrotum.

Macroscopically, the tumor was well capsulated, 12/15/10 mm in size, with yellow brownish colored cut surface. **Microscopically,** well demarcated tumor mass, surrounded by tender fibrotic capsule, comprised of large polygonal cells with abundant eosinophilic cytoplasm and clearly distinguished cell boundaries, was visualized (Figure 4). The nuclei were round, centrally located, relatively monomorphic,

with prominent nucleoli. There were also single binuclear cells. The cells exhibited weak mitotic activity – 1 mitosis per 10 fields on HPF. The stroma was scarce, well vascularized, without desmoplastic or stromal reaction. There were no signs of infiltrative growth. Also no vasoinvasion and no necrotic areas were detected. **Immunohistochemical expression**: Calretinin (prominent); Chromogranin (negative); Synaptophysin (negative); epithelial membrane antigen (EMA) (negative); Ki-67 (≈10% expression).

The postoperative period passed uneventfully and the boy was discharged home on the 3rd day.

Follow-up: One year later, the child was re-admitted at the First Pediatric Clinic for checkup examinations. He was in good condition, and his appearance was much closer to the chronological age. There was no further development of the pubertal signs, and testicle volume was decreased bilaterally back to 3 ml. His height velocity was decreased, and height was not further accelerated (139 cm, 36.7 kg, BMI 19.0 kg/m^2). The hormonal tests were the following: LH <0.1 mIU/ml (r.r. men 8.4-28.7, children <0.1); FSH 0.665 mIU/ml (r.r. men 0.7-11.1, children <0.1); Testosterone <0.7 nmol/l (r.r. men 8.4-28.7, children <0.7). The testicular US examination showed normal shape and size of both testicles.

Discussion

Leydig cell tumors (LCTs) derive from the interstitial Leydig cells, bearing the name of the German anatomist Franz von Leydig who described them first [4]. Little is known about the epidemiology, histogenesis, and possible etiology of these tumors. Most LCTs in children are functionally active, producing high levels of testosterone and low levels of gonadotropins, which give the clinical manifestation of isosexual pseudoprecocious puberty (IPP). hCG, AFP, and lactatedehydrogenase (LDH) are typically normal,but elevated testosterone or estrogen are often observed [3]. Therefore, beside the standard tumor markers, LH, FSH, and testosterone should be analyzed, as well. If inconclusive, estrogen, estradiol, progesterone, and cortisol levels may be helpful.

Benign LCTs are small (<5 cm), sharply delineated solid testicular masses. Tumor cells are arranged in nests and sheets, separated by fibrovascular septa. They are polygonal in shape with abundant cytoplasm and variably prominent nuclei. Other cytological variations are small cells with grooved nuclei and scanty eosinophilic cytoplasm and sarcomatoid cells. Mitoses are rare and nuclear atypia is absent or minimal. Immunohistochemistry, evaluating the expression of vimentin, inhibin, calretinin, and Melan-A can aid the histological diagnosis.

Malignant LCTs are large (>5 cm), occupying the entire testicle, with infiltrative margins, hemorrhage, and necrosis. Their characteristic morphological features are cellular anaplasia, frequent mitoses with atypical mitotic figures, lymphovascular invasion, necrosis, and extratesticular extension. DNA aneuploidy, and increased expression of proliferative markers are seen [5]. Malignant LCTs rapidly lead to metastatic tumor spread to the lymph nodes, lung, bones, and kidney. They are generally treated by orchiectomy with retroperitoneal lymphadenectomy. Interestingly, tumor excision is not always associated with resolution of symptoms and the abnormal laboratory values. Besides, malignant LCTs do not respond to chemotherapy and irradiation [6].

Providing that any testicular mass should be considered malignant until proved otherwise, radical orchiectomy has been the advocated standard treatment in LCTs [7]. Given the in general benign nature of LCTs in pediatric patients, however, some authors recommend conservative, organ-sparing

approach [8-10]. The benefits to testicle-sparing surgery include improving the patient's overall quality of life (QoL), fertility, physiologic endocrine function and negative cosmetic effects of radical orchiectomy.

Partial orchiectomy, providing clear surgical margins, was the treatment chosen in the present case, as well. Both surgery, and the postoperative period ran smoothly, without any complications. The 1-year follow-up confirmed the complete recovery of the testicular morphology and endocrine function with normalization of sex hormones and patient's QoL.

Conclusion

This case indicates that organ-sparing FSA-guided approach for LCTs in children is a safe and feasible mode of treatment. It is presented herein due to its rarity, the typical clinical manifestation of isosexual partial (peripheral) puberty as a first clinical sign of LCT, and to highlight tumor's benign nature, which allowed an organ-sparing surgical approach to be successfully used.

Figures

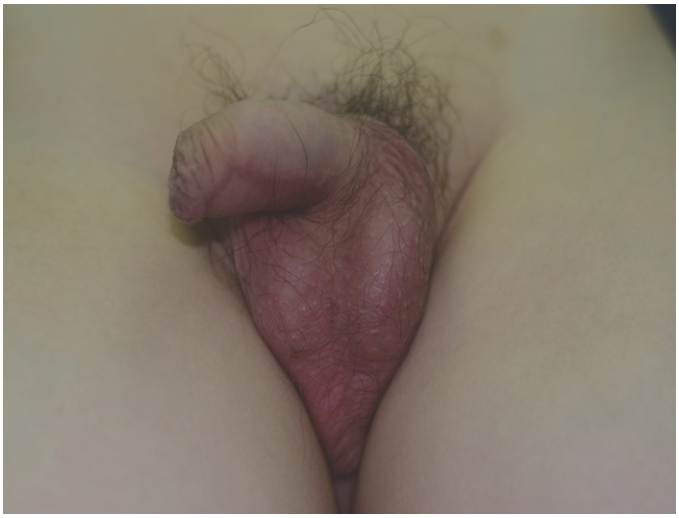

Figure 1: Secondary sexual signs (pubic hair) in a 6-year-old boy with Leydig cell tumor of the left testicle.

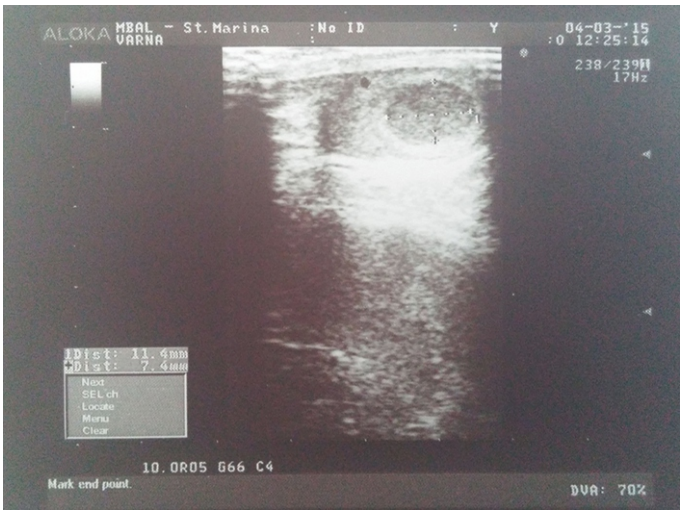

Figure 2: Ultrasound scan of the left testicle – a sharply delineated, oval, hypoechoic zone (a Leydig cell tumor) is clearly visualized.

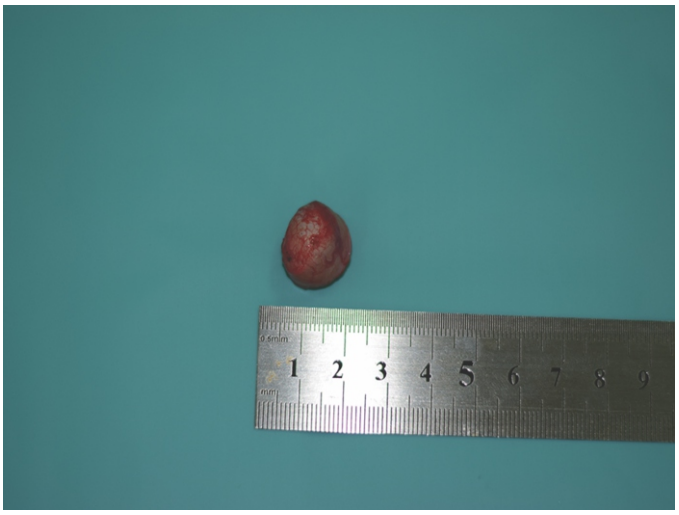

Figure 3: Macroscopic appearance of the excised Leydig cell tumor.

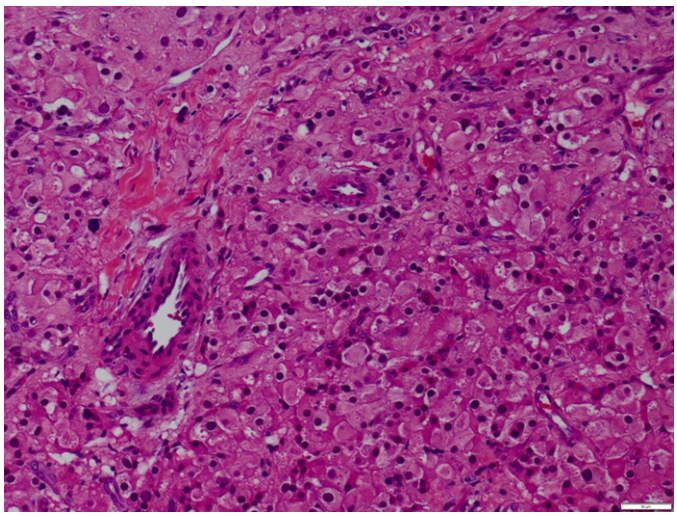

Figure 4: Histological result, demonstrating polygonal cells with round nuclei and abundant eosinophilic cytoplasm (H & E, ×100).

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