LEYDIG CELL TUMOR OF THE TESTIS; A RARE CAUSE OF FEMINIZATION (GYNECOMASTIA) IN A BOY

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ABSTRACT

Leydig cell tumors (LCT) are rare in childhood and account for 1-3% of all testicular tumors and 3-6% of testicular masses. Presentation can include endocrinological manifestation e.g. pubarche or precocious puberty; rarely, gynecomastia. We report a 7-year-old boy who presented with a right testicular mass with an 8-month history of breast enlargement, pubic hair and accelerated growth. Physical examination revealed a tall boy (height: 146.4 cm, +5.5 SD), with bilateral breast enlargement (Tanner 3-4) and a firm enlarged right testis, pubarche (Tanner 2) and a stretched penile length of 9 cm. Scrotal ultrasound revealed an enlarged right testis measuring 3.5 x 2.2 cm with an ill-defined heterogeneous lesion with dense calcifications measuring 2.5 x 1.5 cm. Serum estradiol and testosterone were elevated, with prepubertal levels of gonadotropins. He underwent a right radical orchiectomy and histopathology revealed a benign Leydig cell tumor. Post operatively, serum estradiol and testosterone levels declined.

Keywords: Leydig cell tumor, Gynecomastia, Testicular mass, Virilization

INTRODUCTION

Testicular tumors make up 1.5% of childhood solid tumors and they include germ cell, Sertoli cell and Leydig cell tumors. Leydig cell tumors (LCT) are rare in childhood and account for 1-3% of all testicular tumors and 3-6% of testicular masses. LCT’s are usually unilateral; however, in about 3% of cases they can be bilateral. They are usually benign in nature, especially in childhood; still, 10% can be malignant. There are two peak periods of incidence, the first occurring between 5-10 years and the second between 25-35 years (Al-Agha & Axiotis, 2007; Mati et al., 2002; Muheilan et al., 2017; Farkas et al., 2000; Sternberg et al., 1999; Ciftci et al., 2001; Gheorghisan-Galateanu, 2014). The clinical presentation can vary between simply presenting with testicular mass and endocrinological manifestations, which can include degrees of virilization or feminization (gynecomastia); this depends on the levels and nature of the hormones produced by the LCT (Tazi et al., 2008; Mukhopadhyay et al., 2017; Markou et al., 2002). Here in, we report a 7-year-old boy with a benign LCT who presented with a right testicular mass, in addition to virilizing and feminizing endocrinological manifestations.
CASE PRESENTATION

A 7-year-old boy was referred to the urological pediatric clinic for the evaluation of a right testicular mass noticed after trauma two weeks before referral. The mass was firm and mildly painful. The parents noted bilateral breast enlargement for the past 8 months that was rapidly progressive. It was not painful and not associated with nipple discharge. Penile length has also increased, especially in the two months prior to presentation. It was associated with early morning erections but no discharge. Pubic hair growth and deepening of the voice was also noted. Systemic review was unremarkable, including no symptoms or signs suggestive of increased intracranial pressure. He was not on any medication and the family denied ingestion of testosterone or estrogen containing medications. Perinatal history was unremarkable with no history of surgery or head trauma. There were no similar cases in the family and both parents had normally timed puberty.

Physical examination showed a tall child with a height of 146.4cm (5.5 SD above the mean), which corresponds to the height of child who is around 11 years old. He was not dysmorphic and had no cushingoid features. There was no facial, axillary hair or acne. He had bilateral breast enlargement (tanner 3-4) which was, symmetrical, soft, and non-tender, with no palpable masses or discharge (Figure 1). His abdomen was soft and lax, not tender with no organomegaly or palpable masses. Genital examination revealed a firm right testis, measuring 7 ml, mildly tender (Figure 2), with normal overlying skin. Left testis was normal in consistency, measuring 4ml. Pubic hair was thick but scanty (tanner 2) with a stretched penile length was 9cm. There were no palpable lymph nodes and no skin hyperpigmentation.

FIGURE 1
PHOTOGRAPHS OF THE CHEST REGION, FRONTAL VIEW (A) AND SIDE VIEW (B), SHOWING BILATERAL BREAST ENLARGEMENT (TANNER STAGE 3-4).

Initial laboratory investigations revealed high estradiol 341.7 pmol/L, testosterone of 4.73 nmol/L, luteinizing hormone (LH) <0.07 IU/L and follicle stimulating hormone (FSH) <0.3 IU/L. Gonadotropic releasing hormone stimulation(GnRH) test following a standard protocol Carel et al., 2007 showed a prepubertal gonadotropin, in accordance with peripheral precocious puberty (Table1). Adrenocorticotropic hormone (ACTH) 5 pmol/L, early morning cortisol level of 106.6 nmol/L, dehydroepiandrosterone (DHEAS) 2.28 umol/L, beta human chorionic gonadotropin (β HCG) <2 IU/L, Alpha fetoprotein (AFP) 2.9 KIU/L.
Complete blood count, renal and liver function were normal. Thyroid function tests were normal.

![Figure 2](image1)

**FIGURE 2**
**PHOTOGRAPH OF THE GENITALIA, SHOWING ENLARGED RIGHT TESTIS (ARROW).**

![Ultrasound Images](image2)

**TABLE 1**
**GNRH STIMULATION TEST**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 mins</th>
<th>60 mins</th>
<th>90 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (IU/L)</td>
<td>&lt;0.07</td>
<td>0.14</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>&lt;0.3</td>
<td>0.06</td>
<td>0.08</td>
<td>0.11</td>
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Scrotal ultrasound (Figure 3) revealed an enlarged right testis measuring 3.5 x 2.2 cm with an ill-defined heterogenous lesion with dense calcifications measuring 2.5 x 1.5 cm. The left testis unremarkable. The ultrasound also showed nonspecific pre-aortic/ mesenteric lymph nodes, largest measuring 0.5cm. Bone age was advanced consistent with an age of 13.5 years. CT scan with IV contrast of chest, abdomen and pelvis showed multiple prominent para-aortic lymph nodes, the largest measures 1.1 cm. There was mild hepatomegaly with minimal nonspecific peri portal edema. No focal hepatic lesions were seen. The spleen, pancreas, adrenal glands, kidneys and small and large bowel appeared unremarkable. No bony lesions were seen.
FIGURE 3
SCROTAL ULTRASOUND OF THE PATIENT WITH RIGHT SIED LEYDIG CELL TUMOR SHOWING AN ENLARGEMENT RIGHT TESTIS MEASURING 3.5*2.2CM WITH AN ILL-DEFINED HETEROGENOUS LESION WITH A DENSE CALCIFICATION MEASURING 1.5*2.5CM WITHIN THE TESTICULAR PARENCHYMA.

The child underwent a right-sided radical orchiectomy. The right testis was mobile and not attached to skin or surrounding structures. No para-testicular or cord masses were found. The surgical removed tissue showed a testis 3 x 2 x 1.7 cm; testicular parenchyma was completely replaced by a mass with yellow tan, homogenous cut surface (3.0 x 2.0 x 1.7 cm) with calcification. The mass was limited to the rete testis and epididymis. The spermatic cord was unremarkable. No areas of hemorrhage or necrosis were seen. No lymph nodes were involved. Histopathology (Figure 4) showed testicular tissue infiltrated by polygonal large cells with abundant eosinophilic cytoplasm, distinct cell border, vesicular nuclei and prominent nucleoli. The tumor cells were in a diffuse and insular pattern with large areas of calcifications and focal ossification. Occasional mitoses were identified; however, no necrosis or lymph-vascular invasion was identified. The tumor cells are positive for Calretinin, Inhibin, and CD99 (Membranous), while negative for Melanin A, chromogranin, synaptophysin and EMA. KI-67 proliferative index is expressed in less than 5% of tumor cells. A diagnosis of a benign Leydig cell tumor with peripheral precocious puberty was made.

FIGURE 4
HISTOPATHOLOGY OF THE PATIENT WITH LEYDIG CELLS TUMOR OF THE TESTIS (HEMATOXYLIN & EOSIN)

Post operatively, serum estradiol level declined to <43.6 pmol/L and testosterone level declined to <0.35 nmol/L. Almost 3 months after orchiectomy, he showed no further progression of his symptoms or growth. In fact, the gynecomastia decreased; the right breast was now tanner 2 and the left was tanner 3. The left testis measured 4ml and pubarche was static at tanner 2. Further follow-ups with the pediatric urologist, pediatric oncologist and pediatric endocrinologist were planned.
DISCUSSION

Testicular tumors make up 1.5% of childhood solid tumors and they include germ cell, Sertoli cell and Leydig cell tumors. Leydig cell tumors (LCT) are rare in childhood and account for 1-3% of all testicular tumors and 3-6% of testicular masses. LCT’s are usually unilateral; however, in about 3% of cases they can be bilateral. They are usually benign in nature, especially in childhood; still, 10% can be malignant. There are two peak periods of incidence, the first occurring between 5-10 years and the second between 25-35 years (Al-Agha & Axiotis, 2007; Mati et al., 2002; Muheilan et al., 2017; Farkas et al., 2000; Sternberg et al., 1999; Ciftci et al., 2001; Gheorghisan-Galateanu, 2014).

The clinical manifestations of LCT are variable. It could be asymptomatic, with only a testicular mass or presenting with endocrinological symptoms, such as isosexual virilization or contra-sexual feminization (gynecomastia). The degree of endocrinological manifestations depends on the size of the tumor, as well as the nature and quantity of hormones produced. Gynecomastia is either due to increased estrogen production or aromatization of excessive testosterone (Tazi et al., 2008; Mukhopadhyay et al., 2017; Markou et al., 2002). Bhandarkar et al., reported a case of a three-year-old boy who presented with isosexual precocious puberty, and only after a year was a right testicular mass detected. His biopsy revealed a Leydig cell tumor, making it essential to consider LCTs in boys with peripheral precocious puberty and to carefully examine them. Mameli et al., reported two boys with LCTs that presented with unilateral pubarche with asymmetrical testes that were diagnosed with LCT. In both cases, penile length was normal with no axillary hair or other signs of puberty. Height velocity and bone age were normal, as well as androgen and estrogen levels. Therefore, they recommend testicular ultrasounds in all boys presenting with unilateral pubarche, with or without hyperandrogenism.

Imaging with ultrasonography is the initial tool when investigating testicular masses. Ultrasounds of LCT usually show a hypoechoic testicular mass with a heterogeneous enhancement pattern or peripheral hypervascularity. Magnetic Resonance Imaging (MRI) have a higher tissue resolution and are superior to ultrasounds in demonstrating testicular masses and can also detect small tumors not seen by ultrasound (Maizlin et al., 2004; Lock et al., 2011; Fernandez et al., 2004; Tsitouridis et al., 2014).

A final diagnosis of Leydig cell tumor with peripheral precocious puberty was made based on histopathology and laboratory investigation, respectively. As the LCT was the cause of his peripheral precocious puberty, a radical orchiectomy was sufficient, especially given the significant drop in estradiol and testosterone levels post operatively. Furthermore, as the CT scan revealed no clinical evidence of any metastases to the nearby lymph nodes or distant parts of the body such as the liver, lungs or bones, no further intervention was needed. Surgical resection (orchiectomy) remains the gold standard treatment for both benign and malignant LCT. Metastatic LCT responds poorly to additional systemic chemotherapy or radiotherapy. Long-term regular follow-up is essential to exclude recurrence or metastases (Balzer et al. 2006; Henderson et al., 2006; Carmignani et al., 2007; Bozzini et al., 2013; Zhu et al., 2018; Thambi et al., 2015).
CONCLUSION

Boys presenting right testicular mass must be evaluated carefully for signs of puberty. Gynecomastia in prepubertal boys is serious finding and tumors must be ruled out. Leydig cell tumors, though rare, have been associated with gynecomastia and peripheral precocious puberty and these symptoms can be the presenting feature even before a testicular mass is palpable. Thus, LCT must be considered as a differential diagnosis even if there are no obvious testicular masses. Surgical resection of this benign tumor is usually curative with pubertal regression. This also highlights the importance of precise histopathology reporting, as the treatment plan is based in the tumor type. Nevertheless, post-surgical follow up is mandatory to ensure no further pubertal progression and development of central precocious puberty, as well as recurrence or metastases.

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STATEMENT OF ETHICS

The authors have no ethical conflicts to disclose.

DISCLOSURE STATEMENT

Permission was taken from the child’s guardians to use his photos.

REFERENCES


