

Case — A tale of two boys: An atypical cause of pubertal precocity

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Introduction

Testicular tumors are fairly uncommon in the prepubertal pediatric population, with solid tumors accounting for 1–2% of overall cases.^{1,2} Over the past two decades, it has become well-accepted that most prepubertal pediatric testes tumors are benign.³ This has resulted in differing approaches to the diagnosis and management of testicular masses in such patients compared to historic paradigms.³

Leydig cell tumors (LCT) are neoplastic interstitial neoplasms of the testicle accounting for 1–3% of all testicular tumors in adults and 4–9% in prepubertal children.^{4,5} Herein, we report three patients presenting to our institutions with LCT, including a five-year old boy with a most unusual case of multifocal, bilateral LCT.

Case report

Patient 1

A five-year-and-seven-month-old previously healthy boy presented with a nine-month history of behavioral changes and sleep disturbances. This was associated with a growth spurt, along with recent pubic hair growth and penile enlargement (Fig. 1A). Physical examination yielded an enlarged penis, scant coarse scrotal hairs, with right-sided testicular mass with a volume of 5–6 mL.

Investigations revealed normal luteinizing hormone (LH) (<0.4 IU/L), follicle-stimulating hormone (FSH) (<0.4 IU/L), androstenedione (1.1 nmol/L), 17-OHP (0.7 nmol/L), alpha-fetoprotein (AFP) (2 mcg/L), beta human chorionic gonadotropin (β-HCG) (<1 IU/L) and lactate dehydrogenase (LDH) (582 IU/L). There was an elevated serum testosterone (5.6 nmol/L) (Table 1). Testicular ultrasound examination found

right-sided unilateral testicular mass measuring 6 x 6 x 7 mm (Fig. 2A). This patient had an accelerated bone age of 8 years ± 18 months. Hormonal profile and tumor markers prompted partial orchiectomy, with subsequent pathology confirming the diagnosis of LCT (Fig. 3A). He was followed for five months postoperatively until he was lost to followup.

Patient 2

A five-year-old previously healthy boy presented with one-year history of pubic and facial hair, acne, growth spurt, and penile enlargement (Fig. 1B). Testicular volumes were 5 mL (left) and 6 mL (right). The penile enlargement and pubic hair growth corresponded to Tanner stage 3. Investigations revealed normal LH (<0.1 IU/L), FSH (<0.1 IU/L), AFP (3 mcg/L), β-HCG (<1 IU/L), and LDH (571 IU/L). The bloodwork, however, revealed elevated testosterone (10.2 nmol/L), androstenedione (18.9 nmol/L), and 17-OHP (4.3 nmol/L) (Table 1). Ultrasound demonstrated a large mass (15 x 14 x 10 mm) in the right testicle (Fig. 2B) and three masses (5 x 5 x 3 mm, 6 x 6 mm, 2 mm) in the left testicle (Fig. 2C). This patient also had an accelerated bone age of 13 years six months ± 18.6 months. Bilateral exploration was carried out. Intraoperative ultrasound was used to assure all masses were removed. Pathology confirmed diagnosis of LCT, subsequent to testis-sparing surgery involving bilateral partial orchiectomy (Fig. 3B). He has been followed for >5 years with no recurrence. Leuprolide administration was ceased on his 11th birthday. Genetic testing was carried out for DICER1 in both cases and was negative. The second patient subsequently developed central precocious puberty after LCT resection. This required gonadotropin-releasing hormone (GnRH) treatment.

Patient 3

A 10-year-old male initially presented to his endocrinologist at age six with signs of early puberty, including: testosterone (3.6 nmol/L), mildly accelerated linear growth, and pubic hair. Laboratory studies were all normal in this patient: 17-OHP (2.1 ng/dL) and DHA-S (4.5 micromol/L). This was



Fig. 1. (A) Hair growth limited to one hemiscrotum of patient 1. (B) Pubic hair growth corresponding to Tanner stage 3 in patient 2. (C) Pubic hair growth corresponding to Tanner stage 4 in patient 3. (D) Finger-like structure localized to the right hemiscrotum, 2 x 1.5 cm, in patient 3.

presumed central in origin and initial management included androgen suppression for three years by an endocrinologist, whereby testosterone levels rose despite androgen suppression. Physical characteristics were consistent with advanced bone growth, pubic hair, penile enlargement, and a finger-like scrotal structure (Fig. 1C/D). A magnetic resonance imaging scan of the brain was negative, however, a scrotal ultrasound identified bilateral, multifocal hyperechoic testicular masses, with the largest measuring 10 x 9mm on the left and four additional smaller hyperechoic masses on the right (Figs. 2D, 2E). He was referred to urology for evaluation and management. Serum tumor markers were negative, including AFP (4.5 nmol/L), β -HCG (<1 IU/mL), and LDH (267 IU/L). He underwent bilateral enucleation of testicular masses. The right testicular multifocal masses were approached via an inguinal incision and the specimen were sent as frozen and confirmed to be LCT. The left testicular mass was removed via a scrotal approach (Fig. 3C). The finger-like structure was excised circumferentially (Fig. 4) and was identified as superficial angiomyxoma. He is currently only one month out from surgery and recovering well.

Discussion

LCTs are the most common variation of sex cord stromal tumors, but overall, a rare testicular tumor subtype.⁶ As sex cord stromal tumors, LCTs can manifest in the spermatic

Table 1. Laboratory investigations

Tests (Normal values)	Patient 1	Patient 2	Patient 3
LH (<0.3 IU/L)	0.4	<0.1	-
FSH (<1.6 IU/L)	0.4	<0.1	-
Testosterone (<0.9 nmol/L)	5.6	10.2	3.6
Androstenedione (0.1–0.6 nmol/L)	1.1	18.9	-
17-OHP (0–0.8 nmol/L)	0.7	4.3	2.1
DHA-S (0.7–5.7 micromol/L)	1.1	1.8	4.5
AFP (1–4 mcg/L)	2	3	4.5
β -HCG (<2 IU/L)	<1	<1	<1
LDH (470–900 IU/L)	582	571	267

AFP: alpha-fetoprotein; β -HCG: beta-human chorionic gonadotropin; DHA-S: dehydroepiandrosterone sulphate; FSH: follicle-stimulating hormone; LDH: lactate dehydrogenase; LH: luteinizing hormone; 17-OHP: 17-hydroxyprogesterone.

cords, adrenal glands, and ovaries apart from the testicles. These tumors grow within the interstitium between seminiferous tubules and there are few reports of them in the literature.⁵ They are witnessed in the population in a bimodal age distribution occurring from 5–10 and 30–35 years of age.² LCTs are typically functionally active, secreting testosterone causing precocious puberty. LCTs are typically benign, with only 10% of cases being potentially malignant.⁷ The etiology underlying LCT is not conclusive, although there is incidence in patients with cryptorchidism and Klinefelter syndrome, with no association proven.⁸ DICER1 encodes for RNase III endoribonuclease involved in microRNA production that have tumor suppressors and oncogenic roles, and are therefore associated with increased tumor development risk.⁹ DICER1 mutations are screened in the workup of Sertoli-Leydig malignancies, along with other neoplasms, including: Wilms tumor, thyroid cysts, and pleuropulmonary blastomas.¹⁰ Patients with an LCT usually present with virilization but sometimes can present with feminization (i.e., gynecomastia), superimposed on virilization symptoms. The precocial pubertal presentation can involve penile enlargement and pubic/facial hair growth, as seen in the cases described here. LCTs tend to present as enlarged painless testicles causing discomfort due to swelling.¹¹ Serology is valuable in differentiating origination of various testicular tumors. AFP is generally elevated in yolk sac tumors, a malignant testicular tumor, and should be within normal range in LCT.¹¹ Elevations in testosterone is useful in demonstrating presence of LCT.

Ultrasound examination is used in LCT diagnosis and aids in differentiating extratesticular diseases, including epididymal cysts.¹¹ These tumors have been characterized as well-circumscribed, hypervascularized, hypoechoic lesions, less than 10 mm in diameter without internal calcifications, although there is variation reported in the literature.^{8,12} Confirmative diagnosis of LCT depends on histological and immunohistochemical evaluation.⁸ Microscopically, cells are irregularly set in a sheet-like arrangement.^{5,8} Reinke crys-

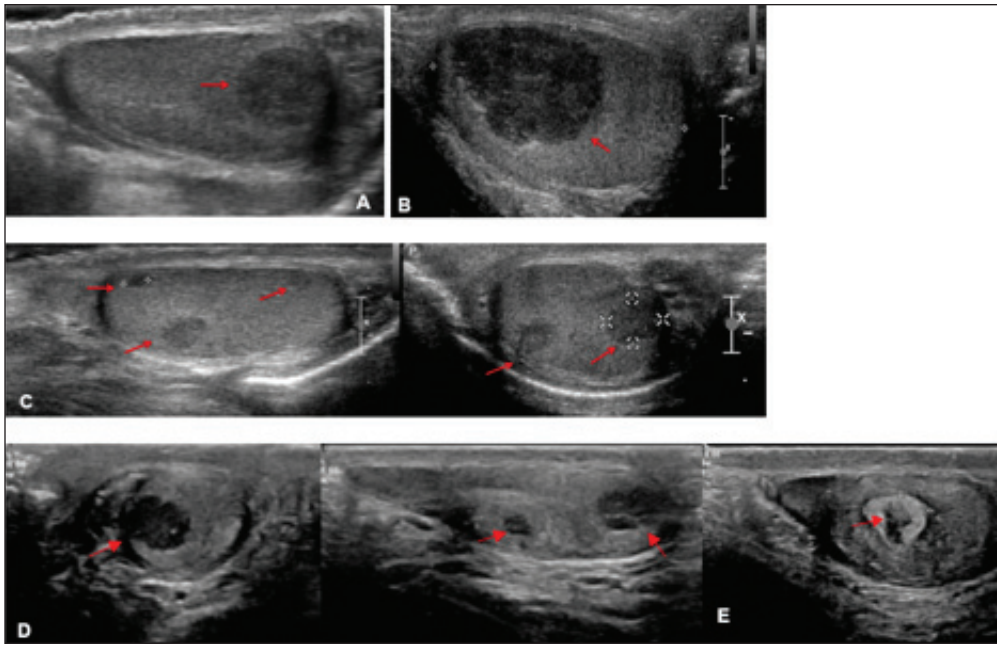


Fig. 2. (A) Ultrasound of right testicle in patient 1 demonstrating a unilateral mass measuring 6 x 6 x 7 mm. (B) Ultrasound of right testicle in patient 2 demonstrating a large mass measuring 15 x 14 x 10 mm. (C) Ultrasound of left testicle in patient 2 demonstrating three masses: 2 mm, 5 x 5 x 3 mm, and 6 x 6 mm. (D) Ultrasound of right testicle in patient 3 demonstrating a hyperechoic mass 10 x 9 mm and multiple small hyperechoic masses. (E) Ultrasound of left testicle in patient 3 demonstrating a large 1 x 7 mm hyperechoic mass.

tals are pale staining inclusions that are pathognomonic for LCT but only found in 30–35% of patients.^{8,13}

Testicular LCTs were traditionally managed with radical inguinal orchiectomy. However, most tumors have been found to be benign, and radical orchiectomy might be considered over-treatment. In turn, LCTs that have favorable pathology or are benign are treated via conservative testes-sparing procedures, whereby tumor enucleation is completed.^{13,14} This approach to treatment has preserved testicle functionality, preserving fertility in these patients.⁶ Observation is thought to be sufficient postoperatively to manage patients with benign LCT.¹³ Malignant LCT is generally managed with radical inguinal orchiectomy with retroperitoneal lymph node dissection (RPLND) for patients with unfavorable prognostic indicators

would present in a multifocal manner and is difficult to differentiate from LCT.⁵ Both cases, however, presented with testosterone elevations and ultrasound findings of lesions less than 10 mm. Both cases were managed with a testis-sparing approach. Parenchyma preservation surgery is pursued to maximally preserve fertility, whereby radical orchiectomy is reserved for malignant or atrophic cases.^{2,15}

Central precocious puberty developed after tumor resection in our second case, as previously shown in the literature.^{3,16} The mechanism is unknown but is theorized due to early maturation of the hypothalamic-pituitary-gonadal (HPG) axis from premature exposure of elevated testosterone via the LCT.^{3,16} GnRH analogues are used in treatment of persistent central precocious puberty, suppressing the HPG axis.³

(i.e., older, unfavorable pathology).⁷ Long-term followup of these patients suggests that this approach does not compromise oncological outcomes.⁶

Our first case demonstrates the classic presentation of an LCT in a pediatric patient with precocious puberty due to a unilateral and unifocal lesion. The second and third cases, however, are unusual and rare presentations of LCT with not only bilateral LCT, but multifocality. LCT traditionally presents as unilateral and benign, with an estimated 3–10% appearing as bilateral in adult series of patients.^{4,15} There are no prior cases found in the literature describing the presentation of a multifocal and bilateral LCT, as seen with our patients. It is important to understand this unique presentation as Leydig cell hyperplasia (LCH)



Fig. 3. (A) Partial orchiectomy of patient 1. (B) Resection of the right testicular tumor in patient 2 during a bilateral partial orchiectomy. (C) Parasagittal incision of right testicular tumor during enucleation via inguinal approach in patient 3.



Fig. 4. Finger-like growth completely excised at base of stalk in patient 3 (2 x 1.5 cm).

Angiomyxomas have been associated with large, cell-calcifying Sertoli cell tumors, adrenocortical rests, and LCTs found within patients diagnosed with Carney complex.¹⁷ Carney complex is an autosomal-dominant syndrome first reported in 1985, and is associated with spotty pigmentation of the skin, endocrinopathy, and endocrine and non-endocrine tumors.¹⁸ These testicular tumors have been reported in the literature to arise as both bilateral and multifocal.¹⁹ The third patient has no family history of Carney complex or other clinical manifestations to support the diagnosis.

Conclusions

LCT may not always present as localized, unilateral testicular masses, as evidenced by this bilateral multifocal presentation. LCT is a rare occurrence and should be considered within the differential diagnosis in boys presenting with precocious or early puberty. Our cases demonstrate use of testis-sparing surgery as an approach to managing LCT to spare fertility. Many clinical principles should be taken away from this case series, namely that central precocious puberty can develop after LCT treatment in a patient with precocious puberty and that there are rare, yet clinically significant genetic syndromes that may manifest in pediatric testicular tumors.

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