Atypical Leydig Cell Tumor in Children: Report of 2 Cases

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abstract

Leydig cell tumors (LCTs) are rare cord-stromal tumors that may occur in testis or ovaries and may produce androgens or estrogens. The majority has been found in men between the ages of 20 and 60 years. Adults with androgen-secreting LCTs are usually asymptomatic; feminizing syndromes may result from the production of estradiol or the peripheral aromatization of testosterone. In children, LCTs usually present between 5 and 10 years of age with isosexual precocious pseudopuberty or gynecomastia. We report 2 cases of LCT in prepubertal boys presenting with advanced unilateral pubarche and testicular volume asymmetry. Both subjects had normal penis size for age; no axillary hair or other signs of puberty were present. Height velocity was normal, and bone age was coincident with chronological age. Androgen levels were normal, as well as estrogen, corticotropin, and cortisol concentration. Testicular ultrasound demonstrated a testicular mass. Histology examination revealed a well-differentiated LCT. This is the first report of 2 pediatric patients with LCT presenting with advanced pubarche in absence of systemic hyperandrogenism. We hypothesize that the neoplastic cells may locally produce high levels of androgens or androgen-like bioactivity molecules that are responsible for the clinical manifestation. We suggest that a testicular ultrasound should be obtained in all children presenting with unilateral pubarche, with or without hyperandrogenism.

Leydig cell tumors (LCTs) are rare sex cord-stromal gonadal tumors. LCTs are steroid-secreting tumors releasing androgens, classically testosterone, but they can also produce estrogens either by direct production of estradiol or peripheral aromatization of the testosterone.[1]

LCTs typically affect males between 20 and 60 years of life. Malignant transformation is rare, and given the slow growth, prognosis is generally good.[2]

The etiology of LCTs remains unknown. Some authors hypothesized that a disorder of the hypothalamic-pituitary axis or structural changes of the luteinizing hormone receptors and G proteins may excessively stimulate Leydig cells and induce oncogenesis.[3] In pediatric subjects, LCTs are rarely reported.[4–6] Overall, LCTs account for 0.4% to 9% of all testis tumors in prepubertal males.

In children, LCTs usually present between 5 and 10 years of age, with isosexual precocious pseudopuberty or gynecomastia in boys or virilizing syndromes in girls, due to their hormonal activity.[7] Gonadotropin-dependent precocious puberty associated with accelerated growth and bone maturation, may develop after surgical therapy.[8]

Radical inguinal orchiectomy is still recommended as standard treatment.

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Dr Mameli conceptualized the study, collected cases, and drafted the initial manuscript; Dr Selvaggio collected cases and reviewed and revised the manuscript; Drs Cerini and Madia drafted the manuscript; Dr Bulfamante performed the histological analysis; Drs Riccipetitoni and Zuccotti critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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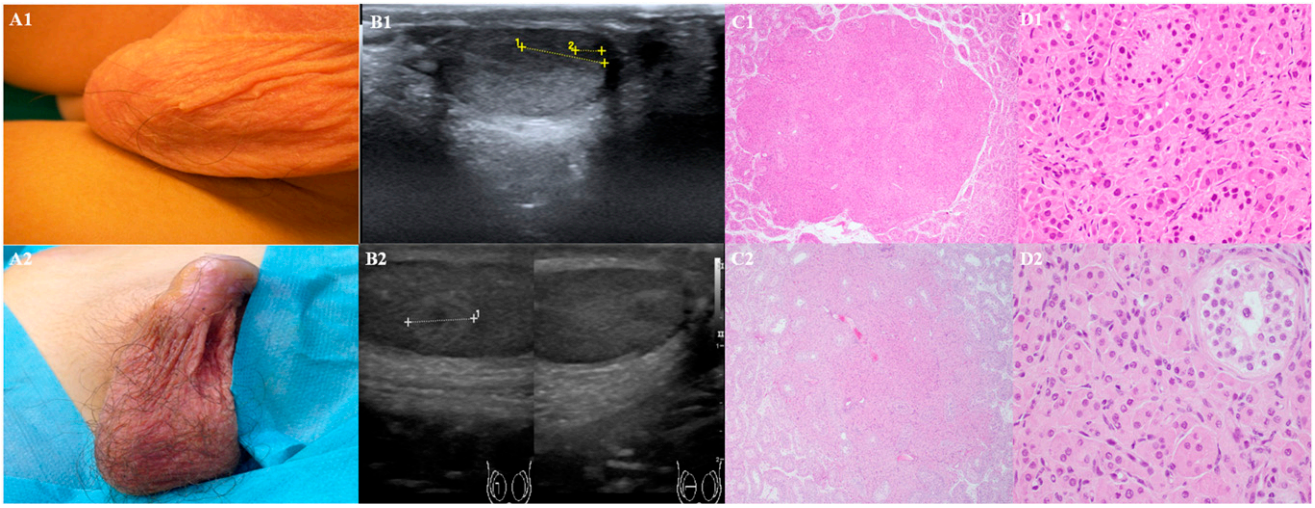

FIGURE 1

1, Patient 1. 2, Patient 2. A, Clinical findings. A1, Patient 1: monolateral curled pubic hair on left testis. A2, Patient 2: monolateral testicular hair adult type. B, Testicular ultrasound. Hypoechoic testicular mass. C, Histology. Hematoxylin and eosin staining, ×4. Neoplastic cells with abundant eosinophilic cytoplasm, distinct cell borders arranged in nests and cords. D, Histology. Hematoxylin and eosin staining, ×40.

TABLE 1 Hormonal Assessment

Subject	LH, IU/L	FSH, IU/L	Testosterone, ng/mL	17-OH-progesterone, ng/mL	Androstenedione, ng/mL	DHEAS, ng/mL
1	<0.1 (0.1–6)	0.5 (0.5–3.7)	0.01 (<5)	0.5 (0.59–3.44)	0.2 (0.6–3.10)	0.8 (0.3–2.5)
2	0.3 (0.1–6)	1.6 (0.5–3.7)	<0.20 (<5)	0.45 (0.59–3.44)	0.61 (0.6–3.10)	1.8 (0.3–2.5)

Data are mean (normal range); testosterone is mean (normal level for prepubertal children).

However, to preserve male fertility, in the past decade a more conservative testis-sparing approach has been successfully chosen for young adults and children.[9]

We report 2 cases of LCTs in prepubertal boys presenting with unilateral advanced pubarche, without hyperandrogenism.

CASE REPORTS

Patient 1 is a 6-year 10-month-old boy who presented with unilateral premature pubarche and history of pubic hair development on the left scrotum since age 6-years 4-months, associated with unilateral testicular swelling.

Physical examination revealed dark, coarse, and curled pubic hair without axillary hair and normal penis size for age (Fig 1). Mild asymmetry of testicular volume was noted: the right and left testicles measured 2 mL and 3 mL, respectively. Neither testis had a palpable mass. Height and weight were at 50th percentile for sex and age; height velocity was normal. Gynecomastia was absent. The hormonal assessment documented normal androgen, estradiol, corticotropin, and cortisol levels. LH, FSH, testosterone, 17-OH-progesterone, androstenedione, and dehydroepiandrosterone sulfate (DHEA-S) plasma levels are shown in Table 1. Tumor markers α-fetoprotein and β-human chorionic gonadotropin were unremarkable. Bone age was 6 years.

Testicular ultrasound of the left testicle identified a 0.3 cm hypoechoic mass located at the inferior pole and grade III varicocele. A left-testis-sparing surgery was performed. The histologic report demonstrated the diagnosis of well-differentiated Leydig cell tumor with negative surgical margins (Fig 1). One month after surgery, pubic hair in the left scrotum decreased, and varicocele resolved.

Patient 2 is a 11-year-old boy who presented with advanced unilateral right pubarche and testicular asymmetry for 1 month. Physical examination revealed testicular hair adult in type, prepubertal penis, and no axillary hair (Fig 1). The right and left testicles were of 3.5 mL and 3 mL volume, respectively, with normal position and no palpable masses. Height and weight were at 75th percentile for sex and age; height velocity was normal. Gynecomastia was absent. The hormonal assessment documented normal androgen, estradiol, corticotropin, and cortisol levels. In particular, testosterone was undetectable. LH, FSH, testosterone, 17-OH-progesterone, androstenedione, and DHEA-S plasma

levels are shown in Table 1. Tumor markers α-fetoprotein, β-human chorionic gonadotropin, and inhibin B were unremarkable. Bone age was 11 years.

Testicular ultrasound revealed a hypoechoic mass measuring 0.6 cm in diameter in the right testis. A right-testis-sparing surgery was performed, and diagnosis of Leydig cell tumor was made. Surgical margins were negative (Fig 1). One month after surgery, pubic hair in the left scrotum decreased.

COMMENTS

LCTs are testicular neoplasms infrequently described in children. They may occur at any age, but most often in prepubertal boys between 5 and 10 years.[7] They are benign during childhood in most cases and typically hormonally active, secreting androgens or, more rarely, estrogens.[7] Malignant transformation has not been clearly proven in children, whereas in adults malignant variants occur in up to 10% of patients.[2]

Twenty-seven cases of LCTs have been described in prepubertal boys.[3,10] Most patients presented with premature pubarche as result of the high level of testosterone. Rarely the tumor is asymptomatic.[10] Only 1 in 27 cases was a nonsecretory tumor with normal testosterone level, despite Tanner stage P2.[11]

We report 2 cases of LCTs in prepubertal boys presenting with advanced unilateral pubarche in the absence of hyperandrogenism.

In both patients, androgens were normal, and in particular, serum testosterone was undetectable or very low. Nevertheless, these patients presented with unilateral pubic hair development on the affected testis and testicular volume asymmetry, with no other signs of puberty. This atypical clinical and hormonal picture suggests that the neoplastic cells were probably producing locally high levels of androgens or substances with androgen bioactivity. The androgen microenvironment of the testis is supposed to be responsible of the unilateral pubic hair development. This is in line with the fact that both patients had no pubic hair in a site other than testis, normal penis growth, and bone age coincident with chronological age.

On the basis of our findings, we infer that pediatric age LCTs may present with different clinical and hormonal profiles: (1) LCTs with systemic hyperandrogenism manifesting with symptoms of precocious puberty, including increased penis size, pubic hair development, accelerated skeletal and muscle growth, advanced bone age, and skin changes, and (2) LCTs without systemic hyperandrogenism presenting only with unilateral pubarche on the affected testicle. In these cases, the effect of androgen production is obvious at the site where the tumor is located.

Taking together these findings suggest that LCTs in pediatric age patients have different characteristics compared with those occurring in adults, in whom an excess of steroid production is often documented at diagnosis, although clinical symptoms of endocrine disturbances may be lacking.[12] On the contrary, in children, signs of local hyperandrogenism could be present even in the setting of normal androgen plasmatic levels. In these latter cases, the effect of androgens or androgen-like substances is obvious and confined to the location of the tumor.

Given the aspecific and remarkable variable clinical presentation, other germinal cells neoplasms, such as yolk sac tumors and granulosa-theca cells tumors, should be considered in the differential diagnosis of a boy presenting with precocious puberty. A high level of clinical suspicion and thorough work-up are crucial for diagnosis and treatment.

We suggest that every male child presenting with unilateral pubarche should be evaluated with testicular ultrasound regardless the finding of systemic hyperandrogenism.

ABBREVIATIONS

DHEA-S: dehydroepiandrosterone sulfate
FSH: follicle-stimulating hormone
LCT: Leydig cell tumor
LH: luteinizing hormone

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