A Testicular Leydig Cell Tumor; An Uncommon Cause of Precocious Puberty: A Case Report With Secondary Central Precocious Puberty

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Abstract- Sexual precocity in boys is defined as any sign of secondary sexual characteristics present before the age of 9. Leydig cell tumors of the testes are a rare cause of peripheral precocious puberty in boys. Here, we report 8 years and 4-month-old boys with signs of peripheral precocious puberty because of a testicular Leydig cell tumor that developed true precocious puberty after surgical removal. Examination of genitalia showed Tanner 4 hair growth. The penis length was 14.5 cm with a 2.5 cm width. The right testis was enlarged but the left testis was measured at 2cm in length and 1 cm in width. Laboratory results showed low serum gonadotropin levels and increased androgen levels. Testicular sonography reported one solid mass measured 31×28×15 millimeters. With a presumptive diagnosis of Leydig cell tumor, the patient underwent radical orchiectomy. Pathologic evaluation confirmed it. Two months after surgery, the diagnosis of central precocious puberty was confirmed according to physical examination and rising of serum gonadotropins. We started treatment with a Gonadotropin-releasing hormone (GnRH) agonist. Leydig cell tumor in children is an uncommon cause of precocious puberty. In every boy with the sign of peripheral precocious puberty and asymmetrical testicular enlargement, the testicular tumor should be considered. It may induce central precocious puberty after surgical resection and this diagnosis should be considered in the patient's follow-up in the next visits.

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Introduction

Sexual precocity in boys is defined when any sign of secondary sexual characteristics presents before the age of 9, and if the source of sex steroids is out of hypothalamus-hypophysis-gonadal axis activation, it's named gonadotropin independent precocious puberty or pseudopuberty. The causes of pseudo puberty in boys are exposure to exogenous androgens, androgen produced from the adrenal gland (congenital adrenal hyperplasia, adrenal tumors), androgen produced from testicular tumors, familial male testotoxicosis, Mc-Cune Albright syndrome, and HCG producing tumors. The most common cause of gonadotropin-independent precocious puberty in boys is virilizing congenital adrenal hyperplasia. Testicular tumors are rare causes of sex steroid production and present with asymmetrical testes enlargement along with signs of puberty. Leydig cell tumors of the testes are uncommon. It accounts for 0.4%-0.9% of all testicular tumors in prepubertal males.

Here, we report 8 years and 4-month-old boys with pseudoprecocity because of Leydig cell tumor and overriding central precocious puberty after tumor resection.

Case Report

The case is an 8 years and 4-month-old boy who came to the pediatric endocrinology clinic in Bushehr city, Iran, with a chief complaint of pubic hair growth about 3 years

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ago. He was the first child of his family, a product of an uncomplicated normal vaginal delivery, from a 20 years old mother and 30-year-old father. The family was Afghan immigrants who have lived in the south of Iran since about ten years ago. His birth weight was 3600 grams. He hadn´t used any medication. He looked much older than his stated age. He had facial acne on his forehead, nose, and cheeks; also he had a small amount of hair over the upper lip. His voice was moderately deep. He had bilateral axillary hair. His height was 150 centimeters. (+2 standard deviation score). His height age was 12 years old. The patient's weight was 48.5 kilograms; weightage was 13 years and 6 months. Midparental height was 169.25 centimeters. ((father height+mother height/2)-6.5 centimeters). His father's height was 168 centimeters (cm) and his mother's height was 157.5 cm. At the first visit, blood pressure was 102/70 mmHg. There was no sign of skin pigmentation. Examination of genitalia showed Tanner 4 hair growth. The penis length was 14.5 cm with a 2.5 cm width. The right testis was enlarged and had firm consistency. It was 3 cm in length and width. The left testis was measured at 2 cm in length and 1 cm in width. One small mass was palpated in the middle part of the right testis. Mass was not tender and its border couldn't define well in palpation. Inguinal lymphadenopathy wasn't detected. No gynecomastia was detected. The rest of the physical examination was not contributory. The parents said that since 2-3 years ago they noticed accelerated growth velocity of their child, but primary health care providers ignored this complaint and said that this is not a sign of any disease, it is not an abnormal finding and he doesn't need to be referred to a physician. They found pubic hair growth and after some time, penile growth and enlargement.

According to the signs and symptoms detected, laboratory tests were requested and radiography of the patient's left hand and wrist for bone age determination was done.

Laboratory results showed low serum gonadotropin levels and increased androgen levels. The levels of 17 hydroxyprogesterone and serum electrolytes were normal, too (Table 1).

Table 1. The laboratory results at the first visit before diagnosis and start of treatment

Test (Normal range)	Patient results
Na (135-145 mmol/l)	140
K (3.6-5.2 mmol/l)	4.8
LH (0.3-2.7 IU/L)	<0.1
FSH(IU/L)	<0.100
Testosterone (<0.07-.02 ng/ml)	9.8
DHEAS (0.06-4.58 µg/ml)	0.2
Androstendion (1-1.8 ng/ml)	41.3
Beta HCG (0-3 Miu/ml)	<0.2
170 HP (<2 ng/ml)	1.4

Bone age according to Greulich and Pyle was 16 years old. Testicular and adrenal sonography reported one solid and heterogeneous hypoechoic mass measured 31×28×15 millimeters with hypervascularity and two foci of hyperechogenicity in the right testes. Total abdominal sonography and CXR were normal.

With a presumptive diagnosis of a Leydig cell tumor of the right testicle, the patient was referred to the urology department for surgical intervention. At surgery, the patient underwent radical orchiectomy with the removal of the right testis and spermatic cord to the level of the inguinal ring. Pathologic evaluation confirmed the diagnosis of a Leydig cell tumor of the right testis (Figure 1).

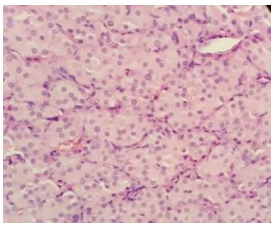

Figure 1. Microscopic picture of tumoral Leydig cells of our patient

Laboratory results one month after right testicular resection showed normal and prepubertal levels of Androstenedione but testosterone level was not in the prepubertal range and gonadotropins were increased (Table 2).

Table 2. laboratory results one month after surgical resection of the tumor

Test (Normal range)	Patient results
LH(0.3-2.7 IU/L)	10.82
FSH (≤3.7 IU/L)	12.51
Testosterone (<0.07ng/ml)	1.7
DHEAS(0.06-4.58µg/ml)	1.61
Androstendion(0.3-3.3 ng/ml)	0/8
Beta HCG(<3 mIU/ml)	< 2
Alpha fetoprotein(<10 ng/ml)	<1.8
LDH(<746 U/L)	312

About two months after surgery the patient was visited again. The size of the Left testis was increased and measured 3×3 centimeters and along with increased gonadotropins level, the diagnosis of central precocious puberty was confirmed and treatment with Gonadotropin-releasing hormone (GnRH) agonist started.

Discussion

Leydig cell tumors (LCTs) are rare sex cord-stromal gonadal tumors in pediatrics, LCTs are rarely reported, and account for 0.4% to 0.9% of all testis tumors in prepubertal boys (1). Peripheral precocious puberty is defined by a rapid somatic growth spurt, deep voice, pubic and axillary hair growth, facial acne, and penile growth with small testes. A hormonal study shows elevated androgens without increased gonadotropin levels. LCTs secret androgens, mainly testosterone, but they can produce and secrete estradiol (2,3,1). It represents in childhood most commonly between 5-10 years of age (1,5). Clinical presentation of LCTs in childhood is isosexual peripheral precocious puberty in boys and gynecomastia (4,3).

LCTs are usually unilateral; however, in about 3% of cases, they can be bilateral (4). They are benign during childhood but about 10% of reported cases have had malignant characteristics (5).

A case of LCT with unilateral isolated pubarche without signs of hyperandrogenism is reported (1). Also, it could be asymptomatic and detected incidentally in palpation with a testicular mass (6,7) or testicular sonography done for another reason (6).

LCTs can cause signs of hyperandrogenism but can't be found in palpation (8). Or without obvious testicular enlargement (3) and is recommended that a scrotal ultrasound scan should be done when peripheral precocious puberty is diagnosed, even in the absence of palpable testicular mass (8).

Our patient presented with a sign of precocious puberty. He had facial acne, accelerated somatic growth, pubic hair, and penile enlargement same as tanner stage 4 (both width and length were increased); but his testes were not enlarged appropriately. One testis was prepubertal and another one only mildly increased in size (stage 2 tanner). According to this finding in physical examination gonadotropin independent precocious puberty was assumed. Laboratory finding was in favor of GIPP too. (Low level of serum gonadotropins and increased androgens). The probable causes were virilizing congenital adrenal hyperplasia (CAH), Mc Cune Albright syndrome, HCG-producing tumors, familial male testotoxicosis, adrenal or testicular androgen-secreting tumors, or exogenous androgen exposure. Serum 17 hydroxyprogesterone (1.4 ng/ml) and HCG (<2 mIU/mL) were in the normal range. And these findings showed that the diagnosis of CAH and HCG-producing tumors are not the cause of his symptoms. Inappropriately testicular enlargement with pseudo-precocious puberty is seen in familial testotoxicosis and HCG-producing tumors. But these two causes are more common in younger ages (before the age of 4 years) (9).

Adrenal sonography didn't find any tumoral mass and adrenal-producing adenoma or adenocarcinoma was excluded.

Asymmetrical testicular enlargement is a sign of testicular tumors. Testicular sonography detected a mass in the right testes and the diagnosis of a Leydig cell tumor was the first and the most likely.

In a case of an asymmetric enlargement of the testes in young boys with idiopathic gonadotropin-independent sexual precocity, a testicular tumor should be considered and testicular sonography other than testicular physical examination should be done. Some tumors may be too small and can't be detected easily on palpation (7,3,8). Our patient's Leydig cell mass was palpable in a physical examination and also induced virilizing signs. The tumor

size was 31 mm and enucleation were not possible. Surgical resection is usually curative with pubertal regression. Post-surgical follow-up is mandatory to ensure no further pubertal progression and development of central precocious puberty, as well as recurrence or metastasis (4). A wide range of tumor dimensions are described, with dimensions less than 1 centimeter noted predominantly in adult patients (1) and children the dimensions reported are between 0.3-3.5 centimeters (1,5,6,7,9-12). The dimension of our patient´s tumor was 31 mm and it was a little greater than the usual sizes reported in children.

Leydig cells predominantly produce testosterone but there are some reports of increased serum Androstendion (12). Our patient had elevated Androstenedione and testosterone secretion, and the increment of androstenedione was more significant than testosterone.

After the surgical removal of the tumor, our patient developed gonadotropin-dependent precocious puberty. The development of central precocious puberty after surgery can occasionally be observed (10). There are a few case reports of this type of puberty in the literature. But it may be more common and should be considered in patients with persistent or recurrent symptoms after successful treatment, and even there is some recommendation of early diagnosis and treatment with GnRH agonist following orchiectomy-owing to the common presentation of gonadotropin-dependent precocious puberty after the treatment of LCTs (10).

Leydig cell tumor in children is an uncommon cause of precocious puberty. In every boy with a sign of peripheral precocious puberty and asymmetrical testicular enlargement, the testicular tumor should be considered. It may not be detected by palpation so testicular sonography is needed to detect nonpalpable hormone-secreting tumors, especially LCTs. It may induce central precocious puberty after surgical resection and this diagnosis should be considered in the patient's follow-up in the next visits.

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