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■ Case report ■

A case of testicular adrenal rest tumor in a male child with congenital adrenal hyperplasia

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= Abstract =

Testicular adrenal rest tumors are a well-known complication in male patients with congenital adrenal hyperplasia. Corticosteroid suppressive therapy usually results in the regression of these tumors. We describe a patient with 21-hydroxylase deficiency who developed bilateral testicular masses. Despite steroid suppressive therapy, the tumors did not regress and hormonal control was poor. Consequently, bilateral partial orchiectomies were performed. **(Korean J Pediatr 2008;51:1018-1022)**

Key Words : Testicular neoplasms, Adrenal rest tumor, Child, Congenital adrenal hyperplasia, Steroid, 21-hydroxylase

Introduction

Congenital adrenal hyperplasia (CAH) is caused by an enzymatic defect in steroid biosynthesis in the adrenal cortex. 21-hydroxylase deficiency is the most common form[1]. In patients with 21-hydroxylase deficiency, precursor steroids, including 17-hydroxyprogesterone (17-OHP), accumulate and are diverted into the sex steroid pathway, resulting in increased androgen production[1].

In CAH, testicular adrenal rest tumors (TARTs) are considered aberrant adrenal tissue that has descended with the testes and has become hyperplastic because of ACTH stimulation[2-4]. Microscopically, the tumors show features of steroid-producing tissue[5]. The growth of TARTs is stimulated by inadequate corticosteroid suppressive therapy and treatment with adequate doses of corticosteroids results in tumor regression[6]. Although the prevalence of TARTs in male children with 21-hydroxylase deficiency has been reported upto 24%[7], there were a few reports of TARTs in Korean children with 21-hydroxylase deficiency[8, 9].

We describe a TART in a Korean patient with 21-hydroxylase deficiency. The patient had bilateral testicular masses and bilateral partial orchiectomies were performed to remove the steroid-unresponsive testicular tumors. Pathology revealed a testicular adrenal rest tumor.

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Case report

A 15-year-old boy was admitted with bilateral testicular masses. He weighed 3.31 kg at birth and presented with poor oral intake, vomiting, dehydration, lethargy, and electrolyte imbalance (hyponatremia and hyperkalemia) immediately after birth. His family history was unremarkable. He was initially treated with NaCl and fludrocortisone, based on a diagnosis of pseudohypoaldosteronism. He was diagnosed with the salt-wasting form of 21-hydroxylase deficiency at 1 year of age and was then treated with corticosteroid (dexamethasone or deflazacort) and fludrocortisone until 10 years of age.

At 10 years of age, he was transferred to our hospital for treatment of nail dysplasia and 21-hydroxylase deficiency. On physical examination, his height was 133 cm (z score of -0.65), and weight was 30 kg (z score of -0.55). The phallus and pubic hair were both at Tanner stage II, and both testes were 3 mL in volume (Fig. 1, Table 1). Predicted adult height (PAH) calculated using the Bayley and Pinneau method was 156.5 cm. He was treated with oral (PO) deflazacort (5 mg) once daily (QD) and fludrocortisone (0.1 mg PO) QD. The plasma 17-OHP level was 55 ng/mL and bone age was compatible to 13 years of age. The elevated 17-OHP level and advanced bone age might result from poor com-

pliance of suppressive therapy. We changed the 5 mg QD deflazacort schedule to 16.6 mg/m^2/day hydrocortisone suppressive medication and continued 0.1 mg/day fludrocortisone treatment.

After treatment for 5 months, the 17-OHP level and plasma renin activity (PRA) were 1.7 ng/mL (treatment target range, <5 ng/mL) and >20 ng/mL/hr (normal range, 0.5-3.3 ng/mL/hr), respectively. The fludrocortisone dosage was increased to 0.15 mg/day due to improper suppression of PRA. As the testicular volume increased to 4 mL despite the PAH of less than the 3rd percentile, daily growth hormone and monthly leuprolide actetate administration were started at doses with 4 IU/day and 1.88 mg/mo, respectively.

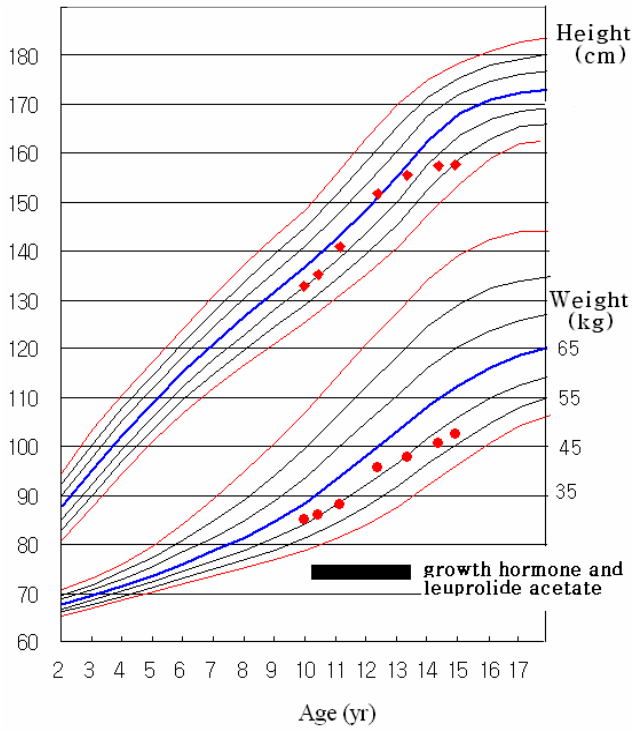

Fig. 1. Growth chart of the patient, from 10 to 16 years of age. He received growth hormone and leuprolide acetate for three yeas.

At 13.4 years of age, GH and leuprolide treatment was discontinued as his bone age accelerated to 15 years. During 3 years of treatment, his height increased from 135.2 cm to 155.5 cm (mean growth velocity, 6.9 cm/yr) and testis size increased to 4 mL. One year after discontinuation of GH and leuprolide, we performed testicular and adrenal magnetic resonance imaging (MRI) because of the increase in testicular volume. Testicular MRI showed bilateral testicular adrenal rest tumor (right, 4.6×2.8×2.9 cm; left, 3.9×3.0×1.9 cm) with compressed normal testicular tissue at peripheral location (Fig. 2). There was no definite mass in both adrenal glands. The serum 17-OHP level was 64 ng/mL and the PRA was 26.5 ng/mL/h. Alpha-fetoprotein, human choriogonadotropin, and lactate dehydrogenase levels were within normal ranges. We performed bilateral partial orchiectomies. Microscopic analysis revealed adrenal rest tumors containing tumor cell nests with fibrous bands, polygonal tumor cells with eosinophilic cytoplasms and focal lymphoid aggregates (Fig. 3). Reinke crystalloids or mitotic activity was not observed. These findings were consistent with the characteristics of adrenal rest tumors. One months after the partial orchiectomies, the volumes of both testes were 5 mL and the reduction in testis size was confirmed by ultrasonography. One

Table 1. Clinical Course, Serial Laboratory Findings and Medications

Age (yr)	Height (cm)	Weight (kg)	BA (yr)	HC (mg/m^2)	FC (mg)	17-OHP (ng/mL)	PRA (ng/mL/hr)	Testes size (mL)	GH/Leup	Events
10.0	133	30	13.0	16.6	0.10	55		3		
10.4	135.2	31		16.2	0.15	1.7	>20	4	4/1.875	
10.7	137.5	31.8		15.9				2		
11.4	143.6	35.4		14.7	0.20		51.2			
11.9	148.6	40.5	13.5	13.5		70	19.8			
12.4	151.8	40.8	15.0	15.2		>200	34.6	4		
13.4	155.5	43		14.7		19			D/C	
13.9	156.8	45.5	16.0	16.0		26	>83	4		
14.4	157.4	45.5		16.0		64	26.5	15		Sono/MRI
14.8										Orchiectomy
14.9	157.8	47.5		15.6		>125	31.6	5		
15.9						27.2	31			

Abbreviations : BA, bone age; HC, hydrocortisone daily dosage per body surface area; FC, fludrocortisone; 17-OHP, 17-hydroxyprogesterone; PRA, plasma renin activity; GH/Leup; daily dosage of growth hormone (IU)/monthly dosage of gonadotropin releasing hormone agonist, Leuprolide (mg); D/C, discontinuation; Sono, sonography; MRI, magnetic resonance imaging

year after the operation, 17-OHP level was 27.2 ng/mL and PRA was 31 ng/mL/hr. Treatment with hydrocortisone (15.6 mg/m^2/day) and fludrocortisone (0.2 mg/day) was maintained.

Discussion

Occasionally, male patients with CAH, particularly the salt-wasting form of 21-hydroxylase deficiency, develop TARTs in adolescence or early adulthood. The prevalence of TARTs in male children with 21-hydroxylase deficiency has been reported upto 24%[7]; these lesions are often bilateral (83%). Concentrations of 17-OHP and androgen are usually elevated. In testicular ultrasonographs, these lesions present as hypoechoic infiltrative nodules and are usually located near the mediastinum testis[10]. TARTs have been detected even in childhood[7], recommending that ulatrasonographic screening should begin no later than adolescence[1]. If TARTs are refractory to medical treatment, partial orchiectomy is recommended[11, 12].

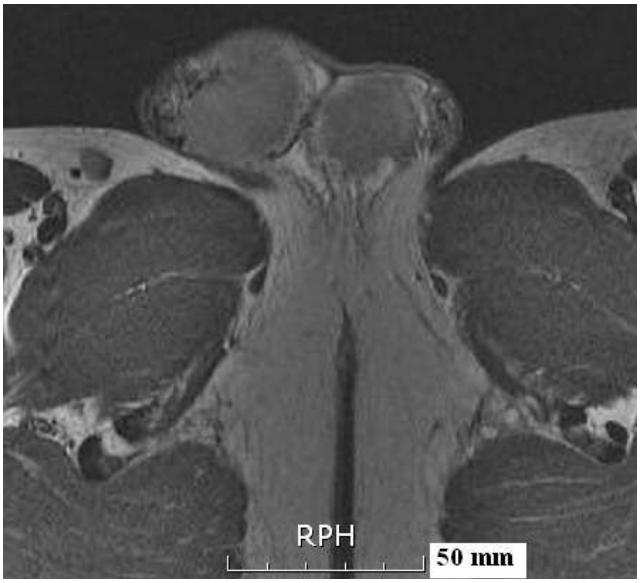

Fig. 2. Testicular magnetic resonance imaging shows bilateral testicular adrenal rest tumor (right, 4.6×2.8×2.9 cm; left, 3.9 ×3.0×1.9 cm) with compressed normal testicular tissue at peripheral location.

TARTs are hormone-dependent and are not considered true autonomous tumors. During the prenatal period, the gonads and adrenals both develop from the adrenogenital ridge and do not separate until the adrenal groove is prominent. Before separation, adrenal cortical tissue may adhere to the gonad. This aberrant adrenal tissue may then descend with the testis or ovary along the courses of their associated arteries[3]. Adrenal rests within the testis occur in 7.5% 15% of neonates and normally regress in early infancy[7]. However, in CAH patients, it is believed that these cells may persist and proliferate with preservation of adrenal-like hormone production properties[4].

Several studies have shown that these tumors are ACTH-dependent, as evidenced by a reduction in tumor size in response to corticosteroid therapy and a recurrence of testicular enlargement in response to ACTH stimulation[4, 6]. TARTs may be stimulated not only by elevated ACTH concentrations but also by elevated angiotensin II levels, based on the presence of angiotensin II receptors[4]. GH can stimulate differentiation and proliferation of cancer cells or precursor cells, but there are no reports on the effect of GH on proliferation or hyperplasia of adrenal rest tumors.

In CAH patients with testicular masses, clinically useful

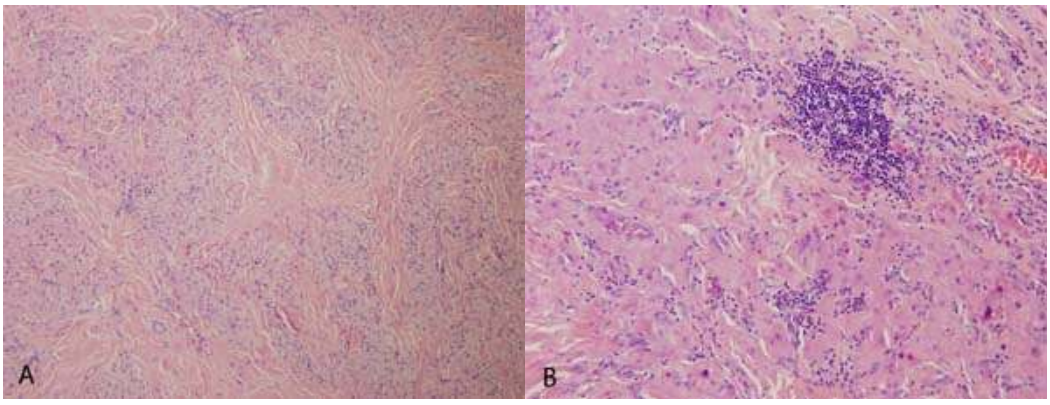

Fig. 3. (A) Testicular mass showing tumor-cell nests with thick fibrous bands (HE stain, ×100). (B) Polygonal tumor cells with eosinophilic cytoplasms. Focal lymphoid aggregate is also evident between the tumor-cell nests (HE stain, ×200).

criteria for differentiating TART from other tumors such as Leydig and germ cell tumors include a clinical history of CAH, bilateralism of tumors and a decrease in the size of tumors in response to corticosteroid therapy[13]. For these reasons, orchiectomy or tumor removal should not be done immediately.

TARTs may produce adrenal steroids such as 21-deoxycortisol, androstenedione and 17-OHP[4]. Therefore, removal of the testicular tumors may decrease the level of androstenedione and 17-OHP. However, 17-OHP levels do not change significantly after surgery in some patients with TARTs[12], as was the case with our patient. These observations suggest that surgical treatment may not be appropriate for improving hormonal control. TARTs may cause testicular tenderness and pain but these symptoms disappear after their removal[12].

Infertility and pituitarygonadal dysfunction may develop in male patients with 21-hydroxylase deficiency. First, sustained suppression of the pituitarygonadal axis by a high level of adrenal androgen secretion results in small testicular size and infertility[3, 6]. Second, TARTs may cause obstructive azospermia or oligospermia[12, 14, 15]. When large TARTs are located in the mediastinum testis proximal to the epididymis, the efferent flow in the seminiferous tubules may be chronically obstructed. Longstanding obstruction of the seminiferous tubules may then result in hypospermatogenesis and peritubular fibrosis. The irreversible end-stage is tubular hyalinization with obstruction of the lumen and complete loss of germ cells and Sertoli cells[15]. Intense corticosteroid treatment sufficient to suppress adrenal steroid secretion may decrease tumor size and improve infertility in some patients with TARTs[6]. If there is no response, tumor enucleation or partial orchiectomy may be performed to preserve fertility[5, 11, 12, 15, 16]. The fertility prognosis of TART patients is uncertain. If irreversible testicular damage caused by longstanding obstruction of the seminiferous tubules is present prior to tumor removal, testicular function cannot be restored by surgery[12].

To our knowledge, this is the third report of a TART in Korea[8, 9]. In the first case reported by Kim and Han[8], contrary to our case, the patient was diagnosed with CAH after removal of TART. And in the second case reported by Cho et al.[9], TART accompanied with adrenal incidentaloma was not decreased with intense hydrocortiosne suppression therapy. Our 21-hydroxylase-deficient patient received corticosteroid suppressive treatment since infancy. The parents reported good drug compliance but we think that the patient did not receive sufficient glucocorticoid and fludrocortisone considering his bone age advancement, short PAH, high level of 17-OHP and sexual maturation at an inappropriately young chronological age. Bilateral testicular masses developed 1 year after discontinuation of GH treatment. We do not know what effect the GH had on the development of the TART. Because of unresponsiveness to medical treatment over a period of 1 year, bilateral partial orchiectomies was performed. Despite the operation, levels of 17-OHP and PRA remained high. We plan to study the patient's pituitarygonadal function and fertility when he is 18 years of age.

We recommend periodic testicular ultrasonography for adolescents with CAH because it enables small testicular lesions to be detected at an early age and facilitates early treatment, which may prevent irreversible testicular damage.

한 글 요 약

선천 부신 과다형성 환자에서 발생한 고환 부신 잔류 종양 1례

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선천 부신 과다형성 환자에서 고환 부신 잔류 종양은 흔하게 발생한다. 대개 이 종양은 적절한 corticosteroid 억제 치료로 호전될 수 있다. 저자들은 양측성 고환 부신 잔류 종양을 보인 21-hydroxylase 결핍증 환아에게서 corticosteroid를 투여하였으나 반응하지 않아 고환 적출술을 시행한 사례를 경험하였기에 보고하는 바이다.

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