

## Case Report

# Androgen-Producing Adrenocortical Carcinoma: Report of 3 Cases with Different Clinical Presentations

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*Adrenocortical carcinoma is extremely rare in children. The majority of cases presented with a combination of clinical features of Cushing syndrome and hyperandrogenism. The authors report three cases of isolated androgen-producing adrenocortical carcinoma with different clinical presentations. The two cases had clinical manifestations of hyperandrogenism: one boy with isosexual pseudoprecocity and one girl with heterosexual pseudoprecocity, both of whom underwent complete tumor removal and were well after surgery. The third patient presented with a huge abdominal mass and weight loss. Local and distant metastases (both lungs) were detected at the time of diagnosis. The patient expired after 36 days of hospitalization. The pathological section in all three patients demonstrated highly pleomorphism, increased mitoses, and scattered areas of necrosis. All cases had high levels of 17-hydroxyprogesterone, dehydroepiandrosterone-sulphate, and testosterone.*

**Keywords:** Adrenocortical carcinoma, Hyperandrogenism, Pseudoprecocity

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Adrenocortical tumors are rare in children with a calculated incidence of 0.3 to 3.0 per million<sup>(1,2)</sup>. Such tumors secrete excess of cortisol, androgen, and aldosterone. The clinical presentation involves a combination of features of hypertension, virilization, and Cushing syndrome<sup>(3-7)</sup>. Pure androgen-producing adrenocortical tumors without excess of cortisol are extremely rare. The presenting symptoms of a pure androgen-producing adrenal tumor are virilization in girls, and pseudoprecocious puberty in boys. To date, not more than 100 cases of a pure androgen-producing adrenocortical tumor in children younger than five years old have been reported<sup>(3-8)</sup>. The authors report three cases of young patients with a pure androgen-producing adrenocortical tumor who presented with different clinical manifestations.

### Case Report

#### Patient 1

A 2-year-old boy presented with penile enlargement, the presence of pubic hair, and increased

weight and height gain, which had been developing for four months. The physical examination revealed a virilized boy with body weight of 16 kg (> 97<sup>th</sup> centile), height 96 cm (> 97<sup>th</sup> centile), blood pressure (BP) 90/60 mmHg, penile length 7 cm, pubic hair Tanner III, and testicular volume 1 mL bilaterally. Investigations showed normal blood chemistry and normal electrolytes. A standard ACTH stimulation test (ACTH 250 µg) revealed cortisol 16.81 µg/dL, 17-hydroxyprogesterone 560 ng/dL, dehydroepiandrosterone-sulphate (DHEA-S) 437 ng/dL, and testosterone 6.39 ng/mL. The boy was initially diagnosed with simple virilizing congenital adrenal hyperplasia. Despite treatment with hydrocortisone 15 mg/m<sup>2</sup>/day for four months, the patient still had progressive virilization with pubic hair Tanner IV (Fig. 1). Magnetic resonance imaging (MRI) demonstrated a well-circumscribed right adrenal mass 5.5 x 5.6 x 6.3 cm. The patient underwent a right adrenalectomy with complete tumor removal. A pathological study demonstrated varying numbers of cells with eosinophilic or bubbly clear cytoplasm and no capsular involvement. After tumor removal, the virilization dramatically decreased and testosterone level decreased to 0.2 ng/mL. At age 3.5 years, penile length was 5.0 cm, no pubic hair, and testes 1 mL bilaterally.

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### **Patient 2**

A 2.5-year-old girl presented with clitoromegaly and the presence of pubic hair for five months. The physical examination revealed height of 95 cm (90<sup>th</sup> centile), weight 14.5 kg (90<sup>th</sup> centile), BP 90/60 mmHg, pubic hair Tanner III, clitoromegaly (2 cm in length) (Fig. 2). Initial investigations showed normal blood chemistry, normal electrolytes, 46XX chromosome,  $\beta$ -hCG < 1 mIU/mL. A standard ACTH stimulation test (ACTH 250  $\mu$ g) revealed peak 17-hydroxyprogesterone 670 ng/dL, DHEA-S 499 ng/dL,



**Fig. 1** A 2-year-old boy with penile enlargement and pubic hair stage Tanner IV



**Fig. 2** A 2.5-year-old girl with pubic hair Tanner III

and cortisol 27.3  $\mu$ g/dL. Testosterone was 3.07 ng/mL. Abdominal ultrasonography showed no adrenal mass. Congenital adrenal hyperplasia was initially diagnosed. She was treated with hydrocortisone 15 mg/m<sup>2</sup>/d for four months without improvement. An MRI abdomen revealed a 2.2 x 2.5 x 2.0 cm right adrenal mass. A right adrenalectomy with complete tumor removal was performed without complication. A pathological section revealed varying numbers of cells with eosinophilic or bubbly clear cytoplasm, and no capsular involvement. Hydrocortisone was tapered off three months after surgery. Virilization subsided as shown by the decrease in size of clitoris to 1 cm and the disappearance of pubic hair.

### **Patient 3**

A 4-year-old girl presented with an abdominal distension and three kg weight loss in four months. On admission, she was ill-looking appearance with body weight 14.5 kg (25<sup>th</sup> centile), height 98 cm (25<sup>th</sup> centile). BP was 100/70 mmHg. Abdominal examination revealed large abdominal mass with massive ascites. Examination of genitalia revealed swelling of labia majora (from massive ascites), presence of pubic hair Tanner III and clitoromegaly (Fig. 3). Investigations showed normal blood chemistry and electrolytes, except for hypoalbuminemia (albumin 2.3 g/dL),  $\beta$ -hCG < 1 mIU/mL, alphafetoprotein 3 ng/mL, 17-hydroxyprogesterone 420 ng/dL, DHEA-S 318 ng/dL, cortisol 23.4  $\mu$ g/dL, and testosterone 4.06 ng/mL. An



**Fig. 3** A 4-year-old girl with pubic hair Tanner III and clitoromegaly. Note the swelling of labia majora from massive ascites

MRI abdomen demonstrated a 12.7 x 15.1 x 20.0 cm mass involving left adrenal and kidney, extending to the right side of abdomen. A chest X-ray showed multiple metastatic nodules in both lung fields. A tissue biopsy demonstrated frequent mitoses and scattered areas of necrosis. After 36 days of hospitalization, the patient expired from ventilator-associated pneumonia and septicemia.

### Discussion

Our patients had clinical features of hyperandrogenism (presence of pubic hair, growth acceleration, penile enlargement in boys, and clitoromegaly in girls) without features of Cushing syndrome. The algorithm for investigations of the presence of pubic hair in prepubertal children is hCG, DHEA-S, 17-OHP, and ACTH stimulation test<sup>(9)</sup>. The abnormally high levels of DHEA-S and 17-OHP suggest a diagnosis of late-onset 21-hydroxylase deficiency congenital adrenal hyperplasia (21-OHD CAH). All of the presented patients, particularly patients 1 and 2, had the high level of 17-OHP and DHEA-S which led to the misdiagnosis to 21-OHD CAH. The misdiagnosis was also aided by the extremely rare incidence of adrenocortical tumor (1:1,000,000) compared to that of CAH (1:15,000). The recent reports of childhood adrenocortical tumors in children under 5 years old are summarized in Table 1.

One of the important clinical clues used to differentiate between virilizing congenital adrenal hyperplasia and an androgen-producing adrenocortical tumor in young children is the clinical condition of virilization. In congenital adrenal hyperplasia, virilization will decrease within two to three months after treatment with a physiological dose of hydrocortisone whereas the virilization will continue to progress in patients with adrenocortical tumor. Therefore, the physicians should be aware of the

possibility of an adrenocortical tumor in young children presenting with virilization. For definite diagnosis, a CT or MRI adrenal glands is indicated. Ultrasonography is not sensitive enough to identify a small adrenal tumor mass, as in the patient 2 whose 2 cm right adrenal tumor could not be detected by abdominal ultrasonography.

Patient 3 presented with a huge abdominal mass and weight loss which mimicked Wilms tumor or neuroblastoma. The presence of pubic hair and mild clitoromegaly were the suggestive signs for excess androgen secreted by adrenal tumor. The pathological section confirmed the diagnosis of adrenocortical carcinoma.

Surgical tumor removal with steroid replacement therapy is the definite treatment for adrenocortical tumor. The majority of these tumors, particular in young children, are malignant. However the prognosis in young children is favorable<sup>(1-8)</sup>. A complete tumor removal without metastasis at the time of diagnosis has been shown to have a better prognosis, even with a tumor size larger than 5 cm, or with the poor histological features. Reports of 10-20 year follow-up of such children have shown that up to 90% of cases survive without recurrence of tumor. The prognosis of the authors' first two patients is favorable as they underwent complete macroscopically and microscopically tumor removal, had no evidence of local or distant metastasis, and the pathological section revealed no capsular or vascular involvement. In patient 3, the prognosis was poor since the tumor was huge and there were local and distant metastases. The pathological section showed highly pleomorphism, an increased number of cell mitoses and necrotic areas. Moreover, her condition at the time of diagnosis was such that she could not undergo surgical tumor removal. Although combination chemotherapy and radiotherapy might be an alternative treatment for an inoperable case, many studies have been shown an unfavorable result<sup>(3-8)</sup>.

**Table 1.** Adrenocortical tumors in children under 5 years old

	Mayer <sup>(4)</sup> (1997)	Wajchenberg <sup>(5)</sup> (2000)	Cordera <sup>(6)</sup> (2003)	Hanna <sup>(7)</sup> (2008)	Chen <sup>(8)</sup> (2011)
Years of study	1972-1996	1982-1999	1946-2002	1976-2005	1991-2010
Duration (yr)	24	17	56	30	20
Total cases	4	22	-	23	34
Pure-androgen-producing tumor	2	13	4	13	19
Cushing syndrome/mixed/others	2	9	-	10	15

### Conclusion

The authors report three cases of pure androgen-producing adrenocortical carcinoma in young children with different clinical presentations, two cases with progressive virilization and growth acceleration, and one case of huge abdominal mass and weight loss. Therefore, in young children who present with virilization similar to that of late-onset congenital adrenal hyperplasia and show no response to glucocorticoid treatment, MRI is indicated to demonstrate adrenocortical carcinoma. Surgical tumor removal with steroid replacement therapy is the definite treatment for adrenocortical carcinoma with a favorable outcome.

### Potential conflicts of interest

None.

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## มะเร็งเปลือกต่อมหมวกไตที่สร้างฮอร์โมนเพศชาย: รายงานผู้ป่วย 3 รายที่มีอาการแสดงแตกต่างกัน

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มะเร็งเปลือกต่อมหมวกไตพบได้น้อยมากในเด็ก ส่วนใหญ่ของมะเร็งเปลือกต่อมหมวกไตแสดงลักษณะทางคลินิกของกลุ่มอาการ Cushing ร่วมกับลักษณะของการมีฮอร์โมนเพศชายมากกว่าปกติ รายงานนี้เป็นการรายงานผู้ป่วยเด็ก 3 รายที่เป็นมะเร็งเปลือกต่อมหมวกไตที่สร้างเฉพาะฮอร์โมนเพศชายสูงมากที่มีอาการนำแตกต่างกันโดยไม่มีลักษณะของกลุ่มอาการ Cushing ผู้ป่วย 2 รายมีลักษณะทางคลินิกของการมีฮอร์โมนเพศชายสูงมากกว่าปกติ โดย 1 รายเป็นเด็กชายที่มาด้วยอาการ *isosexual pseudoprecocity* และเด็กหญิง 1 รายที่มาด้วยอาการ *heterosexual pseudoprecocity* ทั้งสองรายได้รับการผ่าตัดเอาก้อนมะเร็งออกทั้งหมดและอาการต่าง ๆ ดีขึ้นภายหลังการผ่าตัด ผู้ป่วยรายที่สามมาด้วยเรื่องก้อนในท้องและน้ำหนักลด การตรวจเพิ่มเติมพบการกระจายของมะเร็งไปยังอวัยวะข้างเคียงและปอดทั้งสองข้าง ผู้ป่วยรายนี้เสียชีวิตหลังจากรับตัวไว้ในโรงพยาบาล 36 วัน การตรวจชิ้นเนื้อทางพยาธิวิทยาในผู้ป่วยทั้งสามรายพบลักษณะเซลล์มีขนาดที่แตกต่างกัน การแบ่งตัวเพิ่มขึ้นของเซลล์และเนื้อเยื่อตาย การตรวจเลือดในผู้ป่วยทั้งสามรายพบมีระดับ *17-hydroxyprogesterone*, *dehydroepiandrosterone-sulphate* และ *testosterone* สูงมาก

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