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Pubertal outcome in a female with virilizing adrenocortical carcinoma

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Abstract

Adrenocortical tumors are neoplasms that rarely occur in pediatric patients. Adrenocortical carcinoma (ACC) is even more uncommon, and is an aggressive malignancy with 5-year survival of 55% in a registry series. There is a lack of information on long-term endocrine outcome in survivors. We describe a 10-year follow-up in a patient who presented at 3 years 5 months with a 1-year history of axillary odor and 6 months' history of pubic hair development with an increased clitoral size. Androgen levels were increased and a pelvic sonogram revealed a suprarenal mass of the left kidney. The tumor was successfully removed. At 6 years 11 months, androgen levels increased again. Workup for tumor recurrence was negative and the findings likely represented early adrenarche. The patient had menarche at an appropriate time and attained a height appropriate for her family.

Keywords

adrenocortical carcinoma; puberty; virilization

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Introduction

Adrenocortical carcinoma (ACC) rarely occurs in pediatric patients. In the US, Surveillance Epidemiology and End Results (SEER) data from the National Cancer Institute data showed that from 1975 to 1995, 1.3% of childhood malignancies were carcinomas, with only 0.2% being ACCs (1). From 1973 to 2008 the SEER program found that the overall incidence of ACC is 0.21 per million person-years (2). There is a bimodal age distribution in the pediatric population with one peak in early childhood under age 3–4 years, and a second, slightly smaller peak in prepuberty and adolescence (3–5). The overall female:male ratio is approximately 1.6–2:1 with a predominance of females at both age peaks (up to 6.2:1 in adolescence), but a relatively equal sex distribution in the age interval of 4–12 years (2, 6).

ACCs in children can occur as a component of a multisystem syndrome such as Beckwith-Wiedemann Syndrome, multiple endocrine neoplasia (MEN) type 1, Carney's complex, hemihypertrophy syndrome, Li-Fraumeni and other constitutional p53 mutations (3, 6). However, many cases of ACC occur sporadically. ACC is an aggressive malignancy with a 5-year survival of 57% in a recent retrospective analysis of a US-based population multiregional database (2). There is a paucity of information, however, on long-term endocrine outcome in survivors. This is one of the first reports describing detailed long-term endocrine and pubertal outcome with ongoing laboratory and clinical follow-up in a pediatric patient with ACC.

Case presentation

The female child presented at age 3 years 5 months of age with a 1-year's history of axillary odor and 6 months' history of pubic hair development with an increased clitoral size. She had Tanner I breasts, moderate axillary hair and odor, Tanner III pubic hair, and clitoromegaly (4×1 cm). The abdomen was soft, nondistended, and without any palpable masses. Notably, the patient had no acne and no Cushingoid features on physical exam. There was no history of voice change. Blood pressure varied from 102 to 129 systolic over 62–80 diastolic, the upper range slightly elevated for age and height. Laboratory results showed extremely elevated levels of DHEA (11,767 ng/dL; normal <68) and androstenedione (2733 ng/dL; normal <10–17). Testosterone was 72.6 ng/dL (normal <2.5–10), with normal cortisol levels. Values included a post-ACTH stimulation DHEA of 9,940 ng/dL and androstenedione of 2642 ng/dL (see Table 1). A modest increase in her growth velocity was noted from age 2 to 3 years (80th to 90th percentile) with a growth rate of 10 cm that year. Her bone age was advanced at 5 years. Her pelvic sonogram demonstrated an 8.6×6.2×5.9 cm left supra-renal mass, confirmed on CT scan. The 228 g mass was surgically resected. Pathology of the mass revealed an adrenal cortical carcinoma. Metastatic evaluation was negative and thus no additional therapy was recommended.

Within 1 month of resection, DHEA and testosterone had decreased to normal levels for age at 50 ng/dL and 3.7 ng/dL, respectively (see Table 2). Androstenedione took 3 months to decline to undetectable levels. Blood pressure normalized after tumor removal. At age 4 years 3 months, 10 months after resection, her clitoral size was 3×1 cm and pubic hair remained at Tanner III with no further progression. Frequent laboratory evaluation and twice

yearly ultrasounds were normal. At age 6 years 7 months her clitoris size had decreased to 1.5 cm in length with unchanged Tanner staging (pubic hair did not recede from diagnosis even with normal laboratory values). At 6 years 11 months DHEA levels started to increase to slightly more than what would be expected for age, 183 ng/dL (normal <111 ng/dL for age). A repeat CT of the abdomen was negative, and her DHEA levels did not increase further. This was interpreted as representative of early adrenarche. At age 8 years 4 months she was noted to have Tanner II breasts and an increase in pubic hair. Her estradiol increased to pubertal levels at approximately 9 years of age. She had menarche at age 10 years 10 months which was appropriate timing for her family. Her menstrual cycles have remained regular and now at age 13 years 5 months she has attained a height of 163.2 cm (within 2 standard deviations of midparental target height of 172 cm) and has Tanner IV breasts, Tanner V pubic hair, with a clitoris of <1 cm.

Pathology

A 228 g 9.5×8.5×5 cm left adrenal mass was excised. Histologically neoplastic cells were seen with clear to eosinophilic cytoplasm suggestive of adrenal cortical tumor (Figure 1) confirmed immunohistochemically (positive for alpha inhibin (Figure 2), vimentin, and synaptophysin and negative for pan CK, EMA, S100 and peripherin). Scattered highly atypical cells were seen along with multifocal geographic areas of necrosis (Figure 3). Vascular (Figure 4) and capsular invasion were seen. The mitotic count was up to 15 mitoses (Figure 1) per 50 HPF's. Our patient met criteria for stage II (completely resected, tumor 100 g, or volume 200 cm³, with normal postoperative hormone levels) (7, 8).

Discussion

There is a lack of information on endocrine outcome in survivors of ACC with only rare long-terms reports. This case report represents one of the first known long-term detailed follow-up report of a young child with ACC.

Most cases of pediatric ACC are initially diagnosed based on clinical and biochemical laboratory findings. Hagemann et al. (9) have reported that approximately 90% of pediatric ACCs are hormonally active and the type of hormone secretion can lead to varied clinical presentations. As illustrated by this case, signs of androgen hyper-secretion can include accelerated growth velocity, bone age advancement, clitoromegaly, and premature adrenarche.

Conflicting data has been reported with respect to the ability to diagnose ACC of childhood soon after presentation. Ng and Libertino (10) have postulated that the phenotypic presentation of ACC in childhood allows for easier and earlier detection, while Hagemann et al. (9) have suggested that particularly in cases of mixed steroid excesses, variations in clinical manifestations may actually delay diagnosis. Michalewicz et al. (6) pointed out that these children often do not appear to be ill and in fact their accelerated growth in the early stages can initially be mistaken as a sign of health. The International Pediatric Adrenocortical Tumor Registry confirmed a lag in diagnosis ranging from a few days to 90 months with a median of 5 months (6). Our patient had classic evidence of androgen excess without any signs of glucocorticoid excess, but referral to an endocrinologist was delayed at

least a year from onset of symptoms by history. Without evidence of hypercortisolism, the differential diagnosis was confined to an evaluation for causes of heterosexual virilization in a young child. This included assessment for defects in adrenal steroidogenesis causing adrenal hyperplasia or for adrenal tumors. Exogenous administration of androgen compounds was ruled out by history and by elevation of testosterone precursors (11).

Our patient's "classic" case confirms many of the prior epidemiological patterns reportedly associated with ACC. This includes the greater prevalence of females in children with ACC <4 years of age (10). Secondly, like others in her age group with ACC, our patient presented with a virilizing tumor without symptoms of Cushing's syndrome. A significantly greater proportion of functional tumors, particularly those presenting with virilization, are seen in the younger age group. In a large cohort of children with ACC, more than 90% of young children had virilizing features, whereas there was a tendency toward Cushing's syndrome and nonfunctional tumors in adolescents (6). Furthermore, virilization alone in and of itself portends better event-free survival in the setting of localized disease, as experienced in this case (6). Lastly, our patient's excellent response to surgical treatment and event-free survival reflects the findings in the recent Surveillance, Epidemiology, and End Results study (2) which found that 5 year survival for children in our patient's age group (0–4 years) was 91.1%. This was as compared to 5–19 years olds in which 5-year survival was markedly lower at 29.8%. In fact the authors comment that the most significant drop off in survival was noted after age 4 years.

Literature findings have emphasized the importance of complete surgical tumor resection as the most important intervention and as an indicator for improved prognosis (6, 12–14). However, there has not been a consensus as to whether tumor size or histologic features most readily predict survival rates in pediatric ACC (14). Chemotherapy is considered in cases with incomplete resection, metastatic disease, or persistent hormone hypersecretion following apparent complete resection, but has not been shown to improve survival or diminish recurrence. Agents with anecdotal activity are mitotane (o,p-DDD) and cisplatin. Radiation therapy is generally reserved for palliation of refractory disease (15). According to the ARAR0332 protocol (Treatment of Adrenocortical Tumors with Surgery plus Lymph Node Dissection and Multiagent Chemotherapy) (16), a collaboration between Children's Oncology Group (COG) and Brazilian institutions, recommended management for stage II patients is surgery with complete resection of tumor, retroperitoneal lymph node dissection, without chemotherapy. The incidence of lymph node involvement in pediatric ACC is unknown, but appears to be less than in adult ACC; whether ipsilateral retroperitoneal lymph node dissection improves local control is one of the questions asked in the prospective COG protocol described in Ribeiro et al. (8).

Ten years ago, at our patient's diagnosis, we followed the current literature at that time. Our patient is representative of Group B described by Wieneke et al. in 2003 (17). This cohort presented with clinically benign virilization but malignant tumor pathology (including capsular and vascular invasion in a large minority of cases, as in our patient). Most patients in this group were managed by surgery alone, and none had recurrence or metastatic progression. Our patient was managed as such, with no adjunct treatment with chemotherapy

or radiation. Rather, diligent long-term surveillance by both the endocrine and oncology teams was undertaken.

At the time of our patient's diagnosis, there were no formal surveillance guidelines. We performed abdominal ultrasounds every 2 months for the first 6 months, and then every 6 months for the next 3 years. Labwork and examinations were followed monthly by endocrinology for the first 3 months, and then visits were gradually at 6 months, and then yearly as the patient passed the landmark of 5 years "event-free". In recent years, the European Society of Medical Oncology working group has recommended the following surveillance after complete resection of ACC: abdominal CT or MRI, chest CT, and initially elevated steroid values to be repeated every 3 months for 2 years, and less frequently thereafter for at least 10 years (18). The ARAR0332 protocol (16) includes guidelines for follow-up, namely to repeat DHEA, DHEA-S, androstenedione, testosterone, cortisol, deoxycorticosterone, corticosterone, aldosterone at 7 days, then 1, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months post-surgery. ACTH is checked at every other assessment. MRI of primary site (and bone scan if initially positive) are repeated at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months. Chest CT is repeated on the same schedule, except that CXR can be substituted for chest CT in early-stage disease. Our patient had no tumor recurrence. However, the likelihood of a TP53 pathogenic germ line variant is 50%–80% for children with ACC even in the absence of family history (19, 20). Thus it should be recommended that patients and their families be evaluated by a genetic counselor. Li-Fraumeni syndrome (LFS) can predispose to many different cancers including soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumors, and leukemias. Increasing surveillance based on a positive TP53 mutation can help detect cancers early (19, 20).

Our patient's early adrenarche, first noted in her visit at 6 years 11 months with DHEA elevated for age, may be related to early exposure to androgens. This "priming" effect of androgens has also been described in non-classic congenital adrenal hyperplasia (21). Since pubic hair may or may not recede even with tumor removal, it is important to note that physical exam may be unreliable in these patients. It is thus interesting that this early adrenarche was captured solely due to close laboratory follow-up. Our patient's menarche was an appropriate age for her family. Her final height was –8.8 cm below mid parental target height (–1.76 SDs). The gap in advancement in bone age relative to chronological age narrowed with age. While within the acceptable range for mid-parental target height (± 2 SDs), it is possible that our patient may have been closer to target height without androgen excess early in life.

This is one of the first reports describing detailed long-term endocrine and pubertal in a pediatric survivor of ACC. Further studies and documentation of endocrinologic milestones in these children are needed to fully elucidate the effects on the timing of puberty and menarche.

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Figure 1.
Adrenal cortical carcinoma with pleomorphic cells and several mitoses (arrow) (200×).

Figure 2.
Adrenal cortical carcinoma positive immunohistochemically for alpha inhibin.

Figure 3.
Adrenal cortical carcinoma with zonal necrosis (arrow).

Figure 4.
Vascular invasion (arrow) by an adrenal cortical carcinoma (200×).

Table 1

ACTH stimulation test results.

	Preoperative		Postoperative (1 month)	
	0 min	60 min	0 min	60 min
Androstenedione, ng/dL ^a	2733	2642	24	35
<i>pmol/L</i>	<i>75,813</i>	<i>73,289</i>	<i>665</i>	<i>970</i>
Testosterone, ng/dL ^b	72.6 ⁿ	–	3.7	6.3
<i>nmol/L</i>	<i>2.51</i>		<i>0.128</i>	<i>0.218</i>
Dehydroepiandrosterone, ng/dL ^{c,o}	11,767	9940	50	85
<i>nmol/L</i>	<i>408</i>	<i>344</i>	<i>1.73</i>	<i>2.94</i>
Dehydroepiandrosterone sulfate, µg/dL ^d	–	–	<10	–
<i>µmol/L</i>			<i><0.271</i>	
17OHPregesterone, ng/dL ^e	271	334	17	74
<i>nmol/L</i>	<i>8.21</i>	<i>10.1</i>	<i>0.515</i>	<i>2.24</i>
17OH Pregnenolone, ng/dL ^f	116	169	41	168
<i>nmol/L</i>	<i>3.66</i>	<i>5.34</i>	<i>1.29</i>	<i>5.3</i>
Deoxycorticosterone, ng/dL ^g	–	–	16	42
<i>nmol/L</i>			<i>0.484</i>	<i>1.27</i>
11-Desoxycortisol, ng/dL ^h	1.9	–	33	169
<i>nmol/L</i>	<i>0.0548</i>		<i>0.952</i>	<i>4.87</i>
Estradiol, ng/dL ⁱ	–	–	<0.5	–
<i>pmol/L</i>			<i><18.3</i>	
Cortisol, µg/dL ^j	9.9	20.3	14	26
<i>nmol/L</i>	<i>273</i>	<i>560</i>	<i>386</i>	<i>717</i>
Adrenocorticotrophic hormone, pg/mL ^k	–	–	9.2	–
<i>pmol/L</i>			<i>2.02</i>	
Renin, ng/dL/h ^l	–	–	787	–
<i>ng/L·s</i>			<i>2.18</i>	
Dihydrotestosterone, ng/dL ^m	–	–	<2.0	–
<i>nmol/L</i>			<i><0.0690</i>	

[SI conversions are given italicized, underneath all laboratory values]. All laboratory values were obtained from the Esoterix Endocrinology Syllabus, 2015.

^a2–6 years (prepubertal children); 0 min: <10 ng/dL, 60 min: <10–35 ng/dL.

^b1–9 years (prepubertal children): <2.5–10 ng/dL. <9.2 years (Tanner 1): <2.5–10 ng/dL; 9.2–13.7 years (Tanner 2): 7–28 ng/dL; 10.0–14.4 years (Tanner 3): 15–35 ng/dL; 10.7–15.6 years (Tanner 4): 13–32 ng/dL; 11.8–18.6 (Tanner 5): 20–38 ng/dL.

^cPubertal children and adults: 1–5 years: <68 ng/dL; 6–7 years: <111 ng/dL; 8–10 years: <186 ng/dL; 11–12 years: <202 ng/dL; 13–14 years: <319 ng/dL.

^d1–5 years (prepubertal children): <57 µg/dL; 6–7 years (prepubertal children): <72 µg/dL; 8–10 years (prepubertal children): <193 µg/dL. <9.2 years (Tanner 1): 19–144 µg/dL; 9.2–13.7 years (Tanner 2): 34–129 µg/dL; 10.0–14.4 years (Tanner 3): 32–226 µg/dL; 10.7–15.6 years (Tanner 4): 58–260 µg/dL; 11.8–18.6 (Tanner 5): 44–248 µg/dL.

^e2–6 years (prepubertal children); 0 min: 7–114 ng/dL, 60 min: 50–269 ng/dL.

f_2 –6 years (prepubertal children); 0 min: 10–103 ng/dL, 60 min: 45–347 ng/dL.

g_2 –6 years (prepubertal children); 0 min: 4–49 ng/dL, 60 min: 26–139 ng/dL.

h_2 –6 years (prepubertal children); 0 min: 7–210 ng/dL, 60 min: 95–323 ng/dL.

i_1 –9 years (prepubertal children): <15 pg/mL. <9.2 years (Tanner 1): 5.0–20 pg/mL; 9.2–13.7 years (Tanner 2): 10–24 pg/mL; 10.0–14.4 years (Tanner 3): 7.0–60 pg/mL; 10.7–15.6 years (Tanner 4): 21–85 pg/mL; 11.8–18.6 (Tanner 5): 34–170 pg/mL.

j_2 –6 years (prepubertal children); 0 min: 6–19 µg/dL, 60 min: 20–33 µg/dL.

k_6 –48 pg/mL.

l_3 –4 years: 100–650 ng/dL/h.

m_1 –9 years (prepubertal children): <3 ng/dL. <9.2 years (Tanner 1): <3 ng/dL; 9.2–13.7 years (Tanner 2): 5–12 ng/dL; 10.0–14.4 years (Tanner 3): 7–19 ng/dL; 10.7–15.6 years (Tanner 4): 4–13 ng/dL; 11.8–18.6 (Tanner 5): 3–18 ng/dL.

n drawn 2 weeks prior to initial ACTH stimulation test.

o DHEA values unavailable for HPLC/MS-MS for ACTH response.

Table 2

Selected follow up laboratory data over 10 years post ACC resection.

Time post ACC resection	3 months	6 months	10 months	15 months	18 months	3 years 1 month	3 years 6 months	3 years 10 months	5 years 1 month	5 years 11 months	7 years 1 month	8 years 2 months	9 years	10 years
Chronologic age	3 years 8 months	3 years 11 months	4 years 3 months	4 years 8 months	4 years 11 months	6 years 6 months	6 years 11 months	7 years 3 months	8 years 6 months	9 years 4 months	10 years 6 months	11 years 7 months	12 years 5 months	13 years 5 months
Bone age, years	5					10					11–12			
Height, cm	107.3	111	113	116	117	126.4	128.8	131	140.8	148.3	157.8	161.8	162.6	163.2
Height, percentile	97.8	99	98.5	98.6	97.5	90.7	91.7	91	95	98	99	96	88	74
Androstenedione, ng/dL ^a	<10	<10	13	18	13	20	34	27	18	45	174	151	137	138
Testosterone, ng/dL ^b	<277	<277	360	499	360	554	943	748	499	1248	4826	4188	3800	3828
Dehydroepiandrosterone, ng/dL ^c	62	<10	67	57	72	114	183	145	161					
Dehydroepiandrosterone sulfate, µg/dL ^d	2.15	<0.347	2.32	1.97	2.49	3.95	6.35	5.03	5.58					
17OH progesterone, ng/dL ^e	14	<10	13	<10	<0.271	<0.596	0.596	0.487	1.62					
Deoxycorticosterone, ng/dL ^f	0.424	4.2	5.6	4.2	5.6	<2.0	<2.0		11	<10	95	51	104	
Cortisol, µg/dL ^g	7.8	5	8.3	7.9	5.7	7.7	6.3	7						
Adrenocorticotrophic hormone, pg/mL ^h	215	137	228	217	157	212	173	193						
						<5.0	13	15	16	9.5	26	13	18	12
						<1.10	2.86	3.3	3.52	2.09	5.72	2.86	3.96	2.64

[SI conversions are given italicized, underneath all laboratory values]. All laboratory values were obtained from the Esoterix Endocrinology Syllabus, 2015.

^a1–10 years (prepubertal children): <10–17 ng/dL; <9.2 years (Tanner 1): <10–17 ng/dL; 9.2–13.7 years (Tanner 2): <10–72 ng/dL; 10.0–14.4 years (Tanner 3): 50–170 ng/dL; 10.7–15.6 years (Tanner 4): 47–208 ng/dL; 11.8–18.6 (Tanner 5): 50–224 ng/dL.^b1–9 years (prepubertal children): <2.5–10 ng/dL; <9.2 years (Tanner 1): <2.5–10 ng/dL; 9.2–13.7 years (Tanner 2): 7–28 ng/dL; 10.0–14.4 years (Tanner 3): 15–35 ng/dL; 10.7–15.6 years (Tanner 4): 13–32 ng/dL; 11.8–18.6 (Tanner 5): 20–38 ng/dL.^cPubertal children and adults: 1–5 years: <68 ng/dL; 6–7 years: <111 ng/dL; 8–10 years: <186 ng/dL; 11–12 years: <202 ng/dL; 13–14 years: <319 ng/dL.

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$1p$ 34–129 $\mu\text{g/dL}$; 10.0–14.4 years (Tanner 3): 32–226 $\mu\text{g/dL}$; 10.7–15.6 years (Tanner 4): 58–260 $\mu\text{g/dL}$; 11.8–18.6 (Tanner 5): 44–248 $\mu\text{g/dL}$.
 $2p$ 19–144 $\mu\text{g/dL}$; 9.2–13.7 years (Tanner 1): 19–144 $\mu\text{g/dL}$; 9.2–13.7 years (Tanner 2):

$3p$ 11–155 ng/dL ; 10.7–15.6 years (Tanner 4): 18–230
 $4p$ 11–98 ng/dL ; 10.0–14.4 years (Tanner 2): 11–98 ng/dL ; 10.0–14.4 years (Tanner 3): 11–155 ng/dL ; 10.7–15.6 years (Tanner 4): 18–230

$5p$ 20–265 ng/dL .
 $6p$ 7–49 ng/dL ; pubertal children (8:00 a.m.): 2–19 ng/dL .

$7p$ 3.0–2.1 $\mu\text{g/dL}$; 4:00 p.m.: Not Determined.

$8p$ 48–64 pg/mL .