Pedicatric Mixed Functioning Adrenocortical Carcinoma: A Case Report and Review of Literature

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Abstract

Adrenocortical carcinoma (ACC) is a very rare disease in the pediatric age group. The clinic-biological profile, histopathological criteria of diagnosis, and staging of this disease in this age group are different from those of adult ACC. In this paper, we report a case of pediatric ACC presenting as Cushing syndrome that was managed with complete surgical excision. Through this case presentation, we highlight the sequential protocol of investigations and management in a child suspected of having ACC.

Keywords: Pediatric ACC, Cushing’s syndrome

Introduction

Adrenocortical tumors are very rare in the pediatric age group. According to Surveillance Epidemiology End Results data, about 14 new patient cases per year is reported in individuals younger than 20 years in the United States. ACTs represent 1.3% of all carcinomas in this age group.¹ Annual worldwide incidence is around 0.34 per million children below the age of 15 years.² In comparison, in southern Brazil (State of Paraná), the ACT incidence is 4.2 per million in the age range of 0-15 years³ with a higher prevalence in 0 to 4-year-old girls. The prevalence of this disease in this area is 15 times higher than the rest of the world. Clinico-biological profile of childhood ACT is different from its adult counterpart. The incidence of most childhood carcinomas increases with age such that 65% of cases of ACT occur in children younger than 5 years. Such differences suggest that childhood ACT may have a unique cell origin. In this report, we describe the clinical presentation and management of a pediatric ACC.
Case Report

A 13-year-old girl presented to us with a history of weight gain, short stature, and snoring, exertional dyspnea for 8 months. She consulted a general physician and then started oral antibiotics and antitussives, by which her respiratory problems subsided. After a few weeks, referred to us following developing facial hair and generalized rash. There was no associated proximal myopathy, renal calculi, bony pain, headache, palpitations, sweating, or diplopia. She did not have any co-morbid illness and no significant family history. On examination, she was conscious, oriented, and afebrile and did not have any pallor, icterus, cyanosis, lymphadenopathy, and pedal edema. Her pulse rate was 96 per minute and her blood pressure was 140/90 mm of Hg (>95th centile). Her height was 143 cm, weight 46 kg, and bone age was 12 years. She had Cushing stigmata including round face, buffalo hump, and mild purple striae over abdomen (Figure 1). Breast development was in tanner stage 4. Per abdominal examination revealed tinea corporis and cruris but no lump or ascites. Other systemic examinations were essentially normal. Imaging the abdomen with ultrasonography revealed an 85×60 mm sized complex hypoechoic left suprarenal mass. Contrast-enhanced computed tomography of the abdomen showed well-defined large hypo-attenuating retroperitoneal soft tissue mass lesion in the left retroperitoneal region with areas of necrosis. No invasion into the surrounding structures was detected (Figure 1). With clinical and radiological features that were highly suggestive of ACC, we carried out metastatic characterization using high-resolution CT (HRCT) of the thorax and bone scan, which revealed no distant metastasis. Hormonal evaluation is depicted in table 1, showing mixed functioning adrenal mass. With this evaluation, the patient was planned for open left transperitoneal adrenalectomy under general anesthesia. Intraoperatively there was no ascites, liver nodule, or para-aortic lymphadenopathy. In the left suprarenal region the mass presents no adhesions to surrounding structures, left adrenal was not visualized separately, and no inferior vena cava thrombus was identified. One short broad left adrenal vein was found draining to the left renal vein, which was divided between sutures. The specimen weighed 204 grams and their size was 11×10×6 cm (Figure 1). Patient had an uneventful post-operative recovery. She was discharged on postoperative day 6. Microscopic examination showed a tumor composed of lobules and nest of tumor cells divided by thin fibrovascular septa. The tumor cells had moderately pleomorphic nuclei, coarse chromatin, conspicuous nuclei, and moderate to abundant of eosinophilic cytoplasm. Focal areas of clear cell changes were noted. Large areas of necrosis were observed. Mitosis figures were 11 per 50 high power field. Capsular invasion and lymphovascular invasion were also observed. Hence, it was labeled as Adrenocortical
carcinoma (Modified Weiss score- 6/7) (Figure 2). Post-operative hormonal evaluation was done after 4 weeks and serum cortisol and serum DHEAS were within normal limits via a 6-month follow-up, suggesting a biochemical cure.

Discussion

The clinical manifestations and biologic behavior of pediatric ACC seem to be distinct from the ACC observed in adulthood. International Pediatric Adrenocortical Tumor Registry (IPATR) has reported that approximately 90% of pediatric ACCs are functional. Virilization, alone or in combination with signs of overproduction of other adrenal hormones, is the most common clinical presentation (84.3%). Isolated Cushing’s syndrome is rare but approximately 10% of ACCs are nonfunctional. In a study in India, Mishra et al. reported that among a cohort of 16 pediatric ACCs, the distribution of functioning and non-functioning tumors was almost equal (51% vs. 49%). Among functioning tumors, mixed hormone secreting (hypercortisolism + virilizing) was most prevalent (39.1%), followed by cortisol secreting (34.8%) and virilizing tumors (17.4%). Recent literature reports a slightly higher incidence of the functioning tumor. The reason for this shift lies in the extent of hormonal evaluation undertaken by different centers. The proposed explanation for more prevalent virilizing tumors in children is that their ACC originates from the persistent fetal zone of the adrenal cortex, which has the propensity to produce DHEA-S. Imaging modality of choice is CECT abdomen with the

Figure 2. The tumor shows a focal area of capsular invasion (a) and lymphovascular invasion (b). Vast areas of necrosis are seen (c). The tumor is composed of nests and lobules of tumor cells divided by thin fibrovascular septa (d) with cells having pleomorphic nuclei and moderate eosinophilic cytoplasm, (hematoxylin-eosin stain, 40×).
adrenal protocol. Adrenal tumor size is related to ACC such that a tumor size larger than 6 cm is highly suspicious for malignancy and 95% of ACCs are larger than 5 cm.\(^7,8\) Magnetic resonance imaging is superior to CT in detecting IVC involvement.\(^9\) PET CT is complementary to CECT; the sensitivity of PET is 90% as compared to CT 88%. PET can miss lesions smaller than 5 mm and intensity of FDG uptake in patients with ACC is related to survival.\(^10\)

Hormonal evaluation includes test for glucocorticoid excess (dexamethasone suppression test, basal cortisol, basal ACTH), test for sexual steroids (serum DHEAS, serum testosterone, serum OH-progesterone), test for mineralocorticoid excess (serum potassium, serum aldosterone, plasma rennin), and test for mineralocorticoid excess (24 hours urinary metanephrine and normetanephrine, plasma metanephrine).\(^11,12\)

Fine-needle aspiration (FNA) or core biopsy is not recommended for establishing the diagnosis of ACC due to the risk of complication of needle tract metastases and tumor spillage due to capsular breach.\(^13,14\) Wieneke criteria, which includes tumor weight, tumor size, vena caval invasion, capsular and/or vascular invasion, extension into periadrenal soft tissue, severe nuclear atypia, >15 mitotic figures per 20 high-power fields, the presence of atypical mitotic figures and confluent necrosis can help to predict the possibility of malignancy.\(^15\) A score equal to or more than four indicates ACC.

Staging of this disease in the studied age group was different from that of adults. In stage I, tumor is totally excised, tumor volume is <200 ccs, no metastasis occurs, and hormone levels are normal after surgery. In stage II, there is a microscopic residual tumor, tumor volume is >200 ccs, tumor spillage occurs during surgery, and hormone levels are abnormal after surgery. Stage III includes gross residual disease or inoperable tumor. Finally, stage IV is metastatic disease.\(^16\)

Despite extensive technological advances in the genetic field over the last 10 years, the molecular pathogenesis of adrenal tumors still remains largely unknown and routine genetic screening is not recommended.\(^17,18\)

Complete surgical removal is the best option for curing the ACC. R0 resection is a strong predictor of long-term survival. In addition, complete resection of the invaded organs including lymphadenectomy is recommended for this purpose.\(^19\) Role of tumor debulking in the presence of metastasis is debatable as survival is <12 months. Debunking can be an option if >90% of the tumor can be excised in hormone-secreting ACC or to facilitate other therapeutic options.\(^20\)

Radiotherapy in inoperable ACC is not much effective. Tumor response rate up to 42% is observed but radiotherapy is the treatment of choice in bone and brain metastasis and inoperable local recurrences.\(^7,9\) Because of the rarity of ACC, the role of chemotherapy remains undetermined. Mitotane alone or in combination with cisplatin, etoposide, and doxorubicin has been used most commonly with varying effects.\(^21,22,23\)

The 5-year event-free survival and overall survival estimates were 54.2% (95% CI, 48.2% to 60.2%) and 54.7% (95% CI, 48.7% to 60.7%), respectively, in the IPACTR series.\(^4\)
Conclusion
A high index of suspicion in a child with Cushing’s syndrome, appropriate hormonal work-up, and imaging are essential for the diagnosis of pediatric ACC. Histopathological diagnosis requires a pathologist well versed in adrenal pathology to examine all the features of malignancy. Through this case presentation, it was tried to highlight the sequential protocol of investigations and management in a child suspected of having ACC.

Informed Consent
Informed consent was taken from the patient’s father.

Conflict of Interest
None declared.

References