Case Report
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Pediatric 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 years[3] 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.

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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 (Figure1). 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. Intra-operatively 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 (Figure1). 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

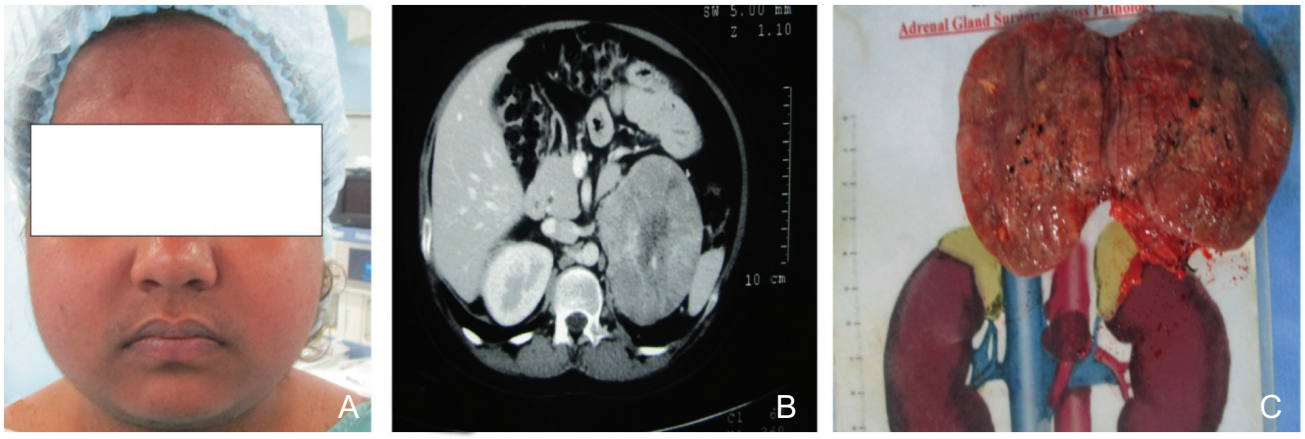

Figure 1. Figure 1. Clinical and intra-operative photographs.(A) Clinical photograph showing typical cushingoid face, (B) Contrast enhanced CT of abdomen showing large heterogeneously enhancing mass with areas of necrosis, (C) Cut surface of surgically resected gland showing greyish white mass with areas of haemorrhage and necrosis.

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.[4] 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%).[5] 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.[6] Imaging modality of choice is CECT abdomen with the

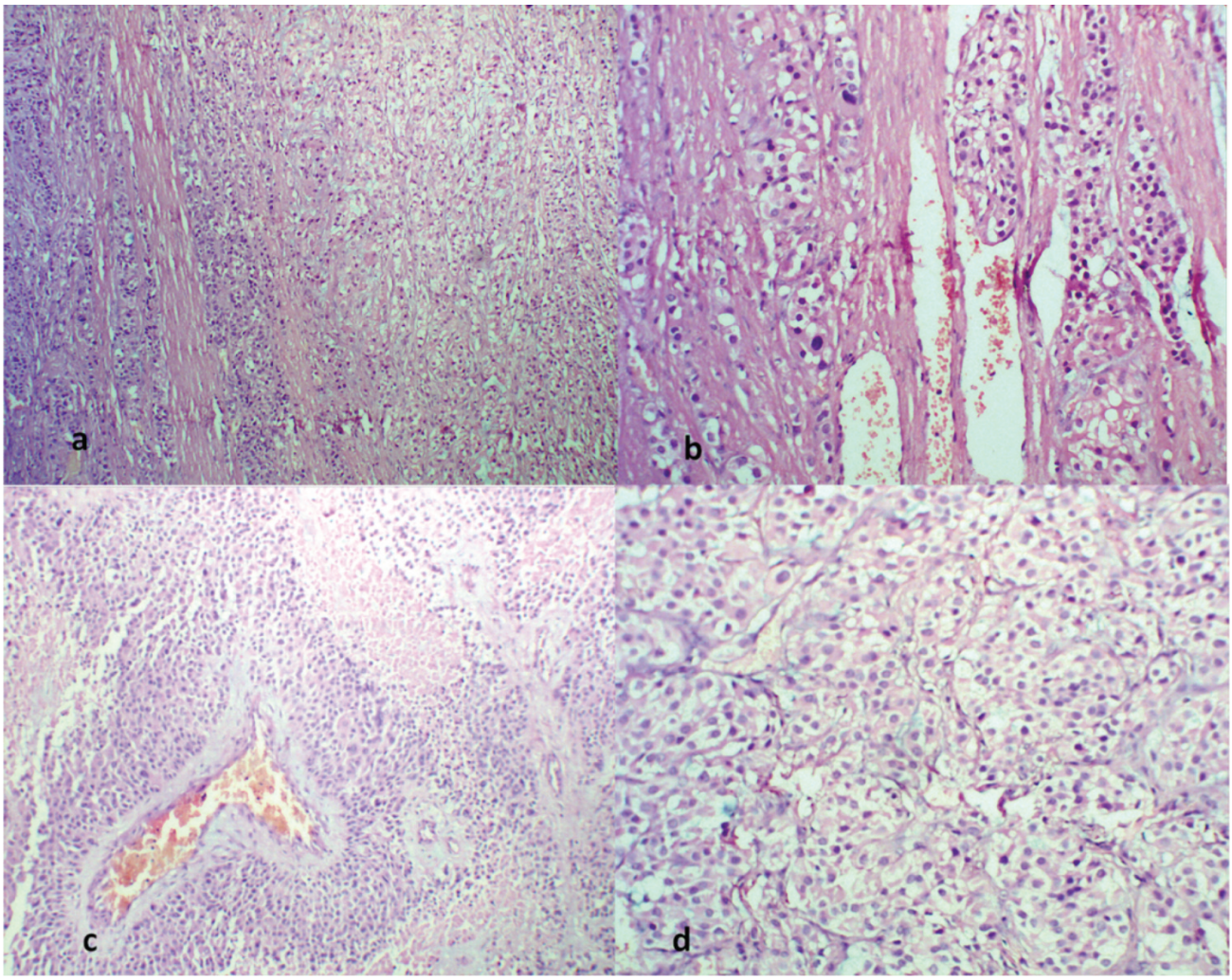

Figure 2. The tumor shows a focal area of capsular invasion (a) and lymphovascular invasion (b). Vast areas of necrosis are seen (c). The tumor is composed of nests and lobules of tumor cells divided by thin fibrovascular septa (d) with cells having pleomorphic nuclei and moderate eosinophilic cytoplasm, (hematoxylin-eosin stain, 40×).

Table 1. Hormonal workup

Parameters	Value	Reference Range	Interpretation
Simple 8 AM serum cortisol	684	138-550 nmol/L	H
Overnight dexamethasone Suppression test (ONDST)	1001	< 50 nmol/L	Non-suppressible
Serum dihydroepiandrosterone sulfate (DHEAS)	24.9	15-24 yr: 1.77-11 25-45 yr: 1.65-9.2 45-65 yr: 0.5-6.9 µmol/L	H
Serum testosterone	19.99	0.29-1.66 nmol/L	H
24 Hr urinary metanephrine and normetanephrine	103 and 223	< 600 mcg/24 hrs	

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 5cm.[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 5mm 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 cava 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. Debulking 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

1. Bernstein L, Gurney J. Carcinomas and other malignant epithelial neoplasms. In: Ries LAG, Smith MA, Gurney JG, et al (editors). Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Cancer Statistics Branch, National Cancer Institute: Bethesda, MD.1999. p.139-48.
2. Young JL Jr, Ries LG, Silverberg E, Horm JW, Miller RW. Cancer incidence, survival, and mortality for children younger than age 15 years. *Cancer.* 1986;58(2 Suppl):598-602.
3. Sandrini R, Ribeiro RC, DeLacerda L. Childhood adrenocortical tumors. *J Clin Endocrinol Metab*. 1997;82:2027-31. doi: 10.1210/jc.82.7.2027.
4. Michalkiewicz E, Sandrini R, Figueiredo B, Miranda EC, Caran E, Oliveira-Filho AG, et al. Clinical and outcome characteristics of children with adrenocortical tumors: A report from the international pediatric adrenocortical tumor registry. *J Clin Oncol*. 2004;22(5):838-45.
5. Sabaretnam M, Mishra A, Agarwal G, Agarwal A, Verma AK, Mishra SK. Adrenocortical carcinoma in children and adults: Two decades experience in a single institution. *Indian J Cancer.* 2016;53:317–21. doi: 10.4103/0019-509X.197737.
6. Buster JE. Fetal adrenal cortex. *Clin Obstet Gynecol.* 1980;23:803-24.
7. Schteingart DE, Doherty GM, Gauger PG, Giordano TJ, Hammer GD, Korobkin M, et al. Management of patients with adrenal cancer: recommendations of an international consensus conference. *Endocr Relat Cancer.* 2005;12(3):667-80.
8. Pena CS, Boland GW, Hahn PF, Lee MJ, Mueller PR. Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT. *Radiology.* 2000;217(3):798-802.
9. Allolio B, Fassnacht M. Clinical review: Adrenocortical carcinoma: clinical update. *J Clin Endocrinol Metab.* 2006;91(6):2027-37.
10. Ahmed M, Al Sugair A, Alarifi A, Almahfouz A, Al Sobhi S. Whole-body positron emission tomographic scanning in patients with adrenal cortical carcinoma: comparison with conventional imaging procedures. *Clin Nucl Med.* 2003;28:494-7.
11. Allolio B, Fassnacht M. Clinical review: Adrenocortical carcinoma: Clinical update. *J Clin Endocrinol Metab*. 2006;91(6):2027-37.
12. Dackiw AP, Lee JE, Gagel RF, Evans DB. Adrenal cortical carcinoma. *World J Surg*. 2001;25(7):914-26.
13. Mody MK, Kazerooni EA, Korobkin M. Percutaneous CT-guided biopsy of adrenal masses: immediate and delayed complications. *J Comput Assist Tomogr.* 1995;19(3):434-9.
14. Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B. Incidentally discovered adrenal masses. *Endocr Rev*. 1995;16(4):460-84.
15. Wieneke JA, Thompson LD, Heffess CS. Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. *Am J Surg Pathol.* 2003;27(7):867-81.
16. Sandrini R, Ribeiro RC, DeLacerda L. Childhood adrenocortical tumors. *J Clin Endocrinol Metab.* 1997;82(7):2027-31.
17. Koch CA, Pacak K, Chrousos GP. The molecular pathogenesis of hereditary and sporadic adrenocortical and adrenomedullary tumors. *J Clin Endocrinol Metab.* 2002;87(12):5367-84.
18. Raymond VM, Else T, Everett JN, Long JM, Gruber SB, Hammer GD. Prevalence of germline TP53 mutations in a prospective series of unselected patients with adrenocortical carcinoma. *J Clin Endocrinol Metab.* 2013;98(1):E119-25. doi: 10.1210/jc.2012-2198.
19. Schulick RD, Brennan MF. Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. *Ann Surg Oncol.* 1999;6(8):719-26.
20. Humphrey GB, et al. Overview on the management of adrenocortical carcinoma (ACC). In: Humphrey GB, Grindey GB, Dehner LP, Acton RT, Pysher TJ, editors. Adrenal and endocrine tumors in children. Cancer Treatment and Research. Vol. 17. Springer: Boston, MA;1983.
21. Zancanella P, Pianovski MA, Oliveira BH, Ferman S, Piovezan GC, Lichtvan LL, et al. Mitotane associated with cisplatin, etoposide, and doxorubicin in advanced childhood adrenocortical carcinoma: mitotane monitoring and tumor regression. *J Pediatr Hematol Oncol.* 2006;28(8):513-24.

22. Hah JO. Intensive chemotherapy with autologous PBSCT for advanced adrenocortical carcinoma in a child. *J Pediatr Hematol Oncol.* 2008;30(4):332-4. doi: 10.1097/MPH.0b013e3181647c03.
23. Arico M, Bossi G, Livieri C, Raiteri E, Severi F. Partial response after intensive chemotherapy for adrenal cortical carcinoma in a child. *Med Pediatr Oncol.* 1992;20(3):246-8.