Adrenocortical Carcinoma in a 6-Month-Old Infant

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Adrenocortical tumors comprise 0.2% of pediatric tumors. Neoplasms of the adrenal cortex are most commonly seen in adults and are rare in children and even rarer in infants. About 50% of adult patients and 90% of pediatric patients with adrenocortical tumors show hormonal dysfunction. Both benign and malignant adrenocortical tumors can be hormonally active. Adrenocortical adenomas and carcinomas can both occur in children. Carcinomas are much rarer than adenomas and have a worse prognosis. Thus, the distinction between benign and malignant tumors has vital importance and depends on the presence or absence of certain pathological and clinical criteria. Congenital adrenal hyperplasia (CAH) may also present with features of virilization, therefore, it is not easy for the clinicians to differentiate between CAH and adrenocortical tumors without histopathological examination. Herein, we report a case of adrenocortical carcinoma (ACC) in a 6-month-old infant. To our knowledge, this is the fifth case to be diagnosed with ACC at such a young age.

Case Report

A 6-month-old girl was brought by the mother with an history of abnormally appearing genitalia and excessive hair growth over the body since birth. She has no history of loss of consciousness, vomiting, diarrhea, and excessive urination. At presentation, the child was active with a weight of 6.2 kg and normal vitals, including blood pressure, which was 90/60 mmHg. Birth history was preterm normal vaginal delivery weighing 1.2 kg at birth. Immunization history and developmental history were appropriate for age. The child had a moon-like face with coarse facial features along with hirsutism [Figure 1a]. On examination, the abdomen was nontender and soft, and no lump was palpable. Genital examination revealed clitoromegaly (clitoris measuring approximately 1.2 cm) and the presence of coarse pubic hair. No gonads were palpable. The anal opening was normal.

Serum 17-alpha-hydroxyprogesterone was raised with a value of 28.24 (normal range: 0.04–0.06 ng/ml); serum cortisol was raised to 29.29 (normal range: 4.3–22.4 µg/dl).

Serum electrolytes, liver function tests, and kidney function tests were within normal limits. Karyotyping was done, which was normal for a female (46XX).

The child was further investigated, and her ultrasound showed a well-defined mass of size 5 cm × 4.8 cm with...
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A chest X-ray was normal. Subsequently, a computed tomography scan of the abdomen was done, which revealed a large well-circumscribed heterogeneous soft-tissue mass lesion, measuring 6 cm × 4.3 cm × 5.2 cm with multiple hypodense nonenhancing areas and foci of calcification in the right suprarenal region pushing the kidney inferiorly [Figure 1b]. It was indenting the inferior surface of the diaphragm and the pleura but not infiltrating it. The right adrenal was not seen separately. The left adrenal gland and kidney were normal in appearance. Other organs did not reveal any lesion on the scan.

The patient was operated. The adrenal mass was completely resected and was sent for histopathological examination.

Grossly, the mass was measuring 6 cm × 5 cm × 3.5 cm and weighing 62 g with an intact capsule, the outer surface was nodular with few areas of congestion. On serial slicing, a tumor was identified, replacing the whole of the adrenal parenchyma. Cut surface showed variegated appearance with areas of necrosis, and few cysts measuring 0.5 cm in diameter. Few septations were also noted.

On microscopy, multiple sections showed a tumor arranged in trabecular, nested, and focal diffuse pattern. The cells showed marked pleomorphism with a large round nucleus, granular chromatin, and prominent nucleoli with moderate to scant amount of eosinophilic cytoplasm. Many large bi- and multi-nucleated and bizarre cells were also noted along with focal areas of necrosis and tumor giant cells [Figure 2a and b].

Immunohistochemical stains were applied, which revealed immunoreactivity for inhibin, Melan A (focal), and synaptophysin [Figure 2c and d]. However, it was negative for chromogranin (to rule out malignant pheochromocytoma). Ki-67 score was 20%–25%, and modified Weiss score was 6/7. Finally, a diagnosis of ACC was given.

When the patient came after 4 months of surgery, her hormonal levels were investigated again, which dropped back to normal limits; however, coarse pubic hair and clitoromegaly have not decreased significantly in a 2-year follow-up period. A repeat ultrasound was also done to rule out the recurrence of the tumor.

**DISCUSSION**

ACC is a rare malignancy and is associated with aggressive biological behavior and poor outcome. Bimodal age distribution is seen with the first peak in early childhood and the second peak in the fourth to fifth decades of life. The tumors are slightly more common in women than men. Adrenal neoplasms can be classified as functional or nonfunctional depending on their ability to secrete various adrenocortical hormones. There are some reported differences in clinicopathological profile, biological behavior, and outcome of ACC occurring in children and adults. However, there are not many published studies which have specifically addressed this issue.[2]

Most of the adrenocortical tumors are sporadic; however, a few of them might be familial. Familial ACC can be associated with Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, multiple endocrine neoplasia type 1, or Carney complex.[3] The molecular pathogenesis of adrenal tumors still remains largely unclear in spite of technological advances in the genetic field in recent years.[2] Abnormalities in the insulin-like growth factor II, p53 tumor suppressor gene,
steroidogenic factor 1 overexpression, and β-catenin gene mutations have been implicated in its pathogenesis.[3]

Familial syndromes should be ruled out by taking a detailed history and performing relevant investigations. Some researchers have suggested that patients with ACC should be at least be screened for TP 53 mutation, as it has great implications for other family members.[2] Our patient did not have any clinically identifiable genetic syndrome or significant family history, and the karyotype was normal.

Table 1[1,4-6] depicts all the cases of ACC diagnosed in infants with ≤ 6 months of age to date with their age at diagnosis, sex, and presenting features. In the literature, only four cases of ACC have been published who presented before the age of 6 months, and the present case is the fifth case. This case presented with features of virilization making it difficult for the clinicians to differentiate it from CAH initially, and histopathologic diagnosis was essential to arrive at a diagnosis.

It is extremely difficult to distinguish between benign and malignant cortical tumors, and different authors have used a variety of parameters to differentiate them. Using Weiss criteria, malignancy can be diagnosed based on at least three of the following features: high nuclear grade, high mitotic rate (>5 mitoses per 50 high-power field), atypical mitotic figures, <25% clear cells, diffuse architecture, tumor necrosis, venous invasion, sinusoidal invasion, and capsular invasion.[7]

ACC in children has less aggressive clinical behavior as compared to their adult counterparts. It has been noted that among patients, the favorable prognostic factors include age <4 years, smaller tumor size, complete tumor resection, signs of virilization alone at presentation, and adenomatous tumor histology. Surgery is the most common treatment but it does not always remove all of cancer, and it can return. Patients with the disseminated or residual disease receive mitotane, cisplatin, etoposide, and/or doxorubicin, and rarely, radiation therapy.[8]

It is observed that, unlike adults, in children, the majority of adrenocortical cancers are functional, with 80%–90% having endocrine manifestations, and virilization is reported to be present in >80% of cases. However, in adults, adrenal hormone overproduction is reported to be around 40%–60%, and most commonly is hypercortisolism. A presumptive explanation for this is attributed to the fact that the fetal adrenal cortex has two different zones: the outer zone being steroidogenically latent until the late gestation and the inner zone producing steroid hormones throughout the gestation. The inner active fetal zone that is responsible for dehydroepiandrosterone sulfate makes up 85%–90% of the total fetal adrenal cortex at birth and subsequently undergoes apoptosis thereafter. Hence, it could explain the hormonally active nature of ACC in children.[1] However, in Table 1, all the cases presenting in <6 months of age presented with features of hypercortisolism, our case presented with features of both virilization as well as Cushingoid features.

**Conclusion**

A careful clinical and radiological examination along with extensive pathological workup is essential in making an accurate diagnosis. Early diagnosis can help in early and correct treatment leading to a favorable prognosis. It is imperative to avoid delay in diagnosing confusing cases presenting with features of virilization in infants.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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