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Adrenocortical carcinoma with extension to the inferior vena cava and right atrium: 20-month-old girl with TP53 mutation

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A 20-month-old female presented with respiratory distress and a right adrenal mass extending into the inferior vena cava and right atrium. The mass was initially thought to be neuroblastoma. Pathology later revealed adrenocortical carcinoma. Inferior vena cava extension is far more common in adrenocortical carcinoma than neuroblastoma, and its presence should prompt clinical and laboratory evaluation for an adrenocortical tumor. The genetic findings in TP53 associated with this disease are discussed.

Case report

A 20-month-old female presented with respiratory distress, fever, and anorexia. Physical examination revealed hypertension, tachycardia, tachypnea, and presumed hepatomegaly. A chest radiograph revealed cardiomegaly and a right paratracheal density (subsequently noted to represent a large azygous vein), prompting an echocardiogram. This demonstrated a large right atrial mass. Contrast-enhanced computed tomography demonstrated a large right suprarenal mass with occlusive thrombus in the inferior vena cava (IVC) extending to the right atrium (Figs. 1, 2). The right adrenal gland was not identified, and pulmonary metastases were absent. Based on the patient's age and the presence of an adrenal mass, a presumptive diagnosis of neuroblastoma was made.

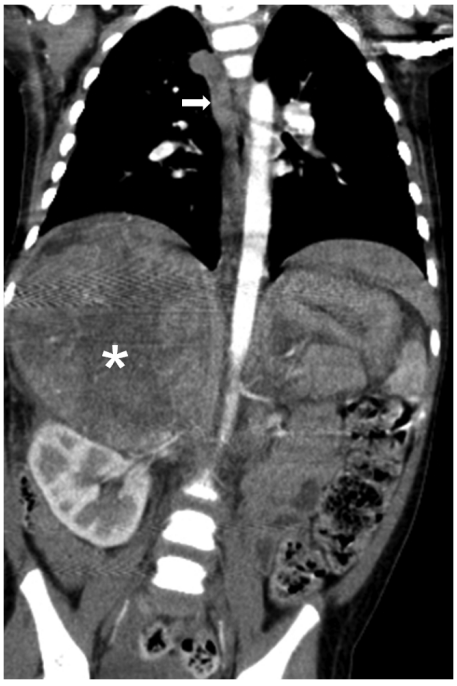

Fig. 1. Contrast-enhanced computed tomographic image of the chest and abdomen. A large suprarenal mass (asterisk) displaces the right kidney inferiorly. The aygous is enlarged (arrow).

The child, who was critically ill, was treated with etoposide and cyclophosphamide in an effort to shrink the tumor

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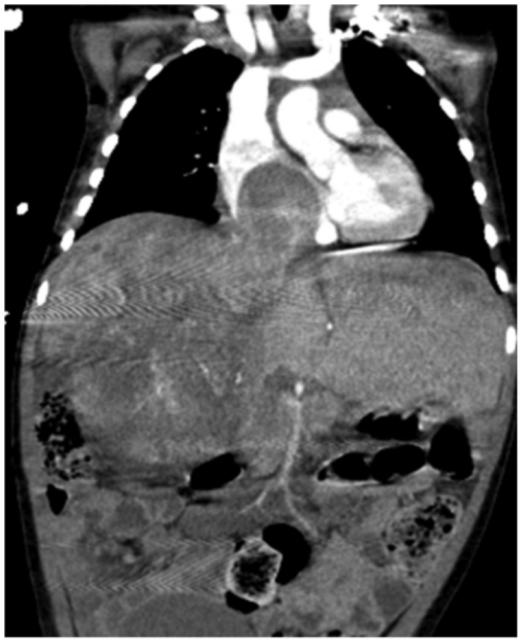

Fig. 2. Tumor extension into the IVC and right atrium is demonstrated.

and stabilize her, despite the absence of a tissue diagnosis. One cycle of chemotherapy complicated by marked marrow suppression resulted in no change in tumor size. MIBG scan and urine catecholamines were negative. Transjugular biopsy of the right atrial mass was performed, and pathology revealed adrenocortical carcinoma (ACC). Laboratory workup was notable for elevated cortisol 25.7 ug/dL (normal, 5-25 ug/dL), testosterone 253 ng/dL (normal, 5-81 ng/dL), and androstenedione 473 ng/dL (normal, 5-51 ng/dL). Mild clitoromegaly was appreciated. There were no other signs of virulization.

Gross tumor resection was performed with normalization of endocrine biomarkers. Despite residual disease, the family declined chemotherapy after one cycle. Germline exome analysis of the TP53 gene identified a disease-causal heterozygous c.818G>A (p.R273H) mutation. The tumor recurred after three months, and the patient died 5 weeks later. No family history of neoplasm was elicited, and the parents declined further genetic testing.

Discussion

ACC is rare in children in the United States, with an incidence of 0.3-0.4 cases/million children. The median age at diagnosis is 3 years, and females are affected twice as often as males (1).

TP53 is a tumor suppressor gene that is mutated in at least 2/3 of children with ACC in North America. Germline TP53 mutations are less frequently identified in children with ACC over ten years of age. Lack of normal p53 protein function leads to proliferation of cells containing damaged DNA, and malignant transformation (2). Most germline TP53 mutations are associated with Li-Fraumeni syndrome, an autosomal dominant disorder characterized by a wide range of early-onset malignancies including ACC, soft-tissue and bone sarcomas, leukemia, brain tumors, and breast cancer (3).

It has been recognized for forty years that there is a much higher incidence of childhood ACC in southern Brazil compared to North America. Ninety percent of affected children in Brazil exhibit a founder germline TP53 mutation (p.R337H) that is not found in North American cases (4).

Whether in North America or Brazil, almost all ACCs secrete excess adrenal hormones causing virilization, feminization, Cushing syndrome, or Conn syndrome. Hypertension is common. Levels of urinary 17-ketosteroids and plasma biomarkers, including testosterone, androstenedione, cortisol, and DHEA-S are often elevated. Prognosis is poor in cases with local invasion or metastases.

In the present case, a presumptive diagnosis of neuroblastoma was made based on the presence of an adrenal mass and the patient's age. However, tumor thrombus involving the IVC and right atrium is exceedingly uncommon in neuroblastoma, with few reported cases in the literature (5). In contrast, there are repeated examples of ACC extending into the IVC and right atrium (6). In a series of 92 patients, venous extension of the tumor was noted in 19.6% of patients. Right atrial extension was much less common, occurring in approximately 1% of cases (7).

Thus, the identification of vascular extension in this patient might have favored the correct diagnosis of ACC since, in a young child with a right-upper-quadrant mass extending into the IVC and right atrium, the diagnosis is much more likely to be ACC than neuroblastoma.

Differentiation of ACC from Wilms tumor requires accurate identification of the organ of origin, which in the presence of a large mass may be difficult using ultrasonography alone and may require imaging with computed tomography or MRI. Vascular extension of the tumor is a well-recognized feature of Wilms tumor, with IVC and right atrial extension occurring in 4% and 1% of cases, respectively (8).

In a child with an adrenal mass and IVC thrombus, ACC should be considered. A prompt, detailed physical examination and laboratory testing for adrenocortical hormone excess should be performed. As childhood ACC is often the first manifestation of Li-Fraumeni syndrome (9), a familial history of cancer should be sought and genetic testing performed.

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