Adrenocortical Neoplasms in Young Children: Age as a Prognostic Factor

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Abstract. Adrenal cortical neoplasms in pediatric patients are rare. The clinical manifestations and biologic behavior of these tumors can be quite distinct from their histologically similar counterparts in the adult population. We report 5 cases of adrenocortical neoplasms in young children and review their clinical presentations, pathology, and follow-up data. Pathologic evaluations included histology and immunostains with p53 and Ki-67. The patients were 3 girls and 2 boys, 13-28 mo of age. The patients all presented with virilization and other hormone-related symptoms for an average duration of 6 mo. Serum testosterone levels were elevated in 3 cases. Imaging studies revealed neoplasms in the left adrenal gland in 3 cases and the right adrenal gland in 2 cases. No evidence of disease was identified at any other site of the body. The tumors were grossly confined to the adrenal glands and ranged in diameter from 3 to 6 cm (mean 4.3 cm). Microscopically, the tumors had histological and immunophenotypic features characteristic of adrenocortical tumors. Additional features noted included capsular and/or vascular invasion, severe nuclear atypia, high mitotic rate (>15 mitotic figures/20 high power fields), and atypical mitotic figures. Necrosis was present in one case. Immunohistochemical staining indices for p53 and Ki-67 were >20%. After follow-up periods ranging from 5 mo to 9.5 yr, all patients were alive and free of disease. Despite histological and immunophenotypical evidence of malignancy, these localized adrenocortical neoplasms had a benign clinical course with no evidence of metastasis or recurrence. Age is an apparent prognostic factor as these patients were <3 yr old. Because of the discrepancy between pathology and clinical outcome, adrenocortical tumors in this age group should be classified as neoplasms of unknown malignant potential.

Keywords: adrenocortical tumors, pediatric oncology, Ki-67, p53

Introduction

Neoplasms of the adrenal cortex are most commonly seen in adults and are rare in children. The average age for adrenocortical carcinoma is about 50 yr. Only about 25 new cases in patients younger than 20 yr are diagnosed per year in the USA [1]. Higher incidence of pediatric adrenocortical tumors occurs in Brazil [2]. The tumors are slightly more common in females. These tumors can be found incidentally at autopsy or as a result of radiographic investigations done for other reasons, or they may be detected because of symptoms or signs related to hormonal dysfunction. About 50% of adult patients and 90% of pediatric patients with adrenocortical tumors show hormonal dysfunction [3]. Both benign and malignant adrenocortical tumors can be hormonally active [4,5].

Adrenocortical tumors (ACTs) in children may occur sporadically or as a component of certain hereditary tumor syndromes, ie, Li-Fraumeni syndrome, multiple endocrine neoplasia-1, Beckwith-Wiedemann syndrome, Carney complex, and congenital adrenal hyperplasia [6,7]. Adreno-
cortical adenomas and carcinomas can both occur in children. Carcinomas are much rarer than adenomas and have a worse prognosis. Patients with malignant adrenocortical tumors have a 5-yr survival rate of 49-55% [3,8]. The poor prognosis is directly related to the presence of residual or metastatic disease. Thus, the distinction between benign and malignant tumors has vital importance and depends on the presence or absence of certain pathologic and clinical criteria. In this article, we present 5 cases of adrenocortical neoplasms in young children and discuss the clinicopathologic features of the tumors and follow-up information.

**Materials and Methods**

Clinical and pathology records of 5 patients who were <3 yr of age and had surgery for adrenocortical neoplasms were reviewed. Existing histologic slides and immunostains were reviewed to confirm the accuracy of the diagnoses. Additional immunostains for Ki-67 and p53 were performed on 5 and 4 cases respectively.

**Results**

The patients were 3 females and 2 males with ages ranging from 13-28 mo. Clinicopathologic features of the 5 cases are listed in Table 1 and the histological features of the tumors are summarized in Table 2. The percentages of tumor cells with positive nuclear staining for Ki-67 and p53 were calculated and the results from areas with highest staining are included in Table 2.

**Case 1.** A 19-mo-old male with right adrenal tumor had symptoms and signs of virilization and Cushing’s disease. Serum testosterone levels were elevated and reached 29 ng/dl (normal for age: <3 to 10 ng/dl). Dehydroepiandrosterone (DHEA) and DHEA-sulfate levels were also increased. Serum cortisol and desoxycortisol levels were increased to 33 μg/dl and 294 ng/dl (normal for age 2.1-18.1 μg/dl and 20-155 ng/dl, respectively). There was no evidence of metastatic disease. The patient underwent surgery for resection of his adrenal tumor. The resected specimen weighed 23 g and measured 6.5 x 5.5 x 3.5 cm. On cut section, the tumor mass had a nodular appearance; it was compressing and flattening the residual adrenal gland. Microscopically, nodules of tumor cells were separated by thick fibrous bands and contained diffuse sheets and nests of monomorphous tumor cells with eosinophilic cytoplasm and central round nuclei. Other cells were large and oncocytoid with abundant granular eosinophilic cytoplasm and markedly pleomorphic and hyperchromatic nuclei. No necrosis or hemorrhage was evident. Mitotic figures were noted (4/hpf). Vascular or capsular invasion was not observed. Oil Red-O stains shows regions of tumor cells that stained 4+ (on a scale of 1 to 4) for intracytoplasmic lipid. The Ki-67 proliferative index was 20%; however, p53 immunostaining was negative. Eight years after the adrenal tumor resection, the patient is in excellent health with no evidence of recurrence or metastasis.

**Table 1. Clinicopathologic features of 5 cases of adrenal cortical neoplasms.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (in months)</th>
<th>Sex</th>
<th>Primary site</th>
<th>Specimen weight (g)</th>
<th>Vena caval invasion</th>
<th>Extension into periadrenal soft tissue and/or adjacent organs</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Male</td>
<td>Right</td>
<td>23</td>
<td>No</td>
<td>No</td>
<td>8 yr</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>Male</td>
<td>Left</td>
<td>59</td>
<td>No</td>
<td>No</td>
<td>9 ½ yr</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>Female</td>
<td>Left</td>
<td>11</td>
<td>No</td>
<td>No</td>
<td>9 mo</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>Female</td>
<td>Left</td>
<td>10</td>
<td>No</td>
<td>No</td>
<td>5 mo</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>Female</td>
<td>Right</td>
<td>51</td>
<td>Yes</td>
<td>No</td>
<td>5 yr</td>
</tr>
</tbody>
</table>
both p53 and Ki-67 (index of 20%). The patient is alive without evidence of disease 9.5 yr after the tumor resection.

**Case 3.** A 28-mo-old female with a history of hirsutism and mood swings was found to have a tumor in the left adrenal gland and underwent adrenalectomy. The resected specimen measured 4.0 x 2.5 x 2.2 cm and weighed 11.0 g. The tumor was encapsulated and compressed the adrenal gland. The tumor cells, arranged in diffuse sheets, were moderate to large in size with abundant predominantly eosinophilic cytoplasm. Cells containing clear cytoplasm were identified, comprising <25% of the tumor. The cells had hyperchromatic and pleomorphic nuclei and some cells were large containing bizarre nuclear morphology (Fig. 1). Mitotic figures were found at a rate of 1-2/hpf, including a few atypical mitotic figures. Small foci of calcifications were present. The tumor had limited areas of capsular invasion as well as invasion into the sinusoidal veins. No necrosis was seen. The tumor cells stained with vimentin, inhibin, and synaptophysin and were negative with chromogranin and S-100 stains. More than 50% of the cell nuclei stained with p53; the Ki-67 (MIB-1) proliferation rate was 20 to 30% (Fig. 1). The tumor was diagnosed as a carcinoma, but at 9 mo after surgery, the patient shows no evidence of disease.

**Case 4.** A 21-mo-old female presented with symptoms and signs of virilization. A solid mass was detected in the left adrenal gland. Adrenalectomy was performed and a lobulated mass was resected, measuring 3.0 x 2.0 x 1.5 cm, and weighing 10 g. The mass had an orange tan-yellow lobulated cut surface. Microscopic sections demonstrated a large tumor compressing the adrenal gland and surrounded by a fibrous capsule. Tumor lobules were separated by broad fibrous bands (Fig. 1). The tumor cells were large with abundant eosinophilic or finely granular cytoplasm. Many cells were highly atypical with bizarre, condensed, or smudgy nuclei. There were gigantic cells with single or multiple abnormal nuclei and prominent nucleoli. There was no necrosis. Capsular and vascular invasion was focally identified (Fig. 1). Twelve mitotic figures/20 hpf were seen, and some of these were atypical. The tumor cells stained strongly with inhibin, vimentin, and melan A. The p53 immunostain was positive and the Ki-67 proliferative index was generally 10 to 20%, with a higher rate identified in localized areas. The patient's serum hormone levels returned to normal after surgery and after a brief follow-up period of 5 mo, the patient has no evidence of disease.

**Case 5.** A 13-mo-old female had developed pubic hair, hirsutism, and body odor at 6 mo of age. The pubic hair became progressively darker and longer. She had an elevated serum testosterone level of 690 ng/dl (normal 2-10 ng/dl) and DHEA-S level of 556 μg/dl (normal <30 μg/dl). A right adrenal tumor was resected. The adrenalectomy specimen measured 6 cm in its greatest dimension and weighed 51 g. Histologically, tumor cells were arranged in nests surrounded by broad fibrous septa. Some tumor cells resembled normal adrenocortical cells. Other cells were large with bizarre pleomorphic nuclei, focal multinucleation, and prominent nucleoli (Fig. 1). The mitotic rate was high, reaching about 20/20 hpf in some areas. Atypical mitoses were frequently found (Fig. 1). Large areas of necrosis (30% of tumor area) and other areas with calcification were seen throughout the tumor mass. No capsular invasion was identified. However, small sinusoidal vessels were focally invaded by tumor cells. The tumor cells were negative for chromogranin, S-100, and cytokeratin immunostains. The Ki-67 proliferation index was very high and focally reached 50%. The tumor was diagnosed as a carcinoma but the patient is alive and well at 5 yr after the surgery.

**Discussion**

Traditionally, adrenocortical tumors (ACT) in adults have been divided into adenomas and carcinomas. While the presence of metastasis remains the absolute evidence of malignancy, classifying localized tumors as benign or malignant may be challenging for both the pathologist and

| Table 2. Microscopic and immunophenotypic features of 5 cases of adrenal cortical neoplasms. |
|---------------------------------|----------|----------|----------|----------|----------|
| Vascular invasion              | -        | +        | +        | +        | +        |
| Capsular invasion              | -        | +        | +        | +        | -        |
| Dense band fibrosis            | -        | +        | +        | +        | +        |
| Nuclear pleomorphism           | +        | +        | +        | +        | +        |
| Prominent nucleoli             | -        | +        | +        | +        | +        |
| Mitoses/20 hpf                 | 5        | 20       | 16       | 12       | 20       |
| Necrosis                       | -        | -        | -        | -        | +        |
| Calcification                  | -        | +        | +        | +        | +        |
| p53                            | Negative | 50%      | 50%      | 30%      | Not performed |
| Ki-67 (maximum index in focal areas) | 20%    | 20%      | 30%      | 20%      | 50%      |

+ present; - absent
Fig. 1. The histology of the adrenocortical tumor in case 3 revealed large cells with eosinophilic and clear cytoplasm and pleomorphic bizarre nuclei (panel A, H&E, x400). Large nucleoli, multinucleation, and atypical mitotic figures were clearly evident in case 5 (panel B, H&E, x400). Broad fibrous bands with vascular invasion (panel C, H&E, x100) were also present in case 4 as well as small areas of capsular invasion (panel D, H&E, x200). In case 3, the tumor cells revealed a high index of immunostaining with p53 (panel E, x400) and the Ki-67 proliferation rate was about 20% (panel F, x400).

the treating physician. Identifying the presence of malignancy is of vital importance to the patients’ prognosis and overall survival. Numerous criteria have been developed to distinguish between benign and malignant tumors. Microscopic criteria, suggestive of malignancy (commonly referred to as the Weiss criteria) include high nuclear grade, mitotic rate ≥5/50 hpf, atypical mitoses, paucity or absence of clear cells, diffuse architecture, necrosis, capsular invasion, and vascular (venous or sinusoidal) invasion. Another feature suggestive of malignancy is spindling of the tumor cells [9,10]. The value of this approach in adults has been documented in numerous articles by independent observers.

Distinguishing benign from malignant tumors may be particularly challenging in children. Earlier studies disclosed that although adrenocortical neoplasms in children may have pathologic features similar to adult tumors, their prognosis in terms of
disease-free survival after complete surgical resection is apparently different. On the basis of pathologic criteria without the incorporation of clinical outcome, it appears that the majority of ACTs in children are interpreted pathologically as malignant in various studies. The prognosis of these tumors in children is, however, more favorable when compared to adults. In a study by Wienecke et al [11], >89% of ACTs were classified pathologically as adrenocortical carcinomas but only 31% of these histologically malignant tumors behaved in a clinically malignant fashion. This implies that the distinction between benign and malignant ACT in children depends on different clinicopathologic features than in adults.

Numerous pathologic parameters have been evaluated for identifying malignancy or to predict prognosis. Features with increased probability of malignant behavior include tumor diameter >10.5 cm, tumor weight >400 g, capsular and/or vascular invasion, extension into the periadrenal soft tissues, severe nuclear atypia, >15 mitotic figures per 20 hpf, and presence of atypical mitotic figures. Invasion of the inferior vena cava and confluent necrosis are also independent predictors of malignant clinical behavior [11]. Increased mitotic activity alone is prognostically unfavorable in adult tumors but not in children [10,11]. The presence of bizarre nuclei or marked nuclear pleomorphism has no predictive value, as it is present in numerous benign and malignant cases, including our own. In conclusion, a child with a completely resectable ACT that weighs <400 g and shows minimal necrosis has the best prognosis [12].

The roles of expression of p53 and a high Ki-67 proliferation index have also been investigated and found to correlate with malignancy [13]. In fact, high Ki-67 proliferation index was labeled as a useful marker of malignancy in numerous studies [14,15]. Ki-67 proliferation rates of more than 5 or 7% are more likely to be associated with malignancy. Other studies underemphasized the importance of these two markers as some adrenocortical adenomas in children were found to be positive for p53 and some carcinomas in children had Ki-67 proliferation rates that were negative or as low as 3.7% [16-18]. Thus, it appears that no feature, short of detection of metastases, discriminates in an absolute fashion between adrenocortical adenomas and carcinomas in pediatric cases.

Few studies have characterized adrenocortical tumors in neonates and children <3 yr of age. The clinical impression that tumors in this age group behave better than in older children has been partly substantiated by case reports. Some of the above-mentioned criteria may play a role in characterizing benignity versus malignancy. Other criteria such as tumor weight need to be modified as a weight >400 g is unexpected in small-sized pediatric subjects. Cases of metastatic adrenocortical carcinomas have been described in this age group with tumors weighing 117 and 125 g [19,20]. In a study of 33 Brazilian children aged 2-mo to 8-yr, tumor weight <100 g was associated with a good outcome [18].

Our 5 cases all occurred in children <3-yr-old. The tumor weights were considerably less than what is reported in the literature as indicative of malignancy. Case 1 can reliably be called adenoma on a histological basis. The remaining cases had high levels of expression of p53 and/or Ki-67 and qualified for the diagnosis of adrenocortical carcinoma with additional histologic criteria. Although two cases had <1-yr follow-up, the clinical course was benign in all cases with no evidence of metastasis or recurrence. These good outcomes may be related to the patients’ young ages and/or low tumor weights, two factors that are interrelated.

Review of our cases indicates that adrenocortical tumors in the very young age group behave clinically differently from those occurring in older children and adults; tumors in young children and infants are most likely associated with the best overall prognosis and may not be as uniformly fatal as they are in older children, even with histologic evidence of malignancy. Although this conclusion may seem ambitious in view of the small number of cases in our study, it is strongly supported by similar cases in the literature [12]. In the study by Wienecke et al [11] an age <5.4 yr was associated with better outcome. In a study of 78 Brazilian children with adrenocortical carcinoma, the survival rate was 82% for children <2 yr-of-age, compared to 29% in older children [21]. Age is an important prognostic factor even in the presence of tumor extension into the inferior vena cava, as seen in one of our cases and also in cases reported by Wienecke.
et al [11]. A few cases of metastatic adrenocortical tumors in young patients have been reported and have been associated with good survival [12,19].

Thus, it appears that the histologic distinction between adrenal cortical adenoma from carcinoma in young children (<3 yr) carries less relevance than in older children or adults. Therefore, it is better to be noncommittal and designate the adrenocortical neoplasms in young children as of “unknown malignant potential.” Such designation necessitates close follow-up by the clinician but reduces the anxiety associated with carcinoma designation. As the age of the child at diagnosis approaches adulthood, the prognosis will vary depending on the histology of the adrenocortical tumors. In older children, combined evaluations of clinical features, tumor size and weight, microscopic appearance, and immunohistochemical/molecular genetic data are necessary to categorize these tumors and predict their prognosis.

References


