Giant virilizing adrenocortical carcinoma in a girl presenting with mutism

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Abstract

Adrenocortical tumors (ACT) are rare tumors of childhood. There are some difficulties in classification of pediatric ACT as adrenoma or carcinoma. Prognostic characteristics as well as treatment choices are controversial. In general, virilizing ACT are presenting at earlier age than non-functional tumors. Here we presented an early presented, delayed diagnosed giant virilizing adrenocortical tumor in a girl presented with mutism. Present case is interesting both in complaints at the presentation and the nature of tumor biology. Based on previously reported prognostic criteria present case had borderline characteristics and treatment option was only total resection of the tumor without adjuvant chemotherapy.

Introduction

Pediatric adrenocortical tumors (ACT) are rare and account only 0.2% of childhood tumors.1 Adrenocortical carcinoma (ACC) is an extremely unusual, and highly malignant childhood tumor. Its incidence is reported 0.3 cases per million per year in children.2 Bimodal age distribution occurs with the first peak occurring before five years of age and the second peak in the fourth to fifth decade of life. Adrenal tumors can be classified as functional (FT) when their hormonal secretions result in clinical consequences: Cushing syndrome, virilization syndrome, feminization syndrome, or a mixed Cushing-virilizing syndrome. Tumors are considered non-functional (NF) when the tumors do not secrete excessive hormones or produce hormonal precursors and/or active hormones in quantities insufficient to have clinical consequences.3 In children patients with functional ACT generally present with virilization signs or stigmata of Cushing syndrome.4,5 In clinical practice signs and symptoms of secreted hormones provide diagnosis of functional adrenocortical tumors at early age comparing to non-functional tumors. We describe a giant virilizing ACC in a girl presented with complaint of mutism caused by deepening in her voice.

Case Report

A 5.5 year-old girl was admitted to our clinic with mutism caused by deepening in her voice. Previous history revealed that she was born as fourth child of non-consanguinous parents, after a 39 weeks pregnancy and uneventful delivery. Her birthweight was 3000 gr. She was admitted to another hospital at the age of 1 year with the complaint of appearance of pubic and axillary hair. She has been evaluated for congenital adrenal hyperplasia and none of imaging studies was performed. Clinical follow up was recommended. However, the parents could not have brought the child to the regular follow up because of social-economic deprivation. During subsequent years, clinical progression of virilization have resulted in deepening of voice and ultimately a voluntary mutism have occured which was the chief complaint for admission to our clinic.

At the time of admission, in physical examination her weight was 28 kg (97 percentile), height was 120.7 cm (90-97 percentile). There were signs of virilization (deepening in voice, hyperpigmentation in genital area and areola, facial acne, hirsutismus and clitoromegaly). Tanner staging of pubertal development was revealed stage 1 breast development, presence of axillary hair and stage 4 pubic hair. Laboratory examination showed elevated adrenal androgens (Table 1). Radiological investigations revealed advanced bone age (10.5 years). Abdominal ultrasonography and computerized tomography showed a large (13x11.4 cm) cystic, heterogeneous mass on right adrenal localization (Figure 1). There was no sign of metastases in PET scan.

Clinical and laboratory findings were consistent with virilizing adrenocortical tumor and the patient underwent surgical resection.

Table 1. Hormonal evaluation before and after surgical resection of tumor

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/dL)</td>
<td>629</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>DHEAS (µ/dL)</td>
<td>1543</td>
<td>&lt;15</td>
<td>0-60</td>
</tr>
<tr>
<td>17(OH) progesteron (ng/mL)</td>
<td>15.5</td>
<td>0.3</td>
<td>0-1.8</td>
</tr>
<tr>
<td>Cortisol (µg/mL)</td>
<td>35.9</td>
<td>1.72</td>
<td>5-15</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>9.22</td>
<td>75.8</td>
<td>0-46</td>
</tr>
</tbody>
</table>

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Figure 1. Computerized tomography image of tumoral mass on the right adrenal localization.
wide eosinophilic-vacuolized cytoplasm and large hyperchromatic nucleus (Figure 2 a,b). Immunohistochemical examination showed positive staining with synaptophysin, negative staining with pan-cytokeratin (PCK), chromogranin, melan A, HMB45 and vimentin (Figure 2 c). Ki-67 proliferation index was 25% (Figure 2 d). The present case consisted of 5 of 9 Weiss criteria.6,7 This criteria was high nuclear grade, mitotic rate six or more per 50 high power fields, atypical mitoses diffuse architecture pattern more than 1/3 of the tumor and confluent necrosis. Both with clinical and histopathologic findings according to Weiss criteria a diagnosis of carcinoma was concluded rather than adenoma. Perioperative and post operative steroid replacement therapy was given to prevent adrenal insufficiency. After operation complete hormonal resolution was observed (Table 1). Patient is under close follow up and in complete remission without adjuvant chemotherapy at fifth month after surgery.

**Discussion**

Adrenocortical carcinoma of childhood is a rare but highly malignant tumor. Functional ACT present with signs and symptoms of virilization or Cushing syndrome according to hormones secreted from tumoral cells.3 Symptoms of virilization or Cushing syndrome provide the pivotal clue to diagnose ACT at earlier age. Present case is interesting both in complaints at the presentation and the nature of tumor biology.

Firstly, signs and symptoms appeared at an early age (1 year) as expected in virilizing ACC. However, because of social and economic deprivation her family could not bring the patient to the regular follow up and diagnosis was delayed. Interestingly her major presenting symptom on admission to our clinic was mutism, caused by coarsening of the voice and unwillingness to speak. On the other hand, despite long period passing from the initial symptoms (at the age of 1) through age at the diagnosis (5,7 years), the biological behaviour of the tumor was not consistent with a typical ACC.

The pathologic classification of pediatric ACT is controversial. It is difficult to differentiate carcinoma from adenoma.8,9 Invasion of surrounding tissues and distant metastases help define these neoplasms as carcinomas. However, in the absence of these characteristics, differentiating between adenomas and carcinomas is critical as well as controversial.13 Weiss criteria both in adults and children are mostly used in histopathologic classification.6,7 Present case included 5 of 9 Weiss criteria. Bugg et al. modified Weiss criteria to analyze pediatric ACT. This classification was based on mitotic index, confluent necrosis, atypical mitoses and nuclear grade. The present case was low grade ACC according to this classification.10,11

Regarding staging in our case, the tumor was resected with negative surgical margins and there was no evidence of metastases. However, tumor size was too large (750 g). Complete hormonal resolution was achieved after surgery. Thus, present case was stage II, low grade adrenocortical carcinoma.11 Since pediatric ACT are extremely rare and clinical expression is heterogeneous, prognostic factors have been difficult to establish in this age group.5,11 Evaluation of prognostic criteria in our case revealed that large tumoral mass (750 gr), high mitotic index, high Ki-67 proliferation index (25%), atypical mitoses, age at the time of the diagnosis and long duration between the initial symptoms and the diagnosis were poor prognostic criteria.11 However, total resection of the tumor with negative surgical margins, absence of vascular and capsular invasion, confluent necrosis, absence of metastasis, complete resolution of the hormonal and the clinical findings were in favor of good prognosis.6,11 It is accepted that, surgery is the single most important procedure in the successful treatment of ACT. The role of chemotherapy in the management of childhood ACT has not been validated.
been established. Similarly, decision in our patient was difficult since the patient exhibit both poor and good prognostic features of an ACT. Taking into consideration the borderline nature of the tumor in the present case and the family’s opposition to chemotherapy, we decided to follow-up the patient without adjuvant treatment. Now patient is in complete remission without any complaint at fifth month after surgical resection. Fortunately, with resolution of hyperandrogenism findings and normalization of hormonal profile the patient’s mood was improved. Based on the clinical and treatment characteristics of present patient we speculate that, the type of the ACT in our case was borderline in nature. In this type of ACT close follow-up after the total resection of the tumor without chemotherapy and radiotherapy can be a management strategy. However, before coming to strict conclusions, it is necessary to see the long-term results of present case and large patient series including cases similar to our patient and carrying borderline characteristics of ACT.

References