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A Rare Form of Cushing's Syndrome in a 10 Year Old Child

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ABSTRACT

Adrenocortical carcinoma as a cause of Cushing's syndrome in a child is a rare occurrence. Functioning adrenal carcinomas are detected usually when they are small while non-functioning tumors are incidentally detected when they grow to a large size. Here we report a case of Cushing's syndrome due to large functioning adrenal carcinoma(>12 cm in size) in a 10 year old female child who presented with clinical features of Cushing's syndrome along with virilisation.A combination of biochemical laboratory reports along with radiological investigations followed by histopathology helped us to arrive at a proper diagnosis. The tumor was ressected and the patient showed clinical signs of improvement. However, the surgical margin showed invasion by the tumor making a likely possibility of recurrence in the near future.

Keywords: Adrenocortical carcinoma;Computed Tomography Scan of abdomen; Cushing's syndrome; recurrent disease; total resection.

INTRODUCTION

With a reported incidence of one to two cases per million, adrenocortical cancer (ACC) is a rare disease with poor prognosis.[1] Age distribution shows two peaks: early childhood and between age 40 and 50 years, with females more frequently affected.[1] Malignant adrenal tumors in children are more likely to be neuroblastomas than cortical carcinomas. Functioning adrenal carcinomas are usually detected when small and Cushing's syndrome is the most common manifestation of these tumors. Diagnosis depends on clinical presentation, imaging with Computed Tomography (CT) / Magnetic Resonance Imaging (MRI) and laboratory findings of elevated hormonal levels.Ultrasonography can demonstrate large adrenal masses but CT scan is more specific as it more clearly localizes the lesion and itsspread to adjacent structures. Moreover, liver metastasis can be easily detected by CT. Total resection is the management modality of choice. Recurrent local and metastatic disease is common for which adjuvant treatment should be provided if available. The overall five-year survival rate of ACC is less than 30% in part owing to advanced stage of the disease at diagnosis and limited efficiency of therapies when initial surgery is not curative.[2]

CASE REPORT

A 10 year old hypertensive female child with normal developmental history presented with complaints of progressive weight gain despite normal appetite for two years followed by excessive growth of hair with multiple papules all over the body for one year. On examination, the child was overweight with a Body Mass Index(BMI) of 28. Her blood pressure was controlled with anti-hypertensive therapy. A typical moon's facies was noted with multiple acnes over the face, chest and both arms. Features suggesting hirsutism were seen over the chin, upper lips and both upper and lower limbs (Figure 1). Breasts were at Tanner stage III. During examination of the abdomen, a non-tender, firm, non-ballotable mass was palpated over the left lumbar region. Initial laboratory studies were normal including her random blood glucose level. Ultrasonography of the abdomen revealed a solid mass at upper part of left kidney.She was then advised for Intravenous Urogram (IVU) which showed drooping of left renal calyces with preservation of excretory function of both the kidneys.

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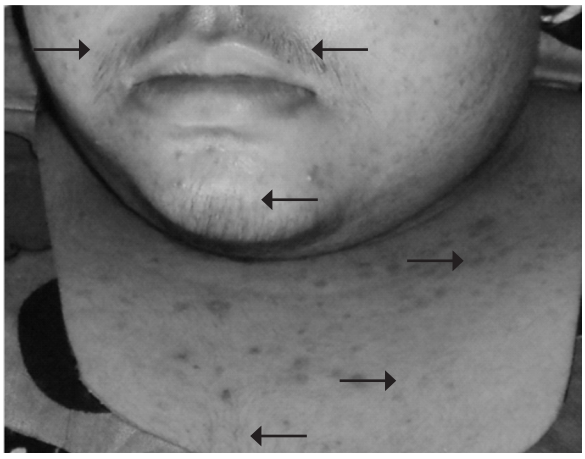

Figure 1.Excessive growth of hair (black arrow) along with acne (notched white right arrow) over the face and upper chest.

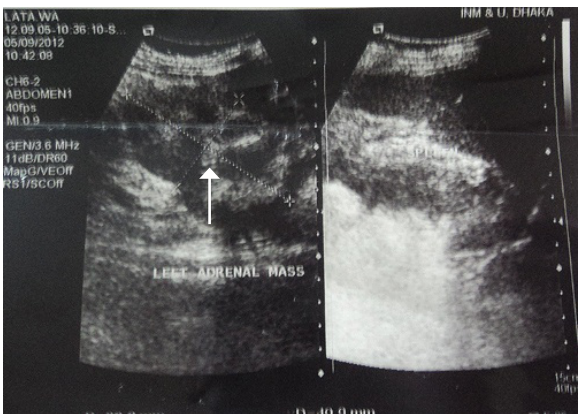

Figure 2. Ultrasonography of abdomen showing the presence of a large suprarenal mass (red arrow).

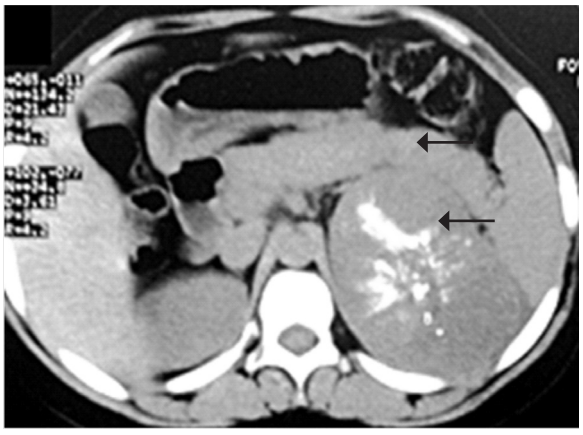

Figure 3. Plain CT scan of abdomen in axial view showing a large mass (arrow) with calcifications pushing the body and tail of pancreas (diamond arrow) anteriorly.

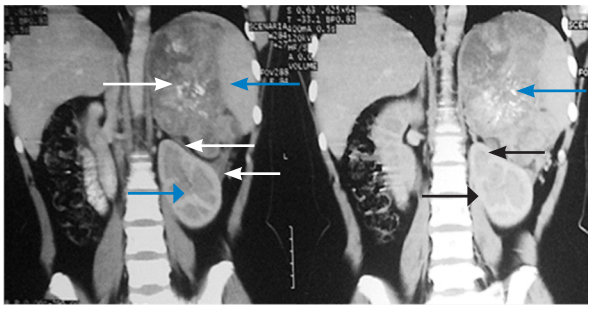

Figure 4. Coronal reconstructed CT images following oral and IV contrast showing a large heterogeneously enhancing mass (black arrows) in the left suprarenal region pushing the left kidney (notched right arrows) downwards and adhering to the renal fascia (blue arrows) and the spleen (red arrows).

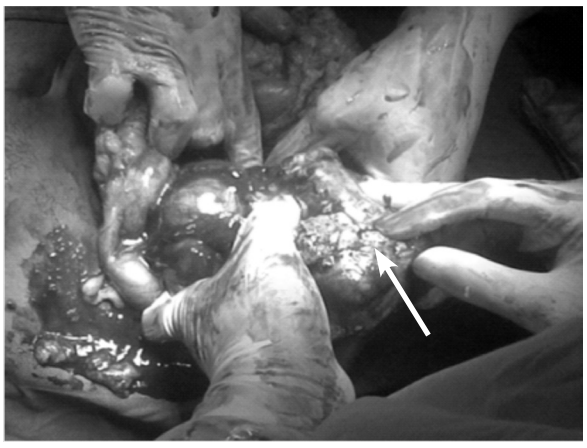

Figure 5. Removal of a large left suprarenal mass (arrow).

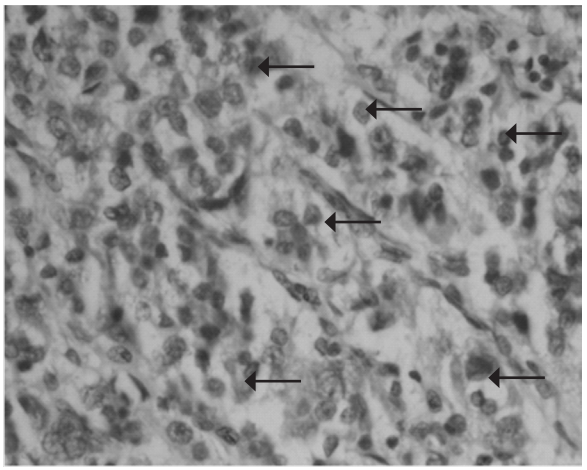

Figure 6. Microscopically, large cells with heterochromatic nuclei (notched left arrows) arranged in sheets and nests were seen.

Patient was advised for further investigation but due to poor socioeconomic conditions, ultrasonography of the abdomen was repeated one year later which suggested the presence of a left supra-renal mass (Figure 2). Then, contrast enhanced CT scan of the abdomen was performed which showed a heterogeneously enhancing large lobulated mixed density mass involving the left supra-renal region and measuring about 12cm x10 cm x9 cm with flecks of calcification within it. The mass was causing downward displacement of left kidney and upward displacement of body and tail of pancreas (Figure 3, 4). Lymphadenopathy was absent. Chest X-ray was normal.

Further laboratory studies showed serum ACTH to be 10.5pg/ml (reference value: upto 46pg/ml), serum cortisol was raised at 1062.0nmol/L (reference range: 140-700nmol/L), urinary free cortisol of 210µg/24hours (reference range: <40µg/24hours in a 10 year child). Fasting plasma glucose was normal at 4.4 mmol/L, postprandial was slightly raised at 9.1mmol/L, serum potassium on two occasions was found to be 2.6mmol/L and 2.8mmol/L. Due to her symptoms coupled with the findings of imaging and laboratory studies, decision was made to excise the mass.

At surgery, a huge mass (Figure 5) was seen in left suprarenal area which was adherent to spleen and left kidney. Left kidney was noted to be slightly enlarged. Left adrenal vein which was found to be dilated was then ligated. Adhesinolysis was done and the tumor was then carefully dissected out from the surrounding structures. Hemostasis was secured. The operation concluded with the placement of two drain tubes in the abdominal cavity. Specimen was then sent for histopathologic examination.

Gross pathological evaluation revealed an encapsulated nodular tissue measuring 13 cm x 9 cm x 9 cm. The cut surface was gray brown and lobular with large areas of necrosis. Microscopically, the tumor was composed of large cells with pleomorphic nuclei arranged in sheets and nests (Figure 6). Large areas of necrosis and hemorrhage were also present with intervening broad fibrous bands. Mitoses were seen about 10/50 HPF. The tumor cells had invaded the capsule. However no vascular invasion was identified. Surgical margin was involved by the tumor. The morphological features were consistent with adrenocortical carcinoma.

Post-operatively, the first sign of improvement we noticed was the gradual decrease in the number and size of acne lesions. Her blood pressure returned to normal. Then gradual reduction of body hairs was noted.

DISCUSSION

Adrenocortical carcinoma (ACC) is a rare malignancy in children.[3] Most adrenocortical tumours are functioning.[4] Though benign adrenocortical tumours are common, adrenocortical carcinoma (ACC) is a relatively rare condition with diverse clinical manifestations due to excessive hormone production by the tumour, with Cushing syndrome and virilisation being the commonest clinical features.[4]Cortisol oversecretion causes clinical Cushing syndrome, and excess androgen leads to virilisation in females, both of which can be the first manifestation in ACC. [4]

Most patients present with steroid hormone excess, for example Cushing syndrome or virilisation, or abdominal mass effects, but a growing proportion of patients with adrenocortical carcinoma (currently >15%) is initially diagnosed incidentally.[5]This patient presented with clinical features of Cushing's syndrome along with virilisation.Individuals often complain of weight gain, hirsutism, proximal muscle weakness, easy bruising, and, in children, growth retardation is commonly seen. Most signs and symptoms are highly prevalent in the general population (hypertension, central obesity, diabetes mellitus or carbohydrate intolerance, osteoporosis, and characteristic phenotypical alterations).[6]

Although ultrasonography can demonstrate large adrenal masses, CT is more specific in demonstrating the lesion, spread to adjacent structures and detecting metastases. Tumors typically appear inhomogeneous in both computerized tomography and magnetic resonance imaging with necroses and irregular borders and differ from benign adenomas by their low fat content.[7] Imaging features suggestive of ACC include irregular margin, inhomogeneous appearance, presence of necrotic areas, calcifications, low-fat content, high attenuation on unenhanced CT with irregular enhancement after contrast.[4]Functioning tumors are detected early when they are of small size, but in this case, the mass had grown to a large size at its first detection.We could also find areas of calcification on CT along with marked heterogenous pattern of contrast enhancement, indicating the malignant nature of left adrenal tumour. Additionally, adhesion to left renal fascia and spleen were very much suggestive of malignant process. Intra-operative findings of adhesion to spleen and renal fascia further support the malignant nature of this tumor.

Pathologically malignant adrenal tumours are differentiated from benign lesions by gross appearance of tumour weight, hemorrhage, capsular involvement as well as microscopic diagnostic score of Weiss.[4] Moreover, broad fibrous bands, nuclear atypia, and necrosis are suggestive of malignancy.[4] The presence of at least one of

the parameters: necrosis, high-mitotic rate, and venous or capsular invasion further contribute to the diagnosis of ACC.[8] Nuclear atypia, necrosis and hemorrhage with intervening fibrous bands were present in our patient. The tumor cells had invaded the capsule. However no vascular invasion was identified.

Surgical treatment is the gold standard for adrenocortical carcinoma.[9] Open adrenalectomy is recommended when malignant adrenal tumor is suspected. Adjuvant treatment with mitotane should be administered when indicated for adrenocortical carcinoma.[9] Combination therapy with mitotane and chemotherapy was reported to be beneficial in patients with advanced and metastatic adrenocortical carcinoma.[9]Local recurrence is frequent, particularly after violation of the tumor capsule. Surgery also plays a role in local tumor recurrence and metastatic disease.[7] In patients not amenable to surgery, mitotane, an adrenolytic agent, is used alone or in combination with cytotoxic drugs remains the treatment of choice. Mitotane is the only adrenal-specific agent available for the treatment of ACC, and although it has been used for several decades, many of its pharmacological properties, as well as its exact mechanism of action, remain to be fully elucidated.[10]Monitoring of drug levels (therapeutic range 14-20 mg/L) is mandatory for optimum results.[7]Adjuvant treatment options after complete tumor removal (e.g. mitotane, radiotherapy) are urgently needed because postoperative disease-free survival at five-year is only around 30%.[7]In our case, chances of disease recurrence is high. But due to the poor socioeconomic condition of the patient's family and unavailability of mitotane, adjuvant treatment could not be provided. However, patient is on a regular follow up every three months to identify the early signs of recurrence.

Adrenocortical carcinoma is a rare malignancy in children and most of them are functioning tumors. Functioning tumors are detected early when they are of small size, but in our case, the mass had grown to a large size at its first detection necessitating reporting of this rare entity. The patient has improved following surgical excision but due to social and economic conditions, adjuvant treatment could not be provided. However, on second follow up, there are no signs of recurrence, although the surgical margin was involved by the tumor.

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