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Clinico-Morphological Profile of Adrenal Tumors in Childhood

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ABSTRACT

The clinical manifestations and biologic behaviour of adrenal tumors in childhood can be quite distinct from their histologically similar counterparts in the adult population.

We report 5 cases of adrenal neoplasms in young children and review their clinical presentations, endocrinological profile, pathology, and follow-up data. Pathologic evaluations included histology and immunostaining with NSE, synaptophysin and chromogranin. The patients included 3 girls and 2 boys, all <11 years of age.

All the patients presented with hormone-related symptoms like Cushing syndrome for an average duration of 6 months. Serum testosterone levels were elevated in 2 cases. Imaging studies revealed neoplasms in the left adrenal gland in 2 cases and in the right adrenal gland in 3 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 size from 1.5 to 4.8 cm diameter. Microscopically, the tumors had histological and immunohistochemical features characteristic of adrenocortical tumors and neuroblastomas.

Keywords: Adrenocortical Tumors, Chromogranin, Cushing Syndrome.

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INTRODUCTION

The adrenal neoplasms in children differ from those found in adults. They can be divided into tumors arising from adrenal cortex and those from medulla. Medullary neoplasms include neuroblastoma, ganglioneuroma and pheochromocytoma. Neuroblastoma is the most common extracranial malignant tumor of childhood and the most common tumor in infancy. It is the second most common abdominal neoplasm in children following Wilms' tumour and overall the third most common paediatric malignancy, after leukaemia and central nervous system tumours.[1] It accounts for almost 15% of childhood cancer fatalities, a number that reflects its aggressive nature and frequency of metastatic disease. Most neuroblastoma deaths occur within 2 years of diagnosis. More than 90% of the diagnosed cases are children aged less than 5 years. Ganglioneuroma and pheochromocytoma are much less common. Adrenocortical neoplasms are rare, potentially fatal and often functional.[1] They account for less than 0.2% of all pediatric neoplasms.[2] Higher incidence of pediatric adrenocortical tumors are seen in Brazil.[3] 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.[4,5] Adreno-cortical adenomas and carcinomas both can 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%.[6,7] 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 its significance in prognosis.

CASE PRESENTATION

Five adrenal neoplasms in children upto the age of 11 years were included in the study over a period of two years. The clinical data, hormonal profile of patients were collected. The cases were diagnosed histopathologically and were subjected to immunohistochemical analysis for the confirmation of diagnosis. The patients were followed up after treatment.

The youngest child in the study was 18 months and the oldest 11 years. There were 2 boys and 3 girls. The clinical variables of the 5 cases are shown in Table 1. Two girls and 1 boy had cushingoid features. One girl had clitoromegaly and increased pubic hair. All the patients were imaged by ultrasound and computed tomogram.

The tumors were surgically resected. The smallest tumor was 1.5x1.5cm and the largest was 4.8x4.3cm.The follow up period was 2 years. Four patients were alive and 1 was dead at the end of the two year period.

The hormonal profile of the patients were recorded. Two patients had cortisol secreting tumors and one presented with androgen secreting tumor. Two patients had raised Vanillyl Mandelic Acid (VMA) and Homovanillic acid (HVA) levels in urine. The VMA/HVA ratio was <1 in one patient. The pathologic variables of the cases are shown in Table 2. Tumor weight varied from 15 to 137.42 grams.

Case 1 showed histologic picture of tumor cells with severe pleomorphism, the cells with clear cytoplasm constituted less than 20%, mitotic rate was 13/50hpf. There was evidence of vascular invasion and necrosis. The Modified Weiss System Score was 6.[8] The case was diagnosed as Adrenocortical Carcinoma and was subjected to immunohistochemistry (IHC) with Neuron Specific Enolase (NSE), Synaptophysin and Chromogranin for confirmation. It was positive for NSE and negative for Synaptophysin and Chromogranin.

Case 2 and 3 revealed features of Adrenocortical Adenoma with Modified Weiss System score <3. Case 2 was positive for NSE and Synaptophysin and negative for Chromogranin. Case 3 was negative for all the three IHC markers. Case 4 and 5 showed small, round, regular tumor cells with presence of Homer Wright rosettes and 'chicken wire' calcification. Necrosis was seen and a diagnosis of Neuroblastoma was given. Both the cases showed positivity for NSE, Synaptophysin and Chromogranin.

Table 1: (Clinical Variables of Cases)

S. No.	Clinical Variable	Case 1	Case 2	Case 3	Case 4	Case 5
1	**Age**	3 years	19 months	18 months	4 years	11 years
2	**Sex**	Female	Male	Female	Male	Female
3	**Symptoms**	Cushing syndrome	Virilization and Cushings disease	Increased pubic hair, clitoromegaly, cushingoid features, hypertension	Palpable abdominal mass	Abdominal mass with watery diarrhea
4	**Radiological finding**	Right renal mass 4.8 x 4.3 cm	Right suprarenal mass 1.8 x 1.8 cm	Left suprarenal mass, 1.5 x 1.5cm	Left suprarenal mass, 2.3 x 2.5cm	Right suprarenal mass, 3.5 x 3.2cm
5	**Hormonal profile**	Serum DHEA –S: 710 µg/dl (Increased) Plasma ACTH: 15 pg/ml (Increased) Cortisol,free,24 hours urine: 639.32 µg/24 hours (Increased)	Serum testosterone 29 ng/dl (Increased) Serum cortisol: 33 µg/dl (Increased)	Serum testosterone : 3.2 nmol/l (Increased) Serum dihydrotestosterone: 3.2ng/ml (Increased) Serum cortisol: normal Serum estrogen: 68 pmol/l (normal)	Urine Homovanillic acid: 28µg/mg creatinine Urine Vanillylmandellic acid: 30 µg/mg creatinine	Urine Homovanillic acid: 40µg/mg creatinine Urine Vanillylmandellic acid: 38 µg/mg creatinine
6	**Follow up**	Alive	Alive	Alive	Alive	Dead

Table 2: Pathologic Variables of Cases

S. No.	Pathologic Variables	Case 1	Case 2	Case 3	Case 4	Case 5
1	**Tumor weight**	137.42 gm	23 gm	15 gm	50gm	80gm
2	**Pleomorphism**	Marked	Mild	Mild	Absent	Absent
3	**Mitosis**	13 /50 hpf	3/50 hpf	2/50 hpf	3/10hpf	4/10hpf
4	**Necrosis**	Present	Absent	Absent	Present	Present
5	**Cells with clear cytoplasm**	<20 %	>35 %	> 40 %	Absent	Absent
6	**Capsular invasion**	Absent	Absent	Absent	Absent	Absent
7	**Vascular invasion**	Present	Absent	Absent	Absent	Absent
8	**Calcification**	Absent	Absent	Absent	Present	Present
10	**NSE**	Positive	Positive	Negative	Positive	Positive
11	**Synaptophysin**	Negative	Positive	Negative	Positive	Positive
12	**Chromogranin**	Negative	Negative	Negative	Positive	Positive

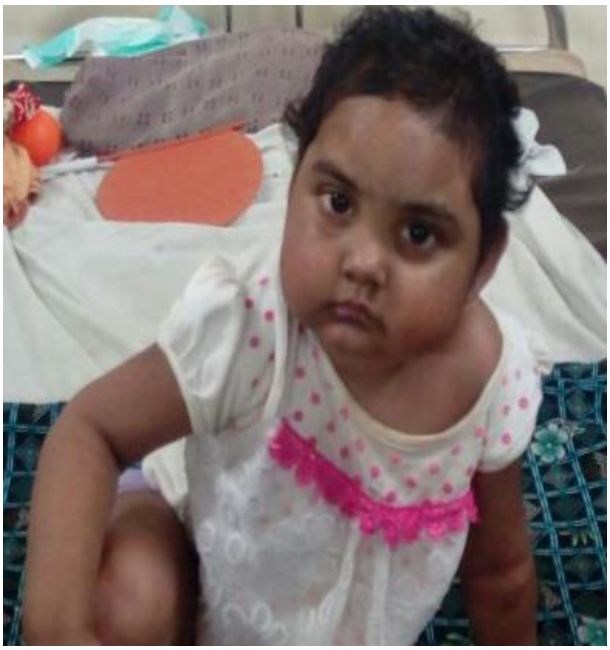

Fig 1: Moon face of Cushing syndrome

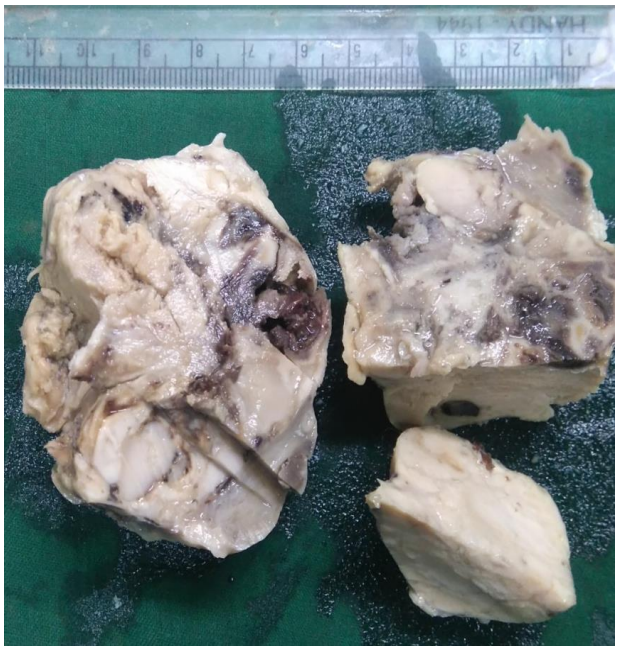

Fig 2: Gross photograph of adrenocortical carcinoma

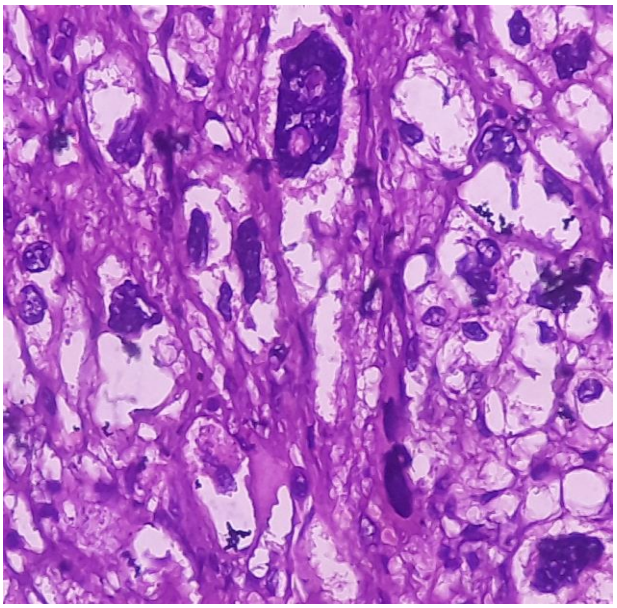

Fig 3: Marked pleomorphism in adrenocortical carcinoma

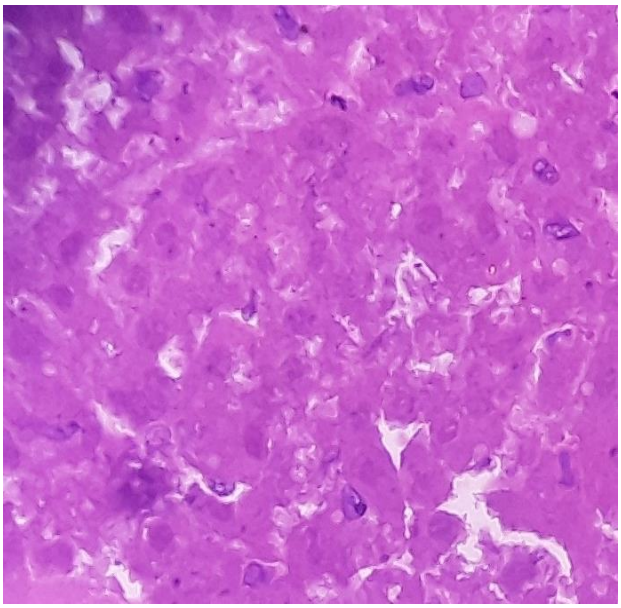

Fig 4: Necrosis in adrenocortical carcinoma

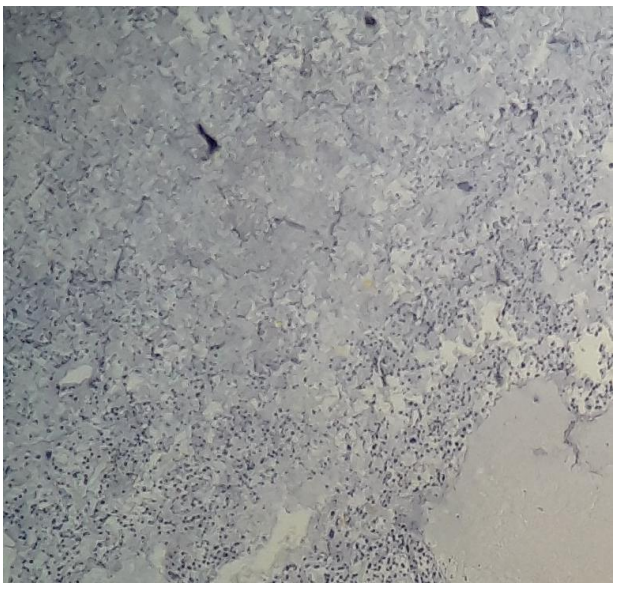

Fig 5: Chromogranin negativity in adrenocortical carcinoma.

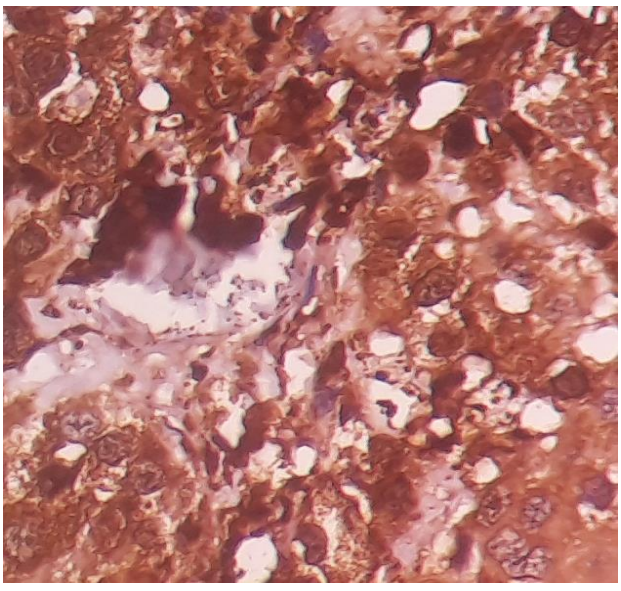

Fig 6: NSE positivity in adrenocortical carcinoma

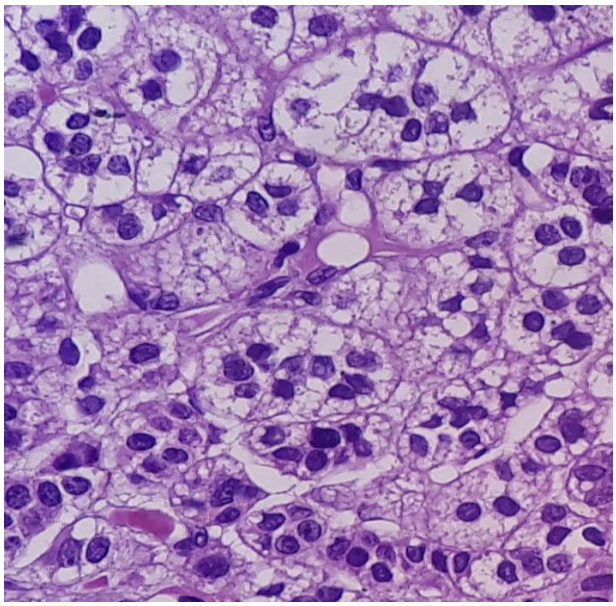

Fig 7: Clear cells area > 35% in adrenocortical adenoma

DISCUSSION

Adrenocortical tumors can be either functional or non-functional. In children, most tumors are functional with 80-90% having endocrinological manifestations at diagnosis and up to 94% secreting excess hormones on further evaluation.[9-11] Most children (50-84%) present with virilization (pubic hair, accelerated growth and skeletal maturation, an enlarged penis or clitoris, hirsutism and acne) due to excess androgen secretion.[9-11] Less frequently, children present with Cushing's Syndrome (15-40%) with hypertension, obesity and decreased linear growth due to excess glucocorticoids, feminization (7%) or gynecomastia due to excess estrogens, signs of hyperaldosteronism (1-4%) including hypertension and hypokalemia, or a mixture of symptoms.[9-11] Cushing's Syndrome appears to occur more frequently in adrenocortical carcinomas, larger tumors (>10 cm), and older children.[9-11] Non-functional tumors also tend to occur more frequently in older children.[9] This in contrast to adults where most of the ACC are non-functional, and if functional, most of them tend to be Cushing's syndrome. Our patient (**Case 2**) was one of the rare case where both androgen and glucocorticoid excesses have started simultaneously, as he had poor growth inspite of virilization which tend to cause growth acceleration. In this study all the 3 adrenocortical tumors were functional. There is often a delay of about eight months between onset of symptoms and diagnosis.[12] ACC tends to grow and metastasize rapidly if untreated. In our case the delay was of 2 months. Usually adrenocortical carcinomas weigh greater than 100gm.In our case it was 137.42 gm. Thus weighing an adrenal mass is important for diagnosing ACCs.

Liou and Kay reviewed the ACTs reported in the pediatric literature and found that the majority occurred during the first 5 years of age with a female: male ratio of 2:1.[13] In our study the cases with adrenocortical tumors presented before 3 years and 2 were female children out of 3. None of our patients had any associated abnormalities. Association of ACT with abnormalities like hemihypertrophy, Li-Fraumeni syndrome, and Beckwith-Wiedemann syndrome has been reported.[13] In all the patients adrenal masses were diagnosed on Ultrasound (US). Computed Tomogram (CT) was done when there was doubt regarding invasion of the inferior vena cava or regional spread. US is the ideal modality for screening the adrenal region and assessment of tumor recurrence postoperatively. However, it cannot reliably identify smaller lesions as accurately as CT[14] which has been reported to be superior in the imaging of tumors measuring 0.5 to 1 cm, assessment of tumor thrombi in the adrenal or renal vein, regional invasion, and distant metastasis. Magnetic resonance imaging (MRI) appears to be accurate in imaging ACTs and has the added ability to show coronal slices which allows better distinction from adjacent tissues. MRI may replace CT as a diagnostic choice in the evaluation of ACTs .Adrenal renography and arteriography are invasive and not usually used in children.

Physicians treating children with ACTs are handicapped by a paucity of data when making difficult clinical decisions. Given the overall poor prognosis of adrenal carcinomas and the known toxicities of treatment, the ability to distinguish adenomas from carcinomas would be a crucial piece of information when considering the risk-benefit analysis for an individual patient. Fine needle aspiration cytology can be performed during initial evaluation. FNAC can only differentiate between metastatic lesion to adrenals and a primary adrenocortical tumor. It cannot differentiate between a benign and malignant lesion, for which distant metastases has to be demonstrated. However, a scoring system like the updated Weiss system on histopathological examination can predict a malignant lesion. This system uses five parameters : > 5 mitoses / 50 high power fields, ≤ 25 % clear tumor cells, abnormal mitoses, necrosis, and capsular invasion. Each parameter is given one point if present. If the score is ≥ 3, it is suggestive of malignancy.[8] Further adrenocortical carcinoma shows negativity for Chromogranin which was well proved here. So IHC with Chromogranin plays a crucial role in diagnosis of adrenocortical tumors.[4]

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 ambiguous in view of the small number of cases in our study, it is strongly supported by similar case studies in the literature.[15] In the study by Wienecke et al[16] an age <5.4 yrs was associated with better outcome. In a study of 78 Brazilian children with adrenocortical carcinoma, the survival rate was 82% for children <2 yrs of age compared to 29% in older children.[17] Neuroblastoma occurring under 2 years of age have the best prognosis. In the study the patient in Case 5 presented at an older age which is rare and had a bad prognosis. VMA/HVA ratio was less than 1, which has been proved to be a poor prognostic factor in previous studies.[18]

CONCLUSION

Adrenal tumors in children carry a better prognosis than those in adults provided they are recognized early, allowing microscopically complete resection. Tumor size and adequacy of excision affect the outcome. Efforts must be made to identify patients with adrenal tumors early, which are facilitated by the secretory nature of these tumors. Features like accelerated body growth, virilization, cushingoid appearance or atypical presentations like pseudo paralysis must lead to clinical suspicion

of ACTs. The prognosis is good in children who present at an earlier age. Tumor weight, hormonal profile, histologic features and immunohistochemistry all aid in the specificity of the diagnosis.

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