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A rare case of Cushing syndrome with virilization

*Hossain MS[1], Jahan S[2], Sultana N[3], Rana MS[4], Debnath BC[5], Hasanat MA[6], Fariduddin M[7]

[1]Md Solaiman Hossain, Resident, Department of Endocrinology, Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh; [2]Sharmin Jahan, Associate Professor, Department of Endocrinology, Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh; [3]Nusrat Sultana, Assistant Professor, Department of Endocrinology, Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh; [4]Md Sohel Rana, Resident, Department of Endocrinology, Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh; [5]Bidyut Chandra Debnath, Endocrine wing, department of Surgery, Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh; [6]Muhammad Abul Hasanat, Professor, Department of Endocrinology, Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh; [7]Md. Fariduddin, Professor, Department of Endocrinology, Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh

Abstract

Cortisol, aldosterone, and androgen are synthesized in the adrenal cortex in different enzymatic processes. Adrenocortical carcinoma is usually a co-secreting tumor, whereas adrenal adenoma is rarely co-secreting. A 10-year-old girl presented with progressive hair growth over the face, upper back, lower back, buttocks, upper and lower limbs (arm and thigh) and pubis, significant weight gain, and deepening of voice for 6 months. Clinical examination revealed a puffy and plethoric face, acne, hirsutism and acanthosis nigricans. She was obese and hypertensive. Tanner stage: B1, P4 and Prader stage: I. There was clitoromegaly. Lab study revealed elevated 24-hour urinary free cortisol with low normal ACTH. In addition, there was markedly elevated total testosterone and DHEA-S. CT abdomen showed a large soft tissue mass at the right suprarenal region. She underwent right-sided open adrenalectomy. Histopathology showed benign encapsulated neoplasm with no atypical mitosis, necrosis, vascular invasion, sinusoidal invasion or capsular invasion. Immunohistochemistry revealed Ki67 of about 1% which corresponds with benign adrenal adenoma. Postoperatively she was on a physiological dose of steroid replacement. Clitoromegaly spontaneously regressed after about four months and hirsutism disappeared after about six months. Her biochemical parameters also became normal at 8 months following surgery. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2023; 2 (1): 28-31]*

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***Correspondence:** Md. Solaiman Hossain, Resident, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Email: dr.solaiman36@gmail.com; cell no: +8801728748988

Introduction

Adrenocortical tumors are rare in children, comprising <0.2 % of all childhood neoplasms. The most frequent clinical presentation is virilization, hypercortisolism or hyperaldosteronism. But a combination of both virilization and hypercortisolism is extremely rare.[1] Adrenocortical carcinoma is usually a co-secreting tumor, while adrenal adenoma is rarely co-secreting. A few cases of adrenal adenoma have been reported with features of virilization and Cushing syndrome.[2-4]

Case presentation

A 10-year-old girl presented with progressive hair growth over the face, upper back, lower back, buttocks, upper and lower limbs (arm and thigh), and pubis along with significant weight gain of about 12 kg in the last six months. She also noticed a deepening of voice for the same duration. She had no history of taking steroids or herbal medication. She was the 1st issue of her non-consanguineous parents. Her neonatal period was uneventful and the milestones of development were age appropriate. Her menstruation had not yet started. On physical examination, her face was puffy and plethoric with acne and hirsutism. The Ferriman-Gallwey score for hirsutism was 16. Acanthosis nigricans was present over the neck and axilla. Her height was 142 cm, weight 41.5 kg, and body mass index (BMI) 20.6 kg/m^2 (>85th percentile). Her systolic blood pressure was 120 mm of

Hg (>75th percentile) and diastolic 130 mm of Hg (>95th percentile). Tanner stage was 1 for breast and IV for pubic hair. Prader stage was 1, clitoromegaly (clitoral index: 150 mm^2) was also present. No lump was palpable on abdominal examination. Her laboratory data are shown in Table: I. The results of routine laboratory evaluations were normal. There was elevated 24-hour urinary free cortisol with low normal ACTH, Overnight 1-mg Dexamethasone Suppression test was positive. In addition, there was markedly elevated serum total testosterone and dehydroepiandrosterone sulfate (DHEA-S).

Table-I: Hormonal change before and after surgery

Tests	Before surgery	After surgery	Reference value
24h UFC	315	ND	50-100 µg/24 hour
ONDST	1044	ND	< 50 nmol/L
S. Cortisol	947.40	160.50	55-469 nmol/L
ACTH	6.74	82.30	0-46 pg/mL
S. Testosterone	828	77.40	3-32 ng/dL
DHEA-S	>1000.0	10.20	13-15 µg/dL
S. FT4	1.10	ND	0.8-1.6 ng/dL
S. TSH	3.88	ND	0.38-4.3 µIU/mL

24H UFC: 24 hours urinary free cortisol)
ONDST: Overnight 1-mg dexamethasone suppression test
ACTH: Adrenocorticotropic hormone
DHEA-S: Dehydroepiandrosterone sulfate
FT4: free T4
TSH: Thyroid-stimulating hormone ND: not done

Computerized tomography (CT) imaging of the abdomen showed well-defined mild heterogeneously enhanced soft density mass (size 7.5x6.2x6.5cm) with a central hypodense area (cystic degeneration or tumor necrosis) seen at the right suprarenal region. There was evidence of calcification within the mass. The absolute enhancement washout of the mass was 81%.

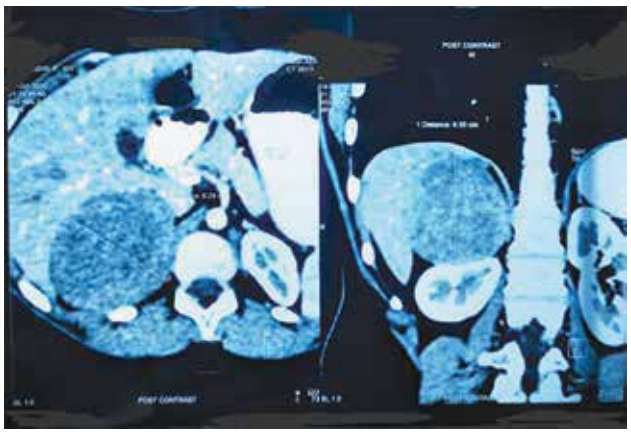
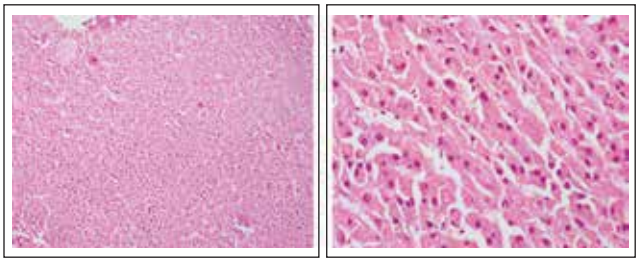


Figure-1: CT abdomen showing right adrenal mass in sagittal and axial view



(a) (b)

Figure 2(a) and 2(b): Histopathology showing cells having abundant Eosinophilic cytoplasm and rounded regular nuclei arranged in nest

She underwent right-sided open adrenalectomy. A capsulated tumor around 6×6 cm in size was resected and sent for histopathological examination. On intraoperative examination, there were no enlarged lymph nodes. Histopathology showed benign encapsulated neoplasm with no atypical mitosis, necrosis, vascular invasion, sinusoidal invasion or capsular invasion. Immunohistochemistry revealed Ki67 about 1% which corresponds with benign adrenal adenoma.

Following surgery, clitoromegaly spontaneously regressed after about four months. The cushingoid features and hirsutism resolved over 6 months following surgery. She lost about 16 kg weight in six months. Her biochemical parameters also became normal at 08 months of follow-up. The patient is maintained on glucocorticoid which is planned to be gradually withdrawn over months.

Figure-3: Appearance of the patient (a) before surgery, (b) after 6 months of surgery

Discussion

Adrenal virilism is the development or premature development of male secondary sexual characteristics

caused by the excessive production of androgens by the adrenal gland. Some common causes of adrenal virilization are adrenal carcinoma and congenital adrenal hyperplasia.[4] In rare cases, adrenal virilism is caused by an adrenal gland tumor. The tumor can be benign (adrenal adenoma) or malignant (adrenal carcinoma). Most tumors are small benign nonfunctional adrenocortical adenoma (ACA). Adrenocortical cancer (ACC) is an extremely rare disease.[5]

In our case, CT of the abdomen revealed a large heterogenous adrenal mass. Upon clinical presentation, ACC tumors are typically large, often measuring >6 cm in diameter. Moreover, the tumors in ACC tend to vary in appearance with frequent heterogeneous enhancement (e.g., internal hemorrhage, calcification, and necrosis).[6] Our patient exhibited large right-sided adrenal tumors along with virilism and Cushing's syndrome, and hence malignancy of the adrenal tumor was suspected. Adrenal adenomas generally secrete only glucocorticoids. In contrast, androgen excess usually occurs in women with adrenal cancer or ACTH-stimulated hyperandrogenism.[6] In our patient, the serum DHEAS levels (>1000.0 ng/mL) were very high before surgery. All these features suggested an adrenal carcinoma. However, histopathology (Weiss score) and immunohistochemistry results (Ki67:1%) later proved the tumor to be of benign nature. Therefore, the final diagnosis was adrenocortical adenoma.

There are few case reports where an adrenal adenoma presented with features of virilization. A 14-year-old Caucasian girl presented with features of virilization. Her androgen levels were extremely high. Adrenal ultrasonography revealed an adrenal mass of 4.6×5.3 cm. The histologic findings showed a benign adrenocortical tumor.[2] In a 23-year-old female patient presenting with hirsutism, laboratory tests revealed a total testosterone level of 4.2 ng/mL, DHEAS level of 574 µg/dL. There was no suppression in cortisol levels with the 2 mg dexamethasone suppression test (5.4 µg/dL). Adrenal MRI revealed a 27×25 mm isointense solid mass lesion in the left adrenal gland. Pathological examination confirmed the diagnosis of benign adrenocortical oncocytoma.[3] Previously one case of a virilizing adrenal adenoma was reported in Bangladesh. A 15 year old girl presented with Cushing's syndrome and virilization, suspected to be due to an adrenal carcinoma. Lab data and imaging character was also favored in adrenal carcinoma, but histopathology of the resected mass revealed a benign adrenocortical adenoma.[4]

Conclusion

The study shows that functioning adrenocortical tumors should be considered in children and adolescents presenting with hyperandrogenism and Cushing's syndrome. Complete adrenocortical function should be evaluated before definitive intervention. Functioning adrenocortical tumor requires surgical removal as early as possible to prevent the untoward effects of virilization or corticosteroid excess.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article

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Disclosure

The authors have no multiplicity of interest to disclose.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Written informed assent was taken from the patient.

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