Case Report

Aldosterone and cortisol co-secreting bifunctional adrenal cortical carcinoma: A rare event

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ABSTRACT

Adrenocortical carcinoma (ACC) co-secreting aldosterone and cortisol is extremely rare. We report the case of a 37-yearold female who presented with paresis and facial puffiness. Evaluation revealed hypertension, hyperglycemia, severe hypokalemia and hyperaldosteronemia with elevated plasma aldosterone to renin ratio (ARR). Urinary free cortisol estimation showed elevated levels. Computed tomography scan revealed a right adrenal mass. Radical adrenalectomy specimen revealed ACC (T3N1). Post-operatively, the patient became normotensive and euglycemic with normalization of urinary cortisol and ARR. This case highlights the need for a complete evaluation in patients of hyperaldosteronism if overlapping symptoms of hypercortisolism are encountered, to avoid post-operative adrenal crisis.

Key words: Adrenal cortical carcinoma, bi-functional tumor, co-secretion

INTRODUCTION

Adrenocortical carcinomas (ACCs) are functional in approximately 60% cases, with a wide range of steroid profile.[1] Most commonly, ACCs secrete cortisol (50%), followed by androgens, whereas aldosterone secretion is quite rare (<2%).[1] Combined hormonal secretion is rare and has been described mostly in adenomas. Among bi-functional ACCs, co-secretion of cortisol with androgens is more common, while co-secretion of aldosterone and cortisol is extremely rare.

CASE REPORT

A 37-year-old female patient presented with a history of easy fatigability and extreme weakness of both lower limbs. There was no history of any abnormal sweating, palpitations or headache. On examination, she was found to have hypertension with grade 3 power in both lower limbs along with facial puffiness. There were no significant abdominal signs.

Laboratory investigations revealed severe hypokalemia (1.5 meq/l) with inappropriate kaliuresis. The random blood sugar level was high with HbA1c being 8.4%. The plasma renin activity (PRA) was normal, with a very high plasma aldosterone concentration (PAC). The PAC/PRA ratio, aldosterone to renin ratio (ARR) was very high (39.8). The facial puffiness along with hypertension and hyperglycemia prompted evaluation for glucocorticoid excess. The 24 h urinary free cortisol was significantly elevated (1781.6 μg/24 h), along with a concomitant high serum cortisol (42.26 μg/24 h). High dose dexamethasone suppression test showed no suppression of cortisol values. Urinary metanephrines and vanillyl mandelic acid were negative, ruling out a pheochromocytoma. Serum levels of androgens were normal [Table 1].

Contrast enhanced computed tomography showed a 6 cm right adrenal mass with a 2 cm right paracaval lymph node [Figure 1]. There was no evidence of adjacent structure involvement or distant metastasis. Pre-operatively, she was optimized with potassium supplementation, oral hypoglycemics and required a combination of three antihypertensives for adequate control of hypertension. She underwent open right radical adrenalectomy [Figure 2a]. At surgery, there were multiple lymph nodes in the right paracaval region, with a large node wedged in the retrocaval region and another in the region of the right renal hilum [Figure 2b]. All the lymph nodes were meticulously

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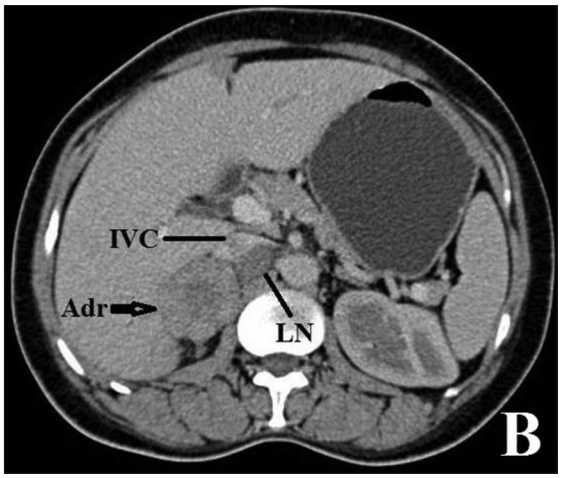

Figure 1: Computed tomography scan revealing right Adrenal mass with large retrocaval lymph node. Adr = Adrenal gland; LN = Lymph node; IVC = Inferior vena cava

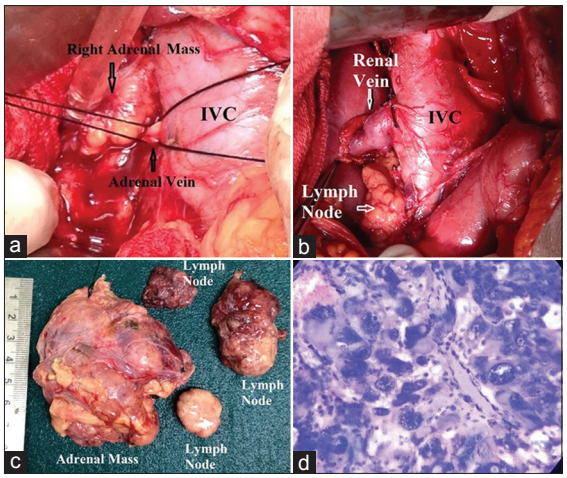

Figure 2: (a) Operative images-right adrenal mass; (b) large retrocaval lymph node; (c) gross specimen-right adrenal mass with lymph nodes; (d) histopathology shows highly pleomorphic cells with anisonucleosis, macronucleoli and numerous abnormal mitotic figures (Weiss score of 4). IVC = Inferior vena cava

Table 1: Pre- and post-operative lab values

Biochemical and hormonal profile	Before adrenalectomy	6 weeks after adrenalectomy	Normal range
S. Potassium	1.5	3.5	3.5-5.0 meq/ml
Urine potassium	83.65	65	25-80 mmol/l
S. Cortisol	42.26	10.34	4-12 ug/dl
24 h free urinary cortisol	1781.6	182	20.9-292.3 μg/24 h
24 h urine VMA	2.70	-	2.8-8.3 mg/24 h
24 h urine HVA	4.95	-	3.2-9.6 mg/24 h
Plasma aldosterone concentration	197.4	16	3-16 ng/dl
Plasma renin activity	3.95	2.9	0.1-3.1 ng/ml/h
PAC/PRA ratio	39.8	5.5	<20
S. Progesterone	0.8	-	0.2-3.3 ng/ml
S. Testosterone	20	-	15-70 ng/dl
S. DHEAS	72	-	35-400 ug/dl

PAC = Plasma aldosterone concentration, PRA = Plasma renin activity, VMA = Vanillyl mandelic acid, HVA = Homovanillic acid

removed [Figure 2c]. Post-operatively serum cortisol level was monitored and supplemented with glucocorticoid injection initially.

Following surgery, she became euglycemic and did not further require any anti-hypertensive medications. Potassium supplements were required post-operatively but at a much lower dose.

Histopathology of the mass revealed right adrenal cortical carcinoma with lympho-vascular invasion–T3N1 with Weiss score of 4 [Figure 2d].

Follow-up at 6 weeks post-operatively showed a falling ARR of 5.5. Serum and urinary cortisol level normalized [Table 1].

She was administered adjuvant chemotherapy with mitotane. 9 months post-operatively she developed liver metastases with repeated episodes of hypokalemia. She however continued to remain euglycemic. She succumbed to the disease 11 months post-operatively.

DISCUSSION

ACC is a rare malignancy which often presents at an advanced stage with signs from tumor compression, invasion or metastasis.[1] They may infrequently present with endocrine symptoms. Most functional ACC are cortisol secreting, which may present as overt or subclinical Cushing's syndrome. Aldosterone producing tumors often present with features of primary hyperaldosteronism, notably hypertension and hypokalemia. Edema or facial puffiness is generally absent due to mineralocorticoid escape phenomenon. In a subset of patients with ACC, there can be features of cortisolism and hyperandrogenism. However co-secretion of aldosterone and cortisol is a very rare occurrence.[1,2]

Understanding co-secretion in ACC

Co-secretion has been described in adrenal adenomas and rarely in ACCs.[2] In patients with co-secretion, the level of hybrid steroids like 18-hydroxy-cortisol (18-OH-F) is much higher than in pure aldosterone secreting tumors.[3] This phenomenon of co-secretion may be explained by the unequal crossover between the genes for 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) resulting in a chimerical CYP11B1/CYP11B2 gene. This crossover results in increased levels of cortisol secretion along with aldosterone.[4] However, a constant occurrence of chimerical gene abnormality is yet to be elucidated. These tumors might have a higher proportion or quantity of cortisol producing cells, which may become clinically significant due to the increased size of the tumor, to secrete relevant amounts of glucocorticoids.[5] There is

no conclusive explanation of hypercortisolism along with hyperaldosteronism in ACCs.

Work-up of patients with co-secretion

The work-up of patients with primary hyperaldosteronism often involves measurement of renin and aldosterone levels, which help in calculating the ARR. ARR can help in diagnosis and in follow-up of patients post treatment. In addition, other adrenal hormones like cortisol and other adrenal steroids also need to be evaluated if symptoms or imaging studies are suggestive of co-secretion. Tests to detect hypercortisolism include the estimation of serum and urinary free cortisol. The dexamethasone suppression test has been shown to be adequate to document and identify the cause of hyper-cortisolism. The evaluation for co-secretion can include measurement of levels of hybrid steroids like 18-OH-F and 18-hydroxy-corticosterone.

Histopathology

In addition to the Weiss scoring used for describing adreno-cortical carcinomas, various Immuno-histochemical studies with antibodies against CYP17A, CYP11B1 and CYP11B2 etc., have been described. However, other than an elevated CYP11B2 activity, the other steroidogenic enzymes have shown varied levels of expression in co-secreting ACCs.[6]

CONCLUSION

Co-secretion of aldosterone and cortisol, although a rare entity has bearing on management of patients presenting with a functional adrenal tumor. Pre-operative detection of co-secretion helps adequate hormonal manipulation to avoid catastrophic adrenal crisis in the post-operative period. The exact pathophysiology behind co-secretion is still debated and needs further research.

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