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Case Report

Double Trouble: Cushing's Syndrome Due to ACTH-secreting Pheochromocytoma

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Abstract

Pheochromocytoma is a catecholamine secreting adrenal tumor originating from chromaffin cells which accounts for 5% of ectopic ACTH syndrome cases and is infrequently reported in medical literature.

Case Description: A 36 year old woman presented with Cushingoid habitus, resistant hypertension, hypokalemia and recent onset diabetes. Endocrinological examination revealed ectopic ACTH production with hypercortisolemia and elevated plasma catecholamines. MRI abdomen showed a large left sided adrenal tumor. After initial medical management, left adrenalectomy resulted in complete remission of Cushing's syndrome and pheochromocytoma.

Conclusion: We present here a case of ACTH producing pheochromocytoma with clinical features of Cushing syndrome.

Keywords: Pheochromocytoma; Ectopic ACTH Syndrome; Cushing's Syndrome

Cushing's syndrome (CS) is a condition associated with high cortisol levels with a incidence of 0.7 to 2.4 cases/million/year [1]. ACTH dependent Cushing's syndrome is divided into Cushing's disease and ectopic ACTH syndrome (EAS). EAS accounts for 20% of all causes of Cushing's syndrome. Most common tumor associated with EAS is bronchial carcinoid followed by neuroendocrine tumors originating from thymus, pancreas, and thyroid. Pheochromocytoma accounts for 5% of EAS cases and is a rarity [2]. Here we describe a case of ACTH producing pheochromocytoma with clinical features of Cushing's syndrome.

Case Description

A 36 year old woman presented with hypertension, recent onset diabetes, cushingoid appearance (moon face, central obesity, wide purplish striae, proximal myopathy, easy bruisability), hirsutism and amenorrhoea beginning 3 months ago. Examination found a body mass index of 24.3 kg/m^2, blood pressure 180/110 mm Hg, pulse rate 94/minute, acneform eruptions over face, supraclavicular fullness, increased dorsocervical fat pad, acanthosis grade 2, hyperpigmentation over knuckles and oral mucosa, hirsutism (modified ferriman gallwey score 12), and clitoromegaly (clitoral index 30 mm^2). Laboratory tests revealed neutrophilic leukocytosis with relative lymphopenia, hypokalemia (2.2 mmol/lit; normal range 3.5 -5.5 mol/lit), raised hepatic enzymes (Alanine transaminase [ALT] 231, Aspartate transaminase [AST] 136) with normal INR and dyslipidemia (cholesterol 328, triglyceride 168, Low density lipoprotein [LDL] 213, High density lipoprotein [HDL] 82). Hypokalemia was corrected after oral and intravenous potassium supplementation and addition of spironolactone. She was started on basal bolus insulin therapy for hyperglycemia and atorvastatin 20 mg for dyslipidemia.

Biochemical investigations revealed severe hypercortisolism with loss of circadian rhythm and non-suppressible cortisol after

dexamethasone suppression tests (Table 1). Plasma ACTH was elevated to 473 pg/ml confirming ACTH dependent Cushing's syndrome. MRI pituitary was done which showed a 4 mm lesion in right half of pituitary gland on dynamic contrast(Image A) but due to deteriorating condition of the patient, inferior petrosal sinus sampling (IPSS) could not be done. In the meantime, the patient had developed hypertensive heart failure and had to be shifted to intensive cardiac care unit. Given the severity of her condition, rapidity of onset of symptoms, difficult to correct hypokalemia and grossly elevated ACTH, we suspected an ectopic source of ACTH production. MRI abdomen showed a 2.9 x 3.5 x 3.9 cm heterogeneously enhancing left adrenal, hyperintense on T2, with minimal hypointensity in out phase T1, adrenal signal intensity index 05%, with normal right adrenal (Image B). 18FDG PET/CT showed metabolically active left adrenal SOL with SUV 16.93 suggesting adrenocortical carcinoma.24hour urinary metanephrine and nor metanephrine was done which showed elevated values. Patient was started on prazosin 5mg and telmisartan 40 mg twice daily, along with ketoconazole (200 mg thrice daily) for medical management of hypertension and hypercortisolemia. She was also given low molecular weight heparin for deep vein thrombosis prophylaxis and sulphamethoxazole-trimethoprim for Pneumoystis carinii pneumonia prophylaxis. After adequate alpha blockade, metoprolol 50 mg once daily was started preoperatively. Left adrenalectomy was performed 28 days after admission which resulted in clinical and biochemical improvement of features of pheochromocytoma and Cushing's syndrome. The resected tumor was 8.5 x 5 x 3 cm^3, ovoid, well-circumscribed, encapsulated mass. Histopathological examination showed large polygonal cells with centrally placed round or oval nuclei and abundant eosinophilic granular cytoplasm arranged in solid nest, trabeculae or zellballen pattern and scant mitotic figures with no lymphovascular invasion suggestive of benign pheochromocytoma (Images C). Immunohistochemistry was positive for synaptophysin, chromoganin, and S100 with Ki67 labelling index of 2% confirming benign pheochromocytoma (Image D). Screening for RET proto-oncogene was done to rule out MEN2 syndrome, which was negative. Postoperatively, there was loss of 12 kg weight within a month with reduction of acne and hirsutism (Image E). Requirement of antihypertensive drugs and oral hypoglycemic drugs decreased to a single drug initially and were gradually stopped. Due to suppressed cortisol level, hydrocortisone in physiological doses was started and will gradually be withdrawn after recovery of axis.

Image A: Pituitary MRI showing 4 mm lesion in right half of pituitary gland.

Image B: MRI abdomen showing 2.9 x 3.5 x 3.9 cm, heterogeneously enhancing left adrenal SOL.

Image C: Hematoxylin and eosin staining showing zellballen pattern.

Image D: Immunostain.

Image E: Pre and postoperative image of the patient.

Due to unavailability of ACTH immunostaining, it could not be done. However, due to clinical and biochemical remission of Cushing's syndrome postoperatively, a diagnosis of ectopic ACTH syndrome was made.

	On Admission	Postoperative	Reference range
Serum Cortisol	63.50	9.04	5-25 ug/dl
ONDST (overnight dexamethasone suppression test)	63.44 ug/dl		
48 hour LDDST (Low dose dexamethasone suppression test)	53.90 ug/dl		
ACTH	473	16	5 -25 pg/ml
DHEAS (Dehydroepiandrosterone sulfate)	250.80	--	74.80 - 410.20 ug/dl
Testosterone	2.20	< 0.20	0.23 - 10.3 ng/ml
24 hour urinary fractionated metanephrines	1938.37	85.13	74 - 297 ug/24 hours
24 hour urinary fractionated normetanephrines	698.47	263.21	73 -808 ug/24 hours
PAC (plasma aldosterone concentration)/ PRA (plasma renin activity)	13.75		< 20
TSH	1.4		0.5 - 4.5 miu/ml
Free T4	1.1		0.89 - 1.80 ng/dl
Prolactin	9.8		1.9 - 25 ng/ml
Serum calcitonin	-	<2.0	< 5.0 pg/ml

Table 1: Hormonal profiles.

Discussion and Conclusion

Cushing's syndrome in pheochomocytoma is rare. ACTH secreting pheochromocytoma forms a distinctive subset of patient with CS with mean age of presentation of 46.8 years (27 - 74 years), with female preponderance. Chen., *et al.* [3] described the diagnostic criteria: (1) clinical and laboratory evidence of hypercortisolism, (2) elevated plasma ACTH levels, (3) biochemical evidence of a pheochromocytoma (elevated urinary catecholamines, metanephrines or vanillylmandelic acid excretion) and MRI evidence of an adrenal mass with ab right T2 signal, (4) resolution of symptoms and signs of adrenocorticoid and catecholamine excess after unilateral adrenalectomy, and (5) rapid normalization of plasma ACTH levels after adrenalectomy. Our patient in discussion fulfilled these criteria. Plasma ACTH

levels are higher in EAS than in CS from a pituitary adenoma tumoral though there remains considerable overlap [4]. In patients with ectopic ACTH, mean plasma ACTH levels were 358 ng/l in the series by Isidori., *et al*. [2] and 204 ng/l in the series by Ilias., *et al*. [5]. An extra pituitary source for ACTH is more likely in a patient of CS when the ACTH level is very high and in the presence of hypokalemia. However, there are many exceptions, and the highest diagnostic accuracy is provided by bilateral inferior petrosal sinus sampling. The presence of a 4 mm lesion in right half of pituitary gland in our patient was a red herring and it is known that pituitary incidentaloma has a prevalence of 10.6% [6]. In our patient, ketoconazole was administered despite increased transaminase levels considering cortisol induced hepatic steatosis and the improvement of cortisol levels during ketoconazole therapy was associated with decline in transaminase levels [7,8] (Table 2). In the published literature, ACTH-producing pheochromocytoma was benign in the vast majority of the patients. Clinical markers which help to predict malignant potential in pheochromocytomas are tumor size, presence of extra-adrenal disease, post-operative hypertension and biochemical markers such as high dopamine, and high norepinephrine and epinephrine to total catecholamine ratio [9].

	At admission	Day 5	After giving Ketoconazole Day 3	After giving Ketoconazole Day 7	After giving Ketoconazole Day 14	Range
Total Bilirubin	0.9	1.4	1.2	0.9	0.3	0.1 - 1.2 mg/dl
ALT	231	452	341	140	29	7 - 55 U/L
AST	136	386	298	88	18	8 - 48 U/L
Alkaline phosphatase	270	290	263	130	199	44 - 147 IU/L

Table 2: Change in Liver Function Test with ketoconazole.

In conclusion, patients with ACTH-secreting pheochromocytoma are seen in only 5% of patients with the ectopic ACTH syndrome, and pose distinctive diagnostic and management challenges, but if diagnosed early and managed well, the results are extremely satisfying.

Learning Points

- Though EAS is a benign entity, timely diagnosis and proper management is necessary for patient survival.
- Inspite of increase in hepatic enzymes, considering cortisol induced steatosis ketoconazole could be started.

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