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# Refractory Hypokalemia- From Ectopic Adrenocorticotropic Hormone Secreting Thymic Tumor

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## Abstract

Ectopic Adrenocorticotropic (ACTH) secreting tumors are unusual causes of Cushing's syndrome. Etiologies include small cell lung cancer (SCLC), medullary thyroid carcinoma and pheochromocytoma (1, 2, and 3) or carcinomas (such as hypernephromas, colon cancer, and paragangliomas). Neuroendocrine tumors of thymus are extremely rare cause of Ectopic ACTH secretion. Patients with ectopic ACTH Secretion more likely present with persistent hypertension and hypokalemic metabolic alkalosis, which is resistant to huge doses of potassium supplementation. Diagnosis is by Serum cortisol, ACTH levels and dexamethasone- CRH suppression test. Overnight dexamethasone suppression test can help differentiating pituitary from ectopic ACTH secretion. Other tests which would help in confirming Cushing's syndrome from ectopic ACTH secretion include, CT scan of the chest looking for thymic or pulmonary etiology and CT abdomen looking at adrenal source. Treatment includes a combination of medical and surgical interventions. We present a rare case of ectopic ACTH secreting thymic Neuroendocrine tumor.

## Case Report(s)

A 46 year old gentleman was admitted with 8 months history of watery eyes, fleeting chest pains with positional variation without any dyspnea. He described a weight loss of 20 pounds over a period of 4-5 months, despite an increase in appetite. Also he complained of pressure in his head, with decreased sense of taste over a period of 2-3 months. His past medical history was significant for appendectomy and single episode of paroxysmal atrial fibrillation. Patient was not on any medications. Social history was significant for 25 pack years history of smoking and daily beer drinking of 4-5 glasses/day. His family history was significant for esophageal cancer in his father at the age of 65. His mother had a brain tumor of unknown etiology. His brother died of a hematological malignancy at the age of 32.

In the emergency department patient was complaining of thumping and tingling in his chest with essentially normal vitals except for hypertension of 180/106 mm/Hg. He had fullness of his face with plethora, when compared to his driver's license picture. Initial lab work showed a significant hypokalemia with potassium of 2.7 mEq/L and metabolic alkalosis with a serum bicarbonate of (HCO3?) of 35 mEq/L (Table 1). The rest of his chemistry and hematology panel including his thyroid function tests were within normal limits. His chest x-ray and EKG were normal. He had a CT scan of his chest with intravenous contrast for evaluation of his symptoms, which revealed a 10.8 x 8.7 cm anterior mediastinal mass, compressing the left innominate vein and superior vena cava without any hilar or mediastinal lymphadenopathy (Figures 2 a & b).

Further in the hospital, patient had episodes of hypertension, without any respiratory compromise from the anterior mediastinal tumor. Hypokalemia was refractory to repletion, and remained low despite huge doses of potassium supplementation. For further evaluation of patient's hypokalemic metabolic alkalosis, Adrenocorticotropic hormone (ACTH) and random serum cortisol were requested which were 358 pg/ml and >65 mcg/dl . 24 hour urinary 5-HIAA levels were mildly elevated (Table 2).

The Patient's hypokalemia and metabolic alkalosis were attributed to be secondary to ectopic ACTH secretion. Patient also had MRI of brain which did not reveal any pituitary tumors. Subsequent biopsy of anterior mediastinal mass, revealed the tumor to be neuroendocrine in origin with immunoreactivity to ACTH, synaptophysin, chromogranin and cytokeratin (Figures 3 a, b, c, d).

With tumor being positive, for neuroendocrine staining and immunoreactivity to cytokeratin, a diagnosis on thymic carcinoid tumor was made. Patient had a median sternotomy and resection of anterior mediastinal mass, following which his metabolic and electrolyte abnormalities were normalized, obviating the need for medical management. Subsequently, he had local radiotherapy and follow up CT scan of chest revealed complete resolution of the primary carcinoid without any metastatic disease.

# Discussion

Our patient had persistent hypokalemia with metabolic alkalosis and hypertensive episodes, indicating a state of hypercortisolism. High plasma ACTH and cortisol levels indicated ACTH dependent etiology for hypercortisolism. MRI of the brain did not reveal any pituitary tumors which excluded Pituitary hyper secretion of ACTH. Presence of anterior mediastinal mass, with elevated ACTH and random cortisol levels with biopsy showing neuroendocrine differentiation, confirmed the etiology of hypokalemic metabolic alkalosis to be thymic neuroendocrine tumor, causing Cushing's syndrome resulting from ectopic ACTH secretion.

Background of Diagnosis

Cushing's syndrome was discovered by Harvey Cushing in 1912. Cushing's syndrome results from autonomous and or excessive endogenous cortisol secretion. 65% of the cases of Cushing's syndrome result from excessive pituitary secretion of cortisol (Cushing's Disease) which is ACTH dependent. Other non pituitary causes of Cushing's syndrome include ectopic ACTH secretion.

Ectopic adrenocorticotropic hormone secretion accounts for less than 10% of all causes of endogenous Cushing's syndrome and is more commonly associated with small cell carcinoma of the lung.

The spectrum of non-pituitary tumors associated with ACTH production includes neuroendocrine tumors of respiratory and gastrointestinal tract, small cell lung cancer (SCLC), medullary thyroid carcinoma and pheochromocytoma (1, 2, 3) or carcinomas (such as hypernephromas, colon cancer, paragangliomas).

Carcinoid is an extremely rare cause of neuroendocrine tumor secreting ACTH, with an incidence of 1-2 cases per 100,000 people. Of them thymic neuroendocrine tumors of the anterior mediastinum can be associated with ACTH secretion (4). Primary carcinoid lesions are either occult or unlocalised in up to 20% of the cases (1, 3). The location and likely presentation of a carcinoid tumor depends on the division of the embryonic gut from which the tumor cells originate. Carcinoid tumors originating from foregut arise in lungs, bronchi, thymus and stomach.

Midgut tumors found in the small intestine, appendix, proximal large bowel are more commonly associated with classic carcinoid syndrome because of their ability to metastasize to liver. Hind gut derivatives arise in distal colon and rectum. Carcinoid tumors have ability to secrete various peptides and bioactive amines. Most commonly secreted substance is 5-hydroxy tryptamine (serotonin) which is responsible for the classic manifestations of carcinoid syndrome (5). Far less common is the neuroendocrine tumor manifesting as Cushing's syndrome, from ectopic ACTH secretion (6).

ACTH and Cortisol metabolism

ACTH is synthesized as a part of large precursor molecule called propiomelanocortin in the anterior pituitary (7). Non pituitary tumors can synthesize propiomelanocortin and some of its translational products, which explains the ectopic ACTH production (8). ACTH is released from anterior pituitary under the influence of Corticotropin Releasing Hormone (CRH) and is inhibited through glucocorticoid negative feedback from cortisol (9). 95 % of cortisol is mainly bound to albumin and cortisol binding globulin and 5 % circulates as free cortisol. Cortisol undergoes glucuronidation in the liver and free cortisol is excreted by the kidney, which is increased in hypercortisolism.

Cortisol is converted to inactive cortisone by 11β -hydroxysteroid dehydrogenase 2 in the kidneys. In Cushing's syndrome most of the excess cortisol remains inactivated leading to effects of mineralocorticoid excess (hypertension and Hypokalemia with alkalosis). Cortisone is activated to cortisol in liver by 11β-hydroxysteroid dehydrogenase 1 (10) (Figure 1).

Pathophysiology of Hypokalemic Metabolic alkalosis

Ectopic ACTH syndrome is associated with increased ACTH production, increased production of ACTH precursor propiomelanocortin (POMC) and increased conversion of POMC to ACTH. Glucocorticoids affect a variety of renal

functions. Metabolic alkalosis and hypokalemia are the two common acid-base and electrolyte abnormalities associated with direct glucocorticoid action in the kidneys (11). Receptors for glucocorticoids are expressed in proximal tubule and collecting ducts and glucocorticoids act via Na+/H+ ion exchanger. Mineralocorticoid receptors are absent in the proximal tubule and are exclusively expressed in the distal nephron segments.

Approximately 80% of the filtered load of HCO3- is reabsorbed in the proximal tubule by Na+:3HCO3- co-transporter (NBC) across basolateral membrane. NBC has 3 isoforms and specifically NBC-1 is up regulated in metabolic acidosis, hypokalemia and glucocorticoids excess states and down regulated in response to $HCO3^{-}$ loading or alkalosis (12). Enhanced renal proximal tubule NBC-1 activity in glucocorticoids excess states could result in increased HCO3- reabsorption. Hypokalemia results from

spillover effect glucocorticoids onto mineralocorticoid receptors, with resulting enhanced potassium secretion in cortical collecting duct. Also, hypokalemia, in turn can increase the bicarbonate reabsorption in the proximal tubule with enhancing NBC-1 expression and activity.

NBC-1 expression also increases bicarbonate absorption in medullary thick ascending limb of loop of henele (mTAL) and inner medullary collecting duct (IMCD). Up regulation of NBC-1 seems to be an early event and precedes onset of hypokalemia (13), indicating that the signal responsible for enhanced NBC-1 expression is likely activated by intracellular potassium depletion rather than hypokalemia.

Clinical symptoms

Cushing's syndrome is characterized by truncal obesity with moon face, facial plethora, buffalo hump with loss of subcutaneous fat, purplish abdominal striae, ecchymoses and proximal myopathy, accompanied by nonspecific symptoms like edema, hypertension, fatigability and weakness, hirsutism, hyper pigmentation, diabetes mellitus, osteoporosis. Loss of potassium with sodium retention with subsequent hypertension and hyporeninemia are the consequences mineralocorticoid excess (11).

It is unusual for the ectopic ACTH to present with classical clinical stigmata of Cushing's syndrome as there is exposure to high levels of glucocorticoids, mineralocorticoids and adrenal androgens within a short period. Patients with ectopic ACTH present with hypokalemia and metabolic alkalosis more commonly and relatively early in the disease course when compared to other causes of Cushing's syndrome. Hypokalemia and metabolic alkalosis are more pronounced in ectopic ACTH secretion and more refractory to supplementation (14). Profound hypokalemia and hypertensive crises from mineralocorticoid action of cortisol may lead to cardiac and vascular complications including ventricular arrhythmias (15). The degree of hypokalemia is directly related to the amount of urine-free cortisol (16). Other lab anamolies include polycythemia, thrombocytosis and leucocytosis. Also marked suppression of immune system can predispose to severe infections and hence septicemia and opportunistic infections including CMV and Pneumocystis jiroveci (carinii) pneumonitis (15).

Diagnosis

Cushing's syndrome is most likely when cortisol levels at midnight are higher than 5µg/100ml, when cortisol levels are higher than 1.4µg/100ml in the combined dexamethasone – corticotrophin-releasing hormone test, when there is elevation of cortisol and ACTH after administration of 1-desamino -8-D-arginine vasopressin (DDAVP) or when there is no elevation of ACTH and cortisol during insulin induced hypoglycemia (15).

If the diagnosis is not clear, overnight dexamethasone suppression testing would help to differentiate pituitary ACTH from ectopic ACTH secretion. With overnight administration of 8 mg of dexamethasone, a decrease in cortisol level to less than 50% of baseline is indicative of pituitary dependent Cushing's disease. A negative response indicates ectopic source of ACTH secretion (17). Sensitivity and specificity of overnight dexamethasone testing is 57-92% and 57- 100% respectively in diagnosing pituitary disease (18). Cushing's syndrome resulting from primary adrenal source is associated with suppressed ACTH levels and ACTH levels are normal or elevated in ectopic ACTH syndrome. CT or MRI of the adrenals is useful in determining adrenal tumors or adrenal hyperplasia. ACTH dependent Cushing's syndrome is more likely pituitary in origin, which is associated with rise of ACTH with CRH administration and a suppression of ACTH and cortisol below 50% of basal value after 8 mg of dexamethasone. Also MRI of the pituitary is helpful in ascertaining the etiology if a pituitary dependent ACTH related Cushing's syndrome is suspected.

When ACTH dependent Cushing's syndrome is suspected it is necessary to confirm or exclude ectopic ACTH secretion especially if there is associated thymic carcinoid or SCLC. Other lab tests for clarifying the diagnosis of ectopic ACTH dependent Cushing's syndrome include plasma chromogranin A, plasma metanephrines, neuron specific enolase, calcitonin and cyfra (15).

ACTH precursors are markedly elevated in ectopic ACTH syndrome, compared to patients with other causes of Cushing's syndrome (19).Management of Cushing's syndrome from Ectopic ACTH secretion Treatment of underlying malignancy is the main stay in management of the Cushing's syndrome secondary to ectopic ACTH secretion. In the case of carcinoid tumors secreting ACTH surgical excision would result in complete resolution of symptoms with return to normal adrenal function (20).Our patient had complete resolution of hypokalemic metabolic alkalosis with surgical excision of anterior mediastinal tumor and biopsy confirmed ACTH secreting carcinoid tumor (Figures 3 a, b, c, d). Medical therapy involves use of steroid synthesis inhibitors, such as Ketoconazole (21), Mitotane, Metyrapone, Octreotide (22), minogluthethemide. Ketoconazole (400-1200mg/day), which acts by blocking corticosteroid production by inhibiting 17-hydroxlase and 11- hydroxylase, is the therapy of choice because of its low incidence of side

effects. Octreotide, acts by binding to the sst2 somatostatin receptor, suppress ACTH release. It is effective both on its own and in combination with Ketoconazole (17). Metyrapone is an alternative agent not as effective as Ketoconazole and can cause significant hypokalemia. Spironolactone, an aldosterone receptor antagonist, is used to decrease urinary potassium wasting secondary to activation of mineralocorticoid receptors (23).

# Conclusion

To conclude, we present a case of persistent hypokalemic metabolic alkalosis resulting from anterior mediastinal thymic neuroendocrine carcinoid tumor. It is imperative to have a high clinical suspicion for recognizing the signs and symptoms of ectopic ACTH mediated Cushing's syndrome. Treatment for carcinoid tumors secreting ectopic ACTH secretion involves surgery and administration of oral medication as deemed necessary. Surgery combined with medical therapy, where ever indicated improves morbidity and quality of life.

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# Illustrations

## Illustration 1

Illustrations for the article

1

**Table 1. Serum levels of Sodium (Na), Potassium (K), Bicarbonate ($HCO3^-$) on admission, during hospital course and few hours post-surgery respectively**

| Electrolytes | On Admission | In hospital | Few hours post surgery |
|---|---|---|---|
| Na | 140 mEq/l | 143 mEq/l | 138 mEq/l |
| K | 2.7 mEq/l | 2.7 mEq/l | 4.7 mEq/l |
| $HCO_3^-$ | 35 mEq/l | 35 mEq/l | 30 mEq/l |

**Table 2. Serum levels of TSH, Random Plasma cortisol, ACTH, 24 hour urinary 5-HIAA on admission**

| | |
|---|---|
| TSH | 1.47 micro IU/ml |
| Random Plasma cortisol | >65 mcg/dl |
| ACTH | 358 pg/ml |
| 24 hr urinary 5-HIAA | 6.8/24hrs |

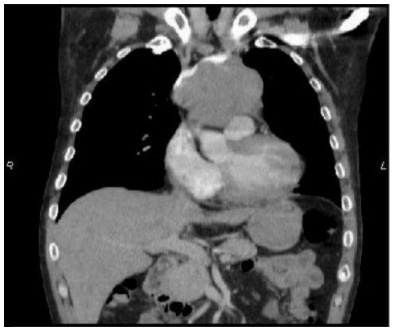
Mineralocorticoid receptor

( Liver, Adipose, CNS, Placenta)

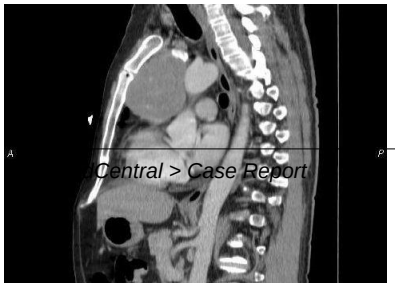
**Legend:** In the liver, inactive cortisone is converted to cortisol in the presence of 11-β-hydroxysteroid dehydrogenase 1 (11- βHSD1); Adipose tissue, CNS and placenta are also involved in formation of cortisol. Subsequently cortisol enters the circulation and in kidneys it is enzymatically inactivated to cortisone by 11-β-hydroxysteroid dehydrogenase 2 (11- βHSD2). Inactive cortisone is also formed in small amounts in colon, salivary, sweat glands and placenta.

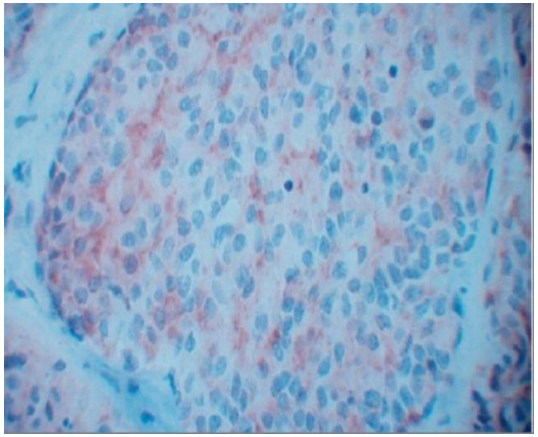
**Figure 2 a & b** coronal and sagittal sections of CT scan of the chest with large anterior mediastinal mass

**2 a**



**2 b**





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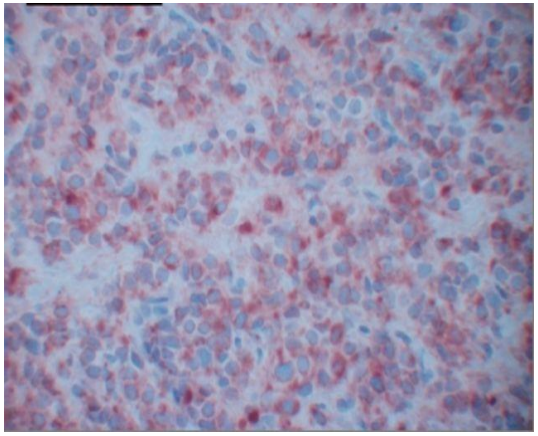

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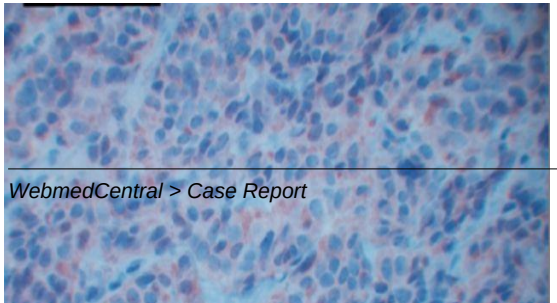

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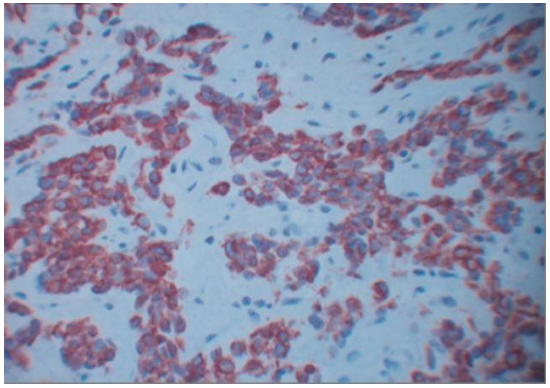

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