

Medullar thyroid carcinoma in mediastinum initially presenting as Ectopic ACTH syndrome

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Submitted: 2010-11-15 Accepted: 2011-06-26 Published online: 2011-08-29

Key words: **ectopic ACTH syndrome; medullar thyroid carcinoma;
adrenocorticotrophic hormone; hypokalemia**

Neuroendocrinol Lett 2011; 32(4):421-424 PMID: 21876495 NEL320411C06 © 2011 Neuroendocrinology Letters • www.nel.edu

Abstract

A rare case with ectopic adrenocorticotrophic hormone syndrome (EAS) caused by medullar thyroid carcinoma (MTC) in mediastinum was reported. This 49 year-old male patient initially presented with serious and intractable hypokalemia. Endocrine evaluations showed increased levels of adrenocorticotrophic hormone (ACTH) and urinary free cortisol, which could not be suppressed more than 50% by high-dose dexamethasone suppression test. Computed tomography (CT) scan detected a 5×5×5 cm mass at the bottom of thyroid in anterior mediastinum. The patient underwent total thyroidectomy with central compartment and ipsilateral modified radical neck dissection. Pathological examination showed an infiltrating thyroid medullary carcinoma with abundant amyloid deposition, meanwhile immunohistochemical positive for ACTH. After surgery, serum levels of kalium, as well as cortisol and ACTH returned to normal range. During follow-up, the patient's clinical manifestation of Cushing syndrome relived.

Abbreviations:

ACTH - adrenocorticotrophic hormone
BISSP - bilateral inferior petrosal sinus sampling
CRH - corticotropinreleasing hormone
EAS - ectopic ACTH syndrome
HDDS - high-dose dexamethasone suppression test
MTC - medullar thyroid carcinoma

present with ectopic adrenocorticotrophic hormone (ACTH) syndrome (Cohen *et al.* 2009; Parenti *et al.* 2006). In this report, we described a rare case with sporadic MTC in mediastinum who initially presented with serious and intractable hypokalemia, and later were confirmed to have ectopic ACTH syndrome (EAS) caused by MTC.

INTRODUCTION

Medullary Thyroid Carcinoma (MTC) derives from parafollicular C-cells of the thyroid, which is of neural crest origin and has the ability to produce calcitonin. MTC is relatively rare, representing 3–5% of all thyroid cancers. Patients with MTC most commonly present with an increasing thyroid nodule and/or combined with palpable cervical lymph nodes, however rarely

CASE REPORT

A 49 year-old male patient was referred to endocrinology department because of dizziness, hypertension, weakness and hypokalemia for 2 months. He had been relatively healthy until 2 months earlier when he suffered from above symptoms. Also his blood pressure elevated to 150–160/95–100 mmHg. In local hospital, labo-

ratory examination showed serious and persistent hypokalemia, with the lowest level at 1.4 mmol/L. After administration of chloratum kalium for 10 g/d, the hypokalemia still could not be rectified. His family history was unremarkable regarding any endocrinological or thyroid disease.

On arrival, the patient clinically presented with slight facial plethora, fat pads in supraclavicular fossa, hyperpigmentation, ecchymoses and moderate edema in the lower extremities. But some other manifestations of typical Cushing syndromes such as central obesity, thick purple and abdominal striae were not presented. Thyroid could not be palpated, and no enlarged superficial lymph nodes were palpable.

After admission, the initial biochemical examination showed serious and refractory hypokalemia (1.91 mmol/L) combined with elevated urinary potassium levels (79.0 mmol/24 h) and metabolic alkalosis. Arterial blood gas analysis showed pH 7.519 and bicarbonate 40.9 mmol/L. Plasma glucose level was at normal level (5.62 mmol/L). Besides, serum carcino-embryonic antigen, α -fetoprotein and human chorionic gonadotropin were all in normal range. Regrettably, the examination of calcitonin was unavailable. Endocrinological evaluation showed that plasma ACTH and cortisol were both at very high level and had circadian rhythm disturbances. Morning plasma ACTH was 61.4 pmol/L (2.2–10.12 pmol/L) and cortisone was >1636.2 mmol/L (241.7–622.3 mmol/L). All these clinical evidences indicated the diagnosis of ACTH-dependent Cushing syndrome. Later the patient underwent high-dose dexamethasone suppression test (HDDS) which showed plasma cortisol suppression less than 50%.

Abdominal computed tomography (CT) scan showed diffuse hyperplasia in bilateral adrenals. Ultrasonic examination and chest CT scan both detected a 5×5×5 cm mass at the bottom of thyroid in anterior mediastinum (Figure 1). Patient underwent the bilateral inferior petrosal sinus sampling (BISSP) for

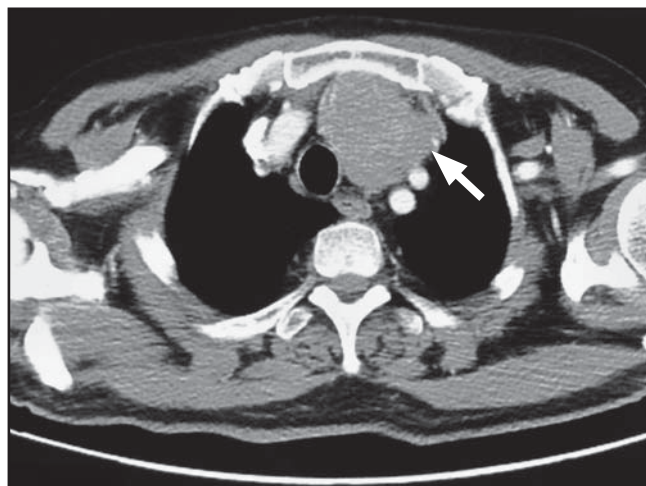


Fig. 1. CT scan detected a 5×5×5 cm mass at the bottom of thyroid in the anterior mediastinum (arrow).

definite diagnosis. The results showed that the highest central to peripheral ACTH gradients varied from 0.89 to 1.27, which was compatible with non-pituitary ACTH production. All these clinical and radiological findings supported the diagnostic hypothesis of EAS and the offending tumor was suspected to be the MTC in the mediastinum.

During hospitalization, the patient complained of polydipsia and polyuria and his fasting plasma glucose level elevated gradually up to 13.5 mmol/L. So the secondary diabetes mellitus was diagnosed and insulin therapy was initiated. Also the symptom such as facial plethora, ecchymoses and lower extremities edema, thick and purple striae all became more and more serious.

Later, the patient underwent total thyroidectomy with central compartment and ipsilateral modified radical neck dissection. The resected tumor in the mediastinal mass measured 5×5×5 cm. The pathological examination showed thyroid tissue with an infiltrating medullary carcinoma with abundant amyloid deposition (haematoxylin & eosin) (Figure 2). Immunohistochemical study revealed that immunoreactivities were positive for ACTH (Figure 3), chromogranin A, but negative for calcitonin and CEA.

After surgery, patient received for 3 days hydrocortisone 100 mg intravenously, and 50 mg for subsequent 3 days to prevent adrenal crisis. Then serum potassium elevated to 3.8–4.3 mmol/l without potassium supplement. Standard replacement with thyroxin was initiated 1 month later. Hormone examination showed both morning serum cortisol (290.7 mmol/L) and ACTH (9.9 pmol/L) in normal range. The treatment also resulted in a dramatic improvement of diabetes mellitus, so insulin therapy was substituted by oral antihyperglycemia drugs. Serum potassium levels remained stable between 3.8 and 4.3 mmol/l. During follow-up, the patient's clinical manifestation of Cushing syndrome relived gradually and his strength improved later.

DISCUSSION

Incidence of ectopic thyroid in anterior mediastinal is about 3–21%, and it usually needs chest CT or magnetic resonance imaging (MRI) to localize. As for this patient, thyroid could not be palpated, but only ultrasonic examination and chest CT detected thyroid and the mass at the bottom of it in the anterior mediastinum.

MTC is usually aggressive and frequently metastatic at the time of diagnosis. The most common clinical presentation of sporadic MTC is a solitary thyroid nodule or a palpable cervical lymph node. Other simultaneous symptoms such as diarrhea and/or a flushing syndrome are usually related to advanced metastatic disease (Fromigué *et al.* 2006). Calcitonin is a specific and highly sensitive biomarker for MTC and basal calcitonin over 100 pg/mL (normal value <10 pg/mL) is strongly suggestive of MTC. Histologically, MTC is

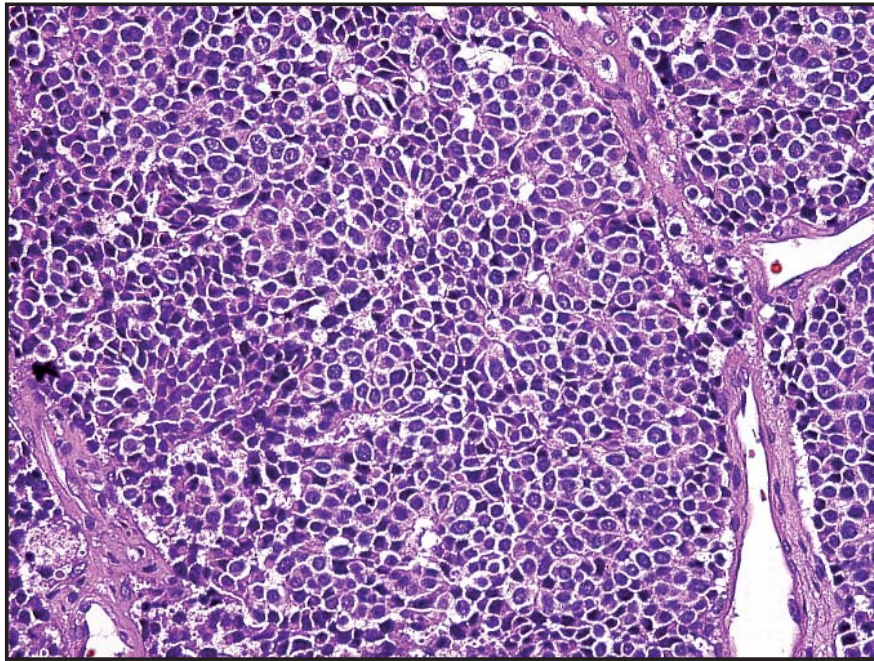


Fig. 2. Pathology examination showed thyroid tissue with an infiltrating medullary carcinoma with abundant amyloid deposition (*hematoxylin & eosin*).

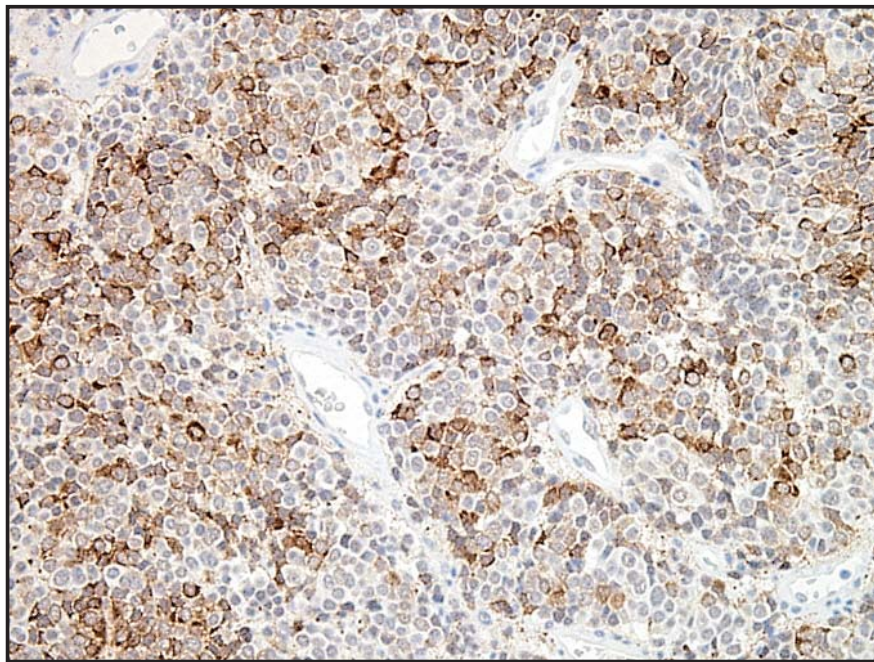


Fig. 3. Immunohistochemical study revealed immunoreactivities positive for ACTH in tumor cells.

characterized by uniform polygonal cells with finely granular eosinophilic cytoplasm and central nuclei. But in most cases, not all, calcitonin immunostaining on tumor tissues is positive (Cohen *et al.* 2009).

EAS is defined as ACTH production from a source outside pituitary gland, leading to clinical manifestation of Cushing syndrome. It occurs in about 10% of all cases with Cushing syndrome. This disease is associated with a variety of solid tumors, mostly of neuroendocrine origin, including small-cell lung carcinomas

(45%), thymic carcinoid tumors (15%), bronchial carcinoids (10%), pancreatic islet cell tumors (10%), other carcinoid tumors (5%) and pheochromocytomas (2%) (Bi *et al.* 2008; Sato *et al.* 2010).

MTC derives from thyroid C cells, which are of neural crest origin. C cells not only have the ability to produce and secrete calcitonin, but also have the potential to secrete some other hormones and humoral agents. In particular, C cells can produce excessive ACTH and/or corticotropinreleasing hormone (CRH),

resulting in Cushing syndrome (Nijhoff *et al.* 2009). EAS in MTC is extremely rare. A large study in France population showed that the frequency of EAS in MTC ranged from 0.6% to 0.7%. The prognosis is darker when EAS is present in patients with MTC, since this disease always had metastases to multiple organs before onset of Cushing syndrome (Barbosa *et al.* 2005).

Ectopic ACTH secretion by malignant tumors typically leads to early-appearing and rapidly augmenting metabolic alterations, for example rapid weight loss, muscle weakness, serious hypokalemia, metabolic alkalosis and glucose abnormal metabolism. But there are often some difficulties in differential diagnosis of EAS from Cushing syndrome because of the overlap in clinical presentation and biochemical features between these clinical conditions. Recently, BIPSS has been considered to be the gold standard for differential diagnosis. A positive conclusion of BIPSS (peak dominant inferior petrosal sinus to peripheral ACTH ratio >2.0 in the basal state and/or >3.0 after CRH infusion) is a very strong indicator of Cushing syndrome, and also a negative response indicates EAS (Chrisoulidou *et al.* 2008; Koo *et al.* 2008; Sawathiparnich *et al.* 2009). Of course, the diagnosis can further be confirmed by positive ACTH immunoreactivity in the tumor tissue and resolution of hypercortisolemia after tumor removal (Park *et al.* 2007).

As for this patient, the initial complaint was hypertension and serious hypokalemia. The presentations of Cushing syndrome are atypical but worsen quickly. Later endocrine evaluation and BIPP, as well as chest CT scan indicated the diagnosis of EAS caused by MTC in mediastinum. Successful removal of MTC resulted in significant improvement of all the symptoms and abnormal biochemical index. The pathology and immunohistological examination of ACTH confirmed our initial judgment.

Once localization diagnosis of MTC was accomplished, surgical removal of these lesions was the optimal treatment of choice and may lead to cure. The recommended procedure is complete surgical resection comprising total thyroidectomy with central lymph node dissection at an early stage (Barbosa *et al.* 2005; Suárez-Llanos *et al.* 2007). The responses of tumors to chemotherapy are always partial and transient, meanwhile radioactive iodine is ineffective because C cells do not take up the agent. As to the therapy on EAS in patients with MTC and advanced metastasis which are incurable with surgery, palliative bilateral adrenalectomy followed by hormone replacement treatment is recommended. All these conservative therapies can lead to a clear improvement of Cushing syndrome and most importantly significantly improve quality of life in short run in patients with advanced metastases (Suárez-Llanos *et al.* 2007). It should be emphasized that whenever surgery is not a curative option, a multidisciplinary approach should be adopted including chemotherapy, radiotherapy, hormone analogues and/or radionuclide

treatment to control tumor growth and associated symptoms. The French MTC consortium showed that serial post-operative calcitonin measurement could allow assessment of the adequacy of surgical extirpation and provide valuable prognostic information (Barbosa *et al.* 2005).

CONCLUSION

In summary, we reported a rare case with EAS caused by MTC in mediastinum. Patient underwent successful operation and remained in remission. We would like to emphasize the importance of detecting rare ectopic organs in EAS when the common sources of ectopic ACTH secretion present negative findings.

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