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Bronchopulmonary carcinoid tumor presenting as dexamethasone suppressible Cushing's syndrome; a case report

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Abstract

Cushing's syndrome is an endocrine condition with complex diagnostic pathways. Cortisol suppression from high-dose dexamethasone suppression tests usually points to the pituitary as the cause. We present a patient with high-dose dexamethasone suppressible Cushing's syndrome from a bronchopulmonary carcinoid tumor. A 30-year-old male presented with signs and symptoms of Cushing's syndrome. Cortisol and ACTH levels were significantly elevated. High-dose dexamethasone test suppressed cortisol production. However, no pituitary source was found. In chest-computed tomography a well-differentiated mass was seen, octreotide scan localized somatostatin-positive tumor in the same place, which revealed a bronchopulmonary carcinoid tumor. Bronchopulmonary carcinoid tumor should be kept in the mind in the differential diagnosis of Cushing's syndrome with suppression of the high-dose dexamethasone test if a pituitary source is not localized.

Keywords: Ectopic Cushing syndrome, Bronchial carcinoid tumor, Hypercortisolism

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Introduction

Cushing's syndrome is a constellation of signs and symptoms resulted from prolonged exposure to excess levels of free plasma glucocorticoids. The prototypic features of Cushing's syndrome are central obesity, moon face, hirsutism, and plethora. It is classified into two groups; ACTH (adrenocorticotropic hormone) – dependent (80%) and ACTH-independent (20%) (1). The causes of ACTH-dependent Cushing's syndrome are associated with bilateral adrenocortical hyperplasia. Their relative frequency is as follows;

- Cushing's disease (pituitary hypersecretion of ACTH) in 65% to 70% of cases.
- Ectopic secretion of ACTH by non-pituitary tumors in 10% to 15 % of cases.
- Ectopic secretion of corticotrophin-releasing hormone (CRH) by non-hypothalamic tumors causing pituitary hypersecretion of ACTH in below 1% of cases.
- Iatrogenic or factitious Cushing's syndrome due to the administration of exogenous ACTH (not glucocorticoids) in <1% of cases.

Non-pituitary tumors secreting ACTH can be divided into two entities; 1) highly malignant tumors such as small cell carcinoma of bronchus and highly proliferative neuroendocrine carcinoma. 2) More indolent tumors such as bronchial carcinoid tumors (BCts) (1,2).

BCTs are characterized as a subclass of bronchopulmonary neuroendocrine cancers which can generate neuropeptides. The global incidence of BCTs is 0.2–2 per 100 000 individuals annually. Around 2% of BCTs secrete adrenocorticotropic hormone and less than 1% of individuals with Cushing's syndrome have BCTs (3,4).

Here we describe a case of ectopic Cushing's syndrome characterized by a typical BCT. This patient reminds that, the evaluation of Cushing's syndrome should be broad and rare causes of Cushing's syndrome should always be considered.

Case Report

The patient is 30 -year- old man, with no positive past-medical history, complained of gradually swelling of face, abdomen and extremities and weight gain (up to 20 kg) from 1 year ago. Patient is a smoker. In visit his blood pressure was 220/110 mm Hg. Other clinical features were moon face, easy bruising, obesity, thick purple striae on abdomen, monomorphic acne on trunk and face. He was referred to an endocrinologist due to the impression

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Implication for health policy/practice/research/ medical education

We described a case of ectopic Cushing's syndrome instigated by a typical bronchial carcinoid tumor. The history of this patient implies that the evaluation of Cushing's syndrome should be wide and rare causes of Cushing's syndrome should always be considered.

of Cushing's syndrome for further evaluation. In physical examination blood pressure of both arms were the same. There was no orthostatic hypotension, peripheral lymphadenopathy or organomegaly. Other clinical findings were unremarkable.

Initial laboratory results included WBC; 11200/µL, hemoglobin level; 16.7 g/dL, Plt: 160000/µL, serum creatinine; 1 mg/dL, Na: 140 mEq/L, K; 4.1 mEq/L, AST; 26 U/L, ALT; 50 U/L, ALP.PH; 65 U/L. Additionally, 24-hour urine free cortisol and ACTH were 1177 µg/d and110 pg/mL respectively.

While both basal cortisol (38.6 µg/dL) and ACTH (110 pg/mL) were high, we conducted a low-dose dexamethasone suppression test.

Serum cortisol after low-dose dexamethasone suppression test was not suppressed (26.2 µg/dL), however, serum cortisol after high-dose dexamethasone suppression test (2 mg dexamethasone 6 hourly for 48 hours) was suppressed more than 50% of baseline (14.8 µg/dL). Pituitary MRI was normal. In chest-CT (computed tomography) scan a solid oval well-circumscribed lesion of 20×15 mm size in left upper lobe with Hounsfield unit of 33-37 was seen. Due to its well-circumscribed border, the lesion seemed to be benign. However, metastatic lesions of slow growing-tumors like carcinoids should be included in differential diagnosis (Figure 1). In abdominal CT, bilateral adrenal hyperplasia was reported. Octreotide scan showed octreotide avid lesion in left hemithorax. The patient was referred to a thoracic surgeon and lung lobectomy was performed and sent for pathologic study. A typical well-differentiated neuroendocrine tumor (grade 1), which is in favor of typical carcinoid tumor was reported (Figure 2). In immunohistochemical staining, chromogranin and synaptophysin were positive. In addition, Ki-67 was positive in 1% of nuclei.

After tumor resection, serological values of ACTH and cortisol started to fall. His clinical condition became better gradually. After surgery oral hydrocortisone prescribed to treat adrenal insufficiency, which was planned to tapper and withhold after six months.

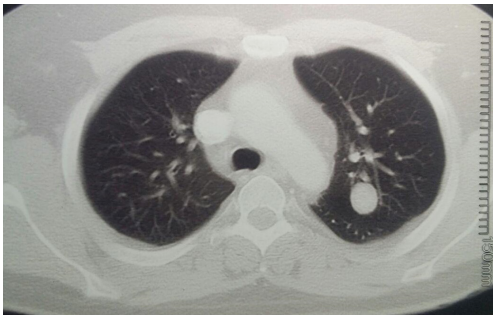

Figure 1. Computed tomography scan of lung without intravenous contrast shows an oval well-circumscribed mass lesion in the left upper lobe

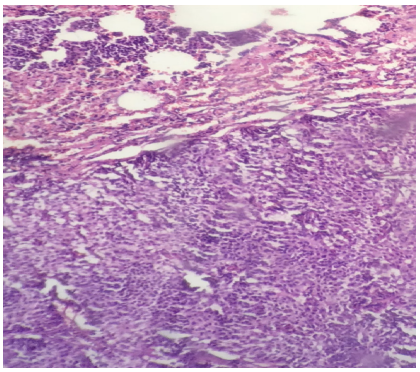

Figure 2. Stained histological biopsy tissue specimens from the left upper-lobe pulmonary lesion, typical well-differentiated neuroendocrine tumor (grade 1) typical carcinoid tumor.

Discussion

Cushing's syndrome is characterized by the symptoms and signs of prolonged exposure to excess levels of free plasma glucocorticoids. It is classified into two groups; ACTH-dependent (80%) and ACTH-independent (20%). Among ACTH-independent causes, 10%-15% belongs to ectopic secretion of ACTH by non-pituitary tumors (1).

Neuroendocrine tumors are rare causes of Cushing's syndrome. Carcinoid tumors of bronchus are characterized by a subcategory of neuroendocrine tumors of bronchopulmonary tree, with a worldwide incidence of 0.2–2 per 100 000 individuals annually (4). A study of 19 Cushing's syndrome case reports related to BCTs demonstrated an equivalent distribution for gender and a mean age of 43 years old. The most common symptoms were arterial hypertension, asthenia and hypokalemia. However, pulmonary manifestations were infrequent (5).

Before evaluation for possible Cushing's syndrome, a careful history of exogenous glucocorticoid intake should be taken (6). The diagnosis of Cushing's syndrome is then established when at least two first-lines tests (late-night salivary cortisol, 24-hour urinary free cortisol [UFC] excretion, overnight 1 mg dexamethasone suppression test or low-dose dexamethasone suppression tests) are abnormal (6). Next step is to determine whether the hypercortisolism is ACTH-dependent (due to a pituitary or non-pituitary ACTH-secreting tumor), or ACTH-independent (due to an adrenal source) by measuring plasma ACTH. The high-dose dexamethasone suppression test is administered to distinguish patients with pituitary ACTH-secreting tumor from patients with non-pituitary

(ectopic) ACTH-secreting tumor.

ACTH producing pituitary adenomas that cause Cushing's disease is relatively resistant to negative feedback regulation by glucocorticoids. However, ACTH secretion can be suppressed in most patients with ACTH producing pituitary adenomas by increasing the dose of dexamethasone. In contrast, most non-pituitary tumors associated with the ectopic ACTH syndrome are completely resistant to feedback inhibition, with the exception of some carcinoid tumors like bronchial carcinoids (2). There is significantly overlapping between patients with ectopic ACTH syndrome secondary to benign carcinoid tumors and ACTH producing pituitary adenomas while biochemical investigations are frequently not conclusive (5).

Computed tomography remains the first stem for evaluation of possible pulmonary neoplasms. A consensus for the diagnostic investigation of bronchopulmonary carcinoid and other neuroendocrine tumors is whole body scintigraphy with indium-111-labeled octreotide (Octreoscan), a somatostatin analogous. It is mainly due to the fact that about 80% of bronchopulmonary carcinoid tumors express somatostatin receptors, making this exam more sensitive and specific (5).

The goal of treatment of all patients with Cushing's syndrome is to reach normalization of hypothalamic-pituitary-adrenal function and subsequent reversal of Cushing's syndrome /symptoms and co-morbidities.

Surgical resection is the treatment of choice when the tumor detected (5). Medical therapy and bilateral adrenalectomy are another treatment options in occult ectopic ACTH-secreting tumors in which the site of the tumor is not known. Somatostatin analogous treatment, adrenal enzyme inhibitors or mitotane are administered for medical treatment (7).

Conclusion

We described a case of ectopic Cushing's syndrome instigated by a typical BCT. The history of this patient implies that the evaluation of Cushing's syndrome should be wide and rare causes of Cushing's syndrome should always be considered.

Authors' contribution

MRK, RSD and SS managed the patient and wrote the first draft. MRK edited the final draft.

Conflicts of interest

There were no points of conflicts.

Ethical considerations

The patient has given his informed consent regarding this case report.

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None.

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