Ectopic Cushing’s Syndrome as the Initial Presentation of Pulmonary Carcinoid

Tumor Managed by Etomidate: A Case Report

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Abstract: Ectopic increase of adrenocorticotropic hormone (ACTH) or ectopic Cushing syndrome is a rare initial presentation of small cell carcinoma and carcinoid tumor of the lung. Here, we reported a 36-year-old male with atypical symptoms of Cushing syndrome managed by Etomidate that had a central pulmonary nodule, and pathologic evaluation of pulmonary lobectomy revealed the diagnosis of well-differentiated, low-grade typical carcinoids of lung.

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Introduction

Medical conditions with excessive endogenous secretion of ACTH outside the pituitary gland are not very common presenting with obesity, hypertension, buffalo hump, moon face, and hirsutism (1). Ectopic increase of adrenocorticotropic hormone (ACTH) or ectopic Cushing syndrome occurs in less than 10 percent of patients with bronchial carcinoids (2). Pulmonary carcinoid is a kind of low-grade malignant lung tumors that tend to be centrally located endobronchial lesions (3). It usually arises from neuroendocrine Kulchitsky cells located in the bronchial epithelium and comprises between 1% and 2% of all primary lung cancers (4). Nearly any neuroendocrine or non-endocrine tumors may be associated with ectopic ACTH syndrome, among which small cell lung carcinoma, pulmonary carcinoid, and medullary carcinoma of the thyroid are the most common (5). It is hard to draw a clear border between ectopic ACTH syndrome and other diseases mainly manifest as Cushing syndrome in the most of times. Cushing’s syndrome due to ectopic ACTH has not classic manifestation. Differentiating between ectopic ACTH secretion and Cushing disease remains a challenging problem (6). Here, we reported a case with overt Cushing syndrome manifestation that was evaluated and finally diagnosed as carcinoid tumor.

Case Report

A 36-year-old male with history of poor control diabetes mellitus was admitted to our department due to progressive muscle weakness in lower extremity, muscle atrophy in upper extremity, and weight loss (about 10 kg) within four months ago. There was no previous personal or familial medical history, rather than the diabetes mellitus of himself. In physical examination, there was facial plethora, severe proximal weakness (positive Gower’s sign), telangiectasia in face, pitting edema in lower limbs (left > right), and no purple striae. The forces of proximal muscle groups in the four limbs were decreased significantly along with two-plus pitting edema in the left lower extremity. Upper extremities examination showed an obvious bilateral muscular atrophy. The baseline laboratory data showed hypokalemia (i.e. K=2.4 mEq/L) and metabolic alkalosis. Because of unilateral lower extremity edema and muscular weakness, he underwent color Doppler
ultrasonography, and Electromyography (EMG)/Nerve conduction velocity (NCV), former confirmed a deep vein thrombosis (DVT) and later showing a chronic motor sensory polyneuropathy with axonal feature and bilateral moderate carpal tunnel syndrome.

Since the Cushing syndrome was highly suspected, serum cortisol and ACTH levels, as well as saliva cortisol level, were assessed randomly, revealing an increased in all of them (54 μg/dL, 251 pg/ml, and 2.1 μg/dL, respectively). Subsequently, the diagnosis of the Cushing syndrome was confirmed by overnight 8-mg dexamethasone suppression test (Cortisol at 6:00 A.M: 45 μg/dL; Cortisol at 3:30 P.M: 30 μg/dL; morning ACTH at 6:00 A.M: 193 pg/mL; ACTH at 3:30 P.M: 98 pg/mL) that showed high cortisol and ACTH levels suggesting ectopic source for it. Other autoimmune laboratories and complement levels were in normal range.

According to severity of Cushing syndrome and no response to ketoconazole, he received Etomidate therapy (0.05 mg/kg IV bolus and 0.03 mg/kg/h infusion and we monitored serum cortisol and electrolytes level. The best response occurs when cortisol level decreases to 20 μg/dl, and the patient feels better after this treatment).

For assessment of source of ACTH, patients underwent brain magnetic resonance imaging, high-resolution CT scan (HRCT) of thorax, and computed tomography (CT) of the abdomen and pelvis. Imaging assessments include adrenal glands were normal except a single 12 mm nodule adjacent to right lung hilum. Also, OctreoScan includes whole-body planar, and SPECT imaging was obtained showing two small avid lesions in the hilum of right lung, which indicated that ectopic ACTH syndrome was caused by pulmonary neuroendocrine tumor (Figure 1).

Figure 1. The Tc-99m-Octreotide scintigraphy and fused SPECT/CT images. It showed two small zones of increased radiotracer uptake in the hilum of the right lung corresponding to the opacities in the CT scan images. The images were shown from left to right in sagittal, coronal and transverse views, respectively.

Afterward, bronchoscopic biopsy was non-diagnostic due to insufficient tissue for pathologic examination, and therefore because of high clinical suspicion and supporting imagings, the patient underwent lobectomy of inferior lobe of right lung with excision of two lymph nodes. Grossly, the resected mass (lobectomy) measured approximately 5.5×10×11 cm in size. The 24 h urine 5-hydroxyindoleacetic acis(5 HIAA) level and the serum chromogranin A level was high (178.35). Histologically, the tumor was primarily made up of small foci of well-differentiated neuroendocrine cell hyperplasia with alveolar hemorrhage and deposition of hemosiderophage (Figure 2), and finally, well-differentiated, low-grade typical carcinoids of lung was diagnosed. After surgery, hydrocortisone150 mg/day IV started and then 20mg /day oral and was discharged after one week; the patient felt better every day; blood glucose was well controlled, and myopathy improved gradually. After 6months of insulin therapy withdrawal, myopathy was completely recovered. The patient was followed-up for one year, and hydrocortisone discontinued. No recurrence of the tumor was found.

Figure 2. Histopathology of resected lung tissue. Figure a, b, and c are representative of bronchi tissue with cellular nesting containing monomorphic, monotone and without mitosis by nuclear chromatin view (Salt and Pepper) in Hematoxylin and Eosin staining x100. Figure d is representative of immunohistochemical staining with Chromogranin marker x400.
Rare initial presentation of pulmonary carcinoid tumor

Discussion

In this case report, we present a patient with ectopic Cushing’s syndrome associated with poorly controlled diabetes, severe weight loss, progressive myopathy, and left lower extremity edema due to pathologically proved pulmonary carcinoid tumor manifested by solitary radioactive pulmonary nodule on the right side. Symptoms of patient were controlled by the administration of Etomidate preoperatively. The type of presentation of pulmonary carcinoid tumor and its management by Etomidate is unique, and there are not frequent reports in this context.

Medical conditions associated with secretion of ACTH outside the pituitary gland are challenging since the symptoms are prominent and need emergent management; however, the definitive diagnosis needs comprehensive evaluations (7). Among all causes, there are several tumors produce ACTH resulting in ectopic Cushing’s syndrome include pulmonary small-cell lung, thymic carcinoid tumors, pancreatic islet cell tumors, and rarely, bronchial carcinoids (8-11). Similar to our report, it was presented by Reza-Albarrán et al., (12) in which the case of a 51-year-old female with Cushing’s syndrome due to ectopic ACTH secretion caused by a pancreatic tumor with a liver metastatic lesion. They reported that Etomidate was indicated in the absence of adequate response to the use of ketoconazole in the control of severe hypercortisolism and its consequent catabolic effects in their case. They also mentioned the benefits of management by Etomidate that control of the serum cortisol levels in ectopic Cushing’s syndrome can be obtained with infusion rates much lower than those used in anesthesia, without respiratory side effects (12). In another case, Johnson and Canada introduced a 73-year-old man with a 5-year history of prostate cancer hospitalized by Cushing’s syndrome symptoms. They indicated that he underwent Etomidate infusion (2 mg/ml) without any obvious problems; however, he was expired because of multiple organ damage despite lowering cortisol level (13). In another case, Drake and colleagues reported a patient with Cushing’s syndrome secondary to ectopic ACTH production from a pancreatic islet cell tumor. They showed the impressive effect of acute and prolonged use of intravenous Etomidate (2.5 mg/h at first and 1.2 mg/h at last) for decreasing the level of serum cortisol that was not changed by octreotide (14). In another case, 41-year-old female with an ectopic ACTH-producing malignant paraganglioma managed by low-dose IV Etomidate (15) successfully similar to our case.

Etomidate inhibits the enzyme, 11-beta-hydroxylase (cortisol and corticosterone generator from 11-deoxycortisol and 11-deoxycorticosterone) leading to control of adrenal synthesis. There is growing evidence showing the potential role for Etomidate in the control of severe hypercortisolism; however, its definitive role has yet to be defined (12). Our case was presented by clinical features of Cushing’s syndrome beside the laboratory findings like hypokalemia and positive high dose dexamethasone suppression test. The patient received Etomidate, a short-acting intravenous anesthetic agent, and his symptoms were controlled appropriately.

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