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A Case of Cushing's Syndrome in ACTH-secreting Mediastinal Paraganglioma

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Paragangliomas are unusual neuroendocrine cell tumors arising from paraganglia, of which ACTH-secreting cases in the mediastinum are exremely rare. A 51-year-old woman was admitted for generalized edema and weakness which began 5 months ago. Chest X-ray and CT scan revealed a tumor mass in the anterior mediastinum. The plasma cortisol and ACTH levels were very high. Other sources secreting ACTH, except mediastinal mass, were not found. Surgical excision of mediastinal mass and left supraclavicular lymph node was performed. The postoperative microscopic finding and immunohistochemical staining revealed organoid tumor cell nests (zellballen) and S-100 protein positive sustentacular cells which are characteristics of paraganglioma. This was thus a case of Cushing's syndrome resulting from ectopic ACTH production in anterior mediastinal paraganglioma.

Key Words : *Cushing's syndrome; ACTH; Mediastinum; Paraganglioma*

INTRODUCTION

Paragangliomas in the mediastinum are rare tumors originated from the neuroendocrine cell. About 90% of paragangliomas exist in adrenal medulla (commonly called pheochromocytoma). The other 10% of tumors are extra-adrenal (paraganglioma), and 90% of these are intra-abdominal, most commonly arising from chromaffin cells near the aortic bifurcation or near the kidney. Other sites include the paravertebral sympathethic ganglia, the urinary bladder, other automatic ganglia (celiac, mesenteric), the thorax (mediastinum, the heart, and paracardic regions) and the neck (in sympathetic ganglia, carotid body, cranial nerve or glomus jugulare)[1].

Mediastinal paragangliomas usually have no symptoms. Occasionally, however, they do present with varying degrees of hypertension, diabetes and hypermetabolism. The tumors produce epinephrine, norepinephrine, or both. Rarely, the tumors produce functioning peptides that can cause Cushing's syndrome[2]. As far as we reviewed, there are no reports of ectopic ACTH syndrome with mediastinal paraganglioma in Korea.

We experienced a case with ACTH-secreting paraganglioma in the anterior mediastinum who was admitted because of Cushing's syndrome. We report this case with a review of the literature.

CASE

A 51-year-old-female was admitted to our hospital with 5 months' duration of generalized edema and weakness. About ten years before admission, she underwent an appendectomy. Two years later, hypertension was detected and she had been taken antihypertensive medications intermittently. Her family members were healthy and she was a housewife and nonsmoker. She denied any history of specific drug administration, including steroid. The patient had not

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any symptoms such as cough, sputum, fever and chest pain, except mild exertional dyspnea.

Her blood pressure was 170/100 mmHg, but other vital signs were stable. On physical examination, she was obese and had a moon face, buffalo hump and purplish abdominal striae. A 2x2 cm-sized hard and fixed mass was palpated on the left supraclavicular lymph node. There were pitting edemas on both lower legs.

The hemoglobin was 11.5 g/dL and the plaelet count was 239,000/mm^3. The serum AST, ALT, ALP and LDH level was 50, 140, 131 and 1,065 U/L, respectively. The renal function test, including serum electrolytes, were within normal limits, except that potassium level was 2.5 mEq/L. Fasting glucose was 472 mg/dL, hemoglobin A_1C was 11.8% and spot urine glucose was above 1,000 mg/dL, but proteinuria was not found.

Chest X-ray (Figure 1) and chest CT scan (Figure 2) revealed a 12x10 cm-sized well-defined and partially capsulated and lobulated homogeneous attenuated mass in the anterior mediastinum. No mediastinal or hilar lymphadenopathies were found. Percutaneous needle biopsy was performed and the microscopical finding revealed a carcinoid or paraganglioma.

The 24h-urine free cortisol was markedly elevated to 16,800 μg/day. The concentration of cortisol at 8:00 AM was 59 μg/dL. There was no suppression of the plasma cortisol level (over 50 μg/dL) after a high-dose dexamethasone suppression test. The plasma ACTH level was also elevated to 278 pg/ml, but pituitary MRI scan did not reveal any evidence of abnormality, therefore ectopic ACTH syndrome was suspected. To find

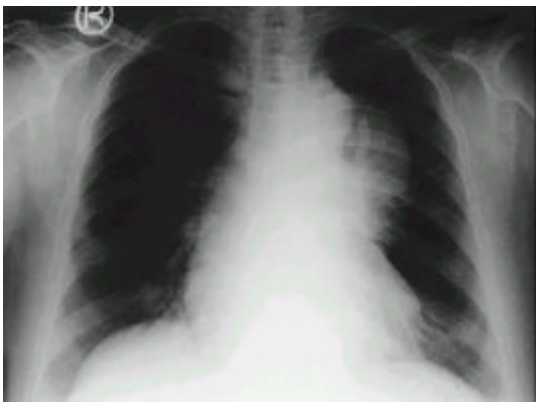

Figure 1. Chest PA shows well-marginated huge left suprahilar mass shadow.

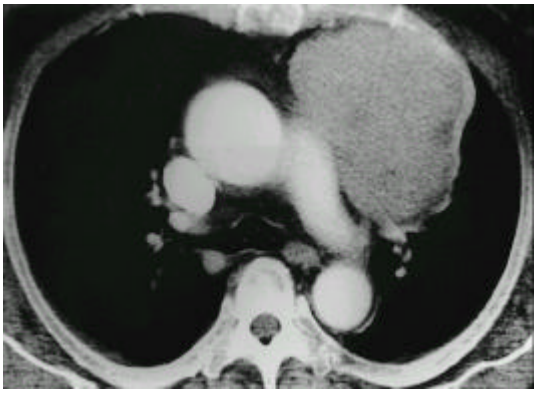

Figure 2. Chest CT shows 12x10cm-sized well-defined, partially capsulated and lobulated homogenous attenuated mass in the anterior mediastinum.

out the other focus of ectopic ACTH secretion, except mediastinal mass, abdominopelvic CT was performed, but there was no evidence of abnormalities, including adrenal gland, pancreas and ovary. The 24h-urine metanephrine, vanillymandelic acid (VMA) and homovanilic acid (HVA) levels were slightly elevated to 3.4, 11.4 and 13.9 mg/day, respectively, which are not typical ranges of pheochromocytoma. However, epinephrine and norepinephrine levels were within normal ranges. The 24h-urine 5-HIAA was elevated to 11.3 mg/day but serum calcitonin and parathyroid hormone levels were within normal ranges.

Surgical excision of mediastinal mass and left supraclavicular lymph node was performed. The gross appearance was a soft, nodular and well-encapsulated 13x10x6 cm-sized mass. Mostly, it consisted of hemorrhagic and necrotic areas. The viable portions existed partially. Light microscopic sections showed a predominantly diffuse pattern of monotonous neoplastic cells arranged in organoid cell nests (classic "Zellballen" pattern) that are characteristics of paraganglioma (Figure 3). Tumor cells were polygonal with a clear or finely granular eosinphilic cytoplasm and a round or ovoid nucleus. There were a few mitotic figures. Immunohistochemical stains revealed a diffuse and strong cytoplasmic immunoreactivity for chromogranin in about 90% of the tumor cells. Immunoreactivity for S-100 protein, confirming the presence of sustentacular cells which are characteristics of paraganglioma, was detected in scattered supporting cells, mostly at the periphery of the tumor cell nests (Figure 4).

She was confirmed as rarely occurring mediastinal paraganglioma secreting ACTH, Cushing's syndrome

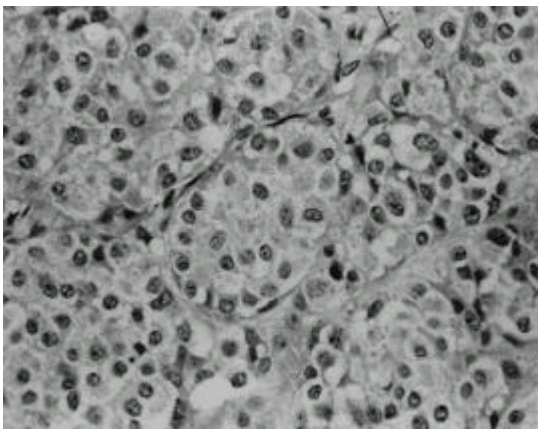

Figure 3. The light microscopic section shows a predominantly diffuse pattern of monotonous neoplastic cells arranged in organoid cell nests (classic "Zellballen" pattern) that are characteristics of paraganglioma.

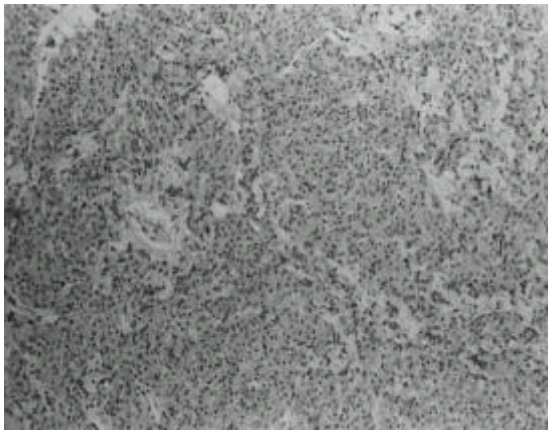

Figure 4. Immunohistochemical stain reveals a positive for S-100 protein in scattered supporting cells.

and secondary diabetes. Unfortunately, she died on the 22th postoperative day because of septic shock and respiratory failure due to uncontrolled mediastinitis with combined pneumonia.

DISCUSSION

Paragangliomas are unusual neuroendocrine cell tumors arising from paraganglia tissue which are widely dispersed groups of specialized neural crest cells. It has been known historically by a variety of names, including glomus tumor, chemodectoma, non-chromaffin paraganglioma, carotid body and tympanic body tumor, and receptoma[3]. The frequent location of paraganglioma in the mediastinum is controversial. In a report of Cesar et al., twelve tumors were located in the posterior mediastinum, and only three were anterior[4]. Gallivan et al. reviewed that anterior mediastinum was the more frequent location. In addition, tumors arising in an anterior mediastinum are claimed to be more often associated with older age, larger size and lower incidence of functionality, and are less amenable to surgical resection[5].

Mediastinal paragangliomas usually cause no symptoms. Occasionally, however, they do present with varying degrees of hypertension, diabetes and hypermetabolism. The tumors produce epinephrine, norepinephrine, or both. VMA and HVA are the chief urinary excretion products but epinephrine and norepinephrine may also be secreted in the urine. The word "functional" is used to describe paraganglioma that secrete catecholmaines and serotonin. The incidence of clinically functional paraganglioma is only 1% to 3%[6]. However, because of potentially serious consequences of a catecholamine crisis during manipulation of a functioning tumor, evaluation of patients should include screening for symptoms and signs and the measurment of appropriate blood and urine product. The tumors may produce functioning peptides that can cause Cushing's syndrome like this case, secretory diarrhea and polycythemia vera. In the thorax, they probably drive from neuroendocrine cells and typically develop in the paravertebral sulci. The 24h-urine metanephrine, VMA, HVA and serum serotonin levels may also be incerased, although slightly in this case. But there was no hypertensive crisis during the operation in this patient.

Paraganglioma in association with other neoplasms (part of multiple endocrine neoplasia syndrome, MEN) and reports of multicentricity have been well documented. Therefore, care should be exercised in differentiating between multicentric neoplasms and metastasis from a malignant tumor. Malignancy is rare and typically defined by the existence of metastasis, rather than cellular characteristics. Lung and bone were the usual sites of metastasis, whereas other sites included lymph nodes, liver, spleen, heart or kidneys[7]. Because paraganglial tissue is not usually found there, its presence in any of these organs constitutes metastasis. Some patients with known lung and bone metastses can live as long as 25 years after the lesions are

discovered[8]. In addition, spontaneous remission of metastatic paraganglioma has been reported[9]. There was no evidence of MEN, but supraclavicular lymph node metastasis was found in this case.

Large masses may be visible on the chest radiograph but, in most patients, CT scans are necessary to visualize the tumors. On MRI, a nonhomogeneous mass with a signal void will be visualized. ^{131}I-metaiodobenzylguanidine(MIBG) scintigraphy is useful for extraadrenal phechromocytoma. It can be used to localize lesions not seen on other scans[10]. The ^{99m}technetium-methoxyisobutylisonitrile (MIBI) scan is also helpful to detect ectopic ACTH-producing tumors undiagnosed with CT and MRI[11].

When the tumors are located in the anterior mediastinum, the most important differential diagnosis is with thymic carcinoid. Carcinoid tumors may display similar histologic features and also neuroendocrine differentiation. However, the presence of bands of connective tissue, nuclear pleomorphism with bizarre forms and absence of festfoons or rosettes are histological features more in favor of paraganglioma. In addition, the positive immunohistochemical reaction for keratin in the tumor cells is a feature that has been more often documented in carcinoid tumor[12]. However, cytokeratin positivity has also been reported in gangliocytic paraganglioma[13]. Paraganglioma located in the posterior mediastinum should be differentiated from metastatic tumors, such as melanoma, renal cell carcinoma and alveolar soft part sarcoma.

Treatment requires surgical excision. However, the patient should first undergo alpha blockade with penoxybenzamine for 1 week and then beta blockade with metoprolol or propranolol. The blood supply of paragangioma is usually rich. When surgery is planned, preoperative embolization of the main arterial supply and the tumor bed is helpful for safe and less morbid removal of large tumors. Unfortunately, surgical resectability may be impaired by tumor fixation to vital structures[14]. Therefore, adjuvant radiotherapy or radiotherapy alone may be beneficial[15,16]. The decision to operate or irradiate should be based on a formula that considers tumor size and location, patient age and health, symptoms or signs, potential morbidity and the expertise and availability of those involved in treatment. Chemotherapy has no defined role for treatment at any stage[17,18].

Mediastinal paraganglioma, because of their unusual anatomic site, may pose problems in diagnosis. A detailed history, hormone study and immunohistochemical studies play an important role in separating these tumors from other neoplasms.

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