Small-cell Lung Cancer in a Young Adult Nonsmoking Patient with Ectopic Adrenocorticotropicin (ACTH) Production

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Abstract

Cushing’s syndrome due to young small-cell lung cancer (SCLC) is recognized as being extremely rare. We herein present the case of a 35-year-old nonsmoking man who presented with thirst and polyuria. Laboratory examinations showed hyperglycemia, hypokalemia and liver enzyme elevation. Imaging examinations revealed the presence of multiple liver tumors and lymph node swelling. The levels of serum neuroendocrine tumor markers were elevated. The patient was diagnosed with SCLC based on the pathological examination of a biopsy specimen from the right supraclavicular lymph node. The physical findings, including proximal myopathy, truncal obesity and pigmentation suggested high levels of glucocorticoids. An immunohistochemical examination of the tumor showed that it was positive for adrenocorticotropicin (ACTH). An endocrinological investigation allowed for the definitive diagnosis of SCLC with ectopic ACTH production.

Key words: Cushing’s syndrome, ectopic ACTH production, small-cell lung cancer, young adult cancer patient

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Introduction

Lung cancer in young adults is uncommon (1). It has been reported that of patients of 40 years of age or younger account for only 2.7% of patients with lung cancer; when limited to small-cell lung cancer (SCLC), they account for only 1.22%. Cushing’s syndrome due to SCLC is extremely rare in young adults. We report a case of SCLC with Cushing’s syndrome due to ectopic adrenocorticotropicin (ACTH) production in a 35-year-old man.

Case Report

A 35-year-old man, who was a non-smoker, was admitted to our hospital after presenting with thirst and polyuria. Laboratory examinations showed that his blood glucose and potassium levels were 965 mg/dL and 3.0 mEq/L, respectively, and that his liver enzyme levels were elevated [glutamic oxaloacetic acid transaminase (GOT) (198 U/L), glutamic pyruvate transaminase (GPT) (266 U/L)]. Abdominal ultrasound revealed multiple low echoic lesions of the liver. Chest and abdominal contrast enhanced computed tomography (CT) revealed multiple low echoic lesions of the liver. Abdominal ultrasound revealed multiple liver tumors and the swelling of the right supraclavicular, left axillary and mediastinum lymph nodes, which were suspected to be metastatic tumors (Fig. 1). Abdominal magnetic resonance imaging (MRI) and gastrointestinal endoscopy could not detect the primary site. A pathological examination of a biopsy specimen from the right supraclavicular lymph node showed a small cell carci-
noma with an oval-shaped nucleus, which was arranged in bundles. An immunohistochemical examination of the tumor revealed that it was positive for AE1/AE2, chromogranin A and synaptophysin. The patient’s serum pro-gastrin-releasing peptide (Pro-GRP) level was 81,500 pg/mL (normal: <65), his serum neuron specific enolase (NSE) level was 24.8 ng/mL (normal: <16.3), and his serum carcinoembryonic antigen (CEA) level was 164.7 ng/mL (normal: <5.0). Based on the imaging and pathologic findings, including immunohistochemical staining and tumor marker examinations, we diagnosed the patient with primary mediastinal small-cell lung cancer with multiple metastases to the liver and of the right supraclavicular, left axillary and mediastinum lymph nodes. The patient had never smoked, had not been exposed to secondhand smoke and did not have a family history of cancer.

At the time of hospitalization, a physical examination revealed hypertension (180/126 mmHg), truncal obesity, proximal myopathy, pigmentation and swelling of the right supraclavicular lymph node. In the attempted differential diagnosis of hypokalemia, laboratory examinations showed that his plasma potassium and chloride levels were elevated and that his plasma renin and aldosterone levels were normal. We considered the findings of the physical and laboratory examinations to be consistent with Cushing’s syndrome. An endocrinological investigation, which was performed in the morning, showed that the patient’s plasma ACTH and cortisol concentrations were 117.2 pg/mL (normal: <56) and 59.7 μg/dL (normal: <19.4), respectively and that his urinary cortisol concentration was 2,070 μg/day (normal: <80.3). His plasma cortisol concentration was not suppressed after a high-dose dexamethasone suppression test. Abdominal CT and brain MRI did not detect an adrenal tumor or a pituitary tumor. These results suggested Cushing’s syndrome associated with ectopic ACTH production. An immunohistochemical examination of a biopsy specimen was diffusely positive for ACTH (Fig. 2). This finding allowed for the definitive diagnosis of SCLC with ectopic ACTH production. Four courses of chemotherapy were administered; however, the tumor showed treatment resistance and patient’s plasma ACTH concentration did not decrease (117.4 pg/mL) after chemotherapy (Fig. 3).

**Discussion**

Cushing’s syndrome caused by SCLC with ectopic ACTH production is reported to occur in approximately 1.6-4.5% of SCLCs (2, 3). Hypokalemia and hyperglycemia are present at a high rate in such patients. The clinical features are peripheral edema (83%), proximal myopathy (61%), moon face (52%), buffalo hump (35%), truncal obesity (35%), pigmentation (22%), psychosis (22%), and hypertension (22%) (2). When ectopic ACTH production is suspected on the basis of such symptoms, an endocrinological investigation should be performed. The examination of ACTH and cortisol concentration and the performance of a high-dose dexamethasone suppression test are useful tools for the diagnosis of Cushing’s syndrome. In addition, it is useful to confirm the absence of adrenal and pituitary tumors by imaging examinations (4). An immunohistochemical examination to detect ACTH allows for the definitive diagnosis (5).

In our case, the physical examinations of the patient led us to suspect Cushing’s syndrome. An endocrinological investigation and the determination, by immunohistochemical

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**Figure 1.** Chest and abdominal contrast enhanced computed tomography revealed multiple ringed enhanced lesion and lymph nodes enlargement of right supraclavicular, mediastinum and left axillary.

**Figure 2.** Biopsy from right supraclavicular lymph node showed ACTH staining was diffusely positive.
staining, that the tumor tissue was ACTH positive, supported the diagnosis. We were able to definitively diagnose the patient with SCLC with ectopic ACTH production. In previous reports, the median age of patient with SCLC with ectopic ACTH production was 60-62 years (2, 3). In contrast, the patient of the present study was 35 years of age.

The median survival time of patients (in lung cancer clinical trials) with limited SCLC who were treated with chemoradiotherapy was reported to be 27 months (6), while that of patients with extensive SCLC who were treated with chemotherapy was reported to be 9.9 months (7).

Paraneoplastic Cushing’s syndrome requires treatment of the underlying malignancy; however, the prognosis of such cases is very poor. Systemic chemotherapy resistance and the high rate of severe infectious complications (2) due to hypercortisolism-induced immunosuppression are two reasons for the poor prognosis. The median survival time of patients with SCLC with ectopic ACTH production who have paraneoplastic Cushing’s syndrome is only 5.5-6.2 months (2, 3). Our patient died of suffocation due to a retropharyngeal abscess after 4 courses of chemotherapy which failed to reduce his plasma ACTH concentration.

In summary, we herein described a case of small-cell lung cancer in a young adult nonsmoking patient with ectopic ACTH production.

The authors state that they have no Conflict of Interest (COI).

References