Small Cell Lung Cancer Expressing Glutamate Decarboxylase with Latent Autoimmune Diabetes in Adults

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Abstract

Small cell lung cancer (SCLC) causes paraneoplastic syndromes, such as diabetes mellitus, by eliciting the expression of various antibodies including anti-glutamate decarboxylase (GAD) antibody. A 62-year-old woman presented to our hospital with a 1-week history of progressive dyspnea and difficulty in walking. Computed tomography showed a tumor obstructing the left bronchus and obstructive lung abscesses with pleural effusions. A biopsy during bronchoscopy revealed SCLC, and the clinical stage was ultimately determined to be IIIB. SCLC was complicated by diabetes mellitus with high titers of serum anti-GAD antibody. An immunohistochemical analysis showed GAD expression in the cancer cells, which is a novel finding.

Key words: small cell lung cancer, glutamate decarboxylase, diabetes mellitus, paraneoplastic syndrome, latent autoimmune diabetes in adults

Introduction

Small cell lung cancer (SCLC) causes paraneoplastic syndromes by inducing the expression of various antibodies such as Hu, Yo, and CV-2 (1). Glutamate decarboxylase (GAD) catalyzes the synthesis of γ-aminobutyric acid, and anti-GAD antibody (GAD-ab) is detected in paraneoplastic syndromes such as diabetes mellitus (DM), stiff person syndrome, and cerebellar ataxia (2). The mechanisms underlying its production in these conditions are unknown. This is the first report of GAD expression in SCLC, which induced high titers of serum anti-GAD-ab that led to DM.

Case Report

A 62-year-old woman presented at our hospital with a 1-week history of progressive dyspnea and difficulty in walking. She had been previously treated with a sulfonylurea for DM 1 year prior to admission. She had no other medical history. Her vital signs were normal, and her consciousness was preserved. The results of her physical and neurological examinations were normal except for reduced thoracic motion and absent breath sounds in her left chest.

A chest radiograph showed a massive left-sided pleural effusion with mediastinal shift. Chest computed tomography showed a tumor obstructing the left bronchus (Fig. 1A), multiple mediastinal lymphadenopathies including station 2R, multiple lung abscesses, and bilateral pleural effusion (Fig. 1B). An aspiration specimen of the abscess revealed Gram-positive cocci, which were subsequently identified as methicillin-sensitive Staphylococcus aureus. Bronchoscopy revealed a necrotic tumor obstructing the left main bronchus (Fig. 1C). A histological examination of the biopsy specimens revealed small to medium-sized cells with a high nuclear-to-cytoplasmic ratio and scant cytoplasm (Fig. 2A). An immunohistochemical analysis showed that these cells expressed chromogranin A (Fig. 2B) and CD56 (Fig. 2C).
which was suggestive of SCLC. They also stained positive in specimens incubated with mouse monoclonal antibody against human GAD65 (1:100; LS-C188636, Funakoshi, Tokyo, Japan) (Fig. 3). The laboratory data revealed the following: neuron specific enolase (NSE), 89.5 ng/mL; progastrin-releasing peptide (ProGRP), 1,230 pg/mL; casual blood glucose, 409 mg/dL; HbA1c, 17.3%; anti-GAD-ab (determined via a radioimmunoassay), 18,500 U/mL; islet antigen 2 antibody and insulin antibody, undetectable; and C-peptide in 24-h urine collections, while fasting, and 2 hours after meals, 6 μg/day, 0.08 ng/mL, and 0.15 ng/mL, respectively. Other laboratory tests revealed no evidence of distant metastases. Therefore, the patient was diagnosed with clinical stage IIIB (cT3N3M0), limited-stage SCLC accompanied by obstructive lung abscesses and latent autoimmune diabetes in adults (LADA) with high-titer anti-GAD-ab.

The patient received antibiotics and thoracic radiation therapy (36 Gy in 12 fractions). These treatments resulted in rapid clinical improvement, allowing for subsequent combination therapy with carboplatin plus etoposide. The insulin dose was adjusted according to the usage of antiemetic glucocorticoids. The patient had a very good partial response to two cycles of chemotherapy and the tumor nearly disappeared. The laboratory data also improved as follows: NSE, 18.9 ng/mL; ProGRP, 23.3 pg/mL; HbA1c, 7.3%; and anti-GAD-ab, 7,400 U/mL. However, the patient required insulin aspart at 26 units/day for DM after the clinical response. The patient is currently being monitored for a relapse as an outpatient because she refused to undergo any further chemoradiotherapy.

Discussion

This is the first report of GAD65 expression in SCLC that induced high titers of serum anti-GAD-ab that led to DM.

There are two isoforms of GAD which differ according to their molecular weights: GAD65 and GAD67 are expressed
in the brain, while GAD65 is also expressed in the pancreas (3). GAD65 and GAD67 are the main targets of autoantibodies in patients with type 1 DM or LADA (4). Anti-GAD-ab (5), which specifically recognizes GAD65, is detected in patients with type 1 DM, slowly progressive insulin-dependent DM, and LADA (6). In a nationwide survey, a high titer of anti-GAD-ab was associated with phenotypes that predict the need for insulin therapy in the future (7). In the present case, LADA was diagnosed according to the poor endogenous insulin secretion, the age of the patient, the presence of anti-GAD-ab, and the necessary insulin therapy for 1 year prior to admission. The optimum treatment for LADA in patients with paraneoplastic syndrome has not yet been established, however, we successfully improved the patient’s HbA1c levels and serum anti-GAD-ab titers using anti-cancer and insulin therapies.

Anti-GAD-ab, especially at a high titer, is detected in patients with paraneoplastic syndromes. In a series of 62 patients in whom anti-GAD-ab was detected at paraneoplastic autoantibody screening, one-third had type 1 DM. The titer of anti-GAD-ab in these patients was extremely high (8). In a series of 61 patients in whom high-titer anti-GAD-ab was detected, 50 patients had symptoms of neurological syndromes associated with anti-GAD-ab production, such as stiff person syndrome and cerebellar ataxia. Four patients also had cancer (SCLC, non-SCLC, or pancreatic or thymic carcinoma), and GAD expression was pathologically confirmed in the pancreatic and thymic carcinoma cases (2). These data indicate that the immune response to GAD in tumor cells may induce paraneoplastic syndromes including DM.

Recent studies show that GAD is also involved in the development and progression of malignant tumors. The expression levels of GAD65 significantly correlate with the depth of tumor invasion and advanced TNM stage in gastric cancer and thus may be useful for reclassifying tumor growth patterns (9). In a clinicopathological study of benign and malignant lesions in the gallbladder, the expression level of GAD65 was significantly higher in the gallbladder adenocarcinoma than in the peritumoral tissues, adenomatous polyps, or areas of chronic cholecystitis. Increased GAD65 expression is a poor prognostic factor for both 1-year survival rates and mean survival times after surgery in patients with cholecystic cancer (10). Similar findings have also been reported in colon (11), breast (12), and prostate cancers (13). To the best of our knowledge, there are no reports of GAD 65 expression in SCLC, and the further accumulation of such cases is needed.

The present case suggests that the high titer of serum anti-GAD-ab induced by GAD65 in SCLC is associated with LADA. Further investigation is required to clarify the involvement of GAD and anti-GAD-ab in SCLC.

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

References