



The diagnostic challenge of small cell lung cancer with anti-gamma-aminobutyric-acid B receptor encephalitis: a case report

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Background: Anti-gamma-aminobutyric-acid B receptor (anti-GABA_BR) encephalitis is a rare type of encephalitis, with an incidence of only 5% in all autoimmune encephalitis (AE). A third of patients had pathologically confirmed small-cell lung cancer (SCLC). Early identification and treatment of tumors can improve the poor prognosis. Most patients attend hospital for the treatment of neurological disorders and rarely present with any respiratory symptoms, but suffer from an underlying tumor. Thus, early proper diagnosis is very important. In this article, we report a special case of a patient with anti-GABA_BR encephalitis with delayed SCLC pulmonary behavior, whose diagnosis process was tortuous and complicated.

Case Description: A 62-year-old man with a history of anti-GABA_BR encephalitis presented with respiratory symptoms. His chest computed tomography (CT) scan showed significant progression of right superior lobe consolidation. A bronchoscopy was performed with no histopathological result, but the microbiological examination of the bronchial lavage fluid showed *Aspergillus niger* infection. With antifungal therapy, the patient's respiratory symptoms were significantly relieved. Given the close relationship between SCLC and anti-GABA_BR encephalitis, we insisted to clarify the pulmonary lesions. The other three biopsies were performed successively, including lung biopsy, endobronchial ultrasonography (EBUS), and transbronchial needle aspiration (TBNA). SCLC was finally proven by pathology, and the patient received systemic chemotherapy.

Conclusions: SCLC is the most common pulmonary neuroendocrine tumor. It secretes onconeural antibodies and is closely associated with paraneoplastic neurologic syndromes (PNSs). Lung tumors, especially SCLC, should be a concern in patients presenting with AE or neurological symptoms, even if they have not any abnormal sign in respiratory system. The early diagnosis and intervention for underlying tumors will improve the clinical outcomes of patients significantly. Thus, the close follow-up is helpful and it is imperative to select and combine the most appropriate examinations for proper diagnosis.

Keywords: Small cell lung cancer (SCLC); anti-gamma-aminobutyric-acid B receptor encephalitis; paraneoplastic neurologic syndromes (PNSs); *Aspergillus niger*; case report

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Introduction

Small cell lung cancer (SCLC) is the most common pulmonary neuroendocrine tumor. It is known for its poor prognosis and high propensity for metastasis. In addition to the direct aggression to the brain, the many neuronal antigens produced by the cancer cells also cause patients to display multiple neurological symptoms.

Anti-gamma-aminobutyric-acid B receptor (GABA_BR) encephalitis is a very rare type of encephalitis and has such a close relationship with SCLC that about 50% of these patients have underlying SCLC (1). Most patients attend hospital for treatment of neurological disorders but are eventually diagnosed with lung cancer by screen. The neurological symptoms usually respond to immunotherapy and the treatment of the cancer (1,2). Thus, early proper diagnosis is very important.

In this article, we report a special case of a patient with anti-GABA_BR encephalitis with delayed SCLC pulmonary behavior; the course was intriguing. We present the following case in accordance with the CARE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-6162/rc>).

Highlight box

Key findings

- We report the case of 1 patient diagnosed with anti-GABA_BR encephalitis, which was pathologically confirmed to be SCLC by 4 biopsies.

What is known and what is new?

- Only a very small number of GABA_BR encephalitis cases have been reported thus far, and only 1/3 to 1/2 of these cases have been pathologically confirmed to have SCLC.
- Such patients may not present with any sign of SCLC at the onset of anti-GABA_BR encephalitis.

What is the implication, and what should change now?

- SCLC in autoimmune encephalitis patients may be insidious; thus, when this kind of patient presents in the clinic, a comprehensive examination should be performed to confirm the coexistence of the tumor.

Case presentation

A 62-year-old man presented with a 1-week history of fever, productive cough, hemoptysis, and right chest pain. He reported no dyspnea, weight loss, or any recent travel history. He had been hospitalized for epileptic seizures 5 months ago. Based on his cerebrospinal fluid assay results, he was diagnosed with GABA_BR encephalitis. Magnetic resonance imaging (MRI) of his brain failed to show any malignant lesions, but bilateral increases in the temporal lobe FLAIR/T2 signal were observed. During his hospital stay, he also received a chest computed tomography (CT) scan, but the results were negative (*Figure 1A,1B*). The patient's neurological symptoms improved significantly after the gamma globulin and methylprednisolone sodium succinate treatment. After discharge, he continued to take phenytoin sodium (100 mg, orally 3 times daily), and the epilepsy did not recur.

When the patient was admitted to our department, his temperature was 38.7 °C, his heart rate was 98 beats per minute (bpm), his respiratory rate was 18 breaths per minute, his blood pressure was 134/80 mmHg, and his oxygen saturation in room air was 96%. The respiratory system examination revealed a rough breathing sound in the right lung. The laboratory outcomes included abnormal leukocyte ($10.32 \times 10^9/L$), C-reactive protein (138.13 mg/L), and neuron specific enolase (33.86 ng/mL) results. The initial chest CT scan showed significant abnormalities with right superior lobe consolidation and right hilar and mediastinal lymph node enlargement (*Figure 1C,1D*).

A bronchoscopy was performed and mucosal inflammation was observed at the opening of the posterior segment of the right upper lobe without tumor evidence, and *Aspergillus niger* was detected in the bronchial lavage fluid by metagenomic next generation sequencing. An ultrasound-guided biopsy on a mass adjacent to the mediastinum was performed (*Figure 1C*, arrow), but no meaningful results were found. After voriconazole administration (400 mg, IV, once daily), the patient's symptoms were gradually relieved.

The patient received a chest CT again 23 days later, and

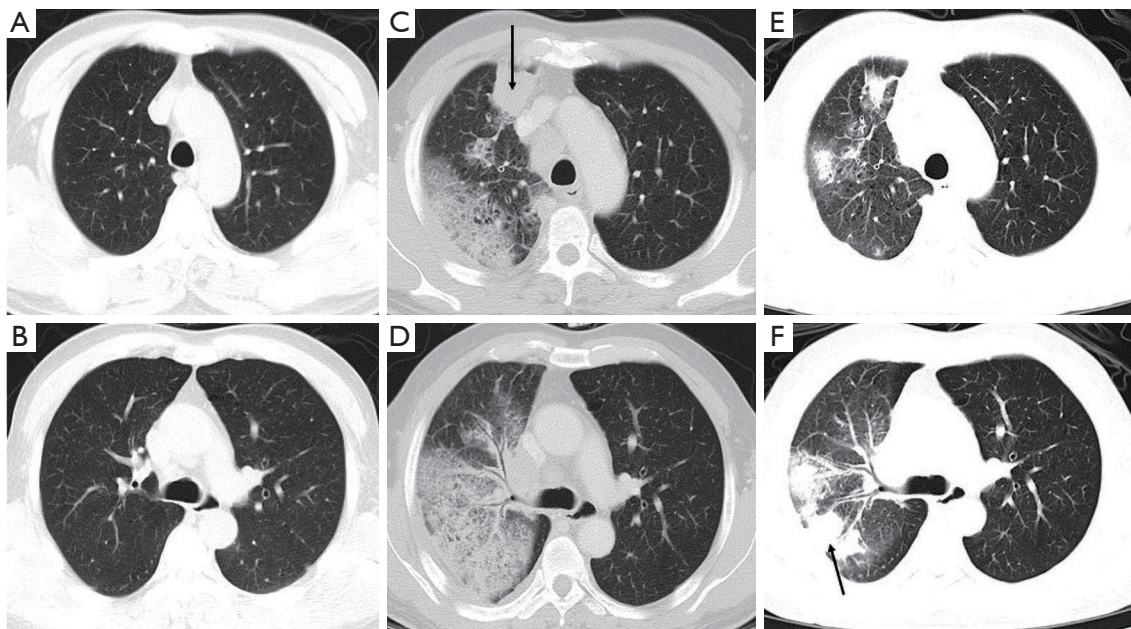


Figure 1 The images of the patient's sequential chest CT scans. In January 2020, there was no significant abnormality (A,B). In June 2020, the first CT scan showed right superior lobe consolidation and right hilar and mediastinal lymph node enlargement (C,D). An ultrasound-guided biopsy of the mass adjacent to the mediastinum (C, arrow) was performed with the discovery of infiltrate of inflammatory cells. After voriconazole administration, the CT scan showed a transformation of the consolidation in the right superior lobe (E,F). A CT-guided lung biopsy was performed on the subpleural nodule (F, arrow), but no tumor cells were found. CT, computed tomography.

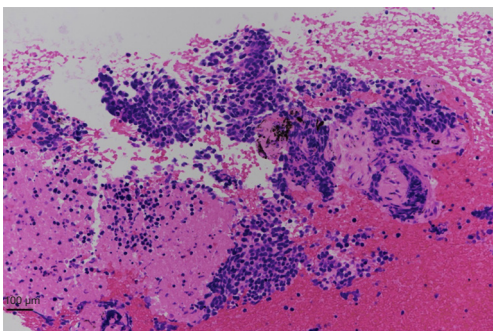


Figure 2 The pathologic diagnosis. The SCLC cells were observed as irregular nests and patches in a section from the 4R lymph node by EBUS and TBNA (hematoxylin and eosin staining, scale bars: 100 μm). SCLC, small cell lung cancer; EBUS, endobronchial ultrasonography; TBNA, transbronchial needle aspiration.

the results revealed a significant, clear transformation of the consolidation in the right superior lobe (Figure 1E,1F). A CT-guided lung biopsy was performed on the subpleural nodule (Figure 1F, arrow). However, the histological results were inconclusive.

To gather more pathological evidence, we conducted a second bronchoscopy with consent of the patient. An endobronchial ultrasonography (EBUS) and a transbronchial needle aspiration (TBNA) on the 4R lymph node were performed. Finally, a histologic examination on the 4R lymph node revealed small lung cancer cell infiltration (Figure 2). The contrast-enhanced CT showed no metastases in the abdomen and pelvis, and the MRI showed no metastases in the brain.

The final diagnosis of the presented case was SCLC. The stage was limited ($T_3N_2M_0$, IIIB). The patient received systemic therapy with cisplatin (30 mg/m^2) plus irinotecan (65 mg/m^2 , IV, days 1 and 8 for 6 cycles). There was no significant adverse event during the treatment.

Based on the chest, abdomen and pelvis CT results at the last cycle, the assessment was stable disease (Figure 3). Unfortunately, after a 2-month interval, the brain metastases were documented by MRI scan. The patient was suggested to visit radiotherapy department, however, he was failed to follow-up.

All procedures performed in this study were in accordance with the ethical standards of the institutional

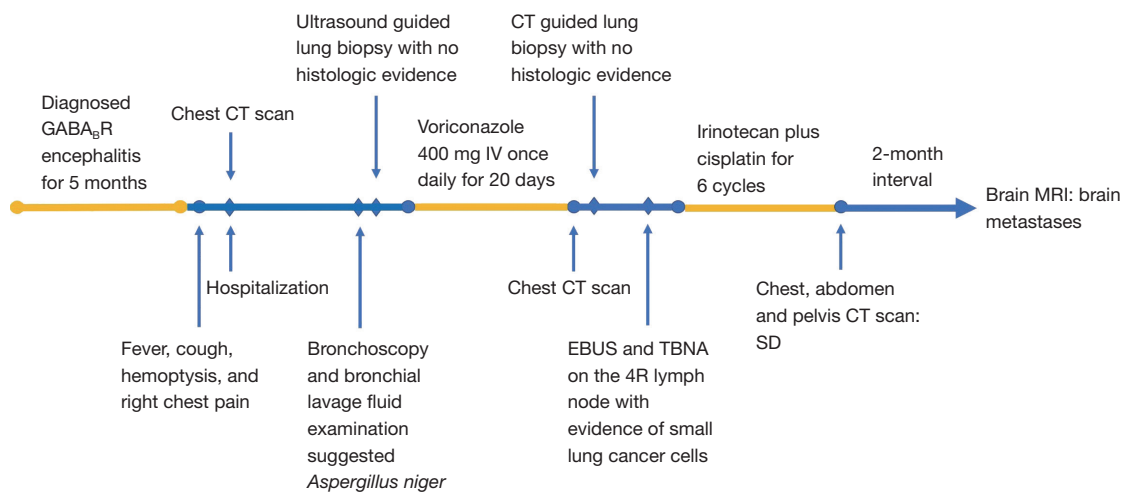


Figure 3 Timeline of the clinical course of the presented case. CT, computed tomography; GABA_BR, gamma-aminobutyric-acid B receptor; IV, intravenously; MRI: magnetic resonance imaging; SD, stable disease; EBUS, endobronchial ultrasonography; TBNA, transbronchial needle aspiration.

and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

SCLC is composed of neuroendocrine cells that can produce biologically active substances, including ectopic hormones and onconeural antibodies (3,4). Onconeural antibodies cause autoimmune syndromes by attacking the nervous system. These syndromes are called paraneoplastic neurologic syndromes (PNSs) (5). SCLC is one of the most common primary tumors associated with PNSs. The mechanisms underlying the development of PNSs are unclear, but autoimmunity is generally believed to be involved in the pathogenesis of PNS (6,7).

GABA_B receptors are G-protein-coupled receptors distributed in the central and peripheral nervous systems. They are highly localized in the hippocampus, thalamus, and cerebellum. Anti-GABA_BR encephalitis is the most rare type of autoimmune encephalitis (AE), accounts for about 5% of all AE, and has a high mortality rate. Its neurological symptoms include short-term memory loss, seizure, and mental disorders. Its incidence is higher in

men than women, and the average age of onset is about 53 years old (8,9). The onset of the disease is usually rapid, and the main manifestations are frequent epileptic seizures.

The diagnosis of GABA_B encephalitis is based on characteristic clinical symptoms, and the detection of specific GABA_B autoantibodies (9). The disease has a close relationship with SCLC, such that about 50% of these patients have underlying SCLC (10). Most patients only present with neurological disorders initially. SCLC is normally discovered within 6 months of the disease onset (10). The neurological symptoms usually respond to immunotherapy and cancer treatment. SCLC is characterized by its rapid growth, tendency to metastasize, and poor survival rates. Patients with limited-stage SCLC are considered curable by using chemotherapy plus thoracic radiotherapy; some patients are eligible for curative surgery followed by systemic therapy with or without mediastinal radiotherapy. Thus, the early proper diagnosis of the disease is very important.

The patient in this case had previously had seizures, but no signs of cancer were detected in the chest CT scan at that time. This suggests that SCLC can induce paraneoplastic disorders at a very early stage, even before the formation of the primary tumor node. If the patient was closely followed up with tumor examinations after that, he would have the chance to get early diagnosis and even get surgery. The patient also had *Aspergillus niger* infection

simultaneously, and a lung biopsy revealed inflammatory pathological manifestations, which further complicated the case. To avoid a misdiagnosis, multiple procedures, including chest CT, bronchoscopy, lung biopsy, EBUS, and TBNA, were carried out with the patient's kindly understanding and consent. Ultimately, SCLC was proven by TBNA. Since SCLC is a highly metabolic disease and the patient's stage is late, brain metastases happened, which indicated the poor prognosis.

Conclusions

This rare case shows that a diagnosis of SCLC should be considered in patients who present with AE, or neurological symptoms. It is essential that the patients are followed up with regular CT examination. The recognition of this disorder and its close relationship to SCLC is important, as this could help to prevent delays in treating more challenging cases of the disease. Also, the neurological symptoms may respond to anti-tumor treatment. Pathology is crucial in the diagnosis and subsequent treatment. As always, timely and correct diagnoses are essential.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-6162/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-6162/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as

revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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