A case of non-small cell lung cancer presenting anti-amphiphysin antibody-positive paraneoplastic neurological syndrome

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A B S T R A C T
Paraneoplastic neurological syndrome (PNS) is associated with malignancies, such as small-cell lung cancer. However, patients with non-small cell lung cancer (NSCLC) rarely develop PNS. We herein report a 72-year-old man with NSCLC who developed disturbance of consciousness on the day of initiation of treatment with an immune checkpoint inhibitor. Blood test results revealed anti-amphiphysin (AMPH) antibody positively, leading to the diagnosis of PNS. The disturbance of consciousness was improved with intravenous administration of steroid and immunoglobulin. To our knowledge, this is the first report of anti-AMPH antibody-positive PNS in a patient with NSCLC.

1. Introduction
Paraneoplastic neurological syndrome (PNS) is caused by an autoimmune process that develops in patients with any types of malignancies [1,2]. Recently, several reports have shown that PNS can be induced by immune checkpoint inhibitors (ICIs) [3–5]. Amphiphysin (AMPH), one of the tumor cell antigens that induces PNS, is enriched in nerve terminals and plays a role in clathrin-mediated endocytosis [6,7]. Although anti-AMPH antibody-positive PNS is common in patients with small cell lung cancer (SCLC) and breast cancer [8], it is rare in patients with non-small cell lung cancer (NSCLC). To our knowledge, this is the first report of anti-AMPH antibody-positive PNS occurred in a patient with NSCLC treated with ICI. The clinical course of the present case suggests that anti-AMPH antibody-positive PNS may develop in patients with NSCLC and may be induced by ICI treatment.

2. Case report
A 72-year-old man with a 50-year-history of smoking was referred to our hospital for weight loss. The patient had a history of hypertension and hyperlipidemia, but he had no history of autoimmune diseases. Computed tomography (CT) revealed a tumor measuring 33 mm in diameter in the right upper lung, multiple swollen lymph nodes, and a small amount of pleural and pericardial effusion (Fig. 1). Brain magnetic resonance imaging (MRI) showed multiple small brain metastases (Fig. 2) without associated symptoms. Endobronchial ultrasound-guided transbronchial needle aspiration of the #7 lymph node revealed AMPH-positive adenocarcinoma (Fig. 3). Therefore, the patient was diagnosed with advanced adenocarcinoma of the lung (ct2aN3M1c: stage IVB). The specimen revealed the presence of epidermal growth factor receptor (EGFR) exon 21 L858R mutation. The specimen was negative for other driver oncogene mutations, including anaplastic lymphoma kinase (ALK) fusion gene, c-ros oncogene 1 (ROS-1) fusion gene, and v-raf murine sarcoma viral oncogene homolog B1 (BRAF). The programmed cell death ligand-1 (PD-L1) tumor proportion score was 20%. We decided to initiate a combination chemotherapy with cytotoxic chemotherapy and ICI before the results of driver oncogene mutations were obtained because of the presence of pleural and pericardial effusion, and rapid weight loss.

Treatment with carboplatin, paclitaxel, bevacizumab, and atezolizumab was initiated as first line chemotherapy. On the day of treatment initiation, the patient developed acute disturbance of consciousness. After treatment initiation, there was no significant changes in MRI findings, anti-nuclear antibody levels, thyroid function, and other blood parameters. However, the patient was positive for anti-AMPH (Table 1). Cerebrospinal examination showed no evidence of tumor cells or...
Therefore, a diagnosis of anti-AMPH antibody-positive PNS was made. The disturbance of consciousness did not completely improve after steroid pulse therapy, but intravenous immunoglobulin (IVIG) therapy resulted in considerable improvement. However, the patient died of lung cancer 6 months after diagnosis.

3. Discussion

PNS can be diagnosed by confirming the presence of malignancies and autoantibodies and ruling out other causes such as central nervous system metastasis, infection, stroke, or metabolic disorders [1,2]. In our case, a diagnosis of PNS was made due to the following reasons. First, anti-AMPH antibodies were detected in the patients’ serum. Second, all other causes were ruled out based on the examination findings. There were no changes in the examination findings before and after the ICI treatment. Small multiple brain metastases were found, but they were too small to be the cause of the disturbance of consciousness. Furthermore, there was no evidence of meningeal carcinomatosis or infection in the cerebrospinal fluid. Third, steroid and IVIG treatment was effective in improving the disturbance of consciousness. There is no established treatment for PNS. However, some reports have indicated that immunosuppressive drugs and IVIG are effective for PNS [1,9]. In our case, steroid and IVIG treatment was effective, supporting that PNS was the cause of the disturbance of consciousness.

To our knowledge, this is the first report of anti-AMPH antibody-positive PNS in a patient with NSCLC. The clinical course of our case suggests two important clinical issues. First, anti-AMPH antibody-positive PNS can occur in patients with NSCLC. Although anti-AMPH antibody positive PNS cases are relatively rare [10,11], previous studies have reported the occurrence of anti-AMPH antibody-positive PNS in patients with SCLC and breast cancer [8,10,11]. However, there is no report of anti-AMPH antibody-positive PNS in patients with NSCLC. Immunohistochemical staining of the tumor cells revealed AMPH positively. This result indicates that tumor cells of NSCLC, as well as SCLC, have the potential to cause anti-AMPH antibody-positive PNS. Second, anti-AMPH antibody-positive PNS can be induced by ICIs. Several reports have suggested that PNS associated with autoantibodies other than anti-AMPH antibody can be induced by ICI treatments [3–5]. However, there is no report of anti-AMPH antibody-positive PNS induced by ICIs. Furthermore, although the typical clinical course of PNS is subacute or chronic, our patient had an acute onset. This acute clinical course indicates that ICIs may activate autoantibodies in PNS, subsequently causing PNS. This is supported by the fact that one of the mechanisms of immune-related adverse events is an increase in pre-existing autoantibodies [2,12]. Therefore, anti-AMPH antibodies may have been present before ICI initiation and were only activated by ICI, which caused disturbance of consciousness in our patient.

The present case report shows that anti-AMPH antibody-positive PNS can develop in patients with NSCLC and can be induced by ICI treatment. Clinicians should consider the possibility of PNS even in patients...
with malignancies that are not strongly associated with PNS when they develop neurological symptoms, especially when initiating treatment with ICIs.

Declaration of competing interest

The authors have no conflicts of interest directly relevant to the content of this article to declare.

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Table 1

Laboratory findings at the onset of PNS.

| [Hematology] | [Serology] | [Cerebrospinal fluid] |
|--------------|------------|-----------------------|
| RBC 481 × 10⁴ /μl | CRP 1.2 mg/dl appearance | watery-clear |
| Hgb 15.7 g/dl | ANA negative pressure | 12 cmH2O |
| WBC 9900 /mm³ | β-D-glucan <6 pg/ml cell count | 15 /μl |
| Neu 77 % | poly % | 13 % |
| Lym 11.5 % | mono % | 87 % |
| Neut 34 × 10⁴ /μl | FT4 1.09 ng/ml protein | 91 mg/dl |
| TP 6.6 g/dl | TSH 1.65 μIU/ml glucose | 50 mg/dl |
| Alb 3.3 g/dl | Hb 15.7 g/dl ANA negative pressure | 12 cmH2O |
| AST 17 IU/l | PNMA2 negative ADA | 20 mg/dl |
| ALT 19 IU/l | Ri negative HSV-PCR negative | | |
| T-Bil 1.2 mg/dl | Yo negative VZV-PCR negative | | |
| LDH 290 IU/l | Hu negative cytology class I | | |
| BUN 13.9 mg/dl | recoverin negative culture | | |
| Cre 0.9 mg/dl | SOX1 negative negative | | |
| Na 138 mmol/l | titin negative | | |
| K 3.8 mmol/l | zic4 negative | | |
| Cl 98 mmol/l | GAD65 negative | | |
| Ca 9.2 mmol/l | Tr negative | | |
| BS 91 mg/dl | NMDA-r negative | | |