

[CASE REPORT]

An Elderly Case of Paraneoplastic Anti-NMDA Receptor Encephalitis Associated with Small-cell Lung Cancer Expressing NR1 Subunits

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Abstract:

A 61-year-old Japanese man presented with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. NR1 antibodies were detected in his cerebrospinal fluid. Chest computed tomography revealed lung tumor. The patient was diagnosed with paraneoplastic anti-NMDAR encephalitis associated with lung cancer and treated with two cycles of intravenous high-dose methylprednisolone and one cycle of intravenous immunoglobulin. However, he died one year later without improvement. An autopsy confirmed small-cell lung cancer (SCLC). Immunohistochemistry revealed the expression of NR1 subunits in the tumor cells, suggesting that SCLC may trigger NR1 autoimmunity though the expression of NR1 subunits as onconeural antigens, expanding the phenotypic spectrum of paraneoplastic neurological syndrome associated with SCLC.

Key words: encephalitis, NMDAR, anti-N-methyl-D-aspartate receptor, small cell lung cancer, SCLC, paraneoplastic syndrome

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder in which IgG antibodies react against the NR1 subunits of the NMDAR (1). Detection of NR1 antibodies confirms the diagnosis and prompts a search for an underlying tumor expressing the NR1 subunits, especially ovarian teratoma in young women (1). The development of anti-NMDAR encephalitis in elderly patients has also been reported, and a small proportion of these cases are associated with cancers (2). However, the pathogenetic links between anti-NMDAR encephalitis and cancers, including NR1-expressing tumor tissues, have not been fully elucidated.

We herein report an elderly case of anti-NMDAR encephalitis associated with small cell lung cancer (SCLC) expressing NR1 subunits.

Case Report

A 61-year-old Japanese man with a history of diabetes and hypertension was admitted to our hospital with decreased consciousness. He had been in his usual state of health until 10 days before his admission, when palpitation developed, without apparent viral prodrome. On the next day, he fell into a catatonic stupor and was admitted to a psychiatric hospital. After admission, he developed generalized convulsive seizures refractory to anti-epileptic drugs and then was transferred to our hospital.

On admission, his temperature was 38.8°C, blood pressure 181/90 mmHg, and pulse 120 beats per minute. A physical examination was otherwise unremarkable, but the blood pressure fluctuated. On a neurologic examination, the patient was unresponsive with eyes closed (Glasgow Coma Scale E 2V2M4). He had nuchal rigidity, orofacial dyskinesias, limb

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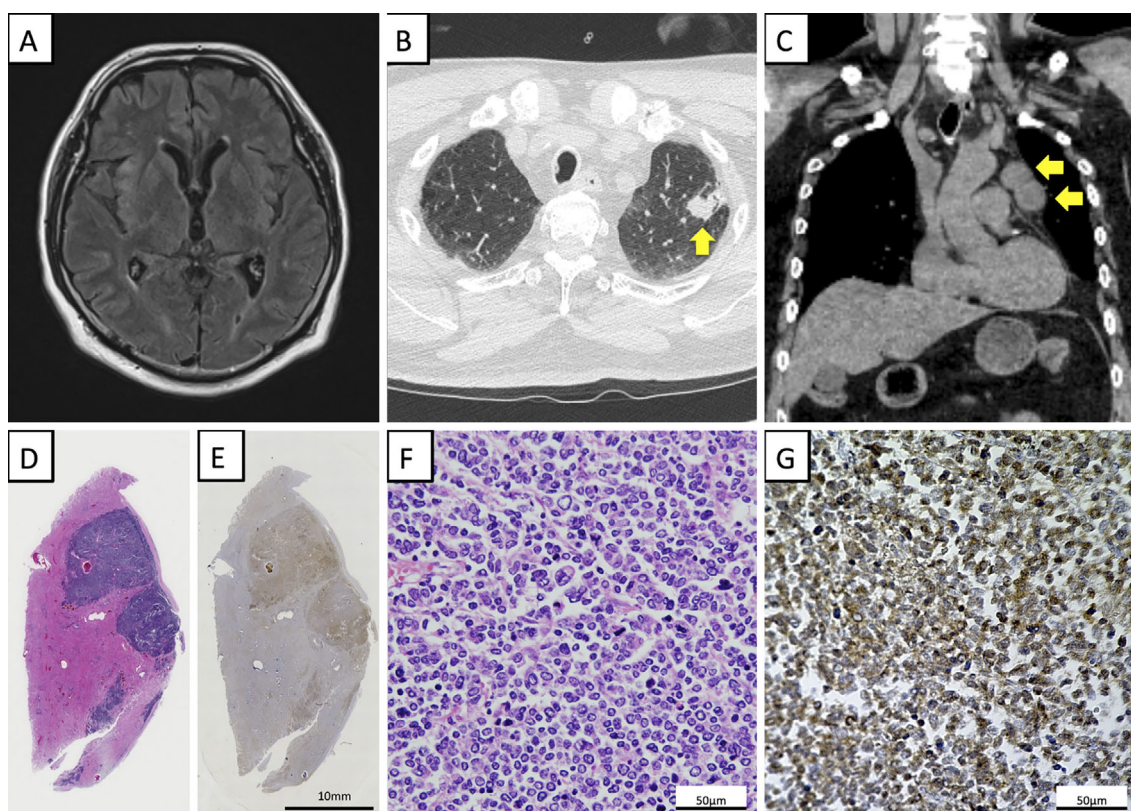


Figure. (A) Fluid-attenuated inversion recovery-weighted brain MRI sequence reveals a high-signal-intensity area in the right insula. Chest CT reveals (B) a mass on the left upper lobe (yellow arrow) and (C) swelling of the lymph nodes (yellow arrows). (D, F) Hematoxylin and Eosin staining reveals neoplastic cells with a high nucleus-cytoplasm ratio and nuclear division. (E, G) Immunohistochemical staining using anti-NR1 antibody reveals NR1-immunoreactive dots on the cell surface. NR1 immunohistochemical staining is conducted using mouse monoclonal IgG2a, clone 54.1, 1:50 (Thermo Fisher Scientific, Rockford, USA) and the avidin-biotin-peroxidase complex method.

athetosis, and recurrent generalized seizures, requiring mechanical ventilation support. Routine blood examinations did not reveal any remarkable abnormalities. His cerebrospinal fluid (CSF) contained 10 white blood cells/mm³ without malignant cells, 54 mg/dL protein, and 110 mg/dL glucose. Brain magnetic resonance imaging (MRI) showed a slightly increased signal intensity in the right insula on T2 and fluid-attenuated inversion recovery imaging (Figure A). Electroencephalography showed generalized delta wave activity without epileptic discharges. Chest computed tomography (CT) revealed a mass and enlargement of hilar lymph nodes (Figure B, C). Elevation of serum progastrin-releasing peptide (324.9 pg/mL, normal range <70 pg/mL) was also observed, suggesting that the lung tumor was SCLC.

Viral or autoimmune encephalitis, including paraneoplastic syndrome, was suspected; therefore, he was treated with acyclovir, multiple antiepileptic drugs, 2 cycles of intravenous high-dose methylprednisolone (1 g/day for 5 days), and 1 cycle of intravenous immunoglobulin under mechanical ventilation support. However, his neurological condition did not improve.

Tests for serum antibodies (anti-Hu, Yo, Ri, Ma, CV2, glutamic acid decarboxylase, SOX1 and amphiphysin) were

negative, as was a CSF herpes simplex virus polymerase chain reaction test, but NR1 antibodies were found by cell-based assays and detected in the CSF. A diagnosis of anti-NMDAR encephalitis was made based on the typical clinical features and NR1 antibody detection in the CSF.

However, further investigations and treatment were not possible due to the patient's poor clinical condition (i.e., suspected advanced cancer and refractory status). He ultimately died one year later due to sepsis without recovery of his impaired consciousness. An autopsy was performed, and SCLC was pathologically confirmed. Immunohistochemistry revealed positivity for chromogranin A, synaptophysin, and CD56, indicating neuroendocrine cancer. Furthermore, NR1 immunohistochemistry showed positive staining, indicating NR1 expression (Figure D-G). Gliosis was confirmed in the hippocampus, amygdala, and claustrum, indicating brain damage associated with anti-NMDAR encephalitis and status epilepticus. Brain metastasis was not apparent.

Discussion

Our elderly patient exhibited characteristic clinical symptoms of anti-NMDAR encephalitis, and NR1 antibodies

were positive in the CSF. Furthermore, he had SCLC, and we confirmed the expression of NR1 subunits in the tissue, thus indicating an association between SCLC and anti-NMDAR encephalitis.

Anti-NMDAR encephalitis has rarely been reported in patients with SCLC (1-4). In a laboratory study, the expression of the NMDAR was confirmed in some commonly used SCLC cell lines (5). However, NR1 subunit expression in tumor tissues has not been comprehensively evaluated in patients with anti-NMDAR encephalitis associated with SCLC. Jeraiby et al. reported a 62-year-old woman with paraneoplastic anti-NMDAR encephalitis associated with SCLC (3). Her serum IgG reacted with SCLC tumor cells obtained via a needle aspiration biopsy. However, binding of antibodies other than NR1 antibodies cannot be excluded. In addition, thus far, only a few patients with anti-NMDAR encephalitis and NR1-positive neuroendocrine tumors have been reported. Neuropsychological improvement was achieved following removal of pancreatic cancer, similar to patients with ovarian teratomas, indicating the association between tumor and encephalitis (6).

A previous study (7) reported that 24 of 264 patients (9.1%) with SCLC presented with paraneoplastic neurological syndrome. Among those, NR1 antibodies were detected in one patient, but the main clinical feature was sensory neuronopathy, which differed from the typical spectrum of anti-NMDAR encephalitis.

Although only a few patients with anti-NMDAR encephalitis have been reported associated with SCLC, an estimated 2.1 million patients have been newly diagnosed with lung cancer in 2018 (8). As reported here, based on the findings that tumor cells can express the NR1 subunits probably on the surface of the cells, cases of anti-NMDAR encephalitis may have been underdiagnosed. Further studies are required to draw a hard conclusion regarding a possible association between anti-NMDAR encephalitis and SCLC.

This study was limited by its retrospective nature and single-case-report format. In addition, no autoantibodies against neuronal surface antigens other than the NMDAR

were studied.

Despite these limitations, this case suggests that NR1 antibodies should be examined even in elderly cases of SCLC presenting with encephalitis. SCLC may trigger NR1 autoimmunity though the expression of NR1 subunits as onconeural antigens, expanding the phenotypic spectrum of paraneoplastic neurological syndrome associated with SCLC.

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

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