Neuroendocrinology Letters Volume 39 No. 2 2018
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Limbic encephalitis associated with antibodies against the α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic acid receptor: a case report

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Submitted: 2017-07-23 Accepted: 2018-01-18 Published online: 2018-07-12

Key words: **Limbic encephalitis; AMPAR antibodies; small cell lung cancer (SCLC)**

Neuroendocrinol Lett 2018; **39**(2):85–87 **PMID:** 30183201 NEL390218A04

Abstract

We report a case of a 51-year-old man with limbic encephalitis (LE) associated with antibodies against the α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic acid receptor (AMPAR). The patient presented with anterograde memory loss for 2 months. Cranial magnetic resonance and electroencephalogram were normal. AMPAR antibodies were found in blood serum and cerebrospinal fluid. All other test results were unremarkable. CT scans found a tumor in the right lobus superior pulmonis. A CT-guided needle biopsy was performed and pathological results showed small cell lung cancer (SCLC). The patient was diagnosed with LE associated with AMPAR antibodies and SCLC. Three months after immunotherapy and tumor removal, patient's memory was partially restored. We recommend that AMPAR antibodies should be detected in patients with classic LE with or without tumor. Prompt treatment of the tumor and immunotherapy are important.

CASE REPORT

INTRODUCTION

Autoimmune synaptic encephalitides are a group of neurological disorders that are associated with autoantibodies against neuronal surface proteins that lead to dysfunction of synaptic transmission in a dose-dependent, reversible, and selective manner (Leypoldt *et al.* 2015). The discovery of these autoimmune diseases has greatly improved the understanding of their pathogenic mechanisms and provided for the possibility of treatment with adequate immunotherapy. The identification of autoantibodies to extracellular epitopes of neurons has increasingly produced a great impact in clinical neurology, and immunotherapy by targeting autoantibodies is potentially beneficial for patients (Vincent *et al.* 2011). Recently, antibodies against α-amino 3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), which mediates the fast excitatory synaptic transmission in the brain and is important for synaptic plasticity, memory, and learning (Sprengel 2006), have been found in patients with otherwise typical limbic encephalitis (Vincent *et al.* 2011). However, the clinical features of limbic encephalitis (LE) associated with AMPAR antibodies are unclear. Here, we report a case of a 51-year-old patient with LE associated with AMPAR antibodies, and summarize the clinical feature of the disease.

CASE REPORT

A 51 year old man was admitted to our hospital, presenting with anterograde memory loss for 2 months. His memory disturbances, particularly short term memory loss and disorientation, had aggravated gradually over the past 2 months. Psychiatric manifestations occurred occasionally. No signs of epilepsy or hyponatremia were observed. The patient's temperature was normal and his past medical history was unremarkable. The patient had no vomiting or headache at the onset of the disease. On neurological examination, the patient had memory disturbance without focal deficit. Cranial magnetic resonance (MR) and electroencephalogram (EEG) were unremarkable. Laboratory testing revealed that the serum sodium level was normal, and the glucose, lactate and protein levels in the cerebrospinal fluid (CSF) were normal. Herpes simplex virus 1 or 2, *Borrelia burgdorferi*, and *Treponema pallidum* were not found, neither in the CSF or the blood. Antibodies in the serum and CSF were positive for AMPAR2, but negative for Yo, Ri, Hu, Ma, N-methyl-D-aspartate receptor, and CV2. CT scans showed oppressive stenosis with nearly total emphraxis in the right lobus superior pulmonis. A CT-guided needle biopsy was performed, and pathological results showed small cell lung cancer (SCLC) (Fig. 1). Based on the characteristic memory loss, positive AMPAR antibodies in the blood and CSF, and histopathology of lung tissues, the patient was diagnosed with a LE associated with AMPAR antibodies and SCLC.

The patient was treated with intravenous immunoglobulin (IVIg, 0.4 g/kg/day) for 5 days. The tumor was surgically removed. Three months after the treatment, the patient's memory was partially restored.

The patient provided informed consent for the use of the case data, and the ethics committee of the First Hospital of Jilin University (Changchun, China) approved this study.

DISCUSSION

The recent characterization of autoimmune synaptic disorders has led to the identification of subtypes of limbic, multifocal, or generalized encephalitis, which often respond to immunotherapy. LE associated with AMPAR antibodies was first reported by Lai *et al.* in 2009, and was often associated with relapses (Lai M *et al.* 2009). Psychosis has been reported as a presenting and dominating symptom (Graus *et al.* 2010). Consistent with previous study, our patient also presented with psychiatric symptoms occasionally. In addition, LE associated with AMPAR antibodies occurred more in women than in men (Dogan Onugoren *et al.* 2015; Bien & Elger 2007). It has been reported that patients with LE associated with AMPAR antibodies had a broad spectrum of neoplasms (including tumors of the lung, breast and thymus) with a tumor rate as high as 70% (Horresh *et al.* 2008). In the present case, the male patient was diagnosed with SCLC by lung CT and histopathological examination of lung biopsy tissues. The histologic types

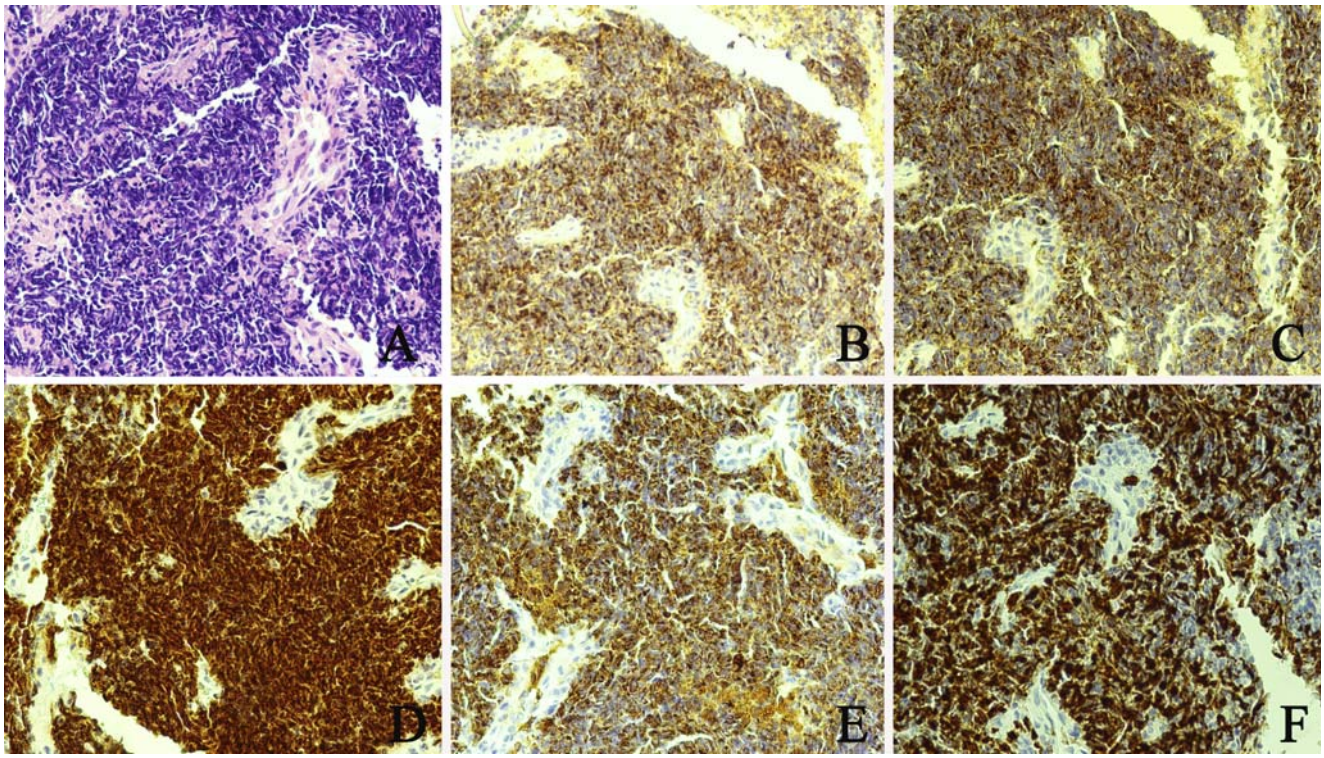

Fig. 1. The histopathological staining of tissues obtained from bronchoscopic biopsy. A: H.E staining; B: CgA(+); C: Sny(+); D: TTF1(+); E: AE1/AE3 (+); F: Ki-67: over 20%. Brown color indicates positive staining. Magnification, × 200.

of tumors were similar to those previously reported in LE associated with AMPAR antibodies (Lai M *et al.* 2009). It has been reported that relapse is a distinctive feature of this disorder (Graus *et al.* 2010). At the latest follow-up (3 months after treatment), our patient did not show relapse of the disease. This may be due to the short follow-up period (Joubert *et al.* 2015). Insufficient immunotherapy might contribute to relapse of the disease (Höftberger *et al.* 2015).

According to our case and cases in the literatures, we summarize clinically relevant findings of LE associated with AMPAR antibodies. (1) Since psychiatric symptoms frequently occur in LE patients, the initial diagnosis of LE may be mistaken for one of several psychiatric diseases, particularly in patients with prominent psychiatric features. (2) Although the clinical diagnosis of LE can be confirmed by MRI findings, brain MRI is normal in certain patients with LE associated with AMPAR antibodies. (3) It has been reported that an underlying tumor is present in 64% of LE patients, and the coexistence of cell surface autoantibodies occurs in 32% of the LE patients. The presence of paraneoplastic symptoms or tumors reflects the concurrent autoimmunity (Höftberger *et al.* 2015).

The first line treatment for LE associated with antibodies to cell surface proteins usually involves high doses of steroids in combination with other immunosuppressive therapies, such as IVIg, plasma exchange, or mycophenolate (Lancaster *et al.* 2011). If the patients fail to respond to first-line treatment within 1–2 weeks, second line therapy, such as rituximab and cyclophosphamide, should be initiated (Höftberger *et al.* 2015). For patients with a tumor, oncologic treatments should be started as early as possible.

In summary, for patients with LE, AMPAR antibodies should be detected. No matter whether the patients had a tumor or not, an extensive screening, including identification of underlying tumors and classic paraneoplastic antibodies should be performed. Moreover, the treatment of the tumor and immunotherapy should be initiated promptly.

CONFLICT OF INTEREST

The authors declare that there was no conflict of interest.

FUNDING

None.

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