

**Case  
Report**

# A Case of Paraneoplastic Limbic Encephalitis in a Patient with Invasive Thymoma with Anti-Glutamate Receptor Antibody-Positive Cerebrospinal Fluid: A Case Report

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**Background:** Thymoma is known to cause autoimmune neuromuscular disease. However, anti-glutamate receptor antibody limbic encephalitis (LE) with thymoma is relatively rare. **Case Presentation:** A 68-year-old woman was admitted with progressive memory impairment and personality change. Brain magnetic resonance imaging (MRI) revealed high intensity in the bilateral limbic areas on T2-weighted fluid-attenuation inversion recovery (FLAIR) images. Chest computed tomography revealed a mass in the anterior mediastinum. Surgical resection of the tumor, which was consistent with a type B3 thymoma, resulted in clinical improvement. After surgery, the cerebrospinal fluid (CSF) was found to be positive for anti-N-methyl-D-aspartate (NMDA) type glutamate receptor antibodies. These findings led to the diagnosis of paraneoplastic LE (PLE) associated with thymoma. **Conclusion:** When a patient presents with neurologic symptoms of unknown origin, the possibility of LE accompanied by thymoma should be considered. Rapid treatment is desirable before the symptoms become irreversible.

**Keywords:** paraneoplastic syndrome, thymoma, limbic encephalitis, anti-glutamate receptor antibody

## Introduction

Thymoma is the most common tumor of the anterior mediastinum. It is known to cause autoimmune

neuromuscular disease. However, limbic encephalitis (LE) associated with thymoma is relatively rare. The detection of anti-glutamate receptor antibodies in such patients is also rare.

## Case Report

A 68-year-old woman presented to Department of Psychiatry of Fukushima Red Cross Hospital in Japan with a 2-week history of progressive impairment of short-term memory. She had undergone right oophorectomy at 48 years of age and hysterectomy and left oophorectomy at 66 years of age.

Her vital signs were normal. She was drowsy and unable to give her address. Her Revised Hasegawa Dementia Scale (HDS-R) score,<sup>1)</sup> which was originally developed for screening dementia, was 7/30. Because of her progressive clinical course, she was referred to Department of

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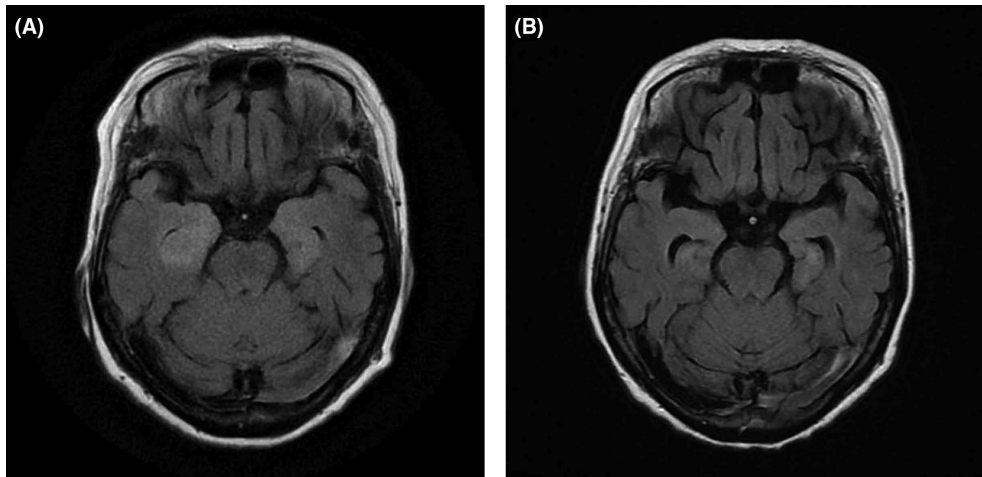
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**Fig. 1** (A) Initial magnetic resonance imaging findings. T2-weighted fluid-attenuation inversion recovery images showing brain edema and hyperintense areas in both limbic areas. (B) Follow-up MRI showing improvement of the lesions.

Neurology and hospitalized. Her neurologic examination was otherwise normal. Brain magnetic resonance imaging (MRI) showed high intensity in the bilateral limbic areas on T2-weighted fluid-attenuation inversion recovery (FLAIR) images (**Fig. 1A**). A diagnosis of possible acute LE was made. Laboratory examination revealed no remarkable abnormalities in the blood count, serum chemistry, inflammation, liver function, renal function, electrolytes, vitamin B1, vitamin B12, thyroid markers, or blood ammonia level. Screening for autoimmune markers (anti-nuclear, anti-DNA, anti-SS-A, and SS-B antibodies) was negative. Tumor markers such as carcinoembryonic antigen, cancer antigen 19-9, and cancer antigen 125 were within normal limits. Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis was unremarkable; few cells were detected, and the protein and glucose levels were normal. CSF cultures were also negative.

After admission, intravenous methylprednisolone (1 g/day for 3 days) and acyclovir (50 mg/kg twice a day) were commenced for treatment of herpes encephalitis. Seven days later, detection of herpes simplex virus in CSF by polymerase chain reaction was negative, and acyclovir was discontinued. However, the patient's level of consciousness did not improve. Chest computed tomography revealed an anterior mediastinal tumor (**Fig. 2**). A thymic neoplasm was then suspected to be contributing to the LE, and she was referred to our department.

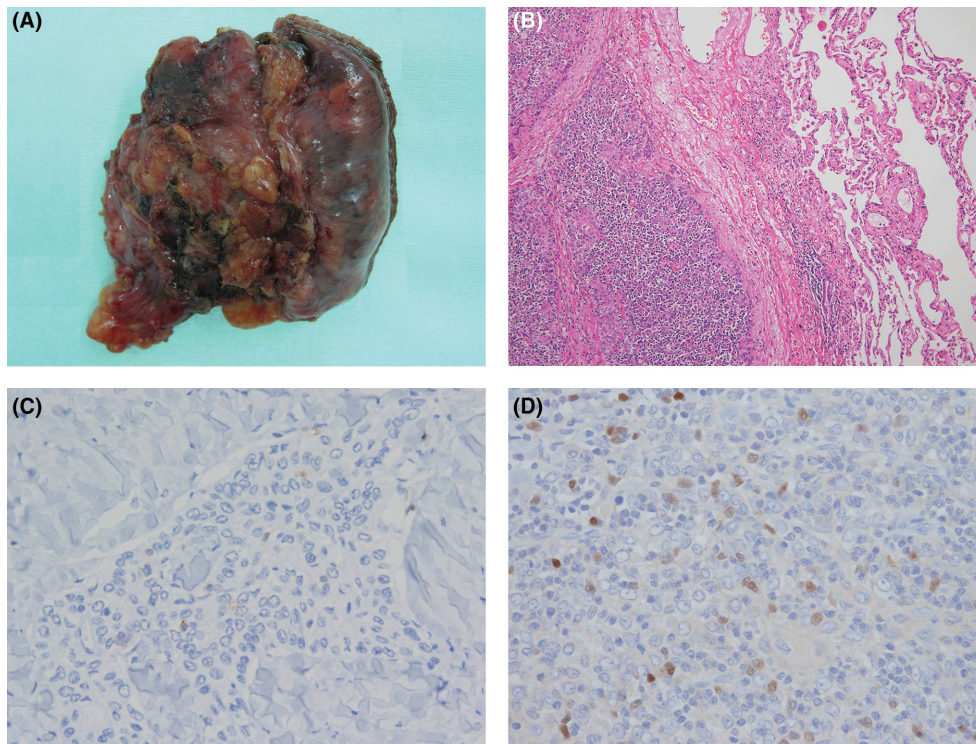
A median sternotomy was performed on day 10 of hospitalization. Intraoperative findings revealed that the mass had invaded the left lung and pericardium. Malignant markers were not observed in the pericardial fluid, and dissemination was not observed in the pleura.



**Fig. 2** A chest computed tomography scan revealed an anterior mediastinal mass (5.0 × 3.5 cm) without pleural effusion or dissemination.

En bloc resection of the tumor, affected lung, and pericardium was performed. Histologic examination revealed invasive thymoma type B3<sup>2)</sup> (**Figs. 3A–3D**).

The patient's postoperative course was uneventful, but her mental status did not improve immediately. Intravenous methylprednisolone (1 g/day for 3 days) was administered again on postoperative day 5. Despite this treatment, her short-term memory impairment did not improve. A third course of methylprednisolone (1 g/day for 3 days) was administered on postoperative day 23, followed by tapering prednisolone therapy (initial dose of 50 mg/day). Her cognitive status and memory began to gradually improve 2 months after surgery, and her HDS-R score finally rose to 28/30. Two months after admission, the CSF finally showed positivity for anti-N-methyl-D-aspartate (NMDA) type glutamate receptor



**Fig. 3** (A) Macroscopically, the resected specimen had invaded the left lung. (B) Histologic examination of the tumor with a few immature T lymphocytes confirmed type B3 thymoma. The tumor cells had invaded the left lung (hematoxylin–eosin stain, original magnification, ×100). (C) The tumor cells stained negative for CD5 (original magnification, ×400). (D) A few immature T lymphocytes stained positive for TdT (original magnification, ×400). TdT: Terminal deoxynucleotidyl transferase

antibodies although all other neural autoantibodies were negative. These results led to the diagnosis of paraneoplastic LE (PLE) associated with thymoma. Follow-up MRI on postoperative day 86 showed improvement in the bilateral temporal lobe lesions (**Fig. 1B**). She was continuing to progress well without complications at the time of this writing (20 months after symptom onset).

## Discussion and Conclusion

The cerebral limbic system is composed of the hippocampus, amygdala, cingulate gyrus, hypothalamus, and other structures. Its function is important for emotion, instinctive behaviors, and memory. LE is characterized clinically by subacute onset of short-term memory impairment and personality changes. LE has various causative factors such as infection, Hashimoto's encephalopathy, systemic lupus erythematosus, Sjogren's syndrome, toxic metabolic encephalopathy (including Wernicke–Korsakoff encephalopathy), primary angiitis of the central nervous system, syphilis, brain tumors, and

paraneoplastic disorders.<sup>3)</sup> Many patients with LE have hyperintensities involving one or both medial temporal lobes on T2 FLAIR MRI.<sup>4,5)</sup> In the present case, T2 FLAIR MRI of the brain was very useful for diagnosis although the cause is difficult to distinguish using only images in such cases.

A paraneoplastic neurologic syndrome (PNS) is a disorder of the nervous system caused by a tumor but not by direct tumor growth, metastases, or metabolic or infectious complications. PNS occurs in 0.01% of patients diagnosed with a malignancy.<sup>6)</sup> It is generally considered that PNS is caused by autoantibodies to commonly expressed neural antigens and tumors. Several antibodies have been reported to date. These antibodies are largely divided into two groups based on the site of the antigen. One group comprises autoantibodies that recognize the cytoplasmic proteins or nucleus of nerve cells (e.g., anti-Hu antibody, anti-Yo antibody); the other comprises autoantibodies that recognize receptors or ion channels on the surface of the nerve cell (e.g., anti-voltage-gated calcium channel antibody, anti-voltage-gated potassium

channel antibody). The former group of antibodies is often associated with malignant tumors. For example, patients with anti-Hu antibody usually have small-cell lung cancer (SCLC), and patients with anti-Yo antibody usually have breast, ovarian, or uterine cancer. These antibodies serve as diagnostic markers, but they are unlikely to be pathologically involved. In other words, it is thought that the antibody alone does not impair the tissue, but rather that CD8-positive T lymphocytes are involved in the pathology. Therefore, neurologic symptoms are less likely to be improved by plasma exchange or immunotherapy. The latter may be associated with malignant tumors, but many are unrelated to them. Because the antigen to which antibodies react is present on the neuronal cell surface, removal of the antibody is often effective and the prognosis of neurologic symptoms is thought to be good.<sup>7)</sup>

PLE, a type of PNS, is a rare complication of cancer. Previous research has shown that neoplasms commonly associated with PLE arise from SCLC, testicular cancer, and breast cancer. Gultekin et al.<sup>3)</sup> reported that among patients with PLE, 40% have SCLC, 20% have testicular tumors, 8% have breast cancer, and only 2% have thymoma. In addition, PLE rarely invades acutely; it is generally indistinguishable from other types of encephalitis such as herpes encephalitis. Although it is well known that thymoma is frequently associated with autoimmune diseases such as myasthenia gravis, it is a relatively rare cause of PLE. Its diagnosis is difficult because the symptoms usually precede the detection of the underlying cancer, and they can resemble those of a variety of conditions. Gultekin et al.<sup>3)</sup> reported that 60% of patients with PLE had anti-neuronal antibodies, and 40% of them were antibody-negative. Anti-glutamate receptor antibodies were present in our patient, leading to the diagnosis of PLE.

The NMDA receptor is a receptor for glutamate, which is a neurotransmitter. Glutamate receptors are classified into the ion channel type and metabolism type, and the ion channel type is further classified into the NMDA type and non-NMDA type.<sup>8)</sup> Anti-NMDA receptor antibody is an antibody to receptors on the surface of nerve cells. Anti-NMDA receptor encephalitis was first reported by Dalmau et al.<sup>9)</sup> in 2007 and has since been increasingly recognized. Many cases in which anti-NMDA receptor encephalitis was associated with ovarian teratoma in young women have been reported, but few such cases in association with thymoma have been reported. Symptoms caused by anti-NMDA receptor encephalitis can be improved by adding anti-tumor therapy and immunotherapy early in the disease course.

Conversely, about 25% of patients reportedly have some sequelae, and the acute mortality rate is 7%.<sup>10)</sup> When examining patients with LE, the clinician must also search for NMDA receptor antibodies.

Anti-NMDA antibody is generally detected by a cell-based assay.<sup>7)</sup> However, the results require a long period of time to obtain, as in the present case. This is not always practical in the clinical setting. Therefore, as in the present case, when the cause of LE cannot be identified at an early stage, it may be necessary to search for the tumor as soon as possible.

Standard therapy for PLE associated with thymoma has not been established. Removal of the underlying tumor is considered to be an effective treatment, possibly because of the removal of the antigenic stimulus.

This case illustrates that the possibility of PLE should be kept in mind, and early diagnosis with prompt therapy in cooperation with other clinical departments is important. We should also remember that PLE is possible when we encounter patients who have neurologic symptoms corresponding to the limbic area. Adequate therapy is desirable before symptoms become irreversible. Because PLE associated with thymoma is a rare disease, the optimal clinical management and prognosis remain unclear. In some patients, neurologic symptoms reportedly occurred following recurrence of the thymoma.<sup>11,12)</sup> Thus, close observation is necessary. Accumulation of more cases and longer-term follow-up are necessary.

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## Disclosure Statement

The authors declare no conflicts of interest.

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