

Voltage-gated potassium channel antibodies associated limbic encephalitis in a patient with invasive thymoma

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Article Abstract

Recently, limbic encephalitis (LE) associated with Voltage-gated potassium channel antibody (VGKC-Ab) has been postulated as a new autoimmune disorder. Most previously reported cases of VGKC-Ab-associated LE were non-paraneoplastic, and reports of a paraneoplastic type are rare. Here we describe a 59-year-old woman with paraneoplastic VGKC-Ab-associated LE preceding the recurrence of invasive thymoma. There was a close temporal relationship between the clinical course and the changes of the VGKC-Ab titer. Unlike many of the non-paraneoplastic VGKC-Ab-associated LE cases, our cases showed the more extensive high intensity lesions on MRI and the absence of seizure and hyponatremia.

1. Introduction

Limbic encephalitis (LE) is clinically characterized by the subacute onset of disorientation, psychiatric symptoms, and impairment of short-term memory. Various conditions have been suggested to be associated with LE. Two recent reports have described the features of the non-paraneoplastic type of LE associated with voltage-gated potassium channel antibodies (VGKC-Ab).^{1,2} Here we describe a case of paraneoplastic VGKC-Ab-associated LE in a patient with invasive thymoma. This is the first reported Japanese case.

2. Case report

A 59-year-old right-handed retired local government official was referred to our hospital with a three-day history of memory impairment. At the age of 56 years, invasive thymoma had been diagnosed and was treated with transsternal extended thymectomy and postoperative radiation therapy. At the age of 57 years, herpes zoster affected the right upper limb. The patient also suffered from post-herpetic neuralgia and was under treatment with carbamazepine. She was also taking antidiabetic and antihypertensive medications. She was a non-smoker and had no history of alcohol intake.

On admission, the vital signs were normal. Her short-term memory was impaired. The Mini-Mental State Examination (MMSE) score was 19/30, and she was disoriented in time. Her daughter reported that the patient had become apathetic. She had no symptom or signs of neuromyotonia; electromyography was not performed. There was no history of seizures and no excessive sweating.

Laboratory tests demonstrated transient leukocytosis (12,000/mm³), an increased

gamma-glutamyl transpeptidase level, and hyperglycemia (280 mg/dl), but other investigations yielded normal results. Serum sodium was also normal. Screening for autoantibodies (including thyroperoxidase antibodies) was negative, except for single-stranded DNA antibodies. Acetylcholine receptor antibodies and Hu and Yo paraneoplastic antibodies were negative. Cerebrospinal fluid examination (including PCR for herpes simplex virus and herpes zoster virus) yielded normal results, except for mild elevation of the protein content (60 mg/ml). The EEG was normal. Her initial chest computed tomography (CT) scan demonstrated no evidence of recurrent thymoma. ⁶⁷Ga scintigraphy and CT scans of the abdomen and pelvis also failed to show any evidence of malignancy. Brain magnetic resonance imaging (MRI) was done at three days after the onset. T2-weighted and fluid-attenuation inversion recovery (FLAIR) images demonstrated bilateral hyperintense areas in the medial part of the temporal lobe. High intensity lesions were also seen in the right insular cortex, as well as bilaterally in the frontobasal cortex and cingulate gyrus (Fig. 1).

Over the next 10 days, there was improvement of her memory and MMSE (to 27/30). At discharge, three weeks after the onset, repeat MRI showed attenuation of the bilateral medial temporal lobe signal changes, especially on the right side. Hyper-intensity of the superficial cortical layers was visible on T1-weighted images. An immunosuppression therapy was advised but refused by the patient and her family.

Six months later, her memory began to decline again and memory impairment was gradually progressive. Ten months after the onset of her illness, repeat chest CT demonstrated the recurrence of invasive thymoma. At that time, the MMSE score was 23/30. On brain MRI, the lesions in the temporal lobes were smaller, but those in the frontobasal lobes were larger, and profound hippocampal atrophy was shown (Fig. 2).

She consented to receive chemotherapy for thymoma and was referred to the department of respiratory disease. She was treated by combination of carboplatin and etoposide. Two months after the recurrence, her mental state partial improved with diminishment of thymoma. Retrospective analysis of serum samples obtained at three times (onset, remission, and recurrence) showed high titers of VGKC antibodies by radioimmunoassay using whole rabbit brain homogenate, as described previously.⁶ The VGKC antibody titer was 403 pM at onset, 373 pM at remission, 917 pM at recurrence, and 649 pM after chemotherapy (normal range <100).

3. Discussion

The most prominent clinical feature in this patient was cognitive dysfunction that caused anterograde amnesia with a remitting and relapsing course. Her signs and symptoms, as well as the MRI findings, were typical of limbic encephalitis. The interesting finding in our patient was the existence of VGKC-Ab, which showed a temporal relationship with her LE symptoms and with the recurrence of thymoma. Recently, a new type of LE associated with VGKC-Ab has been proposed.^{1,2} The main features of this condition are memory disturbance, confusion, seizures, and hyponatremia^{1,2}, while neuromyotonia has only been found in one patient. Compared with non-paraneoplastic VGKC-Ab-associated LE, there have been few reports about paraneoplastic VGKC-Ab-associated LE - only seven patients with thymoma^{3,4} and two with lung cancer⁵ have been reported so far. Detailed clinical features have only been described for one case of thymoma with MG.³ Some features of our case differ from the previously reported non-paraneoplastic type of LE cases, although the most of clinical features of our patient was similar. One of the features was the more extensive high

intensity lesions on MRI, involving the right insular cortex, both frontobasal cortices and cingulate gyrus. Unlike many of the non-paraneoplastic VGKC-Ab-associated LE cases, the serum sodium was normal, and the patient did not develop seizures, which may be relevance. The titer of the VGKC antibodies of this case was not extremely high, starting at around 400 pM, and becoming 900 pM at recurrence of the tumor. Levels around 400 pM may be more common in cases associated with tumors than in the non-paraneoplastic forms.⁴

When VGKC-Ab are detected in patients with paraneoplastic neurological syndromes other than LE, thymoma is found in the majority of cases.^{3, 4, 7-9} VGKC-Ab are also found in 13% of thymoma patients without neurological disorders.⁴ It is thought that the following two disorders are often related to VGKC-Ab and can coexist with thymoma. One condition is acquired peripheral nerve hyperexcitability (APNH), including neuromyotonia, cramp-fasciculation syndrome, and Isaac's syndrome.⁹ The other is Morvan's syndrome, a rare condition that features acquired neuromyotonia, autonomic disturbance, hypersecretion, and cognitive impairment.^{10, 11} Our patients showed spontaneous and treatment-related recovery of clinical findings with the decreasing of the VGKC antibody titer and relapse with the recurrence of invasive thymoma and strikingly increasing anti body titer. Spontaneous recovery of paraneoplastic limbic encephalitis is unusual. This clinical course suggested that VGKC-Ab of our patient related to occurrence of limbic encephalitis and thymoma, although they are detected found in thymoma patients without neurological symptom.⁴

Antibody-mediated VGKC dysfunction is thought to cause hyperexcitability of peripheral motor axons and nerve terminals in patients with APNH.^{9, 12, 13} In VGKC-Ab-associated LE, previous reports¹⁻³ and the findings in our patient have

demonstrated a temporal relationship between the clinical course and changes of the VGKC-Ab titer. Immunohistochemistry using serum samples from a patient with VGKC-Ab and limbic encephalitis showed strong immunostaining of the molecular layer of the dentate gyrus.³ It can be suggested that VGKC-Ab play a pathogenic role in VGKC-Ab-associated LE based on these findings.

Further studies are required to confirm that VGKC antibodies cause limbic encephalitis. LE associated with thymoma may represent a form of VGKC-Ab-mediated autoimmune ion channelopathy, as well as APNH and Morvan's syndrome, and it might show a good response to immunotherapy similar to myasthenia gravis and other autoimmune disorders.

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Competing interests: none declared

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Figure legends

Figure 1. Initial MRI findings

FLAIR images demonstrate bilateral hyperintense areas in the hippocampus and parahippocampal gyrus, as well as a mass effect, especially on the left side. High signal intensity lesions are also present in the right insular cortex, as well as bilaterally in the frontobasal cortex and cingulate gyrus. (A, B) On T1-weighted image, the lesions were demonstrated low intensity. (C)

Figure 2. Follow-up MRI (recurrence at ten months after the onset) findings

FLAIR images show improvement of the lesions in the bilateral temporal lobes (A), but there is expansion of hyperintense areas in the bilateral frontobasal lobes. (B)

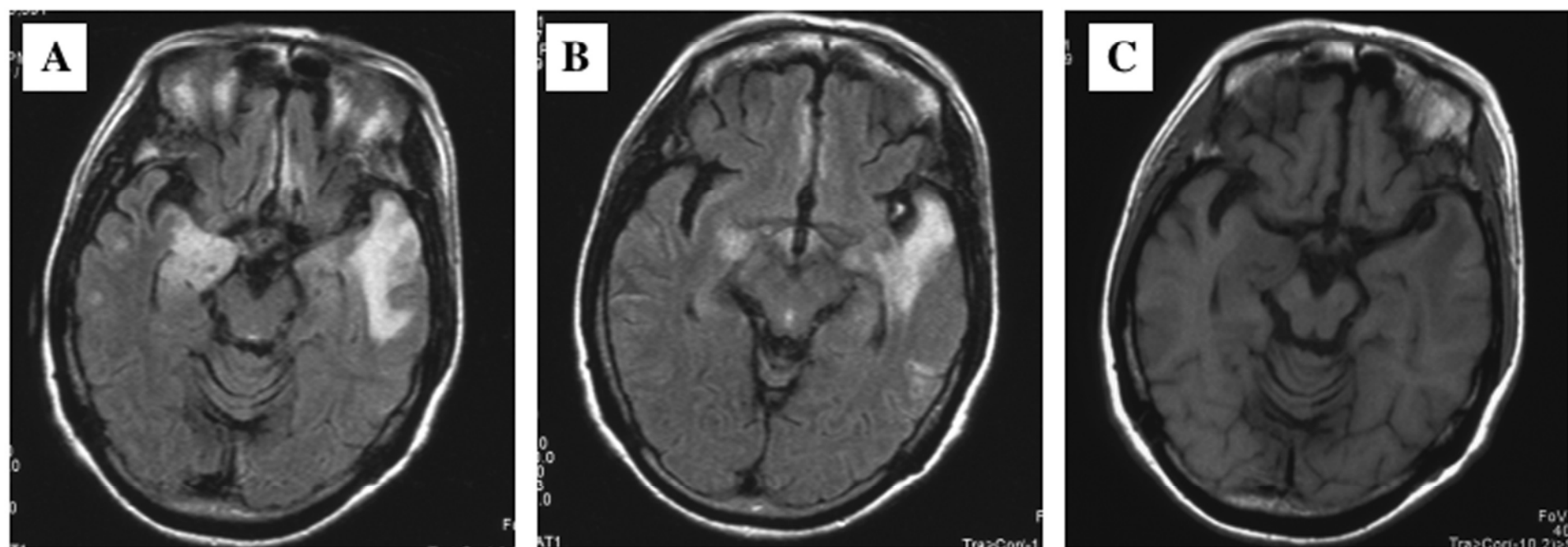


Figure 1.

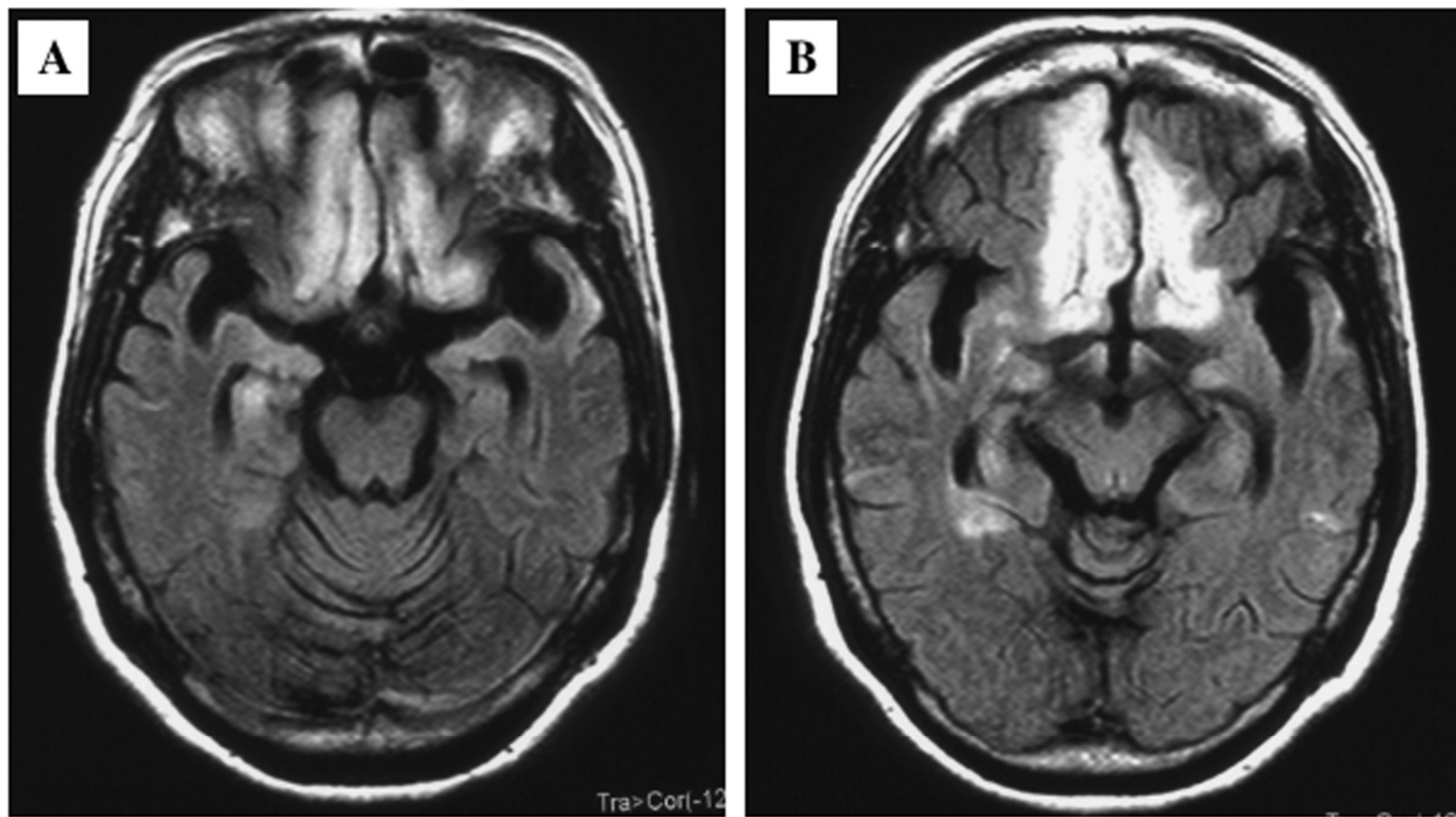


Figure 2.