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【 CASE REPORT 】

Anti-leucine-rich Glioma Inactivated-1 Encephalitis Associated with Essential Thrombocythemia

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Abstract:

Anti-leucine-rich glioma inactivated-1 (anti-LGI1) encephalitis is a subgroup of autoimmune encephalitis. We herein report the case of a 60-year-old man who presented with typical symptoms, including short-term memory loss, mental abnormalities, hyponatremia and seizures characterized by faciobrachial dystonic seizures and who was diagnosed with anti-LGI1 encephalitis. At the same time, he was diagnosed with essential thrombocythemia. A significant improvement was obtained by treatment with corticosteroid, immunoglobulin, mycophenolate mofetil, and hydroxyurea. Autoimmune diseases are associated with a significantly increased risk of developing myeloproliferative neoplasms, which may explain the coexistence of anti-LGI1 encephalitis and essential thrombocythema in this patient; however, but more cases and studies are needed to determine whether there is any correlation between these conditions.

Key words: anti-leucine-rich glioma inactivated-1 encephalitis, essential thrombocythemia, paraneoplastic syndrome, myeloproliferative neoplasms, faciobrachial dystonic seizures

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Introduction

Anti-leucine-rich glioma inactivated-1 (anti-LGI1) encephalitis is a subtype of autoimmune encephalitis characterized by recurrent seizures, psychiatric disturbances, cognitive deficits, hyperhidrosis, sleep disorders, and arrector pili attacks (1). Faciobrachial dystonic seizures (FBDS) are a distinctive clinical manifestation of anti-LGI1 encephalitis-associated seizures. Brain magnetic resonance imaging (MRI) shows increased fluid-attenuated inversion recovery (FLAIR) signal intensity in the hippocampus and medial temporal lobes. Essential thrombocythemia (ET) is a Philadelphia-negative chronic myeloproliferative neoplasms (MPN) characterized by stem cell-derived clonal proliferative myeloid malignancy and a tendency to transform into leukemia in the final stage. Studies have shown that some autoimmune diseases are associated with a significantly increased risk of MPN (2). We herein report the case of a patient with coexisting anti-LGI1 encephalitis and ET. To our knowledge, this is the first case report on autoimmune disease of the central nervous system and MPN.

Case Report

A 60-year-old man with an 18-month history of short-term memory loss, convulsions, mental abnormalities, as well as speech confusion and hallucination, which had persisted for 20 days, was referred to our hospital in November 2016. He had visited two hospitals previously and oxcarbazepine (600 mg/day) and lamotrigine (200 mg/day) had been prescribed to control his seizures. The frequency of the patient's seizures increased, even when he was taking his medications. Twenty days prior to hospitalization, the patient developed agitation, anxiety, speech confusion, irritability, inability to recognize his family members, visuo-spatial disorientation, phonism, and visual hallucination.

A physical examination disclosed apathy, short memory

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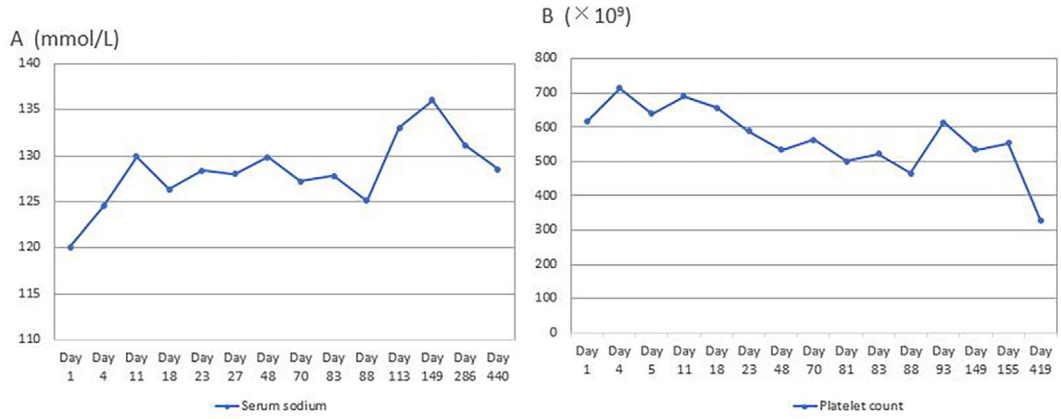

Figure 1. Changes in the serum sodium level (A) and blood platelet count (B).

decline, glossolalia and speech confusion. Involuntary twitching and jerking of his limbs was observed. A Mini-Mental State Examination (MMSE) showed mental impairment, with a score of 12 out of 30. The initial serum sodium level was 120.1 mmol/L (Fig. 1A). The patient's platelet count was 616×10^9/L and then increased to 714×10^9/L, and remained high during the subsequent reexaminations (Fig. 1B). Seven months previously, when the patient was examined at the first hospital, his platelet count had been high (634×10^9/L). Bone marrow biopsy showed active proliferation with a granulocyte (G) ratio of 67%, an erythrocyte (E) ratio of 18.5% and G/E 3.62/1. The megakaryocytic lineage cell count was 548/μL and mature megakaryocytes with hyperlobulated nuclei were observed. The proportion was normal, with no significant left-shift of neutrophil granulopoiesis or erythropoiesis. The platelets were distributed in clumps. Genetic testing detected a Janus kinase 2 (JAK2) V617F gene mutation. According to the 2016 World Health Organization diagnostic criteria for ET (3, 4), and after consulting with a hematologist, this patient was diagnosed with ET. A cerebrospinal fluid (CSF) examination revealed a normal leukocyte count (2/μL, normal range 0-8/μL), a normal glucose concentration (3.72 mmol/L, normal range 2.5-4.5 mmol/L), a reduced chloride level (107.6 mmol/L, normal range 120-130 mmol/L), and a mildly elevated protein level (54.6 mg/dL, normal range 20-40 mg/dL). At the same time, the serum levels of sodium and chloride were 124.5 mmol/L and 88.6 mmol/L, respectively, and the blood glucose level was 4.69 mmol/L. During hospitalization, the patient suffered from faciobrachial dystonic seizures (FBDS) and generalized tonic clonic seizures (GTCS). Video-electroencephalography (VEEG) monitoring revealed normal background activity. During a seizure, the patient suddenly opened his mouth, then presented head torsion, loss of consciousness, corectasis and subsequently generalized convulsions, coexisting with uplifting of the left arm for approximately 2 minutes. VEEG showed decreased voltage in all monitoring leads before attack and a burst of multi-spike activity during the attack period. After the attack, the voltages decreased with low-amplitude irregular slow waves. Cranial MRI showed an increased signal on T2-FLAIR imaging and localized edema in the left medial aspect of the temporal lobe (Fig. 2). Serial arterial spin labeling (ASL) MRI sequences showed hyperperfusion over the left temporal lobe (Fig. 3). Based on the clinical data, we suspected that this patient had anti-LGI1 encephalitis. Subsequently, anti-LGI1 antibodies were detected in both serum and cerebrospinal fluid (CSF) and he was diagnosed with anti-LGI1 encephalitis.

Methylprednisolone pulse therapy was initiated at a dose of 1,000 mg/day for five days. The dosage was then reduced to 500 mg/day for another five days, followed by prednisone per os, tapered off from 60 mg/day. After two weeks of corticosteroid treatment, the seizures accompanied by unconsciousness had almost disappeared. His cognitive decline, speech confusion, and psychotic symptoms were noticeably improved, and his MMSE score had increased to 18/30. Although faciobrachial involuntary dystonic movements and hyperhidrosis still occurred before sleep, the frequency of FBDS decreased. Subsequently, the patient was treated with intravenous immunoglobulin (IVIG; 0.4 g/kg/day) for 5 days. His clinical symptoms improved gradually, and he was discharged.

At the 1-year follow-up visit, the patient had fewer seizures and garrulous words but was still grumpy and irritable. His short-term memory loss had worsened. He was hospitalized again and was treated with IVIG and mycophenolate mofetil. After the third hospital discharge, mycophenolate mofetil, oxcarbezepine, lamotrigine, and hydroxyurea were administered orally as consolidation therapy. During the continuing treatment, his episodic unconsciousness and perspiration symptoms showed significant improvement, but he still had an unstable mood, irritable character, and short-term memory impairment. The blood platelet count declined and his serum sodium level gradually increased (Fig. 1). The abnormal signals of the left medial temporal lobe on brain MRI did not noticeably change, but the hyperperfusion in the ASL sequences over the left temporal lobe disappeared (Fig. 3). Unfortunately, the anti-LGI1 antibody level was not reexamined after immunotherapy; however, the patient's

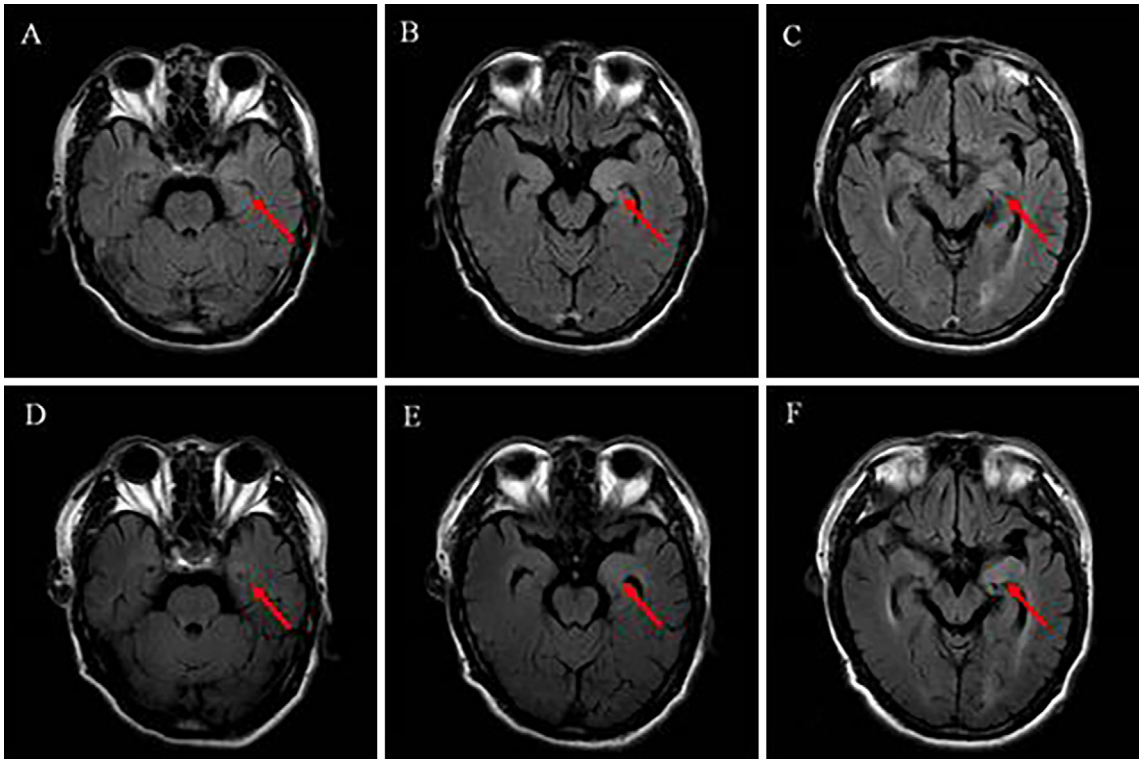

Figure 2. **Brain MRI of the patient with anti-LGI1 encephalitis. A, B, C: Initial axial FLAIR showed swelling and hyperintense signaling in the left medial temporal lobe and hippocampus (red arrow). D, E, F: Axial FLAIR at the 3-month follow-up examination showed the persistence of hyperintense signaling in the left medial temporal lobe and hippocampus (red arrow).**

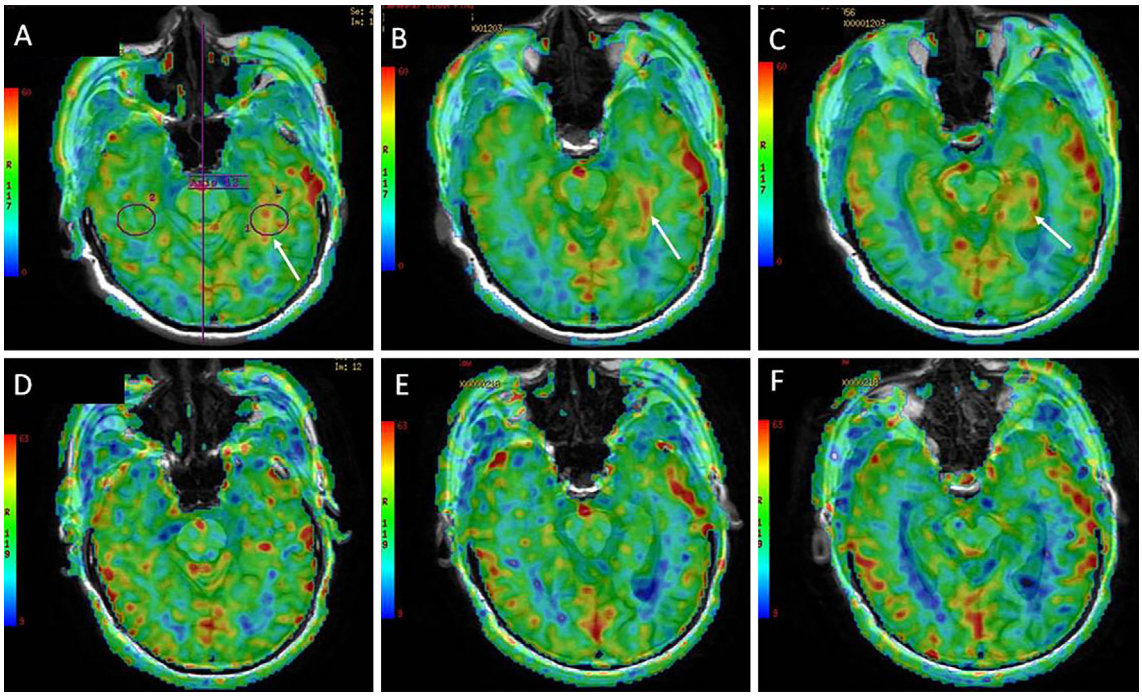

Figure 3. **Serial arterial spin labeling (ASL) MRI sequence changes before and after immunotherapy in the patient with anti-LGI1 encephalitis. A, B, C: ASL showed hyperperfusion over the left temporal lobe in the acute stage of the disease (white arrow). D, E, F: the hyperperfusion in the ASL sequences over the left temporal lobe disappeared after immunotherapy.**

condition showed an obvious improvement.

Discussion

Autoimmune encephalitis is a non-infectious autoimmune encephalopathy associated with the antibodies against neuronal cell-surface or intracellular antigens. In 2007, Dalmau et al. reported some cases of anti-N-methyl-D-aspartate (anti-NMDA) encephalitis (5). The antibodies associated with autoimmune encephalitis are divided into two categories (6, 7): antibodies against neuronal intracellular antigens (8), and antibodies against neuronal cell-surface antigens (5, 9-11). The clinical symptoms of autoimmune encephalitis associated with antibodies against neuronal cell-surface antigens have common characteristics, such as memory deficit, seizure, psychiatric and behavioral manifestations, speech confusion, dyskinesia and hyponatremia. Autoimmune encephalitis mediated by intracellular antibodies is associated with tumors (e.g., small-cell lung carcinoma). Those mediated by antibodies against neuronal cell-surface antigens rarely coexist with tumors. Shin et al. (12) reported that anti-LGI1 encephalitis accounts for 11.2% of all autoimmune encephalitis. Approximately 5-10% of anti-LGI1 encephalitis occurs in thymoma patients (13), but hematological neoplasms are seldom reported in anti-LGI1 encephalitis patients. Previously, there has been one reported case of anti-LGI1 encephalitis associated with acute myeloid leukemia (14). Another case involved paraneoplastic neurological syndrome (PNS) of the central nervous system with voltage-gated potassium channel (VGKC) antibodies (a Charcot-Marie-Tooth syndrome) related to leukemia (15). Two other reported cases involved non-Hodgkin lymphoma associated with limbic encephalitis (16, 17).

In this case, the patient presented with clinical symptoms of anti-LGI1 encephalitis. His initial platelet count on admission was 616×10^{9}/L and remained high during the subsequent reexaminations. Genetic testing detected the JAK2 V617F gene mutation. Experiments and clinical studies have shown the JAK2 V617F gene mutation is usually involved in MPN (18-20). Furthermore, it was observed in 61.9% of ET patients (19). Philadelphia chromosome-negative chronic MPN, including polycythemia vera (PV), ET and primary myelofibrosis (PMF), are stem cell-derived clonal proliferative myeloid malignancies (4). The final stages of these neoplasms are characterized by bone-marrow failure, myelofibrosis and leukemic transformation (21). In a large population-based study including 11,039 MPN patients and 43,550 matched controls, researchers found that some autoimmune diseases were associated with a significantly increased risk of MPN, and that individuals with a history of any autoimmune disease had a 20% increased risk of developing MPN (2). A single institution case-control study in Denmark showed that the risk of developing MPN in subjects with a prior history of autoimmune disease was significantly increased by 86% in comparison to patients with chronic lymphocytic leukemia (CLL) (22). Furthermore, during the follow-up, a positive association between JAK2 V617F-positive MPN and autoimmune disease was observed (22). Barbui et al. (23) reported an association between elevated chronic inflammation marker levels (e.g., hsCRP and pentraxin 3) and the JAK2 V617F mutation allele burden. In this case, the hsCRP level (33.13 mg/L) was higher than the normal range, which may have been involved in the pathogenesis of ET. In addition, TNF-α is capable of facilitating the clonal expansion of JAK2 V617F-positive cells in MPN (24). Because previous reports have been based on epidemiological data, it is not clear how autoimmune diseases affect MPN, including ET, or how MPN affects autoimmune diseases. Further immunological and molecular studies on individual cases are required to clarify the pathophysiology of both disorders.

Conclusions

In this case, anti-LGI1 encephalitis coexisted with ET. More cases and further studies are needed to determine if there is any correlation between these conditions.

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

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