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Case Report

Severe anti-GAD antibody-associated encephalitis after stem cell transplantation

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Abstract

Background: General features of anti-glutamic acid decarboxylase (GAD) antibody-associated limbic encephalitis are seizures, cognitive impairment, and imaging findings at the medial temporal lobes. We report a patient affected with remarkably severe anti-GAD antibody-positive encephalitis after hematopoietic stem cell transplantation (HSCT).

Case Report: A 5-year-old girl received HSCT due to pineoblastoma. Thirteen months after HSCT, she showed seizure clustering and altered mental status. Her anti-GAD antibody level was high, 65,100 U/mL (reference range < 1.5 U/mL). Her disease was diagnosed as autoimmune encephalitis and she received intravenous immunoglobulin (IVIG) and methylprednisolone. After the therapy, she partially recovered. Encephalitis later relapsed, however, and she showed extremely high anti-GAD antibody, 27 months after HSCT. Although lesions were located in the temporal and occipital lobes by MRI at 5 days after the relapse, very severe whole brain encephalitis was revealed at 13 days after the relapse. Seizures and abnormal encephalogram were resistant to IVIG and methylprednisolone. After plasma exchange, these findings were resolved. MRI revealed diffuse cerebral atrophy, 57 months after the relapse. No relapse has occurred for the past 5 years with decreased anti-GAD antibody after starting bimonthly administration of IVIG.

Conclusion: This may be the first case of severe and recurrent anti-GAD antibody-associated autoimmune encephalitis after HSCT with specific MRI findings. No relapse has occurred since starting maintenance IVIG.

Keywords: Anti-glutamic acid decarboxylase antibody; Encephalitis; Hematopoietic stem cell transplantation; Maintenance intravenous immunoglobulin

1. Introduction

Glutamic acid decarboxylase (GAD) is an enzyme that converts excitatory neurotransmitter glutamic acid to inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [1]. Anti-GAD antibody is associated with the following endocrine and neurological disorders: type 1 diabetes mellitus, limbic encephalitis, cerebellar ataxia, autoimmune epilepsy, and stiff-person syndrome (SPS) [1]. Typical symptoms of anti-GAD-associated limbic encephalitis (GAD-LE) are seizures, cognitive impairment, and psychiatric symptoms [1]. Abnormal brain MRI, such as T2/FLAIR hyperintensity of the bilateral

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medial temporal lobes including the hippocampus, has been reported [1]. About half of the patients with GAD-LE obtain favorable outcomes, and others have poor outcomes such as seizures and cognitive impairment [1]. The reported relapse rate of GAD-LE is 17% [1].

Autoimmune diseases may occur after hematopoietic stem cell transplantation (HSCT) [2]. The mechanisms of autoimmunity after HSCT are due to abnormal reconstitution of the immune system ablated by conditioning regimens [2]. There are some case reports on anti-GAD antibody-positive SPS occurring after HSCT [3]; however, encephalitis after HSCT has apparently not been published until now.

Herein, we report the possible first case of severe and recurrent anti-GAD antibody-associated autoimmune encephalitis after HSCT.

2. Case report

A 5-year-old girl who had had epilepsy was diagnosed as pineoblastoma and received chemotherapy, radiotherapy, and HSCT with conditioning chemotherapy. Thirteen months after HSCT, she was admitted to the intensive care unit due to seizure clustering and altered mental status. The EEG showed left-dominant delta activity and diffusion-weighted MRI disclosed hyperintensity of the cerebrum, predominantly in the left hemisphere. She also showed hypoinsulinemic hyperglycemia with very high serum anti-GAD antibody (65,100 U/mL, reference range < 1.5 U/mL). Her condition was diagnosed as type 1 diabetes mellitus and her neurologic symptoms were suggested to come from autoimmune encephalitis with anti-GAD antibody. After intravenous immunoglobulin (IVIG) and methylprednisolone (mPSL) pulse therapy, her mental status gradually and partially recovered, and immunomodulator was discontinued; her full-scale intelligence quotient as measured by the Wechsler intelligence scale for children third edition declined from 76 to 51. At 27 months after HSCT, she again developed status epilepticus and altered mental status, and relapsed encephalitis was diagnosed. Her serum anti-GAD antibody increased even more to 142,000 U/mL, and the antibody level in cerebrospinal fluid (CSF) was 238 U/mL. Her CSF findings were as follows: 3 white

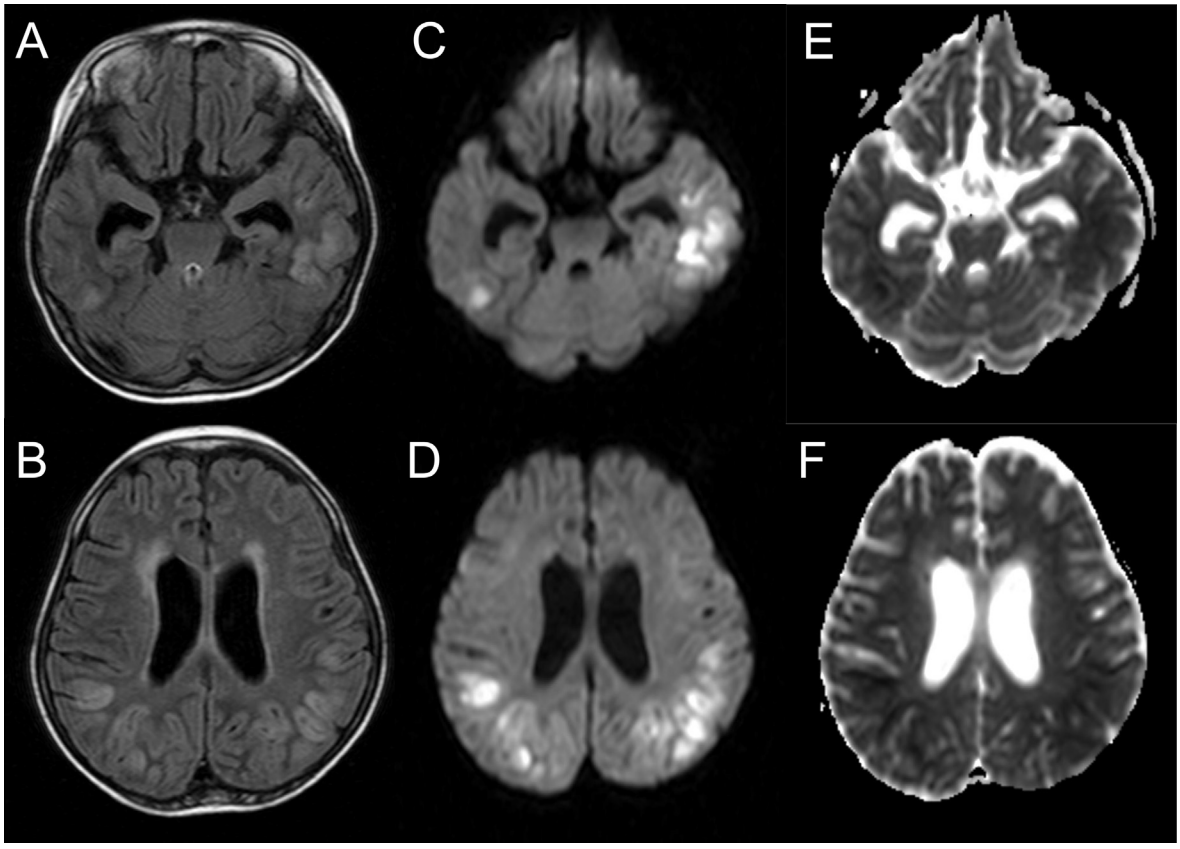

Fig. 1. Axial unenhanced MR imaging at 5 days after the first relapse: fluid-attenuated inversion recovery (FLAIR) (A and B), diffusion-weighted imaging (DWI) (C and D), and apparent diffusion coefficient (ADC). FLAIR images show hyperintensity at the cerebral cortex and subcortical regions of the bilateral temporal and occipital lobes. The lesions show hyperintensity on DWI, and hypointensity on ADC. Cerebral atrophy is not clear.

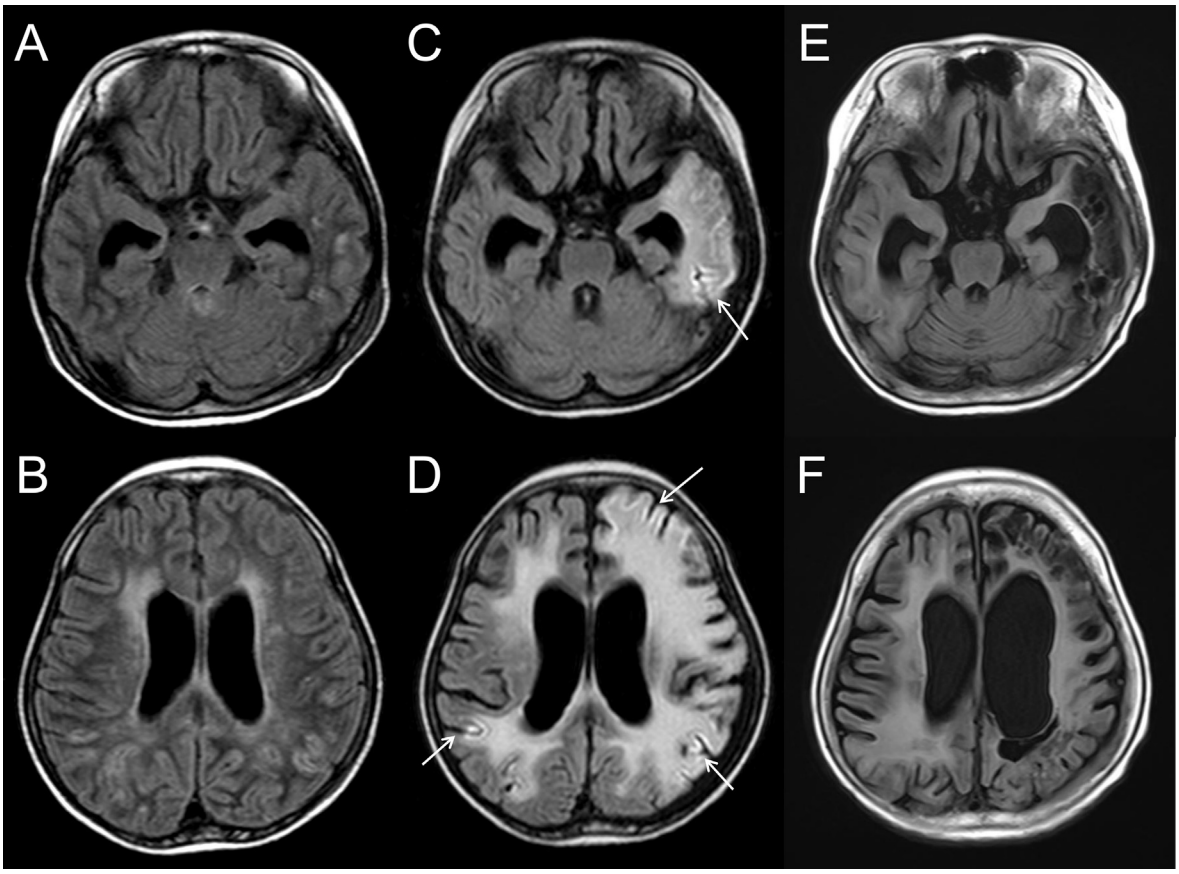

Fig. 2. Axial unenhanced MR FLAIR imaging at 13 days (A and B), 3 months (laminar necrosis [arrows]) (C and D), 57 months (E and F) after the first relapse. Including Fig. 1, cerebral atrophy and cerebral structural disruption progress with time. In a typical case of limbic encephalitis, atrophy occurs in the mediotemporal lobes, and cerebral atrophy appears at several months (not just a few weeks) after the onset of encephalitis. Cerebral atrophy in this case is diffuse and started at only about two weeks after the onset of the first relapse.

blood cells per μL, 8.5 mg/dL of protein, and 116 mg/dL of glucose. The following laboratory values were normal: cytokines (IL-6, IL-10, and TNF-α) in serum and CSF; ratio of matrix metalloproteinase-9 to tissue inhibitor of metalloproteinase-1 (MMP-9/TIMP-1) (data not shown); polymerase chain reaction of herpes simplex virus was negative; EEG showed generalized delta activity and no spike waves. MRI was performed on the day following the relapse and disclosed no interval changes. Although the patient was administered IVIG and mPSL, she developed seizures, and was intubated at 5 days after relapse. MRI at 5 days after relapse revealed hyperintensity on diffusion-weighted imaging, with a decreased apparent diffusion coefficient, located at the cerebral cortex and subcortical regions in both the temporal and occipital lobe symmetrically (Fig. 1). MRI at 13 days after relapse ~~and~~ revealed very severe whole brain encephalitis (Fig. 2A and B). She was administered plasma exchange at 13–15 days after relapse, which led to improved alertness, decreased seizures, and slow waves on her EEG. Although the relapse remitted in about one month, cerebral laminar necrosis, predominantly in the left hemisphere, progressed at about 3 months (Fig. 2C and D), and subsequent destructive changes and diffuse cerebral atrophy were revealed 57 months after the relapse (Fig. 2E and F). To prevent relapse, immunosuppression was attempted with regular administration of tacrolimus, resulting in worsening of chronic sinusitis, and encephalitis relapsed three times. Subsequently, bimonthly administration of IVIG was started, and no relapse has occurred for 5 years since then. After starting maintenance IVIG, anti-GAD antibody gradually decreased from 93,700 U/mL to 16,000 U/mL over a period of one year.

The patient is 15 years old at the time of this writing and some of her abilities, such as eating, have been improving slowly, but she is still unable to communicate or walk independently. She requires almost total assistance.

3. Discussion

The second episode of encephalitis with extremely high anti-GAD antibody caused diffusely destructive changes to the patient's brain. We presume that super-refractory status epilepticus caused the brain

lesions [4]. The effect of unmeasured autoantibodies neurotropic viruses, such as varicella-zoster virus and JC virus, and metabolic encephalopathies associated with abnormal glucose metabolism cannot be denied.

Typical acute limbic encephalitis shows elevated serum MMP-9/TIMP-1 and CSF cytokines (IL-6, IL-10, and TNF-α) [5,6]. In contrast, these parameters in this case were normal during the acute phase of the relapse. The findings in this case suggest that the blood-brain barrier was not injured [5] and that the brain lesion was not derived from cytokine-induced inflammation. Anti-GAD antibody inhibits GABA synthesis and impairs GABA release from presynaptic terminals of GABAergic interneurons [7,8]. High titers of anti-GAD antibody may lead to functional failure of GABAergic neurons. Encephalitis with antibodies to the $GABA_A$ receptor is associated with insufficient GABA action and shows refractory seizures and status epilepticus [9]. The pathophysiology in this case may be the same as for $GABA_A$ receptor-associated encephalitis.

IVIG is a therapeutic strategy for limbic encephalitis [1]. Regarding SPS, an anti-GAD antibody-associated disease, IVIG is effective for improving clinical symptoms and induces a transient decrease in the antibody [10]. The relapse was extinguished after starting IVIG infusion in the present case. However, it is difficult to assess whether the maintenance therapy with regular IVIG was effective or if the events were part of the natural history of encephalitis. There apparently has been no report on the efficacy of maintenance IVIG treatment on autoimmune neurological disorders. In contrast, to prevent relapse of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), an immune-mediated neurological disorder, maintenance IVIG treatment has been established [11]. As maintenance IVIG for CIDP is once every 2–6 weeks because of its catabolism [11], bimonthly IVIG for our patient may have been effective with a similar mechanism.

This may be the first case of severe and recurrent anti-GAD antibody-associated destructive autoimmune encephalitis after HSCT. Accumulation of observations of similar patients is necessary to establish the treatment plan and prognosis.

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