

**Epileptic spasms after stem cell transplantation for chronic Epstein–Barr virus  
infection**

Short running title: Epileptic spasms after SCT

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Abstract:

Stem cell transplantation has been performed for various diseases, contributing to a markedly improved prognosis in some cases. However, several complications, including posterior reversible encephalopathy syndrome, have been noted. Although posterior reversible encephalopathy syndrome was originally defined as a reversible disease, it has recently become clear that it is not reversible in all patients. Epstein–Barr virus causes a wide spectrum of neurological disorders, including epilepsy. To our knowledge, Epstein-Barr virus has not previously been reported to cause epileptic spasms. Here, we describe a girl with epileptic spasms after posterior reversible encephalopathy syndrome associated with stem cell transplantation for chronic Epstein-Barr virus infection. Although direct correlation was not clarified, this is a rare case that may contribute to our understanding of the neurological complications of stem cell transplantation for chronic Epstein–Barr virus infection.

Key words: Epileptic spasms, Intractable epilepsy, Stem cell transplantation, Epstein-Barr virus infection, Posterior reversible encephalopathy syndrome

## Introduction:

Epileptic spasms are typically observed in patients with West syndrome but are also possible seizure manifestations in patients with other forms of generalized or focal epilepsy [1]. The etiology of such spasms is not completely understood.

Epstein–Barr virus is known to cause various conditions, including neurological disorders. Not only acute primary Epstein–Barr virus infections but also chronic active Epstein–Barr virus infections or reactivated Epstein–Barr virus infections can cause neurological complications. Most patients with neurological complications recover from the acute phase, but some have persistent sequelae [2-4].

Stem cell transplantation is an option for some patients with chronic active Epstein–Barr virus infection that is resistant to chemotherapy. Posterior reversible encephalopathy syndrome is a clinicoradiological entity characterized by headaches, altered mental status, seizures, and visual loss. It is associated predominantly with posterior areas of vasogenic edema in various medical conditions such as hypertensive encephalopathy and immunosuppressive drug use, and it may occur in patients treated with stem cell transplantation [5-7]. Most cases have no neurological sequelae, because

the condition is most often reversible [5-6].

Here, we describe a patient with epileptic spasms after posterior reversible encephalopathy syndrome-like episodes developed subsequent to stem cell transplantation for chronic active Epstein–Barr virus infection. This case suggests that intractable epilepsy may occur as a neurological sequela of posterior reversible encephalopathy syndrome-like episodes despite apparent neuroradiological reversibility, although it does not eliminate the possibility of coincidental occurrence. We believe that this case contributes to an understanding of the neurological complications of stem cell transplantation associated with Epstein–Barr virus infection.

Case report:

A 5-year-old girl was referred to our hospital because of prolonged spiking fever for 3 months. She was born after an uneventful pregnancy. Delivery and the infantile period were normal. Birth weight, length, and head circumference were within normal ranges. Psychomotor development was normal, and she had no seizure before the onset.

She was diagnosed with chronic Epstein–Barr virus infection, by serological

examination and bone marrow aspiration (anti-viral titers in blood: Epstein–Barr virus/viral capsid antibody/IgG; 1:640 to 1:1280 during the first month; viral DNA:  $2.7 \times 10^5$  and  $2.5 \times 10^5$  copies/ml on separate blood examinations, as well as  $6.3 \times 10^5$  and  $1 \times 10^5$  copies/ml on separate bone marrow examinations). Although methylprednisolone, immunoglobulin, etoposide, vincristine, actinomycin D, and cyclophosphamide were administered, her fever persisted and hepatosplenomegaly further enlarged. Thus, she was treated with umbilical cord blood transplantation. Twenty-one days after transplantation, she suddenly developed loss of consciousness with vomiting. She presented with hypertension (130/100 mm Hg) and renal dysfunction (blood urea nitrogen: 41.7 mg/dL, serum creatinine: 0.6 mg/dL). Both immediately improved following hypotensive therapy, which included diuretic drugs. At that time, she was treated with continuous administration of cyclosporine A. Her blood concentration of cyclosporine A was within the normal range. Afterward, cyclosporine A was discontinued and tacrolimus was subsequently administered. Her cerebrospinal fluid was not examined at that time, and Epstein–Barr virus-DNA was not detected in her peripheral blood.

Magnetic resonance imaging (MRI) revealed gray matter with white matter lesions in the left occipital lobe on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1). Her mental status change was prolonged. Additionally, she presented with abulia with mutism and did not speak a word for several weeks. Three months later, she was able to participate in a conversation. Five months later, she could walk with support. Ultimately, she was able to walk without support, 9 months later. Since then, she has displayed anorexic behavior and marked mood fluctuations, while apparent changes in her cognitive status have not been found.

At 1.5 years after onset, she developed loss of consciousness for several minutes. Two months later, the loss of consciousness episodes disappeared, and subsequently, spasms presenting with sudden flexions of the axial and proximal limbs and the head developed. Loss of consciousness episodes, distinct from spasms, were observed several times over 2 months. The intermittent spasms occurred in series, which persisted for up to tens of minutes. Several series occurred per day. During spasms, she maintained consciousness and appeared uncomfortable. Interictal electroencephalograms (EEGs) demonstrated that synchronous spike-wave discharges extended from the bilateral

front-polar to centro-parietal area (Fig. 2). Hypsarrhythmia was not seen. Ictal EEG recorded during spasms showed a diffuse slow-wave transient, followed by voltage attenuation with superimposed fast activity (Fig. 2). A MRI study displayed mild cerebral atrophy, and the left occipital lesion observed at onset had disappeared. Epstein-Barr virus was not detected in her peripheral blood or cerebrospinal fluid, and no other abnormal finding was detected in her blood, urine or cerebrospinal fluid, including chromosomal pattern, thyroid function, blood gases, lactic acid level, pyruvic acid level, amino acid and organic acid levels, acyl carnitine level, and very long chain fatty acid level. Anti-viral titers (Epstein–Barr virus/viral capsid antibody/IgG, IgM, IgA, and Epstein–Barr virus/nuclear antigen antibody) in blood were negative. Ophthalmological examination also revealed no remarkable findings. Although carbamazepine, valproate, clobazam, zonisamide, and phenytoin had been administered alone or in combinations, the spasms were intractable. The combination of zonisamide and phenytoin was partially effective, reducing the number of series from more than 10 to about three per day. Neither adrenocorticotrophic hormone therapy nor immune globulin therapy was performed because her parents disagreed with them. The spasms

persisted and were resistant to oral antiepileptic drugs. Unfortunately, she died suddenly at the age of 9. We were unable to determine the cause of death.

#### Discussion:

In patients with epileptic spasms associated with generalized or focal epilepsy other than West syndrome, the clinical and EEG characteristics of the spasms are the same as those of West syndrome, but interictal EEGs show no hypsarrhythmia [1, 8]. The most frequent ictal EEG pattern consists of a diffuse slow-wave transient or a sharp- and slow-wave complex, followed by voltage attenuation with or without superimposed fast activity occurring in clusters [1]. The generative mechanism of the spasms is not well understood [1]. It has been suggested that subcortical structures play a major role in the generation of spasms, while cortical pathology is also involved in the process [9]. In our patient, although her interictal EEG suggested partial seizures of frontal lobe origin, seizure manifestations and ictal EEG patterns were the same as those of epileptic spasms.

Generally, it has been reported that the clinical and radiological prognosis of



posterior reversible encephalopathy syndrome is good, because of the reversibility of the abnormalities [5, 10]. However, it has also been reported that some patients have irreversible courses, clinically and/or radiologically [11-13]. MRI findings demonstrated reversibility in our patient; nonetheless, her mental status change was prolonged and intractable epilepsy subsequently developed. Acute clinical and radiological features were not inconsistent with posterior reversible encephalopathy syndrome, without delayed recovery. The literature describes many cases of posterior reversible encephalopathy syndrome associated with cyclosporine A [5, 10-12, 14]. In addition to cyclosporine A, neurotoxicity has also been reported associated with Epstein–Barr virus [15]. In our patient, cyclosporine A may have affected the etiology of her posterior reversible encephalopathy syndrome-like symptoms. Häusler et al. reported a 5-year-old girl with Epstein–Barr virus reactivated infection in whom the Epstein–Barr virus antigen index in cerebrospinal fluid was positive [2]. She developed mutism and ataxia and lost the ability to eat, walk, and talk for a few weeks. Her clinical findings improved slowly during 4 months of oral prednisolone treatment. Five months after onset, she started to speak single words again. Normal speech was noted 2 months later. The

prolonged duration of her symptoms resembled that of our patient, suggesting that Epstein–Barr virus may lead to neurological complications over the long term. Although we were not able to evaluate Epstein-Barr virus in the cerebrospinal fluid of our patient in the acute phase, a similar mechanism may have affected the etiology of the symptoms in both of these patients.

The etiology of the epileptic spasms in our patient was unclear. A syndrome of irreversible leukoencephalopathy following pediatric allogeneic bone marrow transplantation has been reported [11]. In the syndrome, white matter was involved during the administration of cyclosporine A; patients presented with persistent neurological deficits and psychiatric changes. One female patient with seizures, whose MRI findings displayed persistent lesions, was described, but her seizure manifestations were not reported. To the best of our knowledge, there has been no report of posterior reversible encephalopathy syndrome or Epstein-Barr virus affecting epileptic spasms. Although there was no evidence for Epstein–Barr virus in the central nervous system of our patient in the acute phase, her prolonged neurological disturbances may have been associated with Epstein–Barr virus infection. Chemotherapy might also cause

neurological decline as a late effect, while epileptic spasms have not been found as late effects of chemotherapy in the literature. The impact of the onset of posterior reversible encephalopathy syndrome complicated with cyclosporine A may also cause neurological sequelae. Further studies are needed to examine the mechanisms of the neurological disorders after posterior reversible encephalopathy syndrome in patients with Epstein–Barr virus infection.

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## Figure legends

### Figure 1.

Axial MRI finding at the onset of the PRES-like episode. FLAIR image (TR: 8002, TE: 97.5) shows hyperintense lesions in the white matter and involving grey matter in the left occipital lobe (arrowheads). These lesions had disappeared 1 year later.

### Figure 2.

Her interictal EEG shows bilateral spike-wave discharges from the frontal region extending to the centro-parietal region (left). Ictal EEG shows a diffuse high-voltage slow wave with superimposed fast activity, followed by attenuation, with  $\theta$  activity predominantly in the frontal lobe region (right). Arrowheads indicate the beginnings of the spasms.

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Figure 1

