Central Diabetes Insipidus in an HHV6 Encephalitis Patient with a Posterior Pituitary Lesion that Developed after Tandem Cord Blood Transplantation

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Abstract

A 60-year-old myelodysplastic syndrome patient underwent tandem cord blood transplantation. The primary cord blood graft was rejected, and human herpesvirus 6 (HHV6) encephalitis developed after engraftment of secondary cord blood. Polyuria and adipsic hypernatremia were observed during treatment of the encephalitis. The patient died of bacteremia caused by methicillin-resistant Streptococcus epidermis. HHV6 infection in the posterior pituitary was confirmed on autopsy, as was infection of the hippocampus, but not of the hypothalamus. This is the first case report of central diabetes insipidus caused by an HHV6 posterior pituitary infection demonstrated on a pathological examination.

Key words: CBT, HHV6 encephalitis, CDI, posterior pituitary


Introduction

Human herpes virus 6 (HHV6) infection is common in childhood, and the virus is known to be a causative agent of exanthema subitum (1). Therefore, most adults have antibodies against the virus in their serum, and HHV6 encephalitis is rarely observed in immunocompetent adults (2). However, in immunocompromised hosts such as patients with hematological malignancies and recipients of solid organ transplantation, HHV6 encephalitis can be a fatal complication, even with intensive treatment using antiviral drugs (3-5). Previous research has shown that a reactivation of HHV6 occurs more frequently in patients undergoing cord blood transplantation (CBT) than in those undergoing other types of hematopoietic stem cell transplantation (HSCT), including bone marrow transplantation and peripheral blood stem cell transplantation (6). CBT is also a significant risk factor for early central nervous system complications following reduced intensity stem cell transplantation (7). As the number of CBTs is increasing, it is likely that more cases of HHV6 infection will occur, including cases with unusual symptoms. However, the pathological significance of HHV6 encephalitis in patients with an endocrine system dysfunction has not yet been evaluated in detail.

In the present report, we investigated the lesion responsible for the polyuria and hypernatremia observed after tandem CBT in an HHV6 encephalitis patient using an immunohistological examination of the autopsy specimens.

Case Report

A 60-year-old woman with myelodysplastic syndrome RAEB-1 in a first complete remission was scheduled for CBT in 2004 (Fig. 1). The conditioning regimen for CBT consisted of fludarabine (30 mg/m²) and cyclophosphamide (500 mg/m²) for four days followed by total body irradiation (TBI) using 4 Gy in two fractions. Cyclosporine and short-term methotrexate were used for graft-versus-host disease (GVHD) prophylaxis. No adverse events were observed, except for extended neutropenia that was controllable with antibiotics. As the neutrophil count was 90/μL on day 32,
bone marrow aspiration and fluorescence in situ hybridization were performed with X centromere and Y heterochromatin probes to confirm chimerism. We diagnosed the patient with graft rejection because the chimerism was completely of the recipient type.

We therefore performed rescue CBT 47 days after the initial CBT with a conditioning regimen of fludarabine (40 mg/m²) for five days and busulfan (4 mg/kg) for two days followed by TBI using 2 Gy in one fraction. The GVHD prophylaxis included cyclosporine alone. A high-grade fever due to a pre-engraftment immune reaction was observed on day six. Adenovirus-negative hemorrhagic cystitis occurred on day 11. As the high-grade fever continued, the patient was treated with 40 mg of prednisolone. Fragmented red cells and elevation of the indirect bilirubin level (>1.8 mg/dL) appeared soon after the administration of prednisolone, indicating the occurrence of thrombotic microangiopathy (TMA). Engraftment of the secondary graft was confirmed on day 15. As cytomegalovirus (CMV) antigenemia was observed, we selected foscarnet for treatment in addition to acyclovir on day 21 to prevent myelosuppression induced by ganciclovir. The acyclovir dose was terminated on day 31 as the high-grade fever continued. The patient’s renal function was normal, and no hypercalcemia was observed (BUN: 13.2 mg/dL, Cr: 0.4 mg/dL, Ca: 9.2 mg/dL) appeared soon after the administration of prednisolone, which had been administered for prophylaxis of herpes virus infection. On day 34, disorientation was observed that led us to suspect HHV6 encephalitis. No abnormalities were detected in the patient’s brain on plain CT. A cerebrospinal fluid examination demonstrated almost normal findings (total cell count = 20/μL, protein =35 mg/dL, sugar =139 mg/dL), although HHV6 viral DNA was detected in the same sample on PCR. Ganciclovir was initiated for the treatment of encephalitis instead of foscarnet because the patient’s blood cell count had recovered completely. However, her consciousness level rapidly deteriorated, and hypernatremia (157 mEq/dL) with high serum osmolality (348 mOsm/kg) appeared at the same time, although fluid replacement had been administered since the onset of polyuria. The patient’s blood sugar level was 164 mg/dL, and her calcium level was 10.2 mg/dL. On day 36, bladder tamponade due to sustained hematuria was observed, and bladder washout was performed. Electroencephalogram obtained on day 41 indicated metabolic encephalopathy. Magnetic resonance imaging (MRI) performed on day 43 revealed increased signals in the bilateral hippocampus and right insula on fluid-attenuated inversion recovery (FLAIR) image that were compatible with a diagnosis of HHV-6 encephalitis (Fig. 2A). In spite of receiving intensive treatment for these complications, the patient died of multiple organ failure caused by bacteremia (methicillin-resistant Streptococcus epidermidis) on day 46 after the second CBT.

An autopsy was performed after informed consent was obtained from the patient’s family. HHV-6 was found to be stained diffusely in the neurons of the hippocampus and the insula on immunohistochemistry using a monoclonal antibody (OHV-1; Fig. 3A) (8). Since several reports of virus-related central diabetes insipidus (CDI) have so far been accumulated, as discussed below, another monoclonal antibody (MAB8535, Chemicon International Inc. Temecula, CA, USA) raised against the HHV6B variant was used to stain the hypothalamus and pituitary gland, and the relationship between the HHV6 infection and adipsic hypernatremia was reevaluated in 2012. HHV6 was detected on immunohistochemistry in the posterior pituitary and a portion of the pars intermedia, which did not show abnormal changes at low magnification of Hematoxylin and Eosin staining (Fig. 3B, C). Although HHV6 was detected reproducibly in the hippocampus with MAB8535, the hypothalamus and anterior pituitary gland were negative for the virus (data not shown).

Discussion

Immunocompromised patients sometimes suffer from life-threatening infections with various pathogens that are often resistant to therapy. With respect to the treatment of hematological malignancies, HHV6 encephalitis is one of the complications with the highest mortality rates, particularly following CBT (6). Why HHV6 encephalitis occurs more often after CBT compared to other types of HSCT is still not well understood.
According to a number of previous reports, HHV6 exhibits high tropism, especially to the hippocampus, and the resulting lesions cause representative manifestations, including short-term memory loss and disorientation. HHV6 ubiquitously infects the central nervous system, in addition to the limbic system, and induces varied symptoms such as seizures, visual disturbances, headaches, nausea, vomiting, impaired consciousness, hemiparesis and tachycardia (7, 9).

Abnormal findings on laboratory examinations, including hypo- and hypernatremia, in patients after HSCT have been reported, in addition to the symptoms described above. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is thought to induce hyponatremia in HHV6 encephalitis patients after HSCT (10, 11). SIADH is also a rare complication of exanthema subitum in patients with severe convulsions (12). As patients with HHV6 encephalitis are, in all probability, under complicated treatment with many different intravenous drugs, including ganciclovir and foscarnet, both the viral infection and the therapeutic drugs may impair the innate homeostasis of electrolyte metabolism (13).

In our case, electroencephalograms demonstrated the findings of metabolic encephalopathy. At that point, we suspected that the patient’s polyuria and hypernatremia were side effects of foscarnet.

However, polyuria and hypernatremia are typical manifestations of CDI in the endocrine system that should not be overlooked. The cause of acquired CDI is classified as either traumatic, inflammatory or neoplastic (14). Apart from HHV-6, CMV can also induce hypernatremia due to CDI in acquired immunodeficiency syndrome patients, and Moses et al. confirmed the existence of CMV in the paraventricular areas of the hypothalamus using immunohistochemistry (15, 16).

Tasaka et al. reported an HHV6 encephalitis case of CDI with hypernatremia that developed after CBT (17). MRI revealed the absence of any high-intensity signals in the posterior pituitary, a finding that is compatible with CDI, although an autopsy was not performed in that case. In our case, it was difficult to conclude whether there were any ap-
parent changes on T1-weighted imaging of the pituitary gland because the resolution of the machine was not sufficient to reveal deterioration in the area (Fig. 2B). In addition, transverse FLAIR imaging did not show any high intensity signals in the area (Fig. 2C). Nevertheless, the existence of HHV6 in the posterior pituitary was clearly documented with a monoclonal antibody specific to HHV6 variant B in the autopsy specimens.

As disorientation and hypernatremia occurred simultaneously in our patient, we suspected that HHV6 had infected both the hippocampus and posterior pituitary almost simultaneously. The posterior pituitary develops from the interbrain. On the other hand, the anterior pituitary originates from epithelial cells of the pouch of Rathke. Therefore, it is natural that HHV6 preferentially infects the neurohypophysis in the pituitary gland. Based on the previous and our present report showing that both the hypothalamus and pituitary gland are targets of viruses, a class of idiopathic CDI may include the development of HHV6 infection, as well as SIADH, after exanthema subitum (12, 13).

Hence, although precise endocrine examinations and measurement of the urine osmolality were not performed, we concluded that HHV6 encephalitis was the main cause of the adipsic hypernatremia that developed following polyuria and consciousness disturbance in the present case.

When both hypo- and hypernatremia with an abnormal urine volume are observed in immunocompromised patients, then HHV6 infection of the hypothalamus and/or pituitary gland should be considered in the differential diagnosis.

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

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References