Prolonged Sinus Tachycardia Caused by Human Herpesvirus 6 (HHV6) Encephalomyelitis after Allogeneic Bone Marrow Transplantation

Mitsutaka Nishimoto, Hirohisa Nakamae, Yoshiki Hayashi, Hideo Koh, Takahiko Nakane, Masahiro Yoshida, Masato Bingo, Hiroshi Okamura, Mizuki Aimoto, Satoru Nanno, Takuro Yoshimura, Akiko Inaba, Kiyoyuki Hagihara, Mika Nakamae, Asao Hirose, Yoshitaka Nakao, Yoshiki Terada and Masayuki Hino

Abstract

A 19-year-old man with Philadelphia chromosome-positive acute lymphoblastic leukemia received an allogeneic hematopoietic cell transplant with unrelated bone marrow. On day 20, the patient developed impaired consciousness and disorientation. Examination of the cerebrospinal fluid showed 2×10^4 copies/mL of HHV6B. HHV6 encephalitis was diagnosed, as had HHV6 myelitis based on symptoms that included lancinating pain/pruritus in the lower limbs and dysuria/dyschezia. Concurrently, he showed sinus tachycardia. Even after clearance of the HHV6 genome from the plasma and CSF was achieved by treatment with foscarinet, sinus tachycardia persisted for another 100 days. We suspected prolonged sinus tachycardia due to dysautonomia caused by HHV6 encephalomyelitis.

Key words: human herpesvirus 6 (HHV6), encephalomyelitis, dysautonomia, sinus tachycardia


Introduction

Human herpesvirus 6 (HHV6), a member of the Beta-herpesvirinae subfamily, causes exanthema subitum in infants. HHV6 remains latent in mononuclear cells, salivary glands and cells of the central nervous system after primary infection, and it can reactivate under conditions of severe immunosuppression such as allogeneic hematopoietic cell transplantation (HCT) (1, 2). HHV6 is thought to be associated with post-transplant acute limbic encephalitis, confusion, seizures and loss of short-term memory (3-6). Additionally, a few reports describe myelitis with HHV6 and the clinical symptoms of autonomic neuropathy. However, to the best of our knowledge, there has been no report of prolonged sinus tachycardia due to dysautonomia caused by HHV6 encephalomyelitis.

Case Report

We report a patient who showed protracted sinus tachycardia due to dysautonomia caused by HHV6 encephalomyelitis, following HCT. A 19-year-old man with Philadelphia chromosome-positive acute lymphoblastic leukemia underwent HCT from a serologically HLA-matched (one mismatched HLA-DR allele), unrelated donor. The conditioning regimen consisted of five fractions of total body irradiation (TBI, 12 Gy) on days -8 to -6, etoposide 15 mg/kg on days -5 to -4, and cyclophosphamide 60 mg/kg on days -3 to -2. Cyclosporin A was given (3 mg/kg/day) from day -1 and short-term methotrexate (10 mg/m^2 on day 1; 7 mg/m^2 on days 3 and 5) was administered for prophylaxis against graft-versus-host disease (GVHD). Oral acyclovir (750 mg/day) was given for herpes simplex virus (HSV) prophylaxis from day -7. The transplanted graft dose was 2.17×10^8 nu-
cleared cells/kg. Neutrophil recovery was achieved on day 21. On day 9, high-grade fever, skin rash and watery diarrhea occurred. After diagnosis of GVHD based on skin biopsy, methylprednisolone (1 mg/kg) was started and thereafter these manifestations gradually improved (Fig. 1).

On day 20, the patient developed acute onset of impaired consciousness and disorientation. Examination of cerebrospinal fluid (CSF) by lumbar puncture showed normal pressure (18 cmH$_2$O), leukocytes (1/mm$^3$), protein (31 mg/dL) and glucose (80 mg/dL). CSF culture revealed no evidence of bacteria or fungi. HHV6B was detected in the CSF (2×10$^4$ copies/mL) and plasma (2×10$^3$ copies/mL), without HSV, cytomegalovirus or varicella-zoster in the CSF on real-time polymerase chain reaction (PCR). Brain magnetic resonance imaging (MRI) four days after the onset showed bilateral, hyperintense lesions of the hippocampus, insula and frontal orbital gyrus on fluid-attenuated inversion recovery (FLAIR) (Fig. 2). HHV6 encephalitis was diagnosed, as was HHV6 myelitis based on symptoms that included lancinating pain/pruritus in the lower limbs and dysuria/dyschezia at onset. Simultaneously, he showed marked hyperhidrosis and sinus tachycardia. On day 28, the 24 hours ambulatory electrocardiography showed decreasing heart rate variability such as coefficient of variance of the RR interval (CVRR) (=17.1% at pre-HCT, =12.5% on day 28) and standard deviation of normal-to-normal RR intervals (SDNN) (=102.3 ms at pre-HCT, =40.4 ms on day 28), which were considered to suggest autonomic nerve dysfunction. We started treatment with foscarnet (180 mg/kg/day) from day 21 and clearance of the viral genome of HHV6 from the plasma and CSF was achieved on days 42 and 35, respectively. Foscarnet was discontinued on day 38 because the disorientation and memory impairment had improved. Although a craniocervical MRI was performed because lancinating pain/pruritus persisted in the lower limbs, no significant findings were noted. Since day 73 he was afebrile, hemoglobin level was stable, and volume status was normal. In addition, cardiac function via echocardiography, pulmonary function, and thyroid function tests were all normal; however, idiopathic sinus tachycardia persisted. We therefore suspected prolonged sinus tachycardia due to dysautonomia caused by HHV6 encephalomyelitis. The lower limb symptoms and sinus tachycardia also spontaneously disappeared on about day 130, after discharge on day 120. Complete molecular remission occurred 1 year and 2 months after HCT.
Discussion

HHV6 is considered to be one of the causative agents for acute post-transplant limbic encephalitis, with confusion, seizures and loss of short-term memory. Several recent reports also describe a possible association between HHV6 and lancinating pain and pruritus in the lower limbs (symptoms resembling calcineurin inhibitor-induced pain syndrome; CIPS-like symptoms) with dysuria/dyschezia (7, 8). In the present case, in addition to impaired consciousness and CIPS-like symptoms, concurrent autonomic neuropathy manifested as sinus tachycardia and hyperhidrosis. Heart rate is controlled by autonomic balance and hormones. The medulla oblongata and hypothalamus control involuntary functions such as breathing, heart rate and blood pressure. In general, the causes of sinus tachycardia after HCT include anemia, fever, dehydration, bronchial obstruction, heart failure and/or hyperthyroidism. However, these were not present in the current case. Since there were no significant abnormalities detected in the medulla oblongata and hypothalamus on MRI, sinus tachycardia was considered to be a dysautonomic sign of myelitis. Previous reports attributed the following symptoms to autonomic neuropathy: fixed tachycardia, postural hypotension and paralytic ileus, following either herpes simplex virus (9) or Coxsackie B virus infection (10). In both cases, autonomic function recovered after more than 6 months, indicating that dysautonomia can continue despite resolution of the virus infection. In the present case, sinus tachycardia continued for another 100 days after onset, in spite of disappearance of the HHV6 genome from the CSF on real-time PCR. Sinus tachycardia might thus be caused not only by an inflammatory response to a viral infection, but also by post-inflammatory degeneration of nerve cells.

In conclusion, we should bear in mind that HHV6 encephalomyelitis can cause prolonged sinus tachycardia, as a symptom of dysautonomia, even if the other features have disappeared. More data from similar cases will be necessary to elucidate the mechanism of dysautonomia in HHV6 encephalomyelitis.

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

References