Human herpesvirus 6 is associated with status epilepticus and hyponatremia after umbilical cord blood transplantation

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Status epilepticus after allogeneic hematopoietic cell transplantation (alloHCT) is rare. The authors report a case involving a 65-year-old man with nonconvulsive status epilepticus 34 days after umbilical cord blood transplantation for chronic lymphocytic leukemia. Cerebrospinal fluid and serum were positive for human herpesvirus 6 (HHV6). Magnetic resonance imaging of the brain showed symmetric T2 hyperintensity bilaterally in the mesial temporal lobes, and T2 hyperintensities and restricted diffusion of bilateral putamina. Despite aggressive anticonvulsive therapy, his seizures only abated with initiation of ganciclovir therapy. The patient completed six weeks of combination antiviral therapy (ganciclovir and foscarnet). His cognitive function gradually improved and, after prolonged rehabilitation, the patient was discharged home with residual intermittent memory loss but otherwise functional. HHV6 should be considered in the differential diagnosis of nonconvulsive status epilepticus after alloHCT, especially in patients with hyponatremia. Empirical antiviral therapy targeting HHV6 should be administered to these patients.

Key Words: Human herpesvirus 6; Hyponatremia; Immunocompromised host; Status epilepticus; Umbilical cord blood transplantation

CASE PRESENTATION

A 59-year-old man was diagnosed with chronic lymphocytic leukemia (CLL) in 2007 and managed with various chemotherapy drugs (fludarabine, alemtuzumab, bendamustine, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab). However, the patient required umbilical cord blood transplantation following a reduced intensity conditioning regimen (cyclophosphamide 50 mg/kg on day -6, fludarabine 40 mg/m² daily from days -6 through -2 and total body irradiation 200 cGy on day -1) for treatment of resistant CLL in February 2013. Graft-versus-host disease prophylaxis comprised sirolimus 4 mg daily and mycophenolate mofetil (1500 mg twice per day from days -3 through +30). Cytomegalovirus immunoglobulin (Ig) G and herpes simplex virus IgG were positive, whereas Epstein-Barr virus (EBV) IgG was negative. Infection prophylaxis based on internal hospital guidelines included levofloxacin (250 mg daily), voriconazole (200 mg twice per day for possible invasive fungal infection due to lung nodules before allogeneic hematopoietic cell transplantation [alloHCT]), high-dose acyclovir (800 mg five times per day), and

L'herpèsvirus humain type 6 s'associe à un état de mal épileptique et à une hyponatrémie après la greffe de sang de cordon

L'état de mal épileptique est rare après une greffe de cellules souches hématopoïétiques allogéniques (GCSallo). Les auteurs rendent compte du cas d'un homme de 65 ans présentant un état de mal épileptique non convulsif 34 jours après avoir subi une greffe de sang de cordon pour soigner une leucémie lymphocytaire chronique. Le liquide céphalo-rachidien et le sérum étaient positifs à l'herpèsvirus humain type 6 (HHV6). L'imagerie par résonance magnétique du cerveau a révélé un signal hyperintense symétrique et bilatéral des lobes temporaux médiaux en T2, ainsi que des signaux hyperintenses en T2 et une diffusion bilatérale restreinte du putamen. Malgré un traitement énergique aux anticonvulsivants, les convulsions n'ont diminué qu'après l'amorce d'un traitement au ganciclovir. Le patient a été mis sous bithérapie antivirale (ganciclovir et foscarnet) pendant six semaines. Sa fonction cognitive s'est améliorée graduellement et, après une réadaptation prolongée, il a obtenu son congé à domicile. Il présentait une perte de mémoire résiduelle intermittente, mais était autrement fonctionnel. Il faut envisager un HHV6 dans le diagnostic différentiel de l'état de mal épileptique non convulsif après une GCSallo, particulièrement chez les patients présentant une hyponatrémie. Il faut administrer une anti-virothérapie empirique qui cible l'HHV6 chez ces patients.

sulfamethoxazole/trimethoprim (800/160 mg twice per day on Mondays and Tuesdays). The first month after alloHCT was uneventful. Neutrophil engraftment occurred on day +26 and the patient achieved complete remission of CLL (bone marrow biopsy showed donor chimerism of 94% and no evidence of CLL). The patient was immunocompromised in both cellular and humoral immune systems (CD4⁺ cell count 0.02×10⁹/L, CD8⁺ cell count 0.1×10⁹/L, CD4:CD8 ratio 0.24, CD16⁺56⁺ cell count 0.16×10⁹/L and IgG level of 427 g/L).

The patient was found unconscious and was readmitted to the hospital on day +34. His vital signs, including temperature, were normal. The patient was in nonconvulsive status epilepticus state based on electroencephalography findings and was electively intubated for airway protection. Complete blood count, creatinine, potassium, magnesium, calcium and liver function tests were within normal limits. His sodium level (126 mmol/L) was moderately low. Serum sirolimus was at therapeutic level. There was no evidence for transplantation-associated thrombotic microangiopathy or graft-versus-host disease. Urgent computed tomography and magnetic resonance imaging

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Figure 1) Axial fluid-attenuated inversion recovery-weighted sequence demonstrating hyperintense signal along bilateral putamina (A) and medial temporal lobes (B) (arrows)

(MRI) of the brain were normal for his age. Cerebrospinal fluid (CSF) analysis showed five white blood cells (comprised of lymphocytes and monocytes), no malignant cells, normal protein level (360 g/L) and normal glucose level (4.628 mmol/L). CSF evaluation, including bacterial and fungal cultures, Gram stain, India ink and viral studies (cytomegalovirus, EBV, John Cunningham virus, herpes simplex virus and herpes zoster virus polymerase chain reactions) were all negative.

Despite aggressive antiepileptic therapy (phenytoin 250 mg twice per day and levetiracetam 2 g twice per day), electroencephalography continued to show a pattern of acute repetitive seizures in the right and left frontotemporal regions. High-dose midazolam drip (10 mg/h) was added for seizure control. A repeat MRI on hospital day 5 showed a symmetric hyperintensity bilaterally at the basal ganglia and subtle hyperintensities in bilateral mesial temporal lobes (Figure 1). CSF test results for human herpesvirus 6 (HHV6) were available and positive

(379,300 copies/mL) on day +41. The concurrent serum sample was also positive for HHV6 (8000 copies/mL). Ganciclovir (5 mg/kg intravenous twice per day) was started due to no improvement in his clinical condition, seizure activity and the evolving MRI findings. Seizure activity was no longer detectable, and the patient had become alert and was extubated on day +43. A long hospitalization ensued, which was complicated by deconditioning and multiple reintubations for hypercapnea and respiratory muscle weakness. He completed six weeks of ganciclovir therapy (5 mg/kg twice per day). Foscarnet was added for positive isolation of HHV6 from bronchoalveolar lavage. His cognitive function gradually improved with prolonged rehabilitation. He is now at home with residual intermittent memory loss but otherwise functional.

DISCUSSION

Alteration in consciousness and seizure after alloHCT can be caused by posterior reversible encephalopathy syndrome, immunosuppressive drug toxicities, fludarabine toxicity, transplantation-associated thrombotic microangiopathy or central nervous system infections, including HHV6 (1-3). HHV6, a beta herpes virus, infects 95% of the population by two years of age and is the cause of exanthema subitum (4). After acute infection, HHV6 remains in a latent form in CD34⁺ cells, monocytes and macrophages. On average, 50% of alloHCT recipients – possibly more frequent in umbilical cord blood transplant patients – will reactivate HHV6 in the first month of alloHCT (range two to eight weeks) (5-10). Although the direct causative effect has never been confirmed, HHV6 reactivation is associated with several clinical syndromes, including febrile illness, delayed engraftment, pneumonitis and encephalitis after alloHCT (4,7,9-12). Among these syndromes, there has been accumulating evidence supporting a causal association between HHV6 and encephalitis (4). Moreover, autopsy findings are also suggestive of a pathogenic role for HHV6 (13).

Diagnosis of HHV6-associated encephalitis can be complicated. Patients can present with acute mental status changes, cognitive dysfunction, delirium, hallucinations, anterograde amnesia and seizure (12,14-17). Hyponatremia, resulting from the syndrome of inappropriate antidiuretic hormone secretion or sodium wasting in urine, can be observed (3,12,18). Normal or mildly elevated protein levels and mild pleocytosis are typical CSF findings (5,12). Brain MRI has a role in narrowing the differential diagnosis to limbic encephalitis. It shows T2 hyperintense signal abnormality of one or both hippocampi and variably involving adjacent medial temporal lobe structures of the limbic system, including amygdalae and parahippocampal gyri (limbic encephalitis) (12,14). In addition to HHV6 encephalitis, the differential diagnosis of these findings includes other infectious causes of encephalitis such as herpes zoster virus, varicella zoster virus, cytomegalovirus, EBV or neurosyphilis, autoimmune disorders, conditioning regimen toxicity and paraneoplastic syndromes (19). In vitro and limited clinical data support the antiviral effect of foscarnet and ganciclovir against HHV6 (4,20). The recommended duration of therapy is at least three weeks. Although survival rates appear to be improving, HHV6 encephalitis remains associated with mortality and morbidity (long-term sequelae, such as neuropsychological disorders, are not uncommon) (6,21,22).

HHV6 should be considered in patients with nonconvulsive status epilepticus presenting with sudden unconsciousness after alloHCT. No other apparent cause of seizure and the presence of hyponatremia increase the likelihood of HHV6 infection. Patients should be treated with HHV6-effective empirical antiviral therapy.

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