Fatal herpesvirus-6 encephalitis in a recipient of a T-cell-depleted peripheral blood stem cell transplant from a 3-loci mismatched related donor

ENRICO TIACCI, MARIO LUPPI,* PATRIZIA BAROZZI,* GRAZIELLA GURDO, ANTONIO TABILIO, STELVIO BALLANTI, GIUSEPPE TORELLI,* FRANCO AVERSA
Department of Clinical and Experimental Medicine, Hematology and Immunology Section, University of Perugia; *Department of Medical Sciences, Section of Hematology, University of Modena, Italy

Abstract

Human herpesvirus-6 (HHV-6), like all the other herpesviruses, remains latent in host cells after primary infection but can be reactivated in immunocompromised patients causing fever, skin rash, bone marrow (BM) suppression, pneumonitis, sinusitis and meningoencephalitis. We describe the case of a man with chronic myelogenous leukemia who developed encephalitis associated with acute graft-versus-host disease two months after a T-cell-depleted mismatched peripheral blood stem cell transplant. Magnetic resonance images of the brain revealed multiple bilateral foci of signal abnormality. HHV-6 was the only pathogen detected in cerebrospinal fluid by PCR. Treatment with both ganciclovir and foscarnet was unsuccessful and the patient gradually deteriorated and died. Other cases of HHV-6 encephalitis after bone marrow transplantation are reviewed.

Key words: T-cell-depleted mismatched transplant, HHV-6 encephalitis, GvHD

In the setting of bone marrow transplantation (BMT), infection by the opportunistic pathogen human herpesvirus-6 (HHV-6) is associated with fever, cutaneous rash, sinusitis, pneumonitis and delayed engraftment or marrow suppression; it has also been connected to a single fatal case of meningoencephalitis. However, only a few other cases of HHV-6 encephalitis after BMT have been reported. We describe another case of fatal HHV-6 encephalitis following a mismatched stem cell transplantation. The clinical features of the previously reported cases are reviewed.

Case report

A 47-year old man with blastic crisis of chronic myelogenous leukemia received a T-cell-depleted mismatched peripheral blood cell (PBSC) transplant from his haploidentical 3-loci mismatched daughter, in May 1998. Pre-transplant conditioning included 8 Gy total body irradiation in a single fraction, fludarabine (200 mg/m² over 5 days), thiotepa (10 mg/kg on one day) and rabbit antithymocyte globulin (25 mg/kg over 5 days). Granulocyte colony-stimulating factor (G-CSF) mobilized PBSCs were depleted of T- and B-cells and enriched for CD34+ cells using the Isolox 300i device (Baxter, Irvine, CA, USA). The final inoculum consisted of 1.1 × 10^6 CD34+ cells/kg and 3.4 × 10^4 CD3+ cells/kg recipient b.w. No post-transplant immunosuppressive treatment was given. Anticytomegalovirus (CMV) prophylaxis consisted of ganciclovir (10 mg/kg/day) during the conditioning followed by foscarnet (90 mg/kg/day). The absolute neutrophil count reached 0.5 × 10^9/L on day +11, platelet count reached 25 × 10^9/L on day +39. On day +6, the patient developed signs of hepatic veno-occlusive disease, which resolved with supportive therapy. Acute graft-versus-host disease (a GvHD) was diagnosed on day +35. Initially confined to the skin it extended to the liver on day +67 and to the gut on day +71 despite therapy with methotrexate, cyclosporine and prednisone. Pneumonitis developed on day +62; bronchoalveolar lavage was negative for common bacterial, fungal and viral pathogens (not including HHV-6 or respiratory syncytial virus). On day +67 the patient developed fever, severe mental confusion, visual and auditory hallucinations and 10-20 sec seizures characterized by psychomotor agitation and tonic-clonic jerks of the head and arms. Neurologic examination and CT scan were normal. Magnetic resonance imaging (MRI) on day +68 was negative. Analysis of the cerebrospinal fluid (CSF), obtained via lumbar puncture on day +70, revealed clear CSF, with normal protein and glucose content, negative for common bacterial and fungal pathogens, CMV and herpes simplex virus (HSV). Empirical therapy was acyclovir (30 mg/kg, i.v.), from day +69 to +76. As CMV antigenemia was detected on day +76 (200 positive cells/slide), acyclovir was replaced by ganciclovir (10 mg/kg) from day +77 to +90, which reduced CMV antigenemia to 6 positive cell/slide on day +86. The neurologic signs and mental status of the patient remained unchanged. A second MRI on day +80 showed bilateral foci of signal abnormality in the grey matter i.e. in the medial temporal lobes, the uncus and anterior part of the parahippocampal gyrus (Figure 1). Contrast scanning with gadolinium showed neither lesions nor meningeal enhancement. The patient’s platelet and
Disease/Transportation | Onset (Time after transplantation) | Neurological symptoms | CT | HHV | EEG | Lipid | Other clinical symptoms | Outcome | Diagnosis of HHV6 encephalitis | Ref.
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---
HDL allo-identical | 5 months* | Loss of short term memory| Delusional ideation | Normal | Normal | WBC 3/mL | GIVD | Fatal (1 day after onset of symptoms) | HHV6 late antigen in autopsy brain | (3)
CHU allo-related | 24 days | Confusion | NO | Demyelination/edema in hippocampus | NO | NO | Elevated theta waves in temporal lobes | Foscarnet (180 mg/kg/day) | HHV6 DNA in serum | (5)
B-OHL autologous | 56 days | Muscle tremor | increased tone | Normal | Normal | WBC 5.6 m/L | Protein 5.59 g/L | Pneumonia | Recovery (ganciclovir) | HHV6 DNA in CSF | (6)
T-ALL allo-identical | 15 months | Alopecia, lethargia, seizures | Pancytopenia | Normal | MD | WBC 13/mL | Protein 10.1 g/dL | Fever, rash, pneumonia, seizures | Recovery (ganciclovir) | HHV6 DNA in CSF | (7)
CHU allo-unrelated | 20 days | Generalized seizures, visual hallucinations | Normal | Focal sharply wavelike abnormalities | MD | WBC absent | Protein 0.26 g/L | GIVD | Fatal (2 weeks after onset of ganciclovir plus foscarnet) | HHV6 DNA in CSF | (8)
APL allo-unrelated (12th transplant) | 8 months | Cerebellar syndrome, transient cerebellar syndrome, paresis, ataxia | Cerebellar atrophy | Cerebellar atrophy | Increased theta waves in temporal lobes | WBC 24/mL | Protein 1.3 g/L | Fever, (immunosuppression, immune effusions) | Recovery (ganciclovir) | HHV6 DNA in CSF, PML | (9)
CHU allo-unrelated | 26 days | Loss of short term memory | Edema with hemorrhages in atrophic temporal lobes | Normal | Focal theta waves | WBC 34/mL | Glucose 3.5 m/L | Protein normal | Recovery (ganciclovir) | HHV6 DNA in CSF | (10)
T-ALL allo-identical | 22 days | Confusion, excitement, uncontrollable muscle movements | Normal | NO | Mild diffuse abnormality | WBC 2/mL | GIVD | Recovery (ganciclovir) | Death of organ failure | HHV6 DNA in CSF | (11)
T-ALL allo-unrelated | 10 days | Somnolence, speech abnormalities, increased reflexes | Normal | Normal | Mild diffuse abnormality | WBC absent | Glucose normal | Protein normal | Recovery (ganciclovir) | Death of organ failure | HHV6 DNA in CSF, PML | (11)
T-ALL allo-unrelated | 18 days | Headache, seizures, coma | Subarachnoid bleeding | Normal | Severe diffuse abnormality | WBC 6/mL | Albumin 1.2 g/mL | GIVD | Fatal (7 days after the onset of ganciclovir) | HHV6 DNA in CSF, PML | (11)
T-ALL allo-unrelated | 64 days | Confusion, speech abnormalities, loss of muscle coordination | Low attenuation changes | Old hemorrhage | NO | WBC 4/mL | Albumin 941 mg/dL | Recovery (ganciclovir) | HHV6 DNA in CSF, PML | (11)
T-ALL allo-unrelated | 75 days | Confusion, somnolence, vomiting | Normal | NO | Paraneoplastic pathologic episodes | WBC 4/mL | Albumin 965 mg/dL | GIVD | Recovery (ganciclovir) | HHV6 DNA in CSF, PML | (11)
CHU allo-haplo-identical | 67 days | Confusion, ataxia, hallucinations, cerebellar incoordination, vomiting | Normal | Normal | WBC absent | Glucose normal | Protein normal | Fever, GIVD, skin rash, and liver abnormalities | Recovery (ganciclovir) | HHV6 DNA in CSF, serum | This report

*The authors suggest that an earlier episode of meningocencephalitis, occurring about 15 weeks after transplantation, was due to an undiagnosed chronic HHV-6 infection of the brain (3). The diagnosis in this patient was meningocencephalitis. Abbreviations: Hodgkin's disease (HD); B-cell non-Hodgkin's lymphoma (B-NHL); Chronic myelogenous leukemia (CML); Respiratory syncytial virus (RSV).

white blood cell counts decreased significantly from $133\times10^9/L$ on day +67 to $5\times10^9/L$ on day +88; and from $7.33\times10^9/L$ on day +80 to $2\times10^9/L$ on day +90, respectively. Foscarnet (180 mg/kg/day) was added to ganciclovir from day +80, but after a transient improvement in mental status, the patient deteriorated with progressive stupor and coma, until death on day +90.

PCR analysis and hybridization of the amplified product with an internal oligonucleotide probe was used as described for viral detection in crude extracts of serum and CSF samples collected on days +67 and +70 respectively. Herpesvirus (HSV-1 and 2, VZV, EBV, HHV-8, CMV, HHV-7), adenovirus, and polyomaviruses (JC and BK) DNA were not detected. HHV-6 DNA (ZHV 14 region) was identified in both samples providing the only data for diagnosis, as the CSF biochemistry was not informative and a CT scan and MRI were negative in this early phase of the disease. Cells from the donor were not available for PCR analysis to determine whether HHV-6 had been transmitted from the donor.
Discussion

Few cases of HHV-6 encephalitis have been reported in bone marrow transplant patients and detailed case histories are available for only two plus our present case (Table 1). These data show HHV-6 encephalitis has occurred in autologous and allogeneic (related and unrelated) BM and peripheral blood stem cell transplantation (Table 1). Remarkably 4 of the 8 patients for whom a precise diagnosis was reported were affected by CMV. HHV-6 encephalitis may occur at any time after transplantation. The temporal lobe and hippocampus, as demonstrated either by MRI findings or by the direct immunolocalization of the virus in affected tissues were involved in five cases (4 CML and 1 HD). Of the other eight cases clinical evidence of encephalitis was associated in 1 with cerebellar atrophy, in 2 with hemorrhage and in five with no neuro-radiological abnormalities. All these latter five patients responded well to anti-viral therapy. From the clinical point of view seizures and increased tone are frequently present. This observation may be consistent with HHV-6 localization in the hippocampus.

In our patient as in 8 others, HHV-6 infection was associated with GvHD. The link between HHV-6 infection and GvHD is still under debate with three studies confirming the association and two others not. In vitro studies have clearly demonstrated HHV-6 sensitivity to ganciclovir, and/or foscarnet. The death of 4/11 treated patients despite this anti-viral therapy suggests that in immunosuppressed patients HHV-6 may be resistant to all known anti-virals. New anti-viral agents such as cidofovir may offer hope for these patients.

In conclusion, after primary infection HHV-6 can remain latent in host cells and the grey and white matter of the human brain are common reservoirs. In immunocompromised patients the virus may be reactivated and HHV-6 infection should be carefully considered in the differential diagnosis of causes of encephalitis occurring in the setting of BMT. PCR analysis of CSF for HHV-6 DNA is recommended for early diagnosis. This test is the only diagnostic tool available when biochemical analyses of CSF, CT scan and MRI findings are not informative.

Contributions and Acknowledgments

ET, GG and SB were responsible for the clinical care of the patient. FA was responsible for the clinical care of the patient and critical review of the paper. ML, PB and GT performed the molecular analysis and commented on the draft. AT was responsible for stem cell mobilization and wrote up the report. All the authors read and approved the final version of the paper.

The criteria for the order of names were involvement in patient care, laboratory research, and writing and reviewing the case report. The order of the names was decided on the basis of each individual contribution to the above criteria.

The authors would like to thank Dr. G.A. Boyd and Dr. R. Lupi for their help and comments in writing this paper.

Funding

This work was supported by grants from the Italian Association for Cancer Research (AIRC) to ML and AT.

Disclosures

Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received May 18, 1999; accepted September 21, 1999.

References


Haematologica vol. 85(1):January 2000


