**Haematologica** 2000; 85:94-97
*case of the month*

**Hematology and Medicine**

# 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 herpes viruses, 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.[1-4] However, only a few other cases of HHV-6 encephalitis after BMT have been reported.[5-11] 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 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/m$^2$ 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 Isolex 300i device (Baxter, Irvine, CA, USA). The final inoculum consisted of $11.4\times10^6$ CD34$^+$ cells/kg and $3.4\times10^4$ 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 $0.5\times10^9$/L on day +11, platelet count reached $25\times10^9$/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

*Correspondence: Dr. Antonio Tabilio, Department of Internal and Experimental Medicine, Hematology and Clinical Immunology Section, University of Perugia, Policlinico, Monteluce, 06100 Perugia, Italy*
*Phone: international +39-075-5783990 – Fax: international +39-075-5783691 - E-mail: medemat@unipg.it*

**Table 1. Updated review of the reported cases of HHV-6 encephalitis after BMT.**

| *Disease/ transplantation* | *Onset (Time after transplantation)* | *Neurological symptoms* | *CT* | *MRI* | *EEG* | *Liquor* | *Other clinical symptoms* | *Outcome* | *Diagnosis of HHV-6 encephalitis* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|
| HD/ allo-identical | 5 months* | Loss of short term memory disorientation somnolence incontinence | Normal | Normal | ND | WBC 3/mL Glucose 53 mg/dL Protein 94 mg/dL | GVHD | Fatal (7 days after onset of symptoms) | HHV-6 late antigen in autopsy brain (white-frontal-matter and grey matter-hippocampus) | (3) |
| CML/ allo-related | 24 days | Confusion | ND | Demyelynation/ edema in hippocampus | ND | ND | High fever | No response (foscarnet) | HHV-6 DNA in serum | (5) |
| B-NHL/ autologous | 56 days | Muscle tremor confusion/coma increased tone | Normal | Normal | Focal temporal lobe activity | WBC 5/$m^3$ Glucose 4.68 mmol/L Protein 0.59 g/L | Pneumonia | Recovery (ganciclovir) | HHV-6 DNA in CSF | (6) |
| T-ALL/ allo-identical | 15 months | Ataxia, lethargia, seizures | Pansinusitis | Normal | ND | WBC 53/$m^3$ Glucose normal Protein 101 mg/dL | Fever rash pneumonia (RSV) BM suppression | Recovery (foscarnet) | HHV-6 DNA in CSF Shell vial in CSF | (7) |
| CML/ allo-unrelated | 20 days | Generalized seizures, visual hallucinations | Normal | Foci of signal cortical abnormality (grey matter -frontal, temporo-parietal, occipital lobes) | Periodic sharp waves with temporal predominance | WBC absent Glucose 63 mg/dL Protein 0.26 g/L | GVHD skin and gut | Fatal (2 weeks after onset -ganciclovir plus foscarnet-) | HHV-6 DNA in CSF | (8) |
| AML/ allo-unrelated (2nd transplant) | 8 months | Cerebellar syndrome, transient cranial nerve palsies, amnesia, frontal alterations§ | Cerebellar atrophy | Cerebellar atrophy | Increased theta waves in temporal lobes | WBC 24/$m^3$ Protein 1.5g/L | Fever, skin rash, GVHD, BM suppression, serous effusions | Recovery (foscarnet plus ganciclovir) | HHV-6 DNA in CSF/PBMCs /BM | (9) |
| CML/ allo-unrelated | 26 days | Loss of short term memory, personality change, tonic-clonic seizures, coma | Normal | Edema with hemorrhage in temporal lobes (+32 days after transplantation) | Burst of sharp waves | WBC 8/µL Glucose normal Protein normal | Fever, GVHD | Fatal (immuno-globulins) | HHV-6 DNA in CSF | (10) |
| ?/ allo-identical | 22 days | Confusion, excitement, uncontrollable muscle movements | Normal | ND | Mild diffuse abnormality | WBC 2/mL | GVHD | Recovery (ganciclovir) Death of bleeding | HHV-6 DNA in CSF | (11) |
| ?/ allo-unrelated | 10 days | Somnolence, speech abnormalities, increased reflexes | Normal | Normal | Mild diffuse abnormality | WBC absent Albumin 538 mg/L | GVHD | Improvement (foscarnet) Death of organ failure | HHV-6 DNA in CSF/PBMCs | (11) |
| ?/ allo-unrelated | 18 days | Headache, seizures, coma, increased reflexes | Subarachnoid bleeding | Normal | Severe diffuse abnormality | WBC 6/mL Albumin 12,880 mg/L | GVHD | Fatal (7 days after the onset –foscarnet) | HHV-6 DNA in CSF/ autoptic brain | (11) |
| ?/ allo-unrelated | 64 days | Confusion speech abnormalities, loss of muscle ccordination | Low attenuated changes | Old hemorrhage | ND | WBC 49/mL Albumin 941 mg/L | | Recovery (foscarnet) | HHV-6 DNA in CSF/PBMCs | (11) |
| ?/ allo-unrelated | 75 days | Confusion, somnolence, vomiting | Normal | ND | Pronounced pathologic episodes | WBC 4/mL Albumin 965 mg/L | GVHD | Recovery (foscarnet) | HHV-6 DNA in CSF/PBMCs | (11) |
| CML/ allo-haplo-identical | 67 days | Confusion, visual hallucinations, psicomothor agitation, seizures | Normal | Normal (+68 days after transplantation) Foci of signal cortical abnormality (grey matter temporal lobes) (+80 days after transplantation) | ND | WBC absent Glucose normal Protein normal | Fever GVHD skin and liver Pneumonia Cytopenia | Fatal (13 days after the onset -ganciclovir plus foscarnet-) | HHV-6 DNA in CSF/ serum | This report |

**The authors suggest that an earlier episode of meningoencephalitis, 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 meningoencephalitis. 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[12] for viral detection in crude extracts of serum and CSF samples[13] 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 (ZVH14 region)[12] 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.

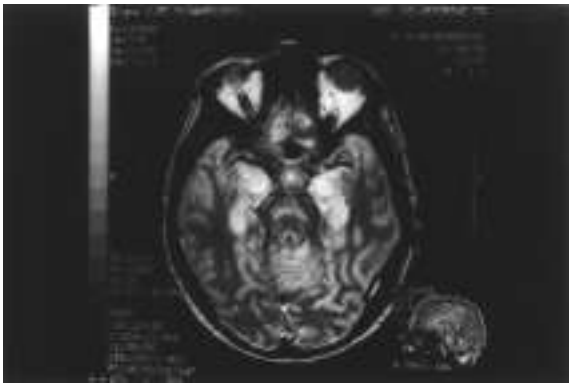

**Figure 1. Proton density MRI shows bilateral hyperintensity of the grey matter involving the uncus and the anterior part of the para-hippocampal gyrus.**

## Discussion

Few cases of HHV-6 encephalitis have been reported in bone marrow transplant patients and detailed cases histories are available for only twelve 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 CML. 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[1,14,15] and two others not.[16,17]

*In vitro* studies have clearly demonstrated HHV-6 sensitivity to ganciclovir, and/or foscarnet.[4] 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.[18] 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 revision 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 up 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

1. Cone RW, Hackman RC, Huang ML, et al. Human herpesvirus 6 in lung tissue from patients with pneumonitis after bone marrow transplantation. N Engl J Med 1993; 329:156-61.
2. Drobyski WR, Dunne WM, Burd EM, et al. Human herpesvirus-6 (HHV-6) infection in allogeneic bone marrow transplant recipients: evidence of a marrow-suppressive role for HHV-6 in vivo. J Infect Dis 1993; 167:735-9.
3. Drobyski WR, Knox KK, Majewski D, Carrigan DR. Brief report: fatal encephalitis due to variant B human herpesvirus-6 infection in a bone marrow-transplant recipient. N Engl J Med 1994; 330:1356-60.
4. Singh N, Carrigan DR. Human herpesvirus-6 in transplantation: an emerging pathogen. Ann Intern Med 1996; 124:1065-71.
5. Chan PK, Peiris JS, Yuen KY, et al. Human herpesvirus-6 and human herpesvirus-7 infections in bone marrow transplant recipients. J Med Virol 1997; 53:295-305.
6. Mookerjee BP, Vogelsang G. Human herpes virus-6 encephalitis after bone marrow transplantation: successful treatment with ganciclovir. Bone Marrow Transplant 1997; 20:905-6.
7. Cole PD, Stiles J, Boulad F, et al. Successful treatment of human herpesvirus 6 encephalitis in a bone marrow transplant recipient. Clin Infect Dis 1998; 27:653-4.
8. Bosi A, Zazzi M, Amantini A, et al. Fatal herpesvirus 6 encephalitis after unrelated bone marrow transplant. Bone Marrow Transplant 1998; 22:285-8.
9. Rieux C, Gautheret-Dejean A, Challine-Lehmann D, Kirch C, Agut H, Vernant JP. Human herpesvirus-6 meningoencephalitis in a recipient of an unrelated allogeneic bone marrow transplantation. Transplan-

tation 1998; 65:1408-11.
10. Tsujimura H, Iseki T, Date Y, et al. Human herpesvirus-6 encephalitis after bone marrow transplantation: magnetic resonance imaging could identify the involved sites of encephalitis. Eur J Haematol 1998; 61:284-5.
11. Wang FZ, Linde A, Hägglund H, Testa M, Locasciulli A, Ljungman P. Human herpesvirus 6 DNA in cerebrospinal fluid specimens from allogeneic bone marrow transplant patients: does it have clinical significance? Clin Infect Dis 1999; 28:562-8.
12. Torelli G, Marasca R, Luppi M, et al. Human herpesvirus-6 in human lymphomas: identification of specific sequences in Hodgkin's lymphomas by polymerase chain reaction. Blood 1991; 77:2251-8.
13. Secchiero P, Carrigan DR, Asano Y, et al. Detection of human herpesvirus 6 in plasma of children with primary infection and immunosuppressed patients by polymerase chain reaction. J Infect Dis 1995; 171:273-80.
14. Wilborn F, Brinkmann V, Schmidt CA, Neipel F, Gelderblom H, Siegert W. Herpesvirus type 6 in patients undergoing bone marrow transplantation: serologic features and detection by polymerase chain reaction. Blood 1994; 83:3052-8.
15. Appleton AL, Sviland L, Peiris JS, et al. Human herpes virus-6 infection in marrow graft recipients: role in pathogenesis of graft-versus-host disease. Newcastle upon Tyne Bone Marrow Transport Group. Bone Marrow Transplant 1995; 16:777-82.
16. Kadakia MP, Rybka WB, Stewart JA, et al. Human herpesvirus 6: infection and disease following autologous and allogeneic bone marrow transplantation. Blood 1996; 87:5341-54.
17. Wang FZ, Dahl H, Linde A, Brytting M, Ehrnst A, Ljungman P. Lymphotropic herpesvirus in allogeneic bone marrow transplantation. Blood 1996; 88:3615-20.
18. Luppi M, Barozzi P, Maiorana A, Marasca R, Torelli G. Human herpesvirus 6 infection in normal human brain tissue. J Infect Dis 1994; 169:943-4.