Human Herpesvirus 6 in Hematological Malignancies

Masao Ogata

Pathogenetic roles of human herpesvirus (HHV)-6 in lymphoproliferative diseases have been of continued interest. Many molecular studies have tried to establish a pathogenic role for HHV-6 in lymphoid malignancies. However, whether HHV-6 plays a role in these pathologies remains unclear, as positive polymerase chain reaction results for HHV-6 in those studies may reflect latent infection or reactivation rather than presence of HHV-6 in neoplastic cells. A small number of studies have investigated HHV-6 antigen expression in pathologic specimens. As a result, the lack of HHV-6 antigen expression in neoplastic cells argues against any major pathogenic role of HHV-6. The role of HHV-6 in childhood acute lymphoblastic leukemia (ALL) has also been of interest but remains controversial, with 2 studies documenting higher levels of HHV-6 antibody in ALL patients, and another 2 large-scale studies finding no significant differences in HHV-6 seroprevalences between ALL patients and controls. Alternatively, HHV-6 is increasingly recognized as an important opportunistic pathogen. HHV-6 reactivation is common among recipients of allogeneic stem cell transplantation (SCT), and is linked to various clinical manifestations. In particular, HHV-6 encephalitis appears to be significant, life-threatening complication. Most HHV-6 encephalitis develops in patients receiving transplant from an unrelated donor, particularly cord blood, typically around the time of engraftment. Symptoms are characterized by short-term memory loss and seizures. Magnetic resonance imaging typically shows limbic encephalitis. Prognosis for HHV-6 encephalitis is poor, but appropriate prophylactic measures have not been established. Establishment of preventive strategies against HHV-6 encephalitis represents an important challenge for physicians involved with SCT. ([J Clin Exp Hematopathol 49(2): 57-67, 2009])

Keywords: human herpesvirus 6, pathogenesis, lymphoproliferative disease, stem cell transplantation, encephalitis

INTRODUCTION

Human herpesvirus (HHV)-6 was isolated in 1986 from the peripheral blood mononuclear cells of 6 patients affected with various lymphoproliferative disorders. This enveloped virion contains about 160 kb of linear double-stranded DNA, and is now classified as a member of the Roseolovirus genus in the Betaherpesvirinae subfamily of human herpesviruses. Type A and type B variants of HHV-6 have been identified, exhibiting different epidemiological and biological characteristics and disease associations. HHV-6B is highly prevalent in the human population, infecting virtually all children within the first few years of life. Like the other herpesviruses, HHV-6 is capable of persisting in the host after primary infection. Under conditions of immunosuppression, HHV-6 can reactivate from latency.

Both HHV-6A and -6B replicate most efficiently in vitro in CD 4+ T cells. The host tissue range of HHV-6 in vivo is broad and includes peripheral blood mononuclear cells, salivary glands, brain tissue, liver cells, lymph node, and endothelial cells. Candidate sites for latency are salivary glands, brain tissue, lymph nodes, and early bone marrow progenitor cells. Primary HHV-6 infection commonly causes exanthem subitum. Associations between HHV-6 infection (reactivation) and development of many diseases have been investigated, including multiple sclerosis, mesial temporal lobe epilepsy, encephalitis in immunocompetent patients, chronic fatigue syndrome, drug-induced hypersensitivity syndrome, Kikuchi’s disease, hematological malignancies, and complications following stem cell or organ transplantation.

To date, huge numbers of investigations have examined the roles of HHV-6 in the development of hematological malignancies (as an oncogenic agent), and the significance of HHV-6 infection during the course of treatment (as an opportunistic pathogen). However, careful interpretation of published data is required. The present work offers an overview of experimental and clinical observations supporting the involvement of HHV-6 in hematological malignancies.
Ogata M

**HHV-6 AS A CAUSATIVE AGENT IN HEMATOLOGICAL MALIGNANCIES**

Two human herpesvirus, Epstein-Barr virus (EBV) and HHV-8, are well-known as oncogenic agents. As HHV-6 strains were first isolated from patients with lymphoproliferative disorders,² pathogenetic roles for HHV-6 in the development of lymphoproliferative diseases have been a matter of continuous interest. A possible pathogenetic role for HHV-6 in lymphoproliferative diseases was first suggested by the ability of its DNA to transform established NIH 3T3 cells and human epidermal keratinocytes in vitro.⁴⁻⁶ Kashanchi et al.⁷ reported that HHV-6 genes encode transactivation proteins, one of which has been shown to possess transformative properties. However, transforming events after HHV-6 infection have not been confirmed in vitro, and no definitive association between HHV-6 and canceration have been provided in vivo. HHV-6 has therefore not yet been defined as an oncogenic pathogen.

**Hodgkin lymphoma**

Both genetic and environmental factors have been implicated in the pathogenesis of Hodgkin lymphoma.⁵ EBV is present in the neoplastic cells of 20–40% of patients with Hodgkin lymphoma,⁶ and has been shown to represent an oncogenic pathogen. HHV-6 DNA shown by PCR have been reported (Table 1).²⁸ FINDINGS suggest an association among EBV, HHV-6 infection facilitates growth of ATL cells.⁴⁵ HHV-6 has been effectively propagated in a T-cell line derived from a patient with ATL.⁶⁵ Persistent HHV-6 infection facilitates growth of ATL cells.⁹ These in vitro findings suggest a possible pathogenetic role for HHV-6 in ATL. Table 3 shows the results of HHV-6 DNA quantification in specimens from patients with ATL and other lymphoid malignancies using real-time PCR in

expression in lymphoid tissue.⁹⁻¹¹ These investigations found a lack of HHV-6 antigen expression in neoplastic cells and limited expression in Reed-Sternberg cells,⁹⁻¹¹ arguing against any major pathogenic role of the virus in lymphomagenesis.

**Non-Hodgkin lymphoma (NHL)**

1) **Angioimmunoblastic T-cell lymphoma (AITL)**

Clinical presentations including high-fever, polyclonal gammapathy, or polymorphic histological appearances raise the possibility of a role for infectious agents in the pathogenesis of AITL. To date, EBV,²⁷,²⁸ HHV-6, and HHV-8 have been reported to show associations with AITL. HHV-6 is found in 22–62.5% of AITL cases by PCR (Table 2).²⁸,³¹,³⁴,³⁸ However, neither EBV²⁷ nor HHV-6¹¹ has been found in malignant cells by histopathological analysis, suggesting a lack of direct causative roles in the development of AITL. Zhou et al.³⁸ reported simultaneous infection with both EBV and HHV-6 B only in specimens showing histological patterns I or II, and a tendency towards an inverse correlation between EBV and HHV-6 B viral loads. These findings suggest an association among EBV, HHV-6 B, and histological progression of AITL.

2) **Non-Hodgkin lymphoma (other than AITL)**

The HHV-6 genome is detected in 22.2–62.1% of cases of NHL by PCR (Table 2).²⁸,³¹,³⁴,⁴⁰,⁴³ Similar to what was outlined in the section on Hodgkin lymphoma and AITL, these results do not necessarily indicate presence of HHV-6 in neoplastic cells. Negative results for the detection of HHV-6 DNA by Southern blot analysis²⁷ and a lack of HHV-6 antigen expression in neoplastic cells¹¹,⁴⁴ suggest that HHV-6 DNA shown by PCR was derived from latent infection.

3) **Adult T-cell leukemia (ATL)**

HHV-6 can infect ATL cell lines.⁴⁵ HHV-6 has been effectively propagated in a T-cell line derived from a patient with ATL.⁴⁵ Persistent HHV-6 infection facilitates growth of ATL cells.⁹ These in vitro findings suggest a possible pathogenetic role for HHV-6 in ATL. Table 3 shows the results of HHV-6 DNA quantification in specimens from patients with ATL and other lymphoid malignancies using real-time PCR in

expression in lymphoid tissue.⁹⁻¹¹ These investigations found a lack of HHV-6 antigen expression in neoplastic cells and limited expression in Reed-Sternberg cells,⁹⁻¹¹ arguing against any major pathogenic role of the virus in lymphomagenesis.

**The possibility remains that the virus infection is associated with the clinicopathological features in patients with Hodgkin lymphoma. Several studies have shown that the frequency of detecting HHV-6 DNA is higher in patients with nodular sclerosis (NS) subtype than with other subtypes.²⁷,³⁴,³⁶ Lacroix et al.²⁷ reported that patients with the NS subtype of Hodgkin lymphoma who were positive for HHV-6 in lymph nodes were younger than those showing negative results. They also showed that the prognosis in these patients was very good, and HHV-6 positivity can be considered as a predictor of good outcomes.**
our institute. A relative high level of HHV-6 DNA was occasionally observed in specimens from ATL patients. However, whether high levels of HHV-6 DNA in pathogenic specimens reflect the presence of HHV-6 in ATL cells or HHV-6 reactivation from a latent state due to altered immune status remains uncertain.

**Acute leukemia**

Various hypotheses have been proposed concerning the involvement of infectious mechanisms in the development of acute leukemia. The role of HHV-6 in acute leukemia, particularly childhood acute lymphoblastic leukemia (ALL), has been a matter of continuous interest, but remains controversial. Ablashi et al. found high levels of HHV-6 antibodies in a small group of children with ALL compared with normal subjects, but a sequential study showed no significant differences in antibody titers between 50 patients with ALL and 50 sex-age matched blood donors. The largest serological case-control investigation showed a slight but significant association between HHV-6 antibody titers and acute myeloid leukemia (AML) patients, while no significant association was found between HHV-6 antibodies and ALL. In 2002, however, Salonen et al. found the presence of IgM antibodies in 40% of children with leukemia and high avidity of IgG compared with controls. The results again raise the possibility of a role for HHV-6 infection in childhood ALL. Bogdanovic et al. analyzed HHV-6 and EBV DNA in Guthrie cards from children, but did not detect the DNA of these viruses in any samples from 54 subjects who later developed leukemia or 47 matched controls. These findings indicate that childhood ALL is unlikely to be associated with in utero infection by HHV-6.

HHV-6 DNA was detected by PCR and in situ hybridization in the bone marrow cells of children with T-ALL in 1991. However, Barozzi et al. found that the presence of

### Table 1. HHV-6 infection in Hodgkin lymphoma

<table>
<thead>
<tr>
<th>References</th>
<th>Detection method</th>
<th>Sample</th>
<th>No. of subjects</th>
<th>Positive rate for HHV-6</th>
<th>HHV-6 variant</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torelli et al. (1991)</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 25</td>
<td>12 %</td>
<td>ND</td>
<td>All cases positive for HHV-6 (n=3) belonged to the NS/LD subtype.</td>
</tr>
<tr>
<td>Sumiyoshi et al. (1993)</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 14</td>
<td>64.3%</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls : 56</td>
<td>98.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern blot</td>
<td>PCR</td>
<td>LN</td>
<td>14</td>
<td>0 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trovato et al. (1994)</td>
<td>PCR</td>
<td>LN</td>
<td>15</td>
<td>7 %</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Ish L.</td>
<td>PCR</td>
<td>LN</td>
<td>15</td>
<td>0 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ish L.</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 52</td>
<td>73 %</td>
<td>2A&amp;EB/36B</td>
<td></td>
</tr>
<tr>
<td>Valente et al. (1996)</td>
<td>PCR</td>
<td>LN</td>
<td>Controls : 19</td>
<td>68.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ISH</td>
<td>LN</td>
<td>57</td>
<td>82.4%</td>
<td></td>
<td>No Hodgkin or Reed-Sternberg cells were positive in any case.</td>
</tr>
<tr>
<td>Southern blot</td>
<td>IHC</td>
<td>LN</td>
<td>NI</td>
<td>0 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt et al. (2000)</td>
<td>PCR</td>
<td>LN</td>
<td>88</td>
<td>13 %</td>
<td>8A/3B</td>
<td></td>
</tr>
<tr>
<td>Shitamizu et al. (2001)</td>
<td>PCR</td>
<td>LN</td>
<td>47</td>
<td>0 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collot et al. (2003)</td>
<td>qPCR</td>
<td>LN</td>
<td>37</td>
<td>35.1%</td>
<td>1A/12B</td>
<td>All Hodgkin lymphoma patients infected with HHV-6 presented with the NS subtype.</td>
</tr>
<tr>
<td>Hernández-Loa et al. (2004)</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 20</td>
<td>40 %</td>
<td>ND</td>
<td>HHV-6 genome was observed most often in the NS group (83.6%). Among NS patients, HHV-6/EBV patients were older than HHV-6/EBV patients.</td>
</tr>
<tr>
<td>Luduix et al. (2007)</td>
<td>qPCR</td>
<td>LN</td>
<td>86</td>
<td>79.1%</td>
<td>5A/6B</td>
<td></td>
</tr>
</tbody>
</table>

HHV-6, human herpesvirus 6; ISH, in situ hybridization; IHC, immunohistochemistry; qPCR, quantitative polymerase chain reaction; LN, lymph node; NI, not informative; ND, not determined; NS, nodular sclerosis; LD, lymphocyte depletion; EBV, Epstein-Barr virus

non-Hodgkin lymphoma; benign lymphadenitis; pediatric Hodgkin lymphoma; normal donor spleen lymphocytes and reactive lymphadenitis
### Table 2. HHV-6 infection in non-Hodgkin lymphoma

<table>
<thead>
<tr>
<th>References</th>
<th>Detection method</th>
<th>Sample</th>
<th>No. of subjects</th>
<th>Positive rate for HHV-6</th>
<th>HHV-6 variant</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AITL, AILD, or IBL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumiyoshi et al. (1993)28</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 8</td>
<td>62.5%</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Sumiyoshi et al. (1993)28</td>
<td>PCR</td>
<td>LN</td>
<td>Controls*: 56</td>
<td>98.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luppi et al. (1993)19</td>
<td>PCR</td>
<td>LN</td>
<td>8</td>
<td>0%</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Luppi et al. (1998)11</td>
<td>PCR</td>
<td>LN</td>
<td>12</td>
<td>58.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohyashiki et al. (1999)40</td>
<td>PCR-ELISA</td>
<td>PB &amp; LN</td>
<td>Patients : 3</td>
<td>100%</td>
<td>3B</td>
<td>Number of HHV-6 genomes in patients was high.</td>
</tr>
<tr>
<td>Ohyashiki et al. (1999)40</td>
<td>PCR-ELISA</td>
<td>LN</td>
<td>5</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collot et al. (2002)14</td>
<td>qPCR</td>
<td>LN</td>
<td>5</td>
<td>20.0%</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td>Visalovic et al. (2004)41</td>
<td>PCR</td>
<td>LN</td>
<td>18</td>
<td>22.2%</td>
<td>NF</td>
<td></td>
</tr>
<tr>
<td>Zhou et al. (2007)18</td>
<td>qPCR</td>
<td>LN</td>
<td>42</td>
<td>45.2%</td>
<td></td>
<td>Only HHV-6B was examined.</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erkek et al. (2001)55</td>
<td>PCR</td>
<td>TT</td>
<td>92</td>
<td>1.1%</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>HIV-associated NHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filleti et al. (1995)43</td>
<td>PCR</td>
<td>TT</td>
<td>27</td>
<td>44.4%</td>
<td>2A/1B/6A &amp; B</td>
<td></td>
</tr>
<tr>
<td>T-cell lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumiyoshi et al. (1993)28</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 33</td>
<td>57.6%</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Sumiyoshi et al. (1993)28</td>
<td>PCR</td>
<td>LN</td>
<td>Controls*: 56</td>
<td>98.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohyashiki et al. (1999)40</td>
<td>PCR-ELISA</td>
<td>PB &amp; LN</td>
<td>6</td>
<td>50%</td>
<td>2B/1 unclassified</td>
<td></td>
</tr>
<tr>
<td>Collot et al. (2002)14</td>
<td>qPCR</td>
<td>LN</td>
<td>8</td>
<td>25.0%</td>
<td>2B</td>
<td></td>
</tr>
<tr>
<td>B-cell lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumiyoshi et al. (1993)28</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 29</td>
<td>62.1%</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Ohyashiki et al. (1999)40</td>
<td>PCR-ELISA</td>
<td>PB &amp; LN</td>
<td>10</td>
<td>20%</td>
<td>1B/1 uncategorized</td>
<td></td>
</tr>
<tr>
<td>Collot et al. (2002)14</td>
<td>qPCR</td>
<td>LN</td>
<td>36</td>
<td>22.2%</td>
<td>1A/7B</td>
<td>The HHV-6 viral load was low.</td>
</tr>
<tr>
<td>Any type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Razzzuate et al. (1996)44</td>
<td>PCR</td>
<td>LN</td>
<td>6</td>
<td>100%</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Luppi et al. (1998)11</td>
<td>IHC</td>
<td>LN</td>
<td>15</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernández-Lou et al. (2004)35</td>
<td>PCR</td>
<td>LN</td>
<td>Patients : 63</td>
<td>27%</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

*benign lymphadenitis; 5 peripheral blood leukocyte from healthy volunteers; *other than AITL or AILD; 6normal donor spleen lymphocytes and reactive lymphadenitis

AITL, angioimmunoblastic T cell lymphoma; AILD, angioimmunoblastic lymphadenopathy with dysproteinemia; IBL, immunoblastic lymphadenopathy; HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma; IHC, immunohistochemistry; qPCR, quantitative polymerase chain reaction; LN, lymph node; PB, peripheral blood; TT, tumor tissue; ND, not determined
HHV-6 DNA is not frequent in patients with ALL compared to normal subjects. Seror et al. recently analyzed HHV-6 DNA copy number by real-time PCR in bone marrow and peripheral blood from 36 children with ALL at diagnosis and during complete remission. Positive rates were 13.9% in leukemia samples and 34.1% in complete remission samples. Viral load was lower at diagnosis than at complete remission. Based on these findings, they concluded that HHV-6 may be unable to infect leukemia cells and reactivation may be observed during complete remission.

**HHV-6 chromosomal integration and development of hematological malignancies**

The unique form of HHV-6 persistence is characterized by integration of the viral DNA sequences into chromosomes. The incidence of chromosomal integration (CI) for HHV-6 is about 2% in the population of the United Kingdom. Whether integrated HHV-6 is capable of replication or is associated with disease remains unclear. Daibata et al. demonstrated integration of HHV-6 genome in a Burkitt’s lymphoma cell line. Furthermore, they showed chromosomal transmission of HHV-6 DNA in ALL. These findings suggest the possibility of an association between chromosomally integrated HHV-6 and development of hematological malignancies. On the other hand, Hobacek et al. recently reported the prevalence of HHV-6 CI among children with ALL or AML. Among 339 patients, 5 patients (1.5%) were confirmed with HHV-6 CI. They concluded that the prevalence of HHV-6 CI in childhood leukemia does not differ from that published for other patients or healthy populations.

**HHV-6 AS AN INFECTIOUS AGENT IN HEMATOLOGICAL MALIGNANCIES**

As described above, many studies have tried to establish links between HHV-6 infections and development of hematological malignancies, with discordant results. However, HHV-6 is increasingly being recognized as an opportunistic pathogen rather than a causal pathogen among clinical hematologists. Particularly in the field of stem cell transplantation (SCT), HHV-6 is now considered as an important pathogen linked to life-threatening encephalitis. On the other hand, the clinical syndrome of HHV-6 reactivation in patients with hematological malignancies who do not receive allogeneic SCT is not well defined.

**HHV-6 reactivation in allogeneic SCT**

Overall, HHV-6 has been shown to reactivate in 40–50% of patients undergoing SCT. Most HHV-6 infections are due to reactivation of HHV-6 type B. HHV-6 appears most frequently around 2–6 weeks after SCT, and onset of HHV-6 reactivation is concentrated around 0–9 days after neutrophil engraftment. HHV-6 can reactivate to high levels within a week, but duration of HHV-6 reactivation is usually short (Fig. 1). Younger age, underlying diseases, sex mismatch, HLA mismatch, steroid treatment, unrelated transplants, cord blood transplantation, and low anti-HHV-6 IgG titer before transplantation have been identified as risk factors associated with HHV-6 reactivation. Steroid administration and cord blood transplantation are also associated with higher-

### Table 3. Quantification of HHV-6 DNA in patients with adult T-cell leukemia and other lymphoid malignancies (data from Oita University)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Sample</th>
<th>No. of subjects</th>
<th>No. of positive cases</th>
<th>Positive rate for HHV-6</th>
<th>HHV-6 DNA among positive samples (copies/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATL LN</td>
<td>6</td>
<td>2</td>
<td>33.3%</td>
<td>180.7</td>
<td>38.6</td>
</tr>
<tr>
<td>ATL PB</td>
<td>11</td>
<td>5</td>
<td>45.5%</td>
<td>2933.3</td>
<td>107.7</td>
</tr>
<tr>
<td>T-cell lymphoma</td>
<td>LN</td>
<td>2</td>
<td>0 %</td>
<td>6.3</td>
<td>4.5</td>
</tr>
<tr>
<td>B-cell lymphoma</td>
<td>LN</td>
<td>12</td>
<td>16.7%</td>
<td>7.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>LN</td>
<td>2</td>
<td>100 %</td>
<td>121.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Reactive lymphadenitis</td>
<td>LN</td>
<td>2</td>
<td>100 %</td>
<td>6.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

ATL, adult T-cell leukemia; LN, lymph node; PB, peripheral blood
Fig. 1. Kinetics of human herpesvirus (HHV)-6 DNA loads in plasma among patients who had received allogeneic stem cell transplantation and showed positive results for HHV-6 DNA by polymerase chain reaction. Taken from [Reference 65].

Table 4. Clinical manifestations potentially associated with human herpesvirus 6 in stem cell transplantation

<table>
<thead>
<tr>
<th>Observed disease</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>60, 71</td>
</tr>
<tr>
<td>Rash</td>
<td>61, 71-74</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>63, 64, 72, 75</td>
</tr>
<tr>
<td>Delayed platelet engraftment</td>
<td>60, 63, 65, 68, 76</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>60, 64, 76</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>63, 65, 66, 68, 69, 77-87</td>
</tr>
<tr>
<td>Lung disease</td>
<td>64, 88-90</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>64, 91</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>63</td>
</tr>
</tbody>
</table>

GVHD, graft-versus-host disease

level HHV-6 reactivation. Cord blood transplant recipients thus display a higher risk of HHV-6 infection in terms of both incidence and level.

To date, many studies have shown the significance of HHV-6 as a pathogen for various complications after SCT (Table 4) [60, 61, 63-66, 68, 69, 71-91]. Due to the significant incidence and poor prognosis, HHV-6 encephalitis is thought to represent the most important complication associated with HHV-6.

HHV-6 encephalitis in SCT

Diagnostic criteria for HHV-6 encephalitis have yet to be established, but HHV-6 encephalitis is generally defined as: the presence of neurological symptoms; positive PCR results for HHV-6 in cerebrospinal fluid; and the absence of other identified etiologies of encephalitis. Retrospective surveillance by a Japanese group has reported an incidence of 0.98%. Five epidemiological studies that monitored HHV-6 viral load have shown associations between HHV-6 reactivation and development of central nervous system (CNS) dysfunction. Incidences ranged from 3.6% to 8.0%. Vu et al. reported an incidence of 11.6% in patients receiving alemtuzumab-supported conditioning. The high incidence of HHV-6 encephalitis among patients receiving cord blood transplant is becoming a major concern in Japan.

A retrospective analysis of 23 patients with HHV-6 encephalitis in Japan revealed that most cases of HHV-6 encephalitis developed in patients who had received transplants from alternative donors including unrelated donor or cord blood, and more than half had received steroid treatment, with onset of encephalitis beginning at a median of day 22 after SCT. Symptoms included coma/impaired consciousness (91%), loss of short-term memory (73%) and seizures (70%). Magnetic resonance imaging (MRI) revealed abnormal findings within the temporal lobes in 73% of patients. Zerr reviewed 48 recipients with HHV-6 encephalitis who had previously been described in the literature and found similar results, with 84% of patients receiving mismatched related or unrelated transplantation. Onset of encephalitis began on a median of day 24. Symptoms were characterized by short-term memory loss, depressed consciousness, confusion, disorientation and seizure. MRI showed abnormal findings in 70% of patients, most commonly within the medial temporal lobes (limbic encephalitis). Fig. 2 shows MRI findings in a patient who developed HHV-6 encephalitis after SCT. The limbic system seems to be an exclusive target of HHV-6 encephalitis. Using immunohistochemical methods, several investigators have found that HHV-6 displays tropism for hippocampal astrocytes in recipients who developed encephalitis. The pathogenic mechanisms underlying HHV-6 encephalitis, however, have not been well defined. HHV-6 encephalitis develops concomitant to peak HHV-6 DNA levels in plasma, and higher levels of HHV-6 DNA in peripheral blood are associated with the development of CNS dysfunction. The findings suggest direct destruction of the CNS by HHV-6. However, not all patients with high HHV-6 load in peripheral blood develop CNS dysfunction, suggesting that additional factors are required for progression to encephalopathy. A recent report showed higher levels of plasma interleukin-6 before HHV-6 reactivation are associated with progression to HHV-6 encephalitis.

The prognosis of HHV-6 encephalitis is poor. A retrospective study in Japan showed sequelae in about half of patients despite receiving antiviral treatment. Zerr reported that 19 of 44 patients with HHV-6 encephalitis who had been previously described in the literature were left with neurological compromise or died of encephalitis. These observations indicate that the efficacy of antiviral treatments appears insufficient once HHV-6 encephalitis has developed.
HHV-6 infection in patients with hematological malignancies who do not receive allogeneic SCT

A few case reports have described patients who developed HHV-6-associated complications, including thrombotic microangiopathy after autologous SCT9,10 or HHV-6 encephalitis in patients with ATL.94 However, few epidemiological studies have examined the incidence or significance of HHV-6 reactivation in patients with hematological malignancies who do not receive allogeneic SCT. Yoshikawa et al.61 found no cases of HHV-6 viremia among patients receiving autologous SCT. Chemaly et al.95 reported 11 of 37 patients with leukemia displayed positive HHV-6 DNA in whole blood specimens. However, that study specifically examined severely immunosuppressed patients with leukemia at risk of mold infection, and the results may therefore not be applicable to the general leukemia population. The clinical significance of HHV-6 reactivation in each hematological malignancy or each therapy should be clarified in the future.

CONCLUSIONS AND FUTURE INVESTIGATIONS

Many studies have tried to establish links between HHV-6 infection and development of hematological malignancies, with discordant results. Interpretation of positive PCR results for HHV-6 in pathologic specimens is complicated by the ubiquitous nature of HHV-6 and its abilities to remain in a latent state, reactivate under altered immune status, and integrate into host chromosomal DNA. Examinations of HHV-6 antigen expression in tumor tissue would improve the interpretation of results. To date, however, relatively few studies9-13 have focused on HHV-6 expression on neoplastic cells, and no evidence has been found for the involvement of HHV-6 in neoplastic cells. More large-scale studies using histopathological methods might identify a pathogenic role for HHV-6 in a subset of lymphoproliferative disorders.

Despite the lack of HHV-6 infection in neoplastic cells, HHV-6 infection may be associated with the clinical course for NS-type Hodgkin lymphoma16 and with pathological features for AITL.38 These findings suggest HHV-6 infection of normal lymphocytes in tumor tissue affects the histological progression or prognosis in a subset of lymphomas. The ability of HHV-6 to modulate the production of and response to cytokines and chemokines6,96,97 may be associated with such behaviors. Further in-depth examinations may identify complementary roles for HHV-6 in the pathogenesis or progression of lymphoma.

HHV-6 is now recognized as a well-known pathogen in the field of allogeneic SCT. About half of SCT recipients experience HHV-6 reactivation. The most important, life-threatening complication associated with HHV-6 reactivation appears to be encephalitis. The pathogenic roles of HHV-6 have not been well clarified but may include direct or immune-mediated destruction of the CNS. Further exploration of the pathogenic roles of HHV-6 in the development of encephalitis may contribute to the development of effective preventative methods and the improvement of prognosis. The efficacy of anti-viral therapy against developed HHV-6 encephalitis appears insufficient, and the establishment of strategies for appropriate pre-emptive or prophylactic methods against HHV-6 encephalitis represents an important challenge for SCT physicians.

REFERENCES


Fig. 2. T2-weighted fluid-attenuated inversion recovery imaging in a patient who developed human herpesvirus 6 encephalitis. Arrows indicate signal hyperintensities in the region of the limbic system. Taken from [Reference 65].

HHV-6 in hematological malignancies
Ogata M

3 Ablishi DV, Balachandran N, Josephs SF, Hung CL, Krueger GR, et al.: Genomic polymorphism, growth properties, and immuno-


8 Campadelli-Fiume G, Miranda P, Menotti L: Human herpesvi-


10 Jarrett RF, Clark DA, Josephs SF, Onions DE: Detection of hu-


12 Donati D, Akhyani N, Fogdell-Hahn A, Carmelli C, Cassiani-


18 Pamaik M, Komaroff AL, Conley E, Ojo-Amazie EA, Peter JB: Prevalence of IgM antibodies to human herpesvirus 6 early anti-


21 Krueger GR, Hueter ML, Rojo J, Romero M, Cruz-Ortiz H: Human herpesviruses HHV-4 (EBV) and HHV-6 in Hodgkin’s and Kikuchi’s diseases and their relation to proliferation and apo-


23 Razzaque A, Williams O, Wang J, Rhim JS: Neoplastic transfor-
mation of immortalized human epidermal keratinocytes by two HHV-6 DNA clones. Virology 195: 113-120, 1993

24 Kashanchi F, Araujo J, Doniger J, Muralidhar S, Hoch R, et al.: Human herpesvirus 6 (HHV-6) ORF-1 transactivation gene ex-


33 Shiramizu B, Chang CW, Cairo MS: Absence of human herpes-

34 Collot S, Petit B, Bordesoule D, Alain S, Toutai M, et al.: Real-
time PCR for quantification of human herpesvirus 6 DNA from
52 Bogdanovic G, Jernberg AG, Pritfakis P, Grillner L, Gustafsson B: Human herpes virus 6 or Epstein-Barr virus were not detected in Guthrie cards from children who later developed leukaemia. Br J Cancer 91: 913–915, 2004
Ogata M

701–705, 2002
90 Buchbinder S, Elmagacli AH, Schafer UW, Roggendorf M: Human herpesvirus 6 is an important pathogen in infectious lung
disease after allogeneic bone marrow transplantation. Bone Marrow Transplant 26: 639–644, 2000

HHV-6 in hematological malignancies