Human herpesviruses-6, -7 and -8 in organ transplant recipients

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Summary  The newer herpesviruses are being increasingly recognized as significant opportunistic pathogens in organ transplant recipients. Published data support the role of human herpesvirus-6 as a potential cause of encephalitis and bone marrow suppression in transplant setting. An association of human herpesvirus-6 with fungal infections and cytomegalovirus infection has also been documented. Human herpesvirus-7 also appears to be an immunomodulatory agent and may facilitate the pathogenicity of cytomegalovirus. Unlike human herpesviruses -6 and -7, human herpesvirus -8 is not ubiquitous; its seroprevalence exhibits wide geographic variation. Human herpesvirus-8 has been causally associated with post-transplant Kaposi's sarcoma. The complete spectrum of pathogenicity and ultimately the effective prophylaxis and management of these viruses has yet to be fully elucidated.

Keywords  transplantation, herpesviruses, human herpesvirus-6, human herpesvirus-7, human herpesvirus-8, Kaposi's sarcoma herpesvirus


INTRODUCTION

Since 1986, three novel herpesviruses, human herpesviruses-6, -7 and -8, have been discovered. It is now known that HHV-8 is causally associated with post-transplant Kaposi's sarcoma. However, controversy abounds regarding the precise role of HHV-6 and HHV-7 in the post-transplant setting. The overview herein attempts to define the clinical relevance of these herpesviruses as pathogens in transplant recipients.

HUMAN HERPESVIRUS-6

Biological features

HHV-6 is a $\beta$-herpesvirus belonging to the genus Roseolovirus. Phylogenetically, HHV-6 is most closely related to HHV-7 and cytomegalovirus (CMV); nucleotide sequencing has shown 66% DNA sequence homology between CMV and HHV-6 [1]. HHV-6 is an enveloped virion with an icosahedral nucleocapsid of 162 capsomeres that contains large double-stranded DNA [2,3]. The extracellular and cytoplasmic nucleocapsids are surrounded by a thick tegument that is a distinctive morphologic feature of HHV-6 virions as compared to the other herpesviruses.

Pathogenesis

The primary target cells for HHV-6 are CD4+ T-lymphocytes, a characteristic that it shares with HIV [7,8]. The propensity to preferentially infect CD4+ T-cells differentiates HHV-6 from other DNA viruses. Unlike with HIV, however, the CD4 molecule is not the membrane receptor for HHV-6 [9]. HHV-6 and HIV can coinfect and simultaneously replicate within the same CD4+ T-cells. Indeed, HHV-6 has been proposed as a cofactor in the acceleration of HIV infection [7,10]. HHV-6 can upregulate CD4 expression and induce CD4 receptors on CD8+ T-cells and natural killer (NK) cells, thus making these cells susceptible to infection with HIV [11]. Although HHV-6 most efficiently replicates in CD4+ T-cells, its cellular host range also includes CD8+ T-lymphocytes,
NK cells, macrophages, megakaryocytes, glial cells, and epithelial cells [12].

Besides directly infecting cells, HHV-6 is a powerful inducer of cytokines, e.g. tumor necrosis factor-α, interferon-γ, and interleukin-1β [13,14]. It has been proposed that the immunomodulatory and marrow suppressive effects of HHV-6 may be partly due to the production of these cytokines [15].

Epidemiology

Seroepidemiologic studies have shown that primary infection due to HHV-6 is usually acquired during the first year of life, saliva being the most likely mode of transmission. As with other herpesviruses, HHV-6 persists in the host in a latent form; seroprevalence in healthy adults exceeds 90% [16,17]. Although the precise site of latency in the body is not known, the epithelial cells of the bronchial and salivary glands represent the most likely sites of latency [18]. Neurons and glial cells are also believed to be sites where HHV-6 may be latent.

Primary HHV-6 infection has been shown to be the cause of roseola (exanthem subitum), a febrile illness of early childhood [19]. In immunocompetent adults, the virus has been associated with an Epstein–Barr virus (EBV)-like mononucleosis syndrome, autoimmune disorders (e.g. Sjögren’s disease), non-Hodgkin’s and Hodgkin’s lymphomas, necrotizing lymphadenitis, and focal encephalitis resembling herpes simplex virus infection [12,20,21]. A pathogenic role of HHV-6 in multiple sclerosis and other demyelinating disorders has also been proposed.

HHV-6 infection has been documented in 38–55% of renal, 31% of liver and 57% of lung transplant recipients [22–28]. It should, however, be realized that most of these studies utilized PCR-based assays for the diagnosis of HHV-6, and these may have overestimated the incidence of HHV-6 infection. In bone marrow transplant recipients, HHV-6 infection has been documented in 38–60% of patients [29–31].

Risk factors for HHV-6 in the post-transplant setting have yet to be fully defined. In a study in liver transplant recipients, patients with hepatocellular carcinoma were more likely to develop HHV-6 viremia than patients without it [32]. It was proposed that the association between HHV-6 and hepatocellular carcinoma is probably mediated through hepatotropic viruses, e.g. hepatitis B and C viruses. HBV and HHV-6 encode gene products that can transactivate the long-terminal repeat of viruses, e.g. HIV. Whether the hepatotropic viruses can also facilitate the emergence of HHV-6 from latency by transactivating its immediate early proteins remains to be proven.

Bone marrow transplant recipients with unrelated donors were more likely to develop HHV-6 encephalitis, as compared to those with HLA identical sibling donors [33]. In another report, detection rates for HHV-6 DNA at 3 and 4 weeks were significantly higher in patients with allogeneic bone marrow transplantation than in those with allogeneic peripheral blood stem cell transplantation [34]. Unlike CMV, which occurs considerably less frequently in autologous bone marrow transplant recipients, the incidence of HHV-6 infection is similar in autologous and allogeneic bone marrow transplant recipients.

There are conflicting data on the role of rejection or augmented immunosuppression in predisposing to HHV-6 infection. Reactivation of HHV-6 after OKT3 receipt has been documented after renal transplantation [35]. In a study in liver transplant recipients, CMV and HHV-6 DNA detection were independently associated with allograft rejection [36]. An inverse association between HHV-6 viremia and rejection was documented in another report; patients with HHV-6 were less likely to develop rejection, suggesting that HHV-6 may indeed be an immunosuppressive virus [32].

Most HHV-6 infections occur between 2 and 4 weeks after transplantation; this characteristic timing of onset distinguishes HHV-6 from CMV, which usually occurs late, i.e. 6–12 weeks post-transplantation [37].

Transmission

Given the high HHV-6 rate of seropositivity in the general population, most infections in transplant patients are proposed to result from reactivation of the latent virus. Genomic analysis of HHV-6 isolates from the blood of a patient, before and after bone marrow transplantation, showed identical strains of HHV-6 [31]. Donor transmission of HHV-6 has also been documented. Following liver transplantation, primary HHV-6 infection has been reported in 61% of the patients who were seronegative for HHV-6 prior to transplantation [27]. Although the precise mode of acquisition of primary HHV-6 infection in seronegative recipients is not known, donor allograft is believed to be the likely source of transmission. HHV-6 has been shown to develop latency in the kidney in vivo [38]. Furthermore, two renal transplant recipients who received the allografts from the same cadaveric donor were documented to have identical genomic patterns of their HHV-6 isolates [24].

Clinical manifestations

The precise clinical manifestations of HHV-6 in organ transplant recipients remain to be fully elucidated; however, there is accumulating evidence to suggest that HHV-6 may be a pathogen in these patients.

Direct sequelae

Although fever of unknown origin, interstitial pneumonitis and hepatitis have been reported in association with HHV-6, bone marrow suppression and encephalitis are the most well
HHV-6 encephalitis has been described as an immunomodulatory and immunosuppressive virus that may facilitate superinfections with other opportunistic organisms in transplant recipients, particularly CMV [13,27,37,39]. Primary HHV-6 infection was identified as a significant risk factor for the development of symptomatic CMV infection, including tissue-invasive CMV disease in liver transplant recipients [27]. In renal transplant recipients at risk for primary CMV infection, HHV-6 infection was significantly associated with the development of CMV viral syndrome and CMV hepatitis [39]. HHV-6 infection was an independently significant predictor of invasive fungal infection in two studies in liver transplant recipients. Liver transplant recipients with HHV-6 had a significantly higher mortality; the independent association between HHV-6 and late mortality approached statistical significance in this study [32].

**Indirect sequelae**

Mental status changes, ranging from confusion to coma, seizure and headache, are the predominant clinical manifestations of HHV-6. Focal neurologic findings are rare. CSF pleocytosis and abnormal neuroimaging findings are characteristically absent. Rarely, low-attenuation CNS lesions, mimicking immunosuppression-associated leukoencephalopathy, may be seen [41].

**Diagnosis**

Serologic, virologic and in situ immunohistochemistry assays have been utilized for the diagnosis of HHV-6. For the serologic diagnosis of HHV-6, enzyme immunoassays have proven more sensitive than the fluorescence assays [43]. As with all herpesviruses (that establish latency), serologic tests, while useful for the determination of seroprevalence, may not be reliable indicators of active infection. Antigenic cross-reactivity or concomitant infection with other herpesvirus may confound the specificity of the serologic assays or the interpretation of changes in HHV-6 antibody titers. IgM per se is also not a reliable marker for HHV-6 infection, since most cases confirmed by culture or seroconversion have no detectable IgM [43]. Furthermore, up to 5% of healthy adults may demonstrate IgM positivity at any time [43].

HHV-6 induces a characteristic cytopathic effect in primary lymphocyte culture, with ‘large ballooning’ refractile cells and loss of normal lymphocyte clumping. Confirmation of HHV-6 in cell culture, however, must be performed by using HHV-6-specific reagents and not merely by the cytopathic effect. HHV-6 isolation in cell culture is labor-intensive and requires 5–21 days for detection. A rapid shell vial (early antigen) assay has been developed that can detect HHV-6 within 72 h [37]. This assay is analogous to the shell vial assay for the diagnosis of CMV. In bone marrow and liver transplant recipients, a

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**Table 1** Association of HHV-6 with clinical sequelae and the level of supportive evidence

<table>
<thead>
<tr>
<th>Evidence from case reports or case series</th>
<th>Proposed association with conflicting supportive evidence</th>
<th>Association with allograft rejection</th>
<th>Association with graft versus host disease</th>
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<td><strong>Association with allograft rejection</strong></td>
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<td><strong>Encephalitis</strong></td>
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<td><strong>Bone marrow suppression</strong></td>
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**Supportive evidence from cohort studies**

- **Encephalitis**
- **Bone marrow suppression**
- **Association with fungal infections**
- **Association with cytomegalovirus infection**
- **Evidence from case reports or case series**
  - **Pneumonitis**
  - **Rash**
  - **Hepatitis**
  - **Gastroenteritis**

**Proposed association with conflicting supportive evidence**

- **Association with allograft rejection**
- **Association with graft versus host disease**

**Indirect sequelae**

HHV-6 has been described as an immunomodulatory and immunosuppressive virus that may facilitate superinfections with other opportunistic organisms in transplant recipients, particularly CMV [13,27,37,39]. Primary HHV-6 infection was identified as a significant risk factor for the development of symptomatic CMV infection, including tissue-invasive CMV disease in liver transplant recipients [27]. In renal transplant recipients at risk for primary CMV infection, HHV-6 infection was significantly associated with the development of CMV viral syndrome and CMV hepatitis [39]. HHV-6 infection was an independently significant predictor of invasive fungal infection in two studies in liver transplant recipients. Liver transplant recipients with HHV-6 had a significantly higher mortality; the independent association between HHV-6 and late mortality approached statistical significance in this study [32].

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sensitivity of 86% and a specificity of 100% have been demonstrated with this assay when compared to the conventional cell culture [44]. Qualitative PCR for the diagnosis of HHV-6 is limited by the fact that it can detect latent virus. Latently infected peripheral blood mononuclear cells, however, contain fewer than 10 HHV-6 genomes per 10^6 cells. Nevertheless, PCR has other advantages; PCR positivity in cell-free specimens can be diagnostically useful. Furthermore, HHV-6 variant discrimination can be readily accomplished by PCR.

Immunohistochemical stains for detecting HHV-6 in formalin-fixed paraffin-embedded tissue are also available. Immunohistochemical staining of tissues with murine monoclonal antibody reactive against the structural protein p101 of variant B and structural protein gp82 of variant A detects cells productively and not latently infected with HHV-6.

Although viral inclusion-bearing cells may occasionally be visualized in histopathologic samples [39], HHV-6 characteristically elicits little inflammatory response. Multinucleated giant cells (similar to the cytopathogenic effect caused by HHV-6 in human T-lymphocytes in vitro) and enveloped virions, with a prominent tegument visualized electronmicroscopically in the tissue, were proposed as morphologic criteria to consider the possibility of tissue-invasive HHV-6 disease [45].

Management

The antiviral susceptibilities of HHV-6 resemble those of CMV, i.e. it is sensitive to ganciclovir and foscarnet and less so to acyclovir [46–49]. Serum levels (1.8–3.6 mg/L) following low-dose acyclovir (200 mg) are inadequate to suppress HHV-6. High-dose acyclovir (800 mg) can achieve plasma concentrations of approximately 1.6 mg/L, which may be partially suppressive for some HHV-6 variant A strains. However, the mean IC_{50} of HHV-6A and HHV-6B variants are 20 μM and 37 μM, respectively [47,48,50–52]. Thus, acyclovir, even in high doses, may not be suppressive for most HHV-6 isolates. The L-valine ester of acyclovir, valacyclovir, upon administration is rapidly converted to acyclovir, achieving peak plasma levels of 38 μM after 200 mg of valacyclovir. These concentrations would be effective for most HHV-6A variants.

Peak serum concentrations following intravenous ganciclovir (5 mg/kg) average 31–43 μM and should be adequate to suppress HHV-6 [47,48,52,53]. The IC_{50} of foscarnet for HHV-6 ranges between 49 and 67 μM; these concentrations are readily achievable with a foscarnet infusion of 90 mg/kg [52,53]. Cidofovir also demonstrates in vitro activity against HHV-6.

Although some reports have documented the successful treatment of transplant recipients with HHV-6 infection, the indications for therapy, the drug of choice and the efficacy of antiviral therapy for HHV-6 have not been adequately assessed in transplant patients. In patients with HHV-6 encephalitis, cure was documented in seven of eight who received ganciclovir or foscarnet for ≥ 7 days as compared to none of four in those who did not receive these drugs or received them for < 7 days (P = 0.01) [41]. Issues concerning prophylaxis, i.e. indications for prophylaxis, timing of initiation, duration, choice of antiviral agent or the efficacy of prophylaxis for HHV-6, remain to be resolved.

**HUMAN HERPESVIRUS-7**

Infection due to HHV-7, like that due to HHV-6, is ubiquitous. Primary infection due to HHV-7 also occurs during childhood, albeit at a slightly later age than with HHV-6. HHV-7 not only exhibits selective tropism for CD4+ T-lymphocytes, but also utilizes the CD4 molecule as its receptor. A causal association between HHV-7 and clinical illness, however, has not been established in the transplant or non-transplant setting.

Unlike with HHV-6, a bimodal peak of HHV-7 DNA detection was documented in one study in bone marrow transplant recipients. The first peak occurred at 3–4 weeks, and the second 9–10 weeks after transplantation. Patients with CMV disease were more likely to have HHV-7 DNA detection than those with asymptomatic CMV infection (31% versus 0%, P = 0.13) [54]. In a study in renal transplant recipients, patients with CMV and HHV-7 coinfection were more likely to have CMV disease than those with CMV infection only [55]. In liver transplant recipients, however, no pathogenic effect of HHV-7 was documented [36].

**HUMAN HERPESVIRUS-8**

HHV-8 or Kaposi’s sarcoma-associated herpesvirus (KSHV) has been causally associated with all forms of Kaposi’s sarcoma (KS), including post-transplant KS. KSHV is a γ-herpesvirus belonging to the genus *Rhadinovirus*. It is most closely related to herpesvirus saimiri, with which it has 51% DNA sequence homology; these herpesviruses are transforming viruses capable of causing tumors in their natural hosts.

**Biological features**

KSHV is unique among herpesviruses in that it contains an unprecedented number of genes transduced from the host cellular genomes during its evolution, a phenomenon known as molecular piracy [56]. While less important for viral replication, three genes encode for cellular homologs that induce angiogenesis, regulate antiviral immunity and alter cellular growth [56]. The histopathologic hallmark of KS is the presence of spindle cells. A majority of these cells stain positive...
for endothelial cell markers; however, some cells express proteins characteristic of smooth muscle cells, macrophages or dendritic cells. These data suggest that KS spindle cells may indeed be derived from a pluripotent mesenchymal progenitor cell [56].

There is some debate over whether KS is a true malignancy or a cytokine-driven hyperplasia. KSHV is a potent inducer of cytokines, e.g. IL-6, basic fibroblast growth factor and IFN-γ, that have been shown to be angiogenic. KS spindle cells produce IL-6, and exogenous IL-6 can enhance the proliferation of KS cells in culture, thus leading many to believe that KS may be a cytokine-driven lesion.

Although most KS lesions in transplant recipients are believed to result from reactivation of latent virus, transmission by transplanted allograft has been documented. Seroconversion occurred a mean of 5 months after transplantation and preceded KS by 11.5 months in another study [57]. Anatomic distribution of KS in an autopsy study and HLA haplotyping suggested that KS arose in the stromal endothelial cells of the donor liver in a liver transplant recipient [58].

Epidemiology and clinical manifestations

The incidence of KS in transplant recipients largely parallels the geographic seroprevalence of KSHV (Table 2). Consequently, wide geographic variations in the rate of KS have been documented. In areas of low seroprevalence of KSHV, e.g. the USA, KS has been observed in < 1% of the transplant recipients and accounts for 3–10% of all malignancies in transplant recipients. On the other hand, in South Africa and Saudi Arabia, up to 5% of the transplant recipients have been documented to develop KS, and KS accounts for 59–87% of the post-transplant malignancies [57,59–61]. The striking male predominance of KS lesions in the non-transplant setting is less pronounced in transplant recipients, the male/female ratio in transplant recipients being 2–3 : 1.

KS is one of the earliest post-transplant malignancies to occur in transplant recipients. The median time to onset was 22 months for KS, 32 months for lymphomas, and 69 months for epithelial malignancies [62]. Liver transplant recipients in one study had a higher frequency of KS than other organ transplant recipients [63]. Notably, KS has only rarely been documented in bone marrow transplant recipients.

Although skin is the most commonly involved site of KS, up to 40% of the transplant recipients may develop visceral lesions, including gastrointestinal, pulmonary, bladder and laryngeal KS. Gastrointestinal involvement may often be occult or associated with non-specific gastrointestinal symptoms and bleeding. Occasionally, perforation, obstruction and protein-losing enteropathy as a result of lymphatic obstruction have been reported.

Management

Although regression of KS with reduction or cessation of immunosuppression has been reported in all forms of KS, higher remission rates have been documented with non-visceral as compared to visceral lesions. However, 50% of the patients have lost their grafts in response to cessation of immunosuppression. In patients with disseminated or visceral KS that failed to respond to modification of immunosuppression, combination chemotherapy has proven effective in some reports [64]. Retransplantation in renal allograft recipients in this setting has nearly always led to recurrence of KS lesions.

The role of a herpesvirus in the pathogenesis of KS and the fact that typically infected cells exist in KS lesions have implications for treatment of KS with antiviral agents. However, only limited experience with antiviral therapy exists in this setting. Nucleoside analogs, e.g. acyclovir and penciclovir, have minimal in vitro activity against KSHV. While the virus is susceptible to ganciclovir and foscarnet, acyclic nucleoside phosphonate analogs, cidofovir and HPMPA ((S)-1-(3-hydroxy-2-phosphonylmethoxypropyadenine), are potent inhibitors of HHV-8 DNA synthesis [65]. Adefovir blocked HHV-8 DNA replication at a four-fold lower concentration than did foscarnet.

In the HIV setting, a significant reduction in the risk of KS has been reported in patients who received ganciclovir. Abatement of KS in association with cidofovir treatment has also been reported in HIV-infected patients [66]. In four thoracic organ transplant recipients who received cidofovir because of KS recurrence or intolerance after cytotoxic chemotherapy, clearance of KSHV was documented from blood in two of two, and from skin lesions in two of four patients [67]. Furthermore, clinical improvement of gastric KS lesions was documented in one patient [67].

Prophylaxis for KS is a worthy goal in patients from highly endemic areas. Should effective antiviral strategies become available in the future, patients with seroconversion or those

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of Kaposi’s sarcoma</th>
<th>Proportion of all malignancies due to Kaposi’s sarcoma</th>
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<tbody>
<tr>
<td>USA</td>
<td>0.5%</td>
<td>3–10%</td>
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<tr>
<td>France</td>
<td>0.6%</td>
<td>8.3%</td>
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<tr>
<td>Italy</td>
<td>1.6%</td>
<td>NA</td>
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<tr>
<td>Israel</td>
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<td>NA</td>
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<tr>
<td>South Africa</td>
<td>4%</td>
<td>59%</td>
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<tr>
<td>Saudi Arabia</td>
<td>5.3%</td>
<td>87%</td>
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NA, data not available.
with increasing KSHV titers by qualitative PCR may be candidates for prophylaxis.

CONCLUSION

Although incontrovertible evidence of pathogenicity has only been documented thus far for human HHV-8, emerging data suggest that all of the novel β-herpesviruses may be clinically relevant opportunistic pathogens in transplant recipients. The indirect sequelae of HHV-6 and -7 infections are intriguing. It is conceivable that the beneficial effect of antiviral prophylaxis for CMV in transplant recipients could in part have been mediated through its effect on the newer β-herpesviruses. In this regard, future trials for CMV chemoprophylaxis may consider monitoring the effect of antiviral agents on HHV-6 and -7 as well. Such data would further elucidate the pathogenicity of these viruses in transplant recipients.

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