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HUMAN HERPESVIRUS 6 INFECTION IN TRANSPLANTATION

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ABSTRACT

Human herpesvirus 6 (HHV-6) is ubiquitous in the human population and causes exanthem subitum, a benign disease seen in infancy. The virus remains latent in the body after primary infection, and reactivates in immunocompromised patients. Infection occurs in nearly half of all bone marrow or solid organ transplant recipients 2–3 weeks following the procedure. It has been suggested that the viral infection and activation result in clinical symptoms including fever, skin rash, pneumonia, bone marrow suppression, encephalitis, and rejection. In order to control the viral infection, several studies investigating the route of viral transmission and diagnostic procedures have been carried out.

Key Words: HHV-6, bone marrow transplantation, solid organ transplantation

INTRODUCTION

Human herpesvirus 6 (HHV-6) was discovered recently as a member of the human herpesvirus family. It was originally designated as "human B –lymphotropic virus"[1], but subsequent studies established that the virus was primarily T-cell lymphotropic, causing it to be re-named HHV-6. The virus is an enveloped virion with an icosahedral nucleocapsid of 162 capsomers enclosing a large double-stranded DNA genome. On the basis of genomic DNA sequences, cell tropism, and reactivity to several monoclonal antibodies, two distinct variants (variant A and variant B) have been described[2]. Primary infection with HHV-6 variant B causes exanthem subitum, which is a common febrile disease of infancy[3),4)]. The clinical course of primary HHV-6 infection is generally benign and self-limited[5]. However, several severe complications have been reported, including encephalitis/encephalopathy[6),7),8)], hepatitis[9)], thrombocytopenia[10)], hemophagocytic syndrome[11)], and myocarditis (unpublished data).

In most children, primary HHV-6 infection occurs between 6 months and two years of age[12),13)]. The virus probably remains latent in the body after the primary infection and then reactivates upon host immunosuppression, similar to other human herpesviruses. All previously-identified human herpesviruses, especially cytomegalovirus (CMV), have been implicated as important causes of morbidity and mortality in immunosuppressed organ transplant recipients. Since HHV-6 shares many characteristics with CMV, including DNA sequence homology, some elements of genomic organization, antigenic cross-reactivity, and similar *in vitro* growth characteristics, it is speculated that HHV-6 is similarly implicated in organ transplant complications. Although the pathogenesis of HHV-6 has not yet been fully delineated, recent evidence suggests

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that the virus is a serious and potentially life-threatening pathogen in the post-transplant period. This review summarizes the epidemiology and clinical correlates of HHV-6 infection in bone marrow transplantation (BMT) and solid organ transplantation. Also, the route of viral transmission and methods for diagnosis of active viral infection are also reviewed briefly.

CLINICAL FEATURES OF HHV-6 INFECTION FOLLOWING BONE MARROW TRANSPLANTATION

BMT has become the standard therapy for treatment of patients with aplastic anemia, leukemia, lymphoma or immunodeficiency syndrome. However, opportunistic infections, especially by herpes viruses, still cause significant morbidity and mortality in marrow transplant recipients. CMV has received much attention in marrow transplant patients because of its role in several severe complications including interstitial pneumonitis. Clinical features of HHV-6 infection after BMT suggested by recent studies are summarized in Table 1. As described before, HHV-6 is very similar to CMV on the basis of biological and molecular analysis. As shown in Table 1, clinical features of HHV-6 infection are also similar to those of CMV infection in bone marrow transplant recipients. Three major clinical events including interstitial pneumonitis, a skin rash resembling acute graft versus host disease (GVHD), and encephalitis are reviewed in this section.

Carrigan et al.[14] first reported the association of severe interstitial pneumonitis with HHV-6 infection in two marrow transplant recipients. The virus was detected repeatedly in respiratory specimens from one patient, and HHV-6-infected cells were demonstrated in lung tissue from both patients by immunohistochemical staining. Subsequently, Cone et al.[15] reported a retrospective study involving 15 cases of post-BMT pneumonia, 15 victims of accidental death, and six fetuses. This study demonstrated that all lung tissues from HHV-6 seropositive individuals contained HHV-6 DNA, including lung tissues from each of 14 seropositive, but clinically normal controls. Moreover, it was also demonstrated that the six patients with pneumonia had relatively high levels of HHV-6 DNA in their lung tissues, while nine patients had lower HHV-6 DNA levels, similar to those found in the accidental death victims. Analyses of clinical and laboratory information from the 15 BMT transplant patients revealed that the six patients with high HHV-

Table 1 Clinical features associated with HHV-6 infection following bone marrow and solid organ transplantation.

Clinical features	Bone marrow transplant	Solid organ transplant	Reference No.
Interstitial pneumonitis	+	+	14, 15
Encephalitis/encephalopathy	+	+	16, 17
Bone marrow suppression	+	+	18, 19
Engraftment failure	+	N/A	20
Skin rash	+	–	21–24
GVHD	+	N/A	25
Thrombotic microangiopathy	+	N/A	26
Fever	+	+	22, 27–29
Rejection	N/A	+	30, 31
Hepatitis	–	+	32

6 DNA levels were more likely to have idiopathic pneumonia as opposed to pneumonia with another etiologic factor identified. However, some other studies, including our recent large case analysis study, have demonstrated that there is no association between HHV-6 infection and pneumonia. In conclusion, although there is some evidence showing that HHV-6 infection plays an important role in causing pneumonia after BMT, the association remains equivocal.

In 1991, we described the reactivation of HHV-6 in three leukemia patients following BMT[21]. The virus was isolated from the recipients' blood 15 days after the procedure. Two of the three patients had fever and macular rash at the time of virus isolation, and were subsequently treated for acute GVHD. These cases allowed us to consider the association between HHV-6 reactivation and acute GVHD. To further explore this association, we prospectively studied 25 BMT recipients on the basis of viral isolation and serological analysis[22]. HHV-6 was isolated from peripheral blood mononuclear cells (PBMC) in ten (40%) of 25 recipients between days 14 and 22 after BMT. Two additional recipients showed a significant increase in antibody titer. Thus, HHV-6 infection was confirmed in 12 (48%) of the 25 recipients. Four of the 12 developed skin rashes, with three of those four having a febrile episode as well during the period when the virus was isolated, whereas none of the remaining 13 manifested these symptoms. These results suggest that HHV-6 infection may occur in almost half of all BMT recipients around 2 to 3 weeks following the procedure, and that it may play an important role in causing acute GVHD. This characteristic timing of onset contrasts that of CMV infection, which usually occurs 6 to 12 weeks after transplantation. Following our suggestion of an association between HHV-6 infection and acute GVHD, several groups have carried out additional analyses to further elucidate the relationship. Some studies demonstrated that HHV-6 is a risk factor in causing acute GVHD[25], while others did not support such a positive association. Currently, the role of HHV-6 in causing GVHD-like skin rashes is being addressed by examining alterations of surface molecules on epidermal cells induced by HHV-6 using *in-vitro* infection model.

Encephalitis caused by HHV-6 has been well-documented in immunocompetent children with primary HHV-6 infection, and the virus genome has been detected in the cerebrospinal fluid of such patients[6),7),8)]. Therefore, it has been proposed that HHV-6 has neurotropism and plays an important role in causing neurological disorders. Several cases with encephalitis, including fatalities linked to HHV-6 infection have been reported in bone marrow transplant recipients[16)]. Although the prognosis in such cases is generally poor, it has been suggested that rapid diagnosis followed by immediate treatment with ganciclovir or foscarnet could improve the prognosis in some patients. Detection of viral DNA in cerebrospinal fluid by PCR has been found to be a useful method for such rapid diagnosis.

ROUTE OF HHV-6 TRANSMISSION IN BONE MARROW TRANSPLANT RECIPIENTS

As previously described, since HHV-6 infection may be associated with severe clinical complications following BMT, it is important to be able to predict viral infection and to clarify the route of viral transmission. There are two likely sources of HHV-6 infection after BMT — reactivation in the recipient and infection acquired from the marrow of a seropositive donor. Therefore, the virus latently infected in PBMC of donors and recipients may be an important source of the virus transmission. In a recent study, we determined that the presence of HHV-6 genome in donor or recipient PBMC before BMT is indeed a valuable predictor of viral infection following the procedure[33)] (Table 2).

Restriction-endonuclease analysis is a valuable tool in identifying the source of HHV-6 isolated from organ transplant recipients. We have successfully isolated three HHV-6 strains from one patient with leukemia both before and after BMT; two strains were obtained before and one after BMT. The cleavage profiles of the two strains obtained before BMT were different from each other, but the third strain isolated after BMT was identical with one of the two previous strains[34]. This finding suggests that latently-infected HHV-6 reactivates in the recipient's body and that possible mutation or superinfection of the virus takes place in an immunocompromised patient. This, however, is as of yet the only report demonstrating direct evidence of viral reactivation in the BMT recipient.

CLINICAL FEATURES OF HHV-6 INFECTION AFTER SOLID ORGAN TRANSPLANTATION

As described in the previous section, the majority of studies investigating post-transplant HHV-6 infection have been focused on bone marrow transplant recipients, with only a limited number of reports relating to HHV-6 infection after solid organ transplantation. The clinical features in both cases are remarkably similar, indicating that HHV-6 infection may be a common pathogenic cause of both sets of post-transplant complications (Table 1).

Recently, living related liver transplantation has become an established therapeutic option for children with end-stage liver disease in Japan. However, opportunistic infection is still a major problem in these patients. Thus, analysis of HHV-6 infection after liver transplantation may be useful in improving the prognosis of these patients. Therefore, we carried out a study to elucidate the rate, time course, clinical features and risk factors of HHV-6 infection after living related liver transplantation[28]. EDTA-treated peripheral blood was collected from 47 donor and recipient pairs at the time of transplantation and biweekly from these recipients following the procedure. HHV-6 infection, as measured in the study by viral isolation and serological assays, was detected in 23 (49%) of the 47 recipients approximately 2 to 4 weeks after transplantation. The rate and time course of viral infection after liver transplantation were consistent with those seen in bone marrow transplant[22] or renal transplant[35] recipients. We evaluated four clinical events — unexplained fever, thrombocytopenia, rejection, and central nervous system involvement — for which an association with HHV-6 infection following solid organ transplantation has been postulated. Only unexplained fever was found to be associated statistically with HHV-6 activity after liver transplantation.

In this study, we observed five cases of primary HHV-6 infection after living related liver transplantation from HHV-6 seropositive mothers[36]. It is generally considered that primary viral infection, especially by herpes viruses, is severe or sometimes fatal in immunosuppressed children. However, there is limited information on primary HHV-6 infection in immunosuppressed infants. All five infants demonstrated seroconversion of HHV-6 antibody, and three of five infants had HHV-6 viremia between 2 to 3 weeks after transplantation. Although five recipients had pyrexia at the time of primary HHV-6 infection, none of the recipients had a skin rash after defervescence. Clinical symptoms disappeared without specific antiviral treatment in all but one of the recipients. These results suggest that primary HHV-6 infection in immunocompromised patients, including organ transplant recipients, is not always severe. Moreover, they also suggest that host immunity may play an important role in the pathogenesis of skin rashes which occur in children with primary HHV-6 infection (exanthem subitum).

The role of rejection or augmented immunosuppression in facilitating HHV-6 infection is controversial. In our previous studies, there was no association found between HHV-6 infection

and rejection in either renal transplant[35] or liver transplant recipients[28]. However, it has been proposed that rejection and increased immunosuppression may lead to a higher incidence of HHV-6 infection in renal transplant recipients[30]. Moreover, in a recent study, vascular adhesion molecule expression was observed in liver tissues infected with HHV-6 after liver transplantation[37]. Therefore, we are now attempting to infect HHV-6 into human umbilical vein endothelial cells to analyze the relationship between viral infection and surface molecule expression.

ROUTE OF HHV-6 TRANSMISSION IN SOLID ORGAN TRANSPLANT RECIPIENTS

It is important to determine whether or not HHV-6 infection via donor graft occurs after solid organ transplantation. We observed the simultaneous isolation of two HHV-6 strains from two renal transplant recipients who received grafts from the same cadaveric donor. Genomic analysis of both isolates showed the same DNA cleavage patterns, suggesting viral transmission via the renal allograft[35].

In liver transplant recipients, it has been suggested that the donor graft transmits HHV-6 during transplantation. As previously described, five liver transplant recipients receiving grafts from HHV-6 seropositive mothers developed primary HHV-6 infection at around the same time (2–3 weeks after the procedure). These results suggest that donor grafts transmit HHV-6. Therefore, it is very important to determine if HHV-6 can latently infect liver tissue. We examined the presence of HHV-6 antigen or viral genome in liver tissues obtained from 25 liver transplant recipients at the time of transplantation, and the presence of the viral genome in PBMC obtained from the recipients at the same time[38]. Immunohistochemical analysis of HHV-6 antigen was negative in all the liver specimens. Although HHV-6 DNA was not detected in liver tissue, it was detected in PBMC in nine of 25 recipients. These results suggest that residual mononuclear cells latently infected with HHV-6 in liver may be important sources of viral transmission via donor grafts.

DIAGNOSIS OF HHV-6 INFECTION AFTER ORGAN TRANSPLANTATION

Laboratory tools currently available for detecting HHV-6 infection include viral isolation, PCR assay, and serologic studies. Although isolation of the virus is the best procedure for detecting active viral infection, it is labor intensive and requires 1 to 2 weeks for results. Since rapid diagnosis of viral infection is important to establish treatment, the PCR assay is a valuable tool. However, because latent HHV-6 infection is believed to occur commonly in the general population, using PCR to detect HHV-6 DNA in blood cells or tissues has limited value in diagnosing active or productive HHV-6 infection. It has been reported that the presence of the viral genome in plasma by PCR is a reliable marker for detecting active viral infection[39]. However, data regarding the reliability of bedside monitoring of active HHV-6 infection is still limited. Therefore, we evaluated the ability of plasma PCR to rapidly identify active viral infection[28]. As shown in Table 3, the presence of HHV-6 DNA in plasma was statistically associated with active HHV-6 infection following liver transplantation ($P<0.01$). The specificity of the assay was 88%, and the positive predictive value was 83%, confirming that this method is useful for monitoring active HHV-6 infection in these patients.

Serological assay is also useful for diagnosis of active viral infection. However, cross-reactivity between HHV-6 and human herpesvirus 7 (HHV-7) antibodies has been demonstrated[40], and interaction between these viruses has been postulated. Although indirect immunofluorescence

Table 2 Comparison of patients at risk for HHV-6 infection following bone marrow transplantation.

Category	HHV-6 infection	
	Yes (n=17)	No (n=13)
HHV-6 DNA in PBMC*		
Positive	16	3
Negative	1	10

P<0.001 by Fisher's exact test.

* If HHV-6 DNA is detected in donor or recipient PBMC, it was considered a positive result.

Table 3 Association between HHV-6 infection and the presence of HHV-6 DNA in plasma by PCR assay.

Category	HHV-6 DNA in plasma	
	Positive	Negative
Recipients with HHV-6 infection	15	8
Recipients without HHV-6 infection	3	21

P<0.01 by Fisher's exact test.

assay is commonly used to determine titers of antibodies against these viruses, the inability of this assay to distinguish cross-reacting HHV-6 and HHV-7 antibodies is problematic. Recently, we demonstrated that a neutralization test, together with an immunoblot detecting antibodies against an HHV-6B-specific major immunogenic protein, is sufficient as a specific serological assay for the diagnosis of active HHV-6 infection[41].

Immunohistochemical stains for detecting HHV-6 in formalin-fixed paraffin-embedded tissues are also available. Such stains, performed with murine monoclonal antibody reactive against the structural protein p101 of variant B detects cells productively infected with HHV-6.

CONCLUSIONS

HHV-6 can be a pathogen in transplant recipients. The true association between each clinical event and the viral infection is still under debate. In order to clarify the pathophysiology behind this phenomenon, however, prompt recognition of the disease spectrum associated with HHV-6 infection is important. Future clinical virologic studies in combination with basic research will provide valuable knowledge to be used in improving the prognosis of transplant recipients.

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