Human Herpesvirus 6 in Hematological Malignancies

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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 on 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.¹ This enveloped virion contains about 160 kb of linear double-stranded DNA,² 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.³ HHV-6B is highly prevalent in the human population, infecting virtually all children within the first few years of life.^{4,5} 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.⁶ The host tissue range of HHV-6 *in vivo* is broad and includes peripheral blood mononuclear cells,⁷ salivary glands, brain tissue, liver cells, lymph node, and endothelial cells.⁸ Candidate sites for latency are salivary glands,^{9,10} brain tissue,^{11,12} monocytes,¹³ and early bone marrow progenitor cells.¹⁴

Primary HHV-6 infection commonly causes exanthem subitum.^{4,5} Associations between HHV-6 infection (reactivation) and development of many diseases have been investigated, including multiple sclerosis,¹⁵ mesial temporal lobe epilepsy,^{12,16} encephalitis in immunocompetent patients,¹⁷ chronic fatigue syndrome,¹⁸ drug-induced hypersensitivity syndrome,^{19,20} Kikuchi's disease,²¹ 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.

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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,¹ 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*.^{22,23} Kashanchi *et al.*²⁴ 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.²⁵ EBV is present in the neoplastic cells of 20–40% of patients with Hodgkin lymphoma,²⁵ and has been shown to represent an oncogenic infectious agent for Hodgkin lymphoma.²⁶ Associations between HHV-6 and Hodgkin lymphoma were first suggested by Torelli *et al.*²⁷ in 1991. They showed higher anti-HHV-6 antibody titers in patients with Hodgkin lymphoma than in normal blood donors, and HHV-6 sequences were detected in 3 of 25 patients with Hodgkin lymphomas. Since then, many studies aimed at identifying the HHV-6 genome in pathologic specimens using polymerase chain reaction (PCR) have been reported (Table 1).^{28–36} Frequencies of positive HHV-6 DNA appear to vary widely among these studies, and may depend on the differences in PCR sensitivity for each study. Variant B has been identified more frequently than variant A. However, it is important to note that positive PCR results do not necessarily indicate the presence of HHV-6 in neoplastic cells. HHV-6 is a ubiquitous pathogen, and remains in a latent state in various host cells including leukocytes. Altered immune status due to disease may thus induce HHV-6 reactivation. As a result, positive PCR results for HHV-6 may merely reflect latent infection or immunological dysfunction. In fact, Sumiyoshi *et al.*²⁸ found amplified HHV-6 DNA using PCR in 64.3% of patients with Hodgkin lymphoma but were unable to detect HHV-6 DNA using Southern blot analysis. They concluded that the presence of HHV-6 DNA shown by PCR was derived from latent infection. Histopathological analysis is a reliable method to demonstrate HHV-6 infection in neoplastic cells. A small number of studies have investigated HHV-6 antigen

expression in lymphoid tissue.^{29–31} These investigations found a lack of HHV-6 antigen expression in neoplastic cells and limited expression in Reed-Sternberg cells,^{29–31} 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.*³⁶ 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.

Non-Hodgkin lymphoma (NHL)

1) Angioimmunoblastic T-cell lymphoma (AITL)

Clinical presentations including high-fever, polyclonal gammopathy, or polymorphic histological appearances raise the possibility of a role for infectious agents in the pathogenesis of AITL. To date, EBV,^{37,38} 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).^{28,31,34,38–41} However, neither EBV³⁷ nor HHV-6³¹ 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, 34, 35, 40, 43, 44} 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 analysis²⁸ and a lack of HHV-6 antigen expression in neoplastic cells^{31, 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.⁴⁶ Persistent HHV-6 infection facilitates growth of ATL cells.⁴⁷ These *in vitro* findings suggest a possible pathogenic 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

Table 1. HHV-6 infection in Hodgkin lymphoma

References	Detection method	Sample	No. of subjects	Positive rate for HHV-6	HHV-6 variant	Observations
Torelli <i>et al.</i> (1991) ²⁷	PCR	LN	Patients : 25 Controls ^a : 41	12 % 0 %	ND	All cases positive for HHV-6 (n = 3) belonged to the NS/LD subtype.
Sumiyoshi <i>et al.</i> (1993) ²⁸	PCR	LN	Patients : 14 Controls ^b : 56	64. 3% 98. 2%	ND	
Trovato <i>et al.</i> (1994) ²⁹	Southern blot	LN	14	0 %	ND	
	PCR	LN	15 ^c	7 %		
	ISH	LN	15	0 %		
Valente <i>et al.</i> (1996) ³⁰	PCR	LN	Patients : 52 Controls ^b : 19	73 % 68. 4%	2A&B/ 36B	No Hodgkin or Reed-Sternberg cells were positive in any case.
	ISH	LN	57	82. 4%		
	Southern blot	LN	NI	0 %		
Luppi <i>et al.</i> (1998) ³¹	IHC	LN	14	14. 3%	ND	Early p 41 antigen was detected in Reed-Sternberg cells in two cases.
Schmidt <i>et al.</i> (2000) ³²	PCR	LN	88	13 %	8A/3B	
Shiramizu <i>et al.</i> (2001) ³³	PCR	LN	47 ^c	0 %		
Collet <i>et al.</i> (2002) ³⁴	qPCR	LN	37	35. 1%	1A/12B	All Hodgkin lymphoma patients infected with HHV-6 presented with the NS subtype.
Hernández-Losa <i>et al.</i> (2004) ³⁵	PCR	LN	Patients : 20 Controls ^d : 52	40 % 33 %	ND	
Lacroix <i>et al.</i> (2007) ³⁶	qPCR	LN	86	79. 1%	5A/63B	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.

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

^anon-Hodgkin lymphoma ; ^bbenign lymphadenitis ; ^cpediatric Hodgkin lymphoma ; ^dnormal donor spleen lymphocytes and reactive lymphadenitis

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.*⁴⁸ found high levels of HHV-6 antibodies in a small group of children with ALL compared with normal subjects, but a sequential study⁴⁹ showed no significant differences in antibody titers between 50 patients with ALL and 50

sex-age matched blood donors. The largest serological case-control investigation⁵⁰ 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.*⁵¹ found the presence of IgM antibodies in 40% of children with leukemia (n= 40) 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.*⁵² 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 develop leukemia or 47 matched controls. These findings indicate that childhood ALL is unlikely to be associated with *in utero* infection by HHV-6.⁵²

HHV-6 DNA was detected by PCR and *in situ* hybridization in the bone marrow cells of children with T-ALL⁵³ in 1991. However, Barozzi *et al.*⁵⁴ found that the presence of

Table 2. HHV-6 infection in non-Hodgkin lymphoma

References	Detection method	Sample	No. of subjects	Positive rate for HHV-6	HHV-6 variant	Observations
AITL, AILD, or IBL						
Sumiyoshi <i>et al.</i> (1993) ²⁸	PCR	LN	Patients : 8	62. 5%	ND	
			Controls ^a : 56	98. 2%		
	Southern blot	LN	8	0 %		
Luppi <i>et al.</i> (1993) ³⁹	PCR	LN	12	58. 3%	ND	
Luppi <i>et al.</i> (1998) ³¹	IHC	LN	5	0 %		
Ohyashiki <i>et al.</i> (1999) ⁴⁰	PCR-ELISA	PB & LN	Patients : 3 Controls ^b : 23	100 % 43. 4%	3 B 9B/2 unclassified	Number of HHV-6 genomes in patients was high.
Collot <i>et al.</i> (2002) ³⁴	qPCR	LN	5	20. 0%	1 B	
Vrsalovic <i>et al.</i> (2004) ⁴¹	PCR	LN	18	22. 2%	ND	
Zhou <i>et al.</i> (2007) ³⁸	qPCR	LN	42	45. 2%	Only HHV-6B was examined.	Simultaneous infection with EBV and HHV-6B was found in specimens with patterns I and II. A tendency toward an inverse correlation between EBV and HHV-6 B viral load was seen.
Mycosis fungoides						
Erkek <i>et al.</i> (2001) ⁴²	PCR	TT	92	1. 1%	ND	
HIV-associated NHL						
Fillet <i>et al.</i> (1995) ⁴³	PCR	TT	27	44. 4%	2A/1B/6A & B	
T-cell lymphoma						
Sumiyoshi <i>et al.</i> (1993) ²⁸	PCR	LN	Patients ^c : 33	57. 6%	ND	
			Controls ^a : 56	98. 2%		
	Southern blot	LN	33 ^c	0 %		
Ohyashiki <i>et al.</i> (1999) ⁴⁰	PCR-ELISA	PB & LN	6	50 %	2 B/1 unclassified	
Collot <i>et al.</i> (2002) ³⁴	qPCR	LN	8 ^c	25. 0%	2 B	
B-cell lymphoma						
Sumiyoshi <i>et al.</i> (1993) ²⁸	PCR	LN	Patients : 29	62. 1%	ND	
			Controls ^a : 56	98. 2%		
	Southern blot	LN	29	0 %		
Ohyashiki <i>et al.</i> (1999) ⁴⁰	PCR-ELISA	PB & LN	10	20 %	1 B/1 unclassified	The HHV-6 viral load was low.
Collot <i>et al.</i> (2002) ³⁴	qPCR	LN	36	22. 2%	1 A/7 B	
Any type						
Razzaque <i>et al.</i> (1996) ⁴⁴	PCR	LN	6	100 %	ND	
	IHC	LN	6	33. 3%		
Luppi <i>et al.</i> (1998) ³¹	IHC	LN	15	0 %		
Hernández-Losa <i>et al.</i> (2004) ³⁵	PCR	LN	Patients : 63	27 %	ND	
			Controls ^d : 52	33 %		

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

^abenign lymphadenitis ; ^bperipheral blood leukocyte from healthy volunteers ; ^cother than AITL or AILD ; ^dnormal donor spleen lymphocytes and reactive lymphadenitis

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

Disease	Sample	No. of subjects	No. of positive cases	Positive rate for HHV-6	HHV-6 DNA among positive samples (copies/ μ g)
ATL	LN	6	2	33.3%	180.7
					38.6
	PB	11	5	45.5%	2933.3
					107.7
					63.1
					35.0
					31.2
T-cell lymphoma	LN	2	0	0%	
B-cell lymphoma	LN	12	2	16.7%	7.5
					6.3
Hodgkin lymphoma	LN	2	2	100%	121.8
					4.5
Reactive lymphadenitis	LN	2	2	100%	6.5
					4.5

ATL, adult T-cell leukemia ; LN, lymph node ; PB, peripheral blood

HHV-6 DNA is not frequent in patients with ALL compared to normal subjects. Seror *et al.*⁵⁵ 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.⁵⁶ Whether integrated HHV-6 is capable of replication or is associated with disease remains unclear. Daibata *et al.*⁵⁷ demonstrated integration of *HHV-6* genome in a Burkitt's lymphoma cell line. Furthermore, they showed chromosomal transmission of HHV-6 DNA in ALL.⁵⁸ 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.*⁵⁹ 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.^{60–66} Most HHV-6 infections are due to reactivation of HHV-6 type B.^{63, 67} HHV-6 appears most frequently around 2–6 weeks after SCT,^{61, 63, 65, 66, 68} and onset of HHV-6 reactivation is concentrated around 0–9 days after neutrophil engraftment.⁶⁵ HHV-6 can reactivate to high levels within a week,^{65, 69} but duration of HHV-6 reactivation is usually short (Fig. 1).⁶⁵ Younger age,⁶³ underlying diseases,⁶³ sex mismatch,⁶³ HLA mismatch,^{65, 66} steroid treatment,^{63, 65} unrelated transplants,^{64, 65} cord blood transplantation,^{66, 70} and low anti-HHV-6 IgG titer before transplantation⁶⁶ have been identified as risk factors associated with HHV-6 reactivation. Steroid administration⁶⁵ and cord blood transplantation⁷⁰ are also associated with higher-

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

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

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.⁸¹ Retrospective surveillance by a Japanese group has reported an incidence of 0.98%.⁸¹ Five epidemiological studies that monitored HHV-6 viral load have shown associations between HHV-6 reactivation and development of central nervous system (CNS) dysfunction.^{63, 65, 66, 68, 69} Incidences ranged from 3.6%

to 8.0%. Vu *et al.*⁸⁴ 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 Japan⁸⁶ 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. Zerr⁸⁰ 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.^{65, 69, 77, 78, 80, 82, 83, 86} Using immunohistochemical methods, several investigators have found that HHV-6 displays tropism for hippocampal astrocytes in recipients who developed encephalitis.^{77, 78, 82} 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,⁶⁵ and higher levels of HHV-6 DNA in peripheral blood are associated with the development of CNS dysfunction.^{65, 87} These 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,⁸⁷ 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.⁸⁷

The prognosis of HHV-6 encephalitis is poor. A retrospective study in Japan⁸⁶ showed sequelae in about half of patients despite receiving antiviral treatment. Zerr⁸⁰ 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.

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 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 SCT^{92, 93} 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 studies²⁹⁻³¹ 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 lymphoma³⁶ 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 chemokines^{38,96,97} 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

- 1 Salahuddin SZ, Ablashi DV, Markham PD, Josephs SF, Sturzenegger S, *et al.* : Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. *Science* 234 : 596-601, 1986
- 2 Josephs SF, Salahuddin SZ, Ablashi DV, Schachter F, Wong-Staal F, *et al.* : Genomic analysis of the human B-lymphotropic virus (HBLV). *Science* 234 : 601-603, 1986

- 3 Ablashi DV, Balachandran N, Josephs SF, Hung CL, Krueger GR, *et al.* : Genomic polymorphism, growth properties, and immunologic variations in human herpesvirus-6 isolates. *Virology* 184 : 545-552, 1991
- 4 Yoshikawa T, Suga S, Asano Y, Yazaki T, Kodama H, *et al.* : Distribution of antibodies to a causative agent of exanthem subitum (human herpesvirus-6) in healthy individuals. *Pediatrics* 84 : 675-677, 1989
- 5 Zerr DM, Meier AS, Selke SS, Frenkel LM, Huang ML, *et al.* : A population-based study of primary human herpesvirus 6 infection. *N Engl J Med* 352 : 768-776, 2005
- 6 Takahashi K, Sonoda S, Higashi K, Kondo T, Takahashi H, *et al.* : Predominant CD4 T-lymphocyte tropism of human herpesvirus 6-related virus. *J Virol* 63 : 3161-3163, 1989
- 7 Kondo K, Kondo T, Shimada K, Amo K, Miyagawa H, *et al.* : Strong interaction between human herpesvirus 6 and peripheral blood monocytes/macrophages during acute infection. *J Med Virol* 67 : 364-369, 2002
- 8 Campadelli-Fiume G, Mirandola P, Menotti L : Human herpesvirus 6 : An emerging pathogen. *Emerg Infect Dis* 5 : 353-366, 1999
- 9 Fox JD, Briggs M, Ward PA, Tedder RS : Human herpesvirus 6 in salivary glands. *Lancet* 336 : 590-593, 1990
- 10 Jarrett RF, Clark DA, Josephs SF, Onions DE : Detection of human herpesvirus-6 DNA in peripheral blood and saliva. *J Med Virol* 32 : 73-76, 1990
- 11 Chan PK, Ng HK, Hui M, Cheng AF : Prevalence and distribution of human herpesvirus 6 variants A and B in adult human brain. *J Med Virol* 64 : 42-46, 2001
- 12 Donati D, Akhyani N, Fogdell-Hahn A, Cermelli C, Cassiani-Ingoni R, *et al.* : Detection of human herpesvirus-6 in mesial temporal lobe epilepsy surgical brain resections. *Neurology* 61 : 1405-1411, 2003
- 13 Kondo K, Kondo T, Okuno T, Takahashi M, Yamanishi K : Latent human herpesvirus 6 infection of human monocytes/macrophages. *J Gen Virol* 72 : 1401-1408, 1991
- 14 Luppi M, Barozzi P, Morris C, Maiorana A, Garber R, *et al.* : Human herpesvirus 6 latently infects early bone marrow progenitors *in vivo*. *J Virol* 73 : 754-759, 1999
- 15 Challoner PB, Smith KT, Parker JD, MacLeod DL, Coulter SN, *et al.* : Plaque-associated expression of human herpesvirus 6 in multiple sclerosis. *Proc Natl Acad Sci USA* 92 : 7440-7444, 1995
- 16 Fotheringham J, Donati D, Akhyani N, Fogdell-Hahn A, Vortmeyer A, *et al.* : Association of human herpesvirus-6 B with mesial temporal lobe epilepsy. *PLoS Med* 4 : e180, 2007
- 17 Yao K, Honarmand S, Espinosa A, Akhyani N, Glaser C, *et al.* : Detection of human herpesvirus-6 in cerebrospinal fluid of patients with encephalitis. *Ann Neurol* 65 : 257-267, 2009
- 18 Patnaik M, Komaroff AL, Conley E, Ojo-Amaize EA, Peter JB : Prevalence of IgM antibodies to human herpesvirus 6 early antigen (p 41/38) in patients with chronic fatigue syndrome. *J Infect Dis* 172 : 1364-1367, 1995
- 19 Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T : Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. *Arch Dermatol* 134 : 1108-1112, 1998
- 20 Tohyama M, Yahata Y, Yasukawa M, Inagi R, Urano Y, *et al.* : Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch Dermatol* 134 : 1113-1117, 1998
- 21 Krueger GR, Huetter 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 apoptosis. *Anticancer Res* 21 : 2155-2161, 2001
- 22 Razzaque A : Oncogenic potential of human herpesvirus-6 DNA. *Oncogene* 5 : 1365-1370, 1990
- 23 Razzaque A, Williams O, Wang J, Rhim JS : Neoplastic transformation 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 exhibits malignant transforming activity and its protein binds to p 53. *Oncogene* 14 : 359-367, 1997
- 25 Diepstra A, Niens M, Vellenga E, van Imhoff GW, Nolte IM, *et al.* : Association with HLA class I in Epstein-Barr-virus-positive and with HLA class III in Epstein-Barr-virus-negative Hodgkin's lymphoma. *Lancet* 365 : 2216-2224, 2005
- 26 Küppers R : B cells under influence : transformation of B cells by Epstein-Barr virus. *Nat Rev Immunol* 3 : 801-812, 2003
- 27 Torelli G, Marasca R, Luppi M, Selleri L, Ferrari S, *et al.* : Human herpesvirus-6 in human lymphomas : identification of specific sequences in Hodgkin's lymphomas by polymerase chain reaction. *Blood* 77 : 2251-2258, 1991
- 28 Sumiyoshi Y, Kikuchi M, Ohshima K, Takeshita M, Eizuru Y, *et al.* : Analysis of human herpes virus-6 genomes in lymphoid malignancy in Japan. *J Clin Pathol* 46 : 1137-1138, 1993
- 29 Trovato R, Di Lollo S, Calzolari A, Torelli G, Ceccherini-Nelli L : Detection of human herpesvirus-6 and Epstein-Barr virus genome in childhood Hodgkin's disease. *Pathologica* 86 : 500-503, 1994
- 30 Valente G, Secchiero P, Lusso P, Abete MC, Jemma C, *et al.* : Human herpesvirus 6 and Epstein-Barr virus in Hodgkin's disease : a controlled study by polymerase chain reaction and *in situ* hybridization. *Am J Pathol* 149 : 1501-1510, 1996
- 31 Luppi M, Barozzi P, Garber R, Maiorana A, Bonacorsi G, *et al.* : Expression of human herpesvirus-6 antigens in benign and malignant lymphoproliferative diseases. *Am J Pathol* 153 : 815-823, 1998
- 32 Schmidt CA, Oettle H, Peng R, Binder T, Wilborn F, *et al.* : Presence of human beta- and gamma-herpes virus DNA in Hodgkin's disease. *Leuk Res* 24 : 865-870, 2000
- 33 Shiramizu B, Chang CW, Cairo MS : Absence of human herpesvirus-6 genome by polymerase chain reaction in children with Hodgkin disease : a Children's Cancer Group Lymphoma Biology Study. *J Pediatr Hematol Oncol* 23 : 282-285, 2001
- 34 Collot S, Petit B, Bordessoule D, Alain S, Touati M, *et al.* : Real-time PCR for quantification of human herpesvirus 6 DNA from

- lymph nodes and saliva. *J Clin Microbiol* 40 : 2445–2451, 2002
- 35 Hernández-Losa J, Fedele CG, Pozo F, Tenorio A, Fernández V, *et al.* : Lack of association of polyomavirus and herpesvirus types 6 and 7 in human lymphomas. *Cancer* 103 : 293–298, 2005
 - 36 Lacroix A, Jaccard A, Rouzioux C, Piguet C, Petit B, *et al.* : HHV-6 and EBV DNA quantitation in lymph nodes of 86 patients with Hodgkin's lymphoma. *J Med Virol* 79 : 1349–1356, 2007
 - 37 Weiss LM, Jaffe ES, Liu XF, Chen YY, Shibata D, *et al.* : Detection and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. *Blood* 79 : 1789–1795, 1992
 - 38 Zhou Y, Attygalle AD, Chuang SS, Diss T, Ye H, *et al.* : Angioimmunoblastic T-cell lymphoma : histological progression associates with EBV and HHV 6 B viral load. *Br J Haematol* 138 : 44–53, 2007
 - 39 Luppi M, Marasca R, Barozzi P, Artusi T, Torelli G : Frequent detection of human herpesvirus-6 sequences by polymerase chain reaction in paraffin-embedded lymph nodes from patients with angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. *Leuk Res* 17 : 1003–1011, 1993
 - 40 Ohyashiki JH, Abe K, Ojima T, Wang P, Zhou CF, *et al.* : Quantification of human herpesvirus 6 in healthy volunteers and patients with lymphoproliferative disorders by PCR-ELISA. *Leuk Res* 23 : 625–630, 1999
 - 41 Vrsalovic MM, Korac P, Dominis M, Ostojic S, Mannhalter C, *et al.* : T- and B-cell clonality and frequency of human herpes viruses-6, -8 and Epstein Barr virus in angioimmunoblastic T-cell lymphoma. *Hematol Oncol* 22 : 169–177, 2004
 - 42 Erkek E, Sahin S, Atakan N, Kocagoz T, Olut A, *et al.* : Examination of mycosis fungoides for the presence of Epstein-Barr virus and human herpesvirus-6 by polymerase chain reaction. *J Eur Acad Dermatol Venereol* 15 : 422–426, 2001
 - 43 Fillet AM, Raphael M, Visse B, Audouin J, Poirel L, *et al.* : Controlled study of human herpesvirus 6 detection in acquired immunodeficiency syndrome-associated non-Hodgkin's lymphoma. The French Study Group for HIV-Associated Tumors. *J Med Virol* 45 : 106–112, 1995
 - 44 Razzaque A, Francillon Y, Jilly PN, Varricchio F : Detection of human herpesvirus 6 sequences in lymphoma tissues by immunohistochemistry and polymerase chain reactions. *Cancer Lett* 106 : 221–226, 1996
 - 45 Zhou CF, Abe K, Wang P, Yamamoto K : Susceptibility of the adult T cell leukemia (ATL) cell lines to HHV-6 B. *Leukemia* 12 : 1001, 1998
 - 46 Zhou CF, Abe K, Wang P, Ojima T, Yamamoto K : Efficient propagation of human herpesvirus 6 B in a T-cell line derived from a patient with adult T-cell leukemia/lymphoma. *Microbiol Immunol* 43 : 425–436, 1999
 - 47 Ojima T, Abe K, Ohyashiki JH, Shirakata M, Yamamoto K : IL-2-regulated persistent human herpesvirus-6 B infection facilitates growth of adult T cell leukemia cells. *J Med Dent Sci* 52 : 135–141, 2005
 - 48 Ablashi DV, Josephs SF, Buchbinder A, Hellman K, Nakamura S, *et al.* : Human B-lymphotropic virus (human herpesvirus-6). *J Virol Methods* 21 : 29–48, 1988
 - 49 Levine PH, Ablashi DV, Saxinger WC, Connelly RR : Antibodies to human herpes virus-6 in patients with acute lymphocytic leukemia. *Leukemia* 6 : 1229–1231, 1992
 - 50 Gentile G, Mele A, Ragona G, Faggioni A, Zompetta C, *et al.* : Human herpes virus-6 seroprevalence and leukaemias : a case-control study. GIMEMA (Gruppo Italiano Malattie Ematologiche dell' Adulto). *Br J Cancer* 80 : 1103–1106, 1999
 - 51 Salonen MJ, Siimes MA, Salonen EM, Vaheri A, Koskiniemi M : Antibody status to HHV-6 in children with leukaemia. *Leukemia* 16 : 716–719, 2002
 - 52 Bogdanovic G, Jernberg AG, Priftakis 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
 - 53 Luka J, Pirruccello SJ, Kersey JH : HHV-6 genome in T-cell acute lymphoblastic leukaemia. *Lancet* 338 : 1277–1278, 1991
 - 54 Barozzi P, Luppi M, Marasca R, Trovato R, Ceccherini-Nelli L, *et al.* : Human herpesvirus-6 genome in acute lymphoblastic leukemia : evidence against an etiologic relationship. *Acta Haematol* 94 : 169–172, 1995
 - 55 Seror E, Coquerel B, Gautheret-Dejean A, Ballerini P, Landman-Parker J, *et al.* : Quantitation of human herpes virus 6 genome in children with acute lymphoblastic leukemia. *J Med Virol* 80 : 689–693, 2008
 - 56 Leong HN, Tuke PW, Tedder RS, Khanom AB, Eglin RP, *et al.* : The prevalence of chromosomally integrated human herpesvirus 6 genomes in the blood of UK blood donors. *J Med Virol* 79 : 45–51, 2007
 - 57 Daibata M, Taguchi T, Taguchi H, Miyoshi I : Integration of human herpesvirus 6 in a Burkitt's lymphoma cell line. *Br J Haematol* 102 : 1307–1313, 1998
 - 58 Daibata M, Taguchi T, Sawada T, Taguchi H, Miyoshi I : Chromosomal transmission of human herpesvirus 6 DNA in acute lymphoblastic leukaemia. *Lancet* 352 : 543–544, 1998
 - 59 Hubacek P, Muzikova K, Hrdlickova A, Cinek O, Hyncicova K, *et al.* : Prevalence of HHV-6 integrated chromosomally among children treated for acute lymphoblastic or myeloid leukemia in the Czech Republic. *J Med Virol* 81 : 258–263, 2009
 - 60 Imbert-Marcille BM, Tang XW, Lepelletier D, Besse B, Moreau P, *et al.* : Human herpesvirus 6 infection after autologous or allogeneic stem cell transplantation : a single-center prospective longitudinal study of 92 patients. *Clin Infect Dis* 31 : 881–886, 2000
 - 61 Yoshikawa T, Asano Y, Ihira M, Suzuki K, Ohashi M, *et al.* : Human herpesvirus 6 viremia in bone marrow transplant recipients : clinical features and risk factors. *J Infect Dis* 185 : 847–853, 2002
 - 62 Ihira M, Yoshikawa T, Suzuki K, Ohashi M, Suga S, *et al.* : Monitoring of active HHV-6 infection in bone marrow transplant recipients by real time PCR ; comparison to detection of viral DNA in plasma by qualitative PCR. *Microbiol Immunol* 46 :

- 701-705, 2002
- 63 Zerr DM, Corey L, Kim HW, Huang ML, Nguy L, *et al.* : Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis* 40 : 932-940, 2005
 - 64 Hentrich M, Oruzio D, Jager G, Schlemmer M, Schleuning M, *et al.* : Impact of human herpesvirus-6 after haematopoietic stem cell transplantation. *Br J Haematol* 128 : 66-72, 2005
 - 65 Ogata M, Kikuchi H, Satou T, Kawano R, Ikewaki J, *et al.* : Human herpesvirus 6 DNA in plasma after allogeneic stem cell transplantation : incidence and clinical significance. *J Infect Dis* 193 : 68-79, 2006
 - 66 Yamane A, Mori T, Suzuki S, Mihara A, Yamazaki R, *et al.* : Risk factors for developing human herpesvirus 6 (HHV-6) reactivation after allogeneic hematopoietic stem cell transplantation and its association with central nervous system disorders. *Biol Blood Marrow Transplant* 13 : 100-106, 2007
 - 67 Reddy S, Manna P : Quantitative detection and differentiation of human herpesvirus 6 subtypes in bone marrow transplant patients by using a single real-time polymerase chain reaction assay. *Biol Blood Marrow Transplant* 11 : 530-541, 2005
 - 68 Ljungman P, Wang FZ, Clark DA, Emery VC, Remberger M, *et al.* : High levels of human herpesvirus 6 DNA in peripheral blood leucocytes are correlated to platelet engraftment and disease in allogeneic stem cell transplant patients. *Br J Haematol* 111 : 774-781, 2000
 - 69 Ogata M, Satou T, Kawano R, Takakura S, Goto K, *et al.* : Plasma HHV-6 viral load-guided preemptive therapy against HHV-6 encephalopathy after allogeneic stem cell transplantation : a prospective evaluation. *Bone Marrow Transplant* 41 : 279-285, 2008
 - 70 Sashihara J, Tanaka-Taya K, Tanaka S, Amo K, Miyagawa H, *et al.* : High incidence of human herpesvirus 6 infection with a high viral load in cord blood stem cell transplant recipients. *Blood* 100 : 2005-2011, 2002
 - 71 Cone RW, Huang ML, Corey L, Zeh J, Ashley R, *et al.* : Human herpesvirus 6 infections after bone marrow transplantation : clinical and virologic manifestations. *J Infect Dis* 179 : 311-318, 1999
 - 72 Volin L, Lautenschlager I, Juvonen E, Nihtinen A, Anttila VJ, *et al.* : Human herpesvirus 6 antigenaemia in allogeneic stem cell transplant recipients : impact on clinical course and association with other beta-herpesviruses. *Br J Haematol* 126 : 690-696, 2004
 - 73 Le Cleach L, Joberty C, Fillet AM, Sutton L, Cordonnier C, *et al.* : Human herpesvirus 6 infection in patients with exanthema after allogeneic bone marrow transplantation. *Arch Dermatol* 134 : 759-760, 1998
 - 74 Yoshikawa T, Ihira M, Ohashi M, Suga S, Asano Y, *et al.* : Correlation between HHV-6 infection and skin rash after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 28 : 77-81, 2001
 - 75 Wilborn F, Brinkmann V, Schmidt CA, Neipel F, Gelderblom H, *et al.* : Herpesvirus type 6 in patients undergoing bone marrow transplantation : serologic features and detection by polymerase chain reaction. *Blood* 83 : 3052-3058, 1994
 - 76 Wang FZ, Dahl H, Linde A, Brytting M, Ehrnst A, *et al.* : Lymphotropic herpesviruses in allogeneic bone marrow transplantation. *Blood* 88 : 3615-3620, 1996
 - 77 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* 330 : 1356-1360, 1994
 - 78 Wainwright MS, Martin PL, Morse RP, Lacaze M, Provenzale JM, *et al.* : Human herpesvirus 6 limbic encephalitis after stem cell transplantation. *Ann Neurol* 50 : 612-619, 2001
 - 79 Zerr DM, Gupta D, Huang ML, Carter R, Corey L : Effect of antivirals on human herpesvirus 6 replication in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 34 : 309-317, 2002
 - 80 Zerr DM : Human herpesvirus 6 and central nervous system disease in hematopoietic cell transplantation. *J Clin Virol* 37 : Suppl 1 : S 52-S 56, 2006
 - 81 Fujimaki K, Mori T, Kida A, Tanaka M, Kawai N, *et al.* : Human herpesvirus 6 meningoencephalitis in allogeneic hematopoietic stem cell transplant recipients. *Int J Hematol* 84 : 432-437, 2006
 - 82 Fotheringham J, Akhyani N, Vortmeyer A, Donati D, Williams E, *et al.* : Detection of active human herpesvirus-6 infection in the brain : correlation with polymerase chain reaction detection in cerebrospinal fluid. *J Infect Dis* 195 : 450-454, 2007
 - 83 Seeley WW, Marty FM, Holmes TM, Upchurch K, Soiffer RJ, *et al.* : Post-transplant acute limbic encephalitis : clinical features and relationship to HHV 6. *Neurology* 69 : 156-165, 2007
 - 84 Vu T, Carrum G, Hutton G, Heslop HE, Brenner MK, *et al.* : Human herpesvirus-6 encephalitis following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 39 : 705-709, 2007
 - 85 Matà S, Guidi S, Nozzoli C, Orsi A, Pratesi A, *et al.* : Human herpesvirus 6-associated limbic encephalitis in adult recipients of unrelated umbilical cord blood transplantation. *Bone Marrow Transplant* 42 : 693-695, 2008
 - 86 Muta T, Fukuda T, Harada M : Human herpesvirus-6 encephalitis in hematopoietic SCT recipients in Japan : a retrospective multicenter study. *Bone Marrow Transplant* 43 : 583-585, 2009
 - 87 Ogata M, Satou T, Kawano R, Takakura S, Goto K, *et al.* : Correlations of HHV-6 viral load and plasma IL-6 concentration with HHV-6 encephalitis in allogeneic stem cell transplant recipients. *Bone Marrow Transplant* 2009 [Epub ahead of print]
 - 88 Carrigan DR, Drobyski WR, Russler SK, Tapper MA, Knox KK, *et al.* : Interstitial pneumonitis associated with human herpesvirus-6 infection after marrow transplantation. *Lancet* 338 : 147-149, 1991
 - 89 Cone RW, Hackman RC, Huang ML, Bowden RA, Meyers JD, *et al.* : Human herpesvirus 6 in lung tissue from patients with pneumonitis after bone marrow transplantation. *N Engl J Med* 329 : 156-161, 1993
 - 90 Buchbinder S, Elmaagacli AH, Schaefer 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
- 91 Amo K, Tanaka-Taya K, Inagi R, Miyagawa H, Miyoshi H, *et al.* : Human herpesvirus 6B infection of the large intestine of patients with diarrhea. Clin Infect Dis. 36 : 120-123, 2003
- 92 Matsuda Y, Hara J, Miyoshi H, Osugi Y, Fujisaki H, *et al.* : Thrombotic microangiopathy associated with reactivation of human herpesvirus-6 following high-dose chemotherapy with autologous bone marrow transplantation in young children. Bone Marrow Transplant 24 : 919-923, 1999
- 93 Belford A, Myles O, Magill A, Wang J, Myhand RC, *et al.* : Thrombotic microangiopathy (TMA) and stroke due to human herpesvirus-6 (HHV-6) reactivation in an adult receiving high-dose melphalan with autologous peripheral stem cell transplantation. Am J Hematol 76 : 156-162, 2004
- 94 Idutsu K, Abe Y, Otonari J, Tachikawa Y, Ohtsuka R, *et al.* : Human herpesvirus 6 encephalitis in a patient with adult T-cell leukemia/lymphoma. Rinsho Ketsueki 48 : 664-666, 2007 (*Abstract in English*)
- 95 Chemaly RF, Torres HA, Hachem R, Kontoyiannis DP, Safdar A, *et al.* : Human herpesvirus-6 DNAemia in immunosuppressed adult patients with leukemia at risk for mold infection. Hematologica 93 : 157-158, 2008
- 96 Krueger GR, Ablashi DV : Human herpesvirus-6 : a short review of its biological behavior. Intervirology 46 : 257-269, 2003
- 97 De Bolle L, Naesens L, De Clercq E : Update on human herpesvirus 6 biology, clinical features, and therapy. Clin Microbiol Rev 18 : 217-245, 2005