Relationship among human herpesvirus 6 reactivation, serum interleukin 10 levels, and rash/graft-versus-host disease after allogeneic stem cell transplantation

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Background: The relationship between herpesvirus reactivation and graft-versus-host disease (GVHD) after allogeneic stem cell transplantation (allo-SCT) is unclear.

Objective: We sought to examine the relationship between human herpesvirus (HHV) reactivation and rash/GVHD after allo-SCT by prospective evaluation.

Methods: Fifteen patients who had received allo-SCT underwent prospective serial examinations for human herpesvirus 6 (HHV-6), HHV-7, cytomegalovirus, and Epstein-Barr virus DNA in the blood by polymerase chain reaction and real-time polymerase chain reaction. Serum interferon gamma, interleukins 4 and 10, tumor necrosis factor alpha, and soluble interleukin 2 receptor (sIL-2R) were also measured.

Results: In 10 of 15 patients, macular/papular eruptions were seen after allo-SCT and GVHD was diagnosed. In 8 patients with rash, HHV-6 DNA levels correlated with the cutaneous manifestation. Interleukin 10 and sIL-2R also increased in association with rash.

Limitations: The number of patients in our study was relatively small. Not all patients were examined for cytokines and sIL-2R.

Conclusions: HHV-6 reactivation may be involved in the pathogenesis of rash/GVHD after allo-SCT. (J Am Acad Dermatol 2008;58:802-9.)

Human herpesviruses such as human herpesvirus 6 (HHV-6), HHV-7, and cytomegalovirus (CMV) infect the majority of the human population. These viruses have a tendency to remain latent in the body after the primary infection and then reactivate in either an immunocompetent or an immunocompromised host, including patients after allogeneic stem cell transplantation (allo-SCT).[1] The morbidity caused by CMV reactivation after allo-SCT is well known and has led to the monitoring of this virus and to the introduction of preemptive therapy.[2] Frequent reactivation of HHV-6 has also been demonstrated in immunocompromised patients after bone marrow transplantation

Abbreviations used:

allo-SCT:	allogeneic stem cell transplantation
CMV:	cytomegalovirus
EBV:	Epstein-Barr virus
GVHD:	graft-versus-host disease
HHV:	human herpesvirus
IFN:	interferon
IL:	interleukin
PCR:	polymerase chain reaction
RISCT:	reduced-intensity stem cell transplantation
SCT:	stem cell transplantation
sIL-2R:	soluble interleukin 2 receptor
TNF:	tumor necrosis factor

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Table I. Profiles of patients and transplantation procedures

Patient No.	Age/Sex	Underlying disease	Transplantation	Pretransplant conditioning	Prophylaxis for GVHD
1	54/M	MM	C (RISCT)	FLU, CPA, TBI	CSP, MMF
2	59/M	NHL	C (RISCT)	FLU, CPA, TBI	CSP, MMF
3	64/F	NHL	C (RISCT)	FLU, CPA, TBI	CSP, MMF
4	57/M	AML	C (RISCT)	FLU, CPA, TBI	CSP, MMF
5	62/M	AML	C (CT)	FLU, BU, Ara-C	CSP, MMF
6	40/F	ALL	C (CT)	CPA, Mesna, TBI	CSP, MTX
7	45/F	AML	P	FLU, BU, TBI	Tacrolimus, MTX
8	51/F	AA	P	FLU, CPA, TBI	CSP, MTX
9	19/M	AML	C (CT)	FLU, BU, Ara-C	CSP, MMF
10	57/F	CLL	P	FLU, BU	CSP
11	67/M	AML	C (RISCT)	FLU, CPA	CSP, MMF
12	22/M	Neuroblastoma	C (CT)	VP-16, Thiotepa, TBI	CSP, MMF
13	53/M	AML	C (CT)	FLU, BU, Ara-C	CSP, MTX
14	58/M	AML	P	FLU, BU, ATG	Tacrolimus, prednisolone
15	58/M	AML	P	FLU, BU	CSP, MTX

AA, Aplastic anemia; *ALL*, acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *Ara-C*, cytosine arabinoside; *ATG*, antithymocyte globulin; *BU*, busulfan; *C*, cord blood stem cell transplantation; *CLL*, chronic lymphoblastic leukemia; *CPA*, cyclophosphamide; *CSP*, cyclosporine; *CT*, conventional transplantation; *FLU*, fludarabine; *GVHD*, graft-versus-host disease; *MM*, multiple myeloma; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *NHL*, non-Hodgkin lymphoma; *P*, peripheral blood stem cell transplantation; *RISCT*, reduced-intensity stem cell transplantation; *TBI*, total body irradiation; *VP-16*, etoposide.

(BMT).[3-7] HHV-6 reactivation has been reported to be associated with febrile illness, rash, encephalitis, bone marrow suppression, interstitial pneumonitis, hepatitis, and thrombotic thrombocytopenic purpura, often with an uncertain causal relationship.[7-17]

Several researchers have suggested a relationship between HHV-6 reactivation and graft-versus-host-disease (GVHD) or rash after allo-SCT based on polymerase chain reaction (PCR) findings, viral isolation, or serological testing.[4-7] However, other researchers observed that there was no significant relationship between HHV-6 reactivation and rash or other clinical symptoms of GVHD.[9,18] Therefore, the role of HHV-6 reactivation on rash or GVHD remains unclear.

In the present study, we prospectively examined HHV-6, HHV-7, CMV, and Epstein-Barr virus (EBV) DNA in the peripheral blood of patients after allo-SCT at regular intervals; we also assessed the relationship among HHV reactivation, serum cytokine levels, and the appearance of rash or GVHD. We observed a close relationship among HHV-6, serum interleukin (IL)-10 and soluble IL-2 receptor (sIL-2R) levels, and rash after allo-SCT.

PATIENTS AND METHODS

Patients

In the period between May 2004 and June 2007, 15 consecutive patients who received allo-SCT for hematologic malignancy or neuroblastoma were enrolled (7 undergoing cord blood SCT, 8 undergoing peripheral blood SCT). The study was approved by the Ethics Committee of Nara Medical University. Characteristics of these patients are shown in Table I. Subjects consisted of 10 men and 5 women with a median age of 51 years (range, 19 to 67 years). Eight patients had acute myeloid leukemia; one, acute lymphoblastic leukemia; one, chronic lymphoblastic leukemia; two, non-Hodgkin's lymphoma; one, multiple myeloma; one, neuroblastoma; one, aplastic anemia.

Stem cell transplantation

Patients' profiles, regimens for pretransplant conditioning, and prophylaxis for GVHD are also shown in Table I. Five patients had received reduced-intensity conditioning stem cell transplantation (RISCT), others received conventional transplantation. Each patient was isolated in a laminar air-flow room, and standard decontamination procedures were followed.[19] Prophylaxis for *Pneumocystis carinii* infection consisted of sulfamethoxazole/trimethoprim. All patients were given acyclovir 1000 mg/d orally during the period between 8 days before and 35 days after allo-SCT for the prevention of herpes simplex virus infection.

Detection of human herpesviruses

Peripheral blood samples for the detection of HHVs were obtained weekly after allo-SCT except for cases 5 and 7; blood examinations of these 2 cases started at the appearance of rash. HHV-6, HHV-7, CMV, and EBV DNA were detected in whole blood by PCR. DNA was extracted from whole blood by means of a QIAamp DNA Blood mini-kit (Qiagen, Tokyo,