Association of Human Herpesvirus 6 Infection With Drug Reaction With Eosinophilia and Systemic Symptoms

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Background: There is a current debate regarding the association of human herpesvirus 6 (HHV-6) infection and drug reaction with eosinophilia and systemic symptoms (DRESS).

Methods: Seven consecutive patients hospitalized with DRESS were enrolled in a prospective study to evaluate evidence of active HHV-6 infection.

Observations: The imputable drugs were carbamazepine (5 patients), ibuprofen (1 patient), and sulfasalazine (1 patient). All patients were seropositive for anti-HHV-6 IgG antibodies. Anti–HHV-6 IgM antibodies were detected in 4 of the 7 patients with a seroconversion in 2 patients. Neither anti-cytomegalovirus nor anti–Epstein-Barr virus early antigen IgM antibody was detected. Human herpesvirus 6 genome was not detected by polymerase chain reaction in the first serum sample of all patients. It was weakly detected in skin lesions in the last patient tested by polymerase chain reaction but was not found in uninvolved skin.

Conclusions: The results suggest an association between HHV-6 active infection (primo-infection or reactivation) and severe DRESS. Absence of anti-cytomegalovirus or anti–Epstein-Barr virus early antigen IgM antibodies argues against a nonspecific viral reactivation. Human herpesvirus 6 infection may play a role in the development of DRESS in susceptible patients. Some drugs with reactive metabolites could favor reactivation and propagation of HHV-6.

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The role of viral infection is suspected in the development of some cutaneous drug eruptions. This is illustrated by the well-known ampicillin-induced exanthema in Epstein-Barr virus (EBV) mononucleosis syndrome. The high prevalence of drug-induced eruption in patients with human immunodeficiency virus (HIV) brings other convincing arguments for the intervention of viral infection in cutaneous drug adverse reactions.

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Recently, we and others reported an association between human herpesvirus 6 (HHV-6) infection and severe drug-induced hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms (DRESS).1,3 Some characteristics of this reactive condition suggest the possible role of an underlying trigger.3 The skin eruption usually begins a long time (a mean time of 4 weeks) after the intake of the drug. Some biological manifestations of DRESS are observed during viral infections, such as mononucleosislike syndrome and visceral involvement.7 We conducted a prospective study to evaluate the prevalence of HHV-6 infection in patients hospitalized in our dermatological department with DRESS syndrome.

RESULTS

Seven patients were included in this study. Clinical and biological manifestations of DRESS were usual (Table): high fever (≥39°C) (7/7 patients); facial edema (7/7 patients); erythoderma followed by an exfoliative dermatitis (6/7 patients); follicular skin eruption (1/7 patients); diffuse lymphadenopathy (5/7 patients); hypereosinophilia (>0.5 × 10⁹/L) (4/7 patients); atypical circulating lymphocytes (4/7 patients); and abnormal results of a liver function test (aspartate aminotransferase, >3 × reference range [40 U/L]) (5/7 patients). Hypogammaglobulinemia oc-
PATIENTS AND METHODS

PATIENTS

All consecutive adult patients hospitalized with DRESS syndrome were enrolled in this study. Criteria for diagnosis included clinical manifestations (fever, facial edema, exfoliative dermatitis, or lymphadenopathy) and biological manifestations (hyperesinophilia, atypical circulating lymphocytes, or liver cytolysis). Anamnestic data (drug intake, delay between first drug intake and the beginning of skin eruption, and delay between the beginning of skin eruption and admission) were collected. Clinical findings (fever, lymphadenopathy, exfoliative dermatitis, erythoderma, and mucous membranes lesions), biological findings (hyperesinophilia, liver analysis, atypical circulating lymphocytes, and blood γ-globulin level), and histological findings were recorded.

STUDY OF HHV-6 INFECTION

Human herpesvirus 6 infection was studied by performing serological tests on serum samples collected on admission and at different times after admission. Serum samples were stored at −20°C until used. The presence of anti–HHV-6 IgG and IgM antibodies was determined in the different serum samples at the same time for each patient using an indirect immunofluorescent antibody assay (immunofluorescence technique, HHV-6 IgM IFA, and HHV-6 IgG IFA; Biotrin International, Dublin, Ireland). Mononuclear cells infected with HHV-6 were used as a target. A polymerase chain reaction (PCR) procedure was performed on the first serum sample of each patient. Detection of HHV-6 DNA in the DNA extracted from skin lesions and uninvolved skin was done in the last patient with DRESS syndrome. The nested PCR was performed as previously reported.7

OTHER SEROLOGICAL ANALYSIS

Anti-cytomegalovirus (CMV) IgG and IgM antibodies were systematically and similarly searched for (Kit CMV-IgG ELA Test PKS médac and Kit CMV-IgM-ELA Test PKS médac; Medac, Hamburg, Germany). Serological analyses for other viral infections (including parvovirus B19, hepatitis B virus [HBV], hepatitis C virus [HCV], HIV, and EBV) were similarly carried out in most patients. The first serum samples of these 2 patients were negative for anti–HHV-6 IgM antibodies, and titers of anti-HHV-6 IgG antibodies were of 160 and 80, respectively. The second serum samples were positive for anti–HHV-6 IgM antibodies, and anti–HHV-6 IgG antibodies were greater than 640. Neither anti-CMV IgM antibodies nor anti-EBV early antigen IgM was detected in any studied sample. The results of serological tests for other viral infections (HBV, HCV, parvovirus B19, and HIV) were either negative or showed previous infection. One patient with anti–HHV-6 IgM antibodies was also HIV positive with a viral load of 5 log10 copies per milliliter (patient 7). Detection of HHV-6 genome by the nested PCR procedure in the first serum samples was always negative in the 7 patients. Human herpesvirus 6 DNA was weakly detected by nested PCR in the skin lesion of the patient infected with HIV (patient 7) although no HHV-6 genome was detected in his normal skin.

Clinicobiological manifestations and histological features were similar in the 2 groups of patients (patients with anti–HHV-6 IgM antibodies and patients without). One patient from the group with anti–HHV-6 antibodies (patient 1) presented on admission with very transitory buccal erosive lesions. Carbamazepine was undetectable by high-performance liquid chromatography in the first serum samples of patients with carbamazepine-induced DRESS.

The role of HHV-6 infection in DRESS is under debate. Since we reported on the first case suggesting this possible association, 4 new cases have been reported.1-4 Our first patient fulfilled the characteristics of DRESS (ie, erythoderma with edema of the face, fever, lymphadenopathy, hepatic failure, atypical circulating lymphocytes, and histological pseudomycosis fungoid pattern).1 The role of HHV-6 was suspected because she developed a hemophagocytic syndrome in the course of an anticonvulsant syndrome induced by phenobarbital.1 We looked for HHV-6 infection because this virus was known to be one of the agents associated with the hemophagocytic syndrome. A seroconversion for HHV-6 occurred on numerous consecutive serum samples. The role of HHV-6 was suspected to induce these 2 reactive conditions.

Hypersensitivity syndrome in the 4 other patients with an active HHV-6 infection was induced by allopurinol (1 patient), sulfasalazine (2 patients), and sodium valproate and ethosuximide (induced by 2 drugs in 1 patient). An active HHV-6 infection was demonstrated by an isolated dramatic rise in anti–HHV-6 IgG antibodies.2-4 Human herpesvirus 6 genome was also detected by PCR procedure and in situ hybridization in the skin lesions in 1 patient, but these studies were not done in uninvolved skin. Human herpesvirus 6 genome was detected from peripheral blood mononuclear cells in another patient. But the value of HHV-6 DNA detection in peripheral blood mononuclear cells is controversial because it can be present in healthy patients.

The absence of an increase in antibodies directed to other viruses (HHV-7, CMV, or EBV) excluded a nonspecific increase of antibodies due to polyclonal reactivation.
In these cases IgM antibodies were not detected, suggesting a reactivation. In our 4 cases the presence of IgM antibodies and the detection of HHV-6 DNA in a skin lesion (1 patient) bring further arguments for an association of HHV-6 active infection and the development of DRESS. Nevertheless, the positive result of the PCR analysis for HHV-6 from lesional skin in the patient with HIV must be interpreted with caution because circulating or infiltrating macrophages and lymphocytes could be responsible for this positive result, which was only observed in the lesional skin. The presence of IgM antibodies suggests a primary infection, but a reactivation cannot be excluded. The negative result of the PCR analysis on the first serum sample does not eliminate a primary infection. The data reported on the primary infection with mononucleosislike syndrome demonstrated that the viremia was of short duration and that the emergence of antibodies correlated with the disappearance of circulating viral genome. However, these negative results may argue for a reactivation.

This association between HHV-6 active infection and cutaneous drug adverse reaction seems to be specific to DRESS. Investigations of patients who developed adverse drug reactions different from DRESS did not show any increase in anti–HHV-6 antibodies.

Human herpesvirus 6 infection is most often asymptomatic and occurs in childhood before age 2 years. Seroprevalence in adults is near 100% as observed in our 7 patients. Symptomatic infection typically induces exanthema subitum, but severe primary infections may cause hepatitis, meningoencephalitis, interstitial pneumonitis, and mononucleosislike syndrome. These latter manifestations are very close to those of DRESS with fever, exfoliative dermatitis, lymphadenopathy, atypical circulating lymphocytes, and hepatic or renal involvement. In immunosuppressed patients (such as transplant recipients) HHV-6 primary infection or reactivation may induce a rejection of transplanted organs and death. Human herpesvirus 6 could be considered a paradigm of infection with high seroprevalence, which may reactivate and propagate in high-risk populations.

Our results support the hypothesis that HHV-6 infection is associated with some DRESS, but it is clear that the evidence of viremia remains the criterion standard for confirmation of an active infection. Comparisons between patients infected with HHV-6 and patients without active HHV-6 infection do not show major differences in clinical, biological, and histological manifestations. However, hypereosinophilia was found more often in the HHV-6–negative group. Hypogammaglobulinemia occurred in the 3 patients without HHV-6 active infection, but these results must be taken with caution because of the low number of patients. This absence of major differences between these 2 groups suggests that HHV-6 is only a trigger in this reactive condition, and other triggers (eg, other viruses, other immunoreactive conditions, or a state of immunosuppression) may play a role on a predisposed genetic background. Interestingly, the mother of one of our HHV-6 IgM–negative patients (patient 3) also had developed a drug-induced reaction to the same drug (carbamazepine), illustrating the importance of genetic background. The presence of hypogammaglobulinemia in anti–HHV-6 IgM–negative patients may argue for another pathway different from viral infection that favors this reactive condition.

### Clinical and Biological Characteristics of the 7 Patients

<table>
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<th>Characteristic</th>
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*HHV-6 indicates human herpesvirus 6; S1, first serum sample collected on admission; S2, second serum sample collected 2 weeks after admission; ND, not done (serum unavailable); plus sign, positive; minus sign, negative; CMV, cytomegalovirus; and EBV EA, Epstein-Barr virus early antigen.*
The pathophysiologic characteristics of DRESS remain unclear. The role of HHV-6 in the development of this syndrome is still hypothetical. Human herpesvirus 6 may interfere in the metabolism of the drug, such as in the enzyme responsible for its detoxification. We looked for carbamazepine by high-performance liquid chromatography in the serum samples of patients for whom this drug was the cause (Gilles Peytavin, PhD, data not shown, 1999); however, we could not find any persistent drug.

Viruses may induce antibodies to cytochrome P450 components. We looked for 1 type of this antibody directed against cytochrome P450 components (CYP2D6) that are detected in hepatitis C viral infection, but these antibodies were not detected in the serum samples by radioligand binding assay (Ana-Maria Yamamoto, MD, PhD, data not shown, 1999). Nevertheless, other components could be involved. Interestingly, Leeder et al recently identified an amino acid sequence (DMVL-NETLRL) that formed an epitope similar to the rat cytochrome P450 3A4, which is recognized by antibodies of some patients with DRESS. Results of a preliminary database search for proteins did not reveal any significant homology with known amino acid sequences of HHV-6 to explain a cross reactivity.

The current explanation for DRESS is immunologic; drug-reactive metabolites modify cellular protein and target an autoimmune response against skin or liver cells. However, reactive metabolites may also mediate immune response and induce reactivation or propagation of HHV-6. This virus remains latent in lymphocytes and monocytes and may persist at low levels in cells and tissues. Moreover, it has been recently demonstrated that the activation of CD4+ lymphocytes with interleukin-2 was essential for an efficient propagation of HHV-6.

The presence of HHV-6 DNA in skin lesions and the similarity between DRESS and severe HHV-6 primary infection in immunocompetent patients or reactivation and primary infection in immunocompromised patients suggest that the virus may itself be responsible for the skin lesions and some of the visceral involvement. This hypothesis is compatible with the fact that the clinical and biological features often progress several weeks after the drug treatment is discontinued.

We can propose that some DRESS may be the result of a cascade of successive events on a predisposed genetic background: (1) HHV-6 infection; (2) generation of anticytochrome P450 antibodies directed to some specific components (possibly cross reactivity between HHV-6 and some cytochrome P450 component amino acid sequences) or abnormal inherited detoxification pathway; (3) drug intake; (4) generation of reactive metabolites; (5) reactivation of HHV-6 infection or HHV-6 primary infection; or (6) development of HHV-6 active infection with strong immune response.

**CONCLUSIONS**

Our results suggest that HHV-6 active infection is associated with some DRESS. Some drugs with reactive metabolites could favor reactivation and propagation of HHV-6. We propose to systematically look for HHV-6 infection in patients with severe DRESS. The pathogenic role of HHV-6 infection in the development of the skin and visceral manifestations still needs to be demonstrated. A simple contingent reactivation from immunologic dysregulation remains another possible but less probable explanation. Knowledge of this association could urge us to propose an alternative therapy to corticosteroid administration in the management of these severe conditions. To identify high-risk patients, a better knowledge of the interaction of HHV-6 infection and drug metabolism is probably required.

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Dr Descamps designed the study, interpreted the data, and wrote the paper; Dr Edlinger performed the serologic analysis; Dr Grossin performed and reviewed with Dr Belaich the histologic analysis; Dr Fillet developed and performed the PCR procedure; and Drs Valence, Lebrun-Vignes, Belaich, and Crickx cared for the patients and contributed to the analysis of the data.

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