Human Herpesvirus 6 Infection as a Risk Factor for the Development of Severe Drug-Induced Hypersensitivity Syndrome

Yosuke Suzuki, MD; Reiko Inagi, PhD; Toshiya Aono, MSc; Koichi Yamanishi, MD; Tetsuo Shiohara, MD

Background: Drug-induced hypersensitivity syndrome is characterized by a severe, potentially fatal, multiorgan hypersensitivity reaction that usually appears after prolonged exposure to certain drugs. Its delayed onset and clinical resemblance to infectious mononucleosis suggest that underlying viral infections may trigger and activate the disease in susceptible individuals receiving these drugs.

Observations: A 60-year-old woman developed an itchy, generalized, erythematous, confluent rash on the 39th day of receiving allopurinol therapy. Even after she discontinued treatment with allopurinol, her skin lesions progressed to a severe blistering skin eruption. After the patient started oral prednisone therapy, her skin lesions resolved with desquamation. After complete resolution, rechallenge with allopurinol led to the development of an erythematous eruption. Titers of human herpesvirus 6 IgG antibodies dramatically increased with the development of the eruption. The results of a polymerase chain reaction and in situ hybridization indicated the presence of human herpesvirus 6 in the skin lesions, although human herpesvirus 7 DNA was detected only by in situ hybridization.

Conclusion: Reactivation of human herpesvirus 6, possibly in concert with human herpesvirus 7, can contribute to the development of a severe drug-induced hypersensitivity syndrome.

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Drug-induced hypersensitivity syndrome is characterized by a severe, potentially fatal, multiorgan hypersensitivity reaction. A limited number of drugs, including dapsone, phenytoin, allopurinol, and minocycline, are implicated in the induction of this syndrome. Although these drugs are most often administered for long periods with no problems, systemic hypersensitivity reactions to them, once induced, are serious and life threatening. Unlike other drug reactions, severe hypersensitivity reactions usually appear after prolonged exposure to the offending drug. The interval between the first dose of the drug and the onset of the reaction is 4 or more weeks. This long latency period suggests an idiosyncratic metabolic mechanism or underlying factors that trigger and activate the disease in susceptible individuals receiving the drugs, which are not per se sufficient to cause an outbreak of hypersensitivity reactions. Among other possible factors, there is an extensive theoretical basis for the hypothesis that underlying viral infections predispose patients to develop severe cutaneous reactions; the most convincing evidence supporting this theory has been the recent recognition that patients with acquired immunodeficiency syndrome have a 1000-fold higher risk of developing a severe drug reaction. The clinical features of hypersensitivity syndrome resemble those of infectious mononucleosis, and while skin eruptions usually occur in 3% to 15% of patients with acute Epstein-Barr virus (EBV) infection, they are observed in 95% to 100% of these patients treated with ampicillin. These observations strongly suggest that underlying viral infections contribute to the pathogenesis of severe cutaneous reactions to drugs.

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Human herpesvirus 6 (HHV-6), first isolated from patients with acquired immunodeficiency syndrome and lymphoproliferative disorders, is a cause of exanthem subitum, which infects at least 90% of individuals with HHV-6 by 2 years of age. The virus can persist in the host in a latent form after primary infection and...
is thought to be reactivated only during immunosuppression. The reactivation of the virus appears to contribute to the development of graft-vs-host disease, because an association between severe graft-vs-host disease and high levels of HHV-6 has been reported by some investigators. Thus, HHV-6 may well be of pathogenic importance in relation to an immunosuppressive state. However, a causal association between drug rash and reactivation of HHV-6 has never been investigated. We describe herein a patient who developed a severe blistering skin eruption 6 weeks after commencing allopurinol therapy in whom we observed the reactivation of HHV-6.

A 60-year-old Japanese woman was admitted to our university hospital on August 9, 1996, because of a 6-day history of an itchy, generalized, erythematous, confluent rash. Seven weeks earlier, the patient had been prescribed 300 mg/d of allopurinol for hyperuricemia, which she had taken until 1 day before admission. On the 39th day of medication, the eruption began with erythema on her neck and became generalized over the next 4 days. Three days before admission, the patient had been prescribed by her general practitioner 10 mg/d of prednisone for the rash, which she took before admission without benefit. Results from a physical examination revealed swelling of her face and erythematous macules, some of which coalesced to form large areas of erythema, particularly on the trunk and arms (Figure 1). The patient had bilateral cervical lymphadenopathy and tonsillar pharyngitis with a fever (body temperature, 38°C). She was negative for Nikolsky sign and her mucous membranes were not affected. The diagnosis of a drug-induced cutaneous reaction was entertained, and allopurinol therapy was discontinued. However, even after the patient stopped treatment with allopurinol, her skin lesions progressed to severe tense bullae covering both arms. Toxic epidermal necrolysis or pemphigoid was also suspected, and a skin biopsy was performed. Results from a skin biopsy specimen demonstrated focal hydropic and vacuolar degeneration of epidermal basal cells, with marked exocytosis of atypical lymphoid cells into the epidermis and a dense perivascular infiltrate composed of predominantly atypical lymphoid cells. These histological findings were compatible with early toxic epidermal necrolysis or erythema multiforme. Negative results of direct immunofluorescence for immunoglobulins and complement excluded pemphigoid. Laboratory investigations on admission revealed the following values: white blood cell count, 21 × 10^9/L (normal range, 3.8 × 10^10/L); with 60% atypical lymphocytes; erythrocyte sedimentation rate, 4 mm/h; cyclic adenosine monophosphate receptor protein, 4.6 nmol/L; aspartate aminotransferase, 241 U/L (normal range, 20-47 U/L); alanine aminotransferase, 364 U/L (normal range, 3-30 U/L); lactate dehydrogenase, 1735 U/L (normal range, 200-470 U/L); and CD4/CD8 lymphocyte ratio, 0.56 (normal range, 1.03-2.36). Oral prednisone, 30 mg/d, was administered on August 16, 1996 (Figure 2). Within 3 days, the patient's general condition and skin improved rapidly, and her skin lesions resolved with desquamation followed by marked scaling of the involved sites. By August 23, the patient had completely recovered. Thirteen days after she discontinued treatment with prednisone, the patient was challenged with 1/10 of a single therapeutic dose of oral allopurinol. Within 4 hours, an erythematous eruption appeared on the previously affected sites. On March 10, 1997, the patient was readmitted for oral rechallenge with allopurinol, because previous studies have demonstrated that the ampicillin rash observed in patients with acute EBV infection cannot be reproduced when challenged after recovery from infectious mononucleosis. In our patient, an erythematous eruption was reproduced in the same location 5 hours after rechallenge with a single therapeutic dose of allopurinol.

Samples of the patient's serum obtained at various time-points after onset of the eruption (August 16, August 26, September 2, and September 17, 1996, and March 7, 1997) were tested for EBV, cytomegalovirus, herpes simplex virus, measles virus, rubella virus, and HHV-6 IgG. As shown in Figure 2, titers of HHV-6 IgG antibodies dramatically increased from 80 to 1280 within the following week, but no specific IgM was detected, suggestive of the reactivation of HHV-6 rather than primary infection. While no marked antibody titer alterations were detected with EBV, cytomegalovirus (Figure 2), herpes simplex virus, measles, or rubella, the antibody titer for HHV-6 increased considerably during the development of the eruption. Nevertheless, we cannot definitely exclude the possibility that the first rash observed on August 3 was due to primary infection with HHV-6, because no materials at the time of the first clinical signs were available to determine whether the patient's eruption was caused by reactivation or primary infection of HHV-6.

**DETECTION OF HHV-6 AND HHV-7 DNA IN SKIN LESIONS**

A more direct approach to delineating the role of HHV-6 in the development of severe hypersensitivity reactions is to determine whether HHV-6 DNA is present in the
pathologic lesions. We examined DNA from paraffin-embedded skin biopsy specimens obtained during the course of the patient's hypersensitivity reactions (August 9, 1996) and after clinical challenge (March 13, 1997) using polymerase chain reaction (PCR). The PCR was performed with primers 5'-GGATCCGATATCACGTACCATCTGT-3' and 5'-GGATCCGATATCACGTACCATCTGT-3' to amplify the HHV-6 glycoprotein H region. The specificity of the PCR products was confirmed by Southern blot hybridization with an alkaline phosphatase–labeled HHV-6 glycoprotein H–specific oligoprobe (5'-alkaline phosphatase–labeled HHV-6 glycoprotein H–specific oligoprobe (5'-AGTTCCAGAC-TGCAATCG-3' and 5'-CACAAAAGGCTGCTATCA-3') for HHV-7 major capsid protein region. The mixture of HHV-6 immediate early–, polymerase–, and glycoprotein H–specific PCR probes was used for in situ hybridization of HHV-6 DNA detection.

As shown in the Table, based on DNA extracted from a biopsy specimen obtained on August 9, PCR results were positive for HHV-6 DNA but negative for HHV-7. The results of in situ hybridization analyses indicated the presence of HHV-6 (Figure 3) and HHV-7 DNA sequences in infiltrating mononuclear cells in the dermis, especially those around the blood vessels, during the development of severe hypersensitivity reactions. Comparable findings from PCR and in situ hybridization were observed only for HHV-6. In the tissue specimen obtained after clinical challenge, HHV-6 DNA was detected by both PCR and in situ hybridization, but HHV-7 was not. The reasons for the discrepant results for HHV-7 DNA between PCR and in situ hybridization are not clear at present because in situ hybridization is generally regarded as less sensitive than PCR.

To ensure that a dramatic rise (more than 30-fold) in HHV-6 antibody titers and the detection of viral DNA in tissue samples are characteristic of hypersensitivity syndrome, we investigated whether significant antibody titer alterations could be observed in other patients with a mild form of drug-induced eruptions, and whether viral DNA could be detected in tissue samples from control patients. The results of the serial HHV-6 antibody measurements of serum samples obtained at various time-points during the course of illness demonstrated no marked antibody titer alterations. We also could not detect HHV-6 or HHV-7 DNA in tissue samples from the control patients at the peak of clinical symptoms either by PCR or in situ hybridization.

**Figure 2.** Clinical course of a patient with a severe drug-induced hypersensitivity syndrome in relation to antibody titers against various viruses. The shaded arrow indicates clinical challenge with 1⁄10 of a single therapeutic dose of allopurinol. The black arrow indicates clinical rechallenge with a single therapeutic dose. As controls, human herpesvirus 6 (HHV-6) antibody titers were sequentially measured in 3 patients with a mild form of drug-induced eruptions who had measurable antibody levels in the initial serum samples. A significant (>4-fold) increase in the titers was not detected in the case patients during an observation period of 2 to 8 weeks; only a 2-fold increase (from 80 to 160) or decrease (from 160 to 80) was noted. CMV indicates cytomegalovirus; EBV, Epstein-Barr virus; VCA, virus capsid antigen; EBNA, Epstein-Barr nuclear antigen; and ND, not determined.
This article presents the first evidence for a possible association between severe drug-induced hypersensitivity syndrome and reactivation of HHV-6. Considering the documented ability of HHV-6 to induce severe infectious mononucleosis, graft-vs-host disease, and interstitial pneumonitis, our case indicates that reactivation of HHV-6, possibly in concert with HHV-7, contributes in some way to the development of drug-induced hypersensitivity syndrome. This view is supported by the lack of detectable HHV-6 DNA sequences in tissue samples obtained from patients with mild drug-induced eruptions; in these patients, no notable antibody titer alterations with HHV-6 were noted during and after the development of the eruptions. In addition, the dramatic increase in titters of HHV-6 IgG antibodies seen in our patient was observed in other patients with a severe drug-induced hypersensitivity syndrome, although the presence of HHV-6 DNA in their skin lesions was not constantly demonstrated by both PCR and in situ hybridization (data not shown). These observations make it unlikely that the reactivation of HHV-6 is a mere epiphenomenon of the drug-induced eruptions. Nevertheless, we cannot entirely exclude the possibility that the presence of HHV-6 DNA sequences in skin biopsy specimens might reflect a passive blood contamination, because neither PCR nor in situ hybridization analyses of the uninvolved skin were performed on our patient. However, this possibility was unlikely, because detection of the HHV-6 genome in peripheral mononuclear cells by PCR was only possible when samples were obtained during convalescence but not at the peak of the clinical symptoms (Y. S. and T. S., unpublished data, 1998).

The similar date of onset of cutaneous manifestations and the dramatic increase in the numbers of atypical lymphocytes (predominantly composed of CD8+ T cells) indicate that skin lesions in this patient could be induced by a massive expansion of virus-specific CD8+ T cells and nonantigen-specific CD4+ and CD8+ T cells. This expansion would selectively eliminate infected cells on the one hand and have particularly devastating consequences for the patient, such as a severe multiorgan hypersensitivity reaction, on the other. A similar hypothesis has been voiced by Chosidow et al. This massive expansion may in turn delay the development of virus-specific antibody responses by causing a striking depletion of CD4+ helper T cells and B cells responsible for antibody production. This mechanism could explain why a dramatic increase in titers of HHV-6 IgG antibodies was delayed for 3 to 4 weeks despite the detection of cells infected with HHV-6 in the skin lesions of our patient on August 9. Thus, it seems safe to assume that in our patient, reactivation of HHV-6 would have occurred at least 1 to 2 weeks before the onset of the rash, because an expansion of virus-specific CD8+ cytotoxic T lymphocytes and bystander T cells and their subsequent infiltration into the skin would be expected to occur in response to reactivation of HHV-6 as a host defense mechanism involved in limiting viral growth. However, because we did not detect HHV-6 DNA in the patient’s skin before the development of hypersensitivity syndrome and prior to rechallenge, we could not directly prove this assumption. This assumption could be directly investigated if it were possible to identify an area of clinically healthy skin that was destined to develop lesions and to perform PCR and in situ hybridization analyses of those lesions.

If reactivation of HHV-6 is involved in the pathogenesis of hypersensitivity syndrome, then the question arises why oral corticosteroids, which may cause viral reactivation, are effective for the treatment of this syndrome. These seemingly contradictory findings are not easily reconciled unless one assumes that epidermal cell injury in this syndrome is mediated by uncontrolled activation of CD8+ cytotoxic T lymphocytes that can rapidly destroy HHV-6–infected cells, and that such harmful immune responses would be reduced to a clinically relevant degree by oral corticosteroid therapy, which may in turn allow for persistent HHV-6 infection. Thus, the balance between viral reactivation and the extent of this T-cell response would determine whether excessive immune protection against a virus with severe immunopathological characteristics or viral persistence due to reduced T-cell responses will predominate.

The observation that rechallenge with allopurinol after clinical resolution in our patient led to the development of an erythematous eruption is in sharp contrast to the hypersensitivity reactions to ampicillin observed in patients with primary EBV infection: skin rashes could not be reproduced when ampicillin was given to those patients after they had recovered from the acute clinical symptoms of infectious mononucleosis. These results indicate that hypersensitivity reactions to ampicillin may occur exclusively with disseminated active EBV infections. Therefore, our case is more likely explained by assuming that after clinical resolution, HHV-6 may be persistently reactivated. In fact, in accordance with this assumption, the results of serologic studies and the detection of HHV-6 DNA in skin samples obtained at various timepoints suggest the persistent reactivation of HHV-6 in this patient for a prolonged period after clinical resolution of severe hypersen-
sensitivity syndrome. However, how can this possibility be reconciled with our view that reactivation of HHV-6 is a risk factor for the development of hypersensitivity syndrome? A likely interpretation of these observations is that reactivation of HHV-6 may not represent a sole triggering factor for an outbreak of the disease and that additional factors, probably acting synergistically with reactivated HHV-6, are needed to activate hypersensitivity syndrome. In this regard, it is of particular interest to hypothesize that reactivation of HHV-6 may have potentially serious interactions with some of the enzymes that detoxify drugs, such as cytochrome P-450, although the specific interactions remain to be assessed. Recent studies have indicated that viral infections may develop autoantibodies directed against cytochrome P-450 enzymes.22,23 Although it remains unknown whether all these antibodies to P-450 can inhibit the function of their antigen, one possible mechanism for the development of hypersensitivity syndrome could be that reactivation of HHV-6 may inhibit P-450, which is involved in the detoxification of drugs, probably via the production of antibodies to P-450.

The role of HHV-7 in the development of drug-induced hypersensitivity syndrome is unclear; however, preceding or concurrent infection with HHV-7 may be a prerequisite for the reactivation of HHV-6, because recent studies24 have shown that HHV-6 is reactivated from latently infected peripheral blood mononuclear cells following reactivation of HHV-7 by T-cell activation. These considerations raise the alternative possibility that reactivation of HHV-6 likely reflects down-stream events caused by drug-induced T-cell activation. Whatever the mechanism responsible for the reactivation of HHV-6 in drug-induced eruptions, reactivated HHV-6 could lead to serious secondary pathogenic events. Prompt recognition of the reactivation of HHV-6 and HHV-7 in patients with hypersensitivity reactions to certain drugs would provide alternative therapeutic approaches to drug-induced hypersensitivity syndrome for which no specific treatment yet exists, because HHV-6 and HHV-7 infections can be effectively controlled by treatment with ganciclovir and foscarnet sodium.25

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Reprints: Tetsuo Shiohara, MD, Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan.

REFERENCES


25. Singh N, Carrigan DR. Human herpesvirus-6 in transplantation: an emerging patho-

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