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CLINICAL REPORT

Human Herpes Virus 6 Encephalitis in Allopurinol-induced Hypersensitivity Syndrome

TARO MASAKI[1], ATSUSHI FUKUNAGA[1], MIKIKO TOHYAMA[2], YOSHIYUKI KODA[3], SHIHO OKUDA[3], NOBUYA MAEDA[3], FUMIO KANDA[3], MASAKI YASUKAWA[4], KOJI HASHIMOTO[2], TATSUYA HORIKAWA[1] and MASATO UEDA[1]*

*[1]Division of Dermatology, Clinical Molecular Medicine, Faculty of Medicine, Kobe University Graduate School of Medicine, [2]Department of Dermatology, Ehime University School of Medicine,[3]Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Clinical Molecular Medicine, Faculty of Medicine, Kobe University Graduate School of Medicine, Kobe and [4]The First Department of Internal Medicine, Ehime University School of Medicine, Ehime, Japan. *E-mail: mueda@med.kobe-u.ac.jp*

Hypersensitivity syndrome is one of the most severe forms of drug eruption, and is characterized by a severe, potentially lethal, multiorgan involvement. Recently, reactivation of human herpesvirus 6 (HHV-6) has been suggested to be involved in this syndrome, although the exact role of HHV-6 remains elusive. In addition to exanthem subitum, neurological illnesses, such as infantile febrile illness without rash and encephalitis in immunocompromised patients have been attributed to HHV-6. A 51-year-old man developed a generalized erythematous eruption during treatment with allopurinol. Prednisolone improved his condition, but after the dose of prednisolone was reduced neurological abnormalities such as mental deterioration and positive meningeal signs developed. HHV-6 DNA in his blood by PCR analysis was positive. Furthermore, we detected HHV-6 DNA in the cerebrospinal fluid. The titers of anti-HHV-6-IgG increased during the course. His neurological symptoms gradually improved and no neurological sequelae were noted. Neurological abnormalities associated with hypersensitivity syndrome are very rare. However, the detection of HHV-6 DNA in the cerebrospinal fluid strongly indicates an involvement of reactivated HHV-6 in encephalitis. *Key words: herpesvirus; cerebrospinal fluid; neurological symptoms.*

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Masato Ueda, MD, Division of Dermatology, Clinical Molecular Medicine, Faculty of Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: mueda@med.kobe-u.ac.jp

Hypersensitivity syndrome is a special kind of drug reaction characterized by an acute, widespread skin eruption, fever, enlarged lymph nodes, and multiorgan involvement. Lymphocytosis, atypical lymphocytes, eosinophilia, high levels of lactate dehydrogenase and hepatitis frequently accompany this syndrome and relapses often occur, even after use of the causative drug is stopped, and especially when corticosteroid treatment is decreased (1). The multiorgan involvement also includes renal failure, restrictive pulmonary insufficiency, and neurological dysfunction. In the acute state, hepatitis and renal failure can be lethal. A limited number of drugs, including dapsone, phenytoin, carbamazepine, minocycline, sulfasalazine and allopurinol, have been implicated in the induction of this syndrome (1). Hypersensitivity syndrome seems to be an idiosyncratic reaction; individual differences in the metabolism of aromatic anticonvulsants or sulfonamides may predispose to such reactions. Recently, reactivation of human herpesvirus 6 (HHV-6) has been suggested to be involved in this syndrome, based mainly on increased titers of HHV-6 IgG antibodies in the sera of patients (2–4). However, the exact role of HHV-6 in hypersensitivity syndrome is still unclear.

Primary HHV-6 infection presents as exanthema subitum (5) or infantile febrile illness without rash (6). The latter condition is sometimes associated with seizures, meningitis and encephalitis. In healthy adults, primary HHV-6 infection is very rare and it may induce hepatitis and a severe infectious mononucleosis-like illness (7). In immunocompromised patients undergoing liver, kidney, or bone marrow transplants, HHV-6 may be reactivated, sometimes causing severe and fatal diseases, including interstitial pneumonitis, graft-vs.-host disease, or encephalitis (8–10).

We present here a patient with hypersensitivity syndrome due to treatment with allopurinol, who suffered a reactivation of HHV-6 and who developed meningoencephalitis during subsequent tapering-off of corticosteroid therapy.

CASE REPORT

A 51-year-old Japanese man with a 6-month history of gout and hypertension had been treated with loxoprofen, colchicine and allopurinol since June 10, 2000, and with nicardipine hydrochloride since June 12, 2000. Loxoprofen and colchicine were then discontinued because the pain had been relieved. On July 1, 2000, 23 days after

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treatment with allopurinol had been initiated, the patient developed a generalized erythematous eruption. On July 3 and 4, 20 mg prednisolone was given intravenously by his general practitioner. Treatment with allopurinol and nicardipine hydrochloride was discontinued on July 10, but the patient developed a high fever, liver dysfunction and an erythrodermic eruption. The patient was admitted to our hospital on July 13, 2000.

Physical examination revealed a fever (body temperature, 37.8°C), swelling of the face and neck, and bilateral cervical lymphadenopathy. A generalized maculopapular rash coalesced to form erythroderma (Fig. 1). No mucosal lesion was observed. A skin biopsy specimen obtained from the patient's forearm showed a lymphocytic infiltration in the epidermis with necrotic keratinocytes, liquefaction degeneration of basal cells, and a perivascular lymphocytic infiltration in the dermis. Laboratory findings on admission are presented in Table 1.

The patient was diagnosed as having hypersensitivity syndrome with hepatitis due to treatment with allopurinol. Treatment with 40 mg/day oral prednisolone was started on July 13 and then tapered-off, as the patient's clinical manifestations had improved. On July 26, 3 days after the dose of prednisolone was reduced to 20 mg/day, the patient suddenly developed a high fever and mental deterioration with decreased consciousness and speech disturbance. The neurological manifestations and findings were as follows. The patient was conscious but was unable to respond to simple commands. Cranial nerves were intact except for a sluggish light reflex. Kernig's sign and nuchal stiffness were positive. Myoclonus appeared on his face and all

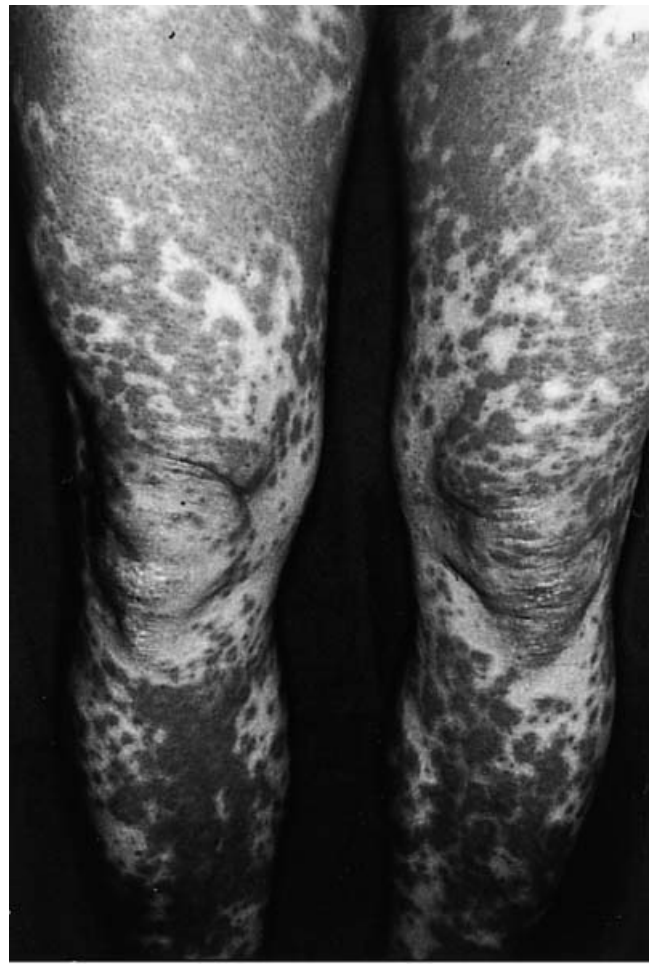

Fig. 1. Erythrodermic erythematous macules on the patient's legs.

Table I. *Summary of the clinical course, treatment and laboratory data in a 51-year-old male treated with allopurinol from June 12–July 10*

Date (month/day)	7/1	7/13	7/14	7/17	7/21	7/25	7/26	7/28	7/30	8/31
Erythema	+++	+++	+++	+	–	–	–	–	–	–
Neurological symptoms	–	–	–	–	–	–	+++	+++	++	–
Prednisolone dose (mg/day)		40	40	40	30	20	20	40	40	5
WBC ($4\sim8.5\times10^9$/L)[a]		14.1	14.9	15.2	7.9	6.1		15.9	9.7	9.0
CRP (mg/dl)		3.86	2.50	0.33	0.73	1.83		1.32	1.63	0.51
LDH (117∼205 U/L)[a]		509	452	363	296	292		346	226	264
ALT (7∼34 U/L)[a]		188	150	181	137	125		196	166	70
AST (9∼36 U/L)[a]		44	27	38	28	32		59	28	14
Anti-HHV-6 IgG			×20	×20	×160	×2,560			×20,480	×25,60
HHV-6 DNA[b]										
Peripheral blood			–		++	–			±	
CSF								–		
CSF										
Mononuclear cell ($<5/mm^3$)[a]								3∼4		
Total protein (0∼50 mg/dl)[a]								77		
Glucose (50∼75 mg/dl)[a]								86	73	

[a]Normal range.
[b]DNA extracted from peripheral blood or cerebrospinal fluid (CSF) was examined by polymerase chain reaction (PCR). WBC: white blood cell; CRP: C-reactive protein; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

extremities intermittently. His muscular strength was normal and deep tendon reflexes were slightly increased. Pathological reflexes were not observed. Electroencephalography revealed a diffuse and non-specific slowing. Results of cerebrospinal fluid (CSF) analysis are presented in Table I. Magnetic resonance imaging demonstrated no neuroimaging abnormalities. Intravenous administration of prednisolone at 40 mg/day, acyclovir, fosfomycin and immunoglobulins were commenced. The neurological symptoms gradually improved and the patient began to speak fluently on July 31 and to walk on August 9. Prednisolone was tapered-off gradually and was finally stopped on September 3; no neurological sequelae were observed.

Culture of HHV-6, PCR assay for HHV-6 DNA, genotyping of HHV-6 and serologic testing for antibodies to HHV-6 were performed as described elsewhere (4). DNA extracted from paraffin-embedded sections and frozen skin tissue biopsied on July 13 was examined for the presence of HHV-6 by PCR, but showed negative results. Analysis of DNA extracted using a QIAmp blood maxi kit (QIAGEN, Tokyo) from whole blood cells showed no band in the first sample (July 14), a strong band on July 21, and weaker bands on July 25 and July 30 (Fig. 2). In the same period of time, the number of peripheral blood mononuclear cells (PBMC), infected latently by HHV-6, dropped from 2.8×10^9/l to 0.8×10^9/l, suggesting that the positive results of HHV-6 DNA in the blood were not due to increased numbers of PBMC. The genotype was identified as HHV-6 variant B. CSF obtained on July 28 showed a positive band for HHV-6 DNA by PCR. We were unable to isolate HHV-6 in culture of the peripheral blood obtained on July 30. Anti-HHV-6 IgG titers are shown in Table I. Antibodies to Epstein-Barr virus did not increase during the course of the patient's illness. We did not measure antibodies to HHV-7, but PCR analysis of HHV-7 DNA did not show positive reactions in the blood.

After prednisolone was stopped, patch testing of oxypurinol (a metabolite of allopurinol), nicardipine hydrochloride, loxoprofen and colchicine mixed in petrolatum at 10% (by volume) was performed, but negative results were obtained. The patient refused oral challenge tests.

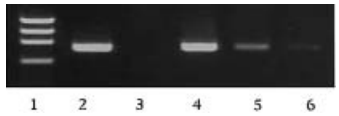

Fig. 2. DNA from peripheral blood cells showed amplified human herpesvirus 6 DNA product. Lane 1: molecular weight markers; lane 2: positive control; lanes 3~6: samples obtained on July 14, July 21, July 25 and July 30, respectively.

DISCUSSION

With the exception of the neurological abnormalities, the clinical and pathological features in this case were typical of hypersensitivity syndrome. Although we were unable to show positive patch tests or to perform challenge tests, allopurinol was strongly suspected to be the causative agent since it is well known that it induces hypersensitivity syndrome, whereas the other medications used by this patient are not known to do so (1).

In several recent studies it has been shown that HHV-6 infection (reactivation) is associated with hypersensitivity syndrome (2–4). Descamps et al. (2) reported a case of hypersensitivity syndrome owing to use of phenobarbital, which showed increased antibody titers to HHV-6. Suzuki et al. (3) reported a case due to allopurinol, which also showed increased titers of HHV-6 IgG. In addition, they detected HHV-6 DNA in skin lesions biopsied 6 days after the initiation of the rash and 3 days after an oral challenge test which induced the symptoms. Tohyama et al. (4) reported on two patients with hypersensitivity syndrome as a result of treatment with sulfasalazine, who both showed increased titers of HHV-6 IgG, and in one case they isolated HHV-6 virus in PBMC. They also detected HHV-6 DNA from frozen skin specimens obtained on the 19th hospital day. Suzuki et al. (3) hypothesized that the rash associated with hypersensitivity syndrome is induced in response to reactivation of HHV-6 as a host defense mechanism involved in limiting viral growth. In contrast, Tohyama et al. (4) hypothesized that hypersensitivity syndrome has two stages: first, T cells are activated as an immune response to reactive drug metabolites, and second, HHV-6 is then reactivated by the activated T cells, thereby affecting the general condition of the patients and causing infectious mononucleosis-like symptoms. In the present case, we were unable to detect HHV-6 DNA using PCR in skin specimens obtained from the patient on the 13th day after the start of the rash. Furthermore, we could not detect HHV-6 DNA by PCR in his peripheral blood on the 14th day after the rash first appeared, but we did detect HHV-6 on the 21st day, when the HHV-6 IgG titer began to increase. The sum of these data fit with the hypothesis of Tohyama et al. (4) that the reactivation of HHV-6 occurs subsequent to the drug-induced T-cell activation.

We assumed that the meningoencephalitis in the present case was due to HHV-6, because it has been shown that HHV-6 DNA in CSF does not occur in latent infection; i.e. detection in a patient with neurologic symptoms is evidence of an active CNS infection caused by HHV-6 (11). In patients with exanthem subitum, primary infection of HHV-6 can cause complications of the CNS, including febrile seizures and encephalitis/encephalopathy. In addition, HHV-6 has been implicated as the causative agent of severe cases

of meningoencephalitis in normal and in immunocompromised patients (9, 10). A review of 14 cases of encephalitis caused by HHV-6 in 13 bone marrow transplant recipients and in one liver transplant recipient revealed various clinical and laboratory characteristics of this condition (10). Changes in mental status ranging from confusion to coma (92%), seizure (25%), headache (25%) and speech disturbance (25%) were the predominant clinical presentations. Focal neurologic symptoms (arm weakness and cranial nerve palsies) were observed in 17% of the patients. Fever was documented in 25% of the patients. CT scans were abnormal in only 1 out of 12 patients and MRIs were abnormal in 2 out of 8 patients. In general, there was no evidence of CSF pleocytosis. Overall, mortality in transplant recipients with HHV-6 encephalitis was 58% (7 out of 12) and death was considered attributable to HHV-6 infection in 42% (5 out of 12) of the patients. Cures were documented in 7 out of 8 patients who received ganciclovir or foscarnet for ≥ 7 days, compared with 0 out of 4 patients who did not receive these drugs or received them for <7 days. In our patient, many features were consistent with those of HHV-6 encephalitis in transplant patients: the main clinical presentation was coma, there were no focal neurologic symptoms, the MRI showed no abnormality, and CSF pleocytosis was lacking. In contrast, the present case showed complete resolution without treatment with ganciclovir or foscarnet. We used intravenous immunoglobulins, but their effects on HHV-6 infections are not currently known. We increased the dose of prednisolone when the patient developed neurological abnormalities because they occurred just after the dose of prednisolone had been reduced. Acyclovir was administered because we suspected herpes simplex meningoencephalitis, but it is known that HHV-6 lacks a thymidine kinase and is therefore not susceptible to acyclovir. Although the patient's neurological symptoms due to HHV-6 improved without any residual sequelae, it was difficult to evaluate whether the treatment we provided was effective, and it could be speculated that meningoencephalitis in hypersensitivity syndrome may be self-limited when the patient is immunocompetent.

A search of the literature revealed 4 cases of hypersensitivity syndrome associated with meningitis, all due to carbamazepine (12–15). In 3 of these cases, the skin rash and meningitis developed simultaneously (12–14), and in the remaining case (15), meningitis developed 2 weeks after the skin rash developed, which is similar to the present case. All patients spontaneously resolved upon discontinuation of the carbamazepine. One patient was left with subtle memory impairment 2 months after the start of the disease (15).

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