

Severe Hypersensitivity Syndrome Due to Sulfasalazine Associated With Reactivation of Human Herpesvirus 6

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Background: A severe adverse reaction to sulfasalazine therapy has been associated with hypersensitivity syndrome, the clinical features of which are similar to infectious mononucleosis. No serologic evidence of viral infections has been reported with this syndrome; however, human herpesvirus 6 infection has not been specifically investigated, which could cause an infectious mononucleosislike syndrome.

Observations: We report 2 cases of hypersensitivity syndrome induced by the use of sulfasalazine. The clinical features of the syndrome appeared 18 and 32 days after administration of sulfasalazine. Clinical signs included a maculopapular rash progressing to exfoliative eryth-

roderma, fever, and lymphadenopathy. Leukocytosis, atypical lymphocytes, liver dysfunction, and renal disturbance were also observed. In 1 patient, human herpesvirus 6 variant B was isolated from peripheral blood mononuclear cells, and in both patients anti-human herpesvirus 6 IgG titers increased considerably.

Conclusions: Two cases of hypersensitivity syndrome due to sulfasalazine use were associated with the reactivation of human herpesvirus 6, which may be a required cause of hypersensitivity syndrome.

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SULFASALAZINE IS a common therapeutic drug used to treat inflammatory bowel disease, rheumatoid arthritis, and psoriatic arthritis. A severe adverse reaction to sulfasalazine has been identified as a type of hypersensitivity syndrome.¹⁻⁴ The reaction, including fever, skin rash, lymphadenopathy, and internal organ involvement, usually occurs 2 to 5 weeks after initiating treatment with sulfasalazine. The clinical features of hypersensitivity syndrome are similar to those of infectious mononucleosis.

*For editorial comment
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Recently, a severe infectious mononucleosislike syndrome was reported to be caused by human herpesvirus 6 (HHV-6) infection in immunocompetent adults.⁵⁻⁷ Its clinical features are characterized by skin rash, generalized lymphadenopathy, high fever, liver dysfunction, leukocytosis, and atypical lymphocytosis. We report 2 cases of sulfasalazine-induced severe hypersensitivity syndrome associated with the reactivation of HHV-6.

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REPORT OF CASES

CASE 1

A 29-year-old Japanese man with an 8-year history of psoriatic arthritis had been treated with numerous agents, including loxoprofen, cyclosporine, and prednisolone, which moderately controlled the disease. Treatment with 0.5 g/d of sulfasalazine was started after all medications except loxoprofen had been discontinued. The dosage was increased to 2 g/d several weeks later. Thirty-two days after treatment with sulfasalazine was initiated, the patient developed a sore throat, nausea, vomiting, diarrhea, and high fever. Sulfasalazine therapy was discontinued 4 days later. Nevertheless, the patient developed a generalized eruption and was admitted to Ehime University Hospital, Ehime, Japan.

Results from a physical examination revealed a high fever (body temperature, 39.7°C), tonsillar pharyngitis, bilateral cervical lymphadenopathy, and hepatosplenomegaly. A generalized maculopapular rash was observed over the patient's face, trunk, and extremities (**Figure 1**). Edema of the

METHODS

ISOLATION AND CHARACTERIZATION OF HHV-6

Peripheral blood mononuclear cells (PBMCs) were separated and cultured with umbilical cord blood mononuclear cells as described previously.⁸ The cytopathic effect of HHV-6 was examined with an inverted microscope. Isolated virus was identified with immunofluorescence assay using anti-HHV-6 monoclonal antibody and polymerase chain reaction (PCR) assay. Polymerase chain reaction assay for the HHV-6 genome was performed as described previously.⁹ The primers were 5'-GTGTTTCCATTGTACTGAAACCGGT-3' and 5'-TAAACATCAATGCGTT-GCATACAGT-3'. The expected product was 776 base pairs (bp). Genotyping of HHV-6 was performed as described previously.¹⁰ Human herpesvirus 6 DNA was amplified using a triple primer mix of 5'-CAGAAGTG-CCAGGGAAATCC-3', 5'-TTATCGGGGCTGTAAGCCAA-3', and 5'-TTTGCT-TCCCGGAGTCATAGA-3'. The PCR product from HHV-6 variant A was 488 bp, and the product from variant B was 259 bp.

SEROLOGIC TESTING

Serum samples from the patients were stored at -80°C until use. IgG antibody to HHV-6 was determined using the indirect immunofluorescent antibody assay described previously.¹¹ Mononuclear cells infected with HHV-6 (HST strain) were used as a target antigen.

face was also present. Abnormal laboratory findings included a white blood cell count of $23.6 \times 10^9/L$ (20% atypical lymphocytes and 11% eosinophils). Liver and renal dysfunction were found, with increased serum creatinine levels of 141.44 $\mu\text{mol/L}$ (1.6 mg/dL), aspartate aminotransferase levels of 88 U/L, alanine aminotransferase levels of 148 U/L, and lactate dehydrogenase levels of 1892 U/L. An analysis of peripheral blood lymphocyte surface markers showed 35% CD4⁺ T cells and 30% CD8⁺ T cells. A skin biopsy specimen obtained from the upper portion of the patient's right arm showed lymphocytic infiltration in the epidermis with necrotic keratinocytes, partial liquefaction degeneration of basal cells, and perivascular lymphocytic infiltration in the dermis (**Figure 2**).

The skin eruption progressed to erythroderma, and the patient was diagnosed as having hypersensitivity syndrome due to sulfasalazine use with multivisceral involvement. Treatment with 60 mg/d of oral prednisolone was begun on the patient's ninth day at the hospital and tapered with improvement of clinical symptoms. By the seventh week of hospitalization, the patient's condition had resolved other than symptoms of psoriatic arthritis.

The presence of atypical lymphocytes and mononucleosislike symptoms led us to examine the possibility of viral infections. Human herpesvirus 6 was isolated from PBMCs obtained on the eighth hospital day and identi-



Figure 1. Widespread erythematous macules and papules coalesced into diffuse erythema with scaling in the forearms in patient 1.

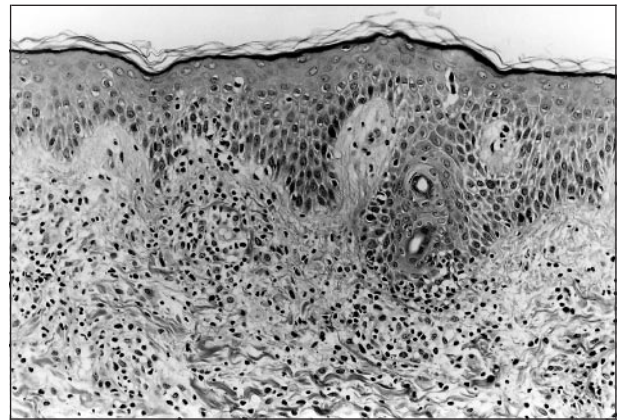


Figure 2. Findings from a microscopic examination of a skin lesion on the upper portion of the right arm of patient 1 shows infiltration of lymphocytic cells in the epidermis with necrotic keratinocytes, partial liquefaction degeneration of basal cells, and perivascular infiltration of lymphocytic cells in the dermis (hematoxylin-eosin, original magnification $\times 100$).

fied as HHV-6 variant B by PCR (**Figure 3**). Furthermore, an anti-HHV-6 IgG titer of 1:160 two days before admission and on the 6th hospital day increased to 1:1280 on the 16th day and 1:5120 on the 22nd day. Results from anti-HHV-6 IgM titers were negative in these samples. Antibody titers against HHV-7, Epstein-Barr virus, cytomegalovirus, rubella, adenovirus, and toxoplasma did not change throughout the clinical course. These data indicated the reactivation of HHV-6 in the patient.

CASE 2

A 22-year-old Japanese woman who presented with abdominal pain and bloody diarrhea was diagnosed as having ulcerative colitis. Treatment with 1.5 g/d of sulfasalazine and 1 mg/d of betamethasone suppository was commenced, and the patient's symptoms resolved 2 weeks later. Betamethasone therapy was discontinued while treatment with sulfasalazine was increased to 2 g/d. Eighteen days after sulfasalazine therapy was initiated, the pa-

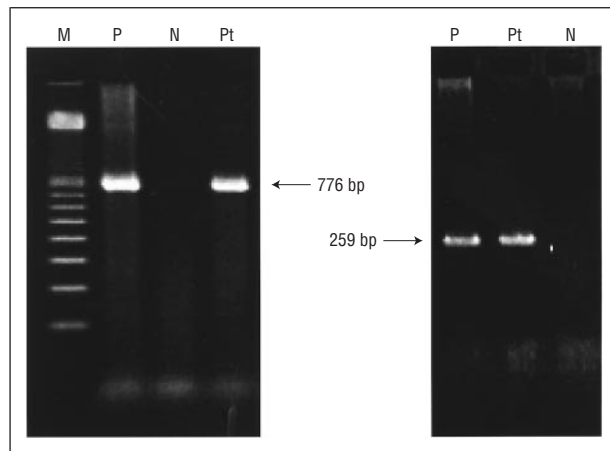


Figure 3. DNA from peripheral blood mononuclear cells (Pt) showed amplified human herpesvirus 6 DNA product with 776 base pairs (bp) using common primers for variant A and variant B (left), and with 259 bp using variant B-specific primers (right). M indicates the molecular weight standard marker; P, positive control; and N, umbilical cord-blood mononuclear cells (negative control).

tient developed a sore throat, nausea, chills, and high fever. Red papules appeared on her abdominal skin and rapidly progressed over her whole body. Seven days after the onset of the disease, sulfasalazine therapy was discontinued, and the patient was treated with 50 mg/d of oral prednisolone for 4 days. Nevertheless, the patient's skin eruption and general condition showed little improvement, so she was admitted to Tokushima University Hospital, Tokushima, Japan.

Results from a physical examination revealed tender generalized lymphadenopathy. The patient's skin was covered with erythematous macules and papules and scattered petechiae. Facial edema was also present. Laboratory data showed a white blood cell count of $14.4 \times 10^9/L$ (48% lymphocytes and 3% atypical lymphocytes). Liver and renal functions were within normal limits.

Treatment with all medications except ketotifen fumarate was discontinued. On the patient's third hospital day, 30 mg/d of oral prednisolone was readministered because of high fever (body temperature, 39.5°C), erythroderma, progressive facial edema, and increasing levels of aspartate aminotransferase and alanine aminotransferase. Over the next 3 days, the patient's liver function worsened. On the sixth hospital day, results from laboratory studies revealed the following values: aspartate aminotransferase, 755 U/L; alanine aminotransferase, 1058 U/L; lactate dehydrogenase, 1712 U/L; and total bilirubin, 41.04 $\mu\text{mol/L}$ (2.4 mg/dL). Methylprednisolone pulse therapy (1 g/d for 3 days) was administered, and the patient's general condition and liver function improved markedly. Prednisolone, 40 mg/d, was continued and tapered with improvement of clinical symptoms.

The patient was diagnosed as having hypersensitivity syndrome due to sulfasalazine use with multivisceral involvement. However, we determined that her anti-HHV-6 IgG titer had increased from 1:320 on the second hospital day to 1:2560 on the sixth hospital day when a preserved serum sample was examined. Anti-HHV-6 IgM titers were negative in these samples. The antibody titers against HHV-7, Epstein-Barr virus, cytomegalovi-

rus, measles, adenovirus, and toxoplasma were within normal ranges throughout the patient's clinical course.

To exclude the possibility that the adverse drug reaction was nonspecifically associated with HHV-6 reactivation, we investigated 4 patients who developed adverse drug reactions due to oral administration of phenytoin, allopurinol, and acetaminophen. They showed skin rash, fever, and mild liver dysfunction, but no mononucleosislike reactions. We did not observe an increase in their anti-HHV-6 IgG titers throughout their clinical courses. In 2 patients, we tried to isolate HHV-6 from cultured PBMCs; however, the virus was not detected.

COMMENT

A drug-associated hypersensitivity syndrome has been reported with administration of sulfasalazine, anticonvulsants, dapsone, allopurinol, and several other medications.^{1-4,12,13} Its clinical features resemble those of infectious mononucleosis and appear 2 to 5 weeks after administration of the drugs. Clinical signs include a maculopapular rash that often progresses to exfoliative erythroderma, fever, lymphadenopathy, and multivisceral involvement. Eosinophilia, atypical lymphocytosis, liver dysfunction, and renal disturbance are also frequently observed with this syndrome. The symptoms are often progressive for several weeks after treatment with the drug is discontinued. Systemic corticosteroid therapy generally improves the condition. We describe 2 patients who experienced the sudden onset of severe infectious mononucleosislike illness 18 and 32 days after the initiation of therapy with sulfasalazine. We believe these cases represent hypersensitivity syndrome due to sulfasalazine therapy.

No serologic evidence of Epstein-Barr virus, cytomegalovirus, or other viral infections have been reported in hypersensitivity syndrome, although HHV-6 infection has not been specifically investigated. In 2 patients, we found an association between HHV-6 infection and hypersensitivity syndrome. Human herpesvirus 6 has been identified as the cause of exanthem subitum.¹⁴ Most people are infected with HHV-6 in early childhood. Then, HHV-6 latently infects monocytes and salivary glands. The mechanism and frequency of the reactivation of HHV-6 are unknown. In immunocompromised patients, it appears that the reactivation of HHV-6 is not infrequent.¹⁵⁻¹⁷ Human herpesvirus 6 was first isolated from immunocompromised patients with lymphoproliferative disease.¹⁸ One of these patients experienced drug-induced dermatopathologic lymphadenopathy with skin eruption.

Several methods may be used to confirm HHV-6 infection, including measurement of anti-HHV-6 titers, PCR analysis, and isolation of HHV-6. The evaluation of HHV-6 antibody titers is controversial. A marked increase in anti-HHV-6 IgG titers strongly indicates a primary or reactivated infection of HHV-6. In general, the appearance of anti-HHV-6 IgM antibodies suggests primary infection, while a remarkable increase in IgG titers without IgM antibodies indicates reactivated HHV-6 infection. However, PCR analysis is more sensitive, detecting HHV-6 DNA in 49% to 88% of PBMCs in healthy seropositive adults.^{19,20} A recent study suggested that the detection of HHV-6 DNA

in serum by quantitative PCR defined the border between latency and active viral replication.²¹ In contrast, isolating the virus is the most reliable method of proving infection, because HHV-6 is rarely isolated from the PBMCs of healthy subjects.²² Our observations of the isolation of HHV-6 from PBMCs and the remarkable increase in anti-HHV-6 IgG titers without the appearance of IgM antibodies indicated reactivated HHV-6 infection.

The clinical symptoms of patients with HHV-6 infection should be evaluated carefully. Other viral infections must be excluded, because coinfections with HHV-6 and other herpesviruses have been reported.²³ The 2 patients in our study showed no increase in anti-HHV-7, anti-cytomegalovirus, and anti-Epstein-Barr virus IgG titers. Accordingly, the reactivation of HHV-6 did not result from coinfection with these viruses. The patients showed similar clinical courses associated with reactivated HHV-6 infection. These findings support the relevance of HHV-6 infection in their clinical diseases. In addition, the increase in the anti-HHV-6 IgG titers was observed more than 2 weeks after the onset of disease. The period from the onset of a primary symptom to the increase in anti-HHV-6 IgG titer seems too long, although the exact time from onset is unknown for reactivated HHV-6 infection. We examined HHV-6 DNA from skin biopsy specimens of patient 1 using PCR. The DNA was detected from frozen skin specimens obtained on the patient's 19th hospital day, but not from paraffin-embedded skin specimens obtained on the 6th day. This observation suggests active replication of the virus after the initiation of clinical symptoms. To confirm this observation, it must be further investigated in other patients.

Recently, a severe infectious mononucleosislike syndrome caused by HHV-6 infection was reported in immunocompetent adults.⁵⁻⁷ Clinical signs included high fever, skin rash, generalized lymphadenopathy, liver dysfunction, and leukocytosis with the appearance of atypical lymphocytes. Although the 3 reported cases were described as primary HHV-6 infection, the possibility of reactivated HHV-6 could not be excluded because of an absent or low anti-HHV-6 IgM response.²⁴ If the infectious mononucleosislike syndrome was precipitated by reactivated HHV-6 infection, possible causes of the reactivation were not delineated. However, 1 of the 3 patients described by Sumiyoshi et al⁶ had been treated with phenobarbital for 3 weeks prior to onset of the illness, and peripheral blood eosinophilia had been found on admission (Y. Sumiyoshi, written communication, June 1997). Phenobarbital has been reported to cause hypersensitivity syndrome¹³; therefore, the patient could have developed hypersensitivity syndrome with reactivated HHV-6 from treatment with phenobarbital.

Hypersensitivity syndrome due to the use of sulfonamides and anticonvulsants may be related to individual genetic polymorphisms in the enzymes involved in the metabolism cascade of these drugs.^{25,26} It is hypothesized that the reactive metabolite binds to tissue macromolecules and causes cell damage or acts as a hapten and elicits an immune response. Mauri-Hellweg et al²⁷ have demonstrated drug-induced activation and proliferation of PBMCs in vitro in patients with hypersensitivity syndrome. However, the pathologic mechanisms mediating the symp-

toms resembling infectious mononucleosis have not been elucidated. Interestingly, it has been considered that the reactivation of HHV-6 from latently infected PBMCs requires T-cell activation.²⁸ On investigation of 4 patients who developed adverse drug reactions but not hypersensitivity syndrome, an increase in anti-HHV-6 IgG titer was not found and the virus was not isolated. It seems likely that the reactivation of HHV-6 is specific to hypersensitivity syndrome. These findings led us to hypothesize that severe drug-induced hypersensitivity syndromes have a 2-stage course: first, T-cell activation develops as an immune response to reactive drug metabolites and second, HHV-6 reactivated by activated T cells affects the general condition of the patients and causes infectious mononucleosislike symptoms.

However, these proposed pathomechanisms do not fully explain the phenomenon of hypersensitivity syndrome, which is induced by only a select group of medications. Many drugs may cause allergic reactions via T-cell activation, but the reactions do not always develop into hypersensitivity syndrome. Therefore, the adverse drug reaction causing hypersensitivity syndrome requires additional factors. Sulfasalazine has been reported to modulate the immune response by inhibiting the secretion of IgA and the production of interleukin 1 and tumor necrosis factor α .^{29,30} These effects of sulfasalazine on the immune system may facilitate the reactivation of HHV-6 by activated T cells and induce the constellation of symptoms and signs of hypersensitivity syndrome.

It should be noted that the patients' clinical conditions improved with the use of systemic corticosteroids. One explanation for this finding might be that the corticosteroids suppressed an excessive immune response to drug metabolites and/or inhibited the production of cytokines caused by massive replicated viruses, which in turn induced severe illness. We would like to suggest possible treatment with an antiviral drug such as ganciclovir for hypersensitivity syndrome, since our observations indicate that HHV-6 infection occurs in a late stage of hypersensitivity syndrome.³¹

In conclusion, we demonstrate that a drug-induced hypersensitivity syndrome due to sulfasalazine use is associated with reactivation of HHV-6 and an infectious mononucleosislike illness. We suggest that HHV-6 infection may be a required cause of hypersensitivity syndrome.

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