Trimethoprim-Sulfamethoxazole-Induced Hypersensitivity Syndrome Associated with Reactivation of Human Herpesvirus-6

Taisuke Morimoto¹, Takeo Sato², Akihiro Matsuoka³, Tetsu Sakamoto¹, Keisuke Ohta¹,
Tsunehiro Ando¹, Soichiro Ikushima¹, Kiyofumi Hagiwara², Hiroaki Matsuno²,
Osamu Akiyama² and Masaru Oritsu¹

Abstract

A 27-year-old man who had a history of bronchial asthma, eosinophilic enteritis, and eosinophilic pneumonia presented with fever, skin eruptions, cervical lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis, and eosinophilia two weeks after receiving trimethoprim (TMP)-sulfamethoxazole (SMX) treatment. After the withdrawal of TMP-SMX and the administration of high-dose steroid, these systemic symptoms gradually resolved. During the disease course, the patient showed a transient increase in anti-human herpesvirus (HHV)-6 antibody titers and HHV-6 DNA in the peripheral blood, indicating the reactivation of a latent HHV-6 infection. This is the first case of TMP-SMX-induced hypersensitivity syndrome associated with the reactivation of a latent viral infection.

Key words: atypical lymphocytosis, drug-induced hypersensitivity syndrome, eosinophilia, human herpesvirus-6, sulfamethoxazole, trimethoprim

(DOI: 10.2169/internalmedicine.45.1352)

Introduction

Drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced severe adverse reaction characterized by generalized symptoms such as fever, skin eruptions, lymphadenopathy, hepatic dysfunction, eosinophilia, and infectious mononucleosis-like atypical lymphocytosis (1, 2). Skin eruptions usually begin with maculopapular erythema and often progress to erythroderma. These symptoms typically develop two to six weeks after the administration of the causative drug and often persist even after the withdrawal of the causative drug. Certain drugs such as sulfas, anticonvulsants, mexiletine, and allopurinol have been associated with DIHS. The incidence of DIHS has been estimated to be between 1 in 1,000 and 1 in 10,000 exposures,

and its mortality rate is approximately 10% (2). Although the pathogenesis of DIHS has not been completely elucidated, several groups have reported the association between DIHS and the reactivation of a latent viral infection (3-5). The reactivation of a latent viral infection is sometimes associated with encephalitis or fulminant type 1 diabetes mellitus (6-9).

Trimethoprim (TMP)-sulfamethoxazole (SMX) is a commonly used antibiotic. It sometimes induces severe adverse reactions such as skin eruptions, pancytopenia, and liver damage. Although cases of TMP-SMX-induced hypersensitivity syndrome have been reported previously (10, 11), the reactivation of a latent viral infection has not been documented to date.

We describe herein a case of TMP-SMX-induced hypersensitivity syndrome. This case was associated with the reactivation of a latent human herpesvirus (HHV)-6 infection.

¹ Department of Respiratory Medicine, Japanese Red Cross Medical Center, Tokyo, ² Department of Allergy and Rheumatology, Japanese Red Cross Medical Center, Tokyo and ³ Department of Dermatology, Japanese Red Cross Medical Center, Tokyo

Received for publication March 17, 2005; Accepted for publication October 23, 2005

Reprint requests should be addressed to Takeo Sato, Department of Allergy and Rheumatology, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo 150-8935

Case report

A 27-year-old man had been treated with prednisolone for eosinophilic pneumonia since he was 25 years old. He had eosinophilic enteritis at age 15, and bronchial asthma at age 22. In January 2004, he had a relapse of eosinophilic pneumonia, and the dose of prednisolone was increased to 30 mg/day. Daily doses of 400 mg of SMX and 80 mg of TMP were administered to prevent opportunistic infections on March 16, 2004. On March 30, 2004, he had a temperature of 40°C. He received acetaminophen and gatifloxacin for 7 days, and thereafter loxoprofen and azithromycin for 3 days, but the fever persisted. On April 9, skin eruptions developed on his hands that rapidly spread to his entire body. On April 12, he was admitted to our hospital.

On admission, he was alert. His body temperature was 40°C. His systolic blood pressure was 140 mmHg. He had cervical lymphadenopathy. Clinical examinations of the chest and abdomen revealed no abnormality. He had maculopapular eruptions in his hands, generalized erythroderma, and mucitis of the nasal and oral cavities.

Laboratory tests revealed the following findings. The total leukocyte count was 10.9×10^9 /L (normal range, 3.7×10^9 to 8.0×10^9) with 7% eosinophils and 17% atypical lymphocytes. The aspartate aminotransferase (AST) level was 26 IU/L (normal range, 10 to 40), the alanine aminotransferase (ALT) level 42 IU/L (normal range, 5 to 40), and the lactate dehydrogenase (LDH) level 714 IU/L (normal range, 105 to 211). The C-reactive protein (CRP) level was 13.4 mg/dL (normal range, 0 to 0.3). The IgG level was 2,445 mg/dL (normal range, 870 to 1,700), and the IgE level 356 U/mL (normal range, 0 to 100). Abdominal echography revealed mild hepatosplenomegaly.

On the 8th day of hospitalization, the dose of prednisolone was increased to 40 mg/day, but eosinophilia and erythroderma persisted. From the 19th day of hospitalization, 500 mg of methylprednisolone was administered for three days, followed by the daily administration of 60 mg of prednisolone. The administration of TMP-SMX was discontinued on the 24th day of hospitalization. He still had maculopapular eruptions in his hands (Fig. 1A) and generalized erythroderma with scales (Fig. 1B) on the 50th day of hospitalization. Skin biopsy revealed epidermal thickening, hyperkeratosis, and the infiltration of inflammatory cells in the subepidermal layer (Fig. 2A), and Civatte bodies and spongiosis in the epidermis (Fig. 2B).

After the above-mentioned treatment, his symptoms gradually resolved (Fig. 3). The dose of prednisolone was tapered; however, it was increased again from 30 mg/day to 40 mg/day on the 88th day of hospitalization because of itching. He was discharged on the 160th day of hospitalization with 35 mg/day of prednisolone.

The results of serological tests for viral infection during the hospitalization were as follows: the HHV-6 IgG antibody was present at 1:320, 1:320, 1:160, and 1:80 dilutions

Figure 1. Maculopapular eruptions in hands (A) and generalized erythroderma with scales (B) on the 50th day of hospitalization.

on the 52nd, 67th, 115th, and 150th days of hospitalization. The HHV-6 IgM antibody was absent on the 52nd day of hospitalization. HHV-6 DNA was detected by polymerase chain reaction (PCR) analysis in the peripheral blood on the 52nd day of hospitalization, and was not detected on the 115th day of hospitalization. The IgG level was 1,413 mg/dL when HHV-6 DNA was first detected. On the 5th and 150th days of hospitalization, Epstein-Barr virus (EBV)-associated antibodies were assayed: viral anti-capsid antigen (VCA) IgG was detected at 1:80 dilution, the anti-EBV nuclear antigen (EBNA) antibody at 1:20 dilution; and VCA IgM was not detected. Cytomegalovirus antigen pp65 was present in 1 per 150,000 white blood cells on the 50th day of hospitalization.

The stimulation index determined by the drug lymphocyte stimulation test (DLST) using TMP-SMX was 7.2 and that using azithromycin 1.1, (normal range, 0 to 1.8).

Discussion

Here, we described a patient who presented with fever, skin eruptions, mucitis, lymphadenopathy, hepatosplenomegaly, eosinophilia, and atypical lymphocytosis

Figure 2. Histopathology of the skin biopsy, showing epidermal thickening, hyperkeratosis (arrow), and the infiltration of inflammatory cells in the subepidermal layer (A, HE stain, $\times 100$). Civatte bodies (arrows) and spongiosis (arrowhead) are present in the epidermis (B, HE stain, $\times 400$).

that developed two weeks after receiving TMP-SMX. These symptoms were resolved after the administration of high-dose steroid and the withdrawal of TMP-SMX. In the present case, the reactivation of a latent HHV-6 infection was indicated by the change in anti-HHV-6 antibody titer and the presence of HHV-6 DNA in the peripheral blood. On the basis of these findings, the patient was diagnosed as having TMP-SMX-induced hypersensitivity syndrome associated with the reactivation of a latent HHV-6 infection.

The differential diagnoses included Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN). In the present case, the diagnoses of SJS and TEN were considered unlikely because SJS and TEN are characterized by an extensive epidermal necrolysis (1), and the reactivation of a latent viral infection is absent in SJS and TEN (12).

Recent reports have shown the association between DIHS and the reactivation of latent viral infections including EBV, HHV-6, HHV-7, and cytomegalovirus infections (3-5, 13-15). These viruses usually infect humans in childhood and thereafter become latent. DIHS may be caused by a T lymphocyte-dependent mechanism, involving pro-inflammatory cytokines such as interleukin (IL)-6 (16), and

T-lymphocyte activation is required for the replication of latent viruses such as HHV-6 (17). Currently, it is presumed that the reactivation of a latent viral infection is not merely a coincidental event but that it is involved in the pathogenesis of DIHS. HHV-6 has various effects on cytokines: increased production of IL-6, IL-8, IL-18, and tumor necrosis factor (TNF)- α (18-20); suppression of IL-12 production (21, 22); modulation of the interferon (IFN)- γ effect on the production of cytokines such as IL-1 β , IL-6, IL-10, IL-12, and TNF- α (23, 24); and increases in serum levels of IFN- γ , IL-4, IL-5, and IL-6 in DIHS associated with HHV-6 reactivation (25, 26). From these findings, we speculated that the pathogenesis of DIHS is as follows: a latent virus is reactivated in a T lymphocyte-dependent manner involving pro-inflammatory cytokine, and the reactivated virus influences the production or regulation of these cytokines, which may be involved in the development of systemic symptoms of DIHS.

Hypogammaglobulinemia was reported as a risk factor for the reactivation of HHV-6 in DIHS (25-27). However, the serum immunoglobulin level was within normal limits in the present case when HHV-6 DNA was detected. In the present case, T lymphocyte activation or certain cytokines might be involved in the reactivation of HHV-6.

The present case had underlying allergic diseases such as bronchial asthma, eosinophilic pneumonia, and eosinophilic enteritis. It is interesting to examine the association between the presence of underlying allergic diseases and the development of DIHS. As the association between these diseases has not been reported, further case studies will be needed to elucidate their association.

TMP-SMX was suspected as the causative drug on the basis of the time course of drug administration and the positive result of DLST. The positive results of DLST or a patch test may be useful in identifying the drug causing DIHS (14, 28). TMP-SMX is a mixture of two antimicrobial drugs that inhibit folate metabolism at different sites: TMP, an analogue of methotrexate, inhibits dihydrofolate reductase, and SMX, a sulfa component, inhibits dihydropteroate synthase. Considering these two drugs, Mainra and Card (11) reported a causal link between DIHS and SMX. SMX is possibly the causative drug because it is a member of the sulfa groups of drugs, which can cause DIHS associated with HHV-6. At present it remains to be elucidated which is the causative drug and whether T lymphocyte activation, cytokines, hypogammaglobulinemia, or other factors are involved in the reactivation of latent HHV-6 infection.

The early identification and withdrawal of the causative drug is important in treating severe drug adverse reactions. The immediate withdrawal of the causative drug is associated with a low mortality rate in SJS or TEN (29). DIHS symptoms are often prolonged even after the withdrawal of the causative drug. Although systemic steroid can resolve DIHS symptoms, it is still unclarified whether systemic steroid should be administered because systemic steroid can promote the reactivation of a latent virus infection presumed

Figure 3. Clinical course of the patient. BT, body temperature; TMP, trimethoprim; SMX, sulfamethoxazole; mPSL, methylprednisolone; PSL, prednisolone; WBC, white blood cell.

to be involved in the development of DIHS. At present, the use of systemic steroid should be limited in cases with severe symptoms such as internal organ damage (2). In cases of DIHS refractory to systemic steroid, intravenous gammaglobulin may be an alternative (30, 31). It may be effective in suppressing a latent viral infection. Its effectivity is worth investigating in the future.

In conclusion, we described a case of TMP-SMX-induced

hypersensitivity syndrome associated with the reactivation of a latent HHV-6 infection. We suggest that the reactivation of a latent virus infection is involved in the pathogenesis of TMP-SMX-induced hypersensitivity syndrome. Further studies are necessary to elucidate its pathogenesis and establish the association between TMP-SMX-induced hypersensitivity syndrome and latent viral infection.

References

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* **331**: 1272-1285, 1994.
2. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology* **206**: 353-356, 2003.
3. Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. *Arch Dermatol* **134**: 1108-1112, 1998.
4. Tohyama M, Yahata Y, Yasukawa M, et al. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch Dermatol* **134**: 1113-1117, 1998.
5. Descamps V, Bouscarat F, Lagrenne S, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. *Br J Dermatol* **137**: 605-608, 1997.
6. Sekine N, Motokura T, Oki T, et al. Rapid loss of insulin secretion in a patient with fulminant type 1 diabetes mellitus and carbamazepine hypersensitivity syndrome. *JAMA* **285**: 1153-1154, 2001.
7. Seino Y, Yamauchi M, Hirai C, et al. A case of fulminant type 1 diabetes associated with mexiletine hypersensitivity syndrome. *Diabet Med* **21**: 1156-1157, 2004.
8. Masaki T, Fukunaga A, Tohyama M, et al. Human herpesvirus 6 encephalitis in allopurinol-induced hypersensitivity syndrome. *Acta Derm Venereol* **83**: 128-131, 2003.
9. Fujino Y, Nakajima M, Inoue H, Kusuha T, Yamada T. Human herpesvirus 6 encephalitis associated with hypersensitivity syn-

- drome. *Ann Neurol* **51**: 771-774, 2002.
10. Hicks ME, Smith CL, Stein GE. Trimethoprim/sulfamethoxazole-induced hypersensitivity syndrome. *Ann Pharmacother* **31**: 1259, 1997.
 11. Mainra RR, Card SE. Trimethoprim-sulfamethoxazole-associated hepatotoxicity - part of a hypersensitivity syndrome. *Can J Clin Pharmacol* **10**: 175-178, 2003.
 12. Aihara M, Mitani N, Kakemizu N, et al. Human herpesvirus infection in drug-induced hypersensitivity syndrome, toxic epidermal necrolysis and Stevens-Johnson syndrome. *Allergol Int* **53**: 23-29, 2004.
 13. Descamps V, Mahe E, Houhou N, et al. Drug-induced hypersensitivity syndrome associated with Epstein-Barr virus infection. *Br J Dermatol* **148**: 1032-1034, 2003.
 14. Kunisaki Y, Goto H, Kitagawa K, Nagano M. Salazosulfapyridine induced hypersensitivity syndrome associated with reactivation of human herpes virus 6. *Intern Med* **42**: 203-207, 2003.
 15. Aihara M, Sugita Y, Takahashi S, et al. Anticonvulsant hypersensitivity syndrome associated with reactivation of cytomegalovirus. *Br J Dermatol* **144**: 1231-1234, 2001.
 16. Chiappini E, Peruzzi M, Galli L, Calabri G, Martino M. Evidence for a T-lymphocyte dependent mechanism involving proinflammatory cytokines in anticonvulsant hypersensitivity syndrome: a case report. *Int J Immunopathol Pharmacol* **15**: 239-242, 2002.
 17. Frenkel N, Schirmer EC, Katsafanas G, June CH. T-cell activation is required for efficient replication of human herpesvirus 6. *J Virol* **64**: 4598-4602, 1990.
 18. Yoshikawa T, Asano Y, Akimoto S, et al. Latent infection of human herpesvirus 6 in astrocytoma cell line and alteration of cytokine synthesis. *J Med Virol* **66**: 497-505, 2002.
 19. Caruso A, Rotola A, Comar M, et al. HHV-6 infects human aortic and heart microvascular endothelial cells, increasing their ability to secrete proinflammatory chemokines. *J Med Virol* **67**: 528-533, 2002.
 20. Mayne M, Cheadle C, Soldan SS, et al. Gene expression profile of herpesvirus-infected T cells obtained using immunomicroarrays: induction of proinflammatory mechanisms. *J Virol* **75**: 11641-11650, 2001.
 21. Smith AP, Paolucci C, Lullo G, Burastero SE, Santoro F, Lusso P. Viral replication-independent blockade of dendritic cell maturation and interleukin-12 production by human herpesvirus 6. *J Virol* **79**: 2807-2813, 2005.
 22. Smith A, Santoro F, Lullo G, Dagna L, Verani A, Lusso P. Selective suppression of IL-12 production by human herpesvirus 6. *Blood* **102**: 2877-2884, 2003.
 23. Arena A, Capozza AB, Luca D. Role of IFN gamma on TNF alpha, IL-1 beta and IL-6 release during HHV-6 infection. *New Microbiol* **19**: 183-191, 1996.
 24. Li C, Goodrich JM, Yang X. Interferon-gamma (IFN-gamma) regulates production of IL-10 and IL-12 in human herpesvirus-6 (HHV-6)-infected monocyte/macrophage lineage. *Clin Exp Immunol* **109**: 421-425, 1997.
 25. Nakashima H, Yamane K, Ihn H, et al. Drug-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and increase in serum IgE level. *Dermatology* **210**: 349-352, 2005.
 26. Aihara Y, Ito SI, Kobayashi Y, Yamakawa Y, Aihara M, Yokota S. Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* **149**: 165-169, 2003.
 27. Kano Y, Inaoka M, Shiohara T. Association between anticonvulsant hypersensitivity syndrome and human herpesvirus 6 reactivation and hypogammaglobulinemia. *Arch Dermatol* **140**: 183-188, 2004.
 28. Galindo BPA, Romero AG, Feo BF, et al. Phenytoin hypersensitivity syndrome with positive patch test. A possible cross-reactivity with amitriptyline. *J Invest Allergol Clin Immunol* **8**: 186-190, 1998.
 29. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* **136**: 323-327, 2000.
 30. Mostella J, Pieroni R, Jones R, Finch CK. Anticonvulsant hypersensitivity syndrome: treatment with corticosteroids and intravenous immunoglobulin. *South Med J* **97**: 319-321, 2004.
 31. Scheuerman O, Nofech-Moses Y, Rachmel A, Ashkenazi S. Successful treatment of antiepileptic drug hypersensitivity syndrome with intravenous immune globulin. *Pediatrics* **107**: E14, 2001.