Salazosulfapyridine Induced Hypersensitivity Syndrome Associated with Reactivation of Human Herpes Virus 6

Yuya Kunisaki, Hiroshi Goto, Kikuo Kitagawa* and Masanori Nagano

Abstract

A 22-year-old woman with ulcerative colitis developed skin eruptions, liver dysfunction, and atypical lymphocytes in the peripheral blood two weeks after she started taking salazosulfapyridine (SASP). Skin eruptions and liver damage were severe. Drug-induced lymphocyte stimulation test (DLST) for SASP was positive. She was diagnosed as having SASP-induced hypersensitivity syndrome (HS). Corticosteroid therapy was needed to suppress these reactions. The transient elevation of HHV-6 IgG titer paralleled the symptoms, which indicated that these reactions were associated with the reactivation of HHV-6. We suggest that HHV-6 IgG titer is one of the modalities for the diagnosis and the prediction of the clinical course of HS.

Key words: severe drug eruption, hypersensitivity syndrome, human herpesvirus 6, salazosulfapyridine

Introduction

Hypersensitivity syndrome (HS) is one of the types of severe drug eruptions, which presents with generalized papulor erythema with infectious mononucleosis-like symptoms and organ damage. This syndrome has a latent phase of two to six weeks and severe systemic inflammation. This reaction is often prolonged and recurs even after the causative drugs are discontinued (1). Recently many reports show that the reactivation of human herpes virus 6 (HHV-6), which causes exanthema subitum in infants, is associated with this syndrome (2, 3).

Salazosulfapyridine (SASP) is a therapeutic drug to treat inflammatory bowel disease. However, many side effects including skin eruptions and hematological disorders have been reported. SASP-induced HS has also been reported recently (4–11). Although HS is not widely known, it causes severe liver damage and sometimes can be life threatening (12). We describe a case of SASP-induced HS associated with reactivation of HHV-6.

Case Report

A 22-year-old woman with one and half month-history of ulcerative colitis (UC) had been treated with SASP (3 g/day), which controlled the disease well. On the 17th day after treatment with SASP was initiated, the patient developed skin eruptions and fever. These symptoms were improved spontaneously and administration of SASP was not discontinued. However, twenty days later, generalized skin eruptions reappeared with high fever and liver dysfunction. The symptoms were progressive even after SASP therapy was discontinued and the patient was admitted to Kyushu Kousei-Nenkin Hospital. Physical examination on admission revealed that she had a high fever (over 39°C), skin eruptions, cervical lymphadenopathy and mild hepatomegaly. The skin eruptions were severe exfoliated erythematous papules and macules with confluence; these progressed over the whole body after admission. Neurologically, paresthesia in the bilateral calves was seen. Abnormal laboratory findings included a white cell count of 21.2 x 10³/µl (11% eosinophil and 12% atypical lymphocyte). Liver and renal dysfunctions were found, with aspartate aminotransferase (AST) levels of 225 IU/l, alanine aminotransferase (ALT) levels of 417 IU/l, lactate dehydrogenase levels (LDH) of 1,177 IU/l, total bilirubin (T.Bil) levels of 2.6 mg/dl and serum creatinine was 0.88 mg/dl. Serum immunoglobulin levels, including IgE were all normal and anti-nuclear antibody was negative. Anti-hepatitis A virus antibody, hepatitis B virus surface antigen and anti-hepatitis C virus antibody
were all negative. No marked change in anti-Epstein-Barr virus and cytomegalovirus antibodies was seen. SASP was discontinued on the day before the admission. Skin eruption and liver dysfunction progressed even after SASP therapy was discontinued. Within several days of hospitalization, there was a rapid increase in the white cell count to 45.6×10^3/μl with 14% of eosinophil. A chest roentgenogram showed slight pleural effusion and cardiac enlargement. The abdominal ultrasonotomography revealed mild hepatomegaly and edema of the gall bladder wall, but no splenomegaly. On the 5th hospital day oral administration of prednisolone (PSL) (60 mg per day) was begun and the systemic reaction was improved temporarily. With PSL tapered into 30 mg per day, fever and skin eruptions, which were not as severe as in the first episode and liver injury reappeared (AST 2,202 IU/l, ALT 1,845 IU/l, T.Bil 9.8 mg/dl). Skin biopsy was performed in the right calf on the 13th hospital day. Result from skin biopsy specimens demonstrated dyskeratosis in the epidermis and marked perivascular infiltration of lymphocytes in the upper layer of the dermis. These histopathological findings were compatible with non-specific chronic dermatitis. Anti-HHV-6 IgM titer was negative. Anti-HHV-6 IgG titer was 640 on the 13th hospital day. Because the systemic reaction including liver dysfunction [prothrombin time was prolonged to 16.6 sec, 54%] was so severe, methyl prednisolone (m-PSL) pulse therapy (1 g × 3 days) was administered on the 13th hospital day. Though the patient’s condition was improved temporarily, fever and the increase in eosinophils appeared again when PSL was tapered to 30 mg per day. A second m-PSL pulse therapy was administered. PSL 60 mg/day was continued and tapered gradually with improvement of the clinical symptoms. Paresthesia was also improved along with the other symptoms. In this case, as DLST for SASP was positive (239%, 1,442 cpm, control; 603 cpm), we diagnosed her illness as SASP-induced HS. The change of anti HHV-6 IgG titer was seen as 640 titer on the 13th hospital day, 1,280 titer on day 35, and 160 titer on day 43 and throughout the clinical course.

Discussion

In this case, skin eruptions appeared two weeks after administration of SASP and the skin eruptions progressed to generalized erythematous papules and macules even after SASP was discontinued. High fever, lymphadenopathy, pleural effusion, liver and renal dysfunction, and atypical lymphocytes in the peripheral blood (infectious mononucleosis-like symptoms) were found. DLST against SASP was also positive. Thus we considered SASP induced hypersensitivity syndrome (HS).

HS is a new entity with severe drug eruptions, which differs from Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). A limited number of drugs including anticonvulsants (phenytoin, carbamazepine) and allopurinol, are implicated in the induction of this syndrome. Though only a few cases have been diagnosed as SASP-induced HS, there may have been other overlooked cases of such HS, based on severe liver damage, skin eruption and infectious mononucleosis-like symptoms. The reported cases with HS in Japan were listed in Table 1. In these cases, the latent
Hypersensitivity Associated with HHV-6

Sulfasalazine 3 g/day

m-PSL pulse m-PSL pulse

Period after initiation of SASP is long, from some weeks to some months. Some cases were improved by only discontinuing SASP, others needed corticosteroid therapy and had a prolonged clinical course.

Interestingly, in the present case, paresthesia in the extremities was found. It was diagnosed as radiculopathy neurologically; to date, such a symptom has not been reported in this syndrome. A few cases of peripheral neuropathy associated with ulcerative colitis have been reported. In most cases, neuropathy followed a course parallel to the activity of UC and it is thought to be an immunologically mediated manifestation (13, 14). In this case, because UC was not active and paresthesia was improved with the other symptoms of HS, we think this radiculopathy might be associated with HS, though we did not do further neurological examinations such as cerebrospinal fluid analysis or nerve conduction velocity test.

In the treatment of HS, corticosteroid is often needed. The symptoms are improved by corticosteroid therapy. However, these often recur when the dose is reduced. As in the present case, rapid tapering of the dose of corticosteroid often causes recurrence. Therefore, it seems that steroid administration for a long period and gradual withdrawal are needed.

Recently it has been reported that reactivation of HHV-6, which is the etiologic agent of exanthema subitum in infants, contributes to the development of HS. Most people are infected with HHV-6 in early childhood and then HHV-6 latently infects peripheral blood mononuclear cells (PBMCs) and the salivary gland. In some cases, a significant elevation of HHV-6 IgG is observed and the peak of this titer corresponds not with the onset but with the period of recurrence or exacerbation. In a previous report, 4 patients with an adverse drug eruption but no hypersensitivity syndrome were investigated, no increase in anti-HHV 6 IgG titer was seen and the virus was not isolated (3). It has been considered that the reactivation of HHV-6 from latently infected PBMCs requires T-cell activation (15). These reports suggest that a causative agent induces T-cell activation and the reactivation of HHV-6 following T-cell activation accelerates the progression of the reaction. In the present case, since the period of the transient elevation of anti-HHV-6 IgG coincided with that of the recurrence of the clinical symptoms and anti HHV-6 IgM was negative, we think the reactivation of HHV-6 was associated with her severe illness.

It has been reported that toxic epidermal necrolysis and other severe cutaneous adverse skin reactions to sulfonamides and anticonvulsants may be linked to a highly specific defect in the detoxication of drug metabolites (16). A
metabolic predisposition to the adverse effect of SASP has been also reported. Sulfapyridine, which is a metabolite of SASP, has a polymorphism in its acetylating process (fast or slow acetylator) in the liver (17, 18). This polymorphism is correlated with dose-dependent adverse reactions, nausea, vomiting and headache. This polymorphism in the metabolic process has not been reported to be associated with HS. In the future, it is necessary to investigate the mechanism of HHV-6 reactivation and the risk factors, including the genetic predisposition, to elucidate the etiology of HS.

Only a few reports have discussed the correlation between anti-HHV-6 antibody and HS. We think that anti-HHV-6 IgG titer is one of the useful modalities for the diagnosis and the prediction of the clinical course of HS.

References

16) Wolkenstein P, Charue D, Laurent P, Revuz J, Roujeau JC, Bagot M. Metabolic predisposition to cutaneous adverse drug reaction. Role in
