

A case of drug-induced hypersensitivity syndrome induced by salazosulfapyridine combined with SIADH caused by interstitial pneumonia

Yusuke Morinaga^{1,*}, Ichiro Abe², Tomohiro Minamikawa³, Yusuke Ueda⁴, Kouhei Nii¹, Kimiya Sakamoto¹, Ritsurou Inoue¹, Takafumi Mitsutake¹, Hayatsura Hanada¹, Jun Tsugawa^{5,6}, Kanako Kurihara^{5,6}, Toshio Higashi^{1,6}

¹ Department of Neurosurgery, Fukuoka University Chikushi Hospital, Chikushino-city, Fukuoka, Japan;

² Department of Endocrinology and Diabetes Mellitus, Fukuoka University Chikushi Hospital, Chikushino City, Fukuoka, Japan;

³ Department of Orthopedics, Fukuoka University Chikushi Hospital, Chikushino City, Fukuoka, Japan;

⁴ Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, Chikushino City, Fukuoka, Japan;

⁵ Department of Neurology, Fukuoka University Chikushi Hospital, Chikushino-city, Fukuoka, Japan;

⁶ Stroke Center, Fukuoka University Chikushi Hospital, Chikushino-city, Fukuoka, Japan.

Summary

We present a case of a patient with drug-induced hypersensitivity syndrome (DIHS) caused by salazosulfapyridine combined with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) caused by interstitial pneumonia (IP). A 67-year-old man with a past history of rheumatism (RA) presented with right hemiparalysis and aphasia as the chief complaints. A diagnosis of left embolic cerebral infarction following trial therapy for RA based on computed tomography findings was made, and external decompression was performed. Salazosulfapyridine was newly started on day 7. Dabigatran was started on day 37. On day 41, the patient developed fever. On day 42, edema and erythema appeared on his face, and erythema and rash appeared on his trunk and extremities, with gradual transition to erythroderma. The drug eruption was initially attributed to the dabigatran. Various symptoms of organ dysfunction (enteritis, myocarditis, interstitial pneumonia, hepatic disorder, stomatitis, and others) then appeared and persisted; hence, a diagnosis of DIHS associated with human herpes virus 6 and cytomegalovirus infection induced by salazosulfapyridine was suggested, and the oral administration of salazosulfapyridine was discontinued on day 53. Hyponatremia was observed in association with exacerbation of IP. Due to low serum osmotic pressure and prompt improvement of the serum sodium level by fluid restriction, the SIADH was attributed to IP. In this case, steroid pulse therapy followed by gradual decrease therapy prevented worsening of the condition.

Keywords: Drug-induced hypersensitivity syndrome, salazosulfapyridine, SIADH, interstitial pneumonia, cytomegalovirus

1. Introduction

Drug-induced hypersensitivity syndrome (DIHS) is an adverse reaction accompanied by fever, rashes, and visceral lesions. DIHS is caused by specific drugs

such as carbamazepine, phenytoin, phenobarbital, zonisamide, allopurinol, salazosulfapyridine, diaphenylsulfone, and mexiletine. The relationship between DIHS and human herpes virus 6 (HHV-6) reactivation is well-known. Symptoms such as fever and hepatitis are closely related to HHV-6 reactivation (1). The combined effect of the immunological response to a drug and the reactivation of HHV-6 can cause severe DIHS (2). If the symptoms of DIHS persist, it is necessary to suspect the involvement of cytomegalovirus reactivation (1). In this report, we

*Address correspondence to:

Dr. Yusuke Morinaga, Department of Neurosurgery, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino-city, Fukuoka Prefecture, 818-8502, Japan.

E-mail: yu_the_morio@yahoo.co.jp

present the extremely rare case of a patient with DIHS associated with HHV-6 and cytomegalovirus infection induced by sulfasalazine combined with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) caused by interstitial pneumonia (IP).

2. Case Report

A 67-year-old male patient with a past history of rheumatism (RA), hypertension, and subarachnoid hemorrhage presented to a health facility with right hemiparesis and aphasia as the chief complaints and was subsequently transferred to our hospital. A diagnosis of left embolic cerebral infarction that occurred during a trial for RA was made. His level consciousness as assessed by the Japan Coma Scale was I-3. Blood pressure was 147/88 mmHg and body temperature was 36.0°C. Left upper limb paralysis and left joint deviation were observed at admission.

Laboratory and radiological investigations were conducted, and the results were as follows. Blood count: white blood cells, $6.1 \times 10^3/\mu\text{L}$; red blood cells, $495 \times 10^4/\mu\text{L}$; hemoglobin, 15.6 g/dL; hematocrit, 46.7%; platelets, $25.2 \times 10^4/\mu\text{L}$; biochemistry: Na, 143 mmol/L; K, 4.4 mmol/L; Cl, 104 mmol/L; hemoglobin A1C, 6.0%; low-density lipoprotein, 156 mg/dL; C-reactive protein, 0.02 mg/dL; coagulation: D-dimer less than 0.3 $\mu\text{g/mL}$. The electrocardiography showed a heart rate of 72 beats per min and no abnormal findings. Magnetic resonance imaging of the head at admission (Figures 1A, B) showed extensive embolic cerebral infarction in the vessel-dominant region of the left middle cerebral artery.

On day 1, external decompression was done to relieve cerebral herniation caused by the cerebral infarction. On day 2, we began a course of levetiracetam at a dose of 1,000 mg/day to prevent convulsions. Based on the history of RA, on day 7, salazosulfapyridine was administered at a dose of 500 mg/day and increased

after 7 days (*i.e.*, on day 14) to 1,000 mg/day. The postoperative computed tomography (CT) following cranioplasty showed no increase in hemorrhagic infarction.

On day 37, dabigatran 300 mg/day was started to prevent the recurrence of cerebral infarction. On day 41, the patient developed fever. The following day (day 42), edema and erythema appeared on his face (Figure 2A), and erythema and rash also appeared on his trunk and extremities (Figure 2B). Due to the gradual onset of erythroderma, topical application of diphenhydramine and oral administration of fexofenadine hydrochloride at a dose of 120 mg/day was started.

The CT performed on day 43 showed inflammatory findings in the ileocecal area (Figure 3A) and a mild nodule shadow at the lower right lung (Figure 3B). We suspected that the drug eruption was caused by the dabigatran, and the oral administration of dabigatran was then stopped. On day 45, the patient developed diarrhea and was started on clostridium butyricum at a dose of 6 g/day. On day 50, his respiratory function deteriorated (saturation of percutaneous oxygen, SpO₂ 90%) and oxygen was administered. On day 51, a drug lymphocyte stimulation test was performed for levetiracetam and dabigatran. Both results were negative. Due to further deterioration of his respiratory function on day 53 (saturation of percutaneous oxygen, SpO₂ 80%), the oral administration of salazosulfapyridine was discontinued. A steroid pulse of methylprednisolone at a dose of 1 g/day for a period of 3 days was administered to prevent exacerbation of the IP (Figures 4A and 4B). Following this, the dose of methylprednisolone was reduced to 40 mg/day. Given the possibility of steroidogenic glucose tolerance abnormality, concurrent insulin therapy was administered in combination with methylprednisolone. Cardiac ultrasound examination performed on day 55 showed a pericardial effusion with normal wall motion. The CT performed on day 59 showed that the IP had



Figure 1. (A) Diffusion weighted image at hospitalization shows acute cerebral infarction consistent with the vessel dominant region of the left middle cerebral artery (left). (B) Magnetic resonance angiography at hospitalization shows the left middle cerebral artery occlusion (right).

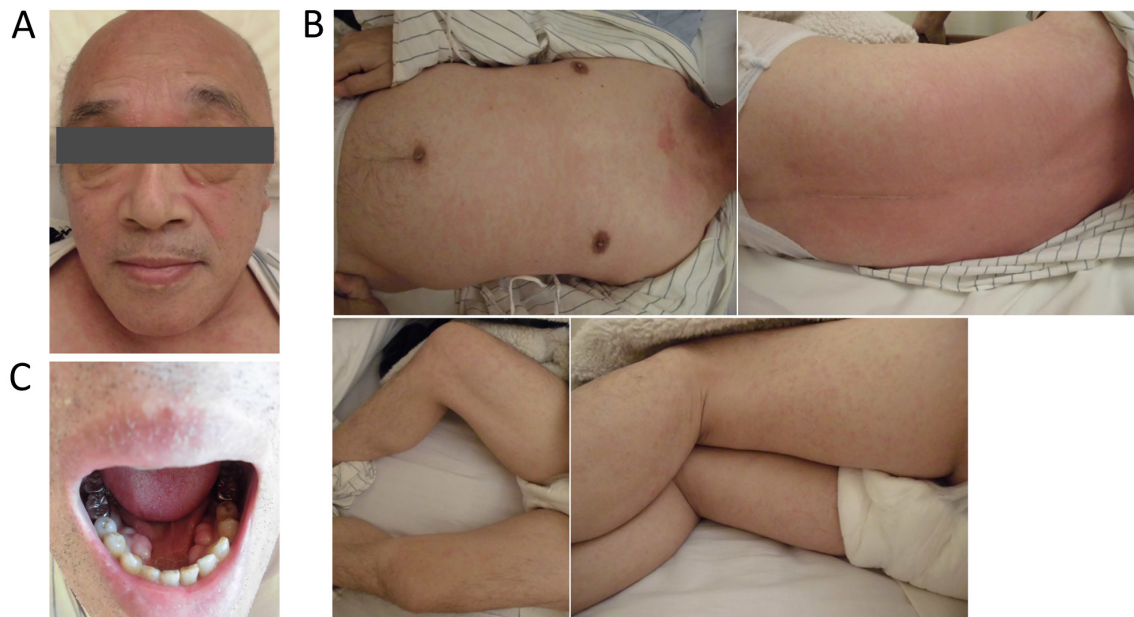


Figure 2. (A) The photograph shows edema and erythema on the patient's face on day 42. (B) The photographs show erythema and rash on the trunk and extremities on day 42. (C)...

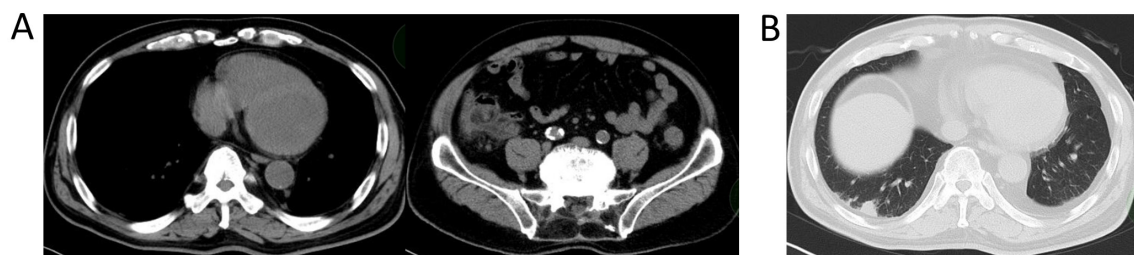


Figure 3. (A) The computed tomography (CT) performed on day 43 shows inflammatory findings in the ileocecal area. (B) The CT performed on day 43 shows mild nodule shadow at the lower right lung.

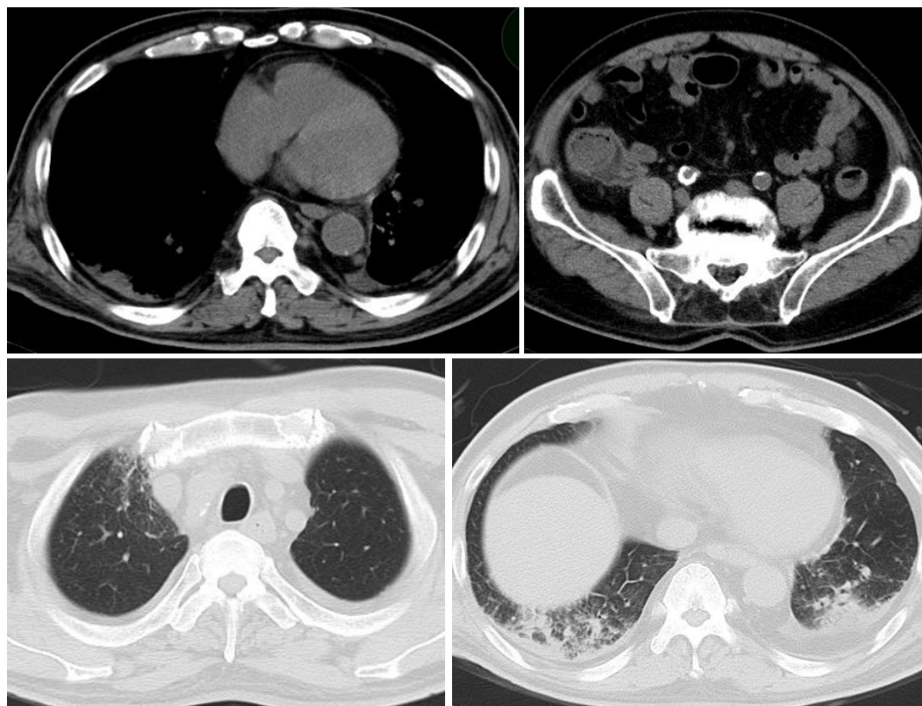


Figure 4. The computed tomography performed on day 43 shows exacerbation of interstitial pneumonia.

worsened and that there was pericardial effusion, while the inflammatory findings in the ileocecal area had decreased (Figures 5A and 5B).

Due to malaise caused by hyponatremia on day 60, fluids were restricted on suspicion of SIADH

caused by the IP. The hyponatremia was then gradually corrected. The patient then developed stomatitis, and a dexamethasone ointment was prescribed. The fever, erythema, and rash recurred on day 66. A CT performed on day 66 (Figures 6A and 6B) showed that

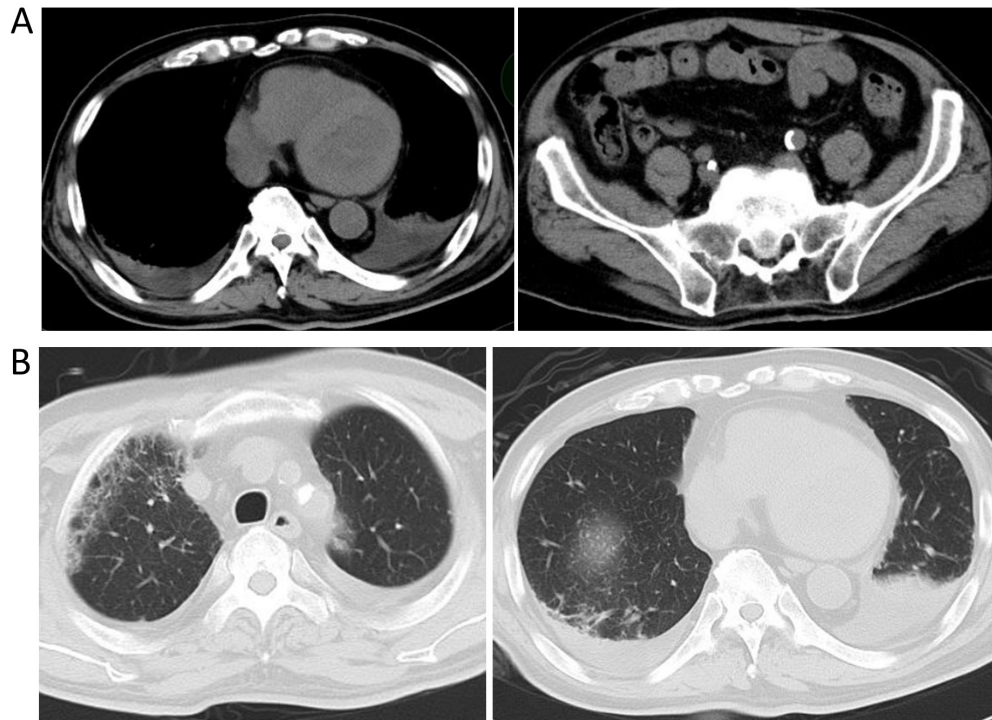


Figure 5. (A) The computed tomography performed on day 59 shows worsened interstitial pneumonia and pericardial effusion, (B) while the inflammatory findings in the ileocecal area appear improved.

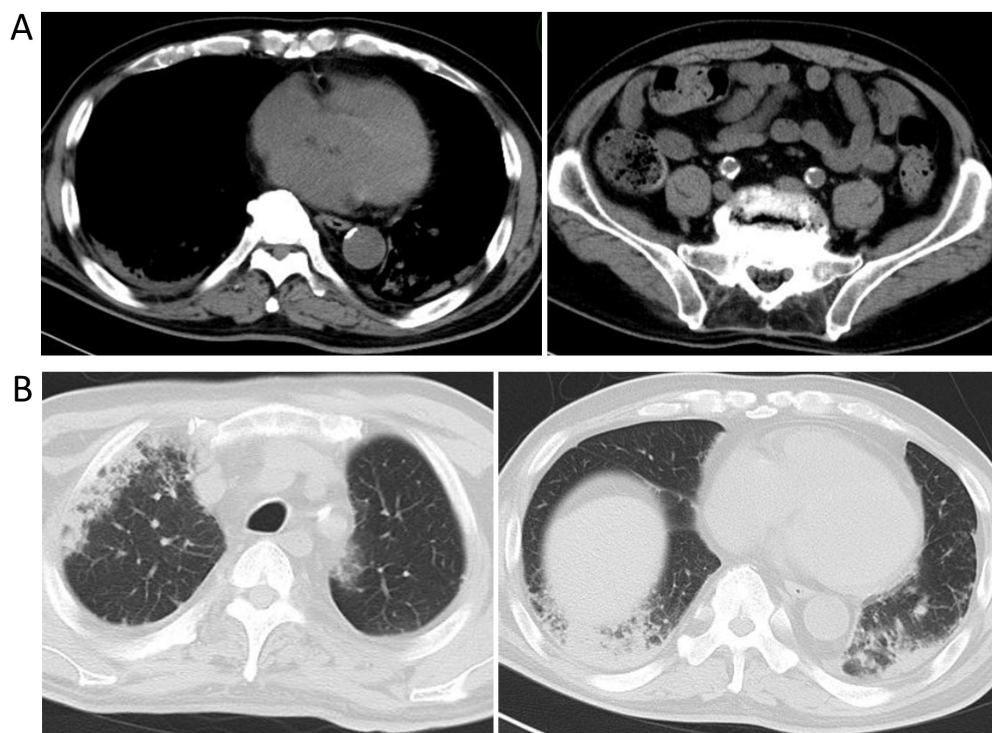


Figure 6. (A) The computed tomography performed on day 66 shows that the pericardial effusion has disappeared, (B) while the interstitial pneumonia has deteriorated.

Table 1. The diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) based on such clinical symptoms and the reactivation of HHV-6

Diagnostic criteria

- 1 Maculopapular rash developing > 3 weeks after starting a limited number of drugs
- 2 Prolonged clinical symptoms 2 weeks after discontinuing the causative drug
- 3 Fever (> 38°C)
- 4 Elevation of liver enzyme (alanine aminotransferase [ALT] > 100 U/L) or involvement of other organs
- 5 Leukocytosis (> $11 \times 10^3/\mu\text{L}$), atypical lymphocytosis (> 5%) or eosinophilia (> $1.5 \times 10^3/\mu\text{L}$)
- 6 Lymphadenopathy
- 7 Human herpesvirus (HHV)-6 reactivation

Diagnosis of typical DIHS requires the presence of all 7 criteria. Atypical DIHS is diagnosed in patients with 1-5.

the pericardial effusion was no longer present. The IP worsened and prednisolone was increased to a dose of 60 mg/day on day 67.

On day 72, we suspected that the patient had DIHS that had been induced by salazosulfapyridine, and antibody examinations for HHV-6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus were performed. The quantification test for HHV-6 DNA was negative (1.4×10^2 copies), and the quantification of HHV-7 DNA was also negative. EB anti-viral capsid antigen (VCA)-immunoglobulin G (IgG) was increased 160-fold and EB anti-VCA-IgM was negative. EB anti-EB nuclear antigen was increased 40-fold, which provided evidence of past EBV infection. As there were positive findings of cytomegalovirus-IgG (enzyme immunoassay) at 15.3 and cytomegalovirus-IgM (enzyme immunoassay) at 1.11, cytomegalovirus reactivation was suspected. Two months following the onset of DIHS, the patient was transferred to a rehabilitation center with a modified Rankin Scale score of 3. After transfer, his skin symptoms recurred intermittently, and psychiatric symptoms were also observed. At 10 months following the onset of DIHS, the patient was still undergoing immunotherapy including prednisolone.

3. Discussion

The period between oral administration of a causative drug and the onset of DIHS (1,2) for many cases is approximately 2 to 6 weeks. Unlike ordinary drug eruptions, DIHS does not occur immediately or within a few days following the oral administration of a drug. There have been reports of DIHS developing after long-term oral administration of a drug or within several weeks of discontinuation of therapy. Systematic symptoms of DIHS include fever, lymphadenopathy, rash (initially mottled papule or erythematous erythematous, often transitioning to erythroderma), hepatic function disorder, renal function disorder, and hematologic abnormalities (leukocytosis, emergence of atypical lymphocytes, and eosinophil multiplication). Incidentally, characteristic erythematous findings such as erythema, edema of the face, red papule of the mouth, pustules, vesicles, and scales, are usually

observed within 1 week of initial drug administration.

The causative drugs are limited. For this reason, DIHS was postulated to be due to an abnormality of metabolic enzymes (3,4). The most frequent causative agent of DIHS in Japan is carbamazepine. The symptoms of DIHS often progress even after stopping the administration of the causative drugs, and complete relief from symptoms often requires longer than 1 month. In typical cases, DIHS is clinically bimodal. This is due to reactivation of HHV-6. In other words, what has been regarded as a very specific course of drug eruption is a complex pathology of drug allergy and virus infection (3,4). Diagnostic criteria for DIHS have been proposed based on such clinical symptoms and the reactivation of HHV-6 (Table 1). Our patient met all seven criteria and was confirmed as a typical case of DIHS induced by salazosulfapyridine.

Reactivation of cytomegalovirus is frequently observed in DIHS (5,6); cytomegalovirus is usually reactivated at the same time or later than HHV-6, suggesting that it could be related to clinical symptoms. Besides fever, mild liver dysfunction, and skin ulcer, severe symptoms such as myocarditis, pneumonia, and gastrointestinal bleeding may occur. If the symptoms of DIHS are prolonged, cytomegalovirus reactivation should be suspected (5,6). Cytomegalovirus infections in DIHS typically: 1) occur among elderly male patients, 2) develop 4 to 5 weeks following the onset of DIHS, 3) develop at the time of reactivation of HHV-6 and are related to HHV-6 DNA loads, and 4) are often prognostic (5). Because cytomegalovirus infection can be treated with appropriate antiviral drugs (ganciclovir), it is important to consider cytomegalovirus reactivation when providing treatment for DIHS. The investigations for cytomegalovirus include IgG antibody titration, measurement of IgM antibody titer, antigenic test, virus DNA, and histopathological examination. Although these methods are the most reliable for the detection of viral DNA, the clinical antigenicity test is also useful (5).

The drug eruption in our patient was suspected to have been induced by dabigatran based on the clinical symptoms that appeared 4 days after its administration. While it is possible that there may have

been cytomegalovirus reactivation, it may have been possible to avoid a severe cytomegalovirus infection such as central nervous system infection (7,8) due to the increased dose of steroids. In addition, due to the early combination of insulin and steroid therapy, there was no transition to fulminant type I diabetic ketoacidosis (9-12). Although diagnosing DIHS was challenging, a severe course of DIHS was avoided by considering the possibility of reactivation of cytomegalovirus.

Hyponatremia was also observed in association with an exacerbation of IP. Due to the serum osmotic pressure, which was as low as 271 mOsm/kgH, and prompt improvement of the serum sodium level by fluid restriction, the SIADH was attributed to IP (13). ADH is neuromodulated by two types of receptors, an osmotic receptor in the hypothalamus and a capacity receptor present in the left atrium, carotid artery, and aorta. Increased plasma osmotic pressure is detected by the osmotic receptor and a reduction in circulating blood volume or blood pressure is detected by the capacity receptor, which both in turn promote ADH secretion (13). Sakuma *et al.* (14) described a patient with phenobarbital-induced hypersensitivity syndrome who had SIADH associated with limbic encephalitis during the course of the disease. However, to the best of our knowledge, there are no reports of DIHS combined with SIADH attributed to IP. In our case, the interstitial capillary blood vessels were impaired following IP in conjunction with reactivation of cytomegalovirus on the background of DIHS. ADH secretion may have been promoted via the capacity receptor due to reduction in the vascular bed in the lung and a decrease in venous return.

In general, steroids (prednisolone 30-50 mg/day) are effective for DIHS treatment, while in severe cases, high-dose steroids and steroid pulse therapy are used. Recently, high-dose intravenous gamma-globulin (IVIG) has been employed, and there are reports of combined use of IVIG with steroid therapy in severe cases (15).

The administration of antiviral drugs is not necessary because HHV-6 reactivation usually occurs on a short-term basis. On the other hand, in the presence of cytomegalovirus infection, with prolongation or severity of symptoms, it is necessary to consider administering ganciclovir (5). In our patient, administration of steroid pulse therapy followed by a gradual decrease in dose prevented severe DIHS. This approach requires further investigation.

In conclusion, we encountered a case of DIHS induced by salazosulfapyridine combined with SIADH attributed to interstitial pneumonia 4 days following the administration of dabigatran that was difficult to diagnose. Timely diagnosis and an increase in the dose of steroids with subsequent tapering prevented worsening of DIHS. In the future, multidrug sensitization, potentially fatal infections, and

convalescent autoimmune diseases may be combined (1,2), and careful follow-up is necessary.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

References

- Tohyama M, Hashimoto K. Drug-induced hypersensitivity syndrome and HHV-6 reactivation. *Uirusu*. 2009; 59:23-30.
- Tohyama M, Hashimoto K, Yasukawa M, Kimura H, Horikawa T, Nakajima K, Urano Y, Matsumoto K, Iijima M, Shear NH. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. *Br J Dermatol*. 2007; 157:934-940.
- Seishima M, Yamanaka S, Fujisawa T, Tohyama M, Hashimoto K. Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. *Br J Dermatol*. 2006; 155:344-349.
- Kano Y, Hirahara K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. *Br J Dermatol*. 2006; 155:301-306.
- Asano Y, Kagawa H, Kano Y, Shiohara T. Cytomegalovirus disease during severe drug eruptions: Report of 2 cases and retrospective study of 18 patients with drug-induced hypersensitivity syndrome. *Arch Dermatol*. 2009; 145:1030-1036.
- Sekiguchi A, Kashiwagi T, Ishida-Yamamoto A, Takahashi H, Hashimoto Y, Kimura H, Tohyama M, Hashimoto K, Iizuka H. Drug-induced hypersensitivity syndrome due to mexiletine associated with human herpes virus 6 and cytomegalovirus reactivation. *J Dermatol*. 2005; 32:278-281.
- Fujino Y, Nakajima M, Inoue H, Kusuha T, Yamada T. Human herpesvirus 6 encephalitis associated with hypersensitivity syndrome. *Ann Neurol*. 2002; 51:771-774.
- Masaki T, Fukunaga A, Tohyama M, Koda Y, Okuda S, Maeda N, Kanda F, Yasukawa M, Hashimoto K, Horikawa T, Ueda M. Human herpes virus 6 encephalitis in allopurinol-induced hypersensitivity syndrome. *Acta Derm Venereol*. 2003; 83:128-131.
- Sekine N, Motokura T, Oki T, Umeda Y, Sasaki N, Hayashi M, Sato H, Fujita T, Kaneko T, Asano Y, Kikuchi K. Rapid loss of insulin secretion in a patient with fulminant type 1 diabetes mellitus and carbamazepine hypersensitivity syndrome. *JAMA*. 2001; 285:1153-1154.
- Seino Y, Yamauchi M, Hirai C, Okumura A, Kondo K, Yamamoto M, Okazaki Y. A case of fulminant type 1 diabetes associated with mexiletine hypersensitivity syndrome. *Diabet Med*. 2004; 21:1156-1157.
- Chiou CC, Chung WH, Hung SI, Yang LC, Hong HS. Fulminant type 1 diabetes mellitus caused by drug hypersensitivity syndrome with human herpesvirus 6 infection. *J Am Acad Dermatol*. 2006; 54:S14-S17.

12. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. *N Engl J Med.* 2000; 342:301-307.
13. Sono K, Kawashima T, Maruyama K, Ashizawa M, Kawashima S, Kikkawa K, Nishi Y, Kuroda T, Goto T, Matuzawa Y, Matumura R, Shirai K. A case of interstitial pneumonia accompanying SIADH. *Nihon Kokyuki Gakkai Zasshi.* 2006; 44:178-184.
14. Sakuma K, Kano Y, Fukuhara M, Shiohara T. Syndrome of inappropriate secretion of antidiuretic hormone associated with limbic encephalitis in a patient with drug-induced hypersensitivity syndrome. *Clin Exp Dermatol.* 2008; 33:287-290.
15. Kano Y, Inaoka M, Sakuma K, Shiohara T. Virus reactivation and intravenous immunoglobulin (IVIg) therapy of drug-induced hypersensitivity syndrome. *Toxicology.* 2005; 209:165-167.

(Received June 16, 2019; Revised August 13, 2019; Accepted August 22, 2019)