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A case of drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) following stomatitis

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Abstract

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a severe form of drug-related rash with distinct features. This condition is characterized by late onset from specific causative drugs, and symptoms worsen despite discontinuation of the causative agent, followed by organ dysfunction. Notably, DIHS/DRESS results from the reactivation of human herpesvirus 6 (HHV-6). Herein, we report a case of DIHS/DRESS in which rash, fever and liver dysfunction were observed during hospitalization for stomatitis, and HHV-6 reactivation was confirmed. A 67-year-old man who had been taking carbamazepine for the sequelae of cerebral hemorrhage was referred to our hospital because of pain in the oral mucosa. Initially, he was diagnosed with a herpes virus infection and treated with acyclovir. Afterward, despite improvement in stomatitis, papules appeared on the trunk of the body and worsened. The symptoms were accompanied by fever and liver dysfunction. Eventually, the patient developed decreased systolic blood pressure, tachypnea, and atrial fibrillation. After pulse steroid therapy was initiated, the patient's clinical condition improved. Real-time polymerase chain reaction was performed suspecting with DIHS/DRESS, and HHV-6 DNA was detected. Based on this process, we diagnosed the patient with DIHS/DRESS induced by carbamazepine.

Keywords: Carbamazepine; Stomatitis; DIHS/DRESS; HHV-6 reactivation; differential diagnosis

1. Introduction

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and

systemic symptoms (DIHS/DRESS) are life-threatening reactions. As a characteristic feature, a rash appears between 2 and 6 weeks after exposure to the causative drug. The anticonvulsants allopurinol and sulfasalazine are the main known causative drugs [1-3]. DIHS/DRESS is distinct from other drug rashes, such as Steven-Johnson syndrome (SJS) and Toxic Epidermal Necrosis (TEN). Human herpesvirus 6 (HHV-6) reactivation is a hallmark of DIHS/DRESS [4, 5]. Symptoms are sustained after discontinuation of the causative drug and become severe due to the HHV-6 reactivation. In typical DIHS/DRESS, fever and rash are the major initial symptoms, and lymphadenopathy and hematologic abnormal findings are present later [6]. It shows a bimodal fever, and organ dysfunction appears at the second fever, accompanied by HHV-6 reactivation [7]. Although the symptoms of oral mucosa may appear, they are rarely considered early symptoms. Here, we report a case that followed the typical clinical course of DIHS/DRESS caused by carbamazepine and where, to our knowledge, stomatitis was considered an initial symptom for the first time.

2. Case report

A 67-year-old man was referred to our hospital with a complaint of oral mucosal pain. A few days before visiting our hospital, the patient had a fever; he was diagnosed with herpes virus infection and treated with acyclovir at another medical clinic. The patient had a medical history of cerebral hemorrhage, hypertension, insomnia, and reflux esophagitis. He had been taking carbamazepine for a month for sequelae of cerebral hemorrhage. At first, he presented with whole-body fatigue, fever (36.6°C), and contact pain of the oral mucosa. Tender lymphadenopathy was observed in the right submandibular lymph node. Multiple stomatitis with redness were recognized in the upper and lower lip mucosa, front of the tongue, and buccal mucosa (Fig.1). On intraoral examination, the characteristics of stomatitis and contact pain were similar to the findings

of herpes simplex virus (HSV) infection, and the patient's contact pain was moderately improved after acyclovir administration. The patient was admitted to our department for nutritional management and was administered valaciclovir, cefditoren pivoxil, and loxoprofen sodium hydrate. Laboratory data showed elevated CRP levels, but no elevation in eosinophils or atypical lymphocytes was noted (Table 1). In addition, there was no increase in HSV and varicella-zoster virus **(**VZV) antibody titers (Table 2). On admission day (AD) 4, a rash with redness appeared on the body trunk (Fig.2). As a late-onset rash was suspected, cefditoren-pivoxil and loxoprofen were discontinued. On AD5, a slight fever of 37°C appeared, which caused valaciclovir to be discontinued. Topical application of a steroid ointment was initiated against the rash. Blood tests were performed for pemphigus vulgaris, but anti-desmoglein 1 antibody, anti-desmoglein 3 antibody, and anti-BP180 antibody tests were negative. Polymerase chain reaction (PCR) was performed on the lip and tongue mucosa, which had a suspected viral infection. However, HSV-1, HSV-2, or VZV DNA was not detected. On AD7, the stomatitis began to disappear, but the abdominal skin rash did not improve. A biopsy was performed, and the histopathological diagnosis was poisoning rash (Fig.3). On AD8, the fever of 37–38°C persisted, and other drugs, including carbamazepine, were discontinued due to the possibility of allergic reactions. On AD11, the rash expanded (Fig.4), and his body temperature increased to late 38°C. Laboratory data revealed liver dysfunction with aspartate aminotransferase (AST) 66 IU/L, alanine aminotransferase (ALT) 104 IU/L, lactate dehydrogenase (LDH) 516 IU/L, and gamma-glutamyl transpeptidase 173 IU/L (Fig.5). At the same time, leukocyte abnormalities were observed, and CRP levels were elevated (Fig.5). Subsequent laboratory data showed leukocytosis exceeding 11,000/mm^3 (Fig.5), but there were no findings of elevated neutrophil fractions, eosinophilia, or dysmorphic lymphocytes. On AD13, the systolic blood pressure decreased to 80 mmHg, and tachypnea and atrial fibrillation were observed. Pulse steroid therapy with 1000 mg

of methylprednisolone sodium succinate per day was immediately initiated. HHV-6 reactivation was suspected, prompting drug-induced lymphocyte stimulation tests (DLST) for drugs including carbamazepine as well as PCR for HHV-6. On AD15, he was transferred to the dermatology department. On AD16, the rash began to disappear, and oral administration of prednisolone 60 mg/day began. On AD23, serum quantitative PCR detected HHV-6 DNA, thus the patient was diagnosed with DIHS/DRESS. On AD31, the patient was discharged due to favorable clinical conditions after oral prednisolone therapy.

3. Discussion

DIHS/DRESS is a severe rash that is caused by a limited number of drugs and is defined as a drug hypersensitivity reaction characterized by organ damage, eosinophilia, lymphadenopathy, and rash [8]. DRESS was first described in 1996 as a DIHS caused by specific drugs [9] and is now considered to have the same disease spectrum as DIHS [10, 11]. Although DIHS requires HHV-6 reactivation (Table 3), DRESS does not list HHV-6 reactivation as a necessary diagnostic criterion (Table 4). However, the other diagnostic criteria are similar. DIHS can be considered a severe case of DRESS [12]. It is generally recognized that there is no obvious difference in the male-to-female ratio, but some reports indicate a slight female predominance [13]. Prevalence can depend on ethnic background but is estimated to be approximately 0.9-9.63 per 100,000 population [14-16]. HHV-6 is the causative virus of the exanthema subitum. Most Japanese adults are infected with this virus. However, it remains dormant in the majority of adults, and reactivation occurs under immunosuppressed conditions [17].

Anticonvulsants, salazosulfapyridine, allopurinol, mexiletine, diphenyl sulfone, and carbapenem have been reported to be causative drugs for DIHS/DRESS (Table 5). These drugs cause marked reductions in IgG levels and B cell counts and are considered to lead to an immunosuppressed state [18]. Patients undergoing immunosuppressive

therapy for autoimmune diseases or HIV patients with reduced $CD4^+$ T-cell counts are generally considered to be in an immunosuppressed condition [19]. However, our patient had no such history and was not under such conditions. As we did not perform immunological tests, the details are unclear. At least, there was no reduction in white blood cell count or neutrophil fraction in the laboratory data.

DIHS/DRESS occurs 2 to 6 weeks from the start of the causative drug [7]. Despite the discontinuation of the causative drugs, clinical and hematological symptoms tend to worsen, and organ damage (especially liver damage) occurs [13]. In our inpatient case, a maculopapular rash appeared approximately a month after carbamazepine administration, and worsened after discontinuation of the drug. Despite discontinuation, the symptoms, including fever of over 38°C, liver dysfunction, leukocyte abnormality, and lymphadenopathy, were rapidly exacerbated and did not improve until steroid therapy was started. Finally, the reactivation of HHV-6 was confirmed by serum quantitative PCR. It is reported that the significant elevation of serum IgG antibody to HHV-6 as well as the detection of serum HHV-6 DNA could be useful tests for the diagnosis of DIHS/DRESS [11]. Based on the clinical course, our case was considered a typical presentation of DIHS/DRESS.

The main differential diagnoses include maculopapular exanthema (MPE), erythema multiforme (EM), and viral eruptions. MPE is a common drug hypersensitivity reaction typically recognized early, approximately 1-2 weeks after initiation of the causative drug. It is characterized by a disseminated, sometimes generalized, symmetric rash of erythema and papules without mucositis or organ damage. In our case, MPE was excluded due to its late onset and the presence of mucositis or organ damage. EM is an inflammatory reaction caused by viral infections or drugs but resolves spontaneously in mild cases. In severe cases, it can progress to SJS, making it difficult to differentiate. In our case, EM was present in the early stages of the disease but did not resolve

spontaneously and could be differentiated by HHV-6 reactivation. Viral rashes can be ruled out by checking HSV and VZV antibody titers. In our case, HSV and VZV antibody titers did not elevate, thus excluding these viral rashes.

SJS/TEN is another delayed drug reaction but is believed to develop earlier than DIHS/DRESS following exposure to the causative agent [20, 21]. Although the diagnostic criteria for SJS/TEN and DIHS/DRESS differ, some causative agents overlap [22], and clinical symptoms may be similar in the early stages. DIHS/DRESS cases with skin symptoms similar to those of SJS/TEN have been reported [23]. DIHS/DRESS usually does not present with ocular symptoms or mucositis, but differentiation can be challenging when stomatitis is the initial symptom, as in our case. The cutaneous manifestations of DIHS/DRESS include edema in the upper dermis and an infiltrate of inflammatory cells, mainly lymphocytes, from the dermis to the epidermis, but no necrosis [13]. In SJS/TEN, on the other hand, the epidermis undergoes progressive necrotic changes, resulting in necrosis of the entire epidermal layer and subepidermal blister formation [24]. However, definitive differentiation can be made by confirming the reactivation of HHV-6. In our case, abdominal skin pathology showed lymphocytic infiltration of the dermis and some epidermis but no necrosis. Ultimately, the diagnosis of DIHS/DRESS was confirmed by PCR, which detected the reactivation of HHV-6. Recently, elevated blood levels of the Th2-type chemokine TARC/CCL17 have been reported in the early stages of DIHS/DRESS. Serum TARC/CCL17 levels in DIHS/DRESS are higher than those in SJS/TEN and disseminated MPE, which may aid in early diagnosis [25].

In recent years, the association between *HLA-A*31:01* and carbamazepine-induced drug eruptions has garnered attention. A genome-wide association analysis using carbamazepine-induced drug eruption cases reported that Japanese patients with the *HLA-A*31:01* type of the *HLA-A* gene predominantly experience carbamazepine-induced drug

eruptions compared to patients without the same type [26]. *HLA-A*31:01* has also been shown to be strongly associated with drug eruptions such as DIHS/DRESS, MPE, and EM, but is not specific for DIHS/DRESS [27]. Although it would be desirable to predict the risk of developing DIHS/DRESS and its severity, *HLA-A*31:01* does not appear to be a marker for DIHS/DRESS caused by carbamazepine at present.

DLST has been proposed as a potential diagnostic tool, but caution is warranted regarding the timing of testing. During the acute phase of DIHS/DRESS, sensitivity and specificity were reported as 40% and 30%, respectively. However, during the convalescent phase, these percentages increased to 73% and 82%, respectively, indicating that DLST should ideally be conducted during the convalescent phase of DIHS/DRESS [28]. Retrospective studies of DIHS/DRESS suggest that conducting DLST after the fifth week of illness onset is more likely to yield a positive result [29]. In our case, the test was conducted during the acute phase, which may have contributed to the negative result.

There are still many unclear points regarding the involvement of HHV-6 reactivation in the pathology of DIHS/DRESS. Tohyama et al. investigated the associations among drug rashes, systemic symptoms, and HHV-6 reactivation [30]. In the HHV-6 reactivated group, the fever period was significantly prolonged, and lymphadenopathy, leukocytosis, atypical lymphocytosis, and severe liver dysfunction were observed [30]. In addition, all patients with organ dysfunction or poor prognosis belonged to the HHV-6 reactivated group [30]. Interestingly, in the patients with organ damage, HHV-6 antigen was detected in the damaged organs [31, 32]. These results indicate that HHV-6 reactivation is closely related to prolongation and exacerbation of the clinical symptoms of DIHS/DRESS. In our case, the patient had a bimodal fever with liver dysfunction and leukocyte abnormality, and as expected, HHV-6 reactivation was confirmed. Delayed treatment may have been fatal.

Oral administration of prednisolone (1–2 mg/kg/day or 40–60 mg/day) is generally

applied to treat DIHS/DRESS [2]. Autoimmune diseases are also known to develop during the progression of this disease, and further, it is associated with immune reconstitution syndrome [33, 34]. Therefore, caution should be exercised when rapidly reducing the steroid dose, as there is a risk of worsening the condition [35]. In the present case, the patient experienced a drop in systolic blood pressure, tachypnea, and atrial fibrillation, and we administered pulse steroid therapy according to the instructions of the Dermatology department. Thereafter, the prednisolone dose was tapered. The mortality rate of patients is reported to range from 5-10% [36]. Early recognition of this syndrome is critical to avoid adverse outcomes.

DIHS/DRESS is reportedly associated with the reactivation of HHV-7, cytomegalovirus (CMV), and Epstein–Barr virus (EBV) [37-39]. Herpesviruses are continuously reactivated during the course of DIHS/DRESS; HHV-6 and EBV reactivation occurs initially, followed by HHV-7 and eventually CMV [40]. A retrospective analysis of 55 patients with DIHS/DRESS has reported that 3 of 11 cases with CMV reactivation died (27.3%) [41], showing that the prognosis in cases with CMV reactivation is poor [41, 42]. In our case, HHV-7 was not detected, and neither CMV nor EBV were tested. However, based on the scoring system [41] established by Mizukawa et al, the severity score of our case was 5 with a risk of CMV reactivation. Therefore, pulse steroid therapy is considered a risk for CMV reactivation and frequent assessment for risk of CMV reactivation is warranted in patients on systemic corticosteroid treatment [41]. HHV-6 is often reactivated 2 to 3 weeks after symptom onset, and fever and liver dysfunction reportedly occur simultaneously [30, 43]. Therefore, it is vital that close attention be paid to HHV-6 reactivation in the acute phase.

Although the initial symptoms of DIHS/DRESS are often fever and rash, stomatitis was identified before the onset of clinical symptoms in the present case. In addition, the stomatitis did not improve after valacyclovir administration. As pemphigus and

pemphigoid were ruled out, stomatitis was considered a symptom of DIHS/DRESS as a drug reaction. Although stomatitis is relatively common in DIHS/DRESS [13], to the best of our knowledge, this is the first case in which stomatitis was observed as an initial symptom of DIHS/DRESS. Therefore, clinicians, including oral surgeons, should consider the possibility of DIHS/DRESS if symptoms of stomatitis followed by rash and fever are present, and reactivation of HHV-6 should be assessed. Further studies are needed to elucidate the pathogenesis of DIHS/DRESS with a focus on stomatitis.

4. Conclusions

We encountered a case of DIHS/DRESS in which stomatitis was considered the initial symptom. Owing to the possibility of DIHS/DRESS, early diagnosis and prevention of serious complications are important when stomatitis is observed in patients taking the causative drugs.

Ethical approval

The patient provided consent for publication.

Acknowledgments

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Conflict of interest

The authors declare no conflicts of interest directly relevant to the content of this article.

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Figure legends

Figure 1

Figure 1 Appearance of the oral mucosa at first visit.

Stomatitis was observed on the upper and lower lips (A and B), tongue, and buccal mucosa (C).

Figure 2

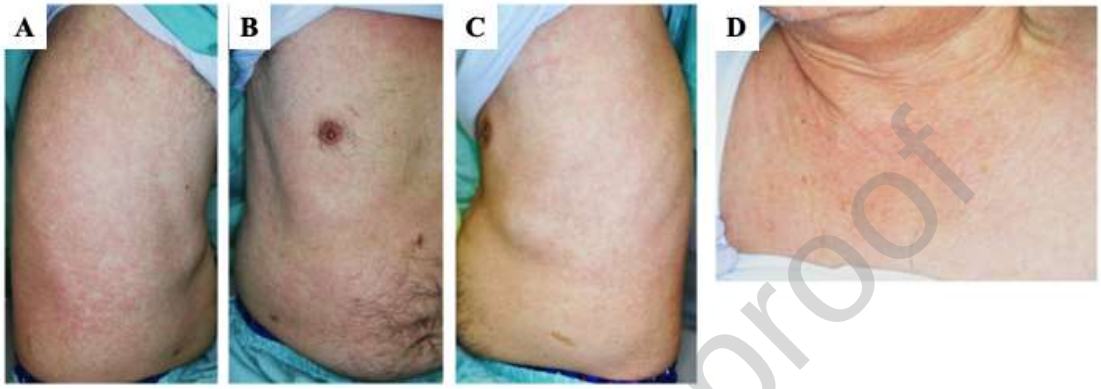

Figure 2 Appearance of rash (AD4).

A rash with redness appeared on the skin of the trunk (A, B, C) and anterior chest (D).

Figure 3

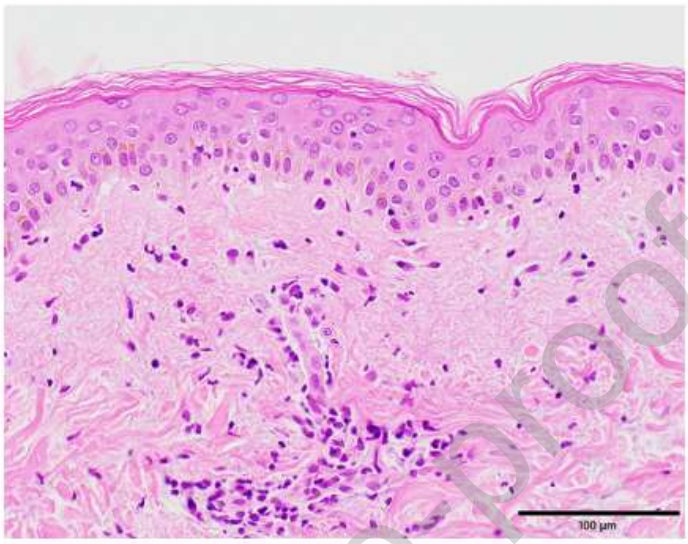

Figure 3 Microscopic photograph of biopsy specimen obtained from the patient's abdominal skin HE staining.

Lymphocyte infiltration into the dermis and partially into the epidermis, which is a characteristic of poisoning rash, has been recognized.

Figure 4

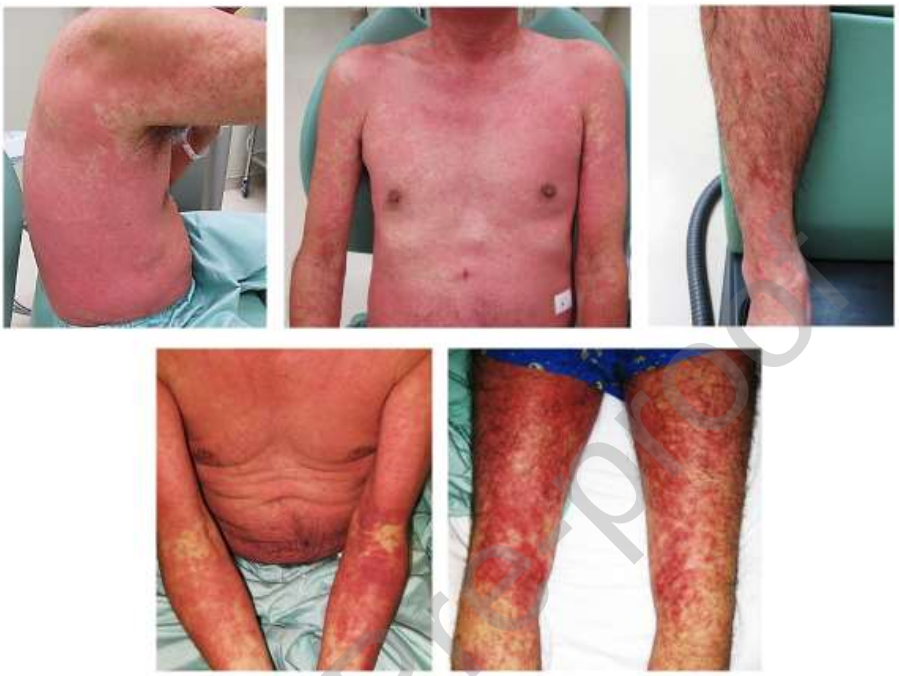

Figure 3

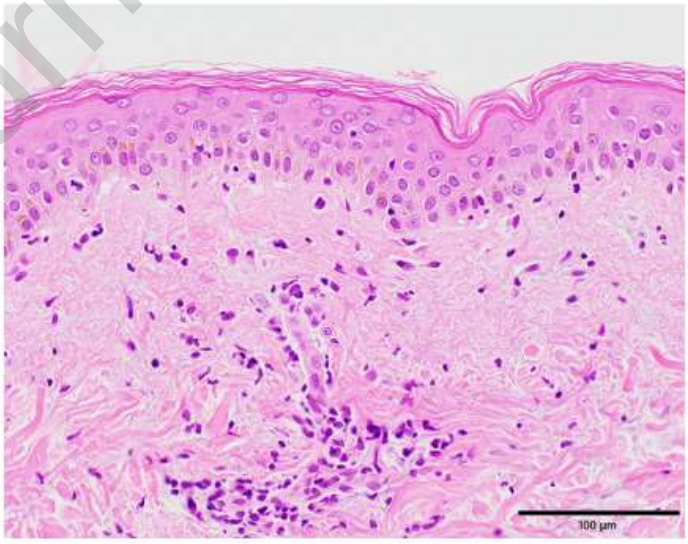

Figure 4 Exacerbation of rash appearance (A, B, C: AD8; D, E: AD11).

Deterioration of the skin rash was observed on almost the entire skin.

Figure 5

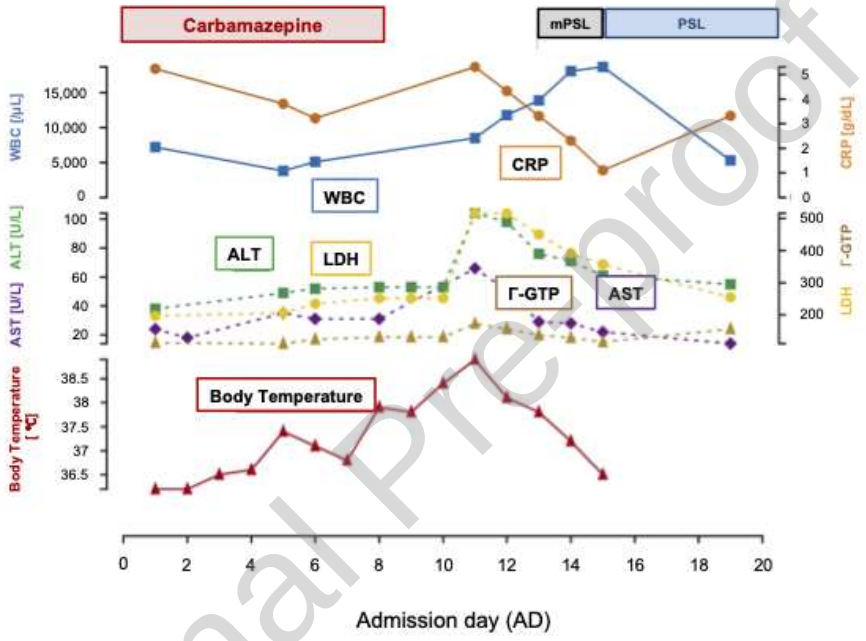

Figure 5 Clinical progress chart.

Elevated hepatobiliary and pancreatic enzymes and bimodal fever were observed simultaneously with rash exacerbation.

Elevated white blood cells and CRP were observed during the exacerbation of the rash.

mPSL: methylprednisolone, PSL: prednisolone

Table 1 Laboratory findings at first visit

Test		Result	Normal range
WBC		$7.2x10^3$ /mm^3	$3.5\text{-}8.5x10^3$ /mm^3
RBC	Low	$3.71x10^6$ /mm^3	$4.31\text{-}6.65x10^6$ /mm^3
Hgb	Low	11.9 g/dL	14.0-17.7 g/dL
Hct	Low	35%	40.4-50.8%
MCV		94.3 fL	85.5-99.6 fL
MCH		32.1 pg	29.2-34.5 pg
MCHC		34 g/dL	33.4-36.1 g/dL
RDW		12.30%	12.0-14.2%
PLT	High	$328x10^3$ /mm^3	$145\text{-}325x10^3$ /mm^3
Pct	High	0.29%	0.132-0.268%
MPV	Low	8.8 fL	9.0-11.1 fL
PDW		9.3 fL	
Baso		1.10%	0-1.5%
Eosin		0.40%	0-6.6%
Neut		77.20%	40.7-74.8%
Lymp	Low	13.50%	19.0-49.8%
Mono		7.80%	1.0-9.0%
TP		6.8 g/dL	6.5-8.3 g/dL
Alb	Low	3.6 g/dL	3.9-4.9 g/dL
Na		142 mmol/L	138-146 mmol/L
K		3.5 mmol/L	3.5-5.0 mmol/L
Cl		103 mmol/L	99-109 mmol/L
BUN		9 mg/dL	8-24 mg/dL
Crea		0.7 mg/dL	0.56-1.18 mg/dL
eGFR		86	60<
T-Bil		0.4 mg/dL	0.3-1.1 mg/dL
AST		24 U/L	13-34 U/L
ALT	High	38 U/L	7-37 U/L
LD		197 U/L	112-213 U/L
γ-GTP	High	113 U/L	9-47 U/L
ALP		305 U/L	106-350 U/L
Amy		43 U/L	32-116 U/L
CRP	High	5.23 mg/dL	<0.3 mg/dL

P-Glu	High	136 mg/dL	72-110 mg/gL

Table 2 Viral antibody titer test

	first visit	about 2 weeks later
HSV-IgG	62.7	57.8
HSV-IgM	0.65	0.66
VZV-IgG	7.5	6.7
VZV-IgM	0.39	0.25

Table 3 Diagnostic criteria for DIHS established by a Japanese consensus group

1. Maculopapular rash developing > 3 weeks after starting with a limited number of drugs
2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
3. Fever (>38℃)
4. Liver dysfunction
5. Leukocyte abnormalities：at least one presentation among a, b, c
a. Leukocytosis (>11,000/mm^3)
b. Atypical lymphocytosis (>5%)
c. Eosinophilia (>1,500/mm^3)
6. Lymphadenopathy
7. HHV-6 reactivation
Typical DIHS：presence of 1-7.
Atypical DIHS：presence of 1-5. Liver dysfunction can be replaced by other organ dysfunction

Table 4 Inclusion criteria for a potential case of DRESS in RegiSCAR

1. Hospitalization
2. Reaction suspected to be drug-related
3. Acute skin rash
4. Fever (>38℃)
5. Enlarged lymph nodes at least two sites
6. Involvement of at least one internal organ
7. Blood count abnormalities Lymphocytes above or below the labotratory limits Eosinophils above the laboratory limits (in percetage ofr absolute count) Platelets below the laboratory limits
Criteria No.1-3 are necessary for diagnosis, and the presence of 3 out of the other 4.

Table 5 Possible causative drugs for DIHS/DRESS

Anticonvulsant
Carbamazepine
Phenobarbital
Zonisamide
Salazosulfapyridine
Allopurinol
Mexiletine
Diphenyl sulfone
Carbapenem