

## Herpes Zoster in Patients with Drug-induced Hypersensitivity Syndrome/DRESS

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Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a severe systemic hypersensitivity reaction caused by specific drugs and involves the reactivation of human herpesvirus 6 (HHV-6) (1, 2). Accumulating evidence suggests that other herpesviruses, such as Epstein-Barr virus (EBV) (3, 4), HHV-7 (5) and cytomegalovirus (CMV) (6) reactivate during the course of DIHS/DRESS, similar to the herpesvirus reactivation observed in recipients who have undergone bone marrow transplantation (BMT) (7). Although varicella-zoster virus (VZV) reactivations are frequently observed in recipients with BMT (8), VZV reactivations have rarely been reported in the setting of DIHS/DRESS (9). In view of the similarity between BMT and DIHS/DRESS (10), it is likely that VZV reactivation might also be present in patients with DIHS/DRESS. Because herpes zoster (HZ) is often observed without any relationship to the underlying disease, it is difficult to determine whether there is any relationship between HZ and DIHS/DRESS. We have therefore retrospectively analysed patients with DIHS/DRESS who developed HZ.

### METHODS

Between 1998 and 2010, 28 patients who developed DIHS/DRESS and were treated in our hospital were enrolled in this study. The criteria used for DIHS/DRESS were the presence of a high fever, a widespread maculopapular and/or diffuse erythematous eruption, lymphadenopathy, leukocytosis with atypical lymphocytosis and/or eosinophilia, liver dysfunction and HHV-6 reactivation (11). To detect HHV-6 reactivation, patients with suspected DIHS/DRESS were tested for anti-HHV-6 IgG antibody titres and/or real-time PCR assays for HHV-6 DNA loads in peripheral leukocytes. HHV-6 reactivation was defined by a >4-fold increase in anti-HHV-6 IgG antibody titres or detection of HHV-6 DNA in the leukocytes. The 6-month observation period after the onset of drug reactions was defined. Patients who were followed up for less than the 6-month

observation period or those who did not satisfy the criteria for DIHS completely were excluded in this study. The DIHS/DRESS patients were classified into two groups: 12 patients who received systemic corticosteroid therapy, and 16 patients who received supportive care for dehydration alone. As a drug eruption control group, patients with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) were selected. SJS/TEN was diagnosed according to the criteria described by Bastuji-Garin et al. (12). There were 8 cases of SJS and 3 of TEN who satisfied the criteria for SJS/TEN and were treated with systemic corticosteroids. The clinical features of each group are summarized in Table I. The clinical diagnosis of HZ was made based on the assessment by the dermatologists at our hospital in the follow-up period. A questionnaire was sent to the control patients who were not regularly followed up.

### RESULTS

Three out of the 28 patients with DIHS/DRESS developed HZ within 6 months after the onset of DIHS/DRESS; all 3 patients had been given systemic corticosteroids. No patient with SJS/TEN developed HZ in the same period (Table II). The 3 patients had had childhood varicella, but not HZ before the onset of DIHS/DRESS. One patient had a renal cell cancer. The causative drug of DIHS/DRESS was anticonvulsants in all 3 patients. HZ developed approximately 60 days after the onset of DIHS/DRESS during the tapering period of administration of systemic corticosteroids in cases 1 and 2; HZ developed 30 days after the cessation of systemic corticosteroids in case 3. There was no identical dermatomal involvement with HZ, and the cutaneous manifestations were mild with no complications. A significant increase in the anti-VZV IgG antibody titre at >2 weeks after the onset of the HZ was seen in all cases. Two patients (cases 2 and 3) were treated with systemic acyclovir and one patient was treated with topical acyclovir alone. Analysis of CMV DNA was

Table I. Characteristics of 28 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) and 11 patients with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). DIHS/DRESS patients are divided into two groups depending on whether or not they received corticosteroids

Diagnosis n (M:F)	Corticosteroid treatment <sup>a</sup> (n)	Age, years Mean ± SD	Underlying disease (n)	Causative drug (n)
<b>DIHS/DRESS</b>				
16 (7:9)	None	56.7 ± 14.8	Cerebral infarction (2), convulsion (5), epilepsy (1), hyperuricaemia (3), neuralgia (2), psychiatric disease (3)	Allopurinol (3), carbamazepine (10), phenobarbital (1), phenytoin (2)
12 (8:4)	0.6–1.0 mg/kg/day (12)	55.2 ± 18.6	Arrhythmia (1), cerebral infarction (2), convulsion (1), epilepsy (3), hyperuricaemia (1), psychiatric disease (3), rheumatoid arthritis (1)	Allopurinol (1), carbamazepine (6), mexiletine (1), phenobarbital (2), phenytoin (1), salazosulphapyridine (1)
<b>SJS/TEN</b>				
11 (5:6)	0.8–1.0 mg/kg/day (8) 1000 mg/day <sup>b</sup> (3)	51.5 ± 21.5	Asthma (1), convulsion (1), cardiovascular disease (2), LE (1), multiple sclerosis (1), pneumonia (2), psychiatric disease (2), ulcerative colitis (1)	Lamotrigine (1), loxoprofen (1), phenytoin (1), salazosulphapyridine (1), sulphamethoxazole trimethoprim (1), unknown (6)

<sup>a</sup>Initial dose. <sup>b</sup>Steroid pulse therapy. SD: standard deviation; M:F: male:female; LE: lupus erythematosus.

Table II. Characteristics of patients with herpes zoster (HZ) in DIHS/DRESS

Case no./ Age, years/sex	Underlying illness	Causative drug Duration <sup>a</sup> , day	Detection of HZ Duration <sup>b</sup> , day	Corticosteroid treatment dose <sup>c</sup>	Dermatome involved	Alteration of anti-VZV IgG antibody titre <sup>d</sup>
1/39/M	Psychiatric disease	Carbamazepine 44	60	+ 40 → 10	Lt. L5	30 → 277
2/63/M	Convulsion due to metastatic tumour	Carbamazepine 27	63	+ 40 → 20	Lt. V2	87 → 514
3/70/F	Cerebral infarction	Phenytoin 43	147	+ 40 → 0	Rt. C5 & C6	36 → 653

<sup>a</sup>Between the initial drug intake and the onset of DIHS/DRESS. <sup>b</sup>Between the onset of drug reaction and that of HZ. <sup>c</sup>At the initial dose and the dose at the onset of HZ (mg/daily). <sup>d</sup>Anti-varicella-zoster virus (VZV) IgG antibody titres were examined at the onset of HZ and more than 2 weeks after that of HZ using an enzyme immunoassay method. Lt: left side; Rt: right side.

carried out in cases 1 and 2. After HHV-6 reactivation, CMV DNA was detected in the blood and then HZ lesions appeared in one patient (case 2).

## DISCUSSION

Our results demonstrated that HZ was present in only 11% of patients who developed DIHS/DRESS in the 6-month observation period after the onset of drug reaction. As VZV reactivation is thought to occur in the absence of skin lesions following renal transplantation (13), it is likely the case also in DIHS/DRESS. Thus significant increases in anti-VZV IgG antibody titre were detected in 2 out of the 11 patients with DIHS/DRESS without any clinical symptom in this observation period (unpublished observation).

The chronological timing of VZV reactivation after BMT is highly variable, ranging from days to several years after BMT (13). In our study, HZ appeared during corticosteroid treatment of DIHS/DRESS in 2 patients and one month after complete recovery in one patient. Alas, our study was not large enough to demonstrate the exact timing of HZ onset.

The administration of systemic corticosteroid for treatment of DIHS/DRESS may have contributed to the increased risk of HZ. Indeed, HZ was not detected in patients with DIHS/DRESS who were treated with only supportive care. On the other hand, HZ was also not observed in patients with SJS/TEN who were given systemic corticosteroids. Presumably, the altered underlying immunological pathomechanism of DIHS/DRESS due to the systemic corticosteroid might have played an important role in the onset of HZ. It has been shown that DIHS/DRESS is a manifestation of newly observed immune reconstitution syndrome (IRS) (14), and HZ is observed as the most common manifestation of IRS after highly active antiretroviral therapy in AIDS (15). Therefore, it is possible that the reduction or withdrawal of corticosteroid in the setting of DIHS/DRESS could contribute to the development of HZ.

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