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.

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. The 3 patients had had 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

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

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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The authors declare no conflicts of interest.

REFERENCES


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

<table>
<thead>
<tr>
<th>Case no./</th>
<th>Years/sex</th>
<th>Underlying illness</th>
<th>Causative drug Durationa, day</th>
<th>Detection of HZ Durationb, day</th>
<th>Corticosteroid treatment dose</th>
<th>Dermatome involved</th>
<th>Alteration of anti-VZV IgG antibody titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/39/M</td>
<td>Psychiatric disease</td>
<td>Carbamazepine</td>
<td>44</td>
<td>+ 40 → 10</td>
<td>Lt. L5</td>
<td>30 → 277</td>
<td></td>
</tr>
<tr>
<td>2/63/M</td>
<td>Convulsion due to metastatic tumour</td>
<td>Carbamazepine</td>
<td>27</td>
<td>+ 40 → 20</td>
<td>Lt. V2</td>
<td>87 → 514</td>
<td></td>
</tr>
<tr>
<td>3/70/F</td>
<td>Cerebral infarction</td>
<td>Phenytoin</td>
<td>34</td>
<td>+ 40 → 0</td>
<td>Rt. C5 &amp; C6</td>
<td>36 → 653</td>
<td></td>
</tr>
</tbody>
</table>

aBetween the initial drug intake and the onset of DIHS/DRESS. bBetween the onset of drug reaction and that of HZ. cAt the initial dose and the dose at the onset of HZ (mg/daily). d 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.