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A Case of Drug-induced Hypersensitivity Syndrome due to Carbamazepine

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Abstract

The patient was a 51-year-old man who had been prescribed carbamazepine for right third-branch trigeminal neuralgia. He had stopped taking the medication after the neuralgia resolved. When the neuralgia recurred, he resumed medication, and about 1 month later he developed fever, fatigue, cervical lymphadenopathy, generalized skin flushing, facial edema and perioral vesicles, and was admitted to Ichikawa General Hospital, Tokyo Dental College. Oral findings showed reddening and erosion of the buccal mucosa. Routine laboratory examination revealed leukocytosis and hepatic dysfunction. Human herpesvirus 6 antibody titer remarkably increased during development of eruptions. These findings led to a diagnosis of drug-induced hypersensitivity syndrome. Carbamazepine was discontinued, and prednisolone (30 mg/day) was started and tapered based on improvement of symptoms. Because skin symptoms recurred after he was discharged 15 days after admission, the dose of prednisolone was increased and the symptoms finally disappeared. The patient has experienced no further recurrence.

Key words: Drug-induced hypersensitivity syndrome (DIHS) — Carbamazepine (CBZ) — Human herpesvirus 6 (HHV-6) — Oral findings

Case Report

Severe drug eruptions can be classified into drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN). Carbamazepine (CBZ) is used for the treatment of trigeminal neuralgia, and is a causative agent for severe drug eruption in the face, head and neck regions. The incidence of drug
eruptions is relatively high, at 2–5%). Over the last 20 years, CBZ has been one of the most common drugs causing drug eruption\(^4\). In recent years, DIHS has been shown to be related to drug allergy and human herpes virus (HHV)-6 which causes exanthem subitum in infants, thus changing the concept of drug allergy\(^5\).

We report herein a case of DIHS with CBZ as the most likely cause.

Patient: 51-year-old man.

Chief complaint: Right mandibular gingival swelling and pain.

Past medical history: Hypertension, Mallory-Weiss syndrome and gastroduodenal ulcer.

Family history: Unremarkable.

History of present illness: The patient experienced swelling in the lingual gingiva of the right mandibular second and third molars and pain in the right third branch trigeminal nerve. He visited his family dentist about 40 days prior to presenting at this department. Although the swelling in the gingiva showed an improvement with administration of antimicrobial agents, the pain did not abate. Therefore, he was referred to our department for detailed examination and treatment. X-ray imaging confirmed an impacted right mandibular third molar, which was then extracted in a conventional manner for diagnostic purposes. However, the trigeminal neuralgia was exacerbated. Therefore, CBZ was administered at 200 mg/day orally for 5 weeks. When trigeminal neuralgia improved, CBZ was discontinued. However, trigeminal neuralgia recurred about 10 months later, and 10 days after this patient revisited our department. As trigeminal neuralgia of central origin was suspected, the patient was referred to the neurosurgery department. On the same day, a neurosurgeon initiated CBZ therapy at 400 mg/day orally. Seven days later the patient visited his family physician complaining of pharyngeal pain, a 37°C fever and arthralgia. A common cold was diagnosed and cold medication prescribed. Seven days later he developed systemic skin erythema and oral mucosal redness. The family physician suspected drug allergy, so the cold medication was discontinued and 30 mg prednisolone (PSL) administered the next day. Since the patient had been taking CBZ for some time, CBZ was not regarded as the cause of the allergy, and oral administration was continued. However, 5 days later, the patient developed a 39.1°C fever and increased systemic skin erythema. Five days later, the family physician therefore referred the patient to the dermatology department of Ichikawa General Hospital, Tokyo Dental College. As mucosal erythema was also confirmed in the oral cavity, a dermatologist referred the patient to the department of oral and maxillofacial surgery for consultation.

1. Present illness

Systemic findings: Generalized skin flushing, broad facial edema and bilateral cervical lymph node enlargement were confirmed (Fig. 1).

Facial findings: Vesicles had formed around the lips, and erythema was confirmed on the facial skin (Fig. 2).

Laboratory findings: Hepatic dysfunction, elevated CRP, elevated WBC and atypical lymphocytes were observed, along with an elevated eosinophil count (Table 1).

Treatment and therapy: Drug-induced hypersensitivity syndrome was suspected based on clinical findings and drug history, and the dermatologist discontinued CBZ from the day of admission. Steroid administration was

<table>
<thead>
<tr>
<th>Table 1 Clinical laboratory test findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP 5.8 g/dl</td>
</tr>
<tr>
<td>Alb 3.6 g/dl</td>
</tr>
<tr>
<td>T-Bil 0.4 mg/dl</td>
</tr>
<tr>
<td>D-Bil 0.2 mg/dl</td>
</tr>
<tr>
<td>LDH 531 IU/liter</td>
</tr>
<tr>
<td>γ-GTP 722 IU/liter</td>
</tr>
<tr>
<td>AST 28 IU/liter</td>
</tr>
<tr>
<td>ALT 85 IU/liter</td>
</tr>
<tr>
<td>BUN 11 mg/dl</td>
</tr>
<tr>
<td>Cr 0.6 mg/dl</td>
</tr>
<tr>
<td>CRP 6.7 mg/dl</td>
</tr>
</tbody>
</table>

Underlined data are abnormal values.
performed in the department of dermatology, followed by initiation of oral PSL administration at 30 mg/day. The facial rash worsened on hospital day 3, and so the PSL dose was increased to 60 mg/day. On hospital day 5, facial and systemic rash showed some improvement, and the PSL dose was reduced to 50 mg/day. As the rash improved, the PSL dose was tapered. The PSL dose was reduced to 5 mg/day on hospital day 15, and the patient was discharged. About 1 week after

Fig. 1 Dermal findings on admission to dermatology department
Redness and vesicle formation were also confirmed in femoral region, and this area was subjected to histopathological analysis.

Fig. 2 Facial findings on admission to dermatology department
Facial edema, redness and perioral vesicle formation were confirmed.

Fig. 3 Oral findings on admission to dermatology department
A: Right buccal mucosa, B: Maxillomandibular gingiva, C: Left buccal mucosa. Entire oral cavity was red and showed partial erosion and edema accompanied by turbidity.
Fig. 6 Histological findings on oral mucosa (HE stain, ×200)
Buccal mucosa and stratum corneum of epidermis were thin and parakeratotic, and marked lymphocyte infiltration and coexisting RBCs were confirmed between mucosal epithelium and stroma. Partial destruction of basal cell layer structure was observed.

Fig. 4 Oral findings during recovery phase
A: Right buccal mucosa, B: Maxillomandibular gingiva, C: Left buccal mucosa.
After skin eruptions healed, no abnormal findings such as erosion or edema were observed in oral cavity.

Fig. 5 Histological findings on skin (HE stain, ×200)
Epidermal liquefaction degeneration and cellular infiltration were confirmed in femoral skin, consisting mainly of lymphocytes containing small numbers of eosinophils around vessels in superficial dermis. Papillary dermis edema and RBC migration were also observed.
discharge, erythema recurred on the scalp, trunk and upper extremities. Prednisolone was administered at 10 mg/day orally for 4 days. As erythema dissipated in 2–3 days, oral PSL therapy was terminated. The rash did not recur. In terms of oral symptoms, erosion, edema, redness and pain were present in the palate, gingiva and bilateral buccal mucosa on the day of admission (Fig. 3). Taste abnormality was also confirmed. Oral surgeons confirmed oral mucosal lesions, performed histopathological analysis, oral cavity rinsing and plaque control, and carried out a follow-up on the patient. The right buccal mucosa was histopathologically analyzed on the same day, and an oral rinse containing benzethonium chloride was prescribed. Although oral mucosal erosion disappeared on hospital day 7, redness persisted and contact pain was confirmed. By the time of discharge, oral symptoms had disappeared and did not recur (Fig. 4). Viral tests showed that the titer of HHV-6 IgG antibody on admission was ×10, increasing to ×2,560 by 2 weeks later. A drug-induced lymphocyte stimulation test (DLST) was conducted at the time of hospitalization, and the results were negative for CBZ (132%). However, patch and oral tests were not conducted. Since CBZ could not be administered with the recurrence of trigeminal neuralgia, right neurovascular decompression was performed 3 months later in the neurosurgery department. Since then, the patient has had no trigeminal neuralgia (Table 2).

Histopathological findings: The femoral skin and buccal mucosa were histopathologically analyzed. In the femoral skin, epidermal liquefaction degeneration and cellular infiltration consisting mainly of lymphocytes containing small numbers of eosinophils around sweat glands and vessels in the superficial dermis were confirmed. Papillary dermis edema and RBC migration were also observed (Fig. 5). In the buccal mucosa, the stratum corneum of the epidermis was thin and parakeratotic, and marked lymphocyte infiltration and coexisting RBCs were confirmed between the mucosal epithelium and stroma. Partial destruction of the basal cell layer structure was apparent (Fig. 6).

Table 2 Clinical laboratory test findings and treatment course

<table>
<thead>
<tr>
<th>(Lab data)</th>
<th>CBZ (× 10^6/μL)</th>
<th>WBC</th>
<th>Eosin %</th>
<th>CRP</th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Hospitalization</td>
<td>12.7↑</td>
<td>15.6↑</td>
<td>22.9↑</td>
<td>13.1↑</td>
<td>5.0↑</td>
<td>0.9↑</td>
</tr>
<tr>
<td>Hospital day 0</td>
<td>24.0↑</td>
<td>7.0↑</td>
<td>20.0↑</td>
<td>4.9↑</td>
<td>0.0↑</td>
<td>8.0↑</td>
</tr>
<tr>
<td>Hospital day 4</td>
<td>0.0↑</td>
<td>5.0↑</td>
<td>4.0↑</td>
<td>0.0↑</td>
<td>0.0↑</td>
<td>8.0↑</td>
</tr>
<tr>
<td>Hospital day 8</td>
<td>6.9↑</td>
<td>6.7↑</td>
<td>0.8↑</td>
<td>0.1↑</td>
<td>8.0↑</td>
<td>28.0↑</td>
</tr>
<tr>
<td>Hospital day 15</td>
<td>4.7↑</td>
<td>28.0↑</td>
<td>19.0↑</td>
<td>8.0↑</td>
<td>28.0↑</td>
<td>28.0↑</td>
</tr>
</tbody>
</table>

CBZ was discontinued, biphasic changes in clinical symptoms, increased HHV-6 antibody titer and abnormal blood test results were confirmed. Furthermore, PSL dose was tapered depending on symptoms.
**Discussion**

In 1951, Allday and Barnes first reported DIHS as dapsone 4,4-diaminodiphenyl-sulphone (DDS) syndrome\(^1\), and similar conditions caused by various causative agents have been reported under various names. In 1994, Roujeau and Stern noted the common clinical symptoms and proposed the term “hypersensitivity syndrome”\(^7\). In 1998, severe drug eruption representing a form of drug allergy was clarified to be related to HHV-6 virus infection\(^10,12\), and elevated HHV-6 IgG and HHV-6 DNA reactivation have been shown to be involved\(^11\). In 2002, the disease was named as DIHS, and diagnostic criteria were presented by a Ministry of Health, Labour and Welfare study group. The diagnostic criteria were reviewed in 2005 (Ministry of Health, Labour and Welfare study group)\(^9\) (Table 3). Clinical symptoms of DIHS include fever, rash, hepatic dysfunction, renal dysfunction and hematological abnormality, and common causative drugs include CBZ, phenytoin, phenobarbital, zonisamide, DDS, salazosulfapyridine, mexiletine, allopurinol and minocycline. One of the characteristics of this condition is delayed onset, which may occur 2–6 weeks after administration of the causative agent. Symptoms rarely improve quickly, even after discontinuing drug administration, and recovery often takes more than a month. In the present patient, erythema that rapidly spread throughout the body, bilateral cervical lymph node enlargement and a 39.1°C fever were observed at 22 days after CBZ administration. Tests confirmed elevated WBCs and eosinophils, atypical lymphocytes and increased levels of ALT and γ-GTP, and a paired serum test showed a high antibody titer for HHV-6 IgG. The patient in this case satisfied all seven diagnostic criteria described above and DIHS was diagnosed. However, the results of the DLST were negative for CBZ. The reason for this was that in regular drug eruption, DLST yields positive results during the acute phase that become negative with time, whereas in DIHS, DLST shows negative results during the acute phase which become positive about 1 month after onset\(^8\). In the present patient, the results were negative because the test was conducted during the acute phase, but the results would probably have been positive if testing had been conducted during the chronic phase. As drug eruptions did not improve, even when the referring physician discontinued cold medication under continuous administration of steroidal drug, CBZ was considered the most likely causative agent.

During the course of DIHS, symptoms such as rash and disorder to multiple organs exhibit biphasic changes, with symptoms tran-

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Table 3 Drug-induced hypersensitivity syndrome (DIHS)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Maculopapular rash developed &gt;3 weeks after starting with a limited number of drugs</td>
</tr>
<tr>
<td>2</td>
<td>Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug</td>
</tr>
<tr>
<td>3</td>
<td>Fever (&gt;38°C)</td>
</tr>
<tr>
<td>4</td>
<td>Liver abnormalities (alanine aminotransferase &gt;100 IU/liter)(^*)</td>
</tr>
<tr>
<td>5</td>
<td>Leukocyte abnormalities (at least one present)</td>
</tr>
<tr>
<td></td>
<td>a. Leukocyte abnormalities (&gt;11 x 10^9/liter)</td>
</tr>
<tr>
<td></td>
<td>b. Atypical lymphocytosis (&gt;5%)</td>
</tr>
<tr>
<td></td>
<td>c. Eosinophilia (&gt;1.5 x 10^9/liter)</td>
</tr>
<tr>
<td>6</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>7</td>
<td>Human herpesvirus 6 reactivation</td>
</tr>
<tr>
<td></td>
<td>• Typical DIHS is defined by the presence of all seven criteria described above.</td>
</tr>
<tr>
<td></td>
<td>• Atypical DIHS is defined by the presence of five of the criteria described above.</td>
</tr>
</tbody>
</table>

\(^*\)This can be replaced by other organ involvement, such as renal involvement.

Diagnostic criteria as revised by Ministry of Health, Labour and Welfare study group in 2005.
siently showing alleviation after 2–3 weeks and then often recurring several days later. How HHV-6 reactivation is involved with DIHS onset remains unclear. However, HHV-6 reactivation has been clarified in recent years to occur 2–6 weeks after onset, driving the biphasic change in clinical symptoms\(^12\). In patients with a history of HHV-6 infection, immune system modulation induces HHV-6 reactivation when drug allergy is induced by agents such as anticonvulsants. HHV-6 reactivation further accelerates immune system modulation via increased inflammatory cytokine production\(^16\) and immunosuppression\(^3\), thus potentially enhancing allergic reactions. Although symptoms showed a transient alleviation in the present patient, erythema recurred on the scalp, trunk and upper extremities at about 1 week after discharge.

Mucosal symptoms of TEN and SJS are very severe, while mucosal symptoms of DIHS are fewer in number compared to these diseases\(^4\). The cause was unknown in this case, however, and oral mucosal redness and erosion were confirmed when the rash was marked. We believe that late termination of CBZ together with HHV-6 infection of the trigeminal domain may have been responsible for the oral symptoms observed here. Based on oral mucosal pathological findings, lesions resembling a rash were observed. Lesions caused by a similar mechanism to the rash thus appear to have been present in the oral cavity.

The treatment of DIHS clearly differs from that for the other two forms of severe drug eruption, TEN and SJS, as DIHS is accompanied by HHV-6 virus infection\(^3\). However, the basic therapeutic plans share many common points. Steroid pulse therapy and bolus administration have been performed for the treatment of DIHS. Steroid administration is considered effective because of the high WBC count and predominance of CD8+ cells, and is often very effective and brings about marked improvements. However, besides decreasing serum IgG and B cell counts, this therapy may enhance HHV-6 reactivation, and risks for renal damage, type 1 diabetes, enteritis, hepatitis, pneumonia, encephalitis and multiple organ failure cannot be ruled out. In recent years, high-dose intravenous therapy with human γ-globulin has been examined for SJS and TEN\(^2,13,19\). In DIHS, steroid therapy alone can induce remission in many patients, but human γ-globulin may be administered to patients with various organ inflammation or those in whom disease progression cannot be stopped by steroid therapy alone. In the present patient, low serum IgG levels were confirmed, but steroid administration was started after discontinuing administration of the causative agent, and because symptoms improved within about 1 month, steroid therapy alone was performed.

We have presented herein the case of a patient who was considered to have DIHS due to CBZ. In this case, lesions similar to dermal lesions were also observed in the oral mucosa. The buccal mucosa was histopathologically analyzed. To our knowledge, there are no other reports of the histopathological analysis of the oral mucosa in DIHS. In the histopathological findings on the buccal mucosa, marked lymphocytes were confirmed between the mucosal epithelium and stroma and partial destruction of the basal cell layer structure was apparent. In fact, if not promptly treated, we must consider the possibility that oral mucosal symptoms may become severe.

Carbamazepine is commonly used in the treatment of trigeminal neuralgia in the field of dentistry, indicating the necessity for sufficient knowledge of drug allergies.

The abstract of the present manuscript was presented orally at the 13th Annual Meeting of the Japanese Society for Oral Mucous Membrane (July 18 and 19, 2003, Nagoya).

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