Case Report

Beneficial Therapeutic Effect of Plasma Exchange Followed by Prednisolone for Drug-Induced Hypersensitivity Syndrome Caused by Allopurinol

Shigeruko Iijima*1, Itaru Ebihara*2 and Hiromichi Yamada*3

Departments of *1Dermatology and *2Nephrology, Mito Saiseikai General Hospital, *3Department of Dermatology, International Goodwill Hospital

Summary The efficacy of plasma exchange for the treatment of severe drug eruption, such as toxic epidermal necrolysis or Stevens-Johnson syndrome, has been well established in many recent reports; however, that for drug-induced hypersensitivity syndrome (DIHS) has not yet to be clarified. We here report an 84-year-old woman with allopurinol-induced DIHS, who had taken a small dose of prednisolone for a long period for systemic lupus erythematosus. The patient developed widespread skin eruptions, fever, eosinophilia, liver injury, renal dysfunction and an increased antihuman herpes virus-6 IgG titer. She was successfully treated with plasma exchange, followed by 30 mg prednisolone. In the past 10 years in Japan, only 11 DIHS patients underwent plasma exchange and 10 patients survived. No cases except ours selected plasma exchange as an initial treatment, which followed by prednisolone. Plasma exchange should thus be considered for the treatment of an early stage of DIHS patients, especially those who are elderly or have frequent infections.

Key words: allopurinol, drug-induced hypersensitivity syndrome, human herpes virus-6, plasma exchange, renal dysfunction

Drug-induced hypersensitivity syndrome (DIHS), also known as a drug reaction with eosinophilia and systemic syndrome (DRESS)1), is a drug-induced severe adverse eruption, equally ranking with toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). The efficacy of plasma exchange for the treatment of TEN or SJS is well established in Japan2) and other countries3); however, that for DIHS has not yet to be clarified. We here present a case of allopurinol-induced DIHS, which resulted in a high fever, rapid increase in the creatinine level, elevation of liver enzymes and eosinophilia, which was successfully treated with plasma exchange in an early phase of the disease, followed by prednisolone. To our knowledge, few DIHS patients have been reported, who have been treated with plasma exchange in Japan. We summarize these cases and discuss the efficacy of plasma exchange in this syndrome.

Patient

An 84-year-old Japanese woman, with a history of systemic lupus erythematosus (SLE) at the age of 57 and essential hypertension at the age of 74, started taking 100 mg allopurinol because of hyperuricemia on April 30, 2005. She had received 2.5 mg prednisolone for SLE and trichlormethiazide for hypertension. Her serum creatinine level was 1.44 mg/dL before taking allopurinol. Itchy skin eruptions appeared on her face on June 9 (day 1), and rapidly spread over her whole body with a fever. She was admitted to a local physician’s clinic on June 11, and all oral medicines including allopurinol were discontinued; however, the fever, skin eruptions and renal function worsened, and thus, she was transferred to our dermatology clinic at Mito Saiseikai General Hospital on June 13 (day 5).

Upon hospital admission, she appeared extremely ill and emergent for treatment. She had a fever of 39.8°C. Skin examination revealed widespread infiltrative exudative erythema on the trunk and extremities and marked edematous erythema on the face (Fig. 1a, b). Small vesicles were superimposed on the erythema of the abdomen, and small crusts...
were seen on the cheeks and nose. She had no lymphadenopathy in cervical, axillary and inguinal nodes.

Laboratory tests included: white blood cells, 19,300/mm³ (neutrophils, 84%; lymphocytes, 8%; monocytes, 3%; eosinophils, 4%; atypical cells, 0%); red blood cells, 383×10⁶/mm³; hemoglobin, 12.2 g/dL; platelet count, 19.8×10⁹/mm³; serum total protein, 5.1 g/dL; albumin, 3.0 g/dL; aspartate aminotransferase, 68 U/L; alanine aminotransferase, 170 U/L; lactate dehydrogenase, 442 U/L; γ-GTP, 88 U/L; blood urea nitrogen, 54.5 mg/dL; creatinine, 2.55 mg/dL; C-reactive protein, 139 mg/dL; IgG, 448 mg/dL; IgA, 100 mg/dL; IgM, 85 mg/dL; C3, 111 mg/dL; C4, 38 mg/dL; CH50, 33.4 CH50/mL; antinuclear antibody, 1:40 in a homogeneous and speckled pattern; anti-dsDNA antibody, <5 IU/mL. Urinalysis revealed no abnormality.

Skin biopsy specimen was taken from the exudative erythema with small vesicles on the trunk (b).

**Fig. 1. Skin eruption on admission.**

Marked edematous erythema on the face with small crusts on the cheeks and nose (a) and widespread infiltrative exudative erythema with small vesicles on the trunk (b).

**Fig. 2. Histology taken from the exudative erythema with small vesicles on the upper abdomen.**

Whole dermal edema and perivascular infiltration composed of lymphocytes, histiocytes and a few eosinophils in the upper dermis. Histology showed whole dermal edema and perivascular infiltration composed of lymphocytes, histiocytes and a few eosinophils in the upper dermis (Fig. 2). Intracorneal microvesicles were present, including some eosinophils. Only a few eosinophilic dyskeratotic cells were observed in the epidermis.

Immediately after admission, we tried to wash out the medication by dripping a 1,500 mL/day infusion intravenously under a suspected diagnosis of allopurinol-induced drug eruption. Three days later, however, the serum creatinine level had increased to 3.01 mg/dL with 28% eosinophils in the white blood cell count of 15,800/mm³ (Fig. 3). The patient then underwent a simple plasma exchange for three consecutive days (day 8–10), after we sufficiently explained both advantages and disadvantages of the simple plasma exchange therapy and obtained written informed consent from the patient and her family. Simple plasma exchange was followed by oral administration of prednisolone at a dose of 30 mg a day. It was performed utilizing plasmaseparator, which had a pore size of 0.2 µm and was made of polyethylene (Plasmacure OP-05, Kuraray Co., Osaka, Japan). The procedures was carried out automatically and continuously with monitor, KM8900 (Kuraray Co., Osaka, Japan) at blood flow 80 mL/min, drained plasma flow 20 mL/min, in a closed circuit. Approximately 3,000 mL of drained plasma was discarded and 30 U of fresh frozen plasma were used as replacement fluid in each session. Exudative erythema was discolored to diffuse dark erythema after the first session of plasma exchange, and the serum creatinine level and
Skin eruption

C-reactive protein level decreased from 3.05 to 2.51 mg/dL and from 14.7 to 2.6 mg/dL, respectively, after the third session of plasma exchange. High fever and chills improved after the third session of plasma exchange and disappeared after prednisolone was started. Oral prednisolone was tapered off on July 4. The next day (day 27), the skin eruptions and fever flared again. Prednisolone at a dose of 10 mg was restarted on July 6, and she was discharged. The dose of prednisolone was slowly tapered this time; however, diffuse infiltrative erythema with itching reappeared on the trunk with 14% eosinophils on July 27 (day 49). 5 days after prednisolone had ceased. A dose of 5 mg prednisolone was effective for the repeated flare-up, and further slow tapering was needed until the end of January 2006.

Additional tests relating to the causative drug showed negative results for patch testing using 1%, 5%, 10%, 20% ointments in petrolatum of allopurinol and its major metabolite, oxipurinol (Wako Pure Chemical Industries, Ltd., Osaka, Japan) on day 135. Drug-induced lymphocyte stimulation tests of allopurinol and oxipurinol were all negative on day 5 and day 135. Virological investigation on day 49 revealed an increase in the specific IgG titer for human herpes virus (HHV)-6 (1:1,280) and a positive result in the real-time PCR assay for HHV-6 DNA (90 copies/μg DNA) using a whole blood sample. Tests for HHV-7 and CMV DNA were not detected.

Thus, we finally diagnosed our patient as having DIHS associated with reactivation of HHV-6.

Discussion

DIHS is a unique serious drug eruption with reactivation of HHV family members, such as HHV-6, cytomegalovirus (CMV) or Epstein-Barr virus. It is caused by some limited drugs, such as anticonvulsants, sulfa drugs, allopurinol, minocycline, and mefloquine, and is characterized by delay onset after taking medication, a prolonged course of the disease, and severe multi-organ involvement manifested by fever, lymphadenopathy, hepatitis, nephrotoxicity, cerebral edema, pneumonitis and myocarditis. Hematological abnormalities, such as leukocytosis, eosinophilia and the presence of atypical cells, are also characteristic. Our patient had skin eruptions as the first symptom, 40 days after taking allopurinol (day 1) and had an increased titer of HHV-6 on day 49. Since skin eruption and fever flared on day 27, the day was assumed to be the date of reactivation of HHV-6. We further presumed that the symptoms before day 27 could be due to drug allergy, and those after the day due to HHV-6 infection.

Therapeutic guidelines for patients with severe drug eruption including DIHS have been recently proposed in Japan. According to the Japanese therapeutic proposal, systemic corticosteroid is the first choice. The recommended dose is 0.5–2.0 mg/kg/day for relatively slowly progressing cases and additional methylprednisolone pulse therapy for rapidly progressing cases. When the patients have a decreased immune state or severe infection, intravenous immunoglobulin or plasma exchange are the best first modalities of treatment without systemic corticosteroid. Our patient was assumed to be in an immunodeficient state, because she was over 80 years old and had been taking prednisolone for a long period. We thus selected plasma exchange first, when she worsened with initial infusion therapy to wash out the medicine.

After the first reports of DIHS by Tohyama and Suzuki in 1998, only eleven DIHS patients underwent plasma exchange in Japan. We summarize those cases in Table 1 and case 11 is our patient. They were 6 males and 5 females. Age ranged from 4 months old to 84 years old, and the oldest was our patient. Two patients had been suffering from chronic renal failure on hemodialysis or continuous ambulatory peritoneal dialysis. Causative drugs were anticonvulsants in 5 cases, allopurinol in 3 cases, sulfa drugs in 2 cases and γ-globulin in one case. The duration until onset of DIHS ranged from 8 days to 4 months. Symptoms included fever and liver injury in all patients and renal dysfunction in 6 cases, complicated with multiple organ failure and fulminating hepatitis in one patient each. Reactivation of HHV-6 was found in 7 cases, that of CMV in two, and no reactivation in three cases. Both HHV-6 and CMV were reactivated in one patient. Plasma exchange was performed as simple plasma exchange in 10
### Table 1. Eleven DIHS patients who underwent plasma exchange during 2001 to 2012.

<table>
<thead>
<tr>
<th>Reported year</th>
<th>Age/sex</th>
<th>Causative drug</th>
<th>Duration until onset</th>
<th>Fever</th>
<th>Liver dysfunction</th>
<th>Renal dysfunction</th>
<th>Reactivation of viruses</th>
<th>Treatment</th>
<th>Time at PE</th>
<th>Reasons for selecting PE</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2001</td>
<td>50/F</td>
<td>carbamazepine</td>
<td>22 days</td>
<td>+</td>
<td>+ (hepatic failure)</td>
<td>NS</td>
<td>HHV-6</td>
<td>mPSL 250 mg→PE →mPSL pulse</td>
<td>NS</td>
<td>to improve hepatic failure, skin rash and fever</td>
<td>survived</td>
</tr>
<tr>
<td>2 2002</td>
<td>21/M</td>
<td>phenobarbital zonisamide</td>
<td>28 days</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>HHV-6</td>
<td>betamethasone 3 mg→HD, mPSL pulse→PE</td>
<td>after flare-up</td>
<td>to improve flared liver injury</td>
<td>dead</td>
</tr>
<tr>
<td>3 2004</td>
<td>15/F</td>
<td>γ globulin</td>
<td>28 days</td>
<td>+</td>
<td>+</td>
<td>NS</td>
<td>HHV-6</td>
<td>PE→PSL 2 mg/kg/day</td>
<td>NS</td>
<td>to eliminate previously administered γ globulin and autoantibodies against RBC, etc.</td>
<td>survived</td>
</tr>
<tr>
<td>4 2005</td>
<td>67/M</td>
<td>phenytoin</td>
<td>4 months</td>
<td>+</td>
<td>+</td>
<td>+ (HD patient)</td>
<td>PE</td>
<td>before flare-up</td>
<td>to improve skin rash, diarrhea, liver dysfunction</td>
<td>survived</td>
<td></td>
</tr>
<tr>
<td>5 2006</td>
<td>53/M</td>
<td>diaphenylsulphone</td>
<td>27 days</td>
<td>+</td>
<td>+</td>
<td>+ +</td>
<td>HHV-6</td>
<td>HD (6 sessions), PE (4 sessions)</td>
<td>after flare-up</td>
<td>to taper the dose of PSL</td>
<td>survived</td>
</tr>
<tr>
<td>6 2006</td>
<td>49/M</td>
<td>allopurinol</td>
<td>8 days</td>
<td>+</td>
<td>+ (multiple organ failure)</td>
<td>+ + (CAPD patient)</td>
<td>CMV</td>
<td>PE (8 sessions), CHDF</td>
<td>after flare-up</td>
<td>to improve multiple organ failure</td>
<td>survived</td>
</tr>
<tr>
<td>7 2006</td>
<td>32/M</td>
<td>allopurinol</td>
<td>1 month</td>
<td>+</td>
<td>+ (fulminant hepatitis)</td>
<td>+ +</td>
<td>—</td>
<td>mPSL pulse, PE, CHDF</td>
<td>before flare-up</td>
<td>to improve fulminant hepatitis</td>
<td>survived</td>
</tr>
<tr>
<td>8 2007</td>
<td>30/F</td>
<td>zonisamide</td>
<td>34 days</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>HHV-6</td>
<td>PSL 40 mg→PE (2 sessions), mPSL pulse</td>
<td>before flare-up</td>
<td>to improve skin rash, liver dysfunction and coagulation abnormality, resistance to previous therapy</td>
<td>survived</td>
</tr>
<tr>
<td>9 2008</td>
<td>4M/F</td>
<td>phenobarbital</td>
<td>11 days</td>
<td>+</td>
<td>+</td>
<td>NS</td>
<td>—</td>
<td>IVIG, mPSL pulse, CyA→PE</td>
<td>after flare-up</td>
<td>to improve fever, skin rash, leukocytosis and liver dysfunction, resistance to previous therapy</td>
<td>survived</td>
</tr>
<tr>
<td>10 2008</td>
<td>43/M</td>
<td>salazosulfa-pyridine</td>
<td>29 days</td>
<td>+</td>
<td>+</td>
<td>NS</td>
<td>HHV-6</td>
<td>PSL 40 mg→5 mg→IVIG, PE (DFPP)</td>
<td>after flare-up</td>
<td>to improve repeated skin rash, frequent infection</td>
<td>survived</td>
</tr>
<tr>
<td>11 2012</td>
<td>84/F</td>
<td>our case</td>
<td>40 days</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>HHV-6</td>
<td>PE→PSL 30 mg</td>
<td>before flare-up</td>
<td>to improve renal dysfunction and eosinophilia</td>
<td>survived</td>
</tr>
</tbody>
</table>

NS, not stated; HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; HHV-6, human herpes virus-6; CMV, cytomegalovirus; IVIG, intravenous immunoglobulin; mPSL, methylprednisolone; Cy A, cyclosporine A; PE, plasma exchange; CHDF, continuous hemodiafiltration; DFPP, double filtration plasmapheresis.
patients and double filtration plasmapheresis in one case, and it was carried out before symptom flare-up in 4 cases and after the flare-up in 5 cases. One of the main reasons for selecting plasma exchange was to improve intractable various symptoms and laboratory data. Resistance to the previous therapy, frequent severe infection and tapering the dose of corticosteroid were the other reasons. Ten of the all patients survived and one patient was dead. Unsuccessful treatments for DIHS were hemodialysis or continuous hemodiafiltration for renal failure. No cases except ours selected plasma exchange as an initial treatment, which followed by prednisolone.

The mechanisms of plasma exchange for the treatment of DIHS have not been clarified yet. Mabuchi et al. reported a DIHS patient with the same histologic features as TEN, and repeatedly examined the serum concentration of sFas-ligand. The concentration was highest on admission, initially decreased by treatment but gradually increased again after reactivation of HHV-6 and CMV. The authors assumed that the accumulation of sFas-ligand was one of the reasons for disease severity. On the other hand, a DIHS patient reported by Higuchi et al. showed that sFas, sFas-ligand, IL-1β, TNF-α and IFN-γ were all within normal limits or were not detected before and after plasma exchange. High mobility group box (HMGB)-1 protein might also be another factor, which is known to be a late and lethal mediator of organ failure. Okamoto et al. detected the protein before plasma exchange in a severe DIHS patient with multiple organ failure, but did not detect after 8 sessions of plasma exchange.

Clearance of causative drugs and activated herpes viruses also seems to be an important mechanism for plasma exchange for DIHS. Because Gyotoku et al. examined the serum levels of oxipurinol repeatedly in their patient, and reported the high detectable levels were maintained until 9 days after cessation of allopurinol. The authors indicated that excretion of the metabolite was markedly disturbed in allopurinol-induced DIHS patients, which was the reason for the progression to serious disease.

Our patient might have been susceptible to severe allopurinol-induced drug eruption because she had insufficient renal function before the medication and had taken thiazide diuretics; however, appropriate selection of plasma exchange in an early stage could contribute to secretion of the metabolite and other causative materials and inhibit the aggregation of symptoms and clinical data. We hope that further case reports will contribute to the beneficial thera-

**References**


