A case of wheat-dependent exercise-induced anaphylaxis sensitized with hydrolysed wheat protein in a soap

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Key words: contact urticaria; hydrolysed wheat protein; wheat-dependent exercise-induced anaphylaxis.

We present a case of wheat-dependent exercise-induced anaphylaxis possibly sensitized with hydrolysed wheat protein through the use of hydrolysed wheat protein-supplemented soap. Physicians should be aware of the potential allergenicity of hydrolysed wheat protein.

Case Report

A 49-year-old woman had been using hydrolysed wheat protein-supplemented soap for 1 year. After 1 month, she developed eyelid oedema and dyspnoea while working after having breakfast (bread and coffee). She experienced similar episodes three times while working and four times while walking over the next 11 months. Additionally, she had facial wheals and nasal discharge after bathing on several occasions. A prick test showed a positive reaction to the soap (0.1% in saline). Serum allergen-specific immunoglobulin (Ig)E tests (ImmunoCAP; Phadia, Uppsala, Sweden) showed specific IgE reactions to wheat (1.35 kUA/l) and gluten (1.78 kUA/l). Provocation tests with noodles made from wheat (120 g) and aspirin (500 mg) induced eyelid oedema, nasal discharge and dyspnoea (Fig. 1). No symptoms were observed with wheat challenge alone or aspirin intake alone, performed on separate days. A face wash challenge test with the soap induced facial wheals. On the basis of her medical history

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and the positive provocation test results, wheat-dependent exercise-induced anaphylaxis and wheat contact urticaria were diagnosed.

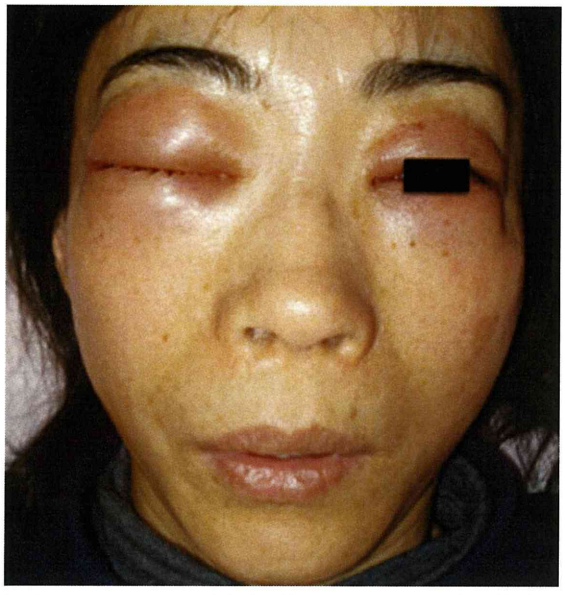

Fig. 1. Provocation test with aspirin + wheat challenge induced eyelid oedema, nasal discharge, and dyspnoea.

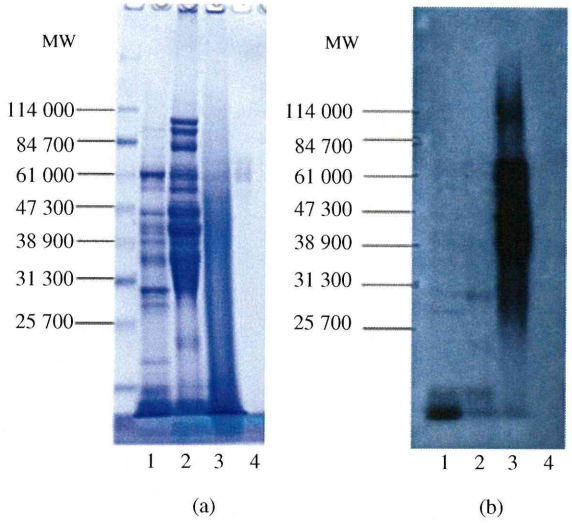

Fig. 2. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis and blotting analyses of wheat protein fractions and commercial hydrolysates. (a) Gel stained with Coomassie Blue. (b) IgE immuno blotting with the patient's serum. Lane 1: salt-soluble wheat proteins. Lane 2: salt-insoluble wheat proteins. Lane 3: Hydrolysed wheat protein. Lane 4: omega-5 gliadin.

Examination of Allergens

Western blotting revealed specific IgE for hydrolysed wheat protein (>25 000 MW), salt-soluble wheat proteins (27 000 and 30 000 MW) and salt-insoluble wheat proteins (30 000 MW) in the patient's sera (Fig. 2), but not for omega-5 gliadin.

Gliadin was undetectable in serum, even during the positive provocation test performed with the methods of Matsuo (1).

Discussion

Wheat contains a variety of proteins (approximately 10%), which can be divided into salt-soluble proteins and salt-insoluble proteins. The latter are referred to as gluten, a mixture of several gliadins and glutenins, which gives the characteristic feature of wheat. Recently, hydrolysed wheat protein has been widely used in cosmetics. It is likely that our patient had been sensitized with hydrolysed wheat protein through using hydrolysed wheat protein-supplemented soap, because she had symptoms after starting to use the soap, a positive skin reaction to diluted soap solution, and serum IgE reacting to hydrolysed wheat protein, as determined by western blotting. The penetration of hydrolysed wheat protein into her skin was confirmed by the wheal formation in the face-washing challenge test. Interestingly, her symptoms were limited to her face. Most patients with wheat-dependent exercise-induced anaphylaxis have specific IgE to omega-5 gliadin and/or high-molecular-weight glutenin; these undigested proteins appear in the sera during positive provocation tests (1, 2). However, gliadins/glutenins were not detected in our patients's serum during the positive provocation test, suggesting that wheat proteins were not only absorbed from the gastrointestinal tract but also penetrated through the oral mucosa and diffused to the face tissue. It is entirely conceivable that the IgE reacting to hydrolysed wheat protein cross-reacted with the wheat proteins.

Wheat-dependent exercise-induced anaphylaxis was diagnosed in our patient, although symptoms were induced with combined wheat and aspirin challenge. Provocation tests employed a combination with aspirin, because symptoms can be induced even in patients with no history of urticaria with non-steroidal anti-inflammatory drugs, and the provocation test with aspirin challenge is performed more safely and more easily than that with exercise challenge (3).

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LETTER TO THE EDITOR

Long-term metronomic docetaxel chemotherapy for inoperative angiosarcoma of the scalp

Dear Editor,

Angiosarcoma of the scalp (AS) is a rare aggressive malignant tumor with poor prognosis. Despite the use of aggressive treatments, AS has a high recurrence rate and shows early metastasis. The median overall survival was reported to be 15 months; all 27 patients with large (>10 cm) tumors died within 24 months.[1] Moreover, topical control of AS is very difficult because of ulceration, bleeding and infection of the tumor. In the advanced stage, the tumor is aesthetically unacceptable and gives rise to a bad odor; achieving hemostasis at this stage is difficult. These manifestations decrease the quality of life of the patient to a great extent. Metronomic chemotherapy is a new modality of long-term drug administration. This chemotherapy allows the continuous and equally spaced administration of low doses of chemotherapeutic drugs and aims to achieve not only antitumor efficacy with very low toxicity but also anti-angiogenic efficacy.[2] Therefore, these continuous direct antitumor effects and the inhibition of tumor angiogenesis necessary for tumor growth seem suitable for maintaining partial response (PR).

Here, we report a case of inoperable AS treated with long-term (~2 years) metronomic docetaxel therapy with an aim to maintain PR.

A 65-year-old woman, who had experienced scalp trauma during childhood, visited us with a 6-month history of a hemorrhagic tumor and gradually enlarging violaceous plaques on the scalp (Fig. 1). Her laboratory data, including blood counts and blood chemistry parameters, were normal. However, physical examination revealed swelling of the cervical lymph nodes. Computed tomography (CT) scans of the head, chest and abdomen showed cervical lymph node enlargement (diameter, 2 cm) but no solid organ metastasis. Examination of a scalp skin biopsy specimen revealed dermal hemorrhage and numerous

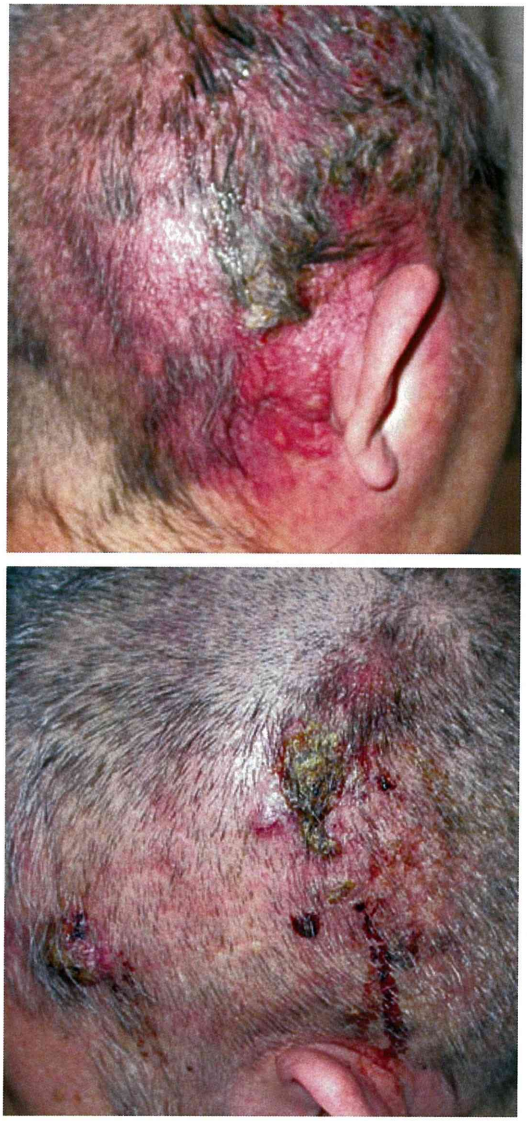

Figure 1. Clinical appearance before docetaxel treatment. Violaceous plaques, dark purple nodule with crust, and edematous erythema can be seen.

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irregular vascular channels lined with atypical enlarged endothelial cells. From these findings, AS with lymph node metastasis was diagnosed. Surgical excision was not possible because the tumor was too widespread to be removed. The patient refused radiotherapy as an alternative therapy. Hence, i.v. and topical injections of interleukin-2 (700 000 IU/day) were administrated for 5 weeks. However, the tumor continuously enlarged; therefore, we decided to initiate biweekly administration of i.v. docetaxel at 40 mg/m^2 body surface area. Three months after the initiation of docetaxel administration, the plaques and cervical lymph nodes decreased in size; we therefore decided to continue this therapy. This PR was maintained without the occurrence of ulceration, bleeding, infection and without additional metastases for 2 years after the initial docetaxel administration (Fig. 2). Although neutropenia (grade 3) appeared 5 months after initiating docetaxel administration, s.c. injections of granulocyte-colony stimulating factor improved the neutropenia without necessitating the discontinuation of docetaxel. Mild peripheral neuropathy (grade 1) and severe edema of the limbs (grade 2) occurred at 18 months after initiating docetaxel therapy; hence, the chemotherapy was discontinued for 2 months, which resulted in a decrease in the edema. Docetaxel was then restarted at a reduced (half) dose (20 mg/m^2). However, edema relapsed 4 months later, so docetaxel was discontinued again. Two months after discontinuing the chemotherapy, she suddenly died at home. Because of her family's refusal for autopsy, the cause of her death remains unclear. On further speculation, tumor-related death seems unlikely because of the absence of organ metastasis at 2 months before her death; however, her preceding docetaxel-induced edema might have induced lethal heart failure.

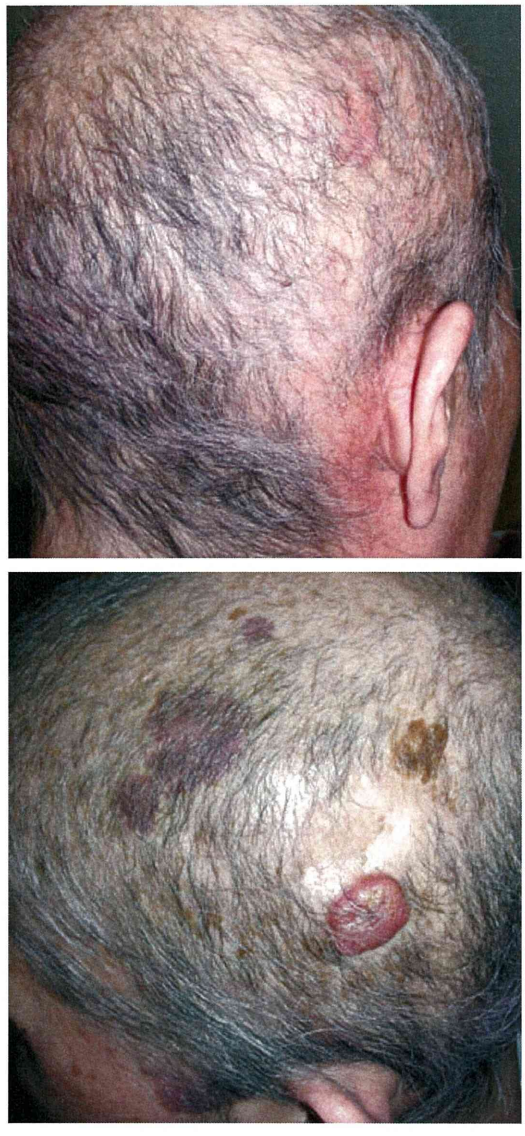

Figure 2. Clinical appearance at 2 years after docetaxel treatment. Right temporal edematous erythema was abolished (upper figure). The enlargement of the red nodule was very slow (lower figure).

Angiogenesis plays a critical role in the growth and metastatic spread of tumors.[3] Recently, anti-angiogenic therapies, including anti-vascular endothelial growth factor therapy, are performed for various cancers.[4] Metronomic chemotherapy, also called tumor dormancy therapy, targets vascular endothelial cells and inhibits angiogenesis by the use of lower-dose chemotherapeutic agents through their anti-angiogenic effect.[2] Because taxanes target microtubules and exhibit anti-angiogenic activity, the taxane docetaxel seems suitable for metronomic chemotherapy.[5] Therefore, despite difficulty of induction of complete remission, we intended to maintain metronomic therapy-induced PR in our patient because of her unresectable tumor.

A previous study showed that the weekly administration of low-dose docetaxel retarded tumor progression in seven of nine patients with AS.[6]

Moreover, Nagano *et al.*[7] have shown that docetaxel monotherapy is effective against AS. However, they administrated docetaxel only for 8 weeks. The effect of long-term administration of docetaxel in cases of AS is unknown.

In conclusion, despite the necessity of care for edema, our case of long-term docetaxel metronomic chemotherapy was effective in retarding AS progression and consequent lung metastasis and in maintaining the quality of life without dyspnea and ulceration, bleeding and infection of the tumor.

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LETTER TO THE EDITOR

Drug-induced hypersensitivity syndrome followed by persistent arthritis

Dear Editor,

Drug-induced hypersensitivity syndrome (DIHS), also known as drug rash with eosinophilia and systemic symptoms (DRESS), is one of the most severe drug eruptions, and may be related to the reactivation of herpes viruses.[1] It is characterized by skin rash, fever, lymphadenopathy, leukocytosis and internal organ involvement.[2] The drugs causing DIHS/DRESS include anticonvulsants, sulfasalazine, allopurinol, diaphenylsulfone, minocycline, and several other medications,[3] such as mexiletine.[4,5] We report a case of DIHS/DRESS with persistent arthritis secondary to the resolution of skin manifestation.

A 64-year-old Japanese woman with premature ventricular contraction developed a fever of 38.5°C and maculopapular rash over her face and trunk 4 weeks after the initiation of oral mexiletine. Withdrawal of mexiletine and i.v. hydrocortisone at 100 mg/day did not improve her eruption. On admission, she had purpuric maculopapular rash on her face, trunk, extremities and oral mucosa (Fig. 1a,b). Laboratory studies showed leukocytosis (17 600/μL) with 8.5% eosinophils and 1.0% atypical lymphocytes, and liver dysfunction (aspartate aminotransferase 107 U/L; alanine aminotransferase 340 U/L). On the 14th day of hospitalization, polymerase chain reaction detected the human herpesvirus 6 (HHV-6) DNA at 3.4×10^2 copies in 1 μL of whole blood, but no other herpes viruses. A skin biopsy from the eruption in the back revealed lymphocytic infiltration in the epidermal–dermal junction and upper dermis (Fig. 1c), and liquefaction degeneration with Civatte bodies. We diagnosed her with DIHS/DRESS although pathological finding of liquefaction degeneration with Civatte bodies is unusual for this syndrome.

Oral prednisolone at 40 mg/day was effective in improving skin eruption, fever, eosinophilia and liver dysfunction. However, maculopapular rash recurred with worsening of laboratory data after a reduction of prednisolone from 30 to 20 mg/day. After increase in prednisolone (20–40 mg/day), there was no sign of DIHS/DRESS relapse, and prednisolone was then weaned carefully, and she was discharged 2 months after hospitalization. A patch test and a drug-induced lymphocyte stimulation test demonstrated positive reactions to mexiletine, but no other drugs.

The patient's bilateral wrists and knees were swollen with pain around the date of discharge (Fig. 1d), and serum matrix metalloproteinase (MMP)-3 level was increased to 582 ng/mL at this time, which was in the normal range (17.8 ng/mL) on admission. Oral prednisolone (5 mg/day) and celecoxib (200 mg/day) were re-administrated to reduce her joint symptoms, and even 1 year later, she still needs an administration of oral prednisolone and celecoxib to keep her joint pain in a lull, and serum MMP-3 is still above normal range (66.6 ng/mL).

It has been reported that DIHS/DRESS is induced by antiviral immune responses and drug-specific immune responses.[6] Except for lymphadenopathy, our case was consistent with the diagnostic criteria[6] for DIHS/DRESS with the prolongation of symptoms for more than 2 weeks after discontinuation of mexiletine, fever (38°C), liver dysfunction, erythematous maculopapular eruptions developing several weeks after taking mexiletine, leukocytosis and HHV-6 reactivation. The course of her disease was unique, however, she developed symmetrical arthritis after the resolution of skin rash of DIHS/DRESS. She showed no X-ray finding of joint destruction and anti-cyclic citrullinated protein antibody, rheumatoid factor and

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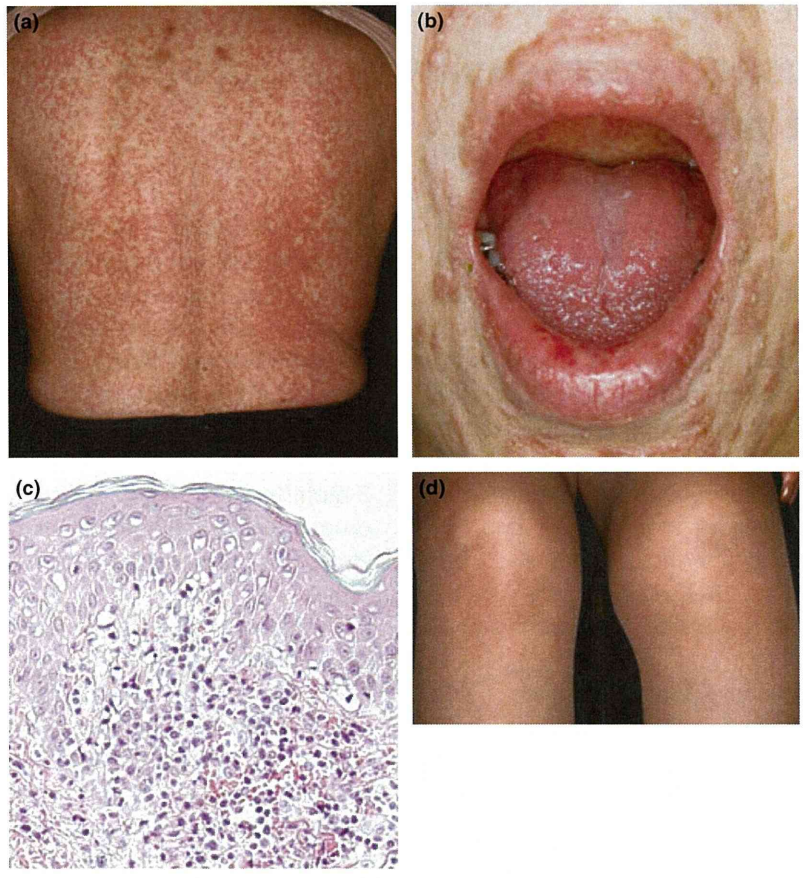

Figure 1. (a) Generalized maculopapular eruption is observed. (b) Papules and erythema are present on her cheeks and lower jaw. Redness of hard palate is noted. (c) Histological findings of the biopsy specimen revealed liquefaction degeneration and lymphocytic infiltration in the epidermal–dermal junction and upper dermis (hematoxylin–eosin, original magnification ×200). (d) The knees are slightly swollen with pain and redness.

anti-galactose defect immunoglobulin G antibody were all within the normal ranges. She did not fulfill the criteria for rheumatoid arthritis. There have been several reports of developing autoimmune disease subsequent to DIHS/DRESS.[7,8] We consider two possibilities of immunological dysregulation that induced persistent arthritis in the patient. One possibility is that a functional defect and reduction of regulatory T cells (Treg) may have triggered a kind of autoimmunity and persistent arthritis after resolution of DIHS/DRESS, because Takahashi *et al.*[9] have reported the finding of an increase of functional Treg in the acute stage of DIHS/DRESS and a gradual loss of their function after resolution of DIHS/DRESS. Another possibility is that a rapid tapering of prednisolone in the early stage may also have induced immunological dysregulation.

Here, we report a case with persistent arthritis after resolution of DIHS/DRESS, which may have resulted from immune system dysregulation along with DIHS/DRESS.

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LETTER TO THE EDITOR

Drug eruption with eosinophilia and systemic syndrome associated with reactivation of human herpesvirus 7, not human herpesvirus 6

Dear Editor,

Drug eruption with eosinophilia and systemic syndrome (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), is a severe type of drug eruption.[1] It is characterized by cutaneous eruption, lymphadenopathy, liver or renal dysfunction, leukocytosis with mainly eosinophilia and sometimes atypical lymphocytes. The causative drugs of DRESS/DIHS are limited to a relatively narrow range of drugs including anticonvulsants, sulfasalazine, diaphenylsulfone, allopurinol, minocycline and several other drugs.[2] DRESS/DIHS develops 2–6 weeks after the initiation of these drugs. Recently, it has been shown that reactivation of human herpesvirus (HHV)-6 may be implicated in the pathogenesis of this disease.[3] We report a rare case of DRESS with HHV-7 reactivation but without HHV-6 reactivation.

A 62-year-old Japanese male began to receive oral carbamazepine therapy at the Department of Urology of our hospital because of pain after surgery for prostate cancer on 30 June 2004. Fever (38.5°C) and systemic diffuse erythema developed on 11 July (day 0). He consulted a local clinic, and was diagnosed as having hepatic dysfunction. Three days later, he was urgently admitted to the Department of Gastroenterology of our hospital and referred to our department. Physical examination revealed mild facial edema and systemic diffuse erythema (Fig. 1a,b). Laboratory findings showed eosinophilia (white blood cell count, $5.6 \times 10^3/\mu L$; eosinophils, 30%) and liver dysfunction (aspartate aminotransferase, 648 IU/L; alanine aminotransferase, 879 IU/L; lactate dehydrogenase, 1055 IU/L). A skin biopsy of erythema showed perivascular lymphocytic infiltration in the upper dermis with small amounts of eosinophils and nuclear dust (Fig. 1c,d).

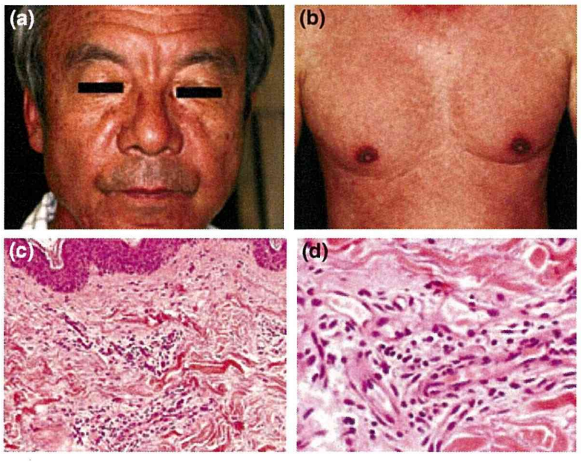

Figure 1. (a) Mild facial edema was observed. (b) Diffuse erythematous skin eruption in the patient. (c,d) The skin biopsy showed perivascular lymphocytic infiltration in the upper dermis. (hematoxylin–eosin, original magnifications: [c] ×100; [d] ×400).

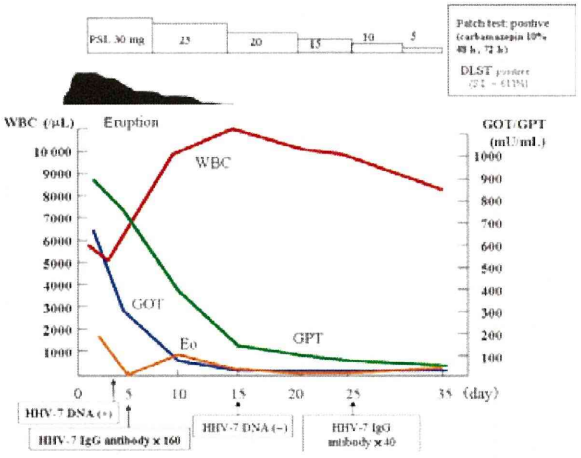

Figure 2. Clinical course in relation to serological data. DLST, drug lymphocyte stimulation test; Eo, eosinophils; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; HHV, human herpesvirus; IgG, immunoglobulin G; PSL, prednisolone; WBC, white blood cell.

The patient was suspected of having DRESS/DIHS because of high fever, systemic diffuse erythema, eosinophilia and hepatic dysfunction on admission. Thus, his carbamazepine therapy was discontinued, and oral prednisolone (30 mg/day) was initiated on day 3, which gradually improved his eruption and high grade fever. Figure 2 shows the clinical course of the patient. On day 4, HHV-7 DNA was detected in the peripheral blood (1.2×10^4 copies/mL) by polymerase chain reaction. High titers of immunoglobulin (Ig)G antibodies to HHV-7 were also recorded (1:160) on day 5. After the remission of the eruption, HHV-7 DNA became negative on day 15, followed by reduction of antibody titers to HHV-7 (1:40) on day 25. During the course of management, HHV-6, cytomegalovirus and Epstein–Barr virus DNA remained undetectable in the peripheral blood, and HHV-6 IgG antibody titers showed no elevation on days 9 (1:20) and 25 (1:10). A patch test was positive for carbamazepine after both 48 and 72 h. A drug-induced lymphocyte

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stimulation test for carbamazepine was also positive (stimulation index, 611%).

The clinical features and laboratory findings of DRESS/DIHS have a lot in common, although there are differences in the diagnostic criteria between DRESS and DIHS.

Our case took carbamazepine p.o. for 11 days before the onset of the disease. Because the diagnostic criteria for DIHS[4] include developing more than 3 weeks after starting with a limited number of drugs, we consider that this case cannot be diagnosed as DIHS strictly. Instead, diagnostic criteria for DRESS are fulfilled and our patient showed solely HHV-7 reactivation as far as we examined.

Human herpesvirus-7 was first isolated from $CD4^+$ T lymphocytes by Frenkel *et al.*[5] Tanaka *et al.*[6] reported that HHV-7 was another causative agent of exanthem subitum in addition to HHV-6. DRESS/DIHS patients with co-reactivation of HHV-6 and HHV-7 have been reported previously.[7] There have also been some reports of DRESS/DIHS patients with reactivation of herpesviruses other than HHV-6, such as cytomegalovirus and Epstein–Barr virus.[8,9] Interestingly, our case showed no reactivation of any herpesvirus examined other than HHV-7. Although the clinical finding of our case was almost identical to typical DRESS/DIHS with HHV-6 reactivation, there was a difference: the lag phase between the onset of skin eruption and HHV-7 reactivation was only 4 days, and relatively short compared to that of typical DRESS/DIHS cases.[10] Accumulation of cases will be necessary to characterize the clinical features of DRESS/DIHS with HHV-7 reactivation.

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A case of drug-induced hypersensitivity syndrome involving multiple-drug hypersensitivity

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● abstracts and key words

We report a case of DIHS in which the patient subsequently developed multiple-drug hypersensitivity.

drug-induced hypersensitivity syndrome, allopurinol, isoniazid, multiple-drug hypersensitivity, lymphocyte transformation test, patch test

Dear Editor,

Drug-induced hypersensitivity syndrome (DIHS) is a life-threatening adverse reaction characterized by skin rashes, fever, leukocytosis with eosinophilia and/or atypical lymphocytosis, lymph node enlargement, and liver and/or renal dysfunction. DIHS usually occurs 3 weeks to 3 months after the start of therapy with certain drugs[1]. Shiohara et al. and Hashimoto et al. reported that there is a close relationship between human herpes virus-6 (HHV-6) reactivation and the development of this syndrome[2,3].

A 31-year-old male with lung tuberculosis and hyperuricemia developed a fever of 38.8°C and a maculopapular rash over his face, trunk, and extremities (Fig.1) at two, four, and six weeks, respectively, after the initiation of therapy involving ethambutol (EB), allopurinol, and isoniazid (INH), rifampicin (RFP) and pyrazinamide (PZA) (Fig.2). Laboratory studies showed leukocytosis (15,400/μl) with eosinophilia (19.4%) and liver dysfunction (AST, 218 U/l; ALT, 287 U/l). On the 16th day of onset, the real-time polymerase chain reaction detected HHV-6 DNA in his whole blood. We diagnosed him as DIHS and oral prednisolone (60 mg /day) was effective. However, the skin eruption relapsed on day 32, one day after the restart of the anti-tuberculosis drug therapy (INH, RFP, EB, and PZA). The skin eruption subsequently disappeared one week after treatment with discontinuation of these anti-tuberculosis drugs.

The patch test and lymphocyte transformation test (LTT) demonstrated positive reactions to INH. We changed the patient's anti-tuberculosis treatment to RFP, EB, and levofloxacin(LVX) on day 47, but itching appeared one month later. We again changed anti-tuberculosis treatment to RFP, EB, and ethionamide(ETH) on day 115. Although his itching disappeared, liver dysfunction and eosinophilia newly developed on day 164. We had to stop the ETH treatment but continued to administer RFP and EB (Fig.2). LTT to INH consistently demonstrated positive reactions for over a year, and transient mildly positive reactions to RFP, EB, and PZA were also detected. Patch tests for INH also demonstrated three positive reactions within a year. LTT to oxypurinol produced a positive result one year later (Fig.2). We also examined his human leukocyte antigen (HLA) genotypes and found that he possessed the HLA-B*1301 and HLA-B*5201 alleles.

We initially thought that this case was INH-induced DIHS, because repeated patch tests and LTT for INH were both consistently positive after the onset of the patient's. We used LTT for oxypurinol to support the diagnosis of allopurinol hypersensitivity. Finally on day 403, the LTT for oxypurinol produced a positive result, more than one year after the onset of the condition. Allopurinol is one of the few causative drugs of DIHS and INH is a very rare of that[4]. Furthermore, it is difficult to think that the patient was newly sensitized with allopurinol after remission of DIHS without further administration of this drug. Though we could not determine the true culprit drug, taken together, we considered that this case was allopurinol-induced DIHS involving multiple-drug hypersensitivity. Results of LTT for DIHS depend on the timing performed and the timing of positive transformation has not been confirmed. In this case, it took more than a year for oxypurinol to produce a positive result.

A unique feature of DIHS is its unexplained cross-reactivity to multiple drugs[1]. We think multiple-drug allergy to RFP, EB, PZA, and INH occurred based on the results of LTT. In addition, though the results of LTT and patch tests were negative, we think that he developed hypersensitivity to LVX and ETH because itching and liver dysfunction occurred and improved after the administration and discontinuation of LVX and ETH, respectively.
In summary, we report a case of allopurinol-induced DIHS complicated by multiple hypersensitivity to drugs that were used during the course of the disease.

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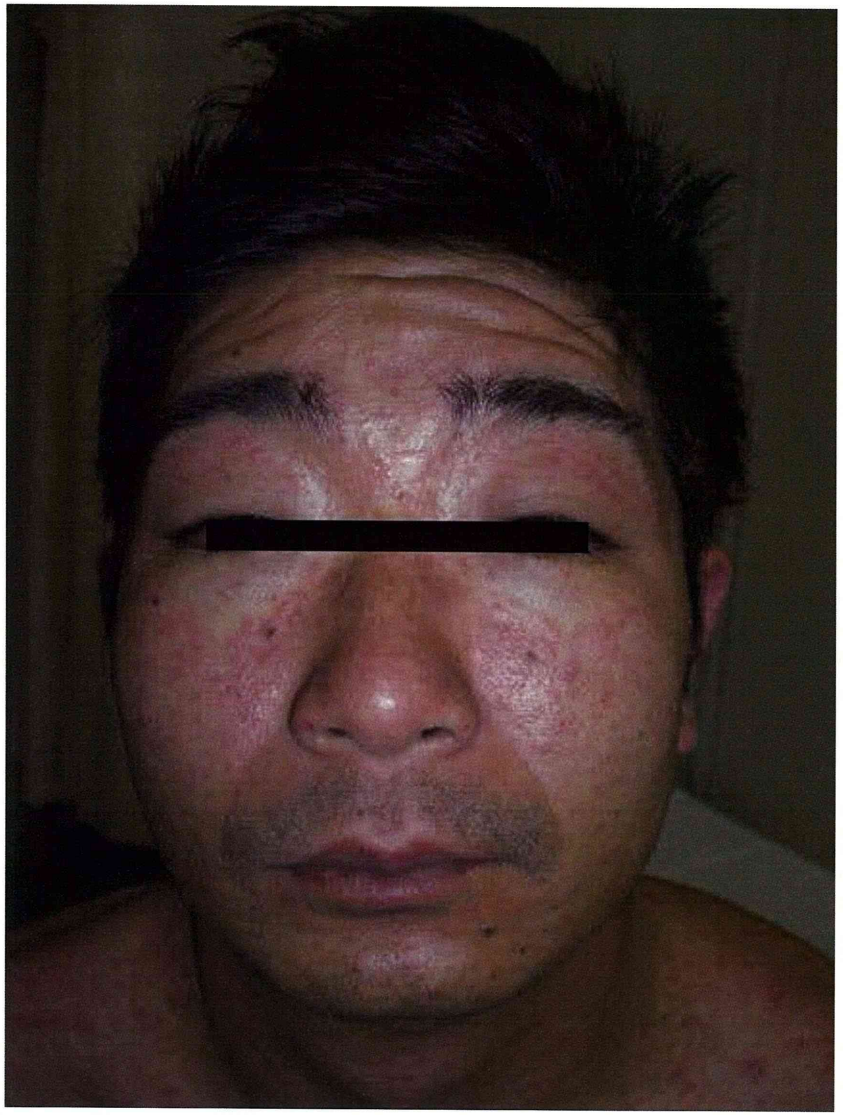
● Figure legends

Figure 1.
(a) Facial edema and diffuse maculopapular rash over his face, which spared the periocular skin.
(b) Diffuse maculopapular rash over his trunk.

Figure 2. Clinical course and results of patch tests and LTT.

LTT, lymphocyte transformation test; INH, isoniazid; RFP, rifampicin; EB, ethambutol; PZA, pyrazinamide; LVX, levofloxacin; ETH, ethionamide



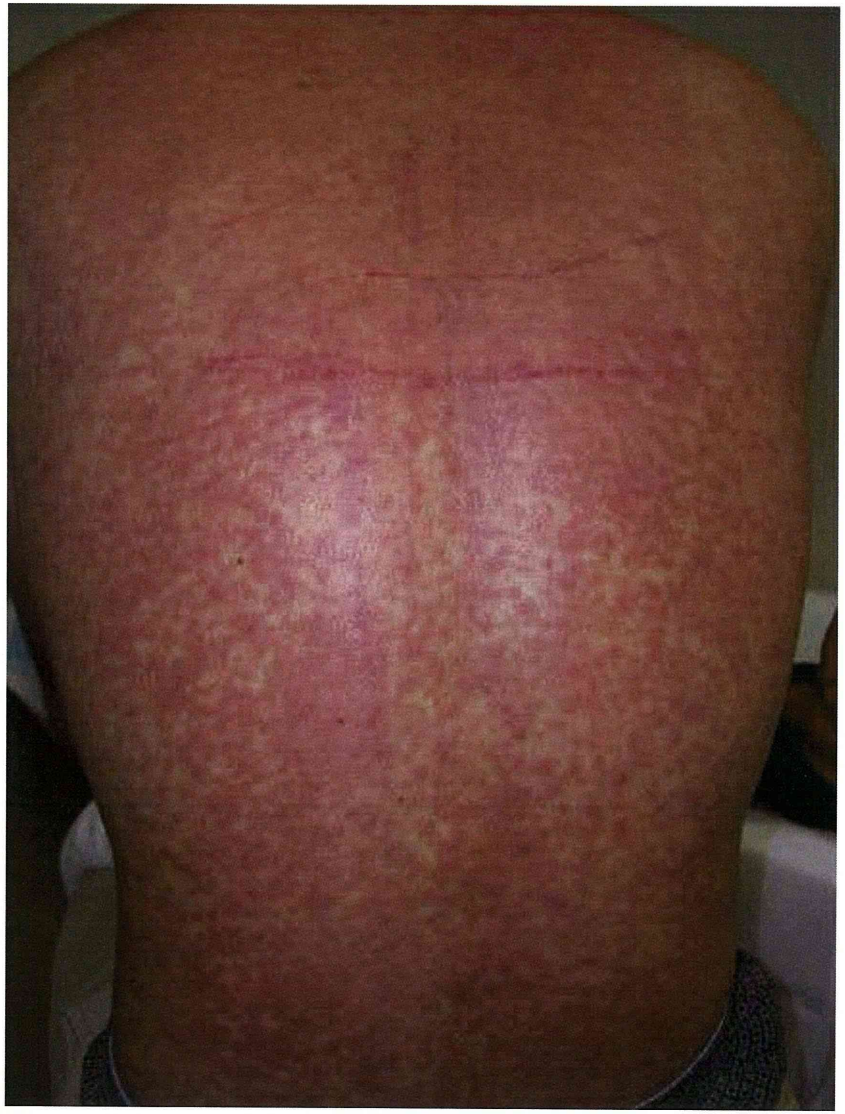


Figure.1 (a) (b)

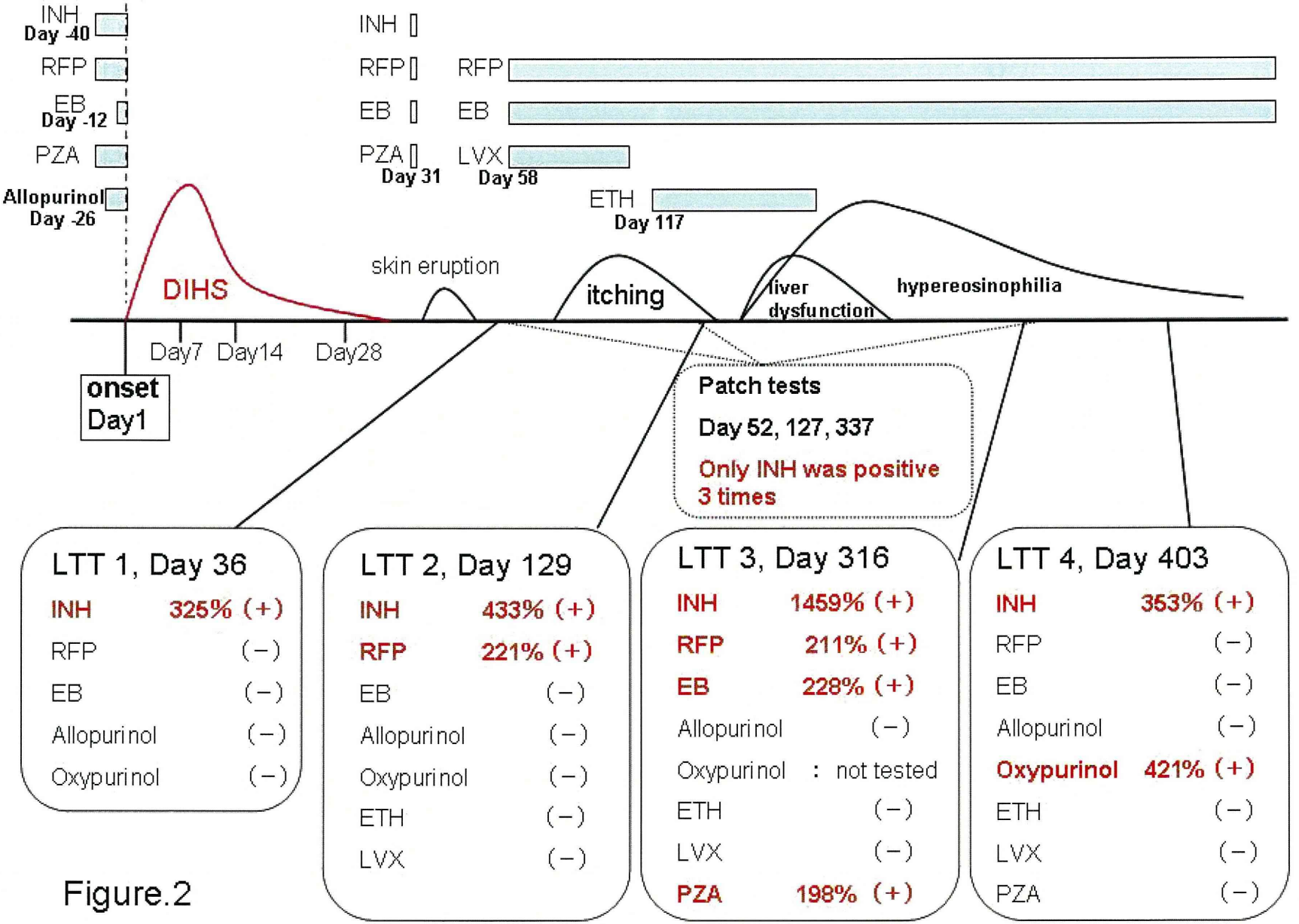

INH
Day -40
RFP
EB
Day -12
PZA
Allopurinol
Day -26
INH
RFP
RFP
EB
EB
PZA
Day 31
LVX
Day 58
ETH
Day 117
DIHS
skin eruption
itching
liver dysfunction
hypereosinophilia
Day7
Day14
Day28
onset
Day1
Patch tests
Day 52, 127, 337
Only INH was positive 3 times
LTT 1, Day 36
INH 325% (+)
RFP (−)
EB (−)
Allopurinol (−)
Oxypurinol (−)
LTT 2, Day 129
INH 433% (+)
RFP 221% (+)
EB (−)
Allopurinol (−)
Oxypurinol (−)
ETH (−)
LVX (−)
LTT 3, Day 316
INH 1459% (+)
RFP 211% (+)
EB 228% (+)
Allopurinol (−)
Oxypurinol : not tested
ETH (−)
LVX (−)
PZA 198% (+)
LTT 4, Day 403
INH 353% (+)
RFP (−)
EB (−)
Allopurinol (−)
Oxypurinol 421% (+)
ETH (−)
LVX (−)
PZA (−)

Figure.2

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Prospective cohort study of herpes zoster in Shozu County: The Shozu Herpes Zoster (SHEZ) Study

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Prospective cohort study of herpes zoster in Shozu County: The Shozu Herpes Zoster (SHEZ) Study

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