Table 1 Characteristics of patients with drug-induced hypersensitivity syndrome/drug rash with eosinophilia with systemic symptoms.

Patient	Age, years/sex	Causative drug	Viral reactivation	Viral DNA loads* (in whole blood) or titres	Time from disease onset to skin biopsy, days	Immunosuppressive treatments at the time of skin biopsy	Time between skin biopsy and viral reactivation, days	FoxP3+/ CD3+ cells in skin lesions,%	Skin rash	Eosinophils, per μL	Liver dysfunction, IU/L
1	62/M	Carbamazepine	HHV-7	1.2×10^4	5	None	−1	14.7	Maculopapular erythema	980	286/723
2	68/F	Carbamazepine	HHV-6	8.8×10^3	15	None	2	17	Maculopapular erythema	1560	34/45
3	75/F	Allopurinol	HHV-6, HHV-7	1.3×10^3 (HHV-6)	13	None	3	27.2	Maculopapular erythema, purpura	1200	57/84
4	61/F	Salazosulfapyridine	HHV-6	7.2×10^4	13	Prednisolone 10 mg/day	4	23.8	Erythroderma	1200	49/107
5	64/F	Mexiletine	HHV-6	3.4×10^5	10	Betamethasone 1.0 mg/day	5	17.3	Maculopapular erythema, purpura	3000	100/182
6	44/M	Carbamazepine	HHV-6, HHV-7	7.4×10^3 (HHV-6)	11	Betamethasone 1.0 mg/day	6	14.7	Erythroderma, pustules	7300	91/130
7	62/M	Lamotrigine	HHV-7	IgG (1 : 20) (day 15); IgG (1 : 1280) (day 29)	13	None	7	13.3	Maculopapular erythema	700	28/104
8	32/M	Allopurinol	HHV-6	4.8×10^3	8	None	9	9.9	Maculopapular erythema	2200	52/304
9	56/M	Cyanamide	HHV-6	2.4×10^4	4	None	10	15.6	Maculopapular erythema	3200	101/119
10	57/F	Salazosulfapyridine	HHV-6	2.6×10^3	10	Prednisolone 10 mg/day	10	7.5	Erythroderma, pustule	5800	257/383
11	13/F	Carbamazepine	HHV-6	2.0×10^4	2	None	13	7.8	Maculopapular erythema	2100	124/295
12	36/F	Lamotrigine	HHV-6	1.4×10^5	6	None	13	6.2	Erythroderma	2400	40/108

*Loads are number of virus copies/mL. HHV, herpesvirus. Maximum value in the category of eosinophil and AST/ALT during the course of DIHS/DRESS.

Table 2 Profiles of patients with graft-versus-host disease after allogenic stem cell transplantation.

Underlying disease	Transplant type	Pre-transplant conditioning	Viral reactivation	Viral DNA loads (of whole blood)	Time from disease onset to skin biopsy, days	FoxP3+/CD3+ cells in skin lesions, %	Grade of GVHD
ALL	CBCT	TBI, FLU, BU	HHV-6	1.6×10^4	7	9.5	I
MDS	PBSCT	TBI, FLU, CPA, Mesna	HHV-6, CMV	5.2×10^3	3	4.2	I
MDS	CBCT	TBI, FLU, CPA, Mesna	HHV-6, CMV	8.0×10^4	3	3	I
AML	PBSCT	TBI, FLU, BU	HHV-6	9.2×10^3	2	2.5	IV
MDS	PBSCT	FLU, BU	CMV	4.4×10^3	5	4.8	II
ALL	CBCT	TBI, CPA, VP-16	HHV-6	1.2×10^3	6	8.2	II
ALL	PBSCT	FLU, BU	ND	ND	4	0.7	IV
ALL	BMT	TBI, CPA, BU, Mesna	ND	ND	29	3.3	III
ALL	BMT	TBI, L-PAM	ND	ND	27	0.6	IV
MM	PBSCT	L-PAM, BTZ	HHV-6	3.4×10^3	6	4.2	II
CML	BMT	TBI, FLU, BU, ATG	HHV-7	8.4×10^3	3	9.8	I
AML	CBCT	FLU, BU, Ara-C	HHV-6	7.2×10^3	4	6.7	I

*Loads are number of virus copies/mL. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Ara-C, cytosine arabinoside; ATG, antithymocyte globulin; BMT, bone marrow transplantation; BTZ, bortezomib; BU, busulfan; CBCT, cord blood cell transplantation; CLL, chronic lymphoblastic leukemia; CML, chronic myeloid leukemia; CPA, cyclophosphamide; FLU, fludarabine; GVHD, graft-versus-host disease; L-PAM, L-phenylalanine monohydrochloride; MDS, myelodysplastic syndrome; MM, multiple myeloma; ND, no data; PBST, peripheral blood cell stem cell transplantation; TBI, total body irradiation; VP-16, etoposide.

Results

Histopathological examination

Histopathological examination of skin biopsies obtained from the erythematous maculopapular rashes of patients with DIHS/DRESS showed perivascular lymphocytic infiltration with eosinophils (8 cases; 66.7%), interface dermatitis with vacuolar degeneration (2 cases; 16.7%) and spongiotic dermatitis with vacuolar degeneration (2 cases; 16.7%). Skin biopsies from rashes in patients with acute GVHD were graded according to the criteria by Lerner *et al.*[15,16] and showed vacuolar degeneration (histological grade I; 6 cases; 50%) and spongiosis with apoptotic cells (histological grade II; 6 cases; 50%). None of the cases showed a cleft between the epidermis and dermis (histological grade III or IV). Tissue from MDE mainly exhibited perivascular lymphocytic inflammation, occasionally with eosinophils.

Increased FoxP3+ Treg/CD3+ T-cell ratio in the skin lesions of DIHS/DRESS

The FoxP3+ Treg/CD3+ T-cell ratio was significantly higher in DIHS/DRESS rashes than in GVHD and MDE tissue (Figs 1 and 2), but the ratio in GVHD was not significantly different from that in MDE. In skin biopsy specimens from GVHD rashes and MDEs, we found small numbers of FoxP3+ Tregs. By contrast, CD4+/CD3+ and CD8+/CD3+ T-cell ratios in the skin lesions were similar for the three groups (Figs 1 and 2). The numbers of CD3+ T cells per 5 high-power fields in skin biopsies of those patients were also not significantly different.

Relationships between FoxP3+ Tregs/CD3+ T cells and the period from onset

Figure 3 shows the relationships between the ratio of FoxP3+ Tregs/CD3+ T cells in the lesional skin and the number of days from disease onset. All patients with DIHS/DRESS in this study had received no major treatment such as high-dose corticosteroid before the skin biopsies were taken. The FoxP3+ Treg/CD3+ T-cell ratio was positively correlated with the number of days from disease onset during the acute phase in DIHS/DRESS, but there was no correlation in either GVHD or MDE.

Discussion

Although DIHS/DRESS and GVHD can have similar presentations, there are a some clinical and histologi-

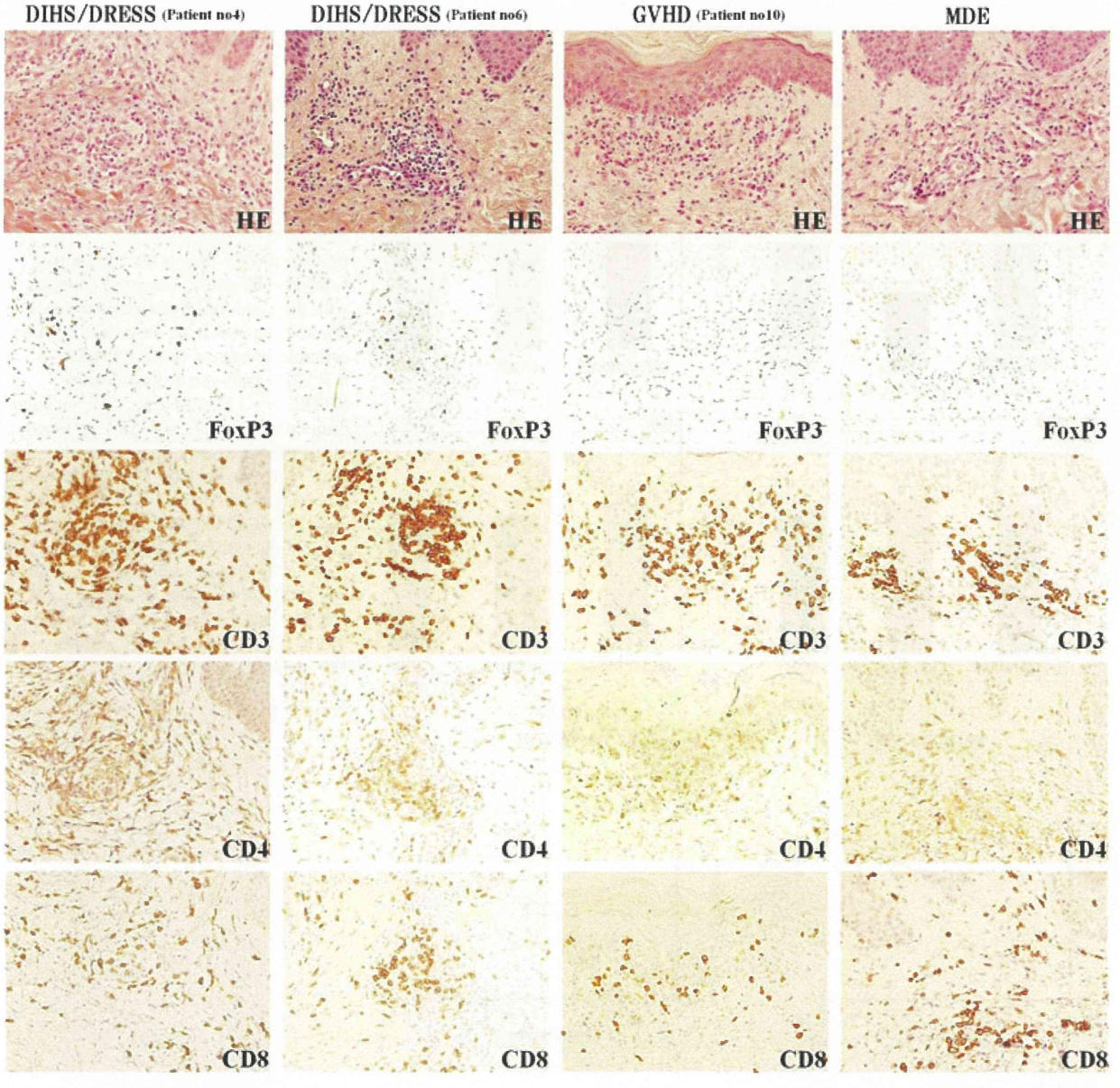

Figure 1 Expression of FoxP3+, CD3+, CD4+ and CD8+ T cells in drug-induced hypersensitivity syndrome (DIHS/DRESS), graft-versus-host disease (GVHD) and maculopapular drug eruption (MDE). Skin biopsies from patients with DIHS/DRESS showed a high number of FoxP3+ T cells in the epidermal-dermal junction and upper dermis compared with those in GVHD and MDE. Sections were counter-stained with haematoxylin, and images show representative serial sections from the same lesion of a patient with each disease (original magnification × 200). Patient numbers correspond with those in the tables.

cal differences between them. The cutaneous presentation of DIHS/DRESS often involves a maculopapular rash or erythroderma, but not blister formation or erosion. The common pathological findings of DIHS/DRESS are superficial perivascular lymphocytic infiltration with extravascular eosinophils, but histologically, severe liquefaction degeneration of the basal layer or epidermal necrosis is rarely found. By contrast, GVHD often presents with blister formation and erosion, and histologically shows lichenoid reaction with epidermal necrosis and/or epidermolysis.

Previous research on the dynamics of skin-infiltrating Tregs in GVHD showed that a decreased number of skin-infiltrating Tregs was associated with severity of GVHD[17]; however, another study showed that Tregs increased with degree of inflammation and grade of GVHD.[18]

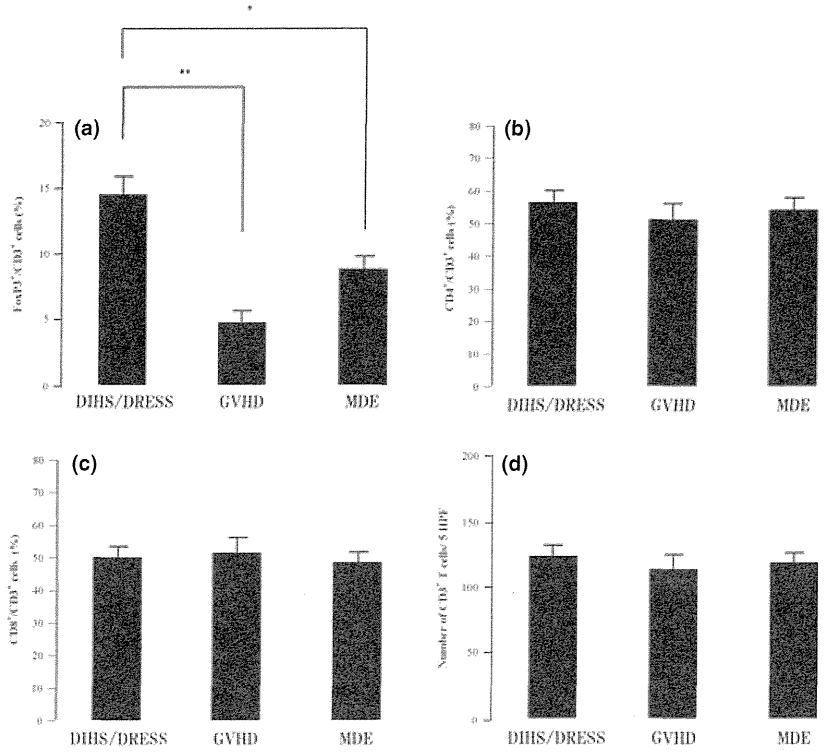

Figure 2 Ratios of FoxP3+ regulatory T cells, CD4+ T cells and ratio of CD8+ T cells to CD3+ T cells in paraffin wax-embedded biopsies taken from patients with drug-induced hypersensitivity syndrome/drug rash with eosinophilia with systemic symptoms (DIHS/DRESS; n = 12),), graft-versus-host disease (GVHD; n = 12) and) and maculopapular drug eruption (MDE; n = 18) are shown. (a) In DIHS/DRESS, a high ratio of FoxP3+ T cells per 100 CD3+ T cells was observed. (b, c) The ratios of CD4+/CD3+ and CD8+/CD3+ T cells infiltrating into the lesional skin of DIHS/DRESS were not statistically different from those in GVHD and MDE. (d) Numbers of infiltrating CD3+ T cells were quite similar in DIHS/DRESS, GVHD and MDE (*$P < 0.05$, **$P < 0.01$).

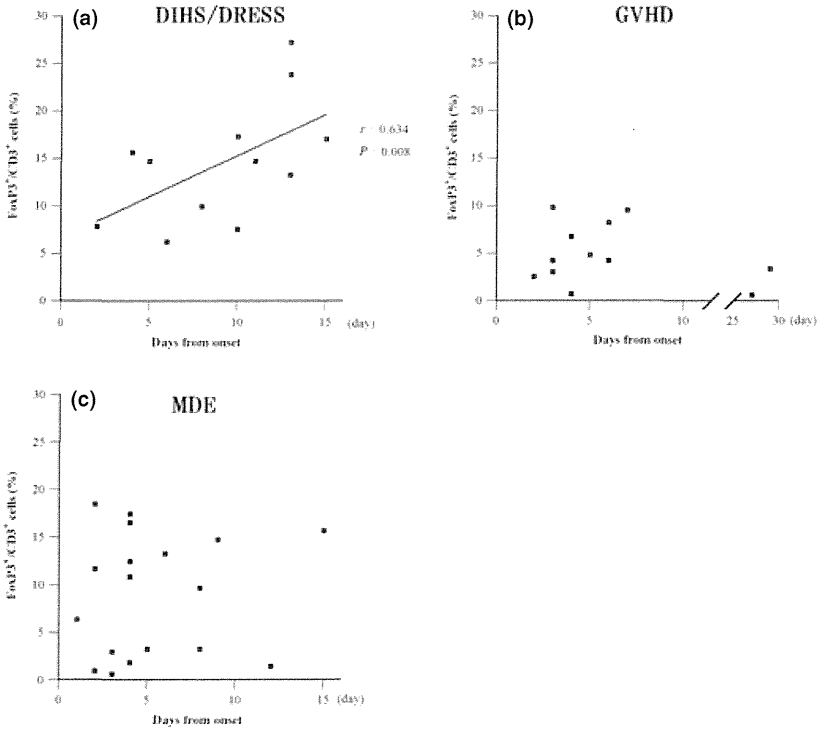

Figure 3 There was a correlation between the FoxP3+ Treg/CD3+ T-cell ratio and the time from disease onset in skin biopsies from patients with drug-induced hypersensitivity syndrome/drug rash with eosinophilia with systemic.

Patients with DIHS/DRESS in the acute stage were found to exhibit increased frequencies of Tregs and gradual loss of their function after resolution in peripheral blood mononuclear cells (PBMCs).[19] However, there have been no studies about the dynamics of skin-infiltrating Tregs in DIHS/DRESS. Therefore, we

focused on the dynamics of infiltrating Tregs in the skin lesions of these diseases, and found considerable differences between DIHS/DRESS and GVHD.

In the current study, the FoxP3+ Treg cell/CD3+ T-cell ratio was significantly higher in lesions from DIHS/DRESS than in those from GVHD and MDE, whereas the numbers of CD3+ T cells infiltrating into the skin lesions were similar in all three conditions (Figs 1 and 2). We also found that the ratio was positively correlated with the number of days from disease onset during the acute phase of DIHS/DRESS (Fig. 3). However, each dot in Fig. 3 represents the FoxP3+/CD3+ ratio from different patient samples, so the data does not show sequential data from individual patients, and thus results must be interpreted with caution. By contrast, the ratios of CD4+CD3+ T cells and CD8+CD3+ T cells in cutaneous lesions were similar for DIHS/DRESS, GVHD and MDE (Fig. 2). These findings suggest that clinical and histological differences between DIHS/DRESS and GVHD may result from differences in the frequency of FoxP3+ Tregs infiltrating into the skin lesions of these diseases. Tregs play a significant role in suppression of various diseases, including allergic responses, autoimmune and infectious disease, and cancers.[20,21] Accordingly, it is likely that an increased number of FoxP3+ T cells infiltrating into DIHS/DRESS skin lesions can protect the epidermis from severe damage compared with that in GVHD skin lesions.

Conclusion

In conclusion, the present study suggests that, despite many similarities, the dynamics of Tregs are different between DIHS/DRESS and GVHD in skin lesions, and that this difference may exert a considerable influence on the development of skin presentations in the two diseases.

What's already known about this topic?

- There are close similarities between DIHS/DRESS and GVHD, including HHV-6 reactivation, skin eruption, and autoimmune disease-like complications.
- However, there are also some clinical and histological differences between these two conditions.
- There are conflicting reports about the dynamics of skin-infiltrating Tregs in GVHD: severity of disease has been associated with both a decreased and an increased number of skin-infiltrating Tregs.
- Patients with DIHS/DRESS patients exhibit increased frequencies of Tregs in PBMCs at the acute stage; however, the dynamics of skin-infiltrating Tregs in DIHS/DRESS are currently unknown.

What does this study add?

- In the current study, levels of FoxP3+ Tregs were significantly higher in the skin lesions of DIHS/DRESS than in those of GVHD.
- The FoxP3+ Treg cell/CD3+ T-cell ratio was positively correlated with the number of days from disease onset during the acute phase of DIHS/DRESS, but not in GVHD or MDE.

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CPD questions

Learning objective

To provide up-to-date information about the immunopathological conditions in drug-induced hypersensitivity syndrome/drug rash with eosinophilia with systemic symptoms (DIHS/DRESS) and graft-versus-host disease (GVHD).

Question 1

Which type of lymphocyte is specifically increased in the skin lesions in DIHS/DRESS?
a) CD4+ T cell.
b) CD8+ T cell.
c) Regulatory T cell.
d) NK cell.
e) B cell.

Question 2

Which of the following diseases often shows epidermal necrosis?
a) DIHS.
b) GVHD.
c) Maculopapular drug eruption.
d) Urticaria.
e) Contact dermatitis.

Question 3

Which type of virus is commonly reactivated in DIHS/DRESS?
a) HSV.
b) VZV.
c) HHV-6.
d) HHV-8.
e) EBV.

Question 4

Which of the following statements about regulatory T cells is true?
a) CD8+.
b) CD20+.
c) CD56+.
d) FoxP3+.
e) Enhance allergic responses.

Question 5

Which of the following features is not seen in DIHS/DRESS?

a) Fever.
b) Eosinophilia.
c) Penicillin allergy.
d) Lymph-node swelling.
e) Delayed onset.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced.

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at www.wileyhealthlearning.com/ced and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

Tinea caused by *T. verrucosum* is very rare in young children.[9] In suspected cases, special attention is required to avoid misdiagnosis. DNA sequence analysis has become the standard method for identifying the causative fungus, but morphological diagnosis remains important.

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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).

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

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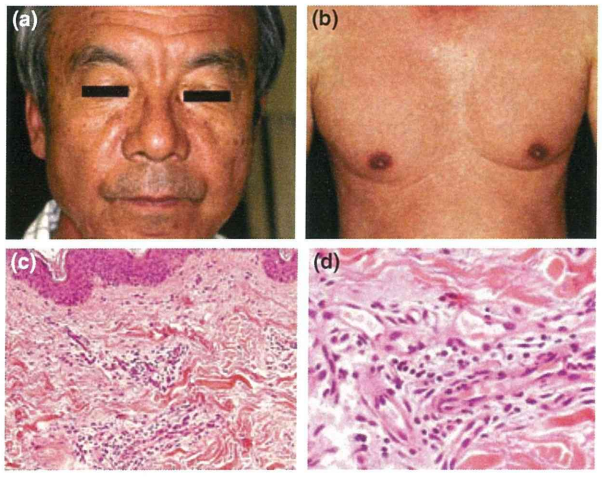

Figure 1. (a) Mild facial edema was observed. (b) Diffuse erythematous skin eruption in the patient. (c,d) The skin biopsy showed perivascular lymphocytic infiltration in the upper dermis. (hematoxylin–eosin, original magnifications: [c] ×100; [d] ×400).

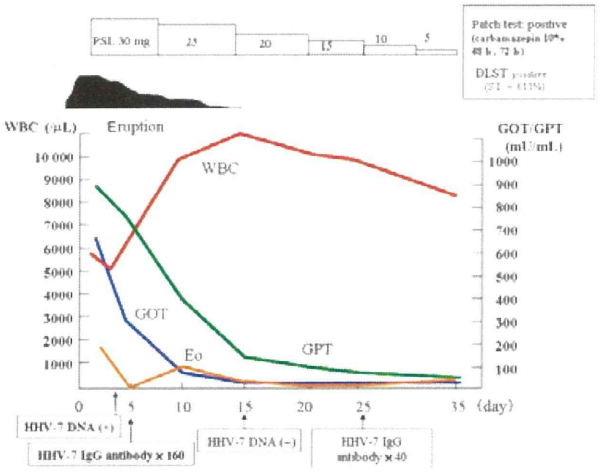

Figure 2. Clinical course in relation to serological data. DLST, drug lymphocyte stimulation test; Eo, eosinophils; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; HHV, human herpesvirus; IgG, immunoglobulin G; PSL, prednisolone; WBC, white blood cell.

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 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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Basophils are required for the induction of Th2 immunity to haptens and peptide antigens

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The relative contributions of basophils and dendritic cells in Th2 skewing to foreign antigen exposure remain unclear. Here we report the ability of basophils to induce Th2 polarization upon epicutaneous sensitization with different antigens using basophil conditionally depleted Bas TRECK transgenic mice. Basophils are responsible for Th2 skewing to haptens and peptide antigens, but not protein antigens *in vivo*. Consistent with this, basophils cannot take up or process ovalbumin protein in significant quantities, but present ovalbumin peptide to T cells for Th2 differentiation via major histocompatibility complex class II. Intriguingly, basophils promote Th2 skewing upon ovalbumin protein exposure in the presence of dendritic cells. Taken together, our results suggest that basophils alone are able to induce Th2 skewing with haptens and peptide antigens but require dendritic cells for the induction of Th2 for protein antigens upon epicutaneous immunization.

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