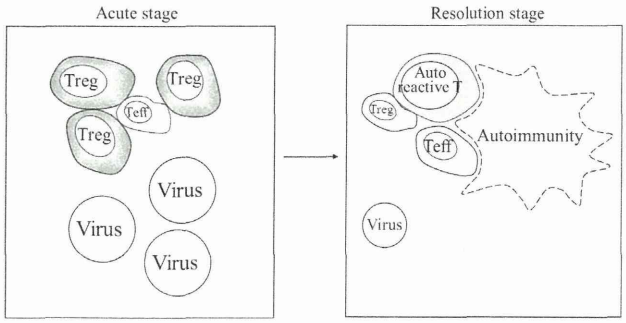

Figure 4 Viral reactivation would be triggered by expansions of Treg cells during the acute stage. Defective Treg function could be associated with the development of autoimmune disease during the resolution stage. Treg = regulatory T cell.

DNA in the blood at onset. These results indicate that patients with high EBV DNA loads may be at risk of subsequently developing SJS. However, contrary to our initial expectation, no patients with TEN demonstrated elevated EBV loads during either the acute stage or long after clinical resolution. High HHV-6 loads were exclusively detected in patients with DiHS during the acute stage. CMV reactivations occurred in ~20% of patients with DiHS as well as those with SJS during the acute stage. Nevertheless, the dynamics of EBV, CMV, and HHV-6 reactivation varied considerably in these patients according to the use of systemic corticosteroids. EBV DNA loads were significantly lower in patients with DiHS treated with systemic corticosteroids than those without them, although CMV and HHV-6 DNA loads were the opposite.

Our series of patients and a review of the English literature demonstrated that less than 10% of patients with DiHS die within 1 year after onset and autoimmune diseases or production of autoantibodies occur as a sequela of DiHS after a disease-free interval of several months to years[27,28] in some patients with DiHS surviving the acute stage: they include type 1 diabetes mellitus,[29,30] autoimmune thyroid disease,[28,31] sclerodermoid GVHD-like lesions,[32] and lupus erythematosus.[27,33] Because EBV reactivations were preferentially observed during the acute stage of DiHS in some patients who subsequently developed these autoimmune diseases, EBV reactivations may act as a trigger for the subsequent development of autoimmune diseases.[28] Interestingly, the increase in various autoantibody titers such as antinuclear antibodies (ANA) and the development of autoimmune diseases during the resolution stage were preferentially observed in DiHS patients who had not received systemic corticosteroids during the acute stage (Figure 4). Consistent with the results of these studies, the generation of autoantibodies to periplakin was also observed in DiHS patients who had not received systemic corticosteroids during the acute stage. These results suggest that immune responses preventable with systemic corticosteroids and/or increased EBV DNA loads during the acute stage could trigger the subsequent generation of autoantibodies and that early intervention by systemic corticosteroids may lead to better long-term outcomes for DiHS patients at risk of subsequently developing autoimmune disease. In addition to the role of EBV reactivations, a gradual loss of Treg function after resolution of DiHS[26] could also increase the risk.

Conclusion

The role of viral infections in the onset, progression, and modulation of a multifactorial disease process in drug eruptions is now well established from a variety of epidemiological, clinical, and experimental studies. Despite the tremendous advances in our understanding of viral pathogenesis, we have to emphasize how much there is still to learn about the ways that link viral infections to drug eruptions. Developing animal models that reliably mimic features of DiHS would represent a useful tool in helping us understand the mechanisms and develop new therapies.

Acknowledgments

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Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution

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Background: Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe systemic hypersensitivity reaction caused by specific drugs, in which herpesvirus reactivations and organ dysfunction occur during the course of the disease. Although recent reports have documented the development of autoimmune disease after complete resolution of DIHS/DRESS, relatively little is known about long-term outcomes after complete resolution of the disease.

Objective: The aim of this study was to retrospectively analyze complications and sequelae in the early and late phases of DIHS/DRESS according to treatment.

Methods: In all, 34 patients were classified into 2 groups: 14 patients with oral corticosteroid treatment; and 20 with noncorticosteroid treatment. The disease time course was divided into 2 periods: the first 6 months after onset of the drug reaction (early phase); and the period thereafter (late phase). Investigations to detect the presence of viral/bacterial infectious diseases, organ dysfunction, and autoantibodies were performed in both early and late phases.

Results: Herpesvirus infections and pneumonia were detected in 6 and 2 patients, respectively, in the corticosteroid treatment group in the early phase. In the noncorticosteroid treatment group, 2 patients developed autoimmune diseases, namely lupus erythematosus and autoimmune thyroiditis. Autoantibodies were detected in 44.4% of patients examined in the late phase of the disease.

Limitations: This study only evaluated a small number of autoantibodies.

Conclusion: The need for anti-inflammatory effects from systemic corticosteroids should be balanced with the risk of infectious diseases and the benefits of preventing the appearance of later autoimmune conditions in patients with DIHS/DRESS. (J Am Acad Dermatol 2013;68:721-8.)

Key words: complication; corticosteroid; drug-induced hypersensitivity syndrome; drug reaction; drug reaction with eosinophilia and systemic symptoms; herpesvirus; outcome; treatment; viral reactivation.

Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe systemic hypersensitivity reaction caused by specific drugs such as anticonvulsants and allopurinol, and is characterized by organ dysfunction and reactivation of human herpesvirus (HHV)-6.[1-3] Reactivation of other herpesvirus, such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) may occur during the course of this drug reaction.[4-6] Despite the complete recovery from DIHS/DRESS, the development of autoimmune sequelae such as autoimmune

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thyroiditis, sclerodermoid lesions, type 1 diabetes mellitus, and lupus erythematosus has been reported.[7-12] The long-term outcomes of DIHS/DRESS after complete resolution of the disease are unclear, because of a lack of long-term follow-up and the potential development of sequelae after a disease-free period of several months to years. In particular, the relationship between administration of systemic corticosteroids—a common treatment for DIHS/DRESS—and long-term outcome is not well documented.[13,14] Long-term outcomes may be influenced by the type and duration of treatment, herpesvirus reactivation, genetic factors, and the presence of underlying disease. To clarify the relationship between treatment and outcome in DIHS/DRESS, we retrospectively analyzed the complications and sequelae in the early and late phases of the disease in relation to treatments in patients with DIHS/DRESS seen at our institution. This study revealed significant differences in outcomes according to treatment for DIHS/DRESS.

CAPSULE SUMMARY

- Drug-induced hypersensitivity syndrome is a severe systemic hypersensitivity reaction, and involves the reactivation of herpesviruses. Various infections and organ failure can develop during the course of this disease.
- Development of autoimmune diseases and autoantibodies were detected in noncorticosteroid-treated patients after complete resolution of the disease.
- Treatments for drug-induced hypersensitivity syndrome should be carefully selected based on an understanding of the differences in treatment modalities.

METHODS

Patients

This study was approved by the institutional review board of Kyorin University School of Medicine, Tokyo, Japan. The medical records of 40 patients who had been admitted into our hospital for DIHS/DRESS between 1998 and 2010 were reviewed. All patients satisfied the diagnostic criteria for DIHS/DRESS proposed by the Japanese Severe Cutaneous Adverse Reaction Group,[15] and the culprit drug had been discontinued once the diagnosis was suspected. Patients were excluded from further analysis if: they were older than 85 years; significant underlying diseases were present, including heart or renal failure; previous treatment before visiting our hospital was unclear; or if the period of observation and follow-up was less than 1 year after the initiation of treatment in our hospital. After the exclusion of ineligible patients based on the exclusion criteria, 34 of the 40 patients given the diagnosis of DIHS/DRESS were enrolled in the study. Using the RegiSCAR scoring system proposed by Kardaun et al,[16] the 34 cases were classified as either definite or probable.

Patients were classified into 2 groups according to whether they had been treated with oral corticosteroids (corticosteroids, n = 14; noncorticosteroid treatment, n = 20). No other immunosuppressive agents had been administered. The initial oral corticosteroid dose was 0.6 to 1.0 mg/kg daily, after which the dose was gradually tapered. Most patients required more than 8 weeks of oral corticosteroids to achieve complete resolution. Patients who had received less than 0.25 mg/kg daily within 3 days before hospital admission were not included in the oral corticosteroid treatment group. A total of 5 patients in the corticosteroid treatment group had also received intravenous immunoglobulin (IVIG) therapy, with a dose of 5 g daily administered for 3 to 5 days on detection of herpesvirus reactivation. In the noncorticosteroid treatment group, 3 patients had received IVIG therapy with intravenous fluids. Two patients were given doses of 5 g daily for 3 and 5 days, respectively, and 1 patient who had 1 kidney because of previous excision of a renal tumor was given a dose of 2.5 g daily for 3 days. The other 17 patients were given supportive treatment with intravenous fluids (Fig 1). Some patients received topical corticosteroids for symptomatic relief. The type of treatment selected was based on the clinical judgment of the consulting dermatologist rather than a predetermined treatment algorithm.

The clinical features and culprit drugs in each group are shown in Table I. The respective mean age was 54.5 ± 19.7 and 56.4 ± 15.2 years in the corticosteroid and noncorticosteroid treatment groups. The type of culprit drugs and the presence of underlying disease were not significantly different between the 2 groups. In most patients, eruptions started as erythematous macules that enlarged and became confluent erythematous lesions. Mucosal lesions were present only in 1 patient in the corticosteroid treatment group. Skin biopsy specimens had been obtained from all patients and histopathological examination revealed scattered exocytosis of mononuclear cells in the epidermis and perivascular lymphocytic and eosinophilic infiltration in the papillary dermis in many specimens. Laboratory data including leukocyte and eosinophil counts,

Abbreviations used:

ATGA:	antithyroglobulin antibody
ATPOA:	antithyroperoxidase antibody
CMV:	cytomegalovirus
DIHS:	drug-induced hypersensitivity syndrome
DRESS:	drug reaction with eosinophilia and systemic symptoms
EBV:	Epstein-Barr virus
HHV:	human herpesvirus
IVIG:	intravenous immunoglobulin

C-reactive protein, alanine aminotransferase, and serum IgG levels in peripheral blood were obtained before treatment and analyzed to exclude differences in disease severity between the 2 groups; no significant differences were observed in any of these parameters between the 2 groups. The culprit drug was confirmed using the lymphocyte transformation test. Positive lymphocyte transformation test results were obtained more than 1 month after the onset of the drug reaction in most patients.

Assessment of clinical courses

The disease time course was divided into 2 periods: the first 6 months after the onset of a drug reaction was regarded as the early phase and the period thereafter was regarded as the late phase. The average time period of clinical observation (from disease onset until end of follow-up) was 53 and 41 months in the oral corticosteroid and noncorticosteroid treatment groups, respectively. Investigations to detect the presence of viral/bacterial infections and organ dysfunction attributable to DIHS/DRESS were performed in both the early and late phases. Mild liver dysfunction and/or erythematous rash commonly observed during the course of the disease were not considered to be complications of DIHS/DRESS.

Detection of viral reactivation

To detect HHV-6 reactivation, patients with suspected DIHS/DRESS were tested for anti-HHV-6 IgG antibody titers by fluorescent antibody assays and/or real-time polymerase chain reaction assays for HHV-6 DNA loads in peripheral leukocytes, based on *Taq*Man technology. HHV-6 reactivation was defined as a greater than 4-fold increase in anti-HHV-6 IgG antibody titers or detection of HHV-6 DNA in leukocytes. In addition, EBV and CMV DNA loads in peripheral leukocytes were also determined by means of polymerase chain reaction assays, based on *Taq*Man technology, during the course of the disease. DNA loads for herpesvirus were evaluated at either biweekly or triweekly intervals.

Detection of antibody

The presence of autoantibodies and increases in autoantibody levels were also evaluated in both phases. In some patients, serum was obtained before treatment and preserved at −80°C for measurement of autoantibodies including antinuclear antibody, antithyroglobulin antibody (ATGA), and antithyroperoxidase antibody (ATPOA), using a fluorescein-labeled antibody for determination of antinuclear antibody levels and radioimmunoassay for measurement of ATGA and ATPOA levels. The aforementioned antibodies were selected based on preliminary results that had shown no alterations in the levels of rheumatoid factor, antitopoisomerase 1, or antimitochondrial or antithyroglobulin receptor antibodies in patients' sera. Autoantibody levels were measured at intervals of several months in the majority of patients. Autoantibody levels were compared with those before the initiation of treatment.

Statistical analyses

Laboratory data from the 2 treatment groups were analyzed using Student *t* test. Values of *P* less than .05 were taken to indicate statistical significance.

RESULTS

The overall mortality was 8.8%. In the corticosteroid treatment group, various infections such as herpes labialis, herpes zoster, CMV diseases, and pneumonia were seen in the early phase. Herpes labialis was detected within 10 days after the onset of DIHS/DRESS. Herpes zoster occurred in 2 patients approximately 2 months after the onset of drug eruptions during corticosteroid tapering, and 1 month after the cessation of corticosteroid therapy in 1 patient. The cutaneous manifestations of herpes zoster were mild and resolved without any complications.[17] CMV diseases were noted in 1 patient, which manifested as gastrointestinal bleeding and skin ulcers on the back 5 weeks after the onset of DIHS/DRESS,[18] followed by acute respiratory distress syndrome, resulting in death. Limbic encephalitis, possibly associated with HHV-6 reactivation, occurred 3 weeks after the onset of DIHS/DRESS in 1 patient, and was complicated by syndrome of inappropriate secretion of antidiuretic hormone.[19] Some of the cases mentioned in the current study have already been published.[7,8,17-19] Most viral infections, including herpes zoster, encephalitis, and gastrointestinal bleeding, were detected when the dose of oral corticosteroid was decreased to 25% to 67% of the initial dose. In addition, 2 cases of pneumonia occurred: 1 patient died of acute respiratory distress syndrome secondary to *Pneumocystis jiroveci* pneumonia 2.5 months after the onset of

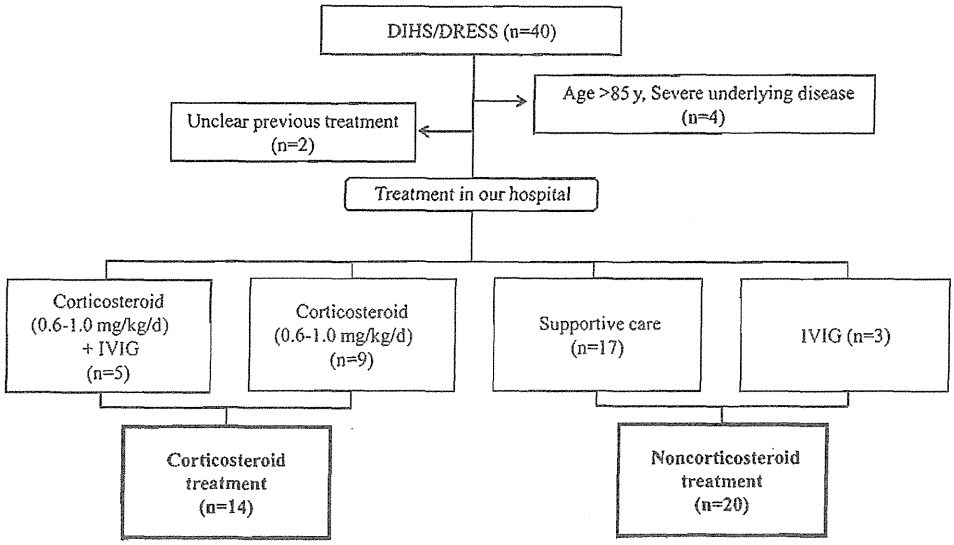

Fig 1. Patient flow diagram. Patients with drug-induced hypersensitivity syndrome (*DIHS*)/drug reaction with eosinophilia and systemic symptoms (*DRESS*) were divided into 2 groups. Administration of intravenous immunoglobulin (*IVIG*) was included in each group.

Table I. Patient characteristics

Treatment group (No. of cases)	Age, y, mean ± SD	M:F	Underlying disease (No. of cases)	Culprit drug (No. of cases)
Corticosteroid (14)	54.5 ± 19.7	10:4	Arrhythmia (1), cerebral infarction (2), colitis (1), convulsion (1), epilepsy (3), hyperuricemia (1), neuralgia (1), psychiatric disease (2), rheumatoid arthritis (1), vasculitis (1)	Allopurinol (1), carbamazepine (6), dapsone (1), mexiletine (1), phenobarbital (2), phenytoin (1), salazosulfapyridine (2)
Noncorticosteroid (20)	56.4 ± 15.2	8:12	Cerebral infarction (3), convulsion (5), encephalitis/asthma (1), epilepsy (1), hyperuricemia (1), hyperuricemia/Sjögren syndrome (1), hyperuricemia/hepatitis C/renal tumor (1), neuralgia (4), psychiatric disease (3)	Allopurinol (3), carbamazepine (14), phenobarbital (1), phenytoin (2)

F, Female; *M*, male.

DIHS/DRESS; and another patient with interstitial pneumonia developed *Cryptococcus* pneumonia 8 months after the onset of DIHS/DRESS. In these 2 patients, infectious pneumonia was observed when the doses of corticosteroid were reduced to 50% and 15% of the initial dose, respectively. Bacterial intramuscular abscess occurred in 1 patient when the dose was decreased to 75% of the initial dose (Table II).

In the early phase of DIHS/DRESS in the noncorticosteroid treatment group, diffuse alopecia developed 4 months after the onset of DIHS/DRESS in 1 patient without evidence of thyroid dysfunction, which persisted for 6 months. Another patient with gastrointestinal bleeding caused by CMV infection required emergency endoscopic clipping and administration of ganciclovir with IVIG.[18] In contrast to the corticosteroid treatment group, no bacterial infections were seen in the noncorticosteroid treatment group in the early phase (Fig 2).

Liver dysfunction was observed in all patients in the early phase. Severe liver dysfunction (alanine aminotransferase >300 IU/L) was detected in 8 patients, and in 4 of these 8 patients the corticosteroid was administered at the initial dose of 0.8 mg/kg daily. The others were managed with supportive treatment monitored by specialists. Liver dysfunction ameliorated within 80 days in most patients, with some fluctuations in the levels. No fatal sequelae were noted in the current study.

Table II. Onset of complications and corticosteroid treatment doses

Case No.	Age, y/gender	Underlying disease	Culprit drug	Complication after treatment	Corticosteroid (prednisolone) Initial dose, mg/d	Dose at onset of complication, mg/d
1	39/M	Psychiatric disease	Carbamazepine	HZ	40	10
2	63/M	Convulsion	Carbamazepine	HZ	40	20
3	70/F	Cerebral infarction	Phenytoin	HZ	40	0
4	69/M	Epilepsy	Phenobarbital	En	60	40
5	74/M	Arrhythmia	Mexiletine	GB → ARDS	50	25 → 20
6	79/M	Neuralgia	Carbamazepine	AC → PP → ARDS	50	40 → 25 → 25
7	28/F	Epilepsy	Carbamazepine	IA	80	60
8	68/M	Rheumatoid arthritis	Salazosulfapyridine	IP → CP	40	15 → 6*

AC, Acute cholangitis; *ARDS*, acute respiratory distress syndrome; *CP*, *Cryptococcus* pneumonia; *En*, encephalitis; *F*, female; *GB*, gastrointestinal bleeding; *HZ*, herpes zoster; *IA*, intramuscular abscess; *IP*, interstitial pneumonia; *M*, male; *PP*, *Pneumocystis jiroveci* pneumonia.
*Administration of corticosteroids continued because of rheumatoid arthritis.

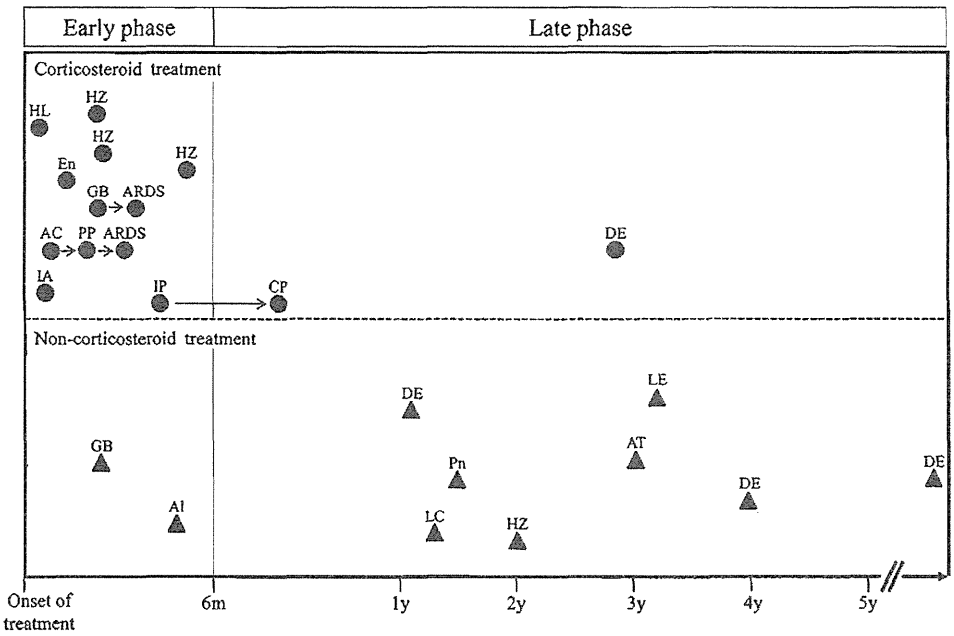

Fig 2. Complications and sequelae were classified into 2 groups in early and late phases according to treatment. *AC*, Acute cholangitis; *AI*, alopecia; *ARDS*, acute respiratory distress syndrome; *AT*, autoimmune thyroiditis; *CP*, *Cryptococcus* pneumonia; *DE*, drug eruption; *En*, encephalitis; *GB*, gastrointestinal bleeding; *HL*, herpes labialis; *HZ*, herpes zoster; *IA*, intramuscular abscess; *IP*, interstitial pneumonia; *LC*, lung cancer; *LE*, lupus erythematosus; *Pn*, pneumonia; *PP*, *Pneumocystis jiroveci* pneumonia.

In the late phase of DIHS/DRESS in the noncorticosteroid treatment group, autoimmune diseases developed in some patients. Lupus erythematosus with severe lupus nephritis developed in a patient 4 years after the onset of DIHS/DRESS treated with IVIG alone.[8] A case of asymptomatic autoimmune thyroiditis (Hashimoto thyroiditis) developed in a patient 3 years after the onset of DIHS/DRESS managed with supportive treatment alone. In this patient, thyroid stimulation hormone level increased 10 months after the onset of DIHS/DRESS, followed by detection of ATGA and ATPOA. One patient with a normal x-ray result on admission died of lung cancer 2 years after the onset of DIHS/DRESS. Drug eruptions were seen in 3 patients, caused by an antibiotic, an antilipemic agent, and a cold remedy, respectively (Fig 2). The lymphocyte transformation test levels were positive in 2 of these 3 cases.

Autoantibodies were more commonly detected in patients in the noncorticosteroid treatment group, particularly in the late phase, with 44.4% of patients

Table III. Detection of autoantibodies

	Detection of autoantibody	
	Frequency Detected antibodies (No. of cases)	
Treatment group (No. of cases)	Early phase	Late phase
Corticosteroid (6)	0% (0/6)	16.7% (1/6) ANA (1)
Noncorticosteroid (10)	20.0% (2/10) ANA (2)	70.0% (7/10) ANA (2) ATGA (4) ATPOA (3)

ANA, Antinuclear antibody; *ATGA*, antithyroglobulin antibody; *ATPOA*, antithyroperoxidase antibody.

Table IV. Herpesvirus reactivations

	Viral reactivation, no. of cases			
Treatment group (No. of cases)	HHV-6, EBV, CMV	HHV-6, EBV	HHV-6, CMV	HHV-6
Corticosteroid (13)	3	2	4	4
Noncorticosteroid (16)	2	7	1	6

CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus; *HHV*, human herpesvirus.

demonstrating autoantibodies. One patient with positive ATPOA in the corticosteroid treatment group had a history of rheumatoid arthritis. Autoantibodies were present in all 3 patients who had been treated with IVIG alone (Table III). The respective ranges for antinuclear antibody, ATGA, and ATPOA detected were 40- to 320-fold, 1.5 to 8.1 U/L, and 1.0 to 19.5 U/L. These autoantibody titers remained elevated during the study period, with some fluctuations in the levels.

Herpesvirus reactivations detected during the course of the disease were classified into 4 groups: HHV-6, EBV, and CMV; HHV-6 and EBV; HHV-6 and CMV; and HHV-6 alone. Our results showed that CMV reactivation was detected in more than half of the patients in the corticosteroid treatment group. EBV reactivation was more frequently observed in patients in the noncorticosteroid treatment group than in the corticosteroid treatment group (Table IV).

DISCUSSION

Little attention has been paid to the long-term outcomes after complete recovery from DIHS/DRESS because many difficulties are encountered in following up with patients who do not seek medical care during a disease-free period after clinical resolution. This study revealed long-term outcomes obtained from a substantial number of patients with DIHS/DRESS who were carefully followed up by the same dermatologists in a single institution.

The prognosis of DIHS/DRESS may be influenced by age, genetic factors, presence of underlying disease, viral reactivation, and type of treatment. In particular, DIHS/DRESS appears to be worse in elderly patients, whereas younger patients recover more quickly. In the current study, there was no significant difference in age between the 2 groups, and laboratory data obtained before the initiation of therapy showed no significant differences between the 2 groups; thus, patient selection bias was unlikely.

Oral corticosteroids remain the mainstay treatment for DIHS/DRESS,[13,14] and a rapid resolution of symptoms is usually observed within several weeks after commencement. In this study, various infections were noted in the corticosteroid treatment group in the early phase, including herpesvirus diseases and *P jiroveci* pneumonia. CMV reactivation was more commonly detected in the corticosteroid treatment group, occurring in 53.8% examined. CMV disease and *P jiroveci* pneumonia were associated with delayed recovery and worse outcomes. Based on our results, most infectious diseases appeared within 3 months after initiation of the oral corticosteroid. As a result, careful follow-up for at least 3 months is recommended to minimize the risk of unfavorable outcomes in patients with DIHS/DRESS. The prolonged administration of oral corticosteroids may be partly responsible for these infections, given that the corticosteroid dose at 0.8 to 1.0 mg/kg daily was relatively high and administered over a long period, with the corticosteroid tapered over 2 months. However, considering the relatively high doses of corticosteroid used to treat other diseases such as collagen diseases and systemic vasculitis, it seems unlikely that corticosteroid alone was responsible for the infections in patients with DIHS/DRESS. In fact, 1 patient with gastrointestinal bleeding and skin ulcers caused by CMV disease had not been treated with oral corticosteroids.[18]

Alternatively, the development of infections in DIHS/DRESS during corticosteroid treatment may be analogous to the pathomechanisms of immune reconstitution inflammatory syndrome.[20] Diseases in the early stage of DIHS/DRESS such as herpes zoster, CMV infection, and *P jiroveci* pneumonia are similar to the range of illnesses in patients with AIDS and immune reconstitution inflammatory syndrome after highly active antiretroviral therapy.[21] As infectious diseases occurred most commonly during corticosteroid tapering down to 25%, the dose reduction of corticosteroids in the setting of DIHS/DRESS might have contributed to the appearance of these infectious diseases. An awareness of these infectious

diseases during tapering will facilitate prompt interventions in patients with DIHS/DRESS.

The development of autoimmune diseases such as lupus erythematosus[8] and autoimmune thyroiditis, along with the presence of autoantibodies, were observed in the noncorticosteroid treatment group in the late phase of DIHS/DRESS. Our previous article reported a patient who developed sclerodermoid graft-versus-host disease–like lesions treated with oral corticosteroids and low-dose IVIG in another hospital.[7] However, surprisingly, no cases of autoimmune disease were seen in the corticosteroid treatment group in the current study, and the appearance of autoantibodies was uncommon. It has been shown that IVIG compensates for the decreased immunoglobulin concentration, provides anti-inflammatory effects, and regulates the immune response in autoimmune diseases. However, according to Joly et al,[22] IVIG in patients with DIHS/DRESS can result in severe adverse events, which may require systemic corticosteroid therapy. In the current study, autoantibodies were detected in all 3 patients treated with IVIG. As only a small number of patients were enrolled in this study, it is difficult to determine the role of IVIG in the management of DIHS/DRESS. Further studies on treatment outcomes and long-term follow-up are thus needed in a larger patient population. Clearly, further work needs to be done regarding the link between the onset of DIHS/DRESS and the occurrence of cancer.

It is unclear why autoimmune diseases develop in the noncorticosteroid treatment group in DIHS/DRESS. We have already reported that regulatory T cells were expanded in the acute stage with normal functions, whereas regulatory T cells were functionally impaired in the resolution stage in patients with DIHS/DRESS.[23] These regulatory T cells most likely increased the susceptibility of patients with DIHS/DRESS to autoimmune diseases. However, autoimmune reactions could not be detected in all patients with DIHS/DRESS. Impaired regulatory T-cell function might thus contribute partially to the development of autoimmune diseases, but other pathomechanisms might also be responsible for the appearance of autoimmune reactions. On the other hand, we speculate that this may be linked to the EBV reactivation, because EBV shows a unique characteristic infection pattern of B cells. EBV infection might be a continuous source of chronic immune stimulation.[24] In fact, EBV has been implicated in the development of autoimmune diseases, such as lupus erythematosus and multiple sclerosis.[25,26] In the current study, EBV reactivation was more frequently detected in patients in the noncorticosteroid treatment group, with 56.3% of patients examined. This frequency was much higher than that in patients in the corticosteroid treatment group. In this regard, we have detected that viral loads of EBV are lower in the corticosteroid treatment group than in the noncorticosteroid treatment group, whereas viral loads of HHV-6 and CMV are higher in the corticosteroid treatment group than in the noncorticosteroid group (in preparation by Ishida). These findings may indicate that the pattern of viral reactivations enhanced by systemic corticosteroids would differ according to the virus.

Although only limited information could be obtained concerning the detection of autoantibodies, the frequency of the detection for autoimmune thyroid antibodies was markedly higher in the noncorticosteroid treatment group than in the corticosteroid treatment group. Considering that EBV antigens were found in target organs in multiple sclerosis,[27] the thyroid gland might be one of the target organs in this setting.

Our findings suggest that patients with DIHS/DRESS should be monitored for the development of autoimmune disease including laboratory examination of autoantibodies, despite clinical symptoms. The beneficial effects of oral corticosteroids in the suppression of inflammation and prevention of autoimmune disease need to be counterbalanced against the risk of infection.

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特集　薬疹を診る―注意点とその対応

重症薬疹の診断と治療

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特集　薬疹を診る―注意点とその対応

重症薬疹の診断と治療

藤山幹子

キーワード●重症薬疹，スティーブンス・ジョンソン症候群，中毒性表皮壊死症，薬剤性過敏症症候群

はじめに

薬疹は薬剤アレルギーの1つであるが，全身症状を伴い，生命予後にまで影響を与えるものを重症薬疹という．重症薬疹にはアナフィラキシー，スティーブンス・ジョンソン症候群（SJS），中毒性表皮壊死症（TEN），薬剤性過敏症症候群（drug-induced hypersensitivity syndrome；DIHS）などがある．

SJSとTENは，10年ほど前までは厳密な区別がなされていなかった疾患で，さらには皮膚粘膜眼症候群という別の病名も用いられていた．現在では2つの疾患として区別され，それぞれの診断基準が作成されている．また，DIHSは以前より特殊な薬疹として認識されていた疾患であるが，その病態が明らかとなり，確立された新しい概念である．

I SJS

SJSの特徴は，発熱と粘膜障害である．薬剤以外にもマイコプラズマ感染症などがきっかけとなり生じることがあるが，ここでは，薬剤により生じるSJSについて述べる．

1. 疫学

2005～2007年に行われた調査においては，日本では人口100万人当たり年間3.1人に発症していた[1]．原因薬剤には，抗菌薬，解熱鎮痛薬，抗てんかん薬が多い．抗菌薬では，セフェム系が24%，ピリドンカルボン酸系が21%を占める．解熱鎮痛薬では，ロキソプロフェンナトリウム26%，アセトアミノフェン19%，イブプロフェン15%であった[1]．SJSの死亡率は約3%である[1]．

2. 診断

発熱，皮膚粘膜移行部の重篤な粘膜障害，体表面積の10%未満の水疱あるいは表皮剝離によるびらんを認めたときにSJSと診断する[2]．

最も重要な所見は皮膚粘膜移行部の粘膜障害であり，眼瞼結膜から眼瞼（図1），口腔粘膜から口唇（図2），外陰部の所見が重要であるが，鼻粘膜にも病変は生じうる．眼の障害は，軽い場合は充血程度であるが，眼瞼結膜の上皮障害による偽膜形成や角膜上皮の欠損を生じると，深刻なドライアイや視力障害などの後遺症を残すことがある．皮膚にも数cm大の紅斑のなかに水疱やびらんを形成するが，体表面積の10%未満にとどまる．また，まれではあるが呼吸器障害を生じることがあり，生命予後に関わってくる．

3. 治療

原因薬剤を中止し，ステロイド薬全身投与により治療を行う．皮疹の範囲や粘膜障害の程度によるが，PSL換算で0.5mg/kg/日以上で開始し，症状の悪化をみたときにはすみやかな増

Diagnosis and management of severe drug rash
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愛媛大学大学院医学系研究科講師（感覚皮膚医学）

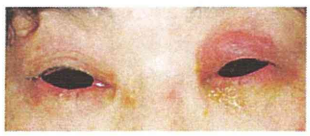

図1　スティーブンス・ジョンソン症候群の眼所見
結膜の充血があり，眼瞼にも紅斑とびらん形成（左眼）が認められる．眼脂を多量に付着する．

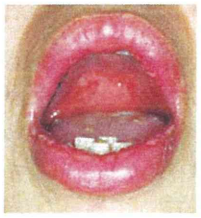

図2　スティーブンス・ジョンソン症候群の口腔所見
早期の所見．口唇，口腔内にびらんを形成する．

量を行う[3]．ステロイドパルス療法を早期から行うこともある．眼病変への対処は重要であり，眼科専門医の診察を受け，感染に注意しながらステロイド点眼薬や眼軟膏を用いて治療する．治療により，粘膜病変の状態の改善，皮膚のびらん面の乾燥，紅斑の消退がみられれば，ステロイド薬は漸減中止する．呼吸器障害を合併する場合やSJSからTENへ移行した場合には，後述するような集学的治療が必要となる．

II TEN

TENは発熱と共に皮膚の広範囲の紅斑と，水疱や水疱がはがれて生じるびらんを体表面積の10%以上に来す疾患である．原因のほとんどが薬剤である．

SJSとTENは，現在のところ同じスペクトラムにある病態と考えられている．事実，TENの多くの症例は皮膚粘膜移行部の粘膜障害を伴い，SJSの皮膚所見が拡大し，10%以上の罹患面積となる．しかし，TENの一部の症例は皮膚障害のみで粘膜障害を示さない．

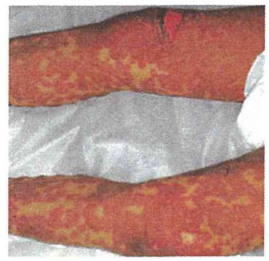

図3　中毒性表皮壊死症（スティーブンス・ジョンソン症候群進展型）
スティーブンス・ジョンソン症候群から進展した．紅斑はすべて水疱となり，融合してきている．

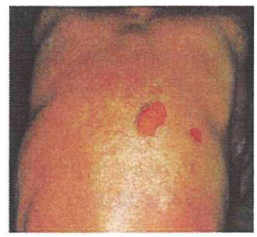

図4　中毒性表皮壊死症（びまん性紅斑型）
びまん性の紅斑のなかに表皮剝離を来している．粘膜障害は認められなかった．

1. 疫学

日本では，人口100万人当たり年間1.3人に発症している[1]．SJSと同様に抗菌薬，解熱鎮痛薬が原因として多い．内訳は，抗菌薬ではセフェム系40%，ピリドンカルボン酸系19%，ペニシリン系19%，解熱鎮痛薬では，ロキソプロフェンナトリウム25%，アセトアミノフェン25%，イブプロフェン11%であった[1]．かつてより救命率は上昇したとはいえ，いまだ死亡率は19%にも上り[1]，処方薬以外にも市販の総合感冒薬や鎮痛薬が原因となりうることは周知されるべきであろう．

2. 診断

発熱と体表面積の10%を超える水疱，表皮剝離，びらんを認めるときにTENと診断する[2]．粘膜障害を伴い，SJSから進展する場合にも（図3），進行のスピードはさまざまである．

広範囲のびまん性の紅斑から表皮剝離を来す場合（図4）には，似た臨床像をとるブドウ球菌性熱傷様皮膚症候群を除外することが必要である．

3. 治療

SJSと同様にステロイド薬全身投与を行うが，PSL換算で1mg/kg/日以上，あるいはステロイドパルス療法が必要となる．びらん面の乾燥化や紅斑の拡大停止がみられないときには，別の治療の併用を考慮する．血漿交換療法はSJSとTENに保険適用がある．二重膜濾過血漿交換よりも単純血漿交換が有効と考えられている．また，現時点では保険適用ではないが，ヒト免疫グロブリン投与もしばしば有効であり，5～20g/日で3～5日投与が推奨されている．

Ⅲ DIHS

DIHSは，発熱と多臓器障害を伴う薬疹で，経過中にヒトヘルペスウイルス6（HHV-6）を主とするヘルペスウイルスの再活性化を伴い，症状が遷延することを特徴とする．HHV-6の再活性化は，発症後2～4週間の間に確認され，発熱，肝機能障害を引き起こす．HHV-6以外にも，サイトメガロウイルスの再活性化が時に病態に関与する．

1. 疫学

DIHSの原因薬剤はいくつかの薬剤に限られている．カルバマゼピン，フェニトイン，フェノバルビタール，ゾニサミド，ラモトリギンなどの抗けいれん薬，アロプリノール，サラゾスルファピリジン，ジアフェニルスルホン，メキシレチン，ミノサイクリンが原因となる．最近，C型肝炎治療薬であるテラプレビルによるDIHSの発症が報告されている．正確な発症頻度はまだ分かっておらず，抗けいれん薬の場合，新たに薬剤を使用する1,000人に1人程度ではないかと考えられている．

薬剤以外では，工業で用いられるトリクロロエチレンが原因となることが知られている．

2. 診断

発熱，急速に拡大する皮疹，原因薬剤中止後も2週間以上遷延すること，リンパ節腫脹，血液学的異常（白血球増多，異型リンパ球の出現，好酸球増多），肝機能障害（あるいは腎機能障害），HHV-6の再活性化をもって診断する[2]．

好酸球増多を除けば，ウイルス感染症でも認められる所見であるため，かつては薬剤の関与が見逃されることが多かった．したがって，DIHSの原因薬剤の内服歴があるかどうかを確認することが最も重要である．また，2～8週間という長い投与期間を経て発症することを知っておく必要がある．

DIHSでは，HHV-6の再活性化が臨床症状の出現後2～4週に生じ，発熱と肝機能障害の再燃を生じる．HHV-6の再活性化は数日で終息するが，臨床経過はさらに遷延することがあり，そのような症例ではしばしばサイトメガロウイルスの再活性化が認められる．サイトメガロウイルス感染に至った場合，発熱，肝機能障害，消化管潰瘍，消化管出血，肺炎，心筋炎，皮膚潰瘍など多彩な病態をとる．ウイルスの再活性化はDIHSの免疫抑制を反映していると考えられ，ウイルス以外にも敗血症やニューモシスチス肺炎などの感染症を生じることがある．

3. 治療

ステロイド薬の全身投与が有効である．PSL換算で0.5～1mg/kg/日を用いる．10日ほど初期量を維持し，発熱，皮疹，全身状態が十分に改善した後に，1～2週間に5～10mgずつ減量を行う．HHV-6の再活性化により，発熱や肝機能障害の再燃を認めることがあるが，通常特別な治療を必要としない．サイトメガロウイルスの再活性化に際しては，ステロイド薬をなるべく減量し，サイトメガロウイルス感染症が生じたときには，ガンシクロビルの投与を行う．免疫抑制状態になりやすい病態を考慮し，ステロイド薬は不必要に長期大量投与とならないよう気を付ける．

おわりに

重症薬疹はまれではあるが，日常診療で用いる一般的な薬剤で生じうる．早期からの専門的治療により，後遺症や死亡例を減らすことが期待できるため，皮膚科医師のみでなく，それら薬剤を処方する医師にも重症薬疹を早期に疑う知識を有することが求められている．薬剤投与後に発熱を認めたときは，粘膜や皮膚についても異常がないか確認し，粘膜障害の程度，皮疹の拡大傾向，水疱形成の有無，あるいは臓器障害に注意し，重症薬疹を疑った時点ですみやかに専門機関に相談することが重要である．

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感染症症候群(第2版)

—症候群から感染性単一疾患までを含めて—

上　病原体別感染症編

IV. ウイルス感染症

DNAウイルス感染症

ヒトヘルペスウイルス6, 7(HHV-6, 7)感染症

薬剤性過敏症症候群

藤山幹子

Ⅳ ウイルス感染症

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ヒトヘルペスウイルス6，7(HHV-6，7)感染症

薬剤性過敏症症候群

Drug-induced hypersensitivity syndrome

藤山幹子

Key words：薬剤性過敏症症候群，drug-induced hypersensitivity syndrome，HHV-6，サイトメガロウイルス

1. 概念・定義

薬剤性過敏症症候群は薬剤アレルギーの一つの病態であり，発疹を伴うため薬疹の一型と認識されている．薬剤性過敏症症候群は従来，原因薬剤が限られており薬剤を2-8週使用した後に遅発性に発症する，原因薬剤中止後に増悪し2週間以上遷延する，多臓器障害を伴うなど，通常の薬疹とは異なる特徴を有する薬疹として認識されていたが，経過中にヒトヘルペスウイルス6(HHV-6)の再活性化を伴うことが明らかとなり，一つの疾患概念として確立された[1]．

2. 疫　　学

原因薬剤は，抗けいれん薬であることが多く，フェニトイン，カルバマゼピン，フェノバルビタール，ゾニサミド，ラモトリギンの投与をきっかけとして発症する．アロプリノール，サラゾスルファピリジン，ジアフェニルスルホン，メキシレチン，ミノサイクリンも原因となる．正確な発症頻度は不明であるが，人種間で差があることが知られている．

3. 病　　態

薬剤性過敏症症候群は，薬剤アレルギーとして始まり，遅れてウイルスの再活性化をきたす疾患である(図1)．再活性化は，HHV-6のみでなく，HHV-7，サイトメガロウイルス，EBウイルスにおいても認められることがあり，HHV-6とサイトメガロウイルスの再活性化により臨床症状を生じうる．

薬剤アレルギーの始まりの症状は，発熱か発疹であることが多い．発疹は，薬疹では最も多くみられる麻疹や風疹様の紅斑であり，次第に融合して拡大する．顔面にも紅斑を認め，強い浮腫で腫れてくる．リンパ節腫脹も特徴であり，肝脾腫がみられることもある．薬剤性過敏症症候群のほとんどの症例で肝機能障害が認められるが，アロプリノールが原因の場合には腎障害のみのこともある．血液では，白血球増多，異型リンパ球の出現，好酸球の増多のいずれかが認められる．

こられの症状が揃った後，HHV-6の再活性化が発症後10-25日までに生じる．再活性化したウイルスの量が多ければ発熱と肝障害を生じ，ウイルス血症の消失とともに軽快する[2]．HHV-6の再活性化の後，引き続いてサイトメガロウイルスの再活性化などが関与すると思われる発熱や皮疹の再燃のほか，皮膚潰瘍，腸炎，肺炎などを生じる可能性がある[3]．

HHV-6の再活性化に際し，まれではあるが中枢神経障害を生じることがある[4-6]．痙攣，意識障害，見当識障害，短期記憶障害などを生じ，髄液中にはHHV-6 DNAが証明される．死亡例の報告もある[4]．また，薬剤性過敏症症候群の経過中に発症した劇症1型糖尿病の報告が増加しているが，その一部の症例では，発症がHHV-6の再活性化の時期に一致している[7]．薬

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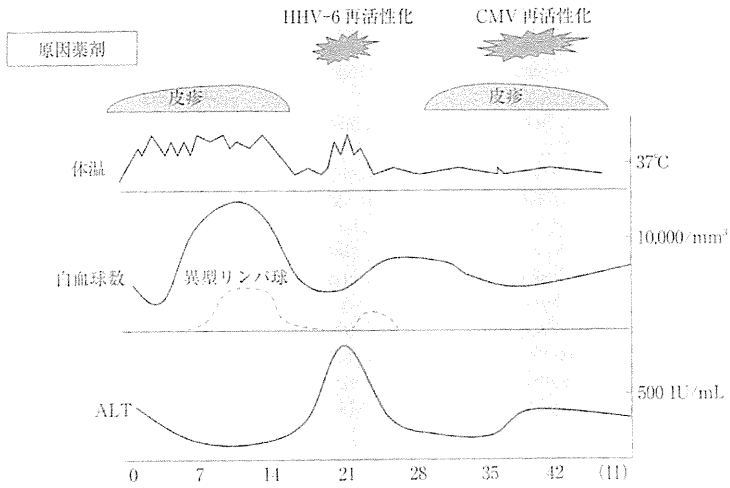

図1　薬剤性過敏症症候群の病態

原因薬剤を2-8週間内服後に，発熱や発疹で発症する．薬剤を中止しても症状は増悪し，リンパ節腫脹や白血球増多，好酸球増多，異型リンパ球が認められるようになる．肝障害も伴う．症状が鎮った後，HHV-6の再活性化を生じ，発熱や肝障害の再燃を認める．HHV-6の再活性化の後にサイトメガロウイルスの再活性化を生じることがある．

剤性過敏症症候群に発症した劇症1型糖尿病では，HLA-B62を有する症例が多い[5]．

4. 診断と鑑別診断

診断においては，薬剤性過敏症症候群の原因となる薬剤の使用歴を確認することが重要である．診断基準があり，1 限られた原因薬剤で遅発性に発症する，2 原因薬剤中止後に増悪し2週間以上遷延する，3 血液障害(白血球増多，好酸球増多，異型リンパ球の出現のいずれか)，4 肝障害(あるいは腎障害)，5 リンパ節腫脹，6 HHV-6の再活性化，をみたすと診断できる[1]．通常HHV-6の再活性化は，抗HHV-6 IgG抗体価の4倍以上の上昇をもって判断する．鑑別診断は，麻疹，デング熱，伝染性単核球症などの発疹を伴うことのあるウイルス性，感染性疾患である．

5. 治療と予後

原因薬剤の中止が重要であり，全身症状の緩和にはステロイド薬の全身投与が有効である．体重1kgあたりプレドニゾロン換算で，1日0.5-1mgを用いる．初期量を1-2週間投与し，発熱，皮疹，全身状態が十分に改善すれば，1，2週間に5-10mgずつ減量を行う．HHV-6の再活性化による症状の再燃は，通常，特別な治療を必要としない．サイトメガロウイルス感染症を生じたときには，ガンシクロビルの投与を行う．

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CORRESPONDENCE

Multiple fixed drug eruption caused by cyclophosphamide and its metabolite

Fixed drug eruption (FDE) is a cutaneous adverse drug reaction characterized by recurrence at the same skin or mucous membrane sites upon re-administration of causative drugs [1]. Cyclophosphamide is converted in the liver to an active form which can inhibit DNA synthesis and modulate immune system responses [2]. To the best of our knowledge, there have only been two reports describing cyclophosphamide-induced FDE [3, 4]. Here we report a case of multiple FDE due to cyclophosphamide, diagnosed by not only clinical features but also a patch test.

An 18-year-old Japanese woman suffering from systemic sclerosis (SSc) and interstitial pneumonia for 5 years was referred to our department because of multiple painful eruptions, mainly on her bilateral inner thighs *(figure 1A)*. At the time, she had undergone 15 courses of cyclophosphamide pulse therapy (500 mg/m^2). After the ninth course however, she developed several painful brownish annular patches about 10 h after cyclophosphamide administration. The eruptions gradually resolved with residual pigmentation but eruptions flared up at the same sites after every pulse therapy session. In addition, the number of patches increased in response to repeated administration of cyclophosphamide. She was therefore suspected of having FDE caused by cyclophosphamide. A skin biopsy of a plaque on her left inner thigh was performed, and histopathological findings were consistent with FDE *(figure 1B)*.

To make a definite diagnosis, a patch test and a lymphocyte stimulation test were performed after informed consent was obtained. Cyclophosphamide and its metabolites – cyclophosphamide monohydrate and carboxyphosphamide – were dissolved and diluted with saline to 5% and 0.5% concentrations, which were the usage concentrations of high-dose pulse therapy (5%) and diluted at 10% (0.5%) respectively, and applied to lesional skin and normal skin of the inner thigh for patch testing. After 48 h, well-defined erythema was observed on the lesional skin areas treated with the 5% cyclophosphamide and 5% cyclophosphamide monohydrate solutions but no reactions were evident on normal skin. The lymphocyte stimulation test was negative because cell proliferation was suppressed with increased drug concentration *(figure 1C)*.

This is the third report of FDE caused by cyclophosphamide. All cases occurred in patients with autoimmune disorders treated with repeated high-dose pulse therapy

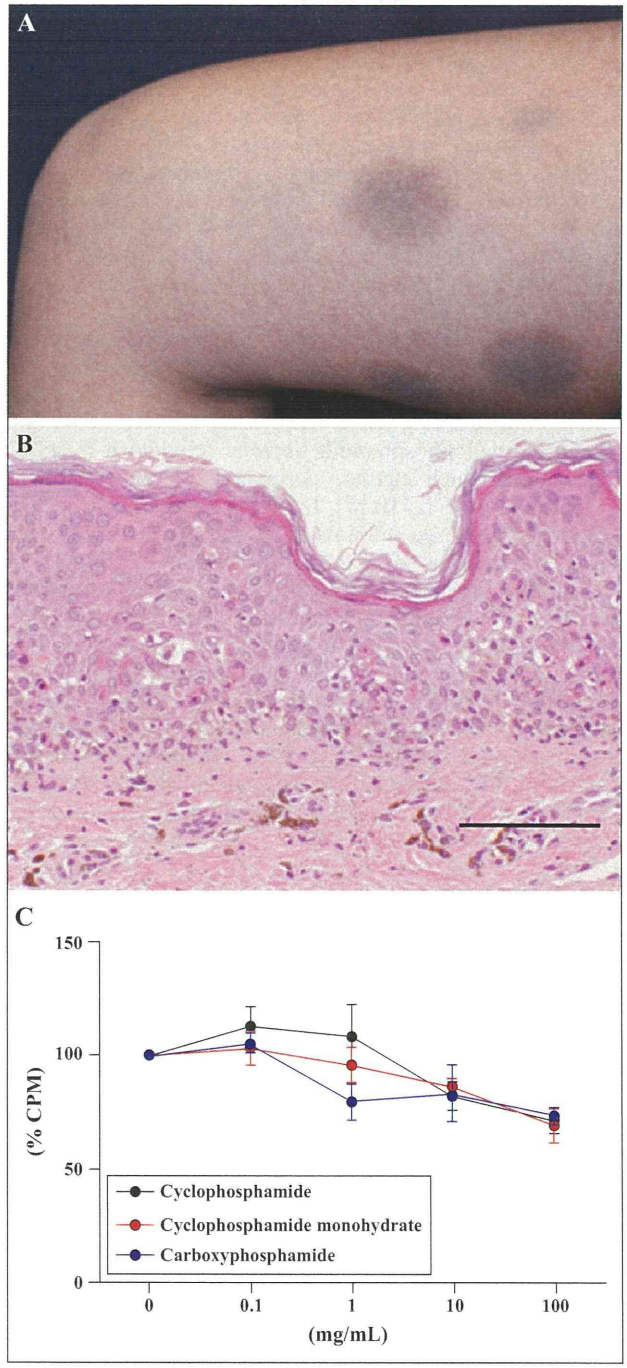

Figure 1.

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Figure 1. A) Clinical findings of FDE. Multiple annular brownish patches appeared on bilateral inner thighs about 10 hours after the administration of cyclophosphamide. **B)** Histological findings of FDE. Skin biopsy was performed from a patch on left inner thigh. Hematoxylin-Eosin stain revealed features of FDE. Scale bar represents 0.1 mm. **C)** Result of the lymphocyte stimulation test. The lymphocyte stimulation test revealed the suppression of cell proliferation with an increase in the concentration of cyclophosphamide and its metabolites. The reference level (100%) is the unstimulated condition.

after the seventh to fourteenth course in the previous cases and after the ninth course in the present case [3, 4]. Cyclophosphamide has been used for the treatment of malignancies and autoimmune disorders for a long time and it has recently been approved for the treatment of SSc in Japan. Cyclophosphamide has both cytotoxic and multiple immunomodulatory effects, whose biological activities are dose dependent. The present case was diagnosed according to the clinical course and the results of the patch tests, despite the absence of proliferation by the culprit drug and its metabolites in the lymphocyte stimulation test, which was likely due to the inhibitory effect of cyclophosphamide on DNA synthesis.

The immunomodulatory effects of cyclophosphamide influence various types of immune cells. Cyclophosphamide promotes proliferation, survival, and activation of Th1 cells which produce IFN-γ while suppressing IL-10 production. Moreover, cyclophosphamide depletes regulatory T and B cell subsets which mediate peripheral tolerance through the production of IL-10 [5]. Intraepidermal $CD8^+$ T cells, which produce large amounts of IFN-γ, play a critical role in the pathogenesis of FDE [1]. Teraki *et al.* reported that the number of $CD4^+$ and $CD8^+$ T cells capable of producing IL-10 significantly increases after oral challenge with the causative drug, suggesting that expansion of IL-10-producing T cells may be responsible for the spontaneous resolution of FDE [6]. Indeed, infiltrated intraepidermal lymphocytes were mainly positive for CD8 during the acute phase (data not shown). In addition, although the pathogenesis of SSc remains unknown, an imbalance between Th1/Th2 or Th17/regulatory T cytokines is closely involved in the development of SSc [7].

These findings can explain why FDE caused by cyclophosphamide has been reported in patients with SSc despite no case of FDE in patients with malignancy. Frequent repetitive administration of cyclophosphamide certainly increases the risk of sensitization, and especially in patients with autoimmune disorders such as SSc, the immunomodulatory effects of high-dose cyclophosphamide may suppress the peripheral tolerance which is prominently involved in IL-10, not only by increasing effector cells but also by suppressing regulatory cells. Thus, physicians who prescribe cyclophosphamide should consider the potential for adverse drug reactions. ■

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