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REVIEW ARTICLE

The role of viral infection in the development of severe drug eruptions

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ABSTRACT

The role of viral infections in the development of drug allergy has recently received increasing attention. Evidence is accumulating that immune responses to drugs can be profoundly influenced by herpesvirus infection that occurs before, concurrent with, or subsequent to drug administration. The current advances in our understanding of the role of viral infections in drug eruptions have been sparked by recent studies on human herpesvirus 6 (HHV-6) reactivation in severe systemic hypersensitivity reactions to drugs, eventually referred to as drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia with systemic symptoms (DRESS). It becomes clear that HHV-6 is not the only herpes virus reactivated during the course of DiHS and other herpes viruses are also reactivated in sequence as shown in graft-versus-host disease (GVHD), which can explain frequent deterioration or several flare-ups of clinical symptoms occurring after withdrawal of the causative drug in DiHS. Here we describe how sequential reactivations of herpesviruses occur during the course of DiHS and discuss how the reactivation events could influence the initiation and maintenance of drug-specific immune responses, resulting in severe immunopathology.

Introduction

The list of drugs causing severe drug eruptions in susceptible individuals is constantly growing and includes hundreds of pharmacologic products. It has long been speculated but not clearly shown that viruses are involved in the development of drug allergy, in particular severe drug eruptions in different ways: for example, prior viral infections could predispose genetically susceptible individuals to the subsequent development of drug allergy.[1,2] Alternatively, dysregulated immune responses to viruses have also been associated with development and/or pathogenesis of drug eruptions. Thus, circumstantial evidence is accumulating that immune responses to drugs can be profoundly influenced by viral infections that occur before, concurrent with, or subsequent to drug administration.[1–3] In this regard, herpesviruses are the increasingly recognized pathogens involved in the development of drug eruptions, because they have the ability to infect the majority of the human population, persist in a latent asymptomatic infection in various immune cells for the lifetime of the host, and be reactivated in an immunosuppressive setting: they include Epstein-Barr virus (EBV), herpes simplex virus (HSV), human herpesvirus 6 (HHV-6), HHV-7, cytomegalovirus (CMV), and varicella-zoster virus (VZV).

In this review, we focus primarily on how herpesvirus infections and dysregulated immune responses to the virus could influence the initiation and maintenance of drug-specific immune responses resulting in severe immunopathology.

Involvement of herpesviruses in drug allergy

A relationship between viral infections and the simultaneous or subsequent development of drug eruptions has been observed in a number of clinical situations. One of the well-known examples is ampicillin rash during infectious mononucleosis (IM), an acute illness which is generally the result of delayed primary infection with EBV and is characterized by pharyngitis, cervical lymphadenopathy, fever, and fatigue (Figure 1).[4] Although earlier studies reported that most IM patients, once treated with ampicillin, developed extensive maculopapular rashes in the 2nd week after the administration of the drug,[5] similar rashes have been reported to occur in IM patients who had received other antibiotics, thus indicating that ampicillin is not the sole factor. Because only 10% of patients recovered from IM showed sensitivity to ampicillin and there is a similar prevalence found in the general population, ampicillin rashes during IM are unlikely to be due to a *de novo* induction of drug antigen-specific T cells uniquely generated by

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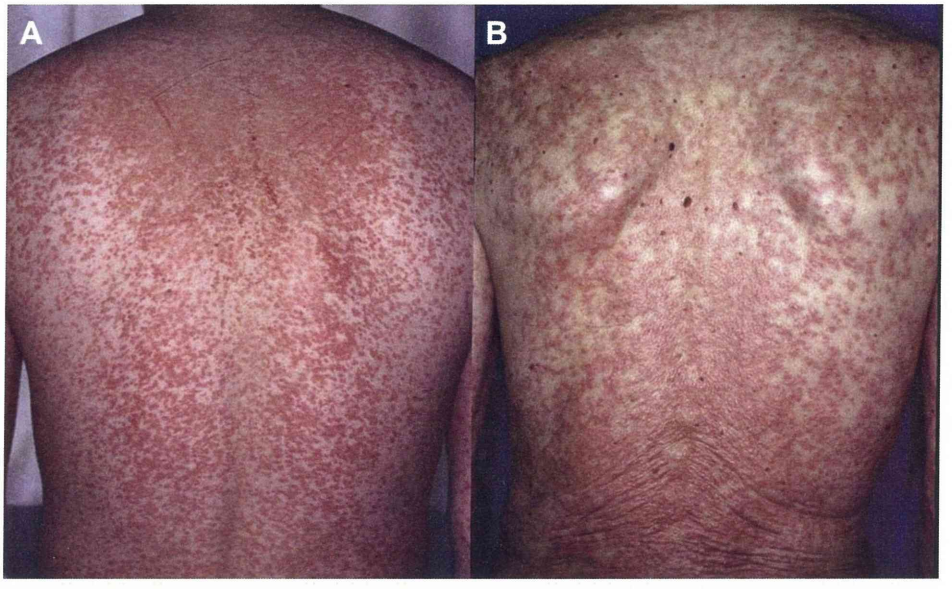


Figure 1 Clinical similarity between ampicillin rash in infectious mononucleosis (A) and drug-induced hypersensitivity syndrome (B).

ampicillin alone in the setting of delayed primary infection with EBV. In view of the observation that large expansions of activated EBV-specific $CD8^+$ T cells and increased natural killer (NK) cell numbers are observed during the disease[4] and that EBV-specific T cells have been shown to cross-react with self-human leukocyte antigen (HLA) alleles of several common HLA-B alleles,[6,7] preferential development of drug rashes during the disease may be due to a selective expansion of $CD8^+$ T cells, which are cross-reactive to the drug, from EBV-specific $CD8^+$ T cells already present in large amounts before administration of the drug. Thus, it remains unclear why only a proportion of IM patients develop drug rashes, but it may be related to the attendant release of interleukin (IL) 6, whose level showed correlation with the symptom severity of IM.[8]

Interestingly, the acute symptoms of IM resolve in 2–6 weeks, but relapse can occur in the first 6–12 months following infection,[8] a finding that can be also observed in a severe systemic hypersensitivity reaction to drug as described later. Given the similarity in sequences of clinical symptoms and clinical manifestations between IM and such a severe systemic hypersensitivity reaction (Figure 1), knowledge on the immune control of primary and persistent herpesvirus infection could be translated into clinical practice contributing to improved patient care in severe drug eruptions.

Severe systemic hypersensitivity reaction associated with herpesvirus reactivation

Fifteen years ago, we[9] and Dr. Hashimoto's group[10] independently published landmark studies that sparked the current advances in our understanding of the role of viral infections in drug allergy. These initial studies detected HHV-6 DNA by polymerase chain reaction (PCR) in blood and skin specimens from patients with the severe systemic hypersensitivity reaction to drug, eventually referred to as drug-induced hypersensitivity syndrome (DiHS). DiHS, also referred to as drug reaction with eosinophilia with systemic symptoms (DRESS), represents the opposite end of a spectrum of severe drug eruptions. The first description of DiHS is credited to Merritt and Putnam, who in 1938 reviewed the toxic symptoms caused by phenytoin and noted that the symptoms could be divided into two cutaneous reactions, a mild, mobilliform eruption and a severe, exfoliative dermatitis with fever and eosinophilia.[11] Since then, it has become clear that the latter reaction is also associated with lymphadenopathy and multivisceral involvement. Although the latter reaction was recognized as a distinct syndrome in the early 1960s, there has been much debate about the diagnosis and considerable confusion about the name of this syndrome. Although the term DRESS is still widely used to describe the clinical symptoms, we proposed the alternative term 'DiHS' based on a retrospective nationwide survey of patients in Japan[12,13]: in the survey, HHV-6 reactivations as evidenced by the significant rise in serologic immunoglobulin G (IgG) titers to HHV-6 or the detection of HHV-6 DNA in the blood were detected at a particular time point, 2–3 weeks after the onset of rash in the vast majority of patients regardless of treatment (Figure 2).[14,15] Based on the survey, a Japanese consensus group named Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR), established a set of criteria for the diagnosis of DiHS in 2006 (Table 1).[16] The clinical and laboratory features of this syndrome in its florid form are currently well recognized in Japan but there has been debate about the inconsistent and variable terminology in other parts of the world. HHV-6 reactivations can be widely used as a specific and sensitive diagnostic clue in Japan, because they are

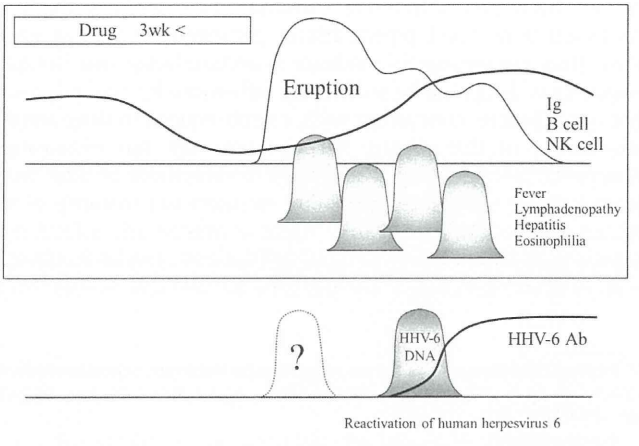


Figure 2 Typical clinical course of drug-induced hypersensitivity syndrome. HHV-6 reactivation occurs 2–3 weeks after onset despite variable clinical symptoms. HHV-6 = human herpesvirus 6.

Table 1 Diagnostic criteria for DiHS established by a Japanese consensus group.[16]

1. Maculopapular rash developing >3 weeks after starting with a limited number of drugs
2. Prolonged clinical symptoms after discontinuation of the causative drug
3. Fever (>38°C)
4. Liver abnormalities (ALT > 100 U/L)[a]
5. Leukocyte abnormalities (at least one present)
   a. Leukocytosis (>11 × 10^9/L)
   b. Atypical lymphocytosis (>5%)
   c. Eosinophilia (>1.5 × 10^9/L)
6. Lymphadenopathy
7. HHV-6 reactivation

Typical DiHS: the diagnosis is confirmed by the presence of the seven criteria above; atypical DiHS: five of the seven.
ALT = alanine aminotransferase; DiHS = drug-induced hypersensitivity syndrome; HHV-6 = human herpesvirus 6.
[a] This can be replaced by other organ involvement, such as renal involvement.

rarely detected in a milder form of this syndrome. Nevertheless, the validity has not necessarily been confirmed in other parts of the world, largely due to an extraordinarily low prevalence of this test. In this regard, we investigated whether our definite DiHS cases could fall into the category "probable/definite DRESS" defined by the DRESS validation score Kardraun SH et al proposed.[17] Our results showed that all of the definite DiHS cases associated with HHV-6 reactivations fell into the category "probable/definite DRESS", although no significant correlation was noted between HHV-6 DNA loads detected in the blood and the DRESS validation score.[18] In considering the rare detection of HHV-6 reactivations in a milder form of DiHS, which could be defined as "probable DRESS", DRESS could represent a condition ranging from a clinically milder form to a florid form of DiHS. Thus, the DRESS validation score is a useful tool for diagnosis of DiHS/DRESS when HHV-6 tests are unavailable.

DiHS typically occurs with fever and rashes 3 weeks to 3 months after starting therapy with a limited number of drugs, mainly anticonvulsants (Table 2). This delayed onset in relation to the introduction of the causative drug is one of the most important features of this syndrome that can be distinguished from other types of drug eruptions, which usually start 1–2 weeks after starting therapy. Importantly, more severe reactions often occur 3–4 days after withdrawal of the causative drug, while most other milder forms of drug eruptions spontaneously resolve: this paradoxical worsening may be mistaken for severe infectious disease. DiHS has also been reported to occur in patients receiving anticonvulsants for up to 40 years. The maculopapular or erythematous eruptions are initially observed on the face, upper trunk, and upper extremities. The cutaneous eruption usually begins as patchy erythematous macules, which may be slightly pruritic and can become confluent (Figure 1). Most erythematous eruptions do not evolve into blisters and no mucous membrane involvement is usually seen,[12,14] a finding that can be used to differentiate this syndrome form Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).[19] Fever usually precedes the rash by some or several days and temperature ranges from 38 °C to 40 °C with spikes that usually generate concern regarding an underlying infection.[14] Periorbital and facial edema with pinhead-sized pustules, reminiscent of acute generalized exanthematous pustulosis, is also one of the characteristic features of early cutaneous lesions in DiHS. Follicular accentuation of the erythematous papules is often observed in the early stage of the rash. The eruption often generalizes into severe exfoliative dermatitis or erythroderma, which usually occurs with continued treatment with the causative drug after this syndrome has developed. Lymphadenopathy can be seen in most patients (>70%), particularly early in the illness, predominantly affecting cervical nodes. Bilateral swelling of the salivary glands with xerostomia has frequently been seen, suggesting reactivation of the mumps virus. These clinical features can often be misdiagnosed as bacterial infection, which may place a substantial burden on physicians to consider unnecessary empirical antibiotic therapy, which may result in the development of additional drug hypersensitivity. This is because patients with DiHS often show unexplained cross-reactivity to multiple drugs with different structures. Other inflammatory conditions that are in the clinical differential diagnoses include measles, IM, Kawasaki syndrome, drug-induced pseudolymphoma, and staphylococcal toxic shock syndrome.[20] Variable clinical symptoms, such as liver and renal symptoms, continue to deteriorate one after another, even for weeks after withdrawal of the causative drug.

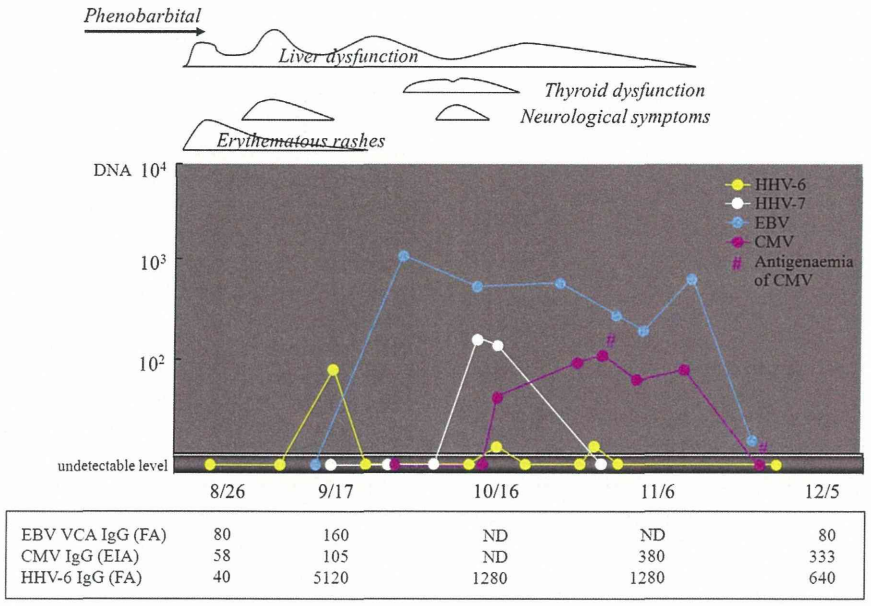
Table 2 The causative drugs of drug-induced hypersensitivity syndrome.

Carbamazepine	Allopurinol
Phenytoin	Dapsone
Phenobartital	Salazosulfapyridine
Zonisamide	Mexiletine
Lamotrigine	Minocycline

In most cases, marked leukocytosis with atypical lymphocytosis or eosinophilia of various degrees can often be seen early in the course, although leucopenia or lymphopenia may precede the leukocytosis in some cases. Depending on the drug, involvement of other organs varies: renal involvement is particularly evident in allopurinol-induced DiHS. Interstitial pneumonia with eosinophilia is often observed in patients receiving minocycline.[20] Myocarditis may also develop at onset or 40 days after onset: clinical symptoms suggestive of myocarditis include heart failure symptoms such as chest pain, unexplained tachycardia, breathlessness, and low blood pressure early in the course. We also reported a patient with DiHS who developed limbic encephalitis and the syndrome of inappropriate secretion of antidiuretic hormone long after resolution of rashes.[21] A decrease in serum IgG, IgA, and IgM levels is typically observed at onset and the lowest levels are usually detected a week after withdrawal of the causative drug. Despite such variable clinical presentations, HHV-6 reactivations can be detected at a particular time point, 2–3 weeks after onset of rash in the vast majority of patients regardless of treatment,[12,14] but not in those with other drug eruptions. Thus, this becomes a gold standard test for identifying patients with DiHS.[16] Nevertheless, it has become clear that HHV-6 was not the only virus reactivated during the course of DiHS. Recently, our studies of real-time measurements for viral loads have demonstrated that other herpesviruses are also reactivated in sequence during the course of DiHS as demonstrated in graft-versus-host diseases (GVHD).[19,22] According to our sequential analysis of viral loads, the cascade of reactivation events initiated by HHV-6 or EBV would extend, with some delay, to HHV-7 as well, and eventually to CMV (Figure 3). The magnitude of HHV-6 reactivations as evidenced by the increase in HHV-6 DNA levels was correlated well with the severity of inflammatory responses,[23] consistent with the previous observations in GVHD. Thus, frequent deterioration or several flare-ups of clinical symptoms occurring after withdrawal of the causative drug in DiHS patients can be explained by sequential reactivations of various herpesviruses in different organs, which may occur totally independently of that detected in the blood.

Mechanisms responsible for sequential reactivation of herpesviruses

Could the sequential reactivation of herpesviruses be a mere epiphenomenon of the underlying immunological disturbance in DiHS? In this regard, earlier studies suggested that DiHS represents



EBV VCA IgG (FA)	80	160	ND	ND	80
CMV IgG (EIA)	58	105	ND	380	333
HHV-6 IgG (FA)	40	5120	1280	1280	640

Figure 3 Sequential reactivations of various herpesviruses during the course of drug-induced hypersensitivity syndrome in a representative case. Occurrence of various clinical symptoms coincident with the reactivation of herpesviruses.

an exaggerated, hyperinflammatory response associated with inflammation-induced viral reactivations and subsequent organ injury.[13] According to this hypothesis, sequential reactivations of herpesviruses could simply be the consequence of drug-induced severe immunopathology and thus not represent a causal factor. Consistent with this view, viral DNA was undetectable at the early phase of DiHS in the blood; indeed, viral DNA levels such as HHV-6 and EBV were undetectable in the vast majority of DiHS patients or low in those few individuals sampled within 7 days after onset. This argues against the idea that viruses and virus-specific $CD8^+$ T cells are responsible for drug-induced immunopathology observed in the early phase of DiHS. Given the extraordinally precursor frequency of drug-reactive T cells at the early phase and the degeneracy of T cell recognition, it is perhaps not surprising that virus-specific T cells become activated following administration of certain drugs, as observed in alloreactive T cells stimulated with viral infections in GVHD.[24,25] In this regard, Picard et al have recently demonstrated that cutaneous and visceral symptoms of DiHS/DRESS are mediated by activated $CD8^+$ effector T (Teff) cells, which are largely directed against herpesviruses such as EBV.[3] Their observations suggest the possibility that herpesvirus reactivations triggered by the causative drug is an initiating event that presumably occurs well before patients become symptomatic and thus activation of $CD4^+$ and $CD8^+$ Teff cells including antiviral Teff and antidrug Teff cells, despite its early appearance after onset, appears to be a secondary event that requires and follows the prior reactivation of herpesviruses. This suggestion would be the opposite of that indicated by earlier studies. If, as suggested here, herpesvirus reactivations represent the actual initiating event in the disease process, it is logical to ask what causes the reactivation events only in susceptible patients receiving the causative drug.

Expansions of regulatory T cells in DiHS

We have recently demonstrated that the clinical phenotype of the severe drug eruptions can be determined when and how regulatory T (Treg) cell function could be impaired: in SJS/TEN, Treg function is profoundly impaired during the acute stage while expansions of functional Treg cells occur in the acute stage of DiHS and the expanded Treg cells are contracted upon clinical resolution and eventually become functionally defective.[26] Various clinical features uniquely observed in DiHS could be explained by the expansions of Treg cells. The frequencies of $CD4^+FoxP3^+$ Treg cells were preferentially increased in the blood of all patients with DiHS at the acute stage before treatment, with a peak median value that was more than three times the baseline value, without affecting their suppressive function. Because the frequencies of Treg cells remained significantly elevated even at 1 week after initial treatment with systemic corticosteroids, expansions of Treg cells are not a universal feature of systemic corticosteroid therapy that improves DiHS. Treg cells were also abundantly detected in skin lesions of DiHS, thereby limiting severe epidermal damage. By contrast, high levels of Treg cells prevent efficient clearance of viral infections by suppressing antiviral immune responses and may allow latent herpesviruses to be reactivated. In view of our preliminary observation that the causative drug has the capacity to expand not only Treg cells, but also Teff cells from DiHS patients after resolution when stimulated the peripheral blood lymphocytes (PBL), Treg cells in DiHS patients would be unique in that they can proliferate in response to relevant drug antigen. Alternatively, other immune cells such as $CD16^+$ monocytes, which may inhibit the induction and proliferation of Treg cells, may be defective in function in patients with DiHS. Thus, herpesvirus reactivations probably triggered by expansions of Treg cells are likely to activate polyclonal population of herpesvirus-specific T cells that include those that are both cross-reactive with the causative drug and noncross-reactive.

Long-term outcomes of viral reactivations

It remains unknown whether sequential reactivations of several herpesviruses could be also observed in other severe drug eruptions, and beyond the acute stage of DiHS. Our quantitative analysis of viral loads during a 2-year period after onset revealed persistently elevated EBV loads in patients with SJS during either the acute stage or long after clinical resolution: in many if not all patients with SJS, increased EBV DNA persisted for up to 2 years after onset, regardless of the clinical course and treatment. By contrast, only a fraction of patients with DiHS had increased levels of EBV

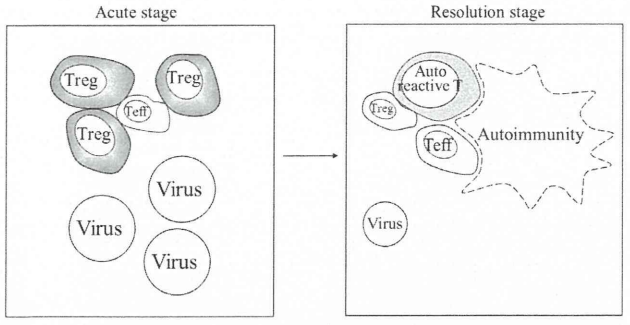


Figure 4 Viral reactivation would be triggered by expansions of Treg cells during the acute stage. Defective Treg function could be associated with the development of autoimmune disease during the resolution stage. Treg = regulatory T cell.

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.

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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

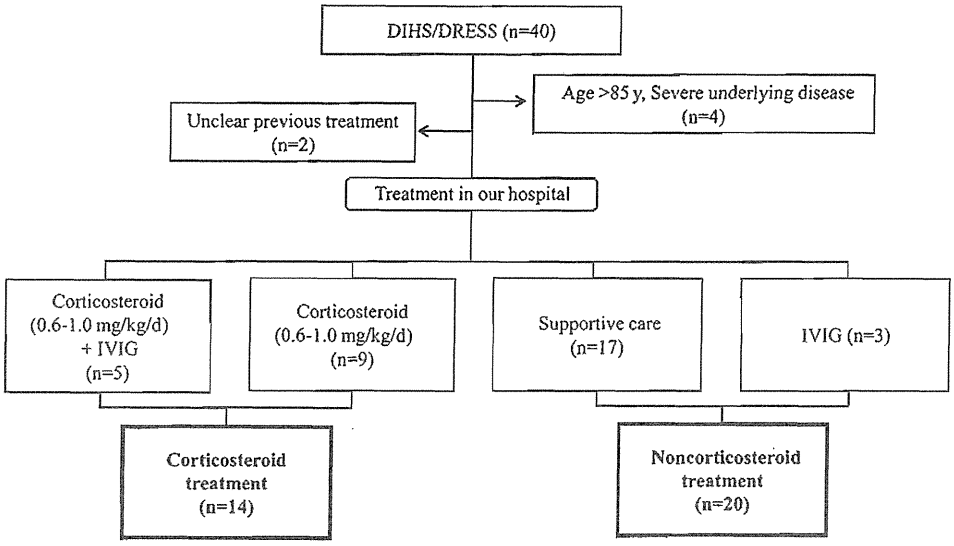

Fig 1. Patient flow diagram. Patients with drug-induced hypersensitivity syndrome (*DIHS*)/drug reaction with eosinophilia and systemic symptoms (*DRESS*) were divided into 2 groups. Administration of intravenous immunoglobulin (*IVIG*) was included in each group.

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	Corticosteroid (prednisolone) 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.

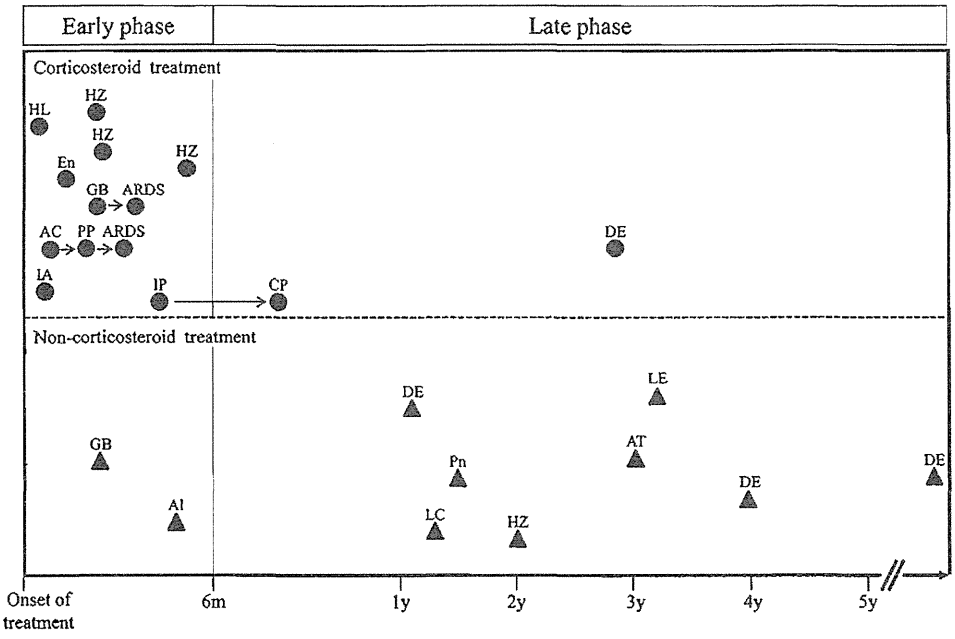

Fig 2. Complications and sequelae were classified into 2 groups in early and late phases according to treatment. *AC*, Acute cholangitis; *Al*, alopecia; *ARDS*, acute respiratory distress syndrome; *AT*, autoimmune thyroiditis; *CP*, *Cryptococcus* pneumonia; *DE*, drug eruption; *En*, encephalitis; *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 non-corticosteroid 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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薬疹の発症機序と皮膚免疫

Pathogenesis of drug eruptions and cutaneous immunity

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◎ Stevens-Johnson 症候群(SJS)/中毒性表皮壊死症(TEN)と薬剤性過敏症症候群(DIHS)は，重症薬疹の双極である．この発症機序として，HLA アリルとの関連について精力的に研究されている．しかし，この関連は薬疹の起こしやすさを決めているだけであり，臨床型を決めているのは別の因子である．そのなかで大きな因子は制御性 T 細胞(Treg)の存在である．DIHS では Treg が増大しているために発症が遅れるし，ウイルスの再活性化が起こる．それに対し SJS/TEN では Treg の機能低下により $CD8^+$ エフェクター T 細胞の過度の活性化が起こる．先行するウイルス感染は Treg の機能を一時低下させることにより，SJS/TEN を起こしやすい状況をつくりだす．このように薬疹の発症には，Treg を介してウイルスが発症のさまざまな過程に関与している．

Key word：薬疹，Stevens-Johnson 症候群(SJS)，中毒性表皮壊死症(TEN)，薬剤性過敏症症候群(DIHS)，ヘルペスウイルス

免疫の研究をはじめた当時，Burnet により提唱されたクローン選択説が絶対の真理として多くの免疫研究者に受け入れられていた．そのとき，著者が抱いた素朴な疑問は，それなら生体はどうして会うことがないはずの未知の薬剤に反応する T 細胞レパートリーをあらかじめ用意しておく必要があるのか，という点であった．それに加えて普通に生活したら絶対に会うはずのない他人のアロ抗原に反応する T 細胞を高頻度にもっている必然性も，クローン選択説ではまったく説明できない現象(厳密にいえば必ずしもそうとはいえないのであるが)と考えたものであった．

30 数年前に抱いたこの疑問はいまも著者の研究の原点になっている．このような疑問をもち続けられたがゆえに，皮疹におけるウイルスの関与も自然に考えることができたといえる．疑問をもち続けることがいかに重要か，今さらながら思う次第である．

本稿を読まれる読者の方々のなかに，Burnet には及びもつかない著者の展開する論旨に疑問をもたれる方も多いに違いない．そのような疑問が将来薬疹の世界にあらたな展開を拡大してくれることを念じつつ，稿をはじめることにしたい．

薬疹はなぜ生じるのか

ここで薬疹という場合，一部の人にのみ生じるある薬剤に対する過敏反応，すなわちアレルギー性薬疹を指すことにする．薬疹を含む薬剤アレルギーが投与された人のうちどのくらいの割合で生じるかについてはさまざまなデータがあるが，高いものでもせいぜい数%(1～8%)程度と考えられている．つまり市場に出ている薬剤は，(頻度の高いものであっても)ほとんどの人に薬剤アレルギーを生じないということになる．それでは薬剤アレルギーを生じる人はどのような要因をもっているのであろうか．

その要因としてもっとも精力的に研究されているのがHLAアリルの解析である．これについては台湾のグループが，HLA-B*1502とカルバマゼピン(CBZ)によるStevens-Johnson症候群(Stevens-Johnson syndrome：SJS)/中毒性表皮壊死症(toxic epidermal necrolysis：TEN)の密接な関係を明らかにした研究[1]からはじまっている．その後，彼らのデータはタイやインドでの研究で確認されたが，白人種ではB*1502の頻度が少ないこともあって確認されなかった．さらに，台湾のグループがHLA-B*5801とアロプロノールとの密接な関係についても報告し[2]，HLAが薬剤と薬疹の臨床型を規定しているようにみえた．つまり，あるHLAアリルを有する人に，ある薬剤による重症薬疹が生じやすいという可能性である．この仮説は，“ある薬剤”と結合しやすく，しかも“あるHLAアリル”とも結合しやすい自己ペプチドをもっている人に，“ある臨床型”の薬疹が生じやすいことを示している．しかし，この論文をつぎつぎと発表していた台湾のグループの研究者と個人的に話したとき，彼らがSJSと薬剤性過敏症症候群(drug-induced hypersensitivity syndrome：DIHS)を区別していなかった(できなかった)ことを知ったのである．

それ以来，HLAアリルは薬疹の臨床型を規定するものではないかもしれないと考えるようになった．その考えが決定的になったのが，それを裏づける著者らのデータが出たときであった．それは著者らの班会議で収集したCBZによる薬疹患者の血液を用いたHLAアリル解析の結果であった．DIHS症例を中心に，その他の臨床型の薬疹の症例も集めて解析したのであるが，結果は臨床型に関係なく，CBZによる薬疹とHLA-A*3101との関係を強く示唆するもの[3]となった．同様の結果は白人を対象とした解析[4]でも得られたことから，HLAは薬疹を起こすかどうかを決めているもっとも重要な因子であるが，DIHS，SJSなどの臨床型はHLA以外の他の要素によって決まってくるということが明らかになったのである．

それではあるHLAアリルをもつ人がすべて，その薬剤による薬疹を生じるのであろうか．しかし，これまでの解析結果はかならずしもそうはなっていない．つまり，薬剤抗原を自己のペプチドとともに認識できるT細胞を有する人すべてに薬疹が生じるわけではない．ある薬剤に反応するT細胞は，まったくその薬剤にアレルギー症状を示していない人や，それまでまったくその薬剤を摂取したことのない人にも存在しているのである．このことは，そのような薬剤特異的T細胞が存在するだけでは薬剤アレルギーは生じないこと，正常の生体にはその活性化を抑える機序が働いていることを示している．この点に関しAzukizawaらは，マウスでTENを生じさせるにはregulatory T細胞(Treg)を除いておくことが重要であることを明らか[5]にしている．おそらく正常の個体ではTregがこの薬剤特異的T細胞の活性化を防いでいるのであろう．

SJS/TENの発症機序

SJS/TENの発症機序に関しては以前から，薬剤抗原を認識するCD8$^+$T細胞の過度の活性化が表皮傷害の原因とする説が広く受け入れられている．しかし，SJS/TENでみられる表皮の広範な壊死(アポトーシス)に関しては諸説あり，いまだ決定的な見解は出されていないと考えるべきであろう．一時はFrenchらのグループが提唱した，FasLが表皮傷害のメディエータである[6]とする説が世界を席巻し，SJS/TENにおける表皮傷害の機序は結論が出たかに思われた．しかし，その後行われた追試はかならずしもFasL/FasがSJS/TENの表皮傷害のおもな機序であるとの彼らの説を支持するものではなかった．同様にChungらにより発表されたgranulysinの関与[7]についても，その後の研究はかならずしも支持するものではなかった．

これらの研究の問題点は彼らが表皮傷害のおもなメディエータとしているFasLやgranulysinはたしかに発症の早期に血清中に検出される[8]が，表皮傷害がもっとも顕著にみられる時期にはあまり検出されないというところにある．しかもSJS/TENの極期におけるもっとも有効な治療法である血漿交換は，これらのメディエータを除去することによって奏効しているわけではないことも明らかになってきたのである．本当にこれらの因子

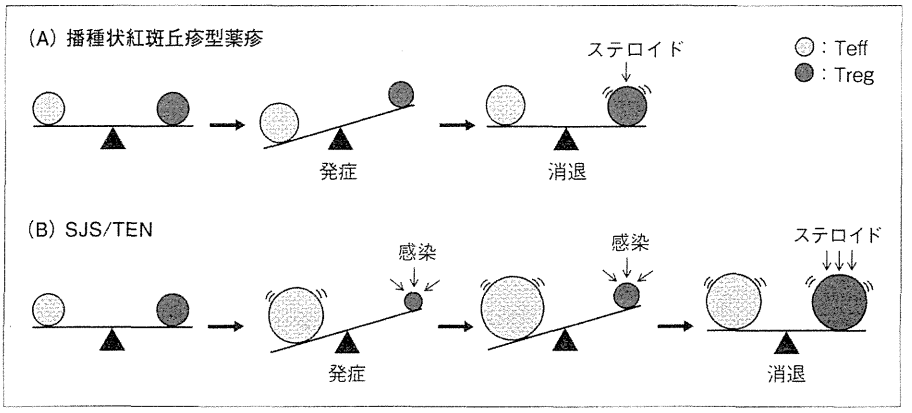

図 1　SJS/TENの発症機序

播種状紅斑丘疹型薬疹(A)ではTeffの活性化が発症をもたらすが，SJS/TEN(B)ではマイコプラズマ感染などにより生じるTregの機能低下が重要な発症因子となる．これが薬剤特異的$CD8^+$ Teffの過度の活性化をもたらす結果として，表皮の著明な傷害が生じる．

がSJS/TENにおける表皮傷害の最終的なメディエータとするなら，これらの所見は矛盾しているということになる．

しかも，これらのメディエータは，当初言われたほど，SJS/TENに特異的ではなく，他の薬疹やウイルス性疾患でも上昇がみられることが明らかになるに及び，当初の熱狂はしだいに失望へと変わっていった．つまり現時点ではまだSJS/TENの表皮傷害の本当のメディエータはわからない，とするのが正直なところなのである．

ただし，注意しなければならないのはSJS/TENのように刻々と変化する病態ではどの時点のサンプルを解析するかにより大きな差があり，典型的な表皮傷害がみられる時期になると表皮傷害に関与するようなT細胞の細胞浸潤はみられなくなるという点である．そう考えれば，早期に起こる$CD8^+$T細胞の浸潤とそれに伴うFasL，granulysin，perforin，granzyme Bなどのさまざまな細胞傷害因子の組合せが，後から生じてくる表皮傷害のメディエータの本態と考えるのがもっとも自然であろう．しかし，それではなぜ，SJS/TENでは他の薬疹と異なり，このような著明な表皮の傷害が起こるのであろうか．

それを説明するもっとも大きな鍵はTregの存在にある．Azukizawaら[5]の研究に刺激されて，多くの研究者はSJS/TENではTregが減っているのに違いないと考えた．しかし，Tregが減っているという結果はどの解析でも得られなかった．著者らはそこで，Tregの数ではなくて機能が低下しているのではないかと推測したのである．著者らの解析結果は，まさに予想どおりのことが起こっていることを示していた．すなわち，TENの極期の末梢血リンパ球(PBL)のTregの数・機能を検討したところ，Tregの数にはまったく減少はみられないのに対し，その機能は著明に低下していた[9]のである．これは，PBLだけでなく病変部局所においても，TENでは浸潤細胞当りのTreg数は著明に減少しており，TENではTregの抑制機能だけではなく，表皮への遊走機能も著明に低下していることが明らかになった．

それではTregのこの機能低下がなぜ生じるのかという点に関し，著者らはそれが基盤にある感染症に起因することを明らかにした(Takahashi，投稿中)．SJS/TENで，しばしばみられるマイコプラズマや単純ヘルペスウイルスの感染はTregの機能を著明に低下させることがわかり，これらの感染がTregの機能を一時的に低下させることにより相対的に$CD8^+$エフェクターT細胞($CD8^+$ Teff)の過度の活性化が生じ，その結果として表皮の著明な傷害がもたらされることが明らかになった(図1)．

SJS/TENのモデルとしての固定薬疹

固定薬疹(FDE)ではSJS/TENに類似した表皮