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Invited Review Article

Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019

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ARTICLE INFO

Article history:

Received 3 February 2019

Available online xxx

Keywords:

Corticosteroids

Drug-induced hypersensitivity syndrome (DiHS)

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Herpesviruses

Regulatory T cells

ABSTRACT

The aim of this review was to provide an updated overview of drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS). Several new insights have been made, particularly with regards to the diagnosis, pathogenesis and care of some important complications and sequelae. The indication of herpesvirus reactivations in diagnosis in the assessment of disease severity is now better specified. Nevertheless, because fatal complications and autoimmune sequelae have been under-recognized, there is a clear need to identify effective parameters for assessing disease severity and predicting prognosis of the disease in the early phase. In this regard, we have established a scoring system that can be used to monitor severity, predict prognosis and stratify the risk of developing severe complications including fatal cytomegalovirus (CMV) disease. Regulatory T cells are likely to be central to the mechanism and would represent potential targets for therapeutic approaches that can ameliorate inflammatory responses occurring at the acute phase while preventing the subsequent development of harmful outcomes, such as CMV disease and autoimmune diseases.

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Introduction

Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) that distinguishes it from other drug reactions is that viral reactivation characteristically follows onset of the disease.^{1–3} Its clinical manifestations in multiorgans are highly heterogeneous and follow a variable and unpredictable course beyond the point where the causative drug would be expected to be eliminated from the body,^{1–4} reflecting sequential reactivation of herpesviruses.^{5,6} Despite its association with herpesviruses, how viral infections contribute to the pathogenesis of DiHS/DRESS remains speculative. Although the nomenclature for this disease continues to evolve, the adoption of “DiHS/DRESS” has been recommended to use among many suggested names in a consensus meeting of a RegiSCAR group and Japanese investigators. Although severe cutaneous adverse drug reactions (cADRs) encompass several clinical entities, DiHS/DRESS and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) represent the opposite ends of a spectrum of severe ADRs. In 1998, we⁷ and Hashimoto's group⁸ independently reported that this syndrome was associated with human herpesvirus 6 (HHV-6)

reactivation and performed a retrospective nationwide survey of these patients in Japan: this retrospective study revealed that HHV-6 reactivation was detected in the vast majority of patients with this syndrome.⁹ We eventually established the diagnostic criteria for DiHS in 2006, including HHV-6 reactivation¹⁰ (Table 1). Although HHV-6 reactivation can be widely used as a specific and sensitive diagnostic clue in Japan and also in EU, the validity of this test has not necessarily been confirmed in other countries largely due to the lower availability of this test in these countries. Because of the lower availability of this test, the RegiSCAR criteria for DRESS do not list HHV-6 reactivation as an essential test for the diagnosis of DRESS^{11,12} (Table 2). According to our retrospective nationwide survey of DiHS patients, DiHS and DRESS could be part of a continuum of the same disease although DRESS may represent a condition including a clinically milder form of DiHS. In this regard, our retrospective study has clearly demonstrated that HHV-6 reactivation can be detected in the majority of probable/definite DRESS patients diagnosed by the DRESS validation score.¹³ This article summarizes the epidemiology, diagnosis, pathogenesis, and also described efforts to develop rational treatments for the disease.

Epidemiology

DiHS/DRESS is much more common than SJS/TEN; its true incidence, however, remains unknown because many cases may

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Peer review under responsibility of Japanese Society of Allergology.

<https://doi.org/10.1016/j.alit.2019.03.006>

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Table 1
Diagnostic criteria for DRESS by the RegiSCAR.²⁰

1. Acute rash
2. Reaction suspected drug-related
3. Hospitalization
4. Fever ($>38^{\circ}\text{C}$)
5. Laboratory abnormalities (at least 1 present)
 - a. Lymphocyte above or below normal
 - b. Low platelet
 - c. Eosinophilia
6. Involvement of >1 internal organ
7. Enlarged lymph nodes >2 sites

The first 3 criteria are necessary for diagnosis, and the presence of 3 out of the other 4.

have been undiagnosed due to its variable clinical presentation and diverse clinical features and laboratory abnormality. Although the reported incidence could be estimated at more than 10 cases per million in 1 year, the incidence would definitely rise once clinical manifestations and laboratory findings of this syndrome have become widely recognized as did in our country between 2006 and 2008.¹⁰ Many reports generally agree that DiHS/DRESS has no age or sex prediction while Kardaun *et al.* described a slight female predominance (male/female ratio, 0.80)¹²; consistent with the report, our case series also demonstrated a female predominance (male/female ratio/0.71).¹⁴ Although the incidence of DiHS/DRESS has been suggested to be highest in elderly black men,¹⁵ it remains undetermined whether a racial predilection would exist. Median age at diagnosis is approximately 51.4 years for men and 55.7 years for women (range, 0–83) and only 7% of patients are younger than 20 years.¹⁴ Our case series also showed no seasonal variations and no increased incidence of a personal and family history of atopy and drug eruption.¹⁴ According to the RegiSCAR study,¹² the frequency of previous rheumatic or collagen vascular disease could be strikingly high (8.5%), as previously reported in SJS/TEN, whereas that of cancer (5.1% vs. 10.6%) was lower than for SJS/TEN.¹² Our case series demonstrated that approximately half of the patients had the episode of an infection within the previous 1 month, particularly virus infection, consistent with the view that viruses have a critical role in the generation and activation of drug-specific T cells.^{16–18} In particular, many patients developed DiHS/DRESS several weeks after herpes zoster. These findings could be interpreted as indicating that viral infection may predisposes individuals with previous rheumatic or collagen vascular disease to develop drug-triggered immunopathology.^{16–18}

Genetic factors

Certain types of drug eruptions induced by limited drugs have been identified in several specific HLA alleles. The most important

Table 2
Diagnostic criteria for DiHS established by a Japanese consensus group.¹⁴

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 ($>38^{\circ}\text{C}$)
4. Liver abnormalities ($\text{ALT}>100\text{ U/L}$)[†]
5. Leukocyte abnormalities (at least one present)
 - a. Leukocytosis ($>11 \times 10^9/\text{L}$)
 - b. Atypical lymphocytosis ($>5\%$)
 - c. Eosinophilia ($>1.5 \times 10^9/\text{L}$)
6. Lymphadenopathy
7. HHV-6 reactivation

The diagnosis is confirmed by the presence of the seven criteria above (typical DiHS) or of five of the seven (atypical DiHS).

[†] This can be replaced by other organ involvement, such as renal involvement.

association between HLA and drug eruptions includes that between HLA-B*15:02 allele and carbamazepine (CBZ)-induced SJS/TEN¹⁹ and that between HLA-B*58:01 allele and allopurinol-induced DiHS/DRESS and SJS/TEN.²⁰ The HLA-A*31:01 has been also reported to be linked to cADRs other than SJS/TEN induced by CBZ in Japanese,²¹ Northern Europeans²² and southern Chinese populations. Evidence has linked the specific HLA alleles with the subsequent risk of developing drug eruptions, but not specific to DiHS/DRESS. We have conducted a prospective study to demonstrate whether prospective screening of HLA-A*31:01 before prescribing CBZ would reduce the incidence of the CBZ-induced drug eruptions. This pre-prescription genotyping significantly reduced the incidence of drug eruptions in the Japanese population.²³ Thus, the HLA-A*31:01 appears to be a specific marker for CBZ-induced drug eruptions but not necessarily a specific marker for CBZ-induced DiHS/DRESS. These findings suggest that the additional factors which determine whether patients have a mild form of drug eruption or develop severe cADRs, such as DiHS/DRESS, are unknown but presumably depend in large part on host immune responses other than genetic factors.

Clinical features

The disease usually starts abruptly with maculopapular morbilliform exanthema with fever of $>38^{\circ}\text{C}$, 2–3 weeks after the introduction of the culprit drug. Sometimes, there may be an upper-airway infection-like prodrome, suggesting viral infections as a possible trigger for this syndrome. The cutaneous lesions usually begin as patchy erythematous macules, pustular, target-like or eczema-like lesions, which may be slightly purpuric and can become confluent. The lesions are symmetrically distributed on the trunk and extremities. The most characteristic cutaneous lesions during the early phase are periorbital and facial edema with pinhead-sized pustules, locally simulating acute generalized exanthematous pustulosis (AGEP). Blisters are occasionally present but mainly limited to the wrists. Mucosal surfaces along with palms and soles are usually spared, but can occasionally show a few lesions, so that their involvement does not necessarily exclude the diagnosis of DiHS/DRESS; but even if present, much less severe and hemorrhagic than SJS/TEN. Lymphadenopathy can be found favoring the cervical, axillary or inguinal regions. Bilateral swelling of the salivary glands has frequently been seen early in the illness, suggesting reactivation of mumps virus. Some patients may also complain of dryness of the mouth due to severe xerostomia which makes swallowing or even taking food difficult. These symptoms usually occur 3 weeks–3 months after starting with a limited number of drugs (Table 3), mainly anticonvulsants. These signs and symptoms seem to depend more on the individual characteristics of the patient than on the causative drug.

Paradoxical worsening of clinical symptoms may occur 3–4 days after withdrawal of the causative drug; this could be mistaken for

Table 3
Drugs frequently causing DiHS/DRESS.

- Carbamazepine
- Phenytoin
- Phenobarbital
- Zonisamide
- Mexiletine
- Lamotrigine
- Dapsone
- Salazosulapyridine
- Allopurinol
- Minocycline
- Abacavir
- Nevirapine

severe infectious disease for physicians who are not familiar to this syndrome and unnecessary empirical antibiotic therapy may be started due to this high level of suspicion of infection. Such empirical therapies could increase the risk of developing additional drug reactions, because patients with DiHS/DRESS often show unexplained cross-reactivity to multiple drugs with different structures, including those used after onset. Thus, patients with DiHS/DRESS should be advised to avoid not only the causative drugs but also any antibiotics and antipyretics unless there is definite evidence for infection. More importantly, relapses or flare-ups of these symptoms frequently occur even days ~ weeks after withdrawal of the original causative drug. Although second drugs including antibiotics and antipyretics used after onset have been erroneously reported as the causative drug, they are not the causative drug responsible for onset of the initial signs and symptoms of DiHS/DRESS. Most antibiotics and antipyretics are likely to represent such second drugs, at which time the initial signs and symptoms of DiHS/DRESS may have been mistaken for an infection.

Laboratory findings

Leukocytosis with atypical lymphocytes and eosinophilia of various degree are unique features of the early phase of DiHS/DRESS, although leukocytopenia can occasionally precede leukocytosis. A recent RegiSCAR study has shown that transient eosinophilia was far more often present (95%) than is usually reported.¹² However, because eosinophilia may often be delayed for 1–2 weeks and even after elevations in liver enzymes return to baseline, frequent monitoring of eosinophilia may be needed not to overlook the transient eosinophilia. The significant decrease in the frequencies of CD56⁺NK cells and CD 19⁺B cells and the marked increase in the frequencies of CD4⁺ CD25⁺ FoxP3⁺ regulatory T cells (Tregs) are specifically found at the acute phase; upon clinical resolution, their frequencies have returned to baseline levels similar to those in healthy controls.^{24,25} Occasionally the number of monocytes is increased at the acute phase. Monocytes are heterogeneous populations and can be separated into distinct subsets: CD14⁺CD16[−]classical monocytes (cMOs) and CD14^{dim}CD16⁺patrolling monocytes (pMOs). pMOs have been reported to patrol the whole body for signs of infection^{26,27} and control peripheral Treg development in immune thrombocytopenia.²⁸ Surprisingly, pMOs are specifically depleted from the circulation at the acute phase and, as a result, the relative increase in the frequencies of cMOs is observed at the same phase.

The elevation in liver enzymes occurs in up to 70% of patients with DiHS/DRESS^{14,29} at the acute phase. The development of severe hepatitis with jaundice increases the risk of reported mortality²⁹ and hepatic necrosis may cause death in the setting of coagulopathy and sepsis.³⁰ In our case series, however, no patients in 55 patients with DiHS/DRESS died due to severe hepatitis.¹⁵ Variable degree of renal involvement can be seen and the mortality of DiHS/DRESS is likely to depend on the degree of renal involvement rather than hepatic involvement.¹⁴

A marked decrease in serum immunoglobulin (Ig) levels is typically observed at the acute phase, although their levels eventually return to normal upon clinical recovery³¹; at its nadir, around 1–2 weeks after onset, the Ig levels, particularly IgG levels, may fall as low as 300–600 mg/dL. Its nadir is immediately followed by transient overshooting Ig synthesis, coincident with HHV-6 reactivation. The decrease in Ig levels observed at the acute phase could be useful biomarker for DiHS/DRESS as well as HHV-6 reactivation. HHV-6 reactivation as evidenced by the significant increase in serum IgG titers to HHV-6 and the detection of HHV-6 DNA in leukocytes can be observed in the vast majority of DiHS/DRESS patients at a certain time point, 2–3 weeks after onset.^{4,5,8–10} Our

recent studies of real-time measurement for viral loads have demonstrated that other herpesviruses, such as Epstein–Barr virus (EBV), HHV-7, cytomegalovirus (CMV) and varicella-zoster virus (VZV), are also reactivated during the course of DiHS/DRESS in a sequential order as demonstrated in graft-vs-host disease (GVHD).^{6,32} Because HHV-6 reactivation can be detected in the vast majority of patients with DiHS/DRESS (>70%) as far as tested at the right timing, this becomes a gold standard test for identifying patients with DiHS/DRESS in Japan.¹⁰ According to our sequential analyses of viral loads in patients with DiHS/DRESS, the cascade of reactivation events is initiated by HHV-6 or EBV extends with some delay, to HHV-7 as well, and eventually to CMV^{6,32} (Fig. 1). Frequent deterioration or several flare-ups of clinical symptoms occurring after withdrawal of the causative drugs in DiHS/DRESS could be explained by sequential reactivations of herpesviruses, which would occur in various organs in a sequential order but totally independent of that observed in blood leukocytes: indeed, the presence of viral DNA in the blood cannot be necessarily associated with the detection of viral DNA in other organs and *vice versa*.

The acute phase of DiHS/DRESS (days 3–10) is characterized by expansions of fully functional Tregs associated with sequential reactivations of herpesviruses.^{24,25} The acute phase is followed by the subacute phase (days 11–36), characterized by a progressive loss of Treg function. During the subacute phase, the frequencies of Tregs have returned to basal levels despite their impaired function and the frequencies of pMOs have gradually restored to baseline levels observed in healthy controls, consistent with the clinical resolution. Thus, these dynamic changes in the frequencies of pMOs appear to be synchronized with a gradual loss of Treg function.²⁵

Diagnosis

Diagnosis of DiHS/DRESS can be made based on diagnostic criteria established by Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) group (for DiHS) (Table 1)¹⁰ and RegiSCAR group (for DRESS) (Table 2),¹² respectively. Although HHV-6 reactivation is not included in the diagnostic criteria for DRESS, there is no fundamental difference between the diagnostic criteria for DiHS and DRESS. Diagnosis of definite (or typical) DiHS requires the presence of seven criteria. Probable (or atypical) DiHS can be diagnosed in patients with typical presentation (criteria 1–5) but in whom HHV-6 reactivation cannot be found due to inappropriate timing of sampling and other reasons. In most patients presenting with typical clinical pictures, little

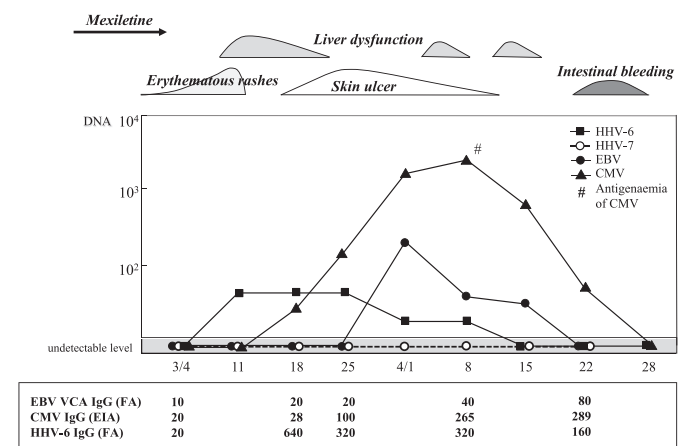


Fig. 1. Representative sequential viral DNA loads in blood of a DiHS/DRESS patient in relation to the clinical symptoms.

disagreements would exist about the diagnosis of DiHS/DRESS among dermatologists without examining HHV-6 IgG titers. However, in patients with milder clinical symptoms, diagnosis of DiHS may be challenging without the data on HHV-6 reactivation. The DRESS validation score¹² is a useful tool for diagnosis of DiHS/DRESS when the evaluation of HHV-6 is unavailable in clinical practice, because our analysis of probable/definite DRESS cases solely diagnosed by the DRESS validation score showed that HHV-6 reactivation was detected in the majority of these patients.¹³

There are a number of differential diagnostic considerations, because the clinical manifestations of DiHS/DRESS can mimic other diseases such as viral infections: they include EBV- or CMV-induced infectious mononucleosis (IM), parvovirus B19 infection, measles infection, dengue virus infection, Coxsackie virus infection, Kawasaki disease and Kikuchi-Fujimoto disease, whose patients can present with fever, skin rashes, lymphadenopathy, and internal organ involvement. In EBV- or CMV-induced IM, a morbilliform eruption, either as a primary eruption to the infection itself or as a secondary eruption after the administration of a penicillin-derived antibiotic such as amoxicillin, may appear on the trunk and upper extremities and then extending to the face. If these symptoms are present in patients on anticonvulsant therapy, those patients should be suspected of having DiHS/DRESS.

The lymphocyte transformation test (LTT) is a reliable *in vitro* method to confirm the causative drug in drug eruptions.³³ We previously demonstrated that positive LTT reactions can only be obtained at the recovery phase, 2 months after onset, but not the acute phase of DiHS/DRESS, while in SJS/TEN and other types of drug eruptions positive LTT reactions were only observed when the test was performed at the acute phase.³³ Thus, negative LTT reactions at the acute phase could alternatively be interpreted as suggesting a diagnosis of DiHS/DRESS.

Even after withdrawal of the causative drug, resolution of symptoms in one organ may be often followed by a stepwise development of other organ failures. Neurologic symptoms manifesting as limbic encephalitis, gastroenteritis, interstitial pneumonia, and myocarditis may also occur long after resolution of rashes: clinical symptoms suggestive of myocarditis include heart failure symptoms such as chest pain, unexplained tachycardia, breathlessness and low blood pressure during the early phase of disease course. Such clinical variability in the presentation and course of clinical symptoms allows for a delay in diagnosis.

Pathogenesis

Although the pathogenesis of DiHS/DRESS remains speculative, it is generally regarded as a T-cell mediated hypersensitivity reaction as in other severe drug eruptions.

If so, we have to ask why sequential reactivations of herpesviruses can be specifically observed in DiHS/DRESS, why severe epidermal damage frequently seen in SJS/TEN cannot be detected in the skin lesions of DiHS/DRESS, and why a positive LTT reaction can only be observed at the resolution phase, but not at the acute phase. Clinical pictures and outcomes of DiHS/DRESS are thought to be fundamentally different from those of SJS/TEN despite the weight of evidence for drug-specific T effector cells (Teffs) as a common principal pathogenic mediator in both diseases. While SJS/TEN is a pathogenic consequence of aberrant activation of Teffs driven by impaired suppressive function of Tregs²⁴. Thus, the difference between the two diseases appear to reside within the Tregs rather than the Teffs (Table 4). One of the puzzling characteristics of DiHS/DRESS is why Tregs are expanded at the acute phase of DiHS/DRESS. In this regard, we hypothesized that impairment of Treg-mediated immunosuppression differently observed in the two diseases could not be intrinsic to Tregs themselves but may be secondary to the

Table 4

Differences in clinical manifestations and laboratory findings in SJS/TEN and DiHS/DRESS.

	SJS/TEN	DiHS/DRESS
Onset	Abrupt (<1–2 wk)	Delayed (>3 wk)
Ig	No change	Decreased
Histology	Severe epidermal injury	No epidermal change
Virus reactivation	Usually absent or EBV	Present (HHV-6, EBV, CMV, etc)
Sequelae	Ocular changes	Autoimmune disease
LTT		
acute	+	–
resolution	–	++

paucity of signals necessary for Treg development, which can be differently regulated by different subsets of monocytes. To test this possibility, we performed a prospective longitudinal study on the frequencies of Tregs, Th17 cells and monocyte subsets after onset of DiHS/DRESS and SJS/TEN and long after their clinical resolution. During the acute phase of DiHS/DRESS (days 0–11), a marked increase was found in Tregs, particularly activated/induced Tregs (iTregs). Such expansions of Tregs (or iTregs) appear to provide a mechanism for why herpesviruses can be sequentially reactivated and why a positive LTT reaction cannot be observed at the acute phase. Upon clinical resolution, however, their frequency and number returned to values similar to those in healthy controls.²⁵ Such dramatic alterations of Tregs were not observed in patients with SJS/TEN throughout the observation period.

Importantly, clinical resolution of DiHS/DRESS was associated with a shift away from Tregs to Th17 cell differentiation. Analysis of intracellular cytokine production by various lymphocyte subsets showed that the frequencies of Th17 cells were significantly increased after clinical resolution of DiHS/DRESS as compared to those at the acute phase and healthy controls.²⁵

As described above, at the acute phase (<days 10) of DiHS/DRESS, pMOs have been specifically depleted from the circulation while cMOs were not significantly altered, causing the relative increase in the frequencies of cMOs with the potent ability to expand Tregs through the production of IL-10, which in turn direct Treg expansions^{25,28} (Fig. 2). pMOs alternatively recruited upon selective depletion of “original” pMOs during the subacute phase (days 11–36) could contribute to the shift away from a Treg to a Th17 responses, probably through their preferential production of IL-6: these alternatively recruited pMOs have been shown to have “pathogenic” features characterized by potent ability to produce IL-6, as those obtained from patients with *Mycoplasma pneumonia* (MP) infection (unpublished data). Consistent with this view, recent

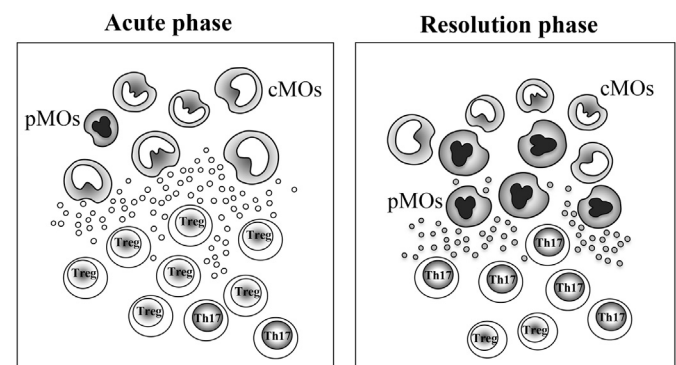


Fig. 2. The relative balance of Tregs to Th17 cells is determined by MOs. In the acute phase, iTregs are expanded by cMOs producing IL-10. In the resolution phase Th17 cells can be induced by “pathogenic” pMOs through their preferential production of IL-6. Filled nucleus indicates pMO, while open nucleus indicates cMO.

studies have shown that iTregs and Th17 cells are not at the final stage of their differentiation and have the potential to convert into Th17 cells and Tregs, respectively, depending on MO subsets.^{34,35} Given that Th17 cells can be induced by IL-6 and TGF- β and propagated by IL-23 and IL-21³⁵, the relative amounts of IL-6 and TGF- β would determine whether Th17 cells or Tregs emerge as the dominant phenotype: high IL-6 levels in the presence of low TGF- β levels could shift the Treg/Th17 balance towards a Th17 response (Fig. 2). Alternatively, recruited pMO-mediated enhancement of Th17 cell development may be inhibited by anti-IL-6 mAb and associated with the inhibition of Treg cell development. Thus, MOs from the acute phase of DiHS/DRESS are more prone to expand iTregs due to the relative increase in cMOs with the potent ability to expand iTregs to cMOs, whereas those at the resolution phase are likely to induce Th17 cell development due to reappearance of “pathogenic” pMOs preferentially producing IL-6 that may be different from the original population. This scenario may explain why a variety of autoimmune responses develop over prolonged periods of time after clinical resolution of DiHS/DRESS.

DiHS/DRESS generally occurs with greater frequency in situations where chemically reactive metabolites are accumulated due to renal or hepatic insufficiency: for example, administration of allopurinol to patients with renal insufficiency results in accumulation of the chemically reactive intermediate oxypurinol, which may cause allopurinol hypersensitivity syndrome. In addition, when initial doses of certain drugs, such as lamotrigine, overwhelm enzymatic detoxifying capacity, DiHS/DRESS could result. Co-administration of lamotrigine and valproic acid may also predispose individuals to cADRs including DiHS/DRESS by overloading the detoxifying capacity.

Polymorphisms in genes encoding drug metabolizing enzymes, such as cytochrome P 450 enzyme and N-acetyltransferase, may also participate in the pathophysiology of DiHS/DRESS. Patients with a low N-acetylating capacity are predisposed towards the development of severe cADRs.

Management

The prognosis of DiHS/DRESS, either short-term or long-term, is highly variable and unpredictable. Complications occurring during DiHS/DRESS have been extensively described in previous studies and have received attention as the cause of mortality in DiHS/DRESS. These complications include myocarditis, *Pneumocystis jirovecii* pneumonia, sepsis, and gastrointestinal bleeding,^{36–42} most of which led to significant morbidity and mortality if unrecognized and

untreated. Therefore, the establishment of a scoring system using routinely obtained parameters by which disease severity and treatment efficacy can be assessed at any time and disease progression to more aggressive stage can be predicted is urgently needed for the successful management of DiHS/DRESS. Based on our case series (n = 55), a composite score was created using demographic data, medical history, and clinical variables (Table 5). The mean age of our case series was 54.5 ± 20.0 years.¹⁴ Clinical symptoms of DiHS/DRESS developed 44.0 ± 6.9 days after starting the culprit drugs. Most patients were followed longitudinally for >1 year after clinical resolution. By comparing the composite score in the early phase (days 0–3) with that at any time after starting therapy, the composite score can provide clinicians with clue for optimizing therapeutic efficacy and preventing treatment-related relapse. In addition to the utility of the scoring system for monitoring the extent of disease severity, our report supports the potential use of this scoring system for identifying individuals with a likelihood of CMV reactivation and complications, either CMV-related or CMV-unrelated, with fatal outcomes.¹⁴ Of the 55 patients investigated for the presence of CMV DNA in sequential blood samples by polymerase chain reaction (PCR) or antigenemia assay, 44 remained quantitatively CMV[−] throughout the period of surveillance. In CMV⁺ cases, who were quantitatively CMV PCR- or antigenemia-positive, CMV DNA or antigenemia was initially detected at 17.2 days (mean) after the initial presentation. CMV⁺ DiHS/DRESS cases were significantly older and had more complications associated with a fatal course. CMV⁺ cases were found to run a more severe and protracted course, as evidenced by longer period of hospitalization. Five of 11 CMV⁺ patients, developed CMV disease or –related complications, while the remaining 6 patients had no evidence of CMV disease and –related complications at any time. Most importantly, none of the 44 CMV[−] patients developed any late-onset complications. CMV disease, such as enterocolitis, or complications developed immediately after the detection of CMV reactivation (mean, 33.2 ± 6.2 days after the initial presentation) in all cases, usually 10.0 ± 4.8 days after the detection of CMV reactivation. DiHS/DRESS patients were also stratified into 3 groups, mild (score <1), moderate (score 1–3) and severe (score 4–6), based on early or late scores to predict the risk of complications. Scores ≥ 4 points were associated with the later development of CMV disease and complications, while no patients with scores <4 developed any complication¹⁴ (Fig. 3).

Systemic corticosteroids have been accepted as the gold standard treatment for ameliorating clinical symptoms of DiHS/DRESS at the acute phase. Rapid resolution of rashes and fever occur within several days after starting systemic corticosteroids. The usual dosage

Table 5

Composite scores for evaluating the severity of drug-induced hypersensitivity syndrome and drug reaction with eosinophilia and systemic symptoms (DiHS/DRESS) and predicting the disease outcomes.

Score	−1	1	2	3
Fixed parameters				
Age (yr)	≤ 40		≥ 75	
Duration of drug exposure after onset		≥ 7 days		
Allopurinol exposure		Yes		
Variable parameters[†]				
Prednisolone intake			Pulse	
Skin involvement				
Erythematous rashes (% body surface area)		$\geq 70\%$	Erythroderma	
Erosive lesions (% body surface area)		10–29%		$\geq 30\%$
Fever ≥ 38.5 °C (duration)		2–6 days	≥ 7 days	
Appetite loss		≥ 5 days with $\leq 70\%$ of regular food intake		
Renal dysfunction (creatinine, mg/dl)		1.0–2.0		≥ 2.1 or HD
Liver dysfunction (ALT, IU/l)		400–1000	≥ 1001	
C-reactive protein (mg/dl)	≤ 2	10–15	≥ 15.1	

Abbreviations: ALT, alanine aminotransferase; CMV, cytomegalovirus; HD, hemodialysis.

[†] Each variable parameter was determined at early (day 0–3 after initial presentation) and later times (2–4 weeks after initial presentation) and on an as-needed basis.

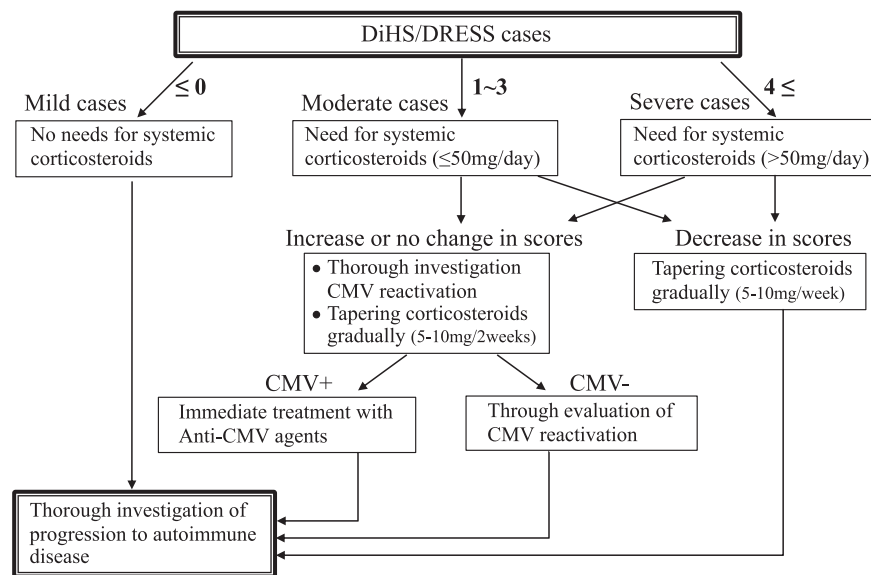


Fig. 3. Proposed flow diagram for diagnosis and prognostication of DiHS/DRESS based on early and late scores.¹⁴

is prednisolone, 40–50 mg/day. Systemic corticosteroids, however, need to be tapered over 6–8 weeks to prevent the relapse of various symptoms of this syndrome and thus are administered for 2–3 months: once systemic corticosteroids have started, drug dose should be reduced gradually even upon resolution of clinical manifestations. This is because patients with DiHS/DRESS are at greater risk of subsequently developing the wide spectrum of immune reconstitution inflammatory syndrome (IRIS) ranging from CMV disease to autoimmune disease⁴³: IRIS is an increasingly recognized disease concept and is observed with a broad-spectrum of immunosuppressive therapy-related opportunistic infectious disease.⁴³ Clinical illness consistent with IRIS includes tuberculosis, herpes zoster, herpes simplex, CMV infection, sarcoidosis, and DiHS/DRESS. Thus, the manifestations of IRIS are diverse and depend on the tissue burden of the preexisting infectious agents during immunosuppressive state. Although IRIS has originally been described to develop in the setting of HIV infection, it becomes widely accepted that the development of IRIS can also be in HIV-negative hosts receiving immunosuppressive agents, such as prednisolone and tumor necrosis factor- α (TNF- α) inhibitors upon their reduction or withdrawal. Given that the causative drugs of DiHS/DRESS have in common immunosuppressive potential to inhibit the differentiation of B cells to Ig-producing cells^{4,16,17,31} and that paradoxical worsening of the clinical symptoms after withdrawal of such drugs is associated with a reduction of viral loads in DiHS/DRESS at the acute phase, it is attractive to suppose that DiHS/DRESS may be another manifestation of the newly recognized IRIS.⁴³ Thus, discontinuation or rapid tapering of prednisolone therapy as well as the withdrawal of the causative drugs with immunosuppressive potential in DiHS/DRESS may be a risk factor for the new development of IRIS, although symptoms may be subclinical at the onset. It should be recognized, therefore, that the use of systemic corticosteroids represents an important factor that increases the risk of disease progression to the full manifestation of IRIS upon withdrawal or reduction of systemic corticosteroids.

In support of this view, CMV reactivation as well as relapses and worsening of clinical symptoms was observed with reduction of corticosteroid dose in our case series. In addition, previously reported cases suggest that the use of pulsed prednisolone may be related to later development of CMV reactivation.¹⁴ Although pulsed corticosteroids or high doses of intravenous

immunoglobulin (IVIG) are shown to be effective in abrogating the acute inflammation of DiHS/DRESS, previously reported cases including our own^{44,45} suggest that such aggressive therapies, particularly in pediatric patients, may paradoxically increase the risk of future development of autoimmune sequelae, particularly type III polyglandular autoimmune syndrome (PAS III): in literature review, five patients with DiHS/DRESS were found to develop autoimmune sequelae consistent with PAS III 2–7 months (average, 4.8 months) after onset of DiHS/DRESS.⁴⁵ Importantly, four out of the 5 patients were treated with pulsed prednisolone or IVIG in the acute phase of DiHS/DRESS.⁴⁵ The timing of these aggressive therapies at the peak of severe liver damage suggest that this could further accelerate the rapid recovery of B cells, thereby causing the subsequent expansions of autoreactive B cells with the specificity to a variety of epitopes including self antigens. To prevent a rapid immune recovery, we recommend that systemic corticosteroids be initiated at a sufficient dose of 40–60 mg/day prednisolone equivalent in DiHS/DRESS and be gradually tapered over >8 weeks. The dose should be slowly and gradually tapered down during a period of 4–8 weeks according to the severity scores of the patients (Fig. 3).

Because previous studies indicated that CMV reactivation could be the cause of several complications, such as gastrointestinal bleeding, renal dysfunction, myocarditis, and sepsis,^{36–40} it is likely that fatal complications occurring in the late phase of DiHS/DRESS could be preventable with anti-CMV therapy. In support of this possibility, fatal outcomes were found exclusively in CMV⁺ cases, especially those in whom anti-CMV therapy was initiated ≥ 3 days after the detection of CMV reactivation, while most cases in whom anti-CMV therapy was started within 2 days after CMV detection recover fully, indicating a great need for starting anti-CMV therapy immediately.¹⁴ Importantly, anti-CMV therapy is effective in preventing the development of not only overt CMV disease but also complications that are generally regarded as being CMV-unrelated. Our data concur with previous observations that anti-CMV therapy may have been also effective at curtailing the risk of other herpesviruses-related complications.

Because inflammation associated with severe tissue damage is thought to be the underlying or preceding events for the subsequent development of autoimmune diseases, severe cADRs associated with severe tissue damage would be accompanied by a

heightened risk of developing some autoimmune diseases. In view of our recent observations that Treg function became gradually defective after clinical resolution (days 11–36 after onset) immediately after the peak of severe liver damage in DiHS/DRESS,²⁵ severe liver damage and a defective Treg function need to be delivered sequentially but not concomitantly to get optimal generation of autoantibodies. Interestingly, our frequent monitoring of viral loads from the early to late resolution phases of DiHS/DRESS revealed that EBV DNA loads were significantly lower in the patients treated with systemic corticosteroids than those without them.³² Given the ability of EBV to act as a trigger for the subsequent development of autoimmune diseases, early intervention by systemic corticosteroids may lead to better long-term outcomes for DiHS/DRESS patients at risk of subsequently developing autoimmune responses,⁴⁶ probably by reducing EBV DNA loads. Because a gradual loss of Treg function occurring after resolution of DiHS/DRESS could increase the risk of developing autoimmune sequelae, systemic corticosteroids administered during the acute phase may have served to prevent not only tissue damage but also the gradual loss of Treg function by restoring the impaired Treg activity. These studies illustrate the complexities in assessing the efficacy of any therapeutic modality at the acute phase of DiHS/DRESS.

Conclusion

Here, we have highlighted several emerging views about the diagnosis, pathogenesis and management of DiHS/DRESS. Although great strides have been made in our understanding of the natural history of the disease, we can still learn important lessons from assessment of immune responses occurring in the acute and late convalescent phases of DiHS/DRESS, respectively. The extent to which the disease may eventually contribute to the development of autoimmune diseases is of growing concern. Systemic corticosteroids continue to be highly successful in the treatment of DiHS/DRESS, but a small portion of patients fail to respond to therapy. Considerations for the development of therapies that can reduce the risk of developing fatal complications and subsequently developing autoimmune diseases in patients with DiHS/DRESS would seem a reasonable path to pursue.

Acknowledgements

This work was supported in part by grants from the Ministry of Education, Culture, Sports, Science and Technology (to T.S.: 24390276) and the Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare of Japan [H26-nanchi(nan)-ippan-081] (to T.S.), and JSPS KAKENHI Grant Number JP 19K08755 (to YM).

Conflict of interest

The authors have no conflict of interest to declare.

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