Drug reaction with eosinophilia and systemic symptoms: A drug-induced hypersensitivity syndrome with variable clinical features

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A R T I C L E  I N F O

Article history:
Received: Jul 6, 2013
Revised: Sep 15, 2013
Accepted: Sep 24, 2013

Keywords:
allopurinol autoimmune diseases eosinophilia hypersensitivity Stevens–Johnson syndrome

A B S T R A C T

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) involves a unique and severe adverse drug reaction. Patients present with fever, rash, lymphadenopathy, hematological abnormalities, systemic illness, and may suffer from prolonged courses. Although the precise pathogenesis of DRESS/DIHS is not fully understood, it is widely considered to be an immunological reaction to a drug or drug metabolites. In this review article, we discuss the historical aspects of nosology, variable clinical and histopathological features, advantages and disadvantages of using an international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) and Japanese DIHS criteria, pathogenesis, treatment, and long-term sequelae of DRESS/DIHS. Early recognition of this syndrome, withdrawal of suspected culprit drugs, and adequate supportive care are mainstays of improving patient prognosis and reducing morbidities and mortality. Moreover, some DRESS/DIHS patients may develop long-term sequelae, especially autoimmune diseases and end organ failure. Physicians should be aware of these possibilities in patients after DRESS/DIHS and cautiously follow-up symptoms and laboratory tests for early detection of these sequelae.

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Introduction

Adverse reactions to drug therapies are a concern for all medical personnel and also for the general public. Drug complications are the most common type of adverse event during hospitalization and the skin is one of the organs most often affected. According to the literature, cutaneous adverse drug reactions affect 2–3% of hospitalized patients. Fortunately, most of these reactions present as benign maculopapular exanthema or urticaria. However, severe cutaneous adverse reactions (SCARs) affect about 1 of every 1000 inpatients.

SCARs to drugs are groups of idiosyncratic hypersensitivity reactions with a heterogeneous clinical presentation. Two of the most notorious SCARs are Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) due to their rapid progression and high morbidity/mortality rates. With extensive reporting and better education of physicians and patients, the incidence of both has gradually decreased. Recently, another SCAR has begun to attract attention due to its unique clinical features and unknown pathogenesis: drug reaction with eosinophilia and systemic symptoms (DRESS); its description reflects the typical presentation of rash, hematologic abnormalities, and systemic illness.

This peculiar syndrome was first reported in the literature in 1937, where it was described as exfoliative dermatitis following administration of sulfanilamide. Until 1950, systemic complications of this drug hypersensitivity, such as lymphadenopathy and visceral involvement, had been widely reported. After this, an increasing number of patients presenting with similar but variable manifestations received diagnoses defined by the drugs that caused the reaction, including phenytoin hypersensitivity, dapsona hypersensitivity (sulfone syndrome), allopurinol hypersensitivity syndrome, and anticonvulsant hypersensitivity syndrome. Because lymphadenopathy was commonly reported in these patients, the term “drug-induced pseudolymphoma” was once confusedly used to describe such condition but then was superseded by “drug-induced hypersensitivity syndrome” (DIHS) to differentiate its acute systemic symptoms from pseudolymphoma. These systemic hypersensitivity syndromes were renamed as “drug rash with eosinophilia and systemic symptoms.”
in 1996,14 but drug “reaction” was later used because of the variation of cutaneous involvement.

Even now, the underlying mechanisms of DRESS/DIHS are only partially understood and many issues about this controversial entity are still being debated. In this article, we will re-examine this severe drug eruption and add new information to help clarify some unrevealed topics about DRESS/DIHS.

Clinical presentation and pathological findings

Clinical symptoms and laboratory findings

DRESS/DIHS symptoms typically occur 2–6 weeks14 after drug intake; however, reactions may not develop until 3 months later, especially when the syndrome is induced by allopurinol.15 A high, spiking fever (usually >38°C) and rash are usually the first signs, and these are followed by other systemic reactions such as cervical, axillary and inguinal lymphadenopathy, arthritis, or general malaise. The rash begins as a nonspecific morbilliform eruption (Figure 1A), which is indistinguishable from other less severe drug reactions, but can progress to a generalized form or even to erythroderma (Figure 1B). Facial and acral edema with periorbital reactions, but can progress to a generalized form or even to DRESS/DIHS symptoms typically occur 2

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involvement rate. However, although the prevalence of hepatitis B virus infection (HBV) is high in Taiwan, the hepatic involvement rate in Taiwan DRESS patients did not absolutely exceed that of other countries. Besides, we found that DRESS/DIHS patients with HBV or HCV infection did not tend to have hepatic involvement. This indicates that chronic HBV or HCV infection may not be a risk factor for liver involvement. Fortunately, most patients recovered from hepatic injury spontaneously, and death from hepatic failure is seldom reported in Taiwan.

Diagnostic criteria and differential diagnosis

Because of the diverse cutaneous presentation and variable systemic involvement, diagnosing DRESS/DIHS is often challenging. In fact, even within the past decade, the existence of this “syndrome” was still being debated. However, discussion and worldwide research efforts have helped identify additional characteristics to improve diagnosis. Most experts agree that DRESS/DIHS has some special features, including delayed onset and prolonged courses,

Figure 1 Clinical presentations of DRESS/DIHS. (A) The skin rash of DRESS usually begins as a nonspecific morbilliform eruption, which is indistinguishable from other less severe drug reactions, but it can then progress to (B) a generalized infiltrated form or even to exfoliative dermatitis (erythroderma). (C) Typical skin lesions for DRESS are facial edema, (D) confluent and infiltrated plaques, (E) purpuric change, and (F) psoriasiform desquamation as a late stage manifestation. (G) Pin-head sized pustules and (H) atypical target lesions may also be observed. (I) Mucosal regions can be involved in DRESS/DIHS but are usually mild as cheilitis.
frequent multiple organ involvement, and sequential HHV reactivation. Better isolation and clarification of this hypersensitivity syndrome also helps physicians manage these patients and predict their clinical course and prognosis. Prior to making the diagnosis of DRESS/DIHS, clinicians should always rule out other conditions, especially infection or autoimmune diseases. In order to establish the correct diagnosis, patients’ symptoms, along with many asymptomatic signs, should be carefully surveyed.

**Diagnostic criteria**

Although there is still no universal consensus about the definition of DRESS/DIHS, two diagnostic criteria are mainly adopted. The international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group has suggested a series of inclusion criteria for suspicious DRESS cases, in which hospitalized patients with a reaction suspected to be drug related must have at least three of the following systemic features: acute skin rash; fever above 38 °C; enlarged lymph nodes; internal organ involvement; and hematological abnormalities, including lymphocytosis or lymphocytopenia, eosinophilia, and thrombocytopenia. Furthermore, a scoring system should be applied to diagnose an included case as DRESS, depending on individual final scores (Table 2). The strength of the RegiSCAR criteria lies in selecting patients with a varied phenotype and making an attempt to exclude other conditions that mimic DRESS. Disadvantages include the need for hospitalization and a lengthy process involving many laboratory tests that are not always readily available. Some cases might be falsely validated as noncases because of inadequate information. Application of these criteria may be limited in a hospital-based setting or used only in expert meetings. Moreover, people who are not familiar with criteria in the RegiSCAR DRESS scoring system may overestimate the value and misclassify no/possible cases to probable/definite cases. Therefore, detailed information about how to apply the RegiSCAR DRESS scoring system is provided in Table 2.

By contrast, the Japanese consensus group established another set of criteria, with the inclusion of HHV-6 reactivation as a diagnostic criterion for DIHS (Table 3). If all criteria are present, especially evidence of HHV-6 reactivation, the diagnosis of typical DIHS is made; otherwise, atypical DIHS is diagnosed when the first five criteria are present. Compared to the RegiSCAR criteria, the Japanese criteria are more easily applied by general physicians or...

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**Table 1** Comparison of clinical features of drug reaction with eosinophilia and systemic symptoms in different studies.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Peyrière et al/ France</th>
<th>Tohyama et al/ Japan</th>
<th>Chen et al/ Taiwan</th>
<th>Walsh et al/ UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top three common culprit drugs</td>
<td>Aromatic anticonvulsants, abacavir, nevirapine</td>
<td>Aromatic anticonvulsants, allopurinol, me GLUT</td>
<td>Allopurinol, aromatic anticonvulsants, dapsone</td>
<td>Aromatic anticonvulsants, minocycline, sulfasalazine</td>
</tr>
<tr>
<td>Fever</td>
<td>69</td>
<td>90</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Skin eruption</td>
<td>Morbilliform exanthem</td>
<td>Morbilliform exanthem</td>
<td>Morbilliform exanthem</td>
<td>Erythematous papules</td>
</tr>
<tr>
<td>Lymphadenopathya</td>
<td>18</td>
<td>54</td>
<td>31</td>
<td>88</td>
</tr>
<tr>
<td>Eosinophiliaa</td>
<td>57</td>
<td>57</td>
<td>52</td>
<td>93</td>
</tr>
<tr>
<td>Atypical lymphocytesa</td>
<td>7</td>
<td>75</td>
<td>63</td>
<td>NA</td>
</tr>
<tr>
<td>Hepatic involvementa</td>
<td>52</td>
<td>34</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Renal involvementa</td>
<td>10</td>
<td>NA</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Mortalitya</td>
<td>10–40</td>
<td>5</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

Data are presented as %.

EM = erythema multiforme; NA = not available.

* Incidence.
Table 2: Scoring system of RegiSCAR for diagnosing drug reaction with eosinophilia and systemic symptoms (DRESS).

<table>
<thead>
<tr>
<th>Assessment/Score</th>
<th>−1</th>
<th>0</th>
<th>1</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥ 38.5°C</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td>Acute episodes</td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>No/U</td>
<td>Yes</td>
<td>Score 2 for extreme eosinophilia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Eosinophils ≥ 1.5 × 10^9/L or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥20% if leukocyte &lt; 4.0 × 10^9/L</td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td></td>
<td></td>
<td></td>
<td>Onset &lt; 21 days prior to hospitalization</td>
</tr>
<tr>
<td>Extent &gt;50% body surface area</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash suggesting DRESS</td>
<td>No</td>
<td>U</td>
<td>Yes</td>
<td>≥2 symptoms: purpuric changes (other than legs), facial edema, infiltration, psoriasiform desquamation</td>
</tr>
<tr>
<td>Biopt suggested DRESS</td>
<td>No</td>
<td>Yes/U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ involvement</td>
<td></td>
<td></td>
<td>Excluding other causes, score maximum of 2</td>
<td></td>
</tr>
<tr>
<td>Liver: any 1 criterion</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney: any 1 criterion</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung: any 1 criterion</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle/Heart: any 1 criterion</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other organs</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash resolution ≥ 15 days</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding other causes</td>
<td>No/U</td>
<td>Yes</td>
<td>Score 1 if ≥3 tests are performed and negative</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A, B, C</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td>At least 2 tests are negative and 1 U: negative</td>
</tr>
<tr>
<td>Mycoplasma/chlamydia</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td>At least 1 test is negative and 1 U: negative</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td></td>
<td></td>
<td>Sampling within 3 days of index date</td>
<td></td>
</tr>
<tr>
<td>Final Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Final scores: <2: excluded; 2–3: possible; 4–5: probable; >5: definite. EBV/CMV and HHV6/7 are also recorded; results, however, do not influence the score. ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CMV = cytomegalovirus; CPK = creatine phosphokinase; CPK-MM = creatine phosphokinase-muscle type; CPK-MB = creatine phosphokinase-brain type; CT = computed tomography; D-bil = direct bilirubin; DRESS = drug reaction with eosinophilia and systemic symptoms; EBV = Epstein-Barr virus; ECG = electrocardiogram; EMG = electromyogram; GFR = glomerular filtration rate; HHV = human herpesvirus; MRI = magnetic resonance image; T-bil = total bilirubin; UNL = upper normal limit.

Table 3: Diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) established by the Japanese group.\(^a\)

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


\(^a\) The diagnosis is confirmed by the presence of all seven criteria (typical DIHS) or the presence of five criteria (1–5, atypical DIHS)

\(^b\) Limited number of drugs for the majority of cases in Japan includes the following eight: carbamazepine, phenytoin, phenobarbital, zonisamide, mexiletine, dapsone, salazosulfapyridine, and allopurinol

\(^c\) This can be replaced by other organ involvement, such as renal involvement.

dermatologists working in local clinics because the suggested laboratory tests are easily available, and those tests need not be repeated. However, some probable cases may not fulfill the diagnostic criteria set by the Japanese consensus group because not all well-known symptoms or signs will be present in all patients. In addition, the list of drugs associated with such hypersensitivity reaction is getting longer, not just with limited drugs. Another important issue is the discrepancy in viewing HHV reactivation between different study groups. Evidence of HHV-6 reactivation is included as a critical criterion to diagnosing typical DIHS for the Japanese consensus, but is not enrolled in the scoring system proposed by RegiSCAR group. This may explain the higher HHV-6 reactivation rate for DRESS/DIHS patients in Japanese studies (62%), compared to that in other studies adopting RegiSCAR criteria (45%), and also may help support our view of taking DIHS as a more typical DRESS. However, the definite role of viral reactivation in DRESS/DIHS is still debatable, and it has still not been conclusively explained whether the reactivation of HHV-6 and other members of the HHV family are part of the disease itself or whether they are better explained as a complication of this syndrome.

Differential diagnosis

The skin rash seen in DRESS/DIHS may be highly variable and dynamic as the disease progresses or fluctuates. When cutaneous manifestation is the first symptom, a diagnosis of maculopapular exanthem is often presumed. When patients have discernible pustules or bullous lesions, acute generalized exanthematous pustulosis (AGEP), SJS/TEN, and generalized bullous fixed drug eruption (GBFDE) should be considered in the differential diagnosis. However, the onset of skin eruption is usually delayed, and neither extensive epidermal necrolysis nor subcorneal pustules are a prominent feature of DRESS/DIHS, except in rare cases.
presenting overlaps between DRESS and other SCARs. Along with the development of fever, lymphadenopathy, or atypical lymphocytosis, acute viral infection should be considered. Primary human immunodeficiency virus, Epstein–Barr virus (EBV) infection, and reactivation of HHV-6 can all present as mononucleosis-like illness with rash and systemic symptoms. When the liver is involved, reactivation of HHV-6 can all present as mononucleosis-like illness the development of fever, lymphadenopathy, or atypical lymphocytosis.

Tests is important to optimize their benefit. Depending on induration and purpuric changes observed in skin lesions, cutaneous T-cell lymphoma or other hematological disorders and systemic vasculitis should be carefully ruled out. In addition, some DRESS patients may eventually progress to erythroderma, which makes correct diagnosis more challenging. Vasculitis with multiple organ involvement can mimic systemic drug hypersensitivity. Churg–Strauss syndrome should be taken into account, especially when patients also present with systemic eosinophilia. Other vasculitic diseases to be differentiated include Wegener’s granulomatosis, polyarteritis nodosa, and even systemic lupus erythematosus.

Histopathological tests may help to identify the pattern and size of involved vessels and a serological examination to establish an autoimmune profile is also essential when such conditions are strongly suspected. If patients experience rapid deterioration to erythroderma, a history of pre-existing skin disorders such as eczema or psoriasis should be sought. Sézary syndrome or other lymphoma/leukemia is not easily distinguishable from a drug eruption. Histologically, atypical lymphocytes with epidermotropism or aberrant intradermal distribution are characteristic. Otherwise, immunohistochemical staining and establishing cell clonality in the blood can aid in the diagnosis for lymphoma/leukemia.

**Diagnostic tools for DRESS/DIHS**

Determining the culprit drug for DRESS/DIHS patients is critical but sometimes difficult. Patients might take several medications just before or during their adverse drug reactions. An additional factor that makes it difficult to find the true drug causing the reaction is the characteristic delayed onset of symptoms in DRESS/DIHS. Although drug provocation testing may serve as the gold standard to establish the diagnosis of drug hypersensitivity, this is not appropriate for SCARs patients because of the potential life-threatening risks. Patch testing and the lymphocyte transformation test are two clinical tests that may benefit these patients. Patch testing has been widely used for diagnosing type IV or delayed type hypersensitivity. A drug patch test is performed by applying a diluted drug in suitable media on the skin, to detect inflammatory effects by drug-specific T-cells. Although it is a safe test, several factors are known to affect its specificity and sensitivity. Prior to when patch testing is ordered for DRESS/DIHS patients, the physician should evaluate some important factors, including the drug category to be tested, drug concentration and vehicle used, and timing of the test after drug hypersensitivity. Overall positive rates for DRESS patch tests are diverse, ranging from 32.1% to 64%. However, some similar results have been repeatedly verified. In the case of anticonvulsants, studies reported to have a 51.5% positive rate; especially for carbamazepine, the positive rate rose to more than 70%. Other drugs reported to produce positive patch tests include β-lactam antibiotics, proton pump inhibitors, and some non-steroidal anti-inflammatory drugs.

By contrast, patch tests always yield negative results in allopurinol-induced DRESS/DIHS. In a systemic review of anticonvulsant hypersensitivity syndrome, performing patch tests during or right after hypersensitivity episodes yielded low rates of positive results. The optimal time for performing this test is 2–6 months after the initiation of drug reaction.

The lymphocyte transformation test (LTT) mainly focuses on detecting drug-specific T-cells by measuring the proliferation of T-cells after encountering the antigens. The specificity of LTT is evaluated to be 85%, but the sensitivity is also variable and is related to both the drug and phenotype of clinical reactions. For β-lactam-delayed-type allergy, the sensitivity rate of LTT was reported to be in the range of 60–70%. However, well-documented data are lacking for other drugs tested by LTT. Other limitations of the LTT include its high laboratory test cost, as well as advanced techniques that demand experience and careful interpretation for reliable results. Nevertheless, LTT should be considered in patch-test-negative patients because overall sensitivity is higher than other tests detecting delayed type hypersensitivity. The optimal time to perform LTT is still being debated, but for DRESS patients, 5–8 weeks after acute episodes has been suggested.

**Pathogenesis**

The precise pathogenesis of DRESS/DIHS is complex and not fully understood. It is widely considered to be an immunological reaction to a drug or to its metabolites because of the signs, such as skin eruption, fever, and reappearance of symptoms upon readministration of the drug. However, exposure to associated drugs does not seem to be enough to develop DRESS/DIHS. Increasing results of pharmacogenetic studies are showing that the occurrence of this syndrome is determined by the combination of susceptible individuals and exposure to specific drugs. However, the mechanisms underlying the flaring of symptoms of DRESS/DIHS cannot be explained solely by an immunological reaction to drugs. The link between DRESS/DIHS and HHV-6 reactivation has evoked much interest in recent years. Some authors consider HHV-6 reactivation a consequence of immunosuppression, either due to drug hypersensitivity or to immunosuppressive treatment; others view this as the early event. Recently, gradual dysfunction of regulatory T-cells was reported and was speculated to be associated with increasing risks of developing autoimmune diseases.

**Immunological hypersensitivity reaction**

DRESS/DIHS only occurs in a relatively small proportion of patients and thus is an idiosyncratic hypersensitivity reaction. This syndrome is classified as type IV or delayed type hypersensitivity because of the need for an incubation period for sensitization. Activated T-cells seem to play a central role in such hypersensitivity. Some have further claimed that DRESS/DIHS has a dominant type IVb reaction, which corresponds to the Th2-type immune response and eosinophil activation. Studies have demonstrated the existence of drug-specific T-cells in patients with drug hypersensitivity and expansion of these T-cells when encountering specific antigens. However, their effector roles in DRESS/DIHS are still elusive. Drugs associated with these reactions may covalently bind protein or DNA to form hapten-carrier complexes (hapten theory) or may directly interact with immune receptors on T-cells (p-i concept) to stimulate the immune cells. The interaction between human leukocyte antigen (HLA), drugs, and T-cell receptors (TCR) is pivotal to such a T-cell-mediated response. When a drug or metabolite interacts with a particular HLA, and if drug presentation to naïve T cells via the TCR stimulates their activation, immune responses are initiated. Individuals possessing specific HLA are predisposed to developing DRESS/DIHS after sensitization by particular drugs; however, these allelic markers are possibly necessary but not sufficient to evoke such allergic reactions.
because of their high negative predictive values but low positive predictive values.54

Scientists first found the correlation between HLA and drugs early in the 21st century. In published data, abacavir-hypersensitive patients carried the allele HLA-B*5701 more frequently than abacavir-tolerant patients did (odds ratio: 117; 95% confidence interval: 29–481).55 Further studies have demonstrated this correlation in Caucasian and Hispanic patients,56 but not in African and Asian populations.57 An international randomized pharmacogenetic clinical trial proved that avoidance of abacavir use in patients with allele HLA-B*5701 reduced the incidence of this hypersensitivity syndrome, which was initially seen in 5% of patients receiving this drug during the first weeks of treatment.38 Recently, the mechanism of T-cell activation by abacavir was explained. Unmodified abacavir binds noncovalently to antigen-binding cleft of HLA-B*5701 and subsequently changes its shape and chemistry, along with changes to the peptide repertoire of HLA-B*5701. This repertoire change alters the “immunological self”, after which loading of novel self-peptides into altered HLA may drive T-cell immune responses.58,59 This finding may also partially explain the occasional occurrence of drug-induced autoimmunity.60 Another well-known association is HLA-B*5801 and allopurinol-induced severe drug hypersensitivity reactions. This correlation was first reported in a case-controlled study of a Han-Chinese population. One-hundred percent of patients diagnosed with allopurinol-induced SJ/TEN and DRESS/DIHS carried the allele HLA-B*5801, compared to only 15% in allopurinol-tolerant controls and 20% in healthy controls.61 Similar strong associations were also demonstrated in other Southeast Asian populations,62 Japanese populations,63 and also European patients64; this was most marked in allopurinol-induced SJ/TEN. Although the mechanism of interaction between specific drugs and HLA variants is still not totally understood, in many countries screening for these alleles is recommended prior to initiating therapy with these drugs. SCAR occurrence may be partially preventable in the future.

Viral reactivation

The association between this drug eruption and HHV was first reported in a patient with phenobarbital-induced hypersensitivity syndrome.22 In that study, the authors reported that the antibody titer of HHV-6 rose during the 2nd–4th week after the initiation of symptoms and this episode of viral infection was claimed to be related to the fulminant hemophagocytic syndrome developing in that patient. Since then, continual evidence supports that viral reactivation might be a unique feature in such drug reaction and typical DIHS was proposed to imply its association with viral reactivation.38

Recently, reactivation of other types of herpesviruses was also discovered through different laboratory modalities; however, the mechanism for sequential viral reactivation and their pathogenetic roles in DRESS/DIHS are still unclear. Decreased B-lymphocyte numbers and total immunoglobulin levels were reported in a comparison of patients with DRESS/DIHS and patients with SJ/S/TEN.65 In addition, reduction of plasmacytoid dendritic cells (pDC) in the peripheral circulation was noted, and the authors speculated that this depressed the antiviral activity in DRESS/DIHS patients because pDCs induce B cell maturation to produce immunoglobulin.66

The role antiviral T-cells play in DRESS/DIHS is still being debated. It has been proposed that T-cells specific to drugs and viruses may have significant cross-reactivity in these patients, so the clinical symptoms during acute episodes and after drug withdrawal are partially induced by antiviral T-cells, which are stimulated by bystander activation.67 Another scenario proposes that antiviral CD8+ T-cells possessing cross-reactivity to drugs play a central role in initiating this drug hypersensitivity reaction when the drugs and specific HLA alleles accidentally activate viral specific T-cells.68 Other researchers have demonstrated EBV replication in patients’ EBV-transformed B lymphocytes after triggering by culprit drugs. These researchers claimed that symptoms of DRESS are mediated by activated CD8+ T-cells whose targets in fact are herpesviruses.69 However, more evidence is needed to clarify the interaction between drugs, HHV, and host immune responses in DRESS/DIHS patients.

Regulatory T-cells

Recently, the roles of regulatory T-cells (Treg) have been studied in DRESS/DIHS patients, and their dynamic changes applied to explain some of the mysterious problems of this drug hypersensitivity reaction. It was observed that Treg cells expanded during acute stages but gradually lost their function during resolution phases of DRESS/DIHS.50 This led to the theory that expanded Treg cells with full capacities suppress activation of effector T-cells. This is reflected as a delayed onset of manifestations of DRESS/DIHS but also paradoxically facilitates viral reactivation. Exhausted Treg cells become dysfunctional, which may partially explain why patients with DRESS/DIHS have an increased risk of developing autoimmune diseases in the future.58

Treatment and disease outcome

The only consensus about DRESS/DIHS patient treatment is to withdraw the offending drugs as soon as possible, along with providing adequate supportive care. Otherwise, it is still inconclusive what treatment benefits DRESS/DIHS patients. Empirical use of antibiotics or anti-inflammatory medications should be avoided to prevent confusion between true deterioration due to newly administered drugs or paradoxical deterioration of clinical symptoms after withdrawal of causative drugs.

Topical corticosteroids can be used to relieve cutaneous symptoms but the risk of superficial infection should always be kept in mind. Systemic corticosteroids are the current mainstream of treatment. A recommended starting dose is 1.0–1.5 mg/kg/day of prednisone or an equivalent drug. This dosage should be slowly tapered over 6–8 weeks to avoid a flare-up of symptoms.72 However, studies focusing on indications and timing of administration and the influence of these factors on long-term outcomes for DRESS/DIHS patients are lacking. Because some patients may completely recover without the need for systemic corticosteroids, it might be unnecessary to give systemic corticosteroids immediately to all patients suspected of having DRESS/DIHS.69

Other alternatives include intravenous immunoglobulin, plasmapheresis, or immunosuppressants; however, reports in the literature have shown variable outcomes and inconclusive results.70,71

The estimated mortality from DRESS/DIHS is 10–40%, according to different studies (Table 1), and the causes for death include hepatic necrosis, shock, pulmonary hemorrhage, or other vital organ decompensation.72,73 Years after the acute stage, patients may have long-term sequelae, comprising newly developed autoimmune diseases and permanent visceral organ failure. In our previous study, the overall cumulative incidence of long-term sequelae for DRESS/DIHS patients was 11.5%. Autoimmune thyroid diseases and renal failure requiring long-term hemodialysis were the most frequent sequelae for young patients and the elderly, respectively.74 Variable autoimmune diseases were reported in the literature, and there were occasional reports of individual patients developing more than one particular disease, either simultaneously or sequentially.22,75 The pathomechanism
of developing autoimmune diseases in DRESS/DIHS patients possibly involves repeated stimulation of T-cells with autoreactive potentials by sequential viral reactivation and dysfunction of regulatory T cells at resolution stages. However, autoimmune diseases after DRESS/DIHS are variable, and they may involve both autoantibody production (for example, autoimmune thyroid diseases or systemic lupus erythematosus) and cell-mediated mechanisms (for example, alopecia areata or scleroderma lesions). These are indications that immune regulation imbalance is multidimensional rather than having a single clear pathogenic process. Physicians should be aware of autoimmune generation in patients after DRESS/DIHS and cautiously follow up symptoms and laboratory tests for early recognition. For elderly patients, physicians should keep in mind that vital organ failure may lead to death, which can occur either at the acute stage of the disease or during the resolution stage of disease.

Conclusion

DRESS/DIHS is a severe adverse drug reaction with unique clinical features and complex pathomechanisms. Early recognition, withdrawal of possible causative drugs, and adequate supportive care are mainstays of improving patient prognosis and reduce morbidity/mortality. Most patients suffering from DRESS/DIHS recover completely, but some may develop long-term sequelae, especially autoimmune diseases and permanent end-organ failure. Patient education and follow-up are necessary, and the search should continue for therapies that can reduce the risk of sequelae.

Acknowledgments

This work was supported by the National Science Council of Taiwan (NSC 99-2628-B-002-084-MY3) and National Taiwan University Hospital. (NTUH 102-S2058).

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