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Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

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Abstract Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe cutaneous drug reaction characterized by fever, lymphadenopathy, hematologic abnormalities, multisystem involvement, and viral reactivation. Although most patients with DRESS syndrome are able to fully recover, a subset of patients go on to have a prolonged course with recurrence, and/or autoimmune complications. Severe systemic involvement is associated with significant morbidity and mortality. Viral reactivation, especially of human herpes virus 6, Epstein-Barr virus, and cytomegalovirus, is a common feature of DRESS, with a high viral load and antibody titers being associated with poor outcomes. Aside from prompt discontinuation of the offending drug, treatment for patients with significant disease consists of systemic therapy with corticosteroids.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome or drug-induced hypersensitivity reaction (DIHS) is a severe cutaneous drug reaction characterized by fever, lymphadenopathy, hematologic abnormalities, multisystem involvement, and viral reactivation. Several features distinguish it from the more commonly encountered morbilliform drug reaction. This review will cover the clinical features, workup, and recommended treatment approach to patients with DRESS.

The morbilliform or maculopapular type of drug reaction is the most common form of cutaneous drug reactions seen in both the inpatient and outpatient setting.[1–3] Patients typically present with coalescing erythematous macules and papules on the upper part of the trunk, face, and extremities. As the name implies, this type of eruption resembles a viral exanthem. In the setting of hematopoietic stem cell transplantation, the cutaneous eruption can be difficult to differentiate from skin changes found in acute cutaneous graft-versus-host disease, both clinically and by histology.[4,5] Most patients with a morbilliform drug reaction will recover fully with discontinuation of the offending drug, supportive treatment with antihistamines, and topical immunomodulating agents, and, if needed, a short course of systemic corticosteroids.[3] Clinicians have long observed, however, that a subset of patients who developed a morbilliform or maculopapular drug reaction had distinctly more severe involvement. These more severely affected patients were more likely to have peripheral eosinophilia, profound systemic clinical manifestations, lymphadenopathy, evidence of systemic inflammation, and poorer outcomes.[6] Over the past two decades, it has become clear that this form of drug reaction—although most commonly presenting with a morbilliform eruption—was clinically, immunologically, and even pharmacogenetically distinct from the more common maculopapular eruption, as well as the severe drug reactions

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[7,8]

DRESS or DIHS is a severe cutaneous adverse reaction (SCAR) characterized by a cutaneous eruption, lymphadenopathy, hematologic abnormalities and multiorgan dyscrasias.[6] It is associated with both short and long-term morbidity, and mortality. DRESS/DIHS is associated with human herpes virus (HHV) reactivation, particularly HHV-6, Epstein Barr virus, and cytomegalovirus (CMV).[9] This phenomenon of viral reactivation has emerged as an important factor in how DRESS/DIHS is defined, and how its pathophysiology is viewed. Characterization of this complex syndrome has led to the development of specific diagnostic criteria.[10–12] The term DIHS is used interchangeably with DRESS, and it is more appropriately linked with the more stringent Japanese criteria (Table 1) that identify a subset of patients on the more severe end of the disease spectrum.[7,13,14] Patients with DRESS/DIHS are also at risk for systemic autoimmune sequelae, which can appear months after resolution of the cutaneous eruption and acute systemic involvement (Figure 1).

There is still much that is unknown about DRESS/DIHS. Its pathophysiology is still not fully understood. Predictors of poor outcomes and the ideal pharmacologic management of patients with DRESS/DIHS are still not known. This review aims to summarize our latest understanding of DRESS, its associations, and its management.

Clinical features and diagnosis

The diagnosis of DRESS/DIHS relies on a combination of clinical and laboratory findings. Fever, eruption, lymphadenopathy, hematologic abnormalities and systemic involvement, and evidence of viral reactivation are the key features of DRESS/DIHS. The eruption in DRESS/DIHS can take on several morphologies. Data from the multinational registry RegiSCAR have shown that a polymorphous maculopapular eruption (85%) and facial edema (76%) were the most commonly seen morphologies of the cutaneous involvement, whereas 15% of their patients had a monomorphic maculopapular dermatitis.[11] As part of the polymorphous maculopapular dermatitis, patients also presented with (in descending order) pustules, purpura, infiltrated plaques, blisters, target-like lesions, urticarial lesions, an exfoliative dermatitis, eczema-like lesions, and lichenoid lesions.[11]

Evidence from retrospective data and different registries suggest that the clinical features in DRESS may vary depending on the offending drug.[15,16] Exposure to allopurinol has been implicated in more severe disease, and it is more likely than some other medications to be associated with the development of renal and hepatic involvement.[11,17] Carbamazepine, another commonly implicated drug in DRESS/DIHS, is associated with hepatic involvement, lymphadenopathy, and atypical lymphocytes.[18] Vancomycin may be more frequently associated with renal involvement and even death.[16,19] In a retrospective series of 29 patients with DRESS, the 4 patients who had vancomycin-associated DRESS had a 4.98-fold median increase in their baseline creatinine, compared with a 2.25-fold median increase in the rest of the cohort.[19]

The initial criteria for the diagnosis of DRESS were proposed in 1996, and required the presence of the following (Table 1)[6]:

- A cutaneous drug eruption
- Systemic involvement in the form of lymphadenopathy ≥2 cm in diameter or hepatitis (transaminase ≥2 times

Table 1 Comparison of criteria for the diagnosis of DRESS/DIHS

Bocquet et al.[6]	Japanese Consensus Group[7]	RegiSCAR[12]
1. A cutaneous drug eruption 2. Systemic involvement lymphadenopathy ≥2 cm in diameter or hepatitis (transaminase ≥2 times upper limit of normal) or interstitial nephritis or interstitial pneumonitis or carditis 3. Hematologic abnormalities eosinophilia $\geq 1.5 \times 10^9$/L or presence of atypical lymphocytes	1. Maculopapular eruption developing >3 weeks after starting a limited number of drugs 2. Prolonged clinical manifestations 2 weeks after discontinuation of the causative drug 3. Fever (>38°C) 4. Liver abnormalities (alanine aminotransferase >100 U/L) * 5. Leukocyte abnormalities (at least 1 present): • Leukocytosis (>11 × 10^9/L) • Atypical lymphocytosis (>5%) • Eosinophilia (>1.5 × 10^9/L) 6. Lymphadenopathy 7. HHV-6 reactivation	1. Acute skin eruption 2. Fever (>38°C) 3. Lymphadenopathy at ≥2 sites 4. Involvement of at least 1 internal organ 5. Lymphocytosis or lymphocytopenia 6. Peripheral eosinophilia 7. Thrombocytopenia
The presence of all 3 is required.	The diagnosis is confirmed by the presence of all criteria (typical DIHS) or the first 5 (atypical DIHS).	The presence of at least 3 of the characteristics is required for the diagnosis of DRESS. In addition, a scoring system[12] is applied to classify patients as *definite, probably,* or *no case.*

DIHS, drug-induced hypersensitivity reaction; DRESS, drug reaction with eosinophilia and systemic clinical manifestations; HHV, human herpes virus.

* This can be replaced by other organ involvement, such as renal involvement.

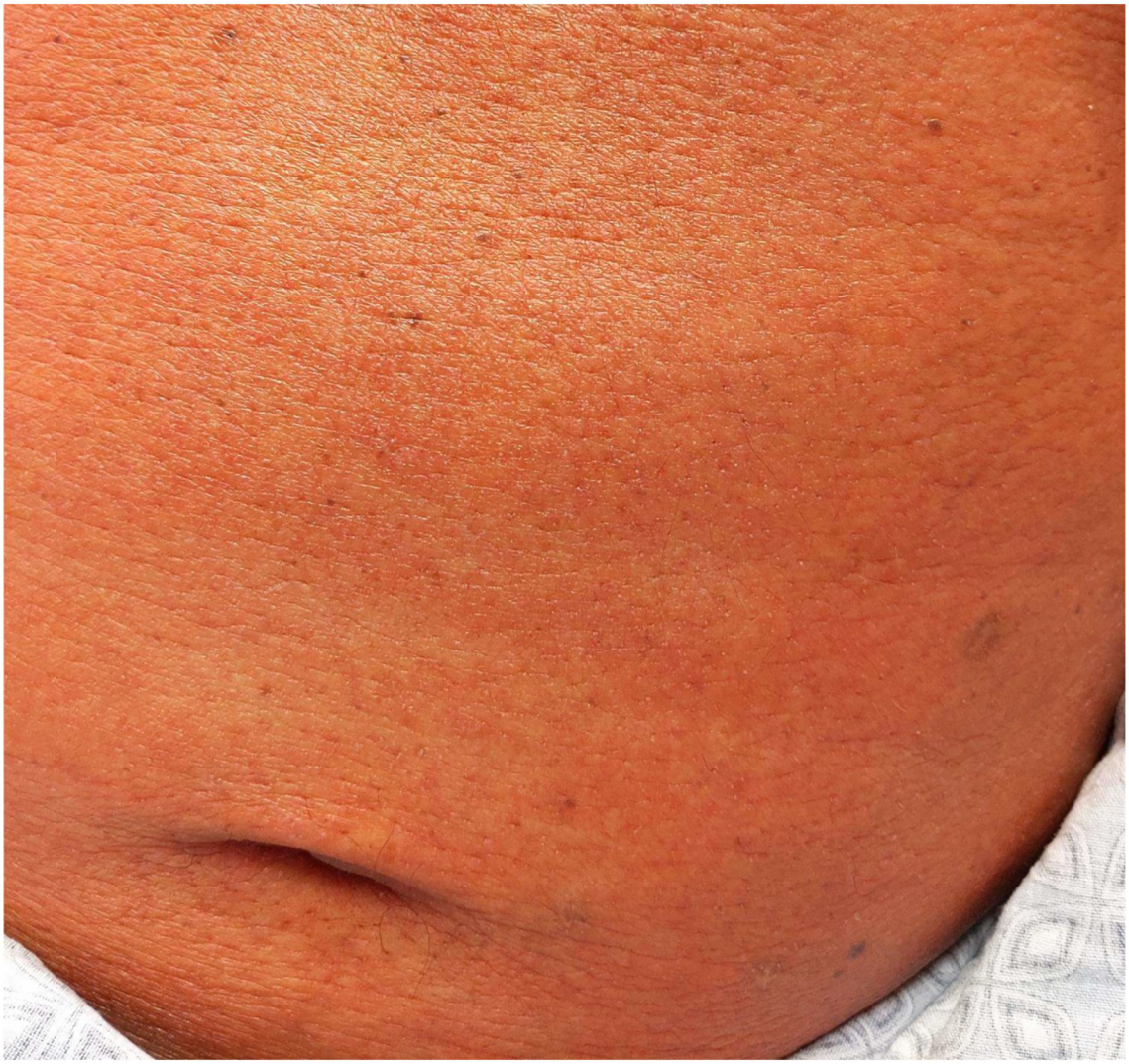

Fig. 1 Patient with the characteristic red eruption of DRESS.

upper limit of normal) or interstitial nephritis or interstitial pneumonitis or carditis
- Hematologic abnormalities (eosinophilia $\geq 1.5 \times 10^9$/L or presence of atypical lymphocytes)

The Japanese SCAR (J-SCAR) consensus group subsequently proposed diagnostic criteria for DIHS, which also had seven components.[10] Some of the key differences between these criteria and those previously described[6] were the following additions:

- Presence of fever
- A 3-week lag time between drug exposure and development of the eruption
- Persistence of the eruption for 2 weeks or more after discontinuation of the offending drug
- Evidence of HHV-6 reactivation

Patients who meet all the seven criteria are considered to have DIHS, whereas those who meet only five of the criteria have atypical DIHS. The European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) consortium has also established its own criteria for the identification of possible DRESS cases.[12] Similar to the Japanese consensus criteria, it expanded the original definition[6] to include seven components, including hospitalization, exposure to a high risk drug, and fever (Table 1). In contrast, however, to the Japanese SCAR consensus, HHV-6 reactivation was not included among the diagnostic criteria. Comparison of the two criteria has demonstrated that a diagnosis of definite DIHS is consistent with probable/definite DRESS, confirming that DRESS and DIHS are not distinct entities, but are part of the same disease spectrum, and the Japanese SCAR consensus likely identifies a patients with more severe involvement.[14] Although the presence of these diagnostic criteria facilitates the identification of patients with DRESS/DIHS, our unpublished data suggest that many clinicians use clinical parameters outside of these criteria to diagnose DRESS. The clinical

findings and the laboratory abnormalities in DRESS/DIHS may evolve over time and may not all be manifest at the time the patient is evaluated. Clinical observations, such as facial edema, can supplement our use of the published criteria to prevent delays in diagnosis and treatment.

A careful history and physical examination that is directed at identifying the offending agent and signs and clinical manifestations of cutaneous and other organ involvement is essential in diagnosing DRESS. Basic laboratory workup is usually guided by the following diagnostic criteria:

- Complete blood count with a differential count to identify eosinophilia and leukocyte abnormalities
- Liver function and renal function panel to identify hepatic and renal dyscrasia
- HHV-6 titers and CMV PCR; consider other viral studies as indicated by history and physical examination[7,10,12]
- Other organ-specific evaluation as indicated by history and physical examination (for example, EKG and echocardiogram to evaluate for cardiac involvement)

A variety of histologic changes in the epidermis and dermis can be found in the skin of patients with DRESS/DIHS, and histology is not specific for DRESS/DIHS.[20] Not surprisingly, the epidermis from patients with clinically more severe DRESS/DIHS is associated with increased confluent keratinocyte necrosis on histology. Spongiotic epidermal change is more likely to be found in those with milder disease.[20] A skin biopsy may be performed, however, to help eliminate other pathologic processes, but it is not required for the diagnosis of DRESS/DIHS.

Serum markers for diagnosing DRESS/DIHS have been suggested but require further investigation. The average serum level of thymus and activation-regulated chemokine/chemokine ligand 17 (TARC/CCL17) among a cohort of 8 patients with DRESS was more than 10 times higher compared with the average serum levels among 7 patients with SJS/TEN or 14 patients with a maculopapular drug reaction.[21] TARC levels were markedly elevated among the patients with DRESS during the acute phase of their disease but decreased with lessening of the eruption.[21] Similarly, serum levels of the high mobility group box 1 protein (HMGB1) were elevated in 17 patients with DRESS and 17 patients with SJS/TEN compared with 11 patients with a maculopapular drug eruption and 14 healthy volunteers.[22] Serum HMGB1 levels among patients with DRESS, however, were significantly higher compared with those in the SJS/TEN group. Although TARC and HMGB1 are promising as a markers for DRESS, their use has not yet been sufficiently validated in a larger cohort.

Epidemiology and course

The true incidence of DRESS/DIHS is still unknown, but it has been reported at around 10 per million.[9] DRESS/DIHS can occur at any age, although the majority of patients reported in the literature have been adults.[23,24] A female predominance has been reported in some registries and series but not others.[9,11,25–27] Numerous medications have been reported to cause DRESS/DIHS. Allopurinol, anticonvulsants, sulfonamides, and antibiotics are the most commonly implicated drugs in DRESS/DIHS (Table 2).[11,27,28] The onset of clinical manifestations in DRESS/DIHS is delayed, typically 2 to 3 weeks from the initial exposure of the drug but can lag up to 3 months or longer after starting the culprit medication.[9,18,29] [9,18,29] The typical course of DRESS is one that is long and drawn out, with disease activity continuing even weeks after discontinuation of the offending drug. Patients may sometimes experience a paradoxical worsening of signs and clinical manifestations in the immediate period after drug withdrawal. Relapses or flares are common in DRESS/DIHS.[30] In a retrospective study of 60 patients with DRESS, 25% of patients had recurrence of their DRESS.[30] In some of these patients, the recurrence was triggered by exposure to a medication unrelated to the original offending agent.

Pathophysiology

The pathophysiology of DRESS/DIHS is still not yet completely understood. Viral reactivation, particularly HHV6, Epstein Barr virus, and CMV, is not only common among patients with DRESS/DIHS and has been implicated in the pathophysiology of this disease.[28] It is also associated with poor outcomes and increased mortality.[26,31] Documentation of viral reactivation is dependent on the timing of the ELISA or PCR, as there is a sequential pattern of HHV reactivation in patients with DRESS/DIHS.[9] Several authors have proposed that the multiorgan immunologic assault that occurs in DRESS/DIHS is mediated by T cells that are cross reactive to viral antigens.[32,33]

Regulatory T (Treg) cells have also been implicated in DRESS/DIHS. The ratio of FoxP3+ Treg cells to CD3+ T cells in the lesional skin of patients with DRESS/DIHS increased compared with lesional skin of patients with acute graft-versus-host disease or a maculopapular drug reaction.[34] In addition, there was a positive correlation between the ratio and the duration of DRESS/DIHS at the time of the biopsy. Early in the course of the disease, peripheral Tregs are greatly expanded in patients with DIHS compared with patients with TEN, maculopapular drug reaction, or normal controls.[35] Toward resolution of the disease, however, this Treg compartment contracts and becomes functionally deficient. At the same time, there is a shift toward an increase in Th17 cells.[36] This dynamics may explain the lag in the onset of DIHS clinical manifestations, as well as the predisposition for late autoimmune sequelae.[9,37] Other authorities have implicated type II innate lymphoid cells (ILC2s) in the pathogenesis of DRESS after demonstrating increased numbers of $ST2^{+}$ILC2s in both the lesional skin of patients compared with healthy volunteers.[38] In addition, ILC2, serum soluble ST2 (sST2), and

Table 2 Common causes of DRESS/DIHS

Antigout medications
Allopurinol
Antimicrobials
Abacavir
Dapsone
Minocycline
Nevirapine
Trimethoprim-sulfamethoxazole
Vancomycin
Antiepileptics
Carbamazepine
Lamotrigine
Phenytoin
Phenobarbital
Anti-inflammatory medications
Sulfasalazine

DIHS, drug-induced hypersensitivity reaction; DRESS, drug reaction with eosinophilia and systemic clinical manifestations.

IL-5 may be increased or elevated in peripheral blood of patients with DRESS in the acute phase, and decreased after steroid treatment. Levels of sST2 also correlated with alanine aminotransferase levels.

Genetic factors play a role in the familial predisposition for developing DRESS/DIHS.[39] Polymorphisms that affect *N*-acetylation and detoxification of toxic drug metabolites are thought to increase susceptibility to developing DRESS/DIHS from specific drugs such as sulfonamides[40] and anticonvulsants.[39] Several HLA alleles have been associated with drug-specific cutaneous adverse reactions, including DRESS.[8] These observations have allowed for effective preventive screening strategies in high-risk populations.[41] HLA molecules on antigen presenting cells are responsible for presenting the drug antigens to their corresponding effector immune cells.[8,42] Some authors have also hypothesized that the impact of specific HLA variants on viral reactivation may explain their association with DRESS.[8,42] HLA-B*5801 has been identified as a genetic marker for allopurinol-associated DRESS in the Han Chinese as well as the Japanese population.[43,44] HLA-A*32:01 has been associated with vancomycin-induced DRESS after comparison of 32 patients with DRESS of predominantly European ancestry and 46 matched vancomycin-tolerant controls.[45] Smaller studies have suggested a link between HLA-B*56:02 and phenytoin-associated DRESS among indigenous Australians,[46] and between HLA-A*3101 and carbamazepine-associated DRESS in Han Chinese and Japanese patients.[47,48]

Prognostic factors

The reported mortality from DRESS/DIHS varies depending on the cohort. Some authors have estimated the mortality from DRESS/DIHS to be around 10%, although other series and registries report mortality to be closer to 5%.[16,26,49,50] Outcomes and mortality in DRESS/DIHS depend greatly on the extent and severity of organ involvement, as well as other sequelae of both the disease itself, and any immunosuppressive treatment.

Viral reactivation, especially HHV-6, Epstein Barr virus, and CMV, is not only common among patients with DRESS/DIHS but is also associated with more severe disease.[26,28,31] Higher viral load and antibody titers are associated with a prolonged course, more extensive systemic involvement, and poorer outcomes among patients with DRESS/DIHS.[31,51] In one retrospective study involving 55 patients, patients who had evidence of CMV reactivation—defined as $\geq$20 genome copies in 10^6 peripheral leukocytes or the detection of CMV-C10/11 antigenemia—had poorer outcomes than those who did not.[26] The mean duration of hospitalization was twice as long in these patients (56.9 vs 25.3 days), as was the mortality rate (27% vs 0).[26] Patients in this cohort who died in this cohort had evidence of CMV reactivation, and were more likely to have had a delay in the initiation of antiviral therapy (ie, $\geq$3 days after detection of CMV reactivation). These authors have also proposed a severity scoring system for patients with DRESS that grades disease severity and predicts the risk of CMV reactivation.[26] This scoring system assigns a higher score or grade based on the patient's age, duration of exposure, the offending drug, exposure to allopurinol, treatment with pulse methylprednisolone, body surface area, duration of fever, appetite loss, degree of hepatic and kidney dysfunction, and C reactive protein levels. This scoring system, however, still requires validation with a larger study.

Sequelae of DRESS/DIHS

Acute sequelae

DRESS/DIHS is a systemic disease and can, therefore, affect practically any organ. Aside from hematologic abnormalities, liver, kidney, and lung in descending order are the other most commonly affected organs.[11,25,52] Pancreas and other gastrointestinal organs, joints and muscles, heart, and the nervous system can also be involved as well, sometimes with fatal consequences (Table 3).[52–54]

Hepatitis

The liver is the most common extracutaneous organ involved in DRESS/DIHS. Prospective observational and retrospective studies and data from registries estimate that as many as 70% to 90% of patients with DRESS/DIHS have hepatic involvement.[11,25,28,52] The most commonly observed hepatic abnormality is a transaminitis, but a small subset of patients go on to develop fulminant hepatic failure. A retrospective, multicenter study of 16 patients who presented with severe acute liver injury or acute liver failure revealed that patients who presented with hepatic encephalopathy on admission either went on to receive a liver transplant or died.[55] In addition,

factor V levels on admission (day 0), prothrombin time (PT) at day 1, and either PT time or factor V levels at day 2 were significantly lower among the patients who deteriorated than in those who improved. Patients who had a worse outcome (transplant or death) also had a higher international normalized ratio at day 2 compared with those who recovered. Systemic corticosteroid treatment did not seem to differ between patients who recovered and those who had poor outcomes, although the numbers are too small to draw any definitive conclusions.[55] Patients who have viral reactivation, especially HHV-6 and CMV, are also more likely to have hepatic involvement, and direct infiltration of the liver with CMV in a patient has been demonstrated.[56]

Renal insufficiency/failure

Renal involvement among patients with DRESS/DIHS has been reported to be anywhere from 11% to 55% of patients.[11,15,19,25,28,29,57] A retrospective study demonstrated that 75% of patients in their cohort who had vancomycin-associated DRESS/DIHS had renal involvement, compared with 50% among those with allopurinol-associated and 25% of those who had trimethoprim-sulfamethoxazole–associated DRESS/DIHS.[19] The degree of renal involvement ranges from a mild elevation of creatinine to severe interstitial nephritis.[52]

Myocarditis

Myocarditis is a rare but fatal complication of DRESS/DIHS that can sometimes be under recognized. The demographics, features, and outcomes among patients with DRESS/DIHS-associated myocarditis have been reviewed.[58,59] A wide variety of medications can be associated with DRESS-associated myocarditis, but minocycline, allopurinol, ampicillin, dapsone, and trimethoprim-sulfamethoxazole have been identified as the most common offending drugs.[58] A retrospective analysis of 43 patients with DRESS-associated myocarditis who were reported in the literature revealed that all of these patients had cardiac signs and clinical manifestations.[58] The most common of signs and clinical manifestations were dyspnea, tachycardia, hypotension, and chest pain, whereas the most common laboratory or imaging abnormality was an abnormal electrocardiography, followed by left ventricular dysfunction on echocardiography and elevated cardiac enzymes.[58] Of the patients with DRESS-associated myocarditis, 44% died during hospitalization. The likelihood of death was 10 times higher among patients with DRESS-associated myocarditis who were not treated with corticosteroids compared with those who were.[58]

Long-term sequelae

Patients who have DRESS/DIHS are at risk for long-term, autoimmune sequelae. These sequelae may appear after a long, symptom-free interval after complete resolution of the acute-phase DRESS/DIHS or may be a continuation of organ involvement that appeared during the acute phase.[50,52] The lag time between resolution of the acute phase and the development of autoimmune sequelae can be as long as 4 years.[52,60]

Investigators from Taiwan noted a cumulative rate of long-term sequelae of 11.5% among 52 patients.[50] The most common sequelae was autoimmune thyroiditis, but they also observed diabetes, autoimmune hemolytic anemia, and alopecia. Two patients who had a history of chronic renal failure developed acute interstitial nephritis during the acute phase of DRESS and required long-term hemodialysis. Other autoimmune sequelae that have been reported include autoimmune blistering disorders, sclerodermoid cutaneous changes, systemic lupus erythematosus, and enteropathy.[23,57,61] Myocarditis, a rare but potentially fatal sequelae of DRESS, usually appears in the acute phase but can appear as late as 2 years afterward.[58] This highlights the need for surveillance even after clinical resolution of the acute phase of DRESS/DIHS.

Management

The main principles in the management of DRESS include the following:

- Identification and discontinuation of the offending drug
- Identification and management of comorbidities
- Supportive measures to control clinical manifestations such as itching
- Control of inflammation with topical and/or systemic medications
- Monitoring for and management of long-term sequelae

Due to the association between increased viral load and poor outcomes, some authors have suggested that adjunctive treatment with systemic antiviral medications may be beneficial in patients with severe DRESS/DIHS.[26,62,63] There is currently a paucity of prospective studies or clinical trials that address the treatment of DRESS/DIHS. Current recommendations on the treatment of DRESS/DIHS rely heavily on expert opinion, retrospective studies, and case series/case reports.[32,49]

Identification and discontinuation of the causative drug

Identification of the causative agent in DRESS may be challenging, especially among patients who are on multiple medications. Latency from the first drug exposure to the onset of DRESS clinical manifestations can vary widely, and looking for a temporal association alone may not be sufficient in discriminating between multiple suspected medications.[16] A recently published retrospective study from South Korea suggests that the median latency for DRESS associated with antibiotics such as cephalosporins (median = 15 days, range 0-36 days) and vancomycin (median = 20 days, range 0-41

days) was shorter than that observed when the offending drug was carbamazepine (median = 33 days, range 13-74 days) or allopurinol (median = 30 days, range 1-162 days).[16] In addition, withdrawal of any suspected offending agent will not result in the immediate improvement of the patients' clinical manifestations due to the natural history of DRESS/DIHS. We therefore rely heavily on identifying any high-risk medications that the patient may be taking (Table 2).

Diagnostic testing by patch testing, intradermal testing, or lymphocyte activation assays to confirm the offending agent in delayed hypersensitivity drug reactions remains controversial.[64] Some authors suggest that patch testing may have some utility when done 6 months after resolution of the signs and clinical manifestations of DRESS for specific drugs.[64] One group performed patch testing on 74 patients with DRESS and found a positive patch test in 64% of the patients[65]; however, the utility of patch testing was dependent on the type of drug that was being tested. The authors noted frequent positive patch testing for beta-lactams, pristinamycin, and omeprazole, but not for allopurinol, a commonly identified culprit in DRESS/DIHS. In addition, 18% of the patients with DRESS in the study had positive patch tests to multiple medications. The ideal concentrations of medications for patch testing in cases of DRESS are also unknown.

Lymphocyte activation test/lymphocyte transformation test (LAT/LLT) has also been used in identifying the causative agent in DRESS, but it also has significant limitations.[66] This test has a high specificity but low sensitivity, and must be timed properly.[66,67] This test is currently not commercially available.

Topical and supportive treatment

Topical corticosteroids and calcineurin inhibitors are part of the management of DRESS/DIHS, although there are no prospective studies that specifically address the use of topical immunomodulatory agents in patients with DRESS/DIHS.[29,49,68] Some authors have suggested that in milder forms of the disease, supportive and topical therapy alone may be sufficient. One group described 12 patients with atypical and typical DIHS who were treated either with supportive therapy alone or topical corticosteroids.[68] They reported that all patients recovered within a median of 18 days (range 7-37 days) after withdrawal of the offending drug, without pneumonia, myocarditis, nephritis, or other systemic disease.

In a retrospective study, another group[29] studied a cohort of 38 patients with a DRESS score of 4 or more (at least probably DRESS) and observed that 66% of the patients in their cohort were treated with high-potency topical steroids alone. Systemic corticosteroid treatment was reserved for patients who had evidence of at least one life-threatening visceral involvement, and therefore had more severe disease. Those treated with topical corticosteroids alone had a significantly lower rate of infections and intensive care unit admissions, shorter hospital stay, and shorter duration of treatment, although one patient (4%) developed progressive disease and died. None of the 13 patients who were treated with systemic corticosteroids died during the study duration.

Table 3 Short- and long-term sequelae of DRESS/DIHS

Arthralgia, reactive arthritis, rheumatoid arthritis
Autoimmune thyroiditis
Colitis/enteropathy
Cutaneous autoimmune disease
Vitiligo, alopecia areata
Diabetes mellitus
Encephalitis
Fulminant hepatic failure
Hemolytic anemia
Myocarditis
Pneumonitis
Renal failure
Systemic lupus erythematosus
Venous thrombosis

DIHS, drug-induced hypersensitivity reaction; DRESS, drug reaction with eosinophilia and systemic clinical manifestations.

Antihistamines can likewise be useful in helping alleviate clinical manifestations such as itching, and antipyretics may be given to control fever.[49] Other supportive measures such as fluid replacement and admission to the intensive care unit should be tailored to the individual patient.

Systemic immunomodulatory treatment

Systemic corticosteroids remain the systemic treatment of choice for DRESS/DIHS.[32] Retrospective studies have shown that systemic corticosteroid therapy is initiated in 34% to 57% of patients with DRESS/DIHS.[25,29,57] Expert opinion recommendations suggest a usual dosing of 40 to 60 mg orally daily, followed by a prolonged taper over 6 to 8 weeks.[32] This allows for the adequate control of cutaneous and systemic inflammation and the prevention of relapse that can occur among patients with DRESS. Other experts recommend a more aggressive approach with intravenous methylprednisolone. In a prospective, open-label, single-arm study, pulse IV methylprednisolone and oral prednisolone were administered to 10 patients with DRESS.[69] There was a rapid resolution of the patients' fever and skin findings and improvement of systemic involvement. One patient, however, still required liver transplantation due to fulminant hepatic failure, and died 4 months later. Another developed steroid-induced psychosis in the immediate treatment period.[69] The optimal dosing and duration of systemic corticosteroid treatment has yet to be determined and needs to be tailored to the individual patient.

There is a great need for studies that identify systemic steroid sparing agents for the treatment of DRESS/DIHS. In a small, single-center, retrospective study, patients who received oral corticosteroid therapy were more likely to develop herpes virus infections and pneumonia, compared with those who did not, although the later were more likely to develop

autoimmune complications.[57] Intravenous immunoglobulin (IVIG) has been reported as treatment for DRESS in case reports, case series, and retrospective studies.[16,70–72]

A prospective, open-label, noncomparative study investigated the efficacy of high-dose IVIG (200 mg/kg per day for 5 consecutive days) as monotherapy among adult patients with DRESS.[73] Six patients had been enrolled before the trial was stopped due to safety concerns. These patients had a median RegiSCAR score of 7 (out of a possible maximum score of 9) and had a median delay of 12.5 days after the onset of DRESS. Two patients had severe malaise after IVIG treatment and dropped out, and another two failed to demonstrate any response to therapy and went on to develop hemophagocytic syndrome. All four required rescue treatment with oral corticosteroids. One patient, who had a partial response to IVIG, developed a pulmonary embolism. Only one patient had a complete response to IVIG monotherapy. Other retrospective data, however, seem to show more promise, especially when IVIG is used in addition to corticosteroids.

Another group recently described a series of seven pediatric patients with severe DRESS who were treated with 1 to 2 mg/kg of IVIG in addition to, or after having failed, systemic corticosteroids.[72] The authors noted resolution of fever, any associated transaminitis, and anasarca, with no mortality.

A variety of other immunosuppressive or immunomodulatory agents have been described as possible treatments for DRESS/DIHS in small case series and case reports. Cyclosporine, plasmapheresis, cyclophosphamide, mycophenolate mofetil, rituximab, and tofacitinib have been successfully used in the treatment of steroid refractory DRESS/DIHS, including those with myocarditis.[49,74–77]

Conclusions

DRESS/DIHS is a severe cutaneous and systemic drug reaction characterized by an eruption, fever, lymphadenopathy, hematologic abnormalities, and other organ involvement. HHV reactivation, especially HHV-6, is common among patients with DRESS/DIHS, is associated with more severe and protracted disease, and has been implicated in the pathophysiology of this disease. Treatment consists of topical and systemic immunomodulatory therapy, and management of concomitant comorbidities. Patients with DRESS/DIHS are at risk for long-term sequelae, and longitudinal, long-term monitoring directed at detecting autoimmune sequelae is recommended for these patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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