REVIEW ARTICLE

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Drug Reaction with Eosinophilia and Systemic Symptoms

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CME

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a T-cell–mediated severe cutaneous adverse reaction characterized by rash, fever, internal organ involvement, and systemic manifestations after prolonged exposure to a medication. DRESS is also known as drug-induced hypersensitivity syndrome and was formerly known as anticonvulsant hypersensitivity syndrome, given its connection to such drugs (details about disease terminology are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

DRESS has an estimated prevalence of approximately 2 cases per 100,000 population and an incidence of 1 in 1000 to 1 in 10,000 cases in patients who received a medication, depending on the culprit medication.[1] Aromatic anticonvulsants confer the highest risk of associated DRESS, followed by allopurinol and sulfonamide antibiotics.[2] In the United States, five drugs account for most cases of DRESS; in order of decreasing prevalence in causing DRESS, these drugs are allopurinol, vancomycin, lamotrigine, carbamazepine, and trimethoprim–sulfamethoxazole.[3] Although DRESS is uncommon, it accounts for up to 23% of cutaneous drug eruptions in hospitalized patients.[4] Recent studies suggest that worldwide mortality from DRESS ranges from 1.2 to 7.1%,[2,5,6] and U.S.-specific mortality of 5% was documented in 2019.[3] A current conservative cost estimate for a single case of DRESS that results in hospitalization in the United States is $22,493.[1]

Clinical Presentation

Patients with DRESS present with a prodromal phase consisting of fever, malaise, sore throat, dysphagia, pruritus, a cutaneous sensation of burning, or a combination of these symptoms. This phase is then typically followed by a morbilliform eruption that begins on the trunk and often the face and eventually spreads to encompass more than 50% of the total body-surface area.[5] Facial edema, which can accentuate or lead to the appearance of new oblique earlobe creases, is characteristic and helps to distinguish DRESS from uncomplicated morbilliform drug rashes.[7] Cutaneous lesions are pleomorphic — urticarial, eczematous, lichenoid, exfoliative, erythrodermic, targetoid, purpuric, vesicular, pustular, or a combination of these — and multiple morphologic features may coexist or develop over time (Fig. 1A).[5] Early erythema may be less obvious in appearance in patients with more deeply pigmented skin, so careful examination with appropriate lighting is important. Pustules, when present, are follicular and generally limited to the face, neck, and chest.[5] In the prospective, validated European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study, 56% of patients with DRESS had mild mucosal inflamma-

KEY POINTS

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

- Drug reaction with eosinophilia and systemic symptoms (DRESS) is a T-cell–mediated severe cutaneous adverse reaction characterized by rash, fever, internal organ involvement, and systemic manifestations after prolonged exposure to a medication.
- DRESS accounts for approximately one fifth of cutaneous reactions among hospitalized patients; antibiotics are one of the most commonly identified triggers.
- Approximately 5% of DRESS cases result in death; the patients who survive may have relapses in addition to medical and psychological sequelae.
- The differential diagnosis includes morbilliform drug eruption; other severe cutaneous adverse reactions, such as the Stevens–Johnson syndrome and acute generalized exanthematous pustulosis; and additional conditions, such as hemophagocytic lymphohistiocytosis, angioimmunoblastic T-cell lymphoma, and acute graft-versus-host disease.
- The validated European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system is a rubric used to diagnose DRESS; however, elements of the diagnostic criteria may manifest at different time points, some late in the course of the disease.
- After identification and removal of the causative drug, treatment of DRESS consists of supportive care and glucocorticoids; glucocorticoid-sparing drugs and targeted biologic treatments are emerging as alternatives and complements to such treatment.
- There is no validated test to establish the cause of DRESS; dermatologists or allergist–immunologists may help assess drug causality and determine alternative drug therapy.

tion and erosion, and 15% of patients had mucositis involving more than one mucosal surface, most commonly the oropharynx.[5]

Generalized lymphadenopathy was present in most patients with DRESS in the RegiSCAR study[5] and preceded cutaneous manifestations in some patients. The rash generally persisted for longer than 2 weeks and often had a prolonged resolution phase marked by superficial desquamation.[5] DRESS can occur without rash or eosinophilia, but this presentation is rare.

DRUG EXPOSURES

Certain drugs have been more commonly associated with DRESS than others (Table 1).[1,2] Although most cases have occurred after 2 to 6 weeks of continuous drug exposure, some drug classes have been associated with distinctive disease latencies. Allopurinol has been associated with the longest disease latency, and beta-lactam antibiotics and iodinated contrast media, the shortest.[8-10] Latency periods longer than 3 months have been reported in rare cases.[11]

Genetic, demographic, and clinical risk factors appear to influence the development of DRESS. For example, elevated serum vancomycin trough levels and an age younger than 50 years have been associated with an increased risk of vancomycin-related DRESS,[12] and kidney impairment has been associated with the risk of allopurinol-related DRESS.[13]

SYSTEMIC INVOLVEMENT

Systemic involvement in DRESS most commonly involves the hematologic, hepatic, renal, pulmonary, and cardiac systems, although involvement of nearly every organ system — including the endocrine, gastrointestinal, neurologic, ocular, and rheumatologic systems — has been described. In the RegiSCAR study, 36% of the patients had involvement of one extracutaneous organ, and 56% of the patients had involvement of two or more organs.[5] Atypical lymphocytosis was the most frequent and earliest hematologic finding, whereas eosinophilia typically occurred later and tended to be persistent.[14]

After the skin, the liver is the most frequently involved solid organ.[2,15] Elevated liver-enzyme levels may precede the onset of rash; although the elevations are usually mild, they may occasionally reach 10 times the upper limit of the normal range.[16] The most common pattern of liver injury is cholestatic, followed by mixed cholestatic and hepatocellular and then hepatocellular.[16] In rare cases, acute liver failure has been profound, leading to liver transplantation.[16] Antibiotics are the most common drug class implicated in cases of DRESS associated with liver dysfunction.

A systematic review involving 71 patients (67 adults and 4 children) with kidney-related sequelae of DRESS[17] noted that 1 in 5 of the patients had isolated kidney involvement, although the majority of the patients had concomitant hepatic injury.

A Pleomorphic Cutaneous Findings Associated with DRESS


Purpuric Lesions

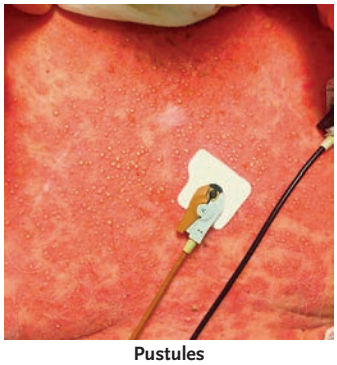

Targetoid Lesions


Erythroderma


Erosion


Facial Edema


Superficial Desquamation


Pustules

B Morphologic Features of Cutaneous Adverse Reactions, Including DRESS


DRESS


Morbilliform Eruption


Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

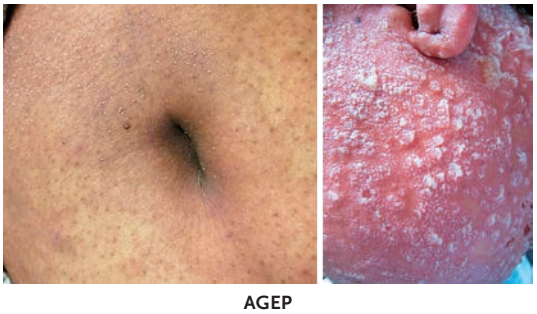

AGEP

Figure 1 (facing page). Clinical Features of DRESS and Other Cutaneous Adverse Reactions.

Panel A shows the pleomorphic cutaneous findings associated with drug reaction with eosinophilia and systemic symptoms (DRESS). Panel B shows the morphologic features of cutaneous adverse reactions, including DRESS — erosive and exfoliative changes in a patient with DRESS, a morbilliform eruption concentrated on the torso in a patient with an uncomplicated drug eruption, labial erosions with hemorrhagic crusting in a patient with the Stevens–Johnson syndrome and full-thickness epidermal necrosis with bullae formation and a positive Nikolsky's sign in a patient with toxic epidermal necrolysis, nonfollicular pustules (1 to 2 mm in diameter) on a background of erythema in a patient with acute generalized exanthematous pustulosis (AGEP), and a patient with severe AGEP with erythroderma, numerous sterile pustules, and lakes of pus. AGEP can also be associated with facial edema and the accentuation of earlobe creases.

Antibiotics were the most common medications associated with kidney injury in patients with DRESS, with vancomycin as the cause in 13%; allopurinol and anticonvulsants were also frequent culprits.[17] Most of the patients with acute kidney injury in that systematic review presented with isolated elevation in the serum creatinine level or a decrease in the glomerular filtration rate.[17] In some cases, kidney involvement included acute kidney injury with proteinuria, oliguria, hematuria, or a combination of the three; isolated hematuria or proteinuria; or anuria.[17] Renal-replacement therapy was used to treat 30% of the affected patients (21 of the 71); many patients appeared to have complete recovery of kidney function, although whether long-term sequelae would develop was unclear.[17]

Pulmonary involvement, which often manifests as shortness of breath, a dry cough, or both, has been reported to develop in up to 32% of patients with DRESS.[5,18] Interstitial infiltrates, acute respiratory distress syndrome, and pleural effusions are the pulmonary abnormalities noted most frequently on imaging; complications have included acute interstitial pneumonitis, lymphocytic interstitial pneumonia, and pleuritis.[5,18] Because pulmonary DRESS is frequently misdiagnosed as pneumonia, its identification requires a high level of suspicion. Furthermore, in almost all cases that include pulmonary involvement, other solid-organ dysfunction has been present.

Myocarditis was reported in up to 21% of patients with DRESS in another systematic review.[19] The appearance of myocarditis was delayed for months in some patients, even after other features of DRESS had resolved.[19] The spectrum of disease ranged from acute eosinophilic myocarditis, which resolved when short-term immunosuppression was administered, to acute necrotizing eosinophilic myocarditis, which led to death in more than 50% of the affected patients and to a median survival duration of just 3 to 4 days.[19,20] Patients with myocarditis generally have presented with dyspnea, chest pain, tachycardia, hypotension, or a combination of these signs and symptoms, along with elevated cardiac enzyme levels, electrocardiographic changes, and echocardiographic abnormalities, including pericardial effusion, systolic dysfunction, septal hypertrophy, and biventricular failure.[2,5,20] Cardiac magnetic resonance imaging may permit visualization of endomyocardial lesions. Although such assessments support the diagnosis of myocarditis, definitive diagnosis requires an endomyocardial biopsy.[20] Pulmonary and myocardial involvement in DRESS are uncommon, and they are reported to be most frequently triggered by minocycline.[18,20]

SCORING AND LABORATORY EVALUATION

The validated European RegiSCAR scoring system is used to diagnose DRESS (Table 2).[5] RegiSCAR criteria include seven features — a core temperature higher than 38.5°C (101.3°F), lymphadenopathy in at least two distinct locations, eosinophilia, atypical lymphocytosis, rash (covering >50% of body-surface area, characteristic morphologic features, or histologic findings consistent with drug hypersensitivity on biopsy), extracutaneous organ involvement, and prolonged time to resolution (>15 days). The score ranges from −4 to 9 and allows for four levels of diagnostic certainty, with a score of less than 2 indicating no disease, a score of 2 to 3 indicating possible disease, a score of 4 to 5 indicating probable disease, and a score of more than 5 indicating definite DRESS. RegiSCAR scoring is most useful for retrospective validation of possible cases, because patients

Table 1. Common Causes of DRESS.

Drug Category and Drug	
Antiinflammatory and analgesic	**Antiviral**
Celecoxib	Boceprevir
Diclofenac	Nevirapine*
Ibuprofen	Telaprevir
Antiarrhythmic	**Antidepressant**
Mexiletine*	Amitriptyline
Antibiotic	**Immunomodulator**
Amoxicillin	Hydroxychloroquine
Ampicillin	Sulfasalazine*
Ceftriaxone	**Iodinated contrast medium**
Dapsone*	Iodixanol*
Ethambutol*	Iohexol*
Isoniazid*	Iomeprol*
Levofloxacin	Ioversol*
Minocycline*	**Proton-pump inhibitor**
Piperacillin–tazobactam*	Omeprazole
Pyrazinamide	**Targeted anticancer therapy‡**
Rifampin*	Daclizumab
Streptomycin	Imatinib
Trimethoprim–sulfamethoxazole*†	Sorafenib
Vancomycin*†	Vemurafenib
Anticonvulsant	**Xanthine oxidase inhibitor**
Carbamazepine*†	Allopurinol*†
Lamotrigine*†	
Oxcarbazepine*	
Phenobarbital*	
Phenytoin*	

* These drugs are associated with a high risk of drug reaction with eosinophilia and systemic symptoms (DRESS).
† These drugs are the five most common drugs associated with DRESS in the United States. In order of decreasing prevalence, they are: allopurinol, vancomycin, lamotrigine, carbamazepine, and trimethoprim–sulfamethoxazole.
‡ The strength of the association of DRESS with these newer therapeutic agents requires further study.

may not initially meet or be eligible to be assessed for all the criteria included in the score.

DIFFERENTIAL DIAGNOSIS

DRESS must be distinguished from other severe cutaneous adverse reactions — namely, the Stevens–Johnson syndrome and its related disease, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis (AGEP) (Fig. 1B and Table S2). The latency period of DRESS is generally longer than that of other severe cutaneous adverse reactions.[9] The Stevens–Johnson syndrome and toxic epidermal necrolysis have rapid evolution, with resolution typically occurring over the course of 3 to 4 weeks. Mucosal involvement in DRESS can arouse concern about one of these conditions, but oral mucosal disease in DRESS tends to be milder and less hemorrhagic.[5] Marked dermal edema in DRESS can result in the formation of tense secondary bullae and erosions that are negative for Nikolsky's sign, in contrast to the full-thickness epidermal separation with application of lateral tension seen in the Stevens–Johnson syndrome and toxic epidermal necrolysis, which is consistent with a positive Nikolsky's sign.[21] AGEP manifests within hours to days after drug exposure and typically resolves over the course of 1 to 2 weeks. In contrast to DRESS, AGEP is characterized by flexural accentuation of the rash, which consists of generalized pustules without predilection for hair follicles. A prospective evaluation of patients with DRESS showed that 6.8% had features of the Stevens–Johnson syndrome, toxic epidermal necrolysis, or AGEP, with the reactions in 2.5% of cases considered to be caused by one of these conditions in addition to DRESS (overlapping severe cutaneous adverse reactions).[5] Use of the RegiSCAR validation criteria may help to distinguish these conditions.[5] Common morbilliform drug eruptions typically manifest 1 to 2 weeks after drug exposure (sooner with drug reexposure) and are not usually associated with elevated aminotransferase levels, eosinophilia, or prolonged recovery times. DRESS must also be distinguished from hemophagocytic lymphohistiocytosis, angioimmunoblastic T-cell lymphoma, and acute graft-versus-host disease (see the Supplementary Appendix).

PATHOGENESIS

IMMUNOPATHOGENESIS OF DRESS

DRESS is classified as a type IV (delayed) hypersensitivity reaction, mediated by T-cell activation and the expansion and release of cytokines after antigen presentation by cells or direct T-cell stimulation.[22] The immunopathogenesis of DRESS, however, is considered to be complex, and much remains unknown. Small-molecule drugs are generally considered to be nonimmunogenic and do not lead to DRESS; several models through

Table 2. RegiSCAR Scoring System for Diagnosis of DRESS.*

Criterion	Subtract 1 Point	0 Points	Add 1 Point	Add 2 Points	Minimum Scorable Points†	Maximum Scorable Points†
Acute skin eruption					−2	+2
Rash is extensive		No or unknown	>50% BSA			
Rash morphology consistent with DRESS	No	Unknown	Yes			
Biopsy suggesting DRESS	No	Yes or unknown				
Fever ≥38.5°C	No or unknown	Yes			−1	0
Lymphadenopathy		No or unknown	Yes		0	+1
Internal organ involvement					0	+2
Liver‡		No or unknown	Yes			
Kidney		No or unknown	Yes			
Lung		No or unknown	Yes			
Muscle or heart		No or unknown	Yes			
Pancreas		No or unknown	Yes			
Other		No or unknown	Yes			
Eosinophilia					0	+2
Eosinophil count — $\times 10^{-9}$ per liter		<0.7	0.7–1.49	≥1.5		
Eosinophil percentage, if leukocyte count <4.0×10⁹ per liter — %			19.9	≥20		
Atypical lymphocytes		No or unknown	Yes		0	+1
Resolution time >15 days	No or unknown	Yes			−1	0
Absence of signs of alternative diagnoses		No or unknown	Yes		0	+1
Presence of antinuclear antibodies						
Positive blood culture						
Positive serologic test for hepatitis A, B, or C viruses						
Positive test for *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*						

* The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score ranges from −4 to 9; the final score can be used to classify a case of DRESS as excluded (<2), possible (2 to 3), probable (4 to 5), or definite (>5).[5] To use this scoring system, start with 0 points, and for each item in the list, either subtract 1 point, add 0 points, or add 1 or 2 points. BSA denotes body-surface area.

† Shown are the minimum or maximum points that can be scored per criterion (e.g., even if three organs are involved, only 2 points can be scored in that category).

‡ Liver involvement is defined by a serum alanine aminotransferase or conjugated bilirubin level more than twice the upper limit of the normal range on two or more successive dates or by aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels all more than twice the upper limit of the normal range.[15]

which drugs are able to elicit a maladaptive immune response manifesting as DRESS have been proposed (Fig. 2).[23] In DRESS, as in other severe cutaneous adverse reactions, cytotoxic T cells are thought to mediate the damage.[24] Activated CD8+ T cells are capable of producing robust amounts of tumor necrosis factor α (TNF-α). In one prospective study, levels of type 1 helper T-cell (Th1) cytokines, interferon-γ, and interleukin-2 were increased in the blood of patients with DRESS as compared with the levels in healthy volunteers.[24]

A prominent type 2 helper T-cell (Th2) signature distinguishes DRESS from other severe cutaneous adverse reactions. Choquet-Kastylevsky

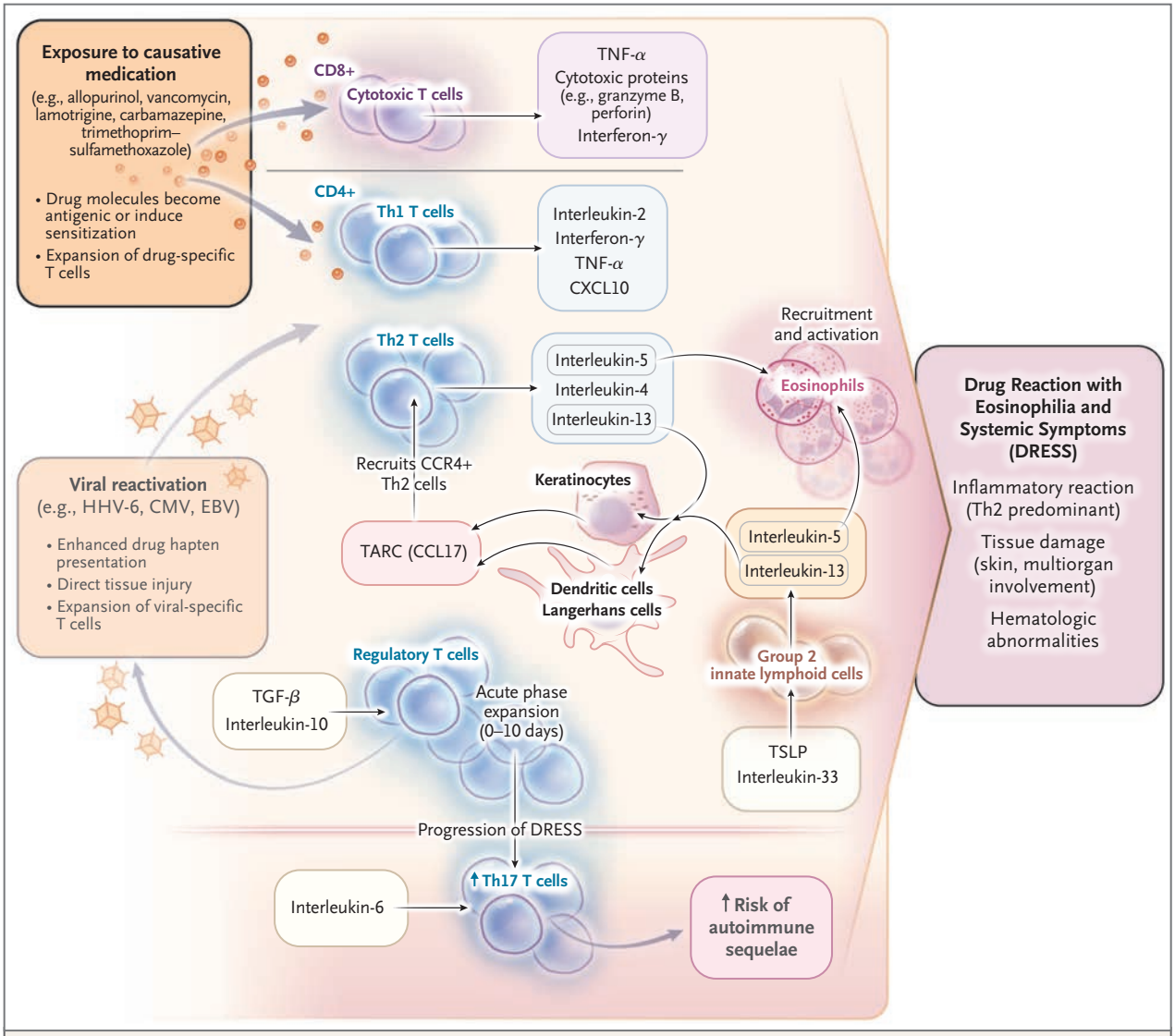


Figure 2. Select Inflammatory and Immunologic Processes Relevant to DRESS.

There are several proposed mechanisms by which drug molecules become antigenic or induce sensitization, leading to an expansion of drug-specific T cells. Both CD4+ and CD8+ T cells play a role in mediating inflammation in DRESS. Type 1 helper T cells (Th1) produce cytokines such as interferon-γ, tumor necrosis factor α (TNF-α), and CXCL10, and type 2 helper T cells (Th2) produce cytokines such as interleukin-5, interleukin-4, and interleukin-13. Interleukin-5 is intimately involved in the recruitment, activation, and survival of eosinophils. Thymus- and activation-regulated chemokine (TARC, or CCL17), which is produced mainly by keratinocytes, dendritic cells (DCs), and Langerhans cells, recruits Th2 cells that express CC chemokine receptor 4 (CCR4). Interleukin-13 can direct DCs toward Th2 polarization and promote TARC production. Group 2 innate lymphoid cells, which are responsive to thymic stromal lymphopoietin (TSLP) and interleukin-33, produce large amounts of interleukin-5 and interleukin-13 as well. The role of viral reactivation in DRESS is not completely understood, but proposed mechanisms include enhanced drug hapten presentation, direct tissue injury, and expansion of virus-specific T cells. Regulatory T cells, which function to hamper immune responses, may proliferate in the early phase of DRESS in response to transforming growth factor-β (TGF-β) and interleukin-10 and promote viral reactivation. In later phases of DRESS, regulatory T cells exposed to inflammatory cytokines such as interleukin-6 may develop a type 17 helper T cell (Th17) phenotype. Some authors have postulated that the proliferation of Th17 cells in the later stages of DRESS could partly explain the risk of autoimmune sequelae after resolution of DRESS. CMV denotes cytomegalovirus, EBV Epstein–Barr virus, and HHV human herpes virus.

et al. observed that levels of interleukin-5 were elevated in patients with drug reactions associated with eosinophilia, although others have reported contradictory findings.[25] Ogawa et al. observed that levels of one of the ligands of CC chemokine receptor 4 (CCR4), thymus- and activation-regulated chemokine (TARC, or CCL17), were elevated in the serum of patients with DRESS but not in patients with the Stevens–Johnson syndrome or toxic epidermal necrolysis or in patients with uncomplicated morbilliform reactions.[26] Dermal dendritic cells are considered the source of TARC.[26] TARC is associated with Th2-predominant inflammatory reactions, and elevated TARC levels have been found to correlate with peripheral eosinophilia and human herpes virus (HHV)–6 reactivation in patients with DRESS.[26,27]

Evidence suggests that an imbalance in the number of regulatory T cells also differentiates DRESS from other severe cutaneous adverse reactions.[28] Takahashi et al. observed that the regulatory T-cell compartment expanded during the acute phase (e.g., days 0 to 11) of DRESS and that the resolution of DRESS was associated with contraction of the regulatory T-cell compartment, with a shift toward predominance of type 17 helper T cells.[28] These authors postulated that such fluctuations in the regulatory T-cell compartment were driven by the relative predominance of classical monocytes early in the disease and patrolling monocytes late in the disease. Furthermore, they hypothesized that the relative abundance of regulatory T cells early in acute DRESS created an environment permissive to HHV reactivation.

VIRAL REACTIVATION

Viral reactivation, especially HHV-6 reactivation, has been closely linked to DRESS, most typically peaking approximately 2 to 3 weeks after the onset of DRESS.[29] However, the exact role of viruses in the initiation and evolution of DRESS is unclear. Furthermore, viral reactivation has been noted in other severe cutaneous adverse reactions.[30] Conversely, DRESS may occur in the absence of viral reactivation.[29,31] HHV-6 reactivation has been associated with flares and increased disease severity, and cytomegalovirus reactivation has been associated with increased mortality in DRESS.[24,32,33] Picard et al. found HHV reactivation in 76% of patients with DRESS, and they found isolated T cells specific to Epstein–Barr virus (EBV) even in patients without evidence of EBV reactivation.[24] These investigators suggested that DRESS-inciting drugs might have precipitated viral reactivation and viral antigen presentation, which in turn generated a multiorgan inflammatory response in genetically susceptible persons.[24] Lee et al. found a higher frequency of CD4+ T cells bearing the HHV-6 entry-specific receptor CD134 in the skin of patients with DRESS than in the skin of patients with erythema multiforme.[34] Recent Delphi-based consensus guidelines recommend testing for reactivation of HHV-6 in patients with DRESS, although validation is needed to determine the clinical utility of such testing.[35]

GENETIC ASSOCIATIONS

Genetic variations that affect drug metabolism and immune responses may increase susceptibility to the development of severe cutaneous adverse reactions. A major function of HLAs is to present peptides and antigens to T-cell receptors and either elicit an immune response or establish immune tolerance.[36] Certain drugs or their metabolites can bind directly to HLA complexes and stimulate a T-cell response.[37] HLA variants are associated with certain types of drug reactions, including DRESS (Table S3). This association is drug specific and population specific; identifying at-risk HLA genotypes through testing may be useful for screening of patients before high-risk drugs are prescribed or in establishing a diagnosis of DRESS.

TREATMENT

Consensus guidance or guidelines for the treatment of DRESS are currently lacking; recommendations are based on observational data and expert opinion. Comparative studies to inform treatment are also lacking, and therefore therapy is not uniform.

REMOVAL OF CAUSATIVE DRUGS

The first and most critical step in treating DRESS is to identify and discontinue the most likely causative drug or drugs. The construction of a drug chart for the affected patient may be helpful (Table S4). Using such a chart, clinicians may docu-

ment the possible causative agents and the temporal relationship between drug exposure and the onset of rash, eosinophilia, and organ involvement. The most likely culprit drug is then identified and discontinued. The adaptation of drug-causality algorithms that are used for other severe cutaneous adverse reactions can also be considered.[38]

PHARMACOLOGIC TREATMENT

Glucocorticoids

Systemic glucocorticoids are the mainstay of treatment for both induction of remission and treatment of relapses of DRESS. Although the typical starting dose of glucocorticoids is 0.5 to 1 mg per kilogram of body weight for prednisone equivalents,[39] experimental studies evaluating the efficacy of glucocorticoids in this clinical context are lacking, as are studies of different doses and courses. The glucocorticoid dose is not tapered until clinical improvement is observed — namely, reduced rash, decreased eosinophilia, and recovery from organ failure. A gradual glucocorticoid taper over the course of 6 to 12 weeks is recommended to reduce the risk of relapse.[40] When induction of remission is not achieved with 1 mg per kilogram per day of prednisone, "pulse" glucocorticoid therapy (equivalent to 250 mg per day of prednisone for 3 days) can be used, also followed by a gradual taper.[39]

Patients with mild DRESS have been successfully treated with high-potency topical glucocorticoids. For example, Uhara et al. reported that 10 patients with DRESS recovered completely without the use of systemic glucocorticoids.[41] The topical approach is not currently broadly recommended because it is not clear which patients can safely forgo systemic treatment.

Glucocorticoid-Sparing and Targeted Treatments

Glucocorticoid-sparing treatments can be considered for DRESS, particularly in patients at high risk for complications from high-dose glucocorticoid use, such as infection. Intravenous immune globulin has been reported as beneficial in select cases,[42] though an open-label study showed a high risk of adverse events (mainly thromboembolic) that led to conversion to treatment with systemic glucocorticoids.[43] The potential benefit of intravenous immune globulin in DRESS is hypothesized to be related to antibody clearance, which may help to fight an associated viral infection or reactivation.[44] Intravenous immune globulin is administered in large volumes; thus, it may not be ideal for patients with congestive heart failure, kidney failure, or liver failure.

Mycophenolate mofetil, cyclosporine, and cyclophosphamide have also been used to treat DRESS. Cyclosporine inhibits T-cell activation by blocking the transcription of genes encoding cytokines, including interleukin-5, which stimulates eosinophils and drug-specific T cells that mediate DRESS.[45] In a study involving 5 patients treated with cyclosporine and 21 patients treated with systemic glucocorticoids, cyclosporine use was associated with a lower incidence of disease progression, better clinical and laboratory findings, and a shorter hospital length of stay than glucocorticoids.[46] However, cyclosporine is not currently considered a first-line treatment for DRESS. Azathioprine and mycophenolate mofetil have largely been used for maintenance rather than induction therapy.

Monoclonal antibodies have been used to treat DRESS, including agents blocking the interleukin-5–interleukin-5-receptor axis (e.g., mepolizumab, reslizumab, and benralizumab), Janus kinase inhibitors (e.g., tofacitinib),[47,48] and anti-CD20 monoclonal antibodies (e.g., rituximab). Of these, the anti–interleukin-5 agents appear to be the most accessible, effective, and safe for induction therapy. With respect to the mechanism of efficacy, interleukin-5 levels have been noted to increase early in DRESS, and these increased levels are suspected to be generated by drug-specific T cells.[25] Interleukin-5 is also the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Anti–interleukin-5 agents are typically added for treatment of eosinophilia or organ dysfunction that persists despite the use of systemic glucocorticoids in DRESS.[49,50]

TREATMENT DURATION

Treatment is highly individual and is guided by monitoring of disease progression and the response to therapy. Patients with DRESS are usually hospitalized, and approximately one quarter of patients receive intensive care.[51] Daily symptom assessments, physical examinations, and measurements of laboratory findings indicative of organ involvement and eosinophilia are typically necessary while the patient is hospitalized,

and weekly assessments are continued after discharge from the hospital. Prolonged and comprehensive monitoring may be necessary, since relapses may occur late, with onset during a glucocorticoid taper or spontaneously after remission, and may appear as a single symptom or organ finding.[52]

DIAGNOSTIC TESTING

Although there are no histologic features that are pathognomonic for DRESS, a cutaneous punch biopsy can be performed to rule out mimicking conditions.[53] A single approved diagnostic test to determine drug causality in DRESS does not exist. However, in vivo drug-allergy testing with delayed intradermal injection or patching may be appropriate in certain situations, depending on the specific clinical history, disease phenotype, and implicated drug.[54] Both delayed intradermal tests and patch tests are performed only when patients are no longer receiving systemic glucocorticoids. Delayed intradermal testing involves placement of a small amount of drug intradermally on the arm, with assessment for a reaction performed after 48 hours. The prevalence of patients with a positive skin-test result varies according to drug, so such testing is useful only in certain situations.[55-57] Although intradermal testing is considered safe and potentially useful in DRESS (with 40% of tested patients receiving positive test results),[56] some guidelines still state that all intradermal testing in the context of current or previous severe cutaneous adverse reactions should be contraindicated.[58,59] Patch testing involves placing a drug, typically solubilized in petrolatum, under an occlusive dressing affixed to the skin before evaluation for a skin reaction, typically at days 2 and 4.[60] Although patch testing is used widely to diagnose allergic contact dermatitis, its diagnostic properties in DRESS are unknown; however, the sensitivity of patch testing has been reported to be as high as 65%, depending on the drug or drug class investigated.[61,62] To reduce the risk of a false negative test result, patch testing should be performed at least 6 months after the resolution of acute DRESS.[63] Patch testing can be useful for cases of DRESS due to anticonvulsants, beta-lactams (notably amoxicillin), iodinated contrast media, and proton-pump inhibitors.[58,61] Although allopurinol and sulfasalazine are frequently associated with DRESS, patch testing has not been shown to be useful in diagnosing DRESS associated with these drugs.[58]

HLA testing may also inform drug causality in specific cases, such as vancomycin-associated DRESS.[64] The enzyme-linked immune absorbent spot (ELISpot) test is an ex vivo assay used to detect serum antigen-specific cytokine-producing cells (most commonly interferon-γ) in the presence of pharmacologic doses of a drug or a metabolite of a drug.[65,66] The interferon-γ–release ELISpot assay has been shown to be positive in the majority of confirmed DRESS cases and can be used to identify the culprit in approximately 20% more cases than delayed intradermal skin testing alone. The lymphocyte transformation test is another test, currently used only in research settings, that measures the proliferation of T cells in the presence of a drug.[67] The lymphocyte transformation test may be useful in DRESS, but its low sensitivity makes it less useful in the acute stage.[68]

Since most common medical conditions that can be treated with medication can be treated with several structurally unrelated drugs, drug challenge with a potential culprit drug is unnecessary in almost all patients who have had DRESS and is, in fact, contraindicated. In rare cases, however, the benefit of drug challenge may outweigh the risk (e.g., in a patient with drug-resistant tuberculosis who must receive a specific antituberculous drug).[69] The absence of a reaction to a single dose of an implicated drug does not rule out DRESS because multiple doses are typically needed to provoke such reactions.[70] The signs and symptoms of DRESS generally recur with shorter latency after drug reexposure.[71]

RECURRENCES, RELAPSES, AND LONG-TERM SEQUELAE

DRESS can have a prolonged course with episodes of remission and relapse, despite withdrawal of a causative drug and prompt initiation of treatment of the relapse.[2,72] Patients who have had DRESS should subsequently avoid the culprit drug and all structurally related drugs.[52] Although the reasons for recurrence and relapse are usually unknown, viral reactivation is hypothesized as contributory.[33,73] An alternative concept is that im-

munosuppression from long-term glucocorticoid use may lead to long-term immune dysregulation.[28,74] Additional explanations for recurrence and relapse include inadvertent exposure to the culprit drug and multiple drug hypersensitivity syndrome, which is characterized by hypersensitivity to multiple unrelated drugs.[75]

Although many patients fully recover from DRESS, some have persistent complications. Chronic complications, which affect more than 10% of survivors, include organ dysfunction, new autoimmune disease (e.g., autoimmune thyroiditis, alopecia areata, vitiligo, type 1 diabetes mellitus, systemic lupus erythematosus, and autoimmune hemolytic anemia), and psychiatric complications (e.g., depression, anxiety, and a phobia of taking medications).[76,77] Such complications can occur years after an episode of DRESS. Although more longitudinal studies are needed to inform follow-up recommendations, monitoring should begin soon after hospital discharge and continue as needed to address the physiological and psychological sequelae of DRESS.[35,78]

SUMMARY

DRESS, the most prevalent severe cutaneous adverse reaction, classically manifests with rash and fever accompanied by facial edema, lymphadenopathy, hematologic changes, hepatitis, acute kidney injury, or a combination of these signs and symptoms, and it is most often associated with antiepileptics, antibiotics, allopurinol, or nonsteroidal antiinflammatory drugs. DRESS is a delayed, type IV hypersensitivity reaction, although its prolonged course after discontinuation of the offending medication, association with viral reactivation, and coexisting long-term autoimmune sequelae suggest that complex immune mechanisms are involved. DRESS must be distinguished from other severe cutaneous adverse reactions, as well as from other life-threatening conditions, such as hemophagocytic lymphohistiocytosis, angioimmunoblastic T-cell lymphoma, and acute graft-versus-host disease. Management of DRESS consists of the prompt discontinuation of potential culprit drugs, supportive care, and immunosuppressive therapy. Systemic glucocorticoids are first-line treatments, although there is emerging evidence for alternative immunosuppressive and targeted treatments, including biologic medications. Although no validated diagnostic tests for DRESS presently exist, consultation and care with a dermatologist or an allergist–immunologist may be useful in assessing drug causality and identifying alternative drugs that are safe for use. DRESS may have a relapsing and remitting course and varied long-term sequelae that require multidisciplinary follow-up care and patient support.

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