[LITERATURE REVIEW]

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

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ABSTRACT

Drug rash with eosinophilia and systemic symptoms syndrome is a severe idiosyncratic drug reaction with a long latency period. It has been described using many terms; however, drug rash with eosinophilia and systemic symptoms syndrome appears to be the most appropriate. This syndrome causes a diverse array of clinical symptoms, anywhere from 2 to 8 weeks after initiating the offending drug. Standardized criteria for the diagnosis have been developed; however, their utility remains to be validated. Unfortunately, the management of drug rash with eosinophilia and systemic symptoms syndrome is not well supported by strong evidence-based data. (*J Clin Aesthet Dermatol.* 2013;6(6):31–37.)

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a distinct, severe, idiosyncratic reaction to a drug characterized by a prolonged latency period. It is followed by a variety of clinical manifestations, usually fever, rash, lymphadenopathy, eosinophilia, and a wide range of mild-to-severe systemic presentations.

EVOLVING NOMENCLATURE

The introduction of new drugs led to a wide range of systemic and cutaneous reactions. When hydantoin was introduced in the 1940s, reports of lymphadenopathy (LAP) soon followed.[1] The lymph node biopsies in these cases demonstrated a lymphomatous appearance, which was termed *drug-induced pseudolymphoma* by Satlztein.[2] This was followed by the introduction of another anticonvulsant drug, carbamazepine, which induced a reaction consisting of a rash, fever, and LAP. Such a reaction was termed *anticonvulsant hypersensitivity syndrome* (AHS).[3] Shortly thereafter, multiple drugs with a similar range of manifestations were observed. Hence the term *drug-induced hypersensitivity* (DIHS), also known as *hypersensitivity syndrome* (HSS), was coined. The term DRESS was introduced by Bocquet et al[4] and was based on the observation of Callot et al[5] who, in 1996, reported a series of 24 patients. Three of these patients had no constitutional symptoms and only pseudolymphomatous pathology, while the remaining 21 patients developed an acute systemic illness with eosinophilia. The "R" in DRESS was changed from *rash* to *reaction* due to its diverse cutaneous presentations. Furthermore, the term drug-induced delayed multiorgan hypersensitivity syndrome (DIDMOHS) was coined by Sontheimer[6] to address this condition. All of these different terms add to the confusion in understanding and diagnosing this condition. A consensus should standardize the diagnosis and management of what the authors refer to as DRESS syndrome in this article.

PATHOGENESIS

The pathogenesis of DRESS syndrome is not well understood and is hypothesized to consist of a complex interaction between two or more of the following:

1. A genetic deficiency of detoxifying enzymes leading to an accumulation of drug metabolites. The metabolites covalently bind to cell macromolecules causing cell death or inducing secondary immunological phenomena. Eosinophilic activation as well as activation of the inflammatory cascade may be induced by interleukin-5 release from drug-specific T-cells.[7]
2. Genetic associations between human leukocyte antigen (HLA) associations and drug hypersensitivity may occur. These include HLA-B*1502, associated with carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis

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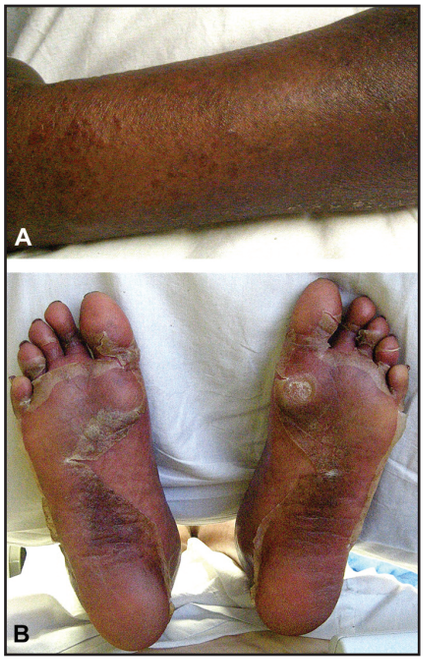

Figures 1A and 1B. Erythematous scaly patch with papules on forearm (A). Desquamation of soles. Upon closer inspection, petechiae were visible (B).
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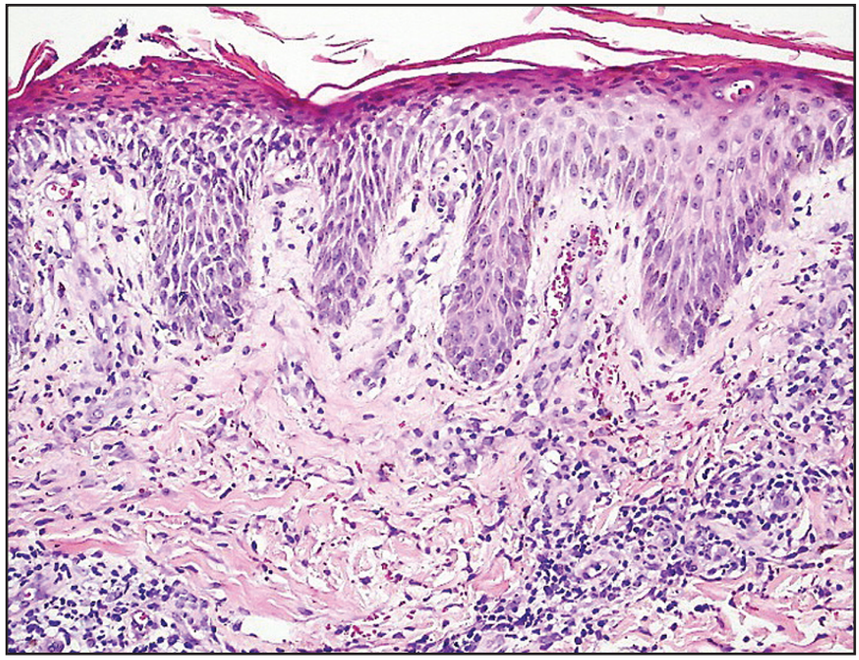

Figure 2. Parakeratosis, intracorneal neutrophilic pustule, spongiosis, and mixed perivascular infiltrate (Hematoxylin and eosin stain; original magnification: ×200.)
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TABLE 1. Drugs and their constellation of manifestations observed as DRESS syndrome[22]

NAME OF DRUG	CONSTELLATION OF MANIFESTATIONS OBSERVED
Lamotrigine	Fever and toxic epidermal necrosis
Allopurinol	Dysfunction and eosinophilia without fever appearing several months after the start of treatment
Minocycline	Peripheral adenopathies, eosinophilia, heart abnormalities, and eosinophilic pneumopathy
Abacavir	Gastrointestinal and acute viral pneumonia-like symptoms of rapid occurrence after the introduction of treatment

(TEN)[8]; HLA-B*1508, associated with allopurinol induced SJS/TEN[9]; and many others.[10–13] It was also observed that the association of HLA-B*1502 and CBZ-induced SJS/TEN could be ethnicity-specific as observed in Chinese populations.[14,15] Furthermore, the association of CBZ-induced drug hypersensitivity reactions seems to be phenotype-specific.[9]

3. A possible virus-drug interaction associated with viral reactivation may also exist. This phenomenon has been previously observed for herpes viruses (notably Epstein-Barr virus [EBV]).[16] The clinical manifestations appear to be a result of an expansion of virus-specific and nonspecific T cells. In fact, drug-specific T-cells have been isolated from the blood and skin of patients in whom DRESS syndrome was induced by lamotrigine and CBZ.[17–19] Shiohara et al[20] reviewed the latest evidence regarding the association of viral infections and drug rashes as well as the mechanisms of how viral infections can induce drug rashes. They observed that sequential reactivations of several herpes viruses (HHV-6, HHV-7, EBV, and cytomegalovirus) can be detected coincident with the clinical symptoms of drug hypersensitivity reactions.[20] The pattern of the herpes virus re-activation was noted to be similar to that

observed in graft-versus-host disease (GVHD),[21,22] thus suggesting that DRESS may resemble GVHD in the sense that antiviral T-cells can cross-react with the drugs and do not only arise from the oligoclonal expansion of drug-specific T-cells. Kano et al[16]Review due also studied whether immunosuppressive conditions that allow HHV-6 reactivation could be specifically detected in the setting of anticonvulsant hypersensitivity syndrome (AHS). In order to test this idea, they performed serological tests for antibody titers for various viruses and found that serum immunoglobulin G (IgG) levels and circulating B-cell counts in patients with AHS were significantly decreased at onset compared with control groups ($P<0.001$ and $P=0.007$, respectively). These alterations returned to normal levels on the patient's recovery. Additionally, they observed that the reactivation of HHV-6 measured by a greater than fourfold increase in HHV-6 IgG titers was exclusively detected in patients with AHS who had decreased IgG levels and B-cell counts. These findings suggest an association between the severity of AHS and possibly DRESS syndrome.

CLINICAL FEATURES

DRESS syndrome is a complex syndrome with a broad spectrum of clinical features. The clinical manifestations are not immediate and usually appear 2 to 8 weeks after introduction of the triggering drug.[23] Common features consist of fever, rash, LAP, hematological findings (eosinophilia, leukocytosis, etc.), and abnormal liver function tests, which can mimick viral hepatitis. The cutaneous manifestations typically consist of an urticarial, maculopapular eruption and, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma (Figures 1, 2).[22,24] Visceral involvement (hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis) is the major cause of morbidity and mortality in this syndrome.[4,25] Many cases are associated with leukocytosis with eosinophilia (90%) and/or mononucleosis (40%).[5]

The life-threatening potential of DRESS syndrome is high and the mortality is estimated to be around 10 percent in multiple studies.[24,26] Antiepileptic medications, such as phenytoin and Phenobarbital, are thought to be the predominant cause of DRESS syndrome with an incidence of 1 per 5,000 to 10,000 exposures.[27]

Peyrière et al[22] investigated the marked variability in the clinical patterns of cutaneous and systemic manifestations of DRESS syndrome in 2006. Their goal was to better define the relationship of the clinical features with the instigating medications.[22] In their retrospective study, 216 cases of drug-induced cutaneous side effects with systemic symptoms were investigated between 1985 and 2000. They compared these records with reports from the literature for the potential DRESS syndrome-inducing drugs. The patients who had febrile skin eruptions accompanied by eosinophilia and/or systemic symptoms occurred during treatment with anticonvulsants, minocycline, allopurinol, abacavir, or nevirapine. The only feature that was found to be consistently present was a 2- to 6-week latency period for carbamazepine. Cutaneous findings were present in the majority of cases (70–100%). However, a wide variety of cutaneous findings were observed; notably, diffuse maculopapular inflammatory reactions (most common), erythroderma, SJS/TEN, erythema multiforme (EM), and pruritic eruptions. Eosinophilia was the most frequently occurring hematological abnormality (>50% of the cases). Other hematological abnormalities observed were thrombocytopenia, anemia, neutropenia, and the presence of large, activated lymphocytes (atypical lymphocytes). LAP was present in a majority (80%) of the cases involving minocycline, while it was a rare finding in cases where other drugs were used. Hepatic involvement in the form of hepatocellular necrosis was the most common visceral abnormality; however, abdominal pain, nausea, and diarrhea were noted with abacavir. Renal dysfunction (mostly proteinuria) was observed most often with allopurinol. Minocycline (eosinophilic pneumopathy, 33% of cases) and abacavir (tachypnea, cough, and pharyngitis) were the drugs associated with lung involvement. It was speculated that the different symptoms associated with each drug were in some way related to the degree of chemical specificity to each drug itself or to its reactive metabolites. It was clear from the study that data from the Peyrière et al study and the literature were similar.[22] Although no clear relationships could be established, some general trends were noted, which have been listed in Table 1.

Following this study, other retrospective analyses were conducted in 60 patients in Taiwan by Chen et al,[28] 38 cases in Korea by Um et al,[29] 30 cases in another study in Taiwan by Chiou et al,[26] and 15 patients in France by Eshki et al[24] (Table 2).

DIAGNOSTIC CRITERIA

The diagnosis of DRESS syndrome is mainly clinical and one must consider the latency period, diversity of symptoms, and exclusion of similar non-drug-induced conditions. Multiple diagnostic criteria have been developed and used in order to standardize the diagnosis and management of DRESS, albeit with limited success. The RegiSCAR group suggested criteria for hospitalized patients with a drug rash to diagnose DRESS syndrome (Table 3).[24] A Japanese group suggested another set of diagnostic criteria, which includes HHV-6 activation (Table 4).[30]

Certain diagnostic tools have been tried to predict the possibility of DRESS in certain patients. Rechallenging with the suspected drug is considered the gold standard for drug eruptions; however, it cannot be used to confirm the culprit drug for DRESS due to the possible life-threatening consequences. Unfortunately, the lymphocyte transformation/activation test is not standardized for most drugs, it is difficult to perform, has low sensitivity and specificity, and was found to be negative during the acute phase of DRESS syndrome.[31]

In an attempt to identify a more effective diagnostic test, Santiago et al[32] evaluated the safety and usefulness of patch

TABLE 2. Retrospective analyses detailing patient characteristics

STUDY (LOCATION AND YEAR)	NUMBER OF PATIENTS (TIME PERIOD WHERE PATIENTS WILL BE ENROLLED)	MOST COMMON CAUSATIVE DRUGS	LATENCY PERIOD RANGE (MEAN) IN DAYS	TREATMENT
Chen et al (Taiwan 2010)[28]	38 (18 men and 20 women) March 2004–January 2009	• Allopurinol (32%) • Phenytoin (18%) • Dapsone (17%) • CBZ, cotrimoxazole, penicillin, NSAIDs (5% each) • Lamotrigine, antituberculous drugs, Chinese drugs (3% each)	3-76 (20.7)	• Systemic CTS—45 (75%) (either methylprednisone or oral prednisone) • IVIG—2 out of the 45—one recovered and one died • Antibiotics—6 patients • Only supportive care—10 patients
Um et al (Korea 2010)[29]	60 (26 men and 34 women) June 1998–May 2008	• Anticonvulsants (47.4%) • Antibiotics (18.4%) • NSAIDs (13.2%) • Allopurinol (5.3%) • Undetermined agents (15.8%)	3-105 (25.2)	• Systemic CTS—42.1% (one patient died of opportunistic infection, one patient had progressive deterioration of liver damage) • Topical CTS + antihistamines—57.9% • Complete recovery—36 (94.8%)
Chiou et al (Taiwan 2008)[26]	30 (15 men and 15 women) Jan 2001–June 2006	• Allopurinol 11 (36.7%) • CBZ 6(20%) • Phenytoin, indomethacin, vancomycin 2 (6.67%) • Levamisole, dapsone 1(3.33%) • Undetermined 3(10%)	3-60 (23.49)	• Systemic CTS—22 (76%) • Oral histamine and supportive care—7 (24%)
Eshki et al (France 2009)[24]	15 (5 men and 10 women) Jan 1995–Dec 2006	• Allopurinol 4 (27%) • Minocycline 3 (20%) • Anticonvulsants 3 (20%) • Sulfonamides 2 (13.3%) • Others 2(13.3%)	5-95 (18)	• Systemic CTS—10 (67%) • IVIG—3 (20%) • Liver transplant—1 (6.7%)

CBZ=Carbamazepine; CTS=corticosteroids; IVIG=intravenous immunoglobulin; EM= erythema multiforme; DM=Diabetes mellitus

TABLE 2 (continued). Retrospective analyses detailing patient characteristics

SKIN MANIFESTATIONS	OTHER SIGNS/SYMPTOMS AND CLINICAL PRESENTATIONS	HISTOPATHOLOGICAL FINDINGS	LABORATORY FINDING	MORTALITY	SEQUELAE
• Diffuse exanthematous eruptions ± facial edema—100% • Followed by exfoliative dermatitis or blister/purpura—6 (10%)	• Fever—52 (87%) • LAP—17 (31%)	**17 had skin biopsy** • 13 (77%) showed various degrees of basal vacuolization, dyskeratosis, lymphocyte exocytosis, dermal edema, superficial perivascular inflammation (mainly eosinophils but no atypical cells), thus diagnosed as EM • 2 (12%)—only perivascular inflammation by mixed cells • 1 (6%)—lymphocytic vasculitis • 1 (6%)—pigment incontinence without obvious interface activity **6 underwent bone-marrow biopsy** • 5 showed hypocellularity with decreased myeloid and erythroid series, all showed increased megakaryocytes and interstitial infiltration • 1 showed hypercellularity and increased M/E ratio to 5:1 with myeloid hyperplasia	• Elevated liver enzymes—48 (80%) • Renal involvement—24 (40%) • Lung involvement—20 (33%) • Cardiac involvement—9 (15%) • Pancreas involvement—3 (5%) • Lymphocytosis—15 (25%) • Lymphocytopenia—27 (45%) • Atypical lymphocytes—38 (63%) • Eosinophilia—31 (52%) • Thrombocytopenia—15 (25%) • IgG to EBV and CMV in 9 patients • IgG to HHV6 positive in 1 patient	10%	• Acute renal failure—5 cases (one died of multi-organ failure and one received dialysis) • Hepatic failure—4 cases • Hyperthyroidism developing into Grave's disease—one patient • Death due to septic shock—3 patients
Not described	• Liver involvement—60 (100%) • LAP—20 (52.6%) • Renal involvement— 6 (15.7%) • Lung involvement—1 (2.6%) • Muscle involvement—1 (2.6%)	Not described	• Eosinophilia—35 (92.1%) • Atypical lymphocytosis—18(47.4%) • Thrombocytopenia—9(23.7%) • Pancytopenia—1(1.7%) • Leukopenia—1(1.7%)	10%	Discussed under treatments
• Exanthematous or maculopapular rash—24(80%) • Erythroderma—7(23.3%) • Vasculitis—7 (23.3%) • Mucosal involvement 17 of 28 patients	• Fever—21 (72.4%) • Jaundice—5 (17.2%) • LAP—5 (17.2%)	**8 skin biopsies done:** • 3 showed lichenoid dermatitis • 4 showed dyskeratotis cells with basal cells, vacuolar changes, and papillary edema consistent with EM • 1 showed leukocytoclastic vasculitis • 1 showed psuedolymphoma	• Elevated liver enzymes—26 (86.6%) • Renal involvement—16 (53.3%) • Cardiac involvement—2 (6.7%) • Lung involvement—1 (3.3%) • Leucocytosis—18 (62%) • Eosinophilia—14 (48%) • Atypical lymphocytes—13 (45%) • Thrombocytopenia—11 (38%) • HHV6 reactivation—positive in 7 out of 11 cases tested	10%	• Most recovered spontaneously • Deterioration of renal function—10/29 patients • Deterioration of liver function—6/29 patients • Type I DM—2/29 patients • Death—3 patients (had underlying disease)
Erythroderma and facial edema	Not quantified—hepatitis, pneumonitis, renal failure, hemophagocytic syndrome, encephalitis	Not described	• Lung involvement—10 (67%) • Liver involvement—7 (47%) • Renal involvement—5 (33%) • Pancytopenia—2 (13%) • HHV6 reactivation—6 of 7 patients tested	20%	Death—3 patients

CBZ=Carbamazepine; CTS=corticosteroids; IVIG=intravenous immunoglobulin; EM= erythema multiforme; DM=Diabetes mellitus

TABLE 3. RegiSCAR criteria for diagnosis of DRESS[24]

Hospitalization
Reaction suspected to be drug-related
Acute rash
Fever >38°C*
Enlarged lymph nodes at a minimum of 2 sites*
Involvement of at least 1 internal organ*
Blood count abnormalities*
Lymphocytes above or below normal limits
Eosinophils above the laboratory limits
Platelets below the laboratory limits

Three out of four asterisked (*) criteria are required for making the diagnosis.

TABLE 4. Japanese group's criteria for diagnosis of DRESS/DIHS[30]

Maculopapular rash developing >3 weeks after starting with the suspected drug
Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug
Fever >38°C
Liver abnormalities (alanine aminotransferase>100U/L)
Leucocyte abnormalities
Leucocytosis (>11 X 109/L)
Atypical lymphocytosis (>5%)
Eosinophilia (>1.5 x 109 /L)
Lymphadenopathy
Human Herpes 6 reactivation

The diagnosis is confirmed by the presence of the 7 criteria (typical DHS).

testing in DRESS, thus attempting to identify a drug-dependent delayed hypersensitivity mechanism. A positive patch test reaction was observed in 18 out of 56 patients (32.1%) (17 with antiepileptics and 1 with tenoxicam). In the antiepileptics group, CBZ alone was responsible for 13 of 17 positive reactions (76.5%). Patch tests with allopurinol and its metabolite were negative in all cases attributed to this drug. It was concluded that patch testing is a safe and useful method in confirming the culprit drug in DRESS induced by antiepileptic drugs, but it had no value in DRESS induced by allopurinol.

The high sensitivity/specificity of some genetic markers provides a plausible basis for the future development of tests to identify individuals at risk for drug hypersensitivity. Genotyping for HLA markers can be used as a screening tool before prescribing such drugs and can therefore prevent DRESS occurrences in specific populations.

MANAGEMENT

DRESS syndrome must be recognized promptly and the causative drug withdrawn. Indeed, it has been reported that the earlier the drug withdrawal, the better the prognosis.[33] Treatment is largely supportive and symptomatic; corticosteroids are often used, but the evidence regarding their effectiveness is scant.[34] Other immunosuppressants, such as cyclosporin, may also be required.[35,36]

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