DRESS Syndrome: Drug Reaction with Eosinophilia and Systemic Symptoms/Drug-Induced Hypersensitivity Syndrome (DHS)

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Background

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DHS), is a rare but potentially lethal adverse drug reaction that classically manifests as a morbilliform rash with associated fever, lymphadenopathy, hematologic abnormalities, and multi-organ manifestations. While anticonvulsants and sulfonamides are the most common offending agents, many other drugs can cause DRESS syndrome. Systemic involvement can manifest with hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine abnormalities [1].

The list of potential offending medications is long (see Table 20.1), but the most common culprits include carbamazepine, phenytoin, phenobarbital, lamotrigine, allopurinol, dapsone, and sulfasalazine [1]. DRESS syndrome is relatively rare, with an incidence of 1/5000 to 1/10,000 prescriptions of each of the causal agents [2–5]. Most cases affect adults without gender predilection, but rare cases have been reported in children [1]. DRESS syndrome carries a 10% mortality risk, usually due to hepatic failure [1].

The pathophysiology of DRESS syndrome remains incompletely understood but involves reactivation of herpesviruses (HHV-6, HHV-7, Epstein-Barr virus [EBV], and cytomegalovirus [CMV]), against which the body mounts a strong immune response [2, 6, 7]. The offending medications may not only affect epigenetic control mechanisms, thereby promoting viral reactivation, but also induce an antiviral T-cell response by interacting with the major histocompatibility complex receptors in

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Table 20.1 Common drugs associated with DRESS

Drug category	Drug name
Anticonvulsant	Carbamazepine, lamotrigine, phenobarbital, phenytoin, valproic acid, zonisamide
Antimicrobial	Ampicillin, cefotaxime, dapsone, ethambutol, isoniazid, linezolid, metronidazole, minocycline, pyrazinamide, quinine, rifampin, sulfasalazine, streptomycin, trimethoprim-sulfamethoxazole, vancomycin
Antiviral	Abacavir, nevirapine, zalcitabine
Antidepressant	Bupropion, fluoxetine
Antihypertensive	Amlodipine, captopril
Biologic	Efalizumab, imatinib
NSAID	Celecoxib, ibuprofen
Miscellaneous	Allopurinol, epoetin alfa, mexiletine, ranitidine

individuals with genetic susceptibility [2]. Two theories currently exist regarding the pathophysiology of DRESS syndrome:

1. Patients with predisposing genetic mutations lack the ability to metabolize certain medications leading to the accumulation of active drug metabolites that then trigger an autoimmune response and/or induce the reactivation of herpesviral infections [1].
2. The reactivation of herpesviruses (mainly HHV-6, but also CMV, EBV, and HHV-7) is triggered by an allergic immune response to a drug with the subsequent activation of T-cell populations (particularly cytotoxic $CD8^+$ lymphocytes) that cause direct tissue damage [1].

In both hypotheses, drug-related reactivation of herpesviral infections directly influences the immune attack on the patient's skin and affected organs leading to the clinical manifestations of DRESS syndrome. Clinical features of DRESS, such as fever, edema, lymphadenopathy, hematologic expansion, and hepatitis, are consistent with those seen in a typical herpesvirus infection and support the hypothesis of a viral infection as a trigger of the syndrome.

Classic Clinical Presentation

The common initial symptoms of DRESS syndrome are fever, malaise, lymphadenopathy, and a skin eruption. A telling feature of DRESS syndrome is the delay of the onset of symptoms in relation to exposure to the offending medication. These symptoms typically occur 2–6 weeks following the initiation of the offending agent, which is prolonged in contrast to other types of drug eruptions [1, 2]. Medications taken for more than 3 months or initiated less than 2 weeks before the onset of DRESS syndrome are unlikely to be the culprit.

A diffuse morbilliform rash with associated pruritus is the most common cutaneous finding [1]. Occasionally the rash can generalize and progress to erythroderma (>90% involvement). The rash typically begins on the face with characteristic associated facial edema that appears similar to angioedema (Fig. 20.1). The rash then progresses

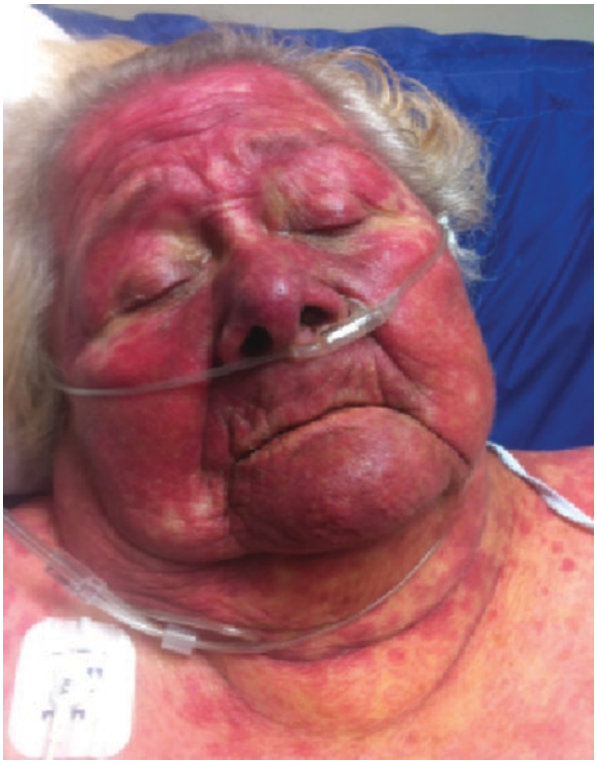

Fig. 20.1 DRESS patient with morbilliform rash and facial edema

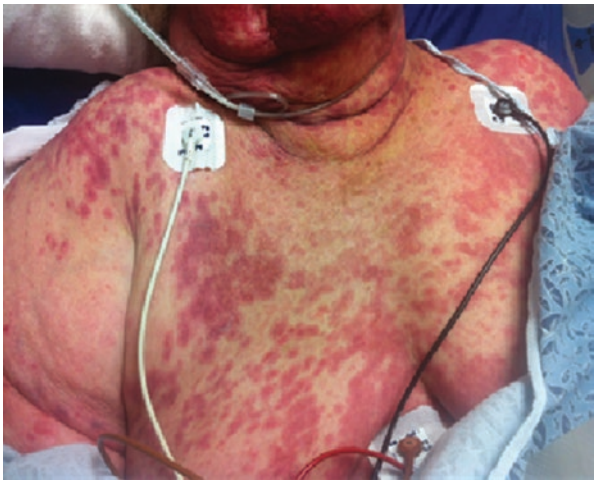

Fig. 20.2 DRESS patient with morbilliform rash progressing from the face to trunk and upper extremities

to the upper trunk and arms (Fig. 20.2) and can also involve the lower extremities (Fig. 20.3). The rash often involves more than 50% of body surface area (BSA) [1]. Other possible cutaneous manifestations include vesicles, bullae, targetoid plaques, purpura, pustules, scaling, and mucosal inflammation with erosions [1] (Fig. 20.4).

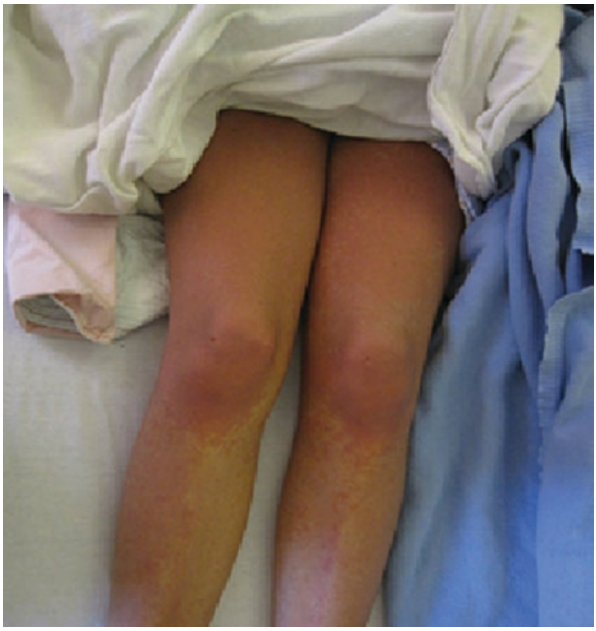

Fig. 20.3 DRESS patient with morbilliform rash that progressed from the face and trunk to lower extremities

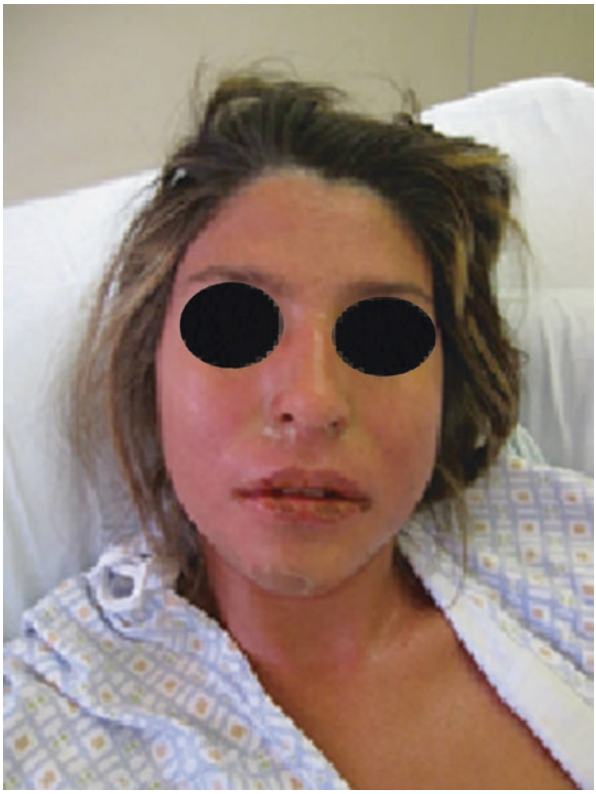

Fig. 20.4 DRESS patient with facial eruption and edema as well as oral and ocular mucosal inflammation and erosion

Atypical Presentation

There are rare cases of DRESS syndrome that exist without "D" (causative drug relation), "R" (rash), "E" (eosinophilia), or "SS" systemic symptoms [9]. In one review of 216 cases over a 15-year period in France, they found a morbilliform eruption in only 70% of cases and eosinophilia in only 50% of cases [10].

Associated Systemic Symptoms

Hematologic and lymphatic involvement are common. Hematologic abnormalities occur in 30–90% of cases and diffuse lymphadenopathy occurs in 30–60% of cases [6, 8, 9]. Hematologic abnormalities include lymphocytosis, eosinophilia, and atypical lymphocytes (mononucleosis-like). Thrombocytopenia and anemia may also be present as part of a hemophagocytic syndrome. Lymphadenopathy is commonly present at cervical lymph nodes but can be found elsewhere and is typically found at multiple sites.

Associated systemic symptoms other than fever, malaise, and rash are directly related to the organ system involved (Table 20.2). Systemic involvement of at least one visceral organ occurs in approximately 90% of patients. The liver is the most common organ affected with 60–80% of cases showing liver impairment. Renal involvement occurs in 10–30% of cases and lung involvement occurs in 5–25% of cases [11–13]. Hepatic necrosis with fulminant liver failure is the most common cause of mortality in DRESS syndrome. Other organ systems that may be involved include the heart, gastrointestinal tract, pancreas, thyroid, neurologic system (brain and peripheral nerves), muscles, and eyes [9]. Clinical symptoms, laboratory abnormalities, and imaging studies will reflect specific organ involvement (Table 20.2). While multiple drugs can cause DRESS syndrome, some specific drugs have a predilection for specific organ dysfunction (Table 20.2) [16].

Key Physical Exam Findings and Diagnostic Features

A thorough history and physical examination should be performed. DRESS syndrome should be suspected in patients who have received a high-risk medication initiated within the past 2–6 weeks who present with a constellation of the following signs and symptoms [2]:

- Morbilliform skin eruption that may progress to confluent and infiltrated erythema or exfoliative dermatitis.
- Facial edema.
- Fever (38–40°C).
- Enlarged cervical lymph nodes and/or generalized lymphadenopathy
- Systemic manifestations with organ involvement (hepatitis, nephritis, pneumonitis, carditis).
- Histopathology of the skin biopsy can help exclude other entities but is most commonly non-specific.

Table 20.2 Systemic manifestations, related drugs, and clinical findings

Systemic manifestation	Common offending drug	Clinical findings
Cutaneous (majority of cases)	Any	Erythematous morbilliform rash Facial edema Generalized erythroderma Pustular eruption Targetoid lesions Mucositis
Hematologic (30–90% of cases)	Any	Leukocytosis with eosinophilia (>700/microL) Atypical lymphocytosis Thrombocytopenia Anemia
Lymphatic (75% of cases)	Any	Cervical or generalized lymphadenopathy
Hepatic (60–80% of cases)	Phenytoin, minocycline, dapsone	Hepatosplenomegaly Hepatitis with elevated liver enzymes Hepatic necrosis with liver failure Hepatic coagulopathy
Renal (10–30% of cases)	Allopurinol, carbamazepine, dapsone	Renal insufficiency Elevated BUN and creatinine Impaired creatinine clearance Urine eosinophils Interstitial nephritis Renal failure
Pulmonary (5–25% of cases)	Minocycline	Acute interstitial pneumonitis Lymphocytic interstitial pneumonia Pleuritis Acute respiratory distress syndrome Atypical chest X-ray or chest CT scan
Cardiac	Ampicillin, minocycline	Myocarditis Cardiomegaly and pleural effusion on CXR ST and TW changes on EKG Systolic dysfunction with decreased EF, wall thickening, and pericardial effusion on echo Elevation of cardiac enzymes (BNP, CK, and troponin)
Gastrointestinal	Any	Gastroenteritis with dehydration Ulcerations/mucosal erosions with GI bleeding Colitis Pancreatitis
Endocrine	Any	Thyroiditis (autoimmune/Graves' thyroiditis) Sick euthyroid syndrome
Neurologic	Any	Meningitis Encephalitis Polyneuritis Brain lesions on MRI
Others	Any	Myositis with rhabdomyolysis Uveitis

Since DRESS syndrome cannot be diagnosed solely on the clinical signs and symptoms, a thorough initial evaluation for DRESS syndrome to exclude other causes would include CBC, BMP, LFTs, urinalysis, 24-h urine protein and urinary eosinophil count, CPK, LDH, ferritin, triglycerides, calcium, PTH, TSH, PT/PTT, lipase, serum protein electrophoresis, CRP, quantitative PCR (HHV-6, HHV-7, EBV, and CMV), blood culture, viral hepatitis serologies, and ANA.

Laboratory studies in DRESS syndrome:

- CBC: eosinophilia, lymphocytosis, atypical lymphocytes
- Liver function tests: ALT > 2× upper limit, Alk Phos >1.5× upper limit)
- Creatinine and urinalysis (moderately increased creatinine, proteinuria, urinary sedimentation rate, eosinophilia)

Imaging/diagnostic studies in DRESS syndrome:

- CXR/CT chest: interstitial pneumonitis and/or pleural effusion
- Echocardiogram and electrocardiogram: pericarditis and/or myocarditis
- Brain MRI: brain lesions
- Skin biopsy: non-specific but can help to exclude other causes

Diagnosis

There is no reliable standard for the diagnosis of DRESS syndrome. Diagnostic criteria are based on clinical and laboratory findings. There are three known scoring systems that may be helpful in making the diagnosis of DRESS syndrome. The most commonly used in the United States and Europe is known as RegiSCAR [11]. The following table (Table 20.3) presents a scoring system for classifying DRESS cases as definite, probable, or no case based on the 201 cases reviewed in the RegiSCAR's multinational registry [11, 18].

Common Mimics and Differential Diagnosis

DRESS has several similarities to other drug-induced rashes and life-threatening rashes that should remain in the differential diagnosis for DRESS. Table 20.4 outlines a few of the features that distinguish DRESS from these similar rashes (Table 20.4).

Management

The cornerstone of treatment of DRESS syndrome is prompt diagnosis, discontinuation of the offending medication, aggressive supportive therapy, and high-dose steroids [8, 16]. Topical corticosteroids can be used for symptomatic relief, but

Table 20.3 Scoring system for classifying DRESS

Clinical feature		Present		Absent
Fever ≥ 38.5°C (101.3°F)		0		−1
Enlarged lymph nodes (>1 cm size, at least 2 sites)		1		0
Eosinophilia: ≥700 or ≥10% (leucopenia)	≥1500 or ≥20%	1	2	0
Atypical lymphocytes		1		0
Rash ≥50% of body surface area		1		0
Rash suggestive (≥2 of facial edema, purpura, infiltration, desquamation)		1		0
Skin biopsy suggesting alternative diagnosis		−1		0
Organ involvement: one	Two or more	1	2	0
Disease duration >15 days		0		−2
Investigation for alternative cause (blood cultures, ANA, serology for hepatitis viruses, mycoplasma, chlamydia) ≥3 done and negative		1		0

Total score < 2, excluded; 2–3, possible; 4–5, probable; ≥6, definite

Table 20.4 Differential diagnosis

Rash	Clinical presentation
Non-specific drug eruption (morbilliform)	Skin eruption may appear similarly Lacking characteristic facial edema, lymphadenopathy, and systemic findings Onset <2 weeks
Stevens-Johnson syndrome (SJS)	Necrosis of the skin Mucosal involvement No facial edema, lymphadenopathy Systemic findings less common/severe Onset 3–30 days
Toxic epidermal necrolysis (TEN)	Necrosis of the skin +/− mucosal involvement No facial edema, lymphadenopathy Systemic findings less common/severe Onset 3–30 days
Acute generalized exanthematous pustulosis (AGEP)	Superficial pustules starting in skin folds Acute onset (<2 days) after drug exposure Fever and facial edema may be present No lymphadenopathy, systemic findings
Cutaneous lymphoma (MF)	Insidious onset Skin biopsy and T-cell clonality can help differentiate as DRESS can show a pseudo-lymphomatous pattern in the skin and lymph nodes histologically Rash morphology usually different

high-dose systemic steroid therapy is generally required, especially when there is systemic organ involvement [16]. Current clinical recommendations are to start systemic steroids at a dose equivalent to at least 1 mg/kg/day of prednisone with increased dosing based on lack of clinical response or when there is significant organ involvement [8]. Steroids should be continued at that dose until adequate

clinical response is obtained. Steroids then need to be tapered slowly, over 3–9 months, in order to prevent relapse [2, 16]. In particularly severe cases or in those unresponsive to oral steroids, high-dose IV methylprednisolone may be required for several days with transition to oral prednisone [16].

No prospective randomized trials are available upon which to base the management of DRESS syndrome. Antiviral agents, such as ganciclovir, foscarnet, or cidofovir, may be indicated if active viral replication is detected. However, there is no current data to support such and the potential toxicities of these agents limit their use [2, 17]. Patients with DRESS syndrome should be managed in an ICU or burn unit for appropriate care and infection control. In addition, appropriate specialists should be consulted based on the affected organ systems.

Disease Progression

Most cases of DRESS syndrome will resolve over the course of 2–9 weeks depending on the severity of the initial disease and institution of appropriate treatment [9]. Without proper treatment, symptoms may be persistent and approximately 20% of cases relapse [14]. Relapse usually occurs due to early termination of steroid therapy, reintroduction to the original offending medication, or reactivation of the involved herpesvirus [14, 15]. Those that develop severe organ involvement can progress to fulminant liver failure requiring liver transplantation, renal insufficiency requiring hemodialysis, or other long-term sequelae based on the affected organ system. Death occurs in 10% of cases, usually secondary to hepatic failure.

Prognosis

The severity of DRESS syndrome and associated complications are related to the organ involvement (Table 20.2) [2]. Most patients with DRESS recover completely in the weeks to months after drug withdrawal and appropriate therapy. Occasionally patients will have a prolonged course with flares despite discontinuation of the offending medication [2, 16]. Patients developing liver failure or multi-organ involvement are at risk for chronic complications or death [2]. Careful continued clinical monitoring is crucial as organ involvement may be delayed, and flares may occur, particularly when the glucocorticoid dose is tapered too fast or other drugs are introduced [2].

Complications

End-organ dysfunction can occur almost at any site, and multi-organ failure can lead to shock and disseminated intravascular coagulation. Liver failure is the most common cause of death, but renal and cardiac involvement can become severe and are often more difficult to control with steroids than the hepatic involvement.

Endocrinopathies, such as thyroiditis, more often occur late and require continued clinical observation for several months. Other complications include dehydration and electrolyte imbalances, secondary bacterial or fungal infections, and sepsis related to the breakdown of the skin barrier.

Bottom Line: DRESS Clinical Pearls

- Consider the diagnosis of DRESS syndrome in a patient with rash, facial edema, lymphadenopathy, eosinophilia, and systemic symptoms/organ involvement.
- Delayed onset of rash after drug exposure. Occurs at 2–6 weeks after drug initiation (longer than most other drug eruptions).
- Promptly discontinue the offending drug.
- Obtain labs to evaluate for systemic organ involvement and appropriate imaging studies as indicated.
- Admit to the intensive care or unit burn unit (if severe erosions) with prompt dermatology consultation.
- Treatment includes high-dose steroid therapy of ≥ prednisone 1 mg/kg/day, perhaps IV methylprednisolone 1 g/day for several days in severe cases.
- Prolonged steroid taper is required to prevent relapse (3–9 months).
- Closely monitor patients' clinical symptoms and labs after resolution for relapse or late complications (i.e., endocrinopathies).

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