DRESS syndrome

Part I. Clinical perspectives

Zain Husain, MD,[a] Bobby Y. Reddy, MD,[b] and Robert A. Schwartz, MD, MPH, FRCP (Edin)[c]
Washington, DC; Boston, Massachusetts; and Newark, New Jersey

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After completing this learning activity, participants should be able to diagnose DRESS syndrome effectively in both in-patient and out-patient settings; identify common culprit medications; and discuss possible acute and chronic cutaneous and systemic manifestations.

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Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also referred to as drug-induced hypersensitivity syndrome, is a distinct, potentially life-threatening adverse reaction. It is seen in children and adults most often as a morbilliform cutaneous eruption with fever, lymphadenopathy, hematologic abnormalities, and multiorgan manifestations. Historically, it was most frequently linked with phenytoin and known as phenytoin hypersensitivity syndrome. However, because many other medications were found to produce the same reaction, another name was in order. Anticonvulsants and sulfonamides are the most common offending agents. Its etiology has been linked with lymphocyte activation, drug metabolic enzyme defects, eosinophilia, and human herpesvirus-6 reactivation. DRESS has a later onset and longer duration than other drug reactions, with a latent period of 2 to 6 weeks. It may have significant multisystem involvement, including hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine abnormalities. This syndrome has a 10% mortality rate, most commonly from fulminant hepatitis with hepatic necrosis. (J Am Acad Dermatol 2013;68:693.e1-14.)

Key words: DRESS syndrome; drug allergy; drug-induced hypersensitivity syndrome; eosinophilia; erythroderma; phenytoin hypersensitivity; severe drug eruption; toxic epidermal necrolysis.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, potentially life-threatening adverse drug reaction with cutaneous manifestations and internal organ involvement that occurs in both adults and children.[1] It was originally observed in patients treated with anticonvulsants in the early 1930s, when phenytoin first became available.[2] In 1950, Chaiken et al[3] reported a case of fever, hepatitis, and exfoliative dermatitis in a patient taking phenytoin, which he described as Dilantin (diphenylhydantoin) hypersensitivity (Dilantin, Pfizer, New York, NY).

Saltzstein et al[4] later described this cutaneous drug reaction as pseudolymphoma because of its clinical and histologic similarities to malignant lymphoma. Many clinical terms have been used since to describe DRESS, including hypersensitivity syndrome and mononucleosis-like syndrome. Reference to the inciting drug was common, as in phenytoin hypersensitivity syndrome and allopurinol syndrome. In 1996, Bocquet et al[5] proposed the term DRESS "to decrease the ambiguity of the denomination of hypersensitivity syndrome" and to give a more accurate description of this clinical entity.

CAPSULE SUMMARY

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening adverse drug-induced reaction, with an estimated mortality of 10%.
- Although the dermatologic manifestations of DRESS can be diverse, the most frequently encountered cutaneous finding is a morbilliform rash.
- Systemic involvement includes hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine abnormalities.
- There is currently no criterion standard for establishing the diagnosis of DRESS syndrome, but 2 recently developed diagnostic criteria are the European Registry of Severe Cutaneous Adverse Reaction and Japanese Research Committee on Severe Cutaneous Adverse Reaction scoring systems.

ETIOLOGY

Key points

- **The list of potential causative agents of DRESS syndrome is considerable, but carbamazepine is the most frequently reported**
- **The onset of symptoms typically occurs 2 to 6 weeks after drug administration**

The etiology of DRESS is generally regarded as a severe hypersensitivity to a medication and its reactive drug metabolites, which may be associated with enzymatic defects in drug metabolism. Many drugs have been implicated (Table I).[5-48] Aromatic anticonvulsants, especially phenytoin, carbamazepine, and phenobarbital, and sulfonamides, such as dapsone and sulfasalazine, are the most

From the Dermatology,[a] Georgetown University School of Medicine, Washington, DC; Medicine,[b] Brigham and Women's Hospital, Boston; and Dermatology and Pathology,[c] Rutgers University New Jersey Medical School, Newark.

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Correspondence to Robert A. Schwartz, MD, MPH, FRCP (Edin), Professor and Head, Dermatology, New Jersey Medical School, 185 S Orange Ave, Newark, NJ 07103-2714. E-mail: roschwar@cal.berkeley.edu.

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Abbreviations used:

ANEM: acute necrotizing eosinophilic myocarditis
CMV: cytomegalovirus
CYP-450: cytochrome P-450
EBV: Epstein–Barr virus
DIHS: drug-induced hypersensitivity syndrome
DRESS: drug reaction with eosinophilia and systemic symptoms
HHV: human herpesvirus
J-SCAR: Japanese Research Committee on Severe Cutaneous Adverse Reaction
T4: thyroxine

common causes of DRESS.[5,33] Immunosuppression may predispose individuals to develop this condition, especially when accompanied by a primary or reactivation human herpesvirus-6 (HHV-6) infection.[44,49-51] DRESS syndrome usually begins within 2 months of ingestion of the offending drug, most often 2 to 6 weeks after its first use.[5,28] However, symptoms may occur more rapidly and be more severe upon reexposure.[5] When the culprit drug is unknown among multiple medications, it is important to note medication administration timing and its relationship to the onset of symptoms, along with the likelihood of a particular drug to cause the syndrome. The incidence of DRESS is unknown; reliable epidemiologic data on disease incidence and the etiologic factors involved are lacking.[32] However, it has been estimated that the overall population risk is between 1 in 1000 and 1 in 10,000 drug exposures.[5,27]

PATHOGENESIS

Key points

- **The precise pathogenesis of DRESS syndrome remains elusive**
- **Mechanisms that have been implicated in DRESS syndrome include drug detoxification enzyme abnormalities with subsequent accumulation of reactive drug metabolites, sequential reactivation of herpesviruses, such as cytomegalovirus, Epstein–Barr virus, human herpesvirus-6 and -7, and genetic predisposition associated with certain human leukocyte antigen alleles**

The pathogenesis of DRESS syndrome is not fully understood.[28,30,52] Several hypotheses have been proposed; one theory is that deficient drug metabolism and reactive metabolites play a major role in the development of DRESS.[5,28,30,50,52,53] Individuals carrying specific mutations in genes that encode drug detoxification enzymes have been shown to have a higher risk of DRESS.[28] These genetic

Table I. Common drugs associated with drug reaction with eosinophilia and systemic symptoms syndrome

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

NSAID, Nonsteroidal antiinflammatory drug.

polymorphisms appear to be inherited in an autosomal dominant fashion, which may explain familial distribution of the disease and possible racial predisposition, as suggested by the many cases reported in black patients.[43,46,52,54-85] Mutations of genes encoding drug detoxification enzymes lead to the accumulation of drug reactive metabolites, which can biochemically interact with and modify cellular proteins, trigger autoimmune responses against skin or liver cells, alter immune responses, and induce the reactivation of viral infections.[53] This has been well described in anticonvulsant-induced DRESS. Several anticonvulsants are metabolized by the cytochrome P450 (CYP-450) system to arene oxide metabolites, which are normally detoxified by epoxide hydroxylase or glutathione transferase. Genetic mutations involving epoxide hydroxylase result in the accumulation of toxic metabolites, which can affect function and elicit immunologic responses.[5,28,55,86] The slow N-acetylator phenotype is also associated with increased risk of DRESS.[30,50,87] This may serve as a predisposing factor for sulfonamide-induced DRESS, in which the CYP-450 oxidative pathway is favored, leading to the excessive production of toxic hydroxylamine metabolites.[87] Drug dosages, genetic variants, and environmental factors that affect the bioactivation and detoxification processes have been shown to play a role.[28] Agents that induce CYP-450 activity or decrease glutathione levels may be risk factors.[88]

An immunologic mechanism is also widely believed to underlie a major component of DRESS

syndrome.[28,31-33,49,52,53,89-92] There are several characteristics of this condition that support an immune-mediated model, including the fact that it occurs in only a limited number of patients and is accompanied by eosinophilia and modification of the lymphocytic system. In addition, it requires sensitization and is reproducible through skin tests, suggesting a delayed cell-mediated immune response. There are reports of more rapid onset on rechallenge.[28] Immunosuppression is frequently observed in DRESS syndrome. Studies have shown decreased total B-lymphocyte counts and serum immunoglobulin levels, including IgG, IgA, and IgM at onset, demonstrating immune suppression that may contribute to the frequent reactivation of herpesviruses observed in DRESS syndrome.[49] There is also expansion of memory T cells that cross-react with both the drug and the virus.[71,75] Several cytokines are elevated in DRESS syndrome, particularly tumor necrosis factor and interleukin-6, which are both proinflammatory. At the time of viral reactivation, the circulating $CD8^+$ T-cells are favored. Regulatory T cells are initially increased in number in the circulation and skin, but decrease in parallel with the functional deterioration of different organs and systems.[93] Cutaneous inflammation observed in DRESS syndrome eruptions may also contribute to immunosuppression. Sugita et al[81] reported a reduction in the number of plasmacytoid dendritic cells (pDCs) in the peripheral blood of patients with DRESS syndrome, but an increase in the expression of these cells in the affected skin.[81] pDCs are major producers of interferon-alfa, which induces the maturation of B cells in order to produce IgG for antiviral defense. As pDCs from the circulation accumulate in the skin, the pDC count in the circulation is reduced, leading to diminished antiviral responses. Drugs such as carbamazepine, phenytoin, lamotrigine, and sulfamethoxazole have been shown to activate drug-specific T cells, which secrete interferon-gamma, interleukin-5, and other cytokines upon drug stimulation.[32,33,92] Elevated levels of interleukin-5, along with eotaxin, are responsible for the significant eosinophilia reported in DRESS syndrome.[89,94,95] Macrophages may also be activated to release tumor necrosis factor, likely playing a role in the severity of tissue damage.[33]

Individuals with specific human leukocyte antigen (HLA) haplotypes are predisposed to developing DRESS syndrome when exposed to an inciting drug. It is thought that the drug interacts with a particular HLA and forms a complex hapten, which is presented to naïve T cells via the T-cell receptor. Subsequently, different immune responses are initiated depending on the HLA expressed on the antigen-presenting cell and the cytokine milieu. HLA alleles have a high negative predictive value but low positive predictive value in relation to adverse drug reactions, suggesting that these allelic markers are necessary but not sufficient to elicit an allergic response.[93] The HLA-B*5701 allele has been associated with an increased risk of developing abacavir-induced DRESS syndrome in white patients. In a study of 22 Japanese patients, Kashiwagi et al[96] determined that HLA-A*3101 is associated with an increased risk of DRESS syndrome and other drug reactions when exposed to carbamazepine, such as erythema multiforme, erythroderma, and Stevens–Johnson syndrome. Hung et al[76] studied the relationship between HLA subtypes and several drugs eliciting severe cutaneous reactions in the Han Chinese population. In one case control study, they found a strong relationship between HLA-B*5801 and allopurinol inducing Stevens–Johnson syndrome/toxic epidermal necrolysis or DRESS syndrome/drug-induced hypersensitivity syndrome (DIHS).[76] HLA-DR3 and HLA-DQ2 alleles have been also shown to be associated in higher frequency of carbamazepine-induced DRESS syndrome.[97]

The reactivation of herpesviruses has also been shown to play a role in the pathogenesis of DRESS syndrome, especially HHV-6. Cytomegalovirus (CMV), Epstein–Barr virus (EBV), and HHV-7 reactivation have been implicated in a minority of cases.[28,30,32,44,49,51,53,67,98-100] There are complex interactions between herpesviruses, antiviral immune, and drug-specific immune responses observed in this condition.[44] Polymerase chain reaction studies have shown sequential reactivation of herpesviruses in DRESS syndrome, similar to that seen in graft versus host disease. The cascade of viral reactivation begins with HHV-6 or EBV early in the course of DRESS syndrome, followed by HHV-7 and eventually CMV.[51,71] HHV-6 reactivation is shown by increased titers of IgG anti–HHV-6 and DNA levels, which are usually detected 2 to 3 weeks after the onset of rash. Clinical similarities between primary HHV-6 infection and DRESS syndrome, including cutaneous and visceral manifestations, such as hepatitis, histiocytic necrotizing lymphadenitis, hemophagocytic syndrome, lymphocytopenia, and pneumonitis, suggest that the virus itself may be largely responsible for manifestations. Further supporting the role of this virus in this hypersensitivity syndrome, HHV-6 DNA and mRNA have been detected in lesional skin from DRESS syndrome patients using polymerase chain reaction and in situ hybridization techniques, respectively.[27,101] Recurrence and exacerbation of DRESS syndrome can be seen with concurrent HHV-6 reactivation.[99]

It is hypothesized that herpesvirus reactivation in DRESS may stem from an allergic immune response to a particular drug with an innate ability to stimulate T cells. These T cells may harbor latent herpesviruses and, when stimulated by the drug, the viral genome is replicated and reactivated in the cell.[93] Viral reactivation may be a result of immunosuppression induced by the culprit drug.[44] Herpesviruses have immunotropic properties and interactions with other latent viruses, thereby modulating immune responses to drugs or directly attacking the immune system.[49] Anti–CYP-450 antibodies may be produced because of the cross-reactivity between the viruses and CYP-450 components.[53]

CLINICAL FEATURES

Key points

- **The most commonly encountered dermatologic manifestation of DRESS syndrome is an erythematous morbilliform rash**
- **The classic cutaneous distribution involves the face, upper trunk, and upper and lower extremities, but it may encompass the entire surface of the skin**
- **The liver is the most frequently affected visceral organ**

DRESS often begins with prodromal symptoms of pruritus and pyrexia. The fever generally precedes cutaneous eruptions by several days, with temperatures ranging from 38°C to 40°C, and may last for several weeks. Although there can be various cutaneous manifestations, a morbilliform rash is the most common and is characterized by a diffuse, pruritic, macular, and occasionally erythrodermatous exanthema.[102] It usually first involves the face, upper aspect of the trunk, and upper extremities, and later spreads to the lower extremities, becoming infiltrative and indurated with associated edema.[31] There may be associated vesicles, bullae, atypical targetoid plaques, and purpura.[5] Sterile follicular and nonfollicular small pustules may be evident.[5] The rash may progress to involve nearly the entire surface of the skin, producing an exfoliative dermatitis or erythroderma that can be associated with mucosal involvement, such as cheilitis, erosions, erythematous pharynx, and enlarged tonsils.[54] There is often significant facial edema, especially in the periorbital and midfacial region, that can be sometimes mistaken for angioedema. Approximately 25% of patients have prominent facial swelling, which can be so marked that the patient becomes disfigured.[46] The rash frequently evolves after its acute presentation, taking on a more violaceous appearance with diffuse scaling. These clinical features may remain for weeks or months after discontinuing the culprit drug (Figs 1-8).[102] In a series of 27 patients with DRESS syndrome, Ang et al[103] reported that 81.5% had an erythematous morbilliform rash involving the face, trunk, and limbs, 7.4% had generalized erythroderma, 7.4% had a pustular eruption, 7.4% had targetoid lesions, 29.6% had mucositis, and 33.3% had swelling of the face.

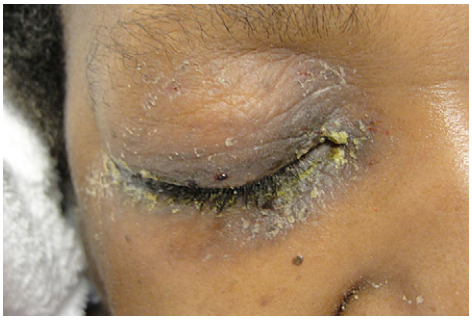

Fig 1. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Well-demarcated periorbital dermatitis.

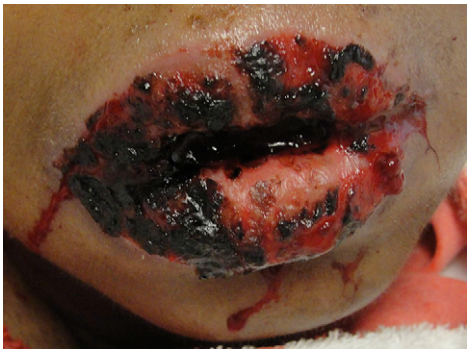

Fig 2. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Prominent lip erosions and hemorrhagic crusts.

Multiple organ systems can be affected in DRESS syndrome. The most common systemic findings involve the lymphatic, hematologic, and hepatic systems, followed by renal, pulmonary, and cardiac manifestations. Severe, atypical cases of DRESS may have neurologic, gastrointestinal, and endocrine dysfunction. Although medications can potentially affect any of the mentioned systems, certain medications have a predilection for involving specific organs (Table II). Lymphadenopathy is a common finding in DRESS syndrome, and is present in nearly 75% of cases.[72] Patients may have limited lymph node involvement or generalized lymphadenopathy with localized tenderness involving the cervical, axillary, and inguinal lymph nodes. Two histopathologic variants have been observed in affected lymph nodes, the benign and pseudolymphoma patterns (see Histopathologic findings).

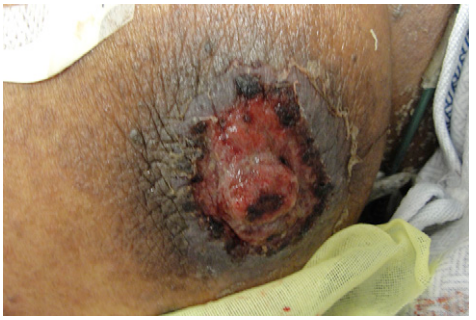

Fig 3. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Prominent areolar erosion.

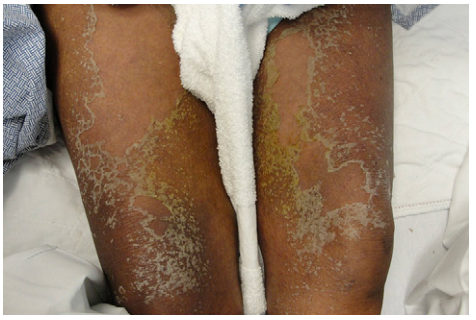

Fig 4. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Diffuse scaling of legs.

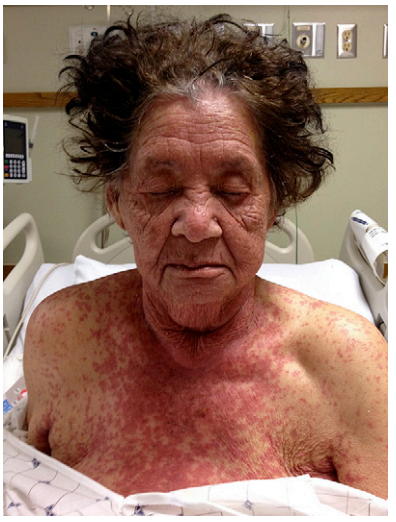

Fig 5. Patient with vemurafenib-induced drug reaction with eosinophilia and systemic symptoms syndrome. Prominent facial edema and morbillform eruption. (Courtesy of Michael Y. Cashman, MD, and Dominique C. Pichard, MD.)

The hematologic system is frequently affected. There can be marked leukocytosis, up to 50.0×10^9 leukocytes/L; atypical lymphocytes are present. In approximately 30% of cases, there is eosinphilia

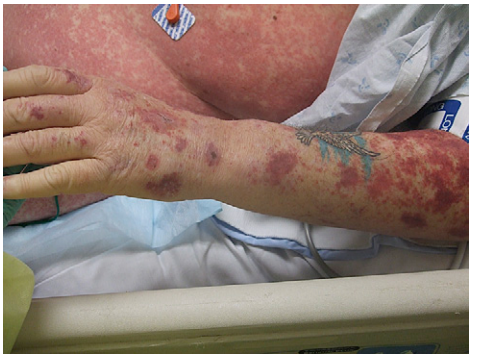

Fig 6. Patient with piperacillin-tazobactam–induced drug reaction with eosinophilia and systemic symptoms syndrome. Purpuric and petecheial lesions on the arm. (Courtesy of Naurin E. Ahmad, MD.)

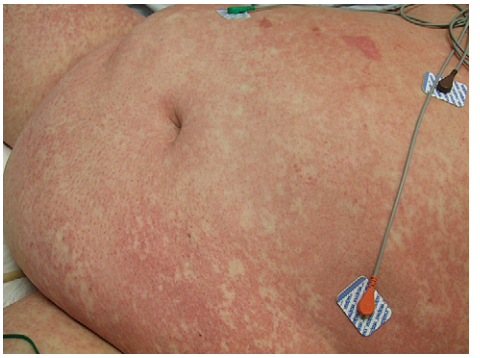

Fig 7. Patient with piperacillin-tazobactam–induced drug reaction with eosinophilia and systemic symptoms syndrome. Morbilliform eruption on the abdomen. (Courtesy of Naurin E. Ahmad, MD.)

with $>2.0 \times 10^9$ eosinophils/L, but it can be delayed for 1 to 2 weeks.[5,102]

Hypereosinophilia likely plays a role in visceral manifestations because eonsinophil granule proteins are toxic to many tissues.[5] Before the initial presentation, there is often a leukopenia or lymphopenia that precedes leukocytosis.[102] There may be thrombocytopenia and a drop in hemoglobin levels.[32] DRESS syndrome may rarely be associated with hemophagocytic syndrome, an uncommon hematologic disorder that manifests as fever, jaundice, and hepatosplenomegaly with hemophagocytosis. There is a decrease in white blood cells and platelets with a concomitant elevation of lactate dehydrogenase. Bone marrow aspirate may reveal an increased number of hemophagocytic macrophages. Hemophagocytic syndrome generally occurs 2 weeks after the onset of drug eruption.[102]

The liver is the most frequently affected visceral organ in DRESS syndrome, often with varying degrees of hepatitis. Phenytoin, minocycline, and dapsone are commonly implicated.[104] Hepatosplenomegaly can be present and is often accompanied by hepatitis

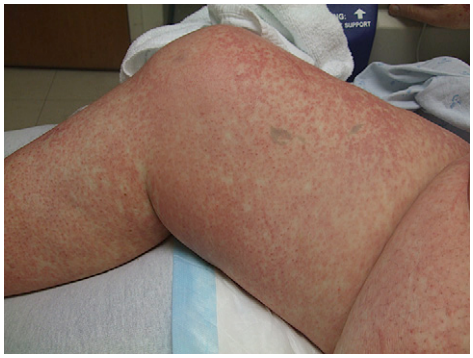

Fig 8. Patient with piperacillin-tazobactam–induced drug reaction with eosinophilia and systemic symptoms syndrome. Morbilliform eruption on right lower extremity. (Courtesy of Naurin E. Ahmad, MD.)

with elevated liver transaminases, alkaline phosphatase, and creatinine.[32] Liver abnormalities with elevated serum alanine aminotransferase (ALT) are found in approximately 70% of patients with DRESS syndrome, although one series of 27 patients found it in more than 95% of them.[103,104] The elevated liver enzymes may persist for several days after withdrawal of culprit drug, but may sometimes take months to completely resolve. The hepatitis is often anicteric and without cholangitis.[64] Viral hepatitis panels are usually negative, but if there is an underlying viral hepatitis infection, the disease course can be more complicated and severe. Severe acute hepatitis (presence of ALT to >10 times the upper limit of normal and/or acute liver failure with coagulopathy and encephalopathy) is seen more commonly in women in the second to fourth decade of life, especially with the use of sulfasalazine.[101] Significant hepatitis can be associated with a chronic course marked by exacerbations and remissions.[105] HHV-6 reactivation has also been shown to cause a hepatitis flare.[99] The most dangerous manifestation is hepatic necrosis, which may be extensive and can lead to liver failure, coagulopathy, and sepsis. It is the primary cause of mortality in DRESS syndrome.[5] Liver transplantation may be the only effective treatment option in cases of fulminant hepatitis.

The kidney is also commonly affected in DRESS syndrome, with 11% of patients exhibiting renal disease.[106] Among the offending drugs associated with kidney injury, allopurinol is the most common, followed by carbamazepine and dapsone.[104] Patients with underlying renal disease and the elderly are at highest risk of developing renal complications.[102] Clinical symptoms are usually absent, but patients can present with mild hematuria and proteinuria. Laboratory abnormalities reflect renal dysfunction and include elevated blood urea nitrogen and creatinine levels and low creatinine clearance.[102] Eosinophils may be present on urinalysis.[102] There are usually no abnormalities evident on kidney ultrasound.[102] In most cases, there is only mild renal impairment, which usually resolves after withdrawal of the offending drug. However, severe interstitial nephritis can develop and progress to kidney failure.[102] Ang et al[103] reported that 4 (14.8%) patients in their series had renal impairment, with half requiring short-term supportive hemodialysis.

Pulmonary manifestations of DRESS syndrome may also occur. Minocycline is the most common drug causing lung pathology.[102] Reported pulmonary complications include impaired pulmonary function, acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress syndrome.[104] Patients can exhibit shortness of breath and a nonproductive cough, but usually recover without lung damage. However, the development of acute respiratory distress syndrome can be life-threatening and requires immediate intubation and mechanical ventilation.[102]

The heart can be affected in DRESS syndrome, with patients usually presenting with myocarditis. Ampicillin and minocycline are the most commonly implicated drugs.[107] DRESS syndrome–associated myocarditis is potentially fatal and can present months after withdrawal of the offending drug and resolution of the clinical and laboratory abnormalities.[107] Patients may present with chest pain, tachycardia, dyspnea, and hypotension. The initial laboratory workup may reveal cardiomegaly and pleural effusions on chest radiograph, while ST segment and T wave changes, sinus tachycardia, and arrhythmias may be identified on electrocardiogram.[102] Echocardiogram may reveal a decrease in ejection fraction.[102] Cardiac enzymes including creatinine kinase and troponin-I may be elevated.[102] Two forms of myocarditis are recognized in DRESS syndrome: hypersensitivity and acute necrotizing eosinophilic myocarditis (ANEM).[107] The former is generally self-limited and responsive to immunotherapy, often accompanied by electrocardiogram changes (T-wave abnormalities, conduction delay, and sinus tachycardia) and an elevation of cardiac enzymes.[107] Echocardiogram often shows systolic dysfunction with low ejection fraction and pericardial perfusion. ANEM shares many of these features, but has more pronounced findings and is associated with >50% mortality and a median survival of 3 to 4 days. Echocardiography often reveals severely decompensated systolic function and increased wall thickness, biventricular failure, and pericardial effusions. Cardiac biopsy provides a definitive diagnosis, but this procedure is invasive and there is a risk of

Table II. Drugs associated with specific internal organ risk in drug reaction with eosinophilia and systemic symptoms syndrome

Medication	Clinical abnormality
Allopurinol	Renal
Ampicillin	Cardiac
Carbamazepine	Renal
Dapsone	Hepatic and renal
Minocycline	Hepatic, pulmonary, and cardiac
Phenytoin	Hepatic

false-negative results because of the patchy nature of the infiltrate.[102,107]

Neurologic manifestations of DRESS syndrome are infrequently encountered. They include meningitis and encephalitis, which often develop 2 to 4 weeks after onset of DRESS syndrome and may be related to HHV-6 reactivation.[102] Clinical symptoms include headache, seizure, coma, speech abnormalities, cranial nerve palsies, and muscle weakness.[102] An electroencephalogram may show diffuse slow waves with occasional solitary spike in frontal and temporal leads.[102] Magnetic resonance imaging scans of the brain reveal bilateral lesions involving the amygdala, medial temporal lobes, insula, and cingulate gyrus.[108] Sakuma et al[109] described an unusual case of DRESS syndrome in which a patient presented with syndrome of inappropriate secretion of antidiuretic hormone with limbic encephalitis.

The gastrointestinal system can also be affected in DRESS syndrome, with gastroenteritis and dehydration being the most common manifestations. Occult abnormalities often require esophagogastroduodenoscopy and colonoscopy for evaluation. CMV ulcers can develop and contribute to acute gastrointestinal bleeding.[102] Arterial bleeding from gastric ulcerations can be seen on endoscopy, with immediate intervention with clipping and blood transfusion usually necessary.[102] There are often simultaneous cutaneous CMV ulcers present on the shoulders and trunk and other signs of disseminated infection.[110] Colitis and pancreatitis are related gastrointestinal complications.[102] Chronic enteropathy has been observed in some patients.

Endocrine abnormalities are rarely seen in acute reactions and are more commonly evident as long-term sequelae. The most commonly affected gland is the thyroid, resulting in thyroiditis or sick euthyroid syndrome.[102] It is important to screen and monitor thyroid laboratory tests, such as thyroid stimulating hormone and free thyroxine (T4) during DRESS syndrome. Ang et al[103] reported 5 patients that developed abnormalities in thyroid function: sick euthyroid syndrome (2), thryoiditis (1), isolated increased free T4 (1), and isolated low thyrotropin (1). Long-term thyroid complications include thyroid dysfunction, sick euthyroid syndrome, and/or thyroiditis, which can result in either hyperthyroidism or hypothyroidism.[28] Antithyroid antibodies are often detected 3 months to 1 year after clinical resolution of DRESS syndrome. The patient may develop Graves disease, usually 2 to 4 months after discontinuing the offending drug. After 5 months, clinical symptoms manifest, such as palpitations, irritability, and difficulty sleeping.[28] Laboratory tests confirm Graves disease. In severe cases, thyrotoxicosis may be present. Hashimoto thyroiditis can also develop with elevated antithyroid peroxidase and antithryoglobulin antibodies.[28] As a result, thyroid function should be routinely screened for at least 2 years in patients recovering from DRESS syndrome.

In addition to thyroid abnormalities, there may be pancreatic involvement in DRESS syndrome, including pancreatitis or type 1 diabetes mellitus (DMTI).[102] There may also be bilateral edema and infiltration of the salivary glands with xerostomia.[72] The symptom-free period between the apparent resolution of DRESS syndrome to the onset of these autoimmune conditions ranges from months to years. Fulminant DMT1 can develop 3 weeks to 10 months after onset of DRESS syndrome and is characterized by rapid onset with absence of diabetes-related autoantibodies, such as antiglutamic acid decarboxylase and islet cell antibodies.[111-114] Herpesvirus reactivation is believed to contribute to the development of DMT1.[102] It usually develops during corticosteroid therapy. Clinical features include vomiting and dull epigastric pain, while laboratory findings include hyperglycemia, hyperosmolarity, metabolic acidosis, and elevated serum amylase and lipase.[52]

HISTOPATHOLOGIC FINDINGS

Key points

- **Skin biopsy specimens of cutaneous lesions in DRESS syndrome typically reveal a perivascular lymphocytic infiltrate in the papillary dermis, with eosinophils, atypical lymphocytes, and spongiosis sometimes presents**
- **The histology of affected lymph nodes in DRESS syndrome may show either benign lymphoid hyperplasia or a pseudolymphoma pattern, which must be carefully distinguished from lymphoma**

The histopathologic analysis of cutaneous and visceral organ specimens may help confirm the diagnosis of DRESS syndrome.[28] The most common skin biopsy findings are a dense, perivascular lymphocytic infiltrate in the papillary dermis, with the presence of

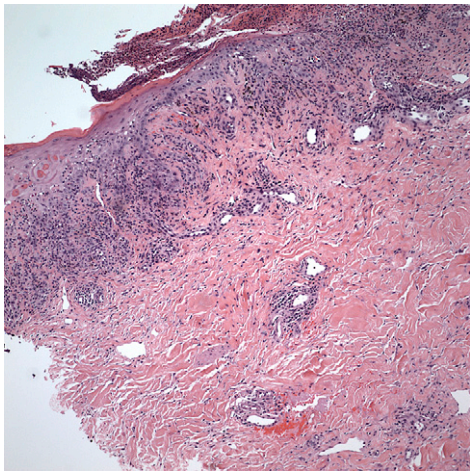

Fig 9. Lesional skin tissue from phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Note the parakeratosis, focal mild acanthosis, band-like lymphocytic infiltrate with epidermotropism, and the tight perivascular lymphohistiocytic infiltrate in the reticular dermis. (Hematoxylin–eosin stain; original magnification: ×40.)

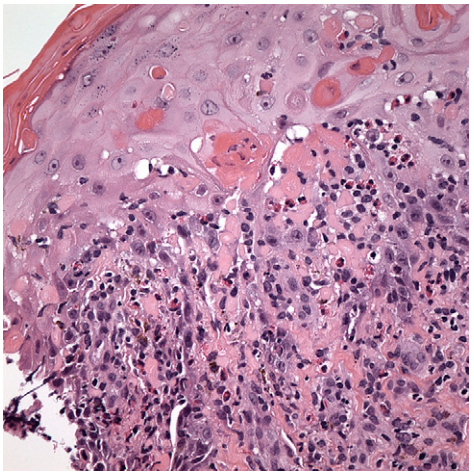

Fig 10. Lesional skin tissue from phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Note the band-like lymphocytic infiltrate with epidermotropism and the prominent eosinophils. (Hematoxylin–eosin stain; original magnification: ×100.)

extravasated erythrocytes, eosinophils, and dermal edema. This infiltrate is generally denser than other drug reactions.[5,26] Eosinophils may be present, which are thought to cause direct toxic damage to tissues as seen in other pathologic conditions with eosinophilia (Figs 9 and 10).[89] Atypical lymphocytes may also be present and can form a lichenoid infiltrate with epidermotropism, resembling mycosis fungoides.[5,26,53] Granulomas may occasionally be observed in the superficial dermis.[101]

The histologic examination of visceral involvement may also be nonspecific, although damaged tissue often contains an accumulation of eosinophils.[89] Lymph nodes are frequently affected in DRESS syndrome, with its histopathology falling under 2 distinct patterns: benign lymphoid hyperplasia, in which lymph node architecture is preserved,[5,115] and a pseudolymphoma with disruption of normal architecture by a polymorphous infiltrate consisting of atypical cells with mitotic figures, plasma cells, histiocytes, and eosinophils with areas of necrosis and edema. However, there are neither Reed–Sternberg cells nor capsular invasion. This pseudolymphoma pattern may be difficult to distinguish from that of a true lymphoma.[5] Biopsy specimens taken from the liver reveal an eosinophilic infiltrate and granulomas with associated hepatocyte necrosis and cholestasis.[5] Similarly, an endomyocardial biopsy reveals an eosinophilic and mixed lymphohistiocytic infiltrate in hypersensitivity myocarditis and ANEM; myocyte necrosis and fibrosis are features seen only in ANEM. Kidney biopsy may show interstitial infiltration by lymphocytes, histiocytes, and eosinophils. The lungs may have interstitial and alveolar infiltration by lymphocytes and eosinophils.[26]

DIAGNOSTIC CRITERIA

Key points

- **There is presently no reliable standard for the diagnosis of DRESS syndrome**
- **The diagnosis is primarily established through clinical and laboratory abnormalities**
- **In recent years, 2 separate scoring systems based on diagnostic criteria have been developed by the European Registry of Severe Cutaneous Adverse Reaction and the Japanese Research Committee on Severe Cutaneous Adverse Reaction**

There is no reliable standard for the diagnosis of DRESS syndrome. Clinicians must exclude other potentially serious conditions, including infections, neoplastic processes, autoimmune disorders, and connective tissue disease. The proposed diagnostic criteria are based on clinical and laboratory findings. Clinical testing and biopsy can be helpful, but are not always specific. Bocquet et al[5] proposed the original criteria to establish the diagnosis of DRESS syndrome, which include the following: (1) drug eruption; (2) hematologic abnormalities (ie, eosinophilia $>1.5 \times 10^9$/L and the presence of atypical lymphocytes); and (3) systemic manifestations (ie, adenopathy with lymph nodes >2 cm; hepatitis with transaminase levels twice the normal values;

Table III. Diagnostic criteria for drug reaction with eosinophilia and systemic symptoms syndrome

Bocquet et al[4]	RegiSCAR[72]	J-SCAR[73]*
Cutaneous drug eruption	Acute rash†	Maculopapular rash developing >3 weeks after starting offending drug
Hematologic abnormalities	Reaction suspected to be drug-related†	Prolonged clinical symptoms after discontinuation of the causative drug
Eosinophils $\geq 1.5 \times 10^9$/L	Hospitalization†	Fever >38°C
Presence of atypical lymphocytes	Fever >38°C‡	Liver abnormalities (ALT >100 U/L) or other organ involvement
Systemic involvement	Enlarged lymph nodes involving ≥2 sites‡	Leukocyte abnormalities (≥1)
Adenopathy: lymph nodes ≥2 cm in diameter	Involvement of ≥1 internal organ‡	Leukocytosis ($>11 \times 10^9$/L)
Hepatitis with liver transaminases ≥2 times normal	Blood count abnormalities‡	Atypical lymphocytes (>5%)
Interstitial nephritis	Lymphocytes above or below normal limits	Eosinophilia ($>1.5 \times 10^9$/L)
Interstitial pneumonitis	Eosinophils over laboratory limits	Lymphadenopathy
Carditis	Platelets under laboratory limits	HHV-6 reactivation

For Bocquet et al[4] criteria, all 3 criteria are required (1 hematologic and 1 systemic feature required).
DIHS, Drug-induced hypersensitivity syndrome; *HHV-6*, human herpesvirus-6; *J-SCAR*, Japanese Research Committee on Severe Cutaneous Adverse Reaction; *RegiSCAR*, European Registry of Severe Cutaneous Adverse Reaction.
*J-SCAR criteria includes DIHS. Typical DIHS is defined as the presence of all 7 criteria, while atypical DIHS is defined as the presence of the first 5 criteria only.
†Necessary criteria for diagnosis according to RegiSCAR.
‡Three of these 4 criteria required for diagnosis according to RegiSCAR.

interstitial nephritis; pneumonitis, and carditis). The presence of at least 3 criteria are required to establish the diagnosis of DRESS syndrome (Table III).

The European Registry of Severe Cutaneous Adverse Reaction study group expanded on the diagnostic criteria proposed by Bocquet et al.[5] It outlines 7 inclusion criteria. The first 3 criteria are necessary for diagnosis and include acute rash, the suspicion of a drug-related reaction, and hospitalization. To establish the diagnosis, the patient must also have 3 of the 4 following systemic features: (1) fever >38°C; (2) lymphadenopathy involving at least 2 sites; (3) involvement of at least 1 internal organ (eg, liver, kidney, heart, pancreas, or other organs); and (4) hematologic abnormalities, including a lymphocyte count above or below the normal limits; an eosinophil count higher than laboratory limits; or a platelet count below laboratory limits (Table III).[111]

Other diagnostic criteria has been proposed by the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) group that highlights the role of HHV-6 in DRESS syndrome, which they refer to as DIHS.[116] There are 7 J-SCAR criteria: (1) maculopapular rash developing 3 weeks after beginning treatment with the causative drug; (2) prolonged clinical symptoms after discontinuing the causative drug; (3) fever >38°C; (4) hepatic abnormalities (ALT >100 U/L) or other organ involvement; (5) leukocyte abnormalities (at least 1 of the following: leukocytosis [$>11 \times 10^9$/L], atypical lymphocytes [>5%], or eosinophilia [$>1.5 \times 10^9$/L]); (6) lymphadenopathy; and (7) HHV-6 reactivation (Table III). If all 7 criteria are present, the patient is diagnosed with typical DIHS; if only the first 5 criteria (1-5) are present, atypical DIHS is diagnosed.[116]

CONCLUSION

DRESS syndrome is a severe drug hypersensitivity reaction with prominent cutaneous and systemic manifestations. Although it is classically caused by anticonvulsants and sulfonamides, many other drugs have been implicated. Its pathophysiology is not completely understood at this time, but is likely related to drug metabolic enzyme deficiencies, lymphocyte activation, reactivation of herpesviruses, and genetic predisposition associated with specific HLA alleles. Clinicians must be aware of this potentially fatal reaction and its common culprit medications. They must pay particular attention to visceral organ involvement and order appropriate laboratory studies. Prompt diagnosis using clinical criteria, laboratory values, and histopathology is imperative.

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