Drug Reaction with Eosinophilia and Systemic Symptoms: An Update and Review of Recent Literature

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, is also known as drug induced hypersensitivity syndrome and by various other names. It is now recognised as one of the severe cutaneous adverse reaction (SCAR) and can be potentially life-threatening. Historically, it was most frequently linked with phenytoin and was initially described as phenytoin hypersensitivity syndrome. However, it was later found to be caused by various other medications. Anticonvulsants and sulfonamides are the most common offender. Characteristically DRESS has a latent period of 2 to 6 weeks. The pathophysiology remains incompletely understood but involves reactivation of viruses and activation of lymphocyte. It is manifested most commonly with a morbilliform cutaneous eruption with fever and lymphadenopathy. The severity of this syndrome is related to the systemic involvement, which can result in multi-organ failure. Most important step in the management of DRESS is early diagnosis and immediate cessation of the suspected offending drug. Patients of DRESS syndrome should be managed in an intensive care set up for appropriate supportive care and infection control. Topical corticosteroids can give symptomatic relief, but systemic therapy with steroid and other immunosuppressant is usually required.

KEY WORDS: Anticonvulsant hypersensitivity syndrome, DIHS, DRESS, drug-induced hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms, phenytoin hypersensitivity syndrome

Introduction

Skin is the most frequently involved organ in adverse drug reaction (ADR). Cutaneous adverse reactions to drugs are observed in 0.1–1% of patients during premarketing clinical trials. The incidence of cutaneous ADR can be as high as 1–8% for certain types of drugs (nonsteroidal anti-inflammatory drugs and antiepileptics) in postmarketing surveys. Studies suggest that roughly a third of drug eruptions require hospital management and are classified as severe, although fortunately, only 2% of cutaneous drug eruptions are really life-threatening.[¹]

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening ADR. Dermatologic manifestations of DRESS can be diverse, with morbilliform rash being the most common presentation. It may have significant multisystem involvement, including haematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine abnormalities. This syndrome has a 10% mortality rate, most commonly from fulminant hepatitis with hepatic necrosis.[²]

History

After the introduction of hydantoins in the 1930s, several ADRs, including rashes, fever, and eosinophilia, started to get reported. In 1950, Chaiken et al reported a case of fever, hepatitis, and exfoliative dermatitis in a patient taking phenytoin, which he/she described as a “febrile drug eruption.”[³] The syndrome is also known as phenytoin hypersensitivity syndrome and by various other names. It is now recognised as one of the severe cutaneous adverse reaction (SCAR) and can be potentially life-threatening.

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as Dilantin (diphenylhydantoin) hypersensitivity.\(^1\) However, it took another 20 years to reach a consensus that phenytoin could produce a characteristic “hypersensitivity syndrome.”\(^2\) After the introduction of hydantoins, several drug reactions, including rashes, fever, and eosinophilia, were reported.

**Drug Reaction with Eosinophilia and Systemic Symptoms: An Evolving Nomenclature**

Existence of many names for a single condition reflects the difficulties in defining the disorder and in clarifying diagnostic criteria. An initial attempt to name this pattern of severe drug reaction was made after the introduction of the first anticonvulsant drug, hydantoin and its derivatives, in the 1940s.

In 1959, Saltzstein collated a number of published reports with seven of his own cases and proposed the term “drug-induced pseudolymphoma” to describe this condition.\(^5\)

In the 1960s came reports of a syndrome similar to Saltzstein’s pseudolymphoma, but with rash and fever in addition to lymphadenopathy, and in 1988, the term “anticonvulsant hypersensitivity syndrome” was first used to label this specific entity.\(^6\)

These group of syndromes had been historically described by various names which include Dilantin hypersensitivity reaction, “phenytoin/Dilantin syndrome,” “Kawasaki-like syndrome,” “mononucleosis-like syndrome,” pseudolymphoma, febrile mucocutaneous syndrome, graft-versus-host-like illness, Kawasaki-like illness, hypersensitivity mimicking infectious mononucleosis-like illness, multisystem hypersensitivity reaction, and drug-induced aseptic meningitis.\(^7,8\)

In 1998, the nomenclature was further confused by Sontheimer’s suggestion of “drug-induced delayed multiorgan hypersensitivity syndrome” to describe this disorder.\(^4\)

At the same time, Bocquet et al coined the term, “drug rash with eosinophilia and systemic symptoms,” for those with systemic involvement, which subsequently got more acceptance.\(^9\) A dermatosis is usual but not mandatory in DRESS; the extent of skin involvement is also variable. Hence, the “R” in DRESS was subsequently changed from “rash” to “reaction.”

However, a Japanese consensus group has defined a similar constellation of symptoms as drug-induced hypersensitivity syndrome (DIHS) and suggested criteria for the same.\(^10\) For the present article, we will consider both conditions interchangeably.

**Epidemiology**

The epidemiologic data on disease incidence and the aetiologic factors involved are lacking, making it difficult to predict true incidence of DRESS. However, it has been estimated that the overall population risk is between 1 in 1000 and 1 in 10,000 drug exposures.\(^11\) However, in clinical practice, a diagnosis of DRESS syndrome is frequently overlooked because of unfamiliarity with the syndrome and its criteria. This happens especially when skin findings are minimal, making the diagnosis difficult.

The risk for developing hypersensitivity within 60 days of the first or second prescription in new users of phenytoin and carbamazepine was estimated to be 2.3–4.5/10,000 and 1–4.1/10,000, respectively.\(^12\) Studies have shown 80% cross-reactivity between the anticonvulsants.\(^11\)

**Aetiology**

DRESS is a severe hypersensitivity reaction to a medication or its reactive metabolites, which may be associated with enzymatic defects in drug metabolism. Aromatic anticonvulsants such as phenytoin, carbamazepine, and phenobarbitone, and sulfonamides such as dapsone and sulfasalazine, are the most frequently reported drugs causing DRESS, among which carbamazepine is the most common offender.\(^2\)

Patrice Cacoub et al carried out a systematic review of DRESS cases reported in the literature by searching PubMed-MEDLINE between January 1997 and May 2009 and found that a total of 44 drugs were associated

| Causal drug                              | Number of cases |
|------------------------------------------|-----------------|
| Allopurinol                              | 15              |
| Anticonvulsants                          |                 |
| Carbamazepine                            | 11              |
| Phenytoin                                | 3               |
| Lamotrigine                              | 2               |
| Phenybarbital                            | 1               |
| Vancomycin                               | 6               |
| Minocycline                              | 4               |
| Trimethoprim-sulfamethoxazole            | 4               |
| Pyrimethamine-sulfadiazine               | 3               |
| Sulfasalazine                            | 3               |
| Omeprazole                               | 2               |
| Antituberculous agents                   | 2               |
| Azathioprine                             | 2               |
| Olanzapine                               | 1               |
| Nevirapine                               | 1               |
| Fluindione                               | 1               |
| Hydroxychloroquine                       | 1               |

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**Table 1: Drug reaction with eosinophilia and systemic symptoms syndrome: Causal drugs identified in 62 patients seen at the Bichat Hospital, Paris, France**
with the 172 cases reported. Carbamazepine was found to be the most commonly reported with a total of 47 cases (27% of total reported cases of DRESS).\[14\]

Although there is a long list of medicine which can be implicated in DRESS, the main drugs are allopurinol, anticonvulsants (phenobarbital, carbamazepine, phenytoin, lamotrigine, and sodium valproate), minocycline, sulfasalazine, disulfone, fluindione, proton pump inhibitors, and streptomycin ranelate[15] [Table 1].[16] Amoxicillin can cause DRESS syndrome but more often acts as an aggravating factor. This aggravating effect can be reminiscent of amoxicillin-induced rash in patients with infectious mononucleosis.[16]

Pathogenesis
The precise pathogenesis of DRESS syndrome remains elusive; however, in anticonvulsant-related cases, complex interplay of three components are considered: (i) deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants; (ii) associated sequential reactivation of herpes virus family and (iii) ethnic predisposition with certain human leukocyte antigen (HLA) alleles[17] [Figure 1].

Theory of deficient drug metabolism and reactive metabolites
Specific mutations in genes encoding drug detoxification enzymes have a higher risk of DRESS. These genetic predispositions are possibly transmitted as an autosomal dominant inheritance.

This may explain familial and racial predisposition as reported in patients of African origin.[18] Excess reactive metabolite formation has been implicated in the pathogenesis of DRESS induced by anticonvulsants. These toxic metabolites are usually detoxified by epoxide hydroxylase. Genetic mutations involving epoxide hydroxylase result in the accumulation of toxic metabolites, which can elicit immunologic responses.[2]

Immunologic mechanism
It is well understood that DRESS is an immune-mediated reaction as it occurs in only a limited number of patients, is accompanied by eosinophilia, and is a modification of lymphocytic response. Since it requires sensitisation and is reproducible through skin tests, a delayed cell-mediated immune response is highly likely.[18] Several proinflammatory cytokines are elevated in DRESS syndrome, particularly tumour necrosis factor and interleukin-6.

Genetic predisposition
Individuals with specific HLA haplotypes are predisposed to developing DRESS syndrome. The HLA-B*5701 allele has been associated with an increased risk of developing abacavir-induced DRESS syndrome in white patients.[2] Kashiwagi et al determined HLA-A*3101 is associated with an increased risk of DRESS syndrome to carbamazepine among Japanese patients.[20] Hung et al found a strong relationship between HLA-B*5801 and allopurinol inducing DRESS syndrome in Chinese population.[21]

Reactivation of herpes viruses
Systemic manifestations of DRESS are related to human herpes virus (HHV) reactivation and to host immune response against the virus. As HHV-6 can be detected in the blood of approximately 60–80% of patients with DRESS, HHV-6 reactivation has been included in the diagnostic criteria for DIHS developed by Japanese experts. Reactivation of other herpes viruses, namely, Epstein–Barr virus (EBV), cytomegalovirus (CMV), and HHV-7, can also be associated with systemic manifestations and flares of DRESS. Two explanations have been put forward to explain viral involvement: (i) an immune response against the drug with secondary viral reactivation related to a cytokine storm and (ii) early viral reactivation responsible for most of the manifestations of DRESS syndrome. There is evidence that certain drugs, able to trigger DRESS, can directly induce viral replication in T-cells in vitro. However, most experts favour the hypothesis that virus reactivation is a simple bystander effect. While the detection of HHV reactivation might be useful in the diagnosis of DRESS, the significance of

Figure 1: Hypersensitivity to aromatic anticonvulsants. Epoxide hydrolase deficiency leads to reactive oxide arenes accumulation, causing immune response. (CYP = cytochrome P450)
virus activation in the pathogenesis of DRESS remains unclear.[22,23]

**Clinical Features**

**Onset**

DRESS syndrome usually begins within 2 months of ingestion of the offending drug, most often 2–6 weeks after its first use. However, symptoms may occur more rapidly and be more severe upon reexposure.[9,19] For phenytoin, the mean interval to onset is 17–21 days; and for carbamazepine, the onset is generally between 21 and 28 days. In previously sensitised individuals, anticonvulsant hypersensitivity syndrome (HSS) may occur within 1 day on rechallenge. Anticonvulsant HSS has no relationship to dosage or serum concentration of anticonvulsants.[8]

**Evolution**

DRESS is characterised by a group of symptoms involving multiple organs, especially the skin, liver, and haematologic system with cutaneous changes being the most apparent.[24] The reaction usually starts with low-grade or high-grade fever, and over the next 1–2 days, a cutaneous reaction, lymphadenopathy, and pharyngitis may develop. This is followed by the involvement of various internal organs, most commonly the liver, although haematologic, renal, or pulmonary impairment may occur.[8,24] The protracted clinical course of DRESS syndrome has been linked to the reactivation of several herpes viruses. They follow an order resembling those that occur in patients with graft-versus-host disease.

**Common Drugs**

Common drugs causing DRESS syndrome are listed in Table 2.[2] The broad spectrum of clinical features and long latency period in HSS/DRESS often results in diagnostic delay.

**Cutaneous manifestations**

Usually, a patient presents with fever, rash, lymphadenopathy, leukocytosis, and abnormal liver tests. The major dilemma in diagnosis is to rule out an infectious aetiology. However, skin changes and blood abnormalities should lead to a thorough history of the patient’s medication to rule out a drug hypersensitivity illness. Commonly, skin features are prominent in DRESS, with urticated, maculopapular eruption being most common, but vesicles, bullae, pustules, cheilitis, purpura, target lesions, and erythroderma were also reported. Facial oedema is a characteristic of DRESS.[25]

Ang et al reported in a series of 27 patients with DRESS syndrome, wherein 81.5% had an erythematous morbilliform rash involving the face, trunk, and limbs, 7.4% had generalised erythroderma, 7.4% had a pustular eruption, 7.4% had targetoid lesions, 29.6% had mucositis, and 33.3% had swelling of the face.[24]

**Systemic involvement**

Although the cutaneous eruption of DRESS is extensive and common, the major morbidity and mortality in DRESS result from systemic involvement. The most common systemic findings include fever (>38°C) and visceral involvement, with most common being lymphatic, haematologic, and hepatic systems, followed by renal, pulmonary, and cardiac manifestations. Severe, atypical cases of DRESS may also have neurologic, gastrointestinal, or endocrine dysfunction. It was noted that certain medications have a predilection for involving specific organs [Table 3].[2] Lymphadenopathy, localised or generalised, is present in nearly 75% of DRESS. Common nodes involved are the cervical, axillary, and inguinal lymph nodes. Histopathologically, two distinct variants are seen, the benign and pseudolymphomatous variants.[27]

Fever is seen in >90% of patients and is usually high (>38°C) and spiking. The spikes in temperature may persist for weeks after the offending drug is discontinued, especially in cases of severe reaction.

**Haematologic abnormality**

Haematologic abnormalities are very common and generally occur 2 weeks after the onset of drug eruption. Leukocytosis, often with very high total count with

| Table 2: Common drugs associated with drug reaction with eosinophilia and systemic symptoms syndrome |
| --- |
| **Category of drug** | **Drug name** |
| Antimicrobial | Ampicillin, dapsone, isoniazid, linezolid, minocycline, rifampin, sulfasalazine, trimethoprim-sulfamethoxazole, vancomycin |
| Anticonvulsant | Carbamazepine, phenytoin, lamotrigine, phenobarbital |
| Antiviral | Abacavir, nevirapine |
| Antidepressant | Fluoxetine |
| Antihypertensive | Captopril |
| Others | Allopurinol, efalizumab, NSAID (celecoxib) |
| **NSAID**: Nonsteroidal anti-inflammatory drug |

| Table 3: Drugs associated with specific internal organ involvement risk in drug reaction with eosinophilia and systemic symptoms syndrome |
| --- |
| **Drugs** | **Specific clinical abnormality** |
| Ampicillin | Cardiac |
| Dapsone | Hepatic and renal |
| Carbamazepine | Renal |
| Phenytoin | Hepatic |
| Allopurinol | Renal |
| Minocycline | Hepatic, pulmonary, and cardiac |
atypical lymphocytes, is usually present. In approximately 30% of cases, there is marked eosinophilia, which may play a role in visceral manifestations because of the proteins released from the granules.[28] There is often a leukopenia or lymphopenia that precedes leukocytosis. There may be thrombocytopenia and anaemia reported sometimes.[29]

**Hepatic abnormalities**

Hepatic disturbance in DRESS occurs commonly with either hepatocellular or cholestatic damage, and in severe cases, fulminant hepatic failure which may necessitate liver transplantation. Phenytoin, minocycline, and dapsone are commonly implicated in liver damage. The mortality rate from DRESS has been estimated at 10%, most patients dying from liver failure.[30] 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 >95% of them.[26,28]

**Renal involvement**

About 11% of patients of DRESS can exhibit renal disease. Allopurinol is the most common offending drug, followed by carbamazepine and dapsone. Patients with underlying renal disease and the elderly are at highest risk of developing renal complications. First manifestations are usually asymptomatic haematuria and proteinuria. Investigations may reveal renal dysfunction including elevated blood urea nitrogen and creatinine levels and low creatinine clearance. Although the renal impairment is mostly mild and resolves after withdrawal of the offending drug, severe interstitial nephritis may develop. Ang et al reported that 4 (14.8%) patients in their series had renal impairment, with two requiring short-term supportive haemodialysis.[26,28]

**Other organ involvement**

Lung involvement of DRESS syndrome may also occur and include impaired pulmonary function, acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress syndrome. Minocycline is the most common drug causing lung pathology.

Cardiovascular system can also be affected, with patients usually presenting with myocarditis. Ampicillin and minocycline are the most commonly implicated drugs. Patients may present with chest pain, tachycardia, dyspnoea, and hypotension. DRESS syndrome with myocarditis is potentially fatal.[31]

Neurologic manifestations are rare and include meningitis and encephalitis, which may be related to HHV-6 reactivation. Gastroenteritis and dehydration are the most common manifestations of gastrointestinal system associated with DRESS. Colitis and pancreatitis are also observed. Chronic enteropathy was reported rarely.[32]

| Table 4: Diagnostic protocol of drug reaction with eosinophilia and systemic symptoms |
|-----------------------------------------------|
| **Mandatory evaluation** | **Additional evaluation (when indicated)** |
| Careful drug history | Histopathology of skin lesion |
| History and examination of skin signs | Viral serology |
| Complete blood count and peripheral blood smear examination | HIV serology |
| Absolute eosinophil count | CT scan of brain and neurological evaluation |
| Liver function tests | Skin patch tests and LTTs to confirm offending drug |
| Renal function tests | Pulmonary function test, CT scan |
| Blood electrolytes | chest, evaluation by pulmonologist |
| USG abdomen | Evaluation by nephrologist |
| Chest X-ray (PA view) | Evaluation by cardiologist |
| ECG, echocardiography | |

It is worthy to monitor thyroid activity during DRESS syndrome, and Ang et al reported five patients who developed abnormalities in thyroid function.[26] Apart from these, there may be pancreatic involvement in DRESS syndrome, including pancreatitis or diabetes mellitus (Type 1).[28]

**Investigations**

Patient suspected of DRESS should undergo extensive evaluation to establish diagnosis, assessment of severity and also for the monitoring purposes [Table 4]. Descamps et al in the consensus French guidelines recommended the following laboratory tests at admission: complete blood cell count, ALT, aspartate aminotransferase, total bilirubin, gamma-glutamyltransferase, alkaline phosphatase, sodium, potassium, creatinine, and creatinine clearance, 24-h urine protein and urinary eosinophil count, creatine phosphokinase, lactate dehydrogenase, and antinuclear factor.[33]

Determination of the offending drug is often very difficult in cases of polypharmacy or when the sign and symptoms begin after a long latency period. Certain clinical tests were developed in determining the causative agent in DRESS syndrome, but they are often unreliable. However, information derived from these tests may be helpful for physician in preventing future episodes. Most commonly used investigations include skin patch test and lymphocyte transformation test (LTTs). A diluted concentration of the drug is used in patch testing. Positive reactions rely on the development of a localised inflammatory response. It is safe; however, its reliability is questionable. A systemic
review revealed that the positive predictive value of patch testing under optimal conditions was as high as 80–90% for certain drugs, but only around 10%–20% for other medications. For optimal results, patch testing should be performed 2–6 months after recovery from the symptoms.\cite{34}

LTT can also help predict the offending drug in DRESS. LTT measures the activation of drug-specific T-cells in response to suspected drug in solution. It quantifies 3 H-thymidine uptake by the T-lymphocytes, which proliferate after encountering the suspected drug. LTT can assess simultaneously the T-cell responses to multiple drugs and also can detect drug reactions of different mechanisms.\cite{35} Facilities for LTT are not available in most places in India, making its utility very limited in real-life scenario. A positive LTT is valuable both in the diagnosis of DRESS syndrome and in determining the eliciting drug. However, because of its limited sensitivity, a negative LTT cannot exclude drug hypersensitivity.\cite{36}

### Histopathology

Histopathology of cutaneous lesions in DRESS syndrome most commonly reveals perivascular dense lymphocytic infiltrate in the papillary dermis, with eosinophils, atypical lymphocytes, and spongiosis of epidermis. Biopsy of the affected lymph nodes in DRESS syndrome may show either benign lymphoid hyperplasia or a pseudolymphomatous pattern.\cite{2}

### Diagnostic Criteria

It must be emphasised that there is presently no gold standard for the diagnosis of DRESS syndrome. The diagnosis is established by clinicians’ judgment of correlating clinical sign and laboratory findings. In an effort to define more accurately the DRESS syndrome, a scoring system has been proposed by the European Registry of Severe Cutaneous Adverse Reaction study group named as the RegiSCAR scoring system.\cite{37} The group expanded on the diagnostic criteria proposed by Bocquet et al\cite{9} in this line, the RegiSCAR’s scoring system has been designed to grade DRESS cases as “no,” “possible,” “probable,” or “definite” case. The original RegiSCAR score was published in a letter by Kardaun et al, in which a two-stage process for collecting cases of DRESS in a registry for further study was discussed: (1) collection of potential cases of DRESS (“inclusion criteria”) \cite{38} followed by (2) confirmation of the diagnosis (“validation criteria”) \cite{39}.\cite{37}

There is still no international consensus on the best criteria for the definition of DRESS/DIHS diagnosis. Bocquet et al\cite{9} and Southeimer and Houpt\cite{4} have proposed different definitions and nosology for DRESS/DIHS, to clarify clinical and pathological characteristics of this syndrome. The Japanese study group of severe cutaneous adverse reactions to drugs (SCAR-J) has adopted other criteria \cite{38}.

### Table 5: Comparison among the proposed diagnostic criteria by Boquet et al and Japanese study group of severe cutaneous adverse reactions to drugs and the inclusion criteria for the RegiSCAR study before application of the validation score for patients with drug reaction with eosinophilia and systemic symptoms

| Investigational group | Bocquet et al\# | J-SCAR* | RegiSCAR* |
|-----------------------|----------------|---------|-----------|
| Rash | Cutaneous drug eruption | Prolonged clinical symptoms 2 weeks after discontinuation of the drug | Hospitalization** |
| | | Maculopapular rash developing >3 weeks after starting suspected drug | Suspected to be drug related** |
| Fever | Fever | Fever >38°C | Acute rash |
| Systemic involvement | Adenopathy: Lymph nodes ≥2 cm in diameter hepatitis with ALT and/or AST ≥2 times normal interstitial nephritis myocarditis | Liver abnormalities (ALT >100 U/L) or other organ involvement | Fever>38°C |
| | | | Involvement of >1 organ |
| Haematologic abnormalities | Eosinophil >1.5×10⁴/L | Eosinophil >1.5×10⁴/L | Eosinophilia |
| | Atypical lymphocytes | Leukocytosis (>11×10⁴/L) | Lymphocytosis and/or lymphopenia |
| | | Atypical lymphocytes (>5%) | Thrombocytopenia |
| Lymphadenopathy | Lymphadenopathy | | Lymphadenopathy that involve ≥2 sites |
| Viral assay | HHV-6 reactivation | | |

\#All three criteria are required (1 haematologic and 1 systemic feature required). \*Diagnosis confirmed based on the presence of seven criteria (typical DIHS) or the first five features (atypical DIHS). \*Inclusion criteria for RegiSCAR: In addition to the mandatory features, **Three of five additional criteria are needed before a validation score may be applied. DIHS: Drug-induced hypersensitivity syndrome, ALT: Alanine aminotransferase, AST: Aspartate transaminase, HHV: Human herpes virus, J-SCAR: Japanese study group of severe cutaneous adverse reactions to drugs.
De, et al.: Drug reaction with eosinophilia and systemic symptoms

Differential Diagnosis

The common differentials of DRESS syndrome include other SCAR, such as Stevens–Johnson syndrome/toxic epidermal necrolysis, acute generalised exanamatosus pustulosis, and erythoderma, which are needed to be based on characteristic cutaneous findings, onset of symptoms, and visceral involvement. It is important to differentiate DRESS syndrome from dermatologic findings associated with viral exanthemata (Kawasaki disease, EBV, hepatitis virus, influenza virus, CMV, and human immuno deficiency virus). It has also to be distinguished from lymphoma or pseudolymphoma, collagen vascular diseases, and serum sickness-like reaction. In serum sickness-like reactions, there is development of arthralgia and lack of internal organ involvement, unlike DRESS. Other differential diagnosis of DRESS includes diseases such as Kawasaki syndrome, Still's disease, syphilis, porphyria, and hypereosinophilic syndrome.

Treatment

The most important challenge in DRESS syndrome is early recognition of the condition and immediate withdrawal of the offending drug. Failing to do so often proves crucial, leading to unwarranted morbidity and mortality.

All patients should be given adequate supportive therapy to stabilise haemodynamics, antipyretics to reduce fever, and emollient and topical steroids to decrease the cutaneous symptoms. Empiric antibiotics should be avoided because it may exacerbate the condition further because of the cross-reactivity between drugs.

Systemic corticosteroids are the gold standard treatment for DRESS. Rapid resolution of rashes and fever occurs within days after initiating corticosteroids. Systemic steroid therapy should begin with a minimum dose of 1.0 mg/kg/day of prednisone or equivalent. Steroids need to be tapered slowly over 6–8 weeks, even upon

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**Table 6: RegiSCAR drug reaction with eosinophilia and systemic symptom validation score**

| Score                                      | −1 | 0 | 1 | 2 | Minimum | Maximum |
|--------------------------------------------|----|---|---|---|---------|---------|
| Fever >38.58°C                             | No/U | Yes |   |   | −1      | 0       |
| Enlarged lymph nodes                       | No/U | Yes |   |   | 0       | 1       |
| Eosinophilia                               | No/U | Yes |   |   | 0       | 2       |
| Eosinophilis, if leukocytes <4000          | 700-1499/µL | 1500/µL | 10-19.9% | 20% or more | 0 | 2 |
| Atypical lymphocytes                        | No/U | Yes |   |   | 0       | 1       |
| Skin involvement                           | No/U | Yes |   |   | −2      | 2       |
| Rash extent (>50% BSA)                     | No/U | Yes |   |   | −2      | 2       |
| Rash suggesting DRESS†                     | No | U | Yes |   |         |         |
| Biopsy suggesting DRESS                   | No | Yes/U |   |   |         |         |
| Organ involvement                          | No/U | Yes |   |   |         |         |
| Liver                                      | No/U | Yes |   |   | 0       | 2       |
| Kidney                                     | No/U | Yes |   |   | 0       | 2       |
| Lung                                       | No/U | Yes |   |   | 0       | 2       |
| Muscle/heart                               | No/U | Yes |   |   | 0       | 2       |
| Pancreas                                   | No/U | Yes |   |   | 0       | 2       |
| Other organ(s)                             | No/U | Yes |   |   | 0       | 2       |
| Resolution >15 days                        | No/U | Yes |   |   | −1      | 0       |
| Evaluation other potential causes          |     |     |     |     |         |         |
| ANA                                        |     |     |     |     |         |         |
| Blood culture                              |     |     |     |     |         |         |
| Serology for Hep A/ Hep B/ Hep C          |     |     |     |     |         |         |
| *Chlamydia/Mycoplasma pneumoniae*          |     |     |     |     |         |         |
| Other serology/PCR                         |     |     |     |     |         |         |
| If none positive and 3 or more of above negative | Yes |   |   |   |         |         |
| Total score                                |     |     |     |     | −4      | 9       |

*After exclusion of other explanations: 1: 1 organ, 2: 2 organs. Final score <2: No case, Final score 2-3: Possible case, Final score 4-5: Probable case, Final score >5: Definite case. Morphology is considered suggestive for DRESS: Scaling/desquamation, e.g., exfoliative dermatitis. Oedema, especially facial oedema (excluding lower leg oedema), purpura (excluding lower leg). Infiltration. U: unknown/unclassifiable, DRESS: Drug reaction with eosinophilia and systemic symptom, BSA: Body surface area, ANA: Antinuclear antibody, PCR: Polymerase chain reaction, Hep A: Hepatitis A virus, Hep B: Hepatitis B virus, Hep C: Hepatitis C virus
Table 7: Comparative clinical features of different types of severe cutaneous adverse reactions

|                    | DRESS                      | AGEP                        | SJS-TEN                    | Erythrodema               |
|--------------------|----------------------------|-----------------------------|----------------------------|---------------------------|
| Onset after exposure | 2-6 weeks                  | 2-3 days                    | 3-4 weeks                  | 1-3 weeks                 |
| Duration           | 12 weeks or more           | Less than a week            | Bulleas, necrosis, atypical target lesions | Months                    |
| Cutaneous manifestations | Facial oedema, morbilliform eruption, pustules, exfoliative dermatitis, rarely bullae | Facial oedema, pustules, tense bullae | | Erythema and scaling affecting more than 90% of the total BSA |
| Mucosal involvement | No/minimal                | +                           | Severe mucocutaneous erosions | No/minimal               |
| Fever              | +++                        | +++                         | +                          | +                         |
| Lymphadenopathy    | Localised or generalised LAP++ | +/-                        | -                          | +                         |
| Liver              | +++                        | +/-                         | +                          | May have hepato-splenomegaly |
| Pulmonary          | Pneumonitis                | +/-                         | Tracheobronchial necrosis  | +/-                       |
| Kidney             | Interstitial nephritis     | +/-                         | Tubular nephritis          | +/-                       |
| Other organ        | Myocarditis, pancreatitis and thyroiditis | +/-                       | -                          | +/-                       |
| Skin histopathology | Dense perivascular lymphocytic infiltrate | Subcorneal pustules | Epidermal necrosis | May reflect underlying aetiology |
| Lymph node histopathology | Lymphoid hyperplasia | +                           | -                          | Mostly nonspecific |
| Eosinophil         | +++                        | +                           | -                          | +                         |
| Atypical lymphocyte | +                         | -                           | -                          | +                         |
| Neutrophil         | +                         | +++                         | May decrease               | +                         |
| Mortality          | 10%                       | 5%                          | Up to 30%                  | 10%                       |

DRESS: Drug reaction with eosinophilia and systemic symptom, AGEP: Acute generalized exanthematous pustulosis, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, BSA: Body surface area, LAP: Lymphadenopathy, - Absent, +/- variable, + mild, ++ moderate, +++ severe

Table 8: Comparative clinical features of drug hypersensitivity syndrome, pseudolymphoma, and serum sickness-like reaction

| Diagnosis                      | Rash                                      | Onset      | Fever | Visceral involvement | Arthralgia | LAP |
|--------------------------------|-------------------------------------------|------------|-------|----------------------|------------|-----|
| DRESS                          | Morbilliform eruption, erythroderma, urticated lesion, pustules, blisters | 2-6 weeks  | ++    | ++                   | -          | +   |
| Pseudolymphoma                 | Single or multiple nodules                | 6 months   | +     | +                    | +          | +   |
| Serum sickness-like reaction   | Urticated lesions, maculopapular eruption | 7-14 days  | +     | -                    | -          | +   |

DRESS: Drug reaction with eosinophilia and systemic symptom, LAP: Lymphadenopathy, - Absent, + mild, ++ moderate, +++ severe

Clinical resolution, to prevent relapse. This is also because patients with DRESS are at greater risk of subsequently developing the wide spectrum of immune reconstitution inflammatory syndrome on rapid withdrawal of steroids.\[11,39,40\]

In more severe cases or cases refractory to oral steroids, patients can be treated with intravenous methylprednisolone. A course of pulsed methylprednisolone, 30 mg/kg intravenously for 3 days, can be administered. During this time, complete blood cell count, liver function tests, lymph nodes, and other organ-specific laboratory tests should be monitored carefully to detect potential relapse, and steroid doses should be adjusted accordingly.\[36\]

Intravenous immunoglobulin (IVIG) was tried in DRESS syndrome, especially in cases who do not respond to systemic steroids or where steroid was contraindicated.\[41\] There are many case reports of DRESS syndrome which were successfully treated with IVIG.\[41-43\] However, a study by Joly et al of six patients with DRESS syndrome failed to demonstrate superiority of IVIG and four of the six patients had to be treated with oral corticosteroids because of the adverse effects of IVIG or uncontrolled DRESS syndrome.\[44\]

Other modalities of treatment tried in DRESS are plasmapheresis and immunosuppressive drugs, such as cyclophosphamide, cyclosporine, interferons, mycophenolate mofetil, and rituximab.\[36\] Cyclophosphamide\[45\] and cyclosporins\[46\] were used in isolated case reports of DRESS with success. N-acetylcysteine may aid in drug detoxification and limit reactive metabolites in anticonvulsant-induced DRESS.\[47\] Valganciclovir may be helpful in minimising complications.
related to HHV-6 reactivation and can be used in combination with prednisone and N-acetylcysteine.[48]

Descamps et al from the consensus group of the French Society of Dermatology suggested a step-wise treatment of DRESS.[33] A multidisciplinary approach is often required for the proper management of DRESS. Long-term follow-up with laboratory testing is important to monitor relapse [Table 9].

### Prognosis

Majority of patients with DRESS syndrome recover completely with early diagnosis, withdrawal of the offending drug, and appropriate treatment. The clinical course varies considerably, with one spectrum of the disease resolving quickly, whereas other more severe spectrum may have life-long, extensive systemic sequelae. The major cutaneous sequela seen in DRESS is chronic exfoliative dermatitis, but there can be pigmentary changes and cutaneous scarring.[36]

Wei et al suggested that poor prognosis of DRESS may be associated with tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleeding, and systemic inflammatory response syndrome.[49] The estimated mortality of DRESS syndrome is 10%; the most common cause of death is related to hepatic necrosis.[50]

### Conclusion

The diagnosis of DRESS should be highly suspected with the presence of skin rash, liver involvement, fever, hypereosinophilia, and lymphadenopathy. The high rate of HHV-6 and other herpes viruses reactivation associated with DRESS implies that it has a complex immunopathogenesis. Immediate withdrawal of causative drug, institutional treatment, and supportive measures, standard wound care, multidisciplinary approach, and prompt initiation of systemic steroid as indicated can reduce the morbidity and mortality to minimum. However, good quality of data in DRESS is missing from the Indian subcontinent regarding the causative drug and prognosis. Further studies are needed from the Indian subcontinent to form a consensus statement applicable for this part of the world.

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### Conflicts of interest

There are no conflicts of interest.

### What is new?

Apart from specific drugs; the pathogenesis is related to altered immune response, sequential reactivation of herpes virus and association with HLA alleles. Early recognition of the syndrome and withdrawal of the offending drug are the most essential steps. Corticosteroids, intravenous immunoglobulin have been used in the management with considerable evidence.

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**Table 9: Therapeutic algorithm of drug reaction with eosinophilia and systemic symptom**

| Step 1 | Confirmation of the diagnosis of DRESS using the RegiSCAR criteria |
|--------|---------------------------------------------------------------|
| Step 2 | a) Admission of the patient |
|        | b) Immediate withdrawal of the culprit drug |
|        | c) Supportive therapies: Correcting fluid and electrolyte balance, thermoregulation, nutrition (oral/parenteral as applicable), care of wound, treatment of infection |
|        | d) Investigations as recommended [Table 4] |
| Step 3 | a) If there is no sign of severe systemic involvement (transaminase levels>5 times of normal, renal involvement, pneumonia, haemophagocytosis, and cardiac severity, etc.), patients can be treated with topical corticosteroids, emollients and H1 - antihistamines |
|        | b) If there is sign of severe systemic involvement, patients can be treated with systemic corticosteroids equivalent to at least 1 mg/kg/day of prednisone |
|        | c) If there is sign of life-threatening systemic involvement (i.e., haemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, and respiratory failure), it can be treated with steroids and IVIG at a dose of 2 g/kg over 5 days |
|        | d) If there is sign of severe systemic involvement with confirmation of major viral reactivation, antiviral medications such as ganciclovir can be given in addition to steroids and/or IVIG |
| Step 4 | Evaluation by appropriate specialists as required by severe signs or symptoms or laboratory investigations |
| Step 5 | Slow tapering of steroids after desired clinical response |
| Step 6 | Long-term follow-up with laboratory testing |

IVIG: Intravenous immunoglobulin, DRESS: Drug reaction with eosinophilia and systemic symptom
De, et al.: Drug reaction with eosinophilia and systemic symptoms

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