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Drug Reaction with Eosinophilia and Systemic Symptoms

■ Synonyms:	Drug-induced hypersensitivity syndrome (DIHS), drug hypersensitivity, drug-induced delayed multi-organ hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome (AHS)
■ Etiology:	A wide range of drugs including antiepileptics, antibacterials, antidepressants, antihypertensives, antituberculosis agents, nonsteroidal anti-inflammatory drugs (NSAIDs), biologics, etc.
■ Incidence:	1/1000–1/10,000 drug exposures
■ Clinical:	Severe cutaneous reaction (e.g., maculopapular rash and generalized erythematous rash), fever, eosinophilia or atypical lymphocytes, and internal organ involvement.
■ Distribution:	Generalized
■ Histology:	Superficial perivascular lymphocytic infiltrate, erythrocyte extravasation, focal interface changes
■ Adverse variables:	End-organ failure
■ Treatment:	Withdrawal of the offending drug, administration of corticosteroids, intravenous immunoglobulin (IVIG)
■ Prognosis:	Relapses may occur, long-term complications may develop
■ Mortality rate:	10 %

Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) was originally described in 1996 by Bocquet et al. in their description of patients who developed fever, a severe cutaneous reaction with infiltrated papules, facial edema or an exfoliative dermatitis, lymphadenopathy, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement within 2 months after initiation of the offending drug [1]. The current literature defines DRESS as a syndrome with varying combination of the following factors: drug-induced immunological background, late onset drug reaction, longer duration than other drug rashes, multi-organ involvement, lymphocyte activation, eosinophilia, and frequent virus reactivation [2].

DRESS is a severe drug-induced adverse reaction that has commonly been associated with anticonvulsants including phenytoin, carbamazepine, phenobarbital, and lamotrigine and with sulfonamides. Additional drugs include allopurinol, nevirapine, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and antituberculosis drugs [3]. The risk factors for DRESS include cranial irradiation, young age, HIV infection, and viral reactivation of Human Herpes Virus HHV4, HHV5, HHV6, and HHV7. Cytomegalovirus (CMV), and Epstein-Barr virus (EBV) [4]. The significance of the human leukocyte antigen (HLA) as a risk factor for developing DRESS has been demonstrated in the scientific literature. In a Taiwanese study of 30 patients with allopurinol-induced DRESS, they reported 100 % prevalence of

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HLA-B*5801 [5]. The association was also reported in a European study of 19 patients with allopurinol-induced DRESS, which demonstrated 12 patients as carriers for HLA-B*5801 [6]. Additionally, HLA-B*5701 has been identified as a risk factor for DRESS in Caucasians receiving abacavir [7, 8]. In addition to HLA genotypes, the role of genetic polymorphisms as a risk factor for DRESS has been hypothesized. Polymorphisms in epoxide hydroxylase, an enzyme responsible for detoxification of aromatic anticonvulsants, result in the buildup of toxic metabolites and subsequent immunologic activity [9]. Furthermore, individuals with genetic variability of N-acetylation, an enzyme reaction involved in the metabolism of sulfonamides, demonstrate an increased susceptibility to the development of DRESS [10].

The pathogenesis of DRESS is not completely understood; however, the current viewpoint associates several factors as implicated in the development of the syndrome including detoxification abnormalities resulting in toxic metabolite accumulation, slow acetylation, and the reactivation of human herpes viruses [9–11].

The incidence of DRESS ranges from 1/1000 to 1/10,000 exposures in patients taking the culprit drug [12]. DRESS was previously reported to have no predilection for gender or age [13]; however, a more recent prospective observational study of 117 patients with DRESS demonstrated a male to female ratio of 0.8 and a borderline significance of younger females than males [14].

DRESS syndrome is characterized by a long latency period; symptoms usually develop 2–8 weeks following the introduction of the offending drug. Early features of DRESS include a fever greater than 38 °C, lymphadenopathy, dysphagia, flu-like symptoms, pruritus, and burning pain [14]. A polymorphous rash, often a morbilliform eruption and frequent facial edema, will subsequently develop; in later stages of DRESS, the rash will progress into an exfoliative dermatitis or erythroderma. Mild involvement of mucous membranes may be present [14]. Organ involvement in DRESS may include the liver, kidney, lung, muscle/heart, pancreas, or additional organs. Laboratory findings in patients with DRESS commonly demonstrate leukocytosis with either eosinophilia or atypical lymphocytes. Because of the diversity in clinical presentation, onset of symptoms, and clinical course, DRESS is challenging to diagnose. The clinical course of DRESS is commonly around 15 days or greater. A prolonged or more severe course of DRESS has been implicated with the reactivation of HHV6 [15].

Skin biopsy demonstrates a dense perivascular lymphocytic infiltrate in the papillary dermis; eosinophils, atypical lymphocytes, spongiosis, and erythrocyte extravasation may be present. Biopsy of affected lymph nodes may show either benign lymphoid hyperplasia or a pseudolymphoma pattern. Biopsy of internal organ involvement may demonstrate an eosinophilic infiltrate.

Three different sets of diagnostic criteria currently exist for DRESS including Bocquet's criteria [1], the RegiSCAR criteria [2], and Japanese DIHS criteria [13]. Bocquet's criteria includes a cutaneous drug eruption, hematologic abnormalities such as eosinophilia or the presence of atypical lymphocytes and systemic involvement including lymphadenopathy (greater than 2 cm in diameter), hepatitis, interstitial nephritis, interstitial pneumonia, or carditis [1]. The RegiSCAR criteria includes at least three of the following seven characteristics: skin eruption, fever greater than 38 °C, lymphadenopathy at two sites or more, involvement of one or more internal organs, lymphocytosis or lymphocytopenia, eosinophilia, and thrombocytopenia [2]. The RegiSCAR scoring system categorizes DRESS cases as definite, probable, possible, or no case based on the following characteristics: fever equal to or greater than 38.5 °C, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin involvement, organ involvement, resolution equal to or greater than 15 days, and evaluation of other potential causes (including antinuclear antibody, blood culture, hepatitis A virus (HAV)/hepatitis B virus (HBV)/hepatitis C virus (HCV) serologies, and *Chlamydia*/*Mycoplasma*) [2]. The Japanese DIHS criteria is defined by a maculopapular rash developing more than 3 weeks after drug onset, prolonged clinical symptoms lasting 2 weeks following discontinuation of the offending drug, fever greater than 38 °C, liver abnormalities, leukocyte abnormalities (including leukocytosis, atypical lymphocytosis, and/or eosinophilia), lymphadenopathy, and HHV6 reactivation [13].

The treatment of DRESS involves the removal of the offending drug and administration of systemic corticosteroids. Corticosteroids combined with intravenous immunoglobulin have also been used successfully for DRESS treatment [16]. In mild cases, topical corticosteroids and antihistamines may be utilized.

Although a rare condition, DRESS syndrome is potentially life-threatening and has an estimated 10 % mortality rate, most frequently due to end-organ failure. In a retrospective review of 172 cases of DRESS, the authors reported no predictive factors for serious cases, as no differences in demographic or clinical variables were found between resolved cases and case fatalities [12]. Of note, however, specific drugs, such as allopurinol and minocycline, have been implicated to result in more serious DRESS cases [17]. Relapses may occur weeks to months after drug withdrawal. It has been hypothesized that when corticosteroids are either tapered or stopped, relapse may occur as these drugs may promote reactivation of herpes virus [11]. Long-term complications of DRESS include autoimmune conditions such as type 1 diabetes mellitus, thyroiditis, or systemic lupus erythematosus [18].

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