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REVIEW

An Overview of Management of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

Eozinofili ve Sistemik Semptomlarla Seyreden İlaç Reaksiyonu (DRESS) Sendromunun Yönetimine Genel Bir Bakış

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS), clinically manifests with fever, lymphadenopathy, a maculopapular rash, and organ involvement. Leukocytosis, leukopenia, atypical lymphocytes, eosinophilia, and changes in liver and kidney function tests are all discovered in laboratory results. Since it might vary according to the very type of medicine and each patient's immunological condition, as well as because many cases go undetected or untreated, the true incidence of DRESS is unknown. Anticonvulsant medications, antibiotics and antituberculosis medications are the most frequently linked to DRESS. It can be difficult to diagnose and is occasionally made late. Using a scoring system based on clinical and laboratory results, the diagnostic criteria put forward by the international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) aid in making the diagnosis. A comprehensive clinical history involving all suspects is the first stage in determining the culprit, with a focus on those most likely to induce DRESS syndrome based on the relevant line of literature and the environment. The diagnostic procedure may also benefit from a skin biopsy. In DRESS situations, patch testing is the preferred method for identifying the offender. Reviewing the available data on the epidemiology, pathogenesis, diagnosis, therapy, clinical and laboratory results of DRESS is the goal of this article.

Keywords: DRESS; Drug; Eosinophilia; Hypersensitivity; Systemic symptom

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DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a hypersensitivity reaction that usually develops against certain drugs and has a severe clinical picture. Clinically, it is characterized by widespread rash, fever, lymphadenopathy, hematological abnormalities (eosinophilia, lymphocytosis) and multiorgan involvement (liver, kidney, lung, heart, and so on.). Although the incidence of DRESS syndrome is low, it is a significant clinical problem due to its severity and potentially life-threatening complications. The mortality rate varies between 10–20% and timely diagnosis and treatment of cases is of vital importance.[1–5]

The aim of this review is to inform the reader about the developments in the diagnosis and treatment of DRESS syndrome in the light of the available literature.

We reviewed the current literature to determine the developments in the diagnosis and treatment of DRESS syndrome. We searched for relevant studies in the PubMed, UpToDate, Web of Science, and Google Scholar databases between January 1, 2010, and December 31, 2024. The search terms were "DRESS" and "Drug-induced hypersensitivity syndrome".

Epidemiology

The lack of reliable data on DRESS syndrome may be due to confusing terminology and the paucity of epidemiological studies. RegiSCAR is an international pharmaco-epidemiological registry for serious adverse drug reactions (SCAR) launched in 2003 and includes DRESS cases. A consortium in Spain called PIELenRed provides reliable data on DRESS syndrome. The annual incidence of DRESS syndrome varies between 0.9 cases per 100,000 and 10 cases per million, while the in-hospital prevalence is reported to be between 2.18 and 9.63 cases per 100,000 patients. The most common comorbidities are HIV infection, atopy and epilepsy. The mortality rate of the syndrome varies between 1.7% and 10%.[6]

DRESS is frequently underdiagnosed in many regions due to insufficient awareness, despite its global presence. Physicians prescribing anticonvulsants need to be vigilant about this syndrome as it can be a common adverse effect of such medications. DRESS occurs in more than 1 in 10,000 patients taking anticonvulsants like carbamazepine. Due to its varying clinical presentations and diverse symptoms, the syndrome is often misdiagnosed, leading to an underestimation of its true prevalence. While it has been noted that DRESS might be more common among elderly Black men, the incidence is likely higher than currently reported. It remains uncertain whether there is a definitive racial predisposition for the condition. Many studies indicate that DRESS does not show a significant age or sex preference, though Kardaun et al.[7] observed a slight female predominance in DRESS syndrome, with a male-to-female ratio of 0.80. In contrast, Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) is more common in women, who are about 1.5 times more likely to be affected than men. The median age at diagnosis is around 51.4 years for men and 55.7 years for women, with only 7% of cases occurring in individuals under 20 years of age.

The RegiSCAR study provided a comprehensive analysis of the epidemiology of DRESS syndrome. This study indicated that the prevalence of DRESS is significant, especially in populations exposed to high-risk drugs. The study emphasized that the risk of developing DRESS is significantly increased in patients with a history of rheumatic disease or collagen vascular disease. These findings provide important data to consider in the diagnosis and management of DRESS syndrome.[8–10]

In Tables 1 and 2, we list the drugs that cause DRESS syndrome most frequently observed and reported in case reports.

Pathophysiology

Three major factors have been identified in the pathophysiology of DRESS, despite the fact that the exact mechanism is still unknown. The first is a genetic susceptibility to specific alleles of the human leukocyte antigen (HLA); the second is associated with a change in the metabolic pathways of medications, primarily aromatic anticonvulsants; and the third is a reactivation of Human herpesvirus 6 (HHV 6), which causes tissue damage through an inflammatory response mediated by T lymphocytes.

HLA haplotypes and DRESS susceptibility have been linked in pharmacogenetic research. There is evidence linking HLA-B 5701 to a higher risk of abacavir-induced DRESS. HLA-DR3, HLA-DQ2, and HLA-A * 31:01 have been linked to DRESS brought on by carbamazepine,[11] whereas HLA-B * 5801 is a risk factor for SJS, TEN, and DRESS brought on by allopurinol among the Han ethnic group of China. The significant negative predictive value of these allelic markers indicates that they are required but insufficient to trigger an allergic reaction.

Hepatic cytochrome P450 (CYP) enzymes metabolize aromatic anticonvulsants like phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and lamotrigine. As a result, a malfunction in the detoxification process mediated by glutathione transferase or epoxide hydroxylase can result in the production of reactive oxygen metabolites, which build up and cause cellular toxicity and alarm signals that can activate T lymphocytes and trigger an immune response.[11,12]

Table 1. Drugs most commonly reported to be associated with DRESS syndrome[6,19–22]

Drug category	Frequent culprit drugs
Antibiotic and other anti-infective drugs	Dapsone, sulfamethoxazole/trimethoprim, abacavir, nevirapine, minocycline, vancomycin
Anticonvulsant drugs	Carbamazepine, lamotrigine, levetiracetam, phenytoin, phenobarbital
Musculoskeletal system drugs	Allopurinol
Treatment for tuberculosis	Rifampicin
Miscellaneous	5-Aminosalicylic acid, sulfasalazine

DRESS: Drug reaction with eosinophilia and systemic symptoms.

Table 2. Drugs less frequently reported to be associated with DRESS syndrome[6,19–22]

Drug category	Frequent culprit drugs
Antibiotic and other antiinfective drugs	Amoxicillin-clavulanic acid, ampicillin/amoxicillin, ampicillin/sulbactam, benzidazole, boceprevir, cefadroxil, cefepime, cefixime, cefotaxime, cefazidime, clindamycin, diaphenylsulfone, hydroxychloroquine, imipenem, levofloxacin, linezolid, meropenem, metronidazole, piperacillin/tazobactam, quinolones, teicoplanin, voriconazole, zalcitabine
Anticonvulsant drugs	Ethosuximide, gabapentin, oxcarbazepine, pregabalin, valproate, zonisamide
Antineoplastic and immunomodulating agents	Azathioprine, chlorambucil, efalizumab, imatinib, lenalidomide, leflunomide, pembrolizumab, rituximab, vemurafenib
Antidepressants and antipsychotic drugs	Amitriptyline, bupropion, clomipramine, fluoxetine, olanzapine, quetiapine, sertraline
Cardiovascular system	Amlodipine, bisoprolol, captopril, diltiazem, losartan, mexiletine, spironolactone, tribenoside
Musculoskeletal system drugs	Aspirin, celecoxib, dexketoprofen, ibuprofen, meloxicam, metamizole, naproxen, phenylbutazone
Treatment for tuberculosis	Ethambutol, isoniazid, pyrazinamide, streptomycin
Miscellaneous	Atorvastatin, cyanamide, epoetin alfa, esomeprazole, iodinated contrast media, methotrexate, ranitidine, rivaroxaban, sitagliptin, strontium ranelate, tacrolimus, thiamine, vitamin B12

DRESS: Drug reaction with eosinophilia and systemic symptoms.

HHV-6 can be triggered after immunosuppression and normally resides latently in T cells and monocytes. Between six and fifteen months of age, the major infection is contracted by droplets. Although it is mostly asymptomatic, 20% of patients may present with neurological symptoms like seizures, fever, and gastrointestinal and respiratory issues. Increased immunoglobulin G (IgG) against HHV-6 and the detection of viral genetic material have shown that HHV-6, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HHV-7 are all reactivated during DRESS.[12]

It has been suggested that a viral reactivation is caused by an immunological response against the medication, which would account for the majority of DRESS's clinical symptoms. The duration required to reactivate and enhance viral replication would result in a lengthy latency period between medication delivery and the beginning of DRESS syndrome symptoms. Certain medications may directly affect the transcription of viral DNA, like in the case of valproic acid, which inhibits histone deacetylases and promotes the reactivation of dormant viruses.[13] The majority of medications linked to DRESS have immunomodulatory qualities, and long-term use of these may have an immunosuppressive effect that promotes viral reactivation. Anticonvulsants, in particular, have the potential to cause temporary hypogammaglobulinemia.

The widespread inflammation and organ failure linked to DRESS are caused by pro-inflammatory cytokines produced in huge quantities by activated T lymphocytes, including interleukin-6 (IL-6), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α). Furthermore, during the acute phase of the disease (0–11 days), these cytokines encourage the growth of populations of regulatory T lymphocytes (Tregs), which are vulnerable to HHV-6 infection. This growth results in a modified function of Tregs, which ultimately contributes to the immune response seen in DRESS following viral reactivation. This reaction, which can be a key distinction between DRESS and other severe skin conditions like SJS/TEN,

is not evident in the former. Additionally, the Treg cells generated by IL-6 appear to play a role in the transition from a Treg to a Th17 response during the subacute stage of the disease (11–36 days), which triggers a response mediated by these cells that promotes inflammation.[14]

Clinicopathological Features

Prodromal symptoms including general malaise, pruritus and fever (between 38 and 40 °C) are typically the first signs of DRESS Syndrome. Skin manifestations typically precede the fever by a few days and might last for weeks. Up to 75% of patients have lymphadenopathies. These are seen in the cervical, axillary, and inguinal areas; they are usually soft in consistency, with a measure of 1 to 2 cm., and can present with either of two histological findings: a benign pattern or features resembling pseudolymphoma.[15]

The majority of patients experience a reaction 2–6 weeks after beginning the medication; this latency period is longer than that of most drug eruptions. However, the symptoms may manifest more quickly and with greater severity in patients who have been exposed to the causative substance again, as well as in those who have changes in their liver and hematological function.

Usually starting as a pruriginous morbilliform rash, skin involvement spreads quickly to become widespread and infiltrating (Fig. 1). First it may affect the face, then the upper extremities, the upper portion of the trunk, and lastly the lower extremities. When a rash affects more than 50% of the body's surface, it is thought to be indicative of DRESS. Atypical target lesions, purpuric lesions, tiny sterile follicular pustules, and vesicles or bullae (likely associated with dermal edema) may also show up. Facial edema, which can be mistaken for angioedema, is symmetrical, chronic, and found in the midface and periorbital region in around half of the patients. Up to 50% of patients have the involvement of the mucous membranes in this regard. It often affects one area (hypertrophic tonsils, erythematous pharynx, or cheilitis), though it can occasionally lead to erosions. With time, the skin rash becomes more purple and has diffuse scaling. In 20–30% of cases, the erythema develops into erythroderma, which is characterized by diffuse erythema and scaling that covers more than 90% of the body surface area. When the offending medicine is stopped, these clinical symptoms may last for weeks or months.[16]

Leukocytosis (followed by leukopenia and lymphopenia), thrombocytopenia, anemia, and the presence of atypical (reactive) lymphocytes are among the hematological signs of DRESS. 60–70% of instances result in eosinophilia,

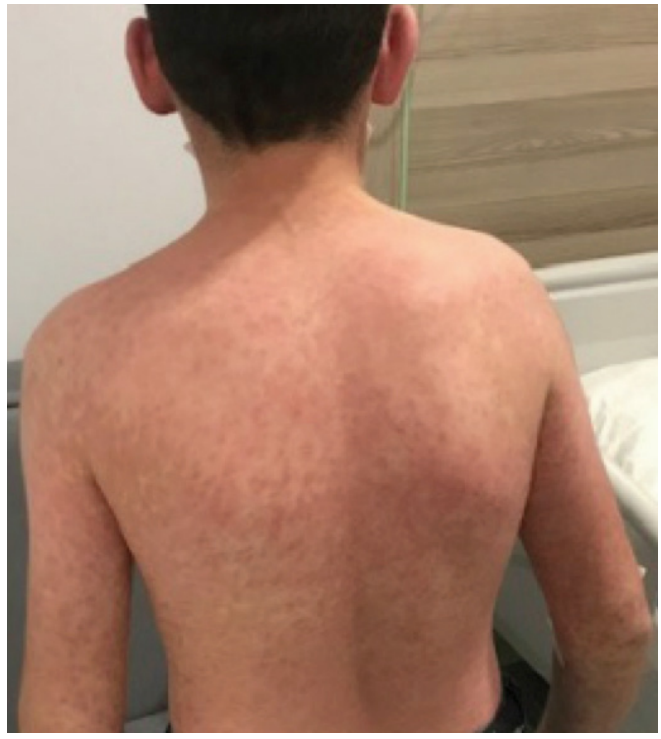

Figure 1. A diffuse maculo-papular rash on the back of one of our patients, typical of DRESS syndrome (Picture supplied by the authors).

which can sometimes take 1–2 weeks to manifest and even happen after liver enzyme levels have stabilized. In rare cases, hemophagocytic syndrome can also manifest as fever, jaundice, hepatosplenomegaly, low ferritin, elevated lactate dehydrogenase (LDH), and raised triglycerides. Up to 90% of patients have at least one organ impacted, with the liver being the most frequently affected (60–80% of cases); hepatitis is usually asymptomatic, but jaundice and hepatomegaly can also be present.

A rise of more than twice the usual value of the enzyme alanine aminotransferase (ALT) and a value of more than 1.5 for alkaline phosphatase are examples of abnormal liver function tests. Although these alterations are usually minor and temporary, the increase in liver enzymes may continue for days or even months after the medication is stopped. Hepatic necrosis, which can be widespread and result in severe liver failure with coagulopathy, encephalopathy, and an ALT more than ten times the upper limit, is the primary cause of death in DRESS.

Up to 30% of instances may result in renal changes, which include proteinuria, changes in the urine sediment due to the presence of eosinophils, and a mild rise in creatinine and BUN (blood urea nitrogen). While severe interstitial nephritis can occur and lead to renal failure, the majority

of kidney disorders is moderate and goes away when the substance causing them is stopped. Allopurinol, carbamazepine, and dapsone are the most frequently recognized medications to cause kidney damage. The elderly and patients with underlying renal disease are more likely to be present with kidney failure.[16,17]

Up to 25% of DRESS cases have pulmonary illness, which manifests as dyspnea, a cough that does not produce anything, hypoxemia, and chest X-ray and CT scans showing interstitial pneumonitis and/or pleural effusion. Minocycline is the medicine most frequently linked to lung injury.[17]

Months after stopping the medication, cardiac involvement, such as pericarditis or eosinophilic myocarditis, may develop and could be lethal. Chest discomfort, tachycardia, dyspnea, and hypotension are some of its common symptoms. The EKG may show arrhythmias, sinus tachycardia, ST and T-wave abnormalities, an increase in cardiac enzymes, and cardiomegaly on the chest X-ray. Minocycline and ampicillin have been linked more often to heart involvement.[15]

An upper gastrointestinal endoscopy and colonoscopy are necessary for the assessment of the gastrointestinal tract, which can also be impacted and show up as gastrointestinal hemorrhage and dehydration.

Thyroiditis is the most frequent finding of endocrine problems, which appear as a long-term sequela 2 to 4 months after stopping the medication.[14–17] Among other things, palpitations, irritability, and disturbed sleep are clinical signs of thyroiditis. For at least two years following the incident, routine thyroid function testing is advised. Between three weeks and ten months following the onset of DRESS, further symptoms such pancreatitis and type 1 diabetes mellitus (DM) may emerge.

Neurological manifestations are infrequent and include meningitis and encephalitis. These may manifest 2 to 4 weeks after the start of DRESS and may be related to the reactivation of HHV-6. Headache, seizures, cranial nerve palsy, and muscle weakness are some of the symptoms that may be present.[14]

RegiSCAR Criteria

DRESS syndrome can be diagnosed using the criteria international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) to drugs. RegiSCAR is the most widely used criterion for the diagnosis of DRESS based on many independent parameters. These include fever >38.5°C, typical skin lesions, hematologic abnormalities, biopsy suggestive of DRESS syndrome, resolution time, lymph node involvement, organ involvement. The RegiSCAR criteria are in Table 3.[18–22] According to RegiSCAR scoring, the diagnosis of DRESS can be definite (score 6 or higher), probable (score 4–5), possible (score 1–3).

Table 3. RegiSCAR criteria used in DRESS syndrome (modified from the reference # 18)

RegiSCAR DRESS criteria			
Features	**No**	**Yes**	**Unknown**
Fever >38.5°C	-1	0	1
Lymph node involvement	0	1	0
Organ involvement*			
One	0	1	0
Two or more		2	
Skin rash, edema, infiltration, scaling	0	1	
>50% body surface	-1	1	
Biopsy suggestive DRESS	-1	0	
Resolution in >15 days	-1	0	-1
Atypical lymphocytes	0	1	0
Eosinophilia	0		
10–19.9% or 700–1499/µL		1	
>20% or >1500/µL		2	
Evaluation of other potential etiologies**	0	1	0

*: Heart, liver, kidney, muscle, pancreas or others; **: ANA, ANCA, HIV serologies; Evaluation: Score 1–3: possible; 4–5: probable; 6 or higher: definite. DRESS: Drug reaction with eosinophilia and systemic symptoms; RegiSCAR: Registry of severe cutaneous adverse reactions.

DRESS Syndrome Treatment Follow-up and Complications

Drug Withdrawal

The most important step in treatment is the immediate identification and discontinuation of the drugs causing DRESS syndrome. Stopping the drugs stops the reaction from progressing and stops the exposure. Symptoms are usually controlled within a few days after stopping the medication.[2]

Topical Treatments

Skin involvement is most common in DRESS syndrome. Topical corticosteroid is the first-line treatment in the least severe patients without organ involvement.[3] In 30.6% of patients, only topical corticosteroid application was sufficient for treatment.[23]

Treatment of Inflammation

In DRESS syndrome, various organs are affected due to systemic inflammation. Organ involvement can be seen in

40–70% of DRESS syndrome patients with liver involvement, renal involvement in 20–40%, cardiac involvement (cardiomyopathy and heart failure) in 5–10%, and lung involvement in 10–20%. Corticosteroids such as prednisone or methyl prednisolone are usually used to prevent organ involvement. The initial dose of systemic corticosteroid treatment is planned according to the clinical situation. The initial dose of prednisone may be 1–2 mg/kg/day (40–80 mg). Methyl prednisolone: 0.8–1 mg/kg/day (approximately 32–80 mg). As clinical response begins to occur within a few days, the treatment dose is reduced by 25–50% of the initial dose every 1–2 weeks and maintenance therapy is initiated. The course of treatment usually lasts 6–8 weeks, but some patients may require longer treatment.[4]

Relapses may occur more frequently when corticosteroids are tapered too rapidly. Therefore, to prevent reactivation of DRESS, corticosteroid taper should be planned gradually and slowly following clinical findings.

The reason for relapse or increase in symptoms during the course of the disease may be rapid reduction of the corticosteroid dose or activation of a viral agent that triggers DRESS syndrome due to immune suppression. It is difficult to distinguish whether symptoms such as increased rash that occur during the follow-up of DRESS syndrome belong to the clinical course of the infection of the viral agent in the etiology of DRESS syndrome or to the worsening of symptoms with the reduction of the steroid dose. When the cause of recurrent symptoms is investigated, there is no additional information on changes in steroid use or antiviral therapy for viral agents detected.[24]

Blood pressure, blood glucose levels, electrolyte balance, liver function tests, renal function and infection screening should be monitored regularly during corticosteroid therapy.

More rarely, IVIG (intravenous immunoglobulin) may be administered if inflammation cannot be controlled or clinical improvement is not observed despite corticosteroids, or if side effects related to corticosteroids occur.[25] There are studies showing that the success rate increases when IVIG is administered with corticosteroids instead of IVIG alone.[26]

Plasmapheresis and immunosuppressive drugs (e.g. azathioprine, methotrexate, cyclosporine) may be administered. There are also other drugs reported in case reports. Inhibition of the interleukin-5 (IL-5) pathway (mepolizumab, reslizumab or benralizumab) may be useful in the treatment of DRESS, especially by suppressing eosinophilia.[27]

Tofacitinib is thought to be a potential treatment option by inhibiting JAK-STAT pathways and preventing activation and inflammation of T cells. It has been reported to be beneficial in eosinophilic myocarditis, which has the highest mortality associated with DRESS syndrome.[28]

Use of Antiviral Therapy

DRESS syndrome may be a disease that can be associated with particularly reactive virus infections. Viruses such as herpes viruses (especially EBV and HHV-6), HSV have been shown to be linked to the development of DRESS syndrome. These viruses are infections controlled by the immune system and can lead to over-activation of the immune response.

The use of antiviral treatment depends on whether DRESS syndrome is virus-related and the clinical condition of the patient. Antiviral treatment is given to control infections caused by viruses, but corticosteroids and immunosuppressive drugs will usually be the first choice for treating DRESS syndrome.[4]

If the action of viruses has been confirmed, especially if HHV-6 or EBV infections have been detected, antiviral therapy may be considered in addition to a treatment that provides immune control, such as corticosteroid therapy, especially in immunocompromised patients. Acyclovir, valacyclovir and famciclovir are common antiviral drugs used for infections such as Herpes Simplex Virus (HSV).

Ganciclovir and valganciclovir are recommended treatment options for HHV-6 or CMV infections.[9,12,29]

HHV-6 was tested (3/7) (42.9%) in cases with progressive liver damage and mortality and was positive in one case (14.3%). One (14.3%) was treated with ganciclovir.[29]

Antihistamines

Antihistamines can be used to manage skin rashes and itching. However, antihistamine treatment only helps to relieve symptoms, they do not treat the underlying inflammation.[3]

Infection Prophylaxis

DRESS syndrome can lead to over-activation of the immune system and therefore to a state of immunosuppression. In combination with corticosteroid therapy, patients may become more susceptible to infections. Therefore, prevention and early diagnosis of infections is of great importance. Antibiotics, antifungal and antiviral prophylaxis and regular screening are important.

Supportive Treatment

Since DRESS syndrome is a multisystemic disease, supportive treatment is important.

Monitoring of Kidney Function

Hydration and monitoring of fluid-electrolyte balance are of great importance in the treatment of DRESS syndrome. Patients should be monitored regularly to prevent fluid loss and maintain electrolyte balance and supportive treatment should be applied when necessary. In DRESS syndrome, treatment is directed towards the causes of impaired fluid-electrolyte balance.

It may be due to the direct effect of drugs, or it may increase sodium and water retention by affecting the aldosterone system. Impaired renal function (interstitial nephritis, acute renal failure), inflammation causing increased vascular permeability, conditions that increase fluid loss such as fever, sweating and gastrointestinal symptoms are mechanisms that trigger fluid accumulation such as fluid retention and edema. In electrolyte and volume imbalances, renal function should be monitored, and dialysis treatment should be applied to the patient when necessary.[3]

Monitoring of Liver Function

In DRESS syndrome, the liver is affected by many different mechanisms. Treatments to prevent these mechanisms of action should be organized and supportive treatment should not be forgotten. Damage to hepatocytes (liver cells) by T cells can lead to hepatitis (inflammation of the liver) and hepatocyte necrosis. Immunosuppressant drugs can help this pathway and also prevent the effect of eosinophils, which play a major role in DRESS syndrome, on the liver. Infiltration of eosinophils into liver tissue controls liver inflammation.

Since liver damage is common, liver enzymes and renal function should be monitored regularly. Special treatment approaches may be required in patients who develop organ failure.

On the other hand, the drugs used bind to liver cells via reactive molecules called haptens and are recognized by the immune system as a foreign substance. This triggers an immune response against liver cells and can lead to liver damage.[30] While some drugs are metabolized by enzymes in the liver, reactive oxygen species (ROS) and free radicals may be produced as a result of overwork of these enzymes. These free radicals can damage liver cells, causing oxidative stress and exacerbating liver damage. Together with these, cytotoxic proteins, perforin and granzyme B increase also reinforced the damage.[31]

Therefore, systemic corticosteroids (Prednisone, Methylprednisolone), antioxidants and free radical scavengers (N-acetylcysteine (NAC), vitamins E and C, sulfur-containing compounds), immune suppressants (azathioprine, methotrexate or cyclosporine), IVIG, plasmapheresis may be used.

Drugs used in DRESS syndrome may affect the microsomal enzyme system (especially CYP450 enzymes) in the liver. These enzymes are needed to metabolize drugs, but some drugs can cause this system to become over-activated. This can damage cells in the liver, because excessive enzyme activity can lead to compounds in the cells becoming reactive and damaging liver tissues.

In DRESS syndrome, inflammation and increased vascular permeability can damage liver tissue. The blood vessels of the liver become more permeable as a result of inflammation, which allows fluid and immune cells to enter the liver.

In addition, in DRESS syndrome, some patients may develop hepatic venous congestion (blockage of the liver veins) or hepatic venous congestion syndrome veno-occlusive disease). The main causes are damage to the vascular endothelium as a result of an excessive immune response, oxidative stress destroying the vessel walls, coagulation disorders leading to clotting and toxic effects of drugs on the liver vessels. This impairs blood flow to the liver and can ultimately prevent oxygen and nutrients from reaching liver cells. As a result, more serious complications such as liver failure and liver death can develop.

Some individuals may have a different level of liver involvement. This is determined by genetic predispositions. Some patients are more sensitive to certain drugs. Genetic variations in HLA (human leukocyte antigen) can cause an excessive immune response to certain drugs. This can make the drugs cause more serious reactions in the body. Drugs that cause DRESS syndrome, especially drugs such as carbamazepine or phenytoin, can cause more severe liver damage in individuals with a genetic predisposition.[32]

In some patients, as liver damage progresses, the liver's capacity to regenerate itself may decrease. Severe inflammation and hepatocyte necrosis can interfere with the liver's natural healing process. If the liver's regenerative capacity is weakened, liver failure may develop. Transplantation may become the only treatment option.

Monitoring of Other Organs

If functional impairments occur in organs such as the lungs or heart, organ-specific treatments (e.g., mechanical ventilation, cardiovascular support) can be applied.

Long-term Follow-up and Reaction Recurrence

Patients with DRESS syndrome should be placed on long-term monitoring. After drug discontinuation, symptoms may completely resolve in some patients, but in some cases,

Table 4. Treatment and follow-up approach according to DRESS syndrome severity and grade proposed DRESS severity grading based on the Delphi consensus statements[3]

Degree of severity and clinical condition	Symptoms and organ involvement	Laboratory values	Monitoring and management	Treatment approach
Mild Mild skin rashes and minimal symptoms	- Skin rashes (maculopapular rashes) - Minimal fever (<38°C) - Mild eosinophilia (eosinophil count <1500/µL) - Absence or minimal organ involvement	Eosinophilia: <1500/µL Liver Enzymes: ALT/AST < 3-fold increase Renal Functions: Normal (Creatinine <1.5 mg/dL) Leukocyte Count: <15,000/µL Hemoglobin: >10 g/dL Neutrophils: >1500/µL, Platelets: >100,000/µL	- Close clinical monitoring - Blood tests (especially eosinophilia and liver function)	- Drug withdrawal - Antihistamines, topical corticosteroids
Moderate Moderate skin rashes and organ involvement	- Skin rashes (maculopapular rashes) - Fever (38–39°C) - Eosinophilia (1500–3000/µL) - Mild hepatitis (elevated liver enzymes) - Nephritis, pulmonary involvement or lymphadenopathy	Eosinophilia: 1500–3000/µL Liver Enzymes: ALT/AST 3–5 fold increase Kidney Functions: Creatinine >1.5–2 mg/dL Leukocyte Count: 15,000–20,000/µL Hemoglobin: 8–10 g/dL Neutrophils: >1000/µL Platelets: >50,000–100,000/µL	-Hospitalization may be required - Weekly blood tests (eosinophilia, liver and kidney function)	- Immediate discontinuation of the drug - Systemic corticosteroid therapy (prednisone/ methylprednisolone) - Organ function supportive therapy (especially liver and kidney support)
Severe Serious organ involvement and complications	- Serious skin rashes (necrotic lesions, bullous rashes) - High fever (>39°C) - Eosinophilia (eosinophil count >3000/µL) - Serious organ failure (liver, kidney, heart, lung) - Multisystem involvement (hepatitis, nephritis, myocarditis, pneumonia)	Eosinophilia: >3000/µL Liver Enzymes: ALT/AST >5-fold increase Kidney Functions: Creatinine >2 mg/dL or acute renal failure (acute kidney injury) Leukocyte Count: >20,000/µL Hemoglobin: <8 g/dL Neutrophils: <1000/µL Platelets: <50,000/µL	- Intensive care unit monitoring may be required - Daily blood tests and organ functions	- Immediate drug withdrawal - IV corticosteroid therapy (methylprednisolone, dexamethasone) -Treatment for organ failure (organ support, intensive care) - Plasmapheresis or IVIG therapy

DRESS: Drug reaction with eosinophilia and systemic symptoms; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

there is a risk of recurrence of the reaction. To reduce the risk of recurrence, these patients should be carefully warned about particularly risky medicines. In addition, these patients should be made aware of all their health conditions when taking medication to avoid medications that may cause a recurrence of DRESS syndrome.

Treatment of Expected Complications

DRESS was defined as conditions observed in the period of 1–24 months after development. The most common of these were hypothyroidism (3.8%), liver failure (3.1%) and diabetes mellitus (2.3%), and less commonly hair

loss, hemolytic anemia, peripheral neuropathy, iatrogenic Cushing's.[21–29] Mortality rate is between 5–10%.[4]

Treatment and follow-up approach according to DRESS syndrome severity and grade proposed DRESS severity grading based on the Delphi consensus statements are shown in Table 4.

Differential Diagnosis of DRESS Syndrome

It's critical to distinguish DRESS from other skin-related illnesses such systemic lupus erythematosus, Kawasaki disease, scalded skin syndrome, and viral infections and vasculitis, which might be accompanied by peripheral eosinophilia. Similar to this, erythroderma may develop as a result of an underlying skin condition, like psoriasis or atopic dermatitis, getting worse.

Other severe drug-related skin reactions like SJS and TEN, which are clinically distinguished by a shorter latency period (5–28 days), necrotic keratinocytes, and epidermal necrosis, can also be mistaken for DRESS. In contrast, non-follicular sterile pustules are a hallmark of generalized acute pustulosis (AGEP), which has a latency period of roughly 48 hours. Usually, it goes away on its own within a few days after the drug in question is stopped.

Prognosis

The majority of individuals require a few weeks to fully recover after stopping the medicine that caused their condition. It is uncertain how often sequelae are. Chronic anemia, autoimmune disorders (autoimmune thyroid disease, diabetes mellitus type I, systemic lupus erythematous (SLE), systemic sclerosis, adrenal insufficiency, and autoimmune hemolytic anemia) and renal failure are examples of long-term consequences.[33]

These symptoms may appear months or years after the original incident, and it is essential to be aware of their connection to medication intake in order to identify and treat a potential DRESS as soon as feasible. Follow-up appointments are advised at 2, 3, 4, 5, 6, 12 months, and then once a year.

Conclusion

Although DRESS syndrome is a serious and potentially fatal reaction, it can be managed with early diagnosis and appropriate treatment. Drug withdrawal, corticosteroids and supportive therapy are the main approaches to the management of DRESS syndrome. Treatment strategies should be individualized according to the severity of organ involvement and other clinical factors. Nevertheless, the management of this syndrome requires a multidisciplinary approach and continuous follow-up and guidance of specialized physicians is of great importance in the treatment of patients.

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