Dress Syndrome

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ABSTRACT

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is a rare, idiosyncratic, life-threatening drug reaction with a variety of clinical manifestations including symptoms of fever higher than 38.5 ºC, pruritic maculopapular or erythematous eruption, hematologic abnormalities, lymphadenopathy, and multiorgan involvement. Its incidence ranges from 1 in 1000 to 1 in 10,000 drug exposures, and it has an estimated mortality rate of up to 10%. To date, many drugs have been reported to cause DRESS syndrome, but the most common ones are the anticonvulsants and sulfonamides, although the pathogenesis is not clearly understood. Deficiency or defects in the epoxide hydroxylase enzyme, which detoxifies the metabolites of aromatic anticonvulsants, an insufficiency in the detoxification of the drug leading to reactive metabolites which may trigger immunologic reactions, predispositions due to some HLA alleles, and reactivation of herpes viruses are suggested to play a role in the pathogenesis. The latent period varies from two to six weeks. Hematologic, hepatic, renal, cardiac, pulmonary, neurologic, gastrointestinal and endocrine involvement; and hemophagocytic syndrome can be seen during the clinical course of DRESS syndrome. The long term sequels of DRESS syndrome include hepatic, renal and adrenal failure; diabetes mellitus type 1 and type 2, Graves disease, autoimmune hemolytic anemia, lupus, systemic sclerosis, and autoimmune enteropathy. Diagnosis of DRESS syndrome is difficult to establish, and requires a high degree of initial clinical suspicion and ruling out of other etiologies. The most important step in the management of DRESS syndrome is early diagnosis and prompt withdrawal of the offending drug. In cases with organ involvement, systemic corticosteroid treatment is required. In serious and steroid-resistant cases, using more potent immunosuppressive agents or intravenous immunoglobulin treatments may be required.

Keywords: DRESS syndrome, cutaneous drug reaction, prognosis

INTRODUCTION

DRESS syndrome is a severe hypersensitivity reaction that may be related to an enzymatic defect in the metabolism of drugs or their reactive metabolites (1-5). It is characterized by fever that is higher than 38.5 ºC, skin rash (generally maculopapular and diffuse erythematous eruptions), hematologic anomalies (eosinophilia and/or mononucleosis, atypical lymphocytes, and/or thrombocytopenia), lymphadenopathy and multiple organ involvement (hepatitis, nephritis, pneumonia, colitis, encephalitis, pancreatitis, thyroiditis, and myocarditis) (5-10). DRESS syndrome observed secondary to anticonvulsant treatment was initially named as “Anticonvulsant Hypersensitivity Syndrome”. Later on Bocquet et al. named it “drug rash with eosinophilia and systemic symptoms” (11). The syndrome that was also known as the drug hypersensitivity reaction syndrome is now known as DRESS syndrome (6). The “R” in the DRESS syndrome was later changed from “rash” to “reaction”.

Epidemiology

The real incidence of DRESS syndrome is not known but it is estimated as 1 in every 1000-10000 subjects exposed to drugs (1,2).

Etiology

Many drugs have been reported to cause DRESS syndrome (Table I) (3,5,7). Aromatic anticonvulsants such as phenytoin, carbamazepine, and sulfonamides such as dapsone and sulfasalazine are the most frequently reported drugs. Carbamazepine is the most frequently encountered cause among these drugs (1,2,5).
Cacoub et al. reported that carbamazepine is the causative drug in 27% of the DRESS syndrome cases (1). From a total of 62 DRESS syndrome cases reported in France, 15 cases were caused by allopurinol and 11 cases were reported to be caused by carbamazepine (5). In a cohort of 69 DRESS syndrome cases, Wolfson et al. reported that antibiotics—mostly vancomycin and β-lactams—were the cause in 74% and anticonvulsants in 20% of the cases (12). The analysis of a total of 16 DRESS syndrome cases reported from our country by Mısırlıoglu et al. showed that the most responsible drug was amoxicillin-clavulanate and carbamazepine (13).

**Pathogenesis**

The pathophysiology of DRESS syndrome has not yet been explained in full. The majority of the data on the pathogenesis of DRESS syndrome has been obtained from cases caused by anticonvulsants. Three hypotheses that have been suggested for the anticonvulsant-related cases include the lack of or defect in the epoxide hydroxylase enzyme that enables the detoxification of the metabolites in aromatic amine anticonvulsants, the ethnic predisposition with certain human leukocyte antigens (HLA); and the reactivation of viruses from the herpes virus family such as Epstein Barr Virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), and HHV-7 (1,5,6,14).

Several factors have been implicated in the function of the epoxide hydroxylase enzyme; polymorphisms in the genes that encode the enzyme which metabolises drugs, such as cytochrome P450 (CYP450) and N-acetyltransferase, decrease the activity of these enzymes leading to the accumulation of these drugs or their active metabolites, thereby stimulating immune responses by interacting with cellular proteins or peptides (3). Genetic mutations that affect the epoxide hydroxylase enzyme have also been reported to result in the accumulation of toxic metabolites leading to the emergence of immunological responses (5,15). The inheritance of these detoxification defects as autosomal dominant is probable. The latter may explain the familial and racial tendency observed in patients of African origin (5). The probability for slow metabolism of the CYP450 system results in the accumulation of toxic hydroxylamine, thereby leading to sulfonamide related hypersensitivity reactions.

HLA alleles play a role in the major histocompatibility complex (MHC), antigen presentations, and the formation of immunological synapses. Therefore, polymorphisms of HLA alleles affect which types of antigens are present and the following T-lymphocyte responses. Polymorphisms in HLA alleles greatly explain the genetic predisposition in DRESS syndrome patients. However, there are still many questions that await answers (3,16). It has been suggested that abacavir-induced DRESS syndrome risk in Caucasians increases in individuals with the HLA-B*5701 allele and that there is a relationship between carbamazepine-induced increased DRESS syndrome risk and HLA-A*3101 in Japanese patients. A strong relationship between allopurinol-induced DRESS

### Table I. The common culprit drugs in DRESS syndrome (3,5).

| Category of Drug          | Drug Name                                                                 |
|---------------------------|---------------------------------------------------------------------------|
| Anti-convulsants          | Carbamazepine, lamotrigine, phenobarbital, phenytoin, oxcarbazepine, gabapentin |
| Anti-bacterial            | Amoxicillin, ampicillin, azithromycin, levofloxacin, minocycline, piperacillin/tazobactam, vancomycin, sulfasalazine |
| Anti-tuberculosis         | Ethambutol, isoniazid, pyrazinamide, rifampin, streptomycin               |
| Anti-retroviral agents     | Abacavir, nevirapine                                                      |
| Anti-hepatitis C virus agents | Boceprevir, telaprevir                                                   |
| Anti-pyretic/analgesics    | Acetaminophen, diclofenac, celecoxib, ibuprofen                           |
| Sulfonamides              | Dapsone, sulfamethoxazole-trimethoprim, sulfasalazine                      |
| Targeted therapeutic agent| Doraferib, vismodegib, vemurafenib                                       |
| Antidepressant            | Fluoxetine                                                                |
| Antihypertensive          | Captopril                                                                |
| Others                    | Allopurinol, Chinese herbal medicine, imatinib, mexitelate, omeprazole, strontium ranelate, celecoxib (NSAID) |

**NSAID**: Nonsteroidal anti-inflammatory drug
syndrome and HLA-B*5801 has been shown in a Chinese society (2,15,17,18). It is also considered that families of individuals with DRESS syndrome are at higher risk due to the genetic predisposition to this syndrome (1,6).

It has been asserted that the relationship between viral infections (EBV, HHV-6, and HHV-7) and the host immune response may play a role in the pathogenesis. In recent years, Japanese experts have suggested that HHV-6 reactivation may be a diagnostic marker, considering that it has been detected in about 60-80% of patients (1,5,6). To date, the mechanism of HHV-6 reactivation is still unknown, but two possible mechanisms have however been suggested including the direct impact of medications or metabolites on viral reactivation and the “cytokine storm”. There is a need to carry out studies on the differences between DRESS syndrome patients with and without HHV-6 reactivation in order to define the exact mechanisms of viral reactivation. While HHV-6 reactivation is not essential for the development of the disease, it can be an aggravating factor that causes a long and rough course (3). The reactivation of other herpes viruses like EBV, CMV, or HHV-7 may be related to the DRESS syndrome's systemic condition and exacerbation (19,20). Hemophagocytic syndrome cases with HHV-6, HHV-7, EBV, and CMV reactivation-induced DRESS syndrome have also been reported (7).

Clinical Findings

The clinical presentation of DRESS syndrome is characterized by fever, widespread skin lesions, internal organ involvement, a long latent period after intake of the culprit drug, a prolonged and protracted clinical course, and possible sequential reactivation of various HHV’s. These findings may persist or exacerbate despite the discontinuation of the inducing medication (1,3). Clinical findings generally develop within two months after the intake of medication and most frequently within 2-4 weeks. However, more serious clinical symptoms may develop faster in case of reexposure (5,16). It is also reported that even though symptoms may develop in a day in sensitised cases, the latent period may extend up to 105 days (21,22). DRESS syndrome is characterised by multiple organ involvement and especially, skin, liver and the hematological system. The reaction generally starts with a fever and cutaneous reaction, lymphadenopathy, and pharyngitis develops within 1-2 days. This is most frequently followed by hematological, renal, and pulmonary involvement including the liver. It has been reported that DRESS syndrome cases with chronic prognosis are related to herpesvirus reactivation (5).

Since skin findings are generally accompanied by fever, rash, lymphadenopathy, leukocytosis, and abnormal liver tests, it is important to eliminate infectious etiology. Skin findings in DRESS syndrome are mainly itchy maculopapular rashes, however, lesions such as vesicle, bulla, pustule, cheilitis, purpura, target lesions, and eczema-like lesions along with erythroderma have been reported. Skin findings are cured with desquamation. Facial edema is a characteristic finding for DRESS and mucosal lesions that affect the mouth and the lips are seen most frequently (3,23).

Ang et al. carried out a study on 27 DRESS syndrome cases and reported erythematous morbilliform rash on the face, body, and extremities of 81.5% of them, pustular eruption in 7.4%, mucositis in 29.6% and facial edema in 33.3% (24).

Even though the presence of skin lesions is the most frequent and widespread finding, systemic involvement is a cause of major mortality and morbidity. Fever higher than 38.5 ºC and visceral involvement are the most commonly observed systemic findings. While lymphatic, hepatic, and hematologic involvements are observed most frequently, renal, pulmonary, and cardiac involvements may also be observed. Neurological, gastrointestinal, and endocrine system involvements have also been reported in severe and atypical DRESS cases. Lymphadenopathy present in 75% of the cases may be localized or generalized. Fever is present in more than 90% of cases and is above 38 ºC. It may remain high for weeks in some cases even when the causative agent is discontinued (5).

Hematologic findings are observed frequently. Ang et al. reported hematologic findings in 81.5% of 27 cases (24). Leukocytes, especially atypical lymphocytosis is frequent. Eosinophilia, leukopenia, lymphopenia, thrombocytopenia, and anemia may also be observed (25,26). Eosinophilia is the most frequently observed finding and is reported in 66-95% of all cases (3).

Hepatic disorders may be hepatocellular, cholestatic, or mixed. Fulminant hepatic failure that requires liver transplantation may be observed in severe cases. Phenytoin, minocycline, and dapsone are the drugs that are most commonly related to liver damage. High alanine
aminotransferase (ALT) is present in 70% of all DRESS syndrome cases and indeed, a series reported a rate of >95% (3,5).

Renal involvement has been reported in 11-28% of cases (5,27). This rate is reported as 12-40% in some other publications (1,28,29). Allopurinol is the medication that is related the most with renal involvement, followed by carbamazepine and dapsone. Underlying renal diseases and advanced age are the major risk factors for renal involvement. The first finding is generally asymptomatic hematuria and proteinuria. An increase of blood urea nitrogen and creatinine along with low creatinine clearance may be observed. Renal findings are generally mild and improve when the related medication is discontinued; however, renal failure and even death have been reported due to renal replacement therapy-requiring cases and severe interstitial nephritis, acute tubular necrosis, or vasculitis (2,3). Ang et al. have reported renal involvement in a series of their cases at a rate of 14.8% and that short term hemodialysis has been required for two of the cases (24).

Pulmonary involvement is observed in about one-third of the cases (3). The most common findings are impairment in pulmonary function, interstitial pneumonia, pleural effusion, and acute respiratory distress syndrome (ARDS) (2,3). Chen et al. reported a rate of 2.6%, whereas Cacoub et al. reported a rate of 5% (1,28). Minocycline and abacavir were the most frequent causes (2,3,5).

Gastrointestinal symptoms including diarrhea have been reported in some of the cases with DRESS syndrome. However, the prevalence of these symptoms is not known since they are rarely reported. Colitis has been reported in some cases. Colon involvement may be mild in some DRESS syndrome cases and can improve spontaneously or it may be severe enough to cause electrolyte disorders. Complications with hemophagocytic syndrome occurred in one of the lost cases due to massive gastrointestinal hemorrhage (2,30). Chung et al. reported a case with severe diarrhea that required intravenous hydrocortisone since it had not recover with oral prednisone (31). They have suggested administering intravenous steroid in such cases due to gastrointestinal motility increase and a decrease of absorption. Infectious diarrhea and especially parasitic infections, inflammatory, and ischemic causes should be eliminated in cases with gastrointestinal involvement (2). Pancreatitis and chronic enteropathy are also reported (3,5).

Cardiovascular system involvement may also occur. Myocarditis is associated with high mortality even though it is rare (55%). Another characteristic of myocarditis is that it recovers after all other laboratory findings are improved. It has been reported that it remains until four months despite successful DRESS therapy, with ampicilllin being the most frequently used (5). Chest pain, nonspecific electrocardiography (ECG) changes, tachycardia, arrhythmia, and a decrease in the left ventricular ejection fraction may occur (15,32). Even though an endomyocardial biopsy can infer an exact diagnosis, the diagnosis is mainly made by clinical echocardiography and other laboratory findings. Troponin and creatine kinase-MB (CK-MB) are increased in the majority of the myocarditis cases; however, there have been reports of rare cases without any increase (2).

Neurological involvement is rare. Headaches, convulsion, coma, and motor dysfunction may occur. HHV-6 reactivation and neurological findings such as meningitis and encephalitis are rarely reported (3,5). Thyroid function monitorization is important since thyroid function disorders may be observed during DRESS syndrome (24). DRESS syndrome may also be associated with some cases of pancreatitis and diabetes development, and spleen involvement has been reported (3,25,33).

Diagnosis

There is no pathognomonic sign or diagnostic test for DRESS. The diagnosis is clinical and established by presence drug exposure in the appropriate clinical setting and latency between drug exposure and symptom onset (2). Careful history taking and clinical observation, and comprehensive laboratory examination are required for diagnosing DRESS syndrome.

Suspicous cases should be evaluated in detail since mortality rates of DRESS syndrome may reach up to 10%. The most widely used diagnostic criterion is the scoring system suggested by RegiSCAR (Table II) (1-3,34,35). Another diagnosis criterion that is also often used is suggested by a Japanese consensus group and is comprised of seven items similar to RegiSCAR. The most important difference is that HHV-6 reactivation is used as a diagnostic criterion and eosinophilia, although reported in up to 95% of cases, is not a constant clinical finding (3,22,36).

Descamps et al. suggested a full blood count, ALT, AST, total bilirubin, GGT, ALP, sodium, potassium,
creatinine and creatinine clearance, protein discharge in urine at 24 h, urinary eosinophil count, creatinine phosphokinase, lactate dehydrogenase, and antinuclear antibody examinations for DRESS syndrome cases (37).

Many diseases may imitate DRESS syndrome (3). Differential diagnosis of infectious diseases (e.g., viral exanthemas, staphylococcal and streptococcal shock syndromes, and meningococcemia), noninfectious drug eruptions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis), autoimmune disease (e.g., Kawasaki disease, Stills’ disease, and hypereosinophilic syndrome), and neoplastic diseases (e.g., leukemia cutis and mycosis fungoides) should be considered (2). Depending on the specific organs involved, the differential diagnosis also includes viral hepatitis, glomerulonephritis, vasculitis, pre- and post-renal causes of acute kidney injury, Kawasaki disease and eosinophilic myocarditis, parasitic infection, and bacterial, viral, and fungal pathogens (2).

It is very difficult to detect the responsible medication when the latent period is too long or in the case of multiple drug use. Skin-patch and lymphocyte transformation tests (LTT) are frequently used for diagnosis. It has been reported that the positive predictive value of the patch test has reached 80-90% with some medications. The test should be applied 2-6 months after the recovery of the symptoms for optimal results (5,38). The highest positivity of skin-patch test has been observed in antiepileptic drug allergies (39,40). Ben Mahmoud et al. reported that the patch test positivity of antiepileptic drug allergies reached 95% (40). The non-irritable maximum concentrations used in skin-patch tests for different drugs are given in Table III (41).

LTT may be helpful in determining the suspicious medication but its sensitivity is limited as a negative lymphocyte transformation test does not eliminate the drug hypersensitivity reaction (38). Acquiring the LTT

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**Table II. RegiSCAR scoring system for diagnosis and classification of DRESS syndrome (1).**

| Score | -1 | 0 | 1 | 2 |
|-------|----|---|---|---|
| Fever ≥38.5 °C | no / B | no / B | yes | |
| Lymphadenopathy | no / B | yes | |
| Eosinophilia | no / B | yes | |
| Eosinophilia (If leukocyte <4.0x10^9 L^-1) | 0.7-1.499 x 10^9 L^-1 | 10%-19.9% | ≥1.5x10^9L^-1 | ≥%20 |
| Atypical lymphocyte | no / B | yes | |
| Skin involvement | | | |
| Skin rash frequency (body area %) | no / B | yes | |
| Skin rash supporting DRESS | no / B | yes | |
| Biopsy supporting DRESS | no / B | yes | |
| Organ involvement * | | | |
| Liver | no / B | yes | |
| Kidney | no / B | yes | |
| Lungs | no / B | yes | |
| Heart / muscle | no / B | yes | |
| Pancreas | no / B | yes | |
| Other organ | no / B | yes | |
| Resolution ≥ 15 days | no / B | yes | |
| Evaluation of other causes | | | |
| Antinuclear antibody (ANA) | | yes | |
| Blood culture | | yes | |
| Serology for HAV/HBV/HCV | | yes | |
| Chlamydia/mycoplasma | | yes | |
| (If none is positive and ≥ 3 negative) | | yes | |

Total score is evaluated as < 2 “no”, 2-3 “possible”, 4-5 “probably”, >5 “certainly” DRESS.

B: unknown or unclassified.

* When other reasons are isolated, 1; one organ involvement, 2; two or more organ involvement

HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus
at the right time in the clinical course of DRESS is very important. LTT has been reported to be most useful in the recovery phase of DRESS where the sensitivity and specificity of the LTT in the recovery were reported 73% and 82%, respectively. This is in contrast to sensitivity and specificity of 40% and 30%, respectively, in the acute phase. Therefore, the optimal time for LTT is five to eight weeks after the onset of skin eruption. However, LTT is primarily indicated for identifying anticonvulsants as the causal drug in DRESS (39).

The other in vitro test used in the diagnosis of DRESS syndrome is interferon γ-enzyme-linked immunospot assay (IFNγ-ELISpot). It has similar sensitivity and specificity compared to LTT. Sensitivity of IFNγ-ELISpot has been reported to be 42% (abacavir) to 64% (allopurinol/oxipurinol) respectively (42).

Histopathological findings are generally not specific. Spongiosis, interface dermatitis, and superficial perivascular infiltration may be observed. Spongiosis is the most frequently observed characteristic of the histopathological presentation and has been observed in 40-80% of cases in previous studies. Atypical lymphocytes at various levels including perivascular infiltration comprised of eosinophils and neutrophils is a universal characteristic of all DRESS syndrome cases (3).

### Long Term Sequels

DRESS syndrome is a life-threatening disease with a mortality rate that reaches up to 10%. In addition, morbidities may also occur due to complications in relation to organ failure or treatment. Permanent damage may develop in cases with internal organ involvement. Transplantation may be required for cases with severe liver failure. Cases with underlying chronic renal disease are at high risk for permanent renal failure and lifelong hemodialysis. Infections such as herpes labialis, herpes zoster, pneumonia, and soft tissue abscess are among the major complications encountered during DRESS syndrome treatment. Infections may be severe and may result in septic shock or death. These infections are observed more often in patients who have been administered systemic corticosteroids. Cases have been reported with fulminant type 1 diabetes mellitus development (43). Even though the exact mechanism is not known, it has been reported that fulminant type 1 diabetes mellitus related to HHV-6 reactivation has developed in patients who have been treated for DRESS syndrome. Thyroid diseases are among the most frequently observed sequels in DRESS syndrome cases with a prevalence of 4.8% and consist of Graves disease, Hashimoto thyroiditis, and painless thyroiditis (35,43). It has been reported that anti-thyroid peroxidase and anti-thyroglobulin antibodies have been detected in seven out of 16 DRESS syndrome patients without clinical thyroid symptoms (44). It has been indicated that the development of thyroid diseases may be related to HHV-6 reactivation (45). Autoimmune diseases such as systemic lupus erythematosus, autoimmune hemolytic anemia, reactive arthritis, alopecia areata, and vitiligo are also reported in addition to thyroid diseases. These autoimmune diseases may develop within several months to several years. Even though the exact mechanism for autoimmune disease development is not known, it is accepted that they develop due to regulatory T-cell dysfunction (43). The existence of anti-plakin auto-antibodies in about 60% of patients in the late period support this (3).

### Table III. The non irritable maximum concentrations used/advised in skin-patch tests for different drugs (43).

| Drug                | Concentration and carrier          |
|---------------------|-----------------------------------|
| Carbamazepine       | 1%, 5%, 10% pet.                  |
| Phenytoin           | 5%, 10% pet.                      |
| Lamotrigine         | 1%, 10% pet.                      |
| Phenobarbital       | 5%, 10% pet.                      |
| Diazepam            | 5%, 10% pet.                      |
| Topiramate          | 30% in water and pet.             |
| Sodium Valproate    | 1%, 10%, 20% pet.                 |
| Abacavir            | 25% pet.                          |
| Pseudoephedrine     | 1% pet (commercial drug)          |
| Chlorpheniramine    | 20% pet (commercial drug)         |
| Desloratadine       | 1% pet (commercial drug)          |
| Hydroxyzine         | 10% pet (commercial drug)         |
| Radiocontrast Agent | undiluted                         |
| Allopurinol         | 1%, 10%, 20% pet.                 |
| Heparin             | undiluted                         |
| Morphine            | 5% pet.                           |
| Proton Pump Inhibitors | 10% pet.                     |
| Chlorhexidine       | 1% pet.                           |
| Hydroxychloroquine  | 5%, 10%                           |

Pet: Petrolatum
**Treatment**

The most important step is to discontinue the culprit drug at once. Supportive treatment is also important. Cases that have improved only with supportive treatment have been reported; however, more studies are needed to verify this observation (3). The main medication for DRESS syndrome cases to date has been systemic corticosteroids that are recommended especially in cases of internal organ involvement (3,5,6,46,47). Even though there is no consensus regarding the optimal corticosteroid dose, its method of administration, treatment duration, and reduction rate, a starting dose of 0.5-1.0 mg/kg/day prednisolone or equivalent with a gradual dose reduction in the medication over a period of 2-3 months after which it is discontinued is suggested (3). Moreover, long term use of systemic corticosteroids may result in many complications in addition to opportunistic infections. Therefore, treatment should be specifically planned for each individual taking into consideration the severity of the disease as well as the underlying comorbidities (47). A group from the French Association of Dermatology suggested the use of systemic corticosteroids in cases of organ involvement such as kidney, lung, and heart, or in cases where serum transaminase levels increase to 5 times the normal levels (37). Pulse parenteral corticosteroid treatment has also been promising in several cases (48).

Another treatment option is intravenous immunoglobulin (IVIG), but the results are contradictory. IVIG applied at a dose of 1-2 g/kg has been used as an additional treatment in cases that have not responded to systemic steroid treatment and have also been preferred in cases with a high risk of infection, with the presence of proven viral reactivations (49). The possible effect of IVIG is suggested to be via immunomodulatory and anti-inflammatory mechanisms. One possible mechanism is that IVIG preparations contain antiviral neutralising antibodies that help clear the viral infection/reactivation, which seems to be important in the pathophysiology of DRESS syndrome (49). Joly et al. reported negative experiences in six DRESS syndrome cases treated with IVIG treatment (50). Of these cases, five had severe side effects and either IVIG treatment complications or the need for using systemic corticosteroid treatment was reported in four patients. Marcus et al. suggested the additional application of IVIG treatment to steroid treatment especially in cases not responding to steroid treatment alone (49). Thus, further studies are required to understand more about IVIG treatment in DRESS syndrome (47).

Agents such as cyclosporine, cyclophosphamide, mycophenolate mofetil, and rituximab may be used in cases when there is a need to use more potent immunosuppressive treatment options. Antiviral agents such as ganciclovir may be required in addition to systemic corticosteroid and IVIG treatment in severe cases where viral reactivation exists. However, the benefit and risk balance should be taken into consideration (47). N-acetyl cysteine may help limit reactive metabolites in cysteine anticonvulsant-related DRESS syndrome as well as drug detoxification (51).

**Prognosis**

The majority of the DRESS syndrome patients may heal completely with early diagnosis, discontinuation of the responsible medication, and proper treatment. Wei et al. reported tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal hemorrhage, and systemic inflammatory response as poor prognosis criteria (52). Furthermore, 10% of cases are associated with hepatic necrosis.

**CONCLUSION**

In the clinical setting, skin rash, liver involvement, fever, hypereosinophilia, and lymphadenopathy should lead to suspicions regarding DRESS syndrome. Moreover, reactivation with HHV-6 and other herpes viruses is an indication of a complex immunopathogenesis. Therefore, the responsible medication should be discontinued immediately. Supportive precautions, in addition to standard wound care, multidisciplinary approaches, and corticosteroid treatment if necessary should be started to minimize mortality and morbidity.

The rational use of drugs is important to prevent all severe drug reactions. The association between causative drugs and genetic factors, including HLA polymorphisms, renders it possible to choose appropriate treatments and improve patient outcomes.

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