Drug rash with eosinophilia and systemic symptoms syndrome (DRESS) is a rare but serious hypersensitivity drug reaction most frequently associated with antiepileptics. We report a case of carbamazepine-induced DRESS syndrome in a 61-year-old man who was recently initiated on carbamazepine (6 weeks back) and presented with a history of acute febrile illness of 10 days duration. General examination showed multiple erythematous coalescent papules and rash over the body with relative sparing of the face with lymphadenopathy. Laboratory results revealed eosinophilia, atypical lymphocytosis, transaminitis, and negative serology for hepatitis. Registry of severe cutaneous adverse reactions (RegiSCAR) scoring system case is categorized as a definite case with a score of 7. Carbamazepine was discontinued and with the initiation of intravenous steroids; the transaminitis improved, fever and rashes resolved.

**Key words:** Carbamazepine, DRESS syndrome, Mini-DRESS, RegiSCAR scoring system, Skirt syndrome

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George et al. DRESS syndrome - A jeopardising clinical entity

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neutrophils – 58,
b

because of a wide range of clinical manifestations including an

symptoms [1]. The term “Rash” was replaced with “reaction” in 1996 and it stood for drug rash with eosinophilia and systemic complications. The acronym DRESS was introduced by Bocquet morbidity and mortality with the potential for long-term DRESS syndrome is a dreaded clinical entity with significant

the given treatment for 10 days and the patient got discharged. Fever, rash, and transaminitis improved with oral prednisolone in tapering dose for 7 days) after withholding (methyl prednisolone – 1 g intravenous for 3 days, followed by

diagnoses and he was started on intravenous corticosteroids

score – 7) was made after excluding all other differential

fatty changes. The blood culture was sterile.

and viral hepatitis were negative. Ultrasound abdomen showed

normal. Screening for tropical infections, exanthematous fever,

lymphocytosis. Electrocardiogram and echocardiography were

normal. Screening for tropical infections, exanthematous fever,

edema of ear may suggest a risk for progression to DRESS [1,2]. Similar to other severe cutaneous adverse drug reactions, DRESS can present with polymorphic rashes, urticaria, pustules, blisters, exfoliative dermatitis, and target lesions making a diagnostic dilemma [1]. Mucosal involvement in DRESS is milder than that seen in Stevens-Johnson syndrome/toxic epidermal necrolysis with pruritus or burning pain. Facial edema is seen in 75% of patients and its association with a morbilliform eruption and edema of ear may suggest a risk for progression to DRESS [1,2].

Clinical features of DRESS include cutaneous eruption, fever, lymphadenopathy, hematologic abnormalities, and visceral involvement. Clinical features usually manifest after 3–8 weeks following exposure to the offending agent [2]. About 99–100% of adult and pediatric patient’s complaints of skin involvement manifest as symmetrical maculopapular (morbilliform) eruption including the trunk and extremities, often covering >50% of the body surface area [1]. The rash appears deeper, more violaceous, or plum hue in comparison with standard morbilliform eruption with pruritus or burning pain. Facial edema is seen in 75% of patients and its association with a morbilliform eruption and edema of ear may suggest a risk for progression to DRESS [1,2].

“mini-DRESS” or “skirt syndrome” have been proposed to refer to milder forms of DRESS [1].

“DiHS” or “DRESS” syndrome involves the liver (≥50% of cases) and can be severe with hepatitis leading to fulminant liver failure. Interstitial kidney and lung disease can also occur in approximately one-third of patients [1]. Pulmonary manifestations consist of nonspecific interstitial pneumonitis, pleural effusion, pneumonia, pulmonary nodules, and acute respiratory distress syndrome [4]. Cardiac involvement is potentially dangerous and can manifest as acute necrotizing eosinophilic myocarditis, cardiac thrombosis, fibrosis,
and congestive heart failure [1]. Mortality of myocarditis reaches about 55% and clinical features include chest pain, dyspnea, and hypotension with elevated cardiac enzymes [5]. Other organs potentially involved are the gastrointestinal system (GIT), pancreas, thyroid, brain, muscle, peripheral nerves, and eye [1,2,4]. GIT involvement consists of colitis, enteritis, esophagitis, or gastritis [6]. Specific drugs noted to have a predilection toward particular internal organs such as sulfasalazine is associated with severe acute hepatitis, allopurinol with kidney injury, minocycline with lung involvement, and ampicillin and minocycline with DRESS-associated myelitis [1]. Its multisystem involvement with highly variable clinical presentation warrants clinicians to be on high alert in diagnosing DRESS syndrome with differential diagnosis such as acute febrile illness, acute viral infections, hepatitis, sepsis, autoimmune disease, and hematologic disorders [7].

Laboratory test has a huge role in the diagnosis of DRESS including complete blood count with differential and peripheral blood smear evaluating for eosinophilia, the presence of atypical lymphocytes and other hematologic abnormalities, liver function tests, and renal function test. Specific laboratory testing such as troponins, creatine kinase-MB, and NT-proBNP if cardiac involvement is suspected, or amylase and lipase if pancreatitis is suspected. Urinalysis and urine sedimentation aids diagnosis of drug-induced acute interstitial nephritis. Current data and recommendations advise testing HHV6, HHV7, CMV, and EBV viral loads through polymerase chain reaction [1]. Antinuclear antibody; blood culture; and hepatitis A, B, and C viral studies are recommended for biological hypersensitivity. Genotyping for HLA and possible HLA genotyping have high sensitivity and specificity, providing a plausible basis for the future development of tests to identify individuals at risk for the development of DRESS syndrome does not have definite histopathological features to pinpoint the diagnosis. Features like dyskeratosis are seen in 53–97% of DRESS cases, whereas, spongiosis in 40–78% of cases, and interface vacuolization is seen in 74–91% of cases. Lymphocytic infiltrate ranging from perivascular to dense is observed, and eosinophils are variably present (anywhere from 20% to 80%) [1]. The diagnostic tests, such as skin testing and in vitro testing, to evaluate for immediate hypersensitivity reactions remain insufficient for diagnosis. Genotyping for HLA markers can be used as a screening tool before prescribing such potent drugs and can, therefore, prevent or at least mitigate DRESS syndrome in specific populations [8].

There are three major scoring systems which include Bocquet’s, published in 1996, the J-SCAR criteria from 2006, and the European RegiSCAR criteria from 2007. RegiSCAR criteria (Fig. 3) are the most accepted and widely used for diagnosis of DRESS [1,2]. RegiSCAR inclusion criteria for potential DRESS syndrome cases require at least three out of the following four signs: Fever above 38°C, enlarged lymph nodes at a minimum of two sites, involvement of at least one internal organ, or blood count abnormalities [8].

Many autoimmune conditions may develop as a delayed complication of DRESS syndrome, including autoimmune thyroiditis, systemic lupus erythematosus, type 1 diabetes mellitus, and autoimmune hemolytic anemia [9]. The escalation of symptoms for DRESS syndrome is typical, even after the cessation of the culprit medicine in the initial course of illness [10].

### Figure 3: The European RegiSCAR criteria

The mainstay of treatment is the discontinuation of the suspected medicine, corticosteroids, and multidisciplinary approach according to the organ involved. Many alternative medications used include cyclophosphamide, cyclosporine, interferons, mycophenolate mofetil, muromonab-CD3, rituximab, and plasmapheresis [1]. Researches are in pipeline regarding Janus kinase (JAK) inhibition in cases of steroid-refractory disease [1]. Viral reactivation can exacerbate DRESS and treatment with antiviral agents, particularly gancyclovir, may also be considered in such cases [1]. Longterm sequelae tend to manifest as autoimmune disease (autoimmune thyroiditis, type 1 diabetes, alopecia, myocarditis, bullous pemphigoid, vitiligo, scleroderma, and systemic lupus erythematosus), while elderly patients may experience end-organ failure. Patients might also suffer from depression, anxiety, and fear of taking medications [1].

### CONCLUSION

DRESS is a rare clinical entity that comes under hypersensitivity reaction toward medications and is featured by fever, mucocutaneous, and multiorgan involvement. RegiSCAR criteria can help in diagnosis and corticosteroid is the mainstay of treatment but resistant cases are not uncommon. Researches are in pipeline regarding JAK inhibition in cases of steroid-refractory disease. Certain genetic markers and HLA genotyping have high sensitivity and specificity, providing a plausible basis for the future development of tests to identify individuals at risk for biological hypersensitivity.

### AUTHORS’ CONTRIBUTIONS

AMG, AK, and SCS involved in evaluation, diagnosis of disease, follow-up, conception, design, acquisition of data, and analysis of data. All authors are accountable for drafting of the manuscript.
critical revision of manuscript for important intellectual content, and the final version to be published.

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