Case Report

Drug rash with eosinophilia and systemic symptoms syndrome in an elderly man on carbamazepine – A jeopardising clinical entity

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ABSTRACT

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

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, a severe form of drug hypersensitivity reaction with significant morbidity and mortality, is associated with long-term complications. This is a less common potentially life-threatening disease condition that occurs primarily after exposure to antibiotics, particularly sulfonamides, nonsteroidal anti-inflammatory drugs, or antiepileptics with a documented mortality rate of approximately 10% [1]. The increasing use of targeted anticancer agents and immunotherapies could raise this number in the coming years [2]. Clinical features of DRESS include cutaneous eruption, fever, lymphadenopathy, hematologic abnormalities, and visceral involvement which manifest after 3–8 weeks of exposure to the offending agent [2]. Laboratory test has a significant role in the diagnosis of DRESS including complete blood count, hematologic abnormalities, liver function tests, renal function test, and specific laboratory tests. Registry of severe cutaneous adverse reactions (RegiSCAR) criteria are the most accepted and widely used for diagnosis of DRESS [2]. Many autoimmune conditions may develop as a delayed complication of DRESS syndrome [1].

We are reporting a case of DRESS syndrome in a person who was recently started on carbamazepine and responded to steroids. The diagnosis of DRESS syndrome is frequently delayed because it occurs in a broad clinical spectrum (fever with rash) and its latent period is prolonged. The awareness of DRESS syndrome among physicians should be increased to reduce morbidity and mortality through early diagnosis and treatment.

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CASE REPORT

A 67-year-old male patient, a known case of chronic obstructive pulmonary airway disease, epilepsy, and Type 2 diabetes mellitus, developed fever 10 days back which was intermittent and high grade. It was associated with malaise, myalgia, and headache for which they consulted a nearby physician and took antipyretics but the fever was not subsiding. After 4 days of persisting fever, he noted the development of multiple small reddish lesions over both upper limbs and it was associated with itching. The lesions progressed rapidly to involve almost all other areas of the body including the chest, abdomen, back of the trunk, both thighs, and leg. Palms and soles had also developed similar lesions toward the end of the course of the illness. He felt a burning sensation in the oral cavity while food intake. No history suggestive of systemic involvement. He was diagnosed to have epilepsy and was started on carbamazepine (200 mg twice daily) 6 weeks back.

General examination showed significant lymphadenopathy involving cervical and inguinal lymph nodes. Multiple erythematous coalesced papules and rashes were present over anterior chest wall, abdomen, back of the trunk, both upper and lower limbs (Fig. 1), palms, and soles with relative sparing of the

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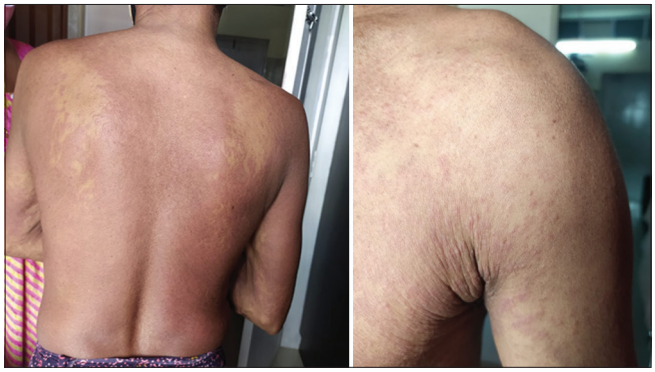

Figure 1: Rashes over chest and back

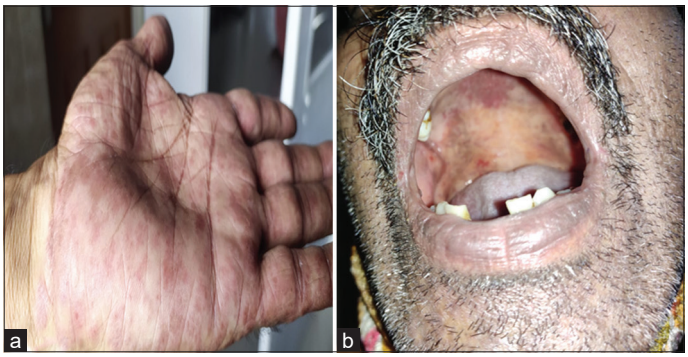

Figure 2: (a) Rashes over palms and soles; (b) oral mucosal involvement

face (Fig. 2a). Oral mucosa showed small erosion present over the hard and soft palate (Fig. 2b). Eyes and genitalia were normal.

Blood investigations showed neutrophilic leukocytosis with eosinophilia (total count – 29,100/mm^3, neutrophils – 58, lymphocytes – 23, eosinophils – 19, and absolute eosinophil count – 5529), erythrocyte sedimentation rate – 30, altered liver function test – serum glutamic-oxaloacetic transaminase – 68 IU/L, and serum glutamic pyruvic transaminase – 138 IU/L. Peripheral smear showed moderate leukocytosis, moderate eosinophilia, and lymphocytosis. Electrocardiogram and echocardiography were normal. Screening for tropical infections, exanthematous fever, and viral hepatitis were negative. Ultrasound abdomen showed fatty changes. The blood culture was sterile.

Diagnosis of carbamazepine-induced DRESS (RegiSCAR score – 7) was made after excluding all other differential diagnoses and he was started on intravenous corticosteroids (methyl prednisolone – 1 g intravenous for 3 days, followed by oral prednisolone in tapering dose for 7 days) after withholding the offending drug. Fever, rash, and transaminitis improved with the given treatment for 10 days and the patient got discharged.

DISCUSSION

DRESS syndrome is a dreaded clinical entity with significant morbidity and mortality with the potential for long-term complications. The acronym DRESS was introduced by Bocquet in 1996 and it stood for drug rash with eosinophilia and systemic symptoms [1]. The term "Rash" was replaced with "reaction" because of a wide range of clinical manifestations including an absence of the rash itself depending on which diagnostic criteria are used. The prevalence of DRESS syndrome approaches 2.18–9.63/100,000 [1]. Incidence for antiepileptic-induced DRESS ranges between 0.001% and 0.0001% in the general population [3]. DRESS is classified under severe cutaneous adverse reaction(SCAR) and comprises a broad group of delayed hypersensitivity reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug-induced hypersensitivity syndrome (DiHS). Clinical features and pathologic mechanisms of DiHS and DRESS are very similar and they are frequently referred to as DiHS/DRESS [3].

The mechanisms underlying DiHS/DRESS are well explained, and it includes the role of CD4 and CD8 and cytomegalovirus (CMV), Epstein–Barr virus (EBV), or human herpes virus (HHV-6/-7) infections with autoimmune sequelae. The basic pathogenesis underlying most of the SCARs is a complex interaction between small-molecule drugs, human leukocyte antigens (HLAs) genes, and T-cell receptors and HLA genotyping could help in the assessment of the SCARs' risk [3]. The terms "mini-DRESS" or "skirt syndrome" have been proposed to refer to milder forms of DRESS [1].

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]. 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 or erythema multiforme [1]. Systemic inflammatory features may precede, occur concurrently with, or lag behind cutaneous manifestations. Fever is the most common sign of disease occurring in ≥90% of patients, followed by hematological derangements with eosinophilia ≥90% (additional abnormalities such as leukocytosis, neutrophilia, atypical lymphocytosis, and monocytosis) and lymphadenopathy – 50–75% of cases [1].

DRESS syndrome can affect most of the internal organs making it accounts for morbidity and mortality. The most commonly involved organ is 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 myocarditis [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 may help to rule out other differential diagnoses [1,2].

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 tools, 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].

Clinical feature	Score
Extent of rash >50% body surface area	1 point
Rash suggestive of DRESS	1 point
Systemic involvement: lymphadenopathy[a], eosinophilia[b], atypical lymphocytosis[b], organ involvement[c]	Maximum 6 points
Relevant negative serological tests[d]	1 point

<2 points: no case; 2–3 points: possible case; 4–5 points: probable case; >5 points: definite case.
[a]≥2 sites, ≥1 cm. A maximum 1 point gained from lymphadenopathy
[b]Eosinophilia: 10–19% of total white cell count = 1 point; ≥20% = 2 points (if total leucocytes <4 × 10^9/L, an eosinophil count of 0.7–1.5 × 10^9/L will gain 1 point, an eosinophil count ≥1.5 × 10^9/L will score 2 points). Atypical lymphocytosis will gain 1 point.
[c]Liver: transaminases >2 × upper limit of normal (ULN) on two successive dates *or* bilirubin × 2 ULN on 2 successive days *or* aspartate aminotransferase (AST), γ-glutamyltransferase (GGT) and alkaline phosphatase >2 × ULN on one occasion. Renal: creatinine 1.5 × patient's baseline. Cardiac: echocardiographic evidence of pericarditis. Maximum of 2 points gained from internal organ involvement.
[d]≥3 of the following performed and negative: hepatitis A, B and C; *Mycoplasma*/chlamydia; antinuclear antibody; blood culture (performed ≤3 days after hospitalization). A maximum of 1 point gained for relevant negative serological tests.

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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