

DRESS Syndrome

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Abstract

Carbamazepine was and still used extensively in clinical practice in varied indications can cause adverse drug reaction showing diverse clinical manifestations of variable severity. "Drug Reaction with Eosinophilia and Systemic Symptoms" (DRESS) syndrome is a severe, potentially life-threatening, acute adverse drug reactions, typically characterized by a long latency period from drug exposure. DRESS syndrome is characterized by the presence of fever, coetaneous eruptions, lymphadenopathy, internal organ involvement (such as hepatitis, carditis, interstitial nephritis, interstitial pneumonitis, etc.) and haematological abnormalities, mainly leucocytosis, eosinophilia and sometimes atypical lymphocytosis.

We report a clinical case of DRESS syndrome with liver injury, evaluated with the RegiSCAR scoring system as a "definite case" possibly induced by carbamazepine in a patient.

Introduction

Carbamazepine is an iminostilbene derivative chemically related to the tricyclic antidepressants synthesized in 1953 by Walter Schindler. It is still one of the most commonly used anti-epileptic even though newer antiepileptic drugs (AEDs) with good efficacy and tolerability are available. Varied incidence of adverse reactions to carbamazepine is reported from clinical studies.¹ Serious adverse reactions to carbamazepine affecting the hematopoietic system (aplastic anaemia, agranulocytosis), skin (Stevens-Johnson syndrome/toxic epidermal necrolysis) and cardiovascular system (heart failure, rhythm disorders) have been observed. Cutaneous reactions induced by carbamazepine may have diverse clinical manifestations and variable severity. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe, potentially life-threatening acute adverse drug reaction, typically characterized by a long latency period (2–6 weeks to 3 months) from drug exposure. The term was introduced by Bocquet et al in 1996.² This clinical entity has been previously described as "anticonvulsant hypersensitivity syndrome", "drug-induced hypersensitivity syndrome", "drug-induced delayed multi organ hypersensitivity syndrome", or more simply "hypersensitivity syndrome".

Although few drugs including aromatic anticonvulsants (carbamazepine, phenytoin and phenobarbital), salazosulfapyridine, dapsone and minocycline have been more frequently associated with DRESS syndrome, reports on various groups of drugs blamed for inducing the syndrome have been emerging. DRESS syndrome is an immune mediated idiosyncratic reaction. Genetic predisposition, defective drug detoxification and accumulation of toxic metabolites and reactivation of herpes virus family have been proposed to be involved in the pathogenesis. Cutaneous eruptions, lymphadenopathy, symptomatic or asymptomatic internal organ involvement (for example hepatitis, carditis, interstitial nephritis, interstitial pneumonitis, etc.) and haematological abnormalities, mainly leucocytosis, eosinophilia and sometimes atypical lymphocytosis are the major clinical features. Each clinical feature maybe of variable onset and degree, leading to confusion and delay in diagnosis. Two sets of diagnostic criteria have been independently introduced by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study group⁴ and the Japanese consensus group to aid in the diagnosis and classification of suspected cases. Although rare, the syndrome may lead to potentially fatal consequences, reported in 10–50% of cases, hence, we report a case of DRESS syndrome.

Case Presentation

A 40 year old male was admitted to hospital with a history of generalised swelling all over the body and reddish discolouration of skin associated with rashes for 2-3 days. The skin rash was accompanied by nausea, vomiting, fever up to 39.7 °C and Acetaminophen was taken as antipyretic. Approximately 2-3 months ago treatment with Carbamazepine for seizure disorder (? generalised tonic clonic seizures). The patient's past, family, personal and drug histories were unremarkable.

Physical examination revealed a very weak pulse, with a non-recordable blood pressure, axillary temperature of 38.8 °C, liver span of 14 cm and generalized non tender lymphadenopathy. He had facial oedema, angular cheilitis and maculopapular exanthema progressing to exfoliative erythroderma. No clinical signs of herpes simplex infection provoked by fever were observed.

His ESR was 20 mm/1st hr., total leucocyte counts were 51.8×10^9 /L with lymphocytic predominance (47%) along with presence of atypical lymphocytes and moderate eosinophilia (11.5%). His routine biochemistry showed mild azotemia (blood urea – 91 mg/dl and serum creatinine – 1.4 mg/dl) and mild transaminitis (AST- 114 IU/L and ALT-132 IU/L). His arterial blood gas analysis was unremarkable. Serological assays for hepatitis B and C virus, human immunodeficiency virus were negative. Antinuclear antibodies were also negative. Blood, urine and stool cultures were negative. Chest radiography and electrocardiography were normal. Abdominal ultrasonography showed hepatomegaly with normal echotexture.

Application of the RegiSCAR scoring system yielded a score of 8 and the clinical case was designated as a "definite case" of DRESS syndrome (Table 1). Carbamazepine was withdrawn immediately and patient was taken on sodium valproate,

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Table 1: Scoring system of RegiSCAR for diagnosing DRESS and case estimation

Score	-1	0	1	2	Min	Max
Fever $\geq 38.5^\circ\text{C}$	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			700-1499/ μL	$\geq 1500/\mu\text{L}$		
Eosinophils, if leukocytes <4000			10-19.9%	$\geq 20\%$		
Atypical lymphocytes	No/U	Yes			0	1
Skin involvement					-2	2
Rash extent ($>50\%$ BSA)	No/U	Yes				
Rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*					0	2
Liver	No/U	Yes				
Kidney	No/U	Yes				
Lung	No/U	Yes				
Muscle/heart	No/U	Yes				
Pancreas	No/U	Yes				
Other organ(s)	No/U	Yes				
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation other potential causes:					0	1
Serological tests like ANA, HAV/HBV/HCV, Chlamydia, Mycoplasma, Blood culture, etc.						
Negative or Positive ≥ 3 of above						

Final score <2 : No case, 2-3: Possible case, 4-5: Probable case, >5 : Definite case; U = unknown/unclassifiable; *After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs

injection methylprednisolone, injection chlorpheniramine and other supportive treatment. Monitoring of haematological and biochemical values was performed for the accurate management of DRESS syndrome. Patient improved and was discharged on 14th day along with a course of corticosteroids for 3 months duration with gradual tapering with regular follow ups which were unremarkable.

Discussion

Persistence or even paradoxical aggravation of symptoms despite removal of offending drugs is a unique feature of DRESS syndrome, and strict monitoring of haematological and biochemical parameters together with supportive care are necessary for the management of the patients. Hepatitis, seen in 50% of cases of DRESS syndrome is usually mild but can be severe.

A systematic review of articles published in English literature during the past 20 years concerning all psychotropic drugs linked to DRESS syndrome, detected 1072 cases of psychotropic drug induced DRESS syndrome, with carbamazepine,

lamotrigine, phenytoin, valproate, and phenobarbital being the most implicated drugs.

Carbamazepine follows a metabolic pathway common to all hydroxylated aromatic compounds. It is metabolized by the liver cytochrome P-450 (CYP) enzyme system with the formation of intermediate arene oxides, and the epoxide hydroxylase is responsible for detoxifying these metabolites. It is speculated that hereditary or acquired abnormalities in the production and/or defective metabolite detoxification in some individuals may predispose to DRESS syndrome.⁵ Arene oxides are capable of binding to cell macromolecules producing cell damage or a secondary immunologic response. Moreover, carbamazepine is an enzyme inducer and can induce its own metabolism with auto induction of CYP3 A4 and CYP B6. Reactivation of herpes virus infections and co-administration of other drugs may also be implicated in the liver and other organ involvement in DRESS syndrome. The viral serological studies carried out in our patient were negative. Patch testing and lymphocyte transformation

test although useful but were not performed in our case because of not affordability. Results from various studies indicate that the test has high specificity but limited sensitivity. Patch testing following DRESS syndrome can be performed after careful evaluation of the risk-benefit ratio for the individual patient due to the possibility of reactivation of cutaneous lesions. The investigation of some genetic markers in drug hypersensitivity patients is a promising tool for their screening and safe evaluation. Recently, genotyping for HLA markers has found a strong association between HLA*31:01 and carbamazepine-induced DRESS syndrome in Europeans.⁵

The reported case of carbamazepine-induced DRESS syndrome presents the difficulties in the etiological assessment and management of severe multi organ adverse drug reactions in poly morbid patients with poly pharmacy. Newly developed autoimmune diseases and permanent visceral organ failure have been observed in patients with DRESS syndrome after the acute stage with a reported incidence of 11.5%. Early recognition of DRESS syndrome is essential to prevent considerable morbidity and mortality. Aromatic anticonvulsants, especially carbamazepine are the commonest cause of DRESS syndrome. Patients on carbamazepine which is increasingly used as a mood stabilizer must be carefully monitored for adverse drug reactions including DRESS syndrome.

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