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Case Report

Carbamazepine-Induced DRESS Syndrome: A Case Report

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Abstract

Adverse drug reactions (ADRs) 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 ADR, typically characterized by a long latency period from drug exposure. DRESS syndrome is defined by the presence of fever, cutaneous eruption, lymphadenopathy, internal organ involvement (such as hepatitis, carditis, interstitial nephritis and interstitial pneumonitis) and hematological 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 (CBZ) in a patient with anxiety disorder, bronchial asthma and polyglandular autoimmune syndrome (PAS) type 3A including type 1 diabetes mellitus and autoimmune thyroiditis. Infections, neoplastic and collagen vascular diseases were excluded. The patient was successfully treated with corticosteroids and hepatoprotectors. During a 3-month follow-up the dosage of corticosteroids was gradually tapered and stopped.

Patients on CBZ which is increasingly used as a mood stabilizer must be carefully monitored for ADRs including DRESS syndrome.

ABBREVIATIONS

CBZ: Carbamazepine; AEDs: Antiepileptic Drugs; FDA: Food and Drug Administration; SSRIs: Selective Serotonin Reuptake Inhibitors; SJS/TEN: Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; ADR: Adverse Drug Reaction; RegiSCAR: Registry of Severe Cutaneous Adverse Reactions; PAS: Polyglandular Autoimmune Syndrome; ref. range: Reference Range; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; GGT: Gamma-Glutamyl Transpeptidase; AP: Alkaline Phosphatase; RUCAM: Roussel-Uclaf Causality Assessment Method: DILI: Drug Induced Liver Injury; CYP: Cytochrome P450

INTRODUCTION

Carbamazepine (CBZ) is an iminostilbene derivative chemically related to the tricyclic antidepressants synthesized in 1953 by Walter Schindler. It was first marketed as a drug in Europe to treat trigeminal neuralgia in 1962 and a few years later was approved as an antiepileptic agent [1]. CBZ is still one of the most commonly used antiepileptics even though newer antiepileptic drugs (AEDs) with good efficacy and tolerability were introduced since the 1990s. CBZ is currently indicated for use in partial seizures, generalized tonic-clonic seizures and mixed seizure patterns and for the treatment of trigeminal and glossopharyngeal neuralgia [2]. CBZ extended-release capsules were approved by the Food and Drug Administration (FDA) in 2004 for the treatment of bipolar I disorder [3], characterized by episodes of full mania alternating with episodes of major depression. CBZ was the first anticonvulsant used as a mood stabilizer in bipolar disorder in the 1970s, both in acute mania and for maintenance therapy [4-6]. CBZ is prescribed off-label in alcohol withdrawal, drug dependence/abstinence [7], and schizoaffective disorder, aggressive behavior in schizophrenia or organic brain disorders [8]. AEDs may be alternatives for patients with anxiety disorders who cannot tolerate selective serotonin reuptake inhibitors (SSRIs) or benzodiazepines [9]. Varied incidence of adverse reactions to CBZ is reported from clinical studies in patients with epilepsy, bipolar disorder and alcohol abstinence syndrome [10]. Serious adverse reactions to CBZ affecting the hematopoietic system (aplastic anemia, agranulocytosis), skin (e.g. Stevens-Johnson syndrome/toxic epidermal necrolysis - SJS/TEN) and cardiovascular system (heart failure, rhythm disorders) have been observed. Cutaneous reactions induced by CBZ may have diverse clinical manifestations and variable severity. Due to

emerging data indicating a strong association between the HLA allele B*1502 and the risk for carbamazepine-induced SJS/TEN in Han Chinese patients, the FDA recommends genotyping all Asians for the allele before starting therapy with CBZ [11].

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, potentially life-threatening acute adverse drug reaction (ADR), 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 [12]. This clinical entity has been previously described as "anticonvulsant hypersensitivity syndrome" [13], "drug-induced hypersensitivity syndrome" [14], "drug-induced delayed multiorgan hypersensitivity syndrome" [15], or more simply "hypersensitivity syndrome" [16]. Although few drugs including aromatic anticonvulsants (carbamazepine, phenytoin and phenobarbital), salazosulfapyridine, dapsone and minocycline have been more frequently associated with DRESS syndrome [17, 18], reports on various groups of drugs blamed for inducing the syndrome have been emerging. DRESS syndrome is an immune-mediated idiosyncratic reaction [19]. 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 [20].

DRESS syndrome is defined by the presence of fever, cutaneous eruption, lymphadenopathy, symptomatic or asymptomatic internal organ involvement (for example hepatitis, carditis, interstitial nephritis, interstitial pneumonitis, etc.) and hematological abnormalities, mainly leucocytosis, eosinophilia and sometimes atypical lymphocytosis. Each clinical feature may be of variable onset, leading to confusion and delay in diagnosis [21]. Two sets of diagnostic criteria have been independently introduced by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study group and the Japanese consensus group to aid in the diagnosis and classification of suspected cases [19,22,23].

Although rare, the syndrome may lead to potentially fatal consequences, reported in 10–40% of cases [12]. Patients who develop hepatitis with jaundice increase their chance for mortality up to 50% [24]. DRESS syndrome has been found to represent the major cause of hospitalization for dermatologic complications in patients treated with anticonvulsants [25,26].

CASE PRESENTATION

A 23-year-old female was admitted to hospital with a history of first degree sunburn of the shoulder area and pruriginous rash involving the abdominal region which had gradually disseminated over most of the body surface for 4-5 days. The skin rash was accompanied by nausea, vomiting, fever up to 39.7 °C and dipyrone was taken as antipyretic. Approximately 2-3 months ago treatment with carbamazepine (prescribed off-label) and trazodone for anxiety disorder was initiated. The patient`s medical history was notable for bronchial asthma in clinical remission in the last year and polyglandular autoimmune syndrome (PAS) type 3A including type 1 diabetes mellitus with peripheral neuropathy and autoimmune thyroiditis on L-thyroxine thyroid hormone replacement therapy.

Physical examination revealed an axillary temperature of 38.8 °C, a heart rate 100 beats per minute, a blood pressure of 100/60 mm Hg, mild liver enlargement and generalized lymphadenopathy. She had facial edema, angular cheilitis and maculopapular exanthema (Figure 1) progressing to exfoliative erythroderma. No clinical signs of herpes simplex infection provoked by sunburn or fever were observed. Erythrocyte sedimentation rate and complete blood count with differential were normal. White blood cells initially in reference range (ref. range) 5.4 x 10^9/L with 1% eosinophils climbed to 21.18 x 10^9/L with 14% eosinophils. An arterial blood gas test, haemostatic profile, creatine kinase with MB fraction and renal function tests were normal. Biochemistry revealed low serum levels of albumin 28.9 g/L (ref. range 38 - 51 g/L) and total protein 45.5 g/L (ref. range 60 - 87 g/L), elevated C reactive protein 14.8 mg/L (ref. range 0.0 – 5.0 mg/L) and increased fasting blood glucose levels up to 13.3 mmol/L (ref. range 2.8 – 6.1 mmol/L). Liver function tests showed increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (AP) and total and conjugated bilirubin (Table 1). Antinuclear antibodies were negative. Serological assays for hepatitis A, B and C virus, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, syphilis, and streptococcal infection were all negative. Blood cultures, urine, stool cultures and nasal-throat swabs were repeatedly negative for bacteria, protozoa or helminth eggs. Vaginal smear culture test was positive for Bacteroides spp. and Peptostreptococcus spp. Microscopic examination revealed "clue cells" on a saline vaginal smear. Abdominal sonography showed mild hepatomegaly. Chest radiography and electrocardiography were normal. The skin biopsy yielded epidermal parakeratosis, irregular acanthosis, spotty spongiosis, low-grade hydropic degeneration of basal keratinocytes and a moderate lichenoid-like infiltrate in upper derma (Figure 2), features consistent with the picture of subacute dermatitis. Infections, neoplastic or collagen vascular diseases were excluded.

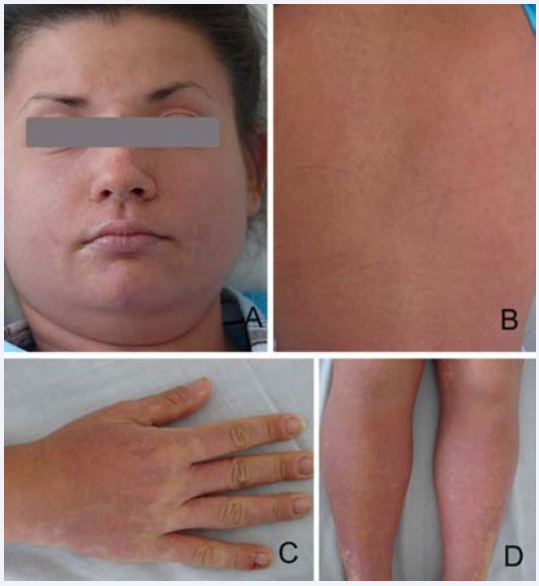

Figure 1 Skin rash. A - facial edema, angular cheilitis; B, C, D - maculopapular exanthema.

Table 1: Hepatic laboratory tests in the reported patient.

Laboratory parameter	Time after drug withdrawal				
	Day 1	Day 3	Day 5	Day 7	Day 12
ALT (U/L)	372.1	781.4	418	252	126
AST (U/L)	140.8	661	167	81	49
Total bilirubin (μmol/l)	70	78	79.5	79.3	-
Direct bilirubin (μmol/l)	46.9	49.2	47.8	49.8	-
GGT (U/L)	751	814	1078	860	1025
AP (U/L)	-	596	755	707	764
LDH (U/L)	-	1014	-	648	506

Abbreviations: ref. range: reference range; ALT: alanine aminotransferase (ref. range 0-32 U/L); AST: aspartate aminotransferase (ref. range 0-31 U/L); total bilirubin (ref. range 3.4-21 μmol/l); direct bilirubin (ref. range 0.8-8.5 μmol/l); GGT: gamma-glutamyl transpeptidase (ref. range 9-39 U/L); AP: alkaline phosphatase (ref. range 64-306 U/L); LDH: lactate dehydrogenase (ref. range 225-450 U/L);

Table 2: Scoring system of RegiSCAR* for diagnosing DRESS and case estimation.

Criteria	Score			Case score
	No	Yes	Unknown	
Fever ≥ 38.5	-1	0	-1	0
Enlarged lymph nodes (≥2 sites;>1 cm)	0	1	0	1
Peripheral eosinophilia 0.7-1.5x10^9/L or 10-19.9% ≥ 1.5x10^9/L or ≥20%	0	1 2	0	 2
Atypical lymphocytes	0	1	0	0
Skin involvement • Extent of cutaneous eruption > 50% • Skin Rash suggesting DRESS • Biopsy suggesting DRESS	 0 -1 -1	 1 1 0	 0 0 0	 1 1 0
Organ involvement One 2 or more	0	 1 2	0	 1
Resolution ≥15 days	-1	0	-1	0
Laboratory results negative for at least 3 of the following: • ANA • Blood culture • HAV/HBV/HCV serology • Chlamydia/mycoplasma serology	0	1	0	1
Total score <2 no case; 2-3 possible case; 4-5 probable case; >5 definite case				7 definite case

*Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. 2007
*Roujeau JC, Allanore L, Liss Y et al, 2009

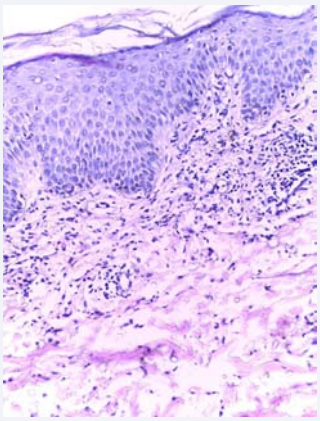

Figure 2 Epidermal parakeratosis, irregular acanthosis, spotty spongiosis, low-grade hydropic degeneration of basal keratinocytes and a moderate lichenoid-like infiltrate in upper derma (HE x 200).

Application of the RegiSCAR scoring system yielded a score of 7 and the clinical case was evaluated as a "definite case" of DRESS syndrome (Table 2). All psychotropic drugs were immediately withdrawn, and after psychiatric consultation, no medication for the anxiety disorder was administered. Treatment with parenteral methylprednisolone 50 mg/24h i.m., peroral cetirizine 10 mg daily, omeprazole 20 mg daily, ursodeoxycholic acid 500 mg b.i.d. and silymarin 90 mg b.i.d. was initiated. Monitoring of hematological and biochemical values was performed for the accurate management of DRESS and the concomitant diabetes complicated by glucocorticosteroid therapy. Insulin daily doses were adjusted on the basis of blood glucose levels and concomitant therapy with L-thyroxine 50 mcg daily was continued. During a 3-month follow-up the dosage of corticosteroids was gradually tapered and stopped as the clinical and laboratory abnormalities of DRESS syndrome resolved. Bacterial vaginosis was treated topically with vaginal tablets metronidazole 100 mg/miconazole 100 mg. There were no recurrences of DRESS syndrome in the following months.

DISCUSSION

DRESS syndrome is an uncommon but potentially serious idiosyncratic ADR. We report a case of DRESS syndrome with a characteristic long latency period, typical clinical features of fever, skin and internal organ involvement with laboratory data of hepatitis, leucocytosis and eosinophilia. The suspected causative drugs CBZ and trazodone were started 2-3 months prior to the onset of the disease, and dipyrone was taken after the first symptoms. Our therapeutic approach consisted of withdrawing the psychotropic medication and administering systemic corticosteroids, antihistamines and hepatoprotectors. In the reported case liver function tests were elevated and some of them continued to rise as long as 12 days after withdrawal of the suspected drugs. Persistence or even paradoxical aggravation of symptoms despite removal of offending drugs is a unique feature of DRESS syndrome [19], and strict monitoring of hematological and biochemical parameters together with supportive care are necessary for the management of the patients. Hepatitis, seen in 50% of cases of DRESS, is usually mild but can be severe [27].

To exclude other probable etiologies of liver damage and to assess causality of drug-induced liver injury the Roussel-Uclaf causality assessment method (RUCAM) was used [28]. Application of RUCAM to the reported case calculated with initial liver enzyme values determined the presence of hepatocellular injury pattern. The RUCAM score was 7 for CBZ and 6 for trazodone, both corresponding to a "probable" drug induced liver injury (DILI). The difference in the scores is based on the labeling information for CBZ and trazodone. Liver damage is included as ADR in the product characteristic of CBZ. Both drugs have been reported in literature in association with various patterns of DILI. [29-31]

Drug causality of DRESS syndrome was evaluated with the Naranjo algorithm [32]. Dipyrone was excluded because it was introduced after the onset of rash and fever. The causal relationship between psychotropic drugs and DRESS was rated as "possible", with a score of 4 for CBZ and 2 for trazodone. A systematic review of articles published in English during the past 20 years (1996-2015) concerning all psychotropic drugs linked to DRESS syndrome, detected 1072 cases of psychotropic drug-induced DRESS, with carbamazepine, lamotrigine, phenytoin, valproate, and phenobarbital being the most implicated drugs [33]. We found no articles specifically mentioning trazodone, an antidepressant with a complex mode of action belonging to the group of 5-HT receptor modulators [34]. It is possible that both CBZ and trazodone contributed to the development of hepatic injury in our patient.

CBZ 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 [35,36]. Arene oxides are capable of binding to cell macromolecules producing cell damage or a secondary immunologic response. Moreover, CBZ is an enzyme inducer and can induce its own metabolism with auto induction of CYP3 A4 and CYP B6 [37,38]. Reactivation of herpes virus infections and co-administration of other drugs may also be implicated in the liver and other organ involvement in DRESS [39-41]. The viral serological studies carried out in our patient were negative. Patch testing and lymphocyte transformation test were not performed. The lymphocyte transformation test is a useful research tool for the diagnosis of drug hypersensitivity reactions. Results from various studies indicate that the test has high specificity but limited sensitivity [42-44]. Patch testing following DRESS can be performed after careful evaluation of the risk-benefit ratio for the individual patient due to the possibility of reactivation of cutaneous lesions [45]. 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 CBZ-induced DRESS in Europeans [46].

The reported case of CBZ-induced DRESS syndrome presents the difficulties in the etiological assessment and management of severe multiorgan ADRs in polymorbid patients with polypharmacy. In our case DRESS syndrome developed in a patient with pre-existing autoimmune diseases (diabetes and thyroiditis). Although glucocorticosteroid treatment aggravated diabetes it was considered essential not only for the proper management of this severe hypersensitivity reaction but also for the prevention of future autoimmune sequelae. Newly developed autoimmune diseases and permanent visceral organ failure have been observed in patients with DRESS after the acute stage with a reported incidence of 11.5% [47]. Early recognition of DRESS syndrome is essential to prevent considerable morbidity and mortality. Aromatic anticonvulsants, especially CBZ [48], are the commonest cause of DRESS. Patients on CBZ which is increasingly used as a mood stabilizer must be carefully monitored for ADRs including DRESS syndrome.

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