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CASE REPORT

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DRESS Syndrome due to Carbamazepine Use in A Drug-Addicted Adolescent

Isilay TURAN, Mehmet Halil CELIKSOY, Sezin NAIBOGLU, Selami ULAS, Cigdem AYDOGMUS

Department of Pediatric Allergy and Immunology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey

Corresponding Author: Mehmet Halil Celiksoy ✉ drmhc@hotmail.com

ABSTRACT

DRESS syndrome is a rare, life-threatening allergic drug reaction of the delayed-type. This reaction is caused by the inhibition of certain enzyme families, itself triggered by the use of other drugs or substances. Marijuana is a substance derived from cannabis. Cannabinoid use increases serum levels of some antiepileptic drugs, such as carbamazepine, by inhibiting the CYP3A enzyme family. Care should be taken in selecting antiepileptic drugs for patients with cannabinoid addiction to avoid triggering severe drug reactions such as the DRESS syndrome.

Keywords: DRESS syndrome, cannabinoid, substance abuse, drug allergy, carbamazepine

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe hypersensitivity reaction to drugs that features high mortality and morbidity rates, as well as limited treatment options (1). The prognosis of DRESS depends on the severity of the associated complications. The complications related to visceral organ involvement typically manifest as hepatitis, but may include lymphadenopathy, interstitial nephritis, interstitial pneumonitis, and myocarditis (2). The most commonly blamed drugs for this reaction are aromatic antiepileptic drugs (3). The time of symptom onset in DRESS syndrome can vary from 2 to 6 weeks after initiation of treatment with the suspected drug (4). The most common symptoms are fever, rash, and lymphadenopathy (4). DRESS syndrome can be diagnosed using Bocquet's criteria for the diagnosis of drug rash and eosinophilia with systemic symptoms/drug-induced hypersensitivity (5), Registry of severe cutaneous adverse reaction criteria for diagnosis of drug rash and eosinophilia with systemic symptoms (RegiSCAR) (6), or the Japanese group criteria for diagnosis of drug rash and eosinophilia with systemic symptoms/induced hypersensitivity (J- SCAR) (7), which evaluate specific clinical and laboratory findings in suspected DRESS syndrome. Treatment is supportive and symptomatic. Identification and immediate withdrawal of the offending drug is the mainstay of treatment for patients with DRESS syndrome, though prognosis is better with early discontinuation of the suspected drug. All potentially involved drugs should be stopped immediately (4). Adequate fluid intake is usually sufficient to maintain fluid and electrolyte balance in patients, as is the use of systemic corticosteroids in mild and moderate cases to ameliorate the clinical symptoms at the acute phase (8).

While DRESS syndrome is a reaction to a medical drug such as antiepileptic medication, the reaction itself is triggered when this drug interacts with another substance like cannabis in the body. Marijuana is a substance derived from cannabis, of which the main constituents are delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) (9). In addition, bonsai is a synthetic cannabinoid derivative. Cannabinoids increase serum levels of carbamazepine by inhibiting cytochrome enzymes that metabolize carbamazepines (9, 10).

ORCID Isilay Turan / 0000-0003-1297-1923, Mehmet Halil Celiksoy / 0000-0002-4164-4668, Sezin Naiboglu / 0000-0002-9593-1136, Selami Ulas / 0000-0003-1486-9690, Cigdem Aydogmus / 0000-0002-6036-7694

This case report presents an instance of DRESS syndrome that developed after carbamazepine ingestion in a cannabis-addicted adolescent girl.

CASE

A 15-year-old female patient presented to the emergency room of our hospital complaining of fever, weakness, and a rash that had persisted for 3 days. The patient's medical history revealed that she had been addicted to cannabis and bonsai for many years, and that she was taking aripiprazole for borderline behavioral disorder and aggression. She had received additional treatment with escitalopram and carbamazepine at an outside center 3 weeks before admission to our hospital. Upon physical examination, her general condition was good and she was conscious. Her body temperature was 39.5°C, heart rate 96/minute, and blood pressure 110/65 mmHg. Her scalp and face were edematous. There was an extensive, faded, erythematous maculopapular rash on her back, arms, legs and trunk (Figures 1A-D). The patient's Nikolsky sign was negative and there was no mucosal or ocular involvement. Numerous lymph nodes of varying sizes were palpated bilaterally in the cervical, submandibular, and inguinal regions. Upon abdominal examination, the patient had hepatosplenomegaly. Other physical findings of the patient were normal.

Laboratory examination revealed an Hgb level of 13.8 g/dL, a leukocyte count of 7150/mm^3, and a platelet count of 131000/mm^3. Total eosinophil count was 2130/mm^3, representing 29.8% of the white blood cells. In the biochemical evaluation, alanine aminotransferase was 81 U/L, aspartate aminotransferase was 56 U/L, and C-reactive protein was 15.3 mg/L. Renal function tests and complete urinalysis were normal. No growth was detected in the urine and blood culture. No virus infections, including Parvovirus B19; Hepatitis A, B and C; Human Immunode-

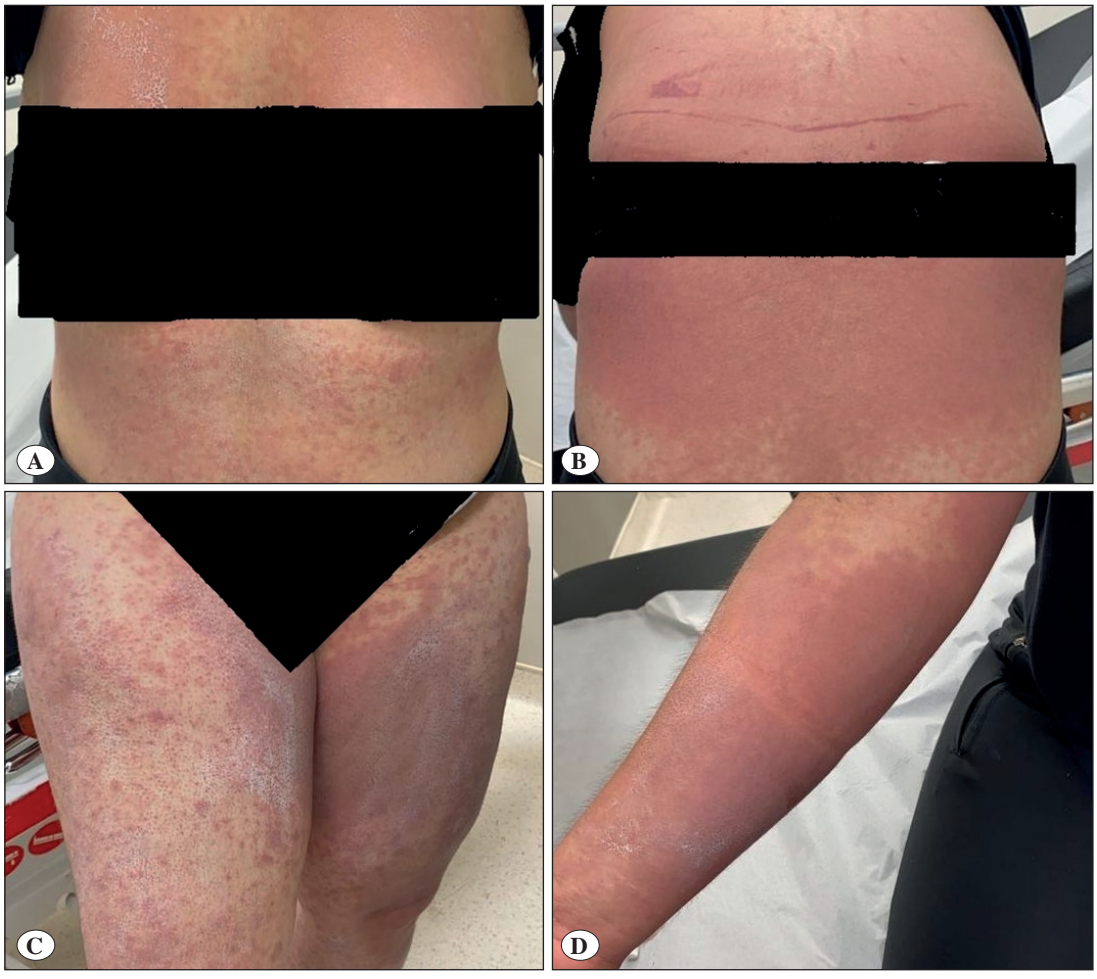

Figure 1. Widespread maculopapular rash over the patient's entire body (**A:** Chest, **B:** Back, **C:** Legs, **D:** Right arm)

ficiency Virus, Human Herpes Virus 6, Cytomegalovirus or Epstein-Barr virus were confirmed. No patch testing was performed.

Ultrasonography demonstrated an enlarged liver with a length of 170 mm (hepatomegaly) and the length of the spleen was 132 mm (splenomegaly). The patient's laboratory values are shown in Table I.

The results of the patient's skin biopsy (basal vacuolar degeneration, necrotic keratinocytes, perivascular lymphocytes in the superficial dermis, extravasated erythrocytes) supported the diagnosis of DRESS syndrome.

The patient was officially diagnosed with DRESS syndrome at 9 points according to the RegiSCAR diagnostic criteria (Table II). Specifically, her fever exceeded 38.5°C (0 points); she presented with enlarged lymph nodes (1 point); eosinophilia (2 points); atypical lymphocytes (1 point); and a skin rash covering more than 50% of the-

Table I: Clinical and laboratory characteristics of the patient with DRESS syndrome.

Age, year	15
Gender	Female
Culprit drug	Carbamazepine
Latent period	3 weeks
Leukocyte (10^9/L)	7.15 (4.19-9.43)
Hemoglobin (g/dL)	13.8 (10.8-13.3)
Platelet (10^9/L)	131 (150-400)
Total eosinophil count (10^9/L)	2.13 (0.02-0.32)
Percentage of total eosinophil (%)	29.8 (0-3.4)
C-reactive protein (mg/L)	15.3 (0-5)
Erythrocyte sedimentation rate (mm/h)	4
Skin rash	Generalized maculopapular rash
Fever	+
Hepatomegaly	+
Splenomegaly	+
Lymphadenomegaly	+
Alanine aminotransferase (U/L)	81 (0-37)
Aspartate aminotransferase (U/L)	56 (0-27)
Urea (mg/dL)	24.0 (10.7-38.5)
Creatinine (mg/dL)	0.64 (0.57-0.87)
DRESS score	9
Diagnosis	Definite (>5)

body surface area (1 point); the skin rash suggested DRESS syndrome (1 point); her biopsy also suggested DRESS syndrome (0 points); there was organ involvement (liver and spleen) (2 points); and she had negative viral titers (HAV/HCV/HBV) (1 point).

The last two medications added to the patient's treatment were escitalopram and carbamazepine. Considering the etiology of DRESS syndrome, carbamazepine treatment was quickly discontinued as the most suspected drug. The patient was treated with pheniramine maleate (2 mg/kg/day) and methylprednisolone (2 mg/kg/day) intravenously. The patient's skin was treated with a moisturizer. On the recommendation of the patient's pediatric psychiatrist, she was administered lorazepam 2x2.5 mg/day and experienced withdrawal symptoms during her hospitalization. Her fever decreased on the first day of steroid treatment. The rash and itching began to decrease on the fourth day of treatment, and by the end of the first week the rash changed shape and exfoliative desquamation began. Corticosteroid therapy was continued for 14 days and tapered over a 6-week period. Pheniramine maleate administration was discontinued at discharge, and outpatient follow-up was continued with oral cetirizine and moisturizer.

Signed informed consent was obtained from the patient's family so that her medical information and photographs could be used for this case report.

DISCUSSION

The pathogenesis of DRESS syndrome is not fully understood, though genetic polymorphism, environmental factors, autoimmune diseases, and previous viral infections are thought to be responsible (3). The drugs most blamed in the etiopathogenesis of DRESS syndrome are antiepileptic drugs, with the incidence of DRESS syndrome due to antiepileptic drugs varying from 1/1000 to 1/10,000 in the general population (3). A deficiency or defect in the enzyme epoxide hydroxylase, which detoxifies the metabolites of aromatic amine anticonvulsants, is most commonly blamed for the syndrome's etiology. Elevated reactive metabolites are thought to cause an immunological response as well due to inadequate detoxification of the responsible drug (11). Carbamazepine is an aromatic anticonvulsant approved for the treatment of epilepsy, trigeminal neuralgia and bipolar disorder (12). Carbamazepine is metabolized mainly by CYP3A4, CYP2C8, CYP3A5, and CYP2B6 to carbamazepine-10,11-epoxide (9,12).

Table II: Scoring system for classifying DRESS cases as definite, probable, possible, or no case.

Score	-1	0	1	2	Minimum	Maximum
Fever ≥ 38.5 C	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			0.7-1.499x10^9	≥1.5x10^9		
Eosinophils, if leucocytes<4x10^9			10-19.9%	≥20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Skin rash extent (% body surface area)		No/U	>50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement[a]					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		No/U	Yes			
Resolution ≥15 days	No/U	Yes			-1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥3 of above negative			Yes		0	1
Total score					-4	9

U: Unknown/unclassifiable, **HAV:** Hepatitis A virus, **HBV:** Hepatitis B virus, **HCV:** Hepatitis C virus. [a] After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score <2, no case; final score 2-3, possible case; final score 4-5, probable case; final score >5, definite case.

Marijuana is a substance derived from cannabis, whose main constituents are THC, CBD and CBN (9). Bonsai is a synthetic cannabinoid derivative that is chemically similar to THC, the active constituent in cannabis (13). THC, CBD, and CBN are metabolized by the cytochrome P-450 enzyme family. CBD is a potent inhibitor of the CYB3 A family (10), specifically CYP3A4/5, while both THC and CBD inhibit CYP2B6. CYP3A4 is the major metabolic pathway for carbamazepine, and CYP3A5 and CYP2B6 are two of its three minor metabolic pathways (9).

Our patient was an adolescent who was being treated for a mood disorder with medically prescribed drugs and she was addicted to cannabis and bonsai. Three weeks before her admission, carbamazepine was added to her treatment due to a mood disorder. According to the RegiSCAR criteria, the patient was diagnosed with DRESS syndrome (score > 5 points) (4,15). Based on the patient's medication history, we suspected that carbamazepine might have caused DRESS syndrome. Indeed, the patient's condition rapidly improved after the drug was discontinued.

The patient's medical history revealed that she was addicted to cannabis and bonsai. The literature has previously reported that cannabinoids cause increased blood and urinary carbamazepine levels by inhibiting drug metabolism in humans and mice (9,10). In their case report, Ridout et al. showed that the blood carbamazepine level in a 37-year-old male patient was 6.8 micrograms/mL during cannabis use. After cessation of cannabis use, the patient's carbamazepine level decreased to 4.8 micrograms/mL (9). We thus concluded that carbamazepine metabolites might have caused DRESS syndrome, due to the inhibitory effect of cannabinoids in our patient.

In summary, DRESS syndrome is rare but potentially fatal. Its diagnosis can be easily missed, because symptoms do not appear until long after the suspected drug's ingestion. Clinicians should check the patient's medical history in detail and they should determine whether the patient is a drug addict. The use of cannabinoids or other drugs, which can increase the metabolites of the illicit drug and lead to DRESS syndrome, should not be overlooked by the clinician. Marijuana and other synthetic cannabinoid derivatives may especially exacerbate adverse allergic drug reactions by inhibiting enzymes related to many drug groups, including antiepileptic medications.

Conflict of Interest

None of the authors has any potential financial conflict of interest related to this manuscript.

Disclosure of Funding

None.

Authorship Contributions

Concept, Design and Supervision: **Isılay Turan, Mehmet Halil Celiksoy,** Collect the patients clinical data: **Isılay Turan, Mehmet Halil Celiksoy, Sezin Naiboglu, Cigdem Aydogmus, Selami Ulas,** Resource and Literature Search: **Isılay Turan, Mehmet Halil Celiksoy,** Writing: **Isılay Turan,** Critical Reviews: **Mehmet Halil Celiksoy.** All authors have read and approved the final manuscript.

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