

Carbamazepine-Induced DRESS Syndrome During Epstein-Barr Virus Reactivation in an Adolescent

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and potentially life-threatening syndrome. Herein, we present the case of a 14-year-old female who developed a diffuse erythematous rash with fever and facial edema 6 weeks after initiating treatment with carbamazepine and sertraline. Laboratory tests showed an inflammatory reaction, elevated liver enzymes, and mild eosinophilia. Serology tests were negative for viral hepatitis, cytomegalovirus, herpes simplex virus, and parvovirus B19, but positive anti-VCA IgM and anti-EBNA IgG confirmed the presence of Epstein-Barr virus reactivation. Drugs were withdrawn, and the patient was treated with corticosteroid. Carbamazepine was identified as the culprit drug after performing patch tests. Even though DRESS is rare in childhood, we present another case of carbamazepine-induced DRESS in an adolescent associated with EBV activation.

ABBREVIATIONS CBZ, carbamazepine; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; NR, normal range

KEYWORDS drug hypersensitivity syndrome; drug-related side effects and adverse reactions; carbamazepine; herpesvirus 4, human; pediatrics

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, referred to as drug-induced hypersensitivity syndrome, is a distinct, potentially life-threatening adverse reaction. It is seen in children and adults most often as a morbilliform cutaneous eruption with fever, lymphadenopathy, hematologic abnormalities, and multiorgan manifestations.¹ The initial event of this reaction is often viral reactivation; the virus in question is typically a member of the herpes family, such as human herpesvirus-6, Epstein-Barr virus (EBV), or cytomegalovirus.² DRESS syndrome is more common in adults and rarely seen in children. The most common clinical presentation of pediatric DRESS includes morbilliform rash in more than 99% of cases.³

Recognizing this syndrome is important as the mortality rate is around 5.4%.⁴ DRESS syndrome must be recognized promptly and the causative drug withdrawn. It has been reported that the earlier the drug withdrawal, the better the prognosis.⁵

Here, we present a case of DRESS syndrome in which the causative agent was carbamazepine (CBZ), which was associated with EBV reactivation, which was confirmed by a positive patch test.

Case Report

A 14-year-old female was admitted to the hospital with fever, facial edema, and a spreading rash, evolving

over 3 days. She was seen 6 weeks prior by a child psychiatrist who prescribed a treatment consisting of CBZ 20 mg/kg/day and sertraline 50 mg/day for depressive syndrome. She had no significant past medical history, no prior medication use, and no known allergies. On physical examination, her temperature was 40°C, a diffuse erythematous rash was noted over the trunk (Figure 1), the face, and extremities with evident facial edema, and she weighed 40 kg. CBZ and sertraline were immediately withdrawn and replaced by fluoxetine with an initial dose of 10 mg/day. The patient received pulsed intravenous methylprednisolone 3 mg/kg/day for 3 days and oral prednisone 0.5 mg/kg/day for 3 weeks, followed by a gradual taper. Initial investigations were compatible with an inflammatory reaction and liver dysfunction as follows: C-reactive protein 65 mg/L (normal range [NR]: 0–8 mg/L), alanine aminotransferase 141 U/L (NR: 5–41 U/L), aspartate aminotransferase 114 U/L (NR: 0–50 U/L), and gamma-glutamyltransferase 110 U/L (NR: 9–50 U/L). Initial full blood count showed a white blood cell count of $6.8 \times 10^3/\mu\text{L}$ (NR: $4.3\text{--}10 \times 10^3/\mu\text{L}$) and mild eosinophilia with 11% (NR: 0–5%). Serology tests were negative for viral hepatitis, cytomegalovirus, herpes simplex virus, and parvovirus B19. Recurrent EBV infection was demonstrated by the presence of IgM anti-VCA antibodies and IgG anti-EBNA antibodies in the serum taken 3 days after the resolution of the skin eruptions. A biopsy of the

Figure 1. Diffuse erythematous rash in the trunk.

skin lesions revealed a combination of mild spongiosis and some necrotic keratinocytes with infiltration of lymphocytes and eosinophils, suggesting a drug reaction.

Within 4 weeks, the outcome was favorable, with a resolution of symptoms. The abnormal laboratory test results described above had normalized. Over a follow-up period of 4 months, the patient had no further episodes of skin rash nor any symptoms of autoimmune disease.

To identify the inducing agent of the hypersensitivity reaction for this patient, patch tests for CBZ and sertraline were performed 6 months after complete recovery and induced a strongly positive skin reaction to CBZ in 48 hours but was negative to sertraline (Figure 2).

In our case, the clinical, biological, and histological data are in accordance with the DRESS diagnosis criteria. According to the Registry of Severe Cutaneous Adverse Reactions scoring system established by Kardaun et al,⁶ our case yielded a score of 6. Thus, the DRESS diagnosis was “definite” (Table 1).

Figure 2. Patch test results: positive to carbamazepine and negative to sertraline.

Discussion

Carbamazepine and sertraline were the suspected culprit drugs in view of a clear temporal relationship between their administration and the onset of the symptoms (6 weeks), as well as the improvement of the clinical and biological disorders some weeks after their withdrawal.

In our case, this adverse drug reaction was reported as “probable” by applying the Naranjo adverse drug reaction probability scale for the suspected drugs⁷ (Table 2). However, the role of CBZ in the occurrence of this adverse drug reaction was confirmed by skin tests. Therefore, the diagnosis of CBZ-induced DRESS was established.

CBZ-induced DRESS is well documented in the adult literature, with many case reports.^{8,9}

In our review of the literature and according to data from MEDLINE, only 1 case of CBZ-induced DRESS during EBV infection was reported with an 8-year-old male during treatment with CBZ for epilepsy 9 weeks after drug withdrawal and corticosteroid treatment.¹⁰ Contrary to our case, this was a primary EBV infection and not reactivation, and patch tests were not performed.

Only 4 documented pediatric cases of CBZ-induced DRESS have been previously reported.^{11–14} Patch tests were not performed in 3 cases, and viral reactivation was not causative.^{11–13} One report of an 8-year-old female who developed a DRESS syndrome 5 weeks after starting CBZ did not have viral reactivation, but patch tests were positive for CBZ.¹⁴

In children, one of the major difficulties in the diagnosis of drug hypersensitivity is the differentiation of maculopapular eruption as an allergic reaction from a viral exanthema, which is very common. Peripheral blood eosinophilia may sometimes be helpful in the differentiation of drug reactions from viral infections. If an allergy is suspected, an allergy workup is recommended. Patch tests are a useful and safe tool for identifying the culprit drug for the DRESS syndrome.¹⁵

The most common causative agents in pediatric DRESS are antiepileptic drugs (50%), including carbamazepine, phenytoin, and phenobarbital.³ The aromatic ring in the chemical structure of carbamazepine leads to a higher risk of hypersensitivity reactions. Age-related differences in drug metabolism may result in increased hypersensitivity to antiepileptic drugs in young children.¹⁵

Human herpes virus HHV-6, HHV-7, herpes simplex virus, cytomegalovirus, and EBV reactivation have been associated with DRESS syndrome.^{16,17} The role of EBV in the pathogenesis of DRESS syndrome is still unclear. It is uncertain whether the commonly encountered viral infections during childhood play a role in or trigger hypersensitivity reactions to antiepileptic drugs in children.¹⁵ Viral infections may change drug metabolism or act as danger signals, leading to an immune response.¹⁸ Descamps et al¹⁹ proposed that EBV amplifies the T-cell

Table 1. Results of the RegiSCAR Scoring System

Items	Scoring for DRESS			Patient Results	Patient Score
	Yes	No	Unknown		
Fever $\geq 38.5^{\circ}\text{C}$	0	-1	-1	Yes	0
Enlarged lymph nodes	1	0	0	Yes	0
Eosinophilia $\geq 0.7 \times 10^9/\text{L}$	1	0	0	Yes	1
$\geq 1.5 \times 10^9/\text{L}$ or $\geq 20\%$	2			No	
Atypical lymphocytes	1	0	0	No	0
Skin rash $> 50\%$ BSA	1	0	0	Yes	1
Rash suggesting DRESS	1	-1	0	Yes	1
Skin biopsy suggesting DRESS	0	-1	0	Yes	1
Organ involvement (score 1 for each organ, maximal score: 2)	1	0	0	Yes	1
	2			No	
Rash resolution ≥ 15 days	0	-1	-1	No	0
Excluded other causes (≥ 3 tests of the following tests were negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture)	1	0	0	Yes	1
Final score*					6

ANA, anti-nuclear antibody; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus

* Final score < 2 : no case, final score 2–3: possible case, final score 4–5: probable case, and final score > 5 : definite case.

Table 2. Naranjo Adverse Drug Reaction (ADR) Probability Scale

Question	Yes	No	Do Not Know or Not Done	Score in Our Case
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score:				+7

Scoring of Naranjo algorithm: >9 = definite ADR; $5-8$ = probable; $1-4$ = possible ADR; 0 = doubtful ADR

activation induced by drugs and participates in developing visceral manifestations.

The concept that DRESS is no more than a viral disease triggered by a direct effect of drugs on virus reactivation and proliferation has been proposed.^{16,20} Immunosuppression from treating DRESS with corticosteroids could contribute to viral reactivations.²¹

Conclusion

Even though DRESS is rare in childhood, we present here another case of carbamazepine-induced DRESS in an adolescent associated with EBV activation and confirmed by a positive patch test. Clinicians should be aware of the severe adverse effects that could be induced by CBZ in pediatric patients.

Article Information

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Ethical approval and Informed consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. However, given the nature of this study, informed consent was not required by our institution.

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