A case of DRESS syndrome associated with carbamazepine treatment

Adem Dursun¹, Ayşe Kaçar Bayram², Nazan Ülgen Tekerek¹, Başak Nur Akyıldız¹, Hüseyin Per²

¹Erciyes University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care, Kayseri, Turkey

²Erciyes University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Kayseri, Turkey

Cite this article as: Dursun A, Kaçar Bayram A, Ülgen Tekerek N, Akyıldız BN, Per H. A case of DRESS syndrome associated with carbamazepine treatment. Turk Pediatri Ars 2018; 53: 48-50

Abstract

Fever and rash associated in a wide clinical spectrum, drug rash with eosinophilia and systemic symptoms syndrome (DRESS) is a potentially life-threatening hypersensitivity reaction. Early diagnosis and treatment and removal of the offending agent can be life-saving. Physicians should be aware of DRESS syndrome, particularly in patients receiving antiepileptic medication and admitted with a symptoms of fever and skin rash. In this study, a girl aged three years who had been under carbamazepine therapy for one month was admitted to our hospital with symptoms of fever and rash and was diagnosed as having DRESS syndrome, is presented to increase awareness of DRESS syndrome among physicians.

Keywords: Carbamazepine, DRESS, fever, rash

Introduction

The discovery of new medicines in medical science has led to some systemic and skin reactions. With use of the first antiepileptic drug hydantoin in the 1940s, lymph node enlargement (LNE) was observed and this was called 'drug-induced pseudolymphoma' (1). Subsequently, it was determined that fever, LNE, and rash developed in relation with carbamazepine and the term 'anticonvulsant hypersensitivity syndrome' was proposed (2). In subsequent years, this term was changed to 'drug-induced hypersensitivity syndrome' when it was understood that these symptoms did not only develop with anticonvulsant drugs, but also with various drugs including allopurinol, minocycline, dapsone and sulphasalazine (3). In 1996, 'drug rash with eosinophilia and systemic symptoms' (DRESS) syndrome was defined by Bocquet et al. (4) as a severe hypersensitivity syndrome characterized

by fever, skin rash, eosinophilia on peripheral blood smear, LNE, and internal organ involvement, which may be life-threatening but is observed extremely rarely.

The diagnosis of DRESS syndrome may be delayed because fever and rash occur in a broad spectrum of conditions including infectious diseases, rheumatic diseases, and allergic diseases, and the latent period following drug use may be prolonged. Difficulties and delays in the diagnosis and inability to establish an appropriate treatment plan increase morbidity and mortality rates.

In this article, a patient who presented with fever and rash was diagnosed as having DRESS syndrome, which might be confused with many conditions and may have fatal outcomes if treatment is delayed, is presented in order to increase awareness.

Address for Correspondence: Hüseyin Per E-mail: huseyinper@yahoo.com

Received: 26.11.2015

Accepted: 31.05.2016

©Copyright 2018 by Turkish Pediatric Association - Available online at www.turkpediatriarsivi.com

DOI: 10.5152/TurkPediatriArs.2017.3671

Case

A 3-year-old girl presented to our hospital with fever and a diffuse skin rash, which had been continuing for the last one week. In her detailed history, it was learned that the patient had used valproic acid in the last six months and carbamazepine was added to treatment one month ago because her seizures could not be controlled. On physical examination, her general status was moderate, her consciousness was clear, her body temperature was 39°C, her apical heart beat was 152 /min, her blood pressure was measured as 85/55 mm Hg, and her respiratory rate was found 35 /min. The patient had edema in her face and scalp. Her lips and tonsils were hyperemic and she had diffuse, confluent, maculopapular erythematous eruptions on her whole body, which faded when compressed. The Nikolsky sign was negative. Bilateral LNE (the largest one being 2 cm) was found in the submandibular region and the liver was palpable 3-4 cm below the right costal margin in the midclavicular line.

The laboratory findings were as follows: hemoglobin: 11.1 g/dL, white blood cells (WBC): 7130 /mm³, platelet count: 115,000/ mm³, total eosinophil count: 3540/mm³. In the biochemical tests, aspartate amino transferase (AST) (278 IU/L) and alanine aminotransferase (ALT) (148 IU/L) were found to be increased, whereas serum electrolytes, bilirubin, alkaline phosphatase, total protein, albumin, gamma glutamyl transpeptidase and renal function tests were found to be normal. C-reactive protein was found as 18.5 mg/L, the erythrocyte sedimentation rate was 12 mm/hour, and anti-neutrophil antibodies were found to be negative. Complete urinalysis was found to be normal and growth did not occur in throat, blood, and urine cultures. Cytomegalovirus, parvovirus B19, Epstein-Barr virus, hepatitis A, B, C, and mycoplasma tests were found to be negative. Lung imaging was found to be normal. On abdominal ultrasonography, the liver was found to have increased dimensions and the liver parenchyma was normal. When the patient was evaluated according to the Registry of Severe Cutaneous Adverse Reactions scale (Regi-SCAR), the total score was found to be 7 and a definite diagnosis of DRESS syndrome was made.

Carbamazepine and valproic acid were discontinued and intensive methylprednisolone (at a dose of 20 mg/kg for three days) was initiated and a maintenance treatment with a dose of 2 mg/kg/day was applied. Plasmapheresis was applied to the patient twice when her eruptions did not fade and her clinical status did not improve at the end of the third day. The eruptions decreased on the

day when plasmapheresis was performed and increased 24 hours later. Thereupon, intravenous immunoglobulin (IVIG) was given at a dose of 600 mg/kg/day for a total of five days. Her clinical status improved on the 8th day of treatment and the patient was discharged on the 20th day.

Discussion

DRESS syndrome is a severe drug hypersensitivity reaction that is rarely observed in childhood and has a mortality rate ranging between 10% and 40% (5). The etiology of the disease has not been elucidated fully. However, the most commonly adopted explanation is deficiency of epoxide hydrolase, which is the enzyme responsible for detoxification of drugs in the liver. Arena oxidase is a harmful by-product formed in the metabolism of aromatic anticonvulsants including carbamazepine, phenytoin and phenobarbital. It is thought that cellular damage and immune response occur in relation with accumulation of this harmful by-product in patients with defective epoxide hydrolase or in patients with epoxide hydrolase deficiency (3). The clinical picture that emerged in our patient was thought to be related with carbamazepine, which was added to treatment in the final period.

DRESS syndrome occurs in a broad clinical spectrum. The symptoms frequently occur 3 weeks-3 months after drug use (6). The most common causes of presentation include high fever (up to 38-40°C) (90-100%) and rash (87%) (7). It has been reported that skin lesions described in patients with DRESS syndrome are maculopapular and may be observed as erythroderma with a lower rate. The lesions frequently begin on the face and upper extremities and show extension to the lower extremities. Necrosis, which is observed in toxic epidermal necrolysis, is not observed in DRESS syndrome. In addition, the fact that the latent period after drug use is long is important in the differential diagnosis with other drug reactions. Edema in the face is a notable sign of the disease (3). In our patient, the initial symptoms included fever and a maculopapular rash and edema in the scalp and face, which is observed rarely, was also accompanying the picture. Hepatic, renal and lung involvement, and LNE are the systemic symptoms that occur in DRESS syndrome. Enlargement of lymph nodes is one of the diagnostic criteria and is observed commonly (70-75%) to the accompaniment of pain. It has been reported to regress with discontinuation of the relevant drug (7). The most common internal organ involvement is with the liver, which occurs in 50-93.8% of patients. One of the most important causes of death

is liver failure (8). LNE, hepatomegaly, and increased transaminases were observed and renal function tests, respiratory system, and cardiovascular system examinations were found to be normal in our patient. The laboratory findings observed in DRESS syndrome include some hematologic disorders. The most common hematologic disorder is eosinophilia with rates reaching up to 95%. In addition, atypical lymphocytes, anemia, leukocytosis, and thrombocytopenia may also accompany (9). An eosinophil count above 1500 /mm³ is considered significant according to the RegiSCAR scoring system. Our patient had a total eosinophil count of 3540 /mm³. Although a reduction in the platelet count was found, anemia or atypical lymphocytes were not found.

The basic step in treatment of the disease is immediate discontinuation of the suspected drug or drugs (10). Although the suspicious drug in our patient was carbamazepine, valproic acid was also additionally discontinued. Systemic corticosteroids (1-1.5 mg/kg/day) usually provide improvement in physical examination and laboratory findings. In resistant cases, intensive methylprednisolone (30mg/kg/day), intravenous immunoglobulin, and plasmapheresis may be tried or these treatment options may be used in combination (3). Intensive methylprednisolone, IVIG and plasmapheresis were applied in combination in our patient because she did not respond to supportive treatment, systemic involvement was present and her general status was not good.

In conclusion, the diagnosis of DRESS syndrome is frequently delayed because it occurs in a broad clinical spectrum and its latent period is prolonged. DRESS syndrome should be kept in mind in the differential diagnosis especially in patients who use anticonvulsant medication and present with fever and rash. The awareness of DRESS syndrome among physicians should be increased and morbidity and mortality rates will decrease with early diagnosis and treatment.

Informed Consent: Written informed consent was obtained from patient's parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.D., H.P.; Design - H.P., A.K.B.; Supervision - B.N.A., N.Ü.T.; Funding - H.P., A.D.; Materials - A.D., H.P., B.N.A.; Data Collection and/or Processing

- A.K.B., N.Ü.T.; Analysis and/or Interpretation - A.D., A.K.B.; Literature Review - H.P., B.N.A.; Writing - A.D.; Critical Review - H.P., B.N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Choudhary S, McLeod M, Torchia D, Romanelli P. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. *J Clin Aesthet Dermatol* 2013; 6: 31-7.
2. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995; 155: 2285-90. [\[CrossRef\]](#)
3. Criado PR, Criado RF, Avancini JM, et al. Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) / Drug-induced Hypersensitivity Syndrome (DIHS): a review of current concepts. *An Bras Dermatol* 2012; 87: 435-49. [\[CrossRef\]](#)
4. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudo-lymphoma and drug hypersensitivity syndrome Drug Rash with Eosinophilia and Systemic Symptoms: DRESS. *Semin Cutan Med Surg* 1996; 15: 250-7. [\[CrossRef\]](#)
5. Ganeva M, Gancheva T, Lazarova R, et al. Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: report of four cases and brief review. *Int J Dermatol* 2008; 47: 853-60. [\[CrossRef\]](#)
6. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int* 2006; 55: 1-8. [\[CrossRef\]](#)
7. Gentile I, Talamo M, Borgia G. Is the drug-induced hypersensitivity syndrome (DIHS) due to human herpesvirus 6 infection or to allergy-mediated viral reactivation? Report of a case and literature review. *BMC Infect Dis* 2010; 10: 49-54. [\[CrossRef\]](#)
8. Knowles SR, Dewhurst N, Shear NH. Anticonvulsant hypersensitivity syndrome: an update. *Expert Opin Drug Saf* 2012; 11: 767-78. [\[CrossRef\]](#)
9. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. RegiSCAR study group. Drug reaction with eosinophilia and systemic symptoms (DRESS): An original multy system adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013; 169: 1071-80. [\[CrossRef\]](#)
10. Bayram AK, Canpolat M, Çınar SL, et al. Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome Induced by Levetiracetam in a Pediatric Patient. *J Emerg Med* 2016; 50: e61-6. [\[CrossRef\]](#)