Carbamazepine-induced DRESS syndrome leading to reversible myocarditis in a child

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Abstract

DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is a rare type of delayed drug hypersensitivity reaction characterised by fever, skin rash, lymphadenopathy, and visceral involvement, which can be life threatening and is a childhood event. An eight-year-old boy was admitted with complaints of extensive rash and fever three weeks after the onset of treatment with carbamazepine for a diagnosis of epilepsy. Fever, as well as patches and plaques with indeterminate limits that tended to merge and were non-blanchable on a widespread erythematous layer, were revealed in physical examination. Extensive cervical, submandibular, and inguinal lymphadenopathy was observed. We present ours as the second case of myocarditis secondary to DRESS syndrome after carbamazepine use in the literature.

Key words: carbamazepine, DRESS syndrome, lymphadenopathy, myocarditis.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but life-threatening reaction to drugs such as phenytoin, phenobarbital, carbamazepine, valproate, and allopurinol. The disease is characterized by skin rashes, fever, haematological abnormalities, lymphadenopathy, and organ failure such as hepatic dysfunction [1]. Carbamazepine is widely used as an anti-epileptic agent in paediatric neurology patients. In the literature there have been many reports showing adverse reactions due to the carbamazepine usage. However, there is only one case reported in the literature that shows myocarditis secondary to DRESS syndrome after carbamazepine use [2]. Herein we present ours as the second case of myocarditis secondary to DRESS syndrome after carbamazepine use in the literature.

Case presentation

The patient was admitted to Yuzuncu Yil University medical faculty paediatric outpatient clinic with complaints of a sudden rash initially on his hands and then spreading all over his body, with a fever of 39°C and pruritus about a week earlier. The patient was admitted to our hospital in Van, Turkey in January 2017. Our hospital is a university referral hospital that serves about one million people. The hospital has 670 beds with six paediatric clinical sections. The patient was an eight-year-old boy. On his medical history, carbamazepine was started due to a diagnosis of epilepsy about four weeks earlier. In the patient’s physical examination a temperature of 39.2°C, heart rate of 123 beats/minute, respiratory rate of 23 breaths/minute, blood pressure of 105/60 mmHg, and O2 saturation of 95% were measured. There were common millimetric lymph nodes in bilateral cervical and inguinal regions. There were patches and plaques with indeterminate limits that tended to merge and were non-blanchable on a widespread erythematous layer in the physical examination (Fig. 1).

In the laboratory review of the patient the following were reported: no hepatosplenomegaly was observed,

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haemoglobin 12.9 gr/dl, leucocytes 14 400/mm³, thrombocytes 433 000/mm³, 30% neutrophil in peripheral spread, 12% stab neutrophil, 44% lymphocytes, 4% monocytes, 16% eosinophil, total eosinophil count 2300/mm³, AST 72 IU/l, troponin I 1.7 ng/ml (normal value: < 0.04 ng/ml), CK-MB 72.5 ng/ml, and CRP 21 mg/dl. Serological studies of Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis A, B, and C, and mycoplasmula were normal. Chest radiography was normal. Electrocardiography revealed sinus tachycardia. Table 1 shows the clinical characteristics and variables of our case. An echocardiogram revealed global hypokinesis, mild mitral regurgitation, and decreased contractility (LV ejection fraction 47%, fractional shortening 23%) consistent with the diagnosis of myocarditis (Fig. 2). A skin biopsy was performed, which demonstrated an inflammatory infiltrate that was predominantly perivascular and lymphocytic in nature (Fig. 3).

The patient was diagnosed with DRESS syndrome and secondary myocarditis, according to both the biopsy results and the RegiSCAR study group scoring system criteria in Table 2. He was treated with methylprednisolone 2 mg/kg/day and diphenhydramine 1 mg/kg i.v. q6h. After carbamazepine was discontinued and the second day of the initiation of the treatment, the clinical symptoms and the general condition improved. Eruptions were completely resolved within seven days. The patient received a total of 45 days of steroid treatment. After two months, echocardiogram showed normal cardiac contractility.

**Discussion**

DRESS syndrome, which is a drug eruption syndrome accompanied by eosinophilia and systemic symptoms, is a febrile dermatosis with cutaneous and visceral organ involvement that can develop in both paediatric and adult patients, which is a rare condition among drug eruptions, and it can be fatal [1]. For the first time, in 1950 Chaiken et al. reported a case of fever, morbilliform rash, and hepatitis developing in a patient using phenytoin, and they named the illness phenytoin hypersensitivity. Then in 1996, Bocquet et al. defined it as DRESS, an abbreviation based on clinical and laboratory findings [3].

Although the aetiology of DRESS syndrome is not fully understood, many drugs are blamed, but it is thought to be a drug reaction that is most often caused by aromatic anticonvulsants [4-6]. Yang et al. reported that carbamazepine and phenytoin, which are anticonvulsant medications, were responsible for 43.6% of all DRESS syndrome cases [7]. Patients with a genetic predisposition develop a severe hypersensitivity reaction within two months of using these drugs (average of 2-6 weeks), and this reaction continues for a long time.

![M-mode echocardiography showing systolic dysfunction](image1)

![Showed various degrees of basal vacuolization, dyskeratosis, infiltration of the epidermis by lymphocytes, dermal edema, superficial perivascular inflammation](image2)

![Table 1. The clinical characteristics and variables of our case](table1)
Table 2. Diagnostic criteria for DRESS syndrome [3]

| Borquet et al. | RegiSCAR study group | Japanese consensus group |
|----------------|----------------------|-------------------------|
| DRESS is confirmed by presence of 1 and 2 and 3 | More than 3 of the criteria are required for the diagnosis of DRESS | Typical DRESS (presence of all 7 criteria): atypical DIHS (all criteria present except lymphadenopathy and HHV-6 reactivation) |
| 1. Cutaneous drug eruption | 1. Hospitalisation | 1. HHV-6 reactivation |
| 2. Adenopathies > 2 cm in diameter of hepatitis (liver transaminases > 2 times upper limit of normal) (or) interstitial nephritis (or) interstitial pneumonitis (or) carditis | 2. Reaction suspected to be drug related | 2. Prolonged clinical symptoms 2 weeks after discontinuation of causative drug |
| 3. Haematological abnormalities; eosinophilia > 1.5 x 10^9/l (or) atypical lymphocytes | 3. Acute rash | 3. Maculopapular rash developing > 3 weeks after starting drug |
| | 4. Fever above 38°C | 4. Fever above 38°C |
| | 5. Enlarged lymph nodes involving at least two sites | | |
| | 6. Involvement of at least one internal organ | 5. Lymphadenopathy | |
| | 6. Blood count abnormalities | 6. ALT > 100 U/l or other organ involvement | |
| | Lymphocytes above or below laboratory limits | 7. Leukocyte abnormalities (at least one) | |
| | Eosinophils above laboratory limits (in percentage or absolute count) | Leucocytosis (> 11 x 10^9/l) | |
| | Platelets below laboratory limits | Atypical lymphocytosis (> 5%) | |
| | | Eosinophilia (1.5 x 10^9/l) | |

DRESS – drug rash with eosinophilia and systemic symptoms, RegiSCAR – European registry of severe cutaneous adverse reactions, DIHS – drug-induced hypersensitivity syndrome, HHV-6 – human herpesvirus 6, ALT – alanine aminotransferase
In conclusion, DRESS syndrome is an uncommon drug reaction in childhood, which could be fatal if not treated. It should be considered in the differential diagnosis of patients with common rash with medication use in anamnesis. Although DRESS syndrome is rare, it is a clinical condition that should be considered as a fatal disease in cases of reuse of the same group of drugs, and it should be promptly recognised and dealt with because of frequent use of the anticonvulsants in many diseases. We think that reporting this case is important because DRESS syndrome is seen very rarely, and ours is the second case with cardiac involvement in the literature.

The authors declare no conflict of interest.

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