CASE REPORT

A case report of drug rash with eosinophilia and systemic symptoms in a patient using carbamazepine

Amin Zand, Shahid Beheshti University of Medical Sciences, Tehran, Iran

.

Email: sandpost3@gmail.com

Date Received: Feb, 2017 *Date Accepted: March, 2017* *Online Publication: December 21, 2017*

Abstract

Drug rash with eosinophilia and systemic symptoms (DRESS) is a critical type of drug reaction with signs such as fever, skin rash, lymphadenopathy, hematological abnormalities particularly eosinophilia, and internal organ involvement like hepatitis two to eight weeks after a drug is first used. The present case is an example of hepatitis as a manifestation of drug reaction with eosinophilia and systemic symptoms syndrome.

Case Presentation

A 17 year-old man is reported as a known case of epilepsy from childhood, who presented anti-epileptic-induced "drug reaction with eosinophilia and systemic symptoms syndrome" with a seven-day history of pruritic rash, periorbital, face and upper extremities edema, hepatitis and fever was admitted at Loghman Hakim Hospital in Tehran, Iran in December, 2015. Laboratory tests showed an eosinophilia and elevated serum liver enzymes. The patient's history showed no drug allergies, but five weeks prior to hospital admission, his therapy regimen had been changed from sodium-valproate to carbamazepine. Carbamazepine was discontinued on hospital admission, and after nine days of high-dose corticosteroid therapy the patient's symptoms and laboratory markers were stable.

Conclusion

Given the high morbidity and mortality rate of DRESS syndrome, physicians should bear in mind this severe hypersensitivity reaction particularly when starting anti-epileptic drugs. Early diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome and initiation of appropriate treatment plays a key role in limiting morbidity and mortality.

Keywords

DRESS syndrome, Hypersensitivity reaction, Rash, Hepatitis, Anti-epileptic, Carbamazepine

Introduction

Bocquet and colleagues in 1996 first presented drug reaction with eosinophilia and systemic symptoms (DRESS). The clinical manifestations include an extensive rash, fever, lymphadenopathy, hematologic disorders like eosinophilia or atypical lymphocytes, hepatitis, and involvement of other internal organs like kidneys, lungs, heart or pancreas (1). The onset of symptoms is often delayed, occurring 2–8 weeks after drug initiation (2). The occurrence of this syndrome is rare. DRESS syndrome is a potentially life-threatening hypersensitivity reaction associated with a variety of medications, particularly anti-epileptic drugs (3). In a study by Ganeva, et al. (4) four cases of DRESS syndrome associated with the use of carbamazepine was reported. In this study the four cases had similar clinical manifestations: a maculopapular eruption progressing to exfoliative erythroderma, fever, and lymphadenopathy. Leukocytosis, atypical lymphocytes and liver injury (in 2 patients) were also observed. The importance of this syndrome and specifically the present case is that:

1. DRESS syndrome is an idiosyncratic drug reaction and is not dependent on the dose of the drug (5).
2. DRESS syndrome has been found to be the major cause of hospitalization for dermatologic complications in patients treated with anticonvulsants (4).
3. Carbamazepine is one of the drugs that has been widely prescribed for epileptic patients, and its adverse side effects such as the DRESS syndrome needs to be studied.
4. Despite the fact that some medications such as corticosteroids can reduce symptoms of delayed hypersensitivity reactions, the only way to treat these reactions is prompt withdrawal of the offending drug (5).

Presentation

A 17 year-old man presented with a seven-day history of pruritic and scaling maculopapular rash and erythroderma with associated periorbital, face and extremities edema, fever, and elevated serum level of transaminases was admitted at Loghman Hakim hospital in Tehran, Iran in December, 2015. He reported having, seven days prior to presentation, pruritic and scaling rash over his face and chest, which progressed to his extremities over the next days. He had a history of brain disorder from childhood compatible with encephalomalacia in the left temporal lobe due to an old ischemic lesion as shown in his brain MRI and suffered from epilepsy that began 12 years ago. He had been treated with sodium-valproate, which was tapered off and changed to carbamazepine 400mg twice a day from 5 weeks prior to his present admission. He had mildly reduced verbal and reading skills since childhood. The patient had no other significant past medical history, drug hypersensitivity, or alcohol or other substance use. Review of systems was positive for a few productive coughs, a sore throat and fever and negative for chest pain, dyspnea, abdominal pain, nausea, vomiting and weight-loss.

On examination, the patient was febrile to 39.0°C with a heart rate of 104 beats/minute, respiratory rate of 18/minute, and blood pressure of 120/70mmHg. The patient's general appearance was well and he was oriented. A fine exanthematous rash was noted on the face, chest, upper (Figure 1) and lower limbs (Figure 2) especially in distal areas without significant involvement of the oral mucosa, palms, or soles. He had periorbital edema that prevented him from opening his eyes well (Figure 3), which was a notable sign in this case. His abdomen was soft and non-distended with no tenderness or hepatomegally. On neurological examination no focal deficits or other abnormal signs were detected. The differential diagnosis of the current presentation are drug-induced hypersensitivity, erythema multiforme, an exanthem caused by viral infections such as Epstein–Barr virus (EBV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV), vasculitis and auto-immune diseases like systemic lupus erythematosus (SLE).

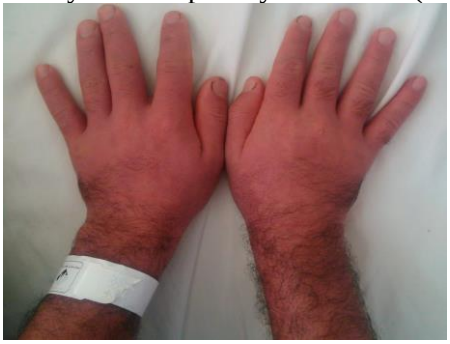

Figure 1. A fine exanthematous rash on the upper limbs.

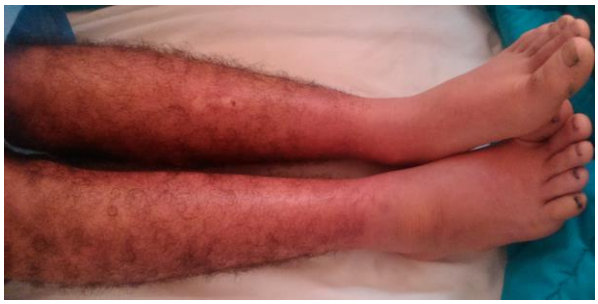

Figure 2. Macular rash with erythroderma on the lower limbs.

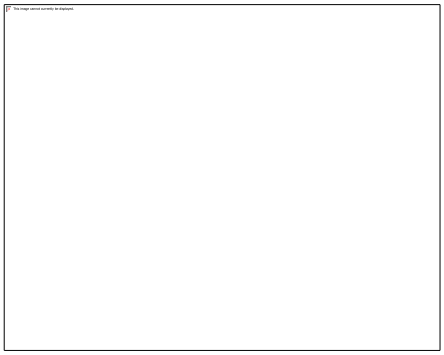

Figure 3. Periorbital edema with mild erythema.

Laboratory findings revealed a white blood cell count of 7.6 thousand/mm3 (normal from 4 to 10 thousand/mm3), with 65% neutrophils, 27% lymphocytes, 4% eosinophils (absolute 0.30 thousand/mm) and 3% monocytes. His basic metabolic lab tests were within normal limits. Liver function tests showed an aspartate aminotransferase (AST) of 149 U/L (normal from 0 to 37), and alanine aminotransferase (ALT) of 254 U/L (normal from 0 to 41). Also, blood cultures were measured twice, which were negative. Evaluations for viral hepatitis with serologies were negative for A, B and C types. HIV testing was negative. Screening for systemic lupus erythematous was done by measuring serum level of antinuclear antibodies (ANA), which was negative. We also requested cardiology consultation for investigation of probable cardiac disorders particularly myocarditis that was performed but ECG and echocardiography did not show any pathologic disorders. The patient was admitted with a diagnosis of drug-induced hypersensitivity. Carbamazepine was discontinued and the patient was monitored for signs of clinical and laboratory improvement.

On the first day of hospitalization, carbamazepine was discontinued and the patient's periorbital and facial swelling deteriorated. Serum level of transaminases began to increase. A repeat complete blood count (CBC) showed eosinophilia at 8.0%. We started prednisolone 20mg orally two times daily to control his deteriorating condition. On the second day, a punch biopsy was taken from the skin of the forearm, which showed a vasculopathic lichenoid reaction pattern compatible with drug reaction (

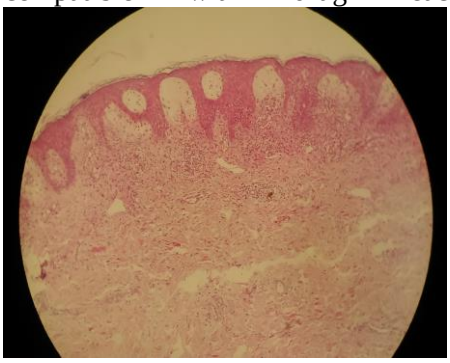

Figure **4**). On the third day, the patient showed a significant clinical recovery from swelling and the rashes were reduced. On the fourth day his levels of transaminases began to improve, and by day 9 his transaminases had greatly improved and prednisolone was tapered to 30mg daily and he was discharged on prednisone 30 mg to be taken once a day until follow-up. After discontinuation of carbamazepine and the administration of prednisolone, the patient showed a dramatic improvement in clinical symptoms, signs and lab tests.

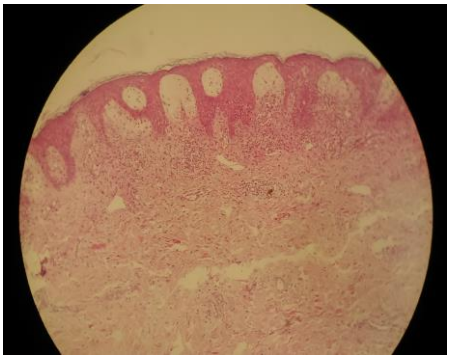

Figure 4. A skin punch biopsy microscopic view showing a non-specific vasculopathic lichenoid reaction pattern to drug (carbamazepine).

Discussion

DRESS syndrome can occur with any medication but the aromatic anticonvulsants (such as phenytoin, phenobarbital and carbamazepine) and sulphonamides are the most common causes of this syndrome (2, 3). Also, according to some case reports allopurinol (6) and dapsone (7) can cause this syndrome, too. The incidence is about one in 1000 to one in 10,000 in reaction to drug (8) and has no age or sex tendency (9).

The pathogenesis of DRESS syndrome is not completely clear. However, three potential factors have been found in its pathogenesis: first, a defect in a drug metabolism pathway that can lead to a failure of toxic reactive intermediates elimination, second, reactivation of human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7), Epstein-Barr virus (EBV), or cytomegalovirus (CMV), which may provoke the reaction, and third, genetic factors that affect immune responses (1, 8, 10, 11). Vitamin D deficiency is a possible factor in the pathogenesis of DRESS due to its protective role against inflammatory and auto-immune disorders, and because its deficiency is more common in people with darker skin phenotypes (12).

The Severe Cutaneous Adverse Reactions (RegiSCAR) study group in 1996, Kardaun et al. (13), introduced a scoring system, which has been commonly used to evaluate potential cases of DRESS syndrome (table 1). The patient in this case report had a score of six points, indicating a 'definite case' (table 1).

Table1. Patient's score according to RegiSCAR scoring system.

RegiSCAR Scoring System	Patient's Data	Patient's Score
Fever: > 38.5°C	Fever: 39°C	**1**
Enlarged lymph nodes	No Lymphadenopathy.	**0**
Eosinophilia	Eosinophilia: 8%	**1**
Atypical lymphocytosis	Without atypical lymphocytosis.	**0**
Skin involvement	A fine exanthematous rash was noted on the face, chest, upper and lower limbs.	**1**
Organ involvement	Liver involvement with presentation of elevated liver enzymes (AST: 149 U/L, ALT: 254 U/L).	**1**
Resolution: > 15 days	Prolonged resolution about 3 weeks.	**1**
Evaluation of other causes (ANA, blood cultures, serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, and chlamydia and/or mycoplasma)	ANA: Negative. Blood cultures at two times were negative. Evaluation for viral hepatitis with serologies was negative for A, B and C types. HIV testing was negative.	**1**
Each of the components of this criteria has 1 score; A final score of: < 2 indicates no case, 2-3 indicates a possible case, 4-5 indicates a probable case, > 5 indicates a definite case.		**Final Score of this Patient: 6 (Definite case)**

Cabrera Fundora EJ, et al. (14) reported a female patient under prescription for carbamazepine for trigeminal neuralgia who presented with skin lesions, which were initially attributed to a hypersensitivity reaction. The lesions worsened in spite of treatment and systemic symptoms ensued. A diagnosis of DRESS syndrome was proposed and steroid treatment was initiated with rapid improvement. The clinical manifestations of

our case and the response found to treatment with steroids were similar to the study by Cabrera Fundora EJ, et al (14).

In managing severe hypersensitivity drug reactions the main treatment is the discontinuation of the probable causative drug. Therefore, the earlier the drug is withdrawn, the prognosis would be better. Systemic corticosteroids are traditionally prescribed in cases with severe conditions such as transaminases greater than five times normal, renal involvement, pneumonia, hemophagocytosis, or cardiac involvement. Other immune suppressants, such as cyclosporine, may also be required (15). In the absence of specific treatment, preventive measures have a key role in the management of DRESS syndrome (16).

Conclusion

The diagnosis of DRESS syndrome must be considered probable in patients with the following signs: skin rash, fever, hepatic involvement, eosinophilia and lymphadenopathy particularly when prescribing any anti-epileptic medication. Early diagnosis of DRESS syndrome is of great importance, since the mortality rate may be up to 10%. After the diagnosis there must be immediate intervention to control life-threatening complications. Reactivation of HHV-6, is one of the potential causative factors in pathogenesis of DRESS syndrome. Thus, the French Society of Dermatology recommended the prescription of steroids with ganciclovir in patients with severe conditions who have a high level of viral reactivation of HHV-6 (17). Sufficient studies about DRESS syndrome using sensitive paradigms like randomized control trials (RCT) have not been done. Thus, further studies are needed to formulate new treatment guidelines for the present syndrome.

Conflict of interests

Authors declare no conflict of interests.

References:

1. Bocquet H BM, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity (Drug rash with eosinophilia and systemic symptoms: DRESS). Sem Cutan Med Surg. 1996;1:250–7.
2. Shiohara T IM, Ikezawa Z, Hashimoto K. The diagnosis of DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Response Br J Dermatol 2007;156:1045-92.
3. Peyrière H DO, Breton H, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2006;155:422-8.
4. Ganeva M GT, Lazarova R, Troeva J, Baldaranov I, Vassilev I, Hristakieva E, Tzaneva V. Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: report of four cases and brief review. International Journal of Dermatology. 2008 Aug;47(8):853-60.
5. Cláudia Sofia Cardoso AMV, and Ana Paula Oliveira. DRESS syndrome: a case report and literature review. BMJ Case Reports 2011 Jun 3.
6. Yaylacı S, Demir MV, Temiz T, Tamer A, Uslan MI. Allopurinol-induced DRESS syndrome. Indian J Pharmacol. 2012 May-Jun;44(3):412-4.
7. Vinod KV, Arun K, Dutta TK. Dapsone hypersensitivity syndrome: A rare life threatening complication of dapsone therapy. J Pharmacol Pharmacother 2013 Apr-Jun;4(2):158-60.
8. Cacoub P MP, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med. 2011;124(7):588-97.
9. Bosdure E CA, Roquelaure B, Reynaud R, Boyer M, Viard L, et al. Oxcarbazepine and DRESS syndrome: a paediatric cause of acute liver failure. Arch Pediatr. 2004;11(9):1073-7.
10. Walsh SA CD. Drug reaction with eosinophila and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin Exper Dermatol. 2010;36:6-11.
11. Criado PR CR, Avancini J, 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.
12. Ben m'rad M L-MS, Blanche P, Franck N, Rozenberg F, Fulla Y, Guesmi M, Rollot F, Dehoux M, Guillevin L, Moachon L. Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. Medicine (Baltimore). 2009;88:131-40.
13. Kardaun SH SA, Valeyrie-Allanore L, et al. Response to Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? [letter to the editor]. Br J Dermatol. 2007;156:575-612.
14. Cabrera Fundora EJ COY, Cabrera Osorio C. Skin reaction to carbamazepine or DRESS syndrome: a case presentation. Medwave. 2016 Feb 25;16(1).
15. Zuliani E, Zwahlen H, Gilliet F, Marone C. Vancomycin-induced hypersensitivity reaction with acute renal failure: resolution following cyclosporine treatment. Clin Nephrol. 2005;64:155-8.
16. Simonart STT. Management of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome): An Update. Dermatology 2003;206:353-6.
17. Descamps V SB, Truchetet F, Avenel-Audran M, Girardin P, Guinnepain MT, Mathelier-Fusade P, Assier H, Milpied B, Modiano P, Lebrun-Vignes B, Barbaud A. groupe Toxidermies de la Société française de dermatologie: Management of drug reaction with eosinophilia and systemic symptoms (DRESS). Ann Dermatol Venereol. 2010;137:703-8.