New Emirates Medical Journal

Content list available at: https://newemiratesmedicaljournal.com

CASE REPORT

EBV Reactivation in A Case of DRESS Syndrome Associated with Lamotrigine: A Case Report

Mahmoud Ahmed Kiblawi[1,*], Mohamad El Saleh[1] and Ashraf El Ghul[1]

[1]*Department of Internal Medicine, Sheikh Shakhbout Medical City, Abu Dhabi, UAE*

Abstract:

Background:

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a rare, T-cell mediated hypersensitivity reaction that develops secondary to a drug reaction. Several drugs have been associated with DRESS syndrome, most commonly carbamazepine. The mechanism is not clearly understood. It is a life-threatening condition that can present with skin rash, hematologic abnormalities, lymphadenopathy, and organ failure.

Case Presentation:

The authors report a case of 43-year-old gentleman who developed DRESS syndrome secondary to lamotrigine and was found to have EBV reactivation. Patient was managed with supportive care; topical steroids and the culprit drug were discontinued. He had full recovery almost 2 weeks following treatment. DRESS syndrome can occur 2 weeks following exposure to an offending drug in susceptible individuals.

Conclusion:

Lamotrigine and EBV reactivation are not frequently reported in patients with DRESS syndrome. Therefore, physicians should be vigilant about this rare drug related hypersensitivity reaction in order to prevent life threatening complications.

Keywords: DRESS Syndrome, Lamotrigine, EBV reactivation, Drug reaction, Hypersensitivity reaction, Rash.

Article History	Received: September 13, 2021	Revised: November 14, 2021	Accepted: December 17, 2021

1. INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a rare, potentially life-threatening condition that arises due to a drug reaction and includes skin rash, hematologic abnormalities, lymphadenopathy, and internal organ involvement [1]. The incidence is unknown. A study done in a West Indian general population suggested an incidence of 0.9/100,000 [2]. A total of 44 drugs were associated to DRESS syndrome in a literature review published in the American Journal of Medicine in 2011 [3]. Out of 172 analysed cases, the most frequently associated drugs in "probable", or "definite" cases were carbamazepine (34 cases), allopurinol (12 cases), sulfasalazine and phenobarbital (7 cases each), and lamotrigine (4 cases) [3].

An association has been found between DRESS syndrome and some viral infections such as Human Herpes Virus 6 (HHV -6) and Epstein Barr Virus (EBV) [4]. However, this association remains unclear and active viremia is not included as a criterion for the diagnosis of DRESS syndrome. The role of viral reactivation remains in debate in the context of DRESS syndrome.

In this case report, we will be presenting the case of a patient who was admitted to our service with DRESS syndrome due to exposure to lamotrigine, with evidence of reactivation of Epstein Barr virus.

2. CASE PRESENTATION

This is a 43-year-old gentleman who presented to the Emergency Department complaining of fever for 2 days duration. It was associated with a diffuse erythematous maculopapular rash all over the trunk and bilateral upper limbs. He denied any history of cough, shortness of breath, headache, vomiting, neck pain, or visual disturbances. He had normal bowel and bladder function. There was no history of exposure to new objects at home or work. He did not suffer any insect

* Address correspondence to this author at the Department of Internal Medicine, Sheikh Shakhbout Medical City, Abu Dhabi, UAE; E-mail: ma7moud@live.ca

bite. He did not have any previous history of allergy to drugs, food, or other items. Patient had past medical history of uncontrolled epilepsy for which he takes antiepileptic medications. These are valproic acid, levetiracetam, and recently just 2 weeks before hospital presentation, lamotrigine was added at his last neurology clinic visit. He was not on other medications. He has no significant family or social history.

Upon examination, the patient had a documented high-grade fever of 38.7°C. Other vital signs (heart rate, blood pressure, respiratory rate) were within normal limits. His general and systemic physical examinations were normal, apart from the mentioned maculopapular rash. Meningeal signs were negative.

Initial laboratory studies were significant for a platelet count of 71 x 10^9/L, lymphocyte 0.97 x 10^9/L, creatinine of 121µmol, aspartate aminotransferase and alanine aminotransferase of 128 IU/L and 188 IU/L respectively, and C-reactive protein 50 mg/L. His white cell count and hemoglobin levels were within normal limits. Blood film did not show any leukemic blast or dysplastic cells. Screening for Coronavirus Disease 19 (COVID-19) by polymerase chair reaction (PCR) was negative and X-ray of the chest was normal.

Patient was admitted to the Internal Medicine service with the impression of acute viral illness, acute kidney injury, hyperkalemia, and transaminitis. Also, acute skin eruption secondary to viral illness *vs*. drug-related reaction to lamotrigine that was recently started. He was managed supportively, and lamotrigine was held on admission.

Following admission, he was initiated on Clobazam following neurology evaluation. His workup showed EBV IgM and IgG capsid antigen positive. Also, EBV nuclear antigen IgG positive. Other labs included human immunodeficiency virus, hepatitis screening, parvovirus, and cytomegalovirus were negative. His blood and urine cultures were negative. His respiratory pathogen panel came back negative. He had ultrasound of the abdomen which was reported normal.

Patient was also seen by the dermatology team and underwent a skin biopsy. He was started on clobetasol propionate 0.05% topical cream and levocetirizine. The final pathology report was suggestive of features consistent with a drug eruption.

During the patient's stay in the hospital, liver function was monitored daily, and it was trending down after discontinuing the lamotrigine. The fever was resolved with supportive care. Creatinine and potassium level normalized with intravenous hydration. His rash subsided 4 days following treatment. Patient was discharged with the instructions of continuing levetiracetam, valproic acid, clobazam, antihistamine as needed, and topic steroids. He was advised to discontinue lamotrigine and follow up after a week in the clinic.

Patient was seen in the Neurology Clinic several times post discharge. His seizures were controlled, and the rash had completely resolved. Repeat labs were done showing normalization of liver function tests and platelet level after 12 days of initial presentation. Patient was doing well overall, and he continued to follow-up regularly with neurology team.

3. DISCUSSION

The association between DRESS syndrome and lamotrigine has rarely been mentioned in the literature. Also, there are no reports to link lamotrigine directly to viral re-activation. However, the reactivation of viral infection in the context of active DRESS syndrome has been reported but the pathogenesis of DRESS syndrome is not completely understood.

DRESS syndrome is a T cell mediated hypersensitivity reaction occurring in susceptible individuals [5]. Studies have shown that there is a marked expansion of T-cells during the acute phase of a severe drug reaction [6]. The effect of the drug on the T-cell antigen-recognition pathway or directly on the T cell receptor stimulates CD4/CD T cells leading to an autoimmune sequela [7]. Studies have also shown that reactivation of some viruses, especially the Herpesviridae family, most commonly HHV-6, may be implicated in the development of immune mediated reactions to anticonvulsant drugs, and DRESS syndrome [8]. Furthermore, latent virus reactivation may occur secondary to the abnormal immune response triggered by the drug effect. This viral reactivation leads to CD8+ immune response that increases the severity of DRESS syndrome [3, 7]. Herpes virus can reactivate 2-4 weeks in patients who develop clinical features of DRESS syndrome [9]. This relates to our patient who was diagnosed with DRESS syndrome 2 weeks after starting lamotrigine and had EBV reactivation at the time of diagnosis.

Other proposed mechanisms include genetic predisposition in susceptible individuals. It is reported that DRESS can occur in patients with genetic deficiency in detoxifying enzymes resulting in drug metabolites accumulation and activation of T cells leading to autoimmune reaction [10, 11]. Furthermore, there is a genetic link between certain drugs and human leukocyte antigen in the development of DRESS syndrome. For example, the presence of the HLA-A*31:01 allele is strongly associated with carbamazepine-DRESS syndrome especially in European and Asian populations [12].

The mortality rate for DRESS syndrome is estimated to be between 5-10%, with the major cause of death being profound shock [3, 5, 13]. Other complications of DRESS syndrome are thought to be the development of autoimmune sequelae in young patients and end-organ damage in elderly patients [3, 5, 13]. For this reason, it is important to establish the diagnosis of DRESS syndrome early to prevent life threatening complications. The European RegiSCAR project gives criteria for the diagnosis of DRESS syndrome that include acute skin rash, involvement of at least one internal organ, lymph node enlargement, deranged blood counts, and fever above 38°C [14]. Our patient would fit the criteria and could be diagnosed with DRESS syndrome.

The mainstay of treatment is to stop the culprit drug and provide supportive care. The patient must also be closely observed for associated complications. The use of steroids can be started to hasten the recovery and slow down the enduring immune reaction. A retrospective observational study of 50 patients diagnosed with DRESS syndrome has concluded that

systemic steroids should be reserved for severe cases in patients who develop organ failure. The findings showed that topical steroid therapy had less frequent complications such as sepsis, relapse, or viral reactivation than systemic therapy [15]. These findings may be related to the severity of the initial presentation of the DRESS syndrome rather than the efficacy of the steroid therapy. Our patient had a full recovery after 12 days of initial hospital presentation.

CONCLUSION

Multiple drugs have been mentioned in the literature to induce DRESS syndrome, but its association with lamotrigine is not frequently reported. Several mechanisms have been proposed in the pathogenesis of DRESS syndrome and it is determined that it results due to an autoimmune T-cell mediated response triggered by the drug or its metabolite. This immune dysregulation can cause latent virus reactivation, which further complicates the process and severity of the disease. We want to stress that DRESS syndrome is a potentially life-threatening condition that requires early detection and intervention. The authors recommend that patients started on new medications associated with DRESS syndrome be monitored every 2 weeks in the first month with routine laboratory investigations, including complete blood count, renal function test, and liver function test. Moreover, the patient needs to be educated about the complications and report back immediately if an adverse reaction occurs. Further studies are required to determine the role of viral infections in the pathogenesis of DRESS syndrome and genetic predisposition in susceptible individuals.

AUTHORS' CONTRIBUTION

M.E. performed a review of literature and wrote the initial manuscript. MAK reviewed the case, initial draft, literature and edited the discussion. A.E. reviewed and approved the final draft of the report. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Verbal and written informed consent was obtained from the patient.

STANDARDS OF REPORTING

CARE guidelines and methodologies were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

Data used in this report is available in the patient's electronic medical record and is available for review.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg 1996; 15(4): 250-7. [http://dx.doi.org/10.1016/S1085-5629(96)80038-1] [PMID: 9069593]

[2] Muller P, Dubreil P, Mahé A, *et al.* Drug hypersensitivity syndrome in a West-Indian population. Eur J Dermatol 2003; 13(5): 478-81. [PMID: 14693494]

[3] Cacoub P, Musette P, Descamps V, *et al.* The DRESS syndrome: a literature review. Am J Med 2011; 124(7): 588-97. Available from: https://www.amjmed.com/article/S0002-9343(11)00258-0/fulltext [http://dx.doi.org/10.1016/j.amjmed.2011.01.017] [PMID: 21592453]

[4] Descamps V, Valance A, Edlinger C, *et al.* Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 2001; 137(3): 301-4. [PMID: 11255328]

[5] Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010; 146(12): 1373-9. Available from: https://jamanetwork.com/journals/jamadermatology/fullarticle/422535 [http://dx.doi.org/10.1001/archdermatol.2010.198] [PMID: 20713773]

[6] Takahashi R, Kano Y, Yamazaki Y, Kimishima M, Mizukawa Y, Shiohara T. Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome. J Immunol 2009; 182(12): 8071-9. Available from: https://www.jimmunol.org/content/182/12/8071 [http://dx.doi.org/10.4049/jimmunol.0804002] [PMID: 19494333]

[7] Niu J, Jia Q, Ni Q, *et al.* Association of CD8(+) T lymphocyte repertoire spreading with the severity of DRESS syndrome. Sci Rep 2015; 5: 9913. [http://dx.doi.org/10.1038/srep09913] [PMID: 25905582]

[8] Kano Y, Inaoka M, Shiohara T. Association between anticonvulsant hypersensitivity syndrome and human herpesvirus 6 reactivation and hypogammaglobulinemia. Arch Dermatol 2004; 140(2): 183-8. Available from: https://jamanetwork.com/journals/jamadermatology/fullarticle/480290 [http://dx.doi.org/10.1001/archderm.140.2.183] [PMID: 14967790]

[9] Cho YT, Yang CW, Chen YC, Chu CY. Comment on "Viral reactivation in hospitalized DRESS patients: A retrospective study from a tertiary medical center in the United States". J Am Acad Dermatol 2020; 83(3): e209-10. Available from: https://www.jaad.org/article/S0190-9622(20)30853-7/fulltext [http://dx.doi.org/10.1016/j.jaad.2020.04.175] [PMID: 32413450]

[10] Choudhary S, McLeod M, Torchia D, Romanelli P. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. J Clin Aesthet Dermatol 2013; 6(6): 31-7. [PMID: 23882307]

[11] Wu X, Yang F, Chen S, *et al.* Clinical, viral and genetic characteristics of drug reaction with eosinophilia and systemic symptoms (DRESS) in shanghai, China. Acta Derm Venereol 2018; 98(4): 401-5. Available from: https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-2867 [http://dx.doi.org/10.2340/00015555-2867] [PMID: 29242946]

[12] Ksouda K, Affes H, Mahfoudh N, *et al.* HLA-A*31:01 and carbamazepine-induced DRESS syndrom in a sample of North African population. Seizure 2017; 53: 42-6. Available from: https://www.seizure-journal.com/article/S1059-1311(17)30448-X/fulltext [http://dx.doi.org/10.1016/j.seizure.2017.10.018] [PMID: 29125944]

[13] Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Long-term

sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. J Am Acad Dermatol 2013; 68(3): 459-65. [http://dx.doi.org/10.1016/j.jaad.2012.08.009] [PMID: 22959230]

[14] Pannu AK, Saroch A. Diagnostic criteria for drug rash and eosinophilia with systemic symptoms. J Family Med Prim Care 2017; 6(3): 693-4. [http://dx.doi.org/10.4103/2249-4863.222050] [PMID: 29417040]

[15] Funck-Brentano E, Duong TA, Bouvresse S, *et al.* Therapeutic management of DRESS: a retrospective study of 38 cases. J Am Acad Dermatol 2015; 72(2): 246-52. [http://dx.doi.org/10.1016/j.jaad.2014.10.032] [PMID: 25592341]