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Case Report

Case Report: Lamotrigine-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (Dress) Associated with Severe Acute Hepatitis

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Abstract

The Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome clinically presents with an extensive cutaneous rash, fever, lymphadenopathy, hepatitis, and hematologic abnormalities. It can also involve multiple organs, particularly the liver, kidneys, heart, lungs, and pancreas, leading to significant systemic damage. Early recognition of this syndrome is crucial, as the mortality rate is approximately 10%, and specific therapies may be required. In this case, the pathogenesis was linked to Lamotrigine use and sequential reactivation of Human Herpesvirus (HHV). Timely identification and discontinuation of the offending drug were essential, while corticosteroids were the primary treatment, alongside Ganciclovir for HHV-6 and HHV-7 reactivation. This case report reviews key concepts related to this serious adverse drug reaction.

Keywords: Keywords: Drug-Induced Liver Injury (DILI), Lamotrigine, Human Herpesvirus-6 (HHV-6/7), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Severe Acute Hepatitis

Background: Hypersensitivity syndrome, characterized by a severe drug reaction manifesting as cutaneous rash, eosinophilia, and systemic symptoms, is known by the acronym DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) (1,2). Skin involvement is typically extensive and is often accompanied by multi-organ involvement, affecting the liver, kidneys, lungs, heart, and lymph nodes, among others.

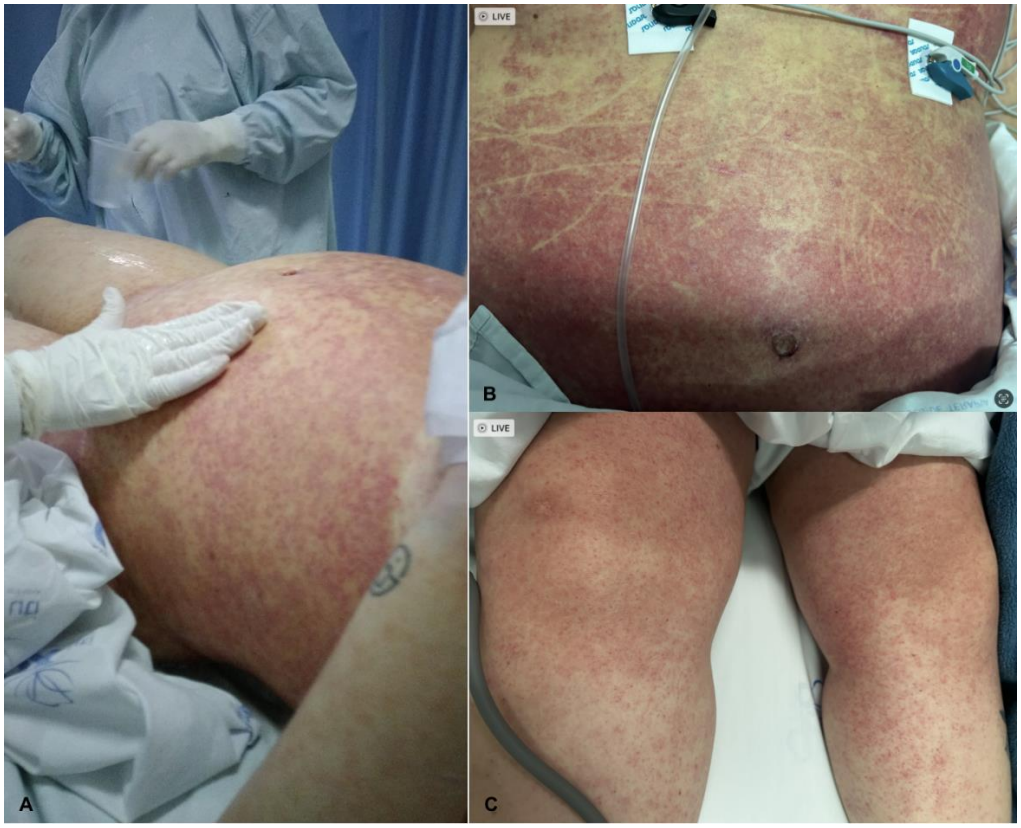
Objective

This report aims to highlight the occurrence of this rare syndrome, which can result from commonly used medications in clinical practice, such as lamotrigine and other anticonvulsants, and which may lead to serious complications, including hepatic, renal, pulmonary, and cardiac impairment. Additionally, we emphasize the importance of investigating and treating the reactivation of Herpesvirus during the progression of DRESS.

Case Report

This is the case of a 41-year-old woman diagnosed with severe bipolar affective disorder, who was receiving a combination of psychiatric medications to manage a recent manic episode. Her treatment included oxcarbazepine, quetiapine, topiramate, and lamotrigine, along with enalapril and propranolol for hypertension. Two weeks after initiating lamotrigine, the patient presented with a diffuse erythematous rash, primarily affecting the trunk and limbs (Fig. 1), accompanied by fever and jaundice (Table 1). Upon admission (D0), all medications except quetiapine were discontinued to mitigate the adverse reactions.

Figure 1: Diffuse Erythematous Rash Associated with DRESS Syndrome on the Trunk and Limbs Two Weeks After Initiation of Lamotrigine



Legend: A - Abdomen B - Abdomen C - Limbs Lower

Initial laboratory results showed a significant elevation in transaminases and total bilirubin, predominantly in its direct form, though there was no evidence of eosinophilia (Table 1). The patient's condition worsened, with the skin lesions progressing and liver function deteriorating. Despite a transient improvement in ALT/AST levels during hospitalization, other parameters such as bilirubin, INR, creatinine, and proteinuria (>500 mg/24h) worsened, alongside the development of anasarca, pulmonary edema, and ascites. Due to the severity of her condition, she was transferred to the intensive care unit (ICU) for advanced respiratory and hemodynamic support. Extensive investigations, including autoimmune and viral panels, were performed, initially ruling out infections such as Herpesvirus 6 and 7.

Table 1: Laboratory Findings on Admission and During Hospitalization of a Patient with DRESS Syndrome Associated with Lamotrigine Use

laboratory tests	**Reference**	**03/25**	**03/26**	**04/04**	**04/11**	**04/21**
Days of Hospitalization		**D0**	**D1**	**D10**	**D17**	**D27**
Hb (g/dL) Ht (%)	12.0 to 15.0 g/dL 36.0 to 46.0%	14.9 42.4	14 39.4	13.1 37.2	10.1 23.1	10.7 29.4
Leukocytes (/ uL)	4,000 to 10,000/ uL	8,360	6,540	28,760	15,320	9,910
Neutrophils (%)	20 to 65%	81%	76%	59%	49%	76%
Eosinophils (%)	0 to 5%	two%	two%	two%	9%	0
Lymphocytes (%) Lymph . Atypicals (%)	20 to 45% 0 to 5%	13% 0	15% 0	29% 0	35% 4%	21% 0
Platelets (/ uL)	150,000 to 600,000/ uL	181,000	179,000	167,000	66,000	226,000
ALT (U/L)	0 to 55 U/L	3.331	1,477	156	97	49
AST (U/L)	5 to 34 U/L	5,640	1,808	117	148	63
Gama-GT (U/L)	9 to 36 U/L		233			200
Phosphatase Alkaline (U/L)	40 to 150 U/L		354			175
Total Bilirubin Bilirubin Direct (mg/dL)	0.2 to 1.2 mg/dL 0.0 and 0.5 mg/dL		10.85 4.63	13.32 9.75	18.45 12.8	12.7 8.78
RNI	0.88 and 1.20		4.8	1.86	1.82	1.23
Protein (g/dL) Albumin (g/dL)	6.0 and 7.8 g/dL 3.5 and 5.2 g/dL			4.0 2.48	4.7 3.0	6.5 3.5
Creatinine (mg/dL)	0.57 and 1.11 mg/dL	1.64	1.32	1.3	0.6	0.5
PCR mg/L	< 5.0 mg/L	45.6		114.4	31.6	12.1

Legend: *Hb: hemoglobin ; Ht : hematocrit ; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Gamma-GT: gamma-glutamyl transferase; CRP: C- reactive protein

The clinical picture was consistent with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and the patient was promptly started on high-dose methylprednisolone pulse therapy (1 g daily for 3 days), followed by oral prednisone at 0.8 mg/kg/day. Despite initial stabilization, on the seventh day of corticosteroid treatment, the patient's condition worsened with increased jaundice (total bilirubin reaching 20 mg/dL), thrombocytopenia,

and atypical lymphocytosis. A repeat viral panel detected reactivation of Human Herpesvirus 6 and 7, which prompted the initiation of intravenous Ganciclovir therapy. This led to rapid hematologic improvement and recovery of both hepatic and renal function.
As the patient's condition improved, proteinuria resolved, and the cutaneous and systemic manifestations of DRESS, including the rash and edema, gradually subsided. Corticosteroids were tapered over three months, ultimately leading to complete resolution of all dermatologic and hepatic abnormalities. This case underscores the importance of early recognition and management of DRESS, including the timely cessation of the offending drug, the use of corticosteroids, and addressing viral reactivations, such as Herpesvirus, which can complicate the clinical course.

Discussion

DRESS syndrome, though rare (with an estimated incidence of 1:1,000 to 1:10,000 drug exposures), must be considered when cutaneous exanthem appears in association with systemic symptoms. Prompt recognition is crucial, as DRESS can cause significant multi-organ dysfunction, even after the withdrawal of the causative drug (1,2,3). High-risk medications, particularly anticonvulsants (e.g., oxcarbazepine, phenytoin, lamotrigine, phenobarbital), antibiotics (e.g., sulfonamides, minocycline, vancomycin), tuberculostatic drugs, and allopurinol, are commonly implicated in the development of DRESS (4,5). The syndrome typically manifests between two and eight weeks after the initiation of the offending agent, a timeframe that aligns with the clinical presentation in most cases.

To facilitate diagnosis, several criteria have been established, including the RegiSCAR and Japanese scoring systems, which combine clinical and laboratory parameters to identify DRESS (4,6,7). The hypersensitivity reaction often begins with fever and a generalized cutaneous rash, progressing to multi-organ involvement. Commonly affected organs include the liver (hepatitis), lungs (pneumonitis), kidneys (nephritis), heart (myocarditis, pericarditis), muscles (myositis), pancreas (pancreatitis), and thyroid (thyroiditis). Hematologic abnormalities, such as eosinophilia, atypical lymphocytosis, neutropenia, thrombocytopenia, or anemia, are also frequently observed. Lymphadenopathy and facial or periorbital edema are characteristic features of the syndrome (7). Due to the potential severity of the condition, hospitalization is often required.

It is important to note that the absence of eosinophilia, as observed in this case, does not exclude the diagnosis of DRESS. Hepatic involvement is the most commonly affected organ system, occurring in up to 90% of cases. Significant elevations in liver enzymes, often more than 10 times the upper limit of normal, are typically observed, with cholestatic patterns in 37% of cases, hepatocellular patterns in 19%, and mixed patterns in 27% (8). In some cases, acute liver failure may develop, necessitating aggressive treatment, including the potential for liver transplantation (9,10,11,12). This underscores the need for early identification and

prompt initiation of immunosuppressive therapy.

The clinical course of DRESS is highly variable. Although discontinuation of the offending drug often leads to symptom resolution and improvement of organ dysfunction, relapse can occur in up to 25% of cases. These relapses may present as recurrent rashes, laboratory abnormalities, or even recurrence of visceral involvement, leading to a prolonged disease course (13,14,15). The unpredictable nature of DRESS supports the use of high-dose corticosteroids, followed by a gradual taper to prevent recurrence.
Another critical aspect of DRESS management is the consideration of viral reactivation, particularly of the Herpesviridae family, including Cytomegalovirus (CMV) and Human Herpesviruses 6 and 7. Viral reactivation can complicate the disease course, as observed in the present case, and may contribute to relapses, prolong the clinical course, and worsen the prognosis. Reactivation is associated with an increased mortality rate, which in severe cases of DRESS can reach up to 10% (15,16). Long-term sequelae are also possible, including the development of autoimmune disorders such as systemic lupus erythematosus (SLE), thyroiditis, vitiligo, and type 1 diabetes mellitus (17).

Conclusion

DRESS syndrome is typically triggered by commonly used medications in clinical practice, such as lamotrigine, and may be exacerbated by the concomitant use of other anticonvulsants. Severe complications can include extensive rashes and hepatitis, which may progress to acute liver failure. The potential for reactivation of Human Herpesvirus types 6 and 7 should be considered, particularly in cases with a prolonged or relapsing course. Early and aggressive intervention is crucial for improving patient outcomes, reducing the risk of complications, and lowering mortality rates associated with this syndrome.

Authors: The case report was conceptualized and researched by Dr. Larissa Martins Flores and Dr. Ava Caroline Martins. The manuscript was written by Dr. Regina Gomes dos Santos and Dr. Cacilda Pedrosa de Oliveira, who also supervised and critically edited the final version.

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CONSENT: Consent per written for presentation and publication it was obtained from the patient. IOG Hospital does not require release from the Ethics Committee in Search.

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