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Case Report

Lamotrigine-induced DRESS Syndrome in an Epileptic Patient: A Rare but Life-threatening Adverse Drug Reaction

Enes Durak, Aslı Aksoy Gündoğdu

Tekirdağ Namık Kemal University Faculty of Medicine, Department of Neurology, Tekirdağ, Türkiye

Enes Durak MD

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Corresponding Author: Enes Durak MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Neurology, Tekirdağ, Türkiye, E-mail: enesdurak@nku.edu.tr

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening hypersensitivity reaction characterized by fever, skin rash, eosinophilia, and multiple organ involvement. Here we report an 18-year-old female patient with epilepsy who developed fever, widespread erythematous rash, facial edema, and elevated liver enzymes six weeks after the initiation of lamotrigine therapy. With a the registry of severe cutaneous adverse reaction score ≥6, a diagnosis of DRESS syndrome was established. Lamotrigine was discontinued, and oral corticosteroid therapy was initiated. Clinical improvement was observed by the third day, liver function tests normalized within 10 days, and cutaneous lesions gradually regressed. In patients receiving lamotrigine, the occurrence of fever and cutaneous rash should raise suspicion for DRESS syndrome in the differential diagnosis. Early diagnosis and treatment are critical for preventing systemic complications.

Keywords: DRESS syndrome, lamotrigine, epilepsy, adverse drug reaction, hypersensitivity

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, idiosyncratic hypersensitivity reaction that typically presents with a delayed onset following exposure to certain pharmacologic agents. This syndrome frequently presents with non-specific prodromal symptoms such as malaise, pruritus, and high-grade fever ranging from 38 to 40 °C. The clinical presentation is characterized by prominent cutaneous manifestations, including morbilliform eruptions, widespread epidermal desquamation, facial edema involving preseptal and periorbital regions, often accompanied by erythroderma.[1] Furthermore, lymphadenopathy, hematologic abnormalities such as eosinophilia and atypical lymphocytosis, and internal organ involvement, particularly affecting the liver, lungs, and kidneys, might be observed.[1,2] This condition typically manifests within 2 to 8 weeks after drug exposure, with a reported mortality rate of up to 10%.[2]

The pathogenesis involves drug-specific T-cell activation, cytokine release, genetic predisposition, and reactivation of herpesvirus.[3] The incidence of DRESS varies depending on the causative drug, ranging from 1/1,000 to 1/10,000.[1] Lamotrigine (LTG), an aromatic antiseizure agent, is increasingly recognized as a potential cause of DRESS, especially when used concomitantly with valproic acid, which inhibits LTG metabolism and increases serum levels.[4] We present a case of LTG-induced DRESS in a young female patient with epilepsy, focusing on the clinical course, diagnostic process, and therapeutic management strategy.

CASE PRESENTATION

An 18-year-old female patient with a known diagnosis of epilepsy presented to the emergency department with a one-month history of generalized rash accompanied by progressively worsening fever over the last ten days. Based on clinical suspicion of drug-induced hypersensitivity reaction, the patient was admitted to the dermatology department and subsequently referred to our neurology clinic for evaluation of potential antiseizure drug-associated adverse effects.

The patient had a one-year history of generalized onset tonic-clonic seizures, with a baseline frequency of approximately 10 episodes per month. Her antiseizure treatment consisted of levetiracetam (LEV) 1000 mg/day, initiated three months prior to evaluation. Due to persistent seizure activity, LTG was added six weeks before admission. Following this adjustment, her seizure frequency had decreased to three episodes per month.

Physical examination revealed right inguinal lymphadenopathy, generalized erythematous and desquamative rash, and preseptal and periorbital edema (Figure 1). Neurological examination was unremarkable, with no focal deficits, cognitive impairment, or signs of meningeal irritation. Ultrasonography demonstrated right inguinal and submandibular lymphadenopathies along with hepatomegaly (165 mm) and splenomegaly (139 mm).

Laboratory investigations showed hepatic involvement with elevated liver enzymes (aspartate aminotransferase 148 IU/L, alanine aminotransferase 165 IU/L, and gamma-glutamyl transferase 77 IU/L), along with markedly elevated lactate dehydrogenase (1017 IU/L). Hematological evaluation revealed peripheral eosinophilia (9.7%) and atypical lymphocytes on peripheral blood smear. Previous reports in skin biopsy have documented mild acanthosis, spongiosis, and intraepidermal vesicle formation accompanied by a dense perivascular inflammatory infiltrate in the dermis composed of lymphocytes, histiocytes, and occasional eosinophils. Additionally, intraepidermal spongiotic vesicles containing eosinophils with a concomitant perivascular lymphohistiocytic and eosinophilic infiltrate in the dermis have been described.[5] In our case, histopathological examination revealed irregular acanthosis; orthokeratotic hyperkeratosis; parakeratosis; exocytosis of neutrophils, leukocytes, and lymphocytes; and vasculopathic changes characterized by basal vacuolar degeneration.

The clinical and laboratory findings, with a the registry of severe cutaneous adverse reaction (RegiSCAR) score of ≥6, confirmed the diagnosis of DRESS (Table 1).[2]

LTG was discontinued, and LEV dose was increased to 3000 mg/day. Oral methylprednisolone therapy was initiated at 1 mg/kg/day. Clinical response was favorable, with resolution of fever by day three of treatment, and normalization of liver enzymes and eosinophil count by day ten. Cutaneous findings and edema gradually improved over two weeks (Figure 2).

After achieving clinical and biochemical stability, the patient was discharged with plans for outpatient continuation of methylprednisolone therapy and close follow-up in the neurology clinic.

Informed consent was obtained from the patient for publication of this case report and accompanying images, which were anonymized. Permission for publication was also granted by the attending dermatologist.

MAIN POINTS

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening hypersensitivity reaction that may occur after lamotrigine initiation.
- Early clinical signs such as fever, facial edema, and widespread erythematous rash should raise suspicion for DRESS, especially in patients using aromatic antiseizure drugs.
- Prompt discontinuation of the culprit drug and initiation of systemic corticosteroids are essential for favorable outcomes.
- The registry of severe cutaneous adverse reaction scoring system is a helpful diagnostic tool in differentiating DRESS syndrome from other systemic conditions.

DISCUSSION

This case illustrates the presentation of LTG-induced DRESS syndrome and underscores the diagnostic and therapeutic challenges associated with aromatic antiseizure drug use. DRESS syndrome is a rare but potentially fatal severe adverse drug reaction that requires early recognition and management.

DRESS syndrome presents a diagnostic challenge due to its variable and delayed-onset clinical presentation. Internal organs, including the liver, lungs, and kidneys, and lymphatic system are among the most commonly affected, with hepatic involvement reported in approximately 65-70% of cases.[2] In the present case, transaminase elevation and hepatomegaly supported hepatic involvement. Lymphadenopathy and widespread maculopapular eruptions are among the diagnostic criteria and were clearly evident in this case. The clinical presentation fulfilled the diagnostic threshold for "definite DRESS" according to the RegiSCAR scoring system (score ≥6). Notably, the absence of neurological symptoms despite systemic inflammation highlights the selective organ involvement.

DRESS syndrome represents a discrete, clinically significant subgroup among SCARs, which also include Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis and acute generalized exanthematous pustulosis.[6] In the case described, a six-week latency period, striking peripheral eosinophilia, demonstrable internal organ involvement, and the absence of notable epidermal detachment collectively favored a diagnosis of DRESS over SJS.

The diagnosis of DRESS is often delayed due to non-specific manifestations, which can mimic other systemic conditions. Therefore, in patients presenting with fever, diffuse rash, and laboratory abnormalities, a thorough drug history is essential. The RegiSCAR scoring system remains a valuable tool for early diagnosis and clinical stratification.

The pathophysiology of DRESS syndrome is mediated by immune and genetic mechanisms. Activated T-cells and monocytes release cytokines such as interleukin-5 and interleukin-13, promoting eosinophilic inflammation and tissue infiltration. As a result, eosinophilia serves as both a pathogenic and diagnostic hallmark of the syndrome.[7] Viral reactivation, especially of herpesviruses, may exacerbate systemic inflammation and contribute to disease severity and recurrence.[8] Genetic predisposition has been associated with an increased susceptibility to DRESS induced by specific drugs. *HLA-A3101, HLA-B5801* and *HLA-B1502* alleles have been linked to the risk of hypersensitivity reactions with LTG, allopurinol, and carbamazepine, respectively.[9-11] These mechanisms collectively

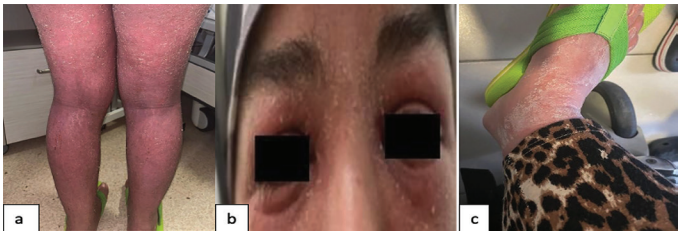

Figure 1. a) Diffuse erythematous and desquamative rash of the lower extremity. **b)** Pronounced preseptal and periorbital edema of the face (anonymized). **c)** Appearance of the rash on the ankles and feet

Table 1. RegiSCAR scoring system[2]

Score	-1	0	1	2
Fever >38 °C	No/Unknown	Yes		
Enlarged lymph nodes		No/Unknown	Yes	
Eosinophils		No/Unknown	0.7-1.499×10⁹/L	≥1.5×10⁹/L
Eosinophils if WBC <4.0×10⁹/L			10-19.9%	≥20%
Atypical lymphocytes		No/Unknown	Yes	
Extent of skin rash		None	>50% of body surface area	
Skin rash suggestive of DRESS	No	Unknown	Yes	
Skin biopsy suggestive of DRESS	No	Yes/Unknown		
Liver involvement (elevated LFTs, ALP, PT, or bilirubin)		No/Unknown	Yes	
Renal involvement (e.g., nephritis, AKI)		No/Unknown	Yes	
Muscle/heart involvement (e.g., myocarditis, pericarditis)		No/Unknown	Yes	
Pancreatic involvement	n	No/Unknown	Yes	
Other organ involvement (thyroiditis, colitis, etc.)		No/Unknown	Yes	
Resolution ≥15 days	No/Unknown	Yes		
Investigation of alternative potential causes (ANA antibodies, blood cultures, hepatitis A/B/C serology, Chlamydia, Mycoplasma): if three or more of the above tests have been performed and all results are negative			Yes	

RegiSCAR: The registry of severe cutaneous adverse reaction, WBC: White blood cell, DRESS: Drug reaction with eosinophilia and systemic symptoms, LFTs: Liver function tests, ALP: Alkaline phosphatase, PT: Prothrombin time, AKI: Acute kidney injury, ANA: Antinuclear antibody

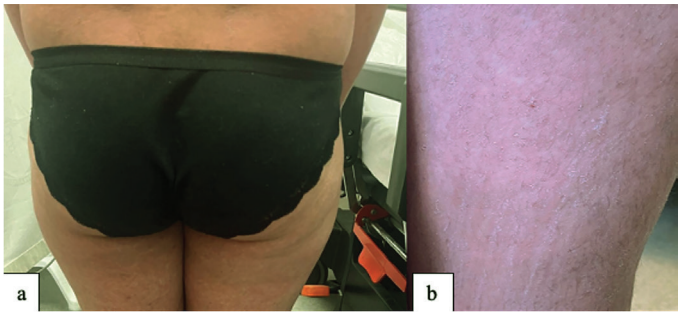

Figure 2. a,b. Marked regression of the cutaneous eruptions following initiation of systemic corticosteroid therapy

explain the multisystem involvement and variable clinical course observed in DRESS syndrome.

LTG is an aromatic antiseizure drug, which is metabolized via hepatic glucuronidation, a process inhibited by valproate, leading to increased LTG serum levels and heightened risk of adverse immune-mediated reactions.[4] In contrast, non-aromatic antiseizure drugs such as LEV have a safer immunologic profile. The patient's condition improved following LTG withdrawal and dose escalation of LEV. Early recognition remains challenging due to symptom overlap with infectious and autoimmune disorders, emphasizing the need for heightened clinical suspicion in patients developing rash and systemic symptoms during antiseizure treatment.

Systemic corticosteroids remain the first-line treatment for moderate to severe DRESS. A gradual tapering is recommended, as abrupt discontinuation may increase the risk of relapse. For steroid-refractory cases or patients with contraindications, second-line options include intravenous immunoglobulin, plasmapheresis, and immunosuppressive agents such as cyclosporine, cyclophosphamide, mycophenolate mofetil, or rituximab.[12] In our case, oral methylprednisolone therapy alone was sufficient to achieve remission.

Long-term follow-up is essential due to potential late-onset autoimmune sequelae, including thyroiditis, autoimmune hepatitis, and systemic lupus erythematosus, which may develop weeks to months after resolution of the acute phase. Therefore, periodic monitoring of thyroid and liver function is strongly recommended.[13]

CONCLUSION

This case highlights the diagnostic and therapeutic challenges of LTG-induced DRESS syndrome in a patient with epilepsy. The favorable outcome was achieved through timely recognition, early withdrawal of the offending drug, appropriate corticosteroid therapy, and close clinical follow-up. Effective management of DRESS requires a multidisciplinary approach involving neurology, dermatology, infectious disease, and hepatology specialists.

Moreover, increased clinician awareness may improve early identification of high-risk individuals and reduce the incidence of severe drug hypersensitivity reactions. Future efforts should focus on improving pharmacogenetic screening and developing biomarkers to predict disease severity and optimize therapeutic approaches.

Ethics

Informed Consent: Informed consent was obtained from the patient for publication of this case report and accompanying images, which were anonymized. Permission for publication was also granted by the attending dermatologist.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.D., A.A.G., Concept: E.D., A.A.G., Design: E.D., A.A.G., Data Collection or Processing: E.D., A.A.G., Analysis or Interpretation: E.D., A.A.G., Literature Search: E.D., A.A.G., Writing: E.D., A.A.G.

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

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