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Case Report

Lamotrigine-induced severe cutaneous adverse reaction in a patient with N-methyl-D-aspartate receptor autoimmune encephalitis

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ABSTRACT

Current case report is regarding a 20-year-old female patient presenting with N-methyl-D-aspartate (NMDA) receptor antibody-positive autoimmune encephalitis and new-onset seizures who developed rapidly progressive erythematous pruritic rash after administration of tablet lamotrigine followed by escalation of its dose and which was combined with tablet sodium valproate and tablet lacosamide. Cutaneous involvement was diffuse but mucosal surfaces were spared. Laboratory investigations revealed mild transaminitis and monocytosis without systemic involvement. A probable lamotrigine-induced severe cutaneous adverse drug reaction was diagnosed based on temporal association and Naranjo causality assessment. Prompt discontinuation of lamotrigine and initiation of systemic corticosteroids resulted in complete clinical resolution. Present case highlights risk of occurance of severe cutaneous adverse drug reactions caused by oral lamotrigine when co-administered with sodium valproate which is known to cause enzyme inhibition as well as in the presence of immune dysregulation. There is a need to take precautions where these conditions exist. Early recognition and timely withdrawal of the offending drug are critical to prevent progression to Steven Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

Keywords: Autoimmune, Cutaneous, Encephalitis, Reaction, Lamotrigine, Valproate

INTRODUCTION

Lamotrigine is a second-generation antiepileptic drug widely used for epilepsy and mood disorders due to its favorable efficacy and tolerability profile. However, it is recognized for causing idiosyncratic cutaneous adverse drug reactions ranging from benign maculopapular eruptions to severe life-threatening conditions such as SJS and TEN.[1,5] The incidence of serious cutaneous reactions is estimated to be higher during the initial weeks of therapy, particularly with rapid dose escalation and concomitant use of sodium valproate.[2-4]

Present study describes a rare and clinically important case of lamotrigine-induced severe cutaneous adverse reaction in a patient with NMDA receptor autoimmune encephalitis, emphasizing the need for heightened vigilance in high-risk populations.

CASE REPORT

A 20-year-old female student presented with a history of newly diagnosed seizure disorder secondary to NMDA receptor antibody-positive autoimmune encephalitis. She was initiated on antiepileptic therapy consisting of lamotrigine, sodium valproate, and lacosamide. Initially she was administered tablet lamotrigine 25 mg two times daily and after a short time, the dose was escalated to 50 mg twice daily.

Approximately one month after initiation of lamotrigine, the patient developed an acute onset of fever followed by a rapidly progressive, pruritic, erythematous rash involving

the face, trunk, and extremities. There was associated throat discomfort and generalized malaise. She had no prior history of drug allergies. On dermatological examination, diffuse erythematous papules with excoriation and scaling were noted over the trunk and limbs. Whereas, mucosal surfaces and mucocutaneous junctions were spared. There was no evidence of epidermal detachment or bullae formation at the site of presentation. Laboratory investigations revealed mildly elevated hepatic transaminases (SGPT 82 U/L) and monocytosis. Renal parameters and hemodynamic status were stable.

Alternative diagnosis like drug reaction with eosinophilia and systemic symptoms (DRESS), viral exanthema, and vasculitic rash were considered but deemed unlikely based on the absence of eosinophilia, lymphadenopathy, organ dysfunction, or systemic instability. Lamotrigine was immediately discontinued, while sodium valproate and lacosamide were continued. Skin biopsy was not performed because of rapid improvement following withdrawal of lamotrigine. The patient was managed with systemic corticosteroids, antihistamines, supportive care, and close monitoring. Oral steroids were administered after gradual discontinuation of initial IV methylprednisolone.

Continuation of valproate without worsening of the rash further reduced the likelihood of valproate-induced cutaneous adverse drug reaction (cADR). Based on the temporal association, clinical features, and exclusion of alternative etiologies, a diagnosis of lamotrigine-induced severe cutaneous adverse drug reaction (SCAR) with concern for early progression toward SJS was considered. SCORTEN (SCOre of TEN) was not applied because full SJS/TEN diagnostic criteria like involvement of multiple mucosal sites was not met, but early withdrawal was undertaken to prevent progression.

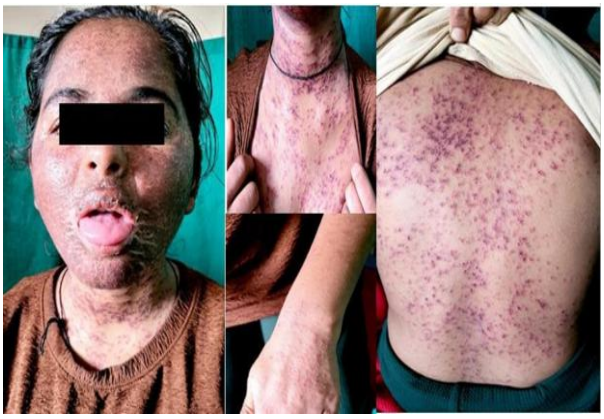

Figure 1: Diffuse erythematous lesions on trunk at presentation, without mucosal involvement.

Causality assessment

Naranjo's causality assessment was performed for all concomitant antiepileptic agents. Lamotrigine scored 'probable' on the Naranjo scale, whereas valproate and lacosamide scored 'possible' and 'doubtful' respectively, supporting lamotrigine as the most likely offending drug.[9] Eventhough the Naranjo algorithm is widely used, it is not specific for severe cutaneous adverse reactions. The ALDEN **(**ALgorithm of Drug causality in Epidermal Necrolysis) score is better suited for confirmed SJS/TEN; it was not applied here because SJS/TEN criteria like involvement of multiple mucosal sites was not fulfilled.

Table 1: Causality assessment of suspected drugs using Naranjo's algorithm.

Drugs	Naranjo score	Interpretation
Lamotrigine	6	Probable
Sodium valproate	3	Possible
Lacosamide	1	Doubtful

Over the following days, the cutaneous lesions showed marked improvement without progression to mucosal involvement or systemic complications. The patient made a complete recovery and was discharged on lacosamide and sodium valproate. No recurrence of cutaneous symptoms was noted during the follow-up.

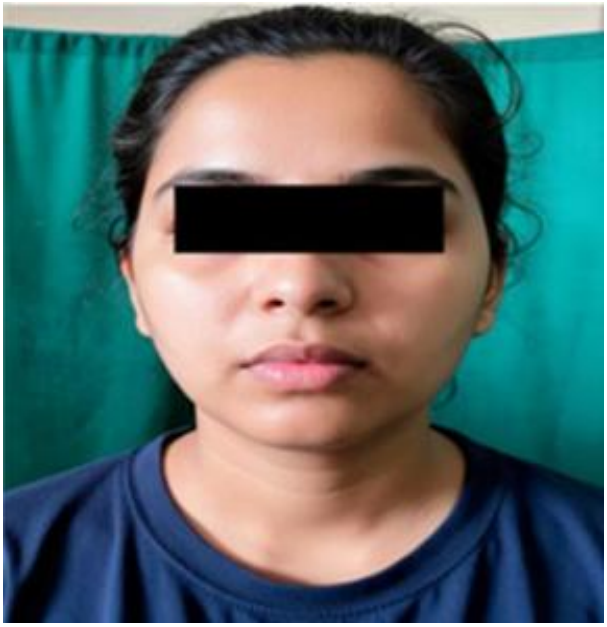

Figure 2: Clinical presentation during follow-up after discharge.

DISCUSSION

Lamotrigine-induced SJS/TEN is a T-cell-mediated type IV hypersensitivity reaction characterized by widespread keratinocyte apoptosis mediated through Fas-Fas ligand interactions and granzyme B pathways.[5,6] Several risk factors for severe cutaneous reactions have been identified, including rapid dose escalation, concomitant valproate therapy, and genetic susceptibility involving specific human leukocyte antigen (HLA) alleles such as HLA-B15:02 and HLA-A31:01.[4,7]

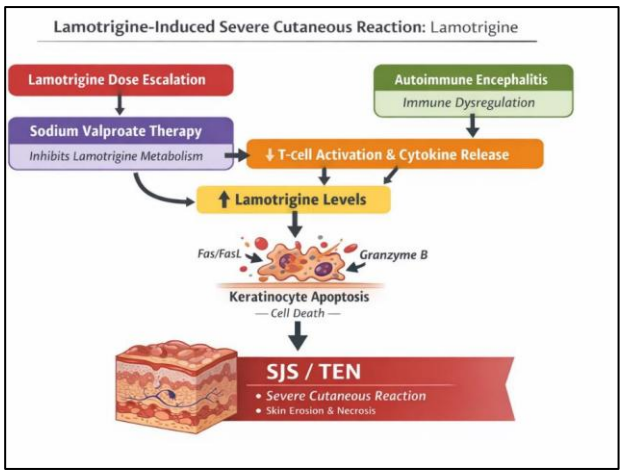

Figure 3: Pathophysiology of SJS/TEN syndrome.[16]

Sodium valproate inhibits lamotrigine glucuronidation through uridine diphosphate-glucuronosyltransferase (UGT1A4), leading to elevated plasma concentrations and increased toxicity.[1,2] Additionally, immune-mediated neurological conditions such as NMDA receptor autoimmune encephalitis represent states of immune dysregulation that may further predispose patients to exaggerated hypersensitivity reactions.[8] Although mucosal involvement was absent, the rapidly progressive nature of the rash with systemic symptoms necessitated early intervention. Prompt withdrawal of tablet lamotrigine has likely prevented the progression to full-blown SJS/TEN.[10-13] This case also reinforces the value of structured causality assessment tools such as the Naranjo algorithm in pharmacovigilance practice.

CONCLUSION

Patients with immune dysregulation receiving lamotrigine, particularly in combination with sodium valproate, represent a high-risk group for severe cutaneous adverse drug reactions. Careful dose titration, close clinical monitoring during the initial treatment period, and immediate drug discontinuation at the first sign of rash are essential to prevent the life-threatening outcomes. This case serves as a clinical alert for the physicians prescribing anti-epileptic drugs in the complex neurological conditions.

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