

Case Report

Delayed Stevens–Johnson Syndrome Secondary to the Use of Lamotrigine in Bipolar Mood Disorder

Kunal Kishor Jha, Durgesh Prasad Chaudhary¹, Tshristi Rijal², Semanta Dahal³

ABSTRACT

Lamotrigine is a mood-stabilizing drug used in maintenance treatment of bipolar I disease. There are adverse effects with lamotrigine such as a headache, blurred vision, diplopia, somnolence, ataxia, dizziness, rash, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis. SJS is a life-threatening, blistering mucocutaneous disease. SJS is characterized by the presence of flat, diffuse erythematous maculopapular rashes with the involvement of < 10% of the body surface area. Standard trigger is drugs including anticonvulsants, antibiotics, and *Mycoplasma pneumoniae* infection. We report a case where a patient developed SJS secondary to delayed-type hypersensitivity reaction after 6 months of the use of lamotrigine, while his initial response during the first 6 months did not show any sign of SJS.

Key words: *Bipolar mood disorder, delayed skin reactions, lamotrigine, Steven–Johnson syndrome*

INTRODUCTION

Lamotrigine is an anticonvulsant and mood-stabilizing drug used in the treatment of epilepsy and bipolar mood disorder.^[1,2] Its prescribing information has warnings about life-threatening skin reaction such as Stevens–Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, and toxic epidermal necrolysis (TEN). SJS is defined as a combination of an acute life-threatening mucocutaneous illness with systemic symptoms due to an idiosyncratic reaction to a drug. The rash is characterized by the presence of flat, atypical target

lesions and epidermal detachment. This rash usually involves < 10% of the body surface area with two or more mucosal sites affected.^[3] The most common drugs causing SJS are sulfonamides, nevirapine, allopurinol, lamotrigine, aromatic anticonvulsants, and oxycam nonsteroidal anti-inflammatory drugs.^[4,5] The incidence of around 2.6–6.1 cases/million people/year has been reported for SJS with a mortality rate of around 5%.^[6] Our patient presented to us with SJS after 6 months of asymptomatic treatment with lamotrigine.

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Department of Critical Care Medicine, Geisinger Medical Center, Danville, PA 17821, USA, ¹Department of Internal Medicine, Norvic International Hospital, Kathmandu, ³Department of Internal Medicine Possible Health, Achham, Nepal, ²Dental Surgeon, Oracare Periodontal Clinic, Kathamandu, Nepal

Address for correspondence: Dr. Kunal Kishor Jha

Department of Critical Care Medicine, Geisinger Medical Center, Danville, PA 17821, USA. E-mail: friendsforever.kunal@gmail.com

CASE REPORT

A 33-year-old male patient, who was diagnosed with bipolar affective disorder (BPAD) for the duration of more than 2 years, was under medications 1 g of sodium valproate, 10 mg of olanzapine, and 1 mg of clonazepam. A few changes were then made to his drug regimen; sodium valproate was stopped, and lamotrigine was introduced, whose target dose of 100 mg was reached gradually in 3 weeks' time. For the next 6 months, the patient did well, and no side effects were reported.

The patient then had a low-grade fever (100°F) for 3 days, for which he did not seek any medical treatment, and then he had a high-grade fever (102°F) accompanied by the rash. His condition worsened, and he developed ulcers on his lips [Figure 1] and pain on swallowing. He also complained of dysuria due to a penile ulcer. Despite his severe medical condition, he did not seek medical assistance for 3 days, after which he presented to us as an outpatient. Examination showed the maculopapular rash on the neck, trunk, and extremities [Figures 2 and 3]. Along with oral ulceration, crusting was present on lips whereas genitalia revealed erythematous papules with erosions. We intervened by stopping lamotrigine; Department of Dermatology was also consulted.

On laboratory investigations, it revealed hemoglobin 10.8 g/dL (12–16 g/dL), white blood cells 12,000/mL (4500–11,000/mL), neutrophils 50%, lymphocytes 40%, eosinophil 6%, monocytes 4%, and platelets 198,000/mL (150,000–400,000/mL). His C-reactive protein was 8 mg/dL (0–10 mg/dL). Other than that, Liver function test (LFT), Renal function test (RFT), Arterial blood gas analysis (ABG), basal serum tryptase, and immunological study were normal. Blood cultures (three samples), urine routine examination, and culture were negative. Serology was negative for hepatitis, chlamydia, *Mycoplasma*, cytomegalovirus, Epstein–Barr virus, and herpes virus. Chest radiograph was normal. Biopsy of the skin lesion was performed for confirmation of diagnosis which revealed focal basal cell vacuolar changes with dense superficial dermal lymphocytic inflammation. Prick test and intradermal skin tests (ID) were not performed. After detailed medical examination and laboratory investigations, diagnosis of SJS was made.

After consultation from the Department of Dermatology, Internal Medicine, and Oral Medicine, ranitidine 300 mg, levocetirizine 10 mg, chlorhexidine mouth rinse, and calamine lotion for skin were prescribed along with the tapering dose of steroids. The dosage of oral prednisone prescribed was 10 mg once daily for the 1st week, and then, it was gradually decreased to 1 mg over a period of 4 weeks, and then, it was



Figure 1: Oral and mucosal ulceration



Figure 2: Maculopapular rashes on the trunk and upper extremity



Figure 3: Maculopapular rash on the lower extremity

stopped. The patient responded well to medications; all the symptoms resolved within 3 weeks. However, postinflammatory pigmentation resolved after 3 months without any medication. Currently, he is on sodium valproate 500 mg and clonazepam 0.5 mg for his original diagnosis of BPAD for the past 1 year without any complaint.

DISCUSSION

SJS, usually triggered by anticonvulsants, antibiotics, and *Mycoplasma pneumoniae* infection, starts with fever, malaise, myalgia, headache, vomiting, and prodromal symptoms.^[3] These symptoms are then followed by diffuse erythematous maculopapular rashes localized to head, neck, trunk, and extremity. The rash later coalesces and makes develop in bullae which further can lead to detachment of the epidermis. There may be involvement of mucosal area as well such as eye, nose, and genitalia leading to difficulty in swallowing and micturition.^[6] SJS usually presents within the first few weeks of starting a culprit medication, but there can be delayed presentation as well on rare occasions.

Delayed cutaneous adverse drug reactions are characterized by idiosyncratic T-cell-mediated immune responses. It encompasses a wide spectrum of diseases including SJS, acute generalized erythematous pustulosis, TEN, and DRESS.^[7,8] Currently, delayed adverse reactions are diagnosed mainly based on patient's medication history, clinical presentation, and clinical course after discontinuation of the culprit medication. It was concluded that the symptoms of our patient were caused by delayed-type hypersensitivity reaction to lamotrigine because the symptoms only appeared after 6 months and the fact that biopsy showed lymphocytic infiltration in the dermis. It suggested an immunologic response requiring time lag to be sensitized, leading to the delayed presentation of SJS. The confirmation of diagnosis can be difficult. The challenge test is not done because it may trigger a new episode of greater severity. LTT stands for Lymphocyte transformation test can be used to quantify the activation of T-cells in response to the drug. It may be useful in the diagnosis of delayed hypersensitivity reactions, but the sensitivity is low in patients with SJS/TEN.^[9,10] Moreover, the LTT should be done within 1 week of the start of the rash.^[11] Difficulties can arise when predicting delayed-type hypersensitivity reaction; however, patch test and lymphoblastic transformation test (LTT) have been used with variable response to confirm the delayed hypersensitivity reactions to the drugs.

Although antiepileptic drugs and mood stabilizers are recognized culprit medications, literature comparing the delayed cutaneous adverse drug reactions associated with these drugs is limited. Better diagnostics are needed to ensure correct diagnosis and appropriate management. The physicians should carry out a skin biopsy to ascertain the presence of the syndrome. Before a diagnosis of SJS can be made, other immunobullous diseases such as staphylococcal scalded skin syndrome, IgA dermatosis, paraneoplastic pemphigus, and

disseminated fixed bullous drug reaction should be ruled out. We are reporting this case because we believe the role of the doctor is more than just prescribing the medications. Doctors have the responsibility to inform the patients about the possible adverse reactions before prescribing medications such as lamotrigine which have been implicated in causing delayed cutaneous adverse drug reactions.

SUMMARY

SJS can also present as delayed-type hypersensitivity reaction; hence, offending drug should be withdrawn immediately as soon as symptoms of maculopapular rash, targetoid lesion, and mucosal lesion appear. Doctors should work with the patients to raise awareness of the adverse reactions of medications such as lamotrigine before prescribing them. They should make sure that they carefully prescribe the right drugs and quantities to prevent the emergence of SJS.

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Conflicts of interest

There are no conflicts of interest.

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