Lamotrigine-induced Stevens-Johnson Syndrome Toxic Epidermal Necrolysis (SJS/TEN) overlap with transaminitis in an Asian female: a case report

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ABSTRACT

Background: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) are a dermatologic emergency characterized by extensive epidermal detachments. The most frequent etiology is drug reaction within an interval of the last 8 weeks. SJS/TEN may occur in any age, race, and gender; however, there is an increased risk in patients over 65. SJS and TEN are differentiated based on the extent of epidermal detachments, which is <10% in SJS, 10-30% in SJS-TEN overlap, and >30% in TEN. This case study aims to evaluate the Lamotrigine-induced Stevens-Johnson Syndrome Toxic Epidermal Necrolysis (SJS/TEN) overlap with transaminitis in an Asian female.

Case Presentation: A 34-year-old woman presented to the emergency room with complaints of rash on the face, neck, arms, body, and back, with itching and burning sensation. The patient also complained of blistered mucosa. The suspected causative drug was lamotrigine, which she consumed within the last 2 weeks. Mucosal involvement was also found on the lips and genital mucosal. The affected body surface area was approximately 20%, with a positive Nikolsky sign. Laboratory studies showed elevated liver function tests. Based on the history, physical examination, and biopsy, the patient was diagnosed with SJS/TEN overlap. The suspected causative drug was immediately stopped, and supportive and systemic corticosteroid treatments were provided. The SCORTEN was 2, with a mortality rate of 12.1%. After a few days, the patient’s condition had improved, the liver function test was normal, and there was no significant complication.

Conclusion: SJS-TEN is a part of epidermal necrolysis, characterized by an extensive epidermal detachment. The management of SJS/TEN includes early detection, immediately stopping the suspected drugs, administering systemic corticosteroids, and other supportive treatments.

Keywords: Lamotrigine, Stevens-Johnson Syndrome, Transaminitis, Toxic Epidermal Necrolysis.


INTRODUCTION

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are acute, life-threatening mucocutaneous reactions characterized by necrosis and extensive epidermal detachment, mostly induced by drug reactions. These conditions are preceded by prodromal symptoms followed by progressive cutaneous lesions and the involvement of at least two mucosae. The difference between SJS and TEN lies in the affected body surface area. SJS’s affected body surface area is <10%, while the SJS/TEN overlap 10-30% and TEN >30%.¹ The pathogenesis of SJS/TEN is still unclear, although it is related to an immune reaction causing a cell-mediated cytotoxic reaction against keratinocytes, leading to massive apoptosis. The most frequent trigger for SJS/TEN is drug consumption, with an interval of 8 weeks before the onset of the lesion. The high-risk drugs inducing SJS/TEN include allopurinol, lamotrigine, cotrimoxazole, carbamazepine, nevirapine, oxicam-class NSAIDs, phenobarbital, and phenytoin.¹

Lamotrigine is a broad-spectrum aromatic anti-epileptic drug that treats epilepsy, bipolar disorders, tonic-clonic seizures, and neuropathic pain and is a mood stabilizer. Lamotrigine suppresses sustained rapid firing of neurons, produces a voltage- and use-dependent blockade of Na⁺ channels, and acts as an antagonist to high-voltage-activated N- and P/Q-type calcium channels.²³ Moreover, it also decreases the synaptic release of glutamate. Lamotrigine is well absorbed orally. The drug has linear kinetics and is metabolized primarily by glucuronidation to the 2-N-glucuronide, which is excreted in the urine. Lamotrigine has a half-life of approximately 24 hours. It decreases to 13-15 hours in patients taking enzyme-inducing drugs. ² The incidence of lamotrigine-induced adverse cutaneous manifestation has been reported at around 3-10%.⁴ Herein, we present a case of a 34-year-old Asian female with SJS-TEN overlap with transaminitis.

CASE REPORT

A 34-year-old woman presented to the emergency room with complaints of rashes on the face, neck, arms, body, and back, with itching and burning sensation. The patient also complained of blistered mucosa on the lips and genital mucosa. The affected body surface area was approximately 20%, with a positive Nikolsky sign. Laboratory studies showed elevated liver function tests. Based on the history, physical examination, and biopsy, the patient was diagnosed with SJS/TEN overlap. The suspected causative drug was immediately stopped, and supportive and systemic corticosteroid treatments were provided. The SCORTEN was 2, with a mortality rate of 12.1%. After a few days, the patient’s condition had improved, the liver function test was normal, and there was no significant complication.

Conclusion: SJS-TEN is a part of epidermal necrolysis, characterized by an extensive epidermal detachment. The management of SJS/TEN includes early detection, immediately stopping the suspected drugs, administering systemic corticosteroids, and other supportive treatments.

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and bleeding lips, along with a burning sensation and erosion in the genital area. She had a fever and flu-like syndrome four days before the lesion appeared. Subsequently, the rash appeared on the trunk and progressively spread to the face, neck, and arms regions. The patient had a history of anxiety and received lamotrigine 100 mg, prescribed by a psychiatrist 12 days before her presentation.

Physical examination showed blood pressure of 127/70 mmHg, respiratory rate 20 times/minute, heart rate 102 times/minute, and temperature of 39.4°C. Other general examinations were within the normal limit. For the dermatological status, multiple erythematous macules, diffuse, geographical shapes accompanied by multiple vesicles and bullae were found on the facial, neck, anterior et posterior trunk, and superior dextra et sinistra extremities regions. In addition, clinicians found erosion and crust on the lips. Hyperemia and erosion were found in the labia majora, and white-yellowish fluor albus were present. Nikolsky's sign was positive, with an affected body surface area (BSA) of 20%.

The laboratory studies showed increased liver enzymes with SGOT 46 and SGPT 35. HbsAg was positive, while anti-HCV was negative. The liver ultrasound was within normal limits. The blood gas analysis showed pH 7.52, PO2 140, PCO2 36.5, HCO3 29.7, and BE 7. Complete blood count, urea, creatinine, electrolytes, and random blood glucose were within normal limits. A 4-mm punch biopsy on the posterior trunk and brachial dextra showed vacuolar interface changes, necrotic keratinocytes, epidermal necrosis, and subepidermal bullae. These findings confirmed our clinical suspicion of SJS/TEN overlap.

Lamotrigine was immediately stopped. The supportive treatments include intravenous fluid with Ringer Lactate 500 ml/8 hours, wound dressing with NaCl 0.9% twice per day, bullae aspiration and treatment of the lips mucosa using Triamcinolone acetonide in orabase ointment twice per day, and gargling using Betadine Gargle. Treatments include systemic dexamethasone with dosage 5 mg/kg/day – 15 mg/kg/day, gentamycin 80 mg/12 hours/IV, cetirizine tablet 10 mg/24 hours, mecobalamin drip 1 ampule in Ringer Lactate/24 hours, and vitamin C 500 mg/24 hours/IV. High-potent topical corticosteroid combined with gentamycin cream was administered twice per day. The labia majora was treated with wound dressing using normal saline (NaCl 0.9%) twice daily and mupirocin 2% ointment twice daily.

The SCORTEN was 2, with a predicted mortality of 12.1%. There was no significant complication during treatment. The patient liver function had returned to normal on discharge. After a one-month follow-up, post-inflammatory hypopigmentation was found in the involved regions.

**DISCUSSION**

The patient's symptoms were preceded by prodromal symptoms, followed by lesions four days after the initial prodromal symptoms. The lesions progressively spread to the face, arms, and back regions. Two mucosas were involved: the erosion on the lips and labia majora. Nikolsky's sign was positive, with a BSA of 20%. Before the lesions appeared, the patient had consumed lamotrigine 100 mg within 12 days, the suspected drug that triggered SJS/TEN overlaps. The clinician's suspicion of SJS/TEN was confirmed with the histopathological result showing features of SJS/TEN.

Lamotrigine is an anti-epileptic drug and acts as a mood stabilizer. One of the adverse effects of Lamotrigine is cutaneous manifestation. The incidence of skin rash induced by lamotrigine is approximately 3-10% and has recently increased. Also, the severity may be dose-dependent; therefore, initially, low and slowly increasing doses may prevent such reactions.

The pathogenesis of lamotrigine-induced SJS/TEN is still unclear; however, it is postulated that lamotrigine inhibits voltage-dependent sodium channels, resulting in a stable neuron membrane in high concentration. Lamotrigine may produce reactive metabolites, which could activate the immune system and lead to tissue damage. The hypersensitivity reaction involves T-cell, namely the...
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Th1 CD4+ (T-cell clones generate only occasional CD8+ cells), which would express the Tα- and Tβ-receptor with Vβ5.1 chain. Drug-specific T-cell clones express lymphocyte antigen receptors in the skin. Lamotrigine stimulates the T-cell to become cytotoxic and secretes perforin, IFN-gamma, IL-5, and macrophage, regulated upon activation, normal T cell expressed, and secreted (RANTES) I-309. Antigen-presenting cells will express lamotrigine as antigen fragments with HLA-DR and HLA-DQ without drug metabolism or processing. T-cell receptors from certain clones will accommodate the lamotrigine analog.5,6

The patient’s liver enzyme was elevated. The HbsAg result was positive, while the anti-HCV was negative. However, another serologic marker was not examined to establish the diagnosis. The patient had no other symptoms, her liver ultrasound result was within normal limits, and her liver function test returned to normal after her SJS/TEN overlap had resolved. An asymptomatic elevated liver enzyme, bilirubin, alkaline phosphatase (ALP), and other hepatic parameters are one of the complications of SJS/TEN. A study reported that the incidence of hepatic involvement in SJS was about 9.62%.7 However, the increased liver enzyme mechanism is still not fully understood. Moreover, a study reported that SJS/TEN patients with underlying liver disease have a higher risk of liver failure. This is due to the liver’s reduced ability to break down, convert, and clear drugs, extending the duration of drugs inside the body, which could also increase the risk of drug-induced liver injury (DILI).7

The main management principle of SJS/TEN is to stop the suspected drug immediately. Supportive treatment such as Ringer Lactate fluid was administered to maintain fluid and electrolyte balance since the erosion occurring in SJS/TEN could lead to significant fluid loss, causing hypovolemia and electrolyte imbalance.1

Wound care was performed with NaCl 0.9% wound dressing on the exfoliated skin for 10-15 minutes twice a day to prevent secondary infection and heat loss and accelerate re-epithelialization. NaCl, 0.9% dressing, is commonly used to dress open wounds to provide a moist environment for wound healing. It will retract fluids from the wound into the gauze, leading to dynamic balance. This occurs because NaCl 0.9% evaporates, making the gauze hypertonic and retracting fluid from the wound through osmosis. In order to be clinically effective, routine replacement of NaCl 0.9% dressing is necessary to maintain adequate tonicity and permeability. NaCl, 0.9% dressing, will also remove blood and exudates.8

There are several systemic treatment options for SJS/TEN. A systemic corticosteroid was chosen. Intravenous dexamethasone during hospitalization was adjusted based on the patient’s clinical condition with a dosage of 5 mg/kg/day – 15 mg/kg/day. In addition, a high-potent topical corticosteroid combined with gentamycin cream was also administered twice per day. Corticosteroids are useful in preventing disease progression when given in the early stages. A large-scale cohort study also reported that moderate-dose corticosteroids provided a good outcome when administered for several days.1

Vitamin C was administered to boost the patient’s immune system. It acts as an antioxidant and photoprotective and has an anti-apoptosis effect on the skin. A study reported that Vitamin C could increase mitogenic and fibroblast motility, leading to accelerated wound healing.9,10 Administration of mecobalamin was used to increase the synthesis of epidermal growth factor (EGF) and provide a reconstructive effect.11 EGF interacts with its receptors throughout the epidermis, especially in the basal layer.12 EGF has a crucial role in wound healing by acting on the epithelial and fibroblast cells, increasing the recovery of injured epithelial.13,14

Cetirizine was administered to reduce the pruritus symptom. Cetirizine is a second-generation antihistamine H1 (H1 receptor antagonist) that acts by reversibly binding with histamine receptors, then stabilizes and maintains histamine in inactive forms. Second-generation H1 antihistamines selectively bind to the peripheral H1 receptors and do not cross the blood-brain barrier; thus, they have less sedation effect than first-generation. H1 antihistamines reduce pro-inflammatory cytokines production, expression of cellular adhesion molecules, reduce the release of mast-cell, basophils, eosinophil cell chemotaxis, and other cell mediators.1,15,16

Sepsis is the most frequent complication and may lead to death. Multiorgan failure and pulmonary complications may also occur in several cases.1 Since the 7th day of admission, the patient’s general condition had improved, and the patient was discharged on the 11th day of admission. The liver function test had returned to normal, and no serious complication was reported.17

The limitation of this study lies in the fact that we did not perform further tests to diagnose the causative drugs in this patient because the patient refused to be tested. We suggest that future studies perform further tests to diagnose the causative drugs, such as closed patches or in vitro tests with drug-specific lymphocyte proliferation assays.

CONCLUSION

Herein, we present a 34-year-old woman with SJS-TEN overlap secondary to Lamotrigine. Although rare, SJS/TEN is a life-threatening condition. Therefore, early detection is essential to prevent serious complications and death. This patient was diagnosed based on history taking, physical examination, laboratory studies, and histopathologic findings. The treatment includes early detection, immediately stopping the triggering drug, supportive treatment, and administering high-dose systemic corticosteroids. The patient had a remarkable improvement within a few days without any significant sequelae.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL CONSIDERATION

This case report has received permission from the patient.

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