

Stevens-Johnson syndrome/toxic epidermal necrolysis induced by lamotrigine in a patient with a cerebral cavernous malformation: a case report

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but serious cutaneous reactions characterized by epidermal and mucocutaneous detachment, most often drug-induced. SJS and TEN are considered the opposite extremes of the same spectrum of disease, where the percentage of skin involvement is <10% in SJS and >30% in TEN; the in-between range is

called an SJS/TEN overlap. We present the case of a 64-year-old patient who was treated with lamotrigine, an anti-epileptic drug, and developed SJS/TEN. After being hospitalized and recovering for three days due to the worsening of the clinical presentation, he was transferred to a burn center. Making an early diagnosis and identifying the appropriate drug is crucial for setting the correct treatment and reducing mortality. Advanced supportive care is required.

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Key words: lamotrigine; Stevens-Johnson syndrome; toxic epidermal necrolysis; cutaneous adverse reactions; drug reactions.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient included in this study.

Consent for publication: the patient gave his consent to use his personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Received: 4 April 2024.
Accepted: 5 September 2024.

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Dermatology Reports 2025; 17:10007
doi:10.4081/dr.2025.10007

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCARs), considered medical emergencies often necessitating hospitalization. The estimated incidence of SJS is approximately 4 cases per million person-years, while the incidence of TEN is 0.8 cases per million person-years. The mortality rate stands at about 5% for SJS and 30% for TEN. Over one hundred drugs have been recognized as triggers of SJS and TEN, including anti-epileptic drugs (AEDs), several antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs). These drugs induce SCARs through an idiosyncratic T-cell-mediated (type IV) hypersensitivity reaction, a type B unpredictable adverse drug reaction that relies on genetic predisposition and does not correlate with agent dosage, unlike the common adverse drug reactions (ADRs).¹ Among the anti-epileptics, those most related to the occurrence of adverse reactions are lamotrigine, carbamazepine, oxcarbazepine, phenytoin, barbiturates, valproate, and felbamate; in particular, lamotrigine and carbamazepine are marked with the FDA-required “black box warning” on the package inserts, urging physicians to conduct a thorough patient evaluation before prescribing these medications. Clinically, SJS/TEN manifestations appear within 8 weeks from the beginning of the assumption of the offending drug, characterized by the sudden onset of fever, flu-like symptoms, and the development of painful, blistering rashes, which can progress to widespread involvement.

Case Report

A 64-year-old man was diagnosed with a cerebral cavernous malformation (CCM) following brain magnetic resonance imaging (MRI). The tumor appeared capable of inducing epileptic seizures due to its “mass-effect”, but since surgical resection was not indicated, conservative management with levetiracetam was thus introduced. Unfortunately, drowsiness and irritability were noted, so the treatment was switched to lamotrigine, with an initial dose of 10 mg twice daily and weekly increments of 10 mg to a

maximum of 60 mg twice daily. After about three weeks, the patient experienced a cluster of symptoms, including a low-grade fever and bilateral conjunctivitis, while cutaneous lesions appeared symmetrically on the face and upper part of the trunk, quickly spreading to cover the entire body, predominantly on the proximal limbs. Skin involvement was represented by coalescing erythematous macules with purpuric spots, surmounted by flaccid bullae, which easily rupture, leaving wide erosions. Nikolsky's sign was positive. Necrotic epidermal "sheets" were detaching, especially from the back and the genital area, including the scrotum and the urethral meatus. Other signs of mucous membrane involvement were bilateral conjunctival hyperaemia, ulceration of oral mucosa, and nasal mucosa with hemorrhagic crusts (Figure 1). Alongside the mucocutaneous lesions, several invalidating symptoms occurred, such as dysphagia, ocular burning, ony-

chodystrophy, and dysuria; no respiratory complications were reported. Blood routine tests showed raised C-reactive protein (7.04 mg/dL), transaminases (AST 136 UI/L, ALT 144 UI/L), LDH (367 mU/mL), glycemia (111 mg/dL), and urea (61 mg/dL). The electrocardiogram trace was normal, with a heart rate of 90 beats/min, and the chest X-ray was within the limits. A nasopharyngeal swab for SARS-CoV-2 was routinely performed and returned a positive result. The history and clinical presentation of the patient raised the suspicion of SJS/TEN induced by lamotrigine. The drug was immediately suspended, and the patient was reallocated to the sub-intensive care unit for close observation to monitor the skin involvement and vital parameters. Intravenous (IV) methylprednisolone (1 mg/kg/day) was administered in parallel to fluid management. The severity-of-illness score for toxic epidermal necrolysis (SCORTEN) was calculated to predict mor-

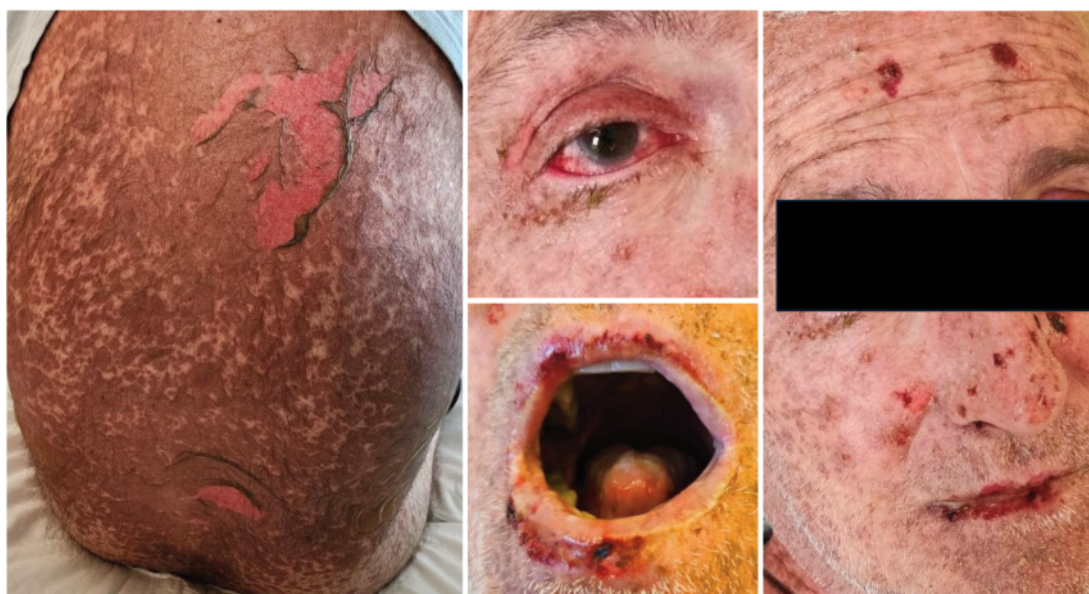


Figure 1. Day 1 of hospitalization. Involvement of both skin (necrotic epidermal "sheets" detaching from the back) and mucous membranes (bilateral conjunctival hyperemia, ulceration of oral and nasal mucosa with hemorrhagic crusts).



Figure 2. Day 2 of hospitalization. The clinical worsening with epidermal peeling increased to more than 50% of the BSA.

tality. Considering an age >40 and a body surface area (BSA)>10%, it accounted for 2, corresponding to a 12.1% mortality rate. The anticonvulsant was replaced with clonazepam, and the day after, the patient was also started with high-dose intravenous human immunoglobulin G (IVIg) (0.5 g/kg/day), analgic therapy, prophylactic antibiotic treatment, and advanced dressings were initiated. Since the patient initially showed a clinical worsening, with epidermal peeling increasing to more than 50% of the BSA (Figure 2), he was transferred to the burn center. After a first re-evaluation, the patient exhibited eupnea and was hemodynamically stable; however, the fever persisted, as did the positivity of the SARS-CoV-2 nasopharyngeal swab. The patient did not develop epileptic seizures while hospitalized.

Discussion

Lamotrigine, a non-aromatic AED approved by AIFA in 1994, is considered quite safe if compared with other anticonvulsants. However, it can bring severe ADRs, being one of the drugs most associated with the development of SJS, TEN, and SJS/TEN overlap syndrome. It is estimated that approximately 10% of seizure patients in therapy with lamotrigine experience an adverse cutaneous reaction.² Although the exact sequence of pathogenetic events is still partially unknown, there is strong evidence that an increased risk of developing SJS/TEN is related to specific human leukocyte antigen (HLA) alleles, which have been studied mainly in Asian populations. *HLA-B*1502* was shown to be associated with carbamazepine-, lamotrigine-, and phenytoin-induced SJS/TEN in Chinese and East Indians, while *HLA-B*58:01* appears to be associated with SJS/TEN in Chinese taking allopurinol.³ Among European and Japanese populations, only the link between *HLA-A*3101* and carbamazepine-induced hypersensitivity reactions has been clearly evidenced.⁴ Accordingly, recent literature advocates a pharmacogenetic screening before the start of AED treatment.⁵ In some countries, preliminary studies showed a positive impact of screening programs with a decrease in the incidence of SJS/TEN through the avoidance of a suspect drug in genetically predisposed patients.⁶ Despite being usually described as a T-cell-mediated HLA-dependent drug hypersensitivity reaction, other environmental factors have been reported as triggers for SJS/TEN. In fact, vaccines⁷ or viral or bacterial infections may interact with the immune system, making it more prone to severe drug reactions⁵ or directly initiate the inflammatory process. According to recent literature, COVID-19 infection may also represent a potential trigger of SJS/TEN, through direct activation of the immune system or increasing the susceptibility to drug reactions.⁸ Moreover, COVID-19 infection seems to increase mortality in patients with SJS/TEN.⁹ In our case, the history of the patient supports lamotrigine as the culprit drug; however, a cooperating role of SARS-CoV-2 cannot be excluded. The activation of cytotoxic T-cells, as well as natural killer cells and NK-T cells, initiates an immune response characterized by a cascade of inflammatory chemokines and cytokines such as perforin-granzyme B, granulysin, TNF- α ,¹⁰ CD40-CD40L,¹¹ and Fas-FasL,¹² resulting in apoptosis and necrosis of keratinocytes. The death of keratinocytes will ultimately lead to skin and mucosal inflammation and detachment.¹³

The clinical course of SJS/TEN is characterized by non-specific prodromal symptoms, including fatigue, fever, pharyngitis, and conjunctivitis, followed by the onset of erythematous, purpuric macules with blistering or necrotic centers, which may confer a targetoid appearance to the lesions.

Cutaneous lesions progress, merging into wide patches and generating flaccid bullae, leaving widespread and painful erosions when blister rupture occurs. Nikolsky's sign is often positive due to skin fragility.

Mucosal involvement with ulceration and erosions is described in over 90% of cases, and in more than half of patients, at least three different mucous membranes are affected, including the conjunctiva, lips, oral cavity, pharynx, genitals, and nose. Mucosal lesions may result in both short- and long-term sequelae, as the healing process can lead to scarring and strictures, ultimately causing functional impairment.

Other signs of systemic involvement, such as hepatitis and lymphadenopathy, can also be found.

As SJS/TEN is invariably associated with the risk of death due to fatal complications, the necessity of a prognostic tool for risk stratification led to the validation of the SCORTEN score, which was developed in 2000¹⁴ to predict mortality in hospitalized patients. SCORTEN is currently the most used prognostic score. It is based on seven factors: age >40, known active malignancy, heart rate (>120 beats/min), blood urea nitrogen (BUN, >28 mg/dL), detached body surface >10%, serum bicarbonate (<20 mEq/L), and serum glucose (>252 mg/dL). This standardized system was conceived considering that early complications are characterized by severe infections, electrolyte imbalance, insulin resistance, adult respiratory distress syndrome, and multiple acute organ failure. Those complications need to be managed in a specialized burn center, which, in our case, has proved to be indispensable.

Conclusions

Early diagnosis, rapid identification, and withdrawal of the culprit drug are key factors in reducing the mortality rate. High-quality supportive care and appropriate management of skin lesions in intensive care units or burn centers are also required.

Considering the life-threatening potential of SJS/TEN, their rapid evolution, and their strong impact on the prognosis, it is extraordinarily hard to realize randomized clinical trials regarding the most appropriate and successful therapy.

A treatment algorithm has not been well established, and the value of reported specific therapies is nowadays controversial; however, high doses of systemic corticosteroids and IVIg are preferred and used worldwide, especially if combined and performed in an early stage.¹⁵

More recently, cyclosporine and TNF- α antagonists have been tried as therapeutic options.¹⁶ Further studies to elucidate the therapeutic efficacies of these treatments in SJS/TEN are needed. Clinicians should be aware of and monitor the first few weeks after the introduction of lamotrigine therapy¹⁷ for possible adverse skin reactions to the drug.

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