Lamotrigine-Induced Stevens–Johnson Syndrome: A Clinical Report

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CASE REPORT

A 33-year-old Black woman presented to the urgent clinic with a 24-hour history of sore throat, fever, chills, and cervical lymphadenopathy that progressively got tender. Streptococcal pharyngitis was clinically diagnosed and was started on cephalexin (Keflex) oral 250 mg as well as an injection of penicillin. Approximately 3–4 days after starting on Keflex, the patient experienced swelling and tingling of her lips and diffuse, maculopapular rash on the palms of the hands, forearm, chest, and back (Figure 1). At that time, she was advised to go to the emergency department.

The hospitalist diagnosed the patient with a possible delayed hypersensitivity reaction to Keflex or penicillin. The patient was started on intravenous (IV) Solu-Medrol 80 mg and IV Benadryl 25 mg both three times per day. Suspecting Candida albicans, thrush, the hospitalist prescribed nystatin (swish and swallow) 5 mL four times a day. These medications were continuously given for the entirety of the patient’s 10-day stay. By day three of treatment, the patient’s lips started bleeding and intraoral ulcers began to erupt, making it difficult to eat or chew (Figure 2). In the patient’s own words, she said “my lips felt like a million needles touching me.”

Triamcinolone 0.1% topical ointment, a compound mucous membrane suspension of diphenhydramine/lidocaine/aluminum-hydroxide/magnesium hydroxide/simethicone, oral famotidine 20 mg, and oral Norco 5 mg were started on day 5. Infectious disease and dermatology specialists were consulted. Vitals, complete blood count (CBC), and basic metabolic panel (BMP) were within normal ranges. Human immunodeficiency virus (HIV), sexually transmitted disease (STD) panel, hepatic panel, and urine analysis were all negative; throat culture was negative for streptococcal pharyngitis and infectious mononucleosis. Final discharge diagnosis was allergic antibiotic drug reaction, oral thrush, and scarlet fever, and the patient was prescribed oral prednisone 10 mg. Two weeks after the initial mucosal ulcerations, the patient’s lips started to heal, but with black scarring. The patient’s sense of taste and the painful ulcerations in the mouth took over one month to heal (Figure 3).

Two weeks post-hospitalization discharge, the patient had a follow-up with the primary care physician. At that time, the patient noted only a recent diagnosis of depression and anxiety by a psychiatrist one-month prior to the onset of the symptoms. She was started on Zoloft 50 mg daily and Lamotrigine 100 mg oral daily.

Figure 1: Patient’s palmar aspect of hands exhibiting erythematos atypical targetoid macules.
Both Zoloft and Lamotrigine were self-discontinued after two weeks. These medications were not noted during her initial visit or hospital course. The patient also noted no known medication use (including no allergy to previous use of Keflex). All vaccinations were up-to-date. Final diagnosis by her primary physician was Stevens–Johnson syndrome (SJS) due to recent use and discontinuation of Lamotrigine.

DISCUSSION

Stevens–Johnson syndrome (SJS) is an immune-complex mediated type 4 hypersensitivity reaction involving skin and mucous membranes that was first described by Hebra in 1866 as “erythema multiforme exudativum” involving mucous membranes. It was named by Albert Mason Stevens and Grant Chambliss Johnson in 1922 in published case reports from Bellevue Hospital, New York where two boys aged 7 and 8 with cutaneous eruptions but no known diagnosis [1]. Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN) are diseases on the spectrum with SJS involving less than 10% of the body and carrying a 1–5% mortality risk. Stevens–Johnson syndrome/toxic epidermal necrolysis overlap occurs with 10–30% body surface area (BSA) involvement and TEN >30% BSA involvement. Toxic epidermal necrolysis carries a mortality risk of 25–35%. Progression from SJS to TEN can be both rapid and unpredictable [2]. Estimated incidence of SJS, TEN, and SJS/TEN ranges from 2–7 cases per million people per year and is higher among patients with HIV or active cancer. Stevens–Johnson syndrome or TEN can occur at any age and is more common in women than men, approximately 1:2 [3].

Stevens–Johnson syndrome is attributed to the body’s inability to detoxify drugs and their peptide metabolites, detected as foreign by the body. This results in cytotoxic T cells attacking keratinocytes and epithelial cells in the mucosa/epidermis, leading to cell death and subsequent sloughing of the skin due to a release of perforin and granzymes, which are cytolytic proteins produced/secreted by T-lymphocytes and natural killer cells [4]. These perforin cytolytic proteins lyse the epithelial cells and form pores allowing granzymes to induce apoptosis. Proinflammatory cytokines such as TNF-alpha and interferon gamma attract immune cells and cause a cascade of further damage [5, 6].

Stevens–Johnson syndrome presents with a prodrome, influenza-like symptoms such as sore throat and malaise, two to three days before the onset of skin manifestations. Stevens–Johnson syndrome lesions are typically painful, often confluent, begin as macules that progress to vesicles/bullae with the rash occurring one to three weeks following the ingestion of the medication [7]. This patient’s new neurologic mediation falls within the time frame. Stevens–Johnson syndrome cutaneous lesions begin as a typical exanthematous eruption, often on the trunk, but can present as pink to dusky macules, often irregular, poorly defined, on the palms and soles with areas of purpura and blistering, leading to detached skin and causing pain/tenderness. As the disease worsens, large areas of blistering occur with subsequent sloughing.
of the skin and may spread to the face and proximal extremities [5–8]. A positive Nikolsky’s sign, patches of skin that slide off with light pressure, can be seen in SJS. Mucosal sloughing occurs in more than 90% of cases. The eyes are involved in greater than 80% of cases often leading to scarring and blindness. The rash also affects the mucosa of the urinary, gastrointestinal, and respiratory tracts. Systemic signs are common and may include fever, tachycardia, hypotension, conjunctivitis, seizures, and coma. Definitive diagnosis is made by skin biopsy, but clinical diagnosis is typically made based on symptoms and timeline [6, 8]. Differential diagnoses for SJS/TEN include: hypersensitivity reaction, drug rash with eosinophilia, and systemic symptoms (DRESS), dermatitis, angioimmunoblastic lymphadenopathy, viral eruption, vasculitis, erythema multiforme, staphylococcal scaled skin syndrome, and toxic shock syndrome. Immediate detection of a life-threatening drug reaction is vital to effective treatment and a delay in discontinuing the offending agent could be deleterious [6, 7]. Treatment includes hospitalization for severe cases, immediate discontinuation of the offending medication or treatment for the underlying condition, and starting on antihistamines, IV fluids, corticosteroids, pain management, or intravenous immunoglobulin (IVIG) [8, 9].

The most common offending agents are allopurinol, non-steroidal anti-inflammatory drugs (NSAIDs) like piroxicam, antibiotics, immune modulators like sulfasalazine, and anticonvulsants. The highest rates of cutaneous drug reactions occur due to antibiotics, particularly sulfonamides. Anticonvulsants can include Lamotrigine, phenytoin, and carbamazepine. Immunizations and infections such as mycoplasma pneumonia, cytomegalovirus, herpes simplex virus (HSV), coxsackievirus, and echovirus are less common causes [8–10]. In this case, the causative agent Lamotrigine, a mood stabilizer and anticonvulsant, has black box warning for SJS. Typical side effects of Lamotrigine include fatigue, dizziness, sleep issues, tremor, headache, and diarrhea. The risk of developing SJS with Lamotrigine is rare and can occur within the first few weeks of use [11]. In this case, however, after discontinuing medication after only two weeks, the patient presented with SJS approximately a month later. There have been very few reports of SJS as a result of monotherapy Lamotrigine--0.03% to 0.08% incidence in adult populations. Reports with combined use of valproic acid and Lamotrigine, however, have more commonly been diagnosed [3, 7, 8, 11]. Since higher doses of Lamotrigine are associated with SJS, it is best to start on the lowest dose and titrate up. It also bears mentioning that the discontinuation of Lamotrigine may not prevent a rash from becoming life-threatening, and since rash severity varies and includes a risk for SJS, patient education should consist of continuous monitoring of the outbreak for improvement after the discontinuation of the medication [11].

CONCLUSION

Stevens–Johnson syndrome is a rare type 4 hypersensitivity, severe mucocutaneous reaction of <10% of the skin that can lead to epidermal detachment due to cytotoxic T-cell mediated destruction of keratinocytes expressing foreign antigen. Medications such as Lamotrigine are the most common cause of SJS. Prodrome symptoms like fever, sore throat, and fatigue precede mucocutaneous symptoms and occur as burning eyes and red/purple macules leading to symptoms ranging from blisters with a positive Nikolsky’s sign to painful crusts/erosions on the skin or eyes/lips. Diagnosis can be made by clinical history or skin biopsy showing epidermal necrosis. Treatment includes supportive care with IV fluids, analgesics, antihistamines, or IV immunoglobulin. In conclusion, drug-induced skin reactions require a detailed history of drug-intake and immediate withdrawal of the offending agent once it is confirmed.

Keywords: Lamotrigine, Stevens–Johnson syndrome, Toxic epidermal necrosis

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