Case Report

Lamotrigine-induced Stevens–Johnson Syndrome Coexisting with Seborrheic Dermatitis in a Dengue virus-infected Patient: A Case Report

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Stevens-Johnson syndrome is a serious skin condition. Lamotrigine-induced Stevens-Johnson syndrome is strongly associated with HLA*B1502 in the Thai population. Stevens-Johnson syndrome has never been reported to coexist with other skin diseases. Here, the authors report a case of Stevens–Johnson syndrome with severe seborrheic dermatitis in a Dengue virus-infected patient. The patient was treated with a high-dose systemic corticosteroid and has shown an excellent response to therapy.

Keywords: Dengue viral infection, Seborrheic dermatitis, Stevens–Johnson syndrome, Lamotrigine, IL-17, Cytokine

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening conditions with extensive epidermal necrosis (EN), both in the epidermis and mucosal epithelium. Patients are classified into one of the three following groups according to the total area in which the necrotic epidermis is detached or detachable[(1)]: SJS, less than 10% of the body surface area (BSA)[(2)]; SJS-TEN overlap, between 10% and 30%[(3)], and TEN, more than 30% of the BSA. The mechanism of the disease is still not completely understood, but genetic susceptibility can contribute to an increased risk of EN. After the early withdrawal of offending drugs, patients with a Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) of 0 to 1 and stable disease can be treated in a general ward. Those with higher scores or rapidly progressing disease should be admitted to a special isolation room or intensive care unit. The specific treatment remains controversial.

Seborrheic dermatitis (SD) is a common, chronic skin disease that presents as erythematous and thick greasy scales over the scalp and face. Multiple drugs can lead to SD-like eruptions. SD is also common in HIV-infected patients. Its pathogenesis is poorly understood but may be related to fungal infection, genetic background, and immunological responses. A high number of *Malassezia furfur* can disturb the protective barrier function of the skin. Malassezin, generated by *M. furfur* or *Malassezia restricta (M. restricta)*, can serve as an agonist of the aryl hydrocarbon receptor, which is involved in the regulation of T-helper 17 cell differentiation and contact sensitivity. Topical medications, including corticosteroids, calcineurin inhibitors, antifungal drugs, and keratolytics, are among the first-line treatments.

Dengue virus (DENV) infection is a particularly common disease in Thailand. The immune system fails to neutralize the secondary infection, making the infection fatal by the induction of the self-immune system, which increases the ability of the virus to infect and destroy the cells. Thrombocytopenia and vascular leakage lead to hypotension and shock once explained by the innate immune system, esp. type I IFN response. However, activation of the adaptive immune-mediated cytokine storm is recently interested. Although common, petechiae and a red rash on the skin are not pathognomonic and cannot help in the diagnosis of DENV. These 3 conditions do not appear to be related to each other. However, the authors report a case of SJS coexisting with SD in a DENV-infected patient.

Case Report

A 30-year-old Thai man suffered from bipolar disorder controlled with nortriptyline, clonazepam, and olanzapine at the psychiatric hospital. The psychiatrist added lamotrigine to control the disease. Two weeks later, the patient presented to the emergency room with a high-grade fever. A blood sample was sent for testing, and the Dengue IgM rapid test was positive. Two days after the onset of fever, he developed bright red rashes with yellowish flakes on his scalp, face, and neck. Simultaneously, bright red rashes appeared over his body, arms, legs, and palms. After 5 days of fever, he followed-up with the psychiatrist, and the doctor discontinued lamotrigine. On day 7, the patient returned for follow-up regarding the DENV infection, but the doctor noticed generalized rashes, slight eye irritation with whitish-yellow exudates, and painful ulcers on his lower lips. There

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was no other mucosal involvement. The patient had never developed this type of rash before. He was admitted to an isolated room in the intensive care unit.

His vital signs were as follows: a body temperature of 36.7 degrees Celsius, blood pressure of 140/90 mmHg, pulse rate of 140 beats per minute, and respiratory rate of 18 breaths per minute. Skin examination revealed confluent bright erythematous patches with coarse yellowish greasy scales over his face, scalp, and upper neck (Figure 2A). Dusky-red maculopapular rashes over his body, extremities, and both palms were also noted. A small area of epidermal detachment was observed on the medial side of both forearms (Figure 2C). Large tender shallow ulcers with a hemorrhagic crusts developed on his lower lip and nearby buccal mucosa (Figure 2B). His SCORTEN score was 1, and his Seborrheic Dermatitis Area and Severity Index (SEDASI) was 52, indicating severe seborrheic dermatitis. An ophthalmologist confirmed the involvement of both eyes. Intravenous dexamethasone and corticosteroid eye drops were started.

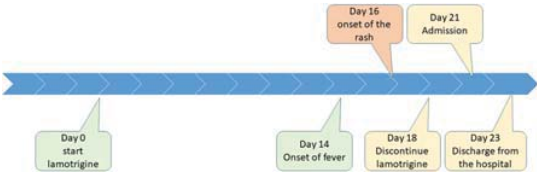

Figure 1. The timeline of the patients' illness.

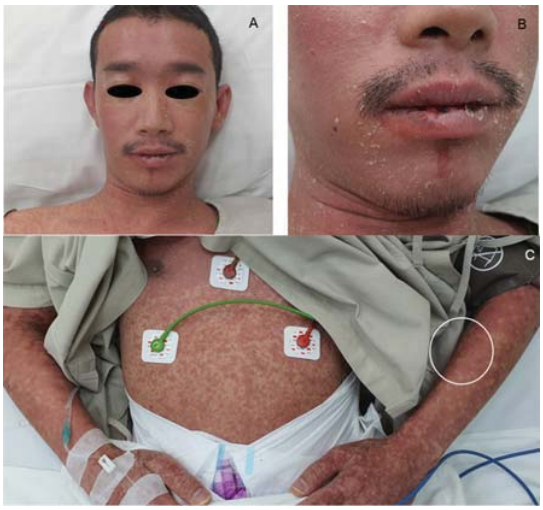

Figure 2. A) Erythematous patched with yellowish coarse greasy scale on face, scalp, and upper neck. B) Painful shallow ulcer with hemorrhagic crust on lower lip. The typical seborrheic dermatitis' scales were moderate. C) The diffused dusky-red papules on trunks and extremities with small area of epidermal detachment on left forearm (white circle).

HSV IFA, HSV (I&II) IgM, and *Mycoplasma pneumoniae* IgM tests were all negative. Anti-HIV was non-reactive. The COVID-19 (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) disease) RT-PCR test was negative (ORF1 a/b gene and E gene results were negative, SAR-COV1 interpretation was undetected).

After treatment with a high-dose systemic corticosteroid for 2 days, the patients' condition drastically improved. SEDASI indicated moderate seborrheic dermatitis. The erythematous confluent patches stopped spreading, and some areas became hyperpigmented with large whitish scales peeling off as in Figure 3.

The patient came back for a follow-up appointment, and all skin lesions had improved. Post-inflammatory hyperpigmentation was observed on the trunk and extremities. His face still showed mild erythema on nasolabial folds without hyperpigmentation. The rash on his palms almost completely subsided and peeled off as sheet-like scales (Figure 4).

Discussion

SJS and TEN are rare but fatal diseases caused by drugs. The most common causes are sulfonamide antibiotics, anti-epileptics, non-steroidal anti-inflammatory drugs, and allopurinol. SJS and TEN are also caused by some infections, such as herpes simplex virus, *M. pneumoniae*, and HIV. Lamotrigine is one of the most frequent causes of cutaneous adverse drug reactions, which mainly present as a maculopapular rash. Severe cutaneous reactions, such as SJS, are rare. The period of high risk is within the first 8 weeks of treatment[1]. In our case, SJS was most likely caused by lamotrigine.

Lamotrigine, a phenyltriazines drug, is an anticonvulsant that prevents depressive episodes in patients with bipolar disorder. Lamotrigine-induced SJS/TEN is highly associated with HLA-B*1502 in Asian people[2]. Multicenter studies conducted in Thailand reported that the HLA-B*1502 allele was found in 40.0% of patients who developed cutaneous adverse drug reactions and 12.0% of tolerant patients[3]. The test for HLA-B*1502 in our patient was negative. Additionally, the tests for common infections, such as HSV IFA, HSV (I&II) IgM, and *M. pneumoniae* IgM, were all negative. Anti-HIV was non-reactive. Olanzapine and SJS are not likely related. There is only one report of an olanzapine-induced fixed drug eruption in medical databases[4].

Seborrheic dermatitis is a very common skin disease related to neuropsychiatric disorders, drugs, and stress. Among primary psychiatric disorders, anxiety with emotional stress is related to SD[5]. The patient in this case experienced severe SD for the first time. However, he may not have recognized mild SD because of its mild symptoms. Because of the chronic nature with a gradual onset, the first sudden onset of severe SD in non-HIV-infected patients is uncommon. The severe SD in this case may have been influenced by

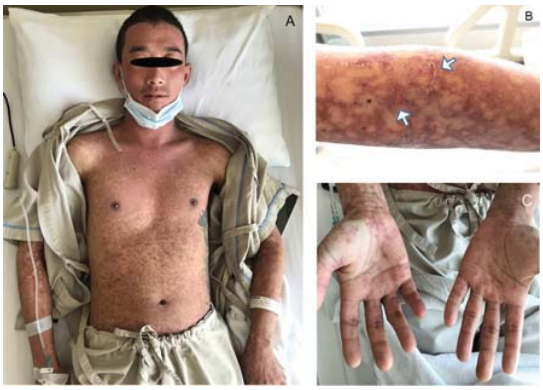

Figure 3. After the treatment with intravenous dexamethasone for 2 days. A) Upper chest wall up to face showed confluent erythematous patches, while the body showed dusky-red macules, and confluent into the patches. B) Confluent maculopapular rashes turned into reticulate hyperpigmentation with large whitish peel-off scales. Small epidermal detachment was presented (white arrow). C) The rash on the palms, turn to early hyperpigmentation.

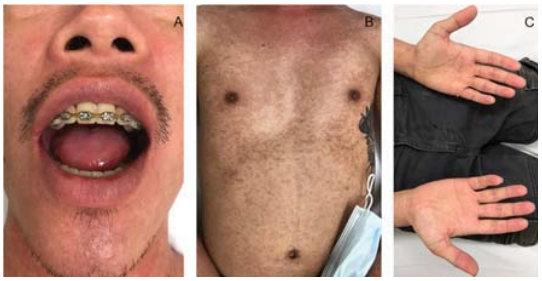

Figure 4. 2 weeks later. A) No mucosal ulcer, facial skin showed no hyperpigmentation with faint erythema on nose. B) Post-inflammatory hyperpigmentation on trunk. C) No erythema, few scales on palms were presented.

physical stress or the fever caused by DENV infection. To date, there have been no reports of either lamotrigine-induced SD or SD coexisting with SJS.

Currently, the diagnosis of DNV infection is challenging. Serology tests are highly useful for early diagnosis than previously by clinical presentations. Dengue NS1 antigens increase in titer during the first few days. The levels of IgM increase during the primary infection, and the presence of IgG with IgM indicate secondary infection. Increased levels of IgG indicate that the patient was previously infected with DNV. In our case, the Dengue NS1 antigen test was negative, Dengue IgG was negative, and Dengue IgM was positive, suggesting that this was the first infection, which explains the mild symptoms without hemoconcentration. False-positive Dengue IgM tests may be observed in patients with flavivirus infection, other hemorrhagic fevers, and more importantly, COVID-19[6,7]. COVID-19 tests were negative in this case.

In the database, there is no report of severe SD coexisting with SJS in the same setting or SJS induced by DENV infection. Because SJS results in a large area of skin necrosis, other skin conditions might be obscured. As all 3 of these diseases might occur simultaneously, the authors reviewed the literature for a relationship between their pathogenic mechanisms and found that interleukin-17 (IL-17) is a mediator of all 3 diseases. IL-17 is an inflammatory cytokine that is produced in response to infections, autoimmune diseases, and malignancies[8]. IL-17 plays an important role in inflammatory skin diseases, such as psoriasis. Recently, it was suggested that the immunopathogenesis of DENV infection might involve antibody-dependent enhancement or cytokine storm[9]. High serum levels of IL-17 are associated with the severity of DENV infection[10]. Peripheral blood mononuclear cells from DENV-infected patients have been shown to exhibit a high frequency of CD4+IL-17+ producing cells by flow cytometry analysis[11]. In SJS/TEN, the serum IL-17 concentration correlates with the severity of the disease[12]. Among the inflammatory cytokines reported to be increased in SD, the enhanced expression of IL-17 in a specific group of T cells was recently reported in Mpzl3 knockout mice with a seborrheic dermatitis-like phenotype[13]. The authors hypothesize that DENV infection increases the serum concentration of IL-17. As the skin lesions erupted 2 days after the presentation of fever, the elevated serum IL-17 levels rather than lamotrigine might have triggered both SD and SJS in this patient. However, lamotrigine-induced SJS increases serum IL-17 levels and exacerbates preexisting mild SD without any link to DENV infection. The excellent response of SJS to a high-dose systemic corticosteroid may support a mechanism of cytokine-driven inflammation, represented by the short half-life of mediators. Future studies should focus on further elucidating the pathogenesis of these disorders.

Conclusion

The authors report a case of HLA-B*1502-negative, lamotrigine-induced SJS coexisting with severe SD in a DENV-infected patient. The authors speculate that the excellent response to high-dose systemic corticosteroids indicates that the condition of the patient was mediated by cytokines.

What is already known on this topic?

Lamotrigine-induced SJS is a life-threatening condition with long-term complications. The HLA-B*1502 screening test should be performed routinely before the initiation of treatment.

What this study adds?

Drug-induced SJS may be associated with other skin conditions, but there is limited information. The authors report the occurrence of SJS and SD in the same setting. Cytokines may play crucial roles in the pathogenesis of these diseases.

Acknowledgements

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Potential conflicts of interest

The authors declare no conflict of interest.

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