Case Study

Acyclovir Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Rare Case Report

T. Amul Prathap[1], D.G. Abinish[2], S. Kalaivani[3], D. Lokeshvaran[4], J. Aswin[5]

[1]DNB (DVL) Department of Dermatology, Assistant Professor, [2-5]Pharm D Intern, Government medical college, Nagapattinam, Tamil Nadu.

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Abstract

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are serious, life-threatening conditions often triggered by drug reactions, characterized by widespread skin detachment and mucosal involvement. This case report describes a 29-year-old woman who developed Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis after receiving prophylactic acyclovir for suspected herpes. The patient initially presented with oral ulcers that rapidly progressed to widespread blisters, ulcers, and severe skin peeling. A thorough diagnostic evaluation, including skin biopsy and the Naranjo algorithm, identified acyclovir as the causative agent. The patient was managed in intensive care with intravenous methylprednisolone 500mg per day for 3 consecutive days as pulse therapy, antibiotics, and other supportive treatments. This case underscores the importance of early recognition, prompt discontinuation of the offending drug, and a multidisciplinary treatment approach. It also highlights the critical need for heightened awareness among healthcare professionals regarding the potential for severe adverse reactions with commonly used medications like acyclovir, to improve patient safety and outcomes.

Keywords: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Acyclovir, Adverse Drug Reaction.

Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe, life-threatening conditions primarily caused by drugs, characterized by extensive skin detachment and mucosal involvement. SJS and TEN occurs at a rate of 1 to 6 and 1 to 2 cases per million annually.[1]The epidemiology of SJS/TEN highlights regional differences in drug associations and genetic risk factors. In Southeast Asia, aromatic anticonvulsants cause over 50% of cases, with carbamazepine alone responsible for 25-33%, compared to only 5-6% in Europe. The HLA-B*15:02 allele, a genetic variant of the Human Leukocyte Antigen (HLA) system commonly found in Southeast Asians but rare in Europeans and Africans, explains this higher risk. Strontium ranelate, associated with HLA-A*33:03 and HLA-B*58:01, also shows regional variation in drug-induced SJS/TEN.[2] In India, the incidence of SJS/TEN is unknown, but it accounts for 6.84% of severe Cutaneous Adverse Drug Reactions (CADR).

Corresponding Author: D.G. Abinish, Pharm D Intern, Government medical college, Nagapattinam, Tamil Nadu.

E-mail: drabinishdgpharmd@gmail.com

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Mortality rates are 12.94% overall, with drugs causing 97.14% of cases. The leading causes are antibiotics, anti-epileptics, and NSAIDs. Ocular complications occur in 40.29% of acute cases, with 60% of chronic cases leading to low vision or blindness.[3] Although antiviral agents like acyclovir are generally well-tolerated with a low incidence of adverse effects, such as mild nausea and headache, rare but serious complications like encephalopathy and seizures can occur, especially with high doses.[4] Despite its overall safety profile, there have been rare reports of fatal cases of SJS/TEN induced by acyclovir.

SJS/TEN often begins with nonspecific symptoms such as fever, sore throat, and general malaise, followed by the rapid development of painful mucocutaneous lesions that can affect the eyes, mouth, and genitals.[5]Diagnosis primarily depends on clinical assessment rather than histopathology. Effective management involves promptly identifying and discontinuing the causative agent, using tools such as the ALDEN (Algorithm of Drug Causality for Epidermal Necrolysis) algorithm for drug causality and the SCORTEN (Severity-of-Illness Score for Toxic Epidermal Necrolysis) scale for prognosis.[6] ALDEN is a specific tool developed to improve the individual assessment of drug causality in SJS/TEN. It categorizes drug involvement as "very probable", "probable", "possible" or "very unlikely" based on multiple criteria, including drug notoriety, pharmacokinetics, and temporal relationship.[7] The SCORTEN tool is used to predict mortality and severity in SJS/TEN patients. It should be calculated within 24 hours of admission and on the 3rd day, with some suggesting a reassessment on day 5. SCORTEN identifies seven risk factors, each scored as one, with mortality rates increasing with higher scores. SJS/TEN has high mortality rates: 1–5% for Stevens-Johnson syndrome, 10–15% for transitional forms, and 25–30% for toxic epidermal necrolysis. Death is most commonly due to sepsis, pulmonary failure, and multiple organ failure.[8]In addition to these diagnostic methods, the Naranjo's Adverse Drug Reaction causality assessment scale[9] and the causality assessment scale provided by the WHO-Uppsala Monitoring Centre also play a crucial role in evaluating drug-related adverse events, offering standardized approaches to determine the likelihood of a causal relationship between a drug and the observed adverse effects.

The initial management of SJS and TEN centers on promptly discontinuing the causative drug, ensuring hospital admission, and addressing any co-morbidities. For severe cases, intensive care or burn unit admission is recommended. Wound care focuses on preventing infection and preserving skin, with varying approaches across centers. Fluid and electrolyte management is crucial due to risks similar to burn victims. While the use of corticosteroids remains debated, cyclosporine shows promise, and other treatments like IVIg and TNF-α inhibitors are under investigation for severe cases.[10]

This case report presents information about a rare and severe case of acyclovir induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.

Case Presentation

A 29-year-old married female presented with chief complaints of blisters and ulcers all over the body for the past 6 days, which initially started as an oral ulcer. The vesicular lesions first appeared on the right upper limb and then spread across the body after the intake of drug therapy for suspected chicken pox. She was immediately admitted to the emergency department and was administered intravenous dexamethasone at a dosage of 8 mg. In addition, she received a combination of 2 units of Ringer's Lactate and 1 unit of Normal Saline, infused at a rate of 75 mL/hr. For immediate relief of symptoms, a single dose of 10 mg cetirizine tablet was also given. Following this initial treatment, she was transferred to the Intensive Care Unit for further management and was subsequently evaluated by a dermatologist. She had a past medical history of a small vesicle on her neck, for which she consulted a doctor who prescribed tablet Acyclovir 500 mg twice daily as a prophylactic treatment for suspected herpes. After administration offirst dose, she developed blisters and ulcers around her mouth and other areas of her body. Despite the worsening condition, she continued the drug, which led to a significant increase in symptoms. By the sixth day, she experienced severe skin peeling throughout her body.

On examination, the patient was conscious, oriented, and febrile. Local examination showed a widespread skin rash, blisters, sores over the face and hands, and swelling and crusting of the mouth and

mucosal membranes. Systemic examination and vitals were found to be normal. Laboratory investigations revealed a normal WBC, RBC, hemoglobin, hematocrit, MCV, MCHC and platelet count. Differential counts show an increased neutrophils of 75.1% and a decreased lymphocyte of 17.8%. All others are found to be normal. Other findings such as RBS, electrolytes, LFT and RFT were found to be normal. Peripheral smear showed mild neutrophilic leukocytosis with massive thrombocytosis. CRP was positive at 96 mg/dL, indicating inflammation. Urine routine showed no albumin or sugar, with 1-2 pus cells suggesting infection or inflammation. HIV test was negative. Lipid profile revealed elevated triglycerides (376 mg/dL) and VLDL of 75 mg/dL, with a lowered HDL of 36 mg/dL. ECG, ECHO and USG was found to be normal.

Dermatological examination revealed generalized hyperpigmentation with islands of sparing, multiple bullae, and vesicles of varying sizes ranging from 2x2 cm to 5x4 cm distributed across the body. Multiple erosions were noted on the genital area and upper limbs, along with oral and lip erosions. The palms and soles showed pigmentation, and similar pigmentation was observed in the genital area. The histopathological examination of the skin biopsy revealed extensive epidermal necrosis, accompanied by basal vacuolar degeneration and a prominent lymphohistiocytic infiltrate within the dermis, reflecting a significant inflammatory response. (Fig.2) Following all examinations and investigations, an ADR causality assessment was conducted to establish a precise diagnosis. The Naranjo algorithm was utilized, resulting in a score of 11, which classified the case as a "definite" drug-induced reaction. This strongly suggested acyclovir as the causative agent for SJS/TEN.Based on the prognostic factors, a SCORTEN score of 1 was found which indicates a 3.2% mortality risk for SJS/TEN. Furthermore, the WHO-Uppsala Monitoring Centre criteria indicated a 'probable/likely' causality, supporting the diagnosis of acyclovir-induced SJS. The clinical presentation and timing of symptom onset relative to drug administration, combined with the absence of any prior history of drug allergies or hypersensitivity, confirmed this as a first-time hypersensitivity event.

After being transferred to the ICU, the patient's treatment was revised, discontinuing dexamethasone 8 mg IV and initiating piperacillin-tazobactam 4.5 g IV three times daily, methylprednisolone 500 mg IV in 1 unit of 5% dextrose over 2 hours only for 3 consecutive days as pulse therapy, and ranitidine 50 mg IV twice daily.[8] Additional medications includedtablet paracetamol 500 mg three times daily, tablet chlorpheniramine maleate 4 mg at bedtime, povidone-iodine ointment, saline-soaked dressings, and B-complex, vitamin C, and calcium tablets for 7 days. On the third day, 0.1% betamethasone ointment was added; on the fourth day, an injection of Astymin Forte was given, and liquid paraffin was started. On the same day an ophthalmologist's examination was done which revealed both eye lagophthalmos, leading to the prescription of Lacryl-PF gel for twice daily and lid taping at bedtime. On the sixth day, the patient had a seizure with fever, chills, and rigor, prompting the initiation of levetiracetam 500 mg IV twice daily and the resumption of dexamethasone 8 mg IV once daily. On the seventh day, the patient was transferred to the Female Medicine Ward.

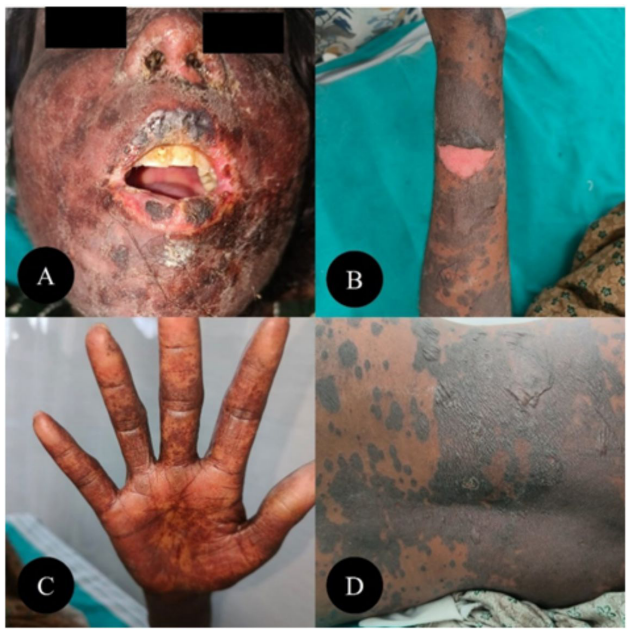

Fig. 1: Clinical presentation of SJS/TEN during admission showing (A) Extensive lesions on the face, (B) erythematous patches on the forearm, (C) pigmentation on the palm, and (D) widespread epidermal detachment on the dorsal portion of the body.

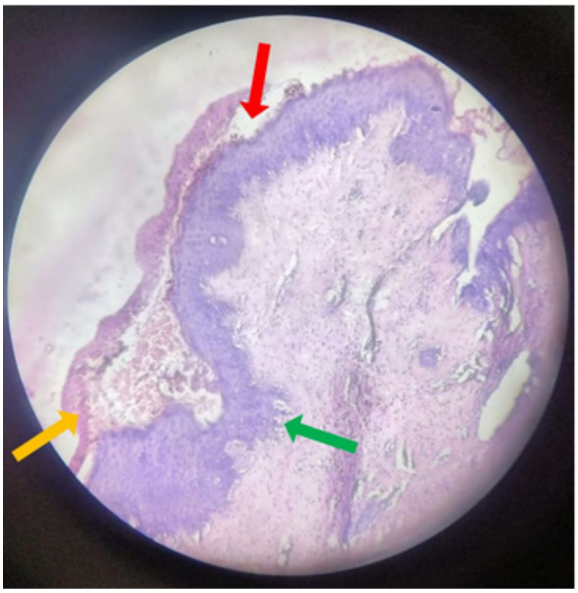

Fig. 2: Skin biopsy showing extensiveepidermal necrosis (↑) with basal cell vacuolar degeneration (↑) and a prominent intraepidermal bulla (↑), indicating a significant inflammatory response.

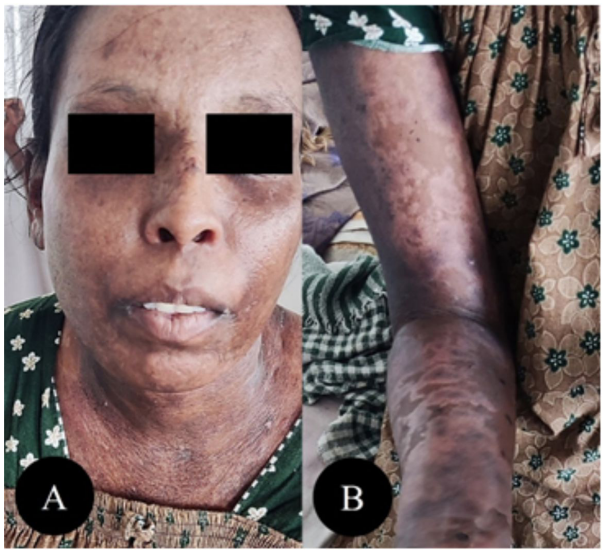

Fig. 3: One week after pulse therapy showing (A) healing lesions on the face with reduced erythema and (B) significant recovery on the forearm with fading pigmentation and re-epithelialization.

Discussion

The intricate pathophysiology of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) underscores the complexity of immune-mediated skin disorders. These conditions are characterized by widespread keratinocyte apoptosis, primarily driven by cytotoxic T cells through mechanisms such as perforin-granzyme and Fas-FasL pathways, alongside the role of granulysin, a potent cytolytic protein. Additionally, metabolic factors like slow acetylation contribute to the disease by generating reactive metabolites that can provoke severe immune responses. The impact of genetic susceptibility is evident, with specific HLA alleles being strongly linked to drug-induced SJS-TEN, particularly within certain ethnic groups. Furthermore, variations in drug metabolism genes, such as CYP2C9, can influence disease severity by impairing drug clearance and exacerbating toxicity.[11]

Clinical presentation in this case included widespread erythematous lesions, blistering, and mucosal involvement after intake of acyclovir, which are hallmark features of SJS. The dermatological findings, combined with systemic involvement, highlight the severity of the condition and the importance of early diagnosis and intervention. The rapid onset of these symptoms following drug intake strongly implicates tablet acyclovir as the causative agent. To assess the likelihood of this adverse drug reaction, the Naranjo algorithm was employed, which is a systematic tool used to determine the probability of drug-induced adverse effects. The patient's case was classified as a "definite" drug-induced Stevens-Johnson Syndrome (SJS) with a Naranjo score of 11, signifying a high likelihood that acyclovir was responsible for the reaction. Also, causality assessment indicated a 'probable/likely' relationship based on the WHO-Uppsala Monitoring Centre criteria. Given the clinical presentation and the timing relative to drug administration, a diagnosis of acyclovir-induced SJS was confirmed. Notably, the patient had no prior history of drug allergies or hypersensitivity reactions, suggesting this was a first-time hypersensitivity event. The clinical presentation and rapid onset of symptoms in this case align with findings by *Sen et al.*,[12] and *Gungam P et al.*,[13] who reported with similar features of SJS and TEN associated with acyclovir diagnosed by using Naranjo's and WHO's causality assessments.

Acyclovir, a synthetic analogue of guanosine, is commonly used to treat infections from herpes simplex and varicella zoster viruses. While it is usually well-tolerated, some individuals may experience adverse drug reactions. These rare side effects can include mild issues like inflammation at the injection site and phlebitis, as well as more serious conditions such as bullous reactions, acute renal failure, neurotoxicity, and, in exceptional cases,

Stevens-Johnson syndrome.[12] This underscores the importance of careful monitoring during acyclovir therapy to promptly identify and manage any unexpected reactions.

The management of SJS and TEN centers on the immediate discontinuation of the suspected drug, though identifying it can be challenging. Key aspects of care include supportive measures such as skin barrier restoration, fluid management, and infection control. While systemic treatments like cyclosporine show potential outcome, they lack conclusive evidence. Treatment varies with skin involvement, and long-term complications may include pigmentation changes and scarring.[8] The pulse therapy of SJS/TEN involves administering 500 mg/day of intravenous methylprednisolone for 3 consecutive days. If no new mucocutaneous lesions develop, oral prednisolone is initiated and gradually tapered.[14] Likewise, in this case the patient received pulse therapy with 500 mg of intravenous methylprednisolone for 3 consecutive days which is an important aspect in reversing this condition. This tailored regimen balanced effective treatment with minimizing side effects, considering the patient's clinical condition.

Comprehensive care involves addressing ocular, gynecologic, oral, respiratory, renal, gastrointestinal, and hepatic complications through a multidisciplinary approach. Nutritional support is critical, with nasogastric or parenteral nutrition often needed. Physical and occupational therapy are crucial for long-term recovery, while pain management and social work support are essential for addressing acute and chronic needs. Effective risk communication and coordinated care planning are vital for patient education and follow-up.[15]

Therefore, this case highlights the critical need for vigilant monitoring of patients receiving acyclovir due to its potential to induce severe adverse reactions such as SJS. Healthcare professionals must exercise heightened awareness when prescribing acyclovir, particularly in individuals with a history of hypersensitivity or those at higher risk. It is essential to monitor for early symptoms of SJS and to educate patients on recognizing these signs promptly. Effective patient education, coupled with early detection and intervention, is crucial for managing and mitigating the impact of such severe reactions, thereby improving overall patient safety and outcomes.

Conclusion

In conclusion, this case underscores the importance of careful monitoring when prescribing acyclovir, despite its general safety. The potential for severe adverse reactions like Stevens-Johnson syndrome (SJS) highlights the need for prompt recognition and swift discontinuation of the offending drug. Healthcare professionals must remain vigilant, educate patients on early symptoms, and ensure a coordinated care approach to manage and reduce the risks of such serious complications, ultimately enhancing patient safety and outcomes.

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