A Suspected Case of Steven-Johnson Syndrome and Toxic Epidermal Necrolysis Overlap Due to Clindamycin Administration – Report of a Rare Case

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Abstract

Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe cutaneous adverse reactions (SCAR) differentiated by degree of skin detachment. Common triggers include anticonvulsants, sulfonamides, antibiotics (penicillin, cephalosporin, quinolones) and acetaminophen. Reports of clindamycin causing cutaneous complications are rare with only 6 published reports, none of which were reported in the Philippines. Though uncommon, it is an important consideration in patients presenting with erythematous to violaceous purpuric macules that progress to full thickness epidermal exfoliation.

A 59-year-old female who presented with erythematous maculopapular rash on both hands, dry crusted lesions on the mouth and positive Nikolsky sign within 28 days of administration of Clindamycin. Algorithm for assessment of drug causality in SJS and TENS (ALDEN) was done and Clindamycin scored 6 points, which points to a definite drug causality of SJS/TEN.

A female in her late 50s presented with fatigue, malaise, and sore throat. Initially managed as a case of sepsis peritonsillar abscess right but later in the course of admission, presented with erythematous maculopapular rash on both hands and dry crusted lesions on the mouth. Patient was clinically diagnosed with Steven-Johnson syndrome and toxic epidermal syndrome and was given a course of intravenous hydrocortisone. Patient unfortunately expired due to overwhelming sepsis.

Severe cutaneous adverse reaction induced by clindamycin are rare but important life-threatening conditions which needs prompt recognition and treatment. SJS/TEN as a secondary diagnosis leads to a delay in management, therefore a high index of suspicion and the utility of validated scoring tools should be maintained throughout the course of treatment.

Keywords: Steven Johnson Syndrome-Toxic Epidermal Necrolysis Overlap, Clindamycin

Introduction

Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) fall under severe cutaneous adverse reactions (SCAR) characterized by extensive necrosis and detachment of the epidermis [8]. SJS and TEN is a disease continuum of disease and is based on the total body surface area involved with skin detachment. SJS is defined as the skin detachment affecting <10 percent of body surface area (BSA). TEN is defined as a skin detachment affecting >30 percent of BSA. SJS/TEN overlap is defined as skin detachment involving 10-30 percent of the BSA [9].

Often triggered by an offending medication, symptoms typically begin within 5 to 28 days after the drug is first introduced. Common implicated medications for SJS and TEN are anticonvulsants (lamotrigine), allopurinol, sulfonamides, certain antibiotics (penicillin, cephalosporins, quinolones,) and acetaminophen [7].

Reports of Clindamycin causing cutaneous complications are rare. To date, there have only been 6 published reports of SJS and TEN caused by clindamycin [1,2,3,4,5,6], none of which was reported in any Asian countries, moreover the Philippines. Although the incidence of SJS and TEN is low and ranges from 1.2 to 6 and 0.4 to 1.2 per million per person-years respectively, its mortality rates are high [10]. In a 7-year retrospective study conducted in the Philippine General Hospital, SJS and TEN accounted for 0.03% of the total admissions. The mortality rate was at 4.7% for SJS and 16.7 for TEN [11].

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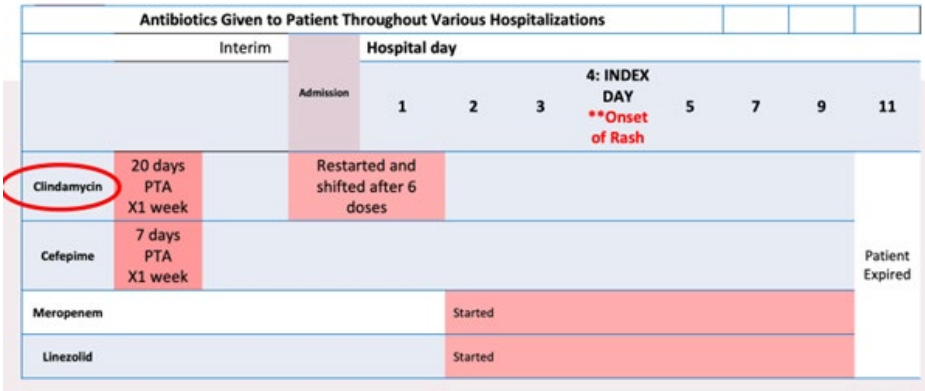

Figure 1. Timeline of the Various Antibiotics Given to the Patient

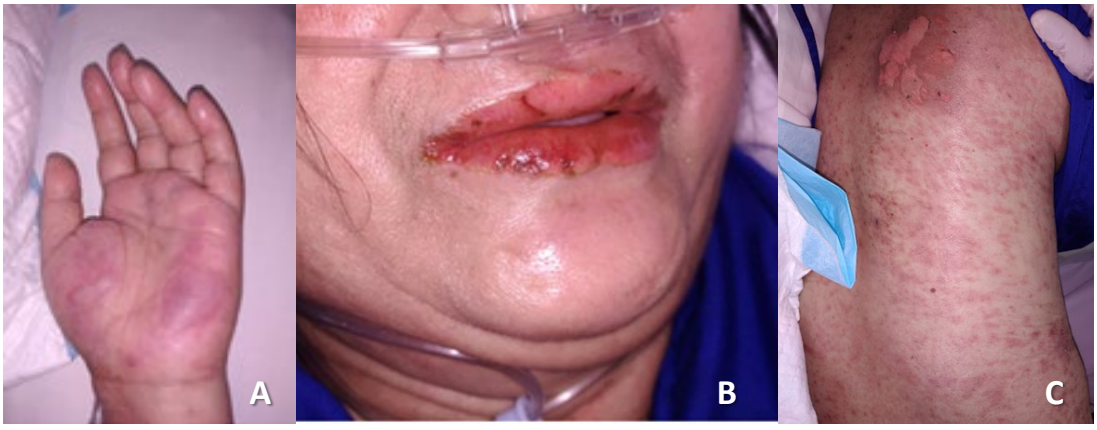

Figure 2. Pictures of the Patient. (A). Erythematous maculopapular rash on hand (B). Dry Crusted Lesions on the mouth, and (C). Flaccid Bullous lesion on the upper back

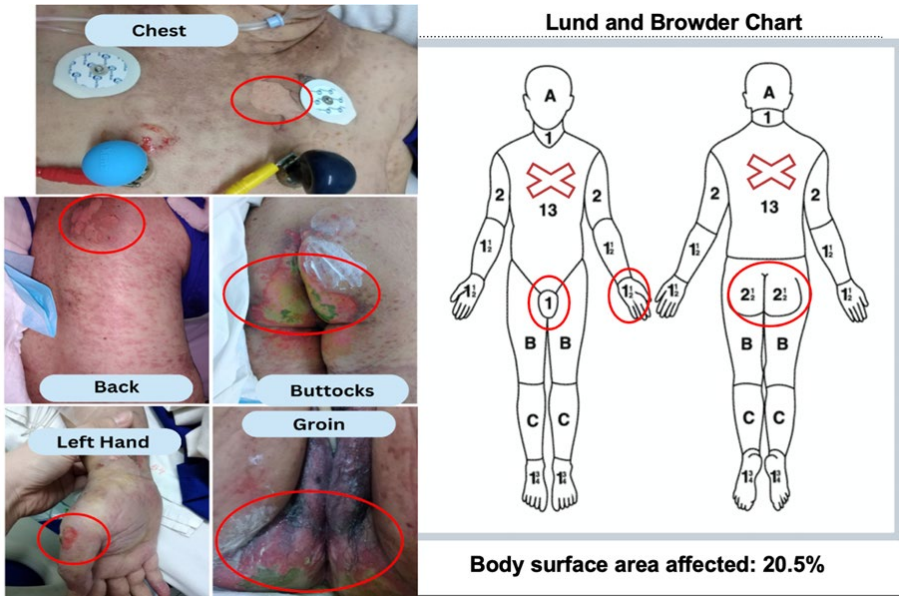

Figure 3. Pictures of the Various Lesions and Their Locations Seen in the Patient

likely, an appropriate therapy should be instituted without delay even if histologic confirmation is pending.

Presented is a case of SJS/TEN overlap in a Filipino patient being treated with Clindamycin.

Case Presentation

A 59-year-old female, diabetic with no known food drug and allergy, was admitted in this institution due to increased fatigue, malaise, and sore throat. Patient reports no family history of SJS nor TENS.

Twenty days prior to present admission, patient was confined at another institution and was managed as a case of acute tonsillopharyngitis. Patient was given Clindamycin IV, that was later stepped down to Clindamycin 300 mg/tab Q8 hours. Patient completed a 7-day course of clindamycin. Patient was discharged as improved as claimed.

Seven days prior to admission, patient was readmitted due to fever and was managed as a case of sepsis secondary to complicated urinary tract infection with growths of *Enterobacter aerogenes* sensitive to cefepime. Cefepime 1 gram IV drip q12 hours was given for seven days.

In the interim body malaise persisted and was associated with recurrence of sore throat.

During the present admission, patient was managed as a probable case of peritonsillar abscess right and was started with clindamycin 600 mg IV drip every 6 hours at the emergency room. On hospital Day 2, clindamycin was shifted to linezolid and meropenem was added to patient's medications. The various antibiotics given to the patient are shown in *Figure 1*.

On the 5th hospital day, clinical examination of the patient revealed erythematous maculopapular rash on both hands (*Figure 2A*) and dry crusted lesions on the mouth (*Figure 2B*). The rash was painful in nature and evolved to pigmented patches in all extremities. Flaccid bullous lesions were also noted in the upper back and shoulder (*Figure 2C*).

In the course of her illness, patient complained of pain particularly at areas with extensive rash, loose watery stools with blood clots, foreign sensation in the eye and persistence of dysphagia. The Nikolsky sign was found to be positive. Skin detachment of approximately 20.5% of the body surface area was reported, suggesting a case of SJS-TEN overlap (*Figure 3*).

Algorithm for determining drug causality for SJS and TEN (ALDEN) was done (see *Tables I and II*). Clindamycin scored 6 points which is indicative of being the causative agent for SJS/TEN overlap in this patient. ALDEN scoring was also done for cefepime, linezolid and meropenem and scored 2, -1 and 1 respectively. Scores 2 and below points to an unlikely etiology of SJS and TEN.

The patient was treated with IV hydrocortisone and intravenous immunoglobulin (IVIG) was prescribed at the later course of her illness. Other treatments implemented were administration of IV fluids and empiric antibiotics

Table I. Matrix for Assessment of Drug Causality in Steven-Johnson Syndrome and Toxic Epidermal Necrolysis (ALDEN) that served as basis for ALDEN scoring in this patient

Algorithm for assessment of drug causality in epidermal necrolysis (ALDEN)

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	−3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely −1	> 56 days	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present	
	Excluded −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar[c] drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative - 2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative - 2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case-control studies[d]	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case-control studies[d]	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[c]	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score	−1
		If at least one has an intermediate score > 3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	
Final score −12 to 10			

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable

ATC, anatomical therapeutic chemical; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

[a] Drug (or active metabolite) elimination half-life from serum and/or tissues, taking into into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance. [b] Suspected interaction was considered when more than five drugs were present in a patient's body at the same time. [c] Similar drug = same ATC code up to the fourth level (chemical subgroups). [d] Definitions for "high risk," "lower risk," and "no evidence of association" in Methods

Reprinted from Algorithm for Assessment of Drug Causality in Steven-Johnson Syndrome and Toxic Epidermal Necrolysis (ALDEN)
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Table II. Matrix for Assessment of Drug Causality in Steven-Johnson Syndrome and Toxic Epidermal Necrolysis (ALDEN) scoring of the Drugs to which the Patient was Exposed to

Algorithm for Assessment of Drug Causality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis				
	Clindamycin	Cefepime	Meropenem	Linezolid
Delay from initial drug component intake to onset of reaction (Index day)	+3	0	0	0
Drug Presented in the Body on Index Day	0	0	0	0
Prechallenge /Rechallenge	4	0	0	0
Dechallenge	0	0	-2	-2
Type of Drug (Notoriety)	-1	2	0	0
Other cause	0	0	0	0
	6	2	-2	-2
Final score -12 to 10 Interpretation: <0 Very unlikely; 0-1 Unlikely; 2-3 Possible, 4-5 Probable, ≥6 Very Probable				

(linezolid and meropenem), correction of electrolyte imbalance and anemia, eye drops and topical preparations. Patient succumbed to sepsis on the 11th day of hospitalization

Discussion

Presented was a case of a woman who was exposed and re-exposed to clindamycin during her various

hospitalizations. She then later developed erythematous maculopapular rash on both hands and dry crusted lesions on the mouth. Presence of intraepidermal blisters were seen on the affected skin and is typical of Steven-Johnson syndrome and toxic epidermal necrolysis.

Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are most commonly drug induced as seen in over 80% of cases.

In a multinational case-control study including 379 cases of SJS/TEN and 1505 control, the following agents were commonly implicated as a cause for SJS: allopurinol, aromatic antiseizure medications and lamotrigine, antibacterial, nevirapine, and NSAIDs.[13]

The risk of SJS/TENS seems to be limited to the first eight weeks of treatment of an offending drug, therefore a thorough review of drug history should be taken. A latent period between the initial drug intake and onset of SJS/TEN always occurs. Drugs used for a longer time are unlikely to be a cause of SJS/TEN.[16]

However other potential etiologies include infection, malignancy, and vaccination. Idiosyncratic reactions are possible thus making the occurrence of SJS/TEN not easily predictable.

Essentially SJS and TEN is a clinical diagnosis. Exposure to a notorious drug and appearance of constitutional symptoms (fever, malaise, arthralgia and sore throat) followed by the typical skin and mucosal lesions within a 5-to-28-day period, points to a SJS/ TENS etiology. Prompt identification and withdrawal of offending agent may improve prognosis.

Pertinent skin signs include erythematous to violaceous and purpuric macules which coalesce to form patches. Flaccid bullae may also be present. Lesions initially involve the trunk which distally involve the limbs. This temporal sequence is usually followed by exfoliation of the skin, and mucosal inflammation (oral, ocular, and genitourinary) is nearly universal. [14.]

Causality attribution is generally determined by two principles which is temporal sequence (started 5 to 28 days prior to the onset of symptoms) and drug notoriety. An algorithm for determining drug causality (ALDEN) has been formulated and is useful for determining the culprit drug causing SJS/TENS.

For the patient, two potential culprits causing SJS/TENS were identified namely clindamycin and cefepime.

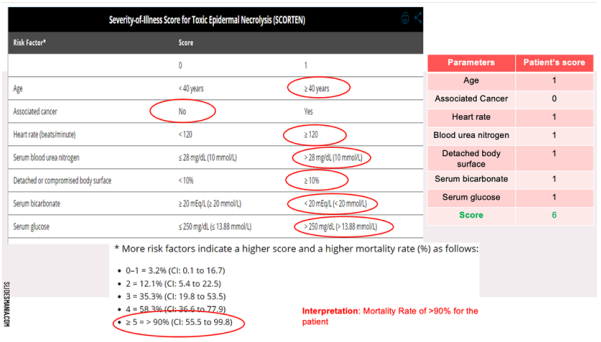
Clindamycin, is a lincosamide antibiotic that acts by primarily binding to the 50s ribosomal subunit of bacteria leading to the disruption of protein synthesis. There are 6 reported cases of Clindamycin induced SJS or TEN in literature. The cases were treated with a combination of varying doses of corticosteroids, IVIG and cyclosporin.

On the other hand, cefepime is a fourth-generation cephalosporin that inhibits bacterial cell wall synthesis. Only four cases of SJS/TENS are attributed to cefepime.[19.]

Table III. List All Case Reports of SJS-TENS Caused by Clindamycin

SJS-TENS secondary to Administration of Clindamycin			
Case Report Number and Title	Date published	Location of Report	Website
1	January 15,1973	Miami USA	https://jamanetwork.com/journals/jama/article-abstract/346521
2	April 26, 1992	Paris France	https://jamanetwork.com/journals/jama/article-abstract/346521
3	April 1995	Belgium	https://pubmed.ncbi.nlm.nih.gov/7748763/
4	May 21, 2007	Freiburg Germany	https://pubmed.ncbi.nlm.nih.gov/7748763/
5	May 15, 2009	Spain	https://pubmed.ncbi.nlm.nih.gov/19624990/
6	September 11, 2018	British Columbia Canada	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6098186/#bib16

Table IV. Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) done in the Patient



The patient was administered cefepime but was discontinued seven days prior to the onset of erythematous rash.

The number of SCAR cases due to clindamycin is greater compared to cefepime. This patient outlines a rare probable 7th instance of SJS-TEN secondary to the administration of clindamycin 22 days prior to admission and readministered five days prior to the onset of the rash (*Table III*). Implementation of the algorithm for assessment of drug causality in SJS and TEN (ALDEN) for clindamycin was done.[17] A score of 6 point to a very probable drug causality (*Table II*). Therefore, it is concluded that clindamycin is the most likely causative agent.

This case also highlights the first reported instance of SJS-TEN precipitated by clindamycin in an Asian individual. In addition, several studies have outlined racial disparities in SJS/TEN with higher incidence amongst Asian and Black populations. Females also tend to be more affected than males with a ratio of 5:3 [18.]

Multiple articles including the UK guidelines for management of SJS and TEN in adults 2016 [15] and the Indian Journal of Dermatology [14] cite that routine drug hypersensitivity testing is not recommended following an episode of SJS/TEN and that histopathology is usually not required for the diagnosis of SJS- TEN.

However, a skin biopsy should be performed for completeness of diagnosis likewise differentiating other

SCAR like morbilliform drug rash, erythema multiforme, drug induced linear IgA disease, acute generalized exanthematous pustulosis, acute graft-versus-host disease or staphylococcal scalded skin syndrome. Hallmark skin biopsy finding include full-thickness epidermal necrosis, subepidermal bulla, and scanty inflammatory infiltrate in the dermis [14].

Due to its high mortality rates, appropriate therapy should be promptly administered the moment a clinical diagnosis has been made. A histologic confirmation is not a prerequisite to treatment and physicians must be vigilant in treating SJS/TEN, even in the absence of completeness of diagnosis.

Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) is an SJS/TEN-specific severity of illness score used to predict in-hospital mortality evaluated during admission. SCORETEN was calculated on the day a clinical diagnosis of SJS/TEN was made. This patient scored 4 which translated to a mortality rate of 58% (*Table IV*). [21]

To date, because of the lack of consensus of the proposed therapeutic modalities, early identification and withdrawal of offending agents, prompt intensive support management remains the criterion standard and key action points that may improve prognosis.

Furthermore, the management of SJS/TEN involves a multi-disciplinary approach that encompasses wound care, surgical approach, fluid and temperature management, nutrition, pain control, prevention, and treatment of infections, repeated bacterial cultures, and management of organ system involved. The role of systemic therapy carries conflicting evidence and revolves around intravenous immune globulin (IVIG), systemic steroids, cyclosporin and pulse corticosteroids.

As seen in this patient, mortality rate is higher amongst patients with a secondary diagnosis of SJS/TEN versus those with a primary diagnosis. This may be because patients with SJS/TEN listed as a secondary diagnosis carry other serious medical problems that warrants admission. Iatrogenically developed SJS/TEN may follow during admission and often complications such as septicemia occur.

Owing to the logistic concerns, the present report could not describe the histopathological findings which remains a limitation of this study.

Conclusion:

Severe cutaneous adverse reaction (SCAR) induced by clindamycin are rare but important life-threatening conditions which needs prompt recognition and treatment. Essentially SJS and TEN warrant a clinical diagnosis encompassing a thorough drug history, presence of constitutional signs symptoms and hallmark skin and mucosal findings. SJS/TEN as a secondary diagnosis leads to a delay in management, therefore a high index of suspicion and utility of validated scoring tools should be maintained throughout the course of treatment. Thus, early recognition and treatment will ensure better health outcome from SJS-TEN.

Conflict of Interest: None Declared

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