Toxic Epidermal Necrolysis/Stevens-Johnson Syndrome at a University Hospital in Saudi: Causative Factors and Outcomes

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ABSTRACT

Introduction: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are rare, life-threatening conditions caused mainly by drugs. Their management relies on the withdrawal of the culprit medication and supportive measures. Different pharmacotherapies have varied effects. However, data related to TEN and SJS in Saudi is limited.

Objective: This study aimed to identify the causative agents, associated factors, and outcomes of TEN/SJS cases admitted to a teaching hospital (King Abdulaziz University) in Jeddah during the last 10 years.

Methods: retrospective descriptive study. The data of patients admitted to the King Abdulaziz University hospital with TEN/SJS diagnosis over the last 10 years were collected

Result: We identified 12 patients with TEN/SJS. Of these, nine survived the condition and were discharged. The culprit medication was identified in eight of them, including antibiotics in six cases and Tegretol and allopurinol in one case each. Most of the patients received systemic steroids and intravenous immunoglobulins.

Conclusion: TEN/SJS is mainly caused by medications of which antibiotics are the most implicated. Consistent with other studies, the mortality rate associated with TEN/SJS in Saudi is 25%.

Limitations: restricted to a single center and small sample size.

Keywords: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Drug reaction

INTRODUCTION

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are rare, life-threatening conditions. They are usually caused by drug exposure and can be precipitated by viral infections, autoimmune diseases, and other unknown factors[1,2]. Several medications are implicated in the onset of TEN/SJS, including antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants. The incidence of TEN/SJS is low worldwide, and there is a paucity of data on its epidemiology and causative agents in Saudi Arabi. There are 2 studies that collected data from other areas. These data can combine to form a cumulative data that help in improving our understanding of this disease.

A recent retrospective survey at the King Fahad Specialist Hospital (KFSH) in the Qassim region between January 2014 and January 2019 identified 10 patients with TEN/SJS, and one of them died[3]. The culprit medications included amoxicillin/clavulanic acid in three cases, carbamazepine in two, and acetaminophen, azithromycin, ciprofloxacin, and levetiracetam in one case each and an unknown cause in one case[3]. Another review of 13 patients diagnosed with TEN/SJS at the King Abdullah Medical City (KAMC), the Holy Makkah, between March 2003 and March 2010 revealed a mortality of 15% (two patients)[4]. The medications associated with TEN were trimethoprim/sulphamethoxazole (TMP/SMZ) in four patients and amoxicillin/clavulanate, diclofenac sodium, ibuprofen, and phenytoin in one patient each. TMP/SMZ was implicated in a patient with SJS and one patient with an SJS/TEN syndrome overlap. Piroxicam and allopurinol were implicated in two patients with SJS/TEN overlap, and the last patient was receiving four drugs (phenytoin used for epilepsy for 30 years, metronidazole, allopurinol, and ibuprofen) at the time of diagnosis. Additionally, several case reports from different areas of Saudi have been published (Table 1).

This study aims to identify the causative agents, associated factors, and outcomes of TEN/SJS cases admitted to a teaching hospital (King Abdulaziz University) in Jeddah during the last 10 years.

METHODS

This study retrospectively analyzed the data of patients diagnosed with TEN/SJS between 2011 and 2020. The study protocol was approved by the Unit of Biomedical Ethics Research Committee at King Abdulaziz University Hospital with a reference number: 529-20. As our hospital is a teaching hospital, all patients sign a informed consent upon admission to use their data for teaching and research purposes. The approvals were taken from the ethics committee and hospital affairs before collecting data. All methods are in accordance with the Declaration of Helsinki. All identifying information (names and ID numbers) were removed before analyzing data and none is represented in this report.

Data on all patients admitted with a TEN diagnosis (Lyell disease) and other related conditions (skin eruption due to drugs and medicaments, erythema multiforme, rash, and other nonspecific skin eruptions) were retrieved from the hospital electronic database and reviewed. The clinical data included the demographic data, length of stay in the hospital, culprit medications, associated comorbidities, treatment modalities, and outcomes.

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Table 1: Published reports of TEN in Saudi

Culprit medication	Reference	Treatment used	Outcome	Region
3 Amoxicillin/ Clavulonic acid, 2 Carbamazepine, 1 Acetaminophen, Azithromycin, Ciprofloxacin, and Levetiracetam and 1 of unknown cause	Alajaji et al, 2020[3]	Steroids and IVIG	9 alive and 1 died	Qassim
6 trimethoprim/sulphamethoxazole (TMP/SMZ), 1 amoxicillin/clavulanate, 1 ibuprofen, 1 diclofenac sodium, 1 phenytoin, 1 Piroxicam and 1 allopurinol and 1 patient was receiving 4 drugs at that time (phenytoin, metronidazole, allopurinol, and ibuprofen)	Nassar et al, 2010[4]	Steroids and IVIG	11 alive and 2 died	Makkah
carbamazepine	Wani et al, 2009[5]	IVIG	alive	Makkah
Possibly captopril	Alkurtass and Al-Jazairi, 2003[6]	supportive	alive	Riyadh
Co-Trimoxazole	Suliman, 2006[7]	supportive	alive	Tabuk
Phenytoin	AlQuliti et al, 2014[8]	Hydrocortisone	Died	Dammam
Lamotrigine	Jan, 2007[9]		Died	Jeddah
Cotrimoxazole (5 children)	Elkharaz et al, 2006[10]	Hydrocortisone and IVIG	alive	Unizah
Cytomegalovirus infection	Khalaf et al, 2011[11]	IVIG	Died	AlKhobar
Sildenafil (high dose)	Al-Shouli et al, 2005[12]	infliximab	alive	Riyadh

Table 2: Demographics of study patients

Case	Gender	Age	Weight	Dx	Outcome	LOS*	Causative agent	Comorbidities
1	F	31	102	SJS	alive	15	unknown	DM**
2	F	31	80	TEN	Died	4	? levofloxacin or amoxicillin/ clavulonic acid	Severe mitral stenosis with pulmonary hypertension and aortic stenosis
3	M	47	70	TEN	alive	27	Trimethoprim/ sulfamethoxazole	
4	F	74	56	TEN	Died	10	Cefixime	DM**, HTN***, dyslipidemia, eczema
5	F	58	70	SJS	alive	13	? antibiotic for middle ear infection	
6	M	3	12	SJS	alive	17	Tegretol	shunted congenital hydrocephalus and repaired meningolcele, developmantaly 6-9 months, sezures on carbamazepine
7	F	29	60	TEN	Died	78	unknown	2 weeks postpartum presented in shock and skin lesions, pancytopenia
8	F	34	68	TEN/SJS	alive	6	ciprofloxacin	pregnant deliverd by CS 6 weeks after episode, Hb 5.9 (refused blood transfusion)
9	F	35	56	SJS	alive	17	ciprofloxacin	
10	F	50	70	SJS	alive	2	? allopuranol or epagliflozin	DM,** HTN***, heart failure
11	F	74	88	TEN	alive	38	allopuranol	HTN***, previous pulmonary embolism on warfarin, heart failure, thyroidictomy for thyroid cancer
12	M	47	60	TEN	alive	6	unknown	hepatitis B

LOS*: length of stay in the hospital, DM**: diabetes mellitus, HTN***: hypertension

RESULTS

After excluding one patient diagnosed with paraneoplastic pemphigus between January 1, 2011 and October 31, 2020, 12 patients were included in the study. Of these, nine were women, and three were men. The patients' ages ranged from 3 to 74 years (median 41 years). The culprit agents were antibiotics in 6 cases (trimethoprim/sulfamethoxazole, cefixime, ciprofloxacin in two cases and an unknown antibiotic in two cases), and Tegretol and allopurinol in one case each. Allopurinol was again suspected but not confirmed to be the cause in one case, while in the remaining three cases, the causative agent could not be identified (Table 2).

The clinical diagnosis was TEN in six cases, SJS in five cases, and TEN/SJS overlap in one case. Nine patients survived the episode and were discharged, while the remaining three (patient numbers 2, 4, and 7) died (mortality rate of 25%). Patient number 2 was a 31-year-old woman suffering from severe mitral stenosis with pulmonary hypertension and aortic stenosis. She had received two antibiotics (levofloxacin and amoxicillin/ clavulanic acid) simultaneously for a chest infection and was waiting for a valvular heart repair surgery. She died four days after admission. Patient number 4 was a 74-year-old woman

with diabetes, hypertension, eczema, and hyperlipidemia. She died 10 days after admission. Patient number 7 was a 29-year-old woman who presented to the emergency department two weeks postpartum in shock, with extensive skin lesions and pancytopenia. She was admitted to the emergency room (ER), resuscitated, and transferred to the intensive care unit (ICU). After recovery and transfer to the medical ward, her condition deteriorated, and she died after 78 days.

All the patients in this study were treated in the ICU and received supportive therapy. They were referred based on clinical signs and symptoms and were assessed by medical internists, ophthalmologists, pulmonologists, dermatologists, gastroenterologists, gynecologists, or urologists. All of them, except two (patients 2 and 6), received systemic corticosteroids. One of them had severe mitral stenosis with pulmonary hypertension and aortic stenosis and eventually died. The other patient was a 3-year-old child with seizures. He had shunted congenital hydrocephalus and repaired meningocele and was developmentally 6-9 months. He recovered and was discharged. Intravenous immunoglobulin (IVIG) was used in nine cases. One patient who did not receive the immunoglobulins died. She was a 74-year-old woman with diabetes, hypertension, and eczema (Table 3). The dosage of immunoglobulins used varied between the patients (Table 3).

DISCUSSION

TEN/SJS are severe mucocutaneous reactions triggered mainly by exposure to medications. In up to a third of the cases, no causative agent can be identified[1,2]. Factors that increase the risk of this reaction include HIV infection, genetic factors, malignancy, high doses of medications, systemic lupus erythematosus, and some physical stimuli[13]. However, studies from Saudi are relatively few. In this retrospective study, we reviewed all TEN/SJS cases admitted to our hospital during the last 10 years. Antibiotics were confirmed to be the causative agents in four cases (ciprofloxacin in two, trimethoprim/sulfamethoxazole in one, and levofloxacin or amoxicillin/ clavulanic acid in one case) and were suspected but not confirmed in another two cases. Tegretol and allopurinol were implicated in one case each. For the remaining four cases, the causative agents were not identified (one of them was suspected to be allopurinol or empagliflozin). These findings are consistent with those of two previous studies from Saudi implicating antibiotics (including trimethoprim/sulphamethoxazole (TMP/SMZ), amoxicillin/clavulanate, and ciprofloxacin) as the most common cause of TEN/SJS[3,4]. A previous study from Japan on 52 cases of SJS and 65 cases of TEN reported medications to be the causative agents in all the TEN cases and most SJS cases[14]. These included antibiotics, NSAIDs, anticonvulsants, and others. Mycoplasma pneumoniae and the antibiotics used to treat it are also known to cause TEN/SJS. A study involving a cohort of cancer patients found antibiotics (most frequently, trimethoprim/sulfamethoxazole), followed by anticonvulsants and antineoplastics agents, to be the most common inducers of TEN/SJS[15]. On the other hand, a study from China found anticonvulsants to be the most common causative agent followed by antibiotics[16]. A study by the Food and Drug Administration from the USA between July 2014 and December 2017 reported that antiepileptic medications were the most reported cause of TEN/SJS[17].

The first large case-control study (SCAR study) to assess TEN/SJS risk associated with exposure to medications was conducted in four European countries from 1989 to 1993. This study confirmed the high relative risk associated with antibiotics (especially cotrimoxazole, aminopenicillins, cephalosporins, quinolones, and cycline antibiotics), carbamazepine, phenytoin, phenobarbital, NSAIDs of the oxicam type, allopurinol, and chlormezanone[18]. A later case-control study (EuroSCAR study), which included 379 patients with SJS or TEN, and 1505 matched hospitalized controls[19], added more medications to the list of causative agents (lamotrigine and sulfasalazine, among others). Another study, including 66 patients and 28 control subjects, found allopurinol to be the most frequently associated drug with SJS or TEN[20].

Consistent with previous studies that have reported a 30% mortality rate associated with TEN/SJS[21,22], our study had a mortality rate of 25% (3 out of 12 patients died). All patients who died were diagnosed with TEN.

Supportive care is the most universally accepted strategy for the management of TEN/SJS[23]. Pharmacological therapy includes systemic corticosteroids, IVIG, cyclosporine[24,25], and new inhibitors of tumor necrosis factor with varied effects. The use of plasmapheresis is equivocal, and thalidomide increases mortality[23]. A study from China comparing treatments based on the clinical outcomes in 39 cases of SJS and 48 cases of TEN found that increasing doses of corticosteroids did not influence the time taken to control SJS lesions but decreased the time taken to control TEN lesions. IVIG shortened the hospital stay for TEN and SJS and the time taken to control TEN[16]. A recent meta-analysis of 67 studies involving 2079 patients who received TEN treatments with immunomodulators concluded that IVIG in

Table 3: Specific medications used for treatment

Case	Outcome	IVIG given	IVIG dose (g/kg)	Duration (Days)	Total IVIG*/Kg (gram)	Steroids	Dose of steroid
1	alive	42 g for 5days	0.4	5	2	hydrocortisone	100 mg TID for 3 days
2	Died	250 g for 7 days	3.125	7	21.88		
3	alive	70 g for 3 days	1	3	3	methylprednisolone	60 mg BID for 5 days
4	Died					hydrocortisone/ methylpred	100 mg for 3 days/ 1g stat
5	alive	140 g for 3 days	2	3	6	hydrocortisone	100 mg for 1 day
6	alive	5 g for 4 days	0.42	4	1.67		
7	Died	30 g for 7 days	0.5	7	3.5	hydrocortisone	100-200 mg daily for several days
8	alive	60 g for 3 days	0.88	3	2.65	hydrocortisone	100 mg for 10 days
9	alive	60 g for 3 days	1.07	3	3.21	prednisolone	20 mg for 18 days
10	alive					prednisolone	50 mg for 7 days
11	alive	44 g for 5 days	0.5	5	2.5	methylprednisolone	in emergency department
12	alive					methylpred/prednisolone	60 mg for 6 days

*IVIG: intravenous immunoglobulins

combination with corticosteroids could reduce the mortality in patients with TEN and SJS/TEN overlap. Thalidomide was found to be associated with a higher mortality rate[26]. Cyclosporine and etanercept emerged as promising therapies, but more studies are required to provide clearer evidence[26].

Our study has some limitations. First, it was restricted to a single center. The second is the small sample size. Finally, because of different coding, we might have missed on some TEN/SJS patients.

CONCLUSION

In conclusion, determining the most common causative agents for TEN/SJS in Saudi Arabia might help in the early prediction of the disease and could lead to preventive measures as cumulative data emerge from this region. These data will also help design a national initiative for the TEN/SJS registry.

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Informed Consent: All patients admitted to the hospital sign a consent for being in a teaching hospital and their data can be used for research purposes.

Potential Conflict of Interest: None.

Competing Interest: None.

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