

Toxic Epidermal Necrolysis in a Paediatric Patient: A Case Report

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ABSTRACT

Toxic Epidermal Necrolysis (TEN) and Stevens Johnson's Syndrome (SJS) are severe adverse cutaneous drug reactions. In addition to severe skin symptoms, it is often accompanied by complications in numerous organs, such as liver, kidney, and lungs. The degree of epidermal detachment less than 10% of body surface area is classified as SJS, greater than 30% as TEN and 10-30% as SJS/TEN overlap. It is thought that this syndrome is a hypersensitivity complex that affects the skin and the mucous membranes. SJS/TEN have been observed with more than 100 drugs. Common culprits are antimicrobials, anti-epileptic drugs and Non-steroidal anti-inflammatory agents (NSAIDs). Diagnosis mainly relies on clinical signs and histopathology of skin lesions. The primary objective for a favourable outcome depends on rapid and aggressive supportive care until the skin regenerates itself in this self-limiting acute skin condition. Here we report an idiosyncratic drug reaction (IDR) in a 9 year old child.

Keywords: Toxic Epidermal Necrolysis, Stevens Johnson's Syndrome, epidermal detachment, idiosyncratic drug reaction.

INTRODUCTION

Toxic Epidermal Necrolysis (TEN) and Stevens Johnson's Syndrome (SJS) are severe adverse cutaneous drug reactions that predominantly involve the skin and mucous membranes. The degree of epidermal detachment less than 10% of body surface area is classified as SJS, greater than 30% as TEN and 10-30% as SJS/TEN overlap. Both are rare, with TEN and SJS affecting approximately 1 or 2/1,000,000 annually, and are considered medical emergencies as

they are potentially fatal. The average reported mortality rate of SJS is 1-5%, and of TEN is 25-35%; it can be even higher in elderly patients and those with a large surface area of epidermal detachment. More than 50% of patients surviving TEN suffer from long-term sequelae of the disease. [1]

In addition to severe skin symptoms, it is often accompanied by complications in numerous organs, such as liver, kidney, and lungs. Patient may initially be present with SJS, which subsequently evolves into TEN or SJS-TEN overlap. [2]

The incidence of TEN is estimated at 1 to 6 cases per million person-years. [3] TEN causes erosions of the mucous membranes, extensive detachment of the epidermis, and severe constitutional symptoms. [4] It is thought that this syndrome is a hypersensitivity complex that affects the skin and the mucous membranes. Although the majority of cases are idiopathic (without a known cause), the main class of known causes is medication, followed by infections and, rarely, cancers. [5]

SJS/TEN have been observed with more than 100 drugs. Common culprits are antimicrobials, anti-epileptic drugs and Non-steroidal anti-inflammatory agents (NSAIDs). [6] Drugs that are at "high" risk of inducing TEN/SJS include: Allopurinol, Trimethoprim-sulfamethoxazole and other sulfonamide-antibiotics, aminopenicillins, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital and NSAID's of the oxicam-type. [7]

The exact mechanism of SJS/TEN still remains largely unknown. Immunological mechanisms, reactive drug metabolites or interactions between these two are proposed. Interactions between CD95 L and Fas (CD 95) are directly involved in the epidermal necrolysis. Granulysin is also considered as a key mediator for disseminated keratinocyte death in SJS/TEN. [8]

Diagnosis mainly relies on clinical signs and histopathology of skin lesions. [9] Typical clinical signs initially include areas of erythematous and livid macules on the skin, on which a positive Nikolsky sign can be induced by mechanical pressure on the skin, followed within minutes to hours by the onset of epidermal detachment characterized by the development of blisters. It should be noted, however, that the Nikolsky sign is not specific for SJS/TEN. Mucosal, including ocular, involvement develops shortly before or simultaneously with skin signs in almost all cases. [10]

TEN is an acute emergency and is potentially life threatening if not treated promptly. However, since the pathophysiology of the disease remained largely unclear (until the recent discovery that the Fas ligand plays a major role in the apoptotic cell death), there is no specific therapy for TEN patients. The primary objective for a favourable outcome depends on rapid and aggressive supportive care until the skin regenerates itself in this self-limiting acute skin condition. [8]

The major cause of death in TEN is sepsis. [11] Meticulous monitoring of the patients in an ICU with daily laboratory examinations of blood and urinary electrolytes, serum creatinine and blood urea, blood glucose, CBC, blood culture and skin swab test are mandatory. Sterile handling of the patients is a must and cannot be over emphasized to minimize nosocomial infection. [12]

Fluids must be replaced intravenously, preferably through a peripheral line, especially during the first

few days to compensate the loss of body fluids through large areas of denuded skin. Strict urinary output should be monitored, if necessary, through a catheter. The electrolyte balance is maintained by daily check up of serum electrolytes.

Meticulous therapy of eye is important to prevent early and long-term ocular complications. Daily examinations by an ophthalmologist and antiseptic and/or antibiotic eye drops are instilled every hour or two. Similarly, mouth and crusted lips should be gently rinsed at least every two hours with physiologic saline and sprayed with antiseptics several times each day. Once the epidermal detachment exceeds 25% of the BSA, no steroids should be used in TEN patients since any benefit of corticosteroids is then far outweighed by its potential risk of developing sepsis. [8]

CASE REPORT

A 9yr old male child was admitted into PICU, Department of Paediatrics, Basaveshwara Medical College Hospital and Research centre, Chitradurga with skin rash, altered sensorium and septic shock. The patient had a history of fever, cough, running nose and vomiting of 2 days duration for which he received Ondansetron 4mg IM and Cefpodoxime at a local hospital. 24 hours later he developed skin rashes, swelling of eyes and lips. On examination, multiple tense vesicles measuring 0.5cm were found predominantly over the neck and trunk and were scarcely distributed over the limbs and face. Edema, erythema and crusting of lips and eyelids were seen. Conjunctivitis and oral ulcers were also present. The child was drowsy with a Glasgow Coma Scale (GCS) of 5 and was in septic shock with a systolic blood pressure of 78 mmHg. Septic Shock responded to oxygen, IV fluids boluses and IV antibiotics.

Lab examinations revealed a normal blood report and elevated blood urea. Dermatologist and Ophthalmologist opinions were taken. As the extent of skin detachment was greater than 30% the case

was diagnosed as Toxic Epidermal Necrolysis.

Treatment given:

External Route

Sl. No.	Drug	Dose	Route	Frequency	Days
1.	Tobramycin(3% w/v)Eye Drops	1 drop	Topical	Q4H	D1-D16
2.	Moxifloxacin(0.5% w/v)Eye Drops	1 drop	Topical	Q4H	D1-D16
3.	Chloramphenicol and Polymyxin-B Sulphate Eye Ointment(10mg+10000units)	1 drop	Local Ocular	1-0-1	D1 - D16
4.	Clobetasol Propionate and Neomycin Sulphate Cream(0.05%+0.5% w/w)	-	Over the lips	1-0-1	D2 - D16
5.	Fusidic Acid and Beclomethasone Dipropionate Cream(2%+0.025% w/w)	-	Applied on the scabs, formed after rupturing of vesicles.	1-0-1	D4-D16
6.	Liquid paraffin	-	Topical	1-1-1	D4-D16

Internal Route

Sl. No.	Drug	Dose	Route	Frequency	Days
1.	Inj. Linezolid(2 mg/ml)	250mg	IV	1-0-1	D1-D11
2.	Syp.B-Complex with Vitamin C	5ml	PO	1-0-1	D5-D16
3.	Syp.Zinc Acetate oral Solution(20 mg/5ml)	2.5ml	PO	1-0-1	D5-D16
4.	Syp.Paracetamol (250mg/5ml)	7ml	PO	1-1-1	D6-D16

By the second day of admission the GCS improved. The vesicles ruptured over the next week and were replaced by scabs which peeled off gradually leaving behind hypopigmented patches. The patient was ambulant, feeding well and afebrile at discharge. Eye drops and ointment were continued. During follow up ectropion of the eyelids and loss of eyelashes were seen.



DISCUSSION

SJS/TEN is life-threatening drug adverse reaction, with higher prevalence rate in Asian than in Western populations.

[13] Patel TK et al., conducted a systematic

review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population and concluded that major causative drugs were antimicrobials (37.27%), antiepileptics (35.73%) and

nonsteroidal antiinflammatory drugs (15.93%).^[14] Yamane Y *et al.*, retrospectively analyzed reports of SJS and TEN published in medical journals from 2000 to 2006. He found that in SJS, 36 cases (69.2%) were considered to be caused by drugs, and five cases (10.4%) were suspected to be caused by Mycoplasma pneumoniae and/or drugs. The causes of the other cases were not determined. In contrast, all TEN cases had received drugs and were suspected to be caused mainly by drugs. In both SJS and TEN, antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDs) and cold medicines were the major causative drugs. Cephalosporins were the most frequent causative drug among antibiotics (10 cases of SJS and TEN).^[15] In a case report on cefpodoxime-induced hypersensitivity reaction by Reehana S *et al.*, 23yrs old female patient suffering from fever was administered Monocef-O 200mg-BD. The patient developed a skin rash involving the forehead and eyes which spread to the whole body resulting in severe itching followed by peeling of skin.^[16] Cefpodoxime is well tolerated by paediatric patients, with adverse events (primarily gastrointestinal tract disturbances and skin rashes) that are consistent with those reported for other oral Cephalosporins.^[17]

Saraogi PP *et al.*, reported an inadvertent provocative oral ondansetron use leading to toxic epidermal necrolysis in an HIV-infected patient.^[18] Manish B and Tripathi CB reported a case of TEN in a 17 year old male which was a probable adverse reaction of Erythromycin, Quinine and/or Ondansetron.^[19] Due to the favourable safety profile and absence of drowsiness as a side effect for Ondansetron, several clinical trials have been conducted in the past 20 years to assess the efficacy of ondansetron use in paediatric gastroenteritis.^[20]

The present case is an example in itself for a rare adverse effect of the drugs. Since the patient was on polypharmacy, the causative drug is uncertain. After admission,

all the suspected offensive drugs were halted, and patient improved.

CONCLUSION

This case is an example for idiosyncratic drug reaction (IDR) where this adverse drug reaction does not occur in most patients treated. Hence these are rare and unpredictable and often life threatening. The reaction of a patient to a drug can be affected by the ethnic pharmacogenetic differences. The primary step is to withdraw the drug. Patient should be transferred to burn units for aseptic handling and sterile environment. Rapid and aggressive supportive care is given until the skin regenerates itself.

Practitioners should be aware of the possible idiosyncratic drug reactions (IDR) of a seemingly innocuous drug. But none are culpable since the reactions are unpredictable and unintentional.

Reports of Idiosyncratic drug reaction (IDR) of drugs by different people with different sensitivity that might not have been seen during clinical trials help to refine or confirm or deny the safety of a pharmaceutical drug. Thus Pharmacovigilance is an essential element for effective use of medicines and for high quality medical care.

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