Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20150236

Review Article

Toxic epidermal necrolysis: a severe cutaneous adverse drug reaction

K. N. Chidananda*, K. Jagadeesh

Department of Pharmacology, Shivamogga Institute of Medical Sciences, Shivamogga, Karnataka, India

Received: 30 December 2014
Accepted: 11 January 2015

***Correspondence to:**
Dr. K. N. Chidananda,
Email: chidu2610@gmail.com

ABSTRACT

Toxic epidermal necrolysis (TEN) is a rare but serious is a rare but potentially life-threatening condition. It is primarily a cutaneous reaction to various precipitating agents, characterized by wide spread erythema and detachment of the epidermis from the dermis. Among the various cutaneous adverse drug reactions, TEN occupy a primary place in terms of mortality. In TEN large sheets of skin are lost from the body surface, thereby decreasing the protecting function of the skin, which results in complications. Usually, TEN is self-limited in absence of complications. If complicated by sepsis, there will be increased chances of mortality. The main treatment would be cessation of the causative drug and early admission of the patient for supportive care and minimizing the occurrence of complications. The present articles reviews the etiology, pathophysiology, differential diagnosis and treatment protocol, with a case of TEN occurrence in a child of 4 years age after consuming phenytoin syrup for febrile convulsions.

Keywords: Toxic epidermal necrolysis, Cutaneous adverse drug reaction, Phenytoin, Febrile, Convulsions

INTRODUCTION

Toxic epidermal necrolysis (TEN) also called as Lyell's syndrome, is a rare, but life-threatening exfoliating disease of the skin and mucous membranes. The disease manifests itself by extensive blistering of the skin with full thickness necrosis of the epidermis and involvement of mucosal surfaces. Skin separation occurs at the dermoepidermal junction. Even in unblistered areas, the epidermis can be removed easily by light tangential pressure (Nikolski's sign).[1] The word toxic implies to the constitutional symptoms while necrolysis refers to the necrosis and detachment of the full thickness of the epidermis.[2] The incidence of TEN varies from 1 to 1.3 cases per million population per year worldwide. TEN can affect an individual of any age, but it is frequent at extremes of age, that is before 5 years and after 64 years. No racial differences have been found in the occurrence of TEN. Mortality varies from 30% to 50%. The primary cause of death is due to sepsis and multi organ failure.[3] Ruskin first described a condition similar to TEN in1948 and Allan Lyell in 1956 reported four patients who had an acute rash followed by skin detachment and mucus membrane involvement. Of the four cases originally described by Lyell, two were eventually attributed to staphylococcal scalded skin syndrome (SSSS). Lyell suggested that the reaction was a toxin associated reaction. Although clinically similar in presentation with sloughing of epidermal sheets, SSSS and TEN can be differentiated from a histologic characteristics, which underlies the importance of the skin biopsy at the time of presentation. In SSSS, there is superficial detachment involving the upper epidermal layers, whereas in TEN there is pan epidermal necrosis.[4] Steven Johnson syndrome (SJS) is the another exfoliative disease of the skin and mucus membrane. It differs from the TEN in only area of skin involved in the body. SJS involves less than 10% total body surface area where as TEN involves more than 30%.[5]

ETIOLOGY

Drugs e.g., antibacterials, antifungals, anticonvulsants, non-steroidal anti-inflammatory drugs, allopurinol are the causative agents in 77% to 94% of TEN cases. Corticosteroids have also been suspected. The other causes for TEN are viral

infections (*Haemophilus influenzae*), vaccinations and host versus skin disease, systemic lupus erythematosus, leukemia, lymphoma, ulcerative colitis and Crohns disease. There also occurs genetic susceptibility with certain antigenic markers of HLA system like B12, A29 and DR7.[6]

Clinical features

The occurrence of TEN following contact with the causative drug may vary from <1 day to 45 days without any signs and symptoms. TEN usually begins with a prodromal phase a Flu like syndrome with fever, rhinitis, cough, myalgia, anorexia, malaise. The first skin and mucosal lesion that characterize the acute phase may occur within 2-3 days and lasts for around 12 days. Skin involvement usually begins with itching, which is soon accompanied by painful eruptions on the face and upper trunk that spreads to the rest of the body with in few days, occurring commonly on the trunk and proximal areas on the limbs. The initial skin lesion is macular type, with irregular outlines and darker center reaching to maximum extent within 2-3 days depending on the drugs half-life (drugs with longer half-life are generally associated with the onset of prolonged skin symptoms and higher mortality). During this spreading stage initial lesions rapidly develop into bullae filled with clear fluid that forms the large plaque of necrotic epidermis, detaching from the underlying dermis and resembling wet clothes, owing to wrinkling. Simultaneously there is a presence of Nikolsky's sign (slight pressure over the apparent intact skin causes epidermis to peel off). Epidermal necrolysis may involve the whole body except the scalp, which remains un affected. The loosening of the epidermal layer results in the discharge of body fluids and there by loss of proteins and electrolytes.

Mucosal lesions usually occur prior to the epidermal necrosis, characterized by erosion and sloughing of the conjunctival, oropharyngeal, nasal, esophageal, urethral, anal and vaginal mucosae. It has special priority for stratified epithelium.

During this period fever remains high even in the absence of infection which is due to release of the pyrogenic agents by the necrotic epidermal tissue, particularly interleukin-1.

In the absence of complications the recovery phase generally lasts from 1 to 3 weeks, for reepithelialization of skin and mucosa. Reepithelialization is faster in the areas not subjected to pressure. Mucosa usually require longer reepithelialization period than cutaneous.[7]

The following criteria must be fulfilled for a case to be diagnosed as TEN.

1. Bullae or erosions involving more than 30% of body surface area or three different anatomical sites.
2. Skin peeling in sheets of more than 3 cm.
3. Involvement of skin not exposed to sunrays.
4. Involvement of mucous membrane frequently.
5. Skin tenderness within 48 hrs of rash.
6. Biopsy confirmation within 48 hrs.
7. Fever.
8. Bullae arising on an erythematous background.
9. Exclusion of SSSS.

Pathophysiology

The pathophysiology of the TEN is not yet fully elucidated and is a subject of controversy. The time between the administration of the triggering agent and onset of symptoms is less in TEN recurrences, strongly supports the existence of primary sensitization and immunological memory. The occurrence of TEN in individuals with auto immune diseases and with particular antigen markers of the HLA system also favors the immunological role in the pathogenesis.

On the other hand, one theory suggests a direct "toxic" effect by medication or a metabolite triggers cell death in epidermal keratinocytes. Alternatively, the drug triggers an immune reaction and the activated immunocytes mediate the cytopathic effects in much the same way that epidermal killing is seen in acute cutaneous graft versus host disease.

Characteristic histologic features include extensive keratinocyte death with separation of the epidermis from the dermis at the dermoepidermal junction. A paucicellular infiltrate, in which macrophages and dendrocytes predominate, has been commonly described. TEN has been characterized pathologically by an increased ratio of dermal dendrocytes to dermal lymphocytes. The death of keratinocytes has been shown to be through apoptosis.[8]

Differential diagnosis[9]

Erythema multiforme (EM)

Is a skin disorder that share some features of the TEN making it sometimes difficult to differentiate between two conditions. There are some criteria's which would differentiate them.

EM is characterized by presence of localized lesion <3 cm wide. It may or may not present as target lesions. Covers <20% of the body. Absence of mucosal involvement.

SJS

It is almost similar to the TEN except it covers <10% total body surface area. Individual lesions are <3 cm wide.

SSSS

Skin infection caused by certain strains of *Staphylococcal aureus* due to release of certain specific exotoxins. This syndrome is commonest in infants and neonates. It has clinical spectrum similar to TEN, its distinctive feature

includes absence of painful experiences and mucosal involvement. The histological difference is partial epidermal necrosis with intra epidermal cleavage at the granular layer level.

Scarlatiniform rash

It is usually caused by Group A *Streptococcus* or *S. aureus*.

It can induce wide spread erythema, which is more marked at the flexural folds, with possible desquamation of the digital pulps, pharyngitis and strawberry like tongue.

Toxic shock syndrome

Is caused *S. aureus*, is characterized by diffuse erythema with desquamation particularly over the palms and soles, fever and systemic involvement that rapidly progress to shock.

Kawasaki disease

Multi system disease of unknown etiology that affects the children <5 years. It is characterized by fever, polymorphic skin rash, conjunctivitis and tongue fissures which is some time mistaken for TEN.

COMPLICATIONS

TEN is considered as self-limiting, if there are no complications. Life-threatening complications are the general rule, which increases the morbidity and mortality. The most common and fatal complication is the infection. Sepsis is the main cause of death and accounting for more than 50% of all fatal cases. Loss of skin barrier through epidermal sloughing, allows the tissue invasion by the endogenous and exogenous organisms.

Cutaneous lesions are first colonized by *S. aureus*, followed by Gram-negative bacteria particularly *Pseudomonas aeuroginosa*. Patient treated with broad spectrum antibiotics or corticosteroids may develop fungal infection by *Candida albicans*. Disseminated Intravascular complication may occur following the sepsis.

Ocular complications are frequent ranging from mild conjunctival hyperemia to purulent conjunctivitis or even fusion of eyelids and eyeball leading to total blindness. These complications are induced by erosion of conjunctiva and subsequent fibrosis.

Respiratory disorders are common finding leading to necessity for the artificial ventilation in 10-20% of the patients. Numerous factors may account for the pulmonary function detoriation, such as shallow respiration, pulmonary edema caused by increased alveolar capillary permeability, aspiration of the oropharyngeal sloughing mucosa, which may lead to bronchiolitis obliterans, pneumonia or acute respiratory distress syndrome.[10]

Digestive tract involvement may not only involve the oropharyngeal sloughing but may also involve more distal region in the esophageal epithelium, which are similar to peptic esophagitis leading to dysphagia, increased gastric bleeding and rarely esophageal rupture. Intestinal lesions are less and may present as bloody diarrhea. Approximately, 50% patients show increased transaminase levels and among them 10% may develop fatal hepatitis.[11]

Hematological complications are common in the form of anemia which is normocytic normochromic, leucopenia is very common, lymphocytopenia occurs in 90% of patients leading to transient decrease in the CD4+ lymphocytes and neutropenia is seen in around 30% patients associated with appearance of sepsis.[12]

Others less complications leading to patient morbidity include vaginal and urethral stenosis, transient alopecia, loss of nails, eyebrows, keloid formation and skin hypo or hyper pigmentation.

Treatment[13]

Important thing is early withdrawal of the offending drug which improves outcome. This is more effective for drugs with shorter half-lives and seems to be less important for drugs with longer half-lives. Hospitalization particularly in in the intensive care units or the burns unit will be helpful in recovering.

Adequate nutrition

Nutrition is an integral part of management, as TEN is a hyper metabolic state and there is increased energy and protein dietary requirements which are proportional to the body surface area affected. Oral intake is often difficult because of upper gastrointestinal tract (GIT) injury; therefore diet and fluid modification are important. Early in the disease when the dysphagia and odynophagia are severe, a fluid diet is preferable. There is a role for enteral feeding if the patient is unable to take orally, but it is important to encourage oral feeds which helps to avoid adhesions in the upper GIT. Glycemic control is a problem as a result of stress and previous treatment with steroids. As hyperglycemia is one of the risk factors for outcome; close control of blood glucose is needed.

Skin care

Careful protection of the exposed dermis and early reepithelializing skin is important to prevent infection. Unbroken epidermis, even if dead, serves as protection for underlying viable and regenerating tissue. Daily baths and the use of clean, sterile, non-adhesive dressings, as required are routine.

Pain management

Pain control is integral part of the management of TEN. It has to be individualized. In a non ICU setting full consciousness is preferable as is oral therapy for reasons mentioned. Short acting, medium potency opioids are best for pain. Anxiolytics such as low dose Benzodiazepines are more effective for patients with high pre procedure anxiety. Longer acting, mild to moderate potency opioids together with antipyretic is of help.

Fluid balance

Careful monitoring of fluid balance is essential as the patients have significant fluid loss and often present with dehydration and renal impairment. This needs to be aggressively corrected as it is one of the risk factors for outcome.

Eye care

Conjunctival involvement is a common problem. This can be mild or severe leading to Keratopathy, limbal stem cell deficiency. Supportive care with 1-2-hourly lubrication and early assessment is needed. There is a role for contact lens use to prevent synechae or minor surgery for release of developing synechae.

Genital care

Good hygiene and the use of non-adhesive dressings are usually adequate to allow healing of mucosal erosions over the genital regions. Every effort should be made to prevent adhesions in areas where two eroded surfaces are opposed. Indwelling catheters should be avoided, as they can be a source of sepsis.

Upper GIT care

Oral intake should be encouraged as this helps to maintain a patent system and prevent adhesions. Mild, medicated mouthwash should be used every two hourly to clean the mouth. A lubricating cream can be used to soften hemorrhagic lip crusts prior to removal. Paraffin gauze dressings and lubricating cream are used to cover erosions and avoid fissuring.

Respiratory system

Respiratory system involvement is common, with 10-20% needs artificial ventilation. They can present with tracheobronchial mucosal necrosis, pulmonary edema, adult respiratory distress syndrome and infectious pneumonia or pneumonitis. Pooling of saliva and secretions may predispose to aspiration and therefore these needs to be cleared frequently.

Prophylactic antibiotics

Antibiotics are best for proven infections. Careful monitoring for any signs of infection is critical to facilitate prompt sepsis intervention with suitable antibiotics after culture and sensitivity.

Systemic steroids

There is controversy regarding use of systemic steroids, but evidence suggests that they are not so beneficial. Low doses of Hydrocortisone have better outcome in but not sepsis confirmed in TEN.

Intravenous immunoglobulin (IVIG)

IVIG blocks Fas/Fas ligand interaction, preventing progression of keratinocyte apoptosis. If used early in TEN it may halt progression of the disease. At doses of <2 mg/kg it is safe and decreases mortality rates. The cost benefit ratio is the factor that restricts its use in developing countries.

Cyclosporine

Given early in the disease, at 3-5 mg/kg daily, intravenously or orally, over 2 weeks, it arrests progression of disease without much risk of sepsis.

Plasmapheresis

Practiced by some clinicians to remove drug metabolites and responsible cytokines from circulation, which would helpful in recovery.

A CASE

A 4-year-old female child was brought to the hospital with history of skin lesions of 4 days duration. There was history of fever and convulsions about a week back for which the child was given paracetamol (Febrex) and phenytoin sodium syrup (Dilantin). On day 4 after starting the above drugs the child developed generalized erythema, followed by blistering of skin and the child was toxic.

Child was hospitalized in the pediatric ICU unit. The causative drug was stopped, investigations were done (Figures 1 and 2).

Investigations

Hemoglobin: 12 g%
Total count: 5000/mm^3, DC N-43, L-50, M-4, E-3
Erythrocyte sedimentation rate: 20 mm/hrs
Platelet: 2.4 lac/mm^3
Red blood cells: 126 mg/dl

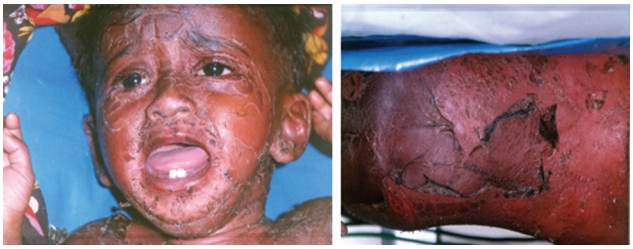

Figure 1: Day 1.

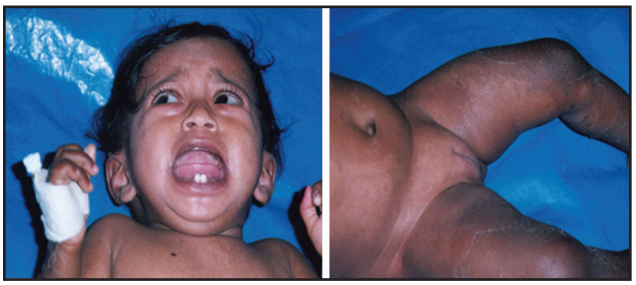

Figure 2: Day 15.

Blood urea: 20 mg/dl
Serum creatnine: 0.43 mg/dl

Serum electrolytes

Na^+: 141 mEq/l
K^+: 4 mEq/l
Cl^-: 100 mEq/l.

Histopathology

- Epidermal keratinocyte necrosis
- Sub epithelial bullae formation
- Vacuolization of basement membrane.

Treatment

- IV fluids
- Cefotaxime - 250 mg IV QID - 5 days
- Corticosteroids - Betamethasone 4 mg/ml 8th hourly IV for 4 days
  - 4 mg/ml 12th hourly for next 3 days
  - 4 mg/ml once daily for another 3 days

The child was completely recovered by 15th day.

CONCLUSION

In all the cases presenting with erythematous and bullous eruptions associated with drug intake, TEN differential diagnosis should be excluded at an early point of time. The offending causative drug should be stopped. The patient should be admitted in a tertiary care center in a burns or intensive care unit and appropriately treated. TEN is self-limiting, unless there occurs complication, among which infection is the most common leading to sepsis. The high morbidity and mortality with TEN makes it necessary to educate all the health care professionals regarding this syndrome.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Cabral L, Riobom F, Diogo C, Teles L, Cruzeiro C. Topical epidermal necrolysis- Lyell's syndrome. Ann Burns Fire Disaster. 2004;17(2):1-26.
2. Qadir SN, Raza N, Qadir F. Drug induced toxic epidermal necrolysis: two case reports. Cases J. 2009;2:7765.
3. Piérard GE, Hermanns-Lê T, Paquet P, Rousseau AF, Delvenne P, Piérard-Franchimont C. Toxic epidermal necrolysis and graft-versus-host reaction: revisiting a puzzling similarity. ISRN Dermatol. 2013;2013:651590.
4. Abood GJ, Nickoloff BJ, Gamelli RL. Treatment strategies in toxic epidermal necrolysis syndrome: where are we at? J Burn Care Res. 2008;29(1):269-76.
5. Tyagi S, Kumar S, Kumar A, Singla M, Singh A. Stevens-Johnson syndrome-A life threatening skin disorder: A review. J Chem Pharm Res. 2010;2(2):618-26.
6. Kaur S, Rajagopaln S, Shafiq N, Dogra S, Pandhi P, Malhotra S. A case of drug induced toxic epidermal necrolysis: pharmacovigilance in action and lessons to learn. J Postgrad Med Educ Res. 2012;46(1):40-2.
7. Spies M, Sanford AP, Aili Low JF, Wolf SE, Herndon DN. Treatment of extensive toxic epidermal necrolysis in children. Pediatrics. 2001;108(5):1162-8.
8. Abe R, Shimizu T, Shibaki A, Nakamura H, Watanabe H, Shimizu H. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble Fas ligand. Am J Pathol. 2003;162(5):1515-20.
9. Halebian PH, Shires GT. Burn unit treatment of acute, severe exfoliating disorders. Annu Rev Med. 1989;40:137-47.
10. McIvor RA, Zaidi J, Peters WJ, Hyland RH. Acute and chronic respiratory complications of toxic epidermal necrolysis. J Burn Care Rehabil. 1996;17(3):237-40.
11. Zweiban B, Cohen H, Chandrasoma P. Gastrointestinal involvement complicating Stevens-Johnson syndrome. Gastroenterology. 1986;91(2):469-74.
12. Goens J, Song M, Fondu P, Blum D, Achten G. Haematological disturbances and immune mechanisms in toxic epidermal necrolysis. Br J Dermatol. 1986;114(2):255-9.
13. Lehloenya R. Management of Stevens-Johnson syndrome and toxic epidermal necrolysis. Curr Aller Clin Immunol. 2007;20(3):124-8.

doi: 10.5455/2319-2003.ijbcp20150236
Cite this article as: Chidananda KN, Jagadeesh K. Toxic epidermal necrolysis: a severe cutaneous adverse drug reaction. Int J Basic Clin Pharmacol 2015;4:1-5.