



Case Study

Piroxicam Induced Toxic Epidermal Necrolysis - A Case Report and Review of Literature

Lavanya J¹, Srinivasa K², Shadab Raheel³ and Lohith Kumar⁴

¹Department of Microbiology, Lady Hardinge Medical College, New Delhi, India

²Associate Professor, Dept. of Pharmacology, CIMS, Chamarajanagar, Karnataka, India

³Senior Resident, Department of Forensic Medicine, VMMC & Safdarjung Hospital, New Delhi, India

⁴Assistant Professor, Dept. of Forensic Medicine, Kodagu Institute of Medical Sciences, Madikeri, India

**Corresponding author*

ABSTRACT

Keywords

Toxic epidermal necrolysis, Piroxicam, Septicemia

Toxic Epidermal Necrolysis (TEN) is a severe hypersensitivity reaction to drugs affecting skin and mucous membrane leading to epidermal detachment. TEN is a potentially fatal cutaneous reaction with a mortality rate up to 40%. We present a case of 35 year old male patient referred to Safdarjung hospital burns ward from Moolchand Hospital with complaints of swelling of gums, lips and eyelids since 2 days along with throat pain and difficulty in swallowing. Patient has history of ingestion of drugs including Tab. Piroxicam., Patient succumbed to death due to extensive exfoliation and septicemia due to TEN induced by Piroxicam tablet ingestion. TEN is an acute, exfoliative, potentially life threatening cutaneous disorder. Prompt recognition of this condition, immediate drug withdrawal and institution of appropriate treatment plays a vital role in reducing mortality.

Introduction

Toxic epidermal necrolysis (TEN), or Lyell's syndrome, is a severe cutaneous disorder characterised by widespread full-thickness epidermal necrosis with involvement of more than 30% of the body surface area. Commonly, there is severe involvement of the mucous membranes (oropharynx, eyes and genitalia). The estimated incidence ranges from 0.4 to 1.2 per million populations per year. It has a high associated mortality approaching 40%.

The main cause in adults is drugs. Patients with HIV infection, systemic lupus erythematosus and bone marrow transplant recipients seem to be predisposed to this disorder. Elderly patients and those with extensive TEN have a worse prognosis. Drug-induced TEN is rare in children, in whom the diagnosis must be distinguished from staphylococcal 'scalded skin syndrome'.¹

One of the most common types of adverse reaction to drug therapy is cutaneous drug eruptions, with an overall incidence rate of 2–3% in hospitalized patients. Skin reactions can occur due to any medicine and certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics contribute to 1–5% of cases. Although most drug-related skin eruptions are not serious, some are severe and potentially life-threatening. Serious reactions include angio-oedema, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis.²

Stevens-Johnson syndrome (SJS; also known as erythema multiforme major) is a manifestation of the same process involved in TEN, with the latter involving more extensive necrotic epidermal detachment. TEN involves more than 30% of the body surface, whereas SJS involves less than 10%.³

We describe a case in which middle aged male with history swelling of gums, lips and eyelids since 2 days along with throat pain and difficulty in swallowing following ingestion of drugs Tab. Piroxicam. Patient was resuscitated but could not be reviewed and leading to septicemic shock and expired after 16 days.

Case report

A 35 year old male patient was admitted to ICU, Moolchand hospital, New Delhi on 14/6/2013 with complaints of swelling of gums, lips and eyelids since 2 days along with throat pain and difficulty in swallowing since 1 day. Patient has history of ingestion of drugs including Tab. Piroxicam.

His initial blood investigations were within normal limits. He was started on i.v antibiotics, antacids, anti-allergic, i.v

steroids and other supportive measures. ENT and Ophthalmology reference was given and their advice was incorporated in the treatment. On day 2 of admission, patient developed rashes over face, neck, chest and trunk along with high grade fever. Antibiotics were escalated and Dermatology reference was given. Patient was given IV IgG for 5 days along with pulse steroid therapy. Later on he developed large areas of epidermal detachment with blisters and areas of denuded skin along with severe conjunctivitis, severe stomatitis with purpuric macules (Figure 1-4). Adequate nutrition and hydration was maintained, with wound care dressing by the surgeon and strict sepsis prevention with isolation was done. Daily IV analgesics were added for pain. His repeated blood, urine and throat swab cultures were sterile. But skin swab culture revealed *Staphylococcus aureus* (MRSA) and persisting high grade fever, antibiotics were escalated after which fever subsided. In view of poor skin healing plastic surgeon was consulted and he underwent thorough dressing in OT under sedation.

Patient was referred to Safdarjung Hospital in critical state on 28/6/2013 with diagnosis of Piroxicam induced Toxic Epidermal Necrolysis with 45% raw areas (15 day old). Patient developed septic shock despite best efforts. Patient was resuscitated but could not be reviewed and declared dead on 29/6/2013.

Discussion

Toxic Epidermal Necrolysis can be induced by

- 1) Drugs – major precipitating cause.
- 2) Infection or
- 3) Idiopathic.

Medications implicated in TEN are⁴

1. Antibiotics like Sulfonamides, Chloramphenicol, Macrolides (eg, erythromycin), Penicillins, Quinolones (eg, ciprofloxacin, trovafloxacin)
2. Antiepileptic drugs like Phenobarbital, Phenytoin, Carbamazepine, Valproic acid and Lamotrigine.
3. nonsteroidal anti-inflammatory drugs (NSAIDs) like Oxicams (eg, piroxicam, tenoxicam) - Implicated more often than other NSAIDs, Phenylbutazone and oxybutazone Ibuprofen, Indomethacin, Sulindac, Tolmetin.
4. Allopurinol.
5. Corticosteroids (topical and systemic), and
6. The antiretroviral drugs nevirapine and abacavir.

Infectious agents (ie, *Mycoplasma pneumoniae*, herpes virus, and hepatitis A), immunizations, and bone marrow or solid organ transplantation have also been associated with TEN.

The aetio-pathogenesis of TEN still remains largely unknown. At present it is assumed that exposure to drugs is the only documented cause of TEN syndrome. These drugs damage the metabolic pathway leading to accumulation in the organism of its toxic metabolites due to enzymatic defects and detoxication disorders⁵

On the basis of extent of epidermal detachment and morphology of the skin lesions, TEN can be classified as follows:⁶

- 1) TEN with spots
- 2) TEN without spots
- 3) Overlap Stevens-Johnson syndrome and TEN (SJS-TEN)

TEN with spots is defined as widespread, irregularly shaped erythematous or purpuric macules with blistering that occurs on all or part of the macule. Blisters become more confluent and result in detachment of the epidermis and erosions on greater than 30% of the body surface area. Mucosal surfaces are usually involved.

TEN without spots is defined as widespread, large areas of erythema with no discrete lesions. Epidermal detachment is greater than 10% of the body surface area. Mucosal surfaces are usually involved.

Overlap Stevens-Johnson syndrome and TEN (SJS-TEN) is characterized by widespread, irregularly shaped erythematous or purpuric macules with blistering that occurs on all or part of the macule. Blisters become confluent and result in detachment of the epidermis and erosions on 10-29% of the body surface area.

Recognising SJS and TEN⁷

We could recognise SJS and TEN early if we are familiar with their clinical features, especially those earlier ones. Many patients with SJS and TEN begin with the prodromal symptoms of fever, headache and myalgia. The SJS and TEN skin eruptions first appear as erythematous then dusky or purpuric macules. The lesions are usually irregularly shaped, discrete in the beginning then coalesce with one another. Atypical target lesions could be seen but they are not the three zone target lesions seen in erythema multiforme. The rash first appears on the face and upper part of the trunk and proximal part of the extremities and spread rapidly to the rest of the body. Lesions soon developed into flaccid blisters. For those non-blistered rash, Nikolsky sign (separation of epidermis from dermis with lateral

pressure) can be demonstrated, which is an important though not pathognomonic sign. Finally the necrotic epidermis comes off leaving large areas of red exudative dermis exposed. The mucous membrane is always involved in SJS and TEN, commonly precede the rash but sometimes after. Erythema is followed by painful erosions on the buccal, ocular and genital mucosae, and usually more than one site are involved. More than 80% of patients have conjunctival involvement, sometimes leads to corneal ulceration, anterior uveitis and synechia. Ocular involvement in SJS and TEN could result in the most debilitating late complications.

Conditions which mimic TEN in appearance and presentation which need to be differentiated before diagnosis are.⁶

- Erythema multiforme major
- Staphylococcal scalded skin syndrome
- Purpura fulminant
- Disseminated intravascular coagulation with skin necrosis
- Acute generalised exanthematous pustulosis
- Generalised bullous fixed drug eruption
- Chemical toxicity (methotrexate, colchicines etc)
- Burns
- Graft-versus-host disease
- Pemphigus

Staphylococcal scalded skin syndrome (SSSS) presents initially as a macular exanthema which might quickly evolve to blistering eruption with positive Nikolsky's sign and mimic SJS and TEN. SSSS more commonly occurs in infants or adults with renal failure. A Tzanck smear will find acantholytic cells in SSSS but not TEN. Skin biopsy with frozen section examination

will find intradermal cleavage with acantholysis in the subgranular layer whereas in SJS and TEN full thickness epidermal necrosis and dermal-epidermal separation are found. The diagnosis of SSSS instead of SJS/TEN will enable the early use of antibiotics against Staphylococcal infection.

Conclusion

The prodrome of fever, myalgia, headache; the appearance of dusky rash on the face and proximal limb; mucosal erosion, and the positive history of drug exposure should alert the physician to the possibility of SJS and TEN. All suspected cases of SJS and TEN should be confirmed by skin biopsy for histologic and immunofluorescence examinations. Mortality rate in TEN is high mainly due to extensive areas of the affected body surface, fluid loss and electrolyte abnormalities and secondary infections. The patient's clinical state, the time of medication therapy and aggressiveness of the undertaken treatment also contribute to the mortality rate. A number of important conditions mimic SJS and TEN. Since 90% SJS and TEN has mucous membrane involvement the absence of such should prompt one to consider alternative diagnosis. The case we described posed a significant dilemma in the diagnosis, as history of ingestion of the drugs responsible for TEN was not available. This case serves as an example to emphasise the necessity of remaining alert when dealing with a drug induced TEN case. Before deriving any conclusion, proper history from parents, along with treatment records should be looked upon to eliminate most of doubts which also helps in concluding opinions and to aid in the administration of justice.



(Figure 1)



(Figure 2)



(Figure 3)



(Figure 4)

References

1. Breathnach SM, Hintner H. Adverse Drug Reactions and the Skin. Oxford: Blackwell Scientific, 1992.
2. Crowson AN, Brown TJ, Magro CM. Progress in the understanding of the pathology and pathogenesis of cutaneous drug eruptions. *Am J Clin Dermatol* 2003; 4: 407–428.
3. Wolkenstein P, Revuz J. Drug-induced severe skin reactions. *Drug Safety* 1995; 13: 56–68.
4. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol* 2001; 137: 765–770.
5. Victor Cohen, Michael Stuart Bronze et al. Toxic Epidermal Necrolysis. *emedicine. medscape.com/ article/ 229698-overview.*
6. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* Dec 14 1995; 333(24):1600-7. [Medline].
7. Dr. HHF Ho. Diagnosis and Management of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Medical Bulletin.* Vol.13 No.10 October 2008.