A case of toxic epidermal necrolysis probably due to etoricoxib

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INTRODUCTION

Toxic epidermal necrolysis (TEN) is a severe adverse skin reaction characterized by generalized keratinocyte necrosis in relation with inappropriate immune activation by certain drugs or their metabolites. It may be associated with immunosuppressive states such as HIV/AIDS, connective tissue disorders, and certain malignancies such as leukemia, lymphoma, and solid tumors. Analysis of several case reports and retrospective studies have identified drugs (nearly 100) implicated in the development of Steven–Johnson Syndrome (SJS)/TEN.

Case Report

A 25-year-old female patient presented with symptoms of extensive brown rashes all over the body with fever. The patient presented with rapidly evolving rashes, initially over the face and upper body but subsequently involving the total body surface area. There was an extensive ulceration of buccal mucosa along with eyelid edema, crusting, and corneal ulceration. Naranjo’s and WHO–UMC score for this adverse event was “seven;” hence, causality was “probable.” SCORTEN (severity-of-illness score) was “one” with a predicted mortality of 3.2%. Due to persistent hypotension and risk of impending sepsis, aggressive fluid resuscitation and antibiotics were initiated. Cyclosporine and systemic steroids were added later, following which the patient had a prompt recovery. She was discharged after 28 days of hospitalization.

Etoricoxib has a 30-fold selective cyclooxygenase-2 (COX-2) enzyme inhibitor that plays a major role in the inhibition of prostaglandin synthesis. Such kind of drugs have been developed in relation with their enhanced gastrointestinal tolerability in addition with effective pain management, although postmarketing surveillance data on etoricoxib have identified cases of SJS/TEN and other skin reactions in the past. In this case report, we discuss a rare incidence of etoricoxib-induced TEN in a 25-year-old woman.

KEYWORDS: Adverse drug reaction, etoricoxib, toxic epidermal necrolysis

Access this article online

Website: http://www.jcrsmed.org

DOI: 10.4103/jcrsm.jcrsm_22_19

How to cite this article: Thakur S, Lahiry S. A case of toxic epidermal necrolysis probably due to etoricoxib. J Curr Res Sci Med 2019;5:118-21.
and peeling of skin at the emergency unit. Her past medical history included few nonspecific symptoms of polyarthralgia involving bilateral upper limb small joints. Associated history of morning stiffness, previous rashes, or photosensitivity reaction was not recorded. However, for achieving pain relief, the patient admitted taking a “better” drug, obtained from a local pharmacy over the counter. It was later confirmed by the medication label that the drug was tablet etoricoxib (60 mg), taken once daily orally with no other concurrent medication.

Subsequently, on Day 13 of continuous such medication intake, she developed a high-grade fever (>38.3°C) with chill and rigor. Her condition quickly worsened with an exaggerated skin reaction consisting of maculopapular rashes, which necessitated hospitalization. The drug was withdrawn as her condition was serious with hypotension. The rashes had first appeared over lower limbs, followed by an eventual spread all over the entire body surface area [Figure 1]. Scattered vesicles and bulla appeared subsequently, some of which got “peeled off” quickly [Figure 2]. There was extensive involvement of buccal mucosa, lips, and erosion of the palate associated with eyelid edema, crusting, and discharge with corneal erosion [Figure 3]. Nikolsky’s sign was clearly elucidated with a detachment of the epidermis from lower layers when rubbed gently. The diagnosis of Staphylococcal Scalded Skin Syndrome (SSSS) was ruled out, attributed to the presence of mucosal involvement, which will be absent in SSSS.13

Primary treatment included replacement of fluid loss (intravenous Ringer’s lactate 500 ml 8 hourly) and maintenance of electrolyte balance and antibiotic therapy (injection clindamycin 600 mg i.v. bid + injection meropenem 1 g i.v. tid). Tablet cyclosporine (100 mg p.o. bid) was added. For local application, lignocaine 2% gel, topical liquid paraffin 15%, and moxifloxacin 0.5% w/v (ophthalmic) were prescribed.

On Day 14, laboratory investigations were mostly normal: sodium – 138.7 meq/L, potassium – 4.4 meq/L, creatinine – 0.6 mg/dL, leukocyte count – 5800/mm³, and platelet – 2.2 lakh/μL. Hemoglobin was 8.9 g/dL. Urine culture-sensitivity analysis revealed “no obvious growth” of any microorganism. Her vitals gradually improved; hence, the treatment was continued.

On Day 20, there was a decline in hemoglobin levels to 7.9 g/dL (by 12%), for which she was transfused with 2 units of whole blood (one bag, each on Days 20 and 21, respectively). Major causes of bleeding or hemorrhage were ruled out. On Day 22, dermatological
consultation was sought and injection meropenem was replaced by the injection linezolid (600 mg. i.v. bid). Tablet betamethasone (2 mg p.o. bid) was added. On Day 23, despite fluid replacement, there was persistent hypotension; hence, Ringer’s lactate was replaced by infusion NS: DNS (2:1) i.v. given 4 hourly. Subsequently, there was a rapid improvement in patient’s condition with the healing of skin lesions [Figures 4 and 5].

On Day 28, betamethasone and antibiotics were withdrawn and liquid diet was permitted. On Day 36, the patient started taking normal oral diet; hence, concomitant medications were switched to oral formulation (tablet clindamycin 300 mg p.o bid + tablet pantoprazole 40 mg p.o bid). Topical formulations (sucralfate[100] + oxetacaine [10 mg] + chlorhexidine [oral] + moxifloxacin 0.5% w.v [ophthalmic]) were continued. She was discharged in a stable condition on Day 41, with proper instructions regarding a possible relapse [Figures 6 and 7].

**DISCUSSION**

The underlying pathophysiology of drug-induced SJS/TEN includes predominantly CD8+ T-lymphocyte and activated macrophages in the epidermis along with CD4+ T-cells in the dermis, indicating a cytotoxic cellular immune reaction at the level of keratinocyte. They are more commonly reported in women than in men.\(^2,4\) Causative drugs or their metabolite act as a hapten and render keratinocyte antigenic. Underlying defect in detoxification system of keratinocyte can also play a major role in drug-induced SJS/TEN.\(^4,9\)

Although etoricoxib is a highly selective COX-2 inhibitor, usually considered “safe” in day-to-day clinical practice, its safety attributed to an anti-inflammatory agent is still a matter of debate.\(^4,6\) Usually, a history of either hypersensitivity and or immunosuppression or genetic susceptibility is positive with such severe mucocutaneous
reaction with this drug.\textsuperscript{2,4} However, the chances of developing such serious unexpected reaction with etoricoxib are still very rare.\textsuperscript{5,6}

In most of the previous cases reported, the time period between suspected drug intake and appearance of skin lesions varied from a few days to 2–3 weeks and even 1 month in few exceptional cases.\textsuperscript{4,5} In the present case, a prodromal phase, characterized by fever and arthralgia, appearing after nearly 2 weeks of continuous drug intake was present. It was quickly followed by the appearance of maculopapular rash systemically, along with the formation of vesicles and bulla, with sloughing of necrotic skin extending to the extremities, back, trunk, and face. There was evidence of oral and nasal mucosal erosions with conjunctival scarring.

In the present case, the causality is “probable” to the drug etoricoxib with a score of 7, on Naranjo Adverse Drug Reaction Probability Scale\textsuperscript{7} and WHO–UMC\textsuperscript{8} Scale, respectively. Based on an assessment of vitals and laboratory test on admission (Day 13), SCORTEN (severity-of-illness score) was “one” with a predicted mortality of 3.2\%.\textsuperscript{9}

The transient fall in the hemoglobin levels may be in parallel with some previous reports of anemia in relation with TEN.\textsuperscript{10} However, there is no definitive explanation to whether there is any underlying bone marrow pathology specific to TEN or related to any secondary phenomenon.\textsuperscript{10} Treatment with antibiotics (linezolid + clindamycin) along with a steroid supplement (betamethasone) was found to be effective in this case. Cyclosporine was added because of its interaction with tumor necrosis factor-\(\alpha\) metabolism promoting shorter reepithelialization time, and the property of lowering mortality has been established previously.\textsuperscript{1,2}

Certain drugs such as sulfonamides, nonsteroidal anti-inflammatory drugs, pyrazolones, barbiturates, and antiepileptics have been associated with triggers of TEN/SJS.\textsuperscript{11,12} However, chances of developing such a rare and idiosyncratic reaction with such drugs are very rare although it mandates a detailed clinical history, including drugs.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Estrella-Alonso A, Aramburu JA, González-Ruiz MY, Cachaferio L, Sánchez MS, Lorente JA. Toxic epidermal necrolysis: A paradigm of critical illness. Rev Bras Ter Intensiva 2017;29:499-508.
2. Fritsch PO, Sidoroff A. Drug-induced Stevens-Johnson syndrome/ toxic epidermal necrosis. Am J Clin Dermatol 2000;1:349-60.
3. Kameshwar JS, Devde R. A case report on toxic epidermal necrolysis with etoricoxib. Indian J Pharmacol 2015;47:221-3.
4. Napoli B, D’Arpa N, D’Amelio L, Chimenti S, Pileri D, Accardo-Palumbo A, et al. Staphylococcal scalded skin syndrome: Criteria for differential diagnosis from Lyell's syndrome. Two cases in adult patients. Ann Burns Fire Disasters 2006;19:188-91.
5. Ward KE, Archambault R, Mersfelder TL. Severe adverse skin reactions to nonsteroidal antiinflammatory drugs: A review of the literature. Am J Health Syst Pharm 2010;67:206-13.
6. Kreft B, Wohlrab J, Bramsiepe I, Eismann R, Winkler M, Marsch WC. Etoricoxib-induced toxic epidermal necrolysis: Successful treatment with infliximab. J Dermatol 2010;37:904-6.
7. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
8. WHO-UMC Causality Criteria. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. [Last accessed on 2017 Mar 19].
9. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Wolkenstein P, Revuz J, Wolkenstein P, SCORTEN: A severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 2000;115:449-53.
10. Rajaratnam R, Mann C, Balasubramaniam P, Marsden JR, Taijbee SM, Shah F, et al. Toxic epidermal necrolysis: Retrospective analysis of 21 consecutive cases managed at a tertiary centre. Clin Exp Dermatol 2010;35:853-62.
11. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5:39.
12. Spornraft-Ragaller P, Ragaller M, Meurer M. Toxic epidermal necrolysis induced by NSAID. Z Rheumatol 2003;62:474-5.