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Case Report

Etoricoxib Induced Toxic Epidermal Necrolysis: A Case Report

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ABSTRACT

Toxic Epidermal Necrolysis (TEN) is a rare and life-threatening skin reaction that can quickly lead to dehydration and infection. TEN is perhaps the most formidable disease encountered by dermatologists, and it remains as puzzling a disorder as it was when described by Lyell. Etoricoxib is a medication that has been associated with TEN. The ideal medical management of TEN should be multidisciplinary and requires early diagnosis and withdrawal of suspected/causative drug(s), supportive care, and specific therapy. Here we present a case of Toxic Epidermal Necrolysis due to Etoricoxib in an immune-compromised patient.

Keywords: Toxic Epidermal Necrolysis, Etoricoxib, Case Report.

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INTRODUCTION

Toxic Epidermal Necrolysis (TEN) is a severe dermatological condition characterized by extensive erythema, necrosis of the epidermis and mucous membranes, and the development of blistering skin detachment. If left untreated, TEN can progress to severe desquamation, sepsis, and potential fatality.[1] This syndrome was independently described by Lyell in Glasgow, Scotland, and Lang and Walker in Cape Town, South Africa in 1956.[2] Lyell is credited with coining the term "Toxic Epidermal Necrolysis" to denote this life-threatening ailment.[3]

Etoricoxib, a medication known for its effectiveness in alleviating inflammation and pain, is a specific inhibitor of the enzyme Cyclooxygenase-2 (COX-2). It belongs to the class of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) recognized for their selectivity in targeting COX-2. Notably, NSAIDs are associated not only with the potential for severe Gastrointestinal (GI) complications but also the risk of inducing life-threatening skin reactions. This includes conditions falling within the Erythema Multiforme (EM) spectrum, which can progress to toxic epidermal necrolysis when selective Cyclooxygenase (COX) 2 inhibitors are employed.

The occurrence of such cases seems unpredictable, affecting patients with or without a history of sulfonamide allergies. These adverse skin reactions can manifest following short-term or long-term use of these medications, with most incidents emerging within the initial two weeks of treatment initiation. The underlying biological mechanism responsible for drug-induced Stevens-Johnson Syndrome (SJS) and TEN is linked to the generation of drug-responsive T cells, primarily concentrated within the dermal and epidermal layers of the skin, specifically within the CD4+ and CD8+ subsets.[4]

Furthermore, the pathophysiology of TEN involves a complex interplay of immune responses, with drug-induced hypersensitivity reactions triggering a cascade of events leading to extensive epidermal and mucous membrane destruction, a hallmark of TEN. It is believed that drug-responsive T cells play a pivotal role in initiating the attack on keratinocytes, ultimately resulting in the extensive skin detachment observed in TEN.[4]

It is imperative for healthcare providers to exercise heightened caution when prescribing medications, especially selective Cyclo-Oxygenase (COX) 2 inhibitors, given the associated risks of severe skin reactions. A comprehensive understanding of the underlying mechanisms and risk factors for TEN is crucial for the timely identification and effective management of cases, with the ultimate goal of mitigating the life-threatening consequences of this rare yet devastating condition.

CASE HISTORY

Patient History

The patient presented to the Father Muller Medical College Hospital with a recent onset of fluid-filled lesions across their entire body, accompanied by raw areas affecting the lips and oral cavity. These lesions initially manifested with widespread pruritus and erythema of the skin, as depicted in Figure 1, illustrating the patient's condition on the day of admission.

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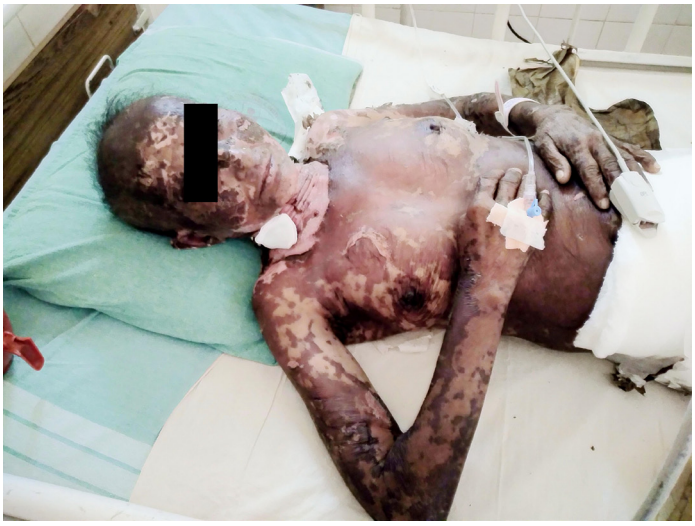

Figure 1: Patient presented to the hospital with multiple skin erosions and lesions.

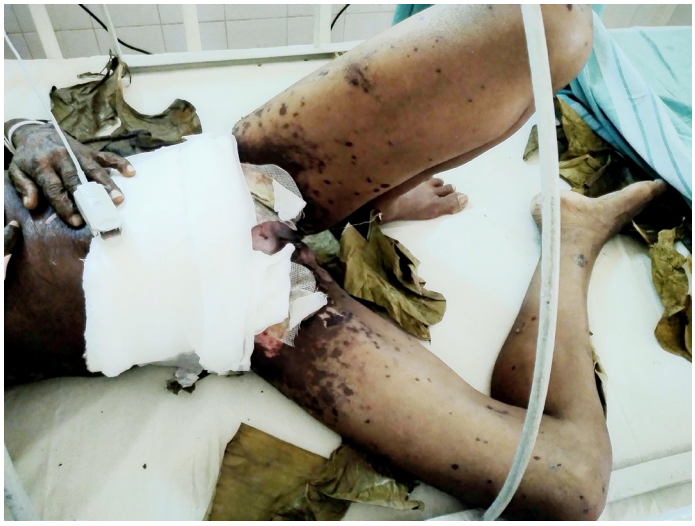

Figure 2: Lesions on the groin region of the patient.

Medical Background

The patient's medical history revealed a diagnosis of stage 4 metastatic cervical cancer in December 2022. Subsequently, the patient underwent six cycles of chemotherapy (comprising paclitaxel, carboplatin, and bevacizumab) from January 1, 2023, to February 9, 2023. Additionally, two cycles of radiation therapy were administered. Commencing on January 13, 2023, the patient initiated a medication regimen consisting of etoricoxib for post-chemotherapy discomfort, which continued until February 9, 2023. Notably, the patient discontinued tapentadol during this period for reasons that remain undisclosed (Refer to Figure 2 for an image depicting the lesions in the patient's groin region.)

Clinical Examination

Upon physical examination, the patient was observed to be of suboptimal nutritional status and exhibited bilateral pedal edema. Cutaneous examination revealed the presence of multiple hyperpigmented macules and patches distributed across the trunk, neck, abdomen, upper and lower extremities, accompanied by a positive Nicholsky sign. Flaccid bullae were noted on the neck and hands, bilateral hand edema, and erythematous macules on the bilateral palms. Large erosions were evident on the back, groin, lower abdomen, buttocks, post-auricular area, and neck. Hyperpigmentation was observed on the scalp. Mucosal examination disclosed mild conjunctival congestion, crusted erosions within the oral cavity and lips, as well as erosions in the genital regions. Additionally, a skin biopsy confirmed the diagnosis of toxic epidermal necrolysis.

SCORTEN Score

The patient's SCORTEN score was calculated to be 3, with individual scores of 1 attributed to age greater than 40 years, the presence of neoplasia, and an initial detachment exceeding 10%.

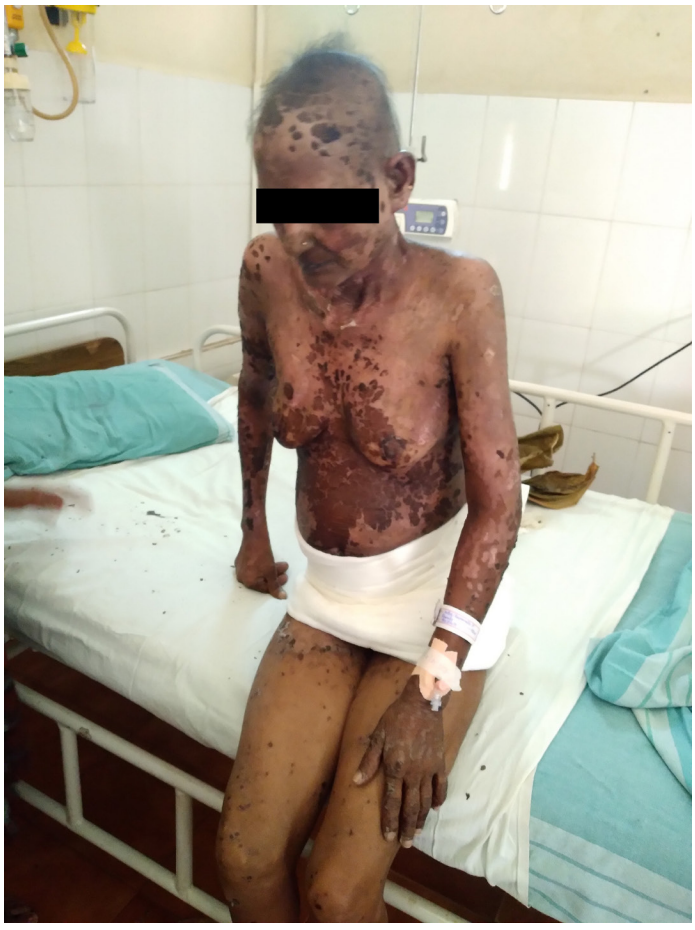

Figure 3: Improved skin lesions of the patient on the day of discharge.

Causality score

The causality in this case is "probable" with a score of 7 on the Naranjo Causality Assessment scale.

Treatment

The primary treatment approach involved intensive fluid resuscitation, the administration of antibiotics, corticosteroids

for inflammation and pruritus control, analgesics, nutritional support, and meticulous wound care. The patient received 600 mg of clindamycin and 1.2 g of amoxicillin-clavulanate to manage the infection. An initial intravenous injection of polymyxin (10 lakh IU) was followed by daily intravenous doses of 5 lakh IU for the subsequent six days to address systemic infections. Wound swab analysis conducted on the third day post-admission revealed the growth of Cornyebacterium striatum, necessitating the addition of 4.5 g of injection piperacillin-tazobactam. Prednisolone (10 mg) was prescribed to alleviate skin inflammation and itching, while eye lubricants were administered to manage ocular manifestations. As a preventive measure to avoid the adherence of loose skin to bed sheets, autoclaved and aseptically handled banana leaves were placed on the bedding.

Outcome

Following the initiation of treatment, the patient's clinical condition showed marked improvement, with a progressive healing of the lesions. On the 19th day of hospitalization, the patient was discharged with stable vital signs and visibly healed lesions, as portrayed in Figure 3, illustrating the patient on the day of discharge.

DISCUSSION

ADRs have been a source of concern due to being regarded as one of the primary causes of morbidity and mortality among hospitalised patients. According to numerous research, ADRs are responsible for around 8% of all hospitalisations.[5] The underlying pathophysiology of drug-induced SJS/TEN involves mostly CD8+ T-lymphocytes and activated macrophages in the epidermis, as well as CD4+ T-cells in the dermis, indicating a cytotoxic cellular immune response at the keratinocyte level. They are more common in women than in men.[6] Although etoricoxib is a highly selective COX-2 inhibitor that is widely deemed "safe" in daily clinical practice, its safety as an anti-inflammatory medication is still debatable. A history of hypersensitivity, immunosuppression, or genetic predisposition is usually associated with such severe mucocutaneous reactions to this medicine.[7]

The worldwide classification of SJS/TEN is based on the involvement of the Body Surface Area (BSA). SJS is defined as involving 10% of BSA, TEN as involving >30%, and overlap syndrome as involving 10%-30%. Septic shock, hypovolemic shock, severe renal failure, fulminant hepatitis, and multi-organ involvement are all common causes of death.[8]

The presented case illuminates the occurrence of Toxic Epidermal Necrolysis (TEN) in the context of an individual undergoing intensive chemotherapeutic management for advanced cervical cancer. The onset of TEN followed the administration of paclitaxel, carboplatin, and bevacizumab, concomitant with the utilization of etoricoxib for post-chemotherapeutic discomfort. Of particular note is the cessation of tapentadol during this period, the rationale for which remains undisclosed, introducing a degree of ambiguity in elucidating potential contributory factors to the development of TEN.

The clinical presentation of TEN, characterized by widespread fluid-filled lesions, mucosal involvement, and a positive Nicholsky sign, adheres to established diagnostic criteria. The calculated SCORTEN score, encompassing age, neoplasia, and the extent of initial detachment, enhances prognostic assessment, underscoring the severity of the case.

The application of the Naranjo Causality Assessment scale, attributing a "probable" relationship (score of 7) between drug administration and TEN development, substantiates the association with chemotherapy and etoricoxib. The absence of explicit reasons for tapentadol discontinuation prompts further exploration into its potential relevance to the pathogenesis of TEN.

Therapeutically, the instituted regimen, comprising intensive fluid resuscitation, antimicrobial agents, corticosteroids, analgesics, and meticulous wound care, adheres to established protocols. The identification of Cornyebacterium striatum in wound swab analysis accentuates the necessity for tailored antimicrobial strategies in addressing secondary infections.

An intriguing facet of this case lies in the incorporation of autoclaved and aseptically handled banana leaves as a preventive measure against the adherence of loose skin to bed sheets. While unconventional, this culturally informed intervention not only offers practical insights into wound care but also underscores the significance of culturally tailored approaches in patient management.

The patient's discharge on the 19th day with stabilized vital signs and visibly healed lesions attests to the efficacy of the comprehensive therapeutic approach. The observed progressive healing throughout the hospitalization period underscores the imperative of a judicious and tailored therapeutic paradigm in addressing the formidable challenges posed by TEN.

Finally, it underscores the significance of patient education, a multidisciplinary approach, and the meticulous risk-benefit analysis when prescribing medications to patients with pre-existing medical conditions, particularly in the context of chemotherapy and pain management. This manuscript contributes to a comprehensive understanding of the intricacies involved in managing TEN, offering valuable insights for healthcare providers and researchers in the field.

CONCLUSION

In conclusion, this case exemplifies the formidable challenges posed by Toxic Epidermal Necrolysis (TEN) in the context of advanced cervical cancer and aggressive therapeutic interventions. Our discussion highlights the critical importance

of early diagnosis, vigilance in medication selection, and the need for thorough risk-benefit assessments, particularly in patients with underlying medical conditions such as cancer. Patient education and informed consent also emerge as crucial elements in fostering collaboration and empowering patients to report adverse reactions.

Collaboration between pharmacists and physicians is instrumental in disseminating information about TEN, its potential triggers, and the importance of close monitoring. Through educational initiatives and disseminating best practices, these professionals can collectively contribute to early detection and optimized management of severe dermatologic emergencies, ultimately enhancing patient safety and outcomes. This case underscores the collaborative effort required across healthcare disciplines to mitigate the challenges posed by conditions of such gravity.

This case report not only adds to the understanding of TEN but also underscores the necessity for further research in identifying additional risk factors and exploring targeted therapies for this devastating condition. As we strive for improved patient care and outcomes, the lessons drawn from this case underscore the importance of early intervention, risk assessment, and a holistic approach in the management of TEN.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TEN: Toxic Epidermal Necrolysis; **SJS:** Steven Johnsons Syndrome; **NSAIDs:** Nonsteroidal anti-inflammatory drugs; **COX-2:** Cyclo-Oxygenase inhibitors; **IU:** international units.

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