International Journal of Research in Dermatology
Racha AS et al. Int J Res Dermatol. 2023 Sep;9(5):307-310
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20232550

Case Report

Cefditoren pivoxil induced toxic epidermal necrolysis: a case report

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Received: 12 June 2023
Accepted: 10 July 2023

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ABSTRACT

Cutaneous adverse drug reactions vary in severity, from mild erythematous skin lesions to life-threatening toxic epidermal necrolysis. Antiepileptics, antipsychotics, antimicrobials, and diuretics are associated with these adverse reactions. We report a case of cefditoren pivoxil-induced toxic epidermal necrolysis in a 46-year-old Indian woman who presented initially with a maculopapular rash that eventually progressed to steroid-refractory toxic epidermal necrolysis. The patient succumbed to her illness on day 33 of the index rash following septic shock.

Keywords: Cefditoren pivoxil, Erythema multiforme, Steroids, Toxic epidermal necrolysis

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare mucocutaneous disease characterized by extensive epidermal necrosis and sloughing of skin and mucosal surfaces. TEN is a delayed hypersensitivity reaction usually associated with drugs.[1] It affects 1-5 persons/million/year.[2]

Dermatological presentations can begin as a morbilliform rash or atypical targetoid macules, which may progress to flaccid blisters, leading to denudation of the epidermis in the sheets.[3] It is a multi-organ disease with ocular, pulmonary, gastrointestinal, renal, and hepatic involvement and is associated with a mortality of 30-50%.[1,4]

Currently, more than 200 preparations have been associated with the potential to cause TEN.[5] Herein, we report a fatal case of toxic epidermal necrolysis in a 46-year-old woman who received cefditoren pivoxil without an indication. The patient's delayed follow-up and multidrug-resistant *Klebsiella pneumoniae* bloodstream infection led to mortality.

CASE REPORT

A 46-year-old Indian woman with chronic liver disease (CLD) presented with itching, pain, and difficulty swallowing for greater than a week. Upon admission (day 12 of index rash) the patient had a maculopapular rash on the body (abdomen, lower limbs, and upper limbs). She was afebrile with neither fatigue nor malaise. During an interview conducted initially by a clinical pharmacist, the patient revealed using supportive medications for CLD for over two months and had no history of drug allergies. She reported a recent hospital visit for jaundice where an oral antibiotic cefditoren pivoxil 200 mg twice daily was prescribed. But, laboratory investigations revealed no objective evidence of infection. Upon further inquiry, she revealed noticing a red rash on the abdomen on day 3 of cefditoren pivoxil therapy; however, she decided to complete the course of 5 days.

Laboratory investigations upon admission to the hospital

Complete blood analysis showed thrombocytopenia (80,000 cells/cmm), red blood cell (RBC) and white blood cell (WBC) counts were normal. The renal function was

normal. Liver function test results revealed elevated Serum glutamic pyruvic transaminase (SGPT) 55 U/l and serum glutamic-oxaloacetic transaminase (SGOT) 88 U/l levels. Tzanck smear was negative for herpes infection. Visual inspection revealed oral mucosal involvement, with creamy white patches on the inner side of her cheeks, and the other mucosa were normal.

The diagnosis of cutaneous adverse drug reactions is challenging and relies on the clinical, and histological features. The patient was provisionally diagnosed as having cefditoren pivoxil-induced drug rash, oral candidiasis and was managed by a multidisciplinary team with the appropriate treatment (Table 1). The patient's symptoms resolved, began to tolerate oral food, and hepatic function also improved (SGPT, 32 U/l, SGOT 43 U/l). On day 5, she was discharged upon request, advised to continue the same oral medications and visit the hospital immediately if the rash worsened or after a week.

Table 1: Therapeutic management of the patient by multidisciplinary team.

S. no.	Drug	Dosage regimen	Duration in hospital (days)	Discharge	Duration to continue
1	Hydrocortisone	100 mg, IV, twice daily	4	On patient request	-
2	Prednisolone	20 mg, PO, once a day	-		10 days
3	Bilastine	20 mg, PO, once a day	4		3 weeks
4	Fexofenadine hydrochloride	120 mg, PO, twice daily	4		3 weeks
5	Clotrimazole	Mouth paint, twice daily	4		1 week
6	Calamine anti-itch lotion	Local application, thrice a day	4		1 week
7	Rifaximin	550 mg, PO, twice daily	4		1 week
8	S-Adenosyl-L-methionine	500 mg, PO twice daily	4		1 week

However, the patient did not visit after a week, and the contact trials failed. On day 29 of the index rash, she was rushed to the emergency department. Epidermal detachment (neck, face, trunk, and upper and lower extremities), bleeding, and swollen erythematous lips were evident (Figure 1). The Nikolsky's sign was positive with oral and ocular mucosal erosion. After the immediate administration of Intravenous Hydrocortisone (100 mg) and pheniramine (22.75 mg), the patient was transferred to a positive-pressure isolation room in the ICU. Liver function tests revealed elevated total bilirubin (21.9 mg/dl), SGPT (60 U/l), and SGOT (67 U/l).

Table 2: Calculation of the ALDEN score for each drug consumed by the patient over the past 2 months.

Drug	ALDEN score	Causal link
Cefditoren pivoxil	2	Possible
Spironolactone	-1	Very unlikely
Ursodeoycholic acid	-2	Very unlikely
Rifaximin	-2	Very unlikely
Furosemide	-3	Very unlikely
Esomeprazole	-4	Very unlikely
S-Adenosyl-L-methioninea	-5	Very unlikely
Carvedilola	-6	Very unlikely

<0: very unlikely, 0–1: unlikely, 2–3: possible, 4–5: probable, ≥6: very probable, [a] drug started after the index rash

The patient initially responded to steroids, but the condition progressed to TEN. This raised concerns on exposure to other drugs and non-compliance with medications on discharge. The ALDEN causality score was assessed for all medications used over the past two months (Table 2).[6] After ensuring compliance and based on the ALDEN score, the patient was diagnosed with cefditoren pivoxil-induced TEN. The patient's SCORTEN was 3 (Table 3), and was managed with fluid resuscitation, protective dressing, eye drops, empiric antibiotics and nutritious food. However, the patient stopped eating because of throat pain, and her family decided against intravenous immunoglobulin (IVIG) treatment. On day 33, the patient succumbed to the illness following septic shock with multiorgan dysfunction syndrome, as the family chose not to resuscitate. Blood culture on day 34 revealed carbapenem resistant *Klebsiella pneumoniae*.

Table 3: Calculation of the SCORTEN in our patient.

S. no.	Prognostic factor	Value	Points*
1	Age (years)	>40	1 (46)
2	Malignancy	Present	0
3	Tachycardia (bpm)	>120	0 (91)
4	Initial detachment >10%	>10	1
5	Serum urea (mg/dl)	>28	1 (35)
6	Serum bicarbonate (mEq/l)	<20	0 (21.5)
7	Blood glucose (mg/dl)	>252	0 (190)
Our patients SCORTEN: 3		Predicted mortality: 35.2%	

*Yes: 1, No: 0

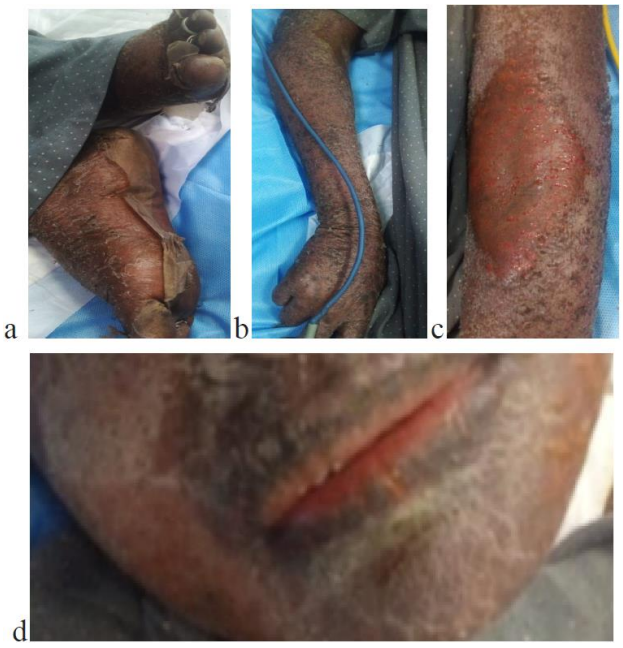

Figure 1: (a) Denudation of epidermis in sheets involving plantar surface of feet, (b) skin eruption with extensive blisters and erosions of right upper limb, (c) bleeding from lesions, and (d) severe scaling on the face with erythematous lips.

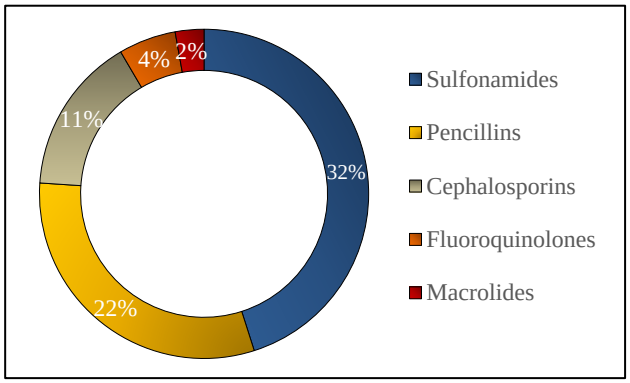

Figure 2: Worldwide prevalence of antibiotic-associated Stevens-Johnson syndrome and toxic epidermal necrolysis.

DISCUSSION

TEN, also known as Lyell syndrome, is a rare and serious cutaneous adverse reaction (SCAR). Antibiotics are associated with 28% of Steven Johnson syndrome (SJS)/TEN cases worldwide (Figure 2).[7] Ceftazidime, cefuroxime, cephalexin, and ceftriaxone are cephalosporins known to cause TEN.[8] Cefditoren pivoxil, a third-generation cephalosporin, has been associated with exanthematous pustulosis.[9]

Our patient was a female aged >40 years, and the rash covered >10% of the body surface area (BSA) resulting in suspicion of SJS but had no constitutional features such as fever, malaise, fatigue, and epidermal detachment, suggestive of erythema multiforme major (EMM) at the primary visit.[1,10,11]

Owing to the lack of cessation of drug use after noticing the rash and diagnostic ambiguity, considering the advantages of early steroid therapy, IV hydrocortisone was instituted (Table 1).

Improvement in her condition without epidermal denudation was associated with a good prognosis, steroid therapy was continued.

However, the patient's arrival at the emergency department with severe epidermal scaling was unanticipated. The symptoms of TEN occur in 1- 4 weeks of starting a new drug. Our patient presented in the late phase of TEN, 30 days after drug use. Drugs with longer half-lives slowly precipitate epidermal necrolysis.[12] Although the half-life of cefditoren pivoxil is 0.8 to 1.3 hours, the plasma levels of cefditoren are greater in females than in males by 14% higher C_{max}.[13] According to information on the product label, moderate hepatic impairment is associated with higher mean C_{max} and AUC, which could have contributed to the delayed elimination half-life and insidious progression to TEN, although our patient initially responded to steroids.

Zhang et al, in a retrospective study, concluded that pre-existing liver disease was an independent risk factor for drug-induced liver injury in patients with TEN and a high serum total bilirubin level is significantly associated with poor prognosis.[14] Our patient with CLD similarly presented with worsened hepatic function after initial improvement due to TEN.

Although the exact mechanism underlying cefditoren pivoxil-induced toxic epidermal necrolysis remains unknown, a few theories state that drugs directly bind to major histocompatibility complex (MHC) 1 and T cell receptors or act as haptens rendering keratinocytes antigenic.[15,16] This ultimately causes the initial activation of T-cells (CD 8+), resulting in keratinocyte apoptosis, releasing cytotoxic agents such as granzyme B, perforin,

IVIG can be a therapeutic option because it suppresses type IV hypersensitivity and hampers apoptosis. It can also suppress antigen-specific CD4+ T-cell responses, CD8+ T-cell activation, and cytotoxic markers (perforin and CD107) at therapeutic doses. In Vitro data suggest that IVIG can block Fas receptors and prevent keratinocyte apoptosis.[18] But IVIG could not be administered to our patient within the first 48 hours, owing to a lack of family consent.

Infectious complications are a dominant cause of mortality and morbidity in these patients owing to damage to protective barriers (skin and mucosa) and alterations in immune mechanisms by drugs.[5] Our patient had a multidrug-resistant *Klebsiella pneumoniae* bloodstream infection which caused septic shock resulting in mortality.

Our case was complicated by an unusual clinical presentation, patient's hesitation for hospital stay, delayed follow-up, hepatic impairment, lack of family consent for IVIG, and septic shock. Although the patient was managed with optimal supportive care and intravenous antibiotics, she experienced septic shock, which progressed to respiratory distress and eventually died.

CONCLUSION

Each drug is different and presents with unique clinical manifestations. Early and appropriate diagnosis, management of ten is vital to prevent mortality caused by drugs.

Recommendations

The strict implementation of antimicrobial stewardship programs to avoid antibiotic use without indications is essential.

It is necessary to counsel patients to monitor the safety of drugs and actions to be taken in case of adverse effects.

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

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Cite this article as: Racha AS, Ashwani P, Swarnalatha P, Singh K. Cefditoren pivoxil induced toxic epidermal necrolysis: a case report. Int J Res Dermatol 2023;9:307-10.