Dermatology Reports

https://www.pagepress.org/journals/index.php/dr/index

eISSN 2036-7406

Please cite this article as:

Alfalah K, Nagshabandi KN, Almusa HA. Generalized bullous drug eruption triggered by ceftriaxone: a case report and literature overview. *Dermatol Rep 2025 [Epub Ahead of Print] doi: 10.4081/dr.2025.10208*

Submitted 02/12/24 - Accepted 14/02/25

Generalized bullous drug eruption triggered by ceftriaxone: a case report and literature overview

Khuzama Alfalah,[1] Khalid Nabil Nagshabandi,[2] Hala Abdullah Almusa[3]

[1]Division of Dermatology, Department of Internal Medicine and Critical Care, King Abdullah Bin Abdulaziz University Hospital, Riyadh; [2]Department of Dermatology, College of Medicine, King Saud University, Riyadh; [3]Department of Dermatology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

Correspondence: Khalid Nabil Nagshabandi, Department of Dermatology, College of Medicine, King Saud University, PJ7C+89Q, 12372 Riyadh, Saudi Arabia.
E-mail: khaloed23@gmail.com
Tel.: +966 582940888

Key words: bullous drug eruption; ceftriaxone; cutaneous hypersensitivity; drug-induced bullous dermatoses; fixed drug eruption; generalized bullous fixed drug eruption (GBFDE).

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: ethics approval is not required for this study in accordance with local or national guidelines.

Consent for publication: written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying images.

Availability of data and materials: all data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Abstract

Ceftriaxone is a widely used third-generation cephalosporin antibiotic known for its efficacy and safety. However, hypersensitivity reactions, including rare cases of generalized bullous fixed drug eruption (GBFDE), have been reported.

We present the case of a 68-year-old female with a history of multiple comorbidities who developed a generalized bullous drug eruption two days after initiating intravenous ceftriaxone for a suspected respiratory infection. Clinical evaluation revealed extensive bullae and erythematous patches sparing mucous membranes, with histopathology confirming drug-induced epidermal changes. Direct immunofluorescence ruled out autoimmune bullous disorders. Prompt discontinuation of ceftriaxone, systemic corticosteroids, and supportive topical treatments led to marked clinical improvement.

This case underscores the importance of recognizing rare but severe cutaneous reactions to ceftriaxone. Early diagnosis and intervention are crucial to minimizing complications and ensuring favorable outcomes.

Introduction

Ceftriaxone is a third-generation cephalosporin antibiotic widely used in clinical practice due to its broad-spectrum activity against various gram-positive and gram-negative bacteria. Administered primarily through parenteral routes, ceftriaxone is particularly effective for treating infections of the respiratory system, urinary tract, skin, soft tissues, and bloodstream, as well as bacterial meningitis. Its extended half-life allows for once-daily dosing, making it a convenient option for both inpatient and outpatient care.[1]

Despite its efficacy and relatively low toxicity, ceftriaxone, like other antibiotics, is associated with adverse reactions, including hypersensitivity reactions. These reactions can manifest in various forms, with cutaneous drug eruptions being one of the most frequently encountered.[2,3] These reactions can present in various forms, and there are multiple reports of ceftriaxone-induced drug eruptions, including severe conditions such as drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and toxic epidermal necrolysis (TEN).[4-6] Bullous-like drug eruptions characterized by widespread blistering and detachment of the skin have also been documented.[7] These severe drug reactions not only compromise the integrity of the skin but pose significant clinical challenges due to their potential

complications, requiring swift recognition and treatment. To date, only one prior case of ceftriaxone-induced generalized bullous fixed drug eruption (GBFDE) has been documented.[7] Herein, we present a new case, adding to the growing literature on cephalosporin hypersensitivity reactions.

Case Report

A 68-year-old female, known to have a medical history of hypertension, diabetes mellitus, atrial fibrillation, and ischemic heart disease, presented to the emergency department with fever, worsening shortness of breath, and signs of fluid overload. She was admitted with an impression of decompensated heart failure and was started on intravenous furosemide. To manage a suspected respiratory infection, the patient was also started on intravenous ceftriaxone. Her home medications included apixaban 5 mg twice daily for atrial fibrillation, bisoprolol 5 mg, nifedipine 90 mg, and valsartan 160 mg. The patient had two previous hospital admissions, all of which were caused by volume overload signs and symptoms and managed with intravenous diuretics. She had no personal or family history of dermatologic conditions or any recent over-the-counter drug or substance use.

Two days after starting ceftriaxone, the patient developed a generalized skin rash. Physical examination showed widespread erythematous-violaceous to dusky patches and plaques of varying sizes, with overlying large, tense, fluid-filled bullae, with clear or slightly yellowish fluid, some of which have collapsed, leaving erosive or crusted areas. The plaques mainly involved the abdomen, back, upper, and lower extremities (Figures 1 and 2). Her palms, soles, and mucous membranes were not involved, and the Nikolsky sign was negative. Laboratory investigations showed a normal neutrophil count. Based on the clinical presentation and the timing of drug administration, the impression of a bullous-like drug eruption and bullous pemphigoid, most likely caused by ceftriaxone, was maintained. Two 4 mm skin punch biopsies of the lesional and perilesional skin were obtained from the right thigh. Histopathological examination showed epidermal vacuolar alteration and bullous formation with dermal eosinophils, consistent with a drug-induced eruption (Figure 3). Direct immunofluorescence was negative for IgA, IgG, IgM, and C3, ruling out an autoimmune bullous disease. No evident full-thickness epidermal necrosis (TEN) was identified, and no evident infectious process was present. The overall morphological features were suggestive of early drug eruption epidermal changes associated with bullous

formation rather than a pustular neutrophilic inflammation. Based on the clinical and histopathological characteristics, with the exclusion of other potential causes, a diagnosis of generalized bullous drug eruption, likely induced by ceftriaxone, was made.

The management plan involved immediate discontinuation of ceftriaxone. The patient was prescribed topical clobetasol propionate 0.05% ointment to be applied twice daily to the affected areas, and fusidic acid was applied to any ruptured bullae. A course of oral prednisolone 40 mg once daily was initiated for five days to control the inflammatory response, along with omeprazole 40 mg for gastric protection. The patient was instructed to monitor for any signs of mucosal involvement or systemic symptoms and to contact the medical team if these developed. Within one week, there was a marked improvement in the rash, with the resolution of bullae. By the end of the second week, all lesions had healed completely, leaving only patches of post-inflammatory hyperpigmentation. No recurrence was observed at follow-up.

Discussion

Generalized bullous fixed drug eruption (GBFDE) is a rare and severe type of fixed drug eruption (FDE) characterized by widespread blistering and erosive lesions at multiple anatomical sites. GBFDE usually appears as well-defined erythematous patches that can develop into bullae and can recur at the same location when the offending drug is used again.[7] Within hours of injection, these lesions may appear and often resolve with some persistent hyperpigmentation. Notably, GBFDE's confined, recurrent nature and lower risk of complete skin detachment distinguish it from other reactions like toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome.[7,8] GBFDE is well-documented with medications such as antibiotics, NSAIDs, and antiepileptics. Ceftriaxone, as reported in our case and similar ones, stands out among cephalosporins due to its ability to act as a hapten, eliciting an immune response. Other antibiotics like sulfamethoxazole-trimethoprim and fluoroquinolones have also been implicated.[7,8]

Despite its broad-spectrum effectiveness and safety, ceftriaxone is still associated with hypersensitivity reactions. T-cell-mediated responses are thought to play a role in the pathophysiology of GBFDE, where skin cell death and bullous development may result from T-cell reactivation at drug re-administration sites. The mechanism underlying GBFDE involves $CD8^+$ memory T cells, which are reactivated upon re-exposure to the causative drug. These T cells release perforin and granzyme, leading to keratinocyte apoptosis and subsequent epidermal

necrosis.[8,9] Ceftriaxone, as a cephalosporin, may act as a hapten, altering self-antigens and eliciting an immune-mediated response. Histological features observed in this case—vacuolar interface changes and eosinophilic infiltration—are consistent with findings from drug-induced bullous dermatoses.[7,10] These features confirm a hypersensitivity reaction rather than autoimmune blistering disorders like bullous pemphigoid.

Drug-associated bullous pemphigoid (DABP) is increasingly recognized in clinical practice. It mimics idiopathic BP in clinical, histological, and immunological presentations but is triggered by medications. The systematic review by Verheyden *et al*. identified 89 drugs implicated in DABP, with dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) being the most notable class.[9] Gliptins, such as vildagliptin and linagliptin, have shown strong associations, particularly in elderly diabetic patients. The underlying mechanism involves DPP-4 inhibitors altering immune regulation, leading to autoantibody production against BP180 and BP230.[9,10]

In our case, the patient developed extensive bullous lesions two days after commencing ceftriaxone for a suspected lung infection. The patient's histopathological results were consistent with those seen in ceftriaxone-induced GBFDE instances that had been previously reported.[7] Her lesions, however, were limited to the skin, protecting mucous membranes and preventing problems like secondary infections, in contrast to patients with mucosal involvement and notable systemic symptoms. Early intervention's effectiveness in reducing the eruption's severity was demonstrated by the improvement that resulted from prompt identification and termination of ceftriaxone in conjunction with anti-inflammatory therapy. Previous reports, including the one by Rathva *et al.* (Table 1), emphasize the importance of being vigilant in vulnerable populations. Ceftriaxone-induced GBFDE can be particularly severe in patients with comorbidities, such as chronic kidney disease. Studies suggest that these comorbid conditions, especially impaired renal function, may enhance antigen presentation and hypersensitivity, increasing the risk of severe drug reactions.[7,10]

Conclusions

Ceftriaxone-induced GBFDE is a rare and uncommon clinical presentation. Clinicians should promptly discontinue the suspected medication and conduct confirmatory histological investigations to distinguish GBFDE from more severe dermatoses. Early dermatological consultation, proper documentation of drug allergies, and patient education on hypersensitivity reactions are crucial for preventing recurrence.

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Figure 1. The lesions are distributed bilaterally on thighs and consist of well-demarcated erythematous plaques interspersed with multiple tense bullae of varying sizes. The bullae contain clear, yellowish fluid and are surrounded by erythematous halos.

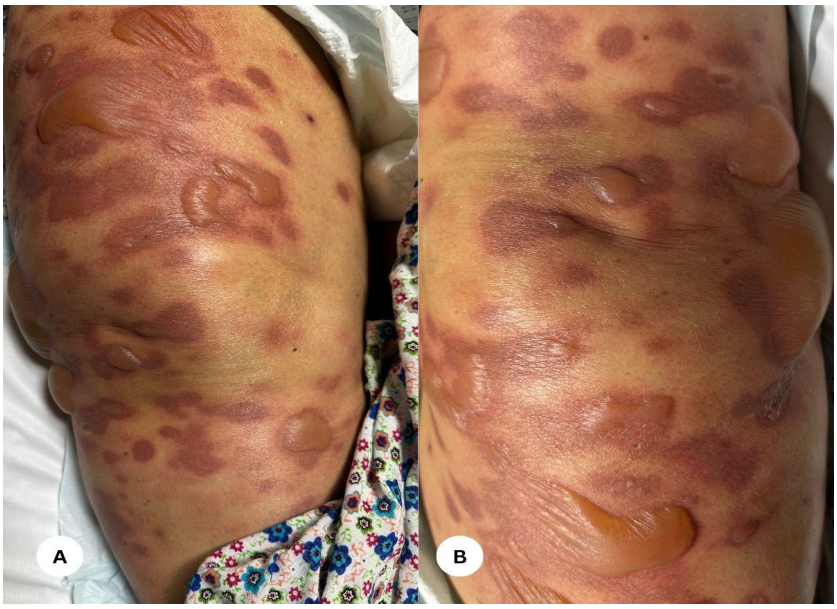

Figure 2. Discrete erythematous macules and patches are scattered across the abdominal surface, with minimal coalescence. The lesions lack vesiculation or bullae but show diffuse erythema. The arms also exhibit erythematous plaques with central ecchymosis and extensive purpuric discoloration, with active fluid-filled bullae visible.

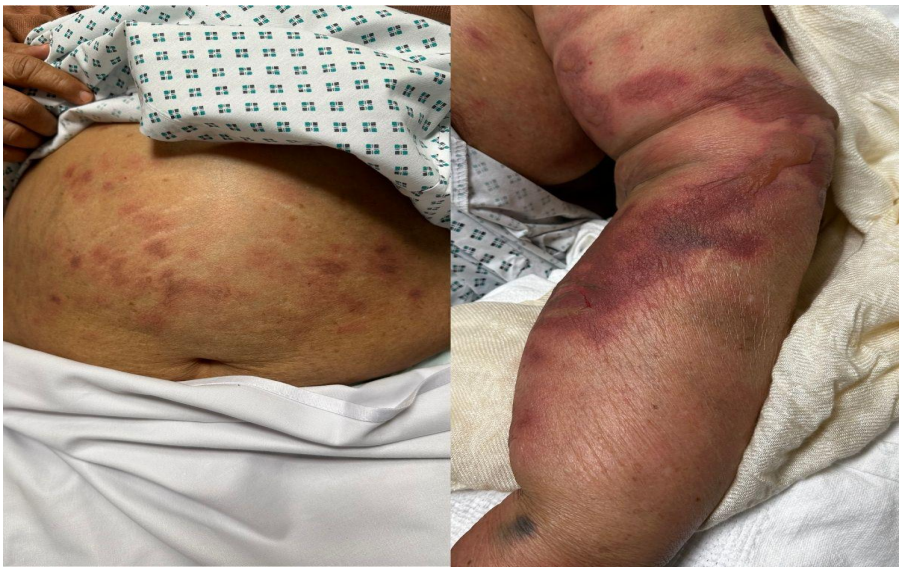

Figure 3. A) Medium-power view of photomicrographs reveals epidermal early vacuolar alteration and bullous formation with underlying few dermal eosinophils; **B)** epidermal sloughing and blister formation with underlying dermal eosinophils. (H&E stain, original magnification x20).

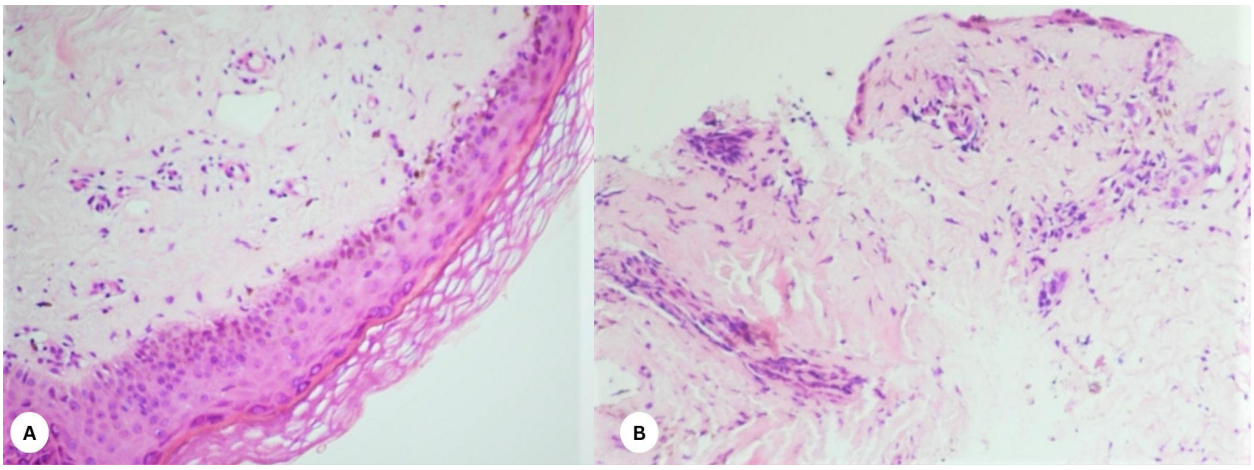

Table 1. Review summary of documented cases of ceftriaxone-induced generalized bullous drug eruption.

Case (Year)	**Age (years) /Gender**	**Initiation of rash after commencing ceftriaxone**	**MM involvement**	**Histopathology**	**DIF**	**Management**	**Prognosis & outcome**
Rathva T *et al.* (2024)	66/Female	1 day	Positive involvement	Not done	Not done	-Discontinuation of ceftriaxone **Systemic therapy**: • Prednisolone 5 mg orally, four doses administered with milk. • Levocetirizine 5 mg twice daily. **Topical therapy**: • Betamethasone cream for localized inflammation. • Fusidic acid cream for antibacterial coverage. **Oral care**: • Triamcinolone oral paste for local application. • Chlorhexidine gargles for antiseptic oral care.	Significant clinical improvement in the patient's condition was observed

Alfalah K *et al.* (Our case) (2024)	68/Female	2 days	Not involved	Epidermal vacuolar alteration and bullous formation with dermal eosinophils	Negative for IgA,IgG,IgM,C3	- Discontinuation of ceftriaxone **Systemic therapy**: • course of oral prednisolone 40 mg once daily initiated for five days to control the inflammatory response. • Omeprazole 40 mg for gastric protection. **Topical therapy**: • Topical clobetasol propionate 0.05% ointment to be applied twice daily to the affected areas. • Fusidic acid applied to any ruptured bullae.	Significant clinical improvement in the patient's condition was observed
DIF, direct immunofluorescence; MM, mucous membrane.							