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Confronting the Therapeutic Challenge of Severe Neutropenia and Extensive Desquamation from Ceftaroline

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Abstract

Ceftaroline is a new-generation cephalosporin used for methicillin-resistant and vancomycin-resistant Staphylococcus aureus (MRSA and VRSA) with a favorable safety profile. Recent studies have shown an increased incidence of neutropenia and rash with ceftaroline, especially when used at a higher dose and for a longer duration. However, concurrent severe neutropenia and extensive desquamation have been rarely described. Herein, we report a 65-year-old male who was treated with a combination of ceftaroline and daptomycin for MRSA bacteremia, osteomyelitis, and endocarditis. The patient developed severe neutropenia with an absolute neutrophil count of four and extensive desquamation involving more than 50% of the body surface area after more than three weeks of ceftaroline use. The patient required discontinuation of ceftaroline, and four doses of filgrastim were given for neutrophil recovery. The desquamation was treated with topical corticosteroids. This case highlights a challenge in treating patients with underlying serious infections complicated by the serious adverse effects of a drug. Early vigilance and careful monitoring are required in patients on long-term ceftaroline to reduce the associated morbidity and mortality.

Keywords: Ceftaroline, Adverse effect, Neutropenia, Rash, Filgrastim

Introduction

Ceftaroline is a broad-spectrum 5th generation cephalosporin approved by FDA in October 2010 to treat community-acquired bacterial pneumonia and acute bacterial skin and soft tissue infections, including MRSA and VRSA. In the premarketing data on ceftaroline, the adverse effects were considered mild, including diarrhea, nausea, and rash [2-4]. The post-marketing data on ceftaroline revealed more adverse effects, mainly neutropenia and cutaneous side-effects, especially in patients on long treatment durations [5-8]. However, there is limited data on the severity of neutropenia and the type of rash with ceftaroline [9-11].

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We, herein, report a case of MRSA bacteremia, osteomyelitis, and endocarditis who developed concurrent severe neutropenia and extensive desquamation on long-term ceftaroline use requiring discontinuation of the drug.

Case Report

A 65-year-old male with a past medical history of hypertension, diabetes mellitus, and intravenous drug use presented to the emergency department with an altered mental state. On physical examination, the patient was drowsy, afebrile, tachycardic, hypertensive, and tachypneic. The laboratory results revealed leukocytosis with left shift, hyponatremia, hypokalemia, hyperglycemia, hyperbilirubinemia, transaminitis, and normal renal functions. The urine toxicology was positive for cocaine and opiates. The computed tomography of the head without contrast showed no intracranial abnormality. The patient was started on empiric treatment for meningitis. The cerebrospinal fluid examination ruled out meningitis. The blood cultures were suggestive of MRSA bacteremia. The patient was started on ceftaroline and daptomycin. The patient showed an improvement in his mental state, became more alert and oriented. After a few days, the patient developed acute lower backache. The magnetic resonance imaging of the lumbar spine suggested right psoas abscess, L1/L2, L2/L3 early discitis, and L1-L3 osteomyelitis. The transesophageal echocardiogram showed mitral valve vegetation with mild mitral regurgitation. The combination of ceftaroline and daptomycin was continued, and the treatment planned for a total of eight weeks. The patient improved clinically with a resolution of bacteremia and infective endocarditis. After three weeks of antibiotic use, the patient developed a skin rash, which started as mild peeling of his hands and feet without erythema, blisters, or itchiness. Later, the rash progressed to extensive desquamation involving more than 50% of his body surface area, including hands, feet, extremities, chest, and upper back [Figure 1]. There was no fever or mucosal involvement. The laboratory results showed leucopenia, neutropenia, eosinophilia, and monocytosis. The liver and renal functions were normal. The patient was started on topical corticosteroids and urea cream after an impression of drug rash by dermatology services. Over a few days, neutropenia worsened with a nadir of 0.8 % neutrophils and an absolute neutrophil count of four. Ceftaroline was discontinued and daptomycin continued as monotherapy. The patient was started on filgrastim after hematology consultation. The rash improved, and the neutrophil count started recovering [Table 1]. The filgrastim was stopped after four doses. The patient remained stable and was continued on single-agent daptomycin to complete eight weeks of treatment.

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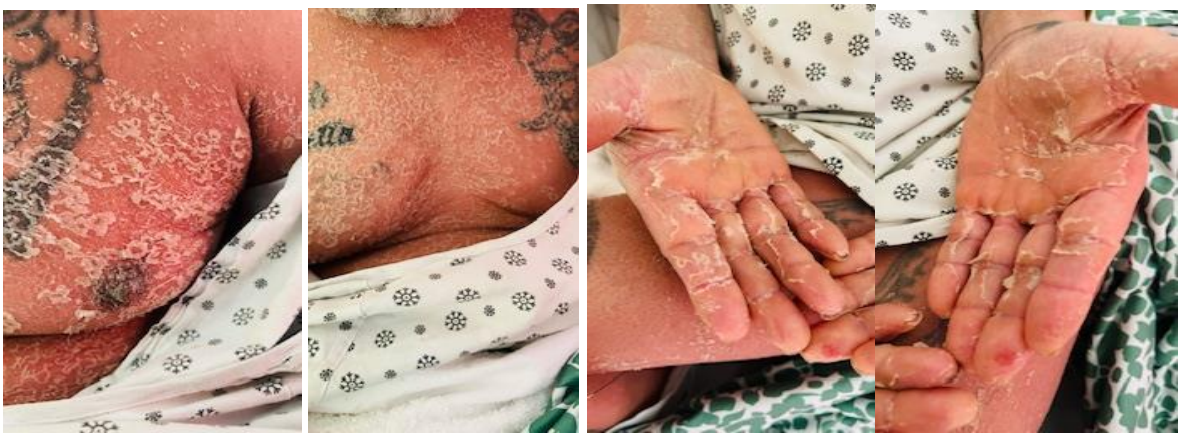

Figure 1: Desquamation of chest and hands

Table 1: Complete blood count abnormalities reflecting severe neutropenia, eosinophilia, and monocytosis.

Components	03/01/24	02/29/24	02/28/24	02/27/24	02/26/24	02/23/24	02/20/24
WBC 4.30 - 11.00 x10(3)/mcL	8.69	4.90	2.56	2.28	2.97	3.63	4.83
Neutrophil % 50.0 - 65.0 %	12.9	**0.8**	1.2	7.0	9.7	38.2	46.8
Neutrophil Abs 1.78 - 5.38 x10(3)/mcL	1.12	0.04	**0.03**	0.16	0.29	1.39	2.26
Lymphocytes 25.0 - 40.0 %	27.4	37.8	36.7	36.0	33.0	22.6	22.4
Eosinophils 0.0 - 5.0 %	13.0	16.1	22.3	**27.2**	23.6	16.3	12.8
Monocytes 4.0 - 10.0 %	39.1	**41.8**	36.7	26.3	30.0	20.9	16.6

Discussion

The non-chemotherapy drug-induced neutropenia is referred as idiosyncratic drug-induced neutropenia (IDIN) and is commonly associated with beta-lactam antibiotics, including penicillin derivatives, cephalosporins, carbapenems, and monobactams. Severe neutropenia, an absolute neutrophil count of < 500 cells/ µL, is associated with significant morbidity and mortality. In approximately 5% of cases, IDIN may be fatal [12]. High doses and long duration of ceftaroline use have been associated with neutropenia [9,10,13,14].

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In a study by Sullivan et al., encompassing fifty-six MRSA-infected patients treated with > 7 days of ceftaroline, the overall rate of incident neutropenia was 7% (four of 56 patients) with ≥3 weeks of ceftaroline exposure. Among four patients with neutropenia, one was severe, and three required filgrastim to aid neutrophil recovery. Only one patient with severe neutropenia also had concurrent eosinophilia and rash. Ceftaroline was discontinued in all four neutropenic patients with resolution of neutropenia after a median of 7 (range 3–11) days [9]. Furtek et al., in their study of 67 patients, found that the overall rate of incident neutropenia was 10%–14% with ≥2 weeks and 21% with ≥3 weeks of ceftaroline exposure. The median duration of ceftaroline use in patients who developed neutropenia was 26 days compared to 15 days in patients without neutropenia. In all cases, neutropenia resolved with ceftaroline discontinuation (14). In our patient, severe neutropenia developed after 3 weeks of ceftaroline use, which required four doses of filgrastim and discontinuation of the drug. The neutrophil recovery in our case was seen after 6 days of ceftaroline discontinuation.

The mechanism whereby ceftaroline leads to neutropenia is poorly understood, however, both immune-mediated and bone marrow effects have been proposed [15]. Some cases also had fever, rash, and/or eosinophilia, suggesting a potential immune or IgE-mediated phenomenon [16].

Rash as an adverse effect of ceftaroline has been poorly described. In a study by Blumenthal et al., rashes were seen in 9 out of 96 patients receiving ceftaroline. Rashes were most commonly maculopapular (n=4), but urticaria (n=1) and rashes with involvement of mucosal lesions (n=1) and skin desquamation (n=1) were also identified. There was no association of rash with the duration or the number of doses of ceftaroline (17). In our case, there was extensive desquamation, which occurred > 3 weeks of ceftaroline use concurrently with neutropenia. The rash resolved after discontinuation of ceftaroline and with topical corticosteroids.
A single report of ceftaroline-induced concurrent rash and severe neutropenia have been described earlier in literature where the patient had an associated fever and required antibiotics and filgrastim for recovery [18].

Conclusion

Ceftaroline-induced neutropenia and desquamation are challenging phenomena. The concurrent occurrence of severe neutropenia and extensive desquamation might represent a serious adverse effect of ceftaroline, that needs to be studied further.

Conflicts of interest

None.

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