Case report

Eosinophilic pneumonia caused by cefepime: A case report and review

Bruce M. Jonesa,b,*, E. Yancey Murrayb, Courtney Crosbyb, Scott Rojasa,c, Christopher M. Blanda,b

aSt. Joseph's/Candler Health System, Inc., 5353 Reynolds Street, Savannah, GA, 31405, USA
bUniversity of Georgia College of Pharmacy, 5356 Reynolds Street, Savannah, GA, 31405, USA
cSouthCoast Health Savannah, 1126 Eisenhower Drive, Bldg 2, Savannah, GA, 31406, USA

Introduction

Cefepime is a fourth-generation cephalosporin that exhibits activity against Gram-positive and Gram-negative bacteria, including Pseudomonas aeruginosa. Due to its broad spectrum of activity, it is indicated for the treatment of febrile neutropenia, intra-abdominal infections, pneumonia, skin and skin structure infections, and urinary tract infections [1]. With increasing evidence of vancomycin and piperacillin/tazobactam induced nephrotoxicity, use of cefepime as an alternative for piperacillin/tazobactam is rising [2]. One of the primary adverse events of concern with cefepime is neurological toxicity, particularly in patients with impaired renal function [1,3]. Historically, drug-induced eosinophilic pneumonia has not been associated with cefepime, despite such reports associated with other antibiotics [4,5]. To our knowledge, we report the first case of cefepime-induced eosinophilic pneumonia.

Case report

A 55-year-old female with a past medical history significant for chronic obstructive pulmonary disease (COPD), coronary artery disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia presented with nonspecific respiratory symptoms, including shortness of breath and nonproductive cough. Social history was significant for being a former smoker. There was no documentation of illicit drug use, although a drug screen was not performed during this admission. The patient had no recent travel or animal exposure. She was recently treated and discharged a month prior for treatment of pneumonia due to Klebsiella pneumoniae. Work-up revealed leukocytosis with a white blood cell count (WBC) of 20.6 × 10³ cells/μL on admission and ground glass infiltrates on chest X-ray similar to previous admission. Vital signs and labs revealed tachypnea (respiratory rate of 30 breaths per minute), mild tachycardia (heart rate of 94 beats per minute), elevated pro-B-type natriuretic peptide (3,956 pg/mL), and elevated procalcitonin (3.6 ng/mL). The patient was admitted for sepsis secondary to community-acquired bacterial pneumonia.

Due to recent hospitalization and intravenous (IV) antibiotic exposure, vancomycin 1000 milligrams (mg) IV every 12 h (preceded by a 1250 mg IV loading dose), piperacillin/tazobactam 3.375 g (g) IV every 8 h as a 4-h infusion, and azithromycin 500 mg IV every 24 h were started empirically on hospital day 1. Methylprednisolone 125 mg IV once followed by 60 mg IV every 8 h was also started on hospital day 1. Initial blood cultures, respiratory multiplex polymerase chain reaction, and Streptococcus pneumoniae urinary antigen testing were all negative. The patient declined and was placed on mechanical ventilation on hospital day 4. Antimicrobials were changed on hospital day 7 to renally-dosed cefepime 1 g IV every 8 h and fluconazole 200 mg IV every 24 h after Hafnia alvei, susceptible to cefepime, and yeast grew from a bronchoalveolar lavage fluid culture performed on hospital day 4, while methylprednisolone was tapered to 40 mg IV daily and continued. The dose of cefepime was increased the following day to 1 g IV every 6 h after improvement in renal function.

Keywords:
Cefepime
Eosinophilic pneumonia
Eosinophilia
Adverse event

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http://dx.doi.org/10.1016/j.idcr.2021.e01166
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The patient remained critically ill on ventilator and vasopressor support with norepinephrine while on cefepime, fluconazole, and methylprednisolone. Repeat chest X-rays taken throughout hospital days 7 through 21 continued to show mostly unchanged bilateral pulmonary infiltrates. On day 10 of cefepime therapy (hospital day 16), the patient became febrile ($T_{\text{max}}$, 101.1 degrees Fahrenheit) for the first time during hospital stay. The patient had persistent leukocytosis throughout cefepime therapy and was unable to be weaned from the ventilator. On cefepime day 12 (hospital day 18), methylprednisolone 40 mg IV daily was discontinued. On day 13 of cefepime therapy (hospital day 19), WBC increased from $16.0 \times 10^3$ cells/µL to $18.0 \times 10^3$ cells/µL, and eosinophils increased from $5.5\% - 7.1\%$. On the following day, the WBC was $18.9 \times 10^3$ cells/µL and eosinophils increased to 11.5 %. *Strongyloides* antibody testing was negative. A computerized tomography (CT) scan of the chest without contrast showed diffuse mixed ground glass and airspace opacities throughout the lungs both in the upper and lower zones and central and peripheral lungs along with intralobular septal thickening (Fig. 1). Cefepime was discontinued with completion of 14 days of therapy and was concern for eosinophilic pneumonia, and methylprednisolone was restarted at 80 mg IV every 8 h. A decrease in WBC from $18.9 \times 10^3$ cells/µL to $9.3 \times 10^3$ cells/µL and eosinophils from 11.5 % to 0.1 % were observed the next day. Of note, the patient did not have eosinophilia in any WBC with differential prior to hospital day 18. The patient also had no documentation of rash or diagnosis of DRESS syndrome.

Despite laboratory improvements, the patient declined rapidly over the next 48 h with increasing oxygen requirements on mechanical ventilation and worsening infiltrates on chest X-ray. Tigecycline 100 mg IV once followed by 50 mg IV every 12 h was started on hospital day 22 for broad spectrum coverage due to concern of exacerbating the eosinophilic pneumonia with other beta-lactams. The patient underwent bronchoscopic evaluation on hospital day 22, which pathology revealed 37 % macrophages and 63 % polymorphonuclear leukocytes that were not differentiated further. Blood cultures and all respiratory cultures from the bronchoscopy were negative for bacterial and fungal growth. The patient was switched to comfort care measures and expired shortly thereafter.

**Discussion and conclusions**

Eosinophilic pneumonia (EP) is a heterogenous group of diseases classified by etiology, onset, and progression. It is characterized by an increase in eosinophils in lung tissue or bronchoalveolar lavage fluid and supported by increased peripheral blood eosinophils along with infiltrates on chest radiographs. EP can be either acute or chronic in presentation, which correlates with the progression rate and duration of the pneumonia [6].

Various etiologies are associated with EP, including tobacco smoke, parasitic and fungal infections, malignancies, and medications [6]. Although the patient did have a history of smoking and COPD, acute eosinophilic pneumonia occurs more frequently in new smokers and chronic eosinophilic pneumonia generally affects non-smokers [6]. Fungal and *Strongyloides* etiologies were excluded by negative cultures and antibody testing, respectively, and there was no documented history of malignancy. At the time of diagnosis, the patient was not receiving any other antibiotics or drugs associated with EP. Previous literature has documented high epithelial lung fluid (ELF) penetration of cefepime, with concentrations exceeding 100 % in ICU patients with pneumonia [?]. In North America, 1.7 % enrolled in cefepime clinical trials had a reported adverse laboratory change in eosinophils [7].

The diagnosis of EP was supported by the presence of bilateral pulmonary infiltrates, peripheral eosinophilia, and recent and sustained course of cefepime. This was determined to be cefepime-induced based on the temporal relationship between the withdrawal of cefepime, the re-initiation of methylprednisolone, and the prompt resolution of the peripheral eosinophilia and leukocytosis. Chest CT was consistent with findings from Souza et al., which evaluated high-resolution CT findings of drug-induced eosinophilic pneumonia in 14 patients. They reported 100 % of patients had parenchymal abnormalities and air-space consolidation, 85 % had ground glass opacities, and 43 % had intralobular septal thickening [8]. Additionally, discontinuing methylprednisolone on day 12 of cefepime therapy may have unmasked the peripheral eosinophilia and leukocytosis. Currently, there are no reports in the literature of EP specifically to cefepime, but it has been reported with other cephalosporins, including cefaroline, cefaclor, and cephalaxin [3,6]. In this case, a Naranjo adverse drug reaction probability score of 6 indicates a probable adverse drug reaction caused by cefepime (adverse event appeared after the suspected drug was given, adverse event improved after cefepime was discontinued, no alternative causes, and presence of objective evidence that confirmed the adverse event) [9].

Cefepime is used commonly for a variety of infections in the hospital due to its broad spectrum of activity. With high ELF penetration in critical illness and documented alteration of eosinophils, we suspect cefepime-induced EP is underreported [7]. Timely identification of cefepime-induced EP is critical to mitigate complications and prevent mortality.

**Conflicts of interest**

B.J. and C.B. have both received grant funding through Merck. B.J. has served on the speaker’s bureau for Allergan. C.B. has served on the speaker’s bureau for Merck. All authors: No reported conflicts of interest.

**Sources of funding**

No sources of funding.

**Consent**

Not required.

**Ethical approval**

Not required.
Author contribution
BJ: study design, data analysis, writing, manuscript review
EM: data collections, writing
CC: data collections, writing
SR: data analysis, manuscript review.
CB: study design, data analysis, manuscript review.

Ethical approval
None required.

Acknowledgements
None.

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