

Eosinophilic pneumonia induced by ceftaroline

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Ceftaroline fosamil, a cephalosporin used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections, was approved by the Food and Drug Administration (FDA) in October 2010 for the treatment of community-acquired pneumonia when it was found noninferior to ceftriaxone.¹ It is also noninferior to the combination of vancomycin and aztreonam in the treatment of acute bacterial skin and skin structure infections, including those caused by MRSA.¹⁻⁵ Recent reports have provided evidence for the use of ceftaroline at higher doses for the treatment of more-serious MRSA infections, including MRSA bloodstream infection and endocarditis.^{6,7} Ceftaroline is sometimes used in treatment-refractory situations when other antibiotics have failed.^{8,9}

Eosinophils are a type of leukocyte associated with allergic processes and parasitic infections. Under normal circumstances, eosinophils reside primarily in tissue (normal range, 1–2%).¹⁰ The hallmark feature of eosinophilic pneumonia is disproportionately high numbers of eosinophils within the alveoli of the lungs, as detected by bronchoalveolar lavage (BAL).^{11,12}

Purpose. A case of eosinophilic pneumonia in a patient receiving ceftaroline for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia is reported.

Summary. A 65-year-old woman was admitted to a medical intensive care unit after arriving at the emergency room with complaints of progressively worsening shortness of breath. Her medical history included chronic obstructive pulmonary disease, acute respiratory distress syndrome, recent traumatic brain injury, tobacco use, and alcohol abuse. Within the first few days of hospitalization, the patient was diagnosed with MRSA pneumonia based on microbiological data from bronchoscopy bronchial washings. Her renal function liver enzyme levels were within normal limits. Empirical antibiotic therapy included i.v. vancomycin and meropenem and was narrowed to i.v. linezolid monotherapy based on culture and sensitivity results. After 10 days of treatment with linezolid, the patient was persistently febrile, and cultures remained

positive. It was decided to switch therapy to a course of i.v. ceftaroline, an anti-MRSA cephalosporin. On the fifth day of treatment with ceftaroline, the patient developed respiratory decompensation and peripheral eosinophilia of 40%. Bronchoalveolar lavage (BAL) results indicated the presence of pulmonary eosinophilia of 13%. Chest radiographs revealed pulmonary infiltrates, and the computed tomography angiography showed no evidence of pulmonary embolism. Ceftaroline was discontinued, and the patient was started on vancomycin and methylprednisolone. The patient responded to methylprednisolone therapy, with repeat BAL and peripheral blood counts showing resolved eosinophilia.

Conclusion. A patient with risk factors for respiratory disease developed eosinophilic pneumonia after receiving ceftaroline for the treatment of MRSA pneumonia. Eosinophilia resolved after ceftaroline was discontinued and i.v. methylprednisolone was initiated.

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One of the first reports of eosinophilic pneumonia caused by drugs and chemical agents was described in 1969 by Liebow and Carrington.¹³ Cases of eosinophilic pneumonia resulted from exposure to simple substances (e.g., nickel) and medications, including penicillin, nitro-

furantoin, and aminosalicic acid. To date, over 100 medications have been associated with eosinophilic pneumonia, with antibiotics and nonsteroidal antiinflammatory drugs being the most commonly implicated.¹⁴ Despite the large number of implicated agents, the number of

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case reports establishing causation is unknown. This patient case report represents only the second case report in the published literature for ceftaroline-induced eosinophilic pneumonia.

Case report

A 65-year-old Caucasian woman weighing 76 kg and standing 162.5 cm tall was admitted to the medical intensive care unit in an 874-bed level 1 trauma center after arriving at the emergency room with complaints of progressively worsening shortness of breath. Her disease course was complicated by a fall approximately one month prior that resulted in a traumatic brain injury, subdural hematoma, subarachnoid hemorrhage, and multiple skull and facial fractures requiring extensive rehabilitation services. Her medical history included chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS) with pneumonia. Medical records indicated that she had a history of tobacco use, smoking one pack every two days for 30 years, and alcohol abuse. There was no mention of illicit drug use or recent travel in her history. On admission, she required intubation due to worsening hypoxia and mental status. Within the first few days of hospitalization, the patient was diagnosed with MRSA pneumonia based on microbiological data from bronchoscopy bronchial washings. Her renal function liver enzyme levels were within normal limits.

The patient had a documented penicillin allergy, reported as a rash. Before admission, she was taking a 7-day course of oral levofloxacin 750 mg daily, which she completed 1 day before admission, for an *Escherichia coli* urinary tract infection. The patient's MRSA pneumonia was treated empirically with vancomycin 1500 mg i.v. every 24 hours and meropenem 1 g i.v. every 8 hours. Despite treatment, the patient was persistently febrile, with temperatures

above 100.4 °F, and had consistently elevated leukocytes and positive respiratory BAL cultures. The microbiology laboratory reported the vancomycin minimum inhibitory concentration (MIC) as 2 µg/mL for the MRSA isolate. Meropenem was discontinued once this positive culture with sensitivities was obtained. Vancomycin was discontinued due to a lack of response, and linezolid 600 mg i.v. every 12 hours was initiated. The pathogen was reported as susceptible to linezolid with an MIC of 4 µg/mL, which is the MIC breakpoint in our microbiology laboratory. After 10 days of treatment with linezolid with little clinical improvement, linezolid was discontinued, and ceftaroline fosamil 600 mg i.v. every 12 hours was initiated.

On the fifth day of ceftaroline treatment, the patient abruptly developed worsening hypoxemia. Increased respiratory support was required with a fraction of inspired oxygen (FiO₂) of up to 100%. Computed tomography and angiography of the chest revealed multiple left-sided infiltrates and right basilar effusions; there was no evidence of pulmonary emboli at that time. Serial chest radiographs revealed bilateral infiltrates, pleural effusions, and interstitial fibrotic changes consistent with a chronic pulmonary process. Aside from the recent antibiotics, including linezolid and vancomycin, no new medications were started during the time frame that was suspect for inciting respiratory decompensation. BAL analysis revealed 13% eosinophils (normal, <1%),¹⁰ 81% neutrophils (normal, <3%),¹⁰ 2% lymphocytes (normal, 10–15%),¹⁰ and 4% macrophages (normal, >85%).¹⁰ Peripheral eosinophilia was noted at 40% (normal, 0–4%).¹⁵ Ceftaroline-induced eosinophilic pneumonia was suspected based on the temporal relationship between symptom onset and initiation of the antibiotic.

To treat her ceftaroline-induced eosinophilic pneumonia, ceftaroline

was discontinued and i.v. methylprednisolone sodium succinate was initiated (hospital day 16). Methylprednisolone sodium succinate 125 mg i.v. every 24 hours was initiated and tapered based on clinical improvement (i.e., 125 mg i.v. every 12 hours for one day, 60 mg i.v. every 12 hours for three to five days, 40 mg i.v. every 12 hours for three to five days, 40 mg i.v. daily for three days, and 20 mg i.v. daily for three days and then switched to oral prednisone, which was tapered over several weeks at discharge (20 mg for five to seven days, 10 mg for 14 days, and 5 mg for 14 days). Antibiotic therapy was switched to vancomycin 1500 mg i.v. every 12 hours to maintain a goal trough concentration of 15–20 µg/mL. After one day of treatment with methylprednisolone, peripheral eosinophil counts decreased and remained at 0% for seven days. As the dose was tapered, peripheral eosinophil counts began to rise to a maximum of 6% over two weeks. The medical team slowed the rate of methylprednisolone-dose reduction, continuing the current treatment for several days in an effort to suppress the rising number of eosinophils. During this period, the patient's ventilation requirements were still high, and she required FiO₂ support and increased levels of sedation. Slight improvements were noted on repeat chest radiographs, such as improvement in bilateral interstitial and alveolar infiltrates, but the patient's underlying COPD complicated the resolution of pulmonary symptoms.

Discussion

Our patient developed eosinophilic pneumonia after receiving treatment with ceftaroline to treat MRSA pneumonia. The manufacturer of ceftaroline lists eosinophilia and other blood dyscrasias (i.e., anemia, thrombocytopenia, and neutropenia) as occurring in fewer than 2% of individuals who take the drug.¹ The monographs for certain medications

specifically list eosinophilic pneumonia as an adverse reaction, including cefdinir (a third-generation cephalosporin)¹⁶ and daptomycin (a cyclic lipopeptide).¹⁷ Other implicated cephalosporins include cephalixin, cephradine, and cefotiam.¹⁸⁻²⁰

To our knowledge, only one other case report of ceftaroline-induced eosinophilic pneumonia in a patient being treated for postoperative MRSA bacteremia has been published.²¹ Eosinophilia attributed to cephalosporins occurs in as many as 4% of patients taking these drugs.²² Phase III clinical trials of ceftaroline provided no evidence of peripheral or pulmonary eosinophilia,^{23,24} though peripheral eosinophilia was noted in a case report published in 2013.⁷ The Phase III clinical trials used ceftaroline 600 mg every 12 hours,^{23,24} while peripheral eosinophilia was associated with ceftaroline 600 mg every 8 hours.⁷

Comparison of our patient case to the case of ceftaroline-induced eosinophilic pneumonia reported by Desai et al.²¹ revealed similarities and differences. The patient described by Desai et al. was a 46-year-old, nonsmoking man with no history of a chronic respiratory disorder. Our patient was older and female with a history of COPD, ARDS, and tobacco use. Smoking may predispose patients to developing acute eosinophilic pneumonia.²⁵ Our patient was being treated for MRSA pneumonia with an FDA-approved dosage of ceftaroline 600 mg every 12 hours, while Desai and colleagues' patient was receiving ceftaroline 600 mg every 8 hours for the treatment of MRSA bacteremia. In both cases, the rationale for switching therapy to ceftaroline was based on an elevated vancomycin MIC of 2 µg/mL. Similarities in clinical findings were also noted between the patients, including hypoxemia with elevated eosinophils and neutrophils on BAL analysis. These findings were reported on the fifth day of ceftaroline therapy

for our patient, whereas respiratory decompensation did not occur until day 39 of ceftaroline therapy in the previously reported case. In both instances, discontinuation of ceftaroline and initiation of i.v. methylprednisolone led to improvement.²¹

Pathophysiology. The underlying pathophysiology of drug-induced eosinophilic lung disease is not fully understood but is thought to be associated with specific cytokines and antigen-presenting cells (APCs).²⁶ The release of eosinophils into the bloodstream is regulated by cytokines, including interleukin-5 (IL-5), which is produced by T-helper type 2 cells and eotaxin. In drug-induced eosinophilic pneumonia, alveolar macrophages, a specific type of APCs, are thought to be responsible for ingesting the circulating drug and presenting it as an antigen via the major histocompatibility complex class II receptor. Recognition of this antigen-receptor complex by T-helper type 2 cells in conjunction with the CD4-lymphocyte receptor leads to activation and release of IL-5, further promoting eosinophil production, chemotaxis, and degranulation.²⁶ The preferential accumulation of eosinophils in the lungs may be attributed to the profuse number of alveolar macrophages found in the lungs.²¹ Corticosteroids have previously been found to be an effective treatment for eosinophilic pneumonia.^{21,27} The number of circulating eosinophils is decreased after steroid administration, which can be attributed to the ability of glucocorticoids to suppress IL-5 release and eosinophil survival.^{27,28}

Diagnosis. Drug-induced eosinophilic pneumonia typically presents as a febrile illness accompanied by respiratory symptoms (e.g., dyspnea, hypoxemia), pulmonary infiltrates, and the presence of eosinophilia on BAL analysis with an onset temporally related to administration of a drug. A presumptive diagnosis of drug-induced eosinophilic pneu-

monia can be made in the setting of pulmonary infiltrates and peripheral eosinophilia with a definitive diagnosis supported by the presence of elevated eosinophils on lung biopsy or in BAL fluid.¹⁴ However, the absence of peripheral eosinophilia does not preclude a diagnosis of eosinophilic pneumonia. Although radiographic abnormalities may accompany the list of abnormalities in acute eosinophilic pneumonia, such a diagnosis is usually made based on the patient's clinical history and the presence of blood eosinophilia.²⁹ Lung biopsy is not required since using BAL is generally accepted practice.

The increase in eosinophils in the BAL fluid is the hallmark sign of eosinophilic pneumonia and a critical clinical indicator that differentiates acute eosinophilic pneumonia from diffuse pneumonia or ARDS. In addition to eosinophilia found during BAL fluid analysis, our patient had elevated neutrophil levels, suggesting acute rather than chronic eosinophilic pneumonia.²⁵

Attributing the development of eosinophilic pneumonia to a specific offending agent is one of the greater diagnostic challenges. The Naranjo et al.³⁰ adverse-drug-reaction probability score was calculated to be 6, indicating that eosinophilic pneumonia was a probable adverse reaction to ceftaroline.

The following criteria have been proposed as necessary to attribute a particular drug or toxin to eosinophilic pneumonia with confidence: (1) the presence of simple, acute, or chronic eosinophilic pneumonia by current diagnostic criteria, (2) the presence of a likely or potential candidate drug or toxin in an appropriate time frame, (3) no other cause of eosinophilic pneumonia (parasites, fungal infection, autoimmune disorder), (4) clinical improvement after cessation of the suspected drug or toxin, and (5) recurrence of eosinophilic pneumonia with rechallenge to the drug or toxin.¹⁴ The patient

satisfied four of these five criteria, as a rechallenge to the drug was not conducted.

Our current patient was shown to have a documented penicillin allergy. The rate of cross-reaction between penicillin and cephalosporins ranges from 1% to 2%.^{22,31} Hogan and colleagues³² explained that “eosinophils are closely associated with the pathogenesis of allergy, specifically in the respiratory tract, with the development of allergic asthma.” Further evidence confirming cefcaroline as the offending agent was the resolution of eosinophilia with cessation of therapy,¹¹ though this also may have been attributable to the administration of i.v. methylprednisolone.

Drug-induced eosinophilic pneumonia is a rare, but serious, adverse drug reaction that may lead to death if unrecognized or untreated, as excess eosinophil accumulation in serum or tissue has been associated with tissue damage, especially if the exposure is prolonged.^{32,33} While it is difficult to predict the timing or severity of eosinophilia that will induce tissue damage, acute eosinophilic pneumonia is often associated with diffuse alveolar damage, resulting in acute lung injury.^{29,34}

Conclusion

A patient with risk factors for respiratory disease developed eosinophilic pneumonia after receiving cefcaroline for the treatment of MRSA pneumonia. Eosinophilia resolved after cefcaroline was discontinued and i.v. methylprednisolone was initiated.

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