Acute Eosinophilic Pneumonia Secondary to Daptomycin: A Report of Three Cases

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We describe 3 cases of daptomycin-induced pulmonary toxic effects that are consistent with drug-induced acute eosinophilic pneumonia. Patients presented similarly with dyspnea, cough, hypoxia, and diffuse ground-glass opacities at chest computed tomography. Clinical suspicion for this adverse drug event and cessation of daptomycin until definitive diagnosis can be made is crucial.

Acute eosinophilic pneumonia (AEP) may occur after exposure to drugs, toxins, or radiation therapy. In fact, more than 300 medications are known to cause AEP. Antimicrobial agents and nonsteroidal anti-inflammatory drugs are among the most common offenders. Daptomycin is a relatively new lipopeptide antimicrobial used for the treatment of gram-positive infections. To our knowledge, only 4 cases of pulmonary toxic effects associated with the use of daptomycin have been reported [1–4]. In this report we describe 3 additional cases of daptomycin-induced pulmonary toxic effects, 2 of which meet definitive criteria for AEP.

CASE REPORTS

Case 1. A 60-year-old man with rheumatoid arthritis, Crohn disease, Cushing disease, and psoriasis developed chronic prosthetic hip infection due to methicillin-susceptible Staphylococcus aureus (MSSA). He underwent surgical débridement of his hip after a long trial of suppressive antibiotic therapy had failed to control his infection. Culturing of intraoperative specimens again revealed MSSA. After this surgery, therapy with daptomycin (6 mg/kg intravenously daily) was initiated. Two weeks later, he presented with a 3-day history of cough, fever, and dyspnea.

At physical examination he was afebrile, tachypneic, and hypoxic. Lung examination revealed diffuse crackles and wheezes. No rashes were noted. A computed tomographic (CT) scan of the chest revealed bilateral scattered ground-glass opacities and peripheral consolidation (figure 1). His white blood cell count was 20 × 10^3/dL, and his platelet count was 401,000 × 10^3/dL. Arterial blood gas examination revealed a pH of 7.45, a partial pressure of carbon dioxide of 31 mm Hg, and a partial pressure of oxygen of 79 mm Hg, measured with 36% fraction of inspired oxygen. Urine antigen tests were negative for Streptococcus pneumoniae and Legionella pneumophila.

Daptomycin treatment was promptly discontinued. Therapy with aztreonam, moxifloxacin, trimethoprim-sulfamethoxazole, and hydrocortisone (50 mg intravenously every 6 hours) was administered. The patient declined bronchoscopy. Within 48 hours, his condition improved dramatically, and supplemental oxygen, antibiotic therapy, and steroids were discontinued. Two days later, daptomycin therapy was resumed. Within 24 hours, fever, dyspnea, and hypoxemia returned, and supplemental oxygen therapy was resumed. His white blood cell count increased to 22,000 × 10^3/dL (21% eosinophils), and his platelet count increased to 702,000 × 10^3/dL. Daptomycin treatment was discontinued, and bronchoscopy was performed. The bronchoalveolar lavage specimen showed 853 nucleated cells/mm^3 (81% eosinophils). All cultures from specimens of his lavage fluid yielded negative results. A silver stain was negative for...
Figure 1. Chest computed tomographic scan from case 1, revealing bilateral scattered ground-glass opacities and peripheral consolidation representative of findings in acute eosinophilic pneumonitis.

Pneumocystis jirovecii. Transbronchial lung biopsies revealed acute fibrinous and organizing pneumonia with reactive alveolar and interstitial epithelial changes.

The patient received a diagnosis of AEP secondary to daptomycin exposure, and daptomycin therapy was discontinued. After this, a tapering dose of prednisone was administered. His condition rapidly improved, and he remained free of pulmonary symptoms when examined 7 days later.

Case 2. A 60-year-old man with diabetes, peripheral neuropathy, gout, and alcoholism developed osteomyelitis and septic arthritis of the first metatarsal head and metatarsophalangeal joint. He underwent surgical débridement for his foot ulcer, and wound specimens obtained intraoperatively grew methicillin-resistant *S. aureus* at culture. Daptomycin therapy (6 mg/kg/day) was initiated. Two weeks later, he presented with a 3-day history of increasing dyspnea, low-grade fevers, chills, and a nonproductive cough.

At physical examination he had a low-grade fever (temperature, 100.5°F) and was hypoxic. Lung examination revealed diffuse crackles. Findings from the heart examination were normal. No rashes were noted. He had a healing ulcer on his right great toe. A chest radiograph revealed diffuse peripheral pulmonary infiltrates. Laboratory evaluation revealed a white blood cell count of 11 × 10^3^/dL with 9% eosinophilia.

Levofloxacin was empirically started to treat presumed community-acquired pneumonia, and therapy with daptomycin was continued. Two days later, his condition clinically deteriorated, and he developed progressive tachypnea and hypoxia. A CT scan of the chest revealed patchy peripheral nodular and ground-glass changes suggestive of pneumonitis. Administration of levofloxacin and daptomycin was discontinued. Within 5 days, his systemic and respiratory symptoms had largely disappeared. A second CT scan showed resolution of the peripheral lung changes. Thereafter, vancomycin therapy was started, and this therapy was continued for 3 weeks while he was an outpatient.

Five months later, recurrent osteomyelitis of the foot was recognized. Daptomycin therapy was reinitiated. Within 3 days, he developed signs and symptoms and radiologic abnormalities nearly identical to those described above. His white blood cell count was 15 × 10^3^/dL but without eosinophilia. Daptomycin therapy was discontinued, and his systemic and respiratory symptoms promptly resolved. Subsequent follow-up imaging studies revealed complete resolution of infiltrates.

Case 3. An 83-year-old man with coronary artery disease, diabetes mellitus, gout, spinal stenosis, and recent C3–4 anterior cervical decompression and fusion developed signs and symptoms of diskitis of his lumbar spine. Empiric therapy with
Daptomycin (6 mg/kg/day) and ceftriaxone (2 g administered intravenously every 24 hours) was initiated after an attempt to find a microbiologic cause for his diskitis was unsuccessful. After approximately 4 weeks of this treatment, he presented with progressive dyspnea, cough, and pleuritic chest pain.

At physical examination he was normotensive and afebrile but tachypneic and hypoxic. Lung examination revealed crackles in the lung bases and dullness to percussion over the left lower lung field without egophony or change in fremitus. Findings from the cardiac examination were normal. No rashes were noted.

His white blood cell count was 10.4 × 10³/dL (9% eosinophils). Results of other laboratory tests were unremarkable. Urine antigen tests were negative for *S. pneumonieae* and *L. pneumophila*. CT imaging revealed diffuse ground-glass and reticular opacities with mild septal thickening with associated small bilateral pleural effusions. Results of a transthoracic echocardiogram were normal.

Treatment with daptomycin and ceftriaxone was discontinued, and treatment with vancomycin, piperacillin-tazobactam, azithromycin, and prednisone was started. Bronchoscopy was performed, and all cultures yielded negative results. Transbronchial lung biopsies revealed acute organizing pneumonia, eosinophilia, chronic inflammation, and benign, nonspecific fibroinflammatory changes (figure 2). Within 6 days of discontinuation of daptomycin therapy, his oxygenation substantially improved. His symptoms and radiologic abnormalities resolved 4 weeks later.

**DISCUSSION**

AEP is a distinct respiratory syndrome. AEP may be idiopathic but is often drug induced. Before a definitive diagnosis can be made, it is necessary to rule out infections known to cause pulmonary eosinophilia and a prior history of atopic disease [5]. The pathophysiology of AEP is thought to be related to antigen (eg, derived from the offending drug or infecting pathogen) presentation by alveolar macrophages. As a consequence, T-helper 2 (Th2) lymphocytes are recruited that, in turn, release interleukin 5. Eosinophil migration into the lung is facilitated by several simultaneous mechanisms; release of interleukin 5 from Th2 lymphocytes promotes eosinophil production and migration to the lungs. Also, activated alveolar macrophages secrete eotaxin, which stimulates eosinophil localization to the lungs [6]. The mechanism of daptomycin-induced pulmonary toxic effects remains unproven. Some authors have speculated that daptomycin’s known ability to bind to synthetic surfactant in vitro may correlate with an ability to bind to human surfactant in vivo and thus accumulate in alveolar spaces in concentrations high enough to injure the epithelium and subsequently result in inflammation [3].

AEP is defined by the presence of (1) febrile illness of less than 5 days duration, (2) diffuse bilateral pulmonary infiltrates, (3) hypoxemia (partial pressure of oxygen of less than 60 mm Hg or pulse oximetry reading of <90% on room air), and (4) bronchoalveolar lavage with greater than 25% eosinophils or eosinophilic pneumonia at lung biopsy [7]. Solomon and Schwarz

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**Figure 2.** Hematoxylin-eosin stain of a lung biopsy specimen from the patient in case 3 at original magnification, ×20. Pathologic changes include acute organizing pneumonia, eosinophilia, chronic inflammation, and benign, nonspecific fibroinflammatory changes.
<table>
<thead>
<tr>
<th>Case or reference</th>
<th>Description</th>
<th>Indication for daptomycin</th>
<th>Antibiotics</th>
<th>Symptom onset</th>
<th>Chest CT findings</th>
<th>Peripheral eosinophil count, no. (%)</th>
<th>Bronchoalveolar lavage findings</th>
<th>Pathologic findings</th>
<th>Use of prednisone</th>
<th>Clinical resolution</th>
<th>Recurrence of symptoms at rechallenge</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>60-year-old man with rheumatoid arthritis, Crohn disease, and Cushing disease who presented with fever (temperature, 102°F), dry cough, and increasing dyspnea</td>
<td>Chronic MSSA infection of prosthesis hip and allergy to vancomycin</td>
<td>Daptomycin 6 mg/kg/day</td>
<td>Day 11 of 42</td>
<td>Bilateral scattered ground-glass opacities and changes consistent with peripheral consolidation most prominent in right upper lobe of lung</td>
<td>2.59 × 10⁹ (12.9)</td>
<td>853 nucleated cells (91% eosinophils); bacterial, fungal, viral and AFB cultures, negative; silver stain, negative</td>
<td>Yes</td>
<td>Yes, within 2 days after initial episode and within 7 days after rechallenge</td>
<td>Yes, within 24 hours</td>
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<td>2</td>
<td>60-year-old man with diabetes and gout who presented with increasing dyspnea, low-grade fevers, chills, and a nonproductive cough</td>
<td>MRSA osteomyelitis/septic arthritis of the first metatarsophalangeal joint</td>
<td>Daptomycin 6 mg/kg/day and levofloxacin 750 mg/day</td>
<td>Day 12 of 42</td>
<td>Patchy peripheral nodular and ground-glass changes suggestive of pneumonitis</td>
<td>0.99 × 10⁹ (9)</td>
<td>Not performed</td>
<td>None</td>
<td>No</td>
<td>Yes, within 5 days after initial episode and within 2 days after rechallenge</td>
<td>Yes, within 3 days he developed signs and symptoms and radiographic abnormalities nearly identical to his initial presentation</td>
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<td>3</td>
<td>83-year-old man with coronary artery disease, diabetes, and gout who presented with dyspnea, dry cough, and pleuritic chest pain</td>
<td>L4-L5 diskitis previously treated with vancomycin until hearing difficulties began</td>
<td>Daptomycin 6 mg/kg/day and ceftriaxone 2 g IV/day</td>
<td>Day 35 of 42</td>
<td>Diffuse, apical, and peripheral ground-glass and reticular opacities with mild septal thickening with associated small bilateral pleural effusions</td>
<td>0.53 × 10⁹ (7)</td>
<td>195 nucleated cells (13% eosinophils); bacterial, fungal, viral, and AFB cultures, negative; silver stain, negative</td>
<td>No</td>
<td>Yes, within 2 weeks</td>
<td>Not rechallenged</td>
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<td>Colb et al [1]</td>
<td>84-year-old man with peripheral vascular disease, hyperlipidemia, and prostatic hyperplasia who presented with weakness, anorexia, weight loss, and depression</td>
<td>Chronic MRSA infection of prosthetic knee, previously treated with vancomycin for 6 weeks</td>
<td>Daptomycin 4 mg/kg/day</td>
<td>Week 1 of therapy of 6-week course. Patient was previously treated with daptomycin for 48 hours 1 month prior</td>
<td>Bilateral, irregularly shaped nodules in the mid- and peripheral lung and multiple mediastinal lymph nodes</td>
<td>0.6 × 10⁹ (80)</td>
<td>Not performed, but CT guided biopsy; bacterial, fungal, and AFB cultures, negative</td>
<td>CT guided biopsy revealed organizing pneumonia and eosinophilic infiltrate</td>
<td>No</td>
<td>Yes, within 2 weeks</td>
<td>Not rechallenged</td>
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<tr>
<td>Study</td>
<td>Patient Description</td>
<td>Diagnosis/Infection Type</td>
<td>Treatment Details</td>
<td>Outcome Details</td>
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<td>Kaikish et al [2]</td>
<td>65-year-old man with a history of obstructive sleep apnea, coronary artery disease, and hypothyroidism who presented with severe shortness of breath that progressed to respiratory failure requiring intubation</td>
<td>MRSA vertebral osteomyelitis complicated by epidural abscess with failure to respond to medical therapy with vancomycin and rifampin at 4 weeks</td>
<td>Daptomycin 6 mg/kg/day Day 14, unknown planned duration of therapy 0.6 × 10^6 (7)</td>
<td>725 nucleated cells (33% eosinophilic, bacterial, fungal, viral, and AFB cultures, negative) Organizing pneumonia with “many” eosinophils and occasional multinucleated giant cells Yes, IV methylprednisolone for 3 days followed by 6-week oral prednisone taper Not rechallenged</td>
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<td>Hayes et al [3]</td>
<td>60-year-old man with a history of endocarditis and cefazolin-induced interstitial nephritis who presented with fever (temperature, 104°F), rigors, and diaphoresis Recurrent MSSA aortic valve endocarditis</td>
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<td>Shinde et al [4]</td>
<td>54-year-old man with a history of MRSA surgical-site infection who presented with a low-grade fever (temperature, 100.4°F) and dry cough for 3 days MRSA surgical-site infection after inguinal hernia repair</td>
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**NOTE.** AFB, acid-fast bacilli; CT, computed tomographic; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible S. aureus.
suggested that a definitive diagnosis of drug- or toxin-induced AEP could be made in patients who meet the above criteria for AEP in addition to the following: (1) exposure to potential candidate drug or toxin in the appropriate time frame; (2) no other cause of eosinophilic pulmonary infiltrates, such as fungal or parasitic pneumonia; (3) clinical improvement after cessation of drug or toxin; and (4) recurrence of symptoms with rechallenge to drug or toxin [8]. Rechallenging patients with the drug is not routinely recommended.

To our knowledge, only 4 prior reports have described drug-induced pulmonary toxic effects related to daptomycin [1–4]. The first and third cases presented in our series meet all of the criteria proposed by Solomon and Schwartz for diagnosing drug-induced AEP. The second patient declined to undergo bronchoscopy; however, clinical and radiologic symptoms suggestive of drug-induced AEP developed rapidly when daptomycin was restarted, and they resolved quickly when it was discontinued a second time. All of the patients in our series and those in previous case reports experienced clinical improvement within 2 weeks of cessation of daptomycin therapy as outlined in table 1. The condition of the majority of patients rapidly improved within the first week, however. Steroids were administered in 4 of the 7 cases.

Eosinophilia and rash are among the other adverse events associated with daptomycin therapy. Eosinophilia occurred in 1% of patients and rash occurred in 4.3% of patients enrolled in phase III clinical trials of daptomycin for the treatment of complicated skin and soft-tissue infection [9]. Peripheral eosinophil counts were obtained for 6 of the 7 cases. Three of these 6 cases demonstrated peripheral eosinophilia by absolute count and percentage, 2 cases demonstrated a normal absolute count with an elevated percentage, and 1 case demonstrated a normal absolute count and percentage. None of the patients had associated rashes at presentation.

CONCLUSION

Daptomycin-induced AEP is a dramatic and potentially fatal adverse drug event if not quickly recognized and appropriately managed. Definitive diagnosis may be elusive because physicians may aptly assume that patients presenting with fever, cough, pleuritic chest pain, hypoxemia, and new pulmonary infiltrates have pneumonia. Daptomycin is not indicated for the treatment of pneumonia; thus, new antimicrobials may be initiated and daptomycin may be stopped in this hypothetical scenario. Physicians may later falsely conclude that the new antimicrobials effectively treated the patient, when, in fact, cessation of the offending drug, daptomycin, was curative.

On the basis of the cases described, these important points can be made: (1) physicians should be aware of daptomycin-induced AEP and have a low threshold for stopping daptomycin treatment while a diagnostic workup (including bronchoscopy) is in process; (2) peripheral eosinophilia may not be present in patients with daptomycin-induced AEP; (3) bronchoscopy with biopsy is the preferred means of diagnosing daptomycin-induced AEP; (4) rechallenging patients with daptomycin is not recommended, because it may result in serious harm; and (5) treatment with steroids may be beneficial in ameliorating pulmonary inflammation, although their role in managing drug-induced AEP requires further study. Understanding the full spectrum of daptomycin-induced pulmonary toxic effects will require a heightened awareness among physicians of this increasingly common disease process.

Acknowledgments

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Potential conflicts of interest. All authors: no conflicts.

References