

Jefferson Health Northeast Internal & Emergency Medicine

Broadening the Dyspnea Differential: Daptomycin-induced acute eosinophilic pneumonitis

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- Acute eosinophilic pneumonitis (AEP) is also known as PIE syndrome (pulmonary infiltrate with eosinophilia)²
- Most common causes of secondary eosinophilic pneumonitis are drug-induced and idiopathic causes (primary eosinophilic pneumonitis).
- Most common drug-induced cause is daptomycin.
- Symptoms are vague and include respiratory distress, fever, and dry cough that can be confused with a myriad of other diagnoses.
- Pulmonary toxicity is time-dependent with an average time of symptom onset to diagnosis of 9.8 days⁷.

Risk factors^{2,7}:

- Male sex
- Prosthetic joint infection
- Age greater than 65
- Renal failure
- Treatment of osteomyelitis +/- diabetic foot infection

Imaging findings:

- Multifocal pneumonia appearance, ground glass opacities, peripheral or pleural-based bilateral non-segmental opacities of the upper lobes, interstitial finding
- Pleural effusions are rare¹

Laboratory findings:

- Peripheral eosinophilia occurs as disease progresses (77-80% of patients)²
- Absolute eosinophils are greater than 1,000 cells/uL (20.7% of patients only have a count greater than 500 cells/uL)
- Elevated erythrocyte sedimentation rate, C-reactive protein, and thrombocytosis¹

Etiology of pulmonary toxicity:

- Unclear
- Caused by drug binding to and building up on pulmonary surfactant leading to alveolar inflammation
- Drug causes disruption of lipid integrity leading to alveolar inflammation³
- Oxidant-induced injury
 - Only seen in daptomycin and nitrofurantoin-induced injury
 - Inflammation from T-helper-2 lymphocytes releasing IL-5 and eotaxin which promote eosinophil involvement^{4,5,7}

Diagnosis:

- Gold standard = bronchoalveolar lavage with pulmonary eosinophilia⁵
- Food and Drug Administration guidelines
- Soloman and Schwarz in Drug-, Toxin-, and Radiation Therapy-Induced Eosinophilic Pneumonia^{6,7} (Table 2)

Treatment:

- Glucocorticoids, unclear duration⁵
- Symptom relief within 48-72 hours, one week for full effect

We present the case involving an 84-year-old female with a medical history of severe atherosclerotic disease, type 2 diabetes mellitus complicated by chronic kidney disease and neuropathy, atrial fibrillation, and hypertension.

Initial Hospitalization

- Admitted for right great toe osteomyelitis complicated by Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.
- Received fifteen days of IV vancomycin prior to switching to IV daptomycin, one day prior to discharge.
- Received a right hallux amputation and a right popliteal stent placement.
- Discharged to subacute rehabilitation on IV daptomycin through a peripherally inserted central catheter to complete a twenty-eight-day course.

Return to the Emergency Department

- Returned eight days post-discharge with four days of dyspnea on exertion, right leg swelling, chest tightness, dry cough, orthopnea
- Vital signs: Oxygen saturation of 80% on room air, BP 182/76, HR 90 beats per minute, RR 26 breaths per minute, and temp 98.2°F. Placed on four liters nasal cannula with improvement.
- Physical exam: No acute distress with moist mucous membranes, coarse breath sounds, mild conversational dyspnea, and non-pitting edema to the right leg with an ACE wrap to the right foot.
- Laboratory workup (Table 1).
- EKG revealed rate-controlled atrial fibrillation with chronic incomplete right bundle branch block.
- Chest x-ray: Increased bilateral reticular markings, patchy airspace densities, and small pleural effusions.
- CT chest angiography: No pulmonary embolism, bilateral ground-glass densities with compressive atelectasis, ill-defined nodular type densities of the upper lobes, and moderate to large pleural effusion, right greater than the left (Figure 1).
- Treatment: 40 mg (milligrams) of IV furosemide
- Admitted for acute hypoxic respiratory failure secondary to acute on chronic heart failure exacerbation.

Second Hospital Course

- Appeared less volume overloaded by morning.
- Continued on her outpatient regimen of daptomycin for her known MRSA bacteremia.
- Possibility of daptomycin-induced AEP was brought up on day one by infectious disease. However, given the improvement in symptoms with diuresis and no eosinophilia, this was thought to be a less likely cause.
- Finished course of daptomycin five days into her hospitalization.
- Developed peripheral eosinophilia one day after discontinuing daptomycin and again two days later (nine days into hospitalization).
- During this time, aggressively diuresed, up to 2 mg of budesonide twice daily for seven days along with daily spironolactone for five days
- Despite this treatment, she remained symptomatic without changes on her chest x-ray.
- Seven days into her hospitalization, she had a chest CT which revealed progressive multifocal irregular ground glass consolidative opacities throughout both lungs with compressive atelectasis, and small bilateral pleural effusions

Table 1: Laboratory values obtained on return to the emergency department

Laboratory test	Value
Creatinine	1.13 mg/dL ¹ (baseline 0.92 mg/dL)
White blood cell count	11.5 B/L ²
Hemoglobin	8.3 g/dL ³
Pro-brain natriuretic peptide	1,785 pg/mL ⁴ (age-adjusted cutoff less than 1,800 pg/mL)
Troponin	36 ng/L ⁵ , delta 1
D-dimer	474 DDU ⁶ (age-adjusted cutoff less than 420 DDU)

Laboratory values are as follows: ¹milligrams per deciliter, ²white blood cells per liter, ³grams per deciliter, ⁴picograms per milliliter, ⁵nanogram per liter, ⁶d-dimer unit

- Pulmonology was consulted for persistent dyspnea and hypoxia and started methylprednisolone 40 mg every eight hours given concern for AEP.
- Within 24 hours, the patient reported feeling better, with clinically significant improvement in dyspnea and increased aeration throughout her lungs on physical exam.
- Weaned off oxygen three days later
- Tapered off methylprednisone to an oral prednisone course over the next four weeks.

Table 2: Criteria for daptomycin-induced pneumonitis as a range (Adapted from Uppart, et al)

Definitive	Probable	Possible	Unlikely
Exposure to daptomycin	Exposure to daptomycin	Exposure to daptomycin	Does not meet listed criteria
Dyspnea with new or increased oxygen requirement or requirement of mechanical ventilation	Dyspnea with new or increased oxygen requirement or requirement of mechanical ventilation		
New infiltrates on chest X-ray or computed tomography	New infiltrates on chest X-ray or computed tomography	New infiltrates on chest X-ray or computed tomography	
Bronchoalveolar lavage with greater than 25% eosinophils	Bronchoalveolar lavage with greater than 25% eosinophils OR peripheral eosinophilia		
Clinical improvement after withdrawal of daptomycin	Clinical improvement after withdrawal of daptomycin	Clinical improvement after withdrawal of daptomycin or patient expiration	
Fever			



Figure 1: CT scan revealing multifocal ground glass consolidations, compressive atelectasis, bilateral pleural effusions

- Expansive use of outpatient IV antibiotics and increased prevalence of resistant bacteria should drive a broad differential diagnosis for dyspnea
- Diagnosis focuses on timeline of symptoms, increased oxygen requirements, new imaging findings, and improvement after cessation of the offending agent.
- As symptoms evolve or do not improve, the clinicians' suspicion of alternative diagnoses should also evolve.
- Based on the clinical diagnostic criteria, her symptoms progressed from possible to probable.
- This case had several factors that muddied her final diagnosis, including initial presentation more concerning for heart failure rather than pneumonitis, completion of daptomycin during her second hospitalization before a probable diagnosis, and transient, delayed peripheral eosinophilia.

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