Jefferson Northeast Internal & Emergency Medicine

Broadening the Dyspnea Differential: Daptomycin-induced acute eosinophilic pneumonitis

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INTRODUCTION

Acute eosinophilic pneumonitis (AEP) also known as PIE syndrome (pulmonary infiltrate with eosinophilia)[2] is a syndrome of rapidly progressive lung disease caused by a build up of eosinophils. The most common causes of secondary eosinophilic pneumonitis are drug-induced and idiopathic causes (primary eosinophilic pneumonitis). The 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. The pathophysiology behind the cause of pulmonary toxicity is unclear. Pulmonary toxicity is time-dependent with an average time of symptom onset to diagnosis of 9.8 days[7]. We discuss a case where the diagnosis of drug-induced eosinophilic pneumonitis was delayed because of concomitant cardiopulmonary disease.

DISCUSSION

Risk factors[2,7]:

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

Imaging findings:

- Broad range: multifocal pneumonia appearance, ground glass opacities, peripheral or pleural-based bilateral non-segmental opacities of the upper lobes, interstitial finding
- Pleural effusions are rare[1]

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 thrombocytosis[1]

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 inflammation[3]
- Oxidant-induced injury
    - Only seen in daptomycin and nitrofurantoin-induced injury[1]
    - Inflammation from T-helper-2 cells lymphocytes releasing IL-5 and eotaxin which promote eosinophil involvement[4,5,7]

Diagnosis:

- Gold standard = bronchoalveolar lavage with pulmonary eosinophilia[5]
- Food and Drug Administration guidelines = Daptomycin-specific
- Soloman and Schwarz in Drug-, Toxin-, and Radiation Therapy-Induced Eosinophilic Pneumonia[6] (Table 2) = Not daptomycin-specific[7]

Treatment:

- Glucocorticoids, unclear duration[5]
- Symptom relief within 48-72 hours, one week for full effect

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/L5, delta 1
D-dimer	474 DDU[6] (age-adjusted cutoff less than 420 DDU)

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

CASE REPORT

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

She was admitted for right great toe osteomyelitis complicated by Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. This was confirmed with laboratory, imaging, and surgical intervention. She received 15 days of IV Vancomycin prior to switching to IV daptomycin, one day prior to discharge. She received a right hallux amputation and a right popliteal stent placement. She was followed by infectious disease, podiatry, and vascular surgery during her stay. She was 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

Eight days post-discharge she returned with dyspnea on exertion and right leg swelling over the last four days. She reported associated chest tightness, dry cough, and orthopnea. Vital signs revealed oxygen saturation of 80% on room, BP 182/76, HR 90, RR 26, and Temp 98.2°F. She was placed on four liters nasal cannula with improvement. On physical exam, she was in no acute distress with moist mucous membranes. She had coarse breath sounds, mild conversational dyspnea, and non-pitting edema to the right leg with an ACE wrap to the right foot. Laboratory workup was obtained (Table 1). EKG revealed rate-controlled atrial fibrillation with chronic incomplete right bundle branch block. Chest x-ray revealed increased bilateral reticular markings, patchy airspace densities, and small pleural effusions. CT chest angiography revealed no pulmonary embolism but did reveal 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. She was treated with 40 mg (milligrams) of IV furosemide and admitted for acute hypoxic respiratory failure secondary to acute on chronic heart failure exacerbation.

Second Hospital Course

She was given an extra 1 mg budesonide and appeared less volume overloaded by the morning. She was continued on her outpatient regimen of daptomycin for her known MRSA bacteremia. Interestingly, infectious disease brought up the possibility of daptomycin-induced eosinophilic pneumonitis on day one of her admission. However, given the improvement in symptoms with diuresis and no eosinophilia, this was thought to be a less likely cause. She finished the course of daptomycin five days into her hospitalization. Curiously, she developed peripheral eosinophilia one day after discontinuing daptomycin and again two days later (nine days into hospitalization).

During her hospitalization, she was aggressively diuresed, up to 2 mg of budesonide twice daily for seven days along with daily spironolactone for five days, in addition to fluid restriction. Despite this, she remained symptomatic without changes on her chest x-ray. She was followed by cardiology, specifically the heart failure team. Seven days into her hospitalization, she had a computed tomography of her chest (Figure 1) which revealed progressive multifocal irregular ground glass consolidative opacities throughout both lungs with compressive atelectasis, and small bilateral pleural effusions. Based on imaging studies and persistent symptoms, she was started on doxycycline for presumed atypical pneumonia. Pulmonology was consulted for persistent dyspnea and hypoxia and started methylprednisolone 40 mg every eight hours. Within 24 hours, the patient reported feeling better, with clinically significant improvement in dyspnea and increased aeration throughout her lungs on physical exam. She was tapered off the methylprednisone to an oral prednisone course over the next four weeks. She was recommended to obtain repeat computed tomography of her chest in four to six weeks to assess for treatment response. She was weaned off oxygen three days after the initiation of steroids and was discharged back to the rehabilitation center.

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CONCLUSIONS

Our case highlights a unique diagnosis. As use of outpatient IV antibiotics expands and prevalence of resistant bacteria increases, this is a diagnosis that should be included on differential diagnoses of those with dyspnea and exposure to an offending agent. This diagnosis focuses on timeline of symptoms, increased oxygen requirements, new imaging findings, and improvement after cessation of the offending agent.

If patients do not continue to improve despite adequate treatment regimens, a shift in focus should occur. Aggressive diuresis should not be prolonged, as in this case, where high-dose diuretics were used for a week before considering an alternative cause. Patients' symptoms, care, and treatment regimens are not stagnant. 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. Our 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.

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			

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