Diagnosis and Management of Daptomycin-Induced Acute Eosinophilic Pneumonia: A Case Report

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Abstract
Daptomycin is a cyclic lipopeptide antibiotic that is indicated for the treatment of complicated skin infections and bacteremia caused by gram positive organisms. Acute eosinophilic pneumonia (AEP) is a rare, but serious adverse effect of daptomycin and caused by accumulation of eosinophils in the lung tissues, and can lead to respiratory failure. Early diagnosis and management of this condition is crucial to avoid severe complications, including death. Herein, we report a case of an elderly man who presented with signs and symptoms of AEP within two weeks of initiation of daptomycin for the treatment of MRSA bacteremia. The patient showed significant clinical improvement and decline in eosinophils upon discontinuation of daptomycin and starting a 5-day steroid course. Acute eosinophilic pneumonia should be kept in mind as a possible, although rare, adverse effect of daptomycin. Early recognition can be established through typical symptoms, eosinophilia, and chest X-ray showing pulmonary infiltrate. Rapid discontinuation of daptomycin with/without steroid therapy and supportive care usually results in significant clinical recover.

Keywords: Daptomycin, Acute eosinophilic pneumonia, Diagnosis, Management

Background

Daptomycin belongs to the cyclic lipopeptide antibiotic class indicated for the treatment of complicated skin infections and bacteremia caused by gram positive organisms, including Methicillin-Resistant Staphylococcus aureus (MRSA) and Vancomycin-resistant Enterococcus (VRE) [1]. Compared to vancomycin, daptomycin demonstrates higher rate of clinical success, a better safety margin, less need for therapeutic drug monitoring, and lower dosing frequency in treating bloodstream MRSA infections [2].

The most concerning adverse effect associated with daptomycin therapy is skeletal muscle injury (myopathy/rhabdomyolysis) with and without acute renal failure [3]. This adverse drug reaction is normally displayed in conjunction with elevation in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal [1]. According to the package insert of daptomycin, the manufacturer recommends that CPK should be monitored weekly and more frequently in patients who have renal impairment or have high risk of developing rhabdomyolysis (e.g., concomitant administration of Statins) [4].

Acute eosinophilic pneumonia (AEP) is a rare and serious pulmonary disease that is caused by accumulation of eosinophils in the lung tissues, and can lead to respiratory failure [5]. This adverse effect has been reported in patients receiving daptomycin. The onset of daptomycin-induced AEP (DAEP) is typically two-four weeks from the initiation of daptomycin therapy, and improve with steroid therapy and discontinuation of daptomycin [6]. Patients suffering from DAEP are usually presented with a wide range of clinical symptoms including dyspnea (69%), fever (60%), nonproductive cough (48%), hypoxic respiratory failure (28%), tachypnea/tachycardia/palpitations (9%), fatigue/lethargy (7.5%), myalgias/chills (5.8%), altered mental status (2.5%), and chest pain (2.5%) [6].

In 2007, AEP was added to the Adverse Reactions, Post-Marketing Experience section of the product label of Daptomycin [7]. Five years later, a review of the literature and the Food and Drug Administration Adverse Drug Reporting System (FAERS) database revealed 7 definite, 13 probable, and 38 possible cases of DAEP [8]. In 2023, the FARES database reported 20 DAEP cases, with 3 deaths and 1 life-threatening hospitalization [9]. With the increase in the incidence rate of DAEP and its serious outcomes, it is important for healthcare providers to be able to diagnose it early and manage it properly. In this report, we present a case of DAEP that was developed within twelve days of daptomycin therapy. The goal is to increase the awareness of clinicians of this serious adverse drug reactions and emphasize the variations in diagnostic symptoms and therapy management.

Case Presentation

The case is a 70-year-old white male, with past medical history significant for COPD, asthma, obesity (BMI 42 kg/m^2), and hypertension. The patient was admitted with septic shock found to have MRSA bacteremia. The patient was febrile (Tmax 102° F) and profoundly hypotensive on admission requiring a short course of norepinephrine and 3L intravenous fluids boluses with initial improvement in pressure. The patient reported focal upper neck pain starting the day prior to

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admission that is severe and worse with side-to-side rotation. The infectious diseases team initiated the patient on vancomycin, ceftriaxone, and metronidazole and later was kept only on vancomycin given the positive MRSA results. Patient responded well to antibiotics and overall clinical picture improved. Upon discharge, vancomycin was transitioned to daptomycin at 8 mg/kg IV every 24 hours for 6 weeks for presumed endovascular infections. Table 1 shows the list of medications that the patient received during this admission. None of these medications is known to cause or contribute to eosinophilic pneumonia.

Twelve days later, the patient was readmitted for progressive dyspnea and significant cough, though unable to get sputum. Pertinent laboratory findings upon admission include: hyponatremia (Na 123 mmol/L) that was improved with IV fluid (Na 131 mmol/L on day 4) and discontinuation of hydrochlorothiazide, chest X-ray shows developing patchy infiltrates at the right lung base (Figure 1), elevated WBC count and eosinophilia on the complete blood count results (Table 2). Microbiology workups ruled out any viral pneumonia. Additionally, the patient was compliant on their asthma/COPD medications and has no prior history of admission due to asthma/COPD exacerbation. These findings, in conjunction with daptomycin use were indicative of an eosinophilic pneumonitis secondary to daptomycin and not a superinfection with another set of bacteria. Utilizing the Adverse Drug Reaction Probability Scale (Naranjo), a score of +5 was obtained, indicating a probable cause [10]. This score was based on +1 from previous conclusive report on this reaction, +2 from occurrence of the adverse effect after daptomycin was administered, +1 due to improvement of the adverse effect when daptomycin was discontinued, and +1 from confirmation of the adverse effect by objective evidence. Given that the patient is requiring a six-week course of antibiotics, the team discontinued daptomycin and switched to vancomycin. The patient received 5 days of prednisone 40 mg inpatient. Subsequently, the patient had clinical improvement with resolution of hypoxia and down-trending eosinophil count (Table 2).

Discussion

Acute eosinophilic pneumonia (AEP) is a subset of pulmonary eosinophilia, a serious and rare heterogenous syndrome associated with increased number of eosinophils in the pulmonary parenchyma [5]. Other important diagnostic criteria for AEP include acute onset of fever, bilateral reticular ground-glass opacities on chest radiography, shortness of breath with or without hypoxemia, and greater than 25% eosinophils in the bronchoalveolar lavage (BAL) [11]. Although approximately 20% of AEP patients present with respiratory distress and require mechanical ventilation, most patients show significant clinical improvement and rapid recovery within 24-48 hours after starting corticosteroids therapy [11]. However, delay in diagnosing AEP can result in death from respiratory failure.

In a review of 135 case reports of drug-induced AEP published between 1990-2017, daptomycin was found to be the leading cause attributing to 18% of the reported cases, followed by minocycline (6%), mesalamine (6%), and nitrofurantoin (5%) [12]. A systematic review of 35 definitive cases of DAEP showed that daptomycin was significantly associated with higher incidence of AEP among male patients with a mean age 65 years, and a mean length of therapy of 2.8 weeks [13]. A recent retrospective cohort study indicated that risk of DAEP is higher in patients who are ≥ 70 year-old, those who received daptomycin therapy for more than two weeks, and those who received a total cumulative dose of > 10 g [14]. Other reported drug classes associated with AEP include antipsychotics (e.g., amitriptyline, risperidone and venlafaxine), antiepileptics (e.g., levetiracetam and valproic acid), and cardiac drugs (e.g., amiodarone). In addition to drugs, AEP can also be induced by toxins, parasites, and fungal infections [11].

The pathophysiological etiology of AEP remains unknown. One proposed mechanism is that AEP is a type of hypersensitivity to the offending agent. This theory was supported by several reports that identified the etiological role of environmental factors such as cigarette smoke in AEP [15]. In case of daptomycin, it binds to pulmonary surfactant, leading to higher concentration on the alveolar epithelium, and injury of the surrounding lung tissues [16]. This cellular injury results in activation of eosinophilic-specific chemoattractants, such as eotaxin, interlukin-5, and serotonin, and consequently leads to eosinophilic accumulation [16].

In summary, AEP is a rare but serious adverse effect of daptomycin, and should be monitored carefully especially in the first several days of drug exposure, and in the presence of eosinophilia. Clinical symptoms significantly improve after drug discontinuation. In severe cases, especially with respiratory distress, initiation of corticosteroids and respiratory support including invasive mechanical ventilation may be warranted. This study reports a case of DAEP in 70-year-old white male 12 days following daptomycin initiation. The diagnosis of DAEP was confirmed by concurrent administration of an offending agent (daptomycin), fever, dyspnea, eosinophilia, patchy pulmonary infiltrates, ruling out other etiologies (such as infections and toxins exposure), and clinical improvement in the symptoms following corticosteroids initiation and daptomycin discontinuation.

Conclusion

Our case adds to the 35 case reports and case series published since 2010, and emphasizes the importance of recognizing and early diagnosis and management of this rare but serious adverse effect of daptomycin. Our case demonstrates the pivotal role clinical pharmacists play in diagnosing and managing adverse drug events. Through daily clinical review of daptomycin therapy, attending pharmacists were able to offer

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early diagnosis of DAEP through changes in laboratory values alongside clinical symptoms listed in physicians' progress notes.

Authors' Note
The data and findings in this manuscript are not currently under revision by other publishers not they have not been presented/published previously.

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Table 1: List of medications that the patient received during the first admission (when daptomycin started)

Drug name	Route	Dose
Albuterol	inhaler	90 mcg/actuation 2 puffs every 6 hours as needed
Mometasone Twisthaler	inhalation	220 mcg/ actuation 1 puff every 12 hours
Irbesartan	oral	300 mg daily
Diltiazem	oral	360 mg daily
Mupirocin	topical	1 application to the affected area inside left nostril 3 times daily
Pantoprazole	Oral	40 mg EC tablet 40 mg 2 times daily before meals
Spironolactone	oral	25 mg tablet 25 mg 2 times daily
Budesonide/formoterol	inhalation	160-4.5 mcg/actuation 2 puffs every 12 hours
Zileuton	oral	600 mg CR tablet 600 mg every 12 hours with meals

CR; controlled release, EC; enteric coated

Table 2: Pertinent laboratory values related to admission and daptomycin therapy

Laboratory Results	Day of re-admission										Reference Range
	-12	1	2	3	4*	5	6	7	10	17	
WBC (x 10^3/µL)	14.8	12.0	13.15	14.4	18.1	15.5	13.2	14.6	14.3	10.6	4.50-11.0
Eosinophils (x 10^3/µL)	0.38	0.3	0.50	-	0.97	1.40	1.26	1.06	1.63	0.71	0.03-0.35
Platelets (x 10^3/µL)	-	480	427	420	385	376	301	317	296	244	150-450
Sodium (mmol/L)	-	128	123	128	131	-	136	-	135	135	135-145
Potassium (mmol/L)	-	4.30	4.10	4.10	4.10	-	3.70	-	3.80	4.00	3.50-5.20
Chloride (mmol/L)	-	93.0	91.0	93.0	96.0	-	101	-	100	100	96.0-106
CO_2 (mmol/L)	-	27.0	26.0	24.0	27.0	-	29.0	-	29.0	28.0	23.0-29.0
BUN (mg/dL)	-	11.0	16.0	14.0	18.0	-	18.0	-	10.0	13.0	7.00-120
Creatinine (mg/dL)	-	0.76	0.74	0.74	0.74	-	0.61	-	0.66	0.85	0.70-1.30

** Daptomycin was discontinued on day 4 of readmission after a total of 15 days of therapy.*

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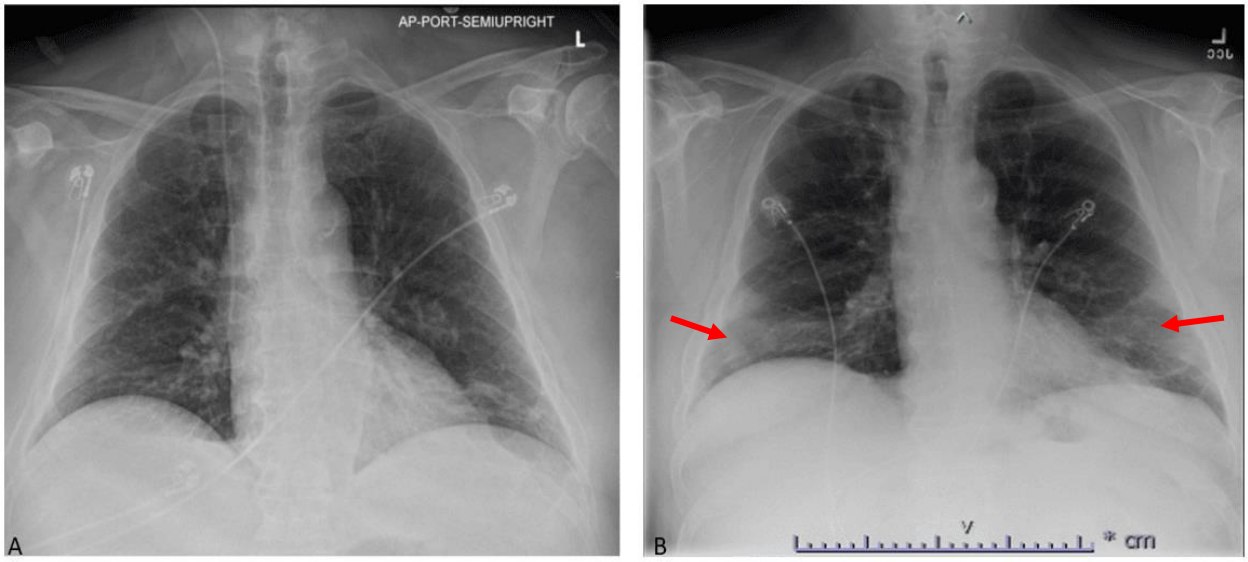

Figure 1: A) Portable anterior-posterior (AP) chest radiograph before starting daptomycin showing no focal opacities; **B)** Portable anterior-posterior (AP) chest radiograph upon admission showing patchy infiltrates and ground glass opacities in the lower lobes.