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Case Report

Daptomycin-Induced Acute Eosinophilic Pneumonia: A Case Report

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Abstract: Acute eosinophilic pneumonia (AEP) is a potentially life threatening adverse event associated with exposure to more than 300different medications including antibiotics such as daptomycin. Definitive diagnosis of this process presents a challenge given the overlap of clinical characteristics with alternative diagnoses and potential lack of awareness. We present a case of daptomycin-induced AEP and a review of the currently available literature regarding diagnosis and treatment of AEP.
Keywords: Daptomycin; acute eosinophilic pneumonia; eosinophilic lung disease; acute respiratory failure; case report.

INTRODUCTION

Daptomycin is a cyclic lipopeptide antibiotic that was approved by the United States Food and Drug Administration in 2003 for treatment of skin and soft tissue infections including osteomyelitis and prosthetic joint infections caused by organisms with reduced susceptibility to vancomycin[10,14]. Its spectrum of activity includes a wide variety of Gram-positive organisms including difficult to treat methicillin-resistant *Staphylococcus aureus*(MRSA). Daptomycin is generally well tolerated with a limited side effect profile; however, it has been linked in a number of case reports to acute eosinophilic pneumonia (AEP), which warrants rapid recognition for appropriate treatment. Here we present a case of AEP associated with daptomycin and review the currently available relevant literature.

CASE REPORT

A 28-year-old Caucasian male presented to our emergency department (ED)with complaints of dyspnea, dry cough and subjective fever. His history was remarkable for recent treatment with daptomycin and piperacillin/tazobactam for polymicrobial osteomyelitis of the foot. During the course of this antibiotic regimen, he was admitted to an outside hospital for “pneumonia” and was treated with a course of levofloxacin without complete recovery. At discharge he required supplemental oxygen therapy and had not returned to his baseline pulmonary status when he presented to our ED.

On initial evaluation, he was a febrile but tachypneic (respiratory rate of 40breaths/min) and hypoxic (SaO2 70% breathing room air). His pulmonary exam was remarkable for bilateral course crackles and rhonchi to the right upper chest. Initial labs revealed a leukocytosis of 15.4 x10^9/L with 19% eosinophils. Chestimaging including chest X-ray and computed tomography showed diffuse peribroncho vascular airspace disease predominantly in the apical regions(Figures1 and 2). He was admitted to the hospital and pulmonary was consulted.

Based on his radiographic findings and recent history of treatment for pneumonia, a diagnostic bronchoscopy was performed and a bronchoalveolar lavage (BAL) revealed 75% eosinophils. Transbronchial biopsy exhibited acute fibrinous and organizing pneumonia with reactive alveolar and interstitial epithelial changes, establishing the diagnosis of drug-induced AEP secondary to daptomycin. The procedure was complicated by hypoxic respiratory failure requiring intubation and transfer to the medical intensive care unit. His daptomycin was discontinued and corticosteroids were initiated. His condition improved and he was extubated on hospital day 3. At follow up visit 6 months later, the patient’s symptoms were completely resolved symptoms and his imaging was improved (Figure 3).

Table-1: Spectrum of activity of daptomycin [1,10]

Methicillin-resistant Staphylococcus aureus (MRSA)
Methicillin-susceptible Staphylococcus aureus (MSSA)
Glycopeptide-intermediate Staphylococcus aureus (GISA)
Vancomycin-resistant Staphylococcus aureus (VRSA)
Coagulase negative Staphylococcus species (CNS)
Vancomycin-resistant Enterococcus (VRE)

Table-2: Criteria for diagnosis of AEP and daptomycin-induced AEP [1,3-5]

AEP	**Daptomycin-induced AEP**
BAL with > 25% eosinophilia	Exclusion of alternate causes of AEP
Fever	Exposure to daptomycin within appropriate time period
Bilateral pulmonary infiltrates	Improvement upon discontinuation of daptomycin
Hypoxemia	Recurrence of symptoms when challenged with daptomycin (not recommended)

Table-3: Summary of reported cases of daptomycin-induced AEP

Age	PMH	Daptomycin Indication	Dose (mg/kg)	Symptom Onset (Days)	CT	Pathology	BAL Eosinophils (%)	Steroid Therapy
69[11]	RA, Chrohn's, Cushing's	MSSA Prosthetic hip	6	11	Ground glass consolidation	Organizing pneumonia	81%	Yes
69[11]	DM, Gout	MRSA Osteomyelitis	6	12	Ground glass	-	-	No
83[11]	CAD, DM, Gout	L4-L5 diskitis	6	35	Ground glass	Organizing pneumonia	13%	No
84[7]	Prostatic Hyperplasia	MRSA Prosthetic knee	4	7	Irregular nodules	Organizing pneumonia	-	No
65[3]	OSA, CAD, Hypothyroidism	MRSA Osteomyelitis	6	14	Bilateral airspace disease	Organizing pneumonia	33%	Yes
60[3]	Endocarditis	MSSA Endocarditis	-	13	Patchy consolidated nodules	Interstitial eosinophils	13%	Yes
54[9]	Postop infection	MRSA Post op hernia	-	14	Patchy infiltrates	Organizing pneumonia	-	Yes
82[7]	Renal failure, Ulcerative colitis, Leukemia	MRSA Prosthetic ankle	-	21	Patchy infiltrates	Inflammatory cells	14%	Yes
87[7]	DVT, renal failure	Infection Prosthetic knee	-	14	Patchy infiltrates	Eosinophils	40%	Yes
78[10]	CAD	Infection Prostatectomy	8	10	Ground glass	Eosinophils	27.5%	No
64[14]	None	MRSE Prosthetic hip	10	4	Ground glass	Eosinophils	47%	No
61[14]	HTN	MRSE Prosthetic knee	10	14	Ground glass	Eosinophils	3%	Yes
28	None	Polymicrobial Osteomyelitis	-	21	Bilateral airspace disease	Organizing pneumonia	75%	Yes

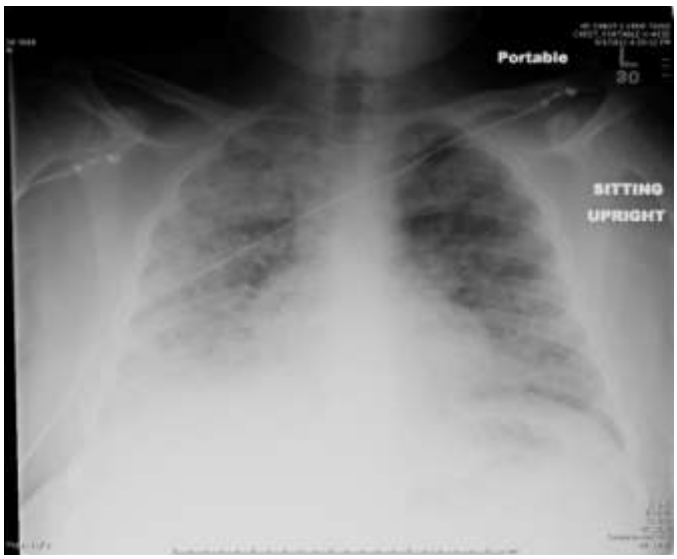

Fig-1: Admission chest radiograph demonstrating diffuse airspace disease

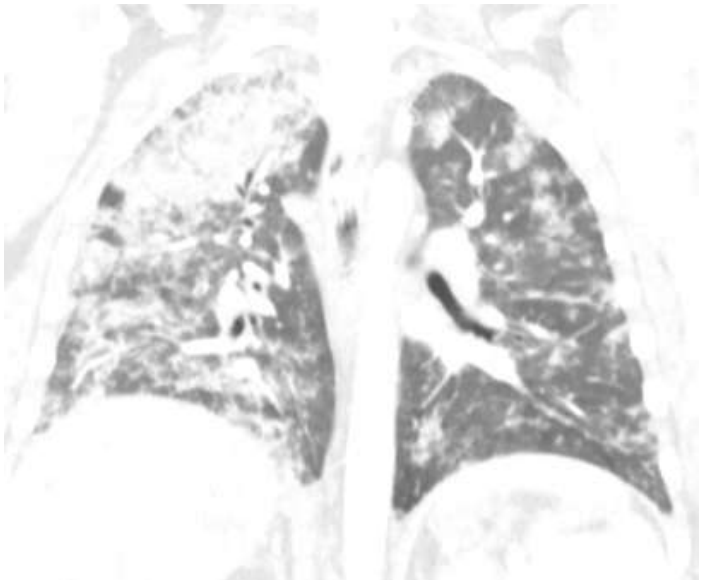

Fig-2: Admission computed tomography of the chest demonstrating diffuse peribronchovascular airspace disease with some upper lobe predominance

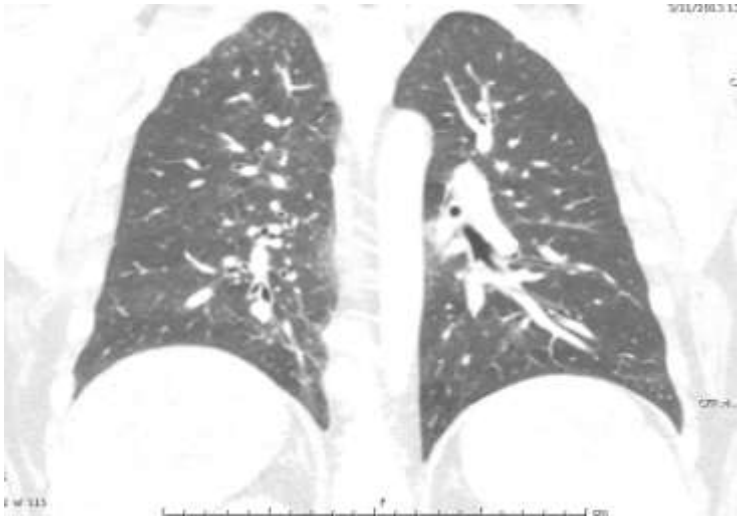

Fig-3: Computed tomography of the chest at 3 month follow up, demonstrating resolution of disease

DISCUSSION

AEP is characterized by eosinophilic infiltration of the pulmonaryparenchyma and potentially results in respiratory failure. This process frequentlyhas idiopathic origins, but has also been linked to medications such as non-steroidal anti-inflammatory drugs, the Bacillus Calmette-Guerin (BCG) vaccine, intramuscular progesterone, and daptomycin [11, 13].

The pathophysiologic mechanisms of daptomycin-induced AEP are still unclear. Daptomycin, which is commonly used in the treatment of infections caused by drug resistant Gram-positive organisms (see Table 1), exerts its drug killing through disruptionin bacterial cell membrane function. When the drug binds calcium, a conformational change allows the compound to bind to neutral or acidic cytoplasmic membranes resulting in deeper membrane insertion and increased membrane permeabilities[10]. Thereare two theories as to the association between daptomycin and AEP. First, in vitro studies suggest daptomycin binds to synthetic surfactant and therefore it is posited that daptomycin may interact with surfactant and alter lipid structure, initiating a pro inflammatory response [1, 9, 10]. The second theory suggests that daptomycin accumulation in alveolar spaces causes damage to surrounding epithelium. Further study is needed to confirm these pathophysiological changes.

AEP is diagnosed based on a constellation of clinical and laboratory findings including the presence of fever, hypoxia, bilateral infiltrates on imaging, and BAL with>25% eosinophils [16, 17] Solomon and Schwartz[5] proposed additional criteria for the diagnosis of daptomycin-induced AEP: 1) consistent time course of exposure todaptomycin; 2) improvement upon discontinuation of daptomycin; 3) other causes ofAEP excluded; and 4)recurrence of symptoms when challenged with drug (though the practice is not recommended). Evaluation of patients with suspected

daptomycin-induced AEP should include BAL with cell count [1]. Lung biopsy can confirm organizing pneumonia and the presence of eosinophils, but is not always necessary if aforementioned criteria are met [5, 11].

There are at least 13 confirmed cases of daptomycin-induced AEP in the literature(Table 3). Patients range in age from 54- to 87-years-old. At 28 years of age, our patientis the youngest reported today. In most cases, daptomycin for used for treatment ofpost-operative prosthetic joint infections caused by *S. aureus*[11]. Other similarities in these13 cases include the onset timeline and constellation of presenting symptoms. Mostpatients presented with dry cough, dyspnea, fever and hypoxemia within 1-2 weeks of treatment with daptomycin. Radiologic changes helpful in the diagnosis of daptomycin induced AEP were mostly atypical bilateral, patchy, ground glass opacities and nodules,and less commonly pleural effusions [11].

Management of daptomycin-induced AEP includes the discontinuation of daptomycin and initiation of corticosteroids. In a number of cases cessation of daptomycin administration resulted in complete resolution of symptoms within 1-5 days without administration of corticosteroids [1, 11, 12, 14]. Specifically, Miller et al. report a case in which the patient's condition resolved within five days of daptomycin discontinuation and did not require corticosteroids [11] However, several patients required corticosteroids for improvement. It is postulated that corticosteroids benefit the patient through eosinophilic apoptosis [15]. Lal and Assimacopoulos reported two cases in which patients benefited from corticosteroid therapy with initial doses of parenteral corticosteroids followed by prolonged (up to 2 years) tapering of the doses [7]. More research is needed to establish the therapeutic benefits and appropriate dosing of corticosteroids for daptomycin-induced AEP.

CONCLUSIONS

It is important for healthcare providers to be aware of the association between daptomycin and AEP. Though uncommon, AEP can easily be misdiagnosed aspneumonia with disastrous consequences, including respiratory failure. Diagnostic criteria have been proposed, but BAL with > 25% eosinophils remains key to the work up of this process. Cessation of the offending drug is the first step in treatment of daptomycin-induced AEP and may result in complete resolution of symptoms within a matter of days. Corticosteroid administration may also play a role in management of daptomycin-induced AEP, however, further research is needed to clarify the most efficacious dosing schedule.

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