Daptomycin-induced acute eosinophilic pneumonia

Preeya Goyal BA, Michael J. Breen PhD, Peter Hountras MD, Rishi Raj MD, Maureen K Bolon MD

ABSTRACT

Acute eosinophilic pneumonia (AEP) is a rare but important and potentially fatal complication of daptomycin therapy. Here, we present the case of an 85-year-old man with a history of resected esophageal cancer and osteomyelitis treated with daptomycin on two separate occasions who presented for workup of recurrent pneumonia. X-ray and computed tomography of the chest showed right upper lobe and left lower lobe infiltrates. Bronchoscopy with bronchoalveolar lavage showed a WBC of 200/µL with 75% eosinophils. No infectious etiology was found despite multiple cultures for pathogens. His presenting symptoms improved over the course of hospitalization despite cessation of all antibiotics. Given the clinical picture and bronchoscopy results, his presentation was attributed to daptomycin-related eosinophilic pneumonia.

Since the approval of daptomycin in 2003, approximately 20 case reports have been published demonstrating AEP associated with daptomycin use. We suggest that daptomycin-associated AEP is an under recognized complication and that the incidence will increase with greater use of the drug. Physicians should be especially cognizant of elderly male patients being treated with prolonged courses.

Key words: daptomycin, eosinophilia, eosinophilic pneumonia, pulmonary eosinophilia

INTRODUCTION

Daptomycin is a cyclic lipopeptide derived from the fermentation of *Streptomyces roseosporus*. Its mechanism of action is based on calcium-dependent depolarization of the bacterial cell wall of gram-positive organisms.[1] Acute eosinophilic pneumonia (AEP) is a rare, potentially fatal complication of daptomycin therapy that should be promptly recognized. Symptoms of daptomycin-induced eosinophilic pneumonia range from fever to severe dyspnea, which can make this diagnosis difficult to recognize. Daptomycin has a wide range of indications, including osteomyelitis, but it is not indicated for pulmonary infections since the drug is inactivated by surfactant.[2]

Corresponding author: Preeya Goyal BA
Contact Information: Preeya.goyal@northwestern.edu
DOI: 10.12746/swrccc2016.0413.174

Daptomycin-induced eosinophilic pneumonia is characterized by febrile illness, hypoxemia, diffuse bilateral pulmonary infiltrates, and bronchoalveolar lavage (BAL) with greater than 25% eosinophils. If this presentation occurs for a maximum of 5 days, it is characterized as acute eosinophilic pneumonia. The BAL criteria can be superseded by a biopsy showing large numbers of eosinophils.[3] The diagnosis of daptomycin-induced eosinophilic pneumonia is made when the patient meets the criteria for eosinophilic

pneumonia and has a history of recent exposure to daptomycin without any other known cause of eosinophilic pneumonia. Additionally, one can see clinical improvement after cessation of daptomycin. Recurrence of symptoms with reinitiation of daptomycin therapy is expected but does not have to occur for diagnostic purposes.[4]

Case

An 85-year-old Caucasian male with a history of resected esophageal cancer, recent osteomyelitis, hypertension, and hyperlipidemia was transferred from an outside hospital for further workup of recurrent pneumonia. He initially presented with symptoms of increased shortness of breath and a cough productive of yellow sputum. This was the third admission for respiratory distress. Six months prior to this hospitalization, he sustained a right olecranon fracture after a fall, which was repaired with plate fixation. The surgery was complicated by infection of the hardware, which was removed. He then developed osteomyelitis of the right arm, which was treated with a five week course of intravenous daptomycin four months prior to admission. He was then treated with negative pressure wound therapy for the failure of the surgical incision to fully close. Three weeks prior to admission, he underwent debridement of the non-healing wound and was started on a second course of daptomycin.

On admission, he was afebrile with a blood pressure of 118/64, heart rate of 68, respiratory rate of 18, and oxygen saturation of 94 % on 2 liters per minute oxygen by nasal cannula. Pulmonary examination revealed decreased breath sounds over the right upper lobe (RUL) and left lower lobe (LLL) and bibasilar crackles. He did not have a leukocytosis but the WBC differential showed an elevated absolute eosinophil count (1.3 K/µL). Right upper lung and left basilar opacities were present on a chest radiograph and computed tomography (CT) of the chest. He was briefly started on imipenem and vancomycin to cover suspected pneumonia and the resolving right elbow osteomyelitis. On the day after admission, all antibiotics were stopped since the clinical presentation and stable chest imaging did not seem consistent with hospital-acquired pneumonia. Given concern for endemic fungal infection, aspiration pneumonia, or eosinophilic pneumonitis, the pulmonary team was consulted for bronchoscopy and additional tests. Polymerase chain reaction testing for respiratory viruses, legionella urine antigen, sputum Gram stain and culture, mycobacterial culture, QuantiFERON gold, cryptococcal antigen, fungal culture, aspergillus galactomannan, pneumocystis direct fluorescent antigen, urine cultures, and blood cultures were all negative. Bronchoscopy BAL demonstrated a WBC of 200/µL with 75% eosinophils.

Given the bronchoscopy results, his symptoms were attributed to daptomycin-related eosinophilic pneumonia. Over his hospital course, symptoms resolved with cessation of antibiotics and a course of prednisone 30 milligrams daily for four weeks with a gradual taper.

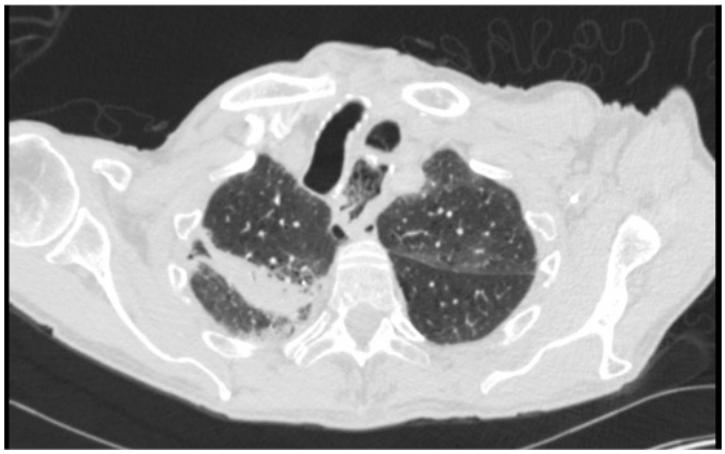

Figure : Computed tomography shows a RUL consolidation consistent with pneumonia and altered tracheal/esophageal anatomy secondary to severe kyphosis. The study also shows LLL consolidation at another level not seen here.

Discussion

Diagnosis

The differential diagnosis for pulmonary eosinophilia is broad, and the diagnosis is often made

by exclusion, as many findings are nonspecific. The differential includes helminth infections, allergic bronchopulmonary aspergillosis, acute and chronic eosinophilic pneumonias, Churg-Strauss syndrome, reactions to medications and toxins, and idiopathic eosinophilic pneumonia.[5] Besides daptomycin, medications, including nonsteroidal anti-inflammatory drugs, anti-psychotics, other antimicrobials like nitrofurantoin and minocycline, and antidepressants, have caused AEP.[4] A disproportionality analysis done in cases of eosinophilic pneumonia reported in the FDA Adverse Event Reporting System found that daptomycin was the drug most frequently associated with AEP.[6]

Mechanism

The exact mechanism of daptomycin-induced eosinophilic pneumonia is unknown. In an animal model of bronchoalveolar pneumonia, daptomycin was completely ineffective against *S. pneumoniae* and methicillin-resistant *Staphylococcus aureus*. *In vitro* experiments using bovine-derived surfactant have demonstrated that daptomycin binds to surfactant molecules and that its bactericidal activity rapidly drops with even low concentrations of surfactant.[2] It is likely then that the drug accumulates in surfactant-lined alveoli, resulting in activation of alveolar macrophages by unclear mechanisms. This triggers an inflammatory response involving Th2 lymphocytes and the production of interleukin-5 and eotaxin, stimulating eosinophil production and migration to the lung.[8] Patients then develop fever, dyspnea, and cough.[9]

Treatment

Symptoms usually resolve after the drug is stopped, but corticosteroid treatment may be needed if symptoms are severe.[6] In general, corticosteroids should be delayed, if possible, until a biopsy or bronchoscopy BAL is performed since corticosteroids may suppress the eosinophilia.[3] In most cases, a relatively short course (e.g., 2 weeks) of corticosteroids is sufficient for complete resolution.[10]

Literature Review

The table summarizes reported cases of daptomycin-associated AEP (Table).[5,9,11-25] Some patterns are readily apparent. There is a strong male predominance (21/23 cases; 91%), and most cases occur in the elderly population. The outliers, a 28-year-old man and a 34-year-old man, had significant comorbidities, namely childhood-onset insulin-dependent diabetes mellitus and DiGeorge Syndrome. The clinical setting in which many of these complications occur is fairly limited, and the majority occur in patients treated for prosthetic joint infection, osteomyelitis, spondylodiscitis, and endocarditis/bacteremia.[17] These types of infections generally require prolonged antibiotic courses ranging from four weeks for endocarditis to six or more weeks for osteomyelitis. Thus, clinicians should be attentive to the possibility of daptomycin-induced AEP in elderly men being treated for the above infections.

Our patient had several uncommon characteristics for daptomycin-associated eosinophilic pneumonia. First, the classic distribution of pulmonary lesions is bilateral, diffuse opacities in the peripheral lung zones.[8] Our patient had a discrete consolidations in the RUL and in the LLL. But his BAL cytology revealed 75% eosinophils and no organisms grew in BAL culture, leaving little doubt as to the diagnosis. Another notable feature is the rapidity of onset following reintroduction of daptomycin. Even initial courses as short as 3-7 days can predispose patients to a robust response after reinitiation of daptomycin.[22,23] Our patient did not report symptoms during his initial five week course of daptomycin, even though his premorbid activity level was relatively good and he might note dyspnea. However, he developed symptoms within a few days of starting his second course of antibiotics. Physicians should proceed cautiously in restarting daptomycin in patients with even mild pulmonary symptoms during prior treatment with this drug.

Table : Cases of daptomycin-associated AEP with indication for and length of daptomycin therapy

Report	Patient age, gender	Indication	Time on drug	Pathology	Treatment
Cobb 2007	84 ♂	Prosthetic joint infection	6 weeks	Bronchiolitis obliterans organizing pneumonia	Drug withdrawal
Hayes 2007	60 ♂	Endocarditis	1 week	AEP	Drug withdrawal, corticosteroids
Kakish 2008	65 ♂	Vertebral osteomyelitis	3 weeks	AEP	Drug withdrawal, corticosteroids
Shinde 2009	54 ♂	Surgical site infection	2 weeks	AEP	Drug withdrawal, corticosteroids
Lal 2010	82 ♂	Prosthetic joint infection	3 weeks	AEP, chronic pneumonitis	Drug withdrawal, corticosteroids
Lal 2010	87 ♂	Prosthetic joint infection	4 weeks	AEP, chronic pneumonitis	Drug withdrawal, corticosteroids
Miller 2010	60 ♂	Prosthetic joint infection	2 weeks	AEP	Drug withdrawal, corticosteroids
Miller 2010	60 ♂	Diabetic foot ulcer, osteomyelitis	2 weeks	AEP	Drug withdrawal
Miller 2010	83 ♂	Discitis	4 weeks	AEP	Drug withdrawal, corticosteroids
Kalogeropoulos 2011	78 ♂	Possible infective endocarditis	10 days	AEP	Drug withdrawal
Rether 2011	69 ♂	Spondylodiscitis, lumbar and psoas abscess	3 weeks	AEP	Drug withdrawal, corticosteroids
Philips 2013	48 ♂	Osteomyelitis	3 weeks	AEP	Drug withdrawal, corticosteroids
Philips 2013	28 ♂	Diabetic foot ulcer, osteomyelitis	4 weeks	AEP	Drug withdrawal, corticosteroids
Yusuf 2014	64 ♂	Prosthetic joint infection	4 weeks	AEP	Drug withdrawal

AEP- acute eosinophilic pneumonia

Table : Cases of daptomycin-associated AEP with indication for and length of daptomycin therapy (continued)

Report	Patient age, gender	Indication	Time on drug	Pathology	Treatment
Yusuf 2014	61 ♂	Prosthetic joint infection	2 weeks	AEP	Drug withdrawal, corticosteroids
Yamamoto 2014	82 ♂	Vertebral septic arthritis, bacteremia	16 days	Pneumonitis	Drug withdrawal
Patel 2014	61♀	Diabetic foot ulcer, osteomyelitis	7 days	AEP	Drug withdrawal, corticosteroids
Rajagopal 2014	63 ♂	Diabetic foot ulcer, osteomyelitis	2 weeks	AEP	Drug withdrawal
Roux 2015	67 ♂	Prosthetic joint infection	17 days	Pneumonitis	Drug withdrawal, corticosteroids
Hagiya 2015	34 ♂	Endocarditis	5 doses, interrupted	AEP, myopathy, eosinophilic sinusitis	Drug withdrawal
Wojtaszczyk 2015	76 ♂	Septic arthritis	1 weeks	AEP	Drug withdrawal, corticosteroids
Chiu 2015	77 ♂	Osteomyelitis	6 weeks	AEP	Drug withdrawal, corticosteroids
Chiu 2015	74 ♀	Prosthetic joint infection	1 week, interruption, 3 days	AEP	Drug withdrawal, corticosteroids

AEP- acute eosinophilic pneumonia

Author Affiliation: Preeya Goyal and Michael Breen are medical students at Northwestern Feinberg School of Medicine in Chicago, Ill. Peter Hountras is a fellow in Pulmonary Medicine at Northwestern School of Medicine in Chicago, Ill. Rishi Raj and Maureen K Bolon are faculty members in the Pulmonary and Critical Care Division in the Northwestern School of Medicine in Chicago, Ill.
Received: 11/23/2015
Accepted: 01/11/2016
Reviewers: Mark Sigler MD
Published electronically: 01/15/2016
Conflict of Interest Disclosures: none

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