Acute Eosinophilic Pneumonia Secondary to Daptomycin Therapy: A Case Report

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Citation

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Abstract

Introduction: Daptomycin is a widely used antibiotic with a unique mechanism of action approved for the treatment of complicated skin and skin structure infections with activity against gram-positive organisms. This case report describes a rare adverse drug reaction (ADR) known as daptomycin-induced acute eosinophilic pneumonia (AEP). Its clinical presentation resembles infectious pneumonia and might lead to unnecessary antibiotic use if not recognized in time.

Case presentation: The patient was an 80-year-old man with poorly controlled hypertension and type 2 diabetes presented with symptoms of dyspnea, runny nose, non-productive cough, sore throat and fever. He was on home infusion of daptomycin for the treatment of methicillin resistant bacteremia secondary to right hand cellulitis initiated during a previous admission, approximately 3 weeks prior. The patient had received daptomycin for a total of 19 days. Upon admission, the patient was treated for presumed healthcare-associated pneumonia with administration of meropenem, vancomycin and doxycycline. However, a chest X-ray followed by computed tomography of the lungs showed the presence of patchy densities and opacity that involved all lobes consistent with daptomycin-induced AEP. His eosinophil count was also elevated which kept increasing with its peak on day twenty three after the first dose. Laboratory studies revealed elevated markers of inflammation such as C-reactive protein, procalcitonin and sedimentation rate. On day six after discontinuation of daptomycin the patient had a complete resolution of symptoms documented by the repeat radiographic studies.

Discussion: In line with Naranjo algorithm, our patient experienced a “probable” daptomycin-induced AEP: (1) Previous case reports of this ADR; (2) ADR appear after daptomycin was administered; (3) ADR improved when daptomycin was discontinued; (4) ADR was confirmed by radiographic studies.

Conclusion: This case report will increase awareness about this rare side effect among healthcare providers and potentially will lower the rate of bacterial pneumonia misdiagnosis, promoting appropriate Antimicrobial Stewardship practice and encouraging avoidance of unnecessary administration of antibiotics.

INTRODUCTION

Daptomycin is the only cyclic lipopeptide antibiotic approved for the treatment of complicated skin and skin structure infections. It has a unique mechanism of action which involves binding to the cell membrane of gram-positive bacteria causing its permeabilization and depolarization that results in inhibition of protein, DNA and RNA synthesis. Specifically, each daptomycin molecule selectively binds two Ca2+ ions of a bacterial cell membrane forming an oligomeric structure that permeabilize and depolarize the cell membrane as well as interfere with cell division and cell wall synthesis. [1] At the same time, when daptomycin makes its way to the lungs and interacts with surfactant it might lead to the production of molecules that act as antigens and activate an inflammatory response. The recruitment of T-helper 2 lymphocytes promotes eosinophil production in large quantity in lungs leading to the condition known as acute eosinophilic pneumonia (AEP) which develops in less than four weeks after the start of daptomycin therapy. [2] We report the case of a patient who developed AEP in the third week of daptomycin therapy.

Since its approval by the Food and Drug Administration for the treatment of complicated skin and skin structure infections caused by susceptible strains of gram-positive microorganisms, including methicillin-resistant strains of

Staphylococcus aureus (MRSA), daptomycin has been widely and successfully used in patients due to its unique mechanism of action. However, numerous adverse reactions have also been reported during post-marketing surveillance and recorded in the package insert in adult patients treated with this medication. [3] The most serious adverse reaction is AEP. AEP is a rare, life-threatening respiratory disease state associated with eosinophilic accumulation in the lungs. The first case of AEP was reported in 1988 by David Badesch and was linked to idiopathic hypersensitivity reaction. [4] It is important to differentiate acute versus chronic eosinophilic pneumonia (CEP) as clinical presentation and treatment duration is different. CEP progresses slowly and is often accompanied by either productive or nonproductive cough, wheezing and dyspnea over several weeks and often requires long term corticosteroid treatment due to frequent relapses. AEP presents as a rapid increase in eosinophils seen in bronchoalveolar lavage with nonspecific symptoms such as fever, chest pain, shortness of breath leading to life threatening hypoxaemia. [5] Unlike CEP, AEP is not well studied so timely clinical diagnosis of the disease is crucial. A systematic review and meta-analysis by Carmi Bartal described 196 case reports of drug-induced eosinophilic pneumonia. About 20% of AEP patients required mechanical ventilation. The study identified two leading drugs associated with this disease: mesalamine (16%) and daptomycin (16%) followed by minocycline (9%), sulfasalazine (7%) and nitrofurantoin (6%). [6]

In order to satisfy FDA criteria for a “probable” AEP secondary to daptomycin therapy, a score of 6-8 points on the Naranjo scale is required. The criteria includes recent exposure to daptomycin, signs and symptoms of the disease, appropriate objective findings and resolution of AEP upon discontinuation of the drug. [10], [11] This case report will describe AEP secondary to daptomycin therapy, a potentially fatal respiratory side effect that accounted for less than 1% occurrence rate during the daptomycin postmarketing surveillance.

CASE PRESENTATION

An 80-year-old male employed as a gardener with past medical history significant for hypertension, type 2 diabetes, gout, and septic arthritis on the right knee, was admitted to our institution with a recent four week history of a rash of his right hand 4th digit initially treated with cephalexin from an urgent care center, followed by doxycycline from his dermatologist, followed by Incision and Drainage (I&D) by a hand surgeon, who advised him to go to the emergency room for further treatment. In our emergency room, he was diagnosed with right hand cellulitis and started on vancomycin IV. His blood cultures grew methicillin resistant Staphylococcus Aureus (MRSA) in 4/4 of his admission blood cultures and his antibiotics were changed to daptomycin 1g (9mg/kg) once daily on hospital day number three and he underwent further I&D on hospital day number four. Cultures from I&D grew MRSA as well. A peripherally inserted central catheter (PICC) line was placed on hospital day number twelve and he was discharged to continue daptomycin via PICC line to complete six weeks. Nine days later, the patient presented to our emergency room with symptoms of dyspnea, runny nose, nonproductive cough, sore throat, feeling chills and rigors for the past few days. His home medications included allopurinol 300 mg daily, amlodipine 10 mg daily, aspirin 81 mg daily, enalapril 20 mg daily, detemir U-100 5 Units at bedtime, glipizide 5 mg daily, sennoside 17.2 mg when needed, multivitamins 1 tablet daily and daptomycin for 6 weeks via PICC line. Patient reported he had stitches removed by a surgeon a few days ago and noted pus coming from the wound site. Patient stated he stopped taking daptomycin due to the aforementioned symptoms two days ago, however his right hand infection got worse with erythema and drainage coming from the wound. Patient had received daptomycin for a total of nineteen days. Upon presentation to the emergency room, his vital signs were normal except for fever 101 F and elevated blood pressure of 196/96 mmHg. Patient was admitted to medicine service with a diagnosis of healthcare-associated pneumonia (HCAP). Meropenem, vancomycin and doxycycline were administered as empiric treatment.

The patient had a documented allergy to ciprofloxacin, sulfa drugs and novocaine. His weight was 107 kg. His serum creatinine was 1.1, blood urea nitrogen was 27, aspartate and alanine aminotransferases were 17 and 20, respectively.

Laboratory workup upon admission included an initial white blood cells count of 6.1 K/UL (normal 4-11 K/UL), C-reactive protein (CRP) of 29.52 mg/L (normal < 3 mg/L), procalcitonin level (PCT) of 0.77 ng/mL (normal < 0.15 ng/mL) and sedimentation rate (ESR) of 75 mm/hr (normal 0-15 mm/hr). His eosinophil level was 7% (normal 0-5%). The respiratory viral panel was negative.

Chest X-ray showed patchy densities in the right lung [Image 1]. Computed tomography (CT) of the chest was performed without contrast. The imaging showed peripheral

pattern of air-space disease and ground-glass opacity more prominent on the right than on the left, but involved all lobes. There was a focus in the lingula measuring 4.1 x 3.5 cm in the axial plane [Image 2] and in the right lower lobe there was a focus measuring 3.5 x 2.5 cm [Image 3]. Some of the areas also had a wedge shape and hyperinfiltration of the lungs with mild increase in the AP diameter of the trachea. Suspicion for eosinophilic pneumonia secondary to daptomycin therapy was raised. Empiric treatment for HCAP was discontinued on hospital day number six and intravenous ceftaroline 600 mg every twelve hours was started for his right hand MRSA infection. Patient's blood cultures grew gram negative rods, subsequently identified as Klebsiella, attributed to a PICC line infection on hospital day number four. After removing the PICC line and starting ceftaroline, blood cultures came back negative the next day.

The patient improved within thirty-six hours of admission. The repeat chest X-ray six days after initial CT showed complete resolution of patchy densities in the right lung and no evidence of acute pulmonary disease. [Image 4] However, an elevated eosinophil count of 13% persisted. [Graph 1]

Image 1

Chest X-ray obtained to rule out pneumonia and pulmonary embolism showed patchy densities in the right lung and patchy atelectasis in both lung bases

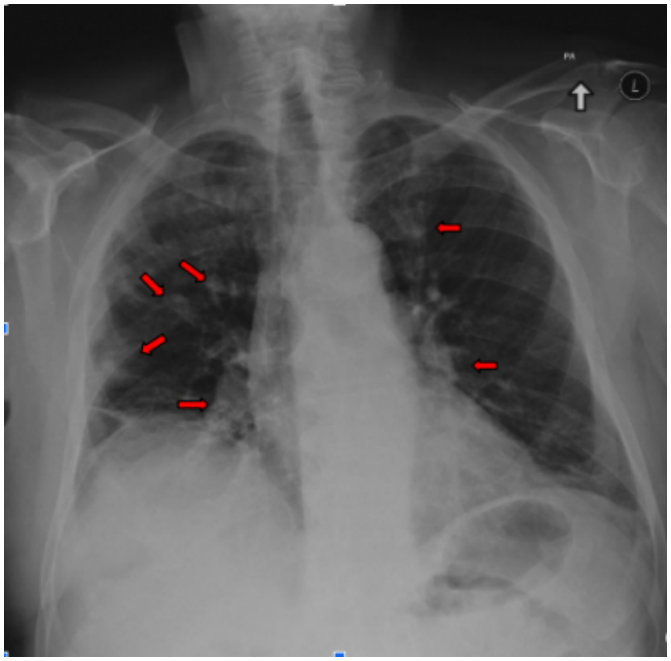


Image 2

Chest Computed Tomography (CT) angiogram obtained to rule out daptomycin induced pneumonia showed multiple peripheral patchy areas of air-space disease and ground-glass opacity

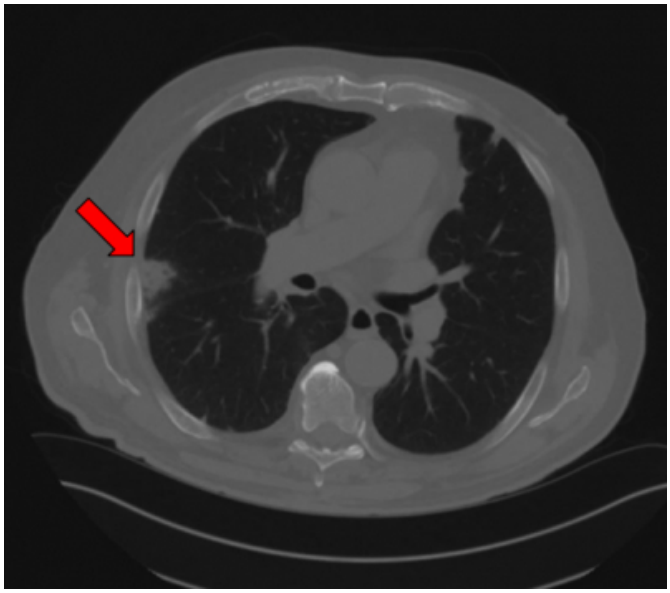


Image 3

Chest Computed Tomography (CT) angiogram obtained to rule out daptomycin induced AEP showed multiple peripheral patchy areas of air -space disease and ground-glass opacity

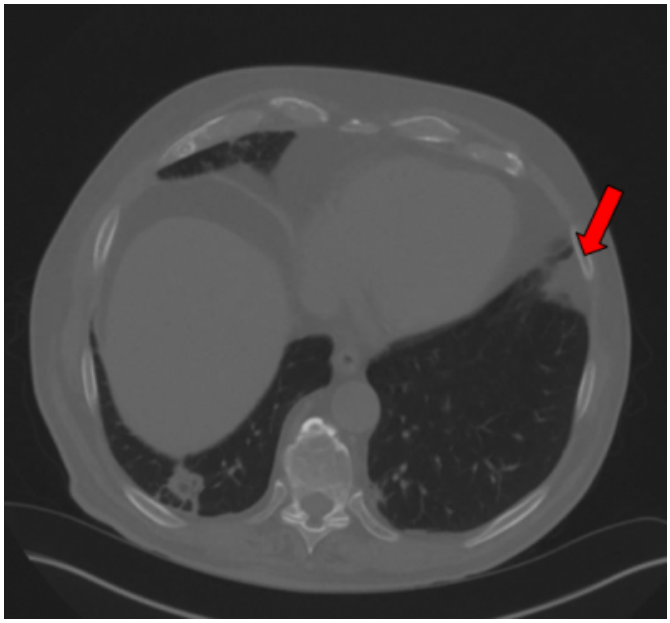
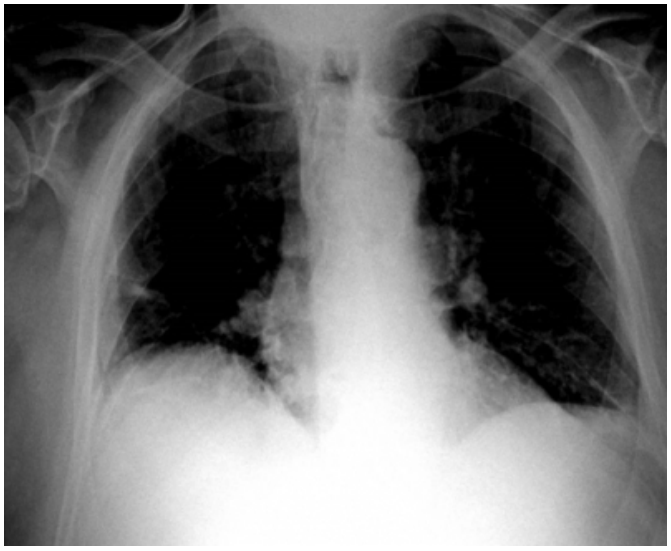


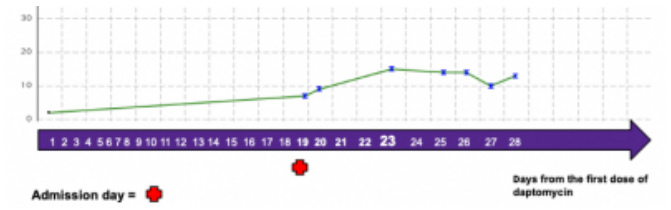
Image 4

Repeat Chest X-ray, after five days of the initial CT, showing almost complete resolution of patchy densities in the right lung



Graph 1

Serum eosinophils count increase from the date of initiation of daptomycin with its peak on day 23 after the first dose



DISCUSSION

Daptomycin has a unique mechanism of action to combat gram positive infections. However, its interaction with pulmonary surfactant may lead to inflammatory response and lung atelectasis due to accumulation of pulmonary infiltrates. [7] Diagnosis of daptomycin-induced AEP is based on clinical presentation, differential diagnosis, clinical history, laboratory results, and radiographic findings. Our patient presented with symptoms of fever, runny nose, dyspnea, non-productive cough, chills and rigors. His laboratory workup included elevated inflammatory markers such as ESR and CRP. Patient's respiratory viral panel was negative which ruled out the possibility of viral pneumonia. [8] Once daptomycin was initiated, his eosinophil count was 2% and it kept increasing with its peak of 15% on day 23 after the first dose. [Graph 1]

One of the crucial objective findings to rule out other causes of AEP was CT scan performed on the hospital stay number two. Multiple peripheral patchy areas of airspace disease and ground-glass opacity were identified on the right lobe and some on the left. Specifically, there was a posterolateral wedged-shaped area of air-space disease in the axial plane [Image 2] and a documented focus on the lingula in the right lower lobe [Image 3]. Differential considerations after obtaining these imaging studies included AEP, bronchiolitis obliterans organizing pneumonia (BOOP), other connective tissue diseases or immunologic-based pneumonitis, and less likely peripheral infection. However, the patient did not have any risk factors for BOOP and his symptoms did not persist for a long period of time despite antibiotic therapy typical for BOOP diagnosis. [9] Nor did he have a history or objective findings consistent with connective tissue or immunologic-based disorders such as rheumatoid arthritis, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjogren's syndrome or dermato-polymyositis. [10]

According to FDA's review of six cases of AEP secondary to daptomycin, the following criteria applies to meet "most likely" AEP diagnosis associated with daptomycin therapy: (1) Current exposure to daptomycin; (2) Fever; (3) Dyspnea with increased oxygen requirement or requiring mechanical ventilation; (4) New infiltrates on chest x-ray or CT; (5) Bronchoalveolar lavage (BAL) with >25% eosinophils; (6) Clinical improvement following daptomycin withdrawal. [11] Although the diagnosis was not confirmed using BAL samples and our patient had dyspnea with Pulse oximetry of 94% on room air, discontinuation of daptomycin monotherapy resolved his symptoms of dyspnea, runny nose, non-productive cough and fever. What is unusual in this case is that the patient assumed his symptoms were associated with daptomycin therapy and he stopped taking this medication before coming to the ED. The fact that he recognized the possible adverse effect of daptomycin during his third week of therapy is consistent with previous reports that described onset of symptoms during two to four week of therapy. However, his symptoms did not resolve after discontinuation of the drug and required additional time to subside. A complete resolution was seen six days after admission. This was confirmed by imaging studies which showed significant improvement, suggesting that eosinophilic pneumonia developed during daptomycin therapy. Our patient had no history of smoking or pulmonary disease and his chest Xray showed the presence of patchy densities in the lungs confirmed by a CT scan as a result of developed AEP. Patient's eosinophil count was found to be elevated and this persisted after discontinuation of therapy.

In line with Naranjo algorithm, our patient experienced a "probable" daptomycin-induced AEP with a total of seven points scored: (1) Previous case reports of this ADR (1 point); (2) ADR appear after daptomycin was administered (2 points); (3) ADR improved when daptomycin was discontinued (1 point); (4) No other alternative causes of this ADR identified (2 points) (4) ADR was confirmed by radiographic studies (1 point). [12]

The FDA recommends discontinuing daptomycin treatment immediately upon onset of signs and symptoms of AEP with administration of systemic steroids to improve recovery. A prompt diagnostic workup is crucial for diagnosis of AEP to avoid a life threatening hypoxaemia and/or an unnecessary treatment of presumed bacterial pneumonia. Fortunately, our patient recognized that his symptoms may be linked to daptomycin and sought medical attention. As AEP was recognized early by healthcare providers, he did not need corticosteroid therapy and his pulmonary function was not compromised enough to require mechanical ventilation. However, the patient's clinical presentation resembled bacterial pneumonia and administration of unnecessary antibiotics were administered for six days. This case report should increase awareness of daptomycin-induced AEP as a rare side effect so healthcare practitioners can recognize this possibility and include AEP in the differential diagnosis early in clinical presentation. This case report potentially will lower the rate of bacterial pneumonia misdiagnosis, promoting appropriate Antimicrobial Stewardship practice and encouraging avoidance of unnecessary administration of antibiotics with broad spectrum coverage.

CONCLUSION

Our patient developed AEP secondary to daptomycin therapy with development of patchy densities and ground-glass opacity that involved all lobes in the lungs documented by a CT scan. Patient's clinical presentation was consistent with previous reports that included fever, runny nose and dyspnea as well as presence of infiltrates in lungs. Discontinuation of daptomycin resulted in resolution of symptoms and improved radiographic imaging. This rare ADR due to daptomycin therapy is classified as "probable" according to FDA criteria as well as Naranjo algorithm. We hope this report will help healthcare providers recognize daptomycin induced AEP early in order to avoid respiratory failure and unnecessary administration of antibiotics for presumed bacterial pneumonia.

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