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Acute Eosinophilic Pneumonia (AEP) Due to Daptomycin: Is Autoimmunity a Clinico-Pathophysiologic Bridge to AEP?

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Abstract

Daptomycin induced acute eosinophilic pneumonia is a rare and potentially life threatening condition characterized by rapid respiratory failure, pulmonary infiltrates and eosinophilia. Risk factors for acute eosinophilic pneumonia include smoking, environmental irritants or inhalants and certain medications such as Daptomycin [1]. In this review of literature, we aim to explore the potential triggers for developing acute eosinophilic pneumonia in patients exposed to Daptomycin. The exact immune mechanism for daptomycin induced AEP is unknown, however the current proposed mechanism describes a T helper 2 lymphocyte response to inactivated daptomycin in the pulmonary surfactant, which leads to eosinophilia. Disordered T regulatory cell function is seen in patients with certain cancers, allergies and autoimmune conditions. We propose that patients with these underlying risk factors may be at increased risk of developing AEP after becoming exposed to Daptomycin. Understanding potential risk factors is crucial for health care workers as it allows them to identify susceptible populations, explore preventative measures and treat accordingly.

Keywords

Daptomycin, Acute Eosinophilic Pneumonitis, Daptomycin Induced Acute Eosinophilic Pneumonia, Drug Induced Pneumonia, Eosinophilic Pneumonia

1. Introduction

Acute eosinophilic pneumonia (AEP) due to Daptomycin is a rare condition. AEP is the culmination of the progressive eosinophilia noted in patients receiving Daptomycin [1]. AEP can lead to increased morbidity and hospital admis-

sions, however full recovery in the majority of patients occurs upon discontinuation of the drug. Although more prevalent in elderly and patients with chronic lung diseases, the underlying risk factors that make certain patients susceptible to AEP are unknown. We report a case and a novel correlative finding from the systematic review of literature.

2. Methods

By using a systematic review of literature; search terms, [daptomycin, acute eosinophilic pneumonitis, acute eosinophilic pneumonia] yielded 24 abstracts for review. Ten cases met the selection criteria after data mining. Inclusion criteria included: Individual case reports; aged 18 and older, exposure to daptomycin; respiratory failure. Exclusion criteria included: case series; pneumonitis caused by alternative cause: different medications, chemical exposure.) The data collected from these publications were as follows: 1) demographic data, 2) presence of absence of comorbidities, 3) allergy to other antibiotics; 4) description of clinical presentation, 5) laboratory values, 6) BAL (bronchoalveolar lavage) findings, 7) chest radiography 8) description of therapy and 9) presence or absence of conditions that represent disorder of T regulatory cells. We present this in the tabular form below (Table 1). The eleventh case is our index case.

3. Results

The purpose of this paper is to describe an association between immune dysfunction and the development of acute eosinophilic pneumonia after exposure to daptomycin.

While research into the exact role of the immune system in daptomycin induced acute eosinophilic pneumonia is needed, The current proposed mechanism of DIAEP is that pulmonary surfactant inactivated daptomycin causes epithelial damage and inflammation via release of eosinophils by TH2 cells [2]. These are the same immune mediators of various allergies, autoimmune diseases and chronic disease. As there are few reported true cases of DIAEP it is important to characterize potential risk factors to be able to identify DIAEP sooner and stop inciting agent.

Allergies are caused by a T Helper 2 (TH2) cell response, which results in a hypersensitivity reaction to said allergen; eosinophilia is wide-spread in allergic conditions. Eosinophils have a role in both innate and adaptive immunity. Thus, they have been implicated in the pathogenesis of various autoimmune conditions such as inflammatory bowel disease (IBD), allergies and asthma [3]. Eosinophils have even been linked to tissue injury in patients with IBD [4].

Nine out of eleven patients in our review of literature had underlying conditions that represent T-regulatory cell dysfunction (allergies, autoimmune disease, chronic kidney disease, cancers.) Patients with conditions such as a history (hx) of autoimmune disease, hx of atopy or multiple allergies, chronic disease or cancers or hx of smoking may be at greater risk of developing DIAEP. These risk

Table 1. Describes case reports used for data mining. Listed are patients demographic data, past medical history, presenting symptoms, lab work, bronchoalveolar lavage (BAL) results, imaging, treatment and list of disorders that represent a disorder of T regulatory cells.

Case Reports	Demographic Data	Comorbidities	Clinical Presentation	Labs	BAL Findings	Imaging	Therapy	±Disorder of Treg cell or Allergy
Portalatin *et al.*, 2021 [5]	53 y/o M, MSSA Paraspinal Abscess on Daptomycin	Hypertension, Prediabetes, Hyperlipidemia, and Ulcerative Colitis	Non-productive cough, dyspnea, and fever (102˚F)	Leukocytosis of 18,120/μL (3800 - 10,800/μL) and peripheral absolute eosinophilia of 790/μL (15 - 500 cells/μL)	Not performed	CT chest showed evidence of diffuse peripheral ground glass, consolidative, nodular opacities in all lobes	Steroid taper/DC Daptomycin w/full recovery	Ulcerative Colitis
Somoza-Cano *et al.*, 2021 [6]	79 y/o M, Chronic L. Knee Prosthetic Infection on Daptomycin	Hypertension, CKD 3B	Subjective fever, wheezing	Moderate anemia, normal white blood cells but with bandemia, elevated erythrocyte sedimentation rate and CRP	Not completed due to early diagnosis and response to steroids.	Chest CT showed diffuse reticulonodular opacities in the lungs with peripheral predominance, areas of ground-glass opacities, and nodularities.	Steroid therapy/DC Daptomycin w/full recovery	Severe Allergy to cephalexin and ciprofloxacin trimethoprim/sulfamethoxazole, CKD
Kumar *et al.*, 2018 [7]	65 y/o M, Vertebral OM w/ Phlegmon on Daptomycin	CKD 3, Liver Cirrhosis, Spinal Stenosis	Progressive dyspnea, fever, and non-productive cough for two days	Polymorphonuclear leukocytosis and eosinophilia	Eosinophil count of >20	Chest CT showed bilateral pulmonary infiltrates	Steroids/DC Daptomycin w/full recovery	Liver Cirrhosis, CKD
Raman *et al.*, 2020 [8]	71 y/o M, Aortic Valve MRSA Endocarditis on Daptomycin	Obesity, Hypertension, HLD, Diabetes	Increased dyspnea and work of breathing	Leukocytosis w/eosinophils 6.3%	Not performed	Chest CT showed bilateral patchy airspace disease and ground-glass opacities	Steroid taper/DC Daptomycin. Patient suffered PEA and expired 2/2 intubation for AHRF	(−)
Nickerson *et al.*, 2017 [9]	70 y/o F, MRSA OM on Daptomycin	Unknown	Cough, SOB and AMS	Peripheral eosinophils were elevated at 11.6%	BAL revealed 5% eosinophils	Unknown	DC Daptomycin w/full recovery	Vancomycin Allergy
Valaiyapathi *et al.*, 2022 [10]	83 y/o M, Prosthetic Knee Joint Infection on Daptomycin	Pituitary hypoplasia	Cough, exertional dyspnea	Longstanding lymphopenia, elevated CRP, normal eosinophil count	BAL demonstrating eosinophilic infiltrate	Chest CT showed bilateral, peripheral infiltrates	Steroids/DC Daptomycin w/full recovery	Hypopituitary
Storandt *et al.*, 2020 [11]	56 y/o M, Spinal Epidural Abscess on Daptomycin	20 pack year smoking hx	Fever	CBC w/eosinophilia	BAL with 46% eosinophils	CXR showed patchy interstitial pneumonic infiltrates bilaterally	Steroids/DC Daptomycin w/full recovery	Smoker

Continued

Rachid *et al.*, 2017 [12]	64 y/o M, Left Groin Graft complicated by MRSA infection on Daptomycin	PAD	Progressive SOB, fever and cough	Leukocytosis, eosinophilia and elevated ESR	BAL not completed due to high oxygen needs	Chest CT showed diffuse bilateral pulmonary infiltrates	Steroids/DC Daptomycin w/full recovery	Severe allergy to Vancomycin -Red Man Syndrome
Abd Algayoum *et al.*, 2022 [13]	71 y/o F, MRSA Knee Bursitis on Daptomycin	Unknown	Progressive dyspnea, dry cough, malaise, weight loss, fever, chills	Mild peripheral eosinophilia	BAL showed leukocytosis and eosinophilia of 25 mm3	Chest CT showed diffuse ground glass opacities	Steroids/DC Daptomycin w/full recovery	(–)
Raza *et al.*, 2019 [14]	72 y/o M, Toe OM on Daptomycin	COPD, PE, Afib, HTN, HLD, PVD, Ex-Smoker	Respiratory distress, nausea, diarrhea	WBC: 10.7 k/ul, absolute eosinophils count: 3.1 k/u	BAL showed a total WBC count of 8504/UL, with 40% neutrophils and 42% eosinophils	Chest CT showed bilateral ground-glass opacities of the lung parenchyma with right lung predominance	Steroids/DC Daptomycin discharged on 2-3 liters NC	Anaphylactic rxn to Vancomycin, Prior smoker
Index Case	65 y/0 M, MSSA Foot OM	COPD, DM, Thyroid Disease, Melanoma and Malignant tubulo-villous polyp	Fever, dry cough, SOB, hypoxia (83%)	WBC: 12.9 k/ul, percent eosinophil count 9%	BAL would have required intubation so not completed	Chest CT showed peripheral ground glass opacities/ infiltrates	Steroids/DC Daptomycin w/full recovery	Thyroid disease, multiple cancers

factors which are already characterized by immune dysregulation may precipitate a stronger inflammatory response to a trigger, in this case daptomycin.

Of the different case studies, three patients had allergies to vancomycin, which is a peptide antibiotic. One patient had severe allergy (urticarial rash and angioedema) to cephalexin, Bactrim, and ciprofloxacin. Three patients had underlying autoimmune disease (pituitary, thyroid, ulcerative colitis).

One patient had both liver cirrhosis and chronic kidney disease (CKD), which both impair T-cell immunity by affecting the levels of naive T cells and memory cells.

Our index patient had multiple cancer diagnoses (melanoma and malignant tubule-villous polyp). Two cases were known/previous smokers.

Interestingly, tobacco can also trigger acute eosinophilic pneumonia as well as other chemicals and inhalants.

One patient had no past medical history (PMH) for review.

Ten out of eleven patients in the case reports showed complete improvement/near resolution of symptoms after discontinuation of daptomycin and steroid initiation.

Results are depicted in Table 1.

4. Case Presentation

A 65-year-old man with past medical history significant for chronic obstructive

pulmonary disease, diabetes, thyroid disease, melanoma and malignant tubulo-villous polyp being treated with intravenous daptomycin for polymicrobial diabetic foot ulcer (DFU). Three weeks into his treatment, the patient presented to the hospital with a two day history of fever, cough, and dyspnea. In the emergency department the patient was in respiratory distress. Vital signs included a systolic blood pressure of 149/97mm Hg, heart rate 110/min, respirations 24/min and pulse oximetry showed 83%.

Cardiac and the remainder of the physical exam were unremarkable.

Chest X ray and CT of the chest (Figure 1 & Figure 2) revealed ground glass pulmonary infiltrates. CBC showed leukocytosis (12.9×10^9/L) and eosinophilia (9%; 1.6×10^9/L). Serum creatinine was 0.9mg/dL. Eosinophilia began in the first week of daptomycin therapy. Blood cultures, sputum and urine cultures were negative.

On hospital day 1, the patient required a 100% non-rebreather mask. Bronchoalveolar lavage (BAL) would have required intubation so was postponed;

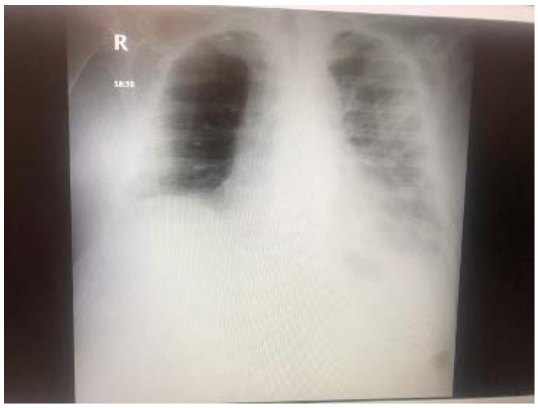

Figure 1. CXR: AP CXR on hospital day #1; Prominent bilateral peripheral opacities, worse on left lung.

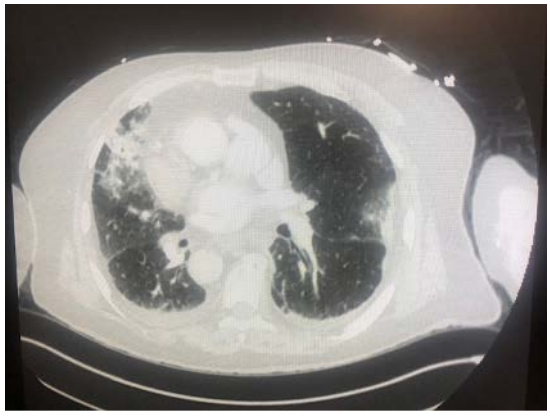

Figure 2. Cross Sectional CT Chest w/contrast: Bilateral patchy areas of ground-glass opacity and interlobular septal thickening.

besides, the peripheral pulmonary infiltrates on chest CT were characteristic and there was a high level of confidence in the diagnosis of daptomycin induced AEP

(DIAEP).

Daptomycin was discontinued and the patient was treated with steroids in addition to empiric broad spectrum antibiotics. At 48 hours, the patient started to improve clinically, and eosinophilia returned to baseline. By day 4, the patient was on room air and the infiltrates on the chest X ray resolved (Figure 3). Patient was discharged home with 2 weeks of prednisone. Upon follow up in the clinic they were asymptomatic and without respiratory symptoms.

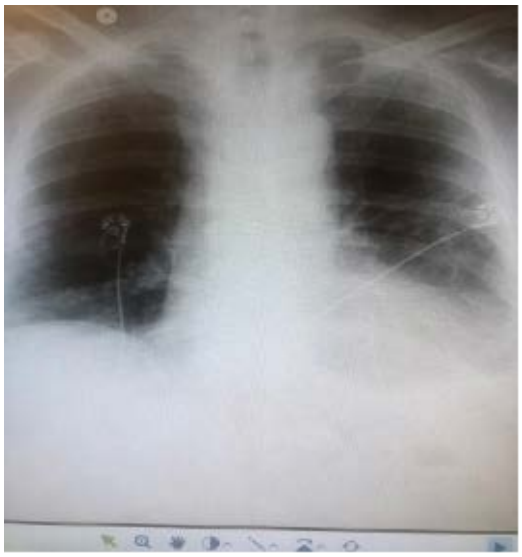

Figure 3. CXR: AP CXR on hospital day #4; Near resolution of bilateral peripheral infiltrates/opacities.

5. Discussion

In this report we described a case of Daptomycin induced AEP (DIAEP). We propose a review of literature derived hypotheses that AEP is indeed a clinical manifestation of underlying autoimmune dysfunction.

Acute eosinophilic pneumonitis (AEP) is an acute febrile illness with diffuse pulmonary infiltrates and pulmonary eosinophilia [1] that are reversed with steroids within 48 - 72 hours [15]. The first case of AEP was published by Allen and Davis (1) in 1989. Tazelar and Colby *et al.* (1990) proposed a histopathological criteria [16]. In clinical practice, modified philit criteria are used to make a definite diagnosis [16]. These criteria are as follows: 1) Acute onset of febrile respiratory illness (≤7 one month); 2) bilateral diffuse opacities on chest radiograph; 3) hypoxemia, with PaO_2 on room air of <60 mm Hg and/or PaO_2/FiO_2 < 300 mm Hg, 4) eosinophilia in bronchoalveolar lavage of >25% [16]. Rapid response to steroid therapy is characteristic [16]. Inhalational exposure is a frequent [17] cause of but not a must as intravenous drugs such as Daptomycin can induce AEP. BAL for detection of pulmonary eosinophilia is not feasible in all patients and there is no correlation with peripheral eosinophilia [17].

Daptomycin is a cyclic lipopeptide antibiotic used to treat Gram positive bacterial infections. Its long half-life makes it an important drug for outpatient an-

tibiotic therapy. It reduces hospital length of stay as well as health care costs. Being lipid soluble, daptomycin diffuses into the alveolar spaces where the cyclic peptide interacts with the surfactant [12] making it ineffective against the bacteria. Hence, daptomycin is not used to treat pulmonary infections. Respiratory secretions are composed of mucus, surfactant and periciliary fluid. These components are arranged in a form of sandwich with surfactant separating the mucus layer from the periciliary fluid [18]. The respiratory mucus is transported from the lower respiratory tract towards the trachea. In this complex, dynamic, chemical milieu of carbohydrates and phospholipids, daptomycin molecules are transported up the respiratory tract, where they are likely to encounter dendritic cells, which are specialized antigen presenting cells in the bronchioles [18].

These dendritic cells when exposed to pathogens or tissue damage will become activated by T cells to release different inflammatory cytokines, which leads to eosinophilia [18]. Not surprisingly, eighty percent [19] of patients on daptomycin develop eosinophilia. This association between our immune system and eosinophilia is well known and must be explored further in the pathogenesis of DIAEP.

In order to explore why patients exposed to daptomycin develop AEP, a review of literature was completed, looking at individual case reports to explore potential risk factors in the way of past medical history that could predispose some to this noninfectious lung disease.

T regulatory cells are responsible for immune tolerance and inflammation. Loss of tolerance occurs when the body's T regulatory cells become overwhelmed or overburdened leading to a quantitative deficit of these cells, or in cases of cellular/tissue damage that leads to an overabundance of autoantibodies when compared to anti-inflammatory cells [20] [21]. T regulatory cell dysfunction is seen in various autoimmune diseases and chronic diseases since failure of tolerance to self is the mechanism of disease. For instance, it is well established that patients with CKD have T cell lymphopenia [22].

Interestingly, patients with inflammatory bowel disease (IBD), an autoimmune disorder, are known to have a prevalence of airway disease that is four times higher than the local prevalence of airway disease. This ten-year retrospective review [23] included tracheal stenosis, bronchitis, granulomatous lung disease, drug induced pneumonitis and pulmonary vasculitis in IBD and non-IBD patients.

Allergies as described in the results section are a result of a TH2 mediated response and T regulatory cells play a key role in maintaining tolerance to allergens [3].

In patients with cancer, it is said that over time as cancer progresses, the amount of T regulatory cells will progress from a low T reg state to a high T regulatory state [24]. Thus, in effect cancer advances from a pro-inflammatory state in many cases.

We acknowledge that while most patients exposed to Daptomycin will not develop AEP, there is a small percentage of patients who will. As such, it is im-

portant to identify those at risk. Based on our research, an unusually high association was found between AEP cases and presence of underlying disorders of T-reg cells dysfunction, 10/11 patients. We, therefore, hypothesized that patients with DIAEP could have predisposition to disorders of T regulatory cells (Treg), such as autoimmune diseases, allergies, hypersensitivities and multiple cancers. To the best of our knowledge, this is the first publication to relate DIAEP to disorders of Treg cells. The purpose of this report is to make the prescribing clinicians aware of this risk factor for DIAEP.

Clinicians should be aware of these risk factors as peripheral eosinophilia is not universal [17] and BAL is not always possible. Luckily, with prompt identification of disease and cessation of Daptomycin coupled with steroid therapy recovery is possible.

6. Conclusion

Patients on daptomycin therapy with underlying T-reg cell dysfunction must be followed closely for development of AEP. We recommend studies to correlate development of AEP and disorders of T-reg cells in patients on Daptomycin therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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