A Case of Daptomycin-Induced Acute Eosinophilic Pneumonitis

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Abstract:

Daptomycin is currently an FDA-approved treatment for various infections, whether they be blood or skin-related. One noted complication is the development of acute eosinophilic pneumonitis which can lead to worsening respiratory complications. Mainstay treatment is to discontinue the offending agent, administer steroids, and conservative management to target respiratory symptoms. We present a case of a patient experiencing increasing oxygen requirements, ultimately requiring intubation, after initiating Daptomycin for a prosthetic joint infection. The antibiotic was discontinued, he was treated with IV steroids and was eventually able to be weaned off the ventilator. Care should be taken when initiating such antibiotics in patients with compromised health. Vitals and respiratory status should be closely monitored and there should be a low threshold for discontinuing the medication should they worsen.

Introduction:

Daptomycin is a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. It binds to bacterial membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death [1]. Daptomycin was approved in 2003 by the Food and Drug Administration (FDA) for treating complicated skin infections, bloodstream infections, and endocarditis. After the first case of Daptomycin-induced acute eosinophilic pneumonitis (AEP) was published in 2007, pulmonary eosinophilia was added to the “Adverse Reactions, Post-Marketing Experience” section of the drug as a rare complication [1,2].

Clinical Couse:

A 62-year-old male with a past medical history of Crohn's disease and obstructive sleep apnea (on BiPAP) underwent a total right hip replacement in January 2024 secondary to an infection in the hip joint in 2018. The patient, unfortunately, developed a prosthetic joint infection (PJI) in February 2024 of the right hip and underwent incision and drainage with joint fluid cultures growing *MSSA* and *S. agalactiae*. The patient was planned to be treated with high-dose intravenous Daptomycin 900 mg (approximately 8 mg/kg/dose) for six weeks, followed by oral Cefadroxil 500 mg twice daily. Within three weeks of initiating treatment, the patient presented to the hospital with dyspnea associated with weakness and cough.

Vitals in the emergency department revealed a heart rate of 102 beats per minute, respiratory rate of 22 breaths per minute, blood pressure of 119/67 mmHg, Temperature 101.2°F, and oxygen saturation at 97% on 6 L of oxygen via nasal cannula. Physical examination revealed crackles in bilateral lung bases. His blood gas analysis on arrival showed pH 7.50, pCO2 25 mmHg, and pO2 61 mmHg with bicarbonate of 20 mEq/l suggestive of respiratory alkalosis. The respiratory panel was unremarkable, and the complete blood count showed a white blood cell count of 10.5K/µL

with eosinophils at 4.1%. His serum chemistry showed mild hyponatremia (130 mmol/l) and mild elevations in AST (132 U/L) and ALT (101 U/L). Chest x-ray (Figure 1) showed severe bilateral pulmonary opacities, suggesting multifocal pneumonia. CT chest (Figure 2 & 3) showed bilateral ground glass mosaic attenuation in the lower lobes with attenuation. CT Abdomen/Pelvis demonstrated right hip prosthesis with a subcutaneous collection suggestive of an underlying infection.

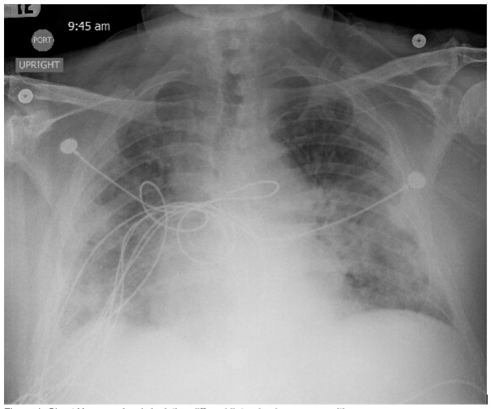

Figure 1: Chest X-ray on day 1 depicting diffuse bilateral pulmonary opacities.

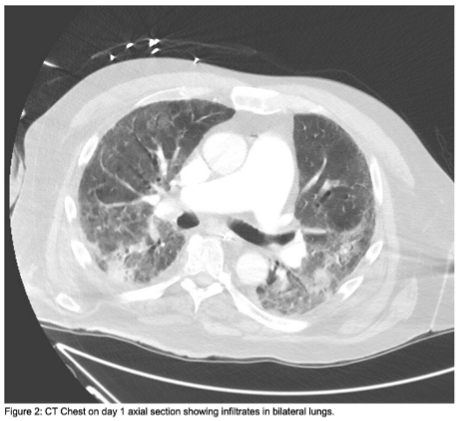
Figure 2: CT Chest on day 1 axial section showing infiltrates in bilateral lungs.

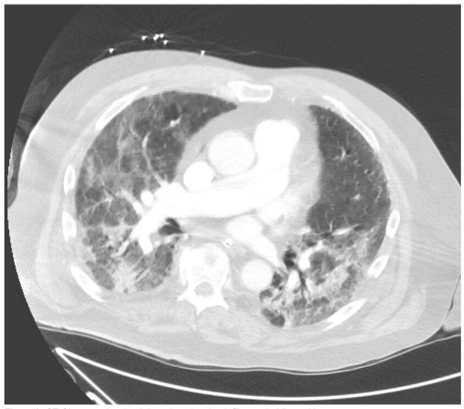
Figure 3: CT Chest on day 1 axial section showing infiltrates in bilateral lungs.

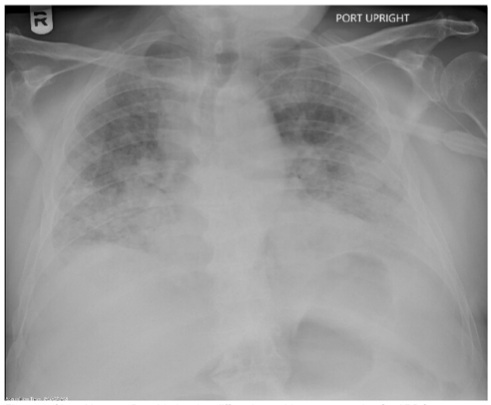

Figure 4: Chest X-ray on Day 14 showing diffuse lung whiteout concerning for ARDS.

Empiric treatment was initiated with Piperacillin/Tazobactam (Zosyn) for concern of multi-lobar pneumonia. Given the lack of response to antibiotics, his increasing oxygen requirements, the presence of fever, lack of viral/bacterial/fungal infection, and new pulmonary infiltrates on chest imaging, the patient met the diagnostic criteria for Daptomycin-induced AEP. Daptomycin was discontinued, and the patient was started on intravenous Methylprednisolone 60 mg daily and intravenous Vancomycin for the PJI. Despite being off Daptomycin for more than 10 days & receiving intravenous Methylprednisolone with doses adjusted daily based on clinical status, his respiratory status continued to deteriorate.

The level of care was escalated, and the patient was transferred to the ICU in anticipation of mechanical ventilation. A bronchoscopy could not be performed due to the severity of his AEP and the patient being highly unstable with increasing supplemental oxygen requirements. He subsequently went into ARDS (Figure 4). IV Methylprednisolone was continued and the patient was diuresed. Ultimately, he required intubation and began mechanical ventilation for which he was on for 12 days.

The patient developed deep vein thrombosis, bilateral pulmonary embolism, and cardiac rhythm abnormalities during the hospital course. The patient was monitored, his respiratory status improved significantly & was eventually able to be discharged to LTAC. Per ID recommendations, he was to continue on chronic oral Cefdinir 300 mg BID for his PJI.

Discussion:

Epidemiology:

The first case of AEP was first noted in 2007 secondary to a case of *MSSA* endocarditis treated with Daptomycin [2]. Other differentials of eosinophilic respiratory complications can include infections from helminths, Allergic Bronchopulmonary Aspergillosis (ABPA), Churg-Strauss syndrome, as well as reactions to other medications/toxins [3]. AEP has a seemingly male predominance, and the severity of the pneumonitis depends on the time exposed to the drug as compared to the dose the patient receives [4].

Pathophysiology:

Several mechanisms have been proposed to explain Daptomycin-induced AEP.

1. Conformational changes of membrane ion channels that allow for altered ion exchange.
2. A higher drug concentration on alveolar epithelium due to surfactant-binding, causing cellular injury.
3. An increased release of eotaxin and interleukin-5 induced by the drug, leading to an eosinophil migration to the lungs and subsequent pulmonary injury [5][6].

As per West et al., the syndromes of this form of pneumonitis can be divided into 3 categories: peripheral eosinophilia, primary Delayed Eosinophilic Pneumonitis (DEP) (usually occurring about four weeks into therapy), and DEP related to re-exposure [7].

Diagnosis:

For patients to be diagnosed appropriately with Daptomycin-induced AEP, the FDA proposed the following guidelines in 2010: the patient is required to be exposed to Daptomycin for long periods, should present with associated fevers and shortness of breath requiring increasing amounts of supplemental oxygenation or mechanical ventilation, and new pulmonary infiltrates or opacities are witnessed on a chest X-ray or CT. Additionally, a bronchoalveolar lavage (BAL) suggestive of > 25% eosinophils and improvement after Daptomycin withdrawal is warranted for a patient to be diagnosed with AEP. Alternatively, Solomon and Schwartz proposed diagnostic criteria in 2006 that did not include patients requiring to be febrile or have dyspnea. Their criteria alluded to the presence of > 25% eosinophils on a lung biopsy or a BAL, the absence of any fungal, bacterial, or viral infection causing pneumonitis, and all prior FDA criteria mentioned above [8].

However, per a vast literature review, a lung biopsy is not indicated to diagnose AEP, and a bronchoscopy will suffice. Given the instability and severity of pneumonitis, our patient could not have a bronchoscopy. A lung biopsy is indicated to explore differential diagnosis in cases with atypical presentations or insufficient imaging features. Interestingly, peripheral eosinophilia is also not required for diagnosis of AEP. In case of any rare diagnosis, other reversible causes must be identified. A comprehensive medical history and physical examination are warranted, with particular attention to smoking history, exposure to any other drugs that can contribute to AEP, and exposure to any fungal or parasitic infections at the patient's place of residence. If clinical

and radiological contexts are appropriate, additional screening tests for eosinophilic granulomatosis with polyangiitis are also applicable [9].

In a prospective cohort study in Lyon, France, about 4600 patients with bone and joint infections who received Daptomycin, like ours, were studied. Out of the 4600, 17 developed Daptomycin-induced AEP; however, only 1 of those patients had a positive bronchoscopy indicating > 25% eosinophils as per the FDA and Solomon and Schwartz criteria. The study discussed how only a minority of their patient cohort fit the proposed criteria, and the researchers proposed a new Lyon criteria. It was argued that the current criteria are very restrictive, particularly the BAL, which indicates > 25% eosinophils, as it is only sometimes done in clinical practice. Fever is a mandatory requirement per the FDA; however, neither of these patients from Lyon presented with fever. The Lyon criteria emphasized radiologic evidence of AEP on CT scan, including bilateral infiltrates, abnormal eosinophilia (either peripheral or from BAL), and symptom improvement once Daptomycin was discontinued. This would diagnose AEP, as per Truongh-Thanh et al., regardless of whether BAL was performed or inconclusive [10].

Complications:
The most common complication occurring in patients with Daptomycin-induced AEP is acute hypoxic respiratory failure requiring mechanical ventilation. In elderly patients, acute renal failure has also been observed in light of receiving higher doses of Daptomycin. Corticosteroids have been primarily used to treat AEP, however, this can exacerbate underlying infections in patients in the critical care setting [11].

Treatment:
Treatment of Daptomycin-induced AEP begins with stopping the offending agent, followed by the mainstay treatment with corticosteroids. The dose of corticosteroids is tailored to the severity of the disease. In hospitalized patients, intravenous Methylprednisolone starting at 60-125 mg every 6 hours is appropriate, followed by oral Prednisone 40 to 60 mg daily tapered over 2- 6 weeks once respiratory status stabilizes, and the patient is extubated [9].

Unlike our patient, clinical improvement is seen within 24 hours to one week of beginning corticosteroid therapy. The duration and dose of steroid therapy are very sparsely studied when it comes to treating Daptomycin-induced AEP. In a retrospective study with prospectively collected data in a Korean military hospital, the efficacies of two groups, being a 2-week versus 4-week course of corticosteroids, were analyzed by Rhee et al. Interestingly, both groups showed similar efficacy in terms of clinical improvement and resolution of radiological findings of AEP. The frequency of adverse effects between the two groups was also comparable. The results of the study indicated that high-dose steroids could be tapered to as close as ten days for treatment of AEP [12].

Conclusion:

AEP is a rare but severe compilation associated with the initiation of Daptomycin. Patients can experience increasing oxygen requirements which can ultimately require intubation. Currently, initial discontinuation of the medication, as well as steroid and conservative respiratory care, are mainstays of management, but further exploration is needed regarding more definitive strategies. Healthcare providers must be mindful of this complication in treating AEP.

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