[CASE REPORT]

Daptomycin-induced Eosinophilic Pneumonia and a Review of the Published Literature

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Abstract:
A 53-year-old man was admitted to the hospital with a diagnosis of cellulitis and osteomyelitis. Twenty-four days after the initiation of daptomycin and sulbactam/ampicillin, he developed a fever and pulmonary infiltration. Bronchoalveolar lavage revealed a high number of eosinophils, while an intracutaneous test revealed positivity for daptomycin. The patient improved after discontinuing antimicrobial therapy. The plasma daptomycin minimum concentration (C_{min}) was elevated (27.4 μg/mL), but plasma protein binding of daptomycin was low (87.8%). Although the pathophysiology of eosinophilic pneumonia remains unclear, antigenic stimulation due to daptomycin accumulation in the alveoli may have caused continuous immune activation.

Key words: daptomycin, eosinophilic pneumonia, therapeutic drug monitoring

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Introduction

Daptomycin (DAP) is a novel cyclic lipopeptide with bactericidal activity that was approved for use in 2003 by the United States (US) Food and Drug Administration (FDA). This drug is effective against endocarditis and skin and skin-structure infections caused by Gram-positive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (1-3). Using data from the US inpatient healthcare utilization system, a previous study reported a dramatic increase in DAP usage between January 2004 and December 2010, when the number of prescriptions increased from 12,688, to 14,231 per year (4).

The primary adverse effect of DAP reported by preclinical studies was skeletal myopathy; in phase III clinical trials, serum creatinine kinase (CK) elevation was reported in 2.8% of patients, while myopathic symptoms occurred in 0.2% of patients (5). In addition to this, the development of eosinophilic pneumonia (EP) is another side effect of treatment with DAP (6). Based on data from the FDA adverse event reporting system, Kim et al. (4) recently reported that, from 2004 to 2010, 63 patients developed DAP-associated EP. Though a prompt improvement after DAP withdrawal was generally observed, some patients with EP developed chronic pneumonitis and required long-term corticosteroid treatment. Some authors speculate that accumulation of the drug in alveolar spaces causes damage to the epithelium (7, 8); however, the mechanism underlying eosinophilic pneumonia induction has yet to be fully elucidated.

In this report, we document the case of a 53-year-old man with chronic kidney disease and obesity who developed acute EP that was likely induced by DAP.

Case Report

This study was approved by the Ethics Review Board of University of Toyama (approval number: clinical 24-118)

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and performed in accordance with the Declaration of Helsinki; patients provided their informed consent regarding the publication of medical data. Patient privacy was fully protected, and personal information was handled in a manner that ensured patients could not be identified.

A 53-year-old Japanese man (height: 175.0 cm, total body weight: 97.0 kg, body mass index: 31.5) with type 2 diabetes and chronic kidney disease was admitted to our hospital with a fever and left lower extremity swelling. Laboratory studies revealed elevated markers of inflammation, including white blood cell count (19.56×10^3 /mm^3), serum C-reactive protein (CRP) (30.69 mg/dL), and procalcitonin (6.30 ng/mL). In addition, blood urea nitrogen (65 mg/dL) and creatinine (8.36 mg/dL) were also elevated. There was a 3.5 cm×3 cm ulcer with purulent drainage at the border on the front of the left foot.

Due to the patient’s history of MRSA-related cellulitis, DAP (7 mg/kg, every 48 hours) and tazobactam/piperacillin (TAZ/PIPC; 4.5 g/day) were initiated after a diagnosis of cellulitis and osteomyelitis. He was followed up without dialysis despite the progression of renal failure. A purulent drainage sample from the ulcer revealed the presence of *Streptococcus agalactiae*, MRSA, *Staphylococcus schleiferi*, Prevotella bivia, and *Peptostreptococcus anaerobius*. In addition, *S. agalactiae* was identified in blood culture. Therefore, on day 7 after admission TAZ/PIPC was discontinued, and sulbactam/ampicillin (SBT/ABPC; 3 g/day) was initiated (administration of DAP was continued). The patient’s fever subsided quickly, and the inflammatory markers gradually improved.

On day 24 after admission, the patient complained of cough with a fever (39.2°C). Laboratory findings revealed increased levels of inflammatory markers, including an elevated white blood cell count (26.36×10^3 /mm^3) with 3.0% eosinophils, serum CRP (31.9 mg/dL), and procalcitonin (1.92 ng/mL). Analyses of arterial blood gases determined after 5 L of O₂ was administered by mask revealed the following: partial pressure of arterial oxygen (PaO₂) was 73.8 Torr, partial pressure of carbon dioxide in arterial blood (PaCO₂) was 30.8 Torr, pH was 7.37, and HCO₃⁻ was 17.4 mmol/L. Chest X-ray (Fig. 1A) and computed tomography (CT) (Fig. 1B) revealed diffuse bilateral patchy consolidations and multiple nodules in the peripheral regions. Test results for antinuclear antibody, myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA), proteinase 3 (PR3)-ANCA, serum cryptococcal antigen, and tuberculosis-specific interferon gamma release assays were all negative, and the levels of serum Krebs von den Lungen-6 (KL-6) were normal (201.5 U/mL). The evaluation of serum immunoglobulin E (IgE) was not performed. Furthermore, all blood cultures were negative, and transthoracic echocardiography did not identify any vegetations, indicating no infective endocarditis. Drug-induced pneumonia was suspected; therefore, the minimum concentration (C_min) of plasma DAP was measured by high-performance liquid chromatography (HPLC) using a Unison UK-C-8 column (3 μm, 150 mm×4.6 mm; Imitakt Corporation, Kyoto, Japan). DAP bulk powder for HPLC was purchased from Wako.
Pure Chemical Industries (Tokyo, Japan). A mobile phase of phosphate buffer (pH 6.5) and acetonitrile [70/30 (v/v)] was used at a flow rate of 1.0 mL/min. The detection wavelength was 223 nm, and the lower limit of quantification was 0.25 μg/mL with an intra/inter-day coefficient of variation below 5%. The plasma DAP C_{min} was 33.4 μg/mL on day 23 after admission. DAP and SBT/ABPC were replaced by TAZ/PIPC on day 27 after admission. Bronchoalveolar lavage (BAL) was performed to assess the presence of infectious etiologies on day 31 after admission. The BAL cell counts identified 4.42×10^5 cells/μL comprising 9.3% macrophages, 7.1% neutrophils, 14.6% lymphocytes, and 69.0% eosinophils. A culture of BAL fluid (BALF) revealed intraoral indigenous (i.e. non-pathogenic) bacteria. Skin tests, including prick-puncture administration and patch tests, and drug lymphocyte stimulation tests (DLST), using DAP, SBT/ABPC, and TAZ/PIPC exhibited negative reactions. However, an intracutaneous test elicited a positive reaction with DAP (rapid type; 30 minutes: 11.5x11.3 mm/15.7x14.7 mm), but not SBT/ABPC or TAZ/PIPC.

After discontinuing DAP and SBT/ABPC, the patient’s fever subsided quickly, and his oxygenation status resolved. Inflammatory markers, including the leukocyte count and serum CRP levels, gradually improved without systemic administration of corticosteroids. In addition, although the peripheral eosinophils increased on day 2 after antimicrobial discontinuation (1.98x10^3 cells/mm^3), they decreased gradually and returned to almost normal levels on day 14 after antimicrobial discontinuation. The clinical course of the patient is summarized in Fig. 2.

**Discussion**

EP has been associated with the use of numerous drugs, including diclofenac, loxoprofen, penicillin, minocycline, cephalosporin, and phenytoin, and should always be considered in the differential diagnosis of acute respiratory failure (9). The first case of DAP-associated EP was reported in 2007, and reports of this disease have recently increased, as DAP has been increasingly used in the treatment of endocarditis and skin and skin-structure infections (6). Kim et al. (4) described six criteria for inclusion in the diagnosis of DAP-associated EP: (1) concomitant exposure to DAP, (2) a fever, (3) dyspnea either with increased oxygen requirement, or requiring mechanical ventilation, (4) new infiltrates on chest X-ray or CT, (5) BAL with >25% eosinophils, and (6) clinical improvement following discontinuation of DAP. In the present case, all of the criteria for the diagnosis of DAP-associated EP were present, but a differential diagnosis was required to distinguish it from SBT/ABPC-associated EP.

Identification of the specific drug associated with the pneumonia is difficult, because rechallenge with the drug is neither warranted nor safe. In addition to this case, diagnostic procedures in 37 previously reported cases of EP implicating DAP are summarized in Table (4, 6-8, 10-25). A diagnosis was made based on the following: DAP rechallenge...
| Case | Age | Sex | Dose of DAP | Duration | Fever | Respiratory symptoms or/and hypoxemia | BAL (% eosinophil) | Imaging findings | Initial treatment | Prognosis | References |
|------|-----|-----|-------------|----------|-------|------------------------------------|-------------------|-----------------|-----------------|-----------|------------|
| 1    | 60  | M   | Unknown     | 2 weeks  | +     | +                                   | 26%               | Bilateral, peripheral and patchy areas of consolidations | Corticosteroid    | Recover   | 6          |
| 2    | 84  | M   | 4 mg/kg     | 6 weeks  | -     | -                                  | Not performed     | Bilateral, sharped nodules and consolidations with air bronchograms | Withdrawal       | Recover   | 10         |
| 3    | 65  | M   | 6 mg/kg     | 2 weeks  | +     | +                                  | 33%               | Bilateral, peripheral diffuse air sarking and bilateral pleural effusion | Corticosteroid    | Recover   | 11         |
| 4    | 54  | M   | Unknown     | 2 weeks  | +     | +                                  | Not performed     | Patchy consolidations and peripheral opacities | Corticosteroid    | Recover   | 12         |
| 5    | 82  | M   | Unknown     | 3 weeks  | +     | +                                  | 14%               | Bilateral, patchy areas of consolidations | Corticosteroid    | Recover   | 13         |
| 6    | 87  | M   | Unknown     | 3 weeks  | +     | +                                  | 40%               | Bilateral, patchy areas of consolidations | Corticosteroid    | Recover   | 13         |
| 7    | 60  | M   | 6 mg/kg     | 2 weeks  | +     | +                                  | 81%               | Bilateral, GGO and peripheral consolidations | Corticosteroid    | Recover   | 7          |
| 8    | 60  | M   | 6 mg/kg     | 2 weeks  | +     | +                                  | Not performed     | Bilateral, peripheral nodular and ground glass changes | Withdrawal       | Recover   | 7          |
| 9    | 83  | M   | 6 mg/kg     | 4 weeks  | -     | +                                  | Unknown           | Bilateral, ground glass and reticular opacities | Corticosteroid    | Recover   | 7          |
| 10   | 78  | M   | 8 mg/kg     | 10 days  | +     | +                                  | 27.5%             | Bilateral, sharped nodular consolidations | Withdrawal       | Recover   | 8          |
| 11   | 69  | Unknown | 6 mg/kg     | 3 weeks  | +     | +                                  | 30%               | Bilateral, patchy areas of consolidations | Corticosteroid    | Recover   | 14         |
| 12   | 63  | F   | 6 mg/kg     | 3 weeks  | +     | +                                  | 60-70%            | Unknown           | Corticosteroid    | Recover   | 4          |
| 13   | 64  | M   | 5.7 mg/kg   | 4 weeks  | +     | +                                  | 44%               | Consolidations   | Corticosteroid    | Recover   | 4          |
| 14   | 79  | M   | 6 mg/kg     | 6 weeks  | +     | +                                  | 9-13%             | Extensive GGO    | Corticosteroid    | Recover   | 4          |
| 15   | 26  | M   | 7.35 mg/kg  | 1.4 weeks| Unknown | Unknown                     | Bilateral         | Consolidations   | Corticosteroid    | Recover   | 4          |
| 16   | 43  | M   | 6 mg/kg     | 1-2 weeks| Unknown | Unknown                     | Bilateral         | Consolidations   | Corticosteroid    | Recover   | 4          |
| 17   | 66  | M   | 6 mg/kg     | 1 week   | Unknown | Unknown                     | Unknown           | Unknown         | Corticosteroid    | Recover   | 4          |
| 18   | 71  | M   | 4 mg/kg     | 7.7 weeks| -     | +                                  | Not performed     | Bilateral, interstitial opacities | Withdrawal       | Recover   | 4          |
| 19   | 77  | F   | 5 mg/kg     | 1 week   | Unknown | Unknown                     | Not performed     | Pneumonitis      | Corticosteroid    | Recover   | 4          |
| 20   | 67  | M   | 6 mg/kg     | 4.3 weeks| Unknown | +                                  | 9%                | Bilateral, consolidations | Corticosteroid    | Recover   | 4          |
| 21   | 73  | M   | 5 mg/kg     | 3.7 weeks| Unknown | +                                  | Unknown           | Bilateral, ground glass appearance | Corticosteroid    | Recover   | 4          |
| 22   | 81  | F   | 6 mg/kg     | 1.6 weeks| Unknown | Unknown                     | 21%               | Bilateral, mid lung consolidations | Corticosteroid    | Recover   | 4          |
| 23   | 61  | M   | 2 weeks     | +       | +     | +                                  | 15.6%             | Bilateral, GGO and consolidations and bilateral pleural effusion | Corticosteroid    | Recover   | 15         |
| 24   | 48  | M   | 6 mg/kg     | 3 weeks  | +     | +                                  | 17%               | Bilateral, patchy airspace opacities | Corticosteroid    | Recover   | 16         |
| 25   | 28  | M   | 6 mg/kg     | 4 weeks  | Unknown | +                                  | 74%               | Bilateral, consolidations | Corticosteroid    | Recover   | 16         |
| 26   | 64  | M   | 10 mg/kg    | 4 weeks  | +     | Unknown                     | 47%               | Bilateral, patchy GGO in the upper part of the lungs | Withdrawal       | Recover   | 17         |
| 27   | 61  | M   | 10 mg/kg    | 2 weeks  | +     | +                                  | 3%                | Bilateral, ground glass consolidation and bilateral effusion | Corticosteroid    | Recover   | 17         |
| 28   | 61  | F   | Unknown     | 1 week   | Unknown | +                                  | 30%               | Bilateral, air space opacities and pleural effusion | Corticosteroid Inhaler | Recover   | 18         |
| 29   | 34  | M   | 10 mg/kg    | 3 days   | +     | -                                  | Not performed     | Peripheral consolidation in the right upper lobe | Corticosteroid    | Recover   | 19         |
| 30   | 62  | M   | Unknown     | 2 weeks  | +     | +                                  | 14%               | Bilateral, GGO and consolidations and pleural effusion | Corticosteroid    | Recover   | 20         |
| 31   | 76  | M   | Unknown     | 2 weeks  | +     | +                                  | 54%               | Bilateral, peripheral GGO and consolidations | Corticosteroid    | Recover   | 21         |
| 32   | 67  | M   | 6 mg/kg     | 17 days  | Unknown | +                                  | 10%               | Bilateral, alveolar and interstitial opacities | Corticosteroid    | Recover   | 22         |
| 33   | 77  | M   | 6 mg/kg     | 6 weeks  | -     | +                                  | 18%               | Bilateral, consolidations | Corticosteroid    | Recover   | 23         |
| 34   | 74  | M   | 6 mg/kg     | 3 days   | +     | +                                  | Not performed     | Increase in air space | Corticosteroid    | Recover   | 23         |
| 35   | 60  | M   | 5 mg/kg     | 24 days  | -     | +                                  | Not performed     | Bilateral tree-in-bud pattern and scattered GGO and right pleural effusion | Withdrawal Inhaler | Recover   | 24         |
| 36   | 67  | F   | 500 mg/day  | 23 days  | +     | +                                  | Not performed     | Diffuse consolidation in the right lobe | Corticosteroid    | Recover   | 25         |
| 37   | 53  | M   | 7 mg/kg     | 24 days  | +     | +                                  | 69%               | Bilateral, peripheral nodules and patchy consolidations | Withdrawal       | Recover   | present case |

* The patient had received corticosteroid therapy before bronchialveolar lavage. DLST: drug-induced lymphocyte stimulation test, GGO: ground glass opacities
bid obesity, severe sepsis, or varying degrees of acute kidney injury (9). Among the 22 patients who received DAP doses ≥6 mg/kg listed in Table, 7 developed EP within 14 days post DAP administration. Of these seven patients, only three exhibited underlying diseases, with one being overweight, and none had a good renal function. In the present case, obesity and kidney failure may indeed have increased the plasma DAP concentration. Furthermore, the intratissue DAP concentration depends on the amount of free DAP in plasma (30).

The findings from the present case report indicate that an increased concentration of available DAP resulted in the excessive accumulation of DAP in the alveoli, continuously activating the immune system. However, the DAP concentrations in BALF were not measured in the present case, and to date there have been no studies about the intrapulmonary pharmacokinetics of DAP. Whether or not DAP plasma levels contribute to DAP concentrations in the BALF and whether or not the drug levels in the BALF contribute to the occurrence of EP itself remain unclear. Further studies are therefore warranted to understand this phenomenon. Bhavnani et al. (31) reported that a DAP Cmin of 24.3 mg/L was associated with an increased probability of CK elevation. These findings suggest that therapeutic drug monitoring may be useful for ensuring safety, even in patients with infections who require long-term antibiotic administration.

In conclusion, we described a rare case of DAP-associated EP. Although the pathophysiology of drug-induced EP was not fully elucidated, one possible mechanism of action was the accumulation of DAP in the alveoli, causing continuous immune activation. Further studies and case reports are warranted to understand this phenomenon.

Author’s disclosure of potential Conflicts of Interest (COI): Yoshihiro Yamamoto: Honoraria, MSD.

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