



Case Report

Eosinophilic pneumonia caused by daptomycin: Six cases from two institutions and a review of the literature



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ABSTRACT

Here we report six cases of daptomycin (DAP)-induced eosinophilic pneumonia (DIEP) encountered at two medical centers and present a review of 43 DIEP patients from 26 studies to compare the clinical characteristics and radiographic findings of acute and chronic eosinophilic pneumonia (AEP; CEP). Four of the six patients did not exhibit respiratory symptoms, and one patient with only fever was misdiagnosed with DAP-induced fever. According to our literature review and the present findings, male sex and old age were dominant risk factors for DIEP. Fever and fine crackles were the most common clinical manifestations. The DAP dose and duration of administration were not significant risk factors for DIEP, and we also could not find any association between allergic predisposition and DIEP. Among the reviewed patients, 51.8% did not show more than 25% eosinophils in bronchoalveolar lavage, which is a criterion for the diagnosis of drug-induced eosinophilic pneumonia. Chest images of all patients showed CEP patterns such as multiple reticulonodular infiltrates in the subpleural region and diffuse bilateral pulmonary infiltrates with ground-glass opacities. However, 66.7% of patients also exhibited pleural effusion, a feature specific to AEP. All patients showed prompt recovery after DAP withdrawal. Our results suggest that clinicians should consider DIEP as a differential diagnosis when patients receiving DAP therapy, particularly men and elderly patients, present with fever, even in the absence of respiratory symptoms. Furthermore, they should be aware that the occurrence of DIEP is independent of the DAP dose and administration duration, and allergic reaction.

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1. Introduction

Daptomycin (DAP) has been used in Japan since 2012, and recent Japanese guidelines recommend the use of DAP to treat various infectious diseases caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

DAP is a novel, cyclic, lipopeptide antibiotic with rapid bactericidal activity against gram-positive bacteria. It causes membrane depolarization through bacterial membrane binding and inhibition of protein, RNA, and DNA synthesis. Musculoskeletal injury and gastrointestinal manifestations such as vomiting, diarrhea, and constipation are well-known side effects of DAP. Eosinophilic pneumonia is another adverse event. DAP-induced eosinophilic pneumonia (DIEP), which was first reported in 2007, potentially leads to severe dyspnea, hypoxemia, and respiratory failure and requires prompt recognition by physicians [1].

Although overseas case reports on DIEP have been increasing, to our knowledge, only five cases have been reported in Japan [2–6]. Here we describe six cases of DIEP encountered among a total of

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492 DAP-treated cases at the University of the Ryukyus ($n = 4$) and Aichi Medical University ($n = 2$) and present a review of the relevant literature, wherein we compared the findings for DIEP in 43 patients (26 studies) with those for acute eosinophilic pneumonia (AEP) and chronic eosinophilic pneumonia (CEP) to elucidate the clinical characteristics and imaging findings of DIEP.

2. Case report

2.1. Case 1

A 64-year-old man with artificial hip arthritis due to methicillin-susceptible *S. aureus* presented with abrupt-onset fever and an increased peripheral eosinophil count (7.7%; $770/\text{mm}^3$) 20 days after the initiation of DAP (8 mg/kg) treatment. Physical examination revealed fine crackles over both lower lung fields, with no cough, respiratory distress, or hypoxemia. High-resolution computed tomography (HRCT) of the chest revealed multiple reticulonodular infiltrates and ground-glass opacities in the subpleural regions of both lung fields (Fig. 1). Bronchoalveolar lavage (BAL) showed 14% eosinophils (244×10^5 mL). DIEP was diagnosed and DAP was discontinued. The patient became afebrile 3 days after DAP withdrawal (Fig. 2). The patient did not have any previous allergic history.

2.2. Case 2

A 74-year-old man with artificial hip arthritis caused by methicillin-resistant *Staphylococcus caprae* presented with slight fever and an increased peripheral eosinophil count (9.1%; $937/\text{mm}^3$) 24 days after the initiation of DAP (5.8 mg/kg) treatment. At the time of presentation, there was no cough or dyspnea [arterial oxygen saturation (SpO_2), 98% in room air], and physical examination did not identify crackles over the lung fields. Therefore, an initial diagnosis of DAP-induced fever was made. The attending physician continued the administration of DAP, because the patient's general condition was good. However, the fever gradually increased, and HRCT revealed multiple, diffuse infiltrations in the subpleural regions of both lungs. On the basis of the clinical course and radiographic characteristics, DIEP was suspected and DAP was promptly discontinued. The patient's fever resolved within 48 h after DAP withdrawal. The patient did not have any previous allergic history.

2.3. Case 3

A 77-year-old man with chronic obstructive pulmonary disease presented with fever, nonproductive cough, and respiratory failure

(SpO_2 , 83% in room air) 14 days after the initiation of DAP (5.3 mg/kg) treatment for artificial hip arthritis due to methicillin-resistant *Staphylococcus capitis*. A differential leukocyte count revealed eosinophilia (6.6%; $330/\text{mm}^3$), and HRCT showed multiple, diffuse infiltrations in both lungs. In addition, BAL showed 19.2% eosinophils (238×10^5 mL). DIEP was diagnosed and DAP was discontinued. The fever and dyspnea resolved 2 days after DAP withdrawal. The patient did not have any previous allergic history.

2.4. Case 4

A 61-year-old man with type 2 diabetes mellitus and chronic kidney failure was referred to our hospital for the further investigation of pain, edema, and inflammation of necrotic foot skin. He was diagnosed with an infected diabetic foot ulcer due to MRSA incubation in the wound. DAP (6 mg/kg) treatment was initiated; however, the patient developed fever, dry cough, and shortness of breath 24 days after treatment initiation. His oxygenation level was normal (SpO_2 , 98% in room air). Blood tests showed an elevated peripheral eosinophil count (7.4%; $888/\text{mm}^3$), and HRCT showed multiple reticulonodular infiltrates and ground-glass opacities in the subpleural regions of both lung fields. DIEP was diagnosed and DAP was promptly discontinued. The patient's symptoms alleviated 4 days after DAP withdrawal. The patient did not have any previous allergic history.

2.5. Case 5

A 67-year-old man with type 2 diabetes mellitus and cardiac angina was diagnosed with pyogenic lumbar spondylitis due to MRSA, and DAP (5.8 mg/kg) treatment was initiated for the management of vertebral osteomyelitis. However, 52 days after treatment initiation, he presented with fever. HRCT revealed peripheral reticulonodular infiltrates and ground-glass opacities in the subpleural regions of both lung fields. There was no dyspnea or a decrease in oxygenation. The peripheral eosinophil count was $310/\text{mm}^3$ (5.2%). Although DIEP was suspected, the patient's general condition was good and DAP was continued for 4 more days (total, 8 weeks). He became afebrile 2 days after DAP withdrawal. The patient did not have any previous allergic history.

2.6. Case 6

A 69-year-old man with type 2 diabetes mellitus was admitted to our hospital complaining of redness and pain in his right leg three weeks after he had undergone bypass surgery for arteriosclerosis obliterans. DAP (5.2 mg/kg) was started promptly, and surgical site infection due to MRSA was diagnosed after he was hospitalized. However, the patient developed fever and increased peripheral eosinophil count (13.5%; $1120/\text{mm}^3$) 5 days after the initiation of DAP. Physical examination revealed fine crackles over both lower lung fields although there was no dyspnea or a decrease in oxygenation, and HRCT revealed multiple, diffuse infiltrations in the subpleural regions of both lungs. In addition, BAL showed 36.5% eosinophils (495×10^5 mL). Hence, DIEP was diagnosed and DAP was discontinued. The fever and dyspnea resolved 4 days after DAP withdrawal. The patient did not have any previous allergic history.

3. Discussion

We described six cases of DIEP that occurred among a total of 492 DAP-treated cases at two medical institutions. The incidence of DIEP was 4 out of 178 cases (2.2%) at the University of the Ryukyus, and 2 out of 314 cases (0.6%) at the Aichi Medical University. However, we did not conduct lung biopsy for the histopathological

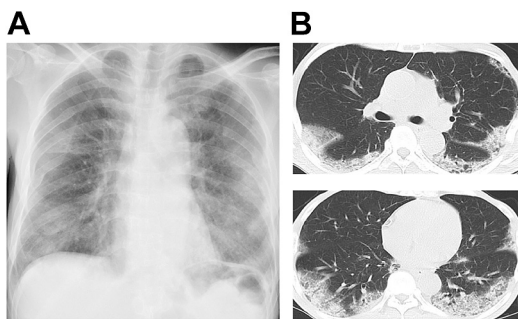


Fig. 1. Chest X-ray (a) and high-resolution computed tomography (b) of case 1. Multiple reticulonodular infiltrates in the subpleural region and diffuse bilateral pulmonary infiltrates with ground-glass opacities of both lung fields were observed.

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