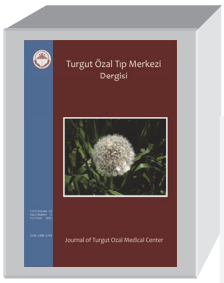

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A Case of Clarithromycin-induced Eosinophilic Pneumonia and Myocarditis

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Abstract
Acute eosinophilic pneumonia (AEP) is a rare disease with unknown etiology that is characterised by pulmonary infiltration in radiography and eosinophilic infiltration into the lungs. Clarithromycin is a commonly used and well tolerated antibiotic. A 31-year-old male asthma patient was admitted with dyspnea, fever, and sputum. Despite the clarithromycin treatment the patient's complaints worsened. Leukocytes was 23400/ml (eosinophil 8%). We re-applied ampicillin-sulbactam and clarithromycin. Since leukocytosis and fever were persisting, antibiotics were withdrawn and cefepim, teicoplanin, and ciprofloxacin were started. Because the patient developed chest pain and his dyspnea worsened, we diagnosed the patient with myocarditis after the cardiac evaluation. The tomography showed pleural effusion and consolidation. Sputum, blood, and tracheal aspirates showed no microorganism production. No parasites were found in feces, either. Leukocyte and eosinophil levels got worsened. The patient was then diagnosed with eosinophilic pneumonia. After methylprednisolon was administrated, laboratory, radiological, and clinical findings improved. This case suggests that eosinophilic pneumonia should be considered in the differential diagnosis of patients with pneumonia who do not respond to treatment.
Key Words: Clarithromycin; Eosinophilic Pneumonia; Myocarditis

Klaritromisinin İndüklediği Eozinofilik Pnömoni ve Myokardit Olgusu

Özet
Akut eozinofilik pnömoni, solunum yetmezliği, radyolojik infiltrasyonlar ve akciğerlerin eozinofil infiltrasyonu ile karakterize, etiyolojisi çoğunlukla bilinmeyen nadir bir hastalıktır. Klaritromisin, yaygın kullanılan, iyi tolere edilen ve yan etkileri nadir bir antibiyotiktir. Astım tanısı bulunan 31 yaşında erkek hasta, nefes darlığı, öksürük, balgam ve ateş şikâyetleri ile başvurdu. Klaritromisin kullanmasına rağmen şikâyetlerinin artması üzerine, astım ve pnömoni tanısıyla yatırıldı. Lökosit: 23.400/ml(eozonifil:%8) idi. Ampisilin-sülbaktam+klaritromisin başlandı. Lökosit ve ateş yüksekliği devam etmesi üzerine mevcut antibiyotikler kesilip cefepim, teiokoplanin ve ciprofloxacin başlandı. Takiplerimizde göğüs ağrısının gelişmesi ve solunum sıkıntısı artması üzerine yapılan kardiyolojik değerlendirmede akut myokardit teşhisi kondu. Bilgisayarlı tomografide bilateral plevral efüzyon ve pnömonik infiltrasyon izlendi. Alınan kan, balgam ve trakeal aspiratlarında bakteri üremedi. Gaitada parazit görülmedi. Lökosit ve eozinofilin artması üzerine hasta eozinofilik pnömoni olarak değerlendirildi. Metilprednizolon başlanmasında sonra çok hızlı klinik, laboratuar ve radyolojik düzelme görüldü. Sunulan olgu tedaviye cevap vermeyen pnömonili bir hastada ayırıcı tanıda eozinofilik pnömoninin düşünülmesi gerektiğini göstermektedir.
Anahtar Kelimeler: Klaritromisin; Eozinofilik Pnömoni; Myokardit

INTRODUCTION

A rare disease of unknown etiology, acute eosinophilic pneumonia (AEP) is characterised by respiratory failure, radiographic infiltrations, and eosinophilic infiltration of the lungs (1-3). Although its etiology is unknown, it is thought that AEP is a hypersensitivity reaction against some agents. Clarithromycin (CLM) is a drug that is widely used in lung infections; it is a well tolerated medication with infrequent side effects. Since there are only two CLM-related AEP cases in the literature, we decided to present our experiences related to this uncommon condition.

CASE REPORT

A 31-year-old male patient, who had been diagnosed with atopy and asthma five years ago, was admitted to our clinic with complaints of shortness of breath, cough, sputum, and fever that had been going on for one week. Experiencing a gradual increase in his complaints despite 1000 mg/day of CLM intake for five days, the patient decided to consult our centre. Apart from the presence of asthma, the patient's medical history was unremarkable. Meanwhile, the patient claimed that his complaints had partially decreased within the two days period between discontinuing CLM and consulting our clinic. The chest radiograph revealed increased heterogeneous density in the middle and lower zones of the left lung (Figure 1).

The patient was hospitalized with a diagnosis of asthma and community-acquired pneumonia. Initially, the number of leukocytes was 23,400/ml (eosinophilia: 8%) while CRP was 6,5 (normal value: 0-0,35) and his body temperature was 38,5°C. We administered 4x1g of ampicillin-sulbactam (iv) accompanied by 2x1 500mg

CLM. As the leukocytes reached 40,000/ml with a body temperature of 39°C within four days, we stopped the antibiotics treatment and started to give cefepime, teicoplanin, and ciprofloxacin. Two days later, the patient started to suffer from chest pain and respiratory distress. The changes in ST, condition of the left bundle branch, bradycardia, CK, and CK-MB elevation observed in the electrocardiography (ECG) as well as the presence of secondary mitral regurgitation in the echocardiography (ECO) suggested acute myocarditis. In the meantime, the computed chest tomography also revealed bilateral pleural effusion and pneumonic inflitration in the neighboring areas of the lungs (Figure 2).

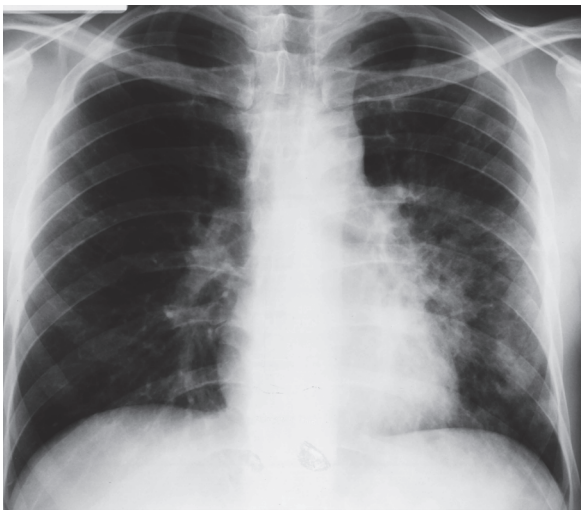

Figure 1. Pneumonic infiltration on the left on admission.

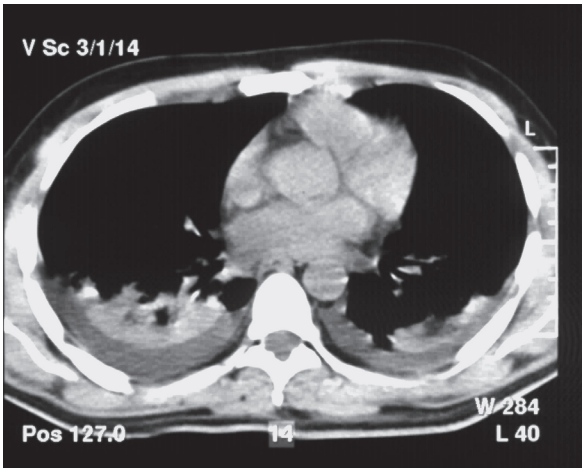

Figure 2. CCT image showing the bilateral pleural effusion and pneumonic inflitration in the neighboring areas of the lungs.

Two days later, the patient was connected to mechanical ventilation upon the development of acute respiratory failure. Although we repeatedly received blood samples and applied blood tests, there were no observable microbial factors either in the blood samples or in the sputum and tracheal aspirate cultures. There were no parasites in the stool, either. The patient's PPD was also negative. Despite the treatment he received, the patient still had a leukocytes level of 43000/ml as the eosinophils level also rose up to 55%. At this point, we started considering myocarditis-related acute pulmonary oedema diagnosis due to eosinophilic pneumonia and myocarditis. Based on these findings, we connected the patient to the mechanical ventilator by adding 80 mg/day of methylprednisolone to the treatment. 24 hours after the initiation of methylprednisolone, we began to observe significant clinical improvement in the patient. The number of leukocytes rapidly decreased down to 12500/ml while eosinophils rate dropped to 10% in a similar fashion. On the fifth day, the patient was disconnected from the mechanical ventilator. We also observed unexpected rapid radiological improvement in the patient's pneumonia. The ECO and ECG findings returned to normal and the methylprednisolone treatment was eventually discontinued. As of now, our patient has not had any problems for nearly ten years.

DISCUSSION

Characterised by lung infiltration of eosinophils, acute respiratory failure that may require mechanical ventilation, presence of rapid response to corticosteroids, and the absence of relapse, AEP was first defined in 1989 (1). AEP can be seen in any age group though the average age of onset is 29 (2). AEP involves hypersensitivity reaction to any given antigens. Patients' medical history may contain having been subject to environmental and occupational exposure to inhalation agents that may precede the symptoms days before the onset of the disease. The cases reported in the literature include medical stories related to exposure to some agents in cave explorations, cleaning gas tanks, or motocross racing as well as exposure to tear gas and even to dust during the September 11 attacks on the World Trade Centre (2).

AEP patients usually present with an acute onset of hypoxemic respiratory failure requiring mechanical ventilation that can sometimes be confused with pneumonia. Other important findings of AEP are cough, dyspnea, fever, and chest pain. As we have seen in our case, the majority of these patients are diagnosed when they do not respond to the treatment of pneumonia following advanced evaluation.

The eosinophil rise in sputum or bronchoalveolar lavage are notable signs of AEP. The overall condition of our patient was not suitable for bronchoscopy. However, we considered the possibility of CLM-related AEP because of the following reasons: the pneumonia infiltration did not to respond broad-spectrum antibiotics; we did not observe any bacteria production in the sputum and blood samples; the eosinophils level in the blood was too high (55%); the patient responded to the methylprednisolone therapy once CLM was discontinued; and most importantly, the complaints got denser once the patient took up using CLM prior to his admittance while these complaints gradually decreased

during the two days between the time he stopped using CLM and his admittance to our hospital although his condition worsened once again (after the challenge test) once we applied CLM to the patient. Meanwhile, the ECHO, ECG, and laboratory findings also made us consider myocardium for our patient.

CLM is a commonly used and generally well tolerated macrolide antibiotic. In addition to its antimicrobial effects, it also has anti-inflammatory properties. It is because of these properties that it can reduce eosinophils count in patients with asthma (4, 5). However, although rare, there are studies reporting CLM-related eosinophilia, vasculitis, Churg-Strauss syndrome, cholangitis, and hepatitis cases in the literature (6-8). More to the point, there are a few reported cases of myocarditis associated with AEP in the literature albeit without any identified etiologic agents (9, 10). There are only two CLM-related AEP cases in the literature while there are no myocarditis-related AEP cases. Of these two cases, the first one was a 17-year-old male patient with a history of asthma and allergic rhinitis similar to our patient (11). The second case was an 80 year-old male patient with no history of asthma. The latter developed AEP during his tuberculosis treatment when CLM was added to the therapy and the patient got better when CLM was replaced with steroids (12). Challenge test, which is a test based on the idea of reusing the medication with potential side effects to ensure that it is the cause of the problem, is an important indicator although it is also considered to be unethical (11). In our case, challenge test was conducted involuntarily but it helped us identify CLM-related AEP.

With this study, we aimed to draw attention to serious side effects (although rare) of CLM and to express that AEP should be considered in the differential diagnosis of pneumonia that does not respond to antibiotics treatment.

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