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CASE REPORT

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A rare cause of interstitial lung disease in rheumatology clinic: case report for sulfasalazine-induced acute pulmonary injury

Romatoloji Kliniğindeki Ender Bir İnterstisyel Akciğer Hastalığı Sebebi: Sulfasalazinin Tetiklediği Akut Akciğer Hasarı Olgusu

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ABSTRACT

Infection, primary lung pathology, rheumatic involvement, malignancy and drug-induced involvement can be suggested as differential diagnosis of a case with rheumatic disease ,who applied to an emergency service with pulmonary symptoms. The drugs cause 2.5-3% of all interstitial lung diseases. Sulfasalazine has been widely used in the treatment of inflammatory rheumatic conditions and it is an extremely rare reason for interstitial lung disase. Here, we aimed to present the rarely seen sulfasalazine-induced interstitial pulmonary disease and its treatment. Sulphasalazine-induced lung disease can mimic the symptoms of infectious and rheumatic lung involvement, and can cause serious diagnostic confusion.

Key Words: Sulphasalazine, Acute Pulmonary Injury, Interstitial Lung Disease, Ankylosing Spondylitis

ÖZ

Enfeksiyon , primer akciğer hastalıkları, romatolojik tutulum, malignite ve ilaca bağlı tutulumların hepsi interstisyel akciğer hastalığı bulgularıyla acil servise başvuran bir romatizma hastasında akla gelebilecek ayırıcı tanılardır. İlaçlara bağlı tutulumlar tüm interstisyel akciğer hastalığı olgularının %2.5 -3 arasındaki sebebini oluşturur. Sülfasalazin inflamatuar romatolojik hastalıkların tedavisinde geniş kullanım alanı olan bir ajan olup interstiyel akciğer hastalıklarına oldukça seyrek de olsa sebep olabilmektedir. Ayrıca sülfasalazine bağlı akciğer tutulumu enfeksiyonlar ve romatolojik tutulumları da taklit edip ciddi tanısal karışıklığa sebep olabilir. Bu yazımızda, nadiren karşılaşılan sülfasalazinin tetiklediği akciğer olgumuz ve bu durumun tedavisine değindik.

Anahtar Kelimeler: Sülfasalazin, İntestisyel Akciğer Hastalığı, Akut Akciğer Hasarı, Ankilozan Spondilit

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INTRODUCTION

In a case with a rheumatic disease who applied to an emergency service due to pulmonary derived symptoms, such as cough and shortness of breath: infection, primary lung pathology, rheumatic involvement, malignancy and drug-induced involvement should be considered in the differential diagnose list. More than 380 drugs can cause toxicity in the lung and the estimated ratio of drugs role for interstitial lung disease (ILD) is 2.5-3% [1, 2]. Differentiating drug-induced lung disease (DILD) from lung involvement of the disease in a rheumatic patient can be quite tricky because of indistinguishable common symptoms. The lack of specific clinical, laboratory, radiological or even histological findings, complicates the diagnosis and treatment process. For this reason, getting medical records as well as examining the onset of complaints and drug use history are necessary, and to be done with utmost care.

In this article we aimed to present the rarely seen sulfasalazine-induced interstitial pulmonary disease and its treatment.

CASE REPORT

A 43-year-old male patient with no known history of lung disease was reported to have cough, sputum, fever and wheezing for 15 days. In his first appliance to the emergency service, infiltration was detected a on chest X-ray and empirical antibiotherapy treatment was started. The patient, whose complaints persisted despite the therapy, referred to the emergency department of the university hospital. A pulmonologist consulted him with his chest X-ray at the emergency service and the patient was admitted to the chest diseases service with an acute pneumonia diagnosis. Ceftriaxone b.i.d. 1 gr and clarithromycin b.i.d. 500 mg (intravenous) were administered. On the 7th day of antibiotherapy his symptoms had not retreated. The patient had consulted by a rheumatologist while he was bedridden and on physical examination, blood pressure was found to be 120/80mmHg, and fever was 38.5°C, pulse was 75/min. There were no pathological findings other than bilateral crepitant rale in auscultation and other physical examination findings were normal. Laboratory findings provided the following results: leukocyte: 9400/μL, hemoglobin: 14g/dL, platelet: 325.000/μL, eosinophil: %1.5, neutrophil: %78, creatinine: 0.69mg/dL, urea: 27 mg/dL, aspartate aminotransferase (AST): 23U/L, alanine aminotransferase (ALT): 32U/L, C-reactive protein (CRP): 2,32 mg/L and erythrocyte sedimentation rate (ESR) 38 mm/h. Proteinuria and active sediment were not found in spot urine. Chest X-ray showed bilateral non-homogeneous reticular opacities in the upper zones. High-Resolution Computed Tomography (HRCT), requested by the chest diseases clinic, showed more common ground-glass opacities and minor fibrotic changes in the bilateral upper lobes (Figure 1). The pulmonary function test (PFT) of the patient was in a restrictive pattern. The carbon monoxide diffusion capacity (DLCO) test showed mild diffusion limitations. There was no cardiac failure found after being consulted with cardiology. HIV serology was negative. Immunological markers were requested, and the results were Rheumatoid factor (RF) (-) antinuclear antibody (ANA) (-), perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) (-), Cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) (-). An expert performed bronchoscopy and a bronchoalveolar lavage (BAL) fluid was obtained from the patient. BAL fluid was slightly hemorrhagic but not as much to consider as a finding of diffuse alveolar hemorrhage. The polymerase chain reaction (PCR) test was negative for Pneumocystis Carinii.

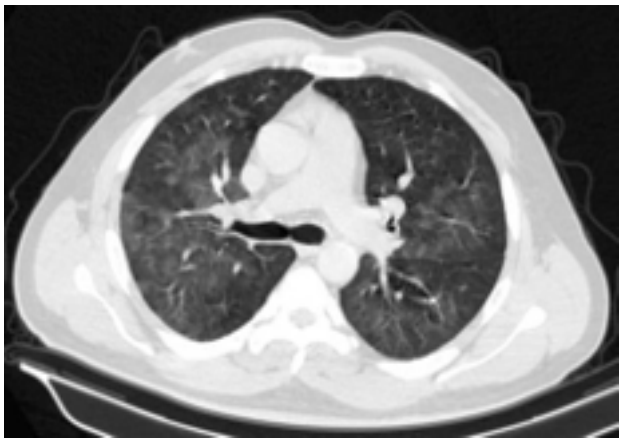

Figure 1: Ground-glass opacities, upper lobes

Evaluated with this information, the patient has no connective tissue diseases and vasculitis that may often cause ILD. Rheumatologic examination revealed chronic knee arthritis and significant inflammatory low back pain for more than five

years. His sibling has a diagnose of psoriasis and were in a follow-up by a dermatology clinic. After a more detailed examination, it was learned that the patient was still using sulfasalazine for three months, which has started by another rheumatology clinic. The patient did not reveal this information to the pulmonologist when giving his medical history. At this time, a sacroiliac X-ray was requested from the patient and bilateral stage 3 sacroiliitis was detected (Figure 2).

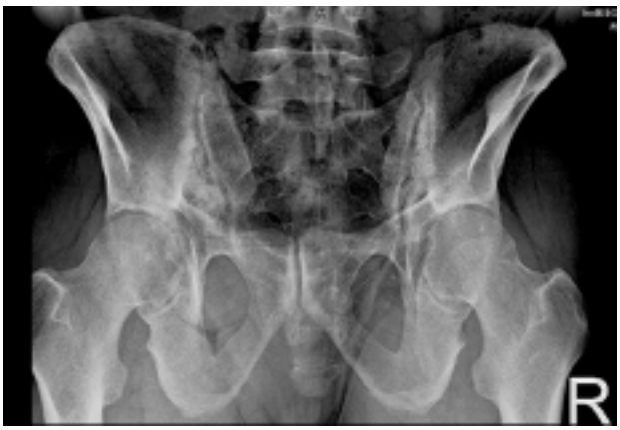

Figure 2: Bilateral grade-3 sacroiliitis

As clinical and radiological findings suggested, sulfasalazine-induced lung injury was considered in the foreground in the patient who was found to be followed up due to spondyloarthritis, and the diagnosis of pulmonary involvement due to primary rheumatic disease was excluded. Sulfasalazine and antibiotherapy were discontinued. Viral infection couldn't be ruled out, so steroid treatment was not started. After five days of sulfasalazine discontinuation, the patient's clinical symptoms wholly resolved. The rate of dyspnea decreased and no fever was observed. A significant regression was seen in the findings of involvement on the HRCT taken 15 days later (Figure 3).

Ethics: Informed consent was taken from the patient, and all procedures followed while writing case report were in accordance with the Helsinki Declaration of 1975 (in its most recently amended version).

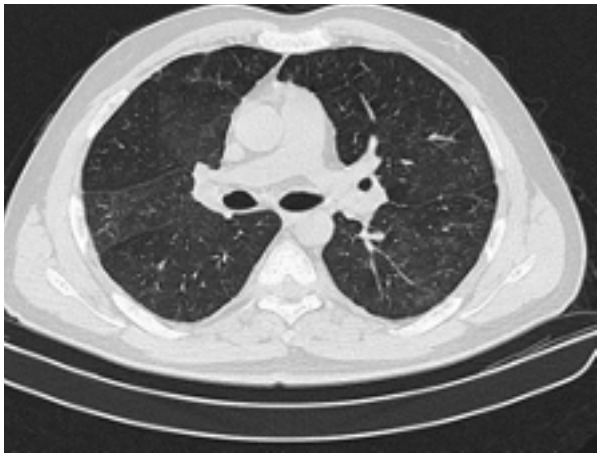

Figure 3: Regression of ground-glass opacities after drug cessation

DISCUSSION

Gas exchange takes place in the alveolocapillary membrane, which is part of the lung interstitium. ILD is the common name for a group of diseases that affects the alveolocapillary membrane in the foreground [3]. The most common cause was idiopathic pulmonary fibrosis, which was reported in most series ranging from 22-37% [4]. Genetic and environmental factors, occupational exposures, infections, malignancy, drug use and autoimmune diseases are other factors that can cause ILD [5].

It has been shown that lung involvement of rheumatic diseases can cause ILD up to 13% of all rheumatic diseases [2]. However, before deciding that ILD is a sign of rheumatic disease, infection, malignancies and pulmonary involvements caused by anti-rheumatic drugs, should be excluded. Radiological and even pathological data may not be helpful to determine the cause of the disease. Because of this, cooperation between rheumatologists and pulmonologist is required, and essential [6].

In cases without known lung disease, the development of new infection should first be excluded in the presence of acute-subacute clinical findings, concomitant fever and ground-glass appearance on HRCT. In our patient, there was no improvement with empirical antibiotic treatment and further investigations were requested. RF, ANCA and ANA tests were negative, microbiological tests could not find the cause and no additional findings were observed in BAL except hemorrhagia. The rheumatologic evaluation found

the spondyloarthritis (SpA) diagnosis of the patient. Acute interstitial pneumonia due to axial spondyloarthritis is an unexpected condition, but rather, bilateral apical fibrosis is more expected in advanced involvement of SpA [7]. Because of this unanticipated situation, the drugs which were being used by the patient were reconsidered as a cause of the drug-induced ILD.

Drug-induced ILD occurs due to the toxic and immunological effects of drugs [8]. They may be seen as cough, bronchospasm, diffuse lung disease, pulmonary edema, pleural diseases, pulmonary vascular diseases and mediastinal diseases [9]. Of the antirheumatic drugs, biological agents, methotrexate and sulfasalazine are often and particularly responsible for side effects in the lungs.

Sulfasalazine has highly miscellaneous side effects. Up to 20% of the patients receiving treatment may experience significant forms of these, such as nausea, vomiting, skin rash, arthralgia, and fever. It is responsible for initiating a number of immune reactions. Typical examples are sulfasalazine-induced ANA positivity, drug-induced lupus and drug-induced vasculitis DRESS syndrome [10], but pulmonary toxicity and blood dyscrasia can be seen in very few cases.

Acute interstitial pneumonitis, eosinophilic pneumonia, pleural effusion, sarcoidosis-like granulomatous lung disease, ANCA-related capillaritis and pulmonary fibrosis, have been identified in patients treated with sulfasalazine [11]. Eosinophilic pneumonia is the most common pulmonary complication: clinical presentation is characterized by fever, lung infiltration and/or skin rash and/or peripheral eosinophilia. Dyspnea, cough and fever trio can be observed in half of the cases [12]. Increased CRP and ESR values often appear, and as they are not specific to the disease, they require careful examination for discriminating from infections. Before the clinical presentation of ILD, usually, 2-6 months of drug use history is present. Radiological findings typically consist of bilateral, peripherally localized, consolidation areas. Upper lobe localization is predominant in these kinds of consolidations and in a few cases, lower lobe or diffuse involvements have been found. A high level of regression will be observed after the discontinuation of sulfasalazine treatment, the predominance of eosinophil and lymphocyte may be seen in BAL fluid; the use of steroids accelerates the treatment [13].

Of the other complications, acute interstitial pneumonia presents with flare-ups within the period following drug intake. Fever and dyspnea gradually increase, and in the pathological specimens, diffuse alveolar damage is detected. The drug should be rapidly discontinued, immunosuppressive agents should be added to the steroid treatments, and when necessary, plasmapheresis should be applied. Despite all, mortality occurs in approximately 50% of cases [14]. Another fatal complication is ANCA-related vasculitis due to sulfasalazine. In general, p-ANCA positivity is found in patients; the drug should be discontinued, and primary ANCA-related vasculitis treatment should be applied [14].

In our case, there was no peripheral eosinophilia and skin rash, but the diffuse involvement was predominant in the upper lobe. BAL had no eosinophilia, and hemorrhagic fluid was detected. Lung biopsy could be very valuable in the differential diagnosis but could not be performed. In our case, sulfasalazine induced acute interstitial pneumonia was considered in higher precedency due to radiological and clinical findings. Regression was observed with the discontinuation of the drug.

As a result, drug-induced lung disease is a rare condition. It can be reversible if diagnosed early and the drug is discontinued, however a delay in diagnosis or treatment causes fatal consequences. Acute phase responses, routine biochemical markers, radiological, or even pathological data often do not produce consistent findings for differential diagnosis. In the emergency service, if the acute pneumonia diagnosed and the patient has a concomitant rheumatic disease, rheumatic lung disease and drug-related lung disease should be kept in mind and obtaining detailed anamnesis (medical records) in this respect, is essential.

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