Fatal Interstitial Pneumonia as an Advers Reaction in Patient with Rheumatoid Arthritis: A Case Report

Romatoid Artritli Hastada İlacın Etkisiyle Fatal Intersitisyel Pnömoni: Olgu Sunumu

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Abstract

Acute interstitial pneumonia developed three weeks after the administration of leflunomide(LEF) in a 53-year-old woman with rheumatoid arthritis. She developed nausea and diarrhea as well as dyspnea before coming to the hospital and LEF treatment was stopped. She suddenly experienced severe dyspnea and her chest x-ray showed reticular shadows in her lower lung fields which had not been detected before. Partial oxygen pressure of her arterial blood fell all of a sudden, which necessitated an emergency admission to the intensive care unit. After endotracheal intubation, mechanical ventilation support was started due to acute respiratory failure. The patient died of respiratory failure 7 days after the onset of acute interstitial pneumonia *(Rheumatism 2008; 23: 103-5)*

Key words: Interstitial pneumonia, rheumatoid arthritis

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Özet

Romatoid artritli 53 yaşındaki kadın hastaya leflunomide verilmesinden 3 hafta sonar akut interstisyel pnömoni gelişti. Bulantı, diare ve dispne gelişen hastada LEF tedavisi kesildi. Hasta şiddetli dispnesi ve akciğer grafisinde retiküler görüntülerin ortaya çıkması ve arteryel parsiyel oksijen basıncının düşmesi üzerine acilen yoğun bakım ünitesine alındı. Akut respiratuar yetmezlik nedeniyle endotrakeal entubasyon ve mekanik ventilasyon desteğine başlandı. Hasta interstisyel pnömoni başlangıcından 7 gün sonra respiratuar yetmezliğe bağlı kaybedildi. *(Rheumatism 2008; 23: 103-5)*

Anahtar sözcükler: Intertisyel pnomoni, romatoid artrit

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease of multifactorial etiology. The disease mainly affects the joints, but other organ systems can also be involved. RA produces a wide variety of intrathoracic lesions, including pleural diseases, rheumatoid nodules, diffuse interstitial pneumonia, pulmonary vasculitis, and airway disease that includes bronchiectasis, bronchiolitis obliterans, and follicular bronchiolitis(1). RA is a heterogenous disease with an unpredictable course, varying from mild to severe disabling (2). The treatment of RA has been evolved over last decades. Every new drug added to the therapeutic armamentarium has significantly improved the outcome of the disease (2). However, RA is still associated with an excess mortality of about 25%. Various second-line or disease-modifying antirheumatic drugs (DMARDs) have been used over the last 50 years to provide symptomatic relief, reduce disease activity and disability, and to prevent radiological progression. All of these drugs show significant toxicity, such that their use requires regular monitoring, although, there is disagreement as to the exact nature and duration of monitoring required. Monitoring schedules have significant cost and resource implications (3). Many rheumatologists believe that if a patient has been taking a DMARD at stable dosage for a long period of time, then the risk of toxicity is likely to be low, and hence monitoring need not be as rigorous (4,5).

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Recently, a new DMARD, leflunomide (LEF), and new class of drugs the biologics (mainly the tumor necrosis factor-blocking agents) have become available for the treatment of RA (3-5). These drugs have proved very efficacious and, together with more aggressive treatment strategy, have had an important impact on outcome of patients with RA (2). LEF inhibits dehydroorotate dehydrogenase, a key enzyme of pirimidine synthesis in activated lymphocytes of RA and to retard structural damage of pulmonary complications, although interstitial lung disease (ILD) is one the very rare side effects reported in the Summary Product Characteristics (7).

We here report the case of a patient with RA who died due to either advers reaction of drugs or lung involvement causing by RA.

Case Report

A 53-year-old female patient with RA acutely developed high fever, dyspnea, cough, 3 weeks after the administration of leflunomide. The Patient had suffered from polyarthritis in january 2005, beginning from her bilateral wrist and proximal interphalengeal and metacarpophalengeal joints. It exacerbated to include bilateral her knees by April. She had morning stiffness lasting more than 1 hour and positive rheumatoid factor (103.4µ/ml). The patient was diagnosed RA according to American College of Rheumatology criteria. She had been given MTX 7.5mg/week. The patient had irregularly took prednizolon since february 2005. Because her arthritis symptoms were aggravated, LEF was prescribed on April 2.2005. An initial dose of 100 mg/day was given for three days followed by 20 mg/day thereafter.

She developed nausea and diarrhea as well as dyspnea before coming to the hospital and 3 weeks after LEF administration and it was immediately withdrawn Two days after LEF cessation, she suddenly experienced severe dyspnea and her chest x-ray showed reticular shadow in her lower lung fields which had not been detected before. Partial oxygen pressure of her arterial blood fell all of a sudden, which necessitated an emergency admission to intensive care unit. After endotracheal intubation, mechanical ventilation support was started due to acute respiratory failure.

She was 157 cm tall and weighed 75 kg. Vital signs were as follows: blood pressure 70/45 mm/Hg and pulse rate 126/min regular, respiratory rate 32/min and body temperature 390 C. Heart sound was normal. Fine crackles were heard over her lower lung fields. We did not detect abnormal findings in neurological examination. The patient had pain, swelling and tendernes in all of her joints predominantly metacarpophalangeal, proxymal interphalangeal, wrist and knee.

Laboratory data were summarized in Table 1. Serum levels of CRP, and erythrocyte sedimentation rate were elevated. Chest roentgenogram revealed reticulo-nodular shadow in her lower lung fields. She didn't have abnormal findings in electrocardiogram and echocardiogram excluding tachycardia. Diffusion capacity was decreased in her respiratory function test. Bacteriological tests of blood were negative. She became more unconscious day by day.

To treat acute interstitial pneumonia, pulse glucocorticoid therapy was started with 1g/day of methyilprednisolne for 3 days followed by 60 mg/day of prednisolone. Cholestyramine was administered per os, although serum levels of LEF cannot be measure. Sulfamethoxazole-trimethoprim compound was prescribed to the patient for the possibility of pneumocystis carinii infection. The patient's condition continued to deteriorate. She died of respiratory failure due to acute interstitial pneumonia on the seventh day of hospitalization.

Table 1. Laboratory Data on Admission to ICU

Features (normal range)	Measured value
White blood cell count (4.4-11.3) K/UL	12.6
Hemoglobin (12.3-15.3)g/dl	11.8
Hematocrit (37.7-53.7) %	35.3
Platelet (142-424) K/UL	223
Total protein (6.40-8.30)g/dl	6.7
Albumın (3.5-5.5)g/dl	3.5
Aspartate aminotransferase (10-40)U/L	15
Alanine aminotransferase (10-35)U/L	41
Lactate dehydrogenase (100-190) U/L	745
Alkaline phosphatase (53-128) U/L	44
Creatine phosphokinase (38-174) U/L	73
Urea (0-50) mg/dl Serum creatinine (0.70-150)mg/dl	29.46 0.91
C-reaktive protein (0.00-5.00)mg/dl	210.85
Sedimentation (8-15) mm	76
Plasma glucose (70-105) mg/dl	114.22
Rheumatoid factor (0-20) IU/ml	103.4
Blood gase analyses PO_2 (83-108)	44.7
Blood gase analyses PCO_2 (32-48)	31.4
Blood gase analyses pH (7.35-7.45)	7.473
Blood gase analyses HCO3 (22-26)	24
Blood gase analyses BEc mmol/L	-0.5

Discussion

RA can be associated with various pulmonary abnormalities, including pulmonary fibrosis, pleural disease, lung nodules, bronchiolitis obliterans with or without organizing pneumonia and pulmonary vasculitis. Although some of these pulmonary disorders are benign and asymptomatic, the development of fibrotic lung disease is notable because it is one of the leading causes of death in these patients irrespective of therapy (8). The clinical features of lung involvement in RA are nonspecific and may develop subacutely over weeks to

months (8). In this case, the rapid development of respiratory failure was not compatible with lung involvement in RA.

A second problem is that pulmonary adverse effects have been attributed to a range of DMARDs. Interstitial pneumonia as an adverse reaction of leflenomide is rare and the incidence of such causes is reported to be 0.02% in western countries. In both the phase II clinical trials with 256 patients enrolled and the long term clinical trials with 110 patients, no such cases were reported (9). According to the website of the company, 45 cases (1.1%) developed acute interstitial pneumonia probably related to LEF (10). On the other hand, MTX pneumonitis an adverse effect of MTX, is unpredictable and may become lifethreatening (6). MTX-induced pulmonary injury is a relatively uncommon complication, with a reported incidence of about 3% to 5.5% of patients treated with MTX. The patient was prescribed the combination therapy including MTX, LEF and corticosteroid. The sings of interstitial pneumonia due to MTX and LEF are similiar (9,11). Clinical features in the disease included fever, nonproductive, cough, dyspnea and tachypne. Therefore, it is difficult to make differential diagnosis accurately in this case. In a case-control study, Alarkon et al. (12) found that the strongest predictors of MTX lung injury were older age, diabetes, rheumatoid pleuropulmonary involvement, previous use of DMARDs, and hypoalbuminemia. In this case there was not any of these risk factors. Furthermore, the majority of patients with MTX pneumonitis recover rapidly after adequate steroid treatment (6). This patient didn't recover in spite of steroid treatment. Therefore, we think that interstitial pneumonia in our patient can be related with LEF. It is possible that, the administration of MTX and LEF combination cause interstital pneumonia in this case. The combination of two antimetabolic agent can be used effectively and safely with careful monitoring (13). It represents a logical alternative for patients who have an incomplete response to monotherapy with maximally tolerated weekly doses of MTX (13). Nevertheless, before the initiating LEF or MTX treatment particularly combination of, the patient must be carefully evaluated with respect to pulmonary involvement of RA.

Leflonomide is absorbed and rapidly converted to A77-1726; peak levels occur between 6-12 hours. The active metabolite, A77-1726, has a long half-life of approximately 15 days (14). LEF can be removed using cholestyramine, 8 g 3 times daily for 11 days. In this case, interstitial pneumonia continued deteriorating even after cholestyramine administration, but serum LEF concentration could not be measured.

We think that, it would be needed to increase the dose of MTX instead of adding LEF to treat the patient. However, we did not arrange treatment of the patient. There has been a growing trend toward early, aggressive treatment of RA with DMARDs. LEF has been shown to reduce signs and symptoms of RA and retard structural damage (7). Clinical trials do not suggest that LEF causes an excess of pulmonary complications, although interstitial lung disease is very rare side effect reported in the Summery of Product Characteristics (7). Among the rare adverse events, fatal interstitial lung disease has been reported during treatment with LEF for RA in Japan (9). In the same way, we have reported the patient with fatal interstitial lung disease by induced LEF. However, both of two patients have been prescribed combination of MTX and LEF. Unlike MTX, interstitial pneumonia as an adverse reaction of LEF was not emphasized because of its low frequency (9). We think that further investigation should be carried out in respect of pulmonary adverse action of LEF, particularly combination with other drugs.

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