

Diffuse alveolar damage in a patient with rheumatoid arthritis under prolonged leflunomide treatment

A Case Report and Literature Review

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Abstract

Patients with rheumatoid arthritis (RA) often have pulmonary involvement, and interstitial lung disease (ILD) is the primary manifestation, in which diffuse alveolar damage (DAD) is a rare histopathologic pattern. Leflunomide (LEF) is a frequently prescribed disease-modifying antirheumatic drug for treating RA. LEF-related ILD in the form of DAD has been reported in patients with RA, with the duration of LEF treatment before symptom onset ranging from 6 to 1204 days.

We present a case of elderly woman with RA under prolonged LEF treatment for >9 years (3291 days), who had acute respiratory failure with the initial presentation of exertional dyspnea, fever, chills, and productive cough for 2 days. The histopathologic result of surgical lung biopsy was compatible with DAD. She was diagnosed as having LEF-related ILD, based on correlated clinical history, compatible histopathologic examination and excluding possible infection after extensive survey.

Although the causative role of LEF cannot be confirmed, this case still hints that LEF-related DAD may occur even if LEF has been prescribed for a prolonged period.

Abbreviation: DAD = diffuse alveolar damage, ILD = interstitial lung disease, LEF = leflunomide, MTX = methotrexate, RA = rheumatoid arthritis.

Keywords: diffuse alveolar damage, interstitial lung disease, leflunomide, rheumatoid arthritis

1. Introduction

Leflunomide (LEF) is a disease-modifying antirheumatic drug for treating rheumatoid arthritis (RA). Its efficacy was established by double-blind, randomized controlled trials.^[1,2] A 5-year follow-up study demonstrated comparative safety profile as in the phase III trial, showing no excessive pulmonary adverse event.^[3] However, LEF-related interstitial lung disease (ILD) was increasingly reported after introduction of LEF in Japan in 2003, and diffuse alveolar damage (DAD) was the principal histopathological change in autopsied cases.^[1] Here we report a

patient with RA who developed ILD after prolonged LEF treatment.

2. Case report

An 80-year-old Taiwanese woman was admitted to our hospital because of shortness of breath. Her medical history was notable for remote pulmonary tuberculosis, which had been cured for 5 years and RA, which had been diagnosed for 11 years. Follow-up chest radiograph taken 2 years earlier showed mild fibrocalcified lesion in right upper lung zone without obvious interstitial changes. She was a nonsmoker and her current medication included oral prednisolone (10 mg/day), cyclosporine (100 mg/day), and LEF (20 mg/day). Methotrexate (MTX) (7.5 mg/week) was prescribed initially after the diagnosis of RA. Due to poor disease control, MTX was replaced with LEF 10 years ago. Her arthralgias remained stable after regimen modification. She had been in her usual state of health until 2 days before admission, when progressive dyspnea on exertion developed, along with productive cough, fever, and chills.

At admission, her vital signs were: temperature 37.3 °C, heart rate 110 beats/min, blood pressure 147/89 mm Hg, respiratory rate 28 breaths/min, and oxygen saturation 95% while breathing supplementary oxygenation at a rate of 10 L/min through a face mask. She was conscious and oriented. Lung auscultation revealed bilateral diffuse crackles. Cardiac examination revealed regular tachycardia, with no murmurs. The remainder of the examination was otherwise unremarkable. Laboratory examinations showed normal leukocyte count (5110/μL), elevated blood urea nitrogen (57 mg/dL), creatinine (1.6 mg/dL), aspartate

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The informed consent was obtained from the patient's next of kin.

The authors have no conflicts of interest to disclose.

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Figure 1. Chest radiograph at admission showed patchy opacities with reticulation in bilateral lower lungs.

aminotransferase (93 U/L), C-reactive protein level (11.7 mg/dL), and mildly increased rheumatoid factor level (44 IU/mL) (normal range, 0–20.1 IU/mL). Chest radiograph at admission (Fig. 1) showed patchy opacities with reticulation in bilateral lower lungs. She was intubated with ventilator support on Day 2 for acute hypoxic respiratory failure. A high-resolution computed tomography of the chest on Day 3 (Fig. 2A) showed diffuse ground-glass opacities with thickened interlobular septa and patchy consolidations at bilateral lower lobes.

Besides empirical intravenous ceftriaxone (2000 mg/d) and levofloxacin (750 mg/d) for presumed severe community acquired pneumonia, intravenous trimethoprim/sulfamethoxazole (trimethoprim component 15 mg/kg/d), and methylprednisolone (60 mg/d) were administered for suspicious *Pneumocystis jirovecii* pneumonia and RA-associated ILD. Cultures of blood, tracheal aspirate, and bronchoalveolar lavage fluid revealed no evidence of bacteria, fungus, or mycobacterium infection. The results of rapid influenza diagnostic test and cytomegalovirus antigenemia assay were both negative. A follow-up high-resolution computed tomography of the chest on Day 16 (Fig. 2B) showed persistent diffuse bilateral ground-glass opacities and interlobular thickening without improvement. Due to poor treatment response, she received thoracoscopic wedge resection of the right upper and middle lung on Day 18. The pathology examination revealed DAD in the acute exudative stage. Microscopically, the airspaces were lined by hyaline membranes, with thickened alveolar septa containing inflammatory exudates, but no obvious fibrotic change. There was no evidence of *Pneumocystis jirovecii*, cytomegalovirus, or other microbial infection (Fig. 3). Her condition deteriorated and she died of superimposed vancomycin-resistant enterococcal bacteremia and septic shock on Day 24.

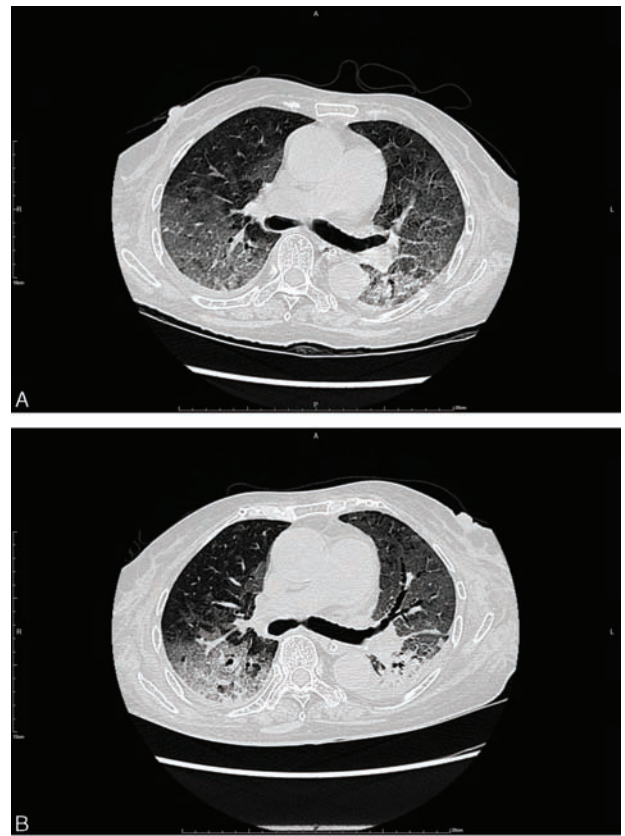


Figure 2. HRCT of the chest on Day 3 (A) showed diffuse ground-glass opacities with thickened interlobular septa, accompanied by patchy consolidations at bilateral lower lobes. A follow-up HRCT of the chest on Day 16 (B) showed persistent diffuse bilateral ground-glass opacities and interlobular thickening without improvement. HRCT, high-resolution computed tomography.

3. Discussion

Patients with RA often have pulmonary involvement, and ILD is the primary manifestation.¹⁴ Besides the underlying RA-associated ILD, the other differential diagnoses include opportunistic infection such as *Pneumocystis jirovecii* or cytomegalovirus

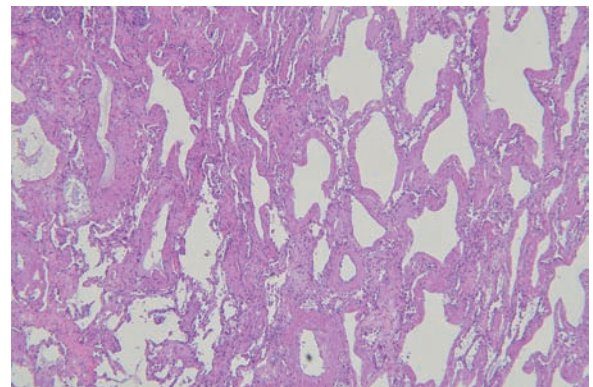


Figure 3. Microscopic examination of the lung (hematoxylin and eosin stain, 40×) revealed the airspaces lined by hyaline membranes, with thickened alveolar septa containing inflammatory exudates, compatible with diffuse alveolar damage in the acute exudative stage. There was no obvious fibrosis or evidence of microbial infection.

infection due to immunosuppressive therapy or drug-induced lung disease by disease-modifying antirheumatic drugs or biologic agent.^[5] In our case, the ILD may be related with LEF, after excluding possible infectious causes and underlying RA-associated ILD.

The prevalence of RA-associated ILD varies according to the different diagnostic modalities and is 19% to 56% by the use of high-resolution computed tomography of the chest, which correlates with the histopathological patterns.^[5] Lee et al found that usual interstitial pneumonia pattern is the most frequent histopathological pattern in patients with RA-associated ILD (56%), followed by nonspecific interstitial pneumonia (33%) and organizing pneumonia (11%).^[6] When a total of 56 patients were reviewed from 4 studies, the histopathological patterns included usual interstitial pneumonia pattern in 34 patients, nonspecific interstitial pneumonia in 21 and lymphocytic interstitial pneumonia in another one, with no DAD pattern was identified.^[6-9] Parambil et al^[10] found 5 patients with RA had DAD on surgical lung biopsy during a 7-year period from 1996 to 2002 at Mayo Clinic, but 1 patient was confounded by LEF treatment. To date, DAD is still a rare histopathological pattern in RA-associated ILD, and the DAD pattern seen in our patient is less likely due to the underlying RA-associated ILD.

LEF is an isoxazole immunomodulatory agent that inhibits dihydroorotate dehydrogenase and thus de novo pyrimidine synthesis after being metabolized to its active metabolite A771726, which has a half-life of 2 weeks.^[11] LEF was launched in the USA in 1998 and in Europe the following year as a disease-modifying antirheumatic drug and approved by Japanese government for treatment of RA in April 2003.^[12] Although ILD was rarely reported as a complication of LEF usage worldwide (0.02%), post-marketing surveillance in Japan revealed that, during the first few months after approval, 16 patients developed de novo or exacerbated ILD, 9 of whom died.^[13] Case reports in Japan were published successively, and DAD was the histopathological pattern in 2 autopsied cases.^[12,14,15]

After that, the Study Committee for Leflunomide-Induced Lung Injury organized by the Japan College of Rheumatology analyzed the data of post-marketing surveillance obtained from Sanofi-Aventis Japan.^[16-18] During the period from September 2003 to June 2006, 61 (1.2%) of 5054 RA patient receiving LEF were reported to have developed ILD. The duration of LEF usage before symptom onset was 138.1 ± 174.7 (6–1204) days.^[16] Cholestyramine wash-out therapy, given orally at 8 g 3 times a day, can reduce plasma level by ~40% in 24 hours, and to undetectable plasma levels in 11 days.^[19] Multivariable logistic regression analysis identified pre-existing ILD, cigarette smoking, a low body weight (<40 kg vs >50 kg) and the use of a loading dose as independent risk factors for LEF-related ILD, among which pre-existing ILD was the most important one.^[17] A Canadian nested case-control study showed that LEF increased the risk of ILD, but the effect was restricted in subjects with previous MTX use or pre-existing ILD.^[20] Patients with a fatal outcome were more likely to have pre-existing ILD, extremely high serum C-reactive protein and low albumin levels, severe hypoxemia and mechanical ventilation and persistent blood lymphopenia throughout the course.^[18] Based on the findings, the Study Committee for Leflunomide-Induced Lung Injury proposes that LEF should not be used in patients with pre-existing ILD and a loading dose is not recommended.^[16]

In vitro studies showed LEF could induce epithelial-mesenchymal transition of mouse pulmonary epithelial cell, which subsequently promoted pulmonary fibrosis. The phenomenon occurs in the presence of other fibrosis-inducing stimuli such as bleomycin but does not do this in the absence of these stimuli.^[21] This may explain why previous MTX use or pre-existing ILD is a risk factor for LEF-related ILD. Outside Japan, cases of LEF-related ILD were reported in Korea, Canada, New Zealand, and Australia with similar higher prevalence rate in Korea (10/1010 = 1%) than in other countries.^[20,22,23] Thus, racial or genetic difference may further predispose the development of LEF-related ILD, and Taiwanese RA patients may also have higher risk due to similar racial and genetic background.

In Taiwan, LEF was licensed in September 2003 for the treatment of MTX-unresponsive or MTX-intolerable RA patients. Theoretically, LEF is more likely to be prescribed in RA patients with previous MTX use or pre-existing ILD (to avoid MTX exposure), who then have increasing risk for LEF-induced ILD. In our patient, LEF may be a potential cause of DAD, supported by the history of previous MTX exposure, lack of infection evidence after extensive survey, and DAD pattern on pathological examination. However, due to prolonged LEF treatment (3291 days), the causative role of LEF in DAD in our patient cannot be confirmed. Nevertheless, our case still hints that LEF-related DAD may occur even if LEF has been prescribed for a prolonged period. When acute ILD develops in a RA patient, surgical lung biopsy may be needed early in the course to help diagnosis and prognosis.

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