Case Report

Leflunomide Induced Acute Interstitial Pneumonia

MICHIO TAKEISHI, YUJI AKIYAMA, HARUHIKO AKIBA, DAISUKE ADACHI, MOTOHARU HIRANO, and TOSHIHIDE MIMURA

ABSTRACT. We describe a 54-year-old woman with rheumatoid arthritis (RA), who developed acute respiratory failure 2 weeks after cessation of 6-week treatment with leflunomide. We diagnosed interstitial pneumonia, probably induced by leflunomide because acute respiratory failure was preceded by elevated serum liver enzyme concentration and hypertension. She showed dramatic improvement with prednisolone and cholestyramine. Prompt treatment may improve the prognosis. In Japan, leflunomide has been implicated as a possible cause to initiate or exacerbate interstitial pneumonia in patients with RA according to postmarketing surveillance. Clinicians should exclude pulmonary disease prior to initiating leflunomide treatment in patients with RA on the basis of a thorough history and physical examination, and chest radiograph. (J Rheumatol 2005;32:1160–3)

Key Indexing Terms:
LEFLUNOMIDE
RHEUMATOID ARTHRITIS
INTERSTITIAL PNEUMONIA
CHOLESTYRAMINE

Leflunomide (LEF) is a newly developed immunoregulatory drug that inhibits the enzyme dihydroorotate dehydrogenase, responsible for the *de novo* synthesis of pyrimidine-containing ribonucleotides[1]. LEF was launched in the USA in 1998 and in Europe the following year, and is now available in 72 countries. A number of clinical trials have evaluated the efficacy and safety of LEF in patients with rheumatoid arthritis (RA)[2-7]. The common adverse events reported are nausea, diarrhea, headache, abnormalities of liver enzymes, rash, alopecia, respiratory infections, and hypertension[8-10]. The available evidence suggests LEF was unlikely to lead to more frequent lung problems. In September 2003 LEF was registered in Japan for treatment of active RA. Soon after, pulmonary adverse effects, sometimes fatal, were reported in some patients who had been prescribed the drug. We describe the first known case of a patient with RA who developed acute interstitial pneumonia (IP), probably induced by LEF, and was successfully treated with prednisolone and cholestyramine.

CASE REPORT

A 54-year-old Japanese woman with seropositive, destructive RA of 12 years' duration was transferred to our hospital because of acute onset of dyspnea with fever and headache on February 18, 2004. She had been seen by a rheumatologist in the local hospital, and failed to respond to multiple disease modifying antirheumatic drugs (DMARD). A LEF loading dose of 100 mg/day for 3 days, followed by a maintenance dose 20 mg/day, was administered on December 22, 2003. She received 6 weeks of LEF therapy, with a dramatic improvement in synovitis and marked fall in C-reactive protein (CRP). At that time, concerns had been expressed over deaths from IP among the RA patients who had been prescribed LEF in Japan. Aventis Pharma Japan advised physicians not to prescribe LEF to patients with IP or pulmonary fibrosis, and to cease treatment in those developing cough or other respiratory ailments. This patient had already had slight fibrosis in the bilateral lower lungs on chest radiographs before LEF therapy. LEF was stopped February 2, 2004, although she showed no respiratory tract symptoms. Two weeks later she was still in good health. On February 17, 15 days after cessation of LEF, she started complaining of general dullness, headache, and fever. Over the next 24 hours, she developed nonproductive cough and dyspnea, and was transferred to our hospital on February 18.

On admission, her temperature was 37.4°C, pulse was 96/min; blood pressure was 186/98 mm Hg. The oxygen saturation was 94.7% while she was breathing O_2 3l/min with nasal cannulation. On examination, she had mild dyspnea, and breath sounds were mildly and symmetrically diminished; fine crackling sounds were audible in both lung fields. A chest radiograph revealed diffuse patchy opacities in both lungs and chest computed tomography (CT) scans revealed subpleural interstitial reticular patterns and superimposed ground-glass opacities, which were most prominent in the bilateral lower lungs (Figure 1A, 1B). Blood gas analysis at the same condition showed PaO_2 76.8 mm Hg, $PaCO_2$ 32.9 mm Hg, and oxygen saturation 94.7%. White blood cell and lymphocyte counts were 5040/μl and 630/μl, respectively. Serum AST (90 IU/l), ALT (86 IU/l), ALP (586 IU/l), γ-guanosine triphosphate (77 IU/l), and KL-6 (1310 EU) were elevated. No abnormal immunologic indicators were observed except for CRP 12.79 mg/dl, erythrocyte sedimentation rate (ESR) 121 mm/h, CA-RF 19.9 AU/ml, and CH50 80.7 U/ml. Influenza virus antigen, beta-1,3-D glucan, and cytomegalovirus antigenemia assay were all negative.

Considering these physical and laboratory findings, we made a diagnosis of LEF induced IP. Administration of prednisolone 40 mg/day was initiated with cholestyramine at 24 g/day on the first hospital day. No medication for infection was administered. After starting prednisolone and cholestyramine, hypoxemia and headache improved significantly, and on the fourth hospital day the oxygen saturation normalized without oxygen administration. The serum ALT concentration improved gradually and

From the Division of Rheumatology, Saitama Medical School, Saitama, Japan.

M. Takeishi, MD; Y. Akiyama, MD; H. Akiba, MD; D. Adachi, MD; M. Hirano, MD; T. Mimura, MD, Professor, Division of Rheumatology.

Address reprint requests to Dr. M. Takeishi, Division of Rheumatology, Saitama Medical School, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama, 350-0495, Japan. E-mail: mtakeish@saitama-med.ac.jp

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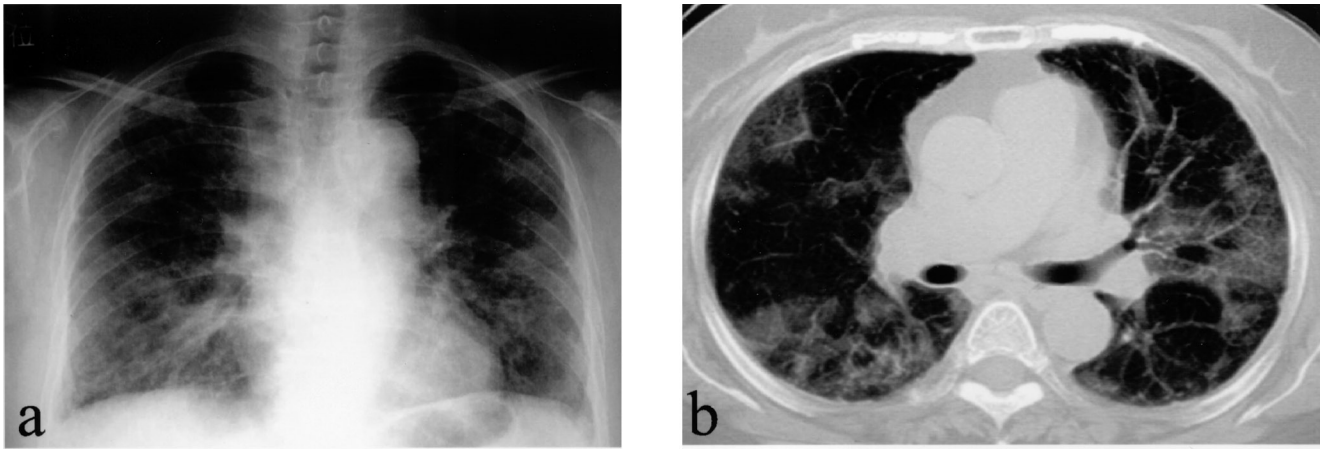

Figure 1. Chest radiograph (A) and CT on admission (B). Radiograph reveals diffuse patchy opacities in both lungs, and CT scan shows subpleural interstitial reticular patterns and superimposed ground-glass opacities, which were most prominent in the lower lungs.

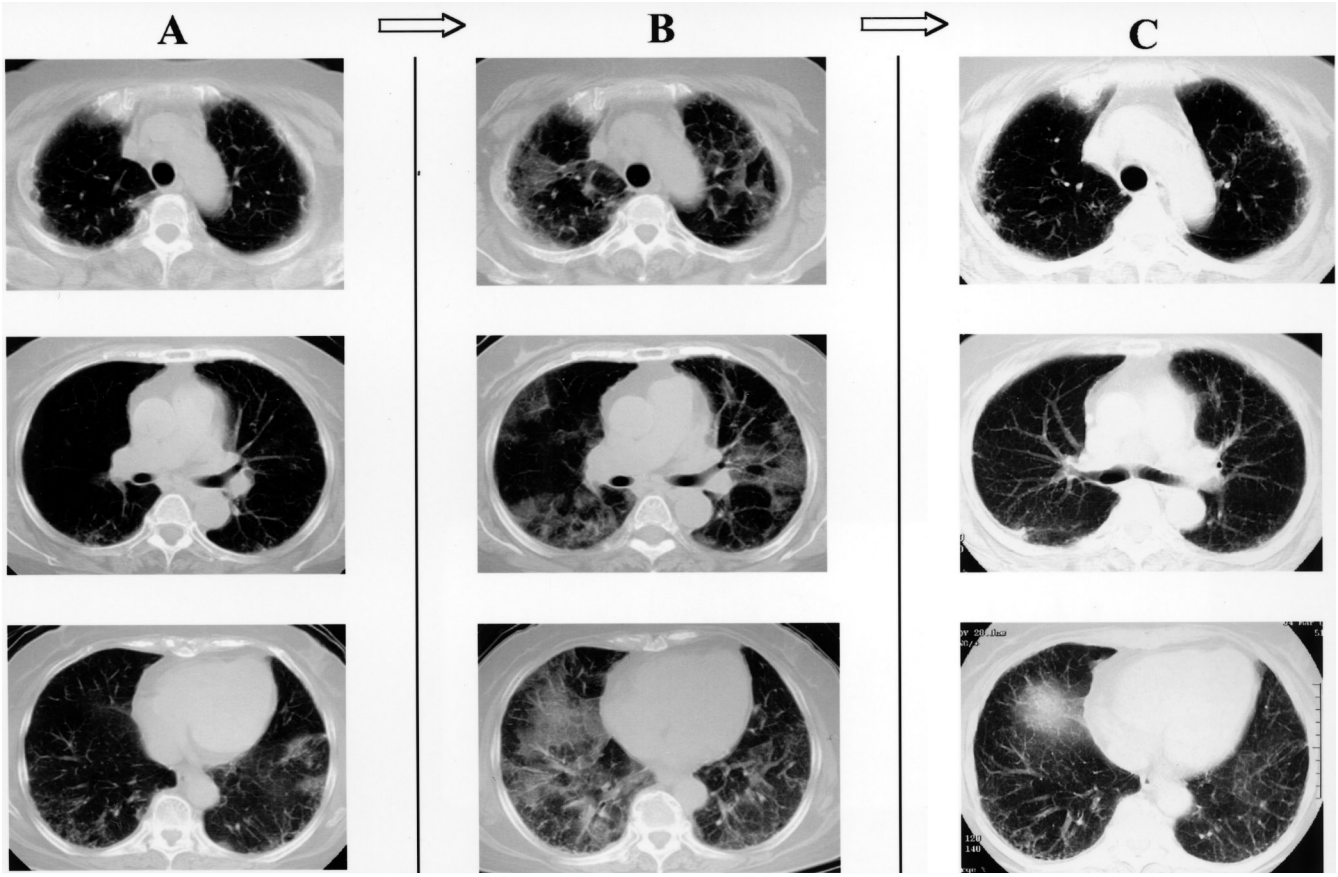

Figure 2. Chest CT findings: A, when LEF was stopped, February 2, 2004; B, on admission, February 18, 2004; C, on discharge March 5, 2004.

became normal on the 14th hospital day. The chest CT findings improved (Figure 2). Prednisolone was tapered to 30 mg daily, and she was discharged (Figure 3).

DISCUSSION

The most common extraarticular manifestation of RA is interstitial lung disease, which is often asymptomatic and becomes symptomatic later in its course when fibrosis is present[11,12]. Occasionally, we encounter cases of acute progressive IP among patients with RA. Because the treatment is completely different, it is important to make an accurate diagnosis to differentiate whether the lung infiltrate is due to a drug reaction such as a methotrexate induced hypersensi-

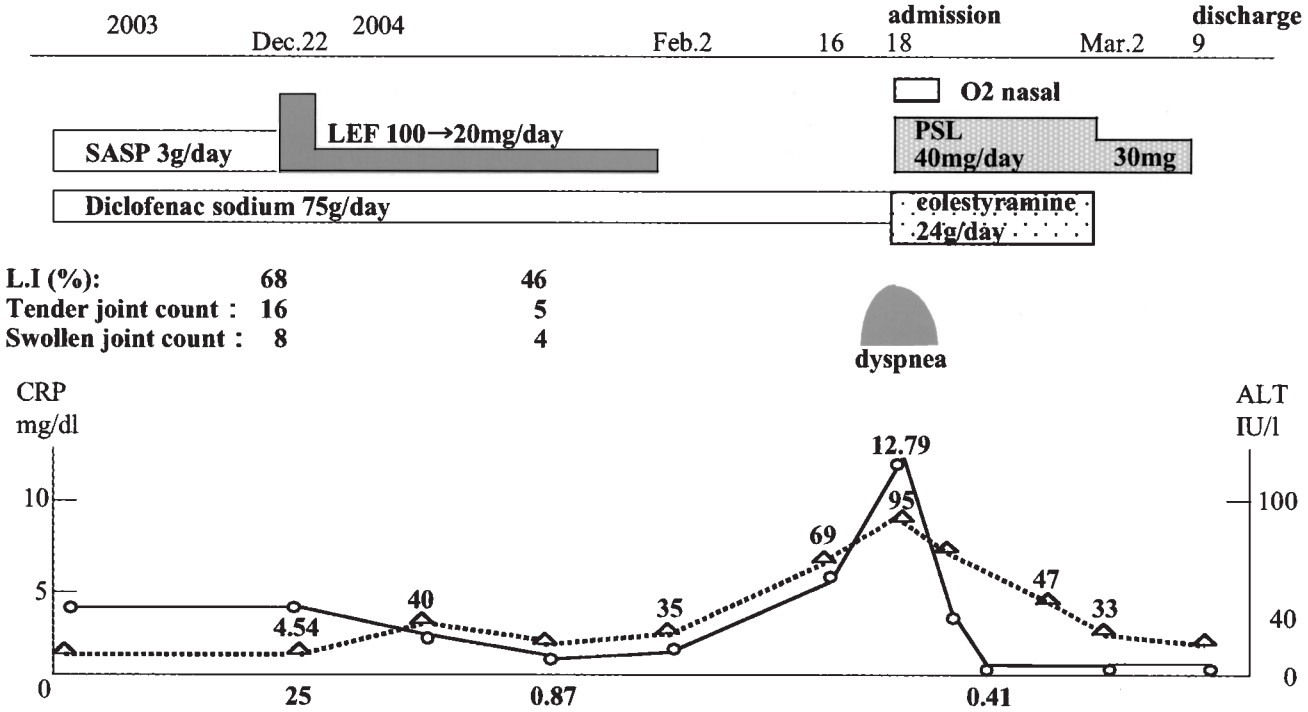

Figure 3. The patient's clinical course. SASP: salazosulfapyridine; LEF: leflunomide; PSL: prednisolone; LI: Lansbury Index.

tivity pneumonitis[13], opportunistic exogenous infections such as *Pneumocystis carinii* pneumonia[14], or underlying rheumatoid associated lung disease. Nevertheless, this differentiation can be difficult because RA patients receive many DMARD, often in combination, and because some of them are immune-compromised. The disease may be fatal unless accurate treatment is started promptly.

LEF is a prodrug that is almost completely converted into its active metabolite, A77 1726, through first-pass metabolism in the gut wall and the liver, and A77 1726 is a highly protein-bound component in plasma. It is important to note that its half-life is about 15 days in humans[15]. In our patient, the concentration of plasma A77 1726 was still 50,183.61 ng/ml on admission, 2 weeks after the cessation of LEF. The liver damage that is the most common adverse event associated with this drug was preceded by acute dyspnea. There were no abnormalities in infection markers such as beta-1,3-D glucan and cytomegalovirus antigenemia. The acute IP responded promptly to corticosteroid and cholestyramine, a drug known to interfere with the enterohepatic cycle of LEF. No other medications were administered. These findings strongly suggest LEF induced IP occurred in our patient. Upon reviewing the chest CT films taken on February 2, 2004, when LEF was discontinued, the slight patchy opacities in the left lower lung are evident (Figure 2). This additional minimal pulmonary involvement, detected only by the CT image, had occurred 2 weeks before the onset of dyspnea. Continuation of LEF would have led to a fatal outcome in this case.

LEF was launched in the USA in 1998, and has been prescribed for 400,000 people in 72 countries. The efficacy and safety experience of LEF has been reported[2-7]. Common adverse effects associated with LEF treatment are diarrhea, nausea, abdominal pain, alopecia, liver enzyme abnormalities, rash, and hypertension[8-10]. Unlike methotrexate, which may cause hypersensitivity pneumonitis in 0.7% to 7.0% of patients[16], LEF was believed not to be associated with pulmonary toxicity[5,7].

The approval of LEF by the Ministry of Health and Labor in Japan in April 2003 was followed by its registration for treating active RA in September 2003. Unexpectedly, deaths from IP probably associated with LEF were reported one after another within a few months after the drug became available in Japan. Of the 400,000 people given the drug, 80 have developed IP, but no deaths had been reported overseas until the cases in Japan. These events raised concerns about the adverse respiratory effects of LEF[17,18]. From September 12, 2003, to January 30, 2004, of the 3470 persons taking the drug in Japan, 18 developed IP; 12 of the 18 had already had lung diseases when they started taking LEF, and 6 died. Although there has been no confirmation that the drug was responsible for the deaths, the pharmaceutical company stated that doctors should not prescribe LEF to RA patients with IP or pulmonary fibrosis, and should cease the treatment immediately in those who develop cough or other respiratory ailments in February 2004.

According to the recent postmarketing surveillance, by June 2004, among 4284 patients, 47 people with IP were

reported, and 22 died (with explanations including no causality 2 cases, cytomegalovirus pneumonia 1, sepsis 1, liver abscess 1, and disseminated intravascular coagulation 1 case). In our patient, plasma concentration of A77 1726 on admission was within mean (SD) steady-state levels[19]. These findings suggest that the mechanism of LEF induced IP is dependent not on dose, but on hypersensitivity, similarly to methotrexate. There are no accurate incidence data for LEF induced IP, since it is highly possible that some of the deaths include those by opportunistic exogenous infections such as *P. carinii* pneumonia or cytomegalovirus pneumonia. It is possible that Japanese people are predisposed in some way to the adverse pulmonary effect, because the incidence of LEF induced IP in Japan is significantly higher than elsewhere. There have been no reports of LEF induced IP since February 2004, when the manufacturer announced the precautions. This is partly explained by the fact that the number of patients starting treatment with LEF has decreased since the pulmonary adverse events were widely reported.

We have described a 54-year-old woman with RA who developed LEF induced IP. Longer followup and further postmarketing surveillance investigations are needed to define the incidence and the mechanism of LEF induced IP.

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