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CASE REPORT

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Leflunomide-related acute interstitial pneumonia in two patients with rheumatoid arthritis: autopsy findings with a mosaic pattern of acute and organizing diffuse alveolar damage

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Abstract We describe two cases of leflunomide-related interstitial pneumonia (IP). A 75-year-old woman with rheumatoid arthritis (RA) developed rapidly progressing IP 45 days after institution of leflunomide. She died of respiratory failure, and an autopsy revealed a mixed pattern of acute and organizing diffuse alveolar damage. A 69-year-old woman with RA also developed acute IP 3 months after institution of leflunomide. Methylprednisolone pulse therapy and cholestyramine ameliorated her IP. The implication of leflunomide in the pathogenesis of IP was suggested.

Key words Drug toxicity · Interstitial pneumonia (IP) · Leflunomide · Rheumatoid arthritis (RA)

Introduction

Leflunomide (Arava; Sanofi-Aventis, Paris, France), one of the newly developed disease-modifying antirheumatic drugs (DMARDs), interferes with the cell cycle of T cells by inhibiting mitochondrial dihydroorotate dehydrogenase (DHODH), an enzyme involved in de novo pyrimidine synthesis.[1] Randomized clinical trials demonstrated the efficacy and safety of leflunomide for the treatment of rheumatoid arthritis (RA).[2,3] Leflunomide was also found to successfully retard the joint destruction associated with RA.[4] These data have placed leflunomide as one of the major DMARDs in the strategy of treating patients with RA, especially those who are resistant or intolerant to methotrexate (MTX), in Western countries.[5,6] During these clinical trials, lung toxicity was found to be rare in the patients treated with the drug.[2–4] This observation led to preferential prescription of leflunomide to RA patients with interstitial pneumonia (IP)/pulmonary fibrosis,[7] which is an established risk factor for MTX-induced IP.[8]

In Japan, marketing of leflunomide was begun in October 2003. In January 2004, the Japanese Ministry of Health, Labour and Welfare cautioned that 16 patients who had been treated with the drug had developed interstitial pneumonia (IP) and that five of these patients died.[9] The drug manufacturer, Sanofi Aventis, has been conducting postmarketing surveillance for all the patients prescribed with leflunomide and has reported that, as of March 31, 2006, 80 of 5911 patients treated with leflunomide in Japan had developed IP. Twenty-seven (34%) of these patients died, and IP was judged to be the primary cause of death in at least 18 patients (http://safety.sanofi-aventis.co.jp/arava/aravad/index.html), which was much higher than the reported mortality rate of MTX-induced IP.[10] A recent population-based epidemiological study also demonstrated that the risk of IP was significantly increased with the use of leflunomide (adjusted relative risk 1.9 [95% confidence interval 1.1–3.6]).[7] One case report[11] and a report of imaging findings of 26 patients with leflunomide-related IP[12] have already been published, but there have been no prior reports of the pathological features of this condition. To gain a more precise understanding of leflunomide-related IP, the histopathological characteristics of affected lungs need to be examined. We report two cases of acute IP during treatment with leflunomide, one of whom died. The causal relationship between IP and leflunomide in these two cases as well as pharmacoepidemiological problems of this adverse drug reaction are discussed.

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Case reports

Case 1

A 75-year-old woman, who was diagnosed with RA and chronic IP in 1995, was treated sequentially with bucillamine, actarit, salazosulfapyridine, and MTX without favorable results. She was referred to the Tokyo Medical and Dental University Hospital (TMDU Hospital) and was admitted on October 30, 2003 for a complete examination. She exhibited bilateral active synovitis in her wrists, knees, ankles, and proximal interphalangeal and metacarpophalangeal joints. Fine crackles were heard in all lung fields. Laboratory examinations revealed an elevated erythrocyte sedimentation rate (ESR) (58 mm/h, normal range [NR] 3–15) and elevated serum levels of C-reactive protein (CRP) (0.6 mg/dl, NR < 0.3), matrix metalloproteinase-3 (MMP-3) (111 ng/ml, NR < 59.7) and rheumatoid factor (80 U/ml, NR < 20). Serum KL-6 levels, an indicator of IP,[13] were as high as 1290 U/ml (NR < 500). Respiratory function tests showed a normal %VC (98.7%) but decreased %DLco (79.1%). Arterial blood gas analysis was within normal range (PaO_2 80 torr; A-aDO_2 20.8 torr). On admission, computed tomography (CT) of the chest revealed increasing subpleural reticulolinear infiltration in the bilateral middle and lower lung fields, compared to the CT taken 2 months before (Fig. 1a). Gallium scintigraphy, also an indicator of IP,[14] showed an elevated pulmonary uptake. We diagnosed active IP and treated her with 40 mg/day of prednisolone (PSL). In addition, MTX was replaced by 20 mg/day of leflunomide with no loading dose. Six weeks after the initiation of this treatment, subpleural infiltration seen by chest CT was markedly improved (Fig. 1b), the serum KL-6 level was reduced to 767 U/ml, and her %DLco recovered to 96.7%. She was discharged on December 10, 2003, with almost complete remission of RA. On January 28, 2004, she complained of shortness of breath and was readmitted to TMDU Hospital. On the second admission, she exhibited a fever of 38°C, tachypnea (30 times/min) and cellulitis of her left lower leg, but no active synovitis. Chest auscultation revealed bilateral fine crackles in all lung fields. Hypoxia (PaO_2 65 torr at room air) and an elevated serum level of CRP (12.2 mg/dl) were also noted. Other laboratory findings included elevated serum KL-6 (723 U/ml) and Surfactant protein D (SP-D) (1369 ng/ml, NR < 110) levels. Respiratory function tests showed a decreased %VC (71.1 %). Chest X-rays and CT scans showed bilateral ground-glass opacity in the middle and lower lung fields, which differed greatly from findings of the chest CT on her first admission (Fig. 1c,d). Conventional bacterial examinations and polymerase chain reaction (PCR) assays for *Mycobacterium tuberculosis*, *Pneumocystis jiroveci*, and cytomegalovirus were all negative. Serum β-D-glucan level remained within normal range. The temporal relationship between the institution of leflunomide and the worsening IP without active arthritis, and the negative results of the bacteriological examinations suggested an association of the drug with IP. Cellulitis of her left lower leg responded well to the treatment with antibiotics. Methylprednisolone (methyl-PSL) pulse therapy (1000 mg/day, three consecutive days) was instituted on February 1, 2004, followed by 60 mg/day of PSL. The serum concentration of leflunomide was rapidly decreased from 5934 ng/ml to 148 ng/ml by plasma exchange and the administration of 24 g/day of cholestyramine. However, hypoxia and the infiltration on chest X-ray worsened

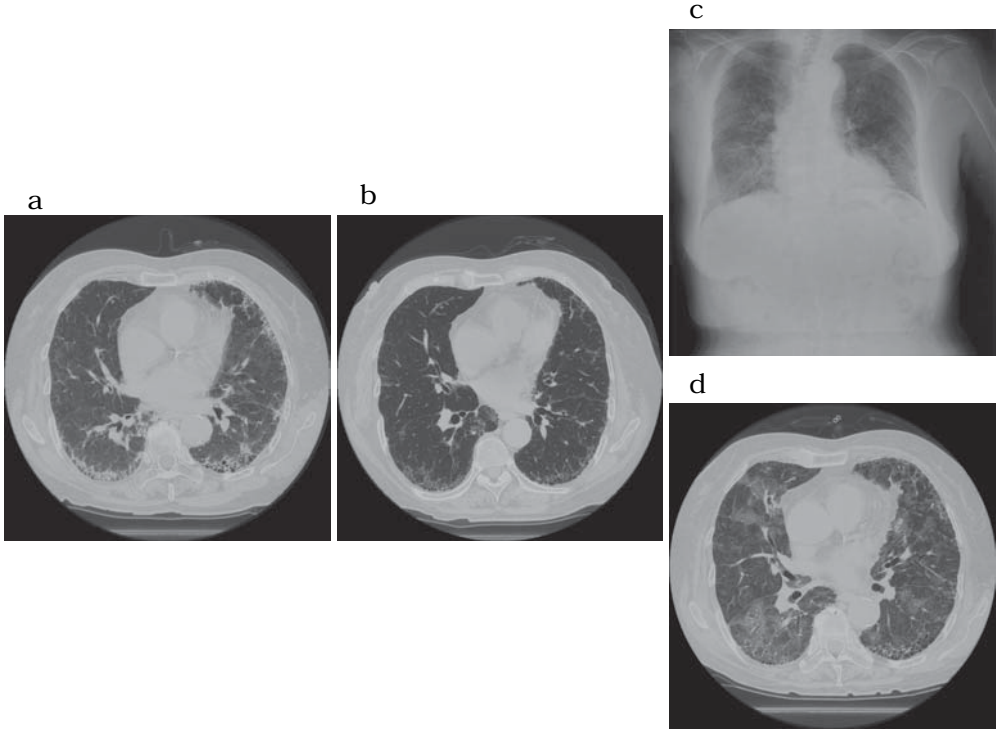

Fig. 1a–d. Radiographic findings in Case 1. A high-resolution computed tomography (CT) scan of the chest on first admission (**a**) showed subpleural reticulolinear densities in the middle and lower lung fields. Results of the chest CT scan markedly improved after treatment with 40 mg/day of prednisolone (**b**). At the second admission, a chest X-ray (**c**) and CT scan (**d**) showed ground-glass opacity in the middle and lower lung fields

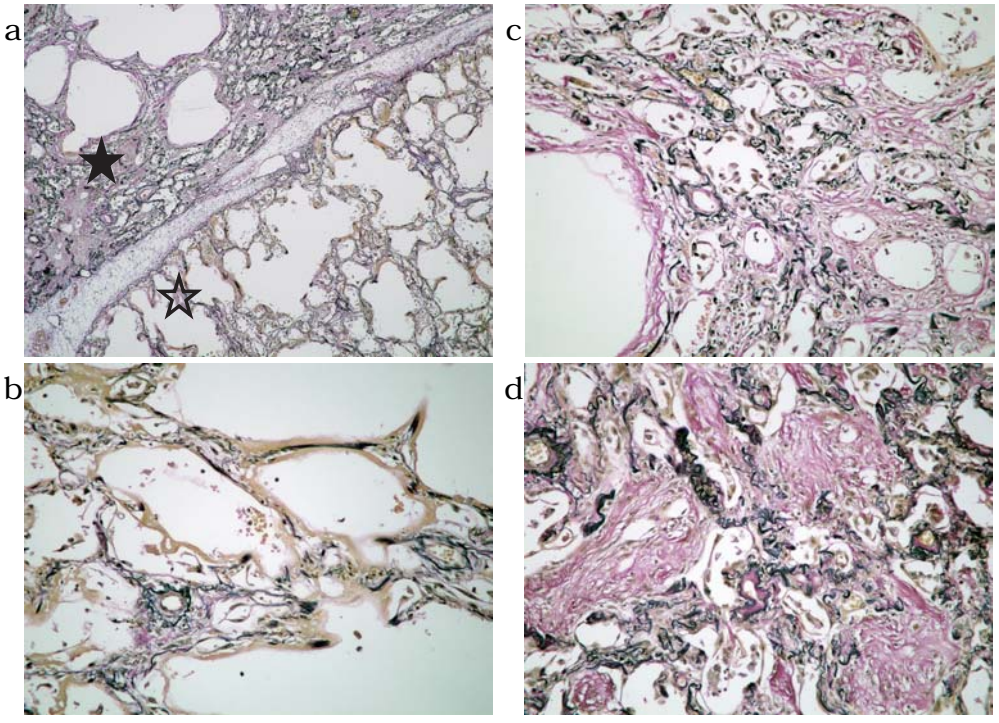

Fig. 2a–d. Microscopic appearance of the lung in Case 1 (Elastica van Gieson stain). **a** A low-power microscopic examination of the lung revealed a mixture of both acute (*open star*) and organizing (*closed star*) diffuse alveolar damage (DAD) pattern. **b** An acute DAD pattern; formation of a hyaline membrane was observed. **c** Chronic DAD pattern; hyaline membrane was replaced by fibrosis and organization. **d** Chronic organizing pneumonia (COP) pattern; intra-alveolar dense fibrosis formation in alveolar ducts was found

and the second methyl-PSL pulse therapy was performed after a week without any improvement of IP. The patient died from respiratory failure on the 46th day of hospitalization.

The autopsy revealed heavy (right, 625 g; left, 530 g) and edematous lungs with bilateral honeycomb changes in the basal area, compatible with the diagnosis of chronic IP. Most of the lung tissue was involved; very little normal lung tissue remained. Microscopic examination revealed the mosaic pattern of acute diffuse alveolar damage (DAD) and organizing DAD, which can be observed in IP induced by various kinds of drugs (Fig. 2a).[15] Acute DAD was characterized by formation of hyaline membranes on the alveolar walls (Fig. 2b). Organizing DAD was characterized by organizing fibrosis that replaced hyaline membranes (Fig. 2c) and intra-alveolar dense fibrosis resembling chronic organizing pneumonia (COP) (Fig. 2d). Some bacterial and fungal growths were also observed, indicating that secondary infections accelerated the respiratory failure.

Case 2

A 69-year-old woman, who was diagnosed with RA in December 2000, did not show IP on chest X-rays. She was treated with 4 mg/week MTX. On November 12, 2003, MTX was replaced by 10 mg/day of leflunomide with no loading dose. Four weeks later the leflunomide dose was increased to 20 mg/day. On February 10, 2004, she complained of shortness of breath and a productive cough, and was referred to the TMDU Hospital. An initial physical examination revealed a low-grade fever (37.3°C) and bilateral active synovitis in her proximal interphalangeal and metacarpophalangeal joints. Chest auscultation revealed coarse crackles throughout the lungs. Laboratory test results showed an elevated serum CRP level (6.7 mg/dl), lymphocytopenia (lymphocytes 364/mm^3), and severe hypoxia (PaO_2 55 torr at room air). A chest X-ray showed a bilateral increase of density over the lung fields and a chest CT scan depicted patchy ground-glass opacity (Fig. 3a,b). Pathological microorganisms, including bacteria, fungi, *Mycobacterium tuberculosis*, or *Mycobacterium avium* complex, were not detected in her sputum by conventional bacteriological examinations. Because the PCR assay for *Pneumocystis jiroveci* was positive, sulfamethoxazole-trimethoprim was administered for 2 days, but could not be continued because of a severe drug-related skin eruption. Serum β-D-glucan levels remained within the normal range. Because she had not exhibited IP before institution of leflunomide therapy and because her IP showed subacute progression, a causal relationship between leflunomide and IP was indicated. Methyl-PSL pulse therapy (1000 mg/day, three consecutive days) followed by 45 mg/day of PSL, along with 24 g/day of cholestyramine, rapidly improved her dyspnea and hypoxia. The serum concentration of leflunomide was rapidly decreased from 89601 ng/ml to 3753 ng/ml. Pulmonary infiltration disappeared on the 29th day of hospitalization (Fig. 3c,d). She was discharged with continuing therapy of 30 mg/day of PSL.

Discussion

We report two cases of RA with acute IP that deteriorated or developed after the institution of leflunomide treatment. In both cases, the temporal relationship between the initiation of leflunomide therapy and the onset of IP could

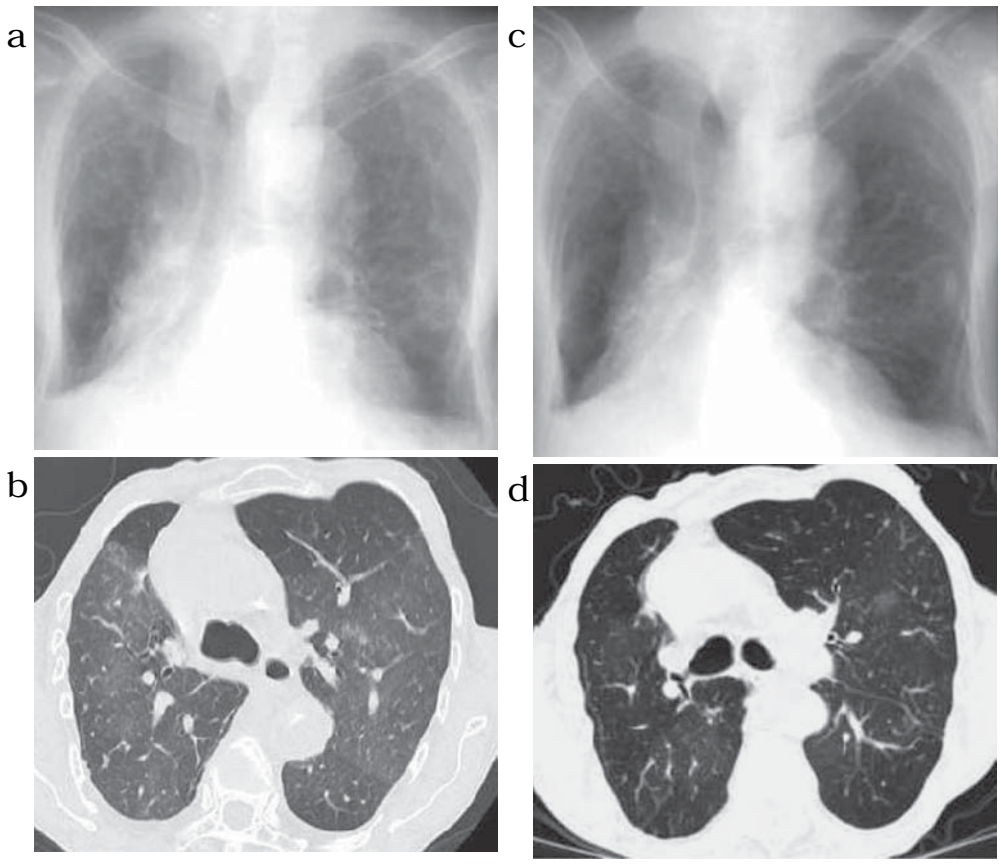

Fig. 3a–d. Radiographic findings in Case 2. On admission, a chest X-ray (**a**) and CT scan (**b**) showed bilateral ground-glass opacity. Twenty-nine days after treatment with prednisolone and cholestyramine, the infiltration disappeared on both chest X-ray (**c**) and CT scan (**d**)

suggest an association between the two. Laboratory examinations and clinical courses exclude the possibility of infectious diseases, such as *Pneumocystis* pneumonia (PCP), as the cause of the interstitial infiltration seen on chest X-rays and CT scans. The pathological findings of both acute and organizing DAD present in Case 1 have been recognized as one of the patterns of drug-induced IP. Although 80 cases of leflunomide-related IP have been reported in postmarketing surveillance conducted in Japan, some investigators have argued against a causal relationship because of the high frequency of IP in patients with RA, as well as the use of more than two DMARDs in combination.[16] In both our cases, however, leflunomide was used as monotherapy and IP was not detected before the institution of leflunomide in Case 2. Although pulmonary infection was observed in Case 1, autopsy findings indicated that it was a secondary event. Therefore, a relationship between leflunomide and IP was suggested in both cases.

The etiology of leflunomide-related IP has not been clarified. Direct toxicity to the lungs and hypersensitivity to the drug could be proposed as etiologies. Opportunistic infections, such as PCP, or cytomegalovirus or fungal infections consequent to bone marrow suppression would worsen the prognosis. From the postmarketing surveillance of leflunomide by Sanofi Aventis, at least 34 (43%) of 80 patients who developed IP with the use of the drug had pre-existing IP or a history of "MTX-induced IP"; these histories significantly increased the risk of IP ($P < 0.0001$ by Fisher's exact probability test). Age (>65-years-old; $P < 0.0001$), male sex ($P = 0.0003$), history of smoking ($P = 0.0002$) and serum albumin level (<3.8 g/dl; $P = 0.0002$) were also significant risk factors by monovariant analysis (Fisher's exact probability test). Loading doses, treatment duration and total cumulative doses were not significant risk factors (http://safety.sanofi-aventis.co.jp/arava/aravad/index.html). Recently, Suissa et al.[7] conducted a nested case-control study and demonstrated the increased risk of IP with the use of leflunomide among the patients with either previous MTX use or history of IP (relative risk 2.6 [95% confidence interval 1.2–5.6]), which is compatible with the results of the postmarketing surveillance in Japan.

Increased susceptibility to gefitinib-induced IP has also been recognized in Japanese patients.[17] Unknown racial and pharmacoepidemiological factors may explain the susceptibility of Japanese patients to drug-induced IP. It is intriguing to note that risk factors for gefitinib-induced IP, MTX-induced IP[18] and leflunomide-related IP included pre-existing IP and male sex. Because of the high mortality rate of leflunomide-related IP, few Japanese rheumatologists use the drug. Therefore, a prospective study to investigate the causal relationship between leflunomide and IP in Japan would now be difficult to implement.

In summary, we report leflunomide-related acute IP in two patients with RA. Considering the high mortality rate of the adverse drug reaction as reported in the postmarketing surveillance in Japan, rheumatologists

should use the drug with great caution especially in those patients with possible risk factors discussed in this case report, and should be alert to this rare but serious adverse drug reaction for appropriate diagnosis and treatment.

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