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ORIGINAL ARTICLE

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Leflunomide-related lung injury in patients with rheumatoid arthritis: imaging features

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Abstract Imaging findings of 26 cases of leflunomide (Arava)-related acute lung injury were analyzed. Thirteen cases had pre-existing interstitial pulmonary disease on chest X-ray or computed tomography. The main features of clinically determined leflunomide-induced acute lung injury were similar to those caused by other drugs: diffuse or widespread patchy ground-glass opacities and/or consolidation, frequently accompanied by septal thickening and intralobular reticular opacities. We categorized these findings into four patterns: diffuse alveolar damage (DAD), acute eosinophilic pneumonia, hyperreaction, and cryptogenic organizing pneumonia. The DAD group had a higher mortality rate, but statistically not a significant one. It is impossible to exclude infectious disease such as pneumocystis carinii pneumonia based on imaging findings, and detailed correlation of imaging findings with clinical and laboratory findings is essential in order to make a correct diagnosis.

Key words Computed tomography (CT) · Diffuse alveolar damage (DAD) · Leflunomide · Lung injury

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Introduction

Leflunomide (Arava, Aventis Pharma, Tokyo, Japan), is one of the newly developed disease-modifying antirheumatic drugs (DMARDs).[1–3] Since the drug was released onto the market in Japan in September 2003, 51 cases of acute lung injury have been reported to the manufacturer of the drug (Aventis Pharma Japan, Tokyo), and 16 of these died due to lung injury in Japan.[4,5] The incidence of leflunomide-related acute lung injury was estimated to be approximately 1% with a mortality rate of approximately 0.3%. The incidence of acute lung injury seems to be higher than in Western countries.

In the present study, we analyzed imaging features of acute lung injury and classified imaging findings into four patterns. We report these imaging features and the role of imaging diagnosis in the evaluation of leflunomide-related lung injury.

Patients and methods

Patient population and method of imaging evaluation

Fifty-one cases were reported as leflunomide-related lung injury to the manufacturer of the drug between September 2003 and July 2004. Diagnosis of rheumatoid arthritis (RA) was made by attending physicians in each hospital based on the American College of Rheumatology (ACR) 1987 revised criteria for RA.

Images were available in 31 cases. Five cases were excluded because of insufficient imaging materials, mainly lack of computed tomography (CT) images at the onset of lung injury or very poor quality CT images. The remaining 26 cases comprised the patient population for the present study.

All evaluated images were provided to the manufacturer by the physicians with written agreement for the further evaluation of the lung injury cases. Physicians also agreed to disclose the evaluated data. The Arava External Safety Review Board was set up by the manufacturer to assess on a regular basis the results from the survey, under authorization by the Ministry of Health, Labour and Welfare. The Respiratory Subcommittee of Arava External Safety Review Board was set up in order to gather, evaluate, and provide information about lung injury for the review board.

Chest X-rays (CXR), CT images, and the clinical and laboratory records of the patients were analyzed by three diagnostic radiologists (F.S., S.N., Y.K.) who were specialists in chest radiology, one rheumatologist (H.Y.), and two respiratory physicians (A.A., S.K.). We investigated whether there were imaging findings suggesting the presence of pre-existing pulmonary diseases when CXR or CT before onset of acute lung injury was available. Chest X-rays and CT images at the onset of acute lung injury were examined by the three diagnostic radiologists and correlated with the clinical findings, then laboratory and microbiological examinations were analyzed by the rheumatologist and two respiratory physicians. A final diagnosis was made by a consensus reached among all six physicians.

In all 26 cases, CXR and CT images at the onset of acute lung injury were available. In 4 of the 26 cases, high-resolution CT (HRCT) images were also available. In 21 cases, CXR or CT images prior to the onset of acute lung injury were available. In 12 cases, CT images were available prior to the onset of acute lung injury. The technical parameters of CT examination, such as slice thickness, varied among patients.

Diagnostic criteria of drug-induced lung injury and pattern recognition

We classified the 26 patients into three groups: clinically definitive drug-induced lung injury (group A); clinically probable drug-induced lung injury (group B); and other diseases (group C). The criteria for the classification were as follows. Group A comprised diffuse or patchy ground-glass opacities or consolidation in bilateral lungs. Frequent thickening of interlobular septa or intralobular reticular appearance was identified, accompanied by ground-glass opacities and consolidation. Detailed correlation of imaging findings with clinical, microbiological, and serological findings could exclude diagnosis of infectious diseases. The criteria for group B were the same as those for group A in terms of imaging findings, but infectious disease could not be excluded based on the clinical and laboratory findings. The criteria for group C were apparent transbronchial spread of shadow such as bronchiolitis or bacteriologic or serological definitive diagnosis of infectious diseases when abnormal opacity appeared. In group C patients, the most probable diagnosis based on imaging findings was described.

Concerning group A and B patients, we described the characteristics and distribution of abnormal shadow in the craniocaudal direction and in the transverse plane, the existence of septal thickening or intralobular reticular appearance, and traction bronchiectasis. These were then categorized into four radiological patterns and correlated with the final outcomes for acute lung injury. Statistical analysis was performed using Fisher's direct exact test.

Results

Diagnosis of drug-induced lung injury

We classified eight cases into group A (Fig. 1), nine into group B, and nine into group C. In group B, the following possible diagnoses cannot be excluded: pneumocystis carinii pneumonia (PCP) (Fig. 2) in five, and one each of cytomegalovirus (CMV) infection, viral infection, bacterial infection, transbronchial infection of undetermined etiology, and interstitial lung diseases related with collagen vascular disease. The most probable diagnoses for individuals in group C are PCP, pneumonia of undetermined etiology, fungal infection, infected bulla, lung abscess, pulmonary edema and aspiration pneumonia, and RA-associated bronchiolitis.

Pre-existing lung diseases

Interstitial lung disease was present on CXR and/or CT images in 12 out of 21 cases. Other pre-existing diseases evident on CXR and/or CT included large bulla, pulmonary emphysema, pulmonary thromboembolism, inactive tuberculosis, bronchiectasis, lingual pneumonia; atelectasis of right middle lobe, RA-related bronchiolitis, and pleural thickening. In 17 clinically definitive (group A) or clinically probable (group B) cases of drug-induced lung injury, 13 had CXR and nine had CT before the onset of acute lung injury. In groups A and B, eight showed pre-existing interstitial changes among the 13 cases in whose CXR or CT images before onset of acute lung injury were available. Other diseases found among individuals in groups A and B were lingual pneumonia, bronchiectasis, inactive tuberculosis, atelectasis of right middle lobe, pleural thickening, and pulmonary thromboembolism.

Imaging features at the onset of lung injury in groups A and B

In groups A and B, the main imaging findings at the onset of acute lung injury were bilateral diffuse or widespread patchy ground-glass opacities and/or consolidation (Fig. 1c,d). The borders of ground-glass opacities or consolidation were sometimes sharply defined. The distribution of the abnormal opacities varied in both craniocaudal distribution and zonal preponderance in the axial plane.

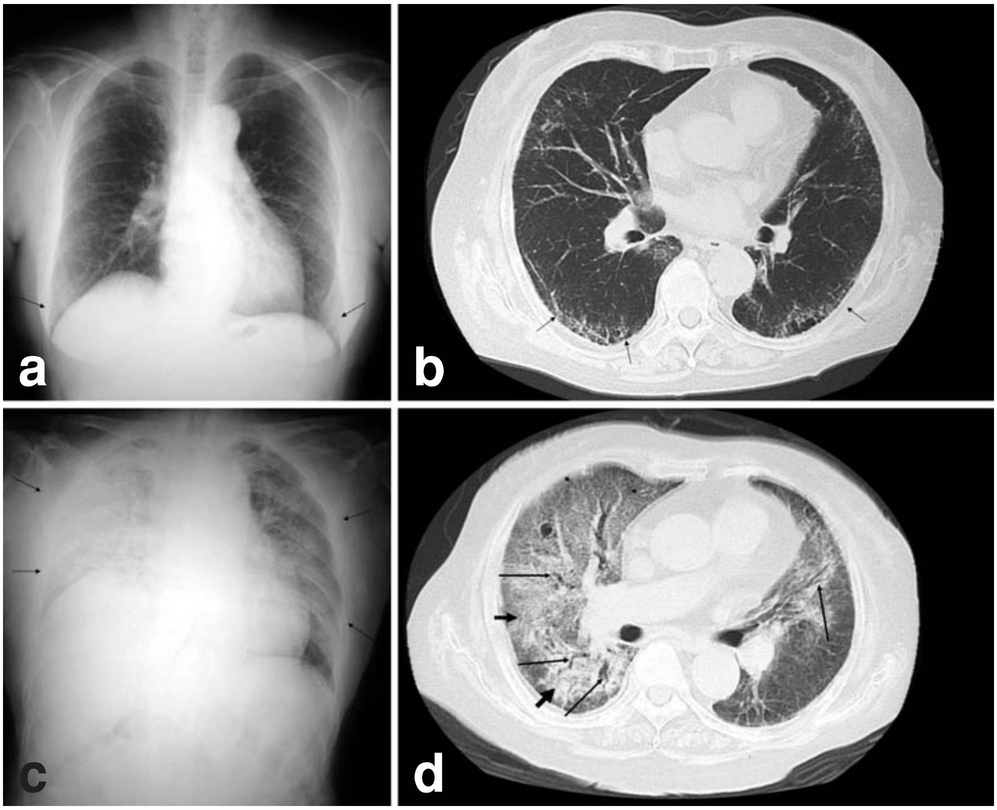

Fig. 1a–d. Leflunomide-induced acute lung injury (group A). **a** Chest X-ray before the onset of acute lung injury. Minimal degree of reticular opacity (*arrows*) is seen in bilateral lower lung fields. There is no evidence of lung volume loss. **b** Chest computed tomography (CT) before the onset of acute lung injury. Ground-glass opacity and reticular opacity (*arrows*) suggesting pre-existing interstitial diseases are seen in the subpleural zone of bilateral lower lobes. **c** Chest X-ray at the onset of acute lung injury. Consolidation (*arrows*) is seen in the bilateral lungs, predominantly on the right side. **d** Chest CT at the onset of acute lung injury. Diffuse consolidation (*bold arrows*) and ground-glass opacity (*arrowheads*) are seen in bilateral lungs. Traction bronchiectasis (*arrows*) and structural distortion is seen within consolidation

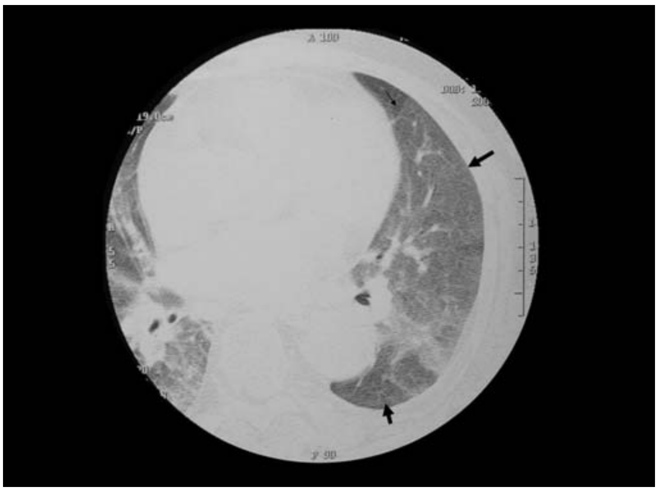

Fig. 2. Pneumocystis carinii pneumonia. Chest high-resolution CT (HRCT) at the onset of lung injury shows widespread ground-glass opacity (*bold arrows*). Foci of ground-glass opacity show linear border (*arrow*)

Among the eight cases in group A, all showed bilateral diffuse or widespread patchy ground-glass opacities, with two cases accompanied by consolidation. Distribution of the shadow showed upper lobe predominance in two cases, lower lobe predominance in three, and generalized distribution in three. Zonal preponderance in the axial plane showed peripheral predominance in one case, perihilar in three, generalized in two, peribronchovascular in one, and mixed in one. Traction bronchiectasis, thickening of interlobular septa, and intralobular reticular shadow were seen in five, three, and three cases, respectively. Three of the traction bronchiectasis cases had had pre-existing interstitial lung disease.

Among the nine cases in group B, all except one showed bilateral diffuse/patchy ground-glass opacities, and three were accompanied by consolidation. The remaining case showed unilateral ground-glass opacities. Distribution of the shadow showed upper lobe predominance in one case, lower lobe predominance in three, and generalized predominance in five. Zonal preponderance in the axial plane showed peripheral predominance in three cases, perihilar predominance in four, generalized predominance in three, and peribronchovascular predominance in two. Traction bronchiectasis, thickening of interlobular septa, and intralobular reticular shadow was seen in five, three, and five cases, respectively. Four of the five cases with traction bronchiectasis had had pre-existing interstitial lung disease.

Imaging patterns in groups A and B

We categorized 17 cases of groups A and B into four imaging patterns: diffuse alveolar damage (DAD) pattern, acute eosinophilic pneumonia (AEP) pattern, hyperreaction (HR) pattern, and cryptogenic organizing pneumonia

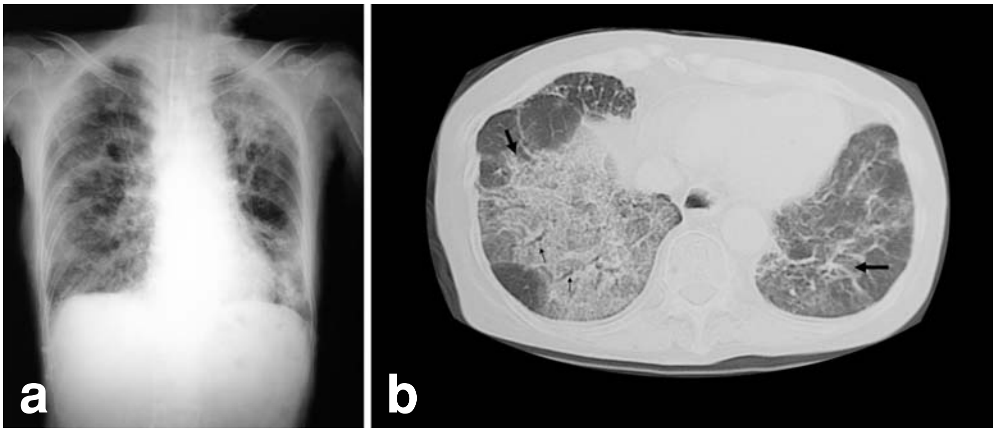

Fig. 3a,b. Diffuse alveolar damage pattern. **a** Chest X-ray at the onset of acute lung injury. Ground-glass opacity is noted in bilateral lungs. **b** Chest X-ray at the onset of acute lung injury. Diffuse ground-glass opacity is seen in the bilateral lungs predominantly on the right side. Traction bronchiectasis (*arrows*) and structural distortion (*bold arrows*) are seen within ground-glass opacity

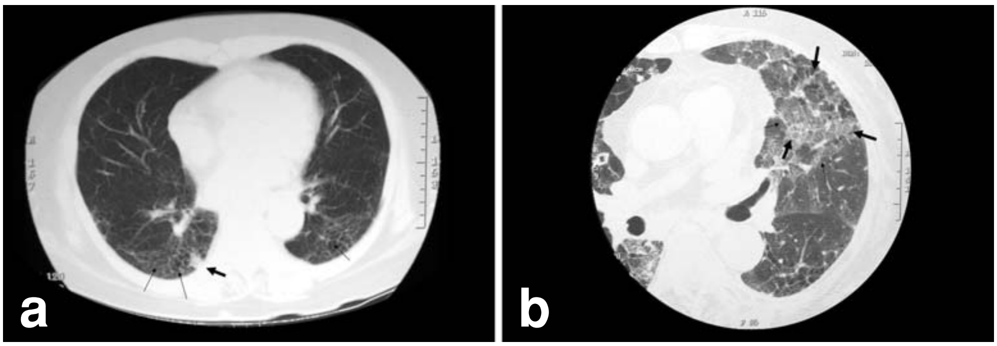

Fig. 4a,b. Acute eosinophilic pneumonia pattern. **a** Conventional chest CT before the onset of acute lung injury, showing pre-existing interstitial lung disease predominantly in bibasilar region (*arrows*). Small foci of dense consolidation was also noted (*bold arrow*). **b** Chest HRCT at the onset of acute lung injury. Linear bordered panlobular ground-glass opacities (*arrows*) with thickening of interlobular septa (*bold arrows*) is evident

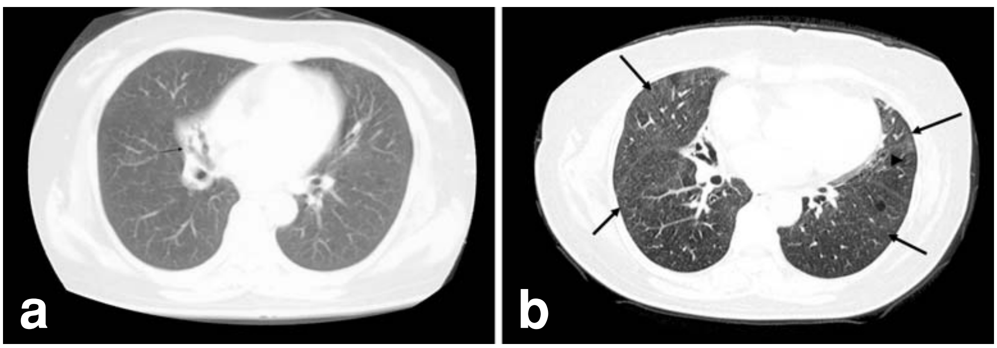

Fig. 5a,b. Hyperreaction pattern. **a** Conventional chest CT before the onset of acute lung injury. Atelectasis of right middle lobe (*arrow*) is seen; however, there is no ground-glass opacity in other lung fields. **b** Chest HRCT at the onset of acute lung injury. Faint ground-glass opacity is diffusely seen in bilateral lungs (*arrows*). There is no structural distortion. A focally spared lobule in the left lung is noted (*arrowheads*)

(COP) pattern, after the pattern recognition in geftinib-induced acute lung injury classification.[6–8] Diffuse alveolar damage (Fig. 3) was defined as diffuse or patchy foci of consolidation or ground-glass opacities with structural distortion such as traction bronchiectasis. Acute eosinophilic pneumonia (Fig. 4) was defined as multilobular ground-glass opacities and consolidation with perilymphatic shadow such as marked thickening of interlobular septa and bronchovascular bundle. Hyperreaction (Fig. 5) was defined as diffuse, faint ground-glass opacities without structural distortion. Cryptogenic organizing pneumonia (Fig. 6) was defined as peripherally located or foci of peribronchovascular consolidation.

Among 17 cases, eight were classified as DAD, three as AEP, five as HR, and one as COP. Six among the DAD group died as a result of acute lung injury, while one death each was recorded against the AEP and HR groups. No deaths occurred among the COP group. Mortality in the DAD group was relatively higher than those of other patterns, but statistically not significant ($P = 0.056$).

Discussion

Leflunomide is one of the new DMARDs for RA. The drug inhibits pyrimidine synthetase[9] and delays the progression

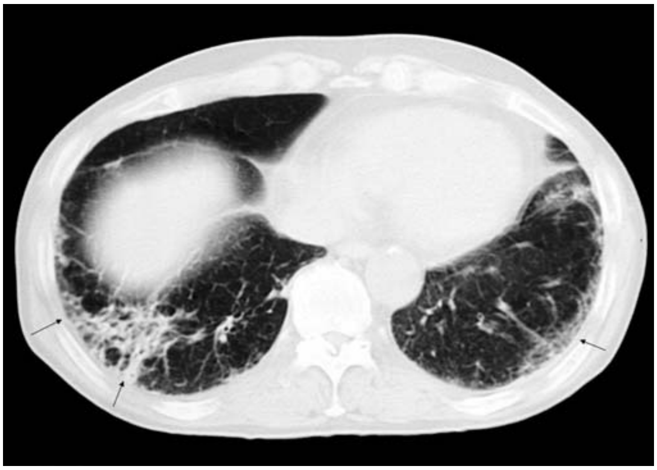

Fig. 6. Cryptogenic organizing pneumonia pattern. Conventional chest CT at the onset of acute lung injury. Dense nonsegmental consolidation (*arrows*) is seen in the subpleural regions of bilateral lower lobes

of cartilage destruction.[10,11] The drug had been expected to be more or equally effective to methotrexate (MTX) and other antirheumatic drugs.[12–17]

Although the drug was thought to be relatively safe, there have been many reports of adverse effects in the gastrointestinal,[18] hepatic,[19–23] hematological,[24–27] dermatological,[28] and neurological systems.[29,30] This drug had been expected to be associated with a lower incidence of lung injury than MTX; however, many cases of acute lung injury have been reported since the drug was released in September 2003.[5] Approximately 5000 patients were treated with leflunomide and the occurrence of lung injury was estimated as approximately 1.1%, which seems to be far higher than the figure recorded in Western countries.[1]

To determine the radiological features of acute lung injury caused by leflunomide, we retrospectively analyzed the imaging findings of 26 cases of leflunomide-related lung injury. The radiological appearance of leflunomide-induced lung injury was similar to that reported previously for other drugs: diffuse or widespread patchy ground-glass opacities and/or consolidation accompanied by thickening of interlobular septa or intralobular reticular shadow.[31–36]

Approximately a third of the lung injuries initially attributed to leflunomide were judged as caused by other diseases, with infectious disease being the most probable diagnosis. The high incidence of infectious disease in our patients group was probably related to an immunocompromised state induced by leflunomide. Increased susceptibility to infection might be one of the important adverse effects of leflunomide other than drug-induced lung injury. Further analysis should be necessary to determine the incidence and hazard of opportunistic infection in adverse effects of leflunomide.

Because the main features of the radiological findings were bilateral ground-glass opacities and/or consolidation, opportunistic infection such as PCP and CMV pneumonia cannot be excluded based on imaging findings only. Detailed correlation of clinical, microbiological, serological, and radiological findings is essential to exclude infectious diseases and make a correct diagnosis of drug-induced lung injury.

We classified these imaging findings into four patterns: DAD, HR, AEP, and COP. The DAD group showed a high mortality rate. Structural distortion is one of the important imaging findings that show irreversible fibrotic change in cases with acute respiratory distress syndrome.[37,38] Structural distortion may newly appear as a progression of drug-induced lung injury or may merely be a manifestation of pre-existing traction bronchiectasis in cases with pre-existing interstitial lung disease.

While the DAD group showed a relatively higher mortality rate, but statistically not a significant one, this may have been influenced by the pre-existence of interstitial lung disease. The DAD pattern on CT images might be an indicator of poor prognosis, although life prognosis may be affected by many factors other than the pattern of lung injury; thus, multivariate analysis may be necessary to determine the actual factors affecting life prognosis after the onset of acute lung injury.

The HR pattern is defined as faint ground-glass opacities without structural distortion. This pattern seems to be the same as hypersensitivity pneumonitis as reported in previous articles.[39] We believe that hypersensitivity pneumonitis is an inadequate terminology for drug-induced lung injury because hypersensitivity pneumonitis should be confined to the disease process caused by inhaled antigen. The pathological basis of the pattern may be lymphocytic infiltration to the alveolar septa and poor granuloma formation frequently seen in MTX lung injury. The HR pattern showed a relatively better prognosis compared with the DAD pattern. The AEP and COP patterns are also common patterns in acute lung injury caused by other drugs and showed better prognosis in our patients.

Compared with that in Western countries, the incidence of leflunomide-induced lung injury in the present study is far higher. Gefitinib-induced acute lung injury occurs at a markedly higher rate in Japan than in Western countries.[6,40] Although the reason is unclear at present, it might be due to racial differences or other unknown factors. Further investigation including genetic analysis should be conducted to elucidate the reasons for the high incidence of drug-induced lung injury in Japanese patients.

Another potential predisposing factor for acute lung injury is pre-existing interstitial lung disease. A higher mortality rate has been reported in gefitinib-induced acute drug injury associated with pre-existing interstitial disease.[6–8] Our study group also had a high incidence of pre-existing interstitial lung diseases. Because our study was a retrospective analysis of cases reported as acute lung injury, further study is essential to determine whether patients with pre-existing interstitial lung disease have a higher morbidity rate regarding leflunomide-related acute lung injury.

The clinical efficacy of HRCT in the diagnosis and evaluation of diffuse lung diseases has been established.[41,42] The prerequisites for HRCT are thin X-ray collimation of less than 2 mm and reconstruction algorithm with high spatial resolution. High-resolution CT can increase precision in the analysis of abnormal opacities on CXR or conventional CT images; however, only a limited number of cases in the present study had HRCT images. High-resolution CT is preferred in evaluating leflunomide-induced lung injury in order to allow a more precise determination of the radiological pattern.[41,42]

High-resolution CT images obtained before the onset of acute lung injury may be helpful in the analysis of CT images at the onset of acute lung injury. Considering the high incidence of interstitial lung disease in RA, HRCT for screening interstitial lung disease may be advisable before administering drugs with possible severe lung toxicity such as leflunomide.

There were many limitations in our present study. First, the study was a retrospective analysis of voluntarily reported cases of leflunomide-related adverse effects to the manufacturer; therefore there could be bias in the selection of patients. Second, there was no single protocol to obtain CXR and CT images, and HRCT images were obtained only in selected cases. Image quality was not sufficient for a detailed analysis in a number of cases. Computed tomography images were not available for some cases before the onset of drug-induced lung injury. Third, since the definitive diagnosis of drug-induced lung injury with invasive methods such as a challenge test is practically impossible, the diagnosis in our study was determined based on the detailed correlation of clinical symptoms, clinical course, and laboratory findings. Fourth, there was no evidence that imaging patterns correctly corresponded to pathologic patterns. According to a previous report,[43] there seemed to be poor concordance between radiological appearance and histopathologic findings in drug-induced lung disease. We were unable to investigate pathologic findings and correlate radiologic findings with pathologic findings because of the limited availability of pathologic materials.

In conclusion, imaging features of clinically determined leflunomide-induced acute lung injury comprised diffuse or widespread patchy ground-glass opacities and/or consolidation frequently accompanied by interlobular septal thickening or intralobular reticular appearance. Radiological patterns were divided into four patterns: DAD, HR, AEP, and COP. Cases with the DAD pattern had a higher mortality rate. Computed tomography, especially HRCT, may be useful in analyzing the images after the onset of drug-related lung injury. Infectious disease such as PCP was the most important differential diagnosis, and detailed correlation of clinical and radiological observations is necessary to make a correct diagnosis.

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