Abstract: We report the case of a young man, affected by rheumatoid arthritis who developed a rapid-onset short-of-breath, hemoptysis, and severe weakness, about 2 weeks after the administration of leflunomide. Chest radiography showed central bilateral opacities and pleural effusion as confirmed by the high-resolution computed tomography that demonstrated diffuse ground-glass and interlobular septal thickening as well. On admission at the Emergency Department, a microhematuria and a severe anemia were also documented. On the basis of the clinico-radiologic presentation, a pulmonary hemorrhage was likely to occur; so to clarify the origin of this process, a complete serologic examination was performed but all the antibodies were negative. Finally a renal biopsy was performed and it showed a pauci-immunologic glomerulonephritis and the bronchioloalveolar lavage confirmed the diffuse alveolar hemorrhage. In conclusion, the diagnosis of leflunomide-pulmonary-renal syndrome was rendered. The treatment with leflunomide was suspended; the conditions of the patient gradually improved and he became completely asymptomatic 1 week later.

Key Words: leflunomide, rheumatoid arthritis, drug pulmonary-related disease, vasculitis, BAL, pulmonary hemorrhage, pulmonary-renal syndrome

Leflunomide is an isoxazole derivative with anti-inflammatory and immunomodulating activities and a half-life of 1 to 4 weeks. It is a disease-modifying antirheumatic agent with an efficacy comparable to methotrexate (MTX) in the treatment of rheumatoid arthritis. In the clinical trials of leflunomide, interstitial lung disease occur very rarely (<1 in 10,000 treated patients per annum). In February 2004, a report in Lancet revealed that several deaths had occurred as result of interstitial pneumonitis in patients participating to a postmarketing surveillance study of leflunomide in Japan. This report indicated that before this, 4,00,000 patients had received leflunomide worldwide and 80 patients had developed interstitial pneumonitis. Sakai et al reported 51 patients with leflunomide-acute lung injury and categorized these findings into 4 patterns: diffuse alveolar damage, acute eosinophilic pneumonia, hyper reaction, and cryptogenic organizing pneumonia. The imaging features comprised diffuse or widespread patchy ground-glass opacities and/or consolidation frequently accompanied by interlobular septal thickening or intralobular reticular appearance. We report the case of a young man who developed a progressive dyspnea with diffuse lung infiltrates, no underlying infections, and an unusual clinico-radiologic presentation as regard the leflunomide pulmonary toxicity.

CASE REPORT

In January 2007, a 30-year-old man, affected by rheumatoid arthritis, 40-pack years tobacco smoker developed a rapid-onset short-of-breath, nonproductive cough, hemoptysis, and severe weakness. On admission at the Emergency Department, the physical examination showed pallor, fever, coetaneous palpable purpurae, and a blood pressure of 100/60 mm Hg. Laboratory test results revealed a severe anemia (5.5 mg/100 mL of hemoglobin), acute renal failure (4.8 mg/dL of serum creatinine), microscopic hematuria, and proteinuria. A severe hypoxemia (pH, 7.46; PaCO2, 32.0 mm Hg; and PaO2, 43.15 mm Hg) was also documented. Chest radiography showed central widespread bilateral opacities, some bronchogram signs, and a mild bilateral pleural effusion (Fig. 1A). A high-resolution computed tomography (HRCT) of the lung (Aquilon16, Toshiba Medical, Tokyo, Japan) was immediately performed and it showed bilateral, widespread ground-glass attenuation, smooth septal interlobular thickening, air-space consolidations, and bilateral pleural effusion (Fig. 1B). The clinico-radiologic findings were highly suggestive of a diffuse alveolar hemorrhage. The renal ultrasound showed a bilateral hyperechogenicity of the renal sinus, probably related to the presence of blood in the urine. Hydronephrosis was absent. Fiber optic bronchoscopy showed a diffuse bleeding from the peripheral airways. Cytologic examination of the lavage fluid revealed an elevated erythrocyte count, hemosiderin-laden alveolar macrophages, and neutrophils. Microbiologic analysis of the bronchoalveolar lavage did not document any colonial growth. A complete serologic examination was performed, particularly the antiglomerular basement membrane antibodies antinuclear antibodies, antineutrophil cytoplasmatic antibodies (pANCA and cANCA), and cryoglobulins. All the dosages were normal. In the clinical...
Wardwell et al. first radiologically documented. The patients showed pulmonary infiltrates that were asymptomatic 1 week later. The supine chest x-rays revealed a diffuse opacification seen in both the lungs consistent with pulmonary infiltrates. Multiple air bronchograms are seen with a diffuse interstitial thickening. The costophrenic angles are blunted. The cardiac silhouette and the mediastinal pedicle are normal in size. B, Chest CT reveals a diffuse ground-glass opacification, with smooth septal thickening and bilateral pleural effusion. C, The histologic section shows inflammatory changes in the little arterial vessels, with lymphocytic and granulocytic infiltration of the wall associated to a fibrinoid necrosis. Mild tubular atrophy associated with initial interstitial fibrosis.

**FIGURE 1. A**, Chest x-rays revealing a diffuse opacification seen in both the lungs consistent with pulmonary infiltrates. Multiple air bronchograms are seen with a diffuse interstitial thickening. The costophrenic angles are blunted. The cardiac silhouette and the mediastinal pedicle are normal in size. **B**, Chest CT reveals a diffuse ground-glass opacification, with smooth septal thickening and bilateral pleural effusion. **C**, The histologic section shows inflammatory changes in the little arterial vessels, with lymphocytic and granulocytic infiltration of the wall associated to a fibrinoid necrosis. Mild tubular atrophy associated with initial interstitial fibrosis.

**DISCUSSION**

Leflunomide is one of the new disease-modifying antirheumatic agents for rheumatoid arthritis, it inhibits pyrimidine synthetase, delays the progression, and it has been expected to be more or equally effective to MTX with a lower incidence of toxicity events. Even though it is relatively safe, many reports describe adverse effects in the gastrointestinal, hepatic, hematologic, dermatologic, pneumologic, and neurologic systems. Since the leflunomide was released in September 2003, several cases of acute lung injury have been reported. Approximately, 5000 patients were treated with leflunomide and the occurrence of lung injury was estimated as approximately 1.1%, particularly acute interstitial pneumonitis have been described. Leflunomide may cause pneumonitis either as monotherapy or, possibly more commonly, after it is added to MTX therapy. In a Japanese postmarketing surveillance program of 3658 patients with rheumatoid arthritis taking leflunomide, 29 cases of interstitial pneumonitis were reported including a fatal outcome. Savage et al. reported a case series of leflunomide-induced pneumonitis in 14 patients who developed an acute respiratory illness requiring the hospital admission. All the patients showed pulmonary infiltrates that were radiologically documented. Wardwell et al. first reported the association of secondary pulmonary alveolar proteinosis with leflunomide therapy in a 42 male under treatment because of rheumatoid arthritis. Chest CT demonstrated bilateral alveolar infiltrates and the transbronchial biopsy a focal early organizing pneumonia. The case that we have reported did not show the clinicoradiologic features of a pneumonitis or of an alveolar proteinosis, rather than of a diffuse pulmonary capillaritis associated with glomerulonephritis that has defined a pulmonary-renal syndrome. A leflunomide-related pulmonary vasculitis associated with glomerulonephritis has not been reported yet. Moreover this drug is proven to be well tolerated and efficient in the remission maintenance of vasculitides as Wegener granulomatosis. Leflunomide-induced vasculitis is probably caused by the alteration of the inflammatory response with constitution of immunocomplexes. Although a leflunomide-induced pulmonary capillaritis has not been described, Smolen et al noted 8 (0.6%) of 133 patients treated with leflunomide developed rash during treatment. However, they did not clarify whether the cutaneous vasculitis was due directly to drug. Chan et al. described the development of leflunomide-induced cutaneous vasculitis and its dose-response relationship. In our case, the presence of neutrophils in bronchoalveolar lavage fluid, of glomerulonephritis, and of cutaneous purpura were highly consistent with the presence of systemic vasculitis. Multidetector CT with high-resolution imaging of the chest represents the cornerstone in the radiologic workup of pulmonary vasculitic disorders. Regardless of the underlying disease, the HRCT findings of diffuse alveolar hemorrhage are essentially similar. In the phase of acute hemorrhage, lobular or lobar areas of ground-glass opacity to consolidation are predominant. In these patients, ground-glass opacity is generated by the subtot alveolar filling with blood and it is accompanied by apparent prominence of segmental and subsegmental bronchi, which has been referred to as the “dark bronchus” sign. Within 2 to 3 days, intralobular lines and smooth interlobular septal thickening superimpose on areas of ground-glass opacity and may give rise to a crazy-paving pattern. In the course of hemorrhage resorption, these patterns may resolve or with severe repeated hemorrhage may progress to interstitial fibrosis, which is readily depictable on HRCT. Regardless of the...
underlying disease, the HRCT findings of diffuse alveolar hemorrhage are essentially similar and the differential includes the ANCA-associated vasculitides, Goodpasture syndrome, and systemic lupus erythematosus.13 Iatrogenic respiratory diseases are important causes of patient morbidity and mortality that can show several and nonspecific radiologic, it really represents a challenge for both clinician and radiologist. The suspension of the drug administration can be sufficient. The strong temporal relationship between the onset of systemic vasculitis and the resolution after the leflunomide withdrawal confirmed that this drug is another cause that extends the already long list of causes of alveolar hemorrhage.

REFERENCES


ERRATUM

The name of the third author was listed incorrectly as “Myrna B. Godoy” for the article titled “Computer-aided detection of pulmonary embolism on CT angiography: initial experience” (*J Thorac Imaging.* 2007;22:324–329). The author’s name is Myrna C. B. Godoy. The corrected citation for the article is as follows:


We regret the error and any inconvenience it has caused.