

Hypersensitivity Pneumonitis Associated with Leflunomide Therapy

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ABSTRACT. Disease progression in rheumatoid arthritis is controlled with disease modifying drugs, many of which have toxic side effects. Pulmonary side effects are common and this has resulted in the development of newer medications with less pulmonary toxicity. We observed that even these newer drugs can be associated with potentially very serious pulmonary toxicity, with hypersensitivity pneumonitis developing after the initiation of leflunomide therapy. We urge caution in the use of leflunomide in patients with pulmonary side effects from other drugs or who have underlying pulmonary disease. (First Release July 1 2007; *J Rheumatol* 2007;34:1934–7)

Key Indexing Terms:

HYPERSENSITIVITY PNEUMONITIS LEFLUNOMIDE RHEUMATOID ARTHRITIS

The cornerstone of management in rheumatoid arthritis (RA) is to reduce longterm disability and progression with disease modifying antirheumatic drugs (DMARD) and to control symptoms with more conventional therapies¹. The most commonly prescribed DMARD is methotrexate (MTX); however, pulmonary toxicity is a major cause for withdrawal^{2,3}.

This has led to the increasing use of novel drugs such as leflunomide, which was originally developed as an immunosuppressant⁴. In initial clinical trials, leflunomide was demonstrated to be safe and effective, with no significant pulmonary toxicity described⁵. It has been recommended for consideration in patients with RA who have failed first-line DMARD drug therapy or, in refractory cases, to be used in addition to other DMARD or biological agents⁶.

We present the case of a 69-year-old man with RA, who experienced pulmonary problems closely linked to the initiation of leflunomide therapy. The temporal association and resolution following withdrawal suggest leflunomide was the causative agent.

CASE REPORT

A 69-year old man with a 19-year history of RA had experienced side effects and intolerance of other DMARD. He was diagnosed in 1986 and initially treated with gold injections for 5 years and then had a trial with myochrisine,

but this was stopped because he developed a rash. His disease activity was controlled with sulfasalazine at a dose of up to 3 g daily for 10 years, but in July 2004 he started taking MTX 7.5 mg OD because of loss of efficacy and development of worsening arthropathy. He stopped this medication because of nausea and fatigue by early January 2005 and his sulfasalazine was also discontinued. He was considered a good candidate for leflunomide therapy and this was commenced at a dose of 20 mg once per day at the start of May 2005.

Three months later he presented to respiratory medicine and was admitted to hospital, with a 1-month history of progressive dyspnea, decreased appetite, and weight loss. There was some associated pleuritic-type chest pain, predominantly right-sided. He had a cough productive of small amounts of white sputum and had taken a course of amoxicillin prescribed by his general practitioner, with no improvement. There was no history of hemoptysis. He had felt nauseated by food and his appetite was greatly reduced, although there was no history of vomiting or diarrhea. Outpatient records confirmed a weight loss of about 6 kg. He felt generally lethargic. There were no other positive symptoms on detailed systemic enquiry. Since starting leflunomide he had no joint pains or swelling and felt his RA was "very well controlled."

Medical history confirmed RA diagnosed with positive serology in 1986 and some mild hypertension. He had no history of previous respiratory disease or tuberculosis (TB) exposure. His medications at presentation were etodolac S/R 60 mg OD, leflunomide 20 mg OD, ranitidine 150 mg BD, paracetamol 1 g QDS, and nifedipine 30 mg OD. None of these medications had been changed in the previous 12 months. He had no drug allergies, but had been intolerant of MTX and myochrisine as described above. He had smoked for 2 years as a young man 40 years previously, drank alcohol on a social basis, and had no social reasons for exposure to respiratory allergens. He was a retired postal worker and had taken early retirement due to problems with his RA and joint pain. There was no history of asbestos exposure. He had no history of infective contacts nor had he traveled overseas in the preceding 12 months. He had previously kept finches but had disposed of the birds 8 years previously and had no contact with birds or pigeon coops since then. He had a history of infective hepatitis in Singapore in the late 1960s. A chest radiograph performed in 1994 was reported as normal.

On examination, he was comfortable while at rest but dyspneic on minimal exertion. He was aphyrexial; his resting respiratory rate was 16. Cardiovascular examination was unremarkable as was gastrointestinal and neurological examination. He was not clubbed, trachea was central, expansion equal bilaterally, and breath sounds vesicular with added fine bibasal crepitations.

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Full blood count revealed normal hemoglobin with a raised white cell count ($15.9 \times 10^9/l$) and a neutrophilia ($11.8 \times 10^9/l$). Eosinophil count was normal. Biochemistry tests were normal. An arterial blood gas sample taken when inspiring room air showed H^+ 29 (37–45 nmol/l), pO_2 9.8 (12–15 kPa), pCO_2 2.7 (4.5–6 kPa), and HCO_3^- 21.0 (21–29 mmol/l). This corrected to normal on an FiO_2 of 0.28. C-reactive protein was elevated at 234 mg/l and the erythrocyte sedimentation rate was 79. D-dimer was 2021 ng/l (normal < 150). Avian precipitins test was negative, culture for pneumocystis on sputum was negative, as were influenza and mycoplasma serology. Sputum culture revealed both yeasts and coliforms, felt to be colonization, and TB culture was negative. A TB skin test was not performed.

Chest radiograph showed some scant patchy infiltrates throughout both lung fields. The differential diagnosis included pulmonary thromboembolism, interstitial changes secondary to RA, and/or drug hypersensitivity. He proceeded to have a computerized tomography (CT) pulmonary angiogram (Figure 1A). This showed no evidence of pulmonary embolism, but did show diffuse ground-glass opacification involving all lobes of the lung but more confluent in the upper zones. There were multiple parenchymal bands in both lower lobes and small bilateral subpleural areas of enhancing atelectasis. There was a single 1.2 cm lymph node at the right hilum and a 3 mm diameter peripheral subpleural nodule in the right upper lobe. The differential diagnosis was felt to include hypersensitivity pneumonitis (HP) and atypical infection.

He was sent for video-assisted thoracoscopic lung biopsy from the right upper lobe. This was examined by a specialist lung pathologist (a member of the UK Interstitial Lung Disease panel), who felt that the histological features were totally in keeping with the diagnosis of HP. A representative section is shown in Figure 2. In addition there was evidence of chronic pleural change in keeping with rheumatoid disease. No specific parenchymal changes suggestive of rheumatoid lung were identified and although granulomas were identified, the pattern of the pathological changes as a whole indicated HP and was not consistent with other granulomatous diseases such as sarcoid.

No specific treatment was instigated (the patient did not receive glucocorticoid or antibiotic treatment) but leflunomide was withdrawn. At followup 3 months after presentation (and withdrawal of leflunomide), his dyspnea had resolved, but he complained of right-side pleuritic chest pain. Repeat chest radiograph showed resolution of the interstitial changes with development of

a small right-side pleural effusion. A repeat CT scan (Figure 1B) showed complete resolution of the interstitial changes, but persistence of the right upper lobe nodule, and confirmed the moderate sized right pleural effusion. The patient was experiencing a flare of his RA with marked joint pains and evidence of active synovitis in the metacarpophalangeal joints. Aspiration of the right pleural effusion resulted in 20 ml of straw-colored fluid; analysis confirmed an exudate (glucose < 1.1 mmol/l, protein 74 g/l, albumin 32 g/l, and lactate dehydrogenase 7280 u/l). This sample contained multinucleated giant cells, elongated histiocytes, lymphocytes, macrophages, and mesothelial cells, all consistent with a reactive rheumatoid effusion.

DISCUSSION

The relationship between the use of various drugs and pulmonary disease is well recognized⁷. However, it is very often a diagnosis of exclusion based on a combination of careful history, radiological evidence, and pathological changes on biopsy.

The radiological patterns of pulmonary disease caused by some drugs such as bleomycin and amiodarone are well known^{8,9}, but in the majority of cases the CT findings are non-specific¹⁰. In this case the CT findings were consistent with widespread inflammatory change and in the absence of infection, malignancy, occupational exposure, thromboembolic disease, or other antigen the most likely diagnosis was felt to be HP.

HP is an inflammatory interstitial lung disease precipitated by exposure and sensitization to an ever-increasing number of antigens¹¹. The pathogenesis of HP involves both type III and type IV hypersensitivity reactions that are mediated by immune complexes and Th1 cells, respectively. Proinflammatory cytokines and chemokines activate alveolar macrophages, cause an influx of CD8-positive lymphocytes into the lungs, facilitate granuloma formation, and promote



A



B

Figure 1. A. Original CT pulmonary angiogram showing diffuse infiltrative parenchymal changes consistent with hypersensitivity pneumonitis. B. Repeat CT scan when leflunomide therapy was stopped, showing complete resolution of interstitial process.

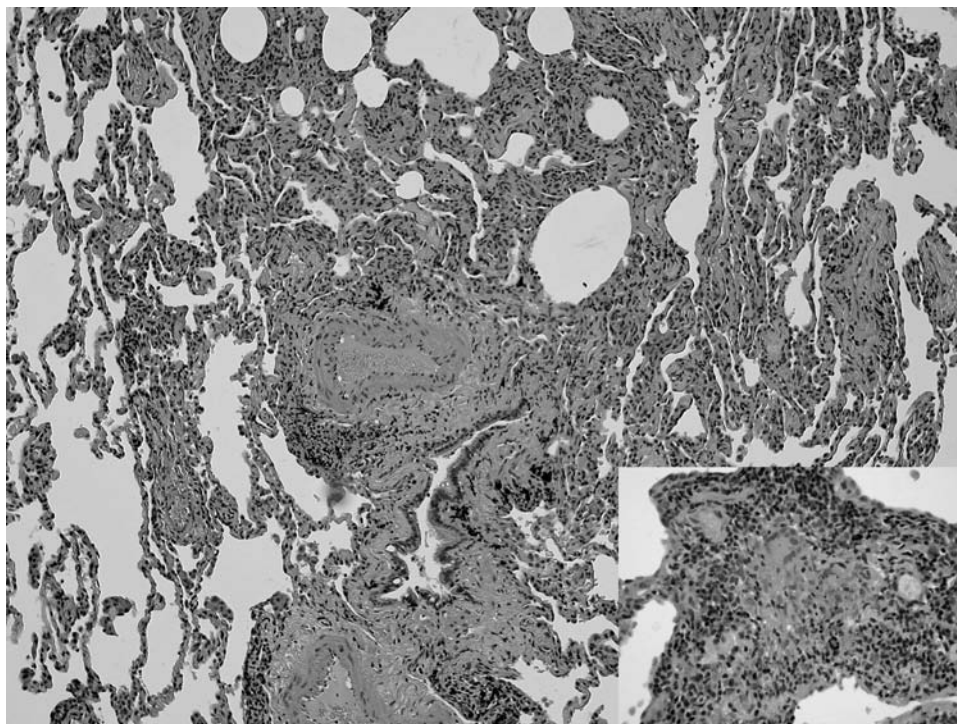


Figure 2. Photomicrograph from video-assisted thoracoscopic lung biopsy showing interstitial pneumonitis with a bronchocentric distribution. Occasional small noncaseating granulomata were identified (insert). These histological features were in keeping with a diagnosis of hypersensitivity pneumonitis (H&E, original magnification $\times 100$, insert $\times 400$).

the development of pulmonary fibrosis¹². The changes on biopsy vary widely from inflammation to fibrosis, which may represent the stage at presentation, with some allergens provoking a more severe immune response and causing early presentation, while others will generate a more indolent response and have more fibrosis at presentation^{13,14}. For clinicians, an early diagnosis of drug-associated HP will allow drug cessation and significantly reduce the risk of progression to irreversible fibrosis¹⁴. This may prove difficult and requires a high index of suspicion, as the symptoms are often vague and nonspecific and may be complicated by other underlying pathology¹⁵.

Pulmonary disease related to leflunomide is being described with increasing frequency. In this case the temporal relationship between the introduction of leflunomide and symptoms as well as the complete resolution of radiological changes on cessation, without the need for steroid treatment, make it the most likely etiological agent. The only way to prove absolute causation would be to rechallenge with leflunomide, and this is judged to be unethical. The resurgence of synovitis and development of a rheumatoid serositic pleural effusion on drug withdrawal represents a flare of disease in the absence of DMARD therapy. The pleuritic chest pain on presentation was felt to be consistent with the pathological diagnosis of HP and has been described¹². This indicates that the original CT changes could not have been due to

active rheumatoid disease, as they were present during disease quiescence and resolved during a flare of symptoms.

The recognition of pulmonary side effects of leflunomide is important for rheumatologists involved in the manipulation of DMARD therapy. There have been previous concerns about this drug in similar circumstances¹⁶⁻¹⁹. However, Suissa, *et al*²⁰ found no excess risk for interstitial lung disease with leflunomide when previous MTX use and previous interstitial lung disease were taken into account. Our case represents the onset of lung disease with no history and many months after the cessation of very low-dose MTX. Although it is difficult to prove the causal relationship between leflunomide and HP and although, if present, this association is likely to be rare²⁰, the sequence of events in our case is suggestive of such an association. Rheumatologists who manage patients with leflunomide should consider drug toxicity in the differential diagnosis of patients with new respiratory symptoms.

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