CASE STUDIES

Leflunomide-induced ILD: A rare and potentially fatal complication

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Abstract

A 48-year-old male with rheumatoid arthritis (RA) developed acute respiratory failure 4 weeks after adding leflunomide to existing methotrexate therapy. On high-resolution computed tomography (HRCT) of thorax, the patient demonstrated dramatic improvement, with nearly complete resolution of lung infiltrates, after treatment with pulse steroids and cholestyramine washout. Leflunomide-induced interstitial lung disease (ILD) is a potentially fatal side effect that can be reversed with prompt management.

Keywords: leflunomide, interstitial lung disease, methotrexate

Introduction

Respiratory involvement in rheumatoid arthritis (RA) can be drug induced or due to disease or infection.[1] The present study reports a case of seropositive rheumatoid arthritis (RA) who developed ILD one month after addition of leflunomide to existing methotrexate therapy.

Case report

A 48-year-old male, a chronic smoker and a known case of hypertension, presented to the clinic with a one-year history of inflammatory polyarthritis. Clinical and lab investigations revealed: rheumatoid factor positive, anti-CCP >200 IU/ml, ANA by immunofluorescence negative, c-reactive protein (CRP) 62 mg/l, and ESR 80 mm/hr. Baseline chest X-ray was normal with no interstitial lung disease (ILD). The disease was diagnosed as RA with disease activity score (DAS28) of 7.57. Intra-articular injection was administered to both the knee joints and was initiated with methotrexate 10 mg/week, which was increased to 15 mg/week on subsequent visit after 1 month. However, the disease activity was still high (DAS28: 5.13) even after 2 months and he had gastrointestinal intolerance to oral methotrexate. Hence methotrexate was made parenteral and leflunomide 10 mg/day was added.

After one month, the patient presented with low-grade fever, non-productive cough and breathlessness at rest of 5 days duration. He was admitted in intensive care unit and provided the support of non-invasive positive-pressure ventilation. On examination, his respiratory rate was 30/minute, pulse 140/min, temp: 98.6°F, BP: 130/90 mm/Hg, oxygen saturation (SpO2) on room air was 89% and 94% with fraction of inspired oxygen (FiO2) of 70%. Chest examination revealed bilateral extensive coarse crepitations. Other system examinations were normal. Investigations revealed: hemoglobin 11.6 g%, WBC count 10270 /mm^3 and platelet count 2.3 lac/mm^3. Renal and liver function tests were within normal limits. Arterial blood gas showed a pH of 7.36, pO2 of 52.1 mm Hg, pCO2 of 42 mm Hg and bicarbonate of 23 mmol/L. ECG was indicative of sinus tachycardia, while ECHO was normal with ejection fraction of 60%. Serum procalcitonin was normal.

Chest X-ray showed bilateral diffuse fluffy lung infiltrates. High-resolution computed tomography (HRCT) of thorax revealed bilateral ground glass opacities in all the lung fields with patchy consolidation (Fig. 1). Possibilities considered were: lower respiratory tract infection, rheumatoid arthritis associated-interstitial lung disease (RA-ILD) and drug-induced ILD. The patient was started on IV antibiotics and cholestyramine washout with 8 g three times a day for 11 days. Methotrexate and leflunomide were stopped. Infection work-up was negative (including blood and urine cultures, and H1N1). Bronchoalveolar lavage was not performed. The patient was subsequently administered with methylprednisolone injection 1 g for

3 days followed by prednisolone 0.5 mg/kg. The patient gradually improved over next 4 days and the respiratory support was removed.

He was prescribed with sulfasalazine for treating arthritis after 1 month of follow-up, as he could not afford rituximab. Repeated HRCT thorax showed near complete resolution of lung infiltrates (Fig. 2).

Discussion

Leflunomide is a pro-drug of teriflunomide (A77-1726) that acts by hindering the *de novo* pyrimidine synthesis by reversible inhibition of dihydroorotate dehydrogenase and tyrosine kinase.[2, 3] It is a disease modifying anti-rheumatic drug used for treating RA in those who have inadequate response or contraindication to methotrexate.[4] The usual dose is 10-20 mg/d in adults. Common adverse effects include gastrointestinal (diarrhea, nausea, vomiting, oral ulcers), transaminitis, infections and hypertension.[5]

Prevalence of leflunomide-induced ILD worldwide is around 0.02% and varies among different populations ranging from 0.3-0.5% in Australia to 0.4-1.1% in Japan. Genetic polymorphisms and differences in average body weight between Asians and Caucasians are possible explanations for the variation in prevalence. Leflunomide-induced ILD

Fig. 1: HRCT of thorax on admission

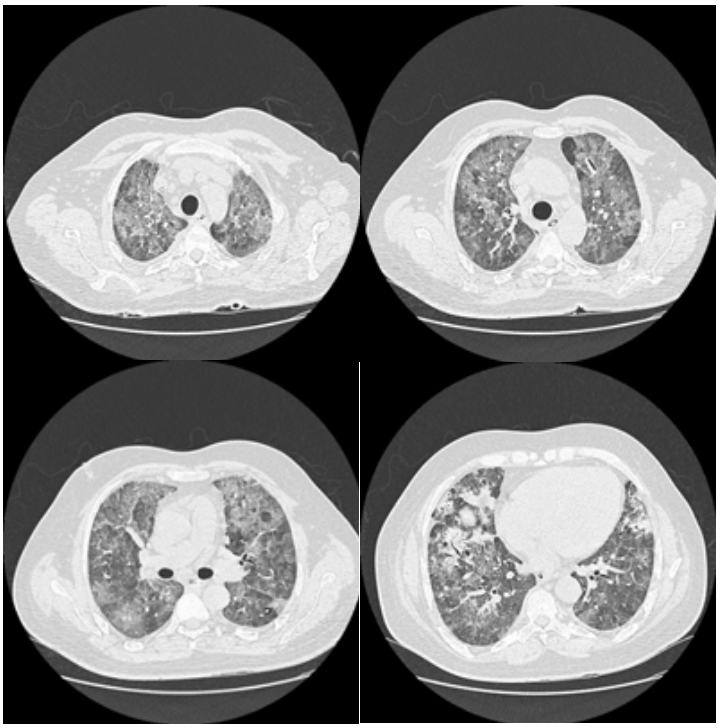
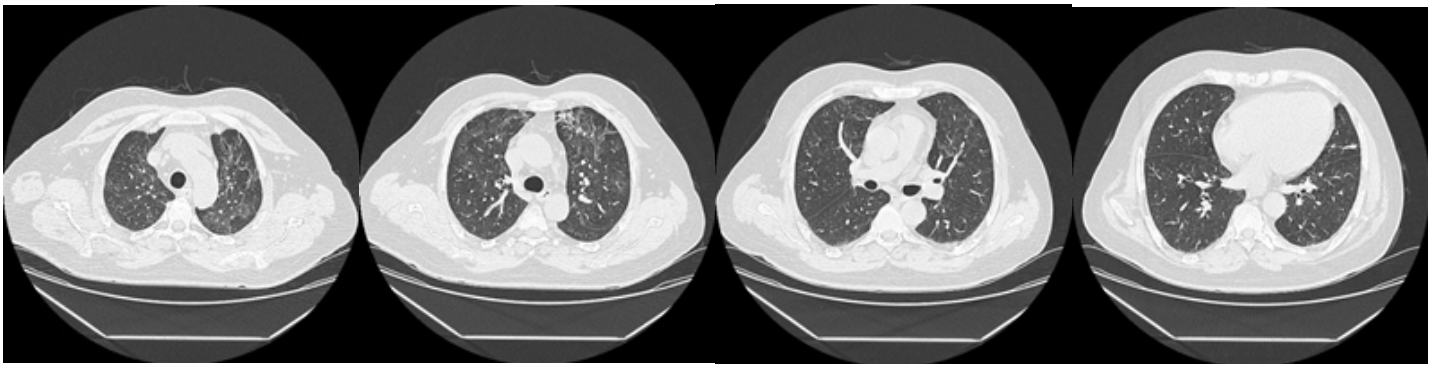


Fig 2: HRCT of thorax after 1 month of admission



generally occurs after a mean duration of 13 (2-133) weeks of treatment and it is associated with a mortality rate of 20-40%.[2] Mice model studies have shown that leflunomide induces epithelial-mesenchymal transition of pulmonary epithelial cells in the presence of other fibrosis-inducing stimuli such as bleomycin.[6] Bilateral diffuse, patchy ground glass opacities or consolidation usually in upper, anterior and central fields are the most common radiologic findings. Honeycombing is seen in 14% patients. No residual changes are usually noted after recovery.[7] Diffuse alveolar damage was the most common finding on histopathology.[2, 3]

Factors that increase risk of ILD include: ethnicity (Japanese> Western), history of methotrexate use, pre-existing ILD (OR -8.2, 95%CI 4.6-14.4), use of a loading dose (OR-4.0, 95% CI 1.2-12.9), low body weight (<40 kg) (OR-2.9, 95% CI 1.1-7.3) and cigarette smoking (OR-3.1, 95% CI 1.7-6.0).[2, 3] Our patient was a smoker and was already on methotrexate. However, he had no pre-existing ILD and loading dose of leflunomide was not used.

Predictors of mortality are pre-existing ILD, severe hypoxemia, need for mechanical ventilation, elevated c-reactive protein, low serum albumin and persistent lymphopenia.[8] Management of leflunomide-induced ILD include drug discontinuation, cholestyramine washout and use of high-dose corticosteroids. Further use of leflunomide in the patient is contraindicated. The present case illustrates a rare and potentially fatal complication of leflunomide therapy that can be managed well, if suspected early.

Competing interests
The author declares that he has no competing interests.

Citation
Jain VK. Leflunomide-induced ILD: A rare and potentially fatal complication. IJRCI. 2017;(5)1:CS3.

Submitted: 28 February 2017, **Accepted:** 23 March 2017, **Published:** 10 April 2017

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