Case Report

Interstitial Pneumonitis Associated with Infliximab Therapy

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ABSTRACT. Interstitial pneumonitis is a well documented, rare complication of methotrexate (MTX). We describe a patient with rheumatoid arthritis (RA) taking MTX for more than 3 years who then developed severe interstitial pneumonitis after a third infliximab infusion. Other similar cases are reviewed. Infliximab may potentiate pulmonary toxicity of MTX. (First Release April 15 2006; J Rheumatol 2006;33:1189–93)

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PNEUMONITIS INFLIXIMAB METHOTREXATE RHEUMATOID ARTHRITIS

Interstitial pneumonitis is a well documented, rare complication of methotrexate (MTX). Its prevalence varies from study to study, but probably occurs in less than 1% of patients. Usually appearing in the first year of treatment, the most common presentation is subacute onset of fever, cough, dyspnea, and pulmonary infiltrates that may be focal or diffuse. Although nondiagnostic, lymphocytosis on bronchoalveolar lavage (BAL) and prominent lymphocytic infiltration on lung biopsy strongly suggest diagnosis of MTX pneumonitis[1]. The usual treatment for it is withdrawal of MTX, in addition to corticosteroids and supportive care. Mortality can reach 20%[1].

We recently observed a patient with rheumatoid arthritis (RA) treated with a stable dose of MTX for more than 3 years who developed severe interstitial pneumonitis shortly after his third infliximab infusion. To date, 7 other similar cases have been reported in the literature. This raises concerns that infliximab may be the primary cause or may potentiate the pulmonary toxicity of MTX.

CASE REPORT

A 70-year-old man with long-standing erosive seropositive RA had persistent synovitis despite oral MTX 22.5 mg per week and prednisone 15 mg. A trial of leflunomide was stopped because of a severe rash. Infliximab was added at 3 mg/kg because of inadequate control with little improvement after 3 doses. However, 9 days after his third infusion, he presented at the emergency room with increasing dyspnea, fever, and fatigue. He had no history of lung disease and was still doing carpentry work on his house just a few days before. Physical examination revealed pulse 100/min, respiratory rate 30/min, temperature 40.2°C, and 94% O_2 saturation on room air. Lungs were clear to auscultation and no other abnormalities were found. Chest radiography showed bilateral interstitial infiltrates in the superior two-thirds of the lung that were not present on previous radiographs (Figure 1). Laboratory studies revealed minor leukocytosis (10.1×10^6) with a predominance of neutrophils (87%) but no eosinophils. Arterial blood gases on room air were: pH 7.46; $PaCO_2$ 33 mm Hg; PaO_2 61 mm Hg; HCO_3 23 mg/dl. Sputum cultures could not be obtained, and the rest of the investigation for infection was negative. At that time, he was treated with oxygen and received a short course of methylprednisolone because he became hypotensive.

High-resolution computer tomography (HRCT) showed bilateral ground-glass infiltrates in the superior two-thirds of the lung, without nodules, lymphadenopathy, bronchiectasis, or fibrosis (Figure 2). BAL revealed alveolitis with predominance of lymphocytes and some eosinophils. Gram stain was negative, but culture revealed aspergillus, and he was given caspofungin. Other cultures including *Pneumocystis carinii*, cytomegalovirus, tuberculosis, and other mycobacterial infections were negative. After discussion with the microbiologist and the pulmonologist, aspergillus was considered to be the colonizing organism. Caspofungin was stopped, and he was treated with oral itraconazole 200 mg per day for prophylaxis. MTX was discontinued, and oral prednisone 50 mg per day was begun and then increased to 100 mg per day for lack of improvement. The patient slowly improved and was discharged one month later with home oxygen therapy and prednisone 50 mg twice a day, which was gradually tapered. Two months later, MTX 22.5 mg orally per week was reintroduced by the pulmonologist. Infliximab was discontinued. Six months later, chest radiography showed important regression of the infiltrates (Table 1 and Figure 3); however, on HRCT scan of the lungs 6 months later, infiltrates and ground-glass areas were about the same.

DISCUSSION

Interstitial pneumonitis is a severe but rare complication of MTX. Patients who develop MTX toxicity tend to do so in the first year of therapy[1]. In our case, the patient had been taking MTX for 10 years, including a stable dose for the past 3 years, making the diagnosis less likely. The bilateral ground-glass infiltrates on chest CT and predominance of lymphocytes with eosinophils on BAL cellular analysis suggested alveolitis of noninfectious cause, and aspergillus found on BAL culture was considered to be a colonizing organism. Moreover, aspergillus antigen detection assay, which has a sensitivity of 94.4% and a specificity of 98.8%, was negative[2].

The time-relation between the introduction of infliximab and appearance of symptoms was highly suggestive of infliximab-induced pneumonitis. We did a Medline search using the words "pneumonitis," "interstitial lung disease," "infliximab,"

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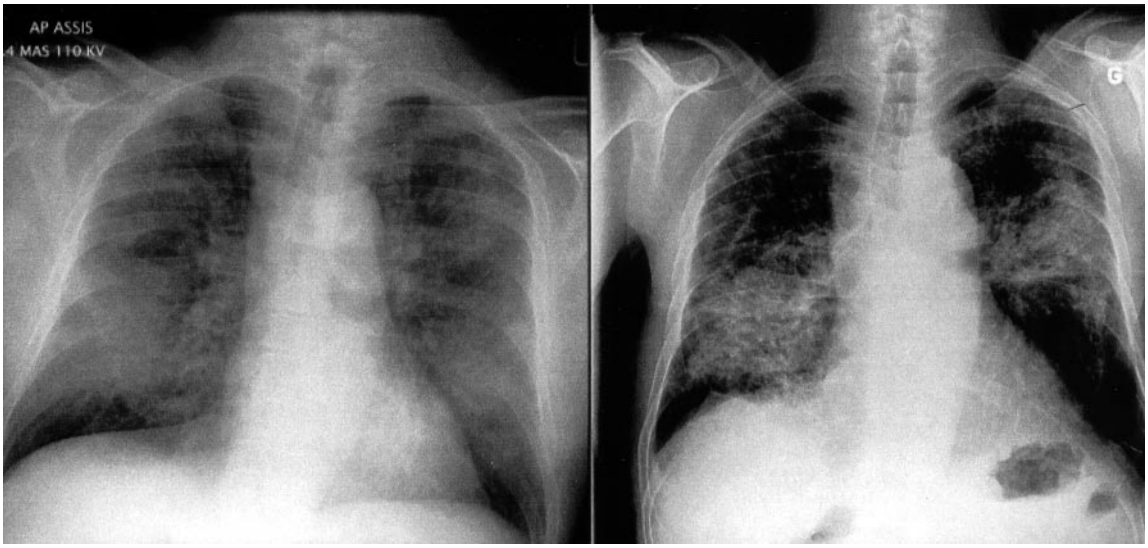

Figure 1. Chest radiograph on admission (left) and 1 month later (right).

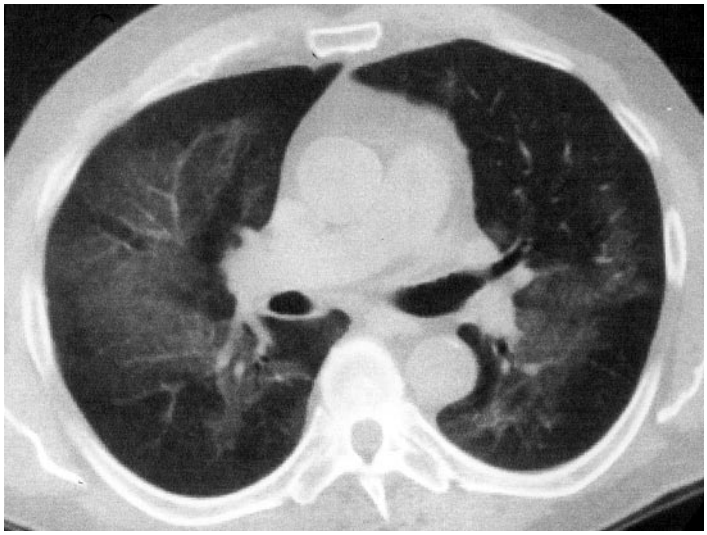

Figure 2. Bilateral ground-glass infiltrates in the superior two-thirds of the lungs.

and "Remicade." Seven other cases of life-threatening diffuse interstitial pneumonitis related to infliximab therapy in patients with RA have been reported[3-5] (Table 2). All patients were treated with stable dose MTX and developed symptoms shortly after a third infliximab infusion, except Patient 7, who was receiving leflunomide instead of MTX and who developed symptoms after a second infusion. All patients had radiologic findings compatible with drug-induced pneumonitis. When available, histology showed proliferation of type II pneumocytes with alveolar damage and varying degrees of fibrosis, which is characteristic of MTX pneumonitis[6]. Only Patient 7 had preexisting lung disease, with CT showing honeycombing and a somewhat more chronic disease. In spite of this finding, the author of the report felt the strong temporal association and rapid development of symptoms suggested causality between the initiation of infliximab and interstitial lung disease[5]. However, we found one case of leflunomide-induced pneumonitis[7]: a 49-year-old Japanese man with RA who developed interstitial pneumonia 17 days after administration of leflunomide[7].

The only cases of pneumonitis related to infliximab monotherapy were eosinophilic pneumonia in a patient with Crohn's disease[8] and pulmonary granulomatosis in a patient with spondyloarthropathy[9]. These are distinctive pathological entities. Many similarities between our case and the 7 others suggest a role of infliximab in development of pulmonary symptoms. First, there is a strong temporal relationship, all patients reporting symptoms shortly after a second or third

Table 1. Evolution of interstitial pneumonitis in our patient.

	Day 1 (admission)	Day 8	Day 22	1.5 mo	6 mo
Respiratory rate	20	20	20	NA	NA
Oxymetry	93%	93%	93%	90% room air	NA
O_2	4 l/min	VM 50%	5 l/min	On exertion only	None
Temperature, °C	36.7	38.4	36.4	NA	NA
Corticosteroids	Pred 15 mg	MP 40 mg IV q6h started	Pred 100 mg/day	Pred 100 and 25 mg every other day	Pred 5 mg/day
Chest radiograph	Interstitial infiltrates, upper 2/3 of lungs	Increase of infiltrates	Unchanged	Substantial clearing of infiltrates	Small improvement vs 1.5 mo

Pred: prednisone; MP: methylprednisolone; NA: not available.

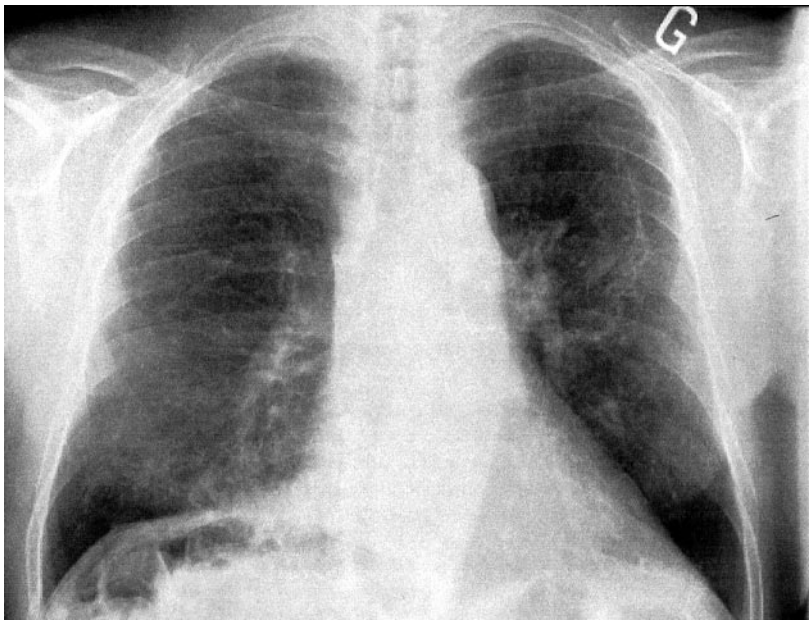

Figure 3. Important clearing of infiltrates at 6 months.

infliximab infusion. Second, patients were taking MTX or leflunomide at a stable dose for many years before pneumonitis developed.

In addition, radiographic findings had not completely disappeared at 6 months and were unchanged on HRCT scan despite symptomatic improvement. This is an unusual course for MTX pneumonitis as complete resolution is expected quickly. Infliximab-induced pneumonitis may be different from MTX-induced pneumonitis, or infliximab may alter the normal course of MTX pneumonitis.

Mechanisms by which infliximab can trigger interstitial pneumonitis or potentiate the pulmonary toxicity of MTX are still unclear, but could be related to deficient apoptosis of infiltrating inflammatory cells. Kuroki, *et al*[10] have demonstrated an accelerated form of bleomycin-induced pneumonitis and pulmonary fibrosis in tumor necrosis factor (TNF) –/– mice in comparison with TNF +/+ mice. TNF promotes tissue repair in the lungs, eliminating inflammatory cells by apoptosis. The mechanisms by which this is done are still not completely understood and are probably complex. The opposite has been shown to happen in the synovium and in the lamina propria of patients with Crohn's disease, in which anti-TNF infliximab induces apoptosis of inflammatory cells[11,12]. This difference may depend on the ability to recognize certain adhesion molecules. Catrina, *et al* demonstrated that infliximab decreases the synovial cellularity mainly by inducing apoptosis of the CD68-positive monocyte/macrophage population[11]. Binding to certain surface markers, infliximab may produce somewhat different effects, depending on the inflammatory cell population of the tissue, having an opposite effect

Table 2. Patients and disease characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Sex	F	F	F	F	F	F	F	M
Age, yrs	64	63	80	72	70	68	84	70
Disease characteristics								
Duration	NA	NA	NA	NA	NA	NA	NA	12 yrs
RF	–	+	+	NA	NA	NA	+	+
Nodular	+	NA	NA	NA	NA	NA	NA	No
Erosive	NA	NA	NA	NA	NA	NA	+	+
Methotrexate								
Dose	25 mg	25 mg	25 mg	10 mg	NA	NA	None	22.5 mg
Po/SC	po	SC	SC	NA	NA	NA		po
Duration	NA	NA	NA	6 yrs	NA	NA		10 yrs
Infliximab								
Dose, mg/kg	3	3	3	3	NA	NA	3	3
No. of infusions	3	3	3	3	3	3	2	3
Other medications	Pred 10 mg/day CSA 5 mg/kg	Pred 15 mg/day	Pred 5mg/day, SSZ 500 bid, HCQ 300/day	None	NA	NA	Leflunomide 10 mg/day	Pred 15mg/day
Clinical presentation								
Symptoms at onset	SOB, fever, night sweats	Fever, SOB	Fever, SOB	Fever, SOB	NA	NA	Fever, SOB, nonproductive cough	Fever, fatigue, SOB
Timing with IFX	1 wk after 3rd infusion	Soon after 3rd infusion	3 wks after 3rd infusion	4 wks after 3rd infusion	After 3rd infusion	After 3rd infusion	2 wks after 2nd infusion	2–3 days after 3rd infusion
Severity	Ventilatory aid	Hypoxemia	Hypoxemia	Ventilation	NA	NA	Hypoxemia	Hypoxemia
Radiographs	Bilateral infiltrates	Normal (CT +)	Bilateral infiltrates	Bilateral infiltrates	NA	NA	Bilateral infiltrates	Bilateral infiltrates
Biopsy	Done	Done	Done	Post-mortem	Done	Not done	Not done	Not done
Treatment	MP 120 mg/day	TMP/SMZ, MP 60 mg q6h	MP 60 mg q6h	MP, broad-spectrum antibiotics	NA	Antibiotics, high-dose corticosteroid	Moxifloxacin, azithromycin	Pred 100 mg/day, itraconazole 200 mg po/day
Evolution	Good	Good	Good	Died	NA	Good	Remains severely dyspneic	Good
Reference	3	3	3	4	4	4	5	Present case

NA: not available, RF: rheumatoid factor, CSA: cyclosporine, Pred: prednisone, SSZ: sulfasalazine, HCQ: hydroxychloroquine, SOB: shortness of breath, IFX: infliximab, CT: computerized tomography, MP: methylprednisolone, TMP/SMZ: trimethoprim/sulfamethoxazole.

on the lungs in comparison to the synovium. In the lungs, TNF inhibits the clearing of inflammatory cells, leading to the free expression of MTX toxicity and development of interstitial pneumonitis. Infliximab, being an anti-TNF agent, might play a permissive role, leading to the free expression of MTX toxicity and development of interstitial pneumonitis. The longer half-life of infliximab could also be responsible for the slow clearing of infiltrates.

In recent years, we have paid attention to the infectious complications of infliximab and other anti-TNF agents, but our experience with these agents is still limited and other potential toxic effects might be unknown. Our experience and the 7 other similar cases suggest that infliximab might also play a role in the development of interstitial pneumonitis similar to that of MTX.

Our observations should prompt awareness about pulmonary symptoms in patients receiving both MTX and infliximab, especially when acute symptoms arise around the time of the first few doses. Rare complications only emerge after several years of use in large cohorts. To date, there is no consensus on preventing or screening for MTX pneumonitis. Preexisting lung disease, old age, and previous use of disease-modifying antirheumatic drugs in RA are the only identified risk factors[6]. Screening of patients with pulmonary function test and chest radiographs (CR) or only spirometry and baseline CR, with further investigations on abnormal findings, is now recommended[6,13]. In the meantime, we recommend that patients be reminded about possible pulmonary toxicity when starting infliximab therapy. They should cease MTX and seek medical help promptly if they develop new severe pulmonary symptoms.

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