**REVIEW**

*Mycobacterium* other than tuberculosis (MOTT) infection: An emerging disease in infliximab-treated patients

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MAC; Infliximab; IRIS; MOTT

**Summary**  
Objectives: Infliximab has revolutionized treatment of rheumatologic diseases and inflammatory bowel disease. However, it increases the risk of tuberculosis. Less is known about the development of *Mycobacterium* other than tuberculosis (MOTT) infection. We review the literature on non-tuberculous mycobacterial infections in infliximab-treated patients and report the first case of disseminated *Mycobacterium avium* complex in an infliximab-treated patient complicated by immune reconstitution inflammatory syndrome.

Methods and results: MEDLINE search with the keywords mycobacteria and infliximab revealed four cases of MOTT in patients treated with infliximab: fatal *Mycobacterium peregrinum* pneumonia in a patient with polymyositis and dermatomyositis; a patient with rheumatoid arthritis with skin and soft tissue infection with *Mycobacterium abscessus*; *Mycobacterium fortuitum* in a patient with rheumatoid arthritis; and a case of pulmonary MAC without dissemination.

Review of US data from 1998 to 2002 published by Wallis et al. revealed that out of more than 233,000 patients treated with infliximab, 30 developed unspecified mycobacterial species infection. No further data was available regarding these cases.

Conclusion: MOTT infection is a rare but emerging complication of infliximab therapy. MOTT cases tend to progress rapidly in infliximab-treated patients and withdrawal of infliximab therapy can result in immune reconstitution.

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Introduction

The TNF-α inhibitor infliximab has had a significant impact in the treatment of rheumatologic diseases and inflammatory bowel disease (IBD). However, the widespread use of this and related agents, etanercept and adalimumab, have increased the incidence of opportunistic infections, such as those caused by mycobacteria. Tuberculosis is the most common infection associated with infliximab use, and the risk is independent of concurrent use of steroids, disease modifying anti-rheumatologic agents such as methotrexate, and the rheumatologic diseases themselves. This risk is less clear for Mycobacterium other than tuberculosis (MOTT), particularly Mycobacterium avium complex (MAC). To date, only one case of pulmonary MAC and three cases of MOTT associated with infliximab use have been reported in the literature.

Immune reconstitution inflammatory syndrome (IRIS) is a well-described entity in HIV-infected patients, particularly those with CD4 counts <50 cells/mm³ with incubating opportunistic infections when initiating highly active antiretroviral therapy. IRIS is felt to be mediated by recognition of circulating antigens by a recovering immune system that heretofore mounted a minimal response. IRIS has been described for a variety of diseases in HIV patients, including MAC lymphadenitis and pulmonary and central nervous system tuberculosis. While IRIS to tuberculosis associated with infliximab use in HIV-uninfected individuals has been described; no cases of IRIS to MAC have been reported for this subset of patients.

Review of literature and correspondence with other investigators revealed no cases of disseminated MAC infection in infliximab-treated patients. We report the first documented case of disseminated MAC in a patient treated with infliximab, and subsequent IRIS after its discontinuation.

Case

A 36-year-old African-American female was admitted to our institution following an abdominal CT scan showing new air space opacities at the base of the lingula. She had a long-standing history of Crohn’s disease, treated with steroids and a subtotal colectomy. She started infliximab five years prior to admission, and had been regularly receiving 5 mg/kg infusions bimonthly for the past two years. She had an excellent clinical response to treatment, with decreased diarrhea and frequency of flares.

She had been feeling poorly several months prior to admission. She lost 10 kg despite a normal appetite. She also had occasional chills and night sweats and an intermittent productive cough without hemoptysis.

She had a history of depression, peripheral neuropathy, vaginal fistulae and herpes simplex esophagitis. She was taking ciprofloxacin, metrizapine, meclizine, mesalamine, acetaminophen, and infliximab at the time of admission. Her most recent infliximab infusion had been two months prior to admission.

On admission, her blood pressure was 106/66 mmHg, pulse 116, and temperature of 35.9 °C. Oxygen saturation was 99%. She weighed 42.8 kg. She was cachectic but comfortable although slightly tachypneic. Her lungs were clear. The rest of her examination was unremarkable.

Her leukocyte count was 10,300/ml, hemocrit of 35% with 90% neutrophils, and normal renal function and electrolytes except for mild hypokalemia of 3.4. Hepatic enzymes were normal.

Hospital course

The patient was admitted under the hospital’s tuberculosis isolation protocol. Sputum smears yielded acid-fast bacilli (AFB) 4+. Chest X-ray and computed tomography (CT) (Fig. 1) were done showing an extensive cavitary lesion involving the left upper lobe and smaller cavitary lesions within the anterior and superior segments of the left lower lobe. Because of the concern not only for tuberculosis but also for MOTT, she was started on empiric treatment with rifampin, isoniazid, ethambutol, pyrazinamide as well as ciprofloxacin and azithromycin.

Initial sputum AFB culture became positive within one week. The gene probe was positive for MAC and negative for tuberculosis. PCR for tuberculosis was sent and was negative. Final sputum cultures grew MAC. AFB blood cultures on admission subsequently grew one out of two sets AFB, identified as MAC on gene probe.

Isoniazid and pyrazinamide were stopped and she was continued on rifampin, ethambutol, ciprofloxacin and azithromycin with gradual improvement in clinical status. Peak blood levels of all administered drugs (obtained because of concerns about gastrointestinal absorption with concurrent Crohn’s disease) were in the therapeutic range. She was discharged to home and no further infliximab treatment was administered; no other systemic immunosuppressive therapy was given. She was also started on total parenteral therapy for severe malnutrition.

She was readmitted three weeks later with a fever of 38 °C, increased cough and worsening diarrhea. Her MAC regimen was continued and she was started on vancomycin and piperacillin–tazobactam. Repeat CT of her chest showed worsening left upper lobe cavitary opacity with new infiltrates in the right upper and middle lobes, and increased left lower lobe infiltrates. Extensive workup for other infections including fungal and viral etiologies was pursued and was negative. She underwent bronchoscopy with broncho-alveolar lavage (BAL) which was smear negative but grew MAC 1+ with identical susceptibility as the original culture. Empiric antibiotics were discontinued and she gradually improved and was transferred to a rehabilitation facility without the introduction of anti-inflammatory or immunosuppressive agents.

Discussion

TNF-α inhibitors have revolutionized the treatment of rheumatologic diseases and IBD. This class of drugs includes infliximab, etanercept, and adalimumab. Infliximab and etanercept are the two most extensively studied TNF-α inhibitors. Infliximab is considered to be more potent than etanercept because infliximab binds both monomeric and trimeric forms of soluble TNF-α, while etanercept only binds the trimeric form. Moreover, etanercept binds less avidly to transmembrane TNF-α than infliximab.
Infliximab is currently used for the induction and maintenance of remission in IBD. Although the overall rate of discontinuation in clinical trials was only 1.9%, a review of a large case series from the Mayo Clinic indicated serious adverse events in 8.6% of patients. In this series, serious infections including pneumonia were the most common event, though no cases of TB were reported. An initial case series of 70 patients administered infliximab who developed TB as reported to the MEDWATCH system were first reported in 2001 and included 56% with extrapulmonary disease and 24% with disseminated TB. Most cases occurred within three months of beginning therapy, suggesting reactivation of latent infection. The FDA Advisory Committee subsequently reviewed the safety of TNF inhibitors in 2001 and noted that in more than 170,000 patients worldwide treated with infliximab, 84 patients developed TB and none developed atypical mycobacterial infection. For etanercept, out of about 104,000 patients, 11 developed TB and eight developed atypical mycobacteria including six cases of MAC and one case each of Mycobacterium kansasii and Mycobacterium marinum. Preventive efforts in this patient population are limited by the frequency of anergy to TB skin testing and thus baseline chest radiographs in patients with risk factors for TB have sometimes been recommended.

A later review evaluating US data from 1998 to 2002 revealed that out of more than 233,000 patients treated with infliximab, 335 developed TB infection and 30 developed unspecified mycobacterial species infection. The data for etanercept showed that out of more than 113,000 patients treated, 30 developed TB and seven developed unspecified mycobacterial species infection. There was a statistically significant difference in the Mycobacterium species infection rate between infliximab and etanercept (p = 0.023 by the Poisson analysis). Personal communication with Dr. Wallis revealed no clear-cut cases of MAC for infliximab.

Three cases of MAC in patients using etanercept are reported in the literature. One patient grew MAC from BAL specimens; but this was felt to be colonization as the lung pathology was thought to be secondary to drug reaction. Another case presented as a psoriasis abscess. Lastly, a patient developed clinical disease with multiple positive MAC sputum cultures.

Only four cases of non-tuberculous mycobacteria are reported in the literature for patients treated with infliximab. Fatal Mycobacterium peregrinum pneumonia in a patient with polymyositis and dermatomyositis was documented. A patient with rheumatoid arthritis developed skin and soft tissue infection with Mycobacterium abscessus. Okubo and his colleagues reported pulmonary MAC in a patient treated with infliximab but without dissemination. Finally, a patient with rheumatoid arthritis developed Mycobacterium fortuitum granulomatous hepatitis.

Paroxysmal reaction (PR) compatible with IRIS was reported in four patients who stopped infliximab after developing tuberculosis. The time frame for developing PR was from 5 to 16 weeks after cessation of infliximab. Belknap and his colleagues reported IRIS in a woman who developed tuberculosis on infliximab three months after discontinuing therapy.

Our patient’s course is compatible with IRIS since she worsened clinically and radiologically after stopping infliximab with no alternative pathogens while on MAC treatment, and MAC was isolated from a subsequent BAL specimen.

While the increased risk for reactivation of latent tuberculosis on treatment with TNF-α inhibitors is well-described, less is known about the risk for MOTT in these hosts. The pathogenesis of MOTT disease is similar to tuberculosis and so the inhibition of TNF-α, which facilitates granuloma formation, increases the likelihood of developing disease. However, the rarity of MOTT infections in TNF-α inhibitor treated patients precludes the definitive demonstration of
increased risk. Whether MOTT infection is reactivation or primary infection is difficult to tease out and is further confounded by the underlying rheumatologic disease and concurrent treatment with other immunomodulating drugs. The higher incidence of TB versus MOTT in TNF-α inhibitor treated patients likely reflects the higher incidence of TB versus MOTT in the general population and is not necessarily an intrinsic consequence of infliximab treatment. One common feature of the MOTT cases described is the rapid progression of disease, which may be associated with TNF-α inhibitor treatment. Moreover, these cases of MOTT illustrate that in patients treated with infliximab who develop lung infiltrates, MOTT should be in the differential diagnosis and, based on our case of disseminated MAC, obtaining AFB blood cultures should be considered. With the development of mycobacterial disease, TNF-α inhibitors should always be discontinued, but IRIS should be considered strongly if clinical and radiologic deterioration occurs in the appropriate time frame after cessation of these drugs.

Conflict of interest

The authors have no conflict of interest.

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References