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REVIEW

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

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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).[1] 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.[1–3] 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.[4] This risk is less clear for *Mycobacterium* other than tuberculosis (MOTT), particularly *Mycobacteriuim 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.[5–8]

Immune reconstitution inflammatory syndrome (IRIS) is a well-described entity in HIV-infected patients, particularly those with CD4 counts $<$50 cells/mm^3 with incubating opportunistic infections when initiating highly active antiretroviral therapy.[9] IRIS is felt to be mediated by recognition of circulating antigens by a recovering immune system that heretofore mounted a minimal response.[9] IRIS has been described for a variety of diseases in HIV patients, including MAC lymphadenitis and pulmonary and central nervous system tuberculosis.[9] While IRIS to tuberculosis associated with infliximab use in HIV-uninfected individuals has been described[10,11]; 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, mirtazipine, 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, hematocrit 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 brocho-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.[1,2,12]