Disseminated Tuberculosis After Treatment with Infliximab

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Medications that block the effect of the pro-inflammatory cytokine tumor necrosis factor α (TNF-α) are increasingly being used in clinical practice. The most widely used of these agents is infliximab, a chimeric immunoglobulin G (IgG) monoclonal antibody targeting TNF-α.[1] Infliximab repeatedly has been shown to be effective in patients who have rheumatoid arthritis (RA) and an unsatisfactory response to methotrexate and in patients who have severe, steroid-dependent, fistulizing Crohn's disease.[2–4] However, TNF-α antagonists have significant potential for adverse events that are often poorly recognized by prescribing physicians. This case report presents one such adverse event, reviews the literature on the adverse event profile of infliximab, and discusses a general framework for monitoring of treated patients.

CASE PRESENTATION
Patient Presentation

A 56-year-old white woman with a history of RA and mild heart failure presented to her family physician in early September because she continued to feel unwell after a flu-like illness. Symptomatic treatment was prescribed for a perceived self-limited condition. Over the next month, the patient experienced an insidious onset of diarrhea, fevers, and malaise. She returned to her physician in mid December, at which time her symptoms had progressed to include weakness, a minimally productive cough, and a 10- to 15-lb weight loss. Outpatient evaluation revealed a right upper lobe process on a chest radiograph and mild hypoxia.

The patient was directed to the local community hospital, where she was admitted and treated with intravenous fluids and broad-spectrum antibiotics for community-acquired pneumonia. Findings on routine blood, urine, and sputum cultures were unrevealing. Despite treatment, the patient's fever persisted and her oxygen requirements escalated, prompting transfer to the regional university hospital. On presentation there, she appeared ill and diaphoretic while receiving supplemental oxygen; her initial laboratory values were significant for hyponatremia with a normal complete blood count.

Medical History

The patient was reported to have New York Heart Association class III heart failure that was well controlled with an angiotensin-converting enzyme inhibitor and furosemide, with a left ventricular ejection fraction estimated at 45%. She also had a life-long history of RA, treated with methotrexate, low-dose prednisone, and the recent addition of infliximab 4 mg/kg by intravenous infusions at 6-week intervals; she had received a total of 4 infusions at the time of presentation. Her medical history was also significant for hypothyroidism, depression, and remote alcohol and tobacco use; her health maintenance records, including tuberculin skin test results, were unknown.

Physical Examination and Laboratory Studies

Physical examination revealed an ill-appearing, middle-age woman in moderate respiratory distress. Her oral temperature was 39.9°C, blood pressure was 133/65 mm Hg, heart rate was 115 bpm, and respiratory rate was 40 breaths/min with an oxygen saturation of 93% while receiving 6 L of oxygen. Her oropharynx was dry with minimal sputum and her neck was supple with an estimated 8 cm of jugular venous distention. Lung examination revealed wheezing throughout with some decreased sounds and mild dullness to percussion at the right upper lobe. Heart sounds were distant and tachycardic, while the abdomen and extremities were normal. Further laboratory tests were significant for hyponatremia at 124 mEq/L (normal, 135–145 mEq/L) and abnormal liver function test results, including an alanine aminotransferase of 357 U/L (normal, 1–45 U/L), aspartate aminotransferase of 487 U/L (normal,

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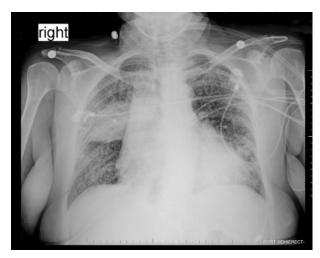
Figure 1. Chest radiograph at hospital presentation shows miliary opacities, wide mediastinum, and a right upper lobe process suggestive of disseminated tuberculosis.
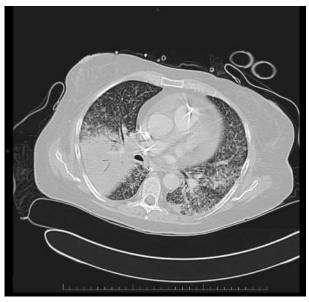

Figure 2. Chest computed tomography scan shows a right upper lobe consolidation, pericardial effusion without tamponade, and miliary airspace disease.

1–40 U/L), total bilirubin of 1.9 mg/dL (normal, 0.1–0.4 mg/dL), alkaline phosphatase of 195 U/L (normal, 40–110 U/L), albumin of 1.9 g/dL (normal, 3.5–5.5 g/dL), and an international normalized ratio of 1.5. The remaining electrolyte values were unremarkable. Repeat cultures of blood, urine, and sputum were unrevealing. Electrocardiography showed a sinus tachycardia with nonspecific repolarization abnormalities. A repeat chest radiograph was significant for diffuse miliary opacities throughout the lung fields (**Figure 1**).

Continued Hospital Course

Soon after transfer to the university hospital, the patient's respiratory status progressively deteriorated and she required admission to the intensive care unit with mechanical ventilation and vasopressors to correct respiratory failure and hypotension. A bedside transthoracic echocardiogram showed a moderate pericardial effusion without tamponade and depressed systolic function that was consistent with previous studies. A Swan-Ganz catheter was placed and showed low central venous pressure, with cardiac output and systemic vascular resistance values suggestive of volume depletion and sepsis. Computed tomography (CT) of the chest (**Figure 2**) and abdomen confirmed the miliary airspace disease and pericardial effusion while also showing several nonenhancing hepatic lesions.

Based on the radiographic findings, history of medical immunosuppression, and the refractory nature of the respiratory disease with scant sputum and a normal neutrophil count, tuberculosis (TB) was placed high on the list of differential diagnoses. The diagnoses of

bacterial pneumonia, histoplasmosis, viral infection, and lymphangitic spread of a malignancy were thought to be less likely. The patient began therapy with isoniazid, rifampin, ethambutol, and pyrazinamide as well as lipid-complex amphotericin, piperacillin-tazobactam, and azithromycin. Conventional antibiotics were continued pending blood culture results, which were ultimately unrevealing. On hospital day 2, fiberoptic bronchoscopy visualized scant respiratory secretions; evaluation of aspirate showed 3+ acid-fast bacilli, which were determined by DNA probe to be *Mycobacterium tuberculosis*.

On hospital day 4, the patient's hepatic function deteriorated. A subsequent CT-guided liver biopsy was performed to assess the hepatic lesions noted on the initial CT; results were significant for necrotic tissue and acid-fast bacilli. Over the next 2 weeks, the patient's course in the intensive care unit was complicated by episodes of hypotension refractory to intravenous fluids, steroids, and 3 vasopressors. The patient developed acute renal failure and hematochezia, both hypothesized to be of ischemic origin. Subsequent lactic acidosis and uremia resulted in a profound anion gap metabolic acidosis, and despite aggressive medical intervention, the patient died after 3 weeks of hospitalization. Autopsy was declined. The diagnosis at the time of death was disseminated TB secondary to medical immunosuppression and presumed reactivation of latent disease.

DISCUSSION
TNF-α Antagonists

Evidence shows that TNA-α has a central role in several inflammatory disease processes, including RA, ankylosing spondylitis, and inflammatory bowel disease (IBD especially Crohn's disease).[4,5] Appreciation of the importance of TNF-α in disease pathogenesis has led to the development of 3 biologic agents that block the effect of this cytokine. The most extensively studied and widely used of these agents is infliximab.[1,5] Trials in the late 1990s demonstrated the utility of infliximab in inducing and maintaining remission in moderate-to-severe, steroid-refractory, and/or fistulizing Crohn's disease.[2,3] In 2000, the US Food and Drug Administration (FDA) approved infliximab for use in conjunction with methotrexate for the treatment of RA. For RA patients with an unsatisfactory response to methotrexate, the addition of infliximab is effective in inhibiting the progression of structural joint damage, reducing signs and symptoms of RA, and improving functional capacity in patients with active RA.[4] The FDA has approved 2 other TNF-α antagonists for treating RA: etanercept and adalimumab. Both have been shown in clinical trials to produce significant clinical improvements comparable with infliximab when added to methotrexate for patients with persistently active RA.[6,7]

The effectiveness of anti-TNF-α therapy for RA is supported by a recent systematic review of the literature that noted that remission or very low disease activity was achieved in 30% to 50% of RA patients treated with an anti-TNF-α agent.[8] Another review article suggests that infliximab has a favorable side-effect profile compared with corticosteroids, which are associated with many side effects after prolonged use.[5] Given the clinical efficacy of the anti-TNF-α drugs, their clinical use is likely to continue to increase, especially as the FDA approved infliximab for treating ulcerative colitis in 2005. However, as the case presented here demonstrates, awareness of the potential for serious complications (eg, infection) is mandated, and screening and monitoring patients receiving treatment is warranted.

Infectious Complications Associated with Infliximab

The evolution of data and clinical experience regarding the use of infliximab has been rapid, with numerous reports in the medical literature. The manufacturer of infliximab (Centocor, Inc.; Horsham, PA) states that serious infections have been reported in patients taking TNF-α antagonists, including sepsis, pneumonia, and fatal infections.[9] Potential reactivation of TB and hepatitis B infection are highlighted based on clinical experiences. Caution is recommended when using infliximab in the presence of chronic, recurrent, or active infection. Additionally, severe hepatic reactions, demyelinating disease, bone marrow suppression, and worsening of congestive heart failure (CHF) have been reported.[1]

Multiple case reports of patients receiving TNF-α antagonists document in particular the dissemination of intracellular pathogens normally controlled by the cell-mediated granulomatous inflammatory process.[10,11] TB, histoplasmosis, listeriosis, and aspergillosis are the most frequently reported infections.[12] In several of these cases, reactivation of a previously controlled infection occurred within several months of the initial dose of anti-TNF-α therapy.[11] Most of these case reports concern infliximab. For all 3 anti-TNF-α agents, the relationships between dose, duration of therapy, and infection risk remain unclear.[11] In controlled trials, serious infections were observed in approximately 5% of all patients treated with infliximab through 2003.[13]

A 2004 report from the Mayo Clinic reviewed the clinical course of 500 patients treated with infliximab for Crohn's disease over a 17-month period.[14] Therapy was generally well tolerated, but serious adverse events were reported in 43 patients (9%). Of these, 30 (6%) were attributable to infliximab. Serum sickness-like reactions occurred in 14 patients, 3 developed drug-induced lupus, and 1 developed a new demyelinating disorder. An infectious event occurred in 48 patients, of which 41 cases (8%) were attributed to infliximab. In 20 patients, serious infections occurred, including fatal sepsis (2 cases), pneumonia (8 cases), abdominal abscesses (2 cases), viral infections (6 cases), cellulitis (1 case), and disseminated histoplasmosis (1 case). Malignant disorders were reported in 9 patients, of which 3 cases were possibly related to infliximab. A total of 10 deaths occurred, of which 5 (1%) were possibly related to infliximab.

Particularly relevant to the case reported here, Keane et al[15] analyzed all reports of TB after infliximab therapy that had occurred as of 2001. They found 70 reported cases of TB among the approximately 147,000 treated patients, a frequency much higher than the reported frequency of other opportunistic infections in patients who received infliximab.[12,15] These patients had received treatment for a median of 12 weeks. In 48 patients, TB developed after 3 or fewer infusions. Extrapulmonary disease occurred in 40 patients (17 with disseminated disease). Of the 70 cases, 64 were from countries with a low incidence of TB. By March 2003, 242 cases of TB associated with infliximab therapy had been reported through the FDA's Adverse Event Reporting System.[12] Interestingly, excess TNF-α in association with TB is thought to cause weight loss and night sweats, yet

in animal models TNF-α has a protective role in the host response to TB infection, suggesting that TNF-α blockade may increase susceptibility to TB.[16]

Prevention of infectious complications. Active, chronic, or recurrent infections should be a near-absolute contraindication for the use of TNF-α antagonists. Importantly, clinicians should be vigilant in screening patients for active infections and educating patients about the typical signs and symptoms of significant infection. TNF-α antagonists should be discontinued in any patient who develops signs of a serious infection.

Prior to initiating treatment with a TNF-α antagonist, all patients should be screened for active and latent TB; a purified protein skin test is mandatory and there should be a low threshold for a screening chest radiograph. A detailed patient history is important because up to 70% of patients with IBD who are considered for infliximab treatment are anergic to skin testing.[17] TB chemotherapy should be initiated in all patients with primary TB and in those at high risk for reactivation; patients with a history of properly treated TB have no need for chemoprophylaxis.[18,19] Physicians should also be cognizant of each individual's risk for infection, such as in residents of the Ohio River Valley and their risk of disseminated histoplasmosis and in patients who travel internationally. Additionally, the FDA advises that patients receiving TNF-α antagonists should be advised to avoid foods that are potential sources of pathogenic bacteria (eg, unpasteurized dairy products) and heat all foods properly to avoid infections with organisms such as *Listeria*.[20]

Other Potential Complications

The teratogenic effect of TNF-α blockade has not been studied in controlled trials; however, infliximab has an FDA category B rating for pregnancy (ie, no evidence of risk to humans). Reviews have found similar rates of birth defects and miscarriages in the general population compared with pregnant women exposed to infliximab.[21]

Heart failure. The use of infliximab is associated with worsening CHF. The manufacturer of infliximab (Centocor) recommends caution and close monitoring for the use of infliximab in patients with known heart failure.[9] Infliximab is contraindicated in patients with New York Heart Association class III and IV CHF.[1,22]

Malignancy. The package inserts for all 3 TNF-α antagonists indicate that there is a risk for lymphoma in patients treated for RA.[9,23,24] This wording was added following clinical trials in which lymphoma occurred in 4 of 1298 treated patients (standardized incidence ratio, 6.35). Interpretation of this risk is difficult, however, because the RA disease process itself has previously been shown to be associated with an increased risk of lymphoma and a cause and effect has not been shown.[1,14,25] Thus, any relationship between infliximab and malignancy is unclear.

Neurologic disease. Some studies have raised concern regarding the use of TNF-α antagonists in patients with certain neurologic diseases, including multiple sclerosis. In a recent review, MacDermott and Lichtenstein[26] conclude that infliximab should be used with caution (or not used) in patients with multiple sclerosis, optic neuritis, or myelitis. Treatment should be stopped in patients who develop significant central nervous system adverse reactions.

Hematologic effects. Cases of leukopenia, thrombocytopenia, and pancytopenia have also been reported.[1,9] The manufacturer of infliximab recommends caution in treating patients with a history of significant hematologic abnormalities; discontinuation should be considered if significant hematologic abnormalities develop during therapy.[1,9]

Hepatotoxicity. Significant adverse hepatic reactions are rare with the chronic use of infliximab; however, Centocor distributed a warning in 2004 regarding severe hepatic reactions after treatment with infliximab.[1] Although rare, some cases of hepatic reaction were fatal or led to transplantation. The FDA has stated that infliximab should be discontinued if jaundice or marked elevations in hepatic enzymes occur, but the FDA did not recommend routine laboratory surveillance. Additionally, known carriers of hepatitis B should be monitored for possible reactivation.[1]

Infusion reactions. In clinical trials, 4.8% of patients treated with infliximab developed acute infusion reactions, compared with 2.1% of controls. These reactions were characterized by nonspecific symptoms, including shortness of breath, hypotension, fever, chills, and urticaria. These symptoms were generally mild; however, medications for the treatment of acute hypersensitivity reactions should be available during infliximab infusions.[12] As noted previously, infliximab is a chimeric protein with components of mouse and human antibody. Consequently, 40% of treated patients develop human anti-chimeric antibodies, which may increase the risk of future infusion reactions. Antibodies are less likely to develop in patients already treated with other immunosuppressive drugs and in patients treated by induction followed by maintenance therapy versus a single dose followed by episodic treatment.[25,27]

CONCLUSION

Research continues concerning the role of the inflammatory cytokines in disease pathogenesis. Clearly,

the success of TNF-α antagonists has ushered in the "biologic" era of treatment for IBD and RA. Hope is well founded that further developments in the understanding of disease mechanisms will lead to additional cytokine modulators to better control dysfunctional immune activity. Although the existing TNF-α–modifying agents are effective, attention must be given to screening and monitoring patients at increased risk for related adverse events, while still allowing as many patients as appropriate to benefit from the use of these agents.　**HP**

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