Disseminated TB Infection during anti-TNF Treatment in an Intractable Rheumatoid Arthritis Patient

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BACKGROUND
Tumor necrosis factor (TNF) antagonists play an important role in the treatment of rheumatoid arthritis (RA), especially for those patients who are resistant to traditional treatment. One important concern prior to starting anti-TNF treatment is the increased risk of TB reactivation in patients with latent TB infection (LTBI). These newly active TB infections tend to occur in extrapulmonary sites and sometimes present with miliary TB.[1] Routine TB screening prior to initiating anti-TNF treatment in RA patients has become standard practice and has successfully decreased the incidence of active TB infections following anti-TNF treatment. Unfortunately currently available TB screening tests are not accurate enough to identify all LTBIrs thus putting some patients at some risk. The patients with undiagnosed LTBI prior to anti-TNF treatment carry a great risk of developing active TB during or after anti-TNF therapy. On the other hand, there was no role of TB screening test in patients with history of TB (LTBI or active TB). These patients must have confirmed adequate treatment before starting TNF antagonists. Once adequate TB treatment was accomplished, these patients can be treated with TNF antagonists with acceptable incidence of TB. Here we present a case of severe RA, who reported complete treatment of LTBI (could not be confirmed), was treated with anti-TNF, and subsequently developed disseminated TB.

CASE PRESENTATION
The patient is a 57-year-old female with past medical history of rheumatoid arthritis, hypertension, asthma and osteopenia. She was sent from the office for abdominal pain, cough, fever and tachycardia. The patient was recently admitted to the medical unit for community acquired pneumonia (CAP) with cough, fever and dyspnea and discharged a week later after finishing a 5 day course of ceftriaxone and zithromax. During the last admission, the patient complained of vague abdominal pain and a cat scan (CT) of the abdomen showed thickened omentum with multiple nodular lesions of unknown etiology. Upper endoscopy and colonoscopy showed no significant findings. The peritoneal fluid exam showed elevated white blood cell counts (WBC) 2,747/mm³, neutrophil 28%, lymphocyte 44%, monocyte 4%, with negative smear for AFB, negative culture and no
malignant cells. The patient stated that she continued to have mild non-productive cough, abdominal pain, and fever since she was discharged. The abdominal pain was localized to the right upper quadrant, constant, worsened after eating and associated with nausea and vomiting. The patient reported normal bowel movements and denied chest pain, dyspnea or hemoptysis. There was no weight loss or history of cancer.

The past medical history was significant for the diagnosis and treatment of LTBI in 1994. The patient’s Quantiferon test was negative (but with a positive mitogen response) prior to the initiation of adalimumab therapy, approximately one and one half years ago prior to this admission. The patient’s home medications included hydroxychloroquine, prednisone, sulfasalazine and adalimumab prescribed by her rheumatologist. She was in remission for her RA with anti-TNF therapy. Social history revealed that the patient was a homemaker, and had immigrated from the Dominican Republic about 15 years ago and had no record of recent travel. She never smoked cigarettes or used any recreational drugs.

On physical exam, the patient was in moderate distress due to abdominal pain, but was able to speak in full sentences. The patient was afebrile. Oxygen saturation was 95-96% on ambient air. There were coarse breath sounds with a prolonged expiratory phase. The abdomen was soft, non tender, with active bowel sounds and no shifting dullness.

The lab results were as follows. WBC 4,700 /mm3, HGB 10.3 gm/dL, PLT 259,000/mm3, ALT 21 IU/L, AST 28 IU/L, TBIL 0.8 mg/dL, Alkaline phosphatase 35 IU/L, Lipase 29 IU/L. The chest CT showed persistent small reticulonodular opacities in upper lungs and a bibasilar small lingular infiltrate versus atelectasis (Image 1). Repeat CT of abdomen and pelvis revealed fatty liver with minimal nodularity, suspicious for early cirrhosis. There was persistent nonspecific anterior omental thickening and nodularity with increasing mild to moderate ascites, suspicious for carcinomatosis (Image 2). A bronchoscopy was performed and the bronchoalveolar lavage fluid smear was negative for AFB.
On day 7 of admission, a sputum specimen sent to NYC-DOH was PCR positive for AFB. Later, the peritoneal fluid culture also became positive for TB. The patient had disseminated TB, with involvement of lung, peritoneum and liver. Adalimumab was discontinued. She was started on rifampin, isoniazid, pyridoxine and ethambutol. Sulfasalazine, plaquenil and prednisone were started to control her arthritis symptoms. Her strain of tuberculosis was resistance to INH and ethambutol, and her TB regimen was changed to rifampin, pyrazinamide and levofloxacin. The patient completed a 9 month course. After completion of treatment, the patient has no respiratory or abdominal symptoms. Her RA is being treated with plaquenil, sulfasalazine and prednisone, and symptoms are controlled.

**DISCUSSION**
Identification of RA patients with LTBI before starting anti-TNF treatment is challenging as currently available screening tests, tuberculin skin test (TST) or IFN-
release assays (IGRA) often produce false negative results either from anergy due to immunosuppression, or from low sensitivity of the test itself.[2] The sensitivity of Quanteferon in the general population is believed to be 73–82%, and in patients with immunosuppression it is thought to be even lower.[2] Failing to identify patients with LTBI before beginning anti-TNF frequently results in reactivation of LTBI and sometimes causes disseminated TB.

According to American Rheumatology guideline for use of biologic agents in the treatment of RA, all RA patients being considered for biologic agent treatment should have LTBI screening before starting biologic agents. In 2012, the American College of Rheumatology updated its guideline and suggested a two-step TB screening test for RA patients with risk of TB exposure. The guideline stated a patient with first TST or IGRA test negative with risk factors of TB exposure should have a repeat TST or IGRA test in 1 to 3 weeks. For patients who have a high risk of TB infection and/or a poor prognosis who have a negative initial screening test (either 2 step TST or IGRA test), some recommend to use both TST and IGRA to screen for LTBI.[3] Although it seems to be a reasonable approach to increase sensitivity of TB screening, there has been no clinical trial to compare the effectiveness between screening with both tests and screening with either of the two tests. For patients who are already on TNF antagonist treatment, with negative baseline TST or IGRA and without a history of TB, annual TB screening as recommended by American College of Rheumatology might help identify new TB infections.

Our patient reported a history of latent TB infection and treatment in 1994 in her home country. She then immigrated to the United States, resided in a medically underserved community with high TB prevalence, and was later diagnosed with RA. She was originally started on etanercept 3 years after her diagnosis of RA. Our patient had a negative PPD (at the time it was not known that she had a history of LTBI), and chest X-ray before initiating etanercept. She stayed on this treatment for about 2 years and then was switched to adalimumab due to progression of RA. The patient had a negative Quantiferon test before switching to adalimumab from etanercept. According to the British Thoracic Society guidelines, patients with a history of TB who were adequately treated previously can begin TNF antagonists without another LTBI treatment.[5]

Information about active TB incidence in patients receiving TNF antagonists with history of treated TB is lacking. Jo KY et al followed 101 patients in Korea receiving TNF antagonists and with history of adequate TB treatment for an average of 31.5 months and only one patient developed active TB. The incidence was 336/100,000 and deemed acceptable.[6]

In addition to TB screening, evaluations of risk factors for TB is just as important in
consideration of prophylactic TB treatment before initiating anti-TNF drugs. Some researchers believe that TNF inhibitor candidates with a negative TST (<5mm) or IGRA should be treated for LTBI if there is high risk for prior TB exposure, an example being i, having had close contact to a TB patient, or having lived in an area of high TB incidence. If a patient has a positive TB screening test, the CDC recommends that the preferred regimen for treatment of latent TB infection is a 9-month course of daily isoniazid. Observational studies suggest anti-TNF therapy can be safely started 1 month after starting isoniazid treatment.

TB can infect many organs and systems and give a variety of atypical presentations with low yield of microbiology confirmation. Oftentimes the diagnosis of TB is extremely challenging. The important lesson is we have to think of TB to diagnose TB. Once a patient is started on anti-TNF treatment, clinicians have to be vigilant about looking for signs and symptoms of possible TB infections. In our patient, a high index of suspicion for TB may have prompted an investigation for TB during her first admission, when fever and dry cough symptoms first were noted. It is also important to bear in mind that TB in patients on anti-TNF treatment oftentimes presents with extrapulmonary infection or even disseminated infection. A better understanding of this feature of TB infection during anti-TNF therapy would have linked both respiratory and abdominal symptoms to TB infection.

CONCLUSION
In conclusion, recommendations suggest a two-step TB screening test (PPD or IGRA) before initiating biologic agent treatment for all RA patients who are at high risk for developing TB. There is currently insufficient data to determine how often a patient already treated for latent TB or active TB will develop active TB on immunotherapy and hence warrants consideration of preventive TB therapy. Tuberculosis should be considered early in patients on anti-TNF treatment with fever and respiratory complaints. In addition, as in our patient, it is important to consider disseminated tuberculosis in these immune-compromised patients.

REFERENCES


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