

Active Tuberculosis in a Patient with Rheumatoid Arthritis Treated with Tumor Necrosis Factor-Alpha Inhibitor

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Therapy with tumor necrosis factor inhibitors is associated with an increased risk of active tuberculosis. In a recent study, the sex and age-adjusted incidence rate of active TB among patients treated with TNFi was 172 per 100,000 patient-years, whereas the incidence in that country's cohort of rheumatic patients not receiving TNFi was 95 cases/100,000 [1]. Active tuberculosis develops within a few months of beginning TNFi therapy, manifesting either as reactivation of latent TB infection or as a primary infection following exposure to patients with active TB [1,2]. The TB associated with TNFi is usually atypical, with more than 50% presenting with extrapulmonary and 25% disseminated disease, causing considerable delay in diagnosis and treatment [1,2].

Professional societies have issued guidelines mandating screening and treatment of latent TB infection before initiating a TNFi [3]. Lack of compliance with these recommendations is associated with emergence of active TB in patients treated with all TNF inhibitors. The risk of developing active TB was seven times

higher when screening recommendations were not followed [1].

We present a patient with debilitating rheumatoid arthritis in whom a two-step tuberculin skin test was initially negative and who developed extrapulmonary active TB during treatment with a TNFi.

PATIENT DESCRIPTION

The patient, a 57 year old social worker who was born in Argentina and immigrated to Israel in 1973, was referred to the pulmonary clinic for evaluation of an abnormal chest computed tomography scan performed because of dry cough, low grade fever and fatigue 3 months after beginning therapy with infliximab for active rheumatoid arthritis.

Rheumatoid arthritis had been diagnosed 15 years earlier and was seropositive, polyarticular and erosive, necessitating knee replacement and total hip surgery. She had been treated with various disease-modifying anti-rheumatic drugs including injectable gold, sulfasalazine, an antimalarial agent, leflenomide, and cyclosporine. When she began the infliximab therapy she was also receiving methotrexate 15 mg/week and prednisolone 10 mg/day

Before beginning infliximab therapy the patient denied having been previously diagnosed with TB, and stated that she did not suffer from night sweats, weight loss, cough or bloody sputum. She did not have a BCG scar on either arm or

palpably enlarged lymph nodes. A two-step tuberculin skin test was performed and was interpreted as negative (0 mm and 3 mm). A chest radiograph was also normal. Laboratory workup revealed: erythrocyte sedimentation rate 60 mm/hr, hemoglobin 10.4 g/dl, white blood cell count $12.32 \times 10^3/\text{ml}$, platelet count $572 \times 10^3/\text{ml}$, serum creatinine 0.7 g/dl, rheumatoid factor titer 41.4 IU (normal range 0–15 IU), and C-reactive protein 2.52 mg/dl (normal range 0–0.5 mg/dl).

Three months after starting infliximab she developed fatigue, low grade fever and dry cough that did not respond to antibiotics prescribed by her family physician. Evaluation for active TB revealed that her TST had increased to 6 mm. Chest CT showed mediastinal lymphadenopathy with a retrocaval lymph node 2.5 cm in diameter and a right hilar lymph node 2.3 cm in diameter. In the right middle lobe and in the lingula there were small areas with a ground-glass appearance. A follow-up CT 3 weeks later showed mediastinal lymphadenopathy with a retrocaval lymph node 1.5 cm in diameter.

She continued to experience worsening dyspnea and repeated episodes of 38°C fever and was admitted to hospital. On admission her temperature was 36.8°C, blood pressure was 115/82 and respiratory rate 12 breaths/min. Lung and heart sounds were normal, the abdomen was soft and no lymph nodes were palpated. Bronchoscopy with bronchoal-

TB = tuberculosis
TNFi = tumor necrosis factor inhibitor

BCG = bacilli Calmette-Guerin

TST = tuberculin skin test

veolar lavage was performed, which did not reveal tumor cells. Stains for acid-fast bacilli and *Pneumocystis jirovecii* were negative. The bronchoalveolar lavage culture for tuberculosis was sterile. A gallium scan did not reveal pathologic uptake. Infliximab treatment was discontinued and the patient was referred to the Ministry of Health tuberculosis clinic and began receiving isoniazide for LTBI because of TST > 5 mm. The treatment was discontinued 2 weeks later when she developed isoniazide-induced hepatitis. Therapy with rifampin was begun; however, she did not tolerate it and discontinued the treatment 2 months later.

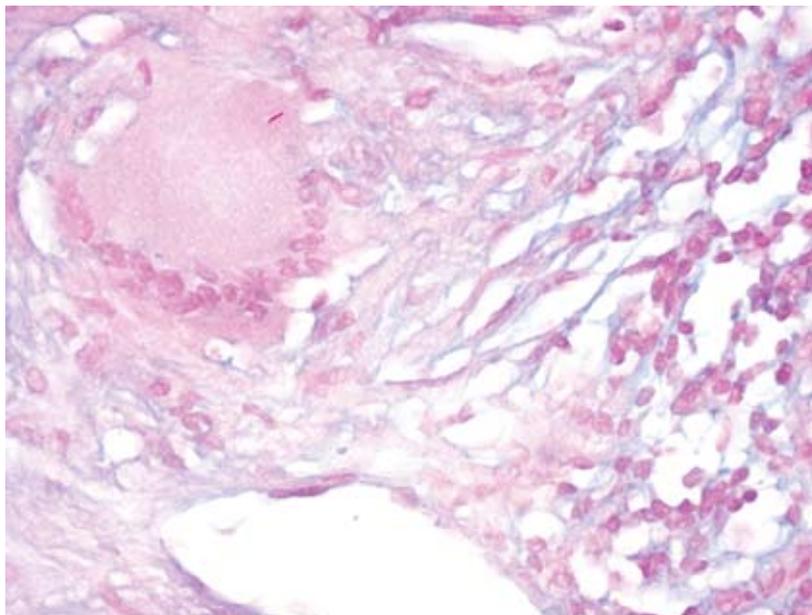
Therapy with etanercept for 6 months was not efficacious and a year after discontinuation of rifampin therapy she began therapy with adalimumab and continued on methotrexate and prednisone.

Six months later the patient presented with weight loss, abdominal pain and diarrhea. Her chest X-ray was normal as was an abdominal ultrasound examination. Upper endoscopy revealed gastritis for which she received omeprazole. Barium swallow was normal, and colonoscopy revealed diverticulosis. Three months later she was admitted again with continued weight loss, night sweats and fever. A perianal abscess was discovered which later drained into a fistula. The patient required surgery and parenteral antibiotics and was discharged for follow-up. Her fever did not abate and the patient was again readmitted for workup of prolonged fever.

Physical examination revealed a hard lymph node (2 x 2 cm) in her right inguinal area. A biopsy of the node was performed and showed necrotizing granulomatous inflammation [Figure]. Acid-fast bacilli were seen on Ziehl-Neelsen staining and the culture from the lymph node revealed *Mycobacterium tuberculosis* sensitive to all first-line anti-tuberculosis drugs. The patient started treatment for active TB with four anti-tuberculosis agents.

LTBI = latent TB infection

Photomicrograph of the core lymph node biopsy of the left groin mass. At the left upper aspect, a Langhans cell shows a mycobacterium at the margin of its cytoplasm (x 340, Ziehl-Neelsen histochemical stain).



COMMENT

We present a patient with severe erosive and deforming rheumatoid arthritis who had not responded to any disease-modifying antirheumatic drug and thus began therapy with a TNF inhibitor. Three months later she developed systemic symptoms, but only 21 months later, despite repeated assessments, active TB was diagnosed in an inguinal lymph node, indicating extrapulmonary TB infection. Before starting TNFi therapy she had undergone a two-step TST test, which showed 0 and 3 mm and definitively ruled out LTBI despite the fact that she was a middle-aged woman, born abroad in surroundings with a higher incidence of TB than in Israel, and worked as a social worker in contact with a high risk population, including prisoners. It was recently demonstrated that the burden of tuberculosis in the Israeli prison system is 3.5 times higher than in the general Israeli population [4]. The interpretation of the pretreatment two-step TST as negative was not

the result of treatment with prednisone and methotrexate [2,3].

The first chest CT scan showed mediastinal lymphadenopathy, however, bronchoalveolar lavage was negative as was a gallium scan. The size of the nodes was reduced in a second scan. This precluded performing lymph node biopsy. However, it is plausible that primary infection was present in the mediastinal lymphadenopathy that progressed to extrathoracic active TB of the peripheral lymph nodes.

It is recommended that treatment for LTBI in patients receiving concomitant prednisone 15 mg/day or methotrexate be initiated at least one month before starting therapy with a TNFi when: a) the TST or the two-step TST is > 5 mm (if the first result was < 5 mm), b) a chest radiograph shows evidence of past tuberculosis, and c) there is a history of exposure to active TB or previous partially treated active TB [2,3]. Lack of adherence to these recommendations, particularly, not performing the two-step TST, is associated with a sevenfold increased risk of developing active TB [1]. Before starting treatment

for LTBI every effort should be made to rule out active TB, which requires introduction of at least four anti-tuberculosis drugs initially to prevent development of drug-resistant strains of *Mycobacterium tuberculosis*.

Performing serial TSTs in patients treated with a TNFi remains a matter of debate. It may be speculated that repeated tuberculin skin testing with purified protein derivative induces a sensitization reaction in susceptible individuals that may confound TST reaction reading. However, in a Scandinavian population such a reaction was found in only 1 of 31 individuals, suggesting that for practical purposes it can be ignored [5].

In a previous study [2], after an initial screening TST we performed a follow-up TST at least 3 months after beginning TNFi therapy. Twenty percent of 40 patients included in the study had conversion of the TST, defined as an

increase of 6 mm of induration between the screening tests and the follow-up test. TB prophylaxis was administered to all of these patients. In our patient, the third TST did not indicate conversion (increment of only 3 mm (from 3 to > 6 mm); however, prophylactic therapy for LTBI was nevertheless prescribed because of an absolute TST value above 5 mm

In summary, we present a patient with extrapulmonary active TB associated with TNF inhibitor therapy. To our knowledge, this is the first reported case of active TB following TNFi in Israel. The case indicates that active TB associated with TNFi treatment is difficult to diagnose, has an atypical clinical course and may manifest as the result of reactivation of LTBI infection or of recently acquired infection [2]. We emphasize the importance of pretreatment screening for latent TB, a high index of suspicion for tuberculosis, and considering performance of serial TSTs.

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