Anti-TNF Treatment and Miliary Tuberculosis in Crohn’s Disease

Branislava Milenković1,2, Aleksandra Dudvarski-Ilić1,2, Goran Janković2,3, Lena Martinović3, Dragana Mijač3

1Faculty of Medicine, University of Belgrade, Belgrade, Serbia; 2Clinic for Pulmonary Diseases, Clinical Centre of Serbia, Belgrade, Serbia; 3Clinic of Gastroenterology and Hepatology, Clinical Centre of Serbia, Belgrade, Serbia

INTRODUCTION

Tumour necrosis factor alpha (TNFα) has a central role in the host immune response to mycobacterial infection. TNFα blockade may therefore result in reactivation of recent or remotely acquired infection. In reported mycobacterium tuberculosis infections, extra-pulmonary and disseminated tuberculosis (TB) was common, appeared rapidly, and if unrecognized, with fatal outcome. We present a female patient with miliary TB following treatment with infliximab for fistulizing Crohn’s disease.

CASE REPORT

A 53-year-old woman presented with a 6-week history of fever, weakness, weight loss (4 kg/6 week), two-week dry cough, but no abdominal pain or diarrhoea. Five years before admission, she was diagnosed with CD with inflammation limited to the terminal ileum and sigmoid colon and has been taking azathioprine 100 mg/day for the last 10 months. Three months before admission to the hospital she developed an enterocutaneous fistula for which therapy with infliximab was started in addition to azathioprine therapy. A tuberculin skin test and a chest x-ray were performed prior to the first infusion with normal findings. She presented with a 6-week history of fever, weakness, weight loss and a 2-week dry cough. Chest x-ray and computed tomography displayed remarkable bilateral hilar and mediastinal lymphadenopathy and uniformly distributed fine nodules throughout both lung fields varying in size from 2 to 3 mm, without any signs of cavitation. Since there were clinical and morphological signs that indicated miliary TB, the treatment with antituberculous therapy was started and six weeks later all of the symptoms completely resolved and the lesions visible on x-ray diminished.

SUMMARY

Introduction Tumour necrosis factor alpha (TNFα) has a central role in the host immune response to mycobacterial infection. TNFα blockade may therefore result in reactivation of recent or remotely acquired infection. In reported mycobacterium tuberculosis infections, extra-pulmonary and disseminated tuberculosis (TB) was common, appeared rapidly, and if unrecognized, with fatal outcome. We present a female patient with miliary TB following treatment with infliximab for fistulizing Crohn’s disease.

Case Outline Five years before admission, the patient was diagnosed with Crohn’s disease, with inflammation limited to the terminal ileum and sigmoid colon and has been on azathioprine 100 mg/day for the last 10 months. Three months before admission to the hospital she developed an enterocutaneous fistula for which therapy with infliximab was started in addition to azathioprine therapy. A tuberculin skin test and a chest x-ray were performed prior to the first infusion with normal findings. She presented with a 6-week history of fever, weakness, weight loss and a 2-week dry cough. Chest x-ray and computed tomography displayed remarkable bilateral hilar and mediastinal lymphadenopathy and uniformly distributed fine nodules throughout both lung fields varying in size from 2 to 3 mm, without any signs of cavitation. Since there were clinical and morphological signs that indicated miliary TB, the treatment with antituberculous therapy was started and six weeks later all of the symptoms completely resolved and the lesions visible on x-ray diminished.

Conclusion The clinical use of TNF-inhibitors is associated with increased risk of developing tuberculosis. Physicians should be aware of the increased risk of reactivation of TB among patients treated with anti-TNF agents and regularly look for usual and unusual symptoms of TB.

Keywords: infliximab; Crohn’s disease; tuberculosis
On admission to hospital, her body temperature was 39.8°C, pulse rate 112/min, respiratory rate 18/min and blood pressure 90/60 mm Hg. Physical examination was normal except for some inspiratory crackles of the basal area of both lungs. Laboratory analyses revealed increased CRP (102 mg/L), ESR 26 mm/hr, leucopenia (2.5×10⁹/L) with 72% neutrophils and 20% lymphocytes (lymphocyte profile showed CD4 count of 350 cells/µL), a normocytic moderate anaemia (Hg 94 g/L), hypoproteinemia (57 g/L) with reduction in the albumin fraction (21 g/L), and abnormal LFTs (alanin aminotransferase 96 UI/L, aspartat aminotransferase 66 UI/L, aspartic transaminase 66 UI/L), elevated LDH 654 (normal range 102-109 UI/L), while all other parameters including basic coagulation tests were normal. Urine analysis was positive for traces of protein and a microscopic examination showed the presence of five white blood cells and two red blood cells per high-power field. Spirometry was normal (FVC=120%pred, FEV₁=119%pred). The carbon monoxide transfer factor diffusing capacity was moderately reduced (55%). Arterial blood gases showed normoxemia, hypocarbia and respiratory alkalosis. On several occasions during hospitalization, sputum, urine and blood cultures were taken but remained sterile. The antibodies to HIV infection were not found. The finding of AFB in a sputum smear was negative. Repeated TST was negative. Chest x-ray displayed remarkable bilateral hilar and mediastinal lymphadenopathy and uniformly distributed fine nodules through both lung fields varying from 2 to 3 mm in size (Figure 1). The nodules were confirmed on CT scanning, but with no signs of cavitation (Figure 2). Abdominal ultrasound and CT confirmed hepatosplenomegaly with micronodular lesions in splenic tissue size up to 5 mm, and enlarged retroperitoneal lymph nodes around coeliac trunk and abdominal aorta. She underwent fiberoptic bronchoscopy which was normal. Bronchoscopically obtained biopsies were not diagnostic with a small amount of biopsy material that revealed only some non-specific inflammatory changes. A bone marrow biopsy was negative for granulomas or malignant cells, as well as for abundant tubercle bacilli.

Since there were clinical and morphological signs that indicated miliary TB, the treatment with antituberculous therapy (isoniasid, rifampicine, streptomycine, pyrazinamide, ethambutol) was started. The diagnosis was confirmed with the use of rapid culture techniques (Bactec) – sputum cultures and BAL cultures, which were positive for M. tuberculosis.

The patient’s symptoms significantly improved three days after the initiation of treatment, but her body temperature continued to spike (39°C) for further 2 weeks. In addition, prednisone 20 mg/day orally was started. During the third week of anti-TB therapy, fever declined and streptomycin was discontinued. Six weeks later her condition improved, all of her symptoms completely disappeared, the lesions visible on x-ray diminished, and the patient was discharged from hospital; on further control examinations she remained with no signs of TB infection.

DISCUSSION

TNFα is a cytokine that mediates multiple proinflammatory processes central to the pathogenesis of CD, rheumatoid arthritis and other inflammatory conditions. Also, it is essential cytokine for the formation and maintenance of granulomas, which are key components of host defences against intracellular pathogens. TNFα appears to play a complex and multifaceted role in the host defence against mycobacterial infection. The introduction of infliximab and the chimeric antibody against TNFα, dramatically improves the management of CD patients [1]. But, it is not surprising that in patients treated with these agents the clinical use of TNF-inhibitors is associated with increased risk of developing serious granulomatous infectious diseases, such as TB, histoplasmosis, and several less common conditions [2, 3]. In such patients, the increased risk of TB reactivation is especially important in Serbia.
because there is still has a higher endemic rate of TB than other industrialized countries [4].

The pattern of TB observed after anti-TNFα treatment may be due to the failure of granulomas to compartmentalize viable M. tuberculosis bacilli, but the underlying mechanism is unclear [5]. Infliximab exerts its action not simply through antibody-mediated neutralization of TNF; it also induces apoptosis of memory T cells and monocytes thereby eliminating excessive cellular responses. Infliximab binds transmembrane TNF and may lead to cell-lysis via complement-dependent cytolyis and antibody dependent cell-mediated citotoxicity. In addition, TNFα-blockade may result in the accumulation of neutrophils, persistent inflammation, and pulmonary cell damage.

Several hundreds of cases of pulmonary and extra-pulmonary TB have been described [2, 6-10]. The first report about the infliximab-associated TB was published by Keane et al. [6]. They reviewed the clinical and laboratory findings in 70 patients treated with anti-TNF agents. In this series more than half (56%) of patients had extrapulmonary disease, while 24% presented with disseminated form of the disease. In unusual cases, such as meningal, lymph node and digestive location of disease, it is sometimes difficult to make a final diagnosis only by using ordinary methods.

The largest and most systematic studies of granulomatous infections in patients treated with the TNF-inhibitors reported 374 cases [2]. The majority (37%) had TB restricted to the lungs and 21% had extra-pulmonary disease. Excess TB cases were observed during the first 3 months of infliximab treatment. In a Raval’s study of 130 cases of infliximab-associated TB, the majority had extrapulmonary and 23% had disseminated disease; 15% were associated with a fatal outcome [7]. The infection was identified most frequently as a cause of death, including six cases in which TB was the specified cause of death.

There are some similarities between previous reports and the case we present hereby; our patient was also treated with concomitant immunosuppressive therapy and presented with disseminated disease. The infection in our patient appeared to be due to a rapid dissolution of granulomas in latent TB rather than a new infection. There was no family history of TB or recent exposure to TB. The onset of symptoms occurred 12 weeks after the start of infliximab, like in Keane’s and Raval’s study, and therefore, it was a case of unrecognized latent TB rather than due to primary infection [2, 6, 7]. Also, in a Daniel’s study, 43% of infliximab-associated cases of TB occurred during the first 90 days of treatment, indicating that they were likely to represent a reactivation of latent infection [11].

In the present case, typical symptoms, the abnormal chest radiograph and CT raised the suspicious of TB. The active disease was confirmed by positive sputum culture. Despite the availability of newer culture media like the BACTEC, these culture techniques still require 1-3 weeks. More rapid diagnostic tests are required because culture confirmation has been reported in 50-75% of miliary TB cases [12].

Tuberculin skin testing is the standard screening test for latent TB infection in high-risk populations. But, negative TST did not exclude the diagnosis of miliary TB in our patient, because a higher proportion of patients with miliary TB fail to react to tuberculin than those with a localized pulmonary or extra-pulmonary disease [13, 14]. In Serbia, where the population may have received prior bacilli Calmette-Guérin vaccination (BCG), the interpretation of TST is further complicated and this test cannot be reliable in establishing the diagnosis [12]. False positive results can occur in recipients if the BCG vaccine was given after the first year of life [7]. Raval et al. [7] found reports of patients with previous BCG vaccination who developed active TB after initiation of infliximab therapy despite having a negative TST. But in general, all patients who have impaired immunity should undergo TST before infliximab to keep to a minimum the risk of false-negative reactions due to anergy [15, 16].

The risk of progressive haematogenous TB dissemination increases with underlying conditions such as severe malnutrition or treatment with immunosuppressive medication, including steroids, cytotoxic agents or TNF-inhibitors. The use of infliximab with corticosteroids or azathioprine may further increase the risk for infection. The risk factors for miliary TB in our patient were cellular immunodeficiency due to malabsorption in gastrointestinal disease and the treatment with azathioprine and anti-TNFα. The majority in the Keane’s study were on concomitant immunosuppressive treatment, identically to our patient [6].

The clinical presentation of miliary TB may vary significantly. Hepatosplenomegaly and lymphadenopathy occurred in the present patient, although splenomegaly (13%), hepatomegaly (16%) and lymphadenopathy (16%) are more common in children than in adults [10, 12, 13].

When miliary TB was suspected in the presented patient, the appropriate antituberculosis treatment was started with gradual improvement of symptoms over several weeks. The initiation of steroids was beneficial for this patient, but the role of corticosteroids in miliary TB remains controversial [9].

Besides its effectiveness in severe Crohn’s disease, infliximab is associated with a high risk of serious infectious complications, particularly tuberculosis. The risk of progressive haematogenous dissemination increases with underlying conditions, such as severe malnutrition or treatment with immunosuppressive medication. The reactivation of TB occurring in patients receiving infliximab may show an unusual clinical manifestation, more disseminated, rapid and atypical presentation, which are fatal if unrecognized and untreated.

Therefore, considering the appropriate approach to the diagnosis of infliximab-associated TB is very important. Physicians should be aware of the increased risk of reactivation of TB among patients treated with anti-TNF agents and they must regularly look for usual and unusual symptoms of TB. When TB is diagnosed, anti-TNF agents have to be discontinued, and appropriate antituberculosis treatment started in order to prevent progression of this serious disease.
REFERENCES