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Case Report

A Case of Peritoneal Tuberculosis Developed after Infliximab Therapy for Refractory RA

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Recently, interferon gamma releasing assay has been recommended to compensate the tuberculin skin test (TST) for screening for latent tuberculosis infection (LTBI). Although it improved the detection of LTBI before treatment with tumor necrosis factor blocker, its application to immune suppressed patients is limited. We report a case of peritoneal tuberculosis (TB) developed in a patient who tested positive for TST and QuantiFERON-TB Gold (QFT-G) before infliximab therapy, to emphasize the importance of monitoring during treatment. A 52-year-old woman presented with abdominal distension. She had been diagnosed with seropositive rheumatoid arthritis six years ago. She had started taking infliximab six months ago. All screening tests for TB were performed and the results of all were negative. At admission, the results of repeated TST and QFT-G tests were positive. Histopathological examination confirmed peritoneal TB. The patient started anti-TB therapy and the symptoms were relieved.

Key Words: Peritonitis, Tuberculous; Infliximab

Introduction

The tumor necrosis factor (TNF) blocker is known to be a promising treatment modality among patients with rheumatoid arthritis (RA) showing poor response to conventional therapy including disease modifying anti-rheumatic drugs (DMARDs)[1]. They improve the clinical outcome of RA dramatically, but also they might increase the risk of opportunistic infection. An increased susceptibility for tuberculosis (TB) or reactivation of latent TB, in particular, has been reported[2-5]. Korea Food and Drug Association (KFDA) thus recommends that all patients should be screened for TB with tuberculin skin test (TST) and chest X-ray before undergoing the TNF blockers therapy[6]. Recently, interferon gamma releasing assay (IGRA) is recommended to compensate the TST for screening the latent tuberculosis infection (LTBI). IGRA detects sensitization to *Mycobacterium tuberculosis* by measuring interferon gamma release in response to antigens representing *M. tuberculosis*. The QuantiFERON-TB gold (QFT-G) is the first IGRA approved by the FDA as an aid for diagnosing *M. tuberculosis* infection. In our case, the peritoneal tuberculosis developed in patient who tested both TST and QFT-G. In order to improve detecting the LTBI or newly developed TB, we strongly recommend to add monitoring guideline. Until now, no guideline has been established for monitoring TB during treatment with TNF blockers. we report this case with review to emphasize the importance of monitoring.

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Case Report

A 52-year-old woman was admitted to the hospital with abdominal distention and low abdominal pain for the past four weeks. She did not have anorexia or weight loss. She was diagnosed as seropositive RA six years earlier and was treated with conventional DMARDs including methotrexate, sulfasalazine, and hydroxychloroquine, proven irresponsive to conventional DMARDs. Screening for TB including chest X-ray, TST, and QFT-G were performed before the infliximab therapy. TST was negative (induration＜3 mm) and QFT-G was negative (Nil, 0.06 IU/mL; TB response, 0.12 IU/mL; mitogen response, 13.35 IU/mL). Thus all the tests were negative, we started Infliximab therapy without TB prophylaxis. Infliximab therapy was continued for six months with an injection of 100-mg intravenous every other week, while the disease activity of RA has been decreased before admission.

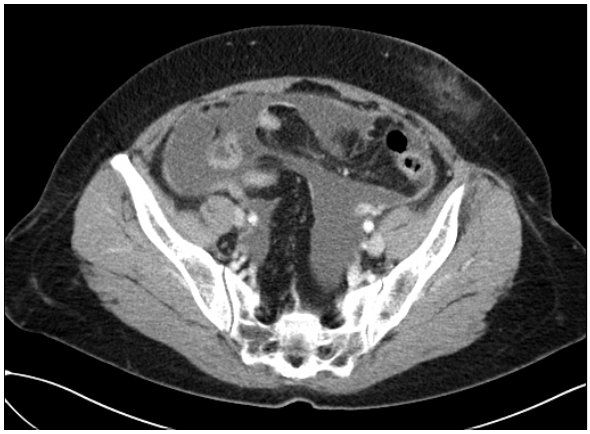

Figure 1. Large amount of ascites, peritoneal irregular thickening and omental nodules suggesting peritoneal tuberculosis in the abdomen computed tomography.

Physical examination revealed ascites. Laboratory evaluation showed 4,600/mm^3 white blood cells with 83% neutrophils and hemoglobin 12.8 g/dL. The erythrocyte sedimentation rate was 42 mm/hr and C-reactive protein was 6.80 mg/dL (normal, 0.1～0.8 mg/dL). Electrolytes, hepatic function tests, and renal function tests were within normal limits, while the serologic tests for antinuclear antibodies, hepatitis virus, and human immunodeficiency virus serology were all negative. Rheumatoid factor was positive (21.4 U/mL; normal, ＜20 U/mL). No organism was detected in blood cultures.

Chest X-ray revealed no active lung lesion. Abdominal computed tomography (CT) scan showed large amount of ascites, irregular peritoneal thickening, and omental nodules (Figure 1). Paracentesis yielded a turbid ascitic fluid with 1,120/mm^3 white blood cells with 83% lymphocytes and elevated adenosine deaminase

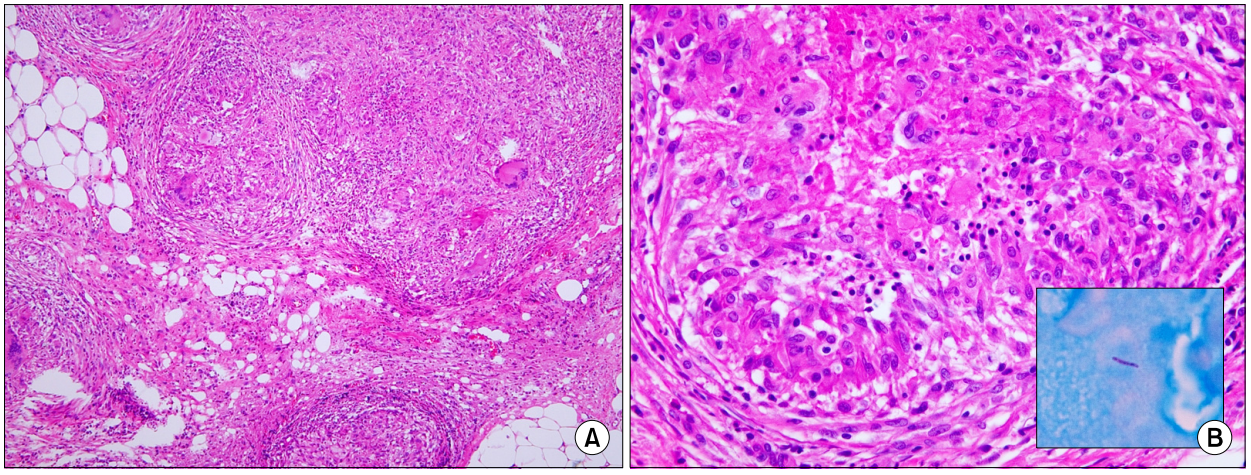

Figure 2. (A) Multiple granulomas surrounded by Langhans giant cells, and few lymphocytes and caseous necrosis (H&E stain, ×100). (B) Caseous necrosis and few lymphocytes in granuloma (H&E stain, ×400). A acid-fast bacillus is seen (inset; Ziehl-Neelsen stain, ×1,000).

(ADA) as 57.4 IU/L (normal, <40 IU/L). Ascites culture for bacteria and *M. tuberculosis* and repeated cytological results performed in ascitic fluid were negative. Sputum cultures were also negative for *M. tuberculosis*. Repeated TST converted positive (induration 18 mm) and QFT-G converted positive (Nil, 0.19 IU/mL; TB response, 0.53 IU/mlL; mitogen response, 6.87 IU/mL).

Laparoscopic biopsy was performed to make a confirmative diagnosis. There were widespread miliary nodules on the peritoneal surfaces in which multiple biopsies were performed. The histopathological examination revealed multiple foci of chronic granulomatous inflammation surrounded by Langhans-type giant cells, a few lymphocytes, and a few caseous necroses. A few acid-fast bacilli were present on Ziehl-Neelsen stain (Figure 2).

Anti-TB therapy with isoniazid 300 mg/day, rifampin 600 mg/day, ethambutol 800 mg/day, and pyrazinamide 1,500 mg/day were implemented. After treatment instauration, the abdominal distention with ascites decreased while the symptom improved. In the follow-up abdominal CT scan, irregular peritoneal thickening and omental nodularity also decreased.

Discussion

TNF is a pro-inflammatory cytokine that plays a major role in the pathogenesis of many autoimmune diseases, especially RA. TNF blockers inhibit this pro-inflammatory pathway and decrease the disease activity of RA. As a result, they improve the outcome of RA dramatically and therefore they have emerged as a new treatment of many autoimmune diseases. Despite the clinical benefit, they also increase the risk of opportunistic infections, especially TB[4,7]. Because TNF has the role of making granuloma in the pathogenesis of TB, blocking of TNF might make TB progress.

There are three types of TNF blockers, including chimeric monoclonal antibody (infliximab), human monoclonal antibody (adalimumab), and human fusion protein (etanercept). They have different effectiveness and side effects due to their different mechanisms of action, biology, or kinetics[8]. For the incidence of TB in patients with RA and treated with anti-TNF therapy has some differences between the used agents, 3- to 4-fold higher with infliximab and adalimumab than etanercept, which could be originated from the difference in the effectiveness of TNF blockade between those agents[2,9].

Most countries have established a guideline to screen for TB before starting TNF blockers to prevent developing TB during treatment[6]. Because South Korea is classified as a country of intermediate TB burden[8], prevention and early diagnosis of TB could be very important issue even at present. KFDA provided guidelines for screening and prophylaxis for latent TB prior to TNF blocker trial. The guidelines recommend TST and chest X-ray before TNF blocker treatment. Because of the defective cellular immune function, inadequate response to TST in RA could be possible[8,10]. In a TB-endemic population, the QFT-G seems to be a more accurate test for detection of LTBI in RA patients compared with the TST, and may potentially improve the targeting of prophylactic therapy before treatment with anti-TNF agents[11].

In our case, despite the patient did TST and QFT-G, the peritoneal TB developed within 6 months of infliximab therapy. In South Korea, only two cases have been reported on peritoneal TB in patients treated with infliximab treatment[12,13]. One of them had RA and the other had AS. Those patients tested only TST without QFT-G before infliximab therapy and the diagnosis of peritoneal TB was made by radiologic findings and ascites ADA results without adequate peritoneal biopsy. Different with these cases, we did QFT-G to compensate the TST. However, there is a limitation when performing QFT-G on immunosuppressed patients. Because many rheumatoid arthritis patients may have been given methotrexate or glucocorticoids, which suppress the immune system prior to the administration of TNF blocker, possibly making it difficult to interpret the QFT-G results. In order to decrease the incidence of TB during TNF blocker therapy, reinforcing the screening test is important, but also follow-up monitoring test is important. Until now, no guideline has been set to

monitor TB during the TNF blocker treatment. Although both TST and QFT-G previously tested as negative, some patients could get TB during the TNF blocker treatment and could show positive conversion to those tests even before active clinical manifestations. In one study, among the patients with rheumatic disease treated with TNF blockers, 32.6% of them showed positive conversion of TST during treatment. An estimated 14% of patients, who got QFT-G before, had positive conversion with follow-up test, and one of them developed miliary TB[14].

The development of TB could be the main reason that TNF blocker therapy should be terminated even in those patients who need TNF blocker such as refractory RA or other refractory autoimmune diseases, and stopping TNF blocker has an influence on the result of RA treatment in that clinical setting. Considering the clinical effects of newly developed TB including patients' discomfort, possible side effects of anti-TB medications and the cost for diagnosis and treatment of TB, the monitoring for TB during TNF blocker therapy, especially with infliximab or adalimumab is clinically important.

The three cases including our case, the peritoneal TB developed within 6 months after infliximab treatment. Usually, the median interval from the start of treatment with infliximab until the development of TB was less than six months[5]. If we monitored TB by some tests within 6 months, we could prevent the development of peritoneal TB before patient's discomfort.

As a conclusion, although every patient who would undergo TNF blocking therapy for refractory autoimmune disease is under monitoring for TB before stating the treatment, there could be some cases who developed new TB infection during TNF blocker therapy. Therefore, there should be an agreement and consideration for making guidelines for monitoring TB in the patients who undergoing TNF blocker therapy.

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