A 58-year-old man with Crohn’s disease received adalimumab for 13 months after screening results for tuberculosis were found to be negative. He was diagnosed with de novo mediastinal lymph-node tuberculosis, which was proved to be bacteriologically identical to that of an individual with smear positive lung tuberculosis by a variable number of tandem repeat analyses. After initiating anti-tuberculosis therapy, the patient developed immune reconstitution syndrome, which was improved by the re-administration of adalimumab. Even in countries with an intermediate tuberculosis burden, including Japan, we need to be alert for de novo tuberculosis as well as its reactivation during tumor necrosis factor-α inhibitor therapy.

Key words: variable number of tandem repeat, immune reconstitution inflammatory syndrome, adalimumab, intermediate tuberculosis burden country

Introduction

Tumor necrosis factor-α (TNF-α) inhibitors are currently considered a part of the standard care for patients with rheumatoid arthritis and other autoimmune diseases. The absolute risk for reactivation of latent tuberculosis infection (LTBI) is common for these drugs (1). Although the development of tuberculosis after the initiation of treatment with TNF-α inhibitors has been reported, reports of genetically determined de novo tuberculosis are rare, and little is known about its clinical symptoms.

A variable number of tandem repeat (VNTR) analysis is a molecular typing technique employed used to subtype bacterial strains for epidemiological investigations (2). It is useful in for identifying the source of infection when combined with contact history.

We herein report a case of de novo tuberculosis with negative tuberculosis screening test before the administration of adalimumab. The history of tuberculosis exposure and VNTR analysis enabled us to diagnose this case as de novo tuberculosis.

Case report

A 58-year-old man with Crohn’s disease for 21 years presented with a month’s history of fever and cough. Thirteen months prior to this presentation, adalimumab had been initiated to control his perianal lesion of Crohn’s disease after showing negative tuberculin skin test screening results and negative chest radiograph screening findings.

On a physical examination, he had a fever (38°C) and dry cough. Laboratory results showed a C-reactive protein level of 3.8 mg/dL, leukocyte count of 4100/μL, and elevated erythrocyte sedimentation rate of 46 mm in the first hour. T-SPOT⡴ was negative. Chest X-ray revealed right hilar lymphadenopathy, which was further defined by a chest computed tomography (CT) scan to be right hilar and mediastinal lymphadenopathy (Fig. 1).

Although the results of acid-fast staining and polymerase
Figure 1. Chest X-ray and CT performed at the onset of symptoms. Chest X-ray revealed right hilar lymphadenopathy. CT showed right hilar and mediastinal lymphadenopathy. In each imaging study, no intrapulmonary lesions were noted.

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Figure 2. A variable nucleotide tandem repeat (VNTR) analysis of Mycobacterium tuberculosis isolates. Genotyping of this patient and his wife’s father showed identical patterns.

Figure 3. Chest X-ray and CT performed 2 two months after the initiation of anti-tuberculosis therapy. Chest X-ray and CT scan demonstrated exacerbated mediastinal lymphadenopathy.

chain reaction (PCR) of his sputum were negative at the first visit, we suspected lymph node tuberculosis and performed endobronchial ultrasonography-guided transbronchial needle aspiration on the mediastinal lymph node. Necrosis with monocyte infiltration was observed on histopathological examination, and a sputum sample obtained after the bronchoscopy was positive for acid-fast bacilli, and Mycobacterium tuberculosis was confirmed (by PCR). From these findings, we diagnosed him with lymph node tuberculosis. Four months before this episode, he had made contact with his wife’s father, who had been diagnosed with smear-positive tuberculosis (Ziehl-Neelsen +7). Sputum samples from his wife’s father were positive for fully susceptible *M. tuberculosis* that was identical to that of the isolate obtained from the patient by a VNTR analysis (Fig. 2).

Anti-tuberculosis therapy with rifampicin, isoniazid, pyrazinamide and ethambutol was initiated after discontinuing adalimumab. Two months later, the amount of acid-fast bacilli in his sputum had gradually decreased, and the treatment was switched to rifampicin, isoniazid and ethambutol. However, CT scan at this point revealed exacerbated mediastinal lymphadenopathy and an intratracheal polyp-like lesion (Fig. 3). The polyp-like lesion was also detected by bronchoscopy (Fig. 4), and histologically revealed to be epi-
formed before starting treatment with TNF-α inhibitors. As with IRIS in HIV-infected patients, the time to the detection of tuberculosis after treatment with infliximab was 12 weeks. Most cases were suspected of being due to reactivation of LTBI, given the old age of most patients, small number with recent reported exposure to tuberculosis, and low incidence of tuberculosis in the countries from which the reports were received (1). However, Byun et al. showed that de novo tuberculosis in patients with inflammatory bowel disease developed within a median of 24 months after TNF-α inhibitor therapy, and de novo tuberculosis was more prevalent than reactivation of LTBI in South Korea, a country with an intermediate tuberculosis burden. In our patient, de novo tuberculosis developed 13 months after TNF-α inhibitor therapy (9). These findings suggest that reactivation of LTBI may develop relatively soon after the initiation of TNF-α inhibitor therapy, whereas tuberculosis that has long interval between the initiation of TNF-α inhibitor therapy and development of the disease may be de novo. As Japan is regarded as a country with an intermediate tuberculosis burden, attention should be paid to the fact that de novo tuberculosis can occur during TNF-α inhibitor therapy.

Discontinuation of TNF-α inhibitor in the setting of active tuberculosis may be associated with paradoxical worsening of tuberculosis, including a worsened fever, hypoxia, lymphadenopathy, and the appearance of new lesions. This phenomenon is known as IRIS and is commonly seen in cases of human immunodeficiency virus (HIV) with tuberculosis co-infection following the introduction of highly active antiretroviral therapy and recovery of the CD4 T-cell population (10). In our patient, IRIS was recognized as lymphadenopathy and the appearance of a new polyp-like lesion in the trachea after discontinuing adalimumab and receiving anti-tuberculosis treatment. As with IRIS in HIV-infected pa-
tients (11), corticosteroid therapy is usually required to treat IRIS that develops after discontinuing anti-TNFα therapy, although there is a lack of good supporting evidence (12). Controversy also exists concerning the continuation of anti-TNFα therapy in patients who develop tuberculosis (13, 14). Wallis et al. reported that TNF antagonists might accelerate the response to tuberculosis treatment by disrupting granuloma formation (15). Matsumoto et al. state that anti-TNF-α therapy for rheumatoid arthritis can be safely continued or restarted in patients with reactivation of latent tuberculosis (16). In our case, anti-TNFα therapy was reintroduced 3.5 months after the initiation of anti-tuberculosis therapy with improvement in both tuberculosis and Crohn’s disease. These findings suggest that continuing TNF-α inhibitor may be beneficial in patients who develop tuberculosis during TNF-α inhibitor therapy.

In conclusion, the present patient presented with *de novo* tuberculosis during treatment with TNF-α inhibitor and was diagnosed via a VNTR analysis. The re-administration of TNF-α inhibitor was safe and effective for the management of IRIS. In high and intermediate tuberculosis-burden countries, including Japan, *de novo* tuberculosis should be remarked, as well as the reactivation of LTBI.

The authors state that they have no Conflict of Interest (COI).

**References**