Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3054-19
Intern Med 58: 3593-3596, 2019
http://internmed.jp

【 CASE REPORT 】

Bacteriologically Determined *De Novo* Tuberculosis during Tumor Necrosis Factor-α Inhibitor Therapy

Gen Takahashi[1], Hiroyuki Kobayashi[1], Yasuyuki Saito[1], Sho Ohsawa[1], Kuniaki Suzuki[1], Shinichi Ishihara[1] and Takeshi Hisada[2]

Abstract:
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

(Intern Med 58: 3593-3596, 2019)
(DOI: 10.2169/internalmedicine.3054-19)

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®. TB 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

[1]Department of Internal Medicine, Isesaki Municipal Hospital, Japan and [2]Department of Respiratory Medicine, Gunma University Graduate School of Medicine, Japan
Received: March 22, 2019; Accepted: July 7, 2019; Advance Publication by J-STAGE: August 21, 2019
Correspondence to Dr. Gen Takahashi, genmail.613@gmail.com

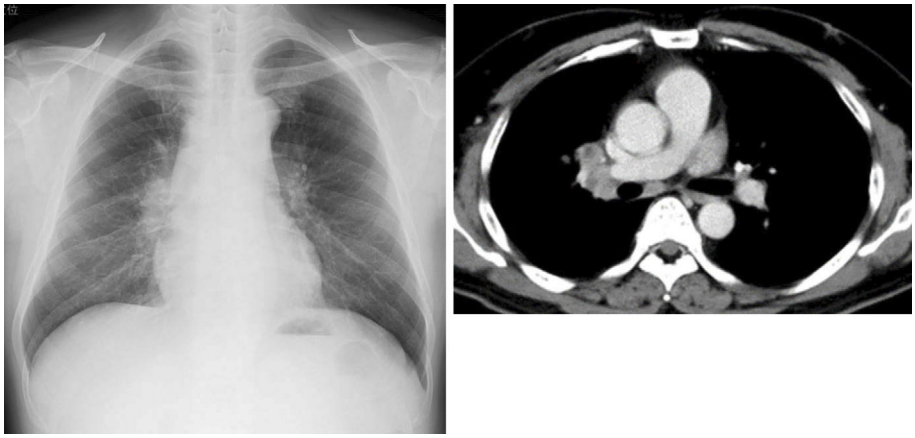

Figure 1. **Chest X-ray and CT performed at the onset of symptoms. Chest X-ray revealed right hilar lymphadenopathy. CT showed right hilar and mediastinal lymphadenopathy. In each imaging study, no intrapulmonary lesions were noted.**

	VNTR																							
	–	JATA 2	–	JATA 7	JATA 9	–	JATA15	–	JATA 1	JATA 3	–	–	JATA 5	JATA 11	JATA 12	JATA 4	JATA 14	JATA 8	JATA 12	–	JATA 10	–	–	JATA 6
	miru4	miru10	miru16	miru26	miru31	miru40	ETR-A	ETR-C	Mtub04	Mtub21	Mtub30	Mtub39	QUB11b	QUB26	QUB4156	Mtub24	QUB11a	QUB15	QUB18	QUB3232	QUB3326	VNTR3820	VNTR4120	VNTR2372
His wife's father	2	1	3	7	5	3	4	4	6	3	4	3	6	8	5	2	9	4	10	16	7	14	12	4
Patient	2	1	3	7	5	3	4	4	6	3	4	3	6	8	5	2	9	4	10	16	7	14	12	4

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.**

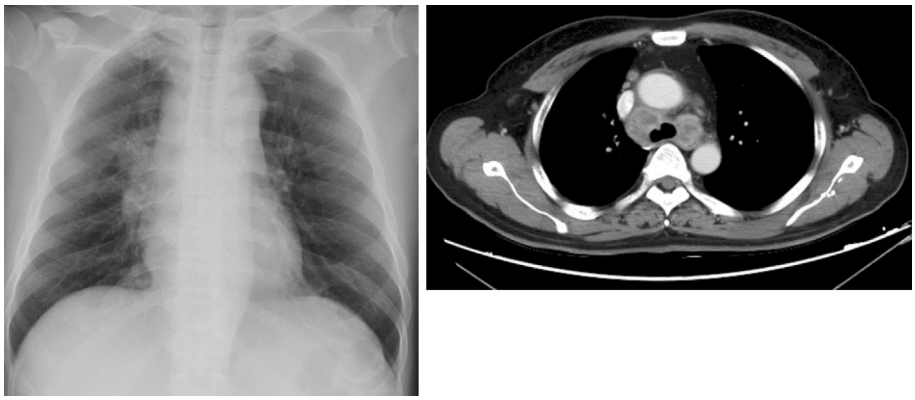

Figure 3. **Chest X-ray and CT performed 2 two months after the initiation of anti-tuberculosis therapy. Chest X-ray and CT scan demonstrated exacerbated mediastinal lymphadenopathy.**

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-

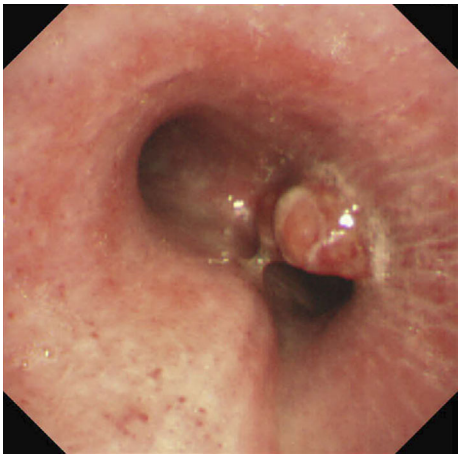

Figure 4. Bronchoscopy performed two months after the initiation of anti-tuberculosis therapy. An intratracheal polyp-like lesion was identified.

thelioid granuloma with necrosis. Acid-fast bacilli were not detected by Ziehl-Neelsen staining of the tissue samples, and tracheal lavage fluid samples were also sterile. Isolated *M. tuberculosis* from his sputum before treatment was confirmed to be susceptible to all anti-tuberculosis drugs. Based on these findings, we attributed the clinical deterioration to immune reconstitution inflammatory syndrome.

Three and a half months after the initiation of anti-tuberculosis therapy, ethambutol was discontinued. However, his Crohn's disease had become exacerbated, so we re-administered adalimumab. After the re-administration of adalimumab, his symptoms of Crohn's disease soon improved. One month later, his mediastinal lymphadenopathy and the intratracheal polyp-like lesion had apparently decreased in size. The patient successfully completed 12 months of anti-tuberculosis therapy and has been alive without recurrence for more than 2 years.

Discussion

Keane et al. analyzed 70 reported cases of tuberculosis after treatment with infliximab, an anti- TNF-α inhibitor, or inflammatory arthritis and inflammatory bowel disease (1). They highlighted the fact that extrapulmonary disease occurred in 57% of patients, nearly a quarter had disseminated tuberculosis, and lymph nodes were the most common extrapulmonary site. These unusual forms of tuberculosis in TNF-α inhibitor therapy may be due to the failure of the development and maintenance of granulomas. Similar to these cases, chest CT in our patient showed right hilar and mediastinal lymphadenopathy without any intrapulmonary lesions. The clinical presentation of tuberculosis during TNF-α inhibitor therapy can be atypical. Thus, when a patient receiving TNF-α inhibitor therapy has a fever, it is important to rule out tuberculosis, especially disseminated and extrapulmonary lesions.

Screening for the presence of LTBI is now routinely performed before starting treatment with TNF-α inhibitors. As has been shown by other reports, tuberculosis occurs following exposure to TNF-α inhibitors, even in patients with no evidence of LTBI (3-5). However, reports of *de novo* tuberculosis confirmed by genetic procedure are extremely rare (6). The present case was diagnosed as *de novo* tuberculosis by a VNTR analysis, one of the methods for fingerprinting of *M. tuberculosis* isolates, in combination with the history of exposure to another patient with smear-positive tuberculosis. A VNTR analysis is a typing method that uses PCR based on variable numbers of tandem repeats of *mycobacterial* interspersed repetitive units (2). In the present case, 24 loci containing variable numbers of tandem repeats were used, and each locus was amplified by PCR with the primers. Isolates were typed by the number of copies of repeated units at 24 loci scattered throughout the genome (7). A VNTR analysis has several advantages over IS6110 restriction fragment length polymorphism typing, including a lower DNA requirement for detection, fast turnaround time, and ability to easily compare digital results between laboratories (8). Genotyping of tuberculosis analyzed by VNTR, when combined with epidemiologic information, aids in the identification of individuals with tuberculosis involved in a chain of transmission.

Keane et al. reported that the median 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

1. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med **345**: 1098-1104, 2001.
2. Supply P, Allix C, Lesjean S, et al. Proposal for standardization of optimized mycobacterial interspersed repetitive unit-variable-number tandem repeat typing of *Mycobacterium tuberculosis*. J Clin Microbiol **244**: 4498-4510, 2006.
3. Singh J, Puri AS, Sachdeva S, Sakhuja P, Arivarasan K. Rectal tuberculosis after infliximab therapy despite negative screening for latent tuberculosis in a patient with ulcerative colitis. Intest Res **14**: 183-186, 2016.
4. Debeuckelaere C, De Munter P, Van Bleyenbergh P, et al. Tuberculosis infection following anti-TNF therapy in inflammatory bowel disease, despite negative screening. J Crohns Colitis **8**: 550-557, 2014.
5. O'Dowd C, Kewin P, Morris J, Cotton M. Tuberculosis complicated by immune reconstitution inflammatory syndrome in a patient on anti-TNFα therapy for Crohn's disease. BMJ Case Rep **2011**: bcr0920103376, 2011.
6. Arend SM, Leyten EM, Franken WP, Huisman EM, van Dissel JT. A patient with de novo tuberculosis during anti-tumor necrosis factor-alpha therapy illustrating diagnostic pitfalls and paradoxical response to treatment. Clin Infect Dis **45**: 1470-1475, 2007.
7. Iwamoto T, Grandjean L, Arikawa K, et al. Genetic diversity and transmission characteristics of beijing family strains of *mycobacterium tuberculosis* in Peru. PLoS One **7**: e49651, 2012.
8. Borgdorff MW, van Soolingen D. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? Clin Microbiol Infect **19**: 889-901, 2013.
9. Byun JM, Lee CK, Rhee SY, et al. The risk of tuberculosis in Korean patients with inflammatory bowel disease receiving tumor necrosis factor-α blockers. J Korean Med Sci **30**: 173-179, 2015.
10. Dhasmana D.J., Dheda K., Ravn P, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients receiving antiretroviral therapy. Drugs **68**: 191-208, 2008.
11. Meintjes G1, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS **24**: 2381-2390, 2010.
12. Tanaka T, Sekine A, Tsunoda Y, et al. Central nervous system manifestations of tuberculosis-associated immune reconstitution inflammatory syndrome during adalimumab therapy: a case report and review of the literature. Intern Med **54**: 847-851, 2015.
13. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) **64**: 625-639, 2012.
14. Ding T, Ledingham J, Luqmani R, et al. Standards, Audit and Guidelines Working Group of BSR Clinical Affairs Committee; BHPR. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology (Oxford) **49**: 2217-2219, 2010.
15. Wallis RS, Kyambadde P, Johnson JL, et al. A study of the safety, immunology, virology, and microbiology of adjunctive etanercept in HIV-1-associated tuberculosis. AIDS **18**: 257-264, 2004.
16. Matsumoto T, Tanaka T. Continuation of Anti-TNF-Therapy for rheumatoid arthritis in patients with active tuberculosis reactivated during anti-TNF Medication is more beneficial than its cessation. J Infect Dis Ther **3**: 35-37, 2015.