Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3295-19
Intern Med 59: 849-853, 2020
http://internmed.jp

【 CASE REPORT 】

Development of Disseminated Tuberculosis with Intestinal Involvement due to Adalimumab Administration Despite Latent Tuberculosis Treatment

Kozo Ikuta[1], Yumiko Ota[1], Shigenobu Kuroki[1], Yoshihide Matsumoto[1], Eri Senda[1], Saki Mukohara[2], Soshi Takahashi[2], Kazuya Monden[3], Akihisa Fukuda[4], Hiroshi Seno[4], Shunichi Kumagai[2] and Seiji Shio[1]

Abstract:
Treatment of latent tuberculosis infection (LTBI) reduces the probability of reactivation of tuberculosis associated with anti-tumor necrosis factor (TNF)α inhibitors, but no chemoprophylaxis is completely protective. We herein report a woman with rheumatoid arthritis who developed disseminated tuberculosis with intestinal involvement during adalimumab administration despite LTBI treatment. Tuberculosis reactivation was not detected in sputum or urine but was detected from the terminal ileal mucosa. Detection of intestinal tuberculosis is rare in patients being treated with anti-TNFα therapy after LTBI treatment. As anti-TNFα inhibitors have become more common, the rate of reactivation of tuberculosis, including intestinal tuberculosis, has increased in patients being treated for LTBI.

Key words: disseminated tuberculosis, intestinal tuberculosis, latent tuberculosis infection, anti-TNFα inhibitor, reactivation of tuberculosis

(Intern Med 59: 849-853, 2020)
(DOI: 10.2169/internalmedicine.3295-19)

Introduction

Anti-tumor necrosis factor (TNF)α inhibitors are effective medications for treating difficult autoimmune and inflammatory diseases, and their application has increased in recent years. However, these agents are also one of the highest risk factors of tuberculosis reactivation in patients with latent tuberculosis infection (LTBI) (1). Therefore, patients in whom anti-TNFα therapy is planned should first be evaluated for LTBI by interferon-gamma release assays (IGRAs), and if positive findings are obtained, these patients should undergo treatment for LTBI before the initiation of further therapy. It should also be noted that although treatment of LTBI decreases the rate of developing active tuberculosis in patients who receive anti-TNFα therapy, chemoprophylaxis cannot completely protect against tuberculosis reactivation (2-5).

We herein report a patient in whom colonoscopic biopsies revealed disseminated tuberculosis with intestinal involvement during the administration of adalimumab despite previous treatment of LTBI.

Case Report

A 79-year-old woman with a 10-year history of rheumatoid arthritis (RA) was admitted to our hospital to investigate the cause of a high fever and general malaise in X year. She had been diagnosed with RA in X-10 year and received etanercept for treatment of RA for three years from X-9 year at a previous hospital. However, whether or not IGRAs had been performed at that hospital was unclear, so chemoprophylaxis for LTBI was not performed.

[1]Division of Gastroenterology, Shinko Memorial Hospital, Japan, [2]The Center for Rheumatic Diseases, Shinko Memorial Hospital, Japan, [3]Department of Respiratory Center, Shinko Memorial Hospital, Japan and [4]Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Japan
Received: May 6, 2019; Accepted: October 10, 2019; Advance Publication by J-STAGE: November 22, 2019
Correspondence to Dr. Kozo Ikuta, kikuta@kuhp.kyoto-u.ac.jp

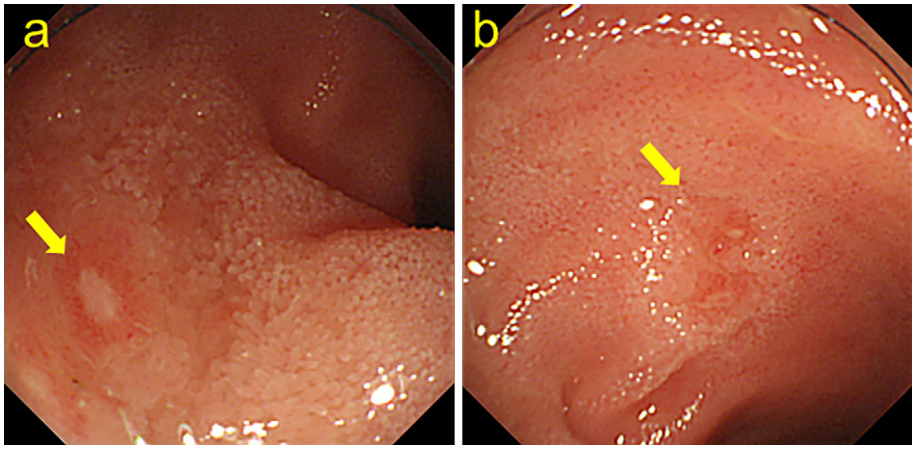

Figure 1. **(a, b) Colonoscopy performed at X-1 year showing small erosions at the terminal ileum (arrow).**

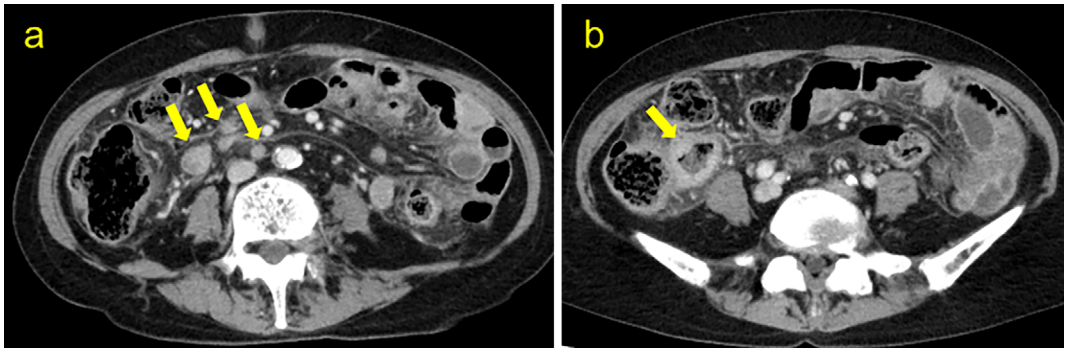

Figure 2. **(a, b) Abdominal CT findings. CT showing para-aortic and mesenteric lymphadenopathy (arrows) (a) and wall swelling of the terminal ileum (arrow) (b).**

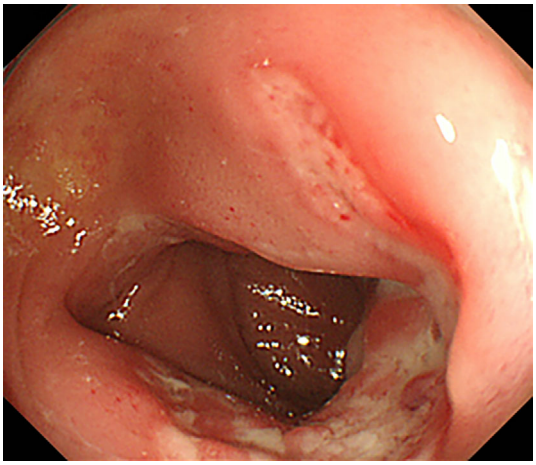

Figure 3. **Colonoscopy showing ring-shaped ulcers at the terminal ileum.**

She was transferred to our hospital in X-6 year, at which point she was immediately found to have LTBI based on a positive T-SPOT®. TB, negative chest X-ray findings, and negative computed tomography (CT) findings. She had been treated with isoniazid 300 mg daily for 6 months while continuing the administration of etanercept.

In X-2 year, she underwent follow-up colonoscopy after endoscopic mucosal resection for colonic polyps at another hospital. Colonoscopy showed no recurrence of colonic polyps but revealed multiple small erosions in the ascending colon. The biopsy specimens showed non-caseous granuloma, Ziehl-Neelsen staining did not show any acid-fast bacilli, and neither chest nor abdominal CT revealed active tuberculosis. Consequently, we diagnosed the colonic erosions as possible Crohn's disease and switched the biologic agent from etanercept to adalimumab, which is effective for Crohn's disease. In X-1 year, re-colonoscopy showed some small aphthous erosions in the terminal ileum (Fig. 1). The biopsy specimens showed ileitis with hyperplasia of lymphoid follicles and aphthous erosions but did not show granuloma. We continued adalimumab.

In X year, she complained of a high fever (over 38℃) and general malaise. Laboratory tests showed a C-reactive protein (CRP) level of 6.96 mg/dL and an erythrocyte sedimentation rate (ESR) of 58 mm/h. Abdominal CT showed para-aortic and mesenteric lymphadenopathy and swelling of the terminal ileum wall (Fig. 2), while colonoscopy showed ring-shaped ulcers at the terminal ileum (Fig. 3). Microscopic images of the biopsy specimens from the ulcer showed nothing but ulcer bed tissue; however, a polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* using the biopsy specimens was positive. In addition, culture of

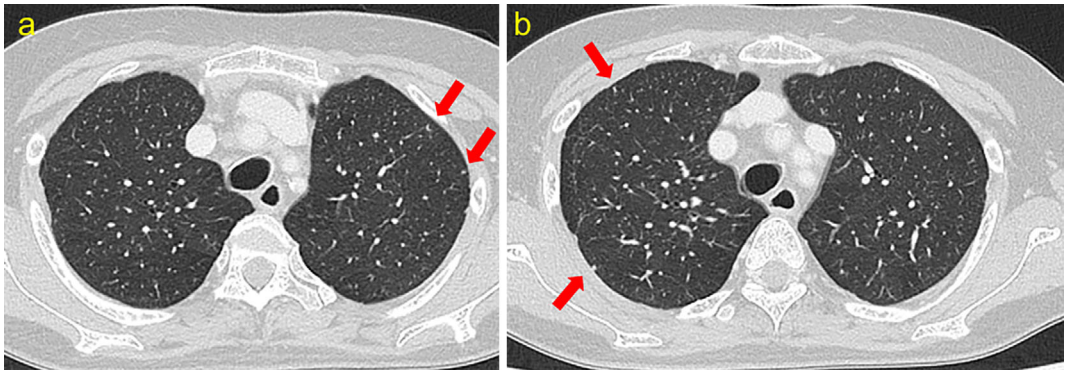

Figure 4. **(a, b) Chest CT showing small granular lesions distributed unrelatedly to the lobule structures in both lungs (arrows).**

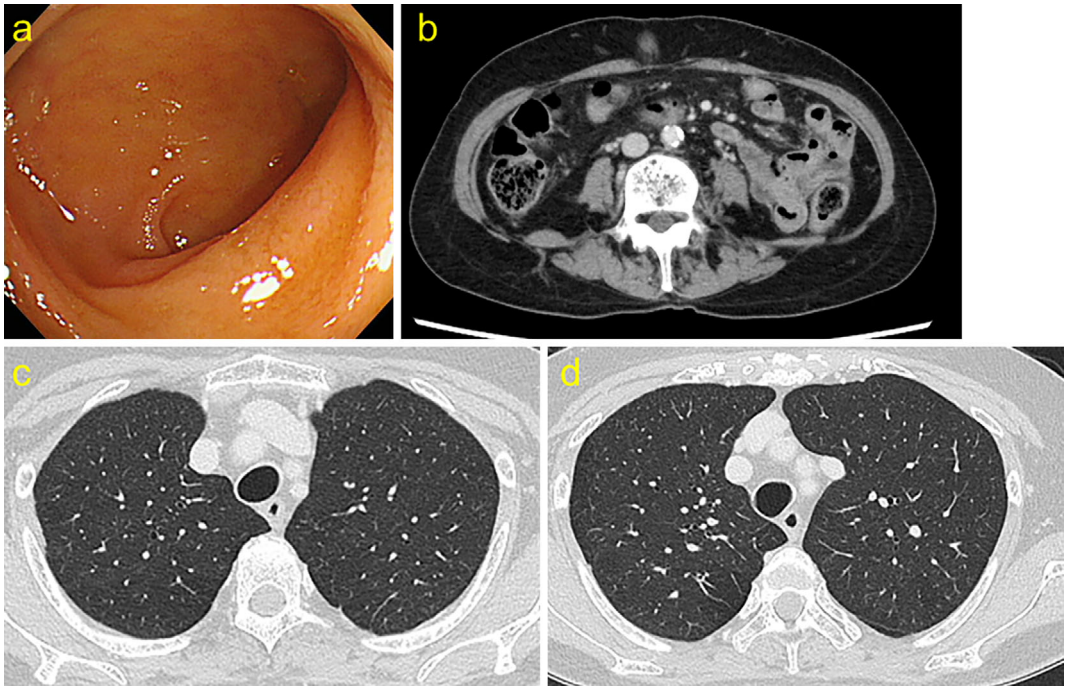

Figure 5. **A colonoscopic image five months after the initiation of anti-tuberculosis therapy and CT findings one year after the initiation. (a) Colonoscopy showing the disappearance of the terminal ileum ulcer. (b) Abdominal CT showing the shrinkage of the lymph nodes. (c, d) Chest CT showing the disappearance of granular lesions.**

intestinal specimens was also positive for *M. tuberculosis*, while PCR and cultures of urine and sputum were negative. With careful observation, chest CT showed small granular lesions distributed unrelatedly to the lobule structures in both lungs (Fig. 4)-findings that had not been detected in X-2 year. While the chest CT findings were not typical enough to clearly identify disseminated tuberculosis, we diagnosed the patient with disseminated tuberculosis with intestinal involvement based on the clinical course and CT findings.

Adalimumab administration was stopped, and anti-tuberculosis therapy was started; no antibiotics other than anti-tuberculosis drugs were administered at this time. This therapy included isoniazid 200 mg, rifampicin 450 mg, ethambutol 750 mg, and pyrazinamide 1 g daily for 2 months followed by isoniazid 200 mg and rifampicin 450 mg daily for 7 months. In the two weeks after the initiation of anti-tuberculosis therapy, the patient's body temperature returned to normal, and the CRP level decreased to 0.95 mg/dL. After five months, colonoscopy revealed the disappearance of the terminal ileum ulcer (Fig. 5a). After one year, abdominal CT revealed shrinkage of the lymph nodes, and chest CT showed the disappearance of the granular lesions (Fig. 5b-d).

Discussion

We herein report a patient who developed disseminated tuberculosis, including intestinal tuberculosis, during the administration of adalimumab after treatment of LTBI.

The disease concept of LTBI was first published in

2000 (6). Patients with LTBI are infected with *M. tuberculosis*, but they do not have obvious symptoms of active tuberculosis, and neither bacteriological examinations nor diagnostic imaging suggest active tuberculosis. IGRAs, including QuantiFERON®-TB and T-SPOT®.TB, have recently been used for the diagnosis of LTBI due to their high specificity and sensitivity for this infection (7). According to the LTBI guidelines, the high risk factors of reactivation of tuberculosis in patients with LTBI are human immunodeficiency virus (HIV) infection/AIDS, being an organ transplantation recipient, chronic renal failure requiring dialysis, silicosis and the use of anti-TNFα inhibitors (1). TNFα is an essential cytokine for the activation of alveolar macrophages and granuloma formation and plays an important role in the containment of *M. tuberculosis*. The administration of anti-TNFα inhibitors leads to the collapse of the granuloma and the reprocessing of *M. tuberculosis* in patients with LTBI (8). Among anti-TNFα inhibitors, monoclonal antibodies, such as infliximab and adalimumab, are associated with a higher risk for the development of tuberculosis than soluble TNF receptors, such as etanercept (9). According to the guidelines of the Japan College of Rheumatology, patients with LTBI who have rheumatoid arthritis should be treated with isoniazid 300 mg daily for 6-9 months beginning 3 weeks before the initiation of anti-TNFα inhibitors. Screening and treatment for LTBI decrease the rate of reactivation tuberculosis; however, chemoprophylaxis cannot completely protect against reactivation tuberculosis (2-5).

In the present case, the patient developed disseminated tuberculosis, including intestinal tuberculosis, during anti-TNFα therapy despite treatment of LTBI. Intestinal tuberculosis was detected by PCR and cultures from biopsy specimens of the terminal ileal mucosa by colonoscopy. However, PCR and cultures from sputum and urine did not reveal tuberculosis reactivation. Previous reports showed that tuberculous patients who develop tuberculosis while undergoing anti-TNFα therapy had a higher rate of extrapulmonary and disseminated tuberculosis than those without immunosuppression (extrapulmonary: 57% vs. 15%, disseminated: 24% vs. 1%) (10). However, to our knowledge, this is the first reported case in which colonoscopy revealed intestinal tuberculosis in a patient with reactivation of tuberculosis who had received anti-TNFα therapy after treatment of LTBI. It should be noted that the terminal ileal mucosa, rather than the sputum or urine, proved the presence of active tuberculosis in this case. Why the tuberculosis was more pronounced in the intestine than in other organs is unclear, although it is possible that the patient had been infected with primary intestinal tuberculosis in the past and it healed naturally.

In the present case, at 3 years after starting etanercept, isoniazid 300 mg/day had been administered for 6 months to treat LTBI. Screening and treatment of LTBI in this case were delayed from the timing recommended in the guidelines. The administration period of isoniazid for treatment of LTBI is nine months in many medical facilities in Japan. This six-month treatment period is consistent with the guidelines but shorter than the usual treatment period. This irregular administration approach might have contributed to tuberculosis reactivation in the present patient.

We closely monitored the patient for the development of immune reconstitution inflammatory syndrome (IRIS) due to the discontinuation of adalimumab. IRIS has been reported as a condition in which immunocompromised patients, such as those with acquired immunodeficiency syndrome, are treated with intensive anti-HIV therapy, such as highly active anti-retroviral therapy (HAART), and when the immune system recovers, the immune response to latent pathogens is enhanced and infectious disease symptoms become apparent (11). IRIS is now known to occur even after dose reduction or discontinuation of immunosuppressants (12). Patients who developed tuberculosis while receiving anti-TNFα therapy have been reported to develop IRIS following the discontinuation of anti-TNFα therapy and resumption of antituberculous therapy (13, 14). At the onset of IRIS, high-dose steroid therapy should be administered, and the resumption of anti-TNFα inhibitors should be considered necessary if IRIS is refractory to steroid therapy (14-16). In the present case, the patient's fever rapidly resolved, as did her general malaise, a few days after the initiation of antituberculous therapy, and no symptoms or new lesions suggestive of IRIS appeared during or after treatment of tuberculosis. We therefore concluded that this patient did not develop IRIS.

Intestinal tuberculosis is sometimes difficult to diagnose correctly because the symptoms are nonspecific, and it can mimic inflammatory bowel diseases, such as Crohn's disease, on colonoscopy images. In the present case, colonoscopy showed small erosions in the terminal ileum and the ascending colon one or two years before she was diagnosed with tuberculosis reactivation. Microscopic images of specimens obtained from biopsies did not show findings suggestive of active tuberculosis, so the erosions were diagnosed as possible Crohn's disease. Given that Hematoxylin and Eosin staining and Ziehl-Neelsen stainings have low sensitivity for the detection of intestinal tuberculosis (17), it is possible that the erosions in the ileum and colon indicated intestinal tuberculosis.

In summary, we encountered a case in which disseminated tuberculosis with intestinal involvement developed during anti-TNFα therapy after LTBI treatment. It should be noted that LTBI treatment cannot completely prevent reactivation of tuberculosis. Intestinal tuberculosis is uncommon in active tuberculosis patients after LTBI treatment. However, as the use of anti-TNFα inhibitors increases, the frequency of reactivation tuberculosis, including intestinal tuberculosis, is expected to increase as well.

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

References

1. Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerg Microbes Infect **5**: e10, 2016.
2. Ramos GP, Stroh G, Al-Bawardy B, Faubion WA, Papadakis KA, Escalante P. Outcomes of treatment for latent tuberculosis infection in patients with inflammatory bowel disease receiving biologic therapy. Inflamm Bowel Dis **24**: 2272-2277, 2018.
3. Parra Ruiz J, Ortego Centeno N, Raya Alvarez E. Development of tuberculosis in a patient treated with infliximab who had received prophylactic therapy with isoniazid. J Rheumatol **30**: 1657-1658, 2003.
4. Raychaudhuri S, Shmerling R, Ermann J, Helfgott S. Development of active tuberculosis following initiation of infliximab despite appropriate prophylaxis. Rheumatology (Oxford) **46**: 887-888, 2007.
5. Bourikas LA, Kourbeti IS, Koutsopoulos AV, Koutroubakis IE. Disseminated tuberculosis in a Crohn's disease patient on anti-TNF alpha therapy despite chemoprophylaxis. Gut **57**: 425; author reply -6, 2008.
6. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med **161** (4 Pt 2): S221-S247, 2000.
7. Amorim RF, Viegas ERC, Carneiro AJV, et al. Superiority of interferon gamma assay over tuberculin skin test for latent tuberculosis in inflammatory bowel disease patients in Brazil. Dig Dis Sci **64**: 1916-1922, 2019.
8. Lin PL, Myers A, Smith L, et al. Tumor necrosis factor neutralization results in disseminated disease in acute and latent *Mycobacterium tuberculosis* infection with normal granuloma structure in a cynomolgus macaque model. Arthritis Rheum **62**: 340-350, 2010.
9. Ai JW, Zhang S, Ruan QL, et al. The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor-alpha antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. J Rheumatol **42**: 2229-2237, 2015.
10. Theis VS, Rhodes JM. Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. Aliment Pharmacol Ther **27**: 19-30, 2008.
11. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med **133**: 447-454, 2000.
12. Sueki H, Mizukawa Y, Aoyama Y. Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients. J Dermatol **45**: 3-9, 2018.
13. Watanabe S, Kaneko Y, Kawamoto H, et al. Paradoxical response with increased tumor necrosis factor-alpha levels to anti-tuberculosis treatment in a patient with disseminated tuberculosis. Respir Med Case Rep **20**: 201-204, 2017.
14. Garcia Vidal C, Rodriguez Fernandez S, Martinez Lacasa J, et al. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. Clin Infect Dis **40**: 756-759, 2005.
15. Lwin N, Boyle M, Davis JS. Adalimumab for corticosteroid and infliximab-resistant immune reconstitution inflammatory syndrome in the setting of TB/HIV coinfection. Open Forum Infect Dis **5**: ofy027, 2018.
16. Walker NF, Stek C, Wasserman S, Wilkinson RJ, Meintjes G. The tuberculosis-associated immune reconstitution inflammatory syndrome: recent advances in clinical and pathogenesis research. Curr Opin HIV AIDS **13**: 512-521, 2018.
17. Dasgupta A, Singh N, Bhatia A. Abdominal tuberculosis: a histopathological study with special reference to intestinal perforation and mesenteric vasculopathy. J Lab Physicians **1**: 56-61, 2009.