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Case report: Disseminated Tuberculosis Following Adalimumab Therapy in a Patient with Rheumatoid Arthritis

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Abstract

Patients with rheumatoid arthritis (RA) who receive anti-tumor necrosis factor-alpha (anti-TNF-α) therapy are at increased risk of tuberculosis (TB), particularly extrapulmonary and disseminated TB. Although baseline TB screening is routinely performed prior to treatment initiation, active TB may develop during therapy. Here, we report the case of a 37-year-old woman with long-standing RA who developed disseminated TB three months after starting adalimumab, despite negative baseline chest radiography and interferon-gamma release assay results. The patient presented with prolonged fever, abdominal distension, and poor appetite. On assessment, pulmonary nodules, ascites, and peritoneal nodular lesions were identified. Histopathological examination revealed granulomatous inflammation with caseous necrosis, and polymerase chain reaction confirmed *Mycobacterium tuberculosis* infection. This report presents the clinical course of this patient and discusses the limitations of current TB screening strategies and the importance of ongoing clinical vigilance during anti-TNF-α therapy.

Key Words: rheumatoid arthritis; adalimumab; anti-tumor necrosis factor-alpha; disseminated tuberculosis; interferon-gamma release assay

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Background

Patients with rheumatoid arthritis (RA) are at increased risk of tuberculosis (TB) compared with the general population owing to disease-related immune dysregulation and the use of immunosuppressive therapies[1-3]. This is particularly important in Asia, where TB remains an endemic infectious disease[2,3]. A nationwide population-based study in Taiwan demonstrated that patients with RA had a 2.28-fold higher risk of developing active TB than the general population, while a recent nationwide cohort study in Korea reported an approximately 3-fold higher risk, even after the implementation of routine latent TB infection screening before biological therapy[2,3].

Tumor necrosis factor-alpha (TNF-α) plays a critical role in host defense against *Mycobacterium tuberculosis* (*MTB) infection* by maintaining granuloma formation. TNF-α inhibition may therefore lead to the reactivation of latent infection or the development of active TB[4-6]. Accordingly, treatment with anti-TNF-α agents has been associated with increased TB risk[7]. An increased risk of TB among RA patients receiving biological therapies was demonstrated in the Taiwanese real-world cohort mentioned above, while the nationwide Korean study reported a 4.68-fold higher risk of active pulmonary TB among patients exposed to biological or targeted synthetic disease-modifying anti-rheumatic drugs[2,3]. Despite recommended baseline TB screening prior to therapy initiation, active TB may still occur.

Objective

Herein, we report the case of a patient with RA who developed disseminated TB shortly after the initiation of adalimumab therapy. We also discuss the limitations of current TB screening strategies and the importance of ongoing clinical vigilance during anti-TNF-α therapy.

Case Report

A woman with RA, diagnosed at the age of 15, was initially treated with methotrexate. Owing to the development of liver function impairment, her treatment was switched to a combination of hydroxychloroquine, nonsteroidal anti-inflammatory drugs, and low-dose prednisolone (<5 mg/day); however, adequate disease control was not achieved. After two consecutive Disease Activity Score in 28 Joints scores of 6.92 and 7.00, anti-TNF-α therapy was initiated when she was 37 years old.

Prior to anti-TNF-α therapy initiation, a risk management plan was performed, including hepatitis serology, chest radiography, and QuantiFERON-TB testing; all results were negative. Treatment with the TNF inhibitor adalimumab was initiated at a dose of 40 mg every two weeks, and a total of seven doses were administered.

Three months after adalimumab therapy initiation, the patient developed intermittent fever, abdominal distension, and a poor appetite, which persisted for one month. She sought medical attention at two other hospitals; however, her symptoms did not improve. She was admitted to our hospital owing to progressive clinical deterioration.

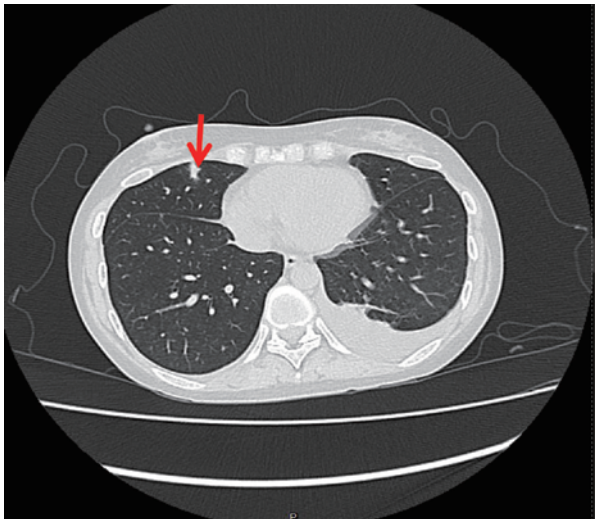


Figure 1. Chest computed tomography revealed multiple solid nodules in both lungs, with a maximum diameter of approximately 0.7 cm (red arrow).

After admission, an extensive diagnostic evaluation for fever of unknown origin was conducted. Chest computed tomography revealed multiple solid nodules in both lungs, with a maximum diameter of approximately 0.7 cm (Figure 1). Abdominal computed tomography demonstrated mild ascites, irregular peritoneal thickening, and multiple small nodules with reticulonodular opacities involving the omentum, spleen, and liver (Figure 2). Thoracentesis was performed to evaluate the pleural effusion, and diagnostic laparoscopy was arranged for further assessment of the omental lesions. During surgery, multiple scattered whitish nodules were observed throughout the peritoneum (Figure 3). Histopathological examination of the peritoneal tissue revealed multifocal chronic granulomatous inflammation with caseous necrosis and palisading multinucleated Langhans-type giant cells (Figure 4). Polymerase chain reaction for *MTB* was positive.

Based on the clinical presentation, radiological results, and pathological findings, the patient was diagnosed with disseminated TB involving the lungs and omentum, complicated by pleural effusion and ascites. Adalimumab was discontinued, and anti-TB

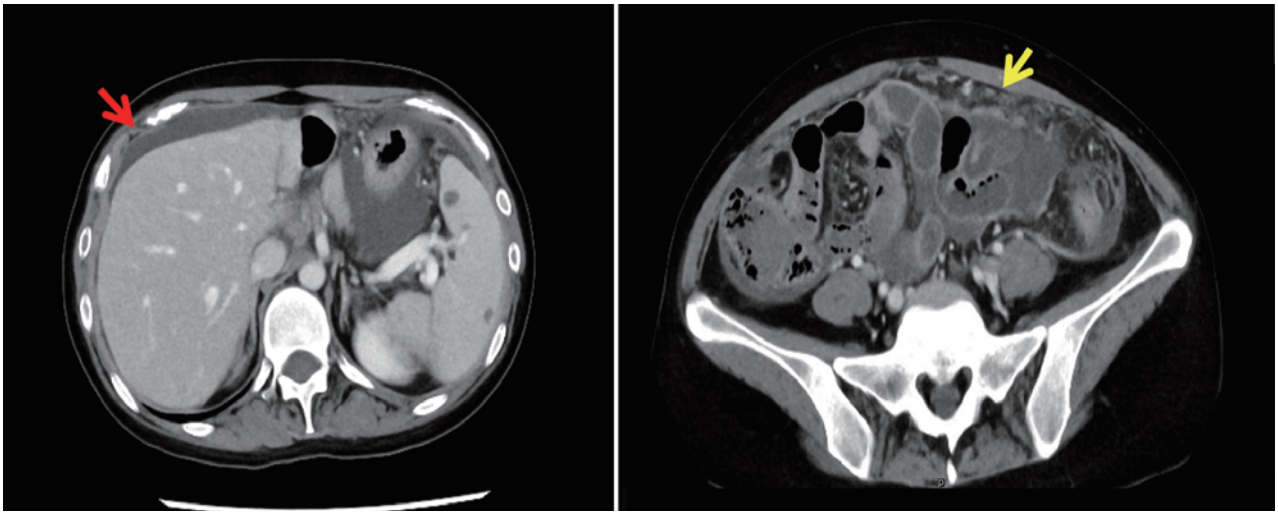


Figure 2. Abdominal computed tomography demonstrated mild ascites (red arrow), irregular peritoneal thickening, and multiple small nodules with reticulonodular opacities involving the omentum (yellow arrow), spleen, and liver.

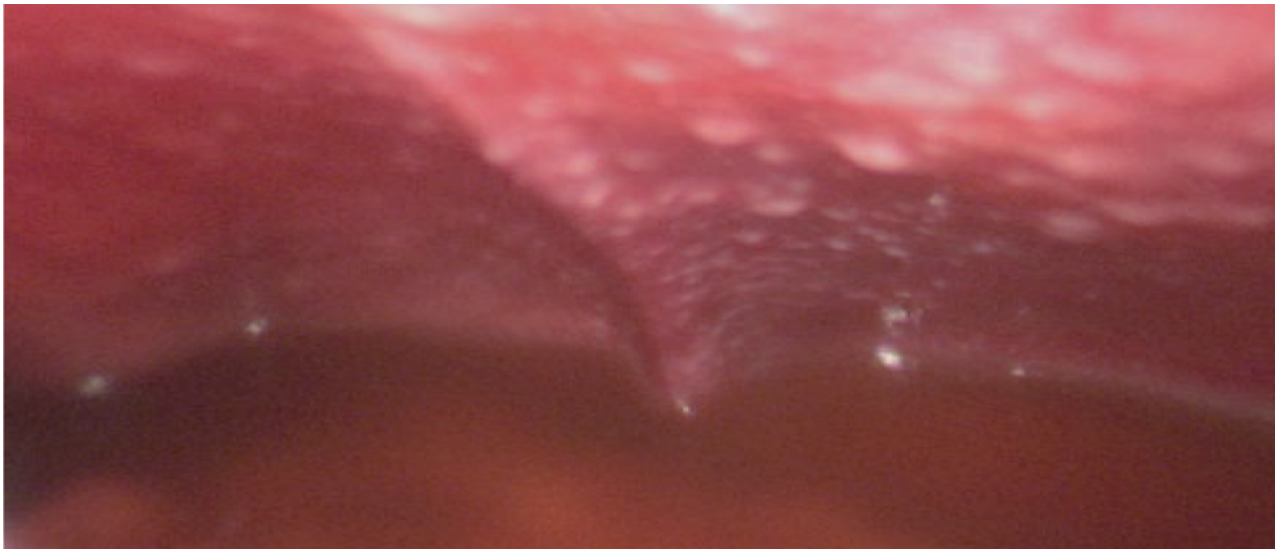


Figure 3. Surgical finding: multiple scattered whitish nodules were observed throughout the peritoneum.

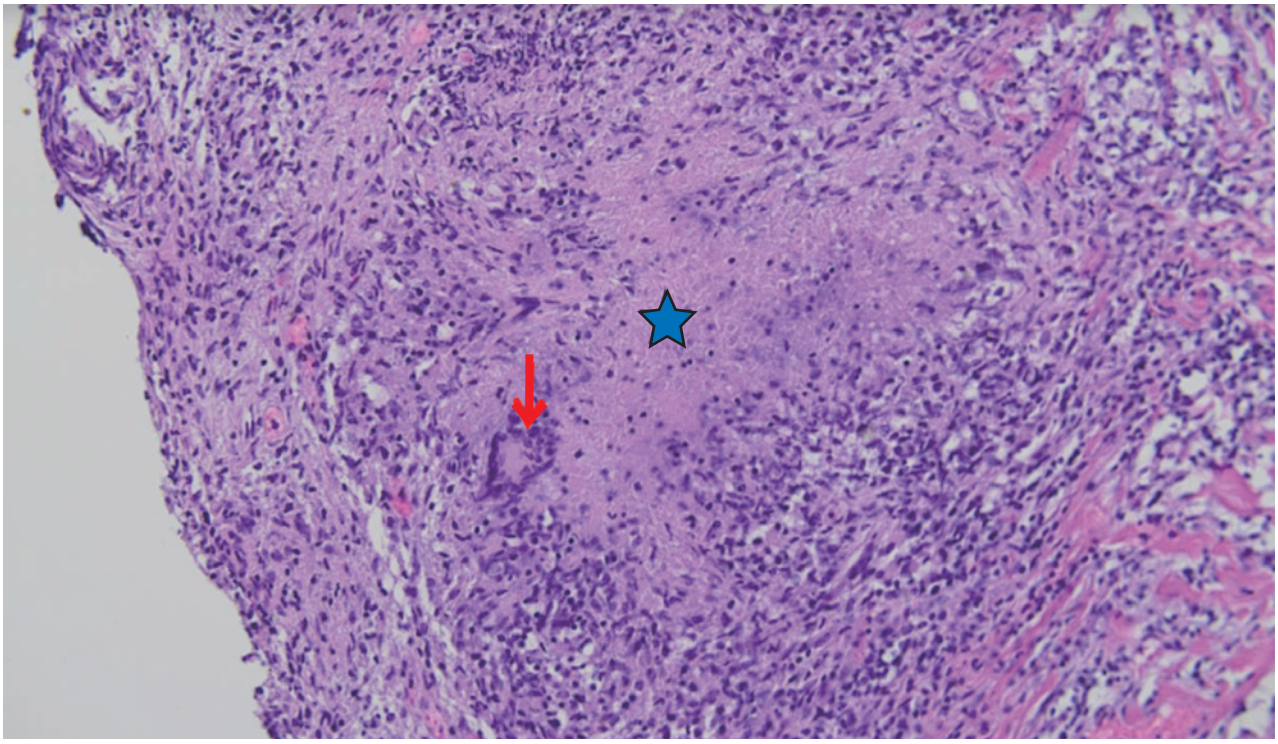


Figure 4. Histopathological examination of the peritoneal tissue revealed multifocal chronic granulomatous inflammation with caseous necrosis (star) and palisading multinucleated Langhans-type giant cells (red arrow).

therapy was initiated with a combination regimen of rifampicin 600 mg, isoniazid 300 mg, pyrazinamide 1,200 mg, and ethambutol 825 mg. The patient completed a seven-month treatment course, with marked clinical improvement.

Discussion

Patients with RA have an increased risk of TB compared with the general population. TNF-α plays a critical role in host defense against *MTB*, primarily by maintaining granuloma integrity and controlling latent infections[4,5]. Consequently, treatment with anti-TNF-α agents has been associated with increased TB risk, particularly extrapulmonary and disseminated disease[7,8].

Among TNF inhibitors, monoclonal antibodies, such as adalimumab, confer higher TB risk than soluble TNF receptor fusion proteins, such as etanercept[7,9,10]. In the present case, disseminated TB involving the lungs, pleura, and peritoneum developed three months after adalimumab therapy initiation, despite negative baseline TB screening. Although it is not possible to definitively differentiate a reactivated latent TB infection from a de novo infection, the early onset and disseminated presentation shortly after anti-TNF-α therapy initiation highlight the limitations of relying solely on baseline screening strategies.

Chest radiography, tuberculin skin tests, and interferon-gamma release assays are commonly used for TB screening; however, these methods have imperfect sensitivity, particularly in patients with immune dysregulation or prior immunosuppressive exposure. A meta-analysis reported a pooled sensitivity of approximately 77% for tuberculin skin tests and sensitivities ranging from 70-78% for QuantiFERON assays, corresponding to false-negative rates of approximately 23% and 22-30%, respectively[11]. Therefore, false-negative results may occur during baseline screening and continued clinical

vigilance following anti-TNF-α therapy initiation is warranted. Previous studies have shown that most anti-TNF-α-associated TB cases occur within the first three to six months of treatment[12], supporting the importance of close clinical observation during this period.

Serial interferon-gamma release assays during anti-TNF-α therapy in selected high-risk populations has been discussed; however, the optimal frequency and clinical utility of this approach remain uncertain[13,14]. Repeat assessment later in the therapy course may help to identify new TB infections, particularly in regions with intermediate TB incidence, such as Taiwan, or in high-burden settings; however, evidence remains limited and practices vary across regions[13,14]. In addition, constitutional symptoms and atypical organ involvement should prompt timely diagnostic evaluation for TB[12,15].

In conclusion, negative baseline TB screening does not preclude subsequent TB development in patients receiving anti-TNF-α therapy. The present case emphasizes the importance of ongoing clinical awareness and structured follow-up to facilitate the early recognition and diagnosis of TB in this high-risk population.

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一名類風濕性關節炎患者於接受 Adalimumab 治療後發生播散性結核病之病例報告

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摘要

類風濕性關節炎患者接受抗腫瘤壞死因子 α（anti-tumor necrosis factor-alpha, anti-TNF-α）治療後，發生結核病的風險增加，尤以肺外及播散性結核為甚。儘管於治療開始前例行進行結核病篩檢，治療期間仍可能發生活動性結核病。本文報告一名 37 歲、病史長久之類風濕性關節炎女性患者，於開始使用 adalimumab 治療三個月後，在基線胸部 X 光及干擾素 γ 釋放試驗皆為陰性之情況下，發生播散性結核病。患者表現為長期發燒、腹脹及食慾不振，影像學檢查顯示肺部結節、腹水及腹膜結節性病灶。病理組織學檢查顯示具乾酪性壞死之肉芽腫性發炎反應，聚合酶連鎖反應證實結核分枝桿菌感染。本文呈現此病例之臨床經過，並探討現行結核病篩檢策略之限制，以及抗 TNF-α 治療期間持續臨床警覺的重要性。