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Case Report

Asymptomatic Pulmonary Tuberculosis in a Child under TNF-alpha Inhibitor Therapy

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Abstract

The use of TNF-alpha inhibitor agents facilitates mycobacterial infections. Unlike in normal population, active tuberculosis in such patients may be asymptomatic. Here we present the case of an asymptomatic child who developed pulmonary tuberculosis during TNF-alpha inhibitor therapy. A 12-year-old child with a diagnosis of juvenile idiopathic arthritis and uveitis was referred to our clinic before initiation of adalimumab therapy. His tuberculin skin test was negative and chest X-ray was normal prior to therapy. On the third month of his therapy, his father was diagnosed with pulmonary tuberculosis, and he was initiated on isoniazid therapy. A month later, the patient's tuberculin skin test was measured as 7 mm, and chest X-ray revealed paratracheal opacity. Computerized tomographic scan confirmed a necrotic mass lesion with a size of 40x27x24 mm which was compatible with tuberculosis. He was thus initiated on antituberculosis therapy. Patients undergoing anti TNF-alpha therapy should be followed up for tuberculosis before and during therapy.

Keywords: Child, TNF-alpha inhibitor, tuberculosis

Introduction

Important accomplishments have been realized in the treatment of many chronic diseases, particularly rheumatoid arthritis, seronegative spondyloarthropathy, and inflammatory bowel disease, with the beginning of use of tumor necrosis factor-alpha inhibitors (TNFAI) in clinical practice. On the other hand, TNFAI have been associated with many side effects, such as increased frequency of infections, neutropenia, local reactions, triggered autoimmunity, and increased risk of malignancy (1).

Tuberculosis (TB) is the leading infectious disease associated with TNFAI. This is because tumor necrosis factor-alpha (TNF-α) has important roles in the response of the immune system against *Mycobacterium tuberculosis* (MTB). TNF-α contributes to the formation of granulomas by increasing the antibacterial efficiency of macrophages and maturing dendritic cells and increasing the release of cytokines and chemokines, migration of lymphocytes to the inflamed area, and their proliferation (2). It has been demonstrated that TNFAI increases reactivation risk, particularly for latent tuberculosis. In this study, a case of a child developing asymptomatic pulmonary tuberculosis during adalimumab therapy is presented.

Case Presentation

A 12-year-old boy followed up for the diagnoses of juvenile idiopathic arthritis and uveitis for 3 years, who had been intermittently given methotrexate and methylprednisolone but planned to initiate treatment with adalimumab due to exacerbated ophthalmological findings, was referred to our clinic of Pediatric Infectious Diseases for monitoring 6 months ago. The initiation of adalimumab was approved because the patient's tuberculin skin test (TST), which was performed at admission, was 0 mm, the result of posteroanterior radiography of the lung was normal, and no suspected tuberculosis was found in the screening of his family (Figure 1a).

The patient had no complaints in our clinical follow-up; however, in the third month of adalimumab therapy, it was learned that his father was diagnosed with pulmonary tuberculosis and isoniazid therapy was initiated for the patient by the Tuberculosis Dispensary with the aim of post-exposure prophylaxis. The patient, who continued adalimumab therapy, visited for routine outpatient clinical control in the first month of isoniazid therapy. His physical examination revealed no pathological findings, and his lung sounds were normal in auscultation. In laboratory analysis, there was no leukocytosis, and erythrocyte sedimentation rate and C-reactive protein values were within the normal reference ranges. The patient's TST was measured as 7 mm, and his chest radiography revealed

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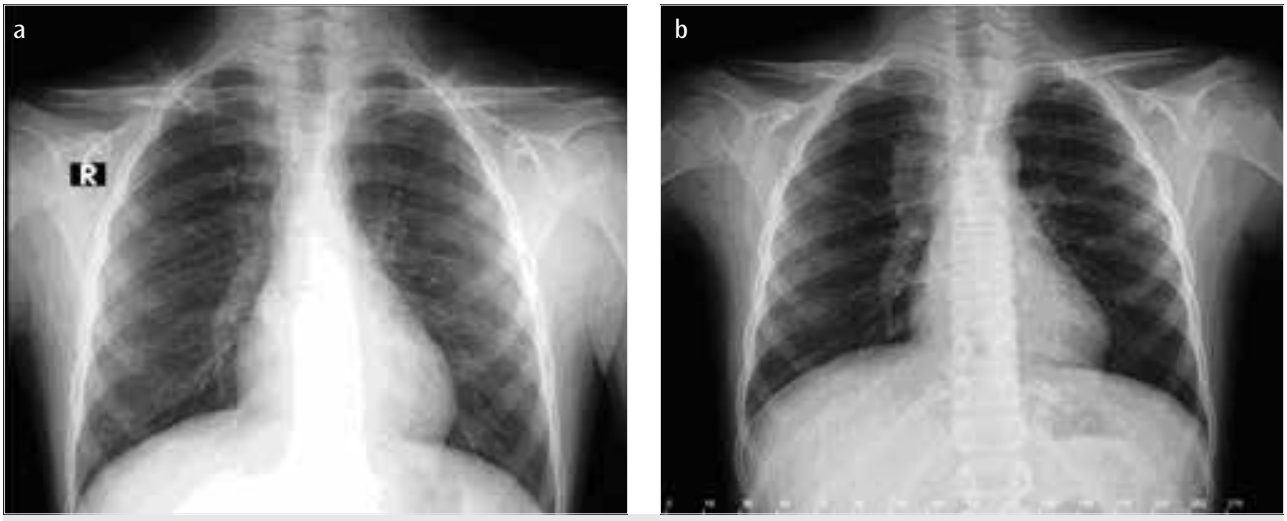

Figure 1. a, b. PA chest radiography findings. (a) Normal PA chest radiography at admission. (b) Paratracheal opacity in the third month of treatment

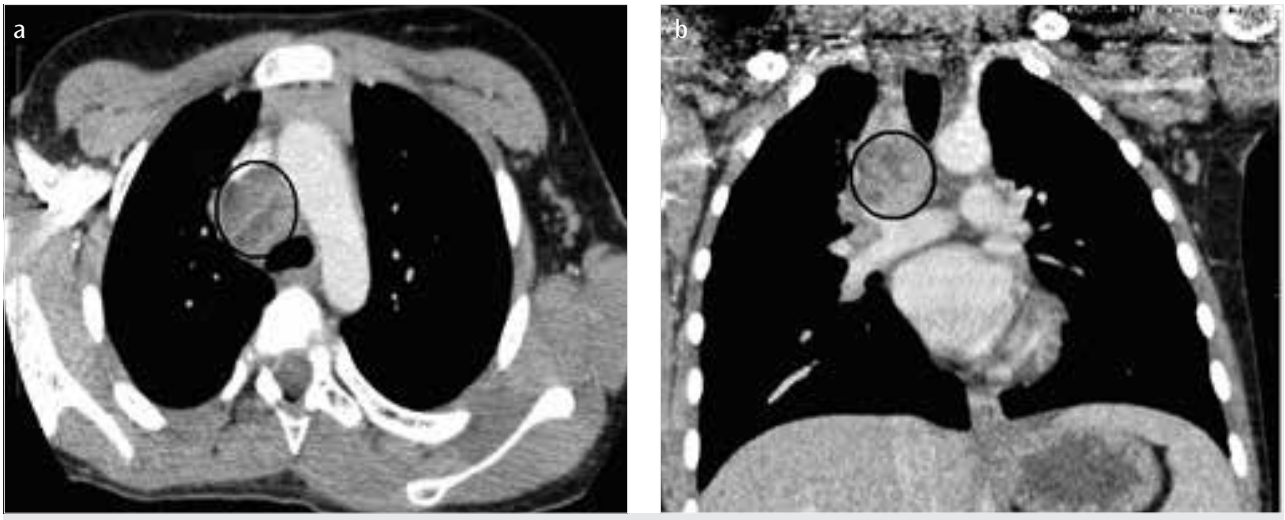

Figure 2. a, b. Thoracic CT findings. A lesion with a size of 40 x 27 x 24 mm, extending from the right upper paratracheal region to the lower paratracheal region and to the right hilar region. (a) Transverse section, (b) Sagittal section

opacity in the paratracheal region. His computed tomography demonstrated a 40 x 27 x 24 mm-sized mass lesion extending from the right upper paratracheal region in the mediastinum to the lower paratracheal region and to the right hilar region, locally including necrotic areas, and showing contrast uptake. Because the patient's condition was first reported to be consistent with tuberculosis lymphadenitis, antituberculosis treatment was initiated including isoniazid, rifampicin, pyrazinamide, and ethambutol, and adalimumab therapy was discontinued (Figure 1b, 2). Tuberculosis screening of family members living in the same house was found to be normal. Chest radiography revealed regression in the second month of treatment and his follow-up continues in our outpatient clinic. Written informed consent was received from the patient's parents.

Discussion

In recent years, adalimumab, infliximab, and etanercept, which antagonize the biological activities of TNF-α, have begun to be used in the treatment of rheumatoid diseases in our country. TNF-α plays an important role in the immune response of the body, and it is necessary to restrict tuberculosis via the formation of granulomas, which isolate bacilli and prevent its spread. Therefore, it is not surprising that the treatment of TNFAI is associated with the progression of tuberculosis and reactivation of latent tuberculosis. In 147,000 patients treated with infliximab over the world, 70 tuberculosis cases were reported. Two months after the present report, this number increased to 117 (3).

In a study evaluating TB incidence in 10,000 patients given TNFAI treatment in England, TB incidence was found to be higher during adalimumab and infliximab therapies than during etanercept therapy. Regarding the mechanisms of action of these agents, while adalimumab and infliximab directly inhibit TNF-α, etanercept exerts its effect by binding to the TNF-R1 and TNF-R2 receptors. The TNF-R1 receptor is known to be responsible for the formation of granulomas in the pathophysiology of tuberculosis. It is likely that etanercept is less likely to increase the risk of tuberculosis because of its lower affinity for TNF-R1, compared with that of adalimumab and infliximab (2).

TNFAI increases the probability of reactivation of latent MTB infection and increases the risk of disease development in patients who are exposed to tuberculosis bacilli. In regions where the risk of tuberculosis is high, only DNA sequencing methods can help to diag-

nose whether the developing tuberculosis is a latent TB activation or a newly acquired TB infection. In our case, the current clinical state of the patient was evaluated to be a new infection because the TST was 0 mm, the result of chest radiography was normal in the pre-treatment evaluation, and the disease developed through active contagion from the father. The development of tuberculosis in our patient despite normal results of screening in other family members living in the same house seems to be associated with the facilitative effect of TNFAI on the disease.

Various studies demonstrated that TB developed earlier after infliximab therapy than after etanercept therapy. In a study conducted in England, the mean time for the development of TB after the use of TNFAI was compared. The development of TB occurred in approximately 5.5 months after infliximab therapy, which was shorter than after etanercept (approximately 13.4 months) and adalimumab (approximately 18.5 months) therapies (4). The time mentioned here is the time taken for the activation of latent TB infection. In our patient, the development of tuberculosis was observed in the third month of adalimumab therapy. However, we thought that the disease of our patient was a newly acquired pulmonary TB because his father was simultaneously diagnosed with pulmonary TB, and latent TB infection was not found in our patient before adalimumab therapy.

The US Centers for Disease Control and Prevention (CDC) recommend screening before the initiation of treatment due to the increased risk of TB in patients using TNFAI such as etanercept, infliximab, and adalimumab. In immunosuppressed patients, a TST value of ≥5 mm is accepted as positive before treatment is initiated (5). Because TB incidence is high in our country, TB screening should be performed for individuals who are candidates for TNFAI treatment. Anamnesis, physical examination, chest radiography, and TST are recommended for this aim. Protective therapy for TB is recommended for patients with positive TST (≥5 mm), fibrotic/calcific lesion on chest radiography, and close contact with a patient having active TB in the last year. Besides these certain indications, treatment can be initiated considering the benefit-risk ratio in patients who are TST negative in both the first and repeat measurements (6). According to national guidelines, TNFAI should be begun after having given isoniazid for at least one month and isoniazid should be used at a dosage of 300 mg/day for 9 months (7). During the use of TNFAI, tuberculosis-related findings such as cough, fever, and weight loss may not be explicit. Although we questioned our patient in detail, none of these complaints were found. Therefore, the most appropriate approach is to follow-up patients closely in terms of the development of TB and to perform screening tests in accordance with the recommendations, even if they are asymptomatic.

In patients found to have active TB under TNFAI treatment, the dose of TNFAI should be decreased or, if possible, discontinued until the detection of drug sensitivity. A clinical picture paradoxically similar to inflammatory syndrome can be observed after the discontinuation of TNFAI treatment in patients with tuberculosis infection. Glucocorticosteroid therapy can be used in patients developing such a reaction (8). After stopping TNFAI treatment in our patient, this type of paradoxical response was not observed. On the contrary, chest radiography revealed regression in the second month of antituberculosis treatment.

Conclusion

In conclusion, the risk of development of tuberculosis is high during the use of TNFAI for various reasons. Contrary to the normal population, the signs and findings of tuberculosis may not be apparent in these patients. Therefore, patients should be examined for latent TB before the initiation of TNFAI, and they should be closely followed up during treatment.

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