

# Fatal Unusual Miliary Tuberculosis in which a Patient Developed Acute Respiratory Distress Syndrome Induced by Infliximab: An Autopsy Case Report

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## Abstract

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Anti-tumor necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) agents increase the risk of tuberculosis (TB), but cases are rarely fatal. This report concerns a patient who was undergoing treatment with infliximab and presented with acute respiratory distress syndrome due to miliary TB without a miliary shadow. The findings of a pathological autopsy revealed innumerable granulomas in the organs, and the miliary nodules in the lung consisted of more unstructured granulomas. Anti-TNF $\alpha$  agents are unusual in the presentation of TB. It is important, particularly for patients receiving anti-TNF $\alpha$  agents, to constantly consider the possibility of TB and to prepare for appropriate management.

**Key words:** tuberculosis, acute respiratory distress syndrome, infliximab, rheumatoid arthritis, immune reconstitution inflammatory syndrome, autopsy

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## Introduction

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Infliximab is an anti-tumor necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) agent approved for the treatment of rheumatoid arthritis (RA). Anti-TNF $\alpha$  agents increase the risk of tuberculosis (TB), but cases are rarely fatal. Keane et al. (1) reported that 70 out of 14,700 patients developed TB during their treatment with infliximab, and 40 of them suffered from extrapulmonary diseases. Twelve patients died, and at least four of the cases appear to have been TB-related deaths. It is important to reduce these risks by screening for latent TB infection. If a patient develops TB, we should look for atypical radiological and clinical manifestations to make an early diagnosis. This report concerns a patient who was undergoing treatment with infliximab who presented with acute respiratory distress syndrome (ARDS) due to miliary TB.

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## Case Report

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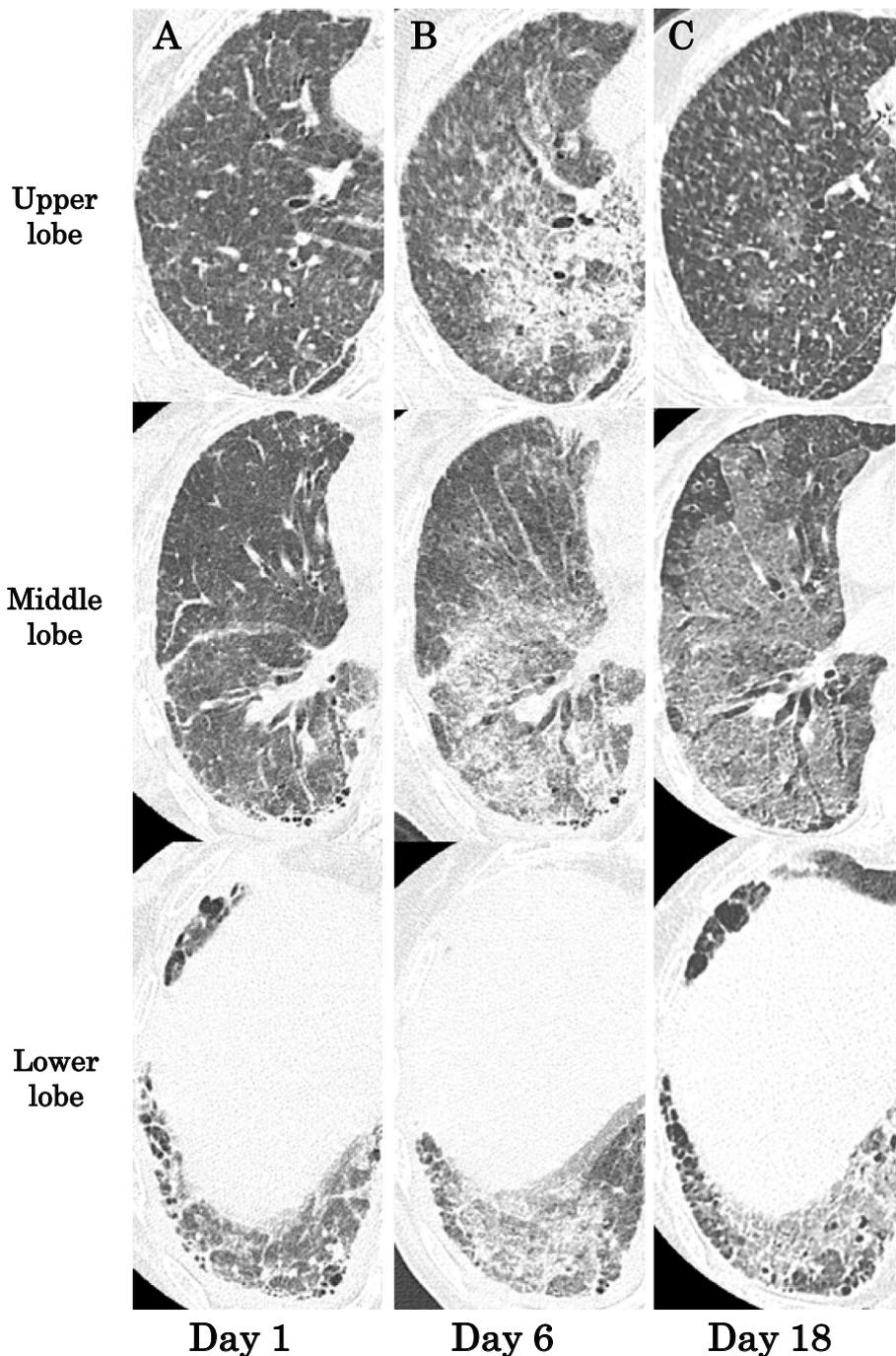
A 78-year-old woman with RA had been treated with infliximab (4 mg/kg) every 8 weeks for 3 years. After the initiation of infliximab, the RA activity was kept under control without remarkable complications. Eight weeks after the last dose of infliximab, she was admitted to our hospital because of a fever that had lasted for 6 weeks. Before the infliximab treatment was initiated, she had not received screening or treatment for a latent TB infection. Upon hospital admission, a laboratory investigation revealed elevated liver enzymes, aspartate aminotransferase of 208 IU/L, alanine aminotransferase of 148 IU/L, lactate dehydrogenase of 464 IU/L, and alkaline phosphatase (ALP) of 1,220 IU/L. Interferon- $\gamma$  (IFN- $\gamma$ ) release assays (QuantiFERON<sup>®</sup>-TB Gold [QFT-G], Cellestis Limited, Carnegie, Victoria, Australia) were positive. A computed tomography (CT) scan showed chronic interstitial pneumonia in the chest (Fig. 1A)

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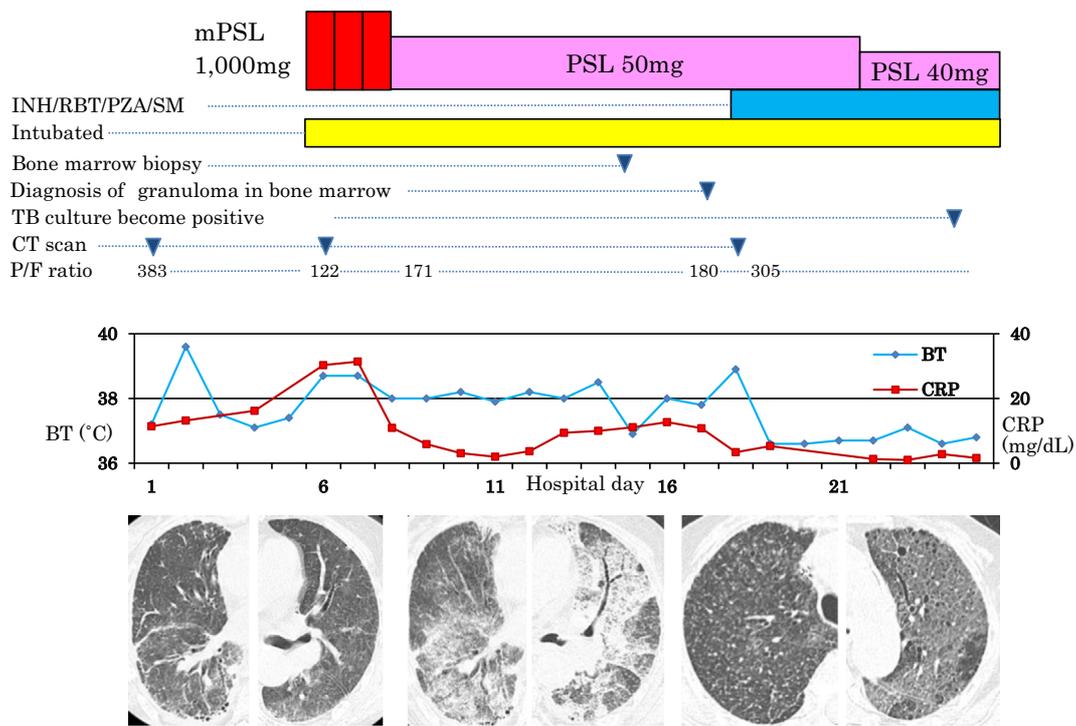


**Figure 1.** Computed tomography images of the development of miliary tuberculosis according to the lobes of the lung. Chest computed tomography (CT) scan on Day 1 showing chronic interstitial pneumonia (A). Chest CT scan on Day 6 showing bilateral, widespread, patchy, ill-defined lung opacification, and interlobular septal thickening, with no clear miliary lesion (B). Chest CT scan on Day 18 clearly showing miliary lesions, especially in the upper lobe (C).

and gallstones and thickening of the gallbladder wall in the abdomen. She was diagnosed with cholecystitis and administered Piperacillin/Tazobactam. However, her fever did not fall, and her respiratory condition further deteriorated. On Day 6, she finally underwent tracheal intubation. An arterial blood gas analysis showed the partial pressure of arterial oxygen ( $\text{PaO}_2$ ) was 61 mmHg and the partial pressure of arterial carbon dioxide was 39 mmHg. The ventilator settings were set to pressure-control ventilation, a fraction of in-

spired oxygen ( $\text{FiO}_2$ ) of 0.5, pressure support of 3 cmH<sub>2</sub>O, and positive end-expiratory pressure of 11 cmH<sub>2</sub>O. Her  $\text{PaO}_2/\text{FiO}_2$  (P/F ratio) was 122 mmHg, suggesting moderate ARDS according to the Berlin Definition (2). A chest CT scan showed bilateral, widespread, patchy, ill-defined lung opacification and interlobular septal thickening, but there were no clear miliary lesions (Fig. 1B).

Because there was the possibility of acute exacerbation of interstitial pneumonia associated with RA triggered by in-



**Figure 2.** Clinical course, laboratory, and radiological findings. A bone marrow biopsy of the anterior superior iliac spine was performed on Day 15 under mechanical ventilation. A diagnosis of tuberculosis was rapidly obtained. Her respiratory condition and fever improved soon after she was administered anti-TB drugs on Day 18. INH: isoniazid, RBT: rifabutin, PZA: pyrazinamide, SM: streptomycin, TB: tuberculosis, CT: computed tomography, mPSL: methylprednisolone, PSL: prednisolone, BT: body temperature, CRP: C-reactive protein, P/F ratio: partial pressure of arterial oxygen/fraction of inspired oxygen

fection, she underwent high-dose corticosteroid therapy and received an antimicrobial agent. Although her respiratory condition improved slightly, with the P/F ratio increasing to 171 mmHg, the fever did not come down. Because of her QFT-positive result on admission and the poor response to treatment thus far, we considered that she might have been suffering from miliary TB induced by infliximab. However, acid-fast staining of the sputum, bronchoalveolar lavage (BAL) fluid, urine, stool, and blood samples were all negative. Furthermore, a *Mycobacterium tuberculosis* polymerase chain reaction (TB-PCR) of a BAL fluid sample was also negative.

The other differential diagnosis was malignant lymphoma, because the serum soluble interleukin-2 receptor (sIL-2R) level was very high (8,096 U/mL). A bone marrow biopsy of the anterior superior iliac spine was performed on Day 15 under mechanical ventilation, revealing epithelioid granulomas compatible with miliary TB. At that point, miliary lesions became apparent on a chest CT scan (Fig. 1C). TB was diagnosed based on the histopathological findings and clinical manifestation.

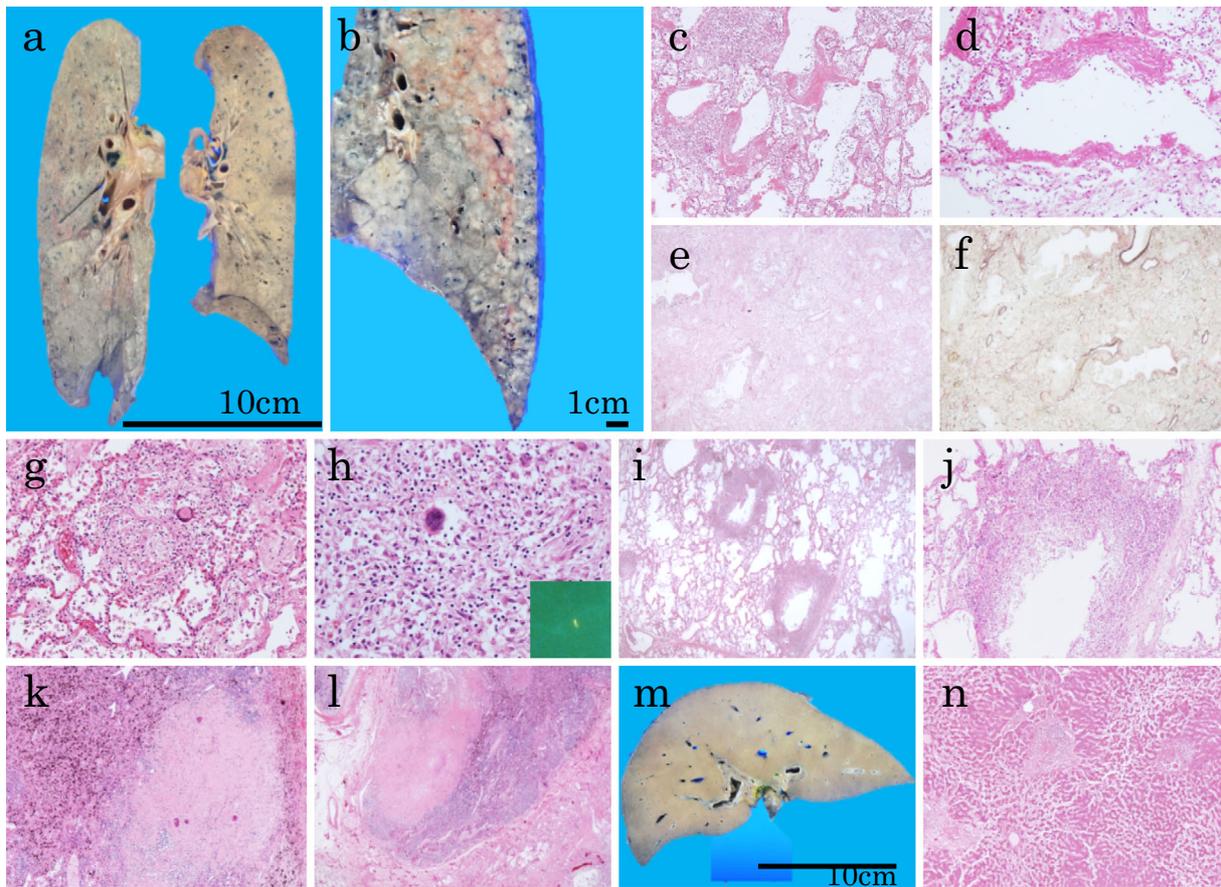
Her P/F ratio increased to 305 mmHg, and the fever improved soon after she was administered anti-TB drugs on Day 18 (Fig. 2). Finally, an acid fast bacterial culture of the BAL fluid at intubation was positive for *M. tuberculosis* in a liquid culture on Day 24. She showed good progress be-

cause of the anti-TB treatment, but unfortunately, pneumothorax occurred before extubation. Although treatment with a chest drain was added, she died due to recurrent pneumothorax and a catheter-related blood stream infection. The clinical course, laboratory, and radiological findings are shown in Fig. 2.

The findings of a pathological autopsy revealed diffuse alveolar damage (DAD), interstitial pneumonia, and innumerable granulomas in the lung, liver, bone marrow, spleen, and lymph nodes. Miliary nodules in the lung consisted of more unstructured granulomas. The DAD showed many hyaline membranes with severe inflammation and an increase in collagen fibers. There were numerous Langhans giant cells and epithelioid granulomas with substantial caseous necrosis in the lymph nodes. A few acid fast bacteria were observed in the lungs, lymph nodes, and liver. The details of the pathological findings are shown in Fig. 3.

## Discussion

Our patient suffered a fatal case of acute respiratory distress syndrome due to miliary TB induced by infliximab. Anti-TNF $\alpha$  agents increase the risk of TB by interfering with the development and maintenance of granulomas. Screening and preventive treatment for a latent TB infection can reduce the risk of developing active TB (3-5). However,



**Figure 3.** Pathological findings. Macroscopically, collapsed air space with necrosis and granuloma presents as a heavy and hard lung (a, b). Loupe images of the lung show the hyaline membrane along the alveolar ducts (c:  $\times 4$ , d:  $\times 10$ ) and severe inflammation (e: Hematoxylin and Eosin staining  $\times 1.25$  f: elastica van Gieson  $\times 1.25$ ). Miliary nodules in the lung consisted of unstructured granulomas and Langhans giant cells with acid fast bacteria identified by Truant's Auramine-Rhodamine stain (g:  $\times 10$ , h:  $\times 10$ ). Poorly formed granulomas were distributed around the bronchiole, which is probably the origin of the tuberculosis discharge (i:  $\times 1.25$  j:  $\times 4$ ). Typical granulomas with large caseous necrosis were found in the lymph nodes (k:  $\times 4$ , l:  $\times 1.25$ ). Distributed granulomas were present around Glisson's capsule in the liver, which appeared normal macroscopically (m, n:  $\times 4$ ).

in the present case, the patient had not received treatment for a latent TB infection, and as a result, she developed active TB.

Her QFT-positive result was initially thought to mean that she had latent TB because no clear active TB lesions were observed in the chest CT scan on hospital admission. However, we gradually recognized that the QFT-positive result might indicate active TB according to the disease progression. It is generally considered that QFT-G cannot distinguish between active TB and latent TB. Furthermore, a previous study indicated that the IFN- $\gamma$  response diminishes with age and the QFT-positive rate among elderly people in Japan (mean age of 80 years) was 22.7%, a significantly lower result than the expected prevalence of TB infection for that age group (6). The accuracy of the interpretation of QFT-G is unclear, particularly with elderly patients, so the risk of TB should not be underestimated.

The patient's pulmonary manifestation was unusual in that she expressed ARDS before a miliary shadow of the lung

became apparent. Because the patient had RA and developed miliary TB presenting with ARDS without a miliary shadow, it was hard to establish from the radiological findings whether she had ARDS caused by miliary TB or ARDS caused by acute exacerbation of RA-related interstitial pneumonia. Furthermore, when the patient was in the early phase of ARDS, typical miliary nodules could not be identified, even by high-resolution CT.

The pathological anatomy showed that the miliary lesions in the lung consisted of unstructured granulomas (Fig. 3). This is similar to TB in human immunodeficiency virus (HIV) patients, which shows unstructured granulomas because TNF $\alpha$  production is reduced (7). Because infliximab also inhibits TNF $\alpha$ , infliximab likely induces an unusual presentation of TB, like that seen in HIV patients.

ALP and sIL-2R are sometimes useful biomarkers of miliary TB. There are some reports that an elevation of ALP in serum was observed in 34-83% of patients (8, 9). It is thought that slight infiltration of the liver by miliary TB oc-

curred. Some studies have reported that serum sIL-2R levels were also elevated in patients with TB (10, 11). It is important to suspect miliary TB when these biomarkers are elevated in patients receiving immunosuppressive therapy.

In our patient, miliary TB was initially diagnosed on the basis of the histopathological identification of granulomas in biopsied bone marrow tissue. There are some reports that a bone marrow biopsy is diagnostic in about 67-86 % of miliary TB patients (9, 12, 13). Given that it is difficult to perform a lung or liver biopsy in patients using a respirator, a bone marrow biopsy is considered a safe and useful procedure for these patients. Furthermore, our patient's results from rapid tests, such as acid-fast staining or TB-PCR, were all negative. It often takes time before TB cultures are identified as positive, even in liquid culture. We probably should have actively considered a bone marrow biopsy for a rapid diagnosis.

Paradoxical reaction or immune reconstitution inflammatory syndrome (IRIS) has been reported among patients who developed active TB during anti-TNF $\alpha$  therapy (14-16). An earlier report showed that the time between the onset of TB and IRIS in infliximab-treated patients was 5-16 weeks, as the effect of infliximab lasts for 4 weeks (14). Our patient received infliximab 8 weeks before hospital admission, so it is likely that IRIS induced the progression of ARDS due to the withdrawal of infliximab in our patient. The unusual presentation and progression of ARDS also resulted in a delayed diagnosis of TB. We believe that these consecutive factors additionally induced severe disease progression in our patient.

This is the first report of autopsy findings in a patient who was undergoing treatment with infliximab and who presented with ARDS due to miliary TB. Anti-TNF $\alpha$  agents induce an unusual clinical, radiological, and pathological presentation of TB. Because their effects delay the diagnosis of TB, the patient's condition deteriorates. It is important, particularly for patients receiving anti-TNF $\alpha$  agents, to constantly consider the possibility of TB and to prepare for appropriate management.

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

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