

[CASE REPORT]

Transbronchial Cryobiopsy for Miliary Tuberculosis Mimicking Hypersensitivity Pneumonitis

Shingo Nasu¹, Kunimitsu Kawahara², Yuki Han³, Norio Okamoto¹, Yoshitaka Tamura³, Hidekazu Suzuki¹, Takayuki Shiroyama¹, Yumiko Samejima¹, Tomohiro Kanai¹, Yoshimi Noda¹, Ayako Tanaka¹, Naoko Morishita¹, Kayo Ueda², Shoji Hashimoto³, Tomonori Hirashima¹ and Takayuki Nagai³

Abstract:

Miliary tuberculosis is a potentially lethal type of tuberculosis that results from the hematogenous dissemination of *Mycobacterium tuberculosis* bacilli. We herein describe the case of a 34-year-old man that presented with a one-month history of cough and fever, while his sputum smear results were negative. Chest computed tomography revealed bilateral centrilobular ground-glass opacification (GGO), suggestive of hypersensitivity pneumonitis; thus, bronchoscopy was performed. Cryobiopsy specimens revealed necrotic granulomas. A re-examination of sputum after bronchoscopy identified *Mycobacterium tuberculosis*, and miliary tuberculosis was diagnosed. A cryobiopsy might be useful for diagnosing miliary tuberculosis pathologically, particularly when miliary nodules may be masked by GGO.

Key words: cryobiopsy, forceps biopsy, miliary tuberculosis, hypersensitivity pneumonitis

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Introduction

Miliary tuberculosis is the hematogenous dissemination of *Mycobacterium tuberculosis* bacilli and it is a potentially lethal type of tuberculosis. The findings of miliary tuberculosis on chest computed tomography (CT) show randomly distributed micro-nodules and may be accompanied by ground-glass opacification (GGO) (1). In approximately two-thirds of miliary tuberculosis cases, sputum smear tests are negative (2). Although transbronchial biopsy can be considered in these cases, the diagnostic yields are not high (62.5-76%) (2, 3).

Recently, transbronchial cryobiopsy has been widely used for the diagnosis of interstitial lung diseases and tumours (4-7). Cryobiopsy specimens are large, with fewer artefacts and more alveolar tissue histopathologically (8). However, there have so far been few reports on cryobiopsy for diagnosing tuberculosis.

We herein report a case of miliary tuberculosis that mimicked hypersensitivity pneumonitis based on radiological and clinical findings, in which cryobiopsy was useful for the diagnosis.

Case Report

A 34-year-old man was admitted to our hospital because of a persistent cough and fever for one month. CT upon admission at our hospital revealed the diffuse distribution of nodules and diffuse centrilobular GGO (Fig. 1A). The centrilobular GGO made it difficult to interpret the distribution of the nodules. However, there were no prior episodes of antigen exposure suspected of hypersensitivity pneumonitis. The laboratory test results revealed C-reactive protein and lactate dehydrogenase levels of 9.44 mg/dL and 707 U/L, respectively; the Krebs von den Lungen (KL)-6 levels were not elevated. Both the sputum smear test and TB-LAMP (Eiken, Tokyo, Japan) were negative. Although the fever

¹Department of Thoracic Oncology, Osaka Habikino Medical Center, Japan, ²Department of Pathology Osaka Prefectural Hospital Organization, Osaka Habikino Medical Center, Japan and ³Department of Infectious Diseases, Osaka Habikino Medical Center, Japan

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Correspondence to Dr. Shingo Nasu, hugurahoma@yahoo.co.jp

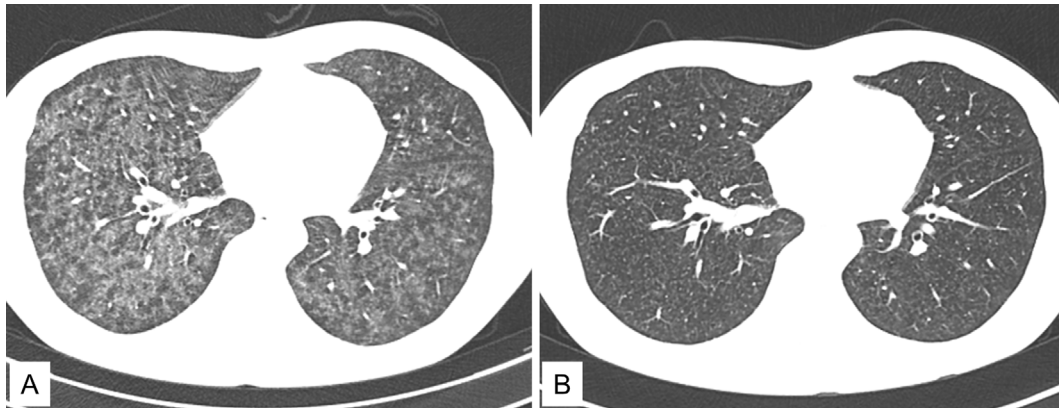


Figure 1. A chest computed tomography (CT) scan of the patient before (A) and one month after the initiation of anti-tuberculosis treatment (B). Chest CT performed one month after the initiation of anti-tuberculosis treatment showed the disappearance of the ground-glass opacification and diffuse, randomly distributed nodules.

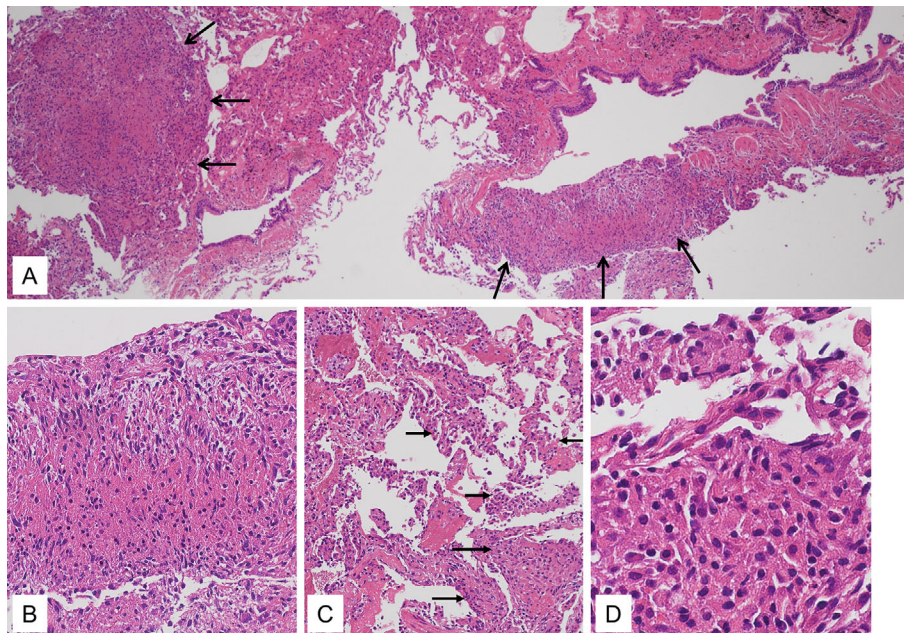


Figure 2. (A) Histological findings of the cryobiopsy specimens revealed numerous granulomas predominantly located around the bronchial walls and vessels (arrows). (B) High-power microscopic view of cryobiopsy specimens revealed necrotic epithelioid cell granuloma in the bronchial wall. (C) (D) Forceps biopsy specimens showed extensive granulomatous pneumonitis, compatible with the ground-glass opacification observed on performing computed tomography (A: Hematoxylin and Eosin (H&E) staining, magnification $\times 40$; B: H&E staining, magnification $\times 200$; C: H&E staining, magnification $\times 100$; D: H&E staining, magnification $\times 400$).

temporarily improved and C-reactive protein decreased to 3.46 mg/dL on Day 2 of admission, the patient's body temperature increased to 38.5 degrees on Day 5.

The centrilobular GGO and temporary clinical improvement after hospitalization suggested hypersensitivity pneumonitis; thus, bronchoscopy was performed on Day 5 of admission. A bronchoalveolar lavage (BAL) fluid analysis revealed an increase in total cell count ($6.43 \times 10^5/\text{mL}$) and lymphocytes (58.6%). A transbronchial lung biopsy was performed using standard biopsy forceps (FB-20C-1; Olympus,

Tokyo, Japan) from the right B²b and B⁸b, and subsequently using a 1.9-mm cryoprobe (20402-040, Erbe Elektromedizin GmbH, Tübingen, Germany) from the right B⁸b. Acid-fast bacilli smear and tuberculosis loop-mediated isothermal amplification (TB-LAMP) of BAL fluid yielded negative results. A histological examination of the cryobiopsy specimens revealed necrotic epithelioid cell granulomas predominantly located around the bronchial walls and vessels; most granulomas were larger than those observed in typical hypersensitivity pneumonitis (Fig. 2A, B) (9). These findings

are characteristic of mycobacterial infections. Additionally, there was neither findings of angitis nor fungus histologically. Grocott staining, periodic acid-Schiff reaction, and Ziehl-Neelsen staining results were negative. An examination of forceps biopsy specimens showed granulomatous pneumonitis without any apparent necrotic foci. Moreover, because of an inadequate amount of granulomas in the specimen fragments, the anatomical distribution of the granulomas was unclear (Fig. 2C, D).

Based on the histopathological findings of a cryobiopsy, miliary tuberculosis was suspected; hence, the sputum was re-examined after bronchoscopy. TB-LAMP of the sputum yielded positive results, and a sputum culture identified the presence of *M. tuberculosis*. Miliary tuberculosis was diagnosed, and treatment was initiated with isoniazid 300 mg, rifampicin 600 mg, ethambutol 1,000 mg. After one month, chest CT showed the disappearance of GGO and the random distribution of the nodules (Fig. 1B). The patient's clinical state improved after anti-tuberculosis therapy.

Discussion

We herein report a case of miliary tuberculosis mimicking hypersensitivity pneumonitis, in which a cryobiopsy was useful for making the diagnosis.

The temporary improvement after hospitalization (which appeared to be due to antigen avoidance), centrilobular GGO on CT, and BAL fluid lymphocytosis, were suggestive of hypersensitivity pneumonitis (10-12). In our case, it was difficult to recognize the distribution of miliary nodules by CT at the time of admission due to extensive centrilobular GGO. One month after the initiation of treatment, GGO disappeared on CT, and it was clear that the nodules were distributed randomly. The rate of GGO in miliary tuberculosis patients has been reported to be 67% (1). GGO is thought to represent a transient exudative reaction (13), and extensive GGO can make the detection of miliary nodules difficult (1).

Cryobiopsy specimens are typically larger than forceps specimens (8). Therefore, in the present case, it is possible that the large samples of external wall lesions taken using the cryoprobe facilitated the histological diagnosis of miliary tuberculosis with hematogenous distributions. The samples obtained by forceps biopsy were insufficient for the histological diagnosis of tuberculosis because they contained few necrotic epithelioid cell granulomas and the granuloma distribution was not clear.

In our case, a tissue culture was not performed because, before performing the cryobiopsy, we had initially suspected that the patient had hypersensitive pneumonitis. Since *M. tuberculosis* is not easily killed by cryopreservation (14), freezing with a cryoprobe is not expected to hinder tissue culturing. Additionally, it has been reported that the diagnostic rate of transbronchial cryobiopsy was 100% (16/16) by culture, while the rate was 81.3% (14/16) by GeneXpert[®] MTB/RIF (Cepheid, Sunnyvale, USA) (15). Hence, we might diagnose *M. tuberculosis* by a tissue culture; however,

the final diagnosis was made on the basis of sputum culture results.

In terms of safety, the major complications after transbronchial cryobiopsy are pneumothorax and bleeding (16); the bleeding risk due to transbronchial cryobiopsy is reportedly higher than that due to transbronchial forceps biopsy (17). Although transbronchial cryobiopsy due to infection, including *M. tuberculosis* infection, is reportedly relatively safe and the complications are controllable (15, 18), it should nevertheless be carefully performed.

It is important to diagnose and treat tuberculosis at an early stage because a misdiagnosis can lead to increased infection transmission. However, there are some cases where it is difficult to demonstrate *M. tuberculosis*. In such cases, the pathological findings can help in the diagnosis of tuberculosis. Therefore, transbronchial cryobiopsy might be more useful than forceps biopsy, especially for miliary tuberculosis.

In conclusion, we encountered a case of miliary tuberculosis that mimicked hypersensitivity pneumonitis based on radiological and clinical findings; cryobiopsy helped in the diagnosis. Cryobiopsy might therefore be more useful than forceps biopsy for diagnosing miliary tuberculosis pathologically.

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

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