



## Efficacy and safety of semi-flexible thoracoscopic cryobiopsy in the diagnosis of elderly tuberculous pleurisy

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### ABSTRACT

**Background:** Thoracoscopic pleural biopsy is an efficient procedure in patients with undiagnosed exudative pleurisy. Rigid or flexible forceps have been widely used for this procedure. Recently, the use of cryo-techniques was reported in pleural biopsy during semi-rigid thoracoscopy; however, the feasibility and safety of pleural cryobiopsy in elderly patients have not yet been fully elucidated.

**Case reports:** We describe two elderly patients who safely underwent semi-rigid thoracoscopic cryobiopsy and were diagnosed with tuberculous pleurisy. Both were >85 years of age, and chest auscultation revealed reduced breath sounds in the right lower zones. Laboratory investigations revealed an elevated level of C-reactive protein without leukocytosis in both patients. Computed tomography scan of the chest revealed right pleural effusion in both patients. Pleural fluid biochemical analysis results were indicative of an exudate. Sputum cultures demonstrated no bacterial growth and smears were negative for the presence of acid-fast bacilli. For definitive diagnosis, pleural biopsy was performed via thoracoscopic cryobiopsy. Specimens obtained from the cryoprobe demonstrated 200–300- $\mu$ m caseating and non-caseating epitheloid cell granulomas with Langerhans type giant cells. Based on the above results, both patients were diagnosed with TB pleurisy. Anti-tuberculosis treatment resulted in good clinical outcome in both patients.

**Conclusion:** Cryobiopsy is easier and more efficient than biopsy with conventional forceps. Our findings in these patients suggest that semi-rigid thoracoscopic cryobiopsy might be a useful alternative diagnostic method for undiagnosed pleural effusion in elderly patients.

### 1. Introduction

Tuberculous (TB) pleurisy is a common manifestation of extrapulmonary tuberculosis and the most common cause of pleural effusion. However, 20%–40% of patients with suspected TB pleurisy remain undiagnosed [1]. The gold standard for diagnosis of TB pleurisy is the isolation of *Mycobacterium tuberculosis* from biological samples, but mycobacterial culture of pleural fluid has low sensitivity (24–58%) [2,3] and involves extended delays in obtaining results (up to 8 weeks); this precludes immediate clinical decisions and timely treatment. Therefore, pleural biopsy via thoracoscopy, which enables assessment of the presence of caseating (necrotizing) granulomas, is also considered adequate for diagnosis of TB pleurisy [4,5].

Medical thoracoscopy, which includes rigid and semi-rigid

pleuroscopy, is reported to offer high diagnostic yield in terms of the diagnosis of TB pleurisy and other types of pleurisy [6–11]. Rigid pleuroscopy is advantageous in that it offers larger biopsy specimens; however, it is not always available and is often more expensive than semi-rigid pleuroscopy. Pulmonologists are generally more familiar with semi-rigid pleuroscopy, which offers better image quality; this method is limited in terms of smaller sample size and more superficial sampling of the pleura.

A novel biopsy technique involving the use of a cryoprobe during transbronchial biopsy is useful for obtaining larger and more representative specimens. A recent study showed the feasibility and safety of cryoprobe use in semi-rigid pleuroscopy [12,13]. However, there have been no report of the use of this procedure focus on elderly patients. Here, we describe two patients over the age of 85 years who were

*Abbreviations:* TB, tuberculous.

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diagnosed with TB pleurisy by using semi-rigid thoracoscopic cryobiopsy under local anesthesia.

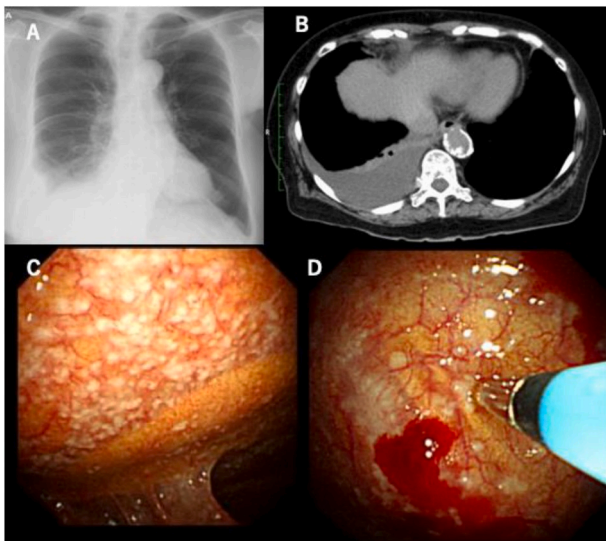
## 2. Case reports

### 2.1. Case 1

An 86-year-old woman had been diagnosed with rheumatoid arthritis 4 years prior to this case, and was prescribed prednisolone 5 mg + salazosulfapyridine 500 mg per day. Here, she presented to the Department of Rheumatology with fatigue, non-productive cough for 7 days, and fever for 3 days. She had no hemoptysis, night sweats, weight loss, or chest pain. She also reported no recent history of exposure to illness or hospitalization. The patient's vital signs were stable on admission. Chest auscultation revealed reduced breath sounds in the right lower zones. Laboratory investigations revealed an elevated level of C-reactive protein (6.61 mg/L) without leukocytosis. Interferon- $\gamma$  release assay (T-SPOT®.TB; Oxford Immunotec, Oxford, United Kingdom) results were positive. Chest radiography showed dullness of the right costophrenic angle, while computed tomography scan of the chest revealed right pleural effusion with right lower lobe compressive atelectasis (Fig. 1A and B). Pleural fluid biochemical analysis revealed that the pleural fluid protein/serum protein ratio was 0.78, with a pleural fluid lactate dehydrogenase level of 784 U/L, indicative of an exudate according to light criteria. The pleural fluid glucose level was 101 mg/dL, which was within normal range. Pleural fluid differential cell count showed predominant lymphocytosis and a high adenosine deaminase level (151.6 IU/L).

Sputum cultures demonstrated no bacterial growth and smears were negative for the presence of acid-fast bacilli. Rheumatoid pleuritis or tuberculous pleurisy was suspected and the patient was transferred to the Department of pulmonology for further examination. Before microbiological tests on pleural fluid were completed, and in an effort to attain a definitive diagnosis for early treatment, thoracoscopy was performed by semi-rigid pleuroscopy under sedation with local anesthesia.

Thoracoscopic findings showed diffuse dissemination of micronodules on the parietal pleura and fibrin adhesions between the visceral and parietal pleura (Fig. 1C). Pleural cryobiopsy was performed by using a 1.9-mm cryoprobe (ERBECRYO, ERBE, US) and the target area of the



**Fig. 1. Imaging and thoracoscopic findings of the patient in case 1.** (A) Chest X-ray shows dullness of the right costophrenic angle. (B) Computed tomography shows right pleural effusion with right lower lobe compressive atelectasis. (C) Thoracoscopic image shows diffuse dissemination of micronodules on the parietal pleura. (D) Thoracoscopic image shows use of the 1.9-mm cryoprobe, attached perpendicularly to the pleura and frozen for 6 seconds.

parietal pleura was frozen for 6 seconds (Fig. 1D).

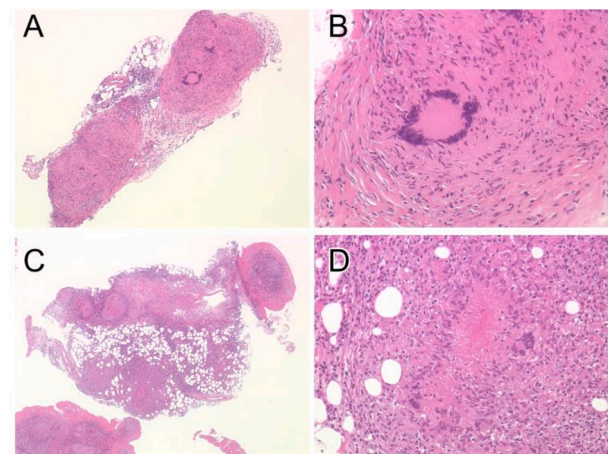
Specimens obtained from the cryoprobe are shown in Fig. 2A and B; these exhibited the size of 0.9 cm; microscopic findings demonstrated 200-300- $\mu$ m caseating and non-caseating epitheloid cell granulomas with Langerhans type giant cells. The Ziehl-Neelsen stain for acid-fast bacilli was positive. Based on the above results, the patient was diagnosed with TB pleurisy; due her use of immunosuppressants, anti-tuberculosis treatment was planned for 10 months. At the most recent outpatient follow-up, she had completed 6 months of treatment and was clinically in good condition. Chest radiography showed regression of the pleural effusion, and her clinical course was consistent with our diagnosis.

### 2.2. Case 2

A 91-year-old man was introduced to our ward for further examination due to a history of exertional dyspnea for 2 months and the finding of massive right pleural effusion in a general health examination. He had been diagnosed with pleurisy of unknown origin during childhood and had no clear history of exposure to illness.

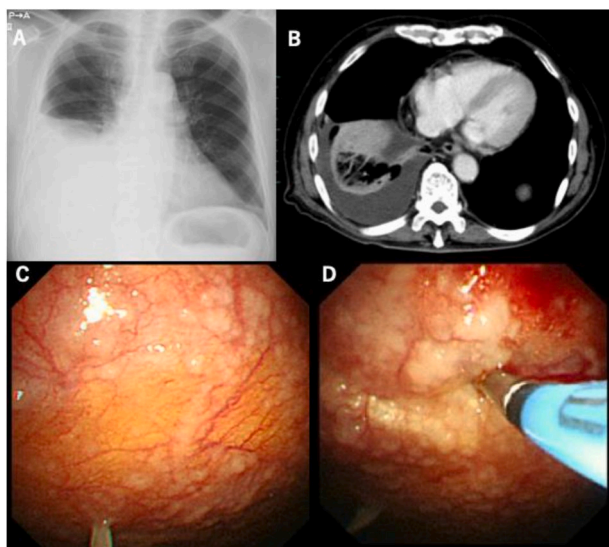
The patient's vital signs were stable on admission. Chest auscultation revealed reduced breath sounds in the right lower zones. Laboratory investigation showed an elevated level of C-reactive protein (2.39 mg/L) without leukocytosis. Interferon- $\gamma$  release assay (T-SPOT®) results were indeterminate. Chest radiography and computed tomography scan of the chest revealed massive right pleural effusion (Fig. 3A and B).

Pleural fluid biochemical analysis revealed that the pleural fluid protein/serum protein ratio was 0.7 with a pleural fluid lactate dehydrogenase level of 180 U/L, indicative of an exudate. Lymphocyte predominance and high adenosine deaminase level (90.1 IU/L) were observed and TB pleurisy was suspected. Sputum and pleural effusion cultures demonstrated no bacterial growth and smears were negative for the presence of acid-fast bacilli. For definitive diagnosis, pleural biopsy was performed via thoracoscopic cryobiopsy (Fig. 3C and D), using a freezing time of 6 seconds. Specimens obtained from the cryoprobe are shown in Fig. 2C and D; these exhibited the size of 0.8 cm; microscopic findings demonstrated epitheloid granulomas with necrosis and many Langerhans type giant cells, highly suggestive of tuberculosis. The Ziehl-Neelsen stain for acid-fast bacilli was negative. Based on the above results, the patient was diagnosed with TB pleurisy. He completed anti-



**Fig. 2. Pathological findings of specimens from semi-flexible thoracoscopic cryobiopsy.**

(A, B) Photomicrographs of the thoracoscopic cryobiopsy specimen from the patient in case 1, which show 200-300- $\mu$ m caseating and non-caseating epitheloid cell granulomas with Langerhans type giant cells. (C, D) Photomicrographs of the thoracoscopic cryobiopsy specimen from the patient in case 2, which demonstrate epitheloid granuloma with necrosis and many Langerhans type giant cells, highly suggestive of tuberculosis.



**Fig. 3. Imaging and thoracoscopic findings of the patient in case 2.** (A–B) Chest X-ray and computed tomography scan show massive right pleural effusion. (C) Thoracoscopic image shows diffuse dissemination of micronodules on the parietal pleura. (D) Thoracoscopic image shows use of the 1.9-mm cryoprobe, attached perpendicularly to the pleura and frozen for 6 seconds.

tuberculosis therapy with complete disease remission and will continue follow-up in the Department of Thoracic Medicine outpatient clinic.

### 3. Discussion

To the best of our knowledge, this is the first case report of the safety and feasibility of semi-rigid thoracoscopic cryobiopsy for undiagnosed exudative pleural effusion in elderly patients. Our patients both presented for treatment of undiagnosed pleurisy and showed exudate pleural effusion with lymphocyte predominance and high adenosine deaminase level. Although previous studies have shown high diagnostic accuracy of adenosine deaminase activity level for the presence of TB pleurisy [14], other diseases such as malignancy or rheumatoid arthritis should be ruled out, because these also are characterized by high adenosine deaminase level [15,16]. Our two patients showed no proof of bacterial growth from pleural fluid culture, so we performed pleural biopsy to obtain a definitive diagnosis.

The biopsy of pleural tissue for combined histological examination and mycobacterial culture of pleural fluid and tissue is the most sensitive of the currently available diagnostic methods for pleural tuberculosis; however, it may yield false negative results in 15–20% of cases [17,18]. The use of cryo-techniques in bronchoscopy has been performed for many years, and recent research has been performed to extend this technique to pleural biopsy by using a semi-rigid pleuroscope to obtain larger specimens for diagnosis.

Before cryoprobe introduction in our facility, biopsy was performed with conventional forceps and an average number of approximately 6 specimens was collected from each patient. The average size of the specimens was approximately 4 mm, which is smaller than the size of cryo-specimens (9 mm). Some previous reports have suggested that smaller specimen size does not affect diagnostic yield [19,20]; however, granulomas were found in 4 of 6 specimens taken by conventional forceps in our patients, whereas they were found in all specimens taken by cryobiopsy. This suggests that more specimens are needed to achieve high diagnostic yield when using conventional forceps; moreover, the use of cryobiopsy might reduce the number of biopsies and shorten the time of the biopsy procedure. Another advantage of cryobiopsy is that collection of a sample with a forceps biopsy may be difficult when the pleura is thickened or exhibits fibrosis. Cryobiopsy only requires

attachment perpendicular to the pleura, followed by freezing to obtain a sample; therefore, it is easier and more efficient.

Thus far, several studies have shown the practicality of cryo-techniques in diagnosing unknown pleural effusion [12,13,21,22], but few studies have reported the efficacy and safety of cryo-techniques when applied to elderly patients with suspected TB pleurisy.

According to a report by the Tuberculosis Surveillance Center in 2016, the largest number of tuberculosis cases in Japan were diagnosed among those aged 75–84 years (4877 cases, 43.5 per 100,000), followed by those aged  $\geq 85$  years (4252 cases, 86.0 per 100,000) [23]. Elderly patients have more comorbidities and delayed treatment increases the risk of mortality, so it is more important to make a precise and timely diagnosis in these patients. In contrast, one report showed that TB pleurisy patients who were  $>60$  years of age were less likely to have granuloma in pleural biopsy specimens, compared with specimens from patients aged 18–34 years (37.9% vs 77.0%) [1]. Although some other reports demonstrated high diagnostic yield by conventional forceps biopsy, most of the research has focused on patients with an average age of 30–50 years. Importantly, our patients were both  $>85$  years of age, and were thus expected to involve greater difficulty in identifying the granuloma and greater risks of complication; our report showed that cryobiopsy was useful for identifying granulomas in elderly patients and could also be performed safely under local anesthesia.

### 4. Conclusions

In summary, we described two elderly patients with suspected TB pleurisy who underwent thoracoscopic cryobiopsy. This method offers larger sample size and can be performed safely to obtain pleural specimens through the semi-rigid pleuroscope. Cryobiopsy is easier and more efficient than biopsy with conventional forceps; thus, it might be an appropriate alternative diagnostic method for undiagnosed exudative pleural effusion in elderly patients.

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### Declaration of competing interest

None.

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