Clinical Analysis of Transbronchial Cryobiopsy in Diagnosis of Diffuse Lung Disease

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Research Article

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Abstract

Background: Rapid advances in TBCB in recent years have allowed its gradual acceptance as a diagnostic method for DLD, and an alternative to surgical lung biopsy . However, the various guidelines have yet to provide clear recommendations for TBCB. This study investigated the diagnostic value of transbronchial cryobiopsy (TBCB) for identifying diffuse lung disease (DLD) .

Methods: The clinical data was reviewed of 34 patients who showed initial signs of diffuse lung lesions, interstitial pneumonia, bronchial asthma, lung cancer/infection, or pulmonary alveolar proteinosis; and underwent TBCB from December 2018 to March 2021. The safety and effectiveness of TBCB in identifying the etiology of DLD was analyzed.

Results: Clear pathomorphological diagnoses were obtained for 27 (79.4%) patients, based on clinical characteristics and pathology: pulmonary fibrosis, adenocarcinoma, alveolar proteinosis, extrinsic allergic alveolitis, tuberculous granulomatous inflammation, and interstitial pneumonia. Four (11.8%) patients required multi-disciplinary discussion for diagnostic confirmation (of diffuse lesions, interstitial pneumonia, and lung infection). The etiology of 3 cases remained unknown. The rate of DLD diagnosis via TBCB was 91.2% (31/34). Associated with the TBCB procedure, 9 (26.5%) patients developed pneumothorax (6 mild, 3 moderate), and 29 (85.3%) post-biopsy bleeding (all grade 1, requiring suction and compression, but no other intervention or surgery). The average hospitalization cost and length of stay were 7988 RMB (1233 USD) and 5.48 days, respectively.

Conclusion: TBCB is safe, cost-effective, requires a short hospitalization, and the diagnostic confirmation rate for DLD is high.

Introduction

Diffuse lung disease (DLD) is a destructive or restrictive lung disease that involves the entire or almost entire lung. There are various radiologic presentations, as DLDs differ widely in etiology, clinical presentation, histopathological characteristics, clinical course, and prognosis [1, 2]. The gold standard for diagnosis of DLD is surgical lung biopsy [2, 3], but this is usually not used in clinical practice due to the associated high risks and cost [3–5]. Alternatives include transbronchial lung biopsy and percutaneous lung biopsy, but each has shortcomings such as low tissue sample size, poor quality, and inability to satisfy pathological diagnosis [5–7].

In 2009, Babiak et al. [8] was the first to use transbronchial cryobiopsy (TBCB) for the diagnosis of DLD. Subsequently, advantages such as little trauma, low cost, multiple specimens, observed alveolar structures, and high diagnostic efficiency has led to the gradual application of TBCB to determine the pathology of lung tumors, interstitial lung diseases, and others.

Rapid advances in TBCB in recent years have allowed its gradual acceptance as a diagnostic method for DLD, and an alternative to surgical lung biopsy [3, 7]. However, the various guidelines have yet to provide

clear recommendations for TBCB. This study investigated the effectiveness of TBCB in the diagnostic differentiation of DLD. Safety was analyzed based on the incidence and severity of complications associated with the procedure.

Methods

Subjects

This study was approved by the Medical Ethics Committee of Taizhou Hospital Affiliated to Wenzhou Medical University. All the patients provided signed informed consent before surgery.

The study population comprised patients with DLD who received treatment at Zhejiang Taizhou Hospital from December 2018 to March 2021. All subjects had chest high-resolution computed tomography (HRCT) showing DLD in both lungs; etiology could not be determined based on clinical data and serological tests alone. The following demographics, medical histories, and other information were collected from all the subjects: gender, age, occupation, previous diagnosis, smoking history, laboratory serology, radiology, and pathology tests.

TBCB procedure

Before the biopsy, patients either did not use anticoagulant or anti-platelet aggregation, or discontinued these drugs for at least 7 days. Relevant preoperative examinations were completed to rule out surgical contraindications. The procedure was performed in the bronchoscopy room. Prior to the operation, the working order of the cryotherapy device (ERBOKRYO CA), cryoprobe (diameter 1.9 mm; both from ERBE Elektromedizin GmbH, Germany), and other devices was confirmed.

During the entire procedure, the patient's blood oxygen saturation (SaO_2), heart rate, and blood pressure were monitored. Oxygen therapy was administered as necessary to maintain SaO_2 at $\geq 92\%$. After appropriate general anesthesia was administered by the anesthesiologist via endotracheal intubation or laryngeal mask, an experienced respiratory physician employed a flexible bronchoscope to examine the alveolar cavity. Alveolar lavage was performed in some patients before the biopsy, that is, 100 to 150 mL of sterile physiological saline (50×2 , or 3 equal portions) was injected into the selected affected segments through corresponding channels before it was drawn into a sterile container by suction for bacterial enumeration and cytological examinations.

Using real-time fluoroscopic guidance, the cryoprobe was inserted into the region selected according to the HRCT, and the biopsy was performed in segmental bronchial tissues (2 cm from the thoracic wall) and the samples were cryopreserved (within 3 to 4 s). Thereafter, the probe and bronchoscope were removed from the trachea with frozen lung tissue attached and samples were collected from the probe after it was warmed. Tissue blocks of a representative patient who underwent TBCB are shown in Fig. 1.

The bronchoscope was immediately inserted in the biopsied subsegment for 3 minutes to observe for bleeding events. If bleeding occurred, a Fogarty catheter was used to control bleeding, or drugs for hemostasis were administered accordingly. From 2 to 4 biopsy tissues were collected for histopathological evaluation.

After surgery, patients were followed for 24 hours and planar chest x-ray was performed when necessary.

Sample processing and diagnosis

The lung biopsy tissues obtained through TBCB were immediately added to 4% formalin buffer and sent to the pathology department. The pathological diagnosis was conducted by 2 experienced pathologists from Zhejiang Taizhou Hospital. The pathologists performed sampling and described the size, quantity, color, and texture of the biopsy specimens; conducted routine dehydration, paraffin embedding, continuous sectioning, hematoxylin and eosin staining, and microscope observation; and concluded with a pathological diagnosis. Immunohistochemistry, special staining, and other related examinations were performed on the samples obtained from some patients to confirm the diagnosis.

In cases with no characteristic pathological presentation, a multi-disciplinary discussion was arranged with senior physicians from multiple departments to obtain a final consensus.

Complications

The primary complications were bleeding and pneumothorax. Bleeding events were classified into 4 grades by severity, from grade nil (0) to grade 3. Specifically, bleeding was absent (grade 0); or mild enough to require suction and compression, but no other intervention or surgery (grade 1); grade 2 bleeding necessitated endoscopic surgery or bronchial artery embolization; and grade 3 bleeding caused unstable breathing and hemodynamics, requiring bronchial artery embolization or other surgical intervention, blood transfusion, or admission to the intensive care unit.

Pneumothorax is usually classified according to the lung compression observed on chest x-rays, as mild ($< 30\%$); moderate ($> 30\%$, but $< 50\%$); or severe ($\geq 50\%$). Other uncommon or rare complications were closely monitored, such as postoperative infection, empyema, respiratory failure, short-term DLD exacerbation, and postoperative death.

Results

In this study, 34 patients underwent TBCB (14 men and 20 women; aged 54 ± 13 y). To reduce the risk of bleeding complications during the procedure, none of the patients used anticoagulant or antiplatelet drugs, and none had thrombocytopenia, coagulation abnormalities, or pulmonary hypertension. Seven patients had a history of hypertension, but preoperative blood pressure was normal. Type I respiratory failure was present in 2 patients, but oxygen saturation was maintained at $\geq 95\%$ with oxygen therapy.

Anesthesia was administered via endotracheal intubation and laryngeal mask in 21 and 13 patients, respectively. The average hospitalization cost and length of stay was 7988 RMB (1233 USD) and 5.48

days.

Overall, 94 lung tissue specimens were collected, and multi-segment biopsy was performed for 4 patients. From 2 to 4 tissue blocks were collected per biopsy. The lengths and areas of the cryobiopsy specimens were 8.2 ± 3.5 mm and 57 ± 40 mm², respectively. Among the 94 specimen blocks, alveoli were present in 91 (96.8%).

As shown in Table 2, TBCB was indicated preoperatively primarily by diffuse bilateral lesions, interstitial pneumonia, and lung infection (15, 11, and 4 cases, respectively). Of these, pathology led to definitive diagnosis in 13, 8, and 2 patients; the final diagnosis depended on multidisciplinary consensus in 2, 3, and 2 patients. Suspected lung cancer in 2 patients was confirmed in both by pathology as lung adenocarcinoma, but pathology also confirmed preoperative diffuse bilateral lesions as lung adenocarcinoma in 2 patients.

Table 1
Demographic and clinical characteristics of the 34 patients *

		Data
Demographics	Age	54 ± 13 y
	Male/female	14 (41.2%)/20 (58.8%)
Anesthesia delivery		
	Endotracheal intubation	21 (31.8%)
	Laryngeal mask	13 (38.2%)
Complications		
	Hypertension	7 (20.6%)
	Type I respiratory failure	2 (5.9%)
	Thrombocytopenia	Nil
	Coagulation abnormalities	Nil
	Pulmonary hypertension	Nil
Hospitalization	Cost	7988 RMD (1233 USD)
	Length of stay	5.48 d
* Data reported as <i>n</i> (%), unless indicated otherwise.		

Table 2

Pathological diagnosis after TBCB of 34 patients, by clinical diagnosis before cryobiopsy ^a

	Total	IPF	LA	PAP	EAA	TB-GD	CTD-NSIP	CTD-UIP	NSIP	Descriptive ^b
Diffuse lesions in both lungs	15	4	2	2	2	2	1	—	1	2
Interstitial pneumonia	11	3	—	1	—	—	1	2	—	3
Lung infection	4	—	—	—	—	1	1	—	—	2
Lung cancer	2	—	2	—	—	—	—	—	—	—
Bronchial asthma	1	—	—	—	1	—	—	—	—	—
Pulmonary alveolar proteinosis	1	—	—	1	—	—	—	—	—	—
Total	34	7	4	4	3	3	3	2	1	7
^a Reported as number of cases, <i>n</i> ; ^b the lesion was found through examination, but the final diagnosis is unclear. The location, size, density, and relationship of the lesion with surrounding tissues is described.										
Abbreviations: CTD, connective tissue disease; EAA, extrinsic allergic alveolitis; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; LA, lung adenocarcinoma; PAP, pulmonary alveolar proteinosis; TB-GD, tubercular granulomatous disease; UIP, usual interstitial pneumonia										

Diagnosis was not confirmed for 7 (20.6%) patients, including 3 cases of unknown etiology. Multidisciplinary discussion was required in 4 cases, which led to final diagnoses of 2 cases each of lung involvement in antisynthetase syndrome, and lung involvement in dermatitis. The HRCT images and micrographs of specimens of representative patients who underwent TBCB are shown in Figs. 2 and 3.

Nine (26.5%) patients developed postoperative pneumothorax, specifically, 6 and 3 cases that were mild and moderate, respectively. Pneumothorax was absorbed after thoracentesis or drainage closure in moderate cases and there was no report of persistent pneumothorax. Overall, 29 (85.3%) patients experienced bleeding events, all of which were Grade 1. There was no occurrence of other rare complications, such as postoperative infection, empyema, respiratory failure, short-term DLD exacerbation, and postoperative death.

Discussion

To further explore the diagnostic value of TBCB in diffuse lung disease. Through the study of 34 patients with unexplained imaging manifestations of two lung diffuse lung disease, 27 patients (79.4%) obtained a clear pathomorphological diagnosis, and 4 patients (11.8%) confirmed the diagnosis through multidisciplinary discussion, with controllable safety, low cost and short hospital stay.

In this study of patients with DLD, there was a wide range of clinical presentations, histopathological characteristics, etiologies, clinical courses, and prognoses. Other studies have suggested a low rate of diagnosis in such patients. According to one study [9], the rates of obtaining a diagnosis via transbronchial or percutaneous lung biopsy are statistically comparable at ~ 25%, while the corresponding rate for surgical lung biopsy is significantly higher (~ 98.7%). In the present study, diagnoses were obtained for 91.2% of the patients who underwent TBCB, that is, a lower rate obtained by surgical lung biopsy but higher than that of either transbronchial or percutaneous lung biopsy reported previously [7, 9].

There are 4 possible explanations for this. First, the dimensions of the cryobiopsy samples in our study were significantly larger than that of forceps biopsy samples. The longest mean dimension of the cryobiopsy samples was 11.7 mm, which is 3-to-5 times larger than samples usually obtained by forceps [5, 7, 9, 10]. The larger specimen provides more lung tissue for pathological diagnosis, and facilitates the observation of heterogeneous lung tissue characteristics under the microscope, which is vital to obtaining a diagnosis.

A second reason for the much higher diagnostic rate of TBCB relative to transbronchial or percutaneous lung biopsies is that, in TBCB, the sample may contain many small airways that can facilitate the evaluation of suspected bronchiolitis. Furthermore, in cryobiopsy, freezing usually does not change lung structure [7, 11] but will decrease compression and deformation, and the specimen quality is better. Finally, in the present study the diagnostic rate was improved by multi-disciplinary discussion when the pathology results alone lacked definitive clarity [9, 12].

The diagnostic rate achieved via TBCB in the present study (including pathological diagnoses after multi-disciplinary discussion) of patients with DLD was comparable to that of the meta-analysis of Ravaglia et al. [9, 12] for patients with interstitial lung disease. The high detection rate and large specimen size obtained via TBCB should be sufficient for future clinical and research needs. Furthermore, the hospitalization and costs associated with TBCB shown by our study were slightly higher than for transcutaneous lung biopsy, but slightly lower than for surgical lung biopsy reported elsewhere in China [13] and consistent with many studies in other countries [9, 14]. TBCB can improve the efficient use of medical resources and decrease medical expenditures.

The incidence and mortality rates of severe complications after surgical lung biopsy have been reported at 12.6% and 2%, respectively [9]. In the present study, there was no occurrence of severe complication or death. The main complication was bleeding, with an incidence of 85.3% (29/34). All bleeding events were grade 1, and ended after onsite management. Sharp et al. [15] reported similar results, but a specific cause was not systematically studied. Bleeding may be due to the removal of the bronchoscope from the airway during the operation, before the biopsy specimen can be removed from the frozen probe. Therefore, the bronchoscope cannot be wedged to stop bleeding immediately. To decrease the risk of a possible bleeding event, all the patients in our study were required to discontinue antiplatelet and anticoagulant drugs for 1 week prior to the TBCB. During the procedure, samples were collected before

the bronchoscope was reinserted into the biopsy site, to observe for active bleeding. When required, a Fogarty catheter was used to control bleeding, or drugs for hemostasis were administered.

One study showed that pulmonary hypertension is the most important factor to influence bleeding during biopsy. Avoiding biopsy at the central lung region and near the pleura may decrease the incidence of bleeding events [3]. In the present study, echocardiography indicated pulmonary hypertension in 31 patients. Biopsy was performed in segmental bronchi, 2 centimeters from the thoracic wall, thereby decreasing the chance of severe bleeding.

Pneumothorax occurred in 26.5% (9/34) of our patients. Thoracentesis or drainage was performed in those with moderate pneumothorax, while persistent pneumothorax did not occur. Cascante et al. [7, 16] reported similar results. Other studies have reported that complications such as postoperative infection, empyema, respiratory failure, short-term DLD exacerbation, and postoperative death are uncommon or rare [9, 17, 18], and these did not occur in our subjects.

This study showed that TBCB has a high probability of providing a definitive diagnosis in patients with atypical DLD on radiology, and has a good safety profile. The limitations of this study include its small sample size and data from a single center. These results warrant confirmation with large-scale clinical data.

Conclusion

DLD has complex etiologies and diagnosis is difficult. In many patients, lung biopsy is essential for obtaining a diagnosis. Sufficient tissues can be obtained in a safe manner via TBCB from patients with DLD for diagnosis, thereby avoiding the risks of surgical lung biopsy. We believe that, with more experience applying this technique, TBCB can become the preferred method to collect lung biopsy specimens for diagnosis in patients with DLD.

Abbreviations

CTD, connective tissue disease; DLD, diffuse lung disease; EAA, extrinsic allergic alveolitis; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; LA, lung adenocarcinoma; NSIP, nonspecific interstitial pneumonia; PAP, pulmonary alveolar proteinosis; TBCB, transbronchial cryobiopsy; TB-GD, tubercular granulomatous disease; UIP, usual interstitial pneumonia.

Declarations

Acknowledgments:

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Authors' contributions:

YFZ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and contributed to obtaining tissue specimens of patients from Taizhou Hospital and to project oversight, organization, data collection, statistical analysis, and writing of the manuscript. XLZ and ZJW contributed to tissue specimen and the writing of the manuscript, statistical, analysis, and data collection. HHZ contributed to tissue specimen experiment and analysis. YZX and JXF contributed to patients' management and manuscript preparation and review. The authors read and approved the final manuscript.

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Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate:

This study was approved by the Clinical Trial Ethics Committee in Taizhou hospital of Zhejiang Province. and all patients included signed their informed consent.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Figures

Figure 1

Three tissue blocks of a representative 52-year-old man with bilateral diffuse lung lesions were extracted after TBCB, with diameters 3, 5, and 4 mm.

Figure 2

A representative 50-year-old woman with bilateral diffuse lung lesions, who presented with a 2-year history of shortness of breath. The pathological diagnosis was pulmonary alveolar proteinosis. (A) Ground-glass opacities, hyperdense shadows were seen in both lungs in chest HRCT, with mosaic attenuation, clear borders, and vascular course in the lesion. (B) Under the microscope, an eosin-stained protein-like substance was observed in the alveolar cavities.

Figure 3

Representative 52-year-old man with bilateral diffuse lung lesions, who presented with cough lasting more than 1 month. The pathological diagnosis was lung adenocarcinoma. (A) Diffuse miliary hyperdense shadows seen in both lungs in chest HRCT, with patchy hyperdense shadows and unclear borders. (B) Dysplastic glandular hyperplasia and interstitial fibrous tissues seen within the bronchial mucosa under the microscope.