Efficacy of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration in the Diagnosis of Thoracic Sarcoidosis

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ABSTRACT

Objective: *To evaluate the efficacy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of thoracic sarcoidosis.*
Methods: *A retrospective dataset of 35 patients who received EBUS-TBNA was analyse d. These patients underwent EBUS-TBNA due to suspected sarcoidosis (radiographic stages I and II) with enlarged hilar or mediastinal lymph nodes (≥ 1.0 cm) revealed by computed tomography. When EBUS-TBNA was considered to be nondiagnostic, surgical biopsy and clinical and radiological follow-up was performed.*
Results: *Twenty-eight of 35 (80%) patients had a final diagnosis of sarcoidosis. Among them, 25 (89.3%) were diagnosed by EBUS-TBNA.*
Conclusion: *Endobronchial ultrasound-guided transbronchial needle aspiration is a safe and effective procedure for the diagnosis of stages I and II of thoracic sarcoidosis.*

Keywords: Diagnosis, endobronchial ultrasound, sarcoidosis, thoracic sarcoidosis, transbronchial needle aspiration

Eficacia de la Aspiración con aguja Transbronquial Guiada por Ultrasonido Endobronquial en el Diagnóstico de Sarcoidosis Torácica

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RESUMEN

Objetivo: *Evaluar la eficacia de la aspiración con aguja transbronquial guiada por ultrasonido endobronquial (EBUS-TBNA, por sus siglas en inglés) en el diagnóstico de la sarcoidosis torácica.*
Métodos: *Se analizó un conjunto de datos retrospectivos de 35 pacientes que recibieron EBUS-TBNA. Estos pacientes experimentaron EBUS-TBNA debido a sospecha de sarcoidosis (etapas radiográficas I y II) con agrandamiento de los ganglios linfáticos o hiliares (≥ 1,0 cm) revelados por tomografía computarizada. Cuando se consideraba que el EBUS-TBNA no conducía a un diagnóstico, se realizaba una biopsia quirúrgica y un seguimiento clínico y radiológico.*
Resultados: *Veintiocho de 35 (80%) pacientes tuvieron un diagnóstico final de sarcoidosis. De ellos, 25 (89.3%) fueron diagnosticados mediante EBUS-TBNA.*
Conclusión: *La aspiración mediante aguja transbronquial guiada por ecografía endobronquial es un procedimiento seguro y eficaz para el diagnóstico de la sarcoidosis torácica en las etapas I y II.*

Palabras claves: Diagnóstico, ultrasonido endobronquial, sarcoidosis, sarcoidosis torácica, aspiración con aguja transbronquial

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INTRODUCTION

Sarcoidosis is a multisystemic granulomatous disorder without known causes. The disease usually involves organs in the chest, particularly the lungs and chest lymph nodes. It has been reported that the incidence of sarcoidosis is on the rise (1, 2). Due to the lack of specific clinical characteristics, sarcoidosis is often mistaken for lung cancer, lymphoma or mediastinal lymph node tuberculosis based on radiographic imaging. In order to exclude other granulomatous diseases, a diagnostic biopsy to assess granulomas is required to confirm sarcoidosis.

Transbronchial lung biopsy (TBLB) is currently the most common procedure in the diagnosis of sarcoidosis. However, its accuracy depends on the disease stage as well as the operator's experience and the number of biopsy samples (3–5). In-

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creasing the number of biopsies improves the diagnostic yield but also increases the risk of complications (2). For patients whose diseases cannot be confirmed by conventional bronchoscopic diagnostic modalities, surgical biopsy *via* mediastinoscopy and thoracoscopy may diagnose sarcoidosis with a high accuracy. However, these procedures have some disadvantages such as surgical trauma caused by endotracheal intubation and neck or chest wall incision under general anaesthesia. In addition, these surgical procedures may cause a non-negligible rate (1.4–2.3%) of complications during or after the operation (5, 6).

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as a safe, accurate and minimally invasive diagnostic approach for the assessment of mediastinal and hilar lymph nodes (7, 8). Currently, EBUS-TBNA is mainly used for the mediastinal nodal staging of lung cancer (9–11). However, recent clinical studies have indicated that EBUS-TBNA has a high sensitivity (83–93%) in the diagnosis of sarcoidosis as well (2, 12–15). The objective of this study was to further evaluate the role of EBUS-TBNA in the diagnosis of sarcoidosis through a retrospective data analysis.

SUBJECTS AND METHODS

The EBUS-TBNA database in the Department of Thoracic Surgery at the People's Hospital of Peking University from September 2009 to June 2011, was reviewed. The patients with clinical and radiographic features of sarcoidosis and enlarged hilar or mediastinal lymph nodes (short axis >10 mm) revealed by computed tomography (CT) were identified and included in the study. The patients with a suspected or known malignancy, or previously established diagnosis of sarcoidosis were excluded. The experimental protocol was approved by the People's Hospital of Peking University's Ethics Committee, and all the subjects gave written informed consent.

The procedure of EBUS-TBNA was as indicated in a previous paper (16). Briefly, patients were placed in a conscious sedated state with midazolam. Local anaesthesia was achieved with 2% nebulized lidocaine solution (10 mL) in the pharynx. A bolus dose of 2 mL of 2% lidocaine was used during the procedure. Vital signs were monitored during the procedure through electrocardiography, pulse oximetry and blood pressure measurement. A standard conventional flexible bron-choscope (model BF-260; Olympus, Tokyo, Japan) was used first to examine the tracheobronchial tree. A dedicated linear array ultrasonic bronchoscope (BF-UC260F-OL8; Olympus) with a dedicated 22-gauge needle (NA-201SX-4022; Olympus) was subsequently used to perform the ultrasonic examination and transbronchial needle aspiration (TBNA). Doppler ultrasound was used to identify the vessels as necessary.

The lymph node stations were identified according to the International Staging System for Lung Cancer (17). The designated lymph node was punctured under direct EBUS guidance. The aspirated materials were smeared onto glass slides. Smears were air-dried and fixed in 95% alcohol followed by haematoxylin-eosin (H&E) staining. Dried smears were evaluated by an on-site cytopathologist to confirm that the obtained cell materials were of adequate quality. Adequate cell material was defined as sufficient for a specific diagnosis or the presence of lymphocytes on the specimen.

For each site, a minimum of three needle passes were performed. If adequate tissue was not identified by on-site cytology after six passes, the procedure was terminated. Histological specimens (obtained using EBUS-TBNA) were fixed with 10% neutral-buffered formalin and stained with H&E. Immunohistochemical staining was performed when necessary. Aspirated materials were also sent for microbiological examination, including special staining for fungi and acid-fast bacilli, and culturing of the specimen for tuberculosis and fungi. Requirement for polymerase chain reaction test for Mycobacterium was based on the operator's judgment.

Cytopathological diagnoses by EBUS-TBNA were categorized as malignancy, specific benign diseases (*eg* sarcoidosis, tuberculosis), non-specific benign lesions (*eg* normal lymph tissue, non-specific inflammation), or inadequate specimen. In the cases of non-specific benign lesions or inadequate specimen, EBUS-TBNA was considered to be non-diagnostic. Those cases were subsequently diagnosed either by surgical biopsy (*via* mediastinoscopy or thoracoscopy) and by clinical and radiological follow-up (for at least 6 months).

The diagnosis of sarcoidosis was based on the criteria that clinical features and radiographic imaging results are consistent with those of sarcoidosis, and non-caseating necrotizing granulomatous lesions were confirmed by EBUS-TBNA, surgical biopsy (*via* mediastinoscopy and thoracoscopy) or pathological examination. The possibility of other granulomatous diseases was ruled out by examining the disease history and microbiological testing. All the patients received long-term clinical and radiological follow-ups.

RESULTS

Endobronchial ultrasound-guided transbronchial needle aspiration was performed on 35 patients with suspected sarcoidosis based on the imaging features and clinical symptoms. Among those patients, 10 of them were male and 25 of them were female with an average age of 48.5 (age range from 14 to 78 years Table 1).

Prior to EBUS-TBNA, all the patients had received conventional chest X-Ray examination, chest CT scan and bronchoscopy. Some of the patients had also received other examinations including bronchoscopic lung biopsy (three cases), bronchial mucosal biopsy (10 cases), conventional TNBA (4 cases) and CT-guided transthoracic needle biopsy (2 cases). Based on the results of chest CT scan, 25 (71.4%) and 10 (28.6%) of them were initially diagnosed as radiological stages I and II sarcoidosis, respectively. Since those approaches could not yield a definitive diagnosis of sarcoidosis, EBUS-TBNA was performed in those patients.

Endobronchial ultrasound-guided transbronchial needle aspiration was performed on a total of 87 lymph node stations in 35 patients. Of these 87 lymph node stations, 64 were in the mediastinal region and 23 were around the hilum or interlobar area (Fig. 1).

Table: Characteristics of the patients with enlarged intrathoracic lymph nodes and suspected sarcoidosis

Characteristics	Data
Age, year	14–78
gender	
Male	10
Female	25
Lymph nodes location	
Total sampled	87
Station sampled	
7	30
2R	2
4R	30
4L	2
10/11R	13
10/11L	10
Lymph node size	
Long axis	25 mm (10–49)
Short axis	18 mm (6–34)

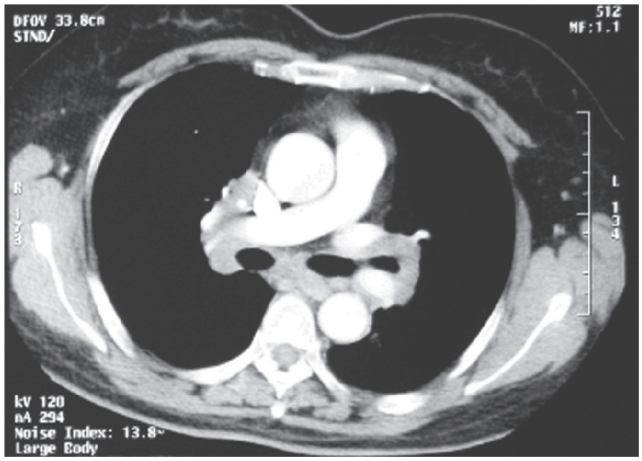
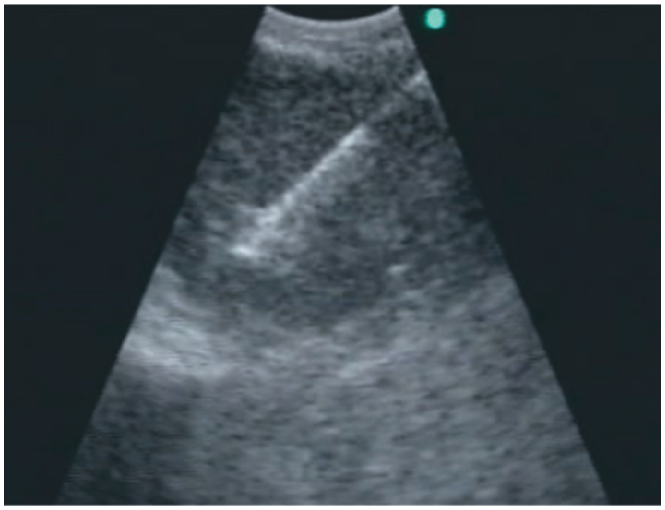
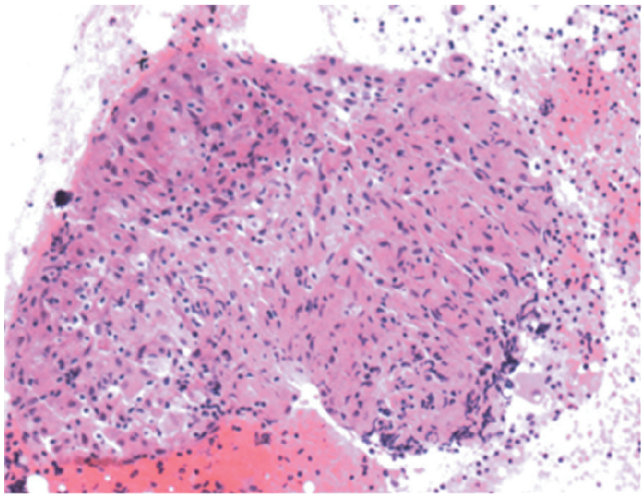


Fig. 1 a): Contrast enhanced CT showing enlarged bilateral hilar and subcarinal lymphadenopathy due to sarcoidosis.



b) Endobronchial ultrasound image demonstrating transbronchial needle aspiration of subcarinal lymph node with a 22 gauge needle.



c) H&E staining of a non-caseating granuloma obtained by endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA).

From each lymph node, 3 to 6 (average 3.5) specimens were obtained. The mean short-axis diameter of the punctured lymph nodes was 18 mm (between 6 and 34 mm). The procedure was well tolerated and no patient experienced hypoxaemia, complications or discomforts during the surgery.

Thirty-one cases were definitively diagnosed after EBUS-TBNA. Among these, 25 were sarcoidosis, three were lymph node tuberculosis and one was cryptococcal infection. The other two cases were metastatic squamous cell carcinoma and adenocarcinoma. However, in this study group, four cases could not be diagnosed by EBUS-TBNA accurately due to the non-specific inflammation in the lymph nodes (two cases) or poor sample quality (two cases). For these four cases, two of them were later confirmed as sarcoidosis by surgical biopsy *via* cervical mediastinoscopy and thoracoscopy. One case was diagnosed as tuberculosis by thoracoscopic biopsy. The other one was closely monitored during a 16-month period of clinical and radiological follow-up and the patient displayed consistent clinical symptoms of sarcoidosis (Fig 2).

Overall, there were 28 cases (80%) of sarcoidosis in those 35 patients. In those 28 cases, 25 of them (89.3%) were accurately diagnosed by EBUS-TBNA. The sensitivity was 89.3% (25/28) and specificity was 66.7% (2/3).

All the patients diagnosed with sarcoidosis received follow-up for eight to 28 months (average 16 months). During the period of follow-up, the results of clinical and radiological assessments supported the initial diagnoses and there was no change in the diagnostic conclusion. These patients did not have fungal or tuberculous infections based on the results of the microbiological examinations.

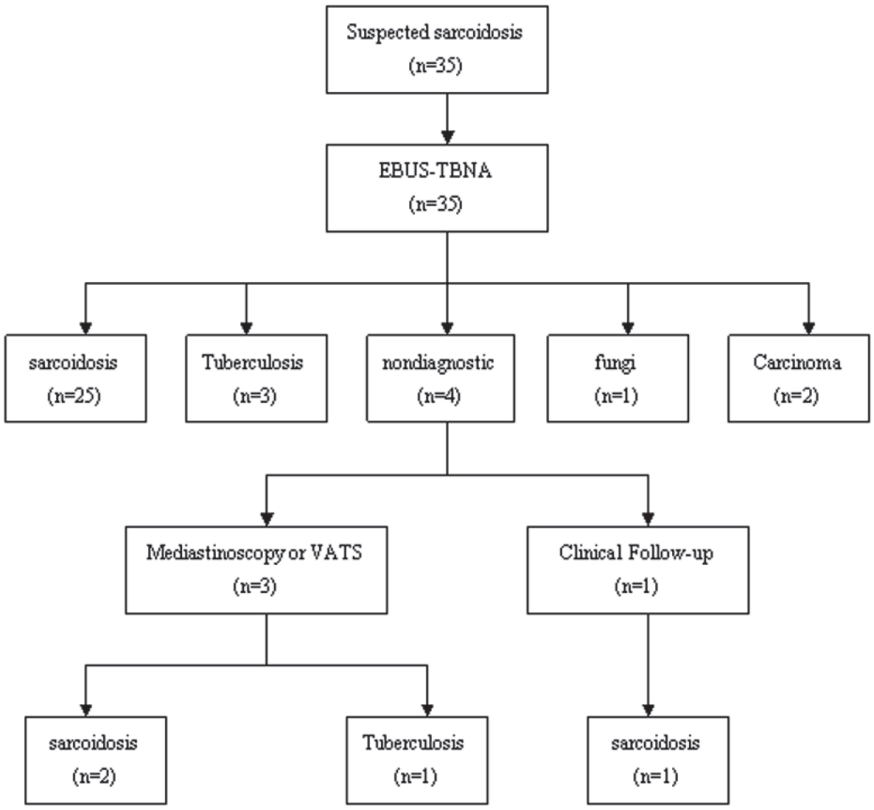


Fig. 2: Flow chart showing confirmation of diagnoses in 35 patients with suspected sarcoidosis. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; VATS, video-assisted thoracoscopic surgery.

DISCUSSION

Sarcoidosis is a systemic disorder that involves multiple tissues in the body. More than 90% of patients with sarcoidosis have enlarged hilar and/or mediastinal lymph nodes (3). The diagnosis of sarcoidosis is based on several criteria including the result of clinical and radiographic assessments, histology of non-caseating granulomatous lesions and the exclusion of other granulomatous diseases. However, a definitive diagnosis of sarcoidosis is usually dependent on the biopsy result of the granuloma. Currently, transbronchial lung biopsy (TBLB), conventional TNBA and mediastinoscopic biopsy are common approaches for the diagnosis of sarcoidosis. Among them, TBLB is the most widely used one. However, the accuracy of TBLB is highly dependent on the disease stage as well as the operator's experience and the number of biopsy samples taken (4). Transbronchial lung biopsy has a relatively high accuracy (75%) in the diagnosis of stage III sarcoidosis with diffuse pulmonary infiltration, while remaining at a low diagnostic rate (40–58%) for stages I and II sarcoidosis whose main symptoms are enlarged hilar and mediastinal lymph nodes (12, 15).

In addition, the risk of complications caused by TBLB increases with an increasing number of biopsy performed (2). According to what has been reported in the literature, TBLB has an overall 65% (46–90%) diagnostic accuracy for sarcoidosis with 2% and 5% complication rates of pneumothorax and bleeding, respectively (2, 14). Compared to TBLB, EBUS-TBNA has a higher diagnostic accuracy for stages I and II sarcoidosis with enlarged hilar and mediastinal lymph nodes (12, 18). Nakajima *et al* evaluated the accuracy of EBUS-TBNA and TBLB in the diagnosis of sarcoidosis in 2009, and concluded that EBUS-TBNA has an advantage over TBLB, particularly in the diagnosis of stage I sarcoidosis without pulmonary abnormalities (12).

Conventional TNBA has an accuracy rate from 42% to 76% in the diagnosis of stages I and II sarcoidosis (19–21). However, unlike in EBUS-TBNA, in conventional TNBA the biopsy needle can only be located based on static CT scans. Therefore, conventional TBNA has a limited accuracy because it relies on blind needle puncture (22, 23). In a prospective randomized clinical study conducted by Tremblay *et al* (13), the authors concluded that EBUS-TBNA had an apparent advantage over conventional TNBA in the diagnosis of sarcoidosis.

Mediastinoscopy has been a gold standard in the diagnosis of mediastinal diseases (24). Although it has a high accuracy in the diagnosis of sarcoidosis (25, 26), medistinoscopy also has limitations such as extensive surgical trauma and a complex procedure that involves endotracheal intubation and

neck or chest wall incision under general anaesthesia. Mediastinoscopy may also cause severe complications (1.4–2.3% of frequency) during or after the operation (6). Furthermore, due to the limited access, biopsy cannot be performed *via* mediastinoscopy in enlarged bilateral interlobar nodes, which are the most common symptoms of stages I and II sarcoidosis involving intrathoracic lymph nodes. Therefore, mediastinoscopy may not be an effective diagnostic approach for patients whose symptoms are limited to the hilar lymhadenopathy. Compared to mediastinoscopy, EBUS-TBNA is a simpler and safer procedure without intubation or anaesthesia and causes less trauma. Furthermore, EBUS-TBNA has more broad applications. It allows biopsy in the mediastinal and hilar lymph nodes (27).

This study includes 87 lymph node biopsies. Twenty-three of them are from hilar/interlobar lymph nodes. Endobronchial ultrasound-guided transbronchial needle aspiration has yielded 89.3% (25/28) sensitivity in the diagnosis of sarcoidosis, which is consistent with those reported in the literature. Sun *et al* (28) reported that EBUS-TBNA provided sensitivity and specificity of 93.69%, 100% in the diagnosis of sarcoidosis, respectively, which was higher than our results. This is caused by the small sample size in our research. When a final diagnosis could not be obtained from ENBU-TBNA or the results were negative, surgical treatment by mediastinoscopy or thoracoscopy and clinical and radiological follow-up would be performed. In this way, the treatment of the suspected cases would not be delayed.

Nevertheless, there are several limitations to this study. The retrospective study lacks randomized controls and has a limited sample number. Therefore, the conclusion needs further evaluations. In addition, the patients included in this study were those with radiographic stages I and II sarcoidosis with mediastinal or hilar lymph nodes larger than 1 cm. Some of the patients had typical imaging features of sarcoidosis; this might have led to an increased accuracy rate of EBUS-TNBA. Moreover, this study focusses on the evaluation of EBUS-TBNA in the diagnosis of sarcoidosis with enlarged mediastinal and hilar lymph nodes. The result does not reflect its role in the diagnosis of stages III and IV sarcoidosis. Recently, a review showed that EBUS-TBNA can be a valuable option for the diagnosis of sarcoidosis even in clinically unselected study populations (29). It was also reported that the combined use of EBUS-TBNA and EUS-B-FNA (endoscopic ultrasound with bronchoscope-guided fine-needle aspiration) was superior to EBUS-TBNA alone, in the diagnosis of mediastinal lymphadenopathy (30).

CONCLUSION

Endobronchial ultrasound-guided transbronchial needle aspiration is a safe and effective approach in the diagnosis and confirmation of stages I and II sarcoidosis (31). Therefore, the use of conventional surgical biopsy, such as mediastinoscopy and thoracoscopy can be reduced in this aspect. However, surgical biopsy may still be required if EBUS-TBNA cannot give a definitive diagnosis due to the limitations of needle aspiration. For a final diagnosis of saroidosis, the results of the biopsy, as those of other diagnostic procedures, need to be assessed in the context of other clinical features such as the disease history and microbiological examination to rule out other granulomatous diseases. Furthermore, all patients diagnosed with sarcoidosis should have extensive clinical and radiological follow-up to make sure that the initial diagnosis is correct.

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