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 data set of 35 patients who received EBUS-TBNA was analyzed. Those patients underwent EBUS-TBNA due to the suspected sarcoidosis (radiographic stage I and II) with enlarged hilar or mediastinal lymph nodes (≥1.0cm) revealed by computed tomography. When EBUS-TBNA was considered to be nondiagnostic, surgical biopsy and clinical and radiological follow-up would be 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: EBUS-TBNA is a safe and effective procedure for the diagnosis of stage I and II thoracic sarcoidosis.

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

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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 in recent years (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). Increasing 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 traumas caused by endotracheal intubation and neck or chest wall incision under general anesthesia. 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 applied in 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.

METHODS

Patients

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. Patients with clinical and radiographic features of sarcoidosis and enlarged hilar or mediastinal lymph node (short axis >10 mm) revealed by computed tomography (CT) were identified and included in the study. 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 Ethical Committee, and all subjects gave written informed consent.

Procedure of EBUS-TBNA

EBUS-TBNA was as indicated in the previous paper (16). As briefly, patients were placed in a conscious sedated state with midazolam. Local anesthesia 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 bronchoscope (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 TBNA. Doppler ultrasound was used to identify 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 hematoxylin-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 of PCR test of Mycobacterium was based on the operator’s judgment.

Cytopathological diagnoses by EBUS-TBNA were categorized as malignancy, specific benign diseases (e.g., sarcoidosis, tuberculosis), nonspecific benign lesions (e.g., normal lymph tissue, nonspecific inflammation), or inadequate specimen. In the cases of nonspecific benign lesions or inadequate specimen, EBUS-TBNA was considered to be nondiagnostic. 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).

**Diagnostic criteria for sarcoidosis**

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 disease history and microbiological testing. All patients received long-term clinical and radiological follow-ups.

**RESULTS**

EBUS-TBNA was performed in 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 average age of 48.5 (age range from 14 to 78, Table 1). Prior to EBUS-TBNA, all patients had received conventional chest X-Ray examination, chest CT scan and bronchoscopy. Some patients had also received other examinations including bronchoscopic lung biopsy (3 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 stage I and stage II sarcoidosis respectively. Since those approaches could not yield a definitive diagnosis of sarcoidosis, EBUS-TBNA was performed in those patients.

EBUS-TBNA was performed on a total of 87 lymph node stations in 35 patients. Of those 87 lymph nodes stations, 64 were in the mediastinal region and 23 were around the hilum or interlobar area (Fig. 1). From each lymph node, 3 to 6 (average 3.5) specimens were obtained. The mean short-axis diameter of the punctured lymph nodes was 18mm (between 6 and 34 mm). The procedure was well tolerated and no patient experienced hypoxemia, complications or discomforts during the surgery.

Thirty-one cases received definitive diagnoses after EBUS-TBNA. Among those, 25 were sarcoidosis, 3 were lymph node tuberculosis and 1 was cryptococcal infection. The other two cases were metastatic squamous cell carcinoma and adenocarcinoma. However, in this study group, 4 cases could not be diagnosed by EBUS-TBNA accurately due to the non-specific inflammation in the lymph nodes (2 cases) or poor sample quality (2 cases).
those 4 cases, 2 of them were later confirmed as sarcoidosis by surgical biopsy via cervical mediastinoscopy and thoracoscopy. One case was diagnosed as tuberculosis by thoracosopic 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). Therefore, this one was also a case of sarcoidosis. 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 patients diagnosed with sarcoidosis received follow-ups for 8 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. Those patients did not have fungal or tuberculous infections based on the results of microbiological examination.

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 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). TBLB has a relatively high accuracy (75%) in the diagnosis of stage III sarcoidosis with diffuse pulmonary infiltration, while remaining a low diagnostic rate (40%-58%) for stage I and II sarcoidosis whose main symptoms are enlarged hilar and mediastinal lymph nodes (12,15). In addition, the risk of complication 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%) of 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 stage 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 have 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 stage I
and II sarcoidosis. 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. In a prospective randomized clinical study conducted by Tremblay et al in 2009, 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. Although it has a high accuracy in the diagnosis of sarcoidosis, mediastinoscopy also has limitations such as extensive surgical trauma and complex procedure that involves endotracheal intubation and neck or chest wall incision under general anesthesia. Mediastinoscopy may also cause severe complications (1.4-2.3% of frequency) during or after the operation. Furthermore, due to the limited access, biopsy cannot be performed via mediastinoscopy in the enlarged bilateral interlobar nodes, which are the most common symptoms of stage 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 lymphadenopathy. Compared to mediastinoscopy, EBUS-TBNA is a simpler and safer procedure without intubation or anesthesia, and causes less trauma. Furthermore, EBUS-TBNA has more broad applications. It allows biopsy in the mediastinal and hilar lymph nodes. This study includes 87 lymph node biopsies.
Twenty-three of them are from hilar/interlobar lymph nodes. ENBU-TBNA has yielded 89.3% (25/28) sensitivity in the diagnosis of sarcoidosis, which is consistent with those reported in literatures. Sun et al (28) reported that EBUS-TBNA provided sensitivity, specificity of 93.69%, 100% in the diagnosis of sarcoidosis, which was higher than our results. This is caused by the small sample size in our research. When ENBU-TBNA was unable to give a final diagnosis or the results were negative, following surgery treatment by mediastinoscopy or thoracoscopy and clinical and radiological follow-up would be performed. In this way, the suspected cases’ treatment would not be delayed.

Nevertheless, there are several limitations in 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 are those radiographic stage I and II sarcoidosis patients with mediastinal or hilar lymph nodes larger than 1cm. Some patients have typical imaging features of sarcoidosis, thus may have led to an increased accuracy rate of EBUS-TNBA. Moreover, this study focuses 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 stage III and IV sarcoidosis. Recently, a review showed that EBUS-TBNA can be a valuable option for 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).

In summary, EBUS-TBNA is a safe and effective approach in the diagnosis and
confirmation of stage I and II sarcoidosis (31). Therefore, 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 make a definitive diagnosis due
to the limitations of needle aspiration. For a final diagnosis of sarcoidosis, the result of biopsy,
as those of other diagnostic procedures, needs 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-ups to make sure that the initial diagnosis is
correct.
REFERENCES


of flexible transbronchial needle aspiration in the diagnosis of stage I sarcoidosis.


Table 1 Characteristics of the patients with enlarged intra-thoracic lymph nodes and suspected sarcoidosis

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>10</td>
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<tr>
<td>Female</td>
<td>25</td>
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<tr>
<td>Lymph nodes location</td>
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<tr>
<td>Total sampled</td>
<td>87</td>
</tr>
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<td></td>
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<tr>
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<td>10</td>
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<tr>
<td>Lymph node size</td>
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<tr>
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<tr>
<td>Short axis</td>
<td>18mm(6-34)</td>
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Fig.1a: 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).

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