Original Article

Use of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) in the Diagnosis of Granulomatous Mediastinal Lymphadenopathy

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Abstract

Introduction: This study assessed the clinical utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of suspected granulomatous mediastinal lymphadenopathy. Materials and Methods: Retrospective chart review of all patients who underwent EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at Singapore General Hospital between December 2008 and December 2011 inclusive. Results: Over a period of 3 years, a total of 371 patients underwent EBUS-TBNA of whom 33 (9%) had the procedure performed for evaluation of suspected granulomatous mediastinal lymphadenopathy — 18 for suspected tuberculosis (TB) and non-tuberculous mycobacterial (NTM) lymphadenitis, and 15 for suspected sarcoidosis. EBUS-TBNA was diagnostic in 9 of the 13 patients with a final diagnosis of TB/NTM. EBUS-TBNA cultures were positive in 6 of them (46%), 1 showed acid-fast bacilli (AFB) although cultures were negative, and 2 had necrotising granulomatous inflammation from EBUS-TBNA biopsies and sputum cultures grew TB. EBUS-TBNA was diagnostic in 9 of the 14 patients with a final diagnosis of sarcoidosis through histology showing non-caseating granulomatous inflammation. The sensitivities of EBUS-TBNA for diagnosis of TB/NTM, sarcoidosis and overall granulomatous mediastinal lymphadenopathy were 69%, 64%, 64%; the negative predictive values were 56%, 17%, 33%; and accuracies were 78%, 67%, 70%, respectively. Conclusion: EBUS-TBNA can be useful in the diagnosis of suspected granulomatous mediastinal lymphadenopathy with sensitivities and accuracies of >60%.

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Key words: Lymphadenitis, Non-tuberculous mycobacterial, Sarcoidosis, Tuberculosis

Introduction

The clinical utility and safety of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis and mediastinal staging of patients with non-small cell lung has been well established with diagnostic accuracies reported at 85% to 100%, and a negative predictive value of 11% to 97.4%.[1] Of all the other conditions, sarcoidosis has been the most extensively studied, and publications have reported diagnostic sensitivities of EBUS-TBNA of 79.5% to 93%.[2-10] These studies were done in patients with a high pretest probability of sarcoidosis and in countries with an incidence rate of 1 to 50 per 100,000, and prevalence rate of 3 to 200 per 100,000 population.[11] Published data on tuberculous mediastinal lymphadenopathy are scarce — one report described the utility of EBUS-TBNA in the diagnosis of tuberculosis in 2 retroviral patients with mediastinal lymphadenopathy for evaluation,[12] whilst 2 other studies have shown sensitivities of EBUS-TBNA for diagnosis of tuberculous mediastinal lymphadenopathy of 84.2% (19 patients) and 94% (156 patients).[9,13] In geographic areas where tuberculosis (TB) is endemic, it can be clinically challenging to distinguish between TB and thoracic sarcoidosis as both may present similarly with mediastinal and hilar lymphadenopathy with or without systemic manifestations of cough, fever,

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and weight loss. In Singapore, the incidence of TB is 35 per 100,000 and that of sarcoidosis is 0.56 per 100,000 population.[14] It would be imperative to differentiate between these 2 conditions as therapeutic management is markedly different. As such, this study set out to evaluate the clinical utility of EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at our institution.

Materials and Methods

A retrospective chart review was carried out on all consecutive patients who underwent EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at the Singapore General Hospital, a tertiary care university-affiliated teaching hospital, between December 2008 and December 2011 inclusive. Completeness of data were ensured by a centralised database that was set up at the time of introduction of EBUS-TBNA to our institution. The database utilised billing to track procedures. All patients had a computed tomography (CT) of the thorax done prior to EBUS-TBNA.

EBUS-TBNA was performed by attending respiratory physicians trained and experienced in this procedure under local anaesthesia with conscious sedation (midazolam and fentanyl). Local anaesthesia was attained using nebulised 1% lignocaine solution (4 mL) and 4% lignocaine solution sprayed into the pharynx (4 mL). Bolus doses of 2 mL 1% lignocaine were administered topically to the airway via the working channel of the bronchoscope as needed. Patients were monitored throughout the procedure by electrocardiogram (ECG), pulse oximetry and blood pressure. A linear array bronchoscope (BF-UC260F-OL8, Olympus, Tokyo, Japan) was introduced via the oral route and used to perform ultrasonic examination. A dedicated 22-gauge needle (NA-201SX-4022, Olympus, Tokyo, Japan) was used to perform biopsies of the pathology in question. Typically, 2 needle passes were performed at each lymph node station with at least 1 core specimen obtained. After obtaining a sample, the needle was withdrawn from the working channel of the bronchoscope and the stylet introduced to expel the core specimen out onto a filter paper which was then put into a bottle of formalin for histological evaluation. The stylet was then removed and 1 mL of normal saline followed by air was introduced into the needle to expel any remaining material into a bottle of normal saline for microbiological evaluation. Rapid on-site evaluation (ROSE) was not utilised routinely. Standard haematoxylin and eosin (H&E) stain was used in processing the histological specimens. Microbiological specimens were sent to the Central Tuberculosis Laboratory, Singapore General Hospital, for identification of acid-fast bacilli (AFB) and mycobacteria cultures. We did not routinely use polymerase chain reaction (PCR) to detect mycobacterium tuberculosis. Patients whose histology from core specimens of the lymph nodes showed necrotising granulomatous inflammation, and/or lymph node aspirate microbiology positive for AFB and mycobacteria culture were considered to have a diagnostic EBUS-TBNA evaluation for TB/NTM mediastinal lymphadenitis. Patients whose histology from the core specimens showed non-caseating granulomatous inflammation with negative microbiology were considered to have a diagnostic EBUS-TBNA evaluation for sarcoidosis. Statistical analysis was done with SPSS 16 statistical software (SPSS Inc, Chicago, Illinois). The study was approved by the Singhealth Centralized Institutional Review Board (2008/458/B).

Results

Over a period of 3 years, a total of 371 patients underwent EBUS-TBNA whose indications are shown in Table 1. Baseline characteristics and clinical presentations of the 33 patients with suspected granulomatous mediastinal lymphadenopathy (18 patients with suspected TB lymphadenitis, 15 with suspected sarcoidosis) are shown in Table 2. A total of 49 lymph node stations were sampled whose characteristics are shown in Table 3. Core biopsies were attained in 45/49 (92%) of the lymph nodes.

EBUS-TBNA results for suspected TB/NTM lymphadenitis are shown in Table 4. Of the 9 patients in whom EBUS-TBNA was diagnostic, EBUS-TBNA cultures were positive in 6 patients — 5 grew mycobacterium tuberculous complex (MTC), and 1 had mycobacterium avian complex (MAC). Two of these 6 patients were HIV positive. The remaining 3 patients had negative EBUS-TBNA cultures. One patient's EBUS-TBNA showed AFB but cultures were negative. This patient was HIV positive and further biopsy of a cervical lymph node grew MAC. The last 2 patients had necrotising granulomatous inflammation from EBUS-TBNA biopsies and sputum cultures were

Table 1. Indications for EBUS-TBNA

Indication	No. of Patients (%)
Suspected or known lung cancer and known cancer with suspected lung metastases	293 (79)
Suspected granulomatous mediastinal lymphadenopathy	33 (9)
Mediastinal lymphadenopathy for evaluation	25 (7)
Mediastinal lymphadenopathy in patients with underlying interstitial lung disease	8 (2)
Suspected lymphoma	7 (2)
Thyroid mass	2 (0.5)
Probable bronchogenic cyst	2 (0.5)
Mediastinal mass of uncertain aetiology	1 (0.3)

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration

Table 2. Baseline Characteristics and Clinical Presentations of 33 Patients who Underwent EBUS-TBNA for Suspected Granulomatous Mediastinal Lymphadenopathy

Characteristics	No. of Patients (%)
Age (years)	47 ± 18
Male	18 (54.5)
Fever	16 (48.5)
Weight loss	12 (36.4)
Cough	18 (54.5)
Dyspnoea	7 (21.2)
Rash	6 (18.2)
Arthralgia/arthritis	3 (9.1)
Uveitis	3 (9.1)
CT thorax findings	
Lung parenchymal abnormalities	1 (3)
Intrathoracic lymphadenopathy	8 (24.2)
Parenchymal abnormalities and lymphadenopathy	24 (72.7)
Median follow-up duration (months, range)	11 (0.5 to 36)

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; CT: Computed tomography

Table 3. Characteristics of the 49 Lymph Nodes Biopsied

Variable	Number
Median size of lymph node (mm, range)	17 (8 to 30)
Median number of passes per lymph node (n, range)	2 (1 to 5)
Lymph node location	(n, %)
2R	2 (4.1)
4R	16 (32.7)
4L	3 (6.1)
7	21 (42.9)
10R	3 (6.1)
10L	1 (2)
11R	2 (4.1)
11L	1 (2)

eventually positive for MTC. They both tested negative for HIV. All cultures of MTC were sensitive to first-line anti-tuberculous drugs. In the 4 patients in whom EBUS-TBNA was non-diagnostic for TB/NTM lymphadenitis, histology from 2 showed lymphocytes, and the other 2 showed necrotic material.

EBUS-TBNA results for suspected sarcoidosis are shown in Table 4. EBUS-TBNA evaluation for sarcoidosis was considered diagnostic if the histology from core specimens of the lymph nodes showed non-caseating granulomatous inflammation and microbiology was negative for mycobacterial disease. In the 5 patients in whom EBUS-TBNA was non-diagnostic, histology was non-diagnostic in 2, and showed lymphocytes in 3 of them.

The sensitivities of EBUS-TBNA for diagnosis of TB/NTM, sarcoidosis, and overall granulomatous mediastinal lymphadenopathy were 69%, 64%, 64%, the negative predictive values were 56%, 17%, 33%, and diagnostic accuracies were 78%, 67%, 70%, respectively. We had no false positives in our study and there were no major complications requiring further intervention from the procedure.

Discussion

The overall sensitivity, negative predictive value, and diagnostic accuracy of EBUS-TBNA in this cohort of patients were 64%, 33%, and 70%, respectively. This is slightly lower than a previous study on granulomatous mediastinal lymphadenopathy which reported a sensitivity, negative predictive value, and diagnostic accuracy of 81%, 43%, and 83%, respectively,[9] but in agreement with the general consensus that EBUS-TBNA is less accurate in conditions not pertaining to mediastinal staging of lung cancer. In the subgroup of patients with sarcoidosis and TB/NTM mediastinal lymphadenitis, we found sensitivities, negative predictive values, and diagnostic accuracies of 64%, 17%, 67%, and 69%, 56%, 78%, respectively. This whilst lower than previous reports,[2-10,12,13] still enabled a definitive diagnosis to be attained in a significant proportion of patients without subjecting them to more invasive investigations which would entail the risks of general anaesthesia, surgical morbidity and mortality, and possible chronic tuberculous sinus formation.[15]

Our comparative lower diagnostic yield could be attributable to the fact that previous studies were largely from dedicated interventional pulmonary units where EBUS-TBNA procedure was performed by world experts. In some cases, the procedure was performed via rigid endoscopy on patients under general anaesthesia.[7] The endoscopists involved in our study, although experienced and trained in EBUS-TBNA, are likely to be more reflective of the practice standard that is more widely available. Another reason for our lower diagnostic yield could be due to the fact that we only used histology without cytology for the diagnosis of granulomatous inflammation. The histopathological hallmark of granulomatous lymphadenitis is the identification of granulomas which are composed of epithelioid and giant cells with or without central necrosis. The use of cytological assessment of lymph node aspirates is more controversial because whilst it may demonstrate epithelioid histiocytes in a background of lymphocytes and plasma cells, the absence of giant cells makes it less specific for true granulomatous disease,[10] although the cytological diagnosis of sarcoidosis has been shown to be feasible.[16] The addition of cytology to histology may be important especially for ROSE of specimen adequacy. Presence of granulomas

Table 4. EBUS-TBNA Results in the 18 Patients with Suspected TB/NTM Lymphadenitis and 15 Patients with Suspected Sarcoidosis

Final Diagnosis (n)	**TB/NTM (13)**	**Not TB/NTM (5)**	**Sarcoidosis (14)**	**Not Sarcoidosis (1)**
EBUS-TBNA diagnostic	9	0	9	0
EBUS-TBNA culture positive	6		0	
EBUS-TBNA histology	• 2 necrotising granulomatous inflammation • 3 necrotic • 1 lymphocytes			
EBUS-TBNA culture negative	3		9	
EBUS-TBNA histology	• 2 necrotising granulomatous inflammation • 1 necrotic, AFB smear positive		9 non-caseating granulomatous inflammation	
EBUS-TBNA non-diagnostic	4	5	5	1
Final diagnosis based on:				
Bronchial washings	1 TB			
Transbronchial lung biopsy			1	
Mediastinoscopy	1 NTM			1 TB
Transthoracic needle biopsy		1 meliodosis		
Video-assisted thoracoscopic surgery		1 infected bronchogenic cyst		
Clinical and radiological follow-up	2 responded to empirical TB treatment	3 benign	4 showed lymph node stability (3 on treatment, 1 not)	

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TB: Tuberculosis; NTM: Non-tuberculous mycobacteria; AFB: Acid-fast bacilli

on ROSE may prompt the endoscopist to consider diagnoses related to granulomatous inflammation, which may not have been a consideration initially and thus direct further investigations accordingly e.g. sending additional specimens for mycobacterial and fungal smears and cultures. However, we would also caution the over- reliance of ROSE cytology interpretation as granulomas and granulomatous inflammation are known to exist around malignancies such as cancer and lymphoma.[10] Therefore, ROSE may be misleading in some situations. We acknowledge that perhaps the addition of cytological evaluation to our histologic one may have increased our EBUS-TBNA diagnostic yield. In spite of these shortcomings, our results still support the use of EBUS-TBNA as an initial mode of evaluation of suspected granulomatous mediastinal lymphadenopathy, and more invasive investigations should be reserved for cases with clinical doubt.

Previous studies have demonstrated that the diagnostic yield for sarcoidosis via EBUS-TBNA can be further improved by combining with random endobronchial and transbronchial lung biopsies.[3,7,8,10] We had a similar finding where the addition of transbronchial lung biopsy increased our diagnostic sensitivity from 64% to 71%.

We were able to obtain a positive microbiological culture in 46%, and combined smear and culture positivity of 54%. This is similar to previously reported microbiological yield for EBUS-TBNA (culture 47%, smear and culture 53%),[13] and compatible with other modalities such as mediastinoscopy (culture 41%),[15] and fine needle aspirates of lymph nodes (culture 49%, smear and culture 57%).[17] The low microbiological yield is postulated to reflect the variable bacillary load within lymph nodes.

The main limitation of our study is its small numbers and retrospective nature. Despite this, we were able to obtain comparable results with the published data. Recent studies have suggested that a bigger EBUS-TBNA needle (19-gauge or 21-gauge) may provide better histologic specimens for better characterisation of diseases including lymphoma and sarcoidosis.[18-20] We believe by adopting these practices, we will be able to further improve our diagnostic accuracy.

Conclusion

EBUS-TBNA has a lower diagnostic yield in patients who do not present with suspected or known lung cancer. The limited negative predictive value mandates that cases without a definitive diagnosis should undergo either

further investigation or clinico-radiological follow-up until resolution. Nevertheless, our study supports the use of EBUS-TBNA, by virtue of being a safe, minimally invasive, and an outpatient procedure, in the diagnosis of granulomatous mediastinal lymphadenopathy with a sensitivity and diagnostic accuracy of >60%, thereby obviating more invasive testing in a significant number of patients.

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