Endobronchial Ultrasound Guided Transbronchial Needle Aspiration in the Diagnosis of Lymphoma.

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Abstract

Background: The diagnostic accuracy of endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of lymphoma in patients with mediastinal lymphadenopathy is not well defined.

Methods: A retrospective review was performed of all patients with mediastinal lymphadenopathy referred for EBUS-TBNA between August 2005 and December 2006, in whom lymphoma was suspected based on prior history or clinical presentation. Mediastinal biopsies were taken using a linear array ultrasonic bronchoscope (Olympus XBF-UC 160F) and a 22 gauge cytology needle (NA-202C Olympus ltd.) with on-site cytopathologic support. The EBUS-TBNA result was compared to a reference standard of pathological tissue diagnosis or a composite of ≥6 month’s clinical follow-up with radiographic imaging.

Results: Of 236 patients who underwent EBUS-TBNA, 25 patients were eligible for inclusion. Indications for EBUS-TBNA were suspected mediastinal recurrence of lymphoma (n=13) and mediastinal lymphadenopathy of unknown cause (n=12). Adequate lymph node sampling was accomplished in 24/25 patients (96%); there were no complications. EBUS-TBNA identified lymphoma in 10 patients and benign disease in 14 patients. There was 1 false negative EBUS-TBNA for lymphoma (lymphoma prevalence 11/25 (44%)). Follow-up over a median of 10.5 months (range 1-19) confirmed stable or regressive lymphadenopathy in all 14 patients without a lymphoma diagnosis, consistent with a benign diagnosis. Overall, EBUS-TBNA had a sensitivity of 90.9%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 92.9% for the diagnosis of lymphoma.

Conclusions: EBUS-TBNA is an accurate, safe and useful tool in the investigation of suspected lymphoma with isolated mediastinal adenopathy, and may diminish the need for more invasive procedures such as mediastinoscopy.
Abbreviations
EBUS= endobronchial ultrasound
EUS-FNA= endoscopic ultrasound fine needle aspiration
F-18 FDG= fluoro-18 deoxy-glucose
SUV= standard uptake value
TBNA= transbronchial needle aspiration
Introduction

Lymphoma typically presents with lymphadenopathy in anatomical sites easily accessible to diagnostic biopsy or fine needle aspiration such as in the neck, axillae or inguinal regions. However, both Hodgkin’s and non-Hodgkin’s lymphoma may present with isolated mediastinal lymphadenopathy [1], and in such cases, mediastinoscopy or thoracotomy may be required to obtain diagnostic material, with the attendant risk of morbidities related to anesthesia, bleeding, infection and post-procedural pain. Transbronchial needle aspiration (TBNA) is a minimally invasive safe technique that allows sampling of mediastinal nodes, often obviating the need for more invasive procedures such as mediastinoscopy [2]. TBNA has expanded the role of bronchoscopy in the diagnosis of mediastinal pathology and lung cancer staging [3]. However, the sensitivity of TBNA in the assessment of mediastinal lymphadenopathy varies from 15-85% and depends on the prevalence of malignant mediastinal lymphadenopathy in the study population, operator experience, needle used, lymph node site and number of aspirates [4-9]. These limitations may explain why surveys demonstrate that only 10-30% of pulmonologists regularly use TBNA [10, 11]. By integrating of ultrasound technology into a flexible bronchoscope, endobronchial ultrasound (EBUS) allows accurate definition of mediastinal structures and enhances site selection for transbronchial sampling. The first device available was a radial probe introduced through the working channel of a flexible bronchoscope prior to subsequent TBNA. This marginally improved the yield of TBNA, particularly in paratracheal lymph nodes [12]. However, the recent development of an integrated linear array ultrasonic bronchoscope now allows for real time ultrasonic visualization of the needle at the area of interest with a consequent improvement in diagnostic yield to 93.5% in mediastinal or hilar lymphadenopathy among a cancer predominant population [13]. The utility of EBUS-TBNA in lung cancer staging has been reported with a sensitivity of 92-95% [14-17], but to our knowledge, there have been no prior studies of the utility of either TBNA or EBUS-TBNA in patients with mediastinal adenopathy secondary to lymphoma. We therefore reviewed our clinical experience to examine the clinical utility of EBUS-TBNA in patients with mediastinal lymphadenopathy secondary to suspected lymphoma.
Materials and Methods

Patients

Consecutive patients with mediastinal lymphadenopathy of unknown cause in whom lymphoma was suspected who were referred for EBUS-TBNA between August 2005 and December 2006 were reviewed. A suspicion of lymphoma was raised either because of a prior lymphoma history, known lymphoma elsewhere, or because of a presentation compatible with new isolated mediastinal lymphoma based on a review of available clinical and radiographic data by the bronchoscopist perfuming the EBUS-TBNA procedure. An example of a compatible presentation was isolated idiopathic bulky mediastinal adenopathy with or without systemic symptoms. Patients were excluded if there was another likely cause for the lymphadenopathy suspected such as lung cancer, or other non-lymphoproliferative malignancy. Our institutional review board approved this analysis.

Imaging evaluation prior to EBUS-TBNA

Prior to EBUS-TBNA, patients underwent CT imaging of the thorax, with or without PET/CT scanning. PET/CT scanning was performed on an integrated scanner (Discovery ST-8, General Electric Medical Systems, Milwaukee, WI) using fluoro-18 deoxy-glucose (F-18 FDG). Quantification of FDG uptake within mediastinal lymph nodes was performed both visually and semi-quantitatively, according to the following equation: $\text{SUV}_{\text{max}} = \frac{\text{mean measured activity within the volume of interest (mCi/mL)}}{\frac{\text{injected dose of FDG (mCi)}}{\text{body weight (g)}}}$. For each lymph node that was subsequently aspirated by EBUS-TBNA, the short-axis diameter of the lymph node (in millimeters) and the intensity of FDG uptake ($\text{SUV}_{\text{max}}$) were recorded by a diagnostic radiologist. A lymph node was considered to be FDG-avid if the intensity of FDG uptake appeared greater than that of the normal surrounding mediastinal blood pool uptake (assessed visually) and if the $\text{SUV}_{\text{max}} \geq 4$.

EBUS-TBNA Procedure

All of the EBUS-TBNA procedures were performed by interventional pulmonology attendings (n=3) with or without supervised fellows. Under general anesthesia with ventilation via a laryngeal mask airway, standard, conventional flexible bronchoscopy (model BF-T160 bronchoscope, Olympus, Japan) was first performed to examine the tracheobronchial tree. A linear array ultrasonic bronchoscope (Olympus XBF-UC 160F) with dedicated 22-gauge needle (NA-202C Olympus ltd.) was subsequently used to perform ultrasonic examination and transbronchial aspiration. The regional lymph node stations of the mediastinum and hilar regions were systematically imaged and measured (short-axis diameter) using the International Staging System (Mountain classification) [18]. All visualized lymph nodes greater than 0.5 cm were sampled using real time ultrasonic needle guidance. Doppler ultrasound was used to identify vessels as necessary. Each nodal station was sampled at least twice, until adequate samples were attained by rapid on-site pathology evaluation (ROSE or if inadequate sample was initially obtained to a maximum of 5 passes per station. Specimen adequacy was defined by the presence of...
lymphoid tissue or tumor. Immunohistochemistry and flow cytometry were requested on all samples, but actually performed on the samples at the discretion of the cytopathologist based on the cytomorphologic characteristics. Adequate samples were defined as positive or negative for lymphoma. Negative samples were subdivided into benign disease, reactive hyperplasia or normal.

All complications were recorded and grouped into major complications (hospital admission, respiratory failure, bleeding requiring transfusion or other intervention, pneumothorax or pneumomediastinum) and minor complications (including post procedure cough, sore throat and bleeding <50cc controlled with simple bronchoscopic tamponade).

**Reference standard evaluation: pathology and clinical follow-up**

For the purposes of the study, a true positive diagnosis of lymphoma was made if there was a positive biopsy of lymphoma within a mediastinal lymph node, either by EBUS-TBNA or on subsequent follow-up by another modality within 6 months. A true-negative diagnosis of benign disease was represented by a negative biopsy, with stability or regression of lymphadenopathy documented on subsequent imaging (by CT and/or PET/CT) and by clinical follow-up over a period of at least 6 months. A diagnosis of sarcoidosis was made if EBUS-TBNA or other tissue sample identified non-caseating granulomas along with a compatible clinical phenotype and adequate exclusion of other causes for granulomatous inflammation (clinical history, follow-up and a combination of negative tissue staining for acid fast bacilli (AFB) and fungal organisms and negative respiratory fungal and mycobacterial cultures).

**Statistical Methods**

Summary statistics were used to report the lymph node characteristics. All the statistics analysis was performed in SAS® Version 9.1 (SAS Institute, Cary, NC).
Results

Out of 236 consecutive patients who underwent EBUS-TBNA during the study period, there were 25 patients with idiopathic mediastinal lymphadenopathy who were eligible for inclusion (Table 1, Figure 1). Thirteen of these patients had a prior history of lymphoma; the other 12 patients had no prior history of lymphoma; however lymphoma was suspected based on radiography and clinical presentation.

Adequate lymphoid tissue was obtained by EBUS-TBNA in 96% (24/25) of patients. Forty-nine lymph nodes were sampled in total (average 1.96 per patient) (Table 2). Based on the results of EBUS-TBNA, other investigations and clinical follow-up, 11 patients had a final diagnosis of mediastinal lymphoma. Follow-up over a median of 10.5 months (range 1-19) confirmed stable or regressive lymphadenopathy in all 14 patients (n=8 sarcoidosis) without a lymphoma diagnosis, consistent with a benign diagnosis (Table 1). 8/13 (61.5%) patients with a prior diagnosis of lymphoma were finally diagnosed with lymphoma and EBUS-TBNA was diagnostic in all. Only 3/12 (25%) patients without a prior history of lymphoma ended up with a final diagnosis of lymphoma and EBUS-TBNA was diagnostic in two and false negative in one other (described below).

Of the eleven patients with a final diagnosis of lymphoma, EBUS-TBNA correctly diagnosed lymphoma in ten. There was one false negative case (described below). Of the ten patients diagnosed with lymphoma by EBUS-TBNA, three patients were diagnosed with Hodgkin lymphoma independently by EBUS-TBNA, of whom one had a prior history of Hodgkin lymphoma (patient 8). One patient with Hodgkin lymphoma was initially diagnosed on EBUS-TBNA based on the cytologic finding of Reed-Sternberg cells (Patient 14, Figure 2), but went on to undergo a mediastinoscopy for further subclassification, with an ultimate diagnosis of Hodgkin lymphoma, nodular sclerosing type. The other patient with Hodgkin lymphoma (Patient 15) was diagnosed definitively by EBUS-TBNA and confirmed by bone marrow and endobronchial biopsies. The other eight patients had a final diagnosis of non-Hodgkin lymphoma. The method of diagnosis of lymphoma by EBUS-TBNA was a combination of cytology, immunohistochemistry with and without flow cytometry in six and four patients respectively (two also had histologic confirmation by biopsy (mediastinoscopy and endobronchial biopsy)) (Table 1).

In the fourteen patients without lymphoma, EBUS correctly diagnosed benign disease (non-caseating granuloma consistent with sarcoidosis) in eight patients, reactive hyperplasia or normal lymphoid tissue in five patients, and an inadequate sample was obtained in one patient (described below). The diagnostic accuracy of EBUS-TBNA in patients with suspected lymphoma was 24/25 (96%) and the sensitivity, specificity positive and negative predictive values were 90.9%, 100%, 100%, and 92.6% respectively (Table 3).

Performance of EBUS-TBNA according to clinical presentation: patients with a prior history of lymphoma (n=13)

Of the 25 patients who underwent EBUS-TBNA for a suspicion of lymphoma, thirteen patients had a prior lymphoma history. Eleven were in remission, one had an autologous bone marrow transplant four months prior and one had active mycosis fungoides. The
mean period of remission in the eleven patients was 2.6 years and they were referred for EBUS-TBNA for new or recurrent mediastinal lymph node enlargement. EBUS-TBNA diagnosed lymphoma recurrence in eight of these eleven patients; there was no evidence of progressive lymphadenopathy on follow-up of the other three patients, and the EBUS-TBNA findings were considered true negative.

One patient with a history of Hodgkins lymphoma who had received an autologous bone marrow transplant with conditioning chemotherapy (melphalan and busulphan) four months earlier presented with cough and pulmonary infiltrates. Tissue sample by EBUS-TBNA was inadequate, due to a dense fibrous capsule surrounding lymph nodes at mediastinal stations 7 and 4R that resisted penetration with the cytology needle. A presumptive diagnosis of busulphan induced pneumonitis was made with response to steroid treatment and stable lymphadenopathy on CT eight months later. The other patient was undergoing treatment for mycosis fungoides and EBUS-TBNA identified reactive lymph node hyperplasia; consistent with clinical and radiological follow-up.

**Performance of EBUS-TBNA according to clinical presentation: patients with no prior history of lymphoma (n=12)**

Twelve of the patients in the study group presented with mediastinal lymphadenopathy with no prior history of lymphoma, but in whom lymphoma was suspected. EBUS-TBNA revealed the diagnosis of Hodgkins lymphoma in two patients, benign lymph node hyperplasia in three patients (transbronchial biopsies were positive for non-caseating granuloma in one patient), and non-caseating granuloma consistent with sarcoidosis in six patients.

One other patient presented with right flank pain and both mediastinal and mesenteric lymphadenopathy. Both EBUS-TBNA and CT-guided biopsy of the mesenteric adenopathy were performed; although the CT-guided biopsy diagnosed mesenteric non-Hodgkins B-cell lymphoma (largest node: 18 mm short axis diameter), EBUS-TBNA revealed normal lymphoid tissue in the mediastinum (subcarinal lymph node station 7: 16 mm short axis diameter). Two subsequent PET scans showed no FDG-avid disease in the mediastinum. The patient declined systemic chemotherapy; at 8 months of follow-up, there had been a progressive increase in size in mesenteric lymphadenopathy but interestingly, the mediastinal lymphadenopathy had reduced in size. Despite this clear discrepancy in the clinical course of the mediastinal adenopathy, for purposes of this analysis, we considered the EBUS-TBNA result a false negative for mediastinal lymphoma.

**Complications**

No complications were identified from the procedure or anesthesia. All procedures were performed as outpatient cases and all patients were discharged after brief observation, as per institutional protocol.
Discussion

Our findings show that EBUS-TBNA is a safe and diagnostically accurate technique for the diagnosis of lymphoma in patients with mediastinal lymphadenopathy. Obtaining adequate pathological specimens is vital in the definitive diagnosis of lymphoma. In patients with mediastinal adenopathy, including those with suspected isolated mediastinal lymphoma, mediastinoscopy has been the procedure of choice to obtain tissue over the past three decades [19]. However, mediastinoscopy does not allow access to peri-hilar lymph nodes and it is technically very difficult to repeat the mediastinoscopy on the same patient due to post-procedural fibrosis. This becomes particularly important in previously treated lymphoma patients with recurrent mediastinal adenopathy. It is also a surgical procedure with attendant risks and complications. In several large series of patients with mediastinal adenopathy undergoing lung cancer staging, definitive diagnosis by mediastinoscopy was achieved in approximately 85-95% of cases with false negatives rates of 5-8% [19-21]. Significant complications occurred in 1-5% [19-21]. Thus, newer, less invasive modalities to obtain pathological specimens have been developed including CT guided transthoracic needle biopsy, and transbronchial and transesophageal lymph node sampling.

The yield of TBNA in patients with lymphoma has not been well defined. We reviewed the literature and identified a number of series reporting the yield of TBNA in mediastinal adenopathy using a variety of cytology (21-22 gauge) and histology needles (19 gauge) [5-8]. These reports included 8 patients with mediastinal adenopathy secondary to lymphoma of which TBNA missed the diagnosis in over 60% [5-7]. In contrast, the performance of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) (22 gauge needle) in one study of 23 patients in lymphoma was reported with sensitivity, specificity and accuracy of 74%, 93% and 81% [22]. These authors also asserted that the addition of flow cytometry and immunohistochemistry improved the yield of EUS-FNA. A more recent study also suggested that the addition of histological sampling using a 19-gauge needle to EUS-FNA in patients with mediastinal adenopathy without ROSE improved the diagnosis of lymphoma [23]. The diagnostic reach of EUS-FNA is however limited to retrotracheal (station 3), left lower paratracheal (station 4L), subcarinal (station 7), lower paraesophageal (station 8) and pulmonary ligament (station 9) lymph nodes.

EBUS-TBNA on the other hand allows access to the upper and lower paratracheal (stations 1, 2, 3P and 4), subcarinal (station 7), peribronchial and perihilar (stations 10, 11 and 12) lymph nodes [17]. Indeed, EUS-FNA and EBUS TBNA appear to be complementary and combining both approaches has been shown to improve the diagnostic yield in patients with mediastinal adenopathy [24]. Although this report is limited by retrospection and size, as far as we are aware, this report is the first published analysis of the diagnostic utility of EBUS-TBNA in patients with mediastinal lymphadenopathy suspected to be due to lymphoma. Our sensitivity, specificity and accuracy of EBUS-TBNA in patients with mediastinal lymphoma are comparable to prior experience with EUS-FNA [24]. In fact, it could be argued that the one false negative result by EBUS-TBNA result (patient 16) we identified may in fact represent a true negative result based on the fact the patients’ mediastinal lymphadenopathy decreased in size in the absence of any chemotherapy. Lymphoma was
diagnosed by EBUS-TBNA more often in patients with a prior history of lymphoma, but
this appears to be related more to the disease prevalence in the subgroup rather than any
limitation attributable to the technique. Overall, the diagnostic yield of EBUS-TBNA for
mediastinal lymphoma was substantially better than the historical data for conventional
TBNA and particularly for non Hodgkin's lymphoma, may even be comparable to the
90% sensitivity reported for mediastinoscopy [25].
Since the commencement of our EBUS program, we have routinely used flow cytometry
and immunohistochemistry in suspected lymphoma on the basis of prior published
experience with EUS-FNA and our data suggests that this is a reasonable clinical
approach [22]. Unlike EUS-FNA, a 19-gauge trucut biopsy needle is not available for
real time EBUS-TBNA at the present time and it is plausible that this additional
histologic sampling will improve the yield and sensitivity of EBUS-TBNA in patients
with mediastinal adenopathy secondary to lymphoma.
In conclusion, in patients with mediastinal adenopathy and suspicion of lymphoma,
EBUS-TBNA with flow cytometry and immunohistochemistry analysis is a safe,
minimally invasive and highly accurate technique that may decrease the need for more
invasive procedures such as mediastinoscopy.

Competing Interests
There are no sources of actual or potential conflict of interest for any authors in the
preparation or submission of this manuscript.
References

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<th>Node Characteristics</th>
<th>EBUS Result (n=#stations)</th>
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<td>8 months:‡ CT Reduction in size</td>
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Table 1

Clinical characteristics, radiographic findings, endobronchial ultrasound transbronchial needle aspiration results and method of final diagnosis of 25 patients with mediastinal adenopathy with a suspicion of lymphoma.

* Atypical cells consistent with follicular lymphoma confirmed by flow cytometry and immunohistochemistry from supraclavicular lymph node aspiration.

** Repeat CT six weeks later identified a new posterior mediastinal mass which also positive for lymphoma by CT guided fine needle aspiration

† Confirmed by mediastinoscopy

‡ Bone marrow and endobronchial biopsies also positive for Hodgkins lymphoma.

§ Despite no lymphoma therapy

¶ Oral EBV associated lymphoproliferative lesion (Spontaneous resolution)

‖ Granuloma identified by other diagnostic test.

BMT= bone marrow transplant, C= cytology, EBUS= endobronchial ultrasound, F= female, Fl= flow cytometry H= histology, I=immunohistochemistry, M= male, N/A= not applicable, NHL= non-Hodgkins lymphoma, NSCLC= non-small cell lung cancer, n/p=not performed, Max PET SUV= Maximum positron emission tomography standardized uptake value for lymph nodes sampled, yrs=years
Table 2
Summary statistics for lymph node size (mm) by endobronchial ultrasound (EBUS) and computed tomography and positron emission tomography standardized uptake values in 25 patients with mediastinal lymphadenopathy who underwent EBUS guided transbronchial biopsy for a suspicion of lymphoma.
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<tr>
<td>EBUS-TBNA Negative</td>
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<td>Adequate Lymphoid Tissue=</td>
<td>24/25 (96%)*</td>
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<td>Sensitivity=</td>
<td>90.9%, 95% CI</td>
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<td>Specificity=</td>
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<td>Negative Predictive Value=</td>
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Table 3
The performance of endobronchial ultrasound transbronchial needle aspiration in a population of 25 patients with suspected lymphoma.
*One patient with inadequate sample excluded from 2X2 table.
Suspected lymphoma
EBUS-TBNA
N=25

Lymphoma
N=10

No Lymphoma
N=14

Inadequate Sample
N=1

Non-caseating granuloma
N=7

Other Benign Histology
Reactive Hyperplasia
N=4
Normal N=3

Lymphoma diagnosed
By other test
(False Negative)
N=1

Figure 1
Patients suspected with lymphoma undergoing endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA).
Figure 2
Radiographic, endobronchial ultrasound, and pathologic images of a 49-year-old male with no significant past medical history, who underwent endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) for the investigation of idiopathic mediastinal lymphadenopathy.
2a. Axial fused PET/CT image show intense uptake of FDG within the enlarged lymph nodes (stations 7 (arrow head) and 11R (arrow)), suspicious for malignancy.
2b. EBUS image shows an enlarged station 7 lymph node (arrow).
2c, d. Fine needle aspirate by EBUS-TBNA shows atypical lymphoid population favoring Hodgkins lymphoma with two Reed-Sternberg variants (2c. arrows) and a multinucleated “lacunar variant” Reed Sternberg cell (2d. arrow). Diff-Quik® stain (400x).
Endobronchial Ultrasound Guided Transbronchial Needle Aspiration in the Diagnosis of Lymphoma.

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