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The role for endobronchial biopsy in the era of endobronchial ultrasound guided transbronchial needle aspiration for the diagnosis of sarcoidosis: A single center experience

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Abstract. *Background and aim:* Endobronchial biopsy (EBBX) has been reported to increase diagnostic yield for pulmonary sarcoidosis. The purpose of this study is to investigate the diagnostic yield for EBBX following endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA). *Methods:* We identified a cohort of patients in the University of Minnesota Sarcoidosis Registry who had EBBx and EBUS-TBNA as part of workup for abnormal chest imaging. Data regarding demographics, biopsy approach and technique were recorded. *Results:* Our cohort included 37 patients (53.24±9.5, Male, 22±0.57; 3.8% were African American). In these patients who had EBBX, EBUS-TBNA was performed in 100% of patients and TBBX was performed in 2 patients (5%). EBBX was positive in 9 patients (24%) and EBUS-TBNA was positive in 34 patients (92%). TBBX was diagnostic in one of two patients. EBBX was the only diagnostic tissue in 3 of the 37 patients (8%). *Conclusion:* The diagnostic yield of EBBX is lower than previously reported, with only 8% of EBBXs demonstrating granulomatous inflammation. However, instrumentation used for obtaining EBBX as well as the presence of visible lesions does influence the diagnostic yield. Studies with adequate power are needed before implementing changes in clinical practice. When performed alongside EBUS-TBNA, EBBX did not significantly add to the diagnostic yield in sarcoidosis unless visible lesions were observed.

Key words: sarcoidosis, lymphadenopathy, interstitial lung disease, EBUS-TBNA, interventional pulmonology

Introduction

In the US, the prevalence of incidental mediastinal lymphadenopathy (MLA) is 0.15-3%. Sarcoidosis is the most common inflammatory cause for MLA and among patients with sarcoidosis, 75-90% will demonstrate MLA (1). Sarcoidosis presents as a clinical spectrum ranging from asymptomatic state to one that is progressive or relapsing. Although not standardized, the diagnosis is primarily based on finding non-caseating granulomatous inflammation in one or more tissue samples, exclusion of alternative causes of granulomatous disease and a compatible clinical presentation. The traditional first-line approach for a histopathological diagnosis was transbronchial forceps biopsy (TBBX) which yielded a diagnostic yield of 50-80% depending on the extent of parenchymal involvement (2-4). To date, bronchoalveolar lavage (BAL), endobronchial biopsy (EBBX), blind transbronchial needle aspiration (TBNA) and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) have been

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studies with a single and combined approach in patients suspected of sarcoidosis. In particular, EBBX has commonly been performed as an additive technique to TBBX as it has been shown to increase the diagnostic yield in patients with or without visible endobronchial involvement (5, 6). Currently, EBUS-TBNA has replaced TBBX as a technique for the diagnosis of sarcoidosis given a diagnostic yield of 87% (95% CI, 94-91%) for non-caseating granulomatous inflammation and low risk for pneumothorax (7-9). To date, there are no published studies to determine whether or not EBBX improves diagnostic yield in the era of EBUS-TBNA. The aim of this study is to investigate the diagnostic yield of EBUS-TBNA and the additive benefit with EBBX in a cohort of sarcoid patients.

Methods

Patient demographics and clinical characteristics and procedural approach, technique and results were summarized in Table 1. This was a single-center retrospective cohort study conducted at the University of Minnesota's Sarcoidosis Center of Excellence, Minneapolis, MN. The human subjects research committee of the local institutional review board approved the study protocol.

We identified a cohort of sarcoid patients who underwent flexible bronchoscopy with EBUS-TBNA and EBBX in the University of Minnesota Sarcoidosis Registry were used for this study. All patients in this registry have histologically evidence of granulomatous inflammation, a compatible clinical presentation, and exclusion of an alternative diagnosis confirming a diagnosis of sarcoidosis. A biopsy was regarded as positive if pathology demonstrated non-caseating granulomatous inflammation (Figure 1) for which no specific cause was present. Endobronchial lesions were considered either visible or non-visible based on nodular or cobblestoning appearance of the

Table 1. Demographic and Clinical Characteristics of the cases (n=37).

	n (%) or mean ± SD
Age (at biopsy)	53.24±9.5
Male	22±0.57
Race	
Caucasian	34 (92)
African American	3 (8)
PFT	
Normal	29±0.78
Obstructive	6±0.16
Restrictive	2±0.05
Smoking Status	
Never	22 (57)
Current	5 (14)
Former	10 (27)
CT findings (35/36)	
MLA only	16 (38)
MLA+perilymphatic nodules	21 (57)
CD4/CD8	3.92±2.11

Data expressed as mean and standard deviations or n (%). Abbreviations: PFT: Pulmonary function test; CT: Chest computed tomography; MLA: Lymphadenopathy; EBUS-TBNA: Endobronchial ultrasound with transbronchial needle aspiration; LN: Lymph node; TBBX: Transbronchial biopsy; EBBX: Endobronchial biopsy; ROSE: Rapid onsite evaluation; FNA: Fine needle aspiration.

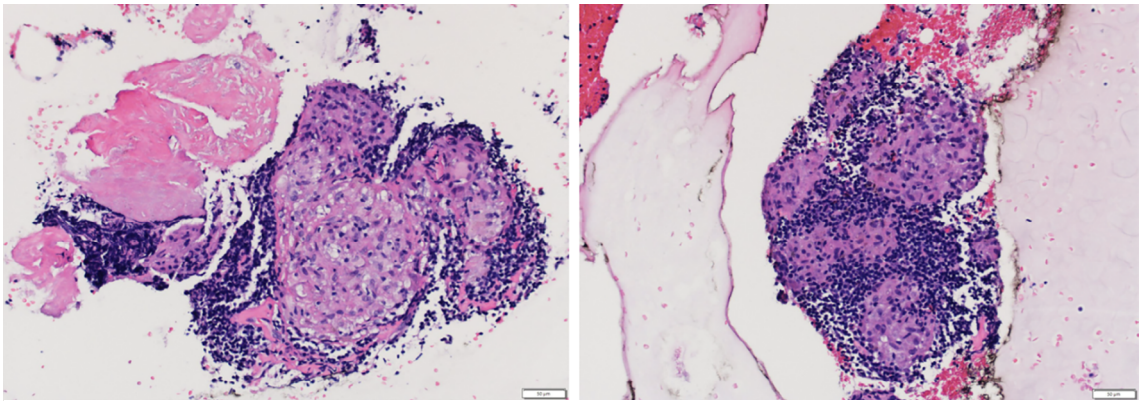

Figure 1. Histopathological specimens acquired from EBUS-TBNA of a mediastinal lymph node illustrating non-necrotizing granulomas in the cytology specimen. Images were from our cohort and taken at 200x (a scale bar is included in each image).

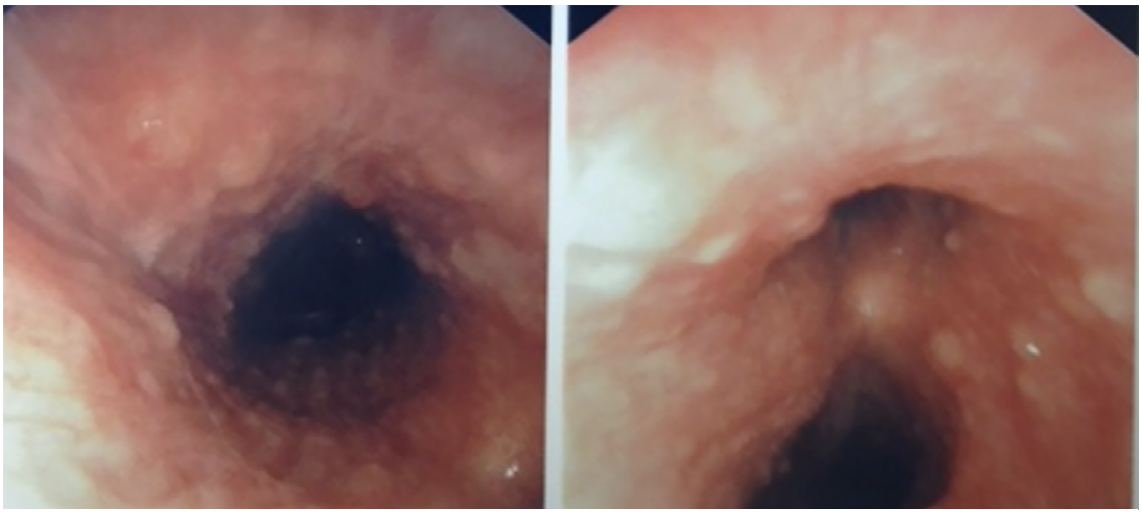

Figure 2. Classic "cobblestoning" finding demonstrated on white light bronchoscopy of the right mainstem and right upper lobe take-off in a patient diagnosed with sarcoidosis. Images were from our cohort and taken with an Olympus bronchoscope (BF-H190 model).

airway mucosa (Figure 2). The database has patients from 1994 to present. Each patient underwent a standardized workup for sarcoidosis which included imaging and pulmonary function testing. Variables used to construct the demographic profile included age, gender, ethnicity, smoking status, pulmonary function testing (normal, obstructive, restrictive, mixed), CT findings (normal, MLA, or presence of perilymphatic lung nodules), and CD4/CD8 ratio from bronchoalveolar lavage. In this report, we present data at the time of diagnosis and thus majority of the cases are not on any treatment. The lines of treatment in our cohort are described in a prior publication (10).

Statistical Analysis: Patient demographics and clinical characteristics and procedural approach, technique and results were summarized and presented using descriptive statistics. Analyses were performed using an updated version of Microsoft Excel. A diagnostic odds ratio (DOR) was calculated to demonstrate diagnostic accuracy between procedure types (11).

Results

A total of 37 sarcoid patients were identified as having an EBBX and EBUS-TBNA as part of their diagnostic evaluation (Mean Age, 53.24±9.5, Male, 22±0.57). There were only three African Americans in the subgroup of sarcoid patients. Pulmonary function testing was largely normal (29, 78%) with six obstructive (16%) and two restrictive (5%). Most patients were non-smokers (22, 57%). The most common chest CT finding was MLA and perilymphatic nodules (21, 57%) than MLA alone (16, 38%). The CD4/CD8 ratio was 3.92±2.11.

Procedural characteristics are presented in Table 2. All patients underwent EBBX and EBUS-TBNA as part of the diagnostic workup. EBUS-TBNA was performed using 22G FNA needle in all patients. An average of 2.62±1.07 lymph nodes were biopsied per case and adequacy for lymph node was 91.8% by ROSE. The diagnostic yield for EBUS-TBNA and EBBX for non-caseating granulomas was 92% (34/37) and 24% (9/37); respectively. A diagnosis with EBUS-TBNA+EBBX occurred in 9 patients; however, EBBX was diagnostic only when visible lesions were present and made the diagnosis alone in only 3 patients (8%).

In this subgroup, TBBX was performed when EBUS-TBNA was unable to be performed due to inability to pass the needle into the LN. This occurred in two patients and diagnostic in only one who had changes in their lung parenchyma.

Discussion

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, most commonly affecting the lungs and intrathoracic lymph nodes. The

Table 2. Procedural Characteristics and diagnostic yield of various procedures performed via bronchoscopy.

	n (%) or mean ± SD
EBUS-TBNA (n=37)	
22G FNA Needle	37 (100)
# LN's Biopsied	2.62±1.06
LN Adequacy by ROSE	34 (91.8)
Diagnostic yield	34 (91.8)
Non-diagnostic EBUS-TBNA	3 (8.2)
Inability to pass the needle	3 (100)
EBBX (n=37)	
Forceps	35 (95)
1.9 mm cryoprobe	2 (5)
Diagnostic yield with positive EBUS-TBNA	9 (24)
Diagnostic yield with negative EBUS-TBNA	3 (8)
Diagnostic yield with visible lesions	9 (100)
Diagnostic yield without visible lesions	0
TBBX (n=2)	
Diagnostic with abnormal CT	1 (50)
Diagnostic with normal CT	0

Data expressed as mean and standard deviations or n (%). Abbreviations: PFT: Pulmonary function test; CT: Chest computed tomography; MLA: Lymphadenopathy; EBUS-TBNA: Endobronchial ultrasound with transbronchial needle aspiration; LN: Lymph node; TBBX: Transbronchial biopsy; EBBX: Endobronchial biopsy; ROSE: Rapid onsite evaluation; FNA: Fine needle aspiration.

diagnosis of sarcoidosis is made on a combination of compatible clinicoradiographic findings and demonstration of non-caseating epithelioid cell granulomas in the absence of a competing diagnosis (12-16). In the pulmonary setting, typical parenchymal findings and mediastinal and/or hilar lymphadenopathy have been conventionally approached using flexible bronchoscopy techniques including TBBX, EBBX, and BAL. These procedures alone or in combination have limitations in terms of diagnostic yield and safety besides the implication on both time and cost. More recently, EBUS-TBNA has emerged as the recommended initial sampling procedure by the American Thoracic Society for suspected sarcoidosis (1). Despite an appreciable learning curve, the advantages of EBUS-TBNA over traditional technique is in its higher diagnostic yield and safety profile. However, as much as there has been an improvement in diagnostic yield from advances in instrumentation, it is unclear if additive procedures, in particular EBBX, to EBUS-TBNA can improve the diagnostic yield for sarcoidosis even further (10).

The exact sequence of the histological approach in the workup of sarcoidosis remains unclear, and only a few studies have explored the comparative and additive benefit of different sampling procedures. Shorr et al performed TBBX and EBBX in 34 patients where EBBX findings were positive in 61.8% while TBBX was positive in 58.8% of patients (5). They report that the addition of EBBX increased the yield of sarcoidosis by 20.6%. Moreover, noted that EBBX provided diagnostic tissue in 30% of patients with normal appearing endobronchial mucosa. These findings were similarly reported in a second study by Goktalay and colleagues (6). In 39 patients who underwent blind TBNA with combined EBBX, they reported that EBBX made the diagnosis alone in 18.6% of patients and a high rate (15.3%) for EBBX being positive in patients with normal bronchial mucosa. In contrast, Goyal and colleagues found that the highest diagnostic yield with EBBX were when mucosal findings were present (17). In their study, they prospectively analyzed the diagnostic yield among different techniques performed at their institution. Interestingly, they performed a combination of TBBX, EBBX and EBUS-TBNA in 22 patients and found no additive benefit for EBBX. Comparatively, our study found a lower additive benefit for EBBX (8% vs 20.6% and 18.6%) when combined with EBUS-TBNA. Additionally, we found that the determining factor for EBBX diagnosis was whether or not visible lesions were present. In patients who had normal endobronchial mucosa, none of the EBBX yielded a diagnosis.

To our knowledge, this current study is unique as it demonstrates the diagnostic yield of EBBX in patients who were diagnosed with sarcoid exclusively by EBUS-TBNA. The results of this study reiterate that flexible bronchoscopy with EBUS-TBNA remains a powerful diagnostic tool (91.8% in the current study) for suspected cases of sarcoidosis. Our main finding is when EBUS-TBNA is successful and diagnostic by ROSE, the additive effects of EBBX were low especially when visible lesions are absent.

There are several limitations to this study. The data are applicable to selected patients who have undergone EBUS-TBNA and EBBX for the diagnosis of sarcoidosis; therefore, may not be limited in generality. This was a retrospective study and patients were selected through a database from a sarcoid

center of excellence institution which, inherently, is subjective to bias. The primary selection criteria were those who had EBUS-TBNA and EBBX, therefore, a fair comparison cannot be made in those patients who had other conventional bronchoscopic procedures as part of the diagnostic workup. Despite these limitations, we feel that our findings are noteworthy and novel when answering the question of whether or not EBBX should be performed in the era of EBUS-TBNA.

Conclusion

In conclusion, data informing expert opinion on performing EBBX concomitantly with EBUS-TBNA is lacking. The existing data implies that EBBX should increase diagnostic yield for pulmonary sarcoidosis following EBUS-TBNA or TBBX; hence, should be routinely performed. Our experience questions the diagnostic impact of EBBX during EBUS-TBNA and more robust studies are needed to confirm our findings.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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