Original Article

Utility of endobronchial ultrasound-guided transbronchial needle aspiration in HIV-infected patients with undiagnosed intrathoracic lymphadenopathy

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ABSTRACT

Background: Intrathoracic lymphadenopathy is a common problem in people living with human immunodeficiency virus (PLHIV). There is, however, limited literature on the utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in these patients. Herein, we describe our experience with EBUS-TBNA in PLHIV. **Materials and Methods:** This is a retrospective study of all PLHIV who underwent EBUS-TBNA for the evaluation of intrathoracic lymphadenopathy. We also perform a systematic review of the English literature for studies reporting the yield of EBUS-TBNA in PLHIV. **Results:** During the study, 1733 EBUS procedures were performed. Among them, 22 (1.3%) were performed in PLHIV. The median age of the individuals (18.2% women) was 46 years. The median CD4 count was 144 cells/mm^3. The common lymph node stations involved were station 7, 4R, and 11 L. On endosonographic examination, heterogeneous appearance and coagulation necrosis sign were observed in 14 (63.6%) and 11 (50%) individuals, respectively. EBUS-TBNA was diagnostic in 17 (77.3%) individuals, with tuberculosis being the most common diagnosis (68.2%). There were no major complications related to the procedure. Our systematic review yielded two studies describing the use of EBUS-TBNA in PLHIV. The mean diagnostic yield of EBUS-TBNA was 71% (95% confidence interval: 56–84). **Conclusions:** EBUS-TBNA is a safe and useful procedure in the evaluation of intrathoracic lymphadenopathy in PLHIV.

KEY WORDS: AIDS, antiretroviral therapy, endobronchial ultrasound, transbronchial needle aspiration, tuberculosis

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INTRODUCTION

Intrathoracic lymphadenopathy is frequently encountered in people living with human immunodeficiency virus (PLHIV).[1,2] The common etiologies of intrathoracic lymphadenopathy include tuberculosis, lymphoma, sarcoidosis, and lung cancer. In addition to these, several unusual causes can be encountered in HIV-infected individuals including nontubercular mycobacterial infection, histoplasmosis, cryptococcosis, Kaposi's sarcoma, Castleman's disease, and the immune reconstitution inflammatory syndrome.[3] Hence, establishing an accurate diagnosis is paramount for appropriate treatment.

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The evaluation of intrathoracic lymphadenopathy can be performed using computed tomography (CT)-guided transthoracic needle aspiration, conventional transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided TBNA (EBUS-TBNA), endoscopic ultrasound (EUS)-guided fine-needle aspiration, and mediastinoscopy. Among these procedures, EBUS-TBNA is currently the preferred procedure as it is readily available, less invasive, and allows sampling of most intrathoracic lymph node stations under "direct" endosonographic vision.[4] There is, however, little information in the literature concerning the utility and safety of this technique in PLHIV. Herein, we describe our experience with EBUS-TBNA in the evaluation of intrathoracic lymphadenopathy in HIV-infected individuals.

MATERIALS AND METHODS

This was a retrospective analysis of individuals who underwent EBUS between July 2011 and November 2017 in the interventional bronchoscopy suite of our department. Procedural consent was obtained from all individuals before the procedure. The study protocol was approved by the institutional ethics committee, and the requirement for informed consent was waived off due to the retrospective nature of the study and anonymized participant data.

Subjects
Consecutive individuals with a diagnosis of HIV infection who underwent EBUS-TBNA for the evaluation of intrathoracic lymphadenopathy were included in this study.

Procedure
We performed EBUS transorally under local anesthesia and conscious sedation, with the patients lying in the supine posture. The convex probe EBUS scope (BF-UC 180F; Olympus Medical Systems, Japan) was used for the procedure, as previously described.[4-6] Sedation depth was assessed using the Ramsay sedation scale. The intensity of the individual's cough and the amount of airway secretions during the procedure were scored by the operator using visual analog scale on a horizontal line 100 mm in length, immediately after the procedure. All individuals were observed for complications (fever, chills, excessive cough, chest pain, bradycardia, hypotension, sustained hypoxemia, bleeding, and need for escalation of care) for at least 2 h after the procedure.

Lymph node stations were categorized according to the classification proposed by the International Association for the Study of Lung Cancer.[7] Lymph nodes at each station were assessed for the following characteristics using EBUS: short-axis diameter (in mm), shape (round or oval), margin (distinct or indistinct), echotexture (homogeneous or heterogeneous), presence of central hilar structure, presence of coagulation necrosis sign, and the presence of central intranodal vessels, as described previously.[8] Subsequently, TBNA was performed by either 21 or 22 G EBUS-TBNA needle (ViziShot, NA-201SX-4021/4022, Olympus Medical Systems, Japan).[9] Samples obtained by EBUS-TBNA were subjected to Xpert MTB/RIF assay, Ziehl–Neelsen staining for acid-fast bacilli, mycobacterial culture, fungal smear and culture, and cytological examination. Rapid on-site cytological evaluation was not available.

The TBNA sample was considered adequate if there was preponderance of lymphocytes (>40 lymphocytes/high-power field).[10] EBUS-TBNA was deemed as diagnostic, if it resulted in a specific diagnosis (tuberculosis, lymphoma, malignancy, sarcoidosis, or others). Additional procedures such as bronchoscopic alveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed, if indicated clinically.

Diagnosis
Tuberculosis was diagnosed if any of the followings was present: acid-fast bacilli on microscopy, granulomatous inflammation with or without necrosis on cytological examination along with the presence of acid-fast bacilli or positive Xpert MTB/RIF. Infection with other microorganisms (nontubercular mycobacteria and fungi) was diagnosed on the basis of appropriate microbiological tests (smear examination and/or culture). A diagnosis of sarcoidosis was made when there was noncaseating granuloma along with consistent clinicoradiological features after excluding conditions with similar presentation (specifically, tuberculosis and fungal infections). A diagnosis of malignancy was established by cytological examination and further typing was performed with immunocytochemistry. A final diagnosis was made based on all available investigations and after follow-up for at least 6 months.

Systematic review
We also performed a systematic review of the PubMed database (from inception till December 18, 2017) for studies reporting EBUS-TBNA in PLHIV using the free text terms: ("hiv" OR "aids" OR "human immunodeficiency virus" OR "acquired immunodeficiency syndrome" OR "antiretroviral therapy" OR "retrovirus") AND ("EBUS" OR "TBNA" OR "endobronchial ultrasound" OR "endosonography" OR "transbronchial needle aspiration"). We excluded studies reporting fewer than five individuals, studies utilizing EUS without EBUS, and studies that did not provide sufficient information for the calculation of the diagnostic yield.

Statistical analysis
Descriptive data are presented as number and percentage or mean (standard deviation) or median (interquartile range, IQR). Statistical analyses were performed utilizing the Statistical Package for the Social Sciences software (IBM SPSS Statistics, version 22; IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

RESULTS

During the study, 1733 individuals underwent EBUS-TBNA for the evaluation of intrathoracic lymphadenopathy and among them 22 (1.3%) had HIV infection [Table 1]. The median (IQR) age of the study population (18% females) was 46 (33–59) years. The median (IQR) CD4 count was 144 (68–288) cells/mm³. Only 4 (18%) individuals were on antiretroviral therapy (ART) at the time of the procedure. The most common clinical diagnosis was tuberculosis followed by lymphoma. The median (IQR) duration of the procedure was 15 min (14–20) [Table 2]. Midazolam and pentazocine were the most commonly used agents for sedation [Table 2]. The median (IQR) Ramsay score was 2 (2–2). A total of 42 lymph nodes were sampled with a median (IQR) of 2 (1–2) nodes per patient and a median (IQR) of 2 (2–3) passes per node.

The common lymph node stations involved were station 7 (81.8%), station 4R (63.6%), and station 11 L (22.7%). The median (IQR) short axis diameter of the involved nodes was 20 (15–28) mm on CT of the chest and 18.4 (14.2–22.9) mm on EBUS evaluation. On endosonographic examination, most lymph nodes were oval (88.1%), had distinct margins (97.6%), with a heterogeneous appearance (57.1%). The lymph node aspirate revealed pus on visual inspection in six individuals (ten lymph nodes), and all of them were diagnosed with tuberculosis eventually. Of the lymph nodes from which pus was aspirated, 80% had a heterogeneous appearance and had the coagulation necrosis sign on EBUS examination. There were no complications during the procedure.

EBUS-TBNA could establish the diagnosis in 17 (77.3%) cases and the most common diagnosis was tuberculosis (68.2%) [Table 2]. In 5 individuals (clinical suspicion of tuberculosis [*n* = 4] and lymphoma [*n* = 1]), the lymph node aspirate was nondiagnostic. Two of these individuals responded to empiric antituberculosis therapy (ATT). Two others remained asymptomatic with

ART alone after follow-up for more than 1 year and were assumed to have nonspecific lymphadenitis. The fifth in whom EBUS was nondiagnostic had a clinical suspicion of lymphoma; however, the final diagnosis remained unknown as the patient expired 1 month after the procedure. Among the individuals with tuberculosis, granuloma formation was observed in only 3 (20%) individuals. However, necrotizing inflammation was observed in 12 (80%) individuals. Staining for acid-fast bacilli and/or mycobacterial culture was positive in 13 (86.7%) individuals.

Our systematic review yielded 61 studies of which two studies met the inclusion criteria [Table 3]. Both the studies were retrospective in nature. The median

Table 1: Baseline characteristics of the study participants (*n*=22)

Characteristic	Total
Age (years)	46 (33-59)
Females, *n* (%)	4 (18.2)
CD4 count (cells/mm³)	144 (68-288)
ART initiated at the time of EBUS, *n* (%)	4 (18.2)
Lymph node stations involved, *n* (%)	42 (100)
4R	14 (63.6)
4L	2 (9.1)
7	18 (81.8)
10R	2 (9.1)
11R	1 (4.5)
11L	5 (22.7)
Clinical diagnosis, *n* (%)	
Tuberculosis	21 (95.5)
Lymphoma	1 (4.5)

All values are presented as median (interquartile range) unless specified. ART: Antiretroviral therapy, EBUS: Endobronchial ultrasound

Table 2: Procedure details and final diagnosis (*n*=22)

Characteristic	Total
Duration of EBUS procedure (min)	15 (14-20)
Sedative agents, *n* (%)	
Atropine and promethazine	22 (100)
Midazolam	14 (63.6)
Dexmedetomidine	8 (36.4)
Fentanyl	10 (45.5)
Pentazocine	12 (54.5)
Ramsay sedation scale score	2 (2-2)
VAS for secretions (mm)	13 (4.5-37)
VAS for cough (mm)	14 (5.5-27.0)
Needle size 21G, *n* (%)	10/19 (52.6)
Needle size 22G, *n* (%)	9/19 (47.4)
Suction applied for TBNA (cm of air)	10 (10-10)
Number of lymph nodes aspirated (%)	42 (100)
Number of nodes sampled per patient	2 (1-2)
Number of passes per node	2 (2-3)
Number of jabs per pass	20 (10-20)
Lymph node size	
Short-axis diameter on CT (mm)	20 (15-28)
Short-axis diameter on EBUS (mm)	18.4 (14.2-22.9)
EBUS characteristics (among sampled nodes), *n* (%)	
Oval shape	20/22 (90.9) (37/42 [88.1])
Distinct margin	21/22 (95.5) (41/42 [97.6])
Heterogeneous appearance	14/22 (63.6) (24/42 [57.1])
Central hilar structure	4/22 (18.2) (6/36 [14.3])
Coagulation necrosis sign	11/22 (50) (17/42 [40.5])
Central intranodal vessels	5/19 (26.3) (5/36 [13.9])
Visual appearance of aspirate (among sampled nodes), *n* (%)	
Lymphoid	13/18 (72.2) (22/35 [62.9])
Pus	6/18 (33.3) (10/35 [28.6])
Blood	2/18 (11.1) (3/35 [8.6])
Diagnosis after EBUS-TBNA, *n* (%)	17 (77.3)
Tuberculosis	15 (68.2)
Lung cancer	1 (4.5)
Lymphoma	1 (4.5)
Unknown	5 (22.7)
Final diagnosis*, *n* (%)	21 (95.5)
Tuberculosis	17 (77.3)
Lung cancer	1 (4.5)
Lymphoma	1 (4.5)
Nonspecific lymphadenitis	2 (9.1)
Unknown	1 (4.5)

*With all available clinical details and investigations including follow-up data. All values are presented as median (interquartile range) unless specified. CT: Computed tomography, EBUS: Endobronchial ultrasound, TBNA: Transbronchial needle aspiration, VAS: Visual analog scale

Table 3: Summary of studies describing endobronchial ultrasound-transbronchial needle aspiration in human immunodeficiency virus-infected individuals

	Han *et al.*	Sánchez-Cabral *et al.*	Current study
n	9	43	22
Country	Singapore	Mexico	India
Methodology	Retrospective	Retrospective	Retrospective
Anesthesia	Local anesthesia with conscious sedation	General anesthesia	Local anesthesia with conscious sedation
Median age (years)	49	35	46
Women (%)	11.1	20.9	18.2
ART initiated (%)	-	-	18.2
CD4 count (cells/mm³), median	127	-	144
Diagnosis by EBUS			
Final diagnosis*,† (%)			
Tuberculosis	33.3	27.9	77.3
Nontuberculous mycobacterial infection	22.2	9.3	0
Fungal infection	0	23.3	0
Other infections	0	16.3	0
Lung cancer	11.1	4.7	4.5
Lymphoma	11.1	4.7	4.5
Other malignancy	0	7.0	0
Other benign condition	0	11.6	0
Nonspecific lymphadenitis	22.2	0	9.1
Unknown	0	9.3	4.5
TBNA diagnostic yield (%)	88.9	60.5	77.3
Complications, *n* (%)	1 (11.1) (death)‡	1 (2.3) (pneumomediastinum)	0 (0)

*Utilizing all available modalities, †Some individuals had multiple diagnoses, ‡Suspected acute coronary event 18 h after an uneventful procedure. ART: Antiretroviral therapy, EBUS: Endobronchial ultrasound, TBNA: Transbronchial needle aspiration

CD4 count in these studies was <150 cells/mm³ with tuberculosis being the most common diagnosis. The mean diagnostic yield of EBUS-TBNA (3 studies [*n* = 74], including the current study) was 71% (95% confidence interval: 56–84). There was one death 18 h after an uneventful procedure that was attributed to an acute coronary event.[11] One patient had pneumomediastinum following the EBUS procedure.[12]

DISCUSSION

The results of our study suggest that undiagnosed mediastinal lymphadenopathy in PLHIV is an uncommon indication for EBUS-TBNA. EBUS-TBNA has a reasonable diagnostic yield in this setting with the procedure diagnostic in about 77% of the individuals.

Majority of patients in the current study were diagnosed with tuberculosis (77.3%) unlike previous studies where infection with nontubercular mycobacteria and fungi were also frequent. This is due to the high burden of tuberculosis in our country. All individuals in whom pus was aspirated during the TBNA had a final diagnosis of tuberculosis. Interestingly, a majority (80%) of these lymph nodes had the coagulation necrosis sign. Although the coagulation necrosis sign has been described in other conditions such as lung cancer,[13] the presence of this sign along with the aspiration of pus in the setting of HIV infection is highly suggestive of tuberculosis, especially in a country with high burden of tuberculosis.

In individuals with a diagnosis of tuberculosis, granuloma formation was uncommon (20%), while necrotizing inflammation (80%) and microbiological evidence of tuberculosis (positive acid-fast stain and/or mycobacterial culture) (86.7%) were more common. In contrast in an earlier publication of 47 individuals with tuberculosis who were diagnosed with tuberculosis by EBUS-TBNA at our center, necrotizing granulomatous inflammation was observed in 33 individuals (70%), while stain for acid-fast bacilli and/or mycobacterial culture was positive in only 12 (25.5%) individuals.[8] Granuloma formation is uncommon in HIV-infected individuals as they do not mount adequate immune response to the infection. It is also well known that the presence of acid-fast bacilli is more common in individuals with necrotizing inflammation as compared to those with well-formed granulomas.[14]

It is a common practice to start empiric ATT in all patients with HIV presenting with mediastinal lymphadenopathy. In the current study, 4 (18.2%) of the 22 individuals with mediastinal lymph node enlargement had diagnosis other than tuberculosis, as identified by EBUS-TBNA and subsequent follow-up (one each had lung cancer and lymphoma while two had nonspecific lymphadenitis). In previous studies, other causes such as nontuberculous mycobacteria and fungal infections were established using EBUS-TBNA. In the setting of HIV infection, especially in patients receiving ART, ATT is associated with several issues including tolerance and drug interaction.[15,16] Therefore, it is imperative that the cause of the mediastinal adenopathy is identified and appropriately managed.

The diagnostic yield of EBUS-TBNA in PLHIV varied from 61% to 89%. In the largest study of EBUS-TBNA in PLHIV (*n* = 43), EBUS-TBNA had a diagnostic yield of

60.5% which increased to 86% and 88.4% on combining EBUS-TBNA with BAL or TBLB, respectively.[12] We did not perform BAL or TBLB because all our individuals presented with isolated mediastinal and/or hilar lymphadenopathy. In contrast, the overall diagnostic yield of EBUS-TBNA performed for intrathoracic lymphadenopathy in a non-HIV setting is about 50%–60%.[5,17] The higher yield in PLHIV is due to the frequent occurrence of infectious diseases, which can be diagnosed with multiple modalities including smear, culture, and nucleic acid amplification techniques. In fact, a diagnostic yield of EBUS-TBNA of about 94% has been reported in the setting of tuberculous mediastinal lymphadenopathy.[18,19]

TBNA can also be performed with the conventional method where lymph node aspiration is performed utilizing anatomical landmarks in the airway. In general, conventional TBNA provides lower diagnostic yield compared to EBUS-TBNA.[6,20,21] In a previous study of 41 PLHIV with intrathoracic lymphadenopathy, conventional TBNA yielded inadequate samples in 20% of the cases and had a diagnostic yield of only 52%.[22]

Finally, EBUS-TBNA is a safe procedure, even in HIV-infected patients with compromised immune status. Complications related to the procedure were mostly minor. None of the individuals developed mediastinitis after the procedure despite a low CD4 count.

Our study has a few limitations. This was a single-center retrospective study with a small sample size. Furthermore, in those patients with a nondiagnostic EBUS, other diagnostic tests including mediastinoscopy could not be performed as most of our patients were not willing for a second procedure. Only few patients could be included in the meta-analysis also, suggesting a need for future studies with larger sample size.

CONCLUSIONS

EBUS-TBNA was found to be a safe and useful procedure in the diagnosis of intrathoracic lymphadenopathy in HIV-infected patients.

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Conflicts of interest
There are no conflicts of interest.

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