Usefulness of Endobronchial Ultrasound in Patients with Human Immunodeficiency Virus Infection and Mediastinal Lymphadenopathy

Olivia Sánchez-Cabral Dina Martínez-Mendoza Sebastian Fernandez-Bussy
Esmeralda Aspuru-García Rosa Rivera-Rosales César Luna-Rivero
José Arturo Martínez-Orozco Gustavo Reyes-Terán

Unidad de Neumología Intervencionista, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico

Keywords

Endobronchial ultrasound-guided transbronchial needle aspiration · Human immunodeficiency virus · Mediastinal lymphadenopathy

Abstract

Background: There are few published studies about the usefulness of endobronchial ultrasound (EBUS) in patients infected with human immunodeficiency virus (HIV). The clinical spectrum of likely diseases in this population is varied and differs from patients not infected with HIV. **Objective:** The aim of this study was to measure the usefulness of EBUS-guided transbronchial needle aspiration (EBUS-TBNA) in HIV-infected patients with mediastinal lymphadenopathy. **Materials and Methods:** We conducted an observational, cross-sectional, retrospective, descriptive study on patients with HIV infection and mediastinal lymphadenopathy who underwent EBUS-TBNA between September 2014 and April 2016. The patients' final diagnosis, regardless of the sample from which it was obtained, was considered the positive gold standard, and the absence of diagnosis was the negative. The study measured diagnostic accuracy of bronchoalveolar lavage (BAL), transbronchial biopsy (TBB), and EBUS-

TBNA. **Results:** A total of 43 procedures were performed; 79.1% (34/43) of the patients were male, and the median age was 35 years (range, 22–66). The overall diagnostic yield including all types of samples was 90.7% (39/43); the yield of BAL was 50% (21), that of TBB 61.9% (26), and that of EBUS-TBNA was 60.5% (26). The combined yield of BAL with TBB was 69.8% (30); the yield of BAL with EBUS-TBNA was 86% (37) and that of TBB with EBUS-TBNA was 88.4% (38). The highest diagnostic accuracy was 97.7% for the combination of TBB and EBUS-TBNA. **Conclusions:** The most common infectious diagnoses were tuberculosis, with a higher diagnostic accuracy using EBUS-TBNA than BAL. With malignancies, both EBUS-TBNA and TBB were useful. EBUS-TBNA is a minimally invasive diagnostic tool that should be considered in these patients.

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Background

Lymph node biopsy via endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has proven useful in mediastinal lesions in patients not infected with human immunodeficiency virus (HIV).

EBUS-TBNA is recommended in the principal clinical practice guidelines as the procedure of choice in patients with suspected cancer-related lymphadenopathy, prior to mediastinoscopy [1, 2]. In benign cases, several studies involving non-HIV patients mainly with suspected tuberculosis and sarcoidosis have shown to be a procedure with a good diagnostic yield and a low complication rate [3–5].

There are few published studies describing the usefulness of EBUS in HIV-positive patients with mediastinal lymphadenopathy. The clinical spectrum in patients with HIV and lymphadenopathy is broad, and coinfections also are more common in this population. Some oncologic diseases especially prevalent among these patients, such as lymphoma and Kaposi sarcoma, can be diagnosed in the mediastinal lymph nodes. As life expectancy increases, so does the incidence of lung cancer in this population, so it will be even more important in differentiating diagnosis [6–8].

Materials and Methods

Objective

We conducted an observational, cross-sectional, retrospective, descriptive study to measure the diagnostic yield of EBUS-TBNA in patients with mediastinal lymphadenopathy and HIV infection.

Study Population

We included HIV-infected patients requiring bronchoscopy guided by EBUS after CT scans indicating mediastinal adenopathy and/or parenchymal lesions between September 2014 and April 2016. The study was approved by the Research and Ethics Committees of the Instituto Nacional de Enfermedades Respiratorias Ismaél Cosío Villegas of Mexico (code C72–16). Bronchoalveolar lavage (BAL), transbronchial biopsy (TBB), and EBUS-TBNA were performed, all under general anesthesia. Samples were subjected to pathology and microbiology analysis. Tests performed for BAL were cultures for pyogenic bacteria and fungi and Xpert MTB/RIF® assay for tuberculosis; for TBB, bacterial and fungal cultures, and for EBUS-TBNA only Xpert MTB/RIF for tuberculosis. The patient's final diagnosis was considered true positive independently of the sample origin, and negative was non-diagnosis. The study measured diagnosis yield (patients with a diagnosis out of all patients), sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of BAL, TBB, and EBUS-TBNA. The microbiology results include the bacterial and fungal cultures and Xpert MTB/RIF for tuberculosis.

Analysis

The variables were analyzed by distribution using descriptive statistics, and comparisons of diagnostic yield are expressed in proportions by sample type and type of diagnosis. The χ^2 test for difference was used to identify the statistically significant association between the diagnostic yield of each method and the gold standard. The IBM SPSS Statistics 21 statistical package and the OpenEpi program, version 3, were used.

Results

During the study period, 43 diagnostic bronchoscopies, including EBUS-TBNA, were performed on HIV-infected patients with mediastinal lymphadenopathy and/or parenchymal lesions. Of these, 79.1% (34/43) were male, the median age was 35 years (range, 22–66), and 65.1% (28/43) were hospital inpatients, while the rest were referred from other hospitals or were outpatients. The most common initial clinical diagnoses were pneumonia in 51.2% (22/43) and probable malignancy in 23.3% (10). Other known diagnoses before the bronchoscopic procedure were tuberculosis and Kaposi sarcoma, both in 4.6% (2/43), and diabetes in 2.3% (1/43), while 39.5% (17/43) had a history of smoking.

The average diameter of mediastinal nodes was 9.5 mm (± 2.7); all patients underwent EBUS-TBNA, although BAL and TBB were performed on only 97.7% (42/43). All EBUS-TBNA samples were sent for pathology evaluation, and 74.4% (32) underwent Xpert MTB/RIF. For BAL samples, 95.3% (41) were sent to pathology and also underwent Xpert MTB/RIF; 90.7% (39) underwent microbiology analysis. For TBB, 93.0% (40) and 90.7% (39) of the samples were sent to pathology and microbiology, respectively. All patients underwent Xpert MTB/RIF testing, via BAL and/or EBUS-TBNA.

Diagnostic Yield

An overall diagnostic yield, including all types of samples, of 90.7% (39/43) was obtained. Yield by sample type was: BAL 50% (21/43), TBB 61.9% (26/43), and EBUS-TBNA 60.5% (26/43), while pathology had a yield of 81.4% (35) and microbiology 60.5% (26). The combined yield of BAL and TBB was 69.8% (30), BAL with EBUS-TBNA 86% (37), and TBB with EBUS-TBNA 88.4% (38). The diagnostic accuracy for BAL, TBB, and EBUS-TBNA was 59.5, 71.4, and 69.8%, respectively. For combinations, BAL and TBB had a diagnostic accuracy of 79.1%, BAL and EBUS-TBNA 95.4%, and TBB and EBUS-TBNA 97.7% (Table 1).

Diagnoses

Among patients with diagnoses (39/43), 74.4% (32) were benign and 16.3% (7) malignant. In 67.4% (29) of the patients, etiological agents could be identified. The median number of microorganisms per patient was 1 (range, 1–3). Mycobacteria were the most frequent (48.5%), followed by fungi (30.3%), pyogenic bacteria (15.2%), and viruses (6.1%). *Mycobacterium tuberculosis* was the most frequently identified mycobacterium in

Table 1. Overall diagnostic yield by type, from bronchoscopy samples in HIV-positive patients

Bronchoscopy samples	n	Diagnostic yield, %	Sensitivity		Specificity		Positive predictive value		Negative predictive value		Diagnostic accuracy		p*
			%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
BAL	21/42	50.0	55.3	39.7, 69.9	100	51.0, 100	100	84.5, 100	19.1	7.7, 40	59.5	44.5, 72.9	0.035
TBB	26/42	61.9	68.4	52.5, 80.9	100	51.0, 100	100	87.1, 100	25.0	10.2, 49.5	71.4	56.4, 82.8	0.007
EBUS-TBNA	26/43	60.5	66.7	50.9, 79.4	100	51.0, 100	100	87.1, 100	23.5	9.6, 47.3	69.8	54.9, 81.4	0.009
BAL+TBB	30/43	69.8	76.9	61.7, 87.4	100	51.0, 100	100	88.6, 100	30.8	12.7, 57.6	79.1	64.8, 88.6	0.001
BAL+EBUS-TBNA	37/43	86.0	94.9	83.1, 98.6	100	51.0, 100	100	90.6, 100	66.7	30, 90.3	95.4	84.5, 98.7	<0.001
TBB+EBUS-TBNA	38/43	88.4	97.4	86.8, 99.6	100	51.0, 100	100	90.8, 100	80.0	37.6, 96.4	97.7	87.9, 99.6	<0.001

HIV, human immunodeficiency virus; BAL, bronchoalveolar lavage; TBB, transbronchial biopsy; EBUS-TBNA, lymph node biopsy by endobronchial ultrasound-guided transbronchial needle aspiration; CI, confidence interval. * χ^2 test for difference in proportions.

Table 2. Etiological agents identified from bronchoscopy samples in HIV-positive patients

Etiological agents	BAL		TBB		EBUS-TBNA		Total		
	n	%	n	%	n	%	n	%	
Mycobacteria									
<i>Mycobacterium tuberculosis</i>	8	66.7	6	50.0	9	75.0	12	75	48.5
<i>M. avium</i> complex	1	25.0	1	25.0	2	50.0	4	25	
Subtotal	9	56.2	7	43.8	11	68.8	16	100	
Fungi									
<i>Pneumocystis jirovecii</i>	4	80.0	4	80.0	0	0.0	5	50	30.3
<i>Cryptococcus neoformans</i>	1	100.0	1	100.0	0	0.0	1	10	
<i>Histoplasma capsulatum</i>	2	100.0	1	50.0	0	0.0	2	20	
<i>Coccidioides immitis</i>	0	0.0	1	50.0	1	50.0	2	20	
Subtotal	7	70.0	7	70.0	1	10.0	10	100	
Bacteria									
<i>Stenotrophomonas maltophilia</i>	1	100.0	1	100.0	0	0.0	1	20	15.2
<i>Nocardia</i> spp.	1	100.0	0	0.0	0	0.0	1	20	
<i>Escherichia coli</i>	2	100.0	0	0.0	0	0.0	2	40	
<i>Pseudallescheria boydii</i>	1	100.0	0	0.0	0	0.0	1	20	
Subtotal	5	10.0	1	10.0	0	0.0	5	100	
Viruses									
<i>Influenza virus A</i>	1	100.0	0	0.0	0	0.0	1	50	6.1
<i>Rhinovirus</i>	1	100.0	0	0.0	0	0.0	1	50	
Subtotal	2	100.0	0	0.0	0	0.0	2	100	
Total	23	69.7	15	45.5	12	36.4	33	100.0	

HIV, human immunodeficiency virus; BAL, bronchoalveolar lavage; TBB, transbronchial biopsy; EBUS-TBNA, lymph node biopsy by endobronchial ultrasound-guided transbronchial needle aspiration.

75.0% (12). Diagnosis was made through Xpert MTB/RIF principally on EBUS-TBNA and BAL samples. The sensitivity of Xpert MTB/RIF in BAL was 66.7%, with a diagnostic accuracy of 90.2%, while the sensitivity of Xpert MTB/RIF in EBUS-TBNA was 81.8%, with a diagnostic accuracy of 93.8%. Among the fungi, *Pneumocys-*

tis jirovecii was the most common (50%), identified in samples from both BAL and TBB. Pyogenic bacteria and viruses were most frequently identified from BAL samples (Table 2).

For malignant diagnoses, Kaposi sarcoma was the most frequent (42.8%), followed by pulmonary adenocar-

Table 3. Malignancy and benign noninfectious diagnoses obtained from bronchoscopy samples in HIV-positive patients

Diagnoses	TBB		EBUS-TBNA		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Malignancy diagnoses						
Kaposi sarcoma	3	100.0	3	100.0	3	42.8
Pulmonary adenocarcinoma	2	100.0	1	50.0	2	28.6
Large B-cell lymphoma	1	50.0	1	50.0	2	28.6
Total	6	85.7	5	71.4	7	100.0
Other benign noninfectious diagnoses						
Fibro-anthraxis	1	50.0	2	100.0	2	40.0
Castleman disease	0	0.0	1	100.0	1	20.0
Granulomatous inflammation	0	0.0	1	100.0	1	20.0
Pneumonia of unidentified etiology	1	100.0	0	0.0	1	20.0
Total	2	40.0	4	80.0	5	100.0

HIV, human immunodeficiency virus; TBB, transbronchial biopsy; EBUS-TBNA, lymph node biopsy by endobronchial ultrasound-guided transbronchial needle aspiration.

cinoma and large B-cell lymphoma, with 28.6% (2) each. In 6 patients, the diagnosis of malignancy was obtained via TBB and in 5 via EBUS-TBNA. Two patients with cancer had positive cultures for *Escherichia coli* via BAL (Table 3).

CT Scans

CT scans were available for 87.7% (36/43) of the patients. For patients with lymphadenopathy and parenchymal lesions, the most common image patterns were nodules in 66.6% (24), ground-glass opacities and consolidations, 25.0% (9) each, and localized pulmonary lesions in 19.4% (7).

One complication was a pneumomediastinum, which resolved spontaneously without any intervention other than supplemental oxygen.

Discussion

This study of HIV patients with lymphadenopathy who underwent EBUS-TBNA is the largest published study to date. Unlike others showing a BAL yield in HIV patients greater than 70% [9, 10], our study puts BAL at 48.8%, which increased to almost 70% with the addition of TBB. However, the increased diagnostic yield of BAL in combination with EBUS-TBNA of 86% is worth noting. In addition, the combination of TBB with EBUS-TBNA was the highest of all (88.4%). One of the 4 patients

for whom no diagnosis could be obtained had been receiving treatment for tuberculosis for 2 months prior to bronchoscopy.

The prevalence of coinfections in this population was 67.4% (29/43), and more than 1 etiologic agent was identified in only 4 patients. The prevalence of mycobacteriosis in our population was 37.2% (16/43), but the prevalence of mycobacteria solely in patients in whom an etiologic agent was identified was 55.2% (16/29). The prevalence of tuberculosis specifically from *M. tuberculosis* was 27.9%. In the prospective study by Sun et al. [4] of 59 patients with suspected tuberculosis, the prevalence was 69.5% (41), diagnosed by various techniques: in 35 by EBUS-TBNA, with which an 85% sensitivity for tuberculosis was obtained. Since then the importance of EBUS-TBNA for the diagnosis of tuberculosis has been described. In our study, EBUS-TBNA also had the highest diagnostic yield for *M. tuberculosis* using Xpert MTB/RIF as well as for the identification of *M. avium* complex. These findings add to those published by Li et al. [5] in their meta-analysis of 14 studies and 684 patients with suspected tuberculosis, in which an 80% diagnostic yield was obtained with EBUS-TBNA, and with minor complications in only 2.2% (15) of the patients. We saw a similar proportion of complications in our population: 1 pneumomediastinum, representing 2.3%.

While *Pneumocystis* pneumonia is common in HIV patients, it is not common in those whose CT scans show

mediastinal lymphadenopathy; nevertheless, in our study, it was diagnosed in 9.3%. This result is consistent with the final recommendations of Fujikura et al. [11] in their case report of a male HIV-positive patient with a diagnosis of pneumonia caused by *P. jirovecii* and *Cytomegalovirus* with mediastinal lymphadenopathy caused by *Nocardia asteroides*, demonstrating the importance of performing EBUS-TBNA in HIV-positive patients with mediastinal lymphadenopathy.

Of the malignancy diagnoses in our study, 85.7% were made through TBB samples and 71.4% via EBUS-TBNA. One of the Kaposi sarcomas and 1 of the diffuse large B-cell lymphomas were also confirmed by surgical biopsy. Regarding the usefulness of EBUS-TBNA in patients with HIV infection and lymphadenopathy, Han et al. [12] showed that in their retrospective study of 513 patients who underwent EBUS-TBNA, out of 9 with HIV infection and mediastinal lymphadenopathy, the need for mediastinoscopy was “reduced” for 8; mycobacterial infections were identified in 5, 1 had lymphoma, and another had small-cell lung cancer.

The prevalence of neoplasms in the HIV population differs from that of the non-HIV population. In our study, the types of neoplasms showed a difference in median age; in patients with adenocarcinoma it was 61.5 years (range, 57.0–66.0), with Kaposi sarcoma 31.0 years (range, 29.0–34.0), and with lymphoma 34.5 years (range, 23.0–46.0). Within this low prevalence of cancer in the HIV population, Kaposi sarcoma is the most frequent [13, 14]. This was also observed in our population with a diagnosis of malignancy: Kaposi sarcoma was the most frequent (50%). There are reports of cases of Kaposi sarcoma with lung involvement in non-HIV patients, mainly those with

an immunocompromising condition, such as hematologic cancers, renal insufficiency and melanomas [15, 16]. In our series, pulmonary adenocarcinoma occurred at the same frequency as lymphoma. In the retrospective study by Grosu et al. [17] that included 181 non-HIV patients, 75 had diagnoses of lymphoma, obtained via EBUS-TBNA in 84% (63), 67% in newly diagnosed cases, and 81% in relapsed patients. Of the 2 lymphomas in our population, 1 was diagnosed through EBUS-TBNA and the other through TBB. As for adenocarcinoma and the age of presentation, cancer diagnoses in HIV patients could undergo a transition due to the effectiveness of antiretroviral therapy and the resulting survival rate, which would allow the emergence of cancers not associated with HIV in this aging population [6].

Conclusions

In patients with HIV infection and mediastinal lymphadenopathy, EBUS-TBNA has a high diagnostic yield, especially when combined with TBB. Of the diagnoses, the most common were benign, the most prevalent being tuberculosis, where the diagnostic accuracy was higher via EBUS-TBNA than BAL, with Xpert MTB/RIF used in both. In malignancies, both EBUS-TBNA and TBB were useful, but BAL was not. In our population, the most frequent cancer was Kaposi sarcoma, followed by pulmonary adenocarcinoma and lymphoma. However, as life expectancy increases, the prevalence of lung cancer in this population will also increase, so EBUS-TBNA is a useful and minimally invasive diagnostic tool that should be considered.

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