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ORIGINAL RESEARCH

The Usefulness of Mediastinal Cryobiopsy in the Diagnosis of Mediastinal Lymphadenopathy in HIV Patients

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Introduction: Mediastinal diseases in HIV patients show complex diagnostic challenges due to opportunistic infections and rare neoplasms. While Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a key technique, its effectiveness is limited as it only provides cytological samples. Endobronchial ultrasound-guided mediastinal cryobiopsy (CryoEBUS) emerges as a promising alternative, yielding larger and higher-quality samples. This study, the first in Mexico and the first worldwide in HIV patients, evaluates its diagnostic efficacy compared to EBUS-TBNA, highlighting its potential to improve disease management in immunocompromised populations.

Materials and Methods: A prospective cross-sectional study has been conducted from April 2023 to October 2023 at a tertiary center for respiratory diseases in Mexico, evaluating the usefulness of the endobronchial ultrasound-guided mediastinal cryobiopsy (CryoEBUS) diagnostic in HIV-positive patients with mediastinal lymphadenopathy ≥1cm. Patients underwent CryoEBUS, with outcomes assessed via pathology and microbiology reports.

Results: Eleven patients were included (64% male, mean age 39.1 years). CryoEBUS yielded diagnostic results in 82% of cases compared to 72% for bronchoalveolar lavage (BAL) and 50% for EBUS alone. Combined CryoEBUS and BAL demonstrated the highest yield (91%).

Conclusion: In patients with HIV and mediastinal lymphadenopathy, mediastinal cryobiopsy has proven to be a useful, effective technique with a high diagnostic yield, especially for benign pathologies. It has also proven to be a safe technique and when combined with other lung sampling techniques, it improves the diagnostic yield of infectious diseases and rare neoplasms.

Keywords: CryoEBUS, HIV, mediastinal disease, immunocompromised

Introduction

Mediastinal diseases in HIV patients show complex diagnostic challenges due to opportunistic infections and rare neoplasms. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a well-established minimally invasive technique for sampling lymph nodes and mediastinal lesions. EBUS-TBNA is currently the technique of choice for mediastinal staging in lung cancer.[1–3] However, EBUS-TBNA despite its excellent accuracy in staging lung cancer, its diagnostic yield for mediastinal diseases with other etiologies is limited due to the fact that endobronchial ultrasound-guided TBNA (EBUS) only provides cytological samples, which may be insufficient when material is needed for histopathological, genetic, or immunological evaluation. Additionally, the core tissues obtained via EBUS-TBNA are sometimes inadequate for immunostaining due to tissue volume, blood contamination, and crushing artifacts.

Overall, the performance of EBUS-TBNA is indisputably good in addressing mediastinal lymphadenopathy with suspected metastasis, particularly non-small cell lung cancer; however, its diagnostic yield for mediastinal lesions secondary to other types of malignancy or benign diseases is not optimal.[4–6].

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Cryobiopsy of the mediastinum is a technique that has demonstrated advantages over fine-needle aspiration mainly due to the larger sample size obtained. This facilitates morphological evaluation of inflammatory and neoplastic pathology, optimizing molecular tests due to the presence of more tumor cells, DNA, and RNA for cancer, metastasis of extrathoracic neoplasms and lymphomas diagnosis, thereby avoiding the need for rebiopsies.[7] Cryobiopsy (CryoEBUS) has emerged as a promising alternative, allowing for the collection of larger and higher-quality histological samples while overcoming the limitations of previous techniques.

This issue is especially relevant when studying certain special populations. Patients living with human immunodeficiency virus (HIV) infection, frequently suffer from infections by opportunistic microorganisms and uncommon neoplasms, for which timely diagnosis is crucial to avoid complications. In HIV patients, early and accurate detection of opportunistic infections and rare neoplasms is crucial, as their immunosuppressed state increases the risk of complex mediastinal diseases. Additionally, considering that the optimal use of antiretroviral therapy maintains high life expectancy in this population, lung cancer is an important disease to rule out.

A prior study in patients with HIV infection has been conducted, it aimed at measuring the use of EBUS-guided transbronchial needle aspiration (EBUS-TBNA) in HIV-infected patients with mediastinal lymphadenopathy. The study demonstrated greater diagnostic precision using EBUS-TBNA, highlighting the significant role of this diagnostic method in managing these patients.[8] However, the diagnostic yield remains suboptimal.

To obtain a larger sample volume and improve the diagnostic usefulness of endobronchial ultrasound, various techniques have been studied.[9] Cryobiopsies are of extraordinarily good histological quality and larger in size than samples obtained with forceps, without crushing artifacts, making them an excellent tool in the diagnosis of peripheral lung lesions, endobronchial tumors, and interstitial lung diseases.[10,11]

To acquire intact samples with sufficient volume for histological and molecular analysis, Zang et al developed a new technique for mediastinal sampling, published in Respiration in 2020, where a transbronchial mediastinal cryobiopsy was performed with real-time endobronchial ultrasound guidance (CryoEBUS).[12]

Multiple studies have demonstrated that this is a safe technique capable of offering better diagnostic yield compared to standard needle aspiration biopsy. From case reports and case series to prospective studies, clinical trials, and even a systematic review, all generally conclude that CryoEBUS was especially useful in cases of lymphomas or non-lung carcinomas and benign cases, with no significant differences found in specific cases of lung cancer.[12–22]

Endobronchial ultrasound-guided mediastinal cryobiopsy (CryoEBUS) emerges as a promising alternative, yielding larger and higher-quality samples. This study, the first in Mexico and the first worldwide in HIV patients, evaluates its diagnostic efficacy, its usefulness and performance in patients with HIV infection, highlighting its potential to improve disease management in immunocompromised populations.

Materials and Methods

This is a prospective cross-sectional study of patients diagnosed with HIV who, for diagnostic reasons, underwent endobronchial ultrasound bronchoscopy with biopsy using the cryobiopsy technique (CryoEBUS). The principal objective was to describe the utility of ultrasound-guided endoscopic mediastinal cryobiopsy compared to fine needle aspiration biopsy in patients with human immunodeficiency virus infection with a diagnostic suspicion of benign and malignant mediastinal diseases. The secondary objectives were to describe the characteristics of the studied population, the ultrasonographic and tomographic features of the biopsied lymph nodes, and to describe the complications.

As a Diagnostic Study, STARD Checklist Was Followed.

The study was performed at the Bronchoscopy Service of a tertiary center for respiratory diseases in Mexico from April 2023 to October 2023. Patients over 18 years old with a human immunodeficiency virus infection diagnosis and evidence of mediastinal lymphadenopathy on chest tomography $\geq$ 1 cm in any lymph node station accessible by bronchoscopy, who were indicated to undergo bronchoscopy with endobronchial ultrasound-guided biopsy as part of their diagnostic approach, were included. (Figure 1) Patients who did not agree to participate in the protocol, had missing data, or met the inclusion criteria but during the endoscopic ultrasound mediastinal evaluation did not show biopsy-eligible lymphadenopathies greater than 1 cm were excluded.

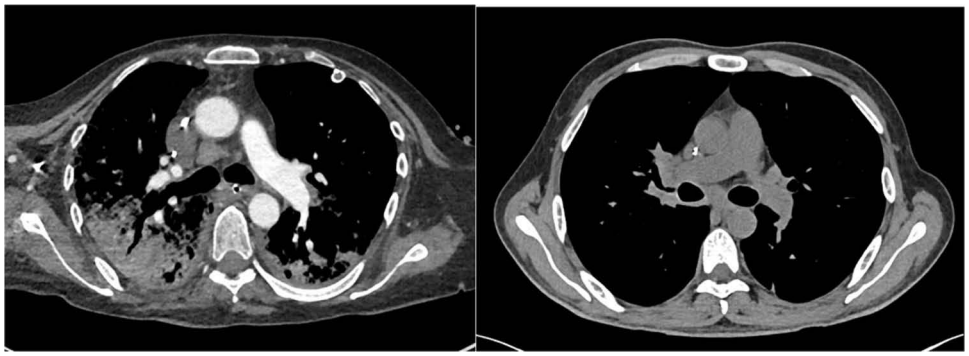

Figure 1 Chest tomography sections of 2 study participants showing the enlargement of lymph node stations 4R (left) and 7 (right).

Eligible patients underwent EBUS with the BFUC190F® bronchoscope (Olympus Medical Systems) under deep sedation with Propofol, midazolam, and neuromuscular blockade after signing informed consent. The procedure was performed by a pulmonologist with several years of experience in endoscopic procedures, conducted in a service with a high number of annual EBUS TBNA procedures. For EBUS-TBCNB, we used a 1.1 mm flexible cryoprobe (Erbecryo 20402–401, Tubingen, Germany). (Figure 2)

EBUS-TBNA was performed according to the guidelines, using a 21 G Olympus needle, 3 biopsies were taken with capillary action and/or suction, indistinctly according to the sample obtained, 20 passes each, 2 were sent to pathology and 1 to microbiology. A channel was then made with the same needle and the flexible cryoprobe 1.1 was inserted, 3 cryobiopsies were taken with a freezing time of 4–8 seconds, and 2 were sent to pathology and 1 to microbiology. For both EBUS-TBNA and CryoEBUS, the largest adenopathy was biopsied and only one per patient. For bronchial lavage, 40 mL of 0.9% saline solution was instilled, 20 mL were recovered and sent to microbiology and pathology.

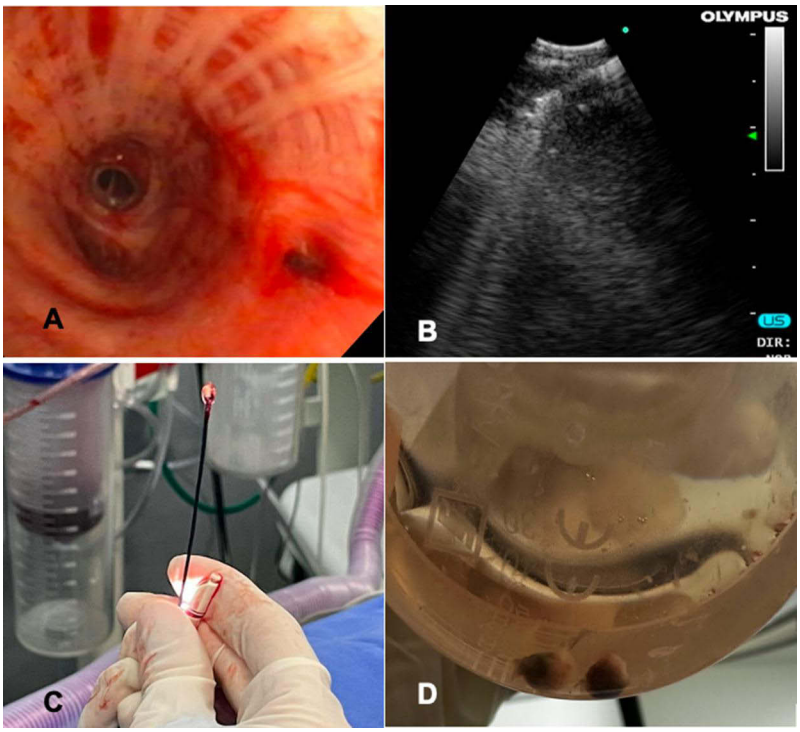

Figure 2 Representative images of a procedure. (**A**) Cryoprobe access channel. (**B**) Cryoprobe inside lymph node. (**C**) Cryoprobe with sample obtained from lymph node. (**D**) Samples obtained in formalin.

Clinical, demographic, and diagnostic data of patients undergoing this procedure during the study period was collected. The outcome variables were the diagnostic yield based on pathology and microbiology reports. Data normality was assessed using the Shapiro–Wilk test. The clinical and demographic characteristics of the study population are expressed as means and standard deviations, or medians and interquartile ranges (p25-p75), number, and frequency. The incidence of positive results in the analysis of bronchoalveolar lavage or EBUS or cryoEBUS biopsy was reported. The prevalences of positive results were compared according to reports from the Microbiology or Pathology laboratory. Stata V14.0 software was used for statistical analysis.

The research protocol was reviewed and approved by the Ethics and Research Committee of the National Institute of Respiratory Diseases (C#4823). All individuals signed informed consent beforehand. The study complies with the Declaration of Helsinki.

Results

Data from 11 patients was analyzed, 7 of whom were male (64%), with an average age of 39.1 ± 10.9 years. The median time since diagnosis was 2 months, with 4 patients being recently diagnosed. Of the total patients, 4 (37%) were on Antiretroviral Therapy (ART). The median CD4 count was 36 (23–166) cells/mm3 [Table 1].

In all patients, a complete ultrasound scan of the mediastinum was performed, the lymph nodes found were characterized and the largest lymph node was punctured, which in 90% of cases was the lymph node in station 7. Regarding tomographic findings, the abnormal lymph nodes reported were 4R, with a range between 10 mm and 46 mm, 2R between 10 mm and 15 mm and 7 between 10 mm and 19 mm. Ultrasound features were characterized by being mostly heterogeneous, without central necrosis, ovoid in shape, with predominantly grade 0 vascularity and with defined edges.

CryoEBUS biopsies were taken from the 11 patients studied and sent to microbiology and pathology laboratories. Only 8 EBUS biopsies were performed, which were sent to the pathology laboratory, while only 3 were dispatched to the microbiology laboratory. Eleven BAL samples were sent to the microbiology laboratory, while only 6 samples were forward to pathology. Analyzing by sample/biopsy type and considering the results from both laboratories, a diagnostic yield of 82% for CryoEBUS, 72% for Bronchoalveolar lavage (BAL), and 50% for EBUS was observed. Considering the positive results from CryoEBUS + BAL, the highest diagnostic yield of 91% was observed [Tables 2–4].

The results obtained were mostly secondary to infectious pathology, such as Pneumocystis Jirovecii, Mycobacterium Avium complex, Mycobacterium tuberculosis, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Histoplasma. Among the non-infectious results, Kaposi's sarcoma was found.

No complications were reported in any of the cases.

Table 1 Demographic and Clinical Characteristics

	Total (n=11)
Age (years)	39.1 ± 10.9
Gender	Male 7 (64%)
CD4+ (cells/mm3)	36 (23–166)
HIV diagnosis (months)	2 (0–19)
Antiretroviral Therapy	4 (37%)
Weight (kg)	62 (54–71)

Clinical and demographic characteristics of the study population are expressed as means and standard deviations, or medians and interquartile ranges (p25-p75), number, and frequency.

Table 2 Cases with Positive Microbiology Results

	CryoEBUS (n=11)	EBUS (n=3)	BAL (n=11)	Cryo-EBUS + LBA (n=11)
Microbiology	5 (45%)	1 (33%)	8 (73%)	9 (82%)

Notes: Patients who underwent each of the procedures and incidence of positive results.
Abbreviations: EBUS, Endobronchial Ultrasound; BAL, Bronchoalveolar Lavage.

Table 3 Cases with Positive Pathology Results

	CryoEBUS (n=11)	EBUS (n=8)	BAL (n=6)	Cryo-EBUS + EBUS (n=8)	EBUS + BAL (n=5)	Cryo-EBUS + BAL (n=6)	Cryo-EBUS + EBUS + BAL (n=4)
Pathology	9 (82%)	3 (38%)	2 (33%)	7 (88%)	4 (80%)	5 (83%)	4 (100%)

Notes: Patients who underwent each of the procedures and incidence of positive results.
Abbreviations: EBUS, Endobronchial Ultrasound; BAL, Bronchoalveolar Lavage.

Table 4 Combined Diagnoses

	CryoEBUS (n=11)	EBUS (n=8)	BAL (n=11)	CryoEBUS + BAL (n=11)
Plasma Cell hyperplasia without growth in BM	3 (27%)	2 (50%)		1 (9%)
Chronic granulomatous inflammation		1 (25%)		
Klebsiella	1 (9%)		1 (9%)	1 (9%)
Klebsiella + Pseudomonas	1 (9%)	1 (25%)		1 (9%)
Mycobacterium avium complex	1 (9%)		1 (9%)	1 (9%)
Pneumocystis pneumonia	1 (9%)		3 (27%)	2 (18%)
Tuberculosis			2 (18%)	1 (9%)
Histoplasmosis + TB	1 (9%)			1 (9%)
Kaposi Sarcoma	1 (9%)			1 (9%)
Pulmonary Aspergillosis			1 (9%)	1 (9%)
Total	9 (82%)	4 (50%)	8 (72%)	10 (91%)

Notes: Distribution of each of the diagnoses analyzed by sample/biopsy kind and considering the results from both laboratories (microbiology and pathology).
Abbreviations: BM, Bone Marrow; TB, Tuberculosis; EBUS, Endobronchial Ultrasound; BAL, Bronchoalveolar Lavage.

Discussion

To our knowledge, this is the first study of endoscopic ultrasound-guided mediastinal cryobiopsy (cryoEBUS) performed inMexico. It is also the first study worldwide to evaluate the role of this new technique in a population of patients living with human immunodeficiency virus (HIV) infection.

Previous literature on cryoEBUS reports an increased diagnostic yield, especially in mediastinal diseases of benign etiology and rare neoplasms. The benign diseases consistently reported in all studies have been sarcoidosis, tuberculosis, and pneumoconiosis. Its performance is also reported as excellent in the diagnosis and staging of lung cancer; however, it does not seem to offer much more than fine-needle aspiration biopsy (EBUS-TBNA). Our study population corresponds to a very specific group, as patients with HIV infection, especially those not on antiretroviral therapy and therefore in a state of severe immunosuppression, are susceptible to acquiring infections from almost any microorganism and it is

very common to observe multiple infections simultaneously. This same immune dysfunction increases the risk of neoplasms, so it is common to see rare neoplasms in these patients.

In the previous study which aimed to measure the diagnostic yield of EBUS-TBNA in patients with mediastinal lymphadenopathy and HIV infection, they found that EBUS-TBNA biopsy significantly increased the diagnostic yield in infectious diseases. However, the highest yield was obtained with a combination of several techniques. In the first cases description regarding the utility of cryoEBUS biopsy in this population of immunocompromised patients, we found similar results, primarily that cryoEBUS biopsy does increase the yield for diagnosing certain diseases, which was evidenced by it, being the only technique that could identify concomitant infection by Histoplasma Capsulatum and Mycobacterium tuberculosis. However, the highest diagnostic yield is still with the combination of techniques. In other reported studies of HIV patients undergoing retrospective EBUS-TBNA, a high prevalence of infectious diagnoses such as tuberculosis was found, followed by lung cancer and lymphoma.[23] The study definitely highlights the quality of lymph node samples in a low lymphocytic condition obtained by EBUS-TBNA.

In another study in a different population than ours, ie with low prevalence of tuberculosis, TBNA appears to be a safe and accurate tool in the investigation of mediastinal lymphadenopathy in HIV-infected patients. It may avoid more invasive procedures such as mediastinoscopy.[23]

Cases of pneumothorax and pneumomediastinum have been reported, which were resolved conservatively. Only one case of a severe complication of hemomediastinum has been reported in a 76-year-old patient with suspected lymphoma.[24] No complications were reported in our study.

This study has multiple limitations: its descriptive nature, without randomizing patients to the two techniques for obtaining material from mediastinal lymph nodes for study (CryoEBUS and EBUS-TBNA); the small sample size; and the fact that not all patients had all samples taken, due to the lack of funding and reliance on hospital resources, meaning the tests performed on the samples depended on medical criteria based on the patient's risk profile. However, it also has relevant strengths worth mentioning. Firstly, it involves a very specific population with close follow-up before, during, and after the procedure.

CryoEBUS emerges as a promising tool for improving diagnostic accuracy in HIV-positive patients with mediastinal lymphadenopathy, also this is a groundbreaking study that also demonstrates the safety of the personnel performing the procedure, even in HIV positive patients without antiretroviral therapy. This study contributes to advancing diagnostic strategies in HIV care, addressing a critical gap in current clinical practice.

Further research is warranted to validate these findings and explore its application in other special populations.

Conclusion

In patients with HIV and mediastinal lymphadenopathy, mediastinal cryobiopsy has proven to be a useful, effective technique with a high diagnostic yield, especially for benign pathologies. It has also proven to be a safe technique and when combined with other lung sampling techniques, it improves the diagnostic yield of infectious diseases and rare neoplasms.

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Disclosure

Dr Adnan Majid reports personal fees from Olympus America and Erbe, during the conduct of the study. The authors declare that they have no other conflicts of interest in this work.

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