J Bras Pneumol. 2020;46(2):e20180183
https://dx.doi.org/10.36416/1806-3756/e20180183

ORIGINAL ARTICLE

The role of endobronchial ultrasound-guided transbronchial needle aspiration in isolated intrathoracic lymphadenopathy in non-neoplastic patients: a common dilemma in clinical practice

Lília Maia Santos[1,2], Viviane Rossi Figueiredo[3], Sergio Eduardo Demarzo[3], Addy Lidvina Mejia Palomino[3], Márcia Jacomelli[3]

1. Programa Complementar em Endoscopia Respiratória, Serviço de Endoscopia Respiratória, Disciplina de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Unidade de Pneumologia, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.
3. Serviço de Endoscopia Respiratória, Disciplina de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

Submitted: 18 June 2018.
Accepted: 20 April 2019.

Study carried out in the Serviço de Endoscopia Respiratória, Disciplina de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To determine the diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in non-neoplastic patients with isolated intrathoracic lymphadenopathy (IL). **Methods:** This was a retrospective study of patients with isolated IL referred for EBUS-TBNA. We calculated the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of EBUS-TBNA in the diagnosis of granulomatous, reactive, and neoplastic lymphadenopathy. In cases of nonspecific granulomas, reactive lymphadenopathy, or inconclusive results, a definitive diagnosis was established by other diagnostic procedures or during a follow-up period of at least 18 months. **Results:** Among the 58 patients included in the study, EBUS-TBNA established a diagnosis of granulomatous disease in 22 (38%), reactive lymphadenopathy in 15 (26%), cancer in 8 (14%), and other diseases in 3 (5%). Results were inconclusive in 10 (17%), the diagnosis being established by other bronchoscopic procedures in 2 (20%) and by surgical procedures in 8 (80%). A final diagnosis of reactive lymphadenopathy was established in 12. Of those, 11 (92%) had their diagnosis confirmed during follow-up and 1 (8%) had their diagnosis confirmed by mediastinoscopy. In another 3, a final diagnosis of sarcoidosis or neoplasm was established. For the diagnosis of granulomatous disease, neoplasms, and reactive lymphadenopathy, EBUS-TBNA was found to have a sensitivity of 73%, 68%, and 92%, respectively; a specificity of 100%, 100%, and 93%, respectively; an accuracy of 86%, 93%, and 93%, respectively; a PPV of 100%, 100%, and 80%, respectively; and an NPV of 78%, 92%, and 98%, respectively. **Conclusions:** In non-neoplastic patients, granulomatous disease and reactive lymphadenopathy appear to be common causes of isolated IL. EBUS-TBNA shows promising results as a first-line minimally invasive diagnostic procedure. The results obtained by EBUS-TBNA can be optimized by examining clinical and radiological findings during follow-up or by comparison with the results obtained with other bronchoscopic methods.

Keywords: Endoscopic ultrasound-guided fine needle aspiration; Lymphadenopathy/diagnosis; Neoplasms.

INTRODUCTION

Isolated intrathoracic lymphadenopathy (IL) can be caused by malignant or benign diseases, and it is often difficult to establish a minimally invasive definitive diagnosis.[1] Tuberculosis, sarcoidosis, and other inflammatory diseases are the most common benign conditions and have a substantial clinical and diagnostic overlap; because they demand completely different therapeutic regimens, this creates a dilemma for pathologists and clinicians.[1-3] Therefore, histopathological/microbiological confirmation is essential for the differential diagnosis.[2]

Lymph nodes (LNs) may become enlarged as a reaction to underlying pulmonary or cardiovascular comorbidities; in such cases, lymph node enlargement is referred to as reactive lymphadenopathy.[4] Reactive lymphadenopathy has been reported to be present in almost 50% of COPD patients and in 35-66% of the patients with chronic heart failure.[4] Other chronic conditions, such as bronchiectasis, pulmonary arterial hypertension, and connective tissue disease, have also been associated with reactive lymphadenopathy.[4]

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as a useful and minimally invasive diagnostic procedure that provides cytological sampling under real-time ultrasound viewing, resulting in improved accuracy and safety during LN sampling.[1-3,5] Nowadays, EBUS-TBNA has an established

Correspondence to:
Márcia Jacomelli. Serviço de Endoscopia Respiratória, Instituto do Coração, Avenida Dr. Enéas de Carvalho Aguiar, 44, Bloco I, 8º andar, Cerqueira César, CEP 05403-900, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5612. E-mail: marcia.jacomelli@hc.fm.usp.br
Financial support: None.

role for IL evaluation, particularly for the diagnosis and staging of cancer patients and for the diagnosis of granulomatous disease, with an accuracy comparable to mediastinoscopy.[4,5] However, less is known about the role of EBUS-TBNA in nonspecific IL.

The objective of the present study was to evaluate the diagnostic yield of EBUS-TBNA in non-neoplastic patients with isolated IL.

METHODS

This was a retrospective longitudinal study of patients with isolated IL undergoing EBUS-TBNA who were seen in the *Serviço de Endoscopia Respiratória, Disciplina de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo*, located in the city of São Paulo, Brazil, between August of 2011 and April of 2017. The data were obtained from the institutional database. The study was approved by the Research Ethics Committee of *Hospital das Clínicas* (Protocol no. 1,630,604).

Patients referred for isolated IL evaluation were included in the study. We defined IL as the presence of at least one mediastinal or hilar LN > 1 cm in short-axis diameter based on CT or with a standardized uptake value > 2.5 on positron emission tomography (PET)/CT. The exclusion criteria were as follows: presence of an endobronchial lesion during conventional video-assisted bronchoscopy performed immediately prior to EBUS-TBNA, history or suspicion of cancer, and loss to follow-up.

To localize enlarged LNs, CT or PET/CT scans of the chest were assessed before the procedure. The LN map recommended by the International Association for the Study of Lung Cancer was used in order to standardize the LN station nomenclature in all procedures and to facilitate communication.[6]

All procedures were performed with topical anesthesia—1% lidocaine using "spray-as-you-go" delivery—and moderate sedation with midazolam (5 mg), fentanyl (100 µg), and slow infusion of propofol (approximately 200 mg). EBUS-TBNA was preceded by conventional video-assisted bronchoscopy (BF-Q180; Olympus Medical Systems Corp., Tokyo, Japan) in order to access the airways and identify any endobronchial lesions to be biopsied. All linear-probe EBUS procedures were performed through natural orifices—nose or mouth—by an experienced bronchoscopist who had been trained in standard and interventional bronchoscopy. In all instances, EBUS sectorial scope (BF-UC180F; Olympus Medical Systems, Tokyo, Japan) and a disposable 22-gauge needle compatible with the ultrasound scope were used: NA-201SX-4022 (Olympus Medical Systems), ECHO-HD-22-EBUS-O (Cook Medical, Winston-Salem, NC, USA), or GUS-45-18-022 (Medi-Globe, Achenmühle, Germany).

TBNA was performed using a 22-gauge needle and negative pressure, and sample collection followed standardized routine protocols. TBNA aspirates were immediately smeared on glass slides and fixed in 95% ethanol for cytology; the remaining aspirates were fixed in 10% formaldehyde and embedded in paraffin for cell-block analysis. When there was suspicion of granulomatous disease, the TBNA aspirate was also flushed into a sterile container with normal saline and sent for fungal and mycobacterial culture; transbronchial biopsy (TBB) was taken, fixed in 10% formaldehyde and embedded in paraffin for histological analysis; and BAL fluid was collected and sent for microbiological and cytological analysis. When there was suspicion of tuberculosis, the specimens obtained were smeared for Ziehl-Neelsen staining and sent for mycobacterial culture on Löwenstein-Jensen medium. Rapid on-site evaluation (ROSE) was not carried out.

When EBUS-TBNA indicated nonspecific granulomas, reactive LNs, or inconclusive results, a definitive diagnosis was established by other endoscopic procedures, by surgical procedures, or by clinical and radiological follow-up for at least 18 months. The diagnostic criteria were as follows: presence of caseating or noncaseating granulomas consistent with tuberculosis, fungal disease, sarcoidosis, or other granulomatous diseases; positive culture for a specific microorganism in the LN sample; and presence of neoplastic cells in the aspirate.

The EBUS-TBNA procedure was considered diagnostic if it resulted in the specific diagnosis of malignancy or inflammatory disease. An LN was considered reactive if further investigation showed it to be reactive or if it remained stable on CT scans and clinical evaluation for at least 18 months of follow-up.

Statistical methods

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for each condition were calculated based on the number of successful diagnoses made by EBUS-TBNA and the number of EBUS-TBNA procedures. We considered true positive cases to be those in which EBUS-TBNA established a correct diagnosis. False positive cases were considered to be those in which a diagnosis was established and then changed due to other procedures or during follow-up. True negative cases were those when the patient did not have the disease according to EBUS-TBNA, other procedures, or follow-up. False negative cases were considered to be those in which EBUS-TBNA could not provide a diagnosis, other procedures or follow-up therefore being required. The variables were described as absolute and relative frequencies. All of the analyses were performed with the IBM SPSS Statistics software package, version 19.0 for Windows (IBM Corporation, Armonk, NY, USA).

RESULTS

During the study period, a total of 196 patients underwent EBUS-TBNA for the diagnosis of isolated IL. Of those, 138 were excluded: 132 due to a history or suspicion of cancer; 3 because they had

an endobronchial lesion detected during conventional bronchoscopy; and 3 who were lost to follow-up (Figure 1). Therefore, 58 patients were included, 33 (56.9%) of whom were female. The mean age of the patients was 53 ± 15 years. The most common comorbidities were HIV and/or HCV infection and autoimmune disease, followed by COPD. All CT scans revealed IL. The most common CT findings were pulmonary nodules, pulmonary masses, pleural effusion, and pulmonary infiltrates. A total of 159 LNs were assessed by EBUS; of those, 79 (49.7%) were sampled by EBUS-TBNA. The sampled LNs had a mean short-axis diameter of 17.8 ± 6.6 mm, and most were subcarinal or paratracheal LNs. The mean number of punctures made in each LN was 3.5 ± 1.5. These characteristics are summarized in Table 1.

EBUS-TBNA diagnosed granulomatous disease in 22 patients (38%), reactive LNs in 15 (26%), neoplasms in 8 (14%), and other diseases in 3 (5%). In 10 cases (17%), EBUS-TBNA samples were not suitable for histopathology. Of those, 8 were also sent for culture and microbiological analysis, the results of which were negative and therefore inconclusive (Figure 1). No major complications were recorded.

With regard to granulomatous diseases, EBUS-TBNA identified mycobacteriosis in 5 patients (22.7%); histoplasmosis, in 1 (4.5%); sarcoidosis, in 1 (4.5%); and silicosis, in 1 (4.5%; Figure 1). Tuberculosis was diagnosed in 4 patients (caseating granulomas identified by cell-block analysis in 2 and positive AFB in aspirate smear in 2). All 4 patients responded to tuberculosis treatment. *Mycobacterium kansasii* was isolated in the aspirate culture in 1 patient. In the remaining 14 patients with nonspecific granulomas by EBUS-TBNA (63.6%), the definitive diagnosis was made by association with other bronchoscopic methods, in 6 (42.9%); surgical biopsy, in 3 (21.4%); and during follow-up, in 5 (35.7%; Table 2).

Of the 15 patients diagnosed with reactive lymphadenopathy, 12 (80%) had their diagnosis subsequently confirmed. Of those, 11 (92%) had their diagnosis confirmed during the follow-up period and 1 (8%) had their diagnosis confirmed by mediastinoscopy. The remaining 3 patients (20%) were diagnosed with sarcoidosis (during the follow-up period), epithelioid hemangioendothelioma (by TBB), or lymphoma (by cerebrospinal fluid analysis; Table 2). Underlying comorbidities were present in 83% of the 12 patients with a definitive diagnosis of reactive lymphadenopathy: infectious/inflammatory disease (pleural tuberculosis under treatment, organizing pneumonia, or myocarditis), in 25%; and chronic diseases (HIV infection, hepatitis C, autoimmune disease, COPD, severe mitral regurgitation, or hypothyroidism), in 58%.

Of the 8 neoplastic results, EBUS-TBNA made a definitive diagnosis in 4: adenocarcinoma, in 2, and non-small cell lung cancer, in 2. Histopathology raised the suspicion of non-Hodgkin lymphoma in 3 cases, all of which were confirmed by surgical biopsy of the LNs. In 1 case, the diagnosis of undifferentiated carcinoma remained the same after surgical biopsy of LNs. In addition, EBUS-TBNA established the diagnosis of substernal goiter in 2 patients and of bronchogenic cyst in 1.

Table 1. General characteristics of the patients, radiological findings, and lymph nodes sampled by endobronchial ultrasound-guided transbronchial needle aspiration (N = 58).[a]

Characteristic	Result
Gender	
Male	25 (43.1)
Female	33 (56.9)
Age, years	53 ± 15
Comorbidities	
HCV/HIV	3 (5.2)
Autoimmune disease	3 (5.2)
COPD	2 (3.4)
Pleural tuberculosis	1 (1.7)
Pulmonary tuberculosis scars	1 (1.7)
Pericardial effusion	1 (1.7)
Heart transplant	1 (1.7)
Diabetes	1 (1.7)
Arterial hypertension	1 (1.7)
CT findings	
Lymph nodes	58 (100)
Pulmonary nodules	12 (20.7)
Bilateral	9 (15.5)
RUL	2 (3.4)
RUL + LUL	1 (1.7)
Size, mm	14 ± 8
Masses	4 (6.9)
Mediastinal	2 (3.4)
Paratracheal	1 (1.7)
Hilar	1 (1.7)
Size, mm	64 ± 14
Pulmonary micronodules	1 (1.7)
Pleural effusion	4 (6.9)
Pulmonary infiltrates	3 (5.2)
Emphysema	1 (1.7)
Pulmonary atelectasis	1 (1.7)
Ground-glass opacities	1 (1.7)
Lymph nodes sampled	79 (49.7)
Location	
Paratracheal region	27 (34.2)
Subcarinal region	41 (51.9)
Hilar region	2 (2.5)
Interlobar region	9 (11.4)
Size, mm	17.8 ± 6.6
Number of punctures	3.5 ± 1.5

RUL: right upper lobe; and LUL: left upper lobe. [a]Values expressed as n (%) or mean ± SD.

On cytology, the presence of red blood cells (n = 9) and few lymphoid cells (n = 1) rendered the samples inadequate for diagnosis, and this could explain the inconclusive results. In 8 of those cases, the samples were also sent for microbiological analysis, but the results were negative. The definitive diagnosis of those inconclusive results by EBUS-TBNA was established by other bronchoscopic methods, in 2 cases (20%); and by surgical biopsy, in 8 cases (80%; Table 2).

Performing BAL or TBB together with EBUS-TBNA helped achieve a definitive diagnosis of nonspecific

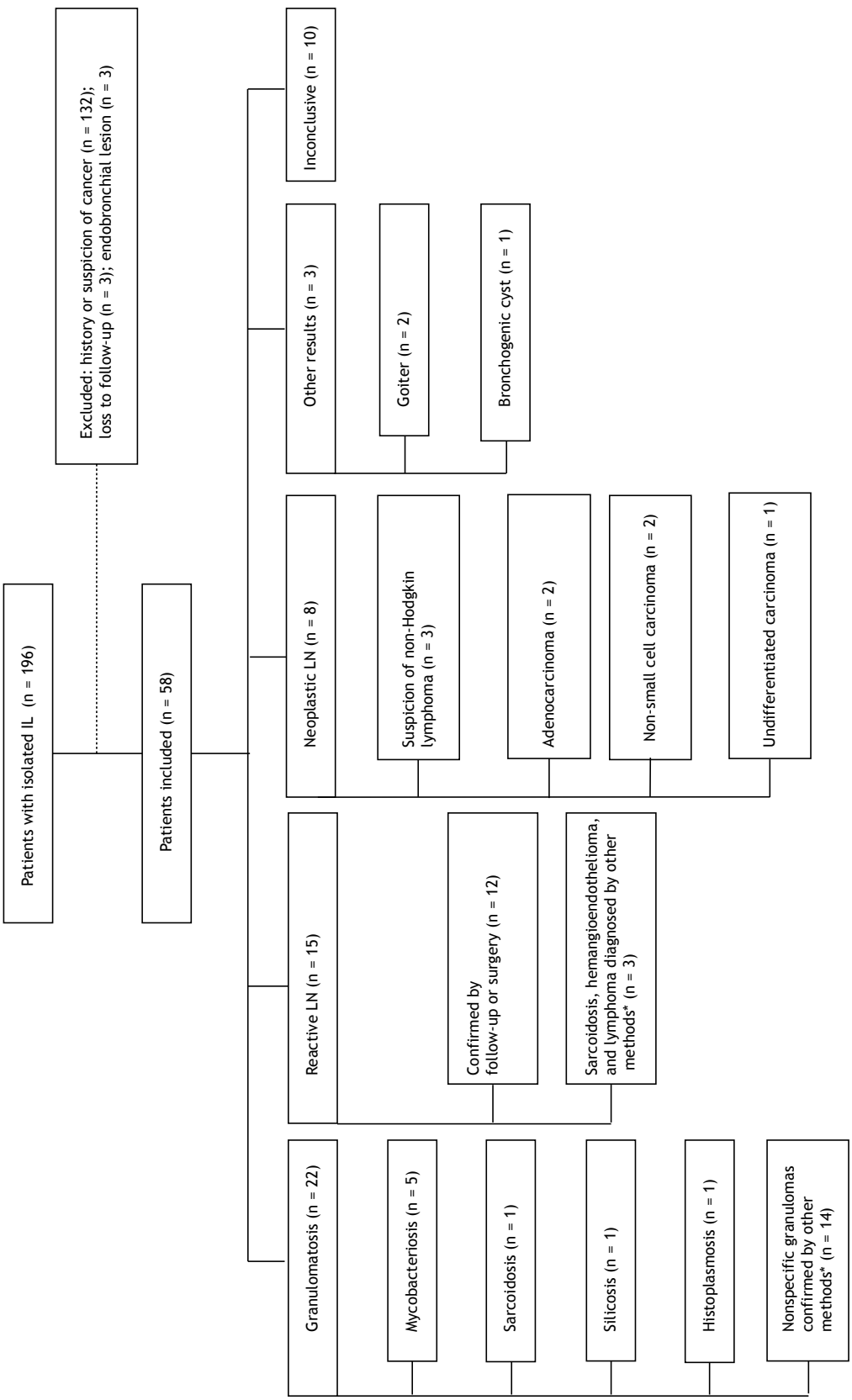

Figure 1. Flow chart of patients who underwent endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of isolated intrathoracic lymphadenopathy. IL: intrathoracic lymphadenopathy; and LN: lymph node. *Other methods (bronchoscopy, surgery, or cerebrospinal fluid analysis).

Table 2. Diagnostic methods other than endobronchial ultrasound-guided transbronchial needle aspiration that established the diagnosis in cases of nonspecific granulomas, reactive lymph nodes, and inconclusive results.

Diagnostic method	Nonspecific granulomas	Inconclusive results	Reactive lymph nodes
BAL	Sarcoidosis (n = 1) (plus clinical and radiological findings)	Aspergillosis (n = 1)	
Transbronchial biopsy	Sarcoidosis (n = 5) (lymphocytosis in BAL fluid and/or elevated CD4/CD8)	Sarcoidosis (n = 1) (lymphocytosis in BAL fluid and/or elevated CD4/CD8)	Epithelioid hemangioma (n = 1)
Mediastinoscopy	*M. avium* (n = 1)	*M. tuberculosis* (n = 1) Sarcoidosis (n = 1) Histoplasmosis (n = 1) Fibrosing mediastinitis (n = 1)	
Surgical biopsy of extrathoracic LN	*M. tuberculosis* (n = 1) Granulomatous slack skin (n = 1)	Reactive lymphadenopathy (n = 1) Sarcoidosis (n = 2)	
Transthoracic biopsy		Lymphoma (n = 1)	
Cerebrospinal fluid analysis			Lymphoma (n = 1)
Follow-up	Sarcoidosis (n = 5)		Sarcoidosis (n = 1)

granuloma, reactive lymphadenopathy, or "inconclusive" results by EBUS-TBNA in 33.3% of the cases.

The sensitivity, specificity, PPV, NPV, and accuracy of EBUS-TBNA for the diagnosis of granulomatosis, neoplasms, and reactive lymphadenopathy are specified in Table 3. The global diagnostic yield was 77.6%, and possible false results were 5%.

DISCUSSION

In our sample of patients with no history or suspicion of cancer, isolated IL mostly revealed benign diseases, which is in accordance with the literature.[1,7] EBUS-TBNA has shown high sensitivity and cost-effectiveness for first-line investigation, rendering mediastinoscopy unnecessary in 87% of the patients with IL.[4] Our study showed that EBUS-TBNA is a useful tool in the differential diagnosis of isolated IL, an important step that informs the utility and applicability of different therapeutic options.

Granulomatous diseases—tuberculosis, fungal infections, and sarcoidosis—are the most common benign causes of IL and, likewise, were the diseases that were most commonly diagnosed by EBUS-TBNA in our study, corresponding to 38% of the cases.[1,7] Granulomatous diseases share various clinical, radiological, and pathological features, which makes their differentiation occasionally arduous, increasing the importance of tissue diagnosis.[8] Morphological characteristics of granulomas—noncaseating in sarcoidosis and caseating in tuberculosis and fungal infections—associated with clinical and radiological findings can help differentiate such disorders. Aspirate smears and cultures can confirm infectious causes and exclude sarcoidosis.[8-11]

The sensitivity of EBUS-TBNA for the diagnosis of granulomatous disease has been reported to range from 64.0% to 80.9%, with an accuracy between 70.0% and 83.3%, and an NPV of 33.0-42.8%,[7,12] the highest results having been shown in a prospective study performed by Çağlayan et al.,[7] in which 72 patients with suspected granulomatous disease were enrolled. In our study, we found sensitivity values within the range reported in the current literature, excellent specificity and PPV, as well as high NPV and accuracy. These results were achieved despite the retrospective nature of our study and a lower suspicion of granulomatous disease than that reported in the aforementioned study.[7]

Sarcoidosis is a multisystem disease that affects the lungs and LNs in almost all patients.[13,14] Its diagnosis is based on clinical and radiological findings, CD4/CD8 ratio (> 3.5) on BAL fluid, tissue confirmation of noncaseating epithelioid cell granulomas, and the exclusion of infectious and malignant conditions.[13-15] Flexible bronchoscopy has a diagnostic yield of approximately 70% for pulmonary sarcoidosis, and EBUS-TBNA can reach a diagnostic yield of 86%.[15] A randomized multicenter clinical trial that included 304 patients with sarcoidosis showed that the overall diagnostic yield of TBB was 53%, with better results in patients with stage II sarcoidosis than in those with stage I sarcoidosis (66% vs. 38%).[13] However, the overall diagnostic yield of EBUS-TBNA was higher (80%), with better results in patients with stage I sarcoidosis than in those with stage II sarcoidosis (84% vs. 77%).[13] Similarly, a systematic review and meta-analysis on the efficacy and safety of EBUS-TBNA in sarcoidosis revealed an overall diagnostic yield of 79%.[14] The sensitivity of EBUS-TBNA for the diagnosis of sarcoidosis has been reported to be between 64% and 84%.[7,12] These excellent results and the knowledge that the combination of EBUS-TBNA with TBB and endobronchial biopsies can

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of granulomatous disease, neoplasms, and reactive lymph nodes.

Diagnosis	Sensitivity	Specificity	PPV	NPV	Accuracy
Granulomatosis	73.3	100	100	77.8	86.2
Neoplasms	66.7	100	100	92.0	93.1
Reactive LNs	92.3	93.3	80.0	97.7	93.1

LN: lymph node; PPV: positive predictive value; and NPV: negative predictive value.

significantly add to the diagnostic yield suggest that EBUS-TBNA should be routinely employed for the diagnosis of sarcoidosis whenever available. In our study, a definitive diagnosis was obtained by EBUS-TBNA in only 1 patient, the remaining diagnoses being confirmed by other bronchoscopic methods, such as lymphocytosis in BAL fluid, elevated CD4/CD8, and/or noncaseating granuloma in TBB; in other cases, there were strong clinical and radiological findings suggesting a diagnosis of sarcoidosis, which was later confirmed during patient follow-up. Although EBUS-TBNA alone was unable to establish the differential diagnosis in 14 cases of granulomatous disease in our study, it was able to detect granulomas in 11 cases diagnosed as sarcoidosis, and its results were inconclusive or indicated reactive LNs in only 5 cases.

IL is the most common form of extrapulmonary tuberculosis, accounting for 30-40% of cases.[9] Unfortunately, its diagnosis is challenging because of the lack of specific clinical and radiological features, as well as common negative sputum smear and culture results due to the absence of parenchymal involvement.[9-11] EBUS-TBNA has been shown to be an effective diagnostic tool in extrapulmonary tuberculosis, with a high sensitivity and a diagnostic yield of 80-94%, because it can reach mediastinal and hilar LNs that are commonly involved, so that the samples can be sent to cytological and microbiological analysis.[10,11,16-18] However, the positive culture rate for tuberculosis in this type of sample is reported to be 14-62%, which might be due to the scarcity of AFB in the LNs or lack of suitable cellular material in samples obtained from necrotic tissue.[9,16,18,19] In our study, EBUS-TBNA diagnosed tuberculosis in 4 cases, half of which were diagnosed by means of aspirate smears together with necrotizing granulomas or reactive LNs. Unfortunately, due to the small number of diagnoses of tuberculosis in our study, we cannot compare our results with those of other studies.

We had a considerable rate of patients diagnosed with reactive lymphadenopathy by EBUS-TBNA (26%), reactive LNs being our second most common cause of isolated IL. The diagnostic yield of EBUS-TBNA was good; 80% of the diagnoses of reactive lymphadenopathy were confirmed, the majority of which (92%) during the follow-up period. Only 1 case was confirmed by mediastinoscopy. Only 2 patients with reactive LNs had no associated comorbidities. The sensitivity and NPV for that diagnosis by EBUS-TBNA were 92.3% and 91.1%, respectively. These results allow us to rely on EBUS-TBNA when it indicates reactive LNs, especially in patients with other inflammatory or chronic diseases and in the absence of a high degree of suspicion of malignancy or alternative diagnoses. Some studies have reported an IL incidence of approximately 35% in HIV patients on the basis of CT findings, and this can be a challenge for clinicians due to a variety of differential diagnoses.[20] Although EBUS-TBNA can help patients avoid surgical procedures in such cases, few studies have evaluated its utility in such patients. According to Han et al.,[20] EBUS-TBNA can prevent mediastinoscopy in 89% of the cases; dispenses with general anesthesia and hospitalization in most centers; and has a low rate of major complications and mortality. In our study, there were only 2 HIV patients: 1 was diagnosed with reactive lymphadenopathy that was confirmed during the follow-up period, and 1 was diagnosed with nonspecific granuloma revealed to be due to *Mycobacterium avium* by mediastinoscopy.

In our study, EBUS-TBNA showed very good specificity in benign diseases, almost all cases being confirmed with no need for more invasive procedures. Furthermore, the accuracy of EBUS-TBNA can be improved with other bronchoscopic procedures, such as BAL, TBB, and endobronchial biopsy, performed during the same procedure when pulmonary infiltrates or secretions are present and especially when nonspecific granulomas, reactive LNs, or inconclusive results are found. In our study, EBUS-TBNA provided a definitive diagnosis in one third of such cases when associated with other bronchoscopic procedures.

Lymphoma is a common cause of mediastinal tumors; however, only 10% are primary mediastinal lymphomas in adults.[21] Despite the relatively lower sensitivity of EBUS-TBNA for lymphoma—because large samples are often required to achieve adequate cellularity and evaluate tissue architecture—EBUS-TBNA has been reported to have a sensitivity ranging from 76.0% to 90.9% and a specificity of 100% when combined with flow cytometry and immunohistochemical analysis.[1,22] In a study by Nunez et al.,[22] 89% of patients with deep-seated lymphadenopathy were diagnosed by endoscopic ultrasound or EBUS-guided fine-needle aspiration. The authors also observed that at least two additional passes can provide an adequate number of cells for flow cytometric analysis, and most of the patients who underwent this diagnostic modality had no need for subsequent surgical LN excision.[22] In our study, EBUS-TBNA failed to yield a definitive diagnosis

of lymphoma; it raised the suspicion of lymphoma in 2 cases, which were subsequently confirmed by surgical biopsy of the LNs. This finding might be due to a low level of suspicion at the time of the procedure and, consequently, the absence of flow cytometry analysis and immunohistochemistry.[1]

The limitations of our study are the typical limitations of any retrospective study. Furthermore, ours was a relatively small population, and some subgroups—particularly malignancy cases—were underrepresented. Finally, ROSE was not available in our routine. We understand the importance of ROSE to raise the suspicion of a particular diagnosis and direct the analysis of the collected material (culture, flow cytometry, or other).

In conclusion, inflammatory and infectious LNs were the most common findings in our non-neoplastic patients with isolated IL. EBUS-TBNA showed good sensitivity and high NPV and should therefore be considered a first-line minimally invasive diagnostic procedure in such cases. Accuracy can be optimized by using clinical and radiological findings appropriately in order to guide further evaluation, follow-up, and the use of bronchoscopic methods.

REFERENCES

1. Yang H, Wang S, Teng J, Han B, Sun J. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing non-specific inflammatory intrathoracic lymphadenitis. Clin Respir J. 2018;12(2):691-698. https://doi.org/10.1111/crj.12580
2. Wang L, Wu W, Teng J, Zhong R, Han B, Sun J. Sonographic Features of Endobronchial Ultrasound in Differentiation of Benign Lymph Nodes. Ultrasound Med Biol. 2016;42(12):2785-2793. https://doi.org/10.1016/j.ultrasmedbio.2016.07.019
3. Ayub II, Mohan A, Madan K, et al. Identification of specific EBUS sonographic characteristics for predicting benign mediastinal lymph nodes. Clin Respir J. 2018;12(2):681-690. https://doi.org/10.1111/crj.12579
4. Evison M, Crosbie PA, Morris J, Martin J, Barber PV, Booton R. A study of patients with isolated mediastinal and hilar lymphadenopathy undergoing EBUS-TBNA [published correction appears in BMJ Open Respir Res. 2014;1(1):e000040corr1]. BMJ Open Respir Res. 2014;1(1):e000040. https://doi.org/10.1136/bmjresp-2014-000040
5. Korrungruang P, Boonsarngsuk V. Diagnostic value of endobronchial ultrasound elastography for the differentiation of benign and malignant intrathoracic lymph nodes. Respirology. 2017;22(5):972-977. https://doi.org/10.1111/resp.12979
6. Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol. 2009;4(5):568-577. https://doi.org/10.1097/JTO.0b013e3181a0d82e
7. Çağlayan B, Salepçi B, Fidan A, Kiral N, Cömert SS, Yavuzer D, et al. Sensitivity of convex probe endobronchial sonographically guided transbronchial needle aspiration in the diagnosis of granulomatous mediastinal lymphadenitis. J Ultrasound Med. 2011;30(12):1683-1689. https://doi.org/10.7863/jum.2011.30.12.1683
8. Dhooria S, Gupta N, Bal A, Sehgal IS, Aggarwal AN, Sethi S, et al. Role of Xpert MTB/RIF in differentiating tuberculosis from sarcoidosis in patients with mediastinal lymphadenopathy undergoing EBUS-TBNA: a study of 147 patients. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33(3):258-266.
9. Kiral N, Caglayan B, Salepci B, Torun Parmaksiz E, Fidan A, Comert SS, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic tuberculous lymphadenitis. Med Ultrason. 2015;17(3):333-338. https://doi.org/10.11152/mu.2013.2066.173.nki
10. Ye W, Zhang R, Xu X, Liu Y, Ying K. Diagnostic Efficacy and Safety of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Intrathoracic Tuberculosis: A Meta-analysis. J Ultrasound Med. 2015;34(9):1645-1650. https://doi.org/10.7863/ultra.15.14.06017
11. Navani N, Molyneaux PL, Breen RA, Connell DW, Jepson A, Nankivell M, et al. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. Thorax. 2011;66(10):889-893. https://doi.org/10.1136/thoraxjnl-2011-200063
12. Low SY, Koh MS, Ong TH, Phua GC, Anantham D. Use of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of granulomatous mediastinal lymphadenopathy. Ann Acad Med Singapore. 2014;43(5):250-254.
13. von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, in 't Veen JC, et al. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA. 2013;309(23):2457-2464. https://doi.org/10.1001/jama.2013.5823
14. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. Respir Med. 2012;106(6):883-892. https://doi.org/10.1016/j.rmed.2012.02.014
15. Dziedzic DA, Peryt A, Orlowski T. The role of EBUS-TBNA and standard bronchoscopic modalities in the diagnosis of sarcoidosis. Clin Respir J. 2017;11(1):58-63. https://doi.org/10.1111/crj.12304
16. Li W, Zhang T, Chen Y, Liu C, Peng W. Diagnostic Value of Convex Probe Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Mediastinal Tuberculous Lymphadenitis: A Systematic Review and Meta-Analysis. Med Sci Monit. 2015;21:2064-2072. https://doi.org/10.12659/MSM.894526
17. Madan K, Mohan A, Ayub II, Jain D, Hadda V, Khilnani GC, et al. Initial experience with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a tuberculosis endemic population. J Bronchology Interv Pulmonol. 2014;21(3):208-214. https://doi.org/10.1097/LBR.0000000000000080
18. Geake J, Hammerschlag G, Nguyen P, Wallbridge P, Jenkin GA, Korman TM, et al. Utility of EBUS-TBNA for diagnosis of mediastinal tuberculous lymphadenitis: a multicentre Australian experience. J Thorac Dis. 2015;7(3):439-448.
19. Thangakunam B, Isaac BTJ, Christopher DJ. Endobronchial ultrasound experience in a high tuberculosis prevalence setting. Indian J Tuberc. 2017;64(3):196-200. https://doi.org/10.1016/j.ijtb.2016.11.035
20. Han AY, Tan AH, Koh MS. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in diagnosis of intrathoracic lymphadenopathy in patients with human immunodeficiency virus infection. Biomed Res Int. 2015;2015:257932. https://doi.org/10.1155/2015/257932
21. Senturk A, Babaoglu E, Kilic H, Hezer H, Dogan HT, Hasanoglu HC, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. Asian Pac J Cancer Prev. 2014;15(10):4169-4173. https://doi.org/10.7314/APJCP.2014.15.10.4169
22. Nunez AL, Jhala NC, Carroll AJ, Mikhail FM, Reddy VV, Xian RR, et al. Endoscopic ultrasound and endobronchial ultrasound-guided fine-needle aspiration of deep-seated lymphadenopathy: Analysis of 1338 cases. Cytojournal. 2012;9:14. https://doi.org/10.4103/1742-6413.95845