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Original Article

Linear Endobronchial Ultrasound as the Initial Diagnostic Tool in Patients With Indications of Mediastinal Disease

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ABSTRACT

Introduction: Linear endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has proven useful for sampling mediastinal masses and nodes and staging lung cancer. The aim of this study was to assess the usefulness of this diagnostic tool in patients with indications of mediastinal disease that could not be diagnosed by noninvasive methods or white light bronchoscopy.
Patients and Methods: All patients undergoing linear EBUS-TBNA for the diagnosis of mediastinal masses and/or adenopathy at our endoscopy unit were included in the study. Diagnoses obtained by linear EBUS-TBNA or any surgical technique performed after a nondiagnostic EBUS-TBNA were considered as final.
Results: In the study population of 128 patients with a mean (SD) age of 62.0 (11.2) years, a total of 294 TBNAs were performed on 12 masses and 282 nodes. Satisfactory samples were obtained in 11 cases (91.7%) from masses and in 233 cases (82.6%) from nodes. Linear EBUS-TBNA was diagnostic, obviating the need for mediastinoscopy in 115 patients (diagnostic sensitivity, 89.8%). The technique confirmed the diagnosis in 85 of the 94 patients with cancer (90.4%), in 8 of the 10 patients with tuberculosis (80.0%), and in the 5 with sarcoidosis.
Conclusions: Linear EBUS-TBNA is a useful diagnostic tool in patients with mediastinal disease for whom a pathologic diagnosis is not achieved by noninvasive methods or white light bronchoscopy.

La ultrasonografía endobronquial lineal como instrumento de diagnóstico inicial en el paciente con ocupación mediastínica

Palabras clave:
Neoplasia broncopulmonar
Punción espirativa
Ultrasonografía endobronquial
Mediastino

RESUMEN

Introducción: La punción aspirativa (PA) guiada por ultrasonografía endobronquial (USEB) lineal permite el muestreo de masas y ganglios mediastínicos, y ha mostrado su utilidad en la estadificación del paciente con neoplasia broncopulmonar. El objetivo del estudio ha sido determinar su utilidad como instrumento diagnóstico en el paciente con ocupación mediastínica cuya causa permanece indeterminada después de obtener muestras con exploraciones no invasivas y broncoscopia con luz blanca.
Pacientes y métodos: Se incluyó en el estudio a todos los pacientes explorados por PA guiada por USEB lineal para el diagnóstico de masa y/o adenopatía/s mediastínica/s. Se consideraron diagnósticos finales aquéllos obtenidos con PA guiada por USEB lineal y los alcanzados con cualquier técnica quirúrgica realizada con posterioridad a la USEB cuando ésta no había sido diagnóstica.

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Resultados: Se estudiaron 128 pacientes (edad media ± desviación estándar: 62,0 ± 11,2 años) en los que se realizaron 294 PA sobre 12 masas y 282 ganglios. En las masas mediastínicas se obtuvieron muestras valorables en 11 casos (91,7%) y en los ganglios, en 233 casos (82,6%). La PA dirigida por USEB lineal fue el instrumento diagnóstico y evitó la mediastinoscopia en 115 pacientes (sensibilidad diagnóstica: 89,8%). La técnica confirmó el diagnóstico en 85 de los 94 pacientes con neoplasia (90,4%), en 8 de los 10 con tuberculosis (80,0%) y en los 5 con sarcoidosis (100%).
Conclusiones: La PA guiada por USEB lineal es un instrumento de diagnóstico útil en los pacientes con afectación mediastínica cuyo diagnóstico anatomopatológico no se alcanza por medio de exploraciones no invasivas ni broncoscopia con luz blanca.

Introduction

Real-time linear endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)—a recently introduced technique for reaching mediastinal tumors and nodes—has proven useful in the study of lung cancer.[1-6] As it is fairly noninvasive and involves no clinically significant complications,[7] this technique has become a very attractive tool for staging lung cancer, which has been the focus of most previous studies.[1-6] Few authors, however, have investigated its use as a diagnostic tool in patients with mediastinal disease, whether malignant or benign.[8-11] The aim of this study was to show the performance of real-time linear EBUS-TBNA for diagnosing mediastinal disease whose cause has not been determined by noninvasive methods or white light endoscopy.

Patients and Methods

Population

All patients referred to the North Barcelona respiratory endoscopy referral unit for the diagnosis of mediastinal tumors and/or adenopathy by real-time linear EBUS-TBNA between April 2005 and March 2008 were included prospectively in the study. The inclusion criteria were the presence of a mediastinal tumor and/or mediastinal adenopathy in the computed tomography (CT) scans, with negative results in the initial non-surgical diagnostic study. This study included cultures of respiratory secretions for potentially pathogenic microorganisms and mycobacteria, in addition to cytology of sputum, bronchial aspirate, bronchial brushings, bronchoalveolar lavage fluid or pleural fluid in the case of effusion; and bronchial biopsy if a bronchial tumor was observed endoscopically. The exclusion criteria were the presence of a coagulation disorder or low platelet levels that contraindicated the TBNA, mechanical ventilation, and a history of cancer unless more than 10 years had passed with no evidence of recurrence during the follow-up. The study was approved by the North Barcelona Ethics Committee and the explorations were carried out with the informed consent of the patients.

Technique

The EBUS-TBNA was performed using local anesthetic (up to 8.2 mg/kg) and deep sedation with midazolam at an initial dose of 0.07 mg/kg, increased by 1 mg/min to achieve the desired effect and later by 1 mg every 5 to 10 minutes to maintain this effect, up to a maximum cumulative dose of 0.67 mg/kg, following the clinical guidelines for respiratory endoscopy.[12] We used a flexible bronchoscope (BF-UC160F-OL8, Olympus Optical Co. Ltd., Tokyo, Japan), which has at the distal tip a linear transducer that scans the paratracheal and peribronchial mediastinal tissue parallel to the insertion direction. The bronchoscope has a working channel for performing the transtracheal and transbronchial needle aspiration under visual control. To obtain the ultrasound image, the tip of the bronchoscope comes into contact with the wall of the trachea or bronchus. To improve the image the tip is covered by a balloon that is filled with saline solution when the ultrasound transducer is not properly positioned against the wall. Doppler mode can also be used to scan the mediastinum when necessary to distinguish the vascular structures from the tumor and/or the mediastinal nodes. In each exploration the bronchoscopist viewed any mediastinal tumors that were present, the right and left paratracheal lymph nodes of the mediastinum, the subcarinal nodes, the nodes in the aortopulmonary window and the lobar nodes. Their lesser diameter was measured (EUS EXERA EU-C80, Olympus Optical Co. Ltd.). Detected tumors and nodes whose lesser diameter was 5 mm or more were punctured with real-time visual guidance, using a cytology needle specially designed for the unit (NA2015X-4022, Olympus Optical Co. Ltd.). The needle was pushed through the channel of the bronchoscope to the trachea, where it was released from its sheath and introduced through the tracheal or bronchial wall under direct ultrasound guidance until the node or tumor was reached. We started with the ones that could involve a more advanced staging. While the needle was moved inside the tumor or node 8 to 10 times, negative pressure was maintained at the proximal end of the catheter. After obtaining the sample, the bronchoscopist withdrew the needle and cytology was performed immediately to determine whether the sample came from a normal node (if neoplastic cells were absent and lymphocytes were predominant) or from a malignant tumor or node (if neoplastic cells were found). A finding of granulomas in the sample was considered to confirm a diagnosis of tuberculosis or sarcoidosis, according to the presence or absence of central necrosis and the results of mycobacterial cultures. Samples that contained only bronchial cells, blood, insufficient material, or atypical cells that were inconclusive were considered unsatisfactory and in this case the aspiration maneuver was repeated on the tumor or node up to 3 times.

Subsequently, the pathology department reassessed the samples to confirm the diagnosis. Diagnoses of mediastinal disease obtained by linear EBUS-TBNA or by any surgical technique performed after a nondiagnostic EBUS-TBNA were considered as final. In cases in which the linear EBUS-TBNA showed only normal nodes, it was considered that the technique had correctly diagnosed benign disease when in the follow-up period—of at least 6 months—the patients showed remission of the mediastinal disease and no diagnosis of malignancy.

Statistical Analysis

For the statistical analysis we used the SPSS statistical package, version 15.0 (SPSS, Inc, Chicago, Illinois, USA). We performed a descriptive statistical analysis of the results obtained, expressing the quantitative variables as mean (SD) if normally distributed and as median and interquartile range if nonnormally distributed; the qualitative variables are expressed as absolute and relative frequencies. The diagnostic sensitivity and the negative predictive value of the technique in assessing cancer were determined, taking as a reference the final diagnosis regardless of the method used to obtain it.

Results

Of all the patients referred to the North Barcelona Respiratory Endoscopy Reference Unit for the diagnosis of mediastinal tumors and/or adenopathy by real-time linear EBUS-TBNA in the study period, 141 met the inclusion criteria. Mediastinal disease was diagnosed in 128 (90.1%) patients, who made up the present series. In the 13 patients not included in the study, normal tissue was obtained in the sampling of mediastinal nodes, and in the subsequent explorations a firm diagnosis was not obtained; a 6-month follow-up was not possible, either because the home of the patients was outside the North Barcelona area or because the patients refused.

The 128 patients included in the study had a mean (SD) age of 62.0 (11.2) years and most were men. In all cases the CT scan showed a mediastinal tumor and/or adenopathy. IA lung nodule or mass was also observed in 88 patients (68.7%) and an alveolar pattern or atelectasis in 9 (7.0%). In 26 patients (20.3%) the CT scan showed no anomalies in the lung fields (Table 1).

A total of 294 NAs were performed on 12 mediastinal masses and 282 nodes in the 128 patients included in the study. Satisfactory samples were obtained from the NA of 11 mediastinal masses (91.7%), 9 of which (75.0%) were diagnosed as lung cancer (Figure 1). Satisfactory samples were aspirated from nodes in 233 cases (82.6%). Malignant cells were obtained in 127 (45.0%) of these, normal cells in 92 (32.6%) (Figure 2) and granulomas in 14 (5.0%) (Table 2). None of the 128 patients undergoing endoscopy developed complications resulting from either the sedation or the procedure.

For 94 patients (73.4%) the final diagnosis was cancer, mainly originating in the lung. The final diagnosis was tuberculosis in 10 cases and sarcoidosis in 5. Linear EBUS-TBNA findings were diagnostic in 115 patients (89.9%), confirming cancer in 85 cancer patients (90.4% of the total with this final diagnosis), tuberculosis in 8 patients (80.0%) and sarcoidosis in 5 patients (100%).

In addition to diagnoses obtained by linear EBUS-TBNA (Table 3), the technique also made it possible to confirm N2 or N3 status in 83 of the 92 patients with a bronchopulmonary tumor in whom the findings were positive for malignancy (90.2%). In 9 of the patients with a final diagnosis of bronchopulmonary tumor (9.8%), the staging by linear EBUS-TBNA showed N0 or N1 status. In 4 of these patients mediastinoscopy confirmed the staging established with EBUS-TBNA. Mediastinoscopy was ruled out in 5 patients with N0 or N1 status diagnosed by EBUS-TBNA due to the presence of severe chronic obstructive pulmonary disease and/or distant metastasis in subsequent studies. These findings ruled out surgical treatment. The thoracotomy confirmed the preoperative staging in 3 of the 4 patients in whom all the examinations had shown the absence of cancer in the mediastinal nodes, and in 1 in whom metastasis was observed in a prevascular N2 node.

Mediastinoscopy was the surgical technique used to diagnose tuberculosis in the 2 patients with this final diagnosis, in whom EBUS-TBNA had showed only normal lymph node cellularity. In 2 of the 4 patients with a final diagnosis of benign tumor, the EBUS-TBNA finding of normal thyroid tissue was diagnostic. In the other 2 patients the samples showed normal lymph node cells and the

Table 1
Clinical and Radiologic Characteristics[a]

No. of patients	128
Mean age, y	61.7 (11.3)
Sex (women)	25 (19.5%)
Computed tomography	
Mediastinal adenopathy/mass	128 (100.0%)
Lung fields	
Pulmonary nodule(s)	41 (32.0%)
Pulmonary mass	47 (36.7%)
Alveolar pattern/atelectasis	9 (7.0%)
Pleural effusion	3 (2.3%)
Interstitial pattern	2 (1.6%)
Normal	26 (20.3%)

[a] Data are expressed as mean (SD) or as number (percentage).

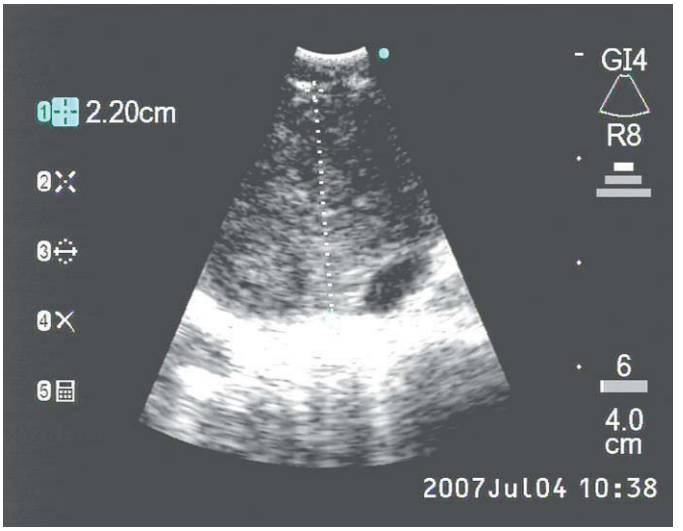

Figure 1. Right paratracheal tumor. Diagnosis based on the aspirated material: adenocarcinoma.

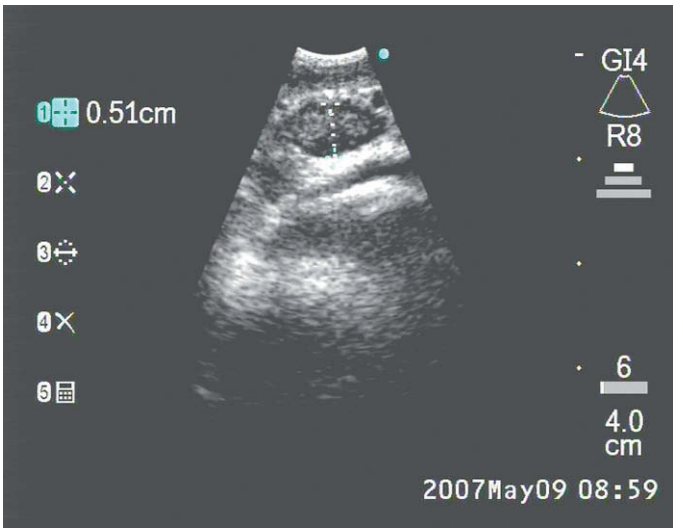

Figure 2. Subcarinal lymph node. Diagnosis of the aspiration: normal lymph node.

Table 2
Characteristics of the Sampled Masses and Nodes[a]

No. of masses and nodes sampled	294
Mediastinal mass	12 (4.1%)
Mediastinal node	239 (81.3%)
Right paratracheal, station 2	4 (1.4%)
Left paratracheal, station 2	1 (0.3%)
Right paratracheal, station 4	62 (21.1%)
Left paratracheal, station 4	25 (8.5%)
Aortopulmonary window, station 5	1 (0.3%)
Subcarinal, station 7	146 (49.7%)
Lesser diameter, mm	12 (5-19)
Lobar node	43 (14.6%)
Station 10	29 (9.9%)
Station 11/12	14 (4.8%)
Lesser diameter, mm	10 (4-16)

[a] Data are expressed as number (percentage) or median (interquartile range).

Table 3
Results of the Linear Endobronchial Ultrasound-Guided Needle Aspiration[a]

Masses sampled	12
Malignancy	9 (75.0%)
Adenocarcinoma	3 (25.0%)
Squamous cell carcinoma	2 (16.7%)
Non–small cell cancer	3 (25.0%)
Small cell cancer	1 (8.3%)
Cellular atypia	1 (8.3%)
Benign tumor	2 (16.7%)
Lymph nodes sampled	282
Normal lymph nodes	92 (32.6%)
Granuloma	14 (5.0%)
Malignancy	127 (45.0%)
Adenocarcinoma	50 (17.7%)
Squamous cell carcinoma	18 (6.4%)
Non–small cell cancer	38 (13.5%)
Small cell cancer	21 (7.4%)
Cellular atypia	5 (1.8%)
Unsatisfactory samples	41 (14.5%)

[a]Data are expressed as number (percentage).

Table 4
Final Diagnosis and Linear Endobronchial Ultrasound-Guided Needle Aspiration as a Diagnostic Technique

Final Diagnosis		Diagnosis by Endobronchial Ultrasonography	
	No.	No.	%
Patients	128	115	89.8
Cancer	94	85	90.4
Adenocarcinoma	38	32	84.2
Squamous cell carcinoma	13	11	84.6
Non–small cell cancer	25	25	100
Small cell cancer	16	15	93.7
Extrapulmonary	2	2	100
Tuberculosis	10	8	80.0
Sarcoidosis	5	5	100
Benign tumor	4	2	50.0
Benign disease	15	15	100

diagnosis was established by thoracotomy. In 15 patients in whom the material obtained by EBUS-TBNA corresponded to normal lymph nodes, the clinical presentation and the absence of abnormalities in the lung fields led us to consider a diagnosis of benign disease, which was confirmed by the remission of the mediastinal disease and the lack of neoplastic disease in the 6 months following the use of the technique.

EBUS-TBNA allowed us to establish the final diagnosis (Table 4), and avoid performing diagnostic mediastinoscopy in 115 patients: 85 (90.4%) with a final diagnosis of cancer and 30 (88.2%) with benign disease. The diagnostic sensitivity was therefore 89.8%. The negative predictive value of the technique for malignancy in our study was 69.8%.

Discussion

Our study shows that real-time linear EBUS-TBNA is a useful diagnostic tool in patients with mediastinal disease for whom a pathologic diagnosis is not achieved by noninvasive methods or white light bronchoscopy, even in cases in which the cause is not a neoplastic process. In the cases studied the technique achieved a diagnostic sensitivity of 89.9% and a negative predictive value for malignancy of 69.8%.

Since real-time linear EBUS-TBNA was introduced, most studies have focused on lung cancer, paying particular attention to staging.[1-6] Our series shows that the technique is extremely useful in the diagnosis of lung cancer when CT scanning shows mediastinal disease and conventional bronchoscopic techniques have shown negative results. In our study, linear EBUS-TBNA established the diagnosis in about 90% of the patients in this situation, with the added advantage of staging the disease during the same procedure. Metastatic adenocarcinoma of the lymph nodes was found in 2 patients (1.6%); immunohistochemical techniques subsequently showed that one of these originated in the breast and the other in the colon. In both patients the CT scan showed mediastinal adenopathy and normal lung fields. In only one such case reported in the literature did linear USEB-TBNA successfully diagnose papillary thyroid carcinoma.[11]

The increasing use of real-time linear USEB-TBNA has led to its application in the diagnosis of nonneoplastic diseases, in which context the yield is high according to the results of the present study. Our series shows its usefulness in diagnosing sarcoidosis, confirmed in 5 patients with clinical and radiologic signs of the disease and with a sample in which nonnecrotizing granulomas were observed and the culture for mycobacteria was negative. Other authors with a greater number of observed cases[8-10,13] have also reported the usefulness of EBUS-TBNA for diagnosing sarcoidosis and our results indicate that in this disease the technique offers better yield than blind NA on mediastinal adenopathy. Similarly, in the present study the diagnosis of lymph node tuberculosis was relatively frequent, with a total of 10 cases (7.8% of the patients included). In 8 cases (80%) the sample obtained by linear EBUS-TBNA was sufficient to establish the diagnosis when it showed the characteristic caseating granulomas in a clinical and radiologic context that indicated the disease. In 2 cases in which only normal cellularity was shown in the samples, it was necessary to perform mediastinoscopy to reach the final diagnosis.

The use of NA in the diagnosis of diseases caused by mycobacteria has been limited so far,[14,15] but the results of our study indicate that when it is guided by linear EBUS it can confirm the diagnosis in a high proportion of cases of such diseases in which there is mediastinal involvement. These cases of lymph node granulomatosis must be differentiated from the occasional finding of isolated granulomas in an NA of mediastinal nodes performed in patients who have been treated for cancer, as was reported recently.[15]

NA guided by ultrasound has been used in the diagnosis of lymphoma in digestive[16] and respiratory[17] endoscopy. Samples obtained by EBUS-TBNA have been useful for diagnosing Hodgkin lymphoma, which was confirmed by the observation of Reed-Sternberg cells in the sample, and non-Hodgkin lymphoma, which was confirmed by using cytology, immunohistochemical techniques and flow cytometry on the sample.[16,17] However, in 2 of the 3 cases described in which this technique was used for the diagnosis, it was necessary to obtain additional biopsies from other sites to subclassify the disease.[17] Despite this limitation, the technique may give better results than mediastinoscopy in specific cases, such as checking for recurrence in the follow-up after a mediastinal exploration has been performed, and when the disease only affects the hilar region. In our series, none of the NA samples indicated lymphoma and in the cases in which they indicated normal lymph nodes no lymphoma was diagnosed in the following 6 months.

The samples obtained using the technique were satisfactory in 83.0% of the cases, a percentage higher than that observed in other series without direct visualization of the target lesion.[18,19] The difference in the results is obviously due to the great advantage of real-time visualization of the node by ultrasound, which shows the structure that is being sampled at all times and reduces the risk of aspirating vascular structures when the technique is combined with the Doppler mode. None of the possible complications described for transtracheal and transbronchial NA, such as pneumothorax, pneumomediastinum, hemomediastinum, bacteremia, or pericarditis[5] were observed in any of our patients; nor have they been reported in previous series in which linear EBUS-TBNA was used.

In conclusion, real-time linear EBUS-TBNA was diagnostic in 115 patients with mediastinal tumors or adenopathy that could not

be diagnosed by noninvasive methods or white light bronchoscopy. These patients comprised 89.9% of the cases studied. In the subgroup of patients with granulomatous diseases of the mediastinal lymph nodes, such as tuberculosis or sarcoidosis, the diagnostic rate was also higher than 80%. The technique made it unnecessary to use diagnostic mediastinoscopy in almost 90% of the patients studied, thus confirming the great importance of ultrasound guidance in diagnostic respiratory endoscopy in patients with mediastinal disease of unknown origin. However, if a result of linear EBUS-TBNA is negative for malignancy, invasive diagnostic techniques must be used, because the negative predictive value in this case—69.8% in our series—is insufficient to rule out cancer.

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