Usefulness of Endoscopic Ultrasound-Guided Fine Needle Aspiration in the Diagnosis of Mediastinal Lesions

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OBJECTIVE: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a safe and effective technique for the diagnosis of focal pancreatic lesions and enlarged abdominal lymph nodes. The aim of this study was to assess the usefulness of EUS-FNA in the diagnosis of mediastinal lesions.

PATIENTS AND METHODS: A retrospective review was performed of all consecutive cases in which EUS-FNA was used for the diagnosis of a mediastinal lesion between January 2001 and September 2003. We used a radial echoendoscope to assess the characteristics of the lesion and a linear-array echoendoscope to perform transesophageal needle aspiration with a 22-gauge needle. Histopathology of the resected specimen was considered as the gold standard in surgically treated patients whereas cytology obtained by EUS-FNA was the gold standard when surgery was not indicated.

RESULTS: EUS-FNA was performed in 59 patients with a total of 89 lesions with mean (SD) dimensions of 2.4 (2.0) cm × 1.6 (1.4) cm. Malignant lesions were larger than benign ones (short axis, 2.7 [1.4] as compared with 1.0 [0.9] cm; *P*<.001). The diagnosis was obtained for 53 patients (90%) and 81 lesions (91%) with a mean of 2 (1) passes per lesion. The sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of EUS-FNA were 81%, 100%, 100%, 75%, and 88%, respectively, when analyzed by lesion, and 88%, 100%, 100%, 80%, and 92% when analyzed by patient.

CONCLUSIONS: EUS-FNA is an effective technique for the diagnosis of mediastinal lesions. The likelihood of malignancy increases with size.

Key words: *Fine-needle aspiration. Endoscopic ultrasound. Mediastinum.*

Valor de la punción aspirativa con aguja fina guiada por ultrasonografía endoscópica en el diagnóstico de las lesiones mediastínicas

OBJETIVO: La punción aspirativa con aguja fina guiada por ultrasonografía endoscópica (USE-PAAF) es una técnica eficaz y segura en el diagnóstico de las lesiones focales del páncreas y las adenopatías intraabdominales. El objetivo de este estudio es describir su utilidad en el diagnóstico de las lesiones mediastínicas.

PACIENTES Y MÉTODOS: Se han revisado todos los casos consecutivos a los que se realizó una USE-PAAF para estudio de una lesión mediastínica desde enero de 2001 hasta septiembre de 2003. Las exploraciones se efectuaron con un ecoendoscopio radial para estudio de las características de la lesión y un ecoendoscopio sectorial para realizar la punción transesofágica usando una aguja de 22 G. Se utilizó como referencia la cirugía en los pacientes operados y el resultado de la citología obtenida con la USE-PAAF en los casos en que el tratamiento quirúrgico no estaba indicado.

RESULTADOS: Se realizó USE-PAAF a 59 pacientes con un total de 89 lesiones, con diámetro medio ± desviación estándar de 2,4 ± 2 × 1,6 ± 1,4 cm. El tamaño de las lesiones malignas fue mayor que el de las benignas (diámetro corto: 2,7 ± 1,4 frente a 1 ± 0,9 cm, respectivamente; p < 0,001). El material obtenido permitió el diagnóstico en 53 pacientes (90%) y en 81 lesiones (91%), y el número de pases fue de 2 ± 1 por lesión. La sensibilidad, la especificidad, el valor predictivo positivo, el valor predictivo negativo y la precisión para el diagnóstico fueron del 81, el 100, el 100, el 75 y el 88%, respectivamente (el 88, el 100, el 100, el 80 y el 92% al analizarlos por paciente).

CONCLUSIONES: La USE-PAAF es una técnica eficaz en el estudio de la patología mediastínica. La probabilidad de malignidad es mayor cuanto mayor es el tamaño de la lesión.

Palabras clave: *Punción aspirativa. Ultrasonografía endoscópica. Mediastino.*

Introduction

Assessment of mediastinal disease is often difficult and imaging techniques such as computed tomography (CT) and magnetic resonance imaging often fail to allow malignant and benign lesions to be distinguished on the basis of morphologic features.[1,2] On the other hand, a firm

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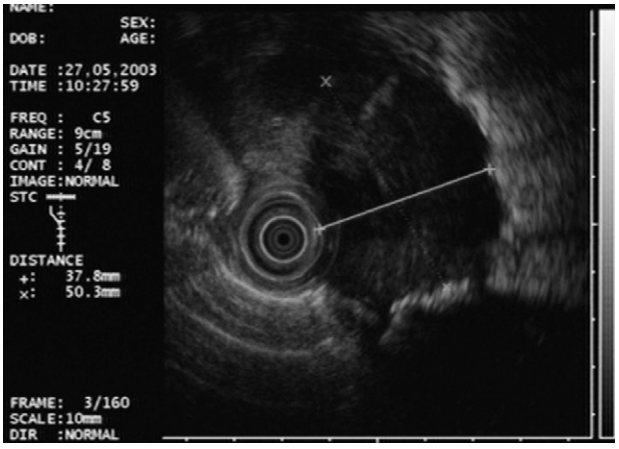

Figure 1. Left paraesophageal mass with malignant characteristics: heterogeneous and poorly circumscribed. The mass was diagnosed as a liposarcoma.

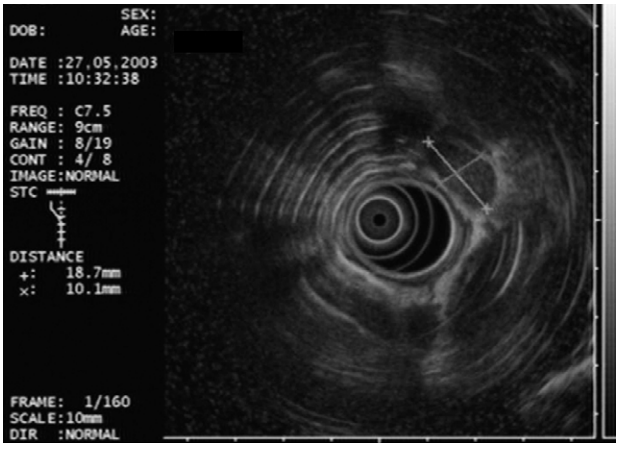

Figure 2. Enlarged lymph node in the 4L lymph node station with ultrasound characteristics of malignancy: round, hypoechogenic, well circumscribed, and with a short-axis diameter of 1 cm.

pathologic diagnosis is essential both for staging mediastinal lymph nodes prior to treatment in patients with non-small cell lung cancer (NSCLC) and for assessment of patients with enlarged lymph nodes or masses of uncertain origin. Consequently, material must often be obtained for cytology or histology, and this requires the use of invasive techniques that are associated with appreciable mortality.

Endoscopic ultrasound (EUS) is a technique that combines gastrointestinal endoscopy with ultrasonography to obtain ultrasound images from within the digestive tract. When the transducer is located in the esophagus, the structures of the middle and posterior mediastinum situated within a radius of 6 cm around the esophagus can be visualized. Real-time EUS-guided fine-needle aspiration (EUS-FNA) has recently been shown to be a very safe and effective technique for the diagnosis of mediastinal involvement in NSCLC and esophageal carcinoma.[3-6] In addition, case series have addressed the usefulness of EUS-FNA in the diagnosis of mediastinal masses.[7-9]

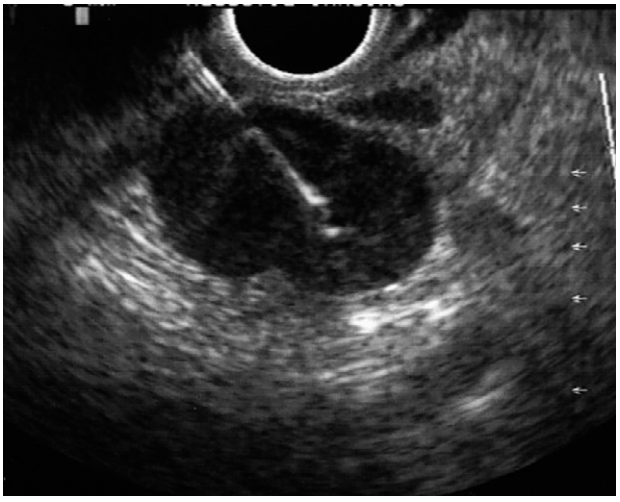

Figure 3. Endoscopic ultrasound-guided fine-needle aspiration of an enlarged mediastinal lymph node. The needle can be seen inside the lymph node.

The aim of the present study was to assess the usefulness of EUS-FNA for cytologic diagnosis of mediastinal lesions in a tertiary level hospital in Spain.

Patients and Methods

Between January 2001 and September 2003, EUS and EUS-FNA were performed in 59 consecutive patients referred for examination of a mediastinal lesion diagnosed by CT or for staging of a pulmonary or esophageal tumor that had been diagnosed and confirmed by cytology or histology using standard techniques (endoscopy with biopsy and bronchoscopy with forceps biopsy and/or bronchial aspiration in pulmonary and esophageal tumors, respectively). The examinations were performed in conscious patients under anesthetist-monitored sedation with propofol and remifentanil. Informed consent was provided by all patients and normal prothrombin time and platelet count were confirmed before the procedures.

First, diagnostic EUS was performed with a radial echoendoscope at frequencies of 5 and 20 MHz (GF UM20 and GF UM160, Olympus America Inc, Melville, New York, USA). In all patients a systematic examination of the posterior and middle mediastinum and the lymph node stations accessible by EUS (4R, 4L, 5, 7, 8, and 9) was undertaken to identify and characterize the morphology of the lesions and establish the relationship between the lesions and neighboring structures (Figures 1 and 2).

EUS-FNA was performed with a linear array echoendoscope (GF UC30P, Olympus America Inc) and an 8 cm, 22-gauge Wilson-Cook needle (Wilson-Cook Medical Inc, Winston-Salem, North Carolina, USA) according to standard techniques: after identifying the lesion to be examined with the radial echoendoscope, the needle was introduced through the working channel of the echoendoscope and advanced into the lesion under real-time ultrasound control (Figure 3). Color Doppler was used in every case to ensure that blood vessels were not present in the needle path. After withdrawal of the stylet (inserted to prevent contamination of the sample with cells from the wall of the digestive tract) from inside the needle, negative pressure was applied using a suction of 3 to 5 mL in a 10-mL syringe connected to the needle while the endoscopist inserted and withdrew the needle repeatedly inside the lesion.

When more than 1 enlarged node was identified in the same station, the node with the greatest likelihood of malignancy was

selected (increased size, round, well circumscribed, and hypoechogenic). When various abnormal lymph nodes were identified in different stations, the node that on the basis of its position would have the greatest clinical impact if it proved to be malignant was selected.

A cytologist was present in the examination room during EUS-FNA in order to immediately assess the sample obtained. Part of the sample was spread on a microscope slide and treated with a rapid stain (Diff-Quick, Diagnostic Grifols SA, Spain), while the rest of the material was stored in alcohol prior to staining with Papanicolaou and in saline for subsequent processing as a cell block preparation (Figure 4). A lesion was considered to be neoplastic when malignant cells were identified, while the absence of malignant cells along with the presence of normal lymphocytes was considered diagnostic of benign lymph node disease. Identification of caseating granulomas and/or positive Löwenstein culture was considered necessary for diagnosis of tuberculosis. For the statistical analysis, all results other than benign lymph node enlargement were considered positive.

Histopathology was used as the diagnostic reference standard in surgically treated patients, while the results of cytology following EUS-FNA, when these were positive for malignant cells, were used in those cases in which surgery was not indicated. This procedure is consistent with that used in the literature, based on the observation that false positives are rare with this technique.[5,9,10] When the results of EUS-FNA were benign and surgical treatment was not indicated, clinical follow-up for at least 1 year and, in cases in which tuberculosis was diagnosed, a favorable response to tuberculostatic treatment were considered as the diagnostic reference standards.

In patients with cystic lesions, prophylactic antibiotic treatment was administered with ciprofloxacin.

Statistical Analysis

The sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values were calculated using standard formulas. Comparison of proportions was performed using the χ^2 test and comparison of means in independent groups using the Student *t* test.

Results

EUS-FNA was performed in a total of 59 patients (50 men and 9 women) with a mean (SD) age of 63 (10) years (range, 36-82 years) and a total of 89 lesions (86 solid masses and 3 cysts). The indications were as follows: staging of previously diagnosed cancer of the lung or esophagus (24 and 7 patients, respectively), diagnosis of a mediastinal lesion of unknown etiology in patients with malignant disease (n=17; suspected lung cancer without histologic confirmation from other techniques, recent history of treated cancer, or presence of a nonmediastinal tumor at the time of examination), and diagnosis of a mediastinal lesion of unknown etiology in patients without suspicion of malignant disease (n=11).

In the patients referred for staging of lung cancer (n=24), the primary lesion was located in the left lung in 13 cases (8 in the upper lobe and 5 in the lower) and in the right lung in 11 (5 in the upper lobe, 4 in the lower, and 2 in the middle lobe). In 13 patients, CT did not detect significantly enlarged lymph nodes. In the remaining 11 cases, CT revealed the presence of 18 abnormally enlarged nodes located in the following regions: subcarinal (n=7), aortopulmonary window (n=5), paraesophageal (n=4), and paratracheal (n=2). All patients had previously undergone bronchoscopy and transbronchial needle aspiration had been performed without guidance in 2 out of 7 enlarged subcarinal nodes without evidence of malignancy.

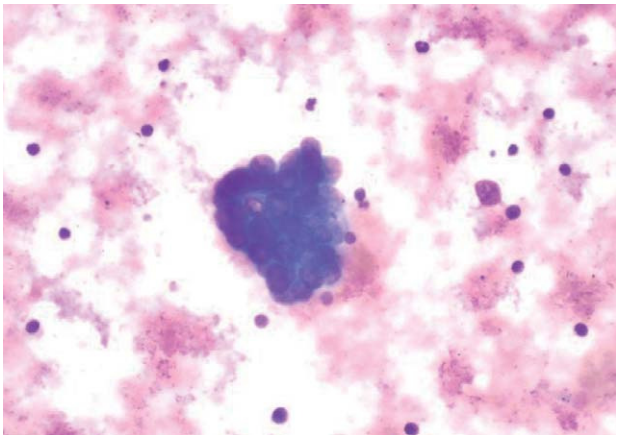

Figure 4. Metastasis of an adenocarcinoma.

The lesions were most often located in the paraesophageal (n=48) and subcarinal (n=25) regions, or the aortopulmonary window (n=13), while 3 cases were in the paratracheal region. The mean size measured by EUS was 2.4 (2) cm × 1.6 (1.4) cm (range, 0.6-8.0 cm for the long axis and 0.4-7.1 cm for the short axis).

The material obtained with EUS-FNA was adequate and allowed diagnosis in 53 of the 59 patients (90%) and 81 of the 89 lesions (91%), corresponding to 78 solid lesions (enlarged lymph nodes and tumor masses) and 3 cysts. A mean of 2 passes were performed per lesion (range, 1-6). All of the cytologic diagnoses obtained with EUS-FNA are shown in Table 1.

TABLE 1
Diagnosis of Patients in Whom Endoscopic Ultrasound-Guided Fine-Needle Aspiration Was Indicated for Examination of a Mediastinal Lesion*

Malignant disease	
Metastasis of lung cancer	19
Adenocarcinoma	7
Squamous cell carcinoma	6
Small-cell carcinoma	5
Non-small cell undifferentiated carcinoma	1
Metastasis of esophageal cancer	4
Squamous cell carcinoma	3
Adenocarcinoma	1
Melanoma	1
Salivary gland carcinoma	1
Nonmalignant disease	
Reactive lymph node	15†
Cyst	3
Bronchogenic	1
Pancreatic pseudocyst	1
Chronic lymphoblastic leukemia	1
Tuberculosis	2
Nondiagnostic	6

*Data are shown as number of patients.
†In 8 patients it was not possible to compare with a diagnostic reference standard (surgery, results of cytology, or clinical follow-up).

TABLE 2
Description of the Lesions in Which Endoscopic Ultrasound-Guided Fine-Needle Aspiration Yielded Insufficient Material for Cytologic Diagnosis*

Patient	Site	Size, mm	Number of Passes	Cytology	Final Diagnosis
1	Paraesophageal	6 × 6	3	Contamination	Surgery: lymph node negative
2a†	Paratracheal	10 × 15	2	Insufficient	EUS-FNA of another enlarged lymph node: adenocarcinoma
2b†	Aortopulmonary window	5 × 2	2	Insufficient	EUS-FNA of another enlarged lymph node: adenocarcinoma
3	Subcarinal	15 × 8	2	Insufficient	Surgery: lymph node negative
4	Cardial	9 × 5	2	Insufficient	Surgery: lymph node negative
5	Paraesophageal	9 × 8	4	Hemorrhagic	Surgery: lymph node negative
6	Paraesophageal	60 × 35	3	Insufficient	Surgery: liposarcoma
7	Paraesophageal	10 × 10	1	Contamination	Surgery: lymph node negative

*EUS-FNA indicates endoscopic ultrasound-guided fine-needle aspiration.
†The patient was correctly diagnosed through needle aspiration of a third enlarged lymph node; therefore, there were only 6 cases in which the material obtained by EUS-FNA did not allow diagnosis.

Histopathology of the surgically resected specimen was available as a diagnostic reference standard for 23 patients (39%) and 36 lesions (40%), while the results of cytology were used for 26 (44%) patients and 2 (3%) lesions, and clinical follow-up was used for 37 (42%) patients and 2 (2%) lesions. However, in 8 patients (3 patients with nonmalignant underlying disease and 5 with malignant disease), with a total of 14 lesions, follow-up was not possible, thereby providing no diagnostic reference standard.

The size of the malignant lesions was significantly greater than that of the benign ones (diameter of the short axis, 2.7 [1.4] cm and 1.0 [0.9] cm, respectively; $P<.001$). All of the solid lesions in which the diameter of the short axis was greater than 2.1 cm were malignant (n=15); in contrast, all of the lesions in which the diameter of the short axis was less then 0.8 cm were benign (n=28). We identified 5 lesions in 5 patients that corresponded to metastases of NSCLC but for which the diameter of the short axis was 1 cm or less; criteria applied in CT would have judged those lesions to be nonspecific or as having a low probability of involving metastasis.

No cases were found in which cytologic diagnosis was not possible using material considered adequate for diagnosis. The cases in which the material was insufficient to establish a cytologic diagnosis—6 patients (10%) and 8 lesions (9%)—were considered as false negatives (Table 2). However, the absence of cytologic diagnosis did not lead to any difference in the treatment of any of the patients. Thus, in 1 patient diagnosis was obtained by aspiration of another enlarged node (metastasis of NSCLC) and the patient therefore received neoadjuvant therapy. The other 5 patients with NSCLC and insufficient material from EUS-FNA underwent surgery and the enlarged mediastinal nodes were negative in all cases. Finally, a patient with a large mediastinal mass was treated surgically and the histologic diagnosis revealed that the mass was a liposarcoma.

In 30 patients (a total of 33 lesions) diagnosis of the disease was obtained and they were considered true positives, while in 15 patients (27 lesions) the enlarged nodes were benign (Table 1). No false positives for malignancy were obtained. Thus, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of EUS-FNA were 81%, 100%, 100%, 75%, and 88%, respectively (88%, 100%, 100%, 80%, and 92% when analyzed on a patient-by-patient basis).

One patient developed self-limited fever and another suffered a hypertensive crisis that required treatment; those were the only 2 complications following the procedure.

Discussion

The incidences of pulmonary and esophageal carcinomas are high and their prognosis is very poor, since at the time of diagnosis they are at advanced stages in more than half of all cases. Current treatments are based on TNM staging at diagnosis and this is especially important in squamous cell carcinoma of the esophagus and in NSCLC, tumors in which surgery offers the greatest possibility of cure. In such cases, the detection of mediastinal lymph node metastases would alter the treatment strategy, which might change from immediate surgery to neoadjuvant treatment followed or not by surgery, and in some cases, to palliative treatment.[11] Enlarged mediastinal lymph nodes are also common in nonmalignant conditions such as tuberculosis, histoplasmosis, sarcoidosis, anthracosis, and silicosis,[12,13] as well as in other extrathoracic malignant diseases.[14,15]

The usefulness of EUS-FNA has been widely demonstrated in the assessment of abdominal disease.[16-18] There have also been studies that demonstrate its efficacy in the assessment of posterior and inferior mediastinal disease,[7-9] in which similar results were obtained to those obtained in the abdomen. A recent study showed that EUS-FNA is superior to application of ultrasound criteria for malignancy in the identification of malignant mediastinal lymph node disease and concluded that it is always necessary to obtain histologic confirmation.[19] In this regard, EUS-FNA is not only less invasive and associated with lower morbidity and mortality than other techniques such as mediastinoscopy, but is also less expensive, since in most cases mediastinoscopy requires general anesthesia and hospitalization whereas EUS-FNA is performed on an outpatient basis with the patient awake and sedated.[20]

In our study, up to 37 diseased nodes had a diameter for the short axis of less than 1 cm and 5 of those were malignant (5.6%). This finding is very important, since the use of CT for diagnosis of diseased mediastinal lymph nodes in NSCLC is based on size criteria (diameter of the short axis ≥1 cm or ≥1.2 cm in the case of subcarinal lesions) and has a diagnostic accuracy of 41% to 49%.[4,21] In contrast, various studies on the usefulness of EUS-FNA in the staging of NSCLC have described a diagnostic accuracy of up to 97%.[5,22] Similar results have been described for transbronchial ultrasound-guided FNA, the diagnostic accuracy of which ranges from 89% to 97%.[23,24] However, that accuracy was slightly lower in cases in which CT did not reveal enlarged lymph nodes (70%),[25] and had a sensitivity and specificity of 50% and 100%, respectively.[26] Few studies have compared those 2 techniques, but the preliminary results that are available suggest that the procedures are complementary, since while transbronchial ultrasound-guided FNA provides better access to anterior paratracheal, subcarinal, and tracheobronchial lesions, EUS-FNA provides better access in paraesophageal lesions and lesions of the aortopulmonary window. In a recent study comparing overall efficacy for the 2 techniques in lymph node stations accessible to both, an overall accuracy of 95% was obtained.[27]

The material obtained with EUS-FNA was adequate and allowed diagnosis in 53 out of 59 patients (90%) and 81 out of 89 lesions (91%), and the mean number of passes performed was similar to that described for needle aspiration in enlarged abdominal lymph nodes.[16,17] Although our results are similar to data published from some studies,[9,28] they are better than those reported in some case series of needle aspiration in enlarged mediastinal nodes.[10] One explanation for these good results is the presence of a cytologist in the examination room.[29]

In our patient series there were no false positives; also, all of the false negatives corresponded to cases in which cytology had been insufficient to obtain diagnosis and in none of those cases did that alter the treatment strategy. In addition, the rate of false negatives was well below the 20% described elsewhere.[10]

There is a consensus that cystic lesions should generally not be punctured due to the risk of complications. However, in some cases an atypical appearance, the presence of underlying disease that may be related to the lymph node enlargement, or other special circumstances may make aspiration not only justifiable but essential. Three patients in our study had cystic lesions. One had a bronchogenic cyst full of dense material that gave it the appearance of a solid tumor. The second had a large pancreatic pseudocyst with substantial mediastinal invasion that led to dysphagia and obliged surgical treatment to be considered. As a result, all diagnostic techniques were considered indicated in that patient prior to reaching a decision on such an invasive therapeutic approach. Finally, the third patient was diagnosed with chronic lymphoblastic leukemia and the cystic mediastinal lesion was found to be a diseased lymph node with a cystic component. If needle aspiration is considered necessary, infectious complications can be avoided through the use of prophylactic antibiotic treatment (usually with ciprofloxacin).[30]

In conclusion, EUS-FNA is a safe and effective technique for assessment of enlarged mediastinal lymph nodes and allows cytologic diagnosis of lymph nodes that are too small for assessment by CT. The probability of malignancy is greater the larger the lesion.

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