

Clinical Utility of Transbronchial Needle Aspiration of Mediastinal Lymph Nodes in the Diagnosis of Sarcoidosis in Stages I and II

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OBJECTIVE: To analyze the individual and combined diagnostic yield and clinical utility of transbronchial needle aspiration and transbronchial biopsy in the histologic diagnosis of sarcoidosis in stages I and II.

PATIENTS AND METHODS: We performed a prospective study enrolling all the patients admitted to our hospital between July 2001 and June 2006 with mediastinal lymph nodes of a diameter of over 10 mm and clinical and radiological indication of sarcoidosis. The patients underwent the following tests in the order specified: a transbronchial needle aspiration of 1 or more lymph nodes using a 19-gauge histology needle until 2 satisfactory specimens were obtained, a bronchoalveolar lavage, and 4 to 6 transbronchial biopsies.

RESULTS: A total of 32 patients were enrolled during the study period. Of these, 26 were finally diagnosed with sarcoidosis. The mean (SD) age of the patients was 38.9 (10.6) years and there were 13 women (50%). The mean (SD) lymph node diameter was 23.5 (6.5) mm. The most common lymph node aspiration sites were the subcarinal station (9 patients, 34.6%) and a combination of the subcarinal and paratracheal stations (7 patients, 26.9%). Computed tomography scans of the chest revealed parenchymal involvement in 12 (46.2%) patients. Fifteen (57.7%) patients were diagnosed by transbronchial biopsy and 16 (61.5%) by transbronchial needle aspiration. These techniques were used in isolation in 7 (26.9%) and 8 (30.8%) patients, respectively ($P > .05$). Diagnosis was achieved with the combined results of transbronchial biopsy and needle aspiration in 23 (88.4%) patients. Overall, the diagnostic yield of the combined techniques was significantly higher than that of either one in isolation ($P = .01$ vs transbronchial biopsy and $P = .02$ vs needle aspiration). In patients with parenchymal involvement, yield was better for the combined techniques only in comparison with transbronchial biopsy ($P = .01$). Only 4 (15%) patients developed complications and 20 (76.9%) tolerated the procedures well.

CONCLUSIONS: Diagnostic yield was significantly higher when transbronchial biopsy and transbronchial needle aspiration were used in combination than when used alone, particularly in patients without parenchymal involvement. There were few complications and tolerance was good.

Key words: Sarcoidosis. Bronchoscopy. Transbronchial needle aspiration. Transbronchial biopsy. Bronchoalveolar lavage.

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Utilidad clínica de la punción transbronquial de adenopatías mediastínicas en el diagnóstico de la sarcoidosis en estadios I y II

OBJETIVO: Analizar tanto la rentabilidad individual como la conjunta y la utilidad clínica de la punción transbronquial (PTB) y la biopsia transbronquial (BTB) en el diagnóstico histológico de sarcoidosis en estadios I y II.

PACIENTES Y MÉTODOS: Se ha realizado un estudio prospectivo en el que se incluyó a todos los pacientes con adenopatías mediastínicas de diámetro superior a 10 mm y sospecha clinicorradiológica de sarcoidosis, ingresados entre julio de 2001 y junio de 2006. Se realizó a todos, por este orden, PTB con agujas Bard-Wang 319 de una o más adenopatías hasta obtener un mínimo de 2 muestras satisfactorias; lavado broncoalveolar, y 4-6 BTB.

RESULTADOS: Se incluyó en el estudio a 32 pacientes, de los que 26 presentaron un diagnóstico final de sarcoidosis. La edad media \pm desviación estándar fue de 38,9 \pm 10,6 años y 13 (50%) eran mujeres. El diámetro medio de las adenopatías fue de 23,5 \pm 6,5 mm. Las estaciones ganglionares más puncionadas fueron la subcarinal, con 9 casos (37,7%), y la combinación subcarinal-paratraqueal derecha, con 7 (26,9%). Se observó afectación parenquimatosa en la tomografía computarizada de tórax en 12 (46,2%). La BTB fue diagnóstica en 15 pacientes (57,7%) y la PTB en 16 (61,5%), y fueron las únicas técnicas diagnósticas en 7 (26,9%) y 8 (30,8%) casos, respectivamente ($p > 0,05$). La combinación de ambas fue diagnóstica en 23 casos (88,4%), significativamente superior a la BTB ($p = 0,01$) y a la PTB ($p = 0,02$) por separado en todos los casos, y sólo a la BTB ($p = 0,01$) en los casos con afectación parenquimatosa. Únicamente 4 pacientes (15%) presentaron alguna complicación y en 20 (76,9%) la tolerancia fue buena.

CONCLUSIONES: La adición de la PTB a la BTB incrementa significativamente el número de diagnósticos de sarcoidosis, sobre todo en pacientes sin afectación parenquimatosa. El número de complicaciones es bajo y la tolerancia, buena.

Palabras clave: Sarcoidosis. Broncoscopia. Punción transbronquial. Biopsia transbronquial. Lavado broncoalveolar.



Figure 1. Endoscopic image from patient with sarcoidosis with an inflamed, irregular mucosa. The bronchial biopsy revealed sarcoid granulomas.

Introduction

Sarcoidosis is a multisystemic disease of unknown etiology that is characterized by noncaseating granulomatous inflammation of affected structures, mainly mediastinal lymph nodes and the lungs.^{1,2} Diagnosis is made on the basis of clinical and radiological findings, the observation of noncaseating granulomas in 1 or more organs, and the exclusion of other granulomatous diseases.¹⁻³ Transbronchial biopsy has traditionally been the method of choice for the histologic diagnosis of sarcoidosis, with a reported diagnostic yield of 52% to 60% for stage I disease and 63% to 76% for stage II disease.⁴ In recent years, however, transbronchial needle aspiration (which involves the insertion of histology needles through a fiberoptic bronchoscope) has proven to be a safe and useful technique. Depending on disease stage, it can increase diagnostic yield by between 14% and 20%.³⁻⁷ Few studies, however, have analyzed the added value of transbronchial needle aspiration over standard transbronchial biopsy in diagnosing sarcoidosis, and most of them have analyzed small series.⁵⁻⁸ The aforementioned studies evaluated the diagnostic yield of the 2 techniques in accordance with disease stage determined by simple radiography, and they all concluded that both transbronchial biopsy and transbronchial needle aspiration should be systematically performed in order to optimize the number of diagnoses made in both stage I and II disease.³⁻⁸ The performance of both techniques, however, would increase the cost and duration of the procedure, and might also increase the risk of iatrogenic adverse events. Furthermore, although transbronchial needle aspiration is highly effective in the diagnosis and staging of lung cancer,⁹⁻¹¹ it is still a very much underused technique.^{10,11} Current guidelines on sarcoidosis management, in fact, do not even mention the

technique.^{2,12} Only 1 Spanish group has published a report on its usefulness in diagnosing sarcoidosis, and that was a short retrospective review of their experience.¹³ The aim of this study was to contribute to the information currently available.

Patients and Methods

We performed a prospective descriptive study enrolling all patients admitted to our hospital between July 2001 and June 2006 with clinical and radiological indication of sarcoidosis and mediastinal and/or hilar lymph nodes of a diameter over 10 mm seen on chest computed tomography (CT) scans. All the patients underwent fiberoptic bronchoscopy.

The endoscopic examination of the airways was performed by experienced bronchoscopists at Hospital Xeral de Vigo, Spain, a tertiary level hospital that serves a population of about 222 000 inhabitants. Following the procedure, a purpose-designed questionnaire was completed to record patient details, age, sex, description and site of the lesions observed on the chest CT scans, bronchoscopic findings, and test tolerance. The results of the different diagnostic techniques performed (transbronchial needle aspiration, bronchoalveolar lavage, and transbronchial biopsy) were added later. When these were not conclusive, the results of the surgical procedure used to make the definitive diagnosis (mediastinoscopy, mediastinotomy, or video-assisted thoracoscopy) were recorded.

The patients were premedicated with 0.5 mg of intramuscular atropine and in most cases administered intravenous midazolam to achieve conscious sedation. Bronchoscopy was performed transnasally with the patient in supine decubitus; local anesthesia was provided with 2% lidocaine. The patients underwent the following tests in the order specified: transbronchial needle aspiration of 1 or more lymph nodes using a 19-gauge histology needle (Bard-Wang, Billerica, Massachusetts, USA) until 2 specimens judged to be satisfactory were obtained, a bronchoalveolar lavage of the middle lobe or lingula, and 4 to 6 transbronchial biopsies of at least 2 different lobes of the same lung. Bronchial biopsy was only performed when the bronchoscopist considered that the bronchial mucosa had an abnormal appearance (Figure 1).

The aspiration site was chosen following detailed analysis of the chest CT scan and identification of the largest and most easily accessible lymph nodes. The procedure was performed following the recommendations of other authors.^{10,11,14} Bronchoalveolar lavage was performed according to the recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).¹⁵ This procedure involved instilling 120 to 180 mL of 0.9% saline solution (in aliquots of 30-50 mL) in segmental or subsegmental bronchi, following centrifugation and preparation of slides for differential cell counting. Following the procedure used in other studies, we only analyzed T-cell subpopulations when the percentage of lymphocytes in the bronchoalveolar lavage fluid was higher than 15%.¹⁶ CD4⁺ and CD8⁺ lymphocyte counts were performed using monoclonal antibodies; a CD4⁺/CD8⁺ ratio of over 3.5 was considered high.²

The bronchial and transbronchial biopsies were performed according to standard procedures using biopsy forceps (100 cm in length and a diameter of 1.8 mm) with an ellipsoid fenestrated jaw (FB-21C-1; Olympus, Tokyo, Japan). Radiologic evaluation was not systematically performed during the transbronchial biopsies.

In all cases, a posteroanterior chest radiograph was performed within 4 hours of the procedure to rule out possible complications.

Radiologic staging to distinguish between stage I and II disease (hilar lymph nodes without parenchymal involvement vs hilar and/or mediastinal lymph nodes with pulmonary infiltrates,

respectively) was based on simple chest radiographs.^{2,12} The patients were divided into 2 groups (parenchymal involvement vs no parenchymal involvement) based on the results of the high-resolution CT scans.

Bronchoscopy tolerance was rated by the bronchoscopist as very good, good, average, and poor. Test duration was not recorded.

A definitive diagnosis of sarcoidosis was made when sarcoid granulomas were identified by bronchoscopic or surgical findings and diseases with a similar clinical and radiological picture had been ruled out.²

The study was approved by the clinical research ethics committee.

Statistical Analysis

Qualitative variables were expressed as absolute frequencies and percentages and numerical variables as means (SD). Discrete variables were compared using the χ^2 or Fisher exact test. Quantitative variables were analyzed using the Mann-Whitney U test. Statistical significance was set at a 2-tailed *P* value of less than .05. The SPSS statistical package, version 9.0 (Chicago, Illinois, USA) and EpiInfo (Centers for Disease Control, Atlanta, Georgia, USA) version 6.04 were used to analyze the data.

Results

Thirty-two patients were enrolled in the study; 6 of these were excluded from analysis because they were diagnosed with different conditions (tuberculosis, lymphoma, lung cancer, lymphomatoid granulomatosis, and 2 cases of pneumoconiosis). The mean age of the 26 patients diagnosed with sarcoidosis was 38.9 (10.6) years and 13 (50%) were women. Seventeen patients (65.4%) were initially classified as having stage I disease and 9 (36.6%) as having stage II disease. High-resolution CT, however, revealed interstitial involvement in 12 patients (46.2%); in other words, this technique detected parenchymal involvement in 3 patients classified as having stage I disease.

The mean diameter of the biopsied lymph nodes was 23.8 (6.3) mm: 25.1 (6.4) mm in patients with parenchymal involvement shown by high-resolution CT and 21.3 (5.7) mm in those without parenchymal involvement (*P*=.17). The most common lymph node aspiration sites were the subcarinal station (9 patients, 34.6%) and a combination of the subcarinal and paratracheal stations (7 patients, 26.9%). These were followed by the right paratracheal station (4 patients, 15.4%), a combination of a hilar lymph node and the subcarinal or right paratracheal station (3 patients, 11.5% and 2 patients, 7.7%, respectively), and the left paratracheal station (1 patient, 3.3%).

The Table shows the diagnostic yield of transbronchial biopsy and needle aspiration in relation to the results of high-resolution CT scans (presence or not of parenchymal involvement). Overall, the diagnostic yield of the combined techniques was significantly higher than that of either one in isolation (*P*=.01 vs transbronchial biopsy and *P*=.02 vs needle aspiration). In patients with parenchymal involvement, yield was better for the combined techniques only in comparison with transbronchial biopsy (*P*=.01).

Bronchoalveolar lavage was performed in the middle lobe and transbronchial biopsies in the right lung in 22

Diagnostic Yield of Transbronchial Needle Aspiration (TNA) and Transbronchial Biopsy (TBB): Overall Results and in Relation to Pulmonary Parenchymal Involvement Shown by High-Resolution Computed Tomography (CT)

	Normal High-Resolution CT Scan (n=16)	Abnormal High-Resolution CT Scan (n=16)	Total (n=26)
TBB			
Diagnostic, n (%)	6 (42.9)*	9 (75)	15 (57.7)*
Only diagnostic procedure, n (%)	3 (21.4)	4 (33.4)	7 (26.9)
TNA			
Diagnostic, n (%)	9 (64.3)	7 (58.3)	16 (61.5)*
Only diagnostic procedure, n (%)	6 (42.9)	2 (16.4)	8 (30.8)
TBB+TNA, n (%)	12 (85.7)	11 (91.7)	23 (88.4)

**P*<.05 for combined TBB+TNA.

patients (84.6%). T-cell subpopulations were analyzed in 21 patients (80.8%) and the mean CD4⁺/CD8⁺ ratio was 3.9 (3.5). The ratio was higher than 3.5 in 9 patients (42.8% of patients in whom T-cell subpopulations were examined and 34.6% of all the patients). A CD4⁺/CD8⁺ ratio of over 3.5 was not used in isolation to diagnose sarcoidosis in any of the patients. Bronchial biopsy was diagnostic in 5 of the 10 patients who underwent the test, and in all cases was used in conjunction with other diagnostic techniques.

Transbronchial biopsy and needle aspiration revealed granulomas in 8 patients; 4 of these had a positive bronchial biopsy result and 3 had bronchoalveolar lavage fluid that indicated sarcoidosis (Figure 2).

Granulomas were detected by mediastinoscopy in the 3 patients in whom bronchoscopy was not diagnostic.

Tolerance was very good or good in 20 patients (76.9%). Two patients (7.6%) developed pneumothorax and 1 of them required chest drainage. One patient had bleeding in excess of 50 mL following a transbronchial biopsy and another developed pneumomediastinum, which resolved spontaneously.

Discussion

Sarcoidosis is generally diagnosed after other possible causes have been ruled out. Diagnostic certainty is attained when there is clinical and radiological indication of the disease, sarcoid granulomas in histologic specimens, and all other conditions with a similar clinical and histologic picture have been ruled out.^{1,2,12} In the absence of histologic confirmation, only very clear signs of Löfgren syndrome and a CD4⁺/CD8⁺ ratio of over 3.5 following analysis of bronchoalveolar fluid are indicators of a probable diagnosis.^{2,12} Even though clinical and radiological findings may indicate sarcoidosis, in most cases histologic confirmation is required to exclude other possible causes such as lymphoproliferative processes, cancer, and other granulomatous processes such as tuberculosis.¹⁸ Between 11% and 26% of patients with a chest radiograph showing diseased bilateral hilar lymph nodes are diagnosed with

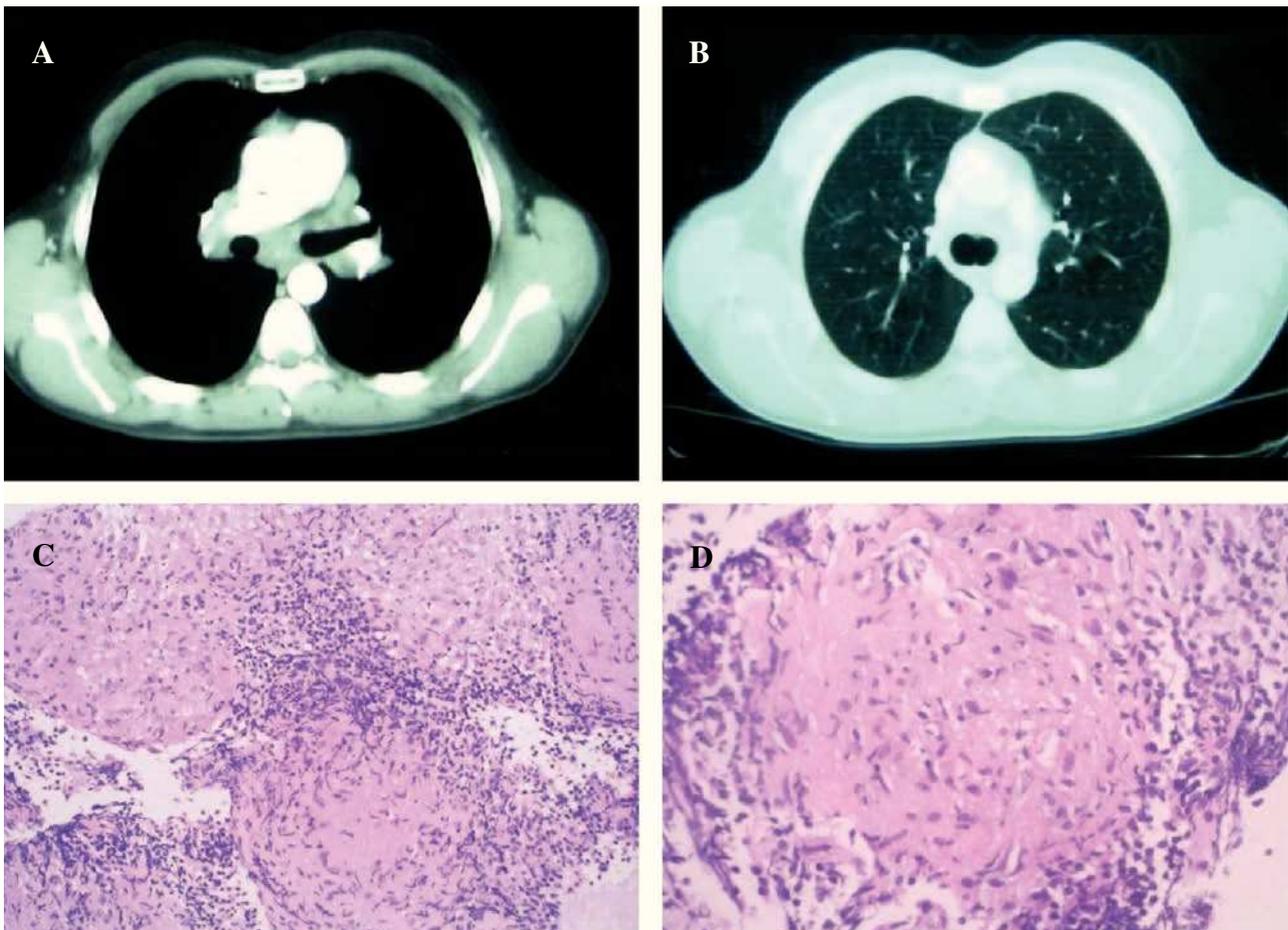


Figure 2. Computed tomography scans showing diseased hilar and mediastinal lymph nodes on both right and left sides (A) and normal lung parenchyma (B) in a patient with stage I sarcoidosis. Samples from a subcarinal lymph node (C) obtained by transbronchial needle aspiration revealed numerous coalesced epithelioid granulomas without necrosis, surrounded by lymphoid tissue (hematoxylin–eosin, original magnification $\times 25$); a lung parenchyma sample (D) obtained by transbronchial biopsy from the same patient revealed compact epithelioid cells, without necrosis, surrounded by a lymphocytic crown (hematoxylin–eosin, original magnification $\times 40$)

conditions other than sarcoidosis.¹⁸ All 32 of our patients had clinical and radiological indication of sarcoidosis but 6 (18.7%) were diagnosed with other conditions (including 4 malignant processes). In similar studies to ours, Bilaceroglu et al⁸ reported alternative diagnoses (benign and malignant) in 28 (25.2%) of 110 patients with suspected sarcoidosis and Leonard et al⁶ only reported 1 alternative diagnosis (lymphoma) in a series of 13 patients (7.6%) with suspected sarcoidosis.

Transbronchial biopsy has traditionally been the method of choice for obtaining lung samples; according to a very recent review, it has a diagnostic yield of between 52% and 76%.⁴ This means that when it is the only technique performed, histologic confirmation is not achieved for a considerable proportion of patients. Since it was introduced just over 20 years ago, transbronchial needle aspiration has proven to be both diagnostically accurate and cost-effective in the diagnosis of diseased hilar and mediastinal lymph nodes. It is particularly effective in tumor processes⁹⁻¹¹ and also performs well in granulomatous processes, and sarcoidosis in particular.³⁻⁸ An exhaustive review conducted by Bilaceroglu et al⁴ reported a diagnostic yield of between

42% and 90% for transbronchial needle aspiration in patients with stage I and II disease (in hilar and/or mediastinal lymph nodes). In 14% to 20% of patients, it was the only technique to provide a histologic diagnosis. The combined use of transbronchial needle aspiration and transbronchial biopsy has a diagnostic yield of 86%.⁴ In our study, transbronchial needle aspiration in isolation detected sarcoid granulomas in 61.5% of patients, and was the only technique to do so in 30.8% of patients. When combined with transbronchial biopsy, however, the rate of successful diagnoses rose to 88%. Despite this success, however, transbronchial needle aspiration is not mentioned either in the latest joint statement on sarcoidosis management issued by the American Thoracic Society and the European Respiratory Society¹² or in the recommendations on the diagnosis and treatment of diffuse interstitial diseases published by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).²

Transbronchial needle aspiration performed with histology needles has certain limitations, including a steeper learning curve than other techniques^{10,11,13} and a higher cost than more common techniques such as bronchial

biopsy and bronchoalveolar lavage. Like other authors,³ we only performed a bronchial biopsy when the mucosa seemed abnormal. This technique is particularly sensitive in this situation and may be the only technique to provide a diagnosis in up to 20% of patients, particularly those with an abnormal mucosa.^{3,4} Bronchial biopsy was not the only means of diagnosis in any of our patients, and in our opinion, it should not replace either transbronchial biopsy or needle aspiration because most transbronchial specimens contain bronchial tissue. Furthermore, the procedure takes up time that may reduce the number of transbronchial biopsy samples that can be taken or needle aspirations performed. It can, however, be a good complementary procedure, and is indicated when, for whatever reason, transbronchial biopsy or transbronchial needle aspiration cannot be performed, or when the mucosa appears abnormal.

A CD4⁺/CD8⁺ lymphocyte ratio of over 3.5 in the bronchoalveolar fluid is highly characteristic of sarcoidosis. Although it has a specificity of 94%, its sensitivity is much lower,^{2,12} and it only provides a probable diagnosis. None of the 3 patients in our series in whom transbronchial biopsy or needle aspiration failed to provide a diagnosis had a particularly high CD4⁺/CD8⁺ ratio. In a study by Leonard et al,⁶ however, 1 patient with a nondiagnostic transbronchial biopsy and needle aspiration (the only one out of 12) had a CD4⁺/CD8⁺ lymphocyte ratio of 8. It should also be remembered that when sarcoidosis is suspected, bronchoalveolar lavage samples must be tested for fungal and mycobacterial cultures to exclude other diseases, and that the technique carries low risk.²

The varying ability of transbronchial needle aspiration to detect granulomas has been attributed to several factors, including the different density and size of the lymph node granulomas, the experience of the person performing the procedure, and the number of aspirations (the ideal number is 2 or 3).^{3,4,8}

Results generally vary according to disease stage, which is established on examination of simple chest radiographs. While transbronchial biopsy has a greater diagnostic accuracy in stage II than in stage I disease, varying results have been reported for transbronchial needle aspiration.⁵⁻⁸ When we analyzed results in view of whether or not parenchymal involvement was visible on the high-resolution CT chest scan, we found that needle aspiration was equally effective for both stages of the disease, and that the diameter of the lymph nodes was similar in both groups. Trisolini et al,⁷ however, suggested that chest lymph node granulomas were less dense in patients with stage II disease.

High-resolution CT is the currently the gold standard imaging method for studying lung involvement in sarcoidosis.^{2,18} It is useful for ruling out interstitial lung disease and is more sensitive than standard radiography in detecting diseased lymph nodes and lung parenchymal abnormalities as it detects parenchymal involvement in a high proportion of patients with stage I sarcoidosis. It can also be used to identify the best part of the lung for performing transbronchial biopsy and bronchoalveolar lavage, and it is essential for orienting transbronchial needle aspiration.^{2,18} We do not agree with the joint recommendation of the American Thoracic Society and

the European Respiratory Society¹² that CT should only be performed in selected cases; we believe that it should be a standard procedure in any patient with clinical or radiological indication of sarcoidosis, and particularly if bronchoscopy is to be performed. Morales et al⁵ showed that CT used to guide transbronchial needle aspiration has a good cost-effectiveness ratio as it eliminates the need for a considerable number of confirmatory surgical procedures.

The use of so many techniques during a single bronchoscopy, however, can be problematic, leading to poor tolerance and increased risk. In our study, all the procedures were well tolerated and the complications were similar to those described for transbronchial biopsy in isolation.¹⁷

The present study has clear limitations, the main one being the small size of our series, mostly attributable to the low prevalence of sarcoidosis in our setting.² Indeed, almost half of the patients enrolled had been referred to the chest surgery department at our hospital for mediastinoscopy following a nondiagnostic endoscopic study in another department. It would therefore seem reasonable to perform a larger multicenter study to confirm our findings. Another limitation is the fact that tolerance was evaluated subjectively by the bronchoscopist, without using specific scales or questionnaires.

In conclusion, and in view of the limitations mentioned, the diagnostic yield of transbronchial needle aspiration is similar to that of transbronchial biopsy in patients with stage I and II sarcoidosis. Furthermore, in almost one third of the patients, it eliminated the need for surgical procedures such as mediastinoscopy. The combined use of both transbronchial techniques had a higher diagnostic yield than either one in isolation. The results were even better in patients in whom the chest radiograph did not reveal parenchymal involvement. There were few complications and tolerance was good. We therefore believe that transbronchial needle aspiration with histology needles should be included in the diagnostic algorithms for sarcoidosis.

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