Determining Factors in Diagnosing Pulmonary Sarcoidosis by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

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Background. **Although the role of endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) in pulmonary sarcoidosis has previously been investigated, the determining factors in diagnosing sarcoidosis by EBUS-TBNA without rapid on-site evaluation (ROSE) are unclear.**

Methods. **Patients with clinically and radiographically suspected sarcoidosis underwent EBUS-TBNA without ROSE in a prospective study. Presence of non-caseating epithelioid cell granulomas was pathologic evidence of sarcoidosis.**

Results. **The EBUS-TBNA was performed in 120 patients, 111 of whom had confirmed sarcoidosis. For the patients with sarcoidosis (62 stage I, 49 stage II) EBUS-TBNA provided sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 93.69%, 100%, 100%, 56.25%, and 94.17%, respectively, in the diagnosis of sarcoidosis. Diagnostic yield of EBUS-TBNA for sarcoidosis was associated with disease stage, but not associated with serum angiotensin converting enzyme level, number of lymph node stations sampled per patient, or total number of passes performed per patient. At EBUS-TBNA, 284 mediastinal and hilar lymph nodes were aspirated in 111 patients. Multivariate logistic regression revealed that short-axis diameter and more than 1 needle pass per lymph node were independent risk factors associated with positive pathology. No major procedure-related complications were observed.**

Conclusions. **Endobronchial ultrasound-guided transbronchial needle aspiration is a safe procedure with high sensitivity for diagnosing sarcoidosis, having a higher diagnostic yield in stage I than stage II. To obtain a higher diagnostic yield of EBUS-TBNA in pulmonary sarcoidosis without ROSE, operators should select the largest mediastinal or hilar lymph node accessible and puncture with 3 to 5 passes.**

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Sarcoidosis is a multisystem disorder of unknown etiology that is characterized by non-caseating epithelioid cell granuloma, primarily affecting the lung and generalized lymphatic system. Enlarged paratracheal or hilar lymph nodes are present in up to 85% of patients [1]. The diagnosis is established when clinicoradiologic findings are supported by cytologic or histologic evidence of non-caseating epithelioid cell granulomas and other causes of granulomas have been excluded [2]. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS -TBNA) is a real-time, accurate, minimally invasive, and safe technique for assessing undiagnosed mediastinal and hilar adenopathy [3–6]. It has been widely used clinically in diagnosing sarcoidosis and has been one of the most important developments in the last decade [7]. While the value of EBUS-TBNA for the diagnosis of sarcoidosis has been investigated by some researchers [8–20], in a recent meta-analysis of its use in sarcoidosis the pooled sensitivity of EBUS-TBNA was 79%, ranging from 54% to 93% [21]. None the less, the accuracy of the diagnosis of EBUS-TBNA in sarcoidosis is quite variable. Thus, we have attempted to determine, by multivariate analysis, the important and related factors for predicting the diagnostic yield of EBUS-TBNA in sarcoidosis.

Patients and Methods

This prospective study reports the results of patients who underwent EBUS-TBNA in whom sarcoidosis was considered to be the leading pre-procedure diagnosis, with clinical and radiologic features suggestive of sarcoidosis. The EBUS-TBNA was conducted on consecutive patients with enlarged mediastinal or hilar lymph nodes (at least 1 node $\geq$ 1 cm in short-axis), based on computerized tomography (CT), from October 2009 to February 2012. Patients were excluded from the study if there was a significant clinical suspicion of malignancy or infection. Follow-up was conducted through February

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2014. All patients were fully informed of the procedure and written consent was obtained. The protocol was approved by the Ethics Committee of Shanghai Chest Hospital (KS10-03).

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

The EBUS-TBNA was performed with the patient under conscious sedation (midazolam) and local anesthesia (lidocaine), as described previously [22, 23]. After white light bronchoscopy was performed orally, target lymph nodes and peripheral vessels were examined by EBUS, using a linear array ultrasonic bronchoscope (BF-UC 260F-OL8; Olympus Ltd, Tokyo, Japan). Scanning was performed at the frequency of 7.5 MHz and images were processed by an Olympus ultrasound processor (EU-C2000; Olympus Ltd). Lymph nodes were classified based on the international staging system [24]. Diameter of target lymph nodes was measured and recorded under frozen ultrasound image. A dedicated 22-gauge needle was used for aspiration (NA-201SX-4022; Olympus Ltd). At least 2 needle aspirations were recommended for each target lymph node. However, if a visible histologic core specimen was obtained, 1 aspiration was acceptable. The bronchoscopist evaluated whether the procedure was sufficient for each sampled area. All procedures were conducted by 2 experienced bronchoscopists (S.J., T.J.). Rapid on-site evaluation (ROSE) was not performed. Cytologic smears were stained by hematoxylin and eosin by 2 pathologists blinded to subject details. Macroscopic tissue fragments were formalin-fixed and paraffin-embedded before being examined by other pathologists under light microscopy. Flush specimens were placed in saline solution for microbiologic assessment. Endobronchial or transbronchial lung biopsies for pathologic examination or bronchial brushings and washings for microbiologic detection (including special staining for acid-fast bacilli and fungi, as were specimens for culture for mycobacteria and fungi) were also performed according to the operator's judgment.

Data Collection and Outcome

Collected data included target location and diameter, aspirations per lymph node, and complications. Pathologic diagnosis by EBUS-TBNA and the final diagnosis were also reviewed. Specimen adequacy was defined by presence of a number of epithelioid cells, histocytes, or lymphocytes. Specimens revealing non-caseating epithelioid cell granulomas were classified as "positive," or "negative" if none found. The final diagnosis of pulmonary sarcoidosis was based on clinic radiologic findings being supported by histologic or cytologic specimens, demonstrating non-caseating epithelioid cell granulomas if a negative microbiologic result was obtained from all samples (Fig 1). Other granulomatous diseases were excluded by reviewing the patient's history and microbiologic results. All patients were followed up clinically and radiographically for at least 12 months.

An EBUS-TBNA diagnosis was subsequently confirmed by results of either other pathologic or microbiologic examination involving common bronchoscopy, CT-guided transthoracic needle aspiration, thoracotomy, mediastinoscopy, or clinical follow-up. Patients' subsequent therapy was performed on the basis of their corresponding final diagnosis.

Statistical Analysis

Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy rate of EBUS-TBNA were calculated according to standard definitions. Univariate and multivariate analyses assessed the independent risk factors for positive pathology. A t test was used for comparison of continuous variables and the χ^2 test or Fisher exact test, when appropriate, was used for categoric variables. Significance was considered for a p value less than 0.05 and all analyses were 2-sided. Significant variables in univariate analysis or those deemed clinically important were then entered in a multivariable logistic regression model. For statistical analyses, SPSS 11.5 (SPSS Inc, Chicago, IL) was used.

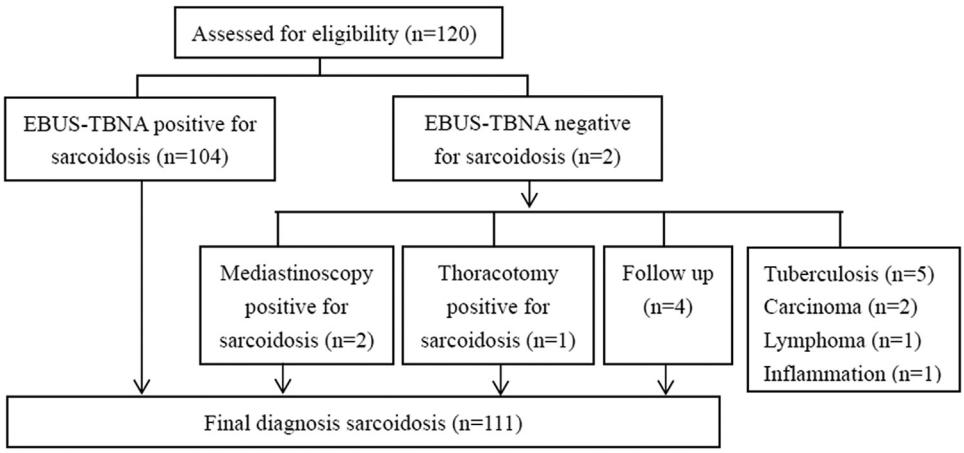

Fig 1. Patients with mediastinal or hilar lymphadenopathy and suspected sarcoidosis undergoing endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).