Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Diagnosing Intrathoracic Tuberculosis

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Background. **Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive procedure that has enabled mediastinal and hilar lymph node assessment with a high sensitivity, but its role in the diagnosis of intrathoracic tuberculosis (TB) has not been established.**

Methods. **We prospectively studied 59 patients suspected of having TB with thoracic lymph node lesions or intrapulmonary lesions accessible by EBUS-TBNA at a clinical center for thoracic medicine from January 2010 to December 2011. Bronchoscopic findings, EBUS-TBNA procedures, pathologic findings, and microbiologic results were recorded.**

Results. **Of 59 eligible patients, 41 patients had TB, 5 had lung cancer, 7 had inflammation, and 6 had sarcoidosis. Sensitivity was 85%, specificity was 100%, positive and negative predictive values were 100% and 75%, respectively, and accuracy was 90% by EBUS-TBNA for TB. Pathologic findings were consistent with TB in 80% of patients (33 of 41), and in 27% (11 of 41) the smear was positive. A total of 37 patients with TB had cultures, of whom 17 (46%) were positive. There were 80 mediastinal and hilar lymph nodes and 5 intrapulmonary lesions that were biopsied in the 41 patients with TB. Multivariate logistic regression revealed that short-axis diameter was an independent risk factor associated with positive pathology, smear, and culture ($p < 0.05$). Additionally, pathology showing necrosis was an independent risk factor associated with a positive culture.**

Conclusions. **Endobronchial ultrasound-guided transbronchial needle aspiration has a high diagnostic yield in the investigation of suspected intrathoracic TB by means of aspiration of intrathoracic lymph nodes and tracheobronchial wall-adjacent lung lesions.**

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The incidence of tuberculosis (TB) in China is rising, becoming one of the 22 high-burden TB countries worldwide [1]. Although the most frequent and easiest ways to diagnose pulmonary TB are through sputum examination for acid-fast bacilli (AFB) by smear or, taking more time, by culture for *Mycobacterium tuberculosis*, such methods are effective only for the diagnosis of pulmonary parenchymal TB, not for tuberculous lymphadenitis (TBLA). Because of its nonspecific clinical and roentgenographic presentation, the diagnosis of mediastinal and hilar TBLA can be challenging [2]. Imaging changes cannot be immediately found after treatment of TBLA by clinical experience, leading to uncertainty when empirical treatment is given. Thus, obtaining pathologic and bacteriologic evidence of TB is essential.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for sampling of intrathoracic lymph nodes and peribronchial tissues has become the standard of care in diagnosing malignancies, sarcoidosis, and other disorders, because it is safe and cost effective [3–5]. However, little data are available on its use in patients infected with TB [6, 7]. Here we prospectively describe the utility of EBUS-TBNA for the diagnosis of intrathoracic TB, including TBLA and intrapulmonary TB.

Patients and Methods

The role of EBUS-TBNA in diagnosing TB was prospectively studied at a clinical center for thoracic medicine. Patient enrollment was performed from January 2010 to December 2011. Follow-up was conducted through December 2012. Endobronchial ultrasound-guided transbronchial needle aspiration was performed according to the following guidelines: (1) enlarged mediastinal/hilar lymph nodes (≥1 enlarged mediastinal or hilar lymphadenopathy >1 cm in short-axis) and/or tracheobronchial wall-adjacent intrapulmonary parenchyma lesions based on computed tomography (CT) or positive intrathoracic lymph nodes/lesions detected (defined as standardized uptake value >2.5) by positron emission tomography within reach of the convex probe for EBUS-TBNA;

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Abbreviations and Acronyms

AFB	= acid-fast bacilli
CT	= computed tomography
CT-TTNA	= CT-guided transthoracic needle aspiration
EBUS-TBNA	= endobronchial ultrasound-guided transbronchial needle aspiration
EUS-FNA	= endoscopic ultrasound-guided fine needle aspiration
TB	= tuberculosis
TBLA	= tuberculous lymphadenitis
WLB	= white light bronchoscopy

(2) clinical and radiologic features suspicious for TB; (3) sputum smears negative for AFB before the procedure; and (4) no contraindication to the procedure.

Interventions

The protocol was approved by the Ethics Committee of Shanghai Chest Hospital (KS10-03). Informed consent was obtained from all subjects. Two bronchoscopists (J.S. and J.T.) performed all EBUS-TBNA procedures upon completion of 30 procedures, comprising the learning curve training [8]. Endobronchial ultrasound-guided transbronchial needle aspiration was performed with the patient under conscious sedation (midazolam) and local anesthesia (lidocaine), as described previously [9]. After oral white light bronchoscopy (WLB), target lesions and peripheral vessels were examined by EBUS, using a linear array ultrasonic bronchoscope (BF-UC260F-OL8, Olympus Ltd, Tokyo, Japan). Scanning was performed at a frequency of 7.5 MHz and images were processed by an ultrasound processor (EU-C2000, Olympus Ltd). Lymph nodes classification was based on the international staging system [10]. Diameter of target lesions was measured and recorded under frozen ultrasound image. A dedicated 22-gauge needle was used for aspiration (NA-201SX-4022; Olympus Ltd) of targeted lesions under guidance of real-time ultrasound. Three needle aspirations were performed for each target lesion. However, if an obvious histology specimen was obtained, two aspirations were acceptable. On-site cytologic evaluation was not performed.

Cytologic smears were stained by hematoxylin and eosin by 2 cytopathologists blinded to subject details. Macroscopic tissue fragments were formalin-fixed and paraffin-embedded before being examined by another 2 pathologists under light microscopy. Flush specimens were placed in saline solution for microbiologic assessment.

Findings by WLB were divided into four categories: (1) no endobronchial lesions; (2) extrinsic compression without mucosal change; (3) submucosal lesions (erythema, edema, mucosal thickening, bronchial narrowing, bleeding, or mucosa eminence); and (4) exophytic lesions. If an endobronchial lesion was seen, an endobronchial biopsy for pathology detection or bronchial brushings and washings for microbiologic detection were also performed according to the operator's judgment. Microbiologic specimens were analyzed by microscopy using Ziehl-Neelsen stains, and Middlebrook 7H9 medium (element of BACTEC MGIT 960 System) was used to culture for mycobacteria.

Assessment of Specimens

A specimen was considered adequate if there were sufficient numbers of representative cellular components present from the target lesion. Pathologic findings of patients with TB were classified into five grades as documented previously [11]: grade I: epithelioid granulomatous reaction with caseation; grade II: epithelioid granulomatous reaction without caseation; grade III: nongranulomatous reaction with necrosis; grade IV: nonspecific; grade V: inadequate sample.

A case was considered to be TB if pathology was grade I through III in the context of clinical features and there was a clinical response including improved symptoms, decreased inflammatory markers, and radiologic features of paracmastic TB on CT to anti-TB treatment through 12 months of follow-up. Microbiologic investigations were considered positive if a smear or culture was positive for AFB. An EBUS-TBNA diagnosis was eventually confirmed by either other pathologic or microbiologic examinations involving WLB, thoracotomy, mediastinoscopy, CT-guided transthoracic needle aspiration (CT-TTNA), or by clinical follow-up. Subsequent therapy was based on the final diagnosis.

Statistical Analysis

Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy rates of EBUS-TBNA for the diagnosis of TB were calculated according to standard definitions. Univariate and multivariate analyses assessed the independent risk factors for pathology, smear, or culture. A t test was used for comparison of continuous variables and the χ^2 test, or Fisher's exact test, when appropriate, for categorical variables. Significance was considered for a p value < 0.05. Significant variables in univariate analysis or those deemed clinically important were then entered in a multivariable logistic regression model. SPSS 11.5 (SPSS Inc, Chicago, IL) was used for statistical analyses.

Results

Of 59 eligible patients, 27 were male, and the median age was 49 years (range, 17 to 70 years). TB was confirmed in 41 patients, lung cancer in 5, inflammation in 7, and sarcoidosis in 6. A TB diagnosis was established by EBUS-TBNA exclusively in 25 patients, by WLB exclusively in 2, by both EBUS-TBNA and WLB in 10, by thoracotomy in 3 (1 had confirmed-negative lymph nodes, suggesting that the EBUS-TBNA results were true-negatives, the other 2 being false-negatives), and by CT-TTNA in one (Fig 1). Endobronchial ultrasound-guided transbronchial needle aspiration provided sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of