Differentiating tuberculosis from sarcoidosis by sonographic characteristics of lymph nodes on endobronchial ultrasonography: A study of 165 patients

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Objective: The differential diagnosis of sarcoidosis and tuberculosis is difficult, especially in countries with a high tuberculosis burden. We hypothesized that sonographic features on endobronchial ultrasonography (EBUS) would help in differentiating tuberculosis from sarcoidosis. In this study, the endosonographic features of tuberculosis and sarcoidosis are compared.

Methods: This was a retrospective analysis of prospectively collected data of patients with intrathoracic lymphadenopathy who underwent EBUS-guided transbronchial needle aspiration (TBNA), and were finally diagnosed with sarcoidosis or tuberculosis. Sonographic features such as size, shape (round or oval), margin (distinct or indistinct), echogenicity (heterogeneous or homogeneous), presence or absence of a central hilar structure, and coagulation necrosis sign were recorded and compared in the 2 groups.

Results: During the study period, 249 EBUS-guided TBNA procedures were performed and a diagnosis of sarcoidosis (n = 118) or tuberculosis (n = 47) was made in 165 patients. A total of 358 lymph node stations were examined. Heterogeneous echotexture (53.4% vs 12.6%, $P < .001$) and coagulation necrosis (26.1% vs 3.3%; $P < .001$) were significantly higher in tuberculous lymph nodes. A combination of a positive tuberculin skin test (TST) and either heterogeneous echotexture or coagulation necrosis sign had specificity of 98% and positive predictive value of 91% for a diagnosis of tuberculosis.

Conclusions: Sonographic features of heterogeneous echotexture or coagulation necrosis in the lymph nodes on EBUS are fairly specific for tuberculosis. Along with a positive TST, these features strongly favor a diagnosis of tuberculosis over sarcoidosis. (J Thorac Cardiovasc Surg 2014;148:662-7)

Sarcoidosis and tuberculosis are 2 granulomatous disorders that closely resemble each other.[1] The presence of intrathoracic lymphadenopathy with or without lung infiltrates is a feature shared by these 2 conditions.[2,3] Differentiation between these 2 granulomatous disorders is mainly dependent on subtle differences in clinical presentation, microbiological investigations for *Mycobacterium tuberculosis*, the presence or absence of hypersensitivity to purified protein derivative (PPD), and the microscopic features of the granulomas identified on cytologic or histologic specimens.[4] Blind transbronchial needle aspiration (TBNA) has been used traditionally to obtain tissue specimens from intrathoracic lymph nodes in patients with suspected sarcoidosis and tuberculosis.[5-7] With the advent of endobronchial ultrasonography (EBUS), the yield of TBNA from mediastinal/hilar lymph nodes has significantly improved.[8,9] In a recent meta-analysis, we found EBUS TBNA to be a safe and efficacious modality in the diagnosis of sarcoidosis.[10]

The sonographic features of intrathoracic lymph nodes on EBUS have been found to be useful in differentiating benign from malignant involvement.[11,12] However, the role of sonographic appearances in the differential diagnosis of 2 common benign causes of mediastinal lymphadenopathy (sarcoidosis and tuberculosis) has not been investigated. Intrathoracic lymph nodes secondary to tuberculosis demonstrate low-density centers on computed tomography (CT) of the chest.[13] We hypothesized that EBUS characteristics of mediastinal lymph nodes could help in differentiating between sarcoidosis and tuberculosis. In this study, the endosonographic features of tuberculosis and sarcoidosis are compared and their usefulness in the differential diagnosis of the 2 clinical mimics is analyzed.

METHODS

Patients

This was a retrospective analysis of prospectively collected data of patients undergoing EBUS TBNA between October 1, 2011, and June 1, 2013. The study protocol was approved by the Ethics Review Committee and written informed consent was obtained from all patients. Consecutive patients presenting to the Bronchoscopy Suite of this Institute who had intrathoracic lymph node enlargement on CT of the chest and were

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Abbreviations and Acronyms

CT = computed tomography
EBB = endobronchial biopsy
EBUS = endobronchial ultrasonography
NAA = nucleic acid amplification
OR = odds ratio
PPD = purified protein derivative
SD = Standard deviation
TBLB = transbronchial lung biopsy
TBNA = transbronchial needle aspiration
TST = tuberculin skin test

scheduled for EBUS TBNA were enrolled in the study. Patients with any of the following were excluded: pregnancy, hypoxemia (pulse oximetric saturation <90 mm Hg in room air), a deranged coagulation profile, or failure to provide informed consent. All patients underwent a detailed clinical evaluation, laboratory tests (complete blood count, coagulation profile, liver and renal function tests, and angiotensin-converting enzyme levels), chest radiography, and CT of the chest. Tuberculin skin testing (TST) with 5 tuberculin units of PPD was performed in all patients and a value of 10 mm or higher was considered positive.

EBUS TBNA Procedure

EBUS procedures were performed by consultants experienced in the EBUS technique or by pulmonary fellows under direct supervision of the consultants. Lymph node stations were classified according to the International Association for the Study of Lung Cancer map, both on CT and EBUS.[14] The procedure was performed on an outpatient basis under conscious sedation and analgesia (intravenous midazolam and pentazocine in doses sufficient to maintain sedation and cough control). Patients were administered 0.6 mg atropine and 25 mg promethazine intramuscularly followed by nebulized lignocaine (4% solution) immediately before the procedure. Topical 10% lignocaine was sprayed over the oropharynx augmented with 2% lignocaine solution instilled over the vocal cords and the airways. Monitoring of pulse rate, respiratory rate, pulse oximetric saturation, and blood pressure was performed throughout the procedure. The convex probe EBUS scope (BF-UC 180F, Olympus Medical Systems, Japan) with a 7.5 MHz convex transducer and a compatible endoscopic ultrasound scanner (EU-ME1, Olympus Medical Systems, Japan) were used.

EBUS TBNA was performed in a standard fashion in the supine position by the oral route using a dedicated, disposable, 21-gauge, Vizishot needle (NA-201SX-4021, Olympus Medical Systems, Japan) under real-time sonographic and endoscopic visualization.[15] The aspirate was then blown on to a glass slide by pushing air using a 20-mL syringe. Aspirated material was also obtained for cell block and mycobacterial cultures (in normal saline using a mycobacterial growth indicator tube [MGIT]). If a histologic core was obtained, it was immediately fixed in 10% formalin. A maximum of 3 aspirates was obtained from each lymph node. In patients with multiple enlarged lymph nodes, the largest lymph nodes were sequentially accessed. On-site cytologic assessment for adequacy of the aspirate was unavailable.

The decision to perform an endobronchial biopsy (EBB) and transbronchial lung biopsy (TBLB) was left to the discretion of the bronchoscopist. In general, EBB was obtained if there were endobronchial abnormalities or in patients with clinical suspicion of sarcoidosis. A TBLB was obtained if there were any parenchymal abnormalities on the CT scan or in those with a clinical diagnosis of sarcoidosis. A conventional fiber optic bronchoscope (BF-1T20 or BF-TE2, Olympus, Japan; FB-19TV, Pentax, Japan) along with standard biopsy forceps (FB19C, Olympus, Japan) were used to perform the biopsies.

EBUS Image Features of Lymph Nodes

The endobronchial ultrasonographic image classification system proposed by Fujiwara and colleagues was used to define the lymph node characteristics.[11] The following nodal features were recorded: (1) size (in millimeters) of the longest dimension (long-axis size) and a dimension perpendicular to it (short-axis size); (2) shape on visual inspection (oval or round); (3) margin (distinct or indistinct): when most of the margin (>50%) was clearly visualized, the lymph node was classified as distinct; (4) echogenicity (homogeneous or heterogeneous): a node was labeled as heterogeneous if there were multiple small areas of varying echogenicity; (5) presence or absence of a central hilar structure, which is a linear avascular hyperechoic area in the center of a lymph node; and (6) the presence or absence of coagulation necrosis defined as the presence of 1 or more large hypoechoic areas within a lymph node with absence of blood flow on Doppler (Figure 1).[16] The EBUS characteristics of the lymph nodes were determined and recorded after being agreed on by at least 2 of the operators.

Diagnosis of Sarcoidosis and Tuberculosis

A final diagnosis of sarcoidosis was made on the presence of all of the following criteria: (1) consistent clinical and radiological presentation; (2) demonstration of nonnecrotizing granulomas on either EBUS TBNA, TBLB, or EBB along with negative acid-fast bacilli and fungal stains; and no growth of mycobacteria on MGIT; (3) clinical and radiological response after treatment with glucocorticoids.[17] A diagnosis of tuberculosis was based on demonstration of all of the following: (1) necrotizing granulomatous inflammation or the presence of acid-fast bacilli on microscopy or a positive culture for *M tuberculosis*; (2) clinicoradiological response to antituberculosis treatment.

Statistical Analysis

Statistical analysis was performed using the commercial statistical package StatsDirect (version 2.7.2, StatsDirect Ltd, Altrincham, United Kingdom, 2005. http://www.statsdirect.com). Data were expressed as the mean ± standard deviation (SD) or number with percentage. Differences between continuous variables in the 2 groups were compared using the Mann-Whitney *U* test; differences between categorical data were compared using the χ^2 test or the Fisher exact test. The performance characteristics of various endosonographic signs and the TST are presented as sensitivity, specificity, and predictive values. Agreement for the sonographic characteristics between lymph node stations in the same patient was evaluated using the kappa statistic. Multivariate logistic regression analysis was performed to define factors predicting the diagnosis of tuberculosis.

RESULTS

A total of 249 EBUS TBNA procedures were performed in 245 patients. Four patients underwent the procedure twice as the first procedure was nondiagnostic. These 4 patients (amounting to 8 procedures) were not considered for analysis. The mean (SD) age of the remaining 241 patients (107 [44.4%] women) was 44.7 (13.9) years. Of the 241 patients, a diagnosis of malignancy was made in 26; in 50 patients, no definite diagnosis was made after EBUS and 6 months of follow-up. A final diagnosis of sarcoidosis or tuberculosis was made in 165 patients (118 sarcoidosis and 47 tuberculosis) from the results of pathologic examination and microbiology. TBLB was performed in 110 of the 165 patients and EBB was performed