The role of EBUS-TBNA and standard bronchoscopic modalities in the diagnosis of sarcoidosis

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Abstract

Background and Aims: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an accurate and minimally invasive technique that has been shown to have excellent diagnostic yield in the diagnosis of mediastinal and hilar lymphadenopathy. However, endoscopic bronchial biopsy (EBB) and transbronchial lung biopsy (TBLB) are still the standard method for making a pathologic diagnosis of sarcoidosis. The aim of this study was to compare the diagnostic yield of EBUS-TBNA and TBLB through a flexible bronchoscope in patients with stage I and II sarcoidosis.

Methods: A total of 653 patients with suspected stage I and II sarcoidosis were included in this retrospective study. After radiological assessment, patients were qualified to bronchoscopy. Patients underwent sequential EBUS-TBNA followed by TBLB and/or EBB. In all patients, 1056 biopsies from mediastinal lymph nodes group were taken.

Results: In all of the biopsied lymph nodes, positive results were obtained in 549 patients (84%). In 180 patients with stage II TBLB, a biopsy was taken from affected part of the lung. Positive results were found in 79 patients (43.9%). EBB was performed in 340 patients, with a positive result in 101 (29.7%). Mediastinoscopy was performed in 60 patients (9.2%) with a negative result in EBUS-TBNA, TBLB and/or EBB. Non-caseating granulomas were found in 48 patients. The sensitivity of TBLB technique alone was significantly lower at 43.9% (79/180) ($P < 0.001$). The sensitivity of EBB was significantly lower than EBUS-TBNA and TBLB and reached 29.7% (101/340) ($P < 0.0001$, $P < 0.003$). The overall diagnostic accuracy for EBUS-TBNA was 84%, and the combination of EBUS-TBNA with standard bronchoscopic techniques had a diagnostic accuracy of 89%.

Conclusion: The diagnostic yield of the EBUS-TBNA for stage I and II sarcoidosis is clearly higher than for TBLB and EBB. The combination of EBUS-TBNA with standard bronchoscopic techniques is safe and feasible, and optimizes the diagnostic yield in patients with pulmonary sarcoidosis and enlarged intrathoracic lymph nodes. EBUS-TBNA in combination with standard bronchoscopy may be considered to be the first-line investigation in patients with suspected sarcoidosis and enlarged intrathoracic lymphadenopathy.

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Key words
bronchoscopy – lung biopsy – sarcoidosis – ultrasound bronchoscopy

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Authorship and contributorship
Dariusz Adam Dziedzic is responsible for study design, data management, and manuscript writing and preparing. Adam Peryt is responsible for study design and data management. Tadeusz Orlowski is responsible for supervising the analyses.

Ethics
The study was approved by the ethics committee of National Research Institute of Chest Diseases, Warsaw, Poland and written consent was obtained from all patients. All authors read and approved the final manuscript.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Background

Sarcoidosis is a multi-system disorder of unknown etiology that is characterized by non-caseating epithelioid cell granulomas. Sarcoidosis can be manifested in hilar and mediastinal lymph nodes, in the lungs, spleen, parotid and thyroid glands, central nervous system and in many other tissues. In a symptomatic stage I (bilateral hilar and/or mediastinal lymphadenopathy) or stage II (bilateral hilar adenopathy

and parenchymal infiltrations on chest radiograph), presumptive diagnosis can often be made based on a typical constellation of clinical and radiological findings, making histological diagnosis unnecessary (1, 2). However, in symptomatic patients, the diagnosis of sarcoidosis requires tissue confirmation of granulomatous inflammation and exclusion of infectious and malignant conditions. Pathological confirmation of pulmonary sarcoidosis is most commonly accomplished by flexible bronchoscopy, which has a yield of approximately 70%, with higher yields in patients with a radiographically more advanced disease (3–5). Flexible bronchoscopy under conscious sedation allows for a transbronchial needle aspiration (TBNA) and transbronchial lung biopsy (TBLB). Endobronchial biopsy (EBB) is also routinely recommended as an additional procedure, and may demonstrate non-caseating granulomas even if no endobronchial disease is evident. Despite the use of combined TBLB and EBB, approximately one third of bronchoscopies do not provide a diagnosis of sarcoidosis (6). Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is gaining momentum as an important new technique for the diagnosis of enlarged lymph nodes because of sarcoidosis.

Materials and methods

From January 2008 to December 2011, 653 patients with clinical and radiological sarcoidosis underwent diagnostic procedures. All patients had computed tomography (CT) examination before invasive procedures. Patients were divided into two groups depending on the stage of the disease: group I – stage I and group II – stage II. In group I (74.8%), only enlarged mediastinal or hilar lymph nodes were found. In the group II (27.6%), enlarged mediastinal lymph nodes and parenchymal infiltrations were observed. After radiological assessment, patients were qualified to bronchoscopy. Patients underwent sequential EBUS-TBNA followed by TBLB and/or EBB under conscious sedation with up to 5 mg midazolam and topical anesthesia with 2% lidocaine. At insertion of a standard bronchoscope, additional 2% lidocaine was applied to the vocal cords and bronchial tree as required. Patients with parenchymal infiltrations underwent TBLB and with endobronchial nodular lesions EBB. In all cases, EBUS-TBNA was performed before standard bronchoscopy in order to avoid airway contamination following TBLB and EBB. Bronchoalveolar lavage was not performed in any patients. According to suggestion of pulmonologists, mediastinoscopy was performed in some patients to exclude other pathologies.

EBUS-TBNA procedure

The equipment included Pentax ultrasonic bronchoscope EB 1970UK, EPK-1000 video processor, EBUS Hitachi HI Vision-5500 processor and 22-gauge aspiration needles with SonoTip IIP syringe (Medi-Globe GmbH, Rosenheim, Germany). During ultrasound examination of the lymph node station, needle aspiration of the largest, accessible lymph node was performed. A dedicated 22-gauge needle was used for lymph node sampling. After the initial puncture, an internal stylet was used to clean out the internal lumen, which tends to become clogged with bronchial membrane. The internal stylet was then removed, and negative pressure was applied with a syringe. After the needle was moved back and forth inside the lymph node, the needle was retrieved and the internal stylet was used once again to push out the core. Using this method, histologic cores as well as cytological specimens can be obtained. The aspirated material was smeared onto glass slides, and smears were air-dried as well as fixed in 95% alcohol. Samples were not evaluated on site.

Standard bronchoscopic procedure

After the EBUS scope was withdrawn, it was immediately replaced with a standard flexible videobronchoscope. Additional topical lidocaine was applied when required. TBLB was performed from the lobe that was demonstrated to be abnormal on imaging. In patients with normal lung parenchyma (stage I sarcoidosis), TBLB was performed from the most convenient location, at the operator's discretion. After the completion of TBLB, EBB was performed. At least four EBB were taken to maximize diagnostic yield even if airway involvement was not found. Since EBUS-TBNA has been introduced, conventional TBNA is not performed routinely.

Mediastinoscopy

Standard cervical mediastinoscopy was performed in all cases in which mediastinoscopy was done. The procedure was done in the operating room under general anesthesia. The paratracheal and subcarinal lymph node stations were systematically dissected, and lymph nodes from stations 2R, 4R, 2L, 4L and 7 were evaluated. All stations were investigated, and if lymph nodes were identified, biopsies were performed irrespective of their size or appearance. The histologic samples

underwent regular pathologic evaluation. Adequate sampling was defined as sufficient material for a specific diagnosis or presence of lymphoid tissue.

Diagnosis of sarcoidosis

A diagnosis of sarcoidosis was made if the clinic-radiological findings were supported by pathological tissue demonstrating non-caseating granulomas without necrosis or the cytological specimen demonstrating non-caseating epithelioid cells based on subsequent clinical assessments if a negative culture result was obtained from all samples. Other granulomatous diseases were excluded by reviewing the patient's history and microbiological results. Cases were classified as inconclusive if no diagnosis could be made by pathological and biological examinations.

Statistical analysis

The diagnostic accuracy rate was calculated using standard definitions. The chi-square test was used for comparison of the modalities for the correct prediction of sarcoidosis. The negative predictive value (NPV) was calculated using the following formula: number of true negatives/(number of true negatives + number of false negatives). The resulting NPV was expressed at 95% confidence interval. A P value of less than 0.05 was taken to denote statistical significance.

Results

Six hundred fifty-three consecutive patients (256 male and 397 female) with suspected sarcoidosis were scheduled to undergo EBUS-TBNA, TBLB and EBB. The mean age was 42 years (range 19–63). Based on radiological findings, 473 patients were considered to have stage I sarcoidosis, while 180 patients were considered to have stage II sarcoidosis. Three hundred sixty-four (56%) had symptoms of cough, fever or weight loss. EBUS was able to detect the enlarged lymph nodes in all of the recruited patients, and EBUS-TBNA was successfully performed in all cases.

Evaluated lymph nodes

In all patients, 1045 biopsies from mediastinal lymph nodes group were taken. The mean number of lymph node stations biopsied per patient was 1.6. The mean size of the lymph nodes sampled was 21 mm (range 12–42 mm). The most often biopsied groups of lymph nodes were 7 and 4R. In the 756 positive lymph nodes, non-caseating granulomas without necrosis were found in station: 2R ($n = 18$), station 2L ($n = 12$), station 4R ($n = 323$), station 4L ($n = 195$), station 7 ($n = 432$), station 11R ($n = 47$) and station 11L ($n = 18$).

Table 1. LN station biopsied

LNs stations	No. of LN biopsied	No. of positive LNs
2R	18	10
2L	12	8
4R	323	230
4L	195	98
7	432	301
11R1	47	32
11L	18	11

LN, lymph node.

Diagnostic rate

Generally, in all of the biopsied lymph nodes, positive results (n – 690) obtained in 549 patients (84%) (Table 1). In 180 patients with stage II TBLB, a biopsy was taken from affected part of the lung. Positive results were found in 79 patients (43.9%). EBB was performed in 340 patients, with a positive result in 101 (29.7%). Airway involvement was found only in 52 patients (15.6%). In 60 patients (9.2%) with negative result in EBUS-TBNA, TBLB and/or EBB, mediastinoscopy was performed. In 48 patients non-caseating granulomas were found and sarcoidosis was confirmed. Non-specific, reactive lymph nodes were found in the remaining 12 patients (Fig. 1). Fifty-eight patients with a negative endoscopic result had no further invasive diagnosis and sarcoidosis was established based only on the clinic-radiological pattern. The sensitivity of EBUS-TBNA for detecting non-caseating granulomas in patients with sarcoidosis was 82.2%. If it is assumed that a patient clinically diagnosed with reactive lymphadenopathy in fact had sarcoidosis, the sensitivity of EBUS-TBNA was 84%. The sensitivity of TBLB technique alone was significantly lower (43.9%, $P < 0.001$). The sensitivity of EBB was significantly lower than EBUS-TBNA and TBLB and reached to 29.7% (101/340) ($P < 0.0001$, $P < 0.003$). The yield per procedure according to the stage of sarcoidosis is summarized in Table 2. There was no significant difference in the diagnostic yields of EBUS-TBNA for stage I and stage II sarcoidosis. However, the sensitivity of standard bronchoscopic techniques was significantly higher for stage II (68%) compared with stage I (14%) ($P < 0.001$). The sensitivity of EBUS-TBNA combined with standard bronchoscopic techniques for the diagnosis of sarcoidosis was 89%, which

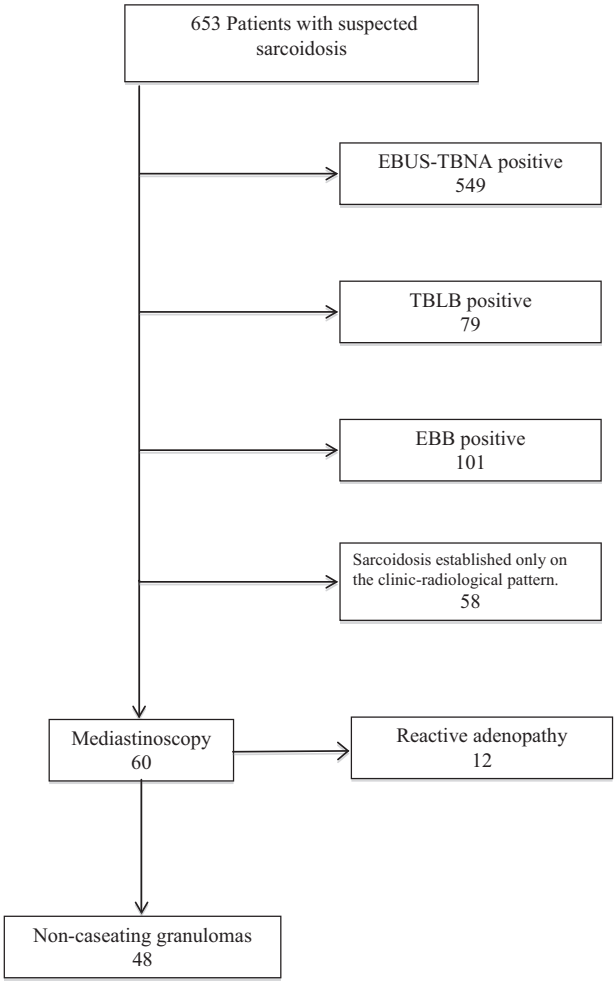

Figure 1. Patients with mediastinal lymphadenopathy and suspected sarcoidosis. EBB, endobronchial biopsy; EBUS-TBNA, endobronchial ultrasoundguided transbronchial needle aspiration; TBLB, transbronchial lung biopsy.

was significantly higher than that of standard bronchoscopic techniques alone (54%) ($P < 0.0001$). The overall diagnostic accuracy for EBUS-TBNA was 84% and the combination of EBUS-TBNA with standard bronchoscopic techniques had a diagnostic accuracy of 89%.

Table 2. Diagnostic yield of each method depending on the stage of sarcoidosis

Methods	Stage I (%)	Stage II (%)	*P* value
EBB	34	25	0.001
TBLB	10.4	43.9	0.0001
EBUS-TBNA	86	84	NS
EBUS-TBNA + EBB + TBLB	90	87	NS

EBB, endobronchial biopsy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; TBLB, transbronchial lung biopsy.

Safety

There were no major complications of the endoscopic procedures. In more than half of patients, some minor complications, including extensive cough and mild hemoptysis, were occurred during 24 h after the procedure.

Discussion

Mediastinal lymphadenopathy represents a diagnostic challenge because of the variety of potential pathological etiologies and the difficulty of access for tissue sampling. Different diagnostic modalities have been used for evaluating mediastinal lymphadenopathy of undetermined origin, including CT, magnetic resonance imaging, bronchoscopy with TBLB, mediastinoscopy and thoracotomy (7). Evaluation of the mediastinum using EBUS-TBNA has been found to be useful for a number of indications. Several publications have shown that EBUS-TBNA established the diagnosis in a high percentage of patients with mediastinal lymphadenopathy of unknown origin (8). Although many of the stage I and II patients may be asymptomatic, differential diagnosis such as tuberculosis, other granulomatous disorders, Hodgkin lymphomas and malignancy cannot be ruled out with certainty.

Computed tomography is the crucial radiological diagnosis of sarcoidosis as it provides visualization of the enlarged mediastinal lymph nodes, and of the changes in the interstitial lung. In many cases, clinical and radiological features are the basis for the diagnosis and further treatment. Hilar or mediastinal lymphadenopathy is present on CT in 47% to 94% of patients with sarcoidosis, irrespective of the radiographic staging (7). Sarcoid lymph nodes are usually non-necrotic and non-compressive, with calcification frequent in longstanding disease (9). Nodules are the hallmark of pulmonary sarcoidosis, seen in 80% to 100% of all patients at high-resolution computed tomography (HRCT) (10). For sarcoidosis, the overall sensitivity (utilizing two observers) was 76% to 83% with clinical data alone, 80% to 88% with clinical and radiographic findings, and 85% to 90% with the addition of CT. However, HRCT is essential in the diagnosis of interstitial pulmonary sarcoidosis. For sarcoidosis, the overall sensitivity was 76% to 83% with clinical data alone, 80% to 88% with clinical and radiographic findings, and 85% to 90% with the addition of CT. The

percentages of correct diagnosis with a high level of confidence were respectively 33% to 42%, 52% to 76%, and 78% to 80% (8, 11). This relatively small difference emphasizes the fact that CT adds little when clinical and radiographic presentation is typical of sarcoidosis, and understates the true diagnostic value of CT in other, less straightforward cases. Moreover, clinical studies support the use of HRCT scanning to predict the likelihood of a positive transbronchial biopsy over chest radiography (12). Some authors suggest the possibility of using positron emission tomography-computed tomography (PET-CT) in the diagnosis of pulmonary and extrapulmonary sarcoidosis. Active granulomatous diseases such as tuberculosis and sarcoidosis cause high fluorodeoxyglucose uptake in the involved lymph nodes (13). With PET-CT, it is postulated that the addition of typical CT findings in patients with multisystemic disease such as hilar and paratracheal lymphadenopathy and parenchymal involvement in pulmonary sarcoidosis can increase usefulness of this modality in evaluation of treatment response in sarcoidosis (14).

However, in case of suspected sarcoidosis, biopsy specimen should be obtained to confirm the diagnosis and to exclude the malignant disease, tuberculosis and histoplasma infection. Therefore, tissue confirmation is crucial in patients with suspicious sarcoidosis. Mediastinoscopy is still a valuable tool in obtaining diagnostic material from the mediastinal lymph nodes (15, 16). The sensitivity of mediastinoscopy in the diagnosis of sarcoidosis is very high and is estimated at 98%. However, mediastinoscopy is invasive, involves general anesthesia, costly, requires inpatient care and has a complication rate of 2%–3% (17–19). This has led to the search for a less invasive tool with high diagnostic yield and minimal complications. So far, the least invasive way to obtain a histological diagnosis was TBLB or EBB, depending on the stage of the disease. The diagnostic value of both methods seems to be far unsatisfactory. The diagnostic yield of TBLB for sarcoidosis by showing non-caseating epithelioid cell granuloma is 37% (stage I: 31%; stage II: 50%) (5, 20, 21). In clinical practice, TBLB is often not performed because of concern about risk of complication (hemoptysis – 4%, pneumothorax – 2%) (22). EBB has lower yield than TBLB that varies between 20% and 62% (23). Visible mucosal abnormalities give higher yields of 54% to 91% although 20%–40% of normal-appearing mucosa can also show granuloma on histology.

In the current study, the sensitivity of TBLB and EBB in all patients (stage I and II) reached 43.9% and 29.7%, respectively. An explanation for the low diagnostic rate of TBLB is that most patients in the present cohort had radiographical stage I sarcoidosis with enlarged intrathoracic lymphadenopathy only. The relatively low diagnostic yield of EBB can be explained by the small group of patients with airway involvement. In most cases, blind epithelial biopsy from normal mucosa of bronchi was performed. Airway nodules were found in only 15.6% of patients during bronchoscopy.

The development of linear echoendoscopes and subsequent procedure (EBUS-TBNA) opened a new diagnostic possibility for sarcoidosis. EBUS-TBNA could diagnose sarcoidosis more precisely, especially for stage I cases that showed hilar adenopathies and no infiltrates on chest roentgenograms (17). Recent trials of endoscopy ultrasound fine needle aspiration in sarcoidosis showed a diagnostic value of 82%, sensitivity of 89%–100% and specificity of 94%–96% (19, 20, 24). Gupta *et al.* (25) found that EBUS-TBNA as a single method is the most useful procedure for demonstrating the granulomatous inflammation in sarcoidosis with diagnostic yield of 74.5%, which is better than 'blind' TBNA (48.4%) or EBB (36.3%) but not TBLB (69.6%). Effectiveness of TBLB (69.6%) is comparable with EBUS-TBNA. Adding TBLB to EBUS-TBNA led to an increase in granuloma detection.

In the current study, it was shown that the diagnostic yield of EBUS-TBNA reached 86%, with no complications noted.

In conclusion, the diagnostic yield of EBUS-TBNA for stage I and II sarcoidosis is clearly higher than for TBLB and EBB. The combination of EBUS-TBNA with standard bronchoscopic techniques is safe and feasible, and optimizes the diagnostic yield in patients with pulmonary sarcoidosis and enlarged intrathoracic lymph nodes. EBUS-TBNA in combination with standard bronchoscopy may be considered to be the first-line investigation in patients with suspected sarcoidosis and enlarged intrathoracic lymphadenopathy.

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