

Clinician's Corner

The Role of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS TBNA) in the Diagnosis of Sarcoidosis



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Bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) provides reliable access to cytologic specimens from the mediastinal and hilar lymph nodes. This technique has substantially changed the clinical approach to patients with suspected sarcoidosis; it provides relatively safe and minimally invasive tissue specimens compared with the more invasive mediastinoscopy, surgical lung biopsy, or bronchoscopic transbronchial lung biopsy. Challenges for EBUS TBNA include obtaining adequate samples to explore a broad differential diagnosis.

The diagnosis of sarcoidosis is based on a compatible clinical and radiographic presentation with the demonstration of granulomas in 1 or more affected tissues. Biopsies of mediastinal or hilar lymph nodes, endobronchial lesions, or lung parenchyma are common sites. Patients with sarcoidosis often come to medical attention when enlarged mediastinal or hilar lymph nodes are discovered on a chest radiograph or chest computed tomography (CT) scan that was obtained for other reasons. If respiratory symptoms are present or radiographs reveal characteristic micronodular infiltrates, subpleural nodules, or nodularity along bronchovascular bundles, then the diagnosis of sarcoidosis is likely. Without these findings, other conditions become more probable, and samples appropriate for their diagnosis must be collected. Lymphoma is the most important other disease that must be diagnosed or definitively excluded. Collecting tissue for flow cytometry to determine clonality is essential.

Fungal infection, either active or healed, is a real alternative to sarcoidosis for many patients. Infections caused by the soil fungi *Histoplasma capsulatum*, *Coccidioides immitis*, or *Blastomyces dermatitidis* are prevalent in different regions of the United States. *Mycobacterium tuberculosis* infection is a major

concern and must also be considered especially when there is necrosis in the node. Collecting tissue to place in transport medium for fungal and mycobacterial culture is important for identifying specific infections.

Bronchoscopy using a flexible instrument allows directed passage through the branching tracheobronchial tree to the level of the subsegments within each lobe. A linear side-scanning ultrasound probe added to the tip of the videobronchoscope offers a thin wedge of imaging at 90 degrees to the axis of the scope and penetrates 3 to 4 cm into the tissues adjacent to the airway. Samples can be taken with ultrasound guidance to localize a submucosal mass or the mediastinal and hilar lymph nodes. The needles used most commonly are 21 or 22 gauge that can extend up to 4 cm into the tissue. The smaller diameter 22-gauge needle is more widely used, because it offers slightly greater flexibility and ease of puncturing the wall with no difference in yield.¹ We routinely use aspiration suction to help draw material into the EBUS TBNA needle, although no differences in yield have been observed between aspiration and capillary filling without suction.²

Processing EBUS TBNA Samples for Sarcoidosis

To guide our sampling of material, cytopathologists provide "rapid on-site evaluation" (ROSE), which is a critical aid to efficient diagnosis and appropriate handling of specimens. The typical EBUS TBNA sample retrieves a few drops of viscous liquid that can be expressed from the needle by replacing the wire stylet or by air pressure. Not using saline or fixative to express material avoids leaving liquid in the channel. A small drop of EBUS TBNA sample is expressed onto a slide and examined on site. The results guide additional samples from



the same lymph node or suggest a change to another location. Material remaining in the EBUS needle can be expressed into fixative for cytology or cell block, into cell culture transport medium for flow cytometry, or into media for microbiological culture. ROSE cytopathology produces final results similar to the results from samples submitted without on-site examination,^{3,4} but we believe ROSE adds substantially to the efficiency of the procedure, optimizes the number of samples needed, and assists the triage of specimens for appropriate testing.

Patients with sarcoidosis typically present with findings such that lung cancer, the most common application for EBUS TBNA, is not the most likely diagnosis. Lymphoma, fungal or mycobacterial infection, or possible metastatic tumor from an extrathoracic source are more likely alternative diagnoses. This differential diagnosis drives the processing of EBUS TBNA samples. In a typical case, the largest and most easily accessible lymph node will be sampled first. In contrast, for patients with the clinical suspicion of lung cancer, the highest stage lymph node is the first target. If non-necrotizing granulomas are identified in the first biopsy, then 2 or 3 more biopsies from that same lymph node are performed for confirmation and additional tests. The analysis of lymphocyte phenotypes from bronchoalveolar lavage specimens typically reveals an elevated ratio of CD4-positive to CD8-positive lymphocytes in patients with sarcoidosis. Although suggestive, this finding alone is not sufficient to establish a diagnosis. The utility of an elevated CD4:CD8 ratio among lymphocytes recovered from mediastinal lymph nodes has not been established, but it would add little to the diagnosis if granulomas were present and would not establish a diagnosis if granulomas were not present. We reserve flow cytometry for cases in which lymphoma is a likely diagnosis. EBUS TBNA from 2 or 3 different lymph nodes bilaterally are performed to confirm that granulomatous inflammation is widespread and is not a localized response to nearby tumor.

Individual center studies, multicenter randomized trials, and literature meta-analyses have demonstrated a sensitivity of 71% to 95% for EBUS TBNA in recovering non-necrotizing granulomas from patients who ultimately were diagnosed with sarcoidosis.⁵ The reported overall sensitivity is approximately 85%; transesophageal fine-needle aspiration yields similar results. EBUS TBNA is superior to blind TBNA⁶ and is more sensitive than transbronchial lung biopsy.⁷ In our experience from 300 EBUS TBNA procedures over 6 years, a definitive diagnosis was obtained in 75% of cases. Granulomatous inflammation was identified in 29% of cases, almost all of which were diagnosed as sarcoidosis.

The most frequent challenges for EBUS TBNA in the diagnosis of sarcoidosis are recovering lymphocytes with no granulomas or obtaining only blood despite an EBUS image that shows the needle in the center of a lymph node. Sampling other lymph nodes often solves the problem of insufficient tissue. A greater challenge is deciphering the finding of non-necrotizing granulo-

mas that may not be of clinical significance. There is virtually no literature that describes the microanatomy of lymph nodes in sarcoidosis or granulomatous infections when the disease is inactive. Often, the lymph nodes remain slightly enlarged on CT scans, and, if discovered without a prior comparison, they appear abnormal. Are lymph nodes with old granulomas of any clinical importance? For most patients, this question can be answered by observation. If the patient has no symptoms or other signs of disease, the lymph nodes were discovered incidentally, and there is no evidence of involvement of other critical organs, then no treatment is indicated.

The technique of EBUS TBNA has changed the management for many patients with sarcoidosis. This approach to the lymph nodes of the mediastinum allows a definitive diagnosis for most patients using a well tolerated, safe, outpatient procedure. Specialized equipment for bronchoscopy and special training for bronchoscopists is needed, but the availability of this procedure is expanding beyond tertiary care centers to many community hospitals. EBUS TBNA samples can be evaluated at most medical centers with cytopathology services. Proper tissue triage and processing are vital to the success of the procedure, and ROSE offers an important service to assure that this is accomplished efficiently. Until recently, many patients who appeared to have sarcoidosis but who did not have tissue sites that could be sampled easily were managed without a secure pathologic diagnosis, despite receiving medications for years that might carry risks and evident side effects. EBUS TBNA has changed this picture, and a definitive diagnosis is now achievable for most patients with sarcoidosis.

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