EBUS-TBNA for the Diagnosis of Sarcoidosis
Is it the Only Game in Town?

Daniel A. Culver, DO, and Ulrich Costabel, MD†*

It is our choices, Harry, that show what we truly are, far more than our abilities.
J.K. Rowling, *Harry Potter and the Chamber of Secrets*

Boujaoude et al[1] revived an unsettled debate about the need for diagnostic certainty when faced with radiologic abnormalities suggesting sarcoidosis, but where malignancy can be plausibly considered. How certain do we need to be about diagnoses in the modern era? Do time-tested clinical diagnoses of sarcoidosis still apply today? The genesis of the renewed discussion in the sarcoidosis arena is the emergence of a new diagnostic tool: endobronchial ultrasonography–guided transbronchial needle aspiration (EBUS-TBNA).[2] The relatively low morbidity, and a reliable access to new tissue previously reserved for surgical specialists, has spawned a bit of a cottage industry to demonstrate that EBUS-TBNA is the emerging imminent gold standard for sarcoidosis diagnosis. Perhaps, the proverbial "camel's nose is already in the tent" analogy holds in the current situation, but it may not be too late to remind ourselves that EBUS-TBNA must still be regarded as a merely one of several tools for making a diagnosis of sarcoidosis.

The usefulness of EBUS-TBNA for diagnosing sarcoidosis was first reported in 2007, in a series of 65 patients where the sensitivity was 92%.[3] In 2009, a widely cited randomized controlled trial demonstrated a 22% absolute improvement in sensitivity for the diagnosis of sarcoidosis using EBUS compared with conventional TBNA (61% vs. 83%).[4] Some,[5,6] but not all,[7] subsequent studies have suggested that EBUS-TBNA is more sensitive compared with standard transbronchial lung biopsies, especially for radiologic stage I disease. As such, EBUS-TBNA has been promulgated as a sufficient stand-alone tool for making the diagnosis of sarcoidosis.[8] This seems premature.

A diagnostic test is of practical value when it can provide information to "rule in" or "rule out" a diagnosis—that is, when it has high predictive values.[9] A limitation of most of the literature addressing the usefulness of isolated EBUS-TBNA in sarcoidosis is that the patient population that was studied is not representative of the patients in whom sarcoidosis is a valid diagnostic possibility. Early studies included populations that were highly enriched for sarcoidosis, with >90% of each population receiving a final diagnosis of sarcoidosis.[2] Some subsequent reports included all patients who had EBUS-TBNA to derive accuracy data for diagnosing sarcoidosis but included a high proportion of patients with a very low pretest probability of sarcoidosis due to radiologic or historic features of malignancy or immunodeficiency.[10–12] Moreover, none of the studies detail the entry criteria that

From the *Department of Pulmonary Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH; and †Department of Pneumology/Allergology, Ruhrlandklinik, University Hospital, University Duisburg-Essen, Essen, Germany.
Disclosure: There is no conflict of interest or other disclosures.
Reprints: Daniel A. Culver, DO, Department of Pulmonary Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, 44195, OH (e-mail: culverd@ccf.org).

led to the suspicion of sarcoidosis and therefore inclusion in the study, rendering generalization of the results difficult.

A more valid way to study the usefulness of EBUS-TBNA would be to study consecutive subjects for whom sarcoidosis is in the differential diagnosis, mirroring the population confronting physicians in regular practice. The radiologic and clinical inclusion criteria that are included in such a study will need to be defined prospectively. Moreover, when interpreting the clinical implications of any such study, it will be important to recognize that the differential diagnosis of granulomatous lymphadenitis is broad, and that the diagnosis of sarcoidosis requires exclusion of other causes for granulomas.[13] Some particular situations that require careful clinical consideration before arriving at a diagnosis include relatively poor sensitivity of stains and cultures from cytologic specimens for granulomatous infections, sarcoid-like reactions due to malignancy, and granulomatous lymphadenitis that is unrelated to a coexisting parenchymal lung disease. All of these have been misdiagnosed as sarcoidosis in our experience after a "diagnostic" EBUS-TBNA.

A second argument, championed by Dr Reich, is that many cases of sarcoidosis do not require tissue confirmation. The vast majority of sarcoidosis experts agree with the precept that asymptomatic stage I sarcoidosis patients with a negative physical examination do not require invasive biopsy confirmation of the diagnosis.[13,14] Although it may be possible to find anecdotal examples of missed diagnoses with this approach, it is less easy to demonstrate that delayed diagnosis in those settings led to irremediable harm to the patient. An exception to the standard of radiologic diagnosis may be when faced with an extremely anxious patient in whom the burden of worry is so substantial as to outweigh the risks of the procedure. An additional point here, although not systematically studied, is that the widespread use of a high-resolution chest computed tomography scanning technique may allow a confident diagnosis of sarcoidosis to be made when classic imaging features are present, and there are no epidemiologic or clinical features to argue against the disease. Whether EBUS-TBNA ever gives an unsuspected diagnosis such as lymphoma in that setting is unlikely.

A final aspect of the debate about EBUS-TBNA relates to generalizability and scalability. Almost all of the current literature relies on experienced operators and cytopathologists in tertiary medical centers. In 1 recent study that examined EBUS-TBNA in less-experienced hands, the yield was as low as 27%.[15] In the study from Calgary, the rate of positive calls for granulomas was 83% when usual cytopathologists reviewed the material but increased to 96% with overreads by dedicated research cytopathologists.[4] It will be important to demonstrate that the diagnostic superiority of EBUS-TBNA is similar in moderate-volume and low-volume centers, unless the goal is to limit bronchoscopy for sarcoidosis to only tertiary centers. In addition, although EBUS-TBNA is less invasive compared with mediastinoscopy, the apparent cost savings evaporate when deep sedation or general anesthesiology is used, as it is in many US centers. All of the data in the lung cancer literature suggesting cost savings with an EBUS strategy were collected from centers using moderate sedation. As sarcoidosis is a worldwide disease that occurs in less economically privileged countries and can be managed perfectly adequately in many smaller centers, a drive to declare EBUS-TBNA as a best practice for sarcoidosis diagnosis has obvious implications in an era of performance measurement and quality indicators.

Perhaps the biggest utility of EBUS-TBNA for sarcoidosis diagnosis (with or without on-site cytologic evaluation) lies in knowing when to stop at EBUS alone and when more information is needed. That skill, in turn, is a cerebral one, not a technical ability.

Similar to Harry Potter, who defeats Lord Voldemort and his Flesh Eaters through nimble intellect rather than superior wizardry, the diagnosis of sarcoidosis must couple technical advances with shrewd diagnostic acumen.

REFERENCES

1. Boujaoude Z, Dahdel M, Pratter M, et al. Endobronchial ultrasound with transbronchial needle aspiration in the diagnosis of bilateral hilar and mediastinal lymphadenopathy. *J Bronchol Interv Pulmonol*. 2012;19:19–23.
2. Costabel U, Bonella F, Ohshimo S, et al. Diagnostic modalities in sarcoidosis: BAL, EBUS, and PET. *Semin Respir Crit Care Med*. 2010;31:404–408.
3. Wong M, Yasufuku K, Nakajima T, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *Eur Respir J*. 2007;29:1182–1186.
4. Tremblay A, Stather DR, Maceachern P, et al. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle

aspiration in patients with suspected sarcoidosis. *Chest*. 2009;136:340–346.
5. Navani N, Booth HL, Kocjan G, et al. Combination of endobronchial ultrasound-guided transbronchial needle aspiration with standard bronchoscopic techniques for the diagnosis of stage I and stage II pulmonary sarcoidosis. *Respirology*. 2011;16:467–472.
6. Oki M, Saka H, Kitagawa C, et al. Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. *J Thorac Cardiovasc Surg*. 2012;143:1324–1329.
7. Plit M, Pearson R, Havryk A, et al. Diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration compared with transbronchial and endobronchial biopsy for suspected sarcoidosis. *Intern Med J*. 2012;42:434–438.
8. Plit ML, Havryk AP, Hodgson A, et al. Rapid cytological analysis of endobronchial ultrasound-guided aspirates in sarcoidosis. *Eur Respir J*. 2012 Nov 22. [Epub ahead of print].
9. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatr*. 2007;96:338–341.
10. Gindesgaard CB, Schousboe LP, Christensen. RK. Endobronchial ultrasound-guided transbronchial needle aspiration in an unselected cohort. *J Bronchol Interv Pulmonol*. 2013;20:140–146.
11. Tian Q, Chen LA, Wang HS, et al. Endobronchial ultrasound-guided transbronchial needle aspiration of undiagnosed mediastinal lymphadenopathy. *Chin Med J (Engl)*. 2010;123:2211–2214.
12. Cetinkaya E, Gunluoglu G, Ozgul A, et al. Value of real-time endobronchial ultrasound-guided transbronchial needle aspiration. *Ann Thorac Med*. 2011;6:77–81.
13. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of sarcoidosis and other granulomatous disorders. *Sarcoidosis Vasc Diffuse Lung Dis*. 1999;16:149–173.
14. Judson MA. The diagnosis of sarcoidosis. *Clin Chest Med*. 2008;29:415–427, viii.
15. Lange TJ, Kunzendorf F, Pfeifer M, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in routine care—plenty of benign results and follow-up tests. *Int J Clin Pract*. 2012;66:438–445.