"Sarcoidosis Americana-Route Europa"

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"The real problem is not whether machines think, but whether men do," wrote B.F. Skinner, a renowned American psychologist, in his masterpiece *Contingencies of Reinforcement: A Theoretical Analysis*. In a rather unrelated context, however, the universality of this profound truth is beginning to reverberate.

Technological advances over the last decade have transformed the armamentarium of diagnostic tools into a plethora of fancy gadgets. Many medical facilities increasingly resemble futuristic sets from sci-fi thrillers. Newer technologies are being introduced at a hectic pace, often replacing the established ones. These technologies are valued highly if they translate into health care improvements. Unfortunately, this is not always the case. For the pulmonologists in practice, bronchoscopy has long been a valuable tool to help unravel the mysteries of clandestine illnesses. However, the increasing use of some of the newer bronchoscopic techniques in situations in which a noninvasive approach would be perfectly reasonable is the classic case of our increasingly superfluous reliance on technology.

The subject of many recent commentaries and opinion pieces, this topic was once again kindled by a recent publication in *JAMA: The Journal of the American Medical Association* titled "Endosonography versus Conventional Bronchoscopy for the Diagnosis of Sarcoidosis: The GRANULOMA Randomized Clinical Trial."[1,2] von Bartheld et al[3] in Europe highlighted the improved diagnostic yield of endosonography in patients with suspected stage I/II pulmonary sarcoidosis. At a time when the practice and skill of performing a conventional transbronchial needle aspiration (C-TBNA) is rapidly waning, this study appropriately drew attention to the excellent yield of this real-time visualization technique. Prima facie, this and many other similar publications in this field make endosonography an attractive option for sampling of mediastinal lymph nodes in suspected sarcoidosis.[3–11] For obvious reasons, there is merit in proceeding with this promising technique whenever diagnostic uncertainty and consequences of delayed treatment risk an adverse outcome. There are several potential reasons for performing bronchoscopy in a potential or known case of sarcoidosis: to make a diagnosis, to confirm the diagnosis in a patient with extrathoracic granulomatous disease, and to evaluate a potential complication of the disease or treatment, such as infection. Endobronchial ultrasound-guided TBNA (EBUS-TBNA) can be certainly added to the list of bronchoscopic procedures used to evaluate sarcoidosis patients. However, this report once again stirs up the hornet's nest on the perceived need for obtaining a tissue biopsy for a condition that may not meet the above description: stage 1 sarcoidosis (S1S). The usual argument from proponents of the tissue diagnosis is that mediastinal

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adenopathy, as noted in S1S, could mimic serious disorders such as lymphoma. Undiagnosed and untreated, this could result in irreparable harm. Advocates of a "clinical diagnosis" of S1S suggest that its presentation is so characteristic that the need for a histologic confirmation with any invasive procedure is unwarranted. Seminal work by Winterbauer et al[12] has stood the test of time and, in the right clinical context, argues strongly against the need to histopathologically augment the diagnosis of S1S. Reiteration for this also comes from the statistical arguments propounded by Reich and colleagues. They point out that one would have to subject 10,000 patients with S1S to an invasive diagnostic procedure to identify, at the most, 5 with an alternative pathology, a ratio that would be difficult to savor even for the healthiest health care economies.[13,14] Cumulative results from prospective studies conducted to assess the yield of EBUS-TBNA in patients with suspected sarcoidosis are summarized in Table 1. Among 746 patients with suspected sarcoidosis, many of which included patients with historical features of malignancy and immunodeficiency, an alternative diagnosis was obtained in only 10%. More importantly, the diagnosis of a malignancy was obtained in only 9 (1.2%) patients.[3–11] Frequently, alternative diagnoses were obtained from surgical biopsy specimens after a nondiagnostic EBUS-TBNA. These studies do not stratify the likelihood of alternative diagnoses by the stage of sarcoidosis, and hence generalization of results is difficult. However, all these studies included patients with multiple stages of sarcoidosis. Accordingly, the likelihood of coming up

TABLE 1. Prospective Studies With EBUS-TBNA in Suspected Sarcoidosis[3–11]

	Suspected Sarcoidosis	Final Diagnosis of Sarcoidosis	Alternative Diagnosis
Garwood et al[4]	49	48	1 reactive adenopathy
Oki et al[5]*	15	14	1 malignant melanoma
Wong et al[6]†	65	61	3 indefinite 1 GPA
Tremblay et al[7]	50	47	3 indefinite
Kim et al[8]	25	25	0
Tournoy et al[9]‡	137	115	5 tuberculosis 11 indefinite 2 extrinsic allergic alveolitis 1 lymphangitis carcinomatosa 1 pneumoconiosis 2 aseptic lymphadenitis
Navani et al[10]§	39	27	8 tuberculosis 2 reactive adenopathy 2 lymphoma 1 metastatic adenocarcinoma
Oki et al[11]‖	62	54	1 lymphoma 1 IgG4-related adenopathy 2 tuberculosis 4 nonspecific lymphadenitis
von Bartheld et al[3]	303	278	15 reactive adenopathy/nonspecific fibrosis 2 tuberculosis 2 lymph node metastasis of non–small cell lung cancer 2 lymph node metastasis from other cancers 1 GPA 1 pneumoconiosis 1 atypical pneumonia 1 diagnosis unknown

*After a negative EBUS-TBNA and a negative TBNA, surgical biopsy led to the diagnosis of malignant melanoma.

†Inadequate sample from EBUS-TBNA and GPA diagnosed by video-assisted thoracoscopic surgery.

‡EBUS gave no formal alternative diagnoses and all alternative diagnoses in this study were based on surgical biopsy.

§Lymphoma diagnosed by EBUS-TBNA and confirmed by bone marrow biopsy (the study included 6 patients with immunosuppression for another disorder, infection with HIV, or prior malignancy).

‖Except tuberculosis, the other alternative diagnoses were obtained by means of either surgical biopsy or clinical follow-up.

EBUS-TBNA indicates endobronchial ultrasound-guided transbronchial needle aspiration; GPA, granulomatosis with polyangiitis.

with an alternative diagnosis of malignancy in SIS has to be $<1.2\%$. This aligns with the statistical arguments highlighted above and once again argues against the necessity of obtaining histologic specimens for suspected SIS. In addition, one has to keep in mind that other conditions cause granulomatous reactions in lymph nodes (Table 1). These include tuberculosis and fungal infections. The EBUS-TBNA sample has a fairly low yield for these infections; hence, cultures of bronchoscopy samples must be sent.[15] In addition, granulomatous reactions to cancer can occur, especially for lymphoma and breast cancer.[16,17] A recent study from the Mayo Clinic found that EBUS-TBNA established a definitive diagnosis of a lymphoproliferative disorder in only 38% of procedures. In particular, the sensitivity was lower for new patients (7 of 32 cases) than for those with established diagnosis; all of these further dilute the added value of EBUS-TBNA.[18]

Every time a new diagnostic test enters the realm of usage, 2 key questions must be asked:

1. What does this test add to the care being provided to the particular patient in question?
2. Does this translate into cost-effective improvements in health care overall?

In our humble opinion, utilizing an invasive diagnostic modality for S1S does not stand to logic, neither for an individual patient nor at a broader policy level. By no means a castigation of the technique, we argue that appropriate patient selection is and should always remain the key. In the current economic environment, a discussion on exercising prudence while subjecting patients to such unnecessary diagnostic tests is increasingly relevant. A recent endeavor from the American Board of Internal Medicine, aptly titled "Choose Wisely," is an initiative on this front to encourage conversations about the need—or lack thereof—for many frequently ordered tests or treatments. In partnership with ACCP/ATS, their first pulmonary list of potentially avoidable tests is expected to be published in October 2013 (http://www.abimfoundation.org/Initiatives/Choosing-Wisely.aspx).

The scientific community across the globe appreciates that research studies aim to reflect an acceptable balance of internal validity and feasibility. With the inherent diversity in populations and practices, a fair bit of skepticism on the part of readers about the generalizability of every study merits consideration. Endosonography, in the European study referenced earlier, included EBUS-TBNA and transesophageal ultrasonography-guided fine-needle aspiration (EUS-FNA). Notably, two thirds of the interventions in the endosonographic group were performed through the transesophageal route. An excellently designed study, it was good enough to merit publication in one of the premier medical journals in the United States, *JAMA*. However, for a non-European audience, recognition of a significant difference in the practice of endoscopy outside Europe is paramount. In Europe, endoscopic training is comprehensive; in the context of mediastinal lymph node sampling, it includes training in both EBUS-TBNA and EUS-FNA. In contrast, in the United States, endoscopic sampling of mediastinal lymph nodes by pulmonologists is traditionally performed by either C-TBNA or EBUS-TBNA. The EUS-FNA training is not routine, in keeping with the fellowship trends in the United States. Combining the learning curve for EUS-FNA with the often underreported complications from this procedure, it is easy to visualize why the results may not hold in a different landscape.[19,20]

We, as physicians, are rapidly evolving from a breed of diagnosticians to a species of technology savants. However, we better be careful, lest the technology savants may soon metamorphose into technology servants.

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