Cryobiopsy for Interstitial Lung Disease: The Heat Is On

Interstitial lung diseases (ILDs) are increasingly recognized as a heterogeneous group of lung disorders with a broad spectrum of outcomes and consequences. Clinicians confronted with patients with ILDs are frequently challenged to sort out the complex group of acute and chronic presentations to reach a specific diagnosis often required before initiating appropriate pharmacological therapy. Despite a thorough history, physical examination, high-resolution computed tomography (HRCT), BAL cellular profile, and appropriate serological testing, clinicians are often unable to reach a specific diagnosis. It is at this point that we consider histopathological examination of the lung as a diagnostic step. Thus, reaching a specific diagnosis is challenging. Indeed, for patients with fibrotic ILD of unknown cause with HRCT showing a pattern other than usual interstitial pneumonia, a recently updated clinical practice guideline for the diagnosis of idiopathic pulmonary fibrosis (IPF) makes a conditional recommendation for a surgical lung biopsy to ascertain the diagnosis of IPF (1).

Obtaining an adequate sample of lung tissue that yields diagnostic histopathological features requires invasive procedures that are associated with risks and complications. The conditional recommendation for the surgical lung biopsy made in the guideline is for the patient suspected of having IPF who has minimal risks associated with surgery. The approximately 1.5% mortality rate associated with this elective surgery must be taken into account when weighting the need to ascertain the histopathological diagnosis against the risks of the procedure (2). Those at higher risk include patients with comorbid conditions, poor overall health status, physical frailty, and a more severe degree of lung function impairment. In practice, up to 15% of patients are left without a specific diagnosis: so-called unclassifiable ILD (3).

Less invasive methods have therefore been considered with the hope of providing a test that is as accurate as surgical lung biopsy with a better safety profile. Using the principles of "cryotechnology" (4), transbronchial lung cryobiopsy (TBLC) performed during bronchoscopy has been proposed as such a tool because it provides biopsies that are considerably larger than those obtained by conventional TBLC (5). A number of studies have examined the diagnostic yield and safety of TBLC for ILD diagnosis, with varying findings (6–10). Diagnostic yield (a measure distinct from diagnostic accuracy) seems to be reasonable, but safety concerns with bleeding and air leaks have been raised. For the patient clinically suspected to have IPF and having an HRCT pattern other than UIP, the 2018 guideline made no recommendation regarding TBLC. Regardless, the results derived from TBLC histopathology have been used in multidisciplinary discussions (MDDs) in tertiary centers and have been advocated by investigators and experts familiar with the technique as an appropriate alternative to surgical lung biopsy (5).

In this issue of the *Journal* (pp. 1249–1256), Romagnoli and colleagues (11) report the results of a prospective study undertaken to compare histopathological features in paired lung biopsy specimens obtained from the same patient subjected to both procedures—TBLC immediately followed by surgical lung biopsy—to evaluate intrapatient concordance of the pathological diagnosis. In this unique study, the histopathological features were assessed by a blinded external pathology expert. TBLC and surgical lung biopsy were poorly concordant, with only 38% agreement (95% confidence interval, 18–62%) for the histopathological pattern. Retrospectively, the surgical lung biopsies carried more weight than TBLC for the final diagnosis in the MDD.

The findings reported by Romagnoli and colleagues are not surprising. It seems logical that the histopathology of smaller lung biopsies obtained would tend to show different patterns from those seen in larger biopsies taken from the periphery of the lung in ILD, and these data provide evidence against the routine use of TBLC in ILD diagnosis in clinical practice. Clinicians should hold themselves to a high standard when beginning to use diagnostic tools in practice. An example is a recently developed molecular classifier for histopathological usual interstitial pneumonia pattern, which underwent evaluation of the diagnostic properties of the test before being available for clinical use (12). We should expect no less for newer applications of diagnostic tools.

Even if TBLC is less accurate, one could argue that if safer than surgical lung biopsy, it may be an appropriate test for some patients. Although the safety outcomes in the study by Romagnoli and colleagues are reassuring, with a low pneumothorax rate and only minimal bleeding, partly owing to the specific design, prior studies have shown higher rates of complications with bleeding, particularly at less experienced centers (10). The safety and efficacy of this procedure remain to be established in further well-designed prospective studies.

Performing both TBLC and surgical lung biopsy on the same patients surely is complex to organize, and recruitment must have been challenging in the two-center study reported by Romagnoli and colleagues. From a patient perspective, a double procedure without evident clinical benefit must have been a hard case to sell! To this end, Romagnoli and colleagues are commended for their clinical approach and the clear design of their study.

In essence, rigorous studies with adequate patient sample size are warranted to settle the issue of the diagnostic accuracy of TBLC in ILD. Until then, the evidence surfaced in the report by Romagnoli and colleagues and the accumulated data on TBLC to date are concerning and should dissuade us from advocating for the use TBLC to diagnose ILD in clinical practice. We also urge caution when considering any type of biopsy to diagnose ILD. In many cases, a

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thorough history and physical examination, recognized patterns of HRCT images obtained with proper technique and in both inspiration and exhalation (1), broad serological testing, BAL cellular profile, consultation with a rheumatologist, and an MDD can yield the specific diagnosis of ILD without subjecting patients to the risks of invasive procedures to obtain lung biopsy for diagnostic interventions. ■

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Harnessing Immune Response to Malignant Lung Nodules
Promise and Challenges

Incidental and screen-detected lung nodules are a common problem (1) and one that is driving the search for diagnostic biomarkers that can distinguish malignant from benign lung nodules with acceptable accuracy. Many investigators are pursuing this line of work, and the importance of this pursuit is increasing, in part because of the increasing adoption of lung cancer screening. The vast majority of indeterminate lung nodules discovered incidentally or in the context of lung cancer screening are not cancer (2, 3). Nevertheless, many patients with benign lung nodules may undergo unnecessary and invasive diagnostic procedures. Standard computed tomography (CT) imaging lacks the ability to accurately differentiate between malignant and benign lung nodules. Although positron emission tomography scans have a very good negative predictive value, their use is limited for smaller nodules; there is a high (>20%) risk of false-positive findings,

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