Impact of Lung Biopsy Information on Treatment Strategy of Patients with Interstitial Lung Diseases: The Glass Is Half Full

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Interstitial lung disease (ILD) represents a varied group of conditions for which diagnosis is often challenging. Although international guidelines would suggest that a substantial proportion of individuals should be biopsied to obtain a confident diagnosis (1, 2), few patients actually undergo this procedure (3). Central to this paradox are concerns over the safety of biopsy (4) and the value added by biopsy, especially given unease around interobserver variability in interpretation of histopathology (5). Although retrospective studies have previously hinted at a change in therapy following biopsy ranging from 40% to 60%, these often did not specifically detail how therapy changed, did not do so in the context of multidisciplinary discussion (MDD), and were commonly performed before antifibrotic drugs were widely implemented (6, 7). No robust studies have examined how lung biopsy affects management in the post-antifibrotic era and in the setting of the most recent clinical practice guidelines.

In this issue of *AnnalsATS*, Tomassetti and colleagues (pp. 737–745) examine the impact of biopsy findings on the management of patients with ILD without a definite usual interstitial pneumonia (UIP) pattern on radiology (8). A substudy of a single-center, retrospective initiative designed to evaluate the prognostic value of transbronchial lung cryobiopsy (TBLC) (9), this work included 426 consecutive patients from Italy who underwent TBLC or surgical lung biopsy (SLB) for suspected ILD, of which nearly 80% had fibrotic disease. Each case was reviewed in MDD to establish a diagnosis and management plan based on clinical and radiologic information. Pathology information was then introduced by a pathologist blinded to clinical and radiologic information, with subsequent reevaluation of the diagnosis and plan. A change in therapy was judged as conversion from expectant management to initiation of treatment or vice versa, or a change in choice of therapy between immunosuppressive and antifibrotic therapy.

Tomassetti and colleagues found that biopsy led to a meaningful change in management in approximately one-third of cases, a finding that remained consistent in the major subgroup limited to patients with fibrotic disease. Among cases where there was a change in management, approximately 40% were in the setting of an altered diagnosis, whereas 60% were associated with a more confident diagnosis. In addition, the percentage of cases where treatment changed was similar regardless of whether TBLC or SLB was used.

Although the authors defined a change in treatment strategy among 20% of biopsied cases as being clinically meaningful, clinicians may disagree on what threshold is worthwhile when balanced against the risk of lung biopsy. The current findings imply that two-thirds of individuals undergoing biopsy do so without significant change in therapy, all while being subjected to procedural complications including up to approximately 10% risk of moderate or severe airway bleeding and 20% risk of pneumothorax in TBLC, as well as a relatively small but nonzero risk of death with both TBLC and SLB (4, 10). In addition, the cost of biopsy must be considered as well as the added strain of this procedure on the healthcare system.

Despite this, there are several strong arguments to support the ongoing pursuit of lung biopsy and pathologic confirmation of disease in less than definite cases. Reclassification from non–idiopathic pulmonary fibrosis (IPF) to IPF, representing approximately 7% of cases in the current study, is crucial in a minority of patients to avoid the harm of immunosuppressive therapy in this condition (11). Similarly, diagnostically challenging cases of mild disease that are identified as IPF may lead to early initiation of antifibrotic therapy, which yields benefit even in those with mild or preserved lung function (12). Finally, the endpoint of the current study does not capture those individuals with mild disease where biopsy may not change management immediately but may do so at a later date if there is progression that demands therapy.

In addition to changes in pharmacologic treatment, biopsy yields information that is beneficial to a patient's care and should not be discounted. Histopathology provides meaningful prognostic information, especially in the setting of an unfavorable UIP pattern (13). Recognition of a UIP pattern also identifies those individuals more likely to progress, who may benefit more from aggressive treatment and close follow-up, and who may be better served by early referral for lung transplantation. Finally, a confirmed diagnosis in a minority of patients may lead to other treatment recommendations apart from pharmacotherapy, such as a renewed search for an antigen and redoubled efforts for

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antigen remediation in cases of fibrotic hypersensitivity pneumonitis. These arguments, in addition to treatment change in one-third of cases, may be enough to convince many clinicians of the merits of seeking lung biopsy.

The authors describe using antifibrotics only in cases of IPF at the time this study was conducted, which does not incorporate new indications for antifibrotics in progressive fibrotic disease (14), systematic sclerosis-associated ILD (15), and unclassifiable progressive ILD (16). Although the progressive fibrotic phenotype should more easily lend itself to antifibrotic therapy, it does not obviate the need for biopsy and ongoing efforts to diagnose ILD subtypes (17). In addition to identifying patterns more prone to progression and potentially leading to earlier initiation of appropriate therapy, biopsy findings may help clinicians decide between starting antifibrotic or immunosuppressive therapy in cases where both might be indicated, such as fibrotic hypersensitivity pneumonitis.

The current study has several strengths and constitutes the first robust examination of how lung biopsy leads to change in therapy in a large, relevant population that is reflective of current clinical practice. However, the findings are based on experience at a single center and require external validation, especially in the setting of the expanding role of antifibrotic therapy in ILD. Moreover, the study was not specifically designed to evaluate a difference in change in management following TBLC as compared with SLB; although no statistically significant difference was detected (31.5% change in treatment with TBLC compared with 38% with SLB), this represents an underpowered analysis and cannot be used to equate TBLC with SLB in its ability to alter management decisions.

In addition, although incorporation of histopathology findings in MDD clearly helped determine treatment, there is, nonetheless, some suggestion in the data from the underlying paper from which the present substudy is derived (9) that the biopsy results may not be entirely accurate, particularly with respect to UIP suggestive of IPF. In patients undergoing SLB who ultimately received a diagnostic label of IPF, most of whom were biopsied in the pre-antifibrotic era, the 5-year survival was 53% and median survival was 5 years, whereas in those who underwent TBLC during a timeframe that coincides with the use of antifibrotics, the 5-year survival was 68% and median survival was 7 years. These numbers are considerably better than those reported by most investigators (18) and suggest that UIP and MDD diagnosis of IPF were being overcalled, particularly by TBLC. Arguably, this finding might not matter if the miscalls are other forms of progressive fibrosing interstitial pneumonias for which antifibrotic therapy is probably the preferred therapeutic approach, but this is not true of other ILD subtypes where immunosuppressive therapy is often the recommended starting point. This whole issue emphasizes the need for specific pathologic criteria for different types of fibrosing interstitial pneumonias in TBLC, something that is largely lacking or controversial (19).

Despite some concern around diagnostic accuracy, Tomassetti and colleagues provide a much-needed study that adds valuable data to guide clinicians when considering the practical utility of lung biopsy in ILD. Although the findings need to be confirmed in geographically diverse settings, the current study offers reassurance that lung biopsy is not an antiquated diagnostic tool to be avoided, but plays an ongoing and important role that meaningfully changes the course of treatment in a significant subgroup of patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Chyle in the Wrong Place: Why Knowing the Target Matters

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Management of chylous effusions has remained a conundrum for many years; it is particularly challenging for nontraumatic causes owing to varied etiologies and complex underlying pathophysiologies. Nontraumatic causes account for 25–50% of chylous pleural effusions (1). Treatment options traditionally included treating the underlying cause, if one is identified, and conservative and surgical approaches, the latter being mainly ligation of the thoracic duct, carrying a mortality up to 10% (2). Since the groundbreaking work by Cope and colleagues in 1999 of using thoracic duct embolization (TDE) as an alternative to ligation of the thoracic duct (3), nonsurgical lymphatic interventions have been a particular focus of interest in changing the outlook of patients with persistent chylous effusions.

The key factor for treatment success in lymphatic interventions for chylous effusions is finding the exact abnormality in the lymphatic tract, which is in itself a complex and variable anatomical pathway. To put this in perspective, TDE success rates have been reported to be 52–78% in the presence of an abnormal thoracic duct and as low as 16% if the thoracic duct is anatomically normal (4). This suggests that there are other underpinning mechanisms, especially in cases of normal thoracic duct anatomy, for which a different targeted intervention is needed. To guide such treatment, advances in our understanding of imaging modalities are required to carefully delineate the precise underlying anatomical abnormality and thus increase the overall success of interventions. Invasive lymphangiography and now newer noninvasive imaging techniques (5) have not only improved our understanding of complex pathophysiology of these effusions but also paved the way for novel targeted interventions. One such intervention is image-guided interstitial lymphatic embolization (ILE), which uses a percutaneous approach to deliver an embolization agent into aberrant lymphatic vessels visualized on lymphangiogram (6). ILE is a promising technique, owing to its feasibility in targeting smaller lymphatic vessels that are too small for catheterization using standard techniques (7). This is a relatively new addition to the artillery of noninvasive techniques offering targeted treatment options for this complex disease.

In this issue of *AnnalsATS*, Gurevich and colleagues (pp. 756–762) present their experience using an algorithm-based approach to map out management plans for nontraumatic chylous effusions (8). The authors used novel dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL) to delineate primary site(s) of the lymphatic defect resulting in the clinical syndrome of chylous effusion and/or ascites (i.e., thoracic, retroperitoneal, or transdiaphragmatic), and this information subsequently guided a lymphatic intervention. A retrospective analysis was conducted of 52 patients, with chylothorax and/or chylopericardium, who were treated according to the underlying pathological abnormality as detected by DCMRL, with a 93% success rate in detection of an aberrant lymphatic pathway causing "true chylothorax."

The authors subdivided these patients into three distinct categories using DCMRL preintervention. A true chylous effusion with abnormal thoracic duct was treated with TDE; if additional retroperitoneal aberrant lymphatic channels were contributing, both TDE and ILE were performed. Chylous ascites leading to effusion due to abnormal transdiaphragmatic channels was managed with abdominal lymphatic channel embolization/pleurodesis/peritoneovenous shunts. The algorithm thus promoted a shift away from offering TDE to all patients in a nontargeted manner.

The authors should be congratulated on a carefully conducted study in a difficult-to-assess and often rare population, focusing on targeted management of chylous effusions based on distinct underlying mechanisms of these heterogenous cases. This algorithm has the potential to sow the seeds of a shift from a one-size-fits-all approach to more tailored management.

The study has distinct strengths, including the definition of discrete clinical groups using noninvasive imaging and the

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