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Time to Trust Transbronchial Cryobiopsy in Identification of Usual Interstitial Pneumonia Pattern?

Usual interstitial pneumonia (UIP) refers to a morphologic pattern characterized by a combination of *1*) patchy interstitial fibrosis sharply demarcated from areas of normal lung ("patchy fibrosis"), *2*) temporal heterogeneity of fibrosis characterized by scattered fibroblastic foci in a background of dense acellular collagen, and *3*) architectural derangement mainly represented by cysts covered by cells that usually express bronchiolar stem cells markers (honeycombing) (1, 2). The patchy interstitial process often emanates from the subpleural zones and septa or, occasionally, from one edge of an airway. Therefore, the distribution of the lesion is better described as periacinar instead of perilobular (1) (Figure 1). UIP pattern is the histopathologic background of idiopathic pulmonary fibrosis (IPF) but it may be observed in biopsies obtained from subjects affected by a variety of other entities (collagen vascular diseases, chronic hypersensitivity pneumonitis, etc.). Ancillary

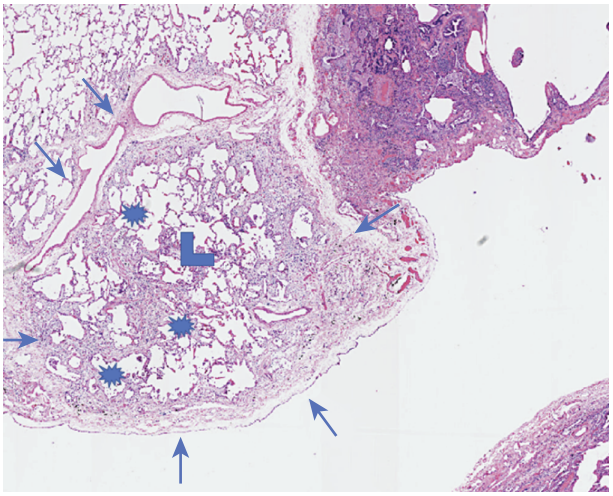

Figure 1. Usual interstitial pneumonia pattern. The boundaries of a secondary pulmonary lobule (marked by arrows) with fibrosis beneath the pleura and along the interlobular septa are shown. Tongues of fibrosis, however, also run along the periphery of an acinus (stars) surrounding a small bronchiole (arrowhead). An adjacent lobule is occupied by honeycombing (hematoxylin and eosin, low power).

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findings such as lymphoid follicles, inflammation, giant cells, granulomas, and coexistence of bronchiolocentric damage raise the possibility of a diagnosis of non-IPF. This pattern, because of the patchwork distribution and mainly subpleural disposition of the lesions, needs volume to be identified under the microscope, and surgical lung biopsy (SLB) is considered the most valid technique thus far. However, this approach, in the best scenario, has a mortality rate of approximately 1.5%; this rate increases significantly when patients are older or the likelihood of having IPF is high (3). Transbronchial lung cryobiopsy (TBLC) performed during bronchoscopy is increasingly used as a surrogate of surgery because it provides biopsies that are considerably larger than those obtained by conventional transbronchial biopsy. It has also a significantly better safety profile when a training program for operators is established and maintained and specific procedures are used (4). TBLC has a diagnostic yield above 80% (4) and provides data that contribute significantly to the prognostic distinction between IPF and other interstitial lung diseases (5). Diagnostic accuracy is also fair, as recently, a good agreement between SLB and TBLC for both histopathologic interpretation and MDD diagnosis was demonstrated (6). Pathologists, however, may feel reluctant to formulate a diagnosis of UIP on TBLC samples 7, 8), this concern being possibly explained by the fact that TBLC usually retrieves samples torn off from the centrilobular zones (9).

In this issue of the *Journal*, Cooper and colleagues (pp. 1306–1313), comparing samples obtained by TBLC and subsequently by SLB in the same patient, provide solid data that contrast with this feeling (10). UIP was identified in 33/65 (50.8%) SLBs, and 81.5% were concordant with the corresponding TBLC. High diagnostic confidence was reported more frequently for the interpretation of SLB than for TBLC (46.2% vs. 12.3%, $P = 0.007$), and the UIP guideline criteria (11) of predominantly subpleural and paraseptal fibrosis, observed in all SLB cases, were identified in only 8/33 TBLCs (24.2%). In the majority of cases, UIP pattern in cryobiopsy samples was therefore defined, according to the current guidelines, as "probable UIP" (11, 12). The study generates interesting cues.

The combined findings of "fibroblast foci," "patchy fibrosis," and "absence of features to suggest a non-UIP diagnosis" in TBLC samples were strongly predictive of definite UIP in the corresponding SLB (10). This result may be in part due to the high incidence of IPF in the cohort analyzed. An alternative explanation could be linked to morphological considerations: the combined findings generating "probable UIP" pattern have a peripheral acinar distribution, as recognized by Colby and colleagues (1) (Figure 1). Because the periphery of the acinus includes paraseptal, subpleural, and peribronchiolar regions, samples obtained by TBLC, although not quite perilobular, might be adequate enough to identify UIP. In accordance with this argument, the presence of pleura on biopsy has been found independently related with honeycombing (13), eliciting that the dysplastic bronchiolar proliferation may also happen in less peripheral regions of the pulmonary lobule (2, 14). The last explanation could also support a provocative thesis: the distinction between "definite" and "probable" UIP is no longer useful and tenable.

Visceral pleura was documented in about 9% of these samples. In previous studies, approximately 20–30% of the samples obtained by cryobiopsy showed pleura (4, 5), and UIP pattern was identified with high confidence in at least 60% of cases. In these studies, the interobserver agreement between pathologists for the diagnosis of UIP versus non-UIP was 0.72 (5). To stay closer to the chest wall with the cryoprobe, accepting an increased rate of pneumothorax (and significantly reducing the risk of major bleeding) could therefore be crucial for obtaining samples representative of the peripheral regions of the secondary pulmonary lobules. Not surprisingly, another relevant observation was that the likelihood of concordance between TBLC and SLB increased substantially when five TBLC samples were obtained. The diagnostic yield may rise strikingly when a second biopsy, if taken from a different site, is performed (4). However, the optimal number of specimens to optimize the diagnostic yield while minimizing complications is still to be known.

The authors translate the current guidelines categories of definite and probable UIP (11) into high and low pathologic confidence, but this assumption might be questionable. In a recent published cohort of TBLC and SLB cases (5), data on pathologists' self-reported confidence were collected (not published). The proportion of cases of UIP/IPF diagnosed by pathologists with high confidence (by at least one of the three pathologists) was similar to that for TBLC (89%) and SLB (91%) and significantly higher if compared with the tabular criteria (11). Self-reported confidence and tabular criteria should not be viewed as the same thing. The first involves explicit and "tacit" knowledge and leads to recognizing entities under an overall aspect or gestalt (15).

In conclusion, this paper gives us important information confirming the role of TBLC in the diagnosis of IPF but opens questions regarding the criteria used to identify and grade the UIP pattern. These questions will probably receive solid answers when new approaches including genomic analysis and machine learning to identify a molecular UIP signature in smaller lung biopsy samples (16), combined with HRCT and clinical factors, will significantly change the criteria used to identify the morphological and biological background of progressive lung fibrosis. ■

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Surrogate Markers for Pulmonary Hypertension May Inform Prognosis in Lung Cancer

Lung cancer is the most commonly diagnosed cancer worldwide (1). Individuals with lung cancer frequently have comorbidities, including chronic obstructive pulmonary disease (COPD) and cardiovascular disease, which place them at increased risk of pulmonary hypertension (PH) (2). PH is a heterogeneous disease that negatively impacts morbidity and mortality. In patients with lung cancer, the presence of PH may contribute to worse outcomes after surgical resection and, if severe, preclude resection altogether (3). Despite the high prevalence of lung cancer and the potential impact of comorbid PH on treatment decisions, the prevalence of PH in patients with lung cancer is not well defined. Additionally, there is a lack of published data describing the relevance of comorbid PH to the natural history of lung cancer.

In this issue of the *Journal*, Eul and colleagues (pp. 1316–1319) present a retrospective analysis of the prevalence of computed tomography (CT) surrogate markers for PH and their impact on survival in patients with lung cancer (4). In the first part of their analysis, they measured pulmonary artery (PA) and ascending aorta (A) diameter on baseline high-resolution CT in 670 patients with lung cancer. They determined that 43.7% of patients had a mean PA diameter of $\geq$28 mm, and 22.5% had a PA/A ratio of $>$1. These thresholds, particularly PA/A $>$1, have been shown to correlate with mean PA pressure $\geq$25 mm Hg and thus suggest PH (5, 6). A subset of patients ($n = 132$) in this study were evaluated with echocardiography. PA diameter and PA/A were positively correlated with echocardiographic PA systolic pressure (PASP) after adjustment for sex, age, body mass index, tumor type, Union for International Cancer Control tumor–node–metastasis stage, and arterial Po_2. Those with PA/A $>$1 had a mean echocardiographic PASP of 38.6 mm Hg compared with 28.5 mm Hg in the group with PA/A $\leq$1; this finding was statistically significant. Taken together, these findings suggest that patients with lung cancer may have an increased risk of PH.

As the authors point out, a major limitation of the study is the use of noninvasive means to diagnose PH without confirmatory right heart catheterization, which remains the gold standard for diagnosis according to the sixth World Symposium on Pulmonary Hypertension (7). A meta-analysis including 2,134 subjects found a summary sensitivity and specificity of 79% and 83% for mean PA diameter and 74% and 81% for PA/A, suggesting a rate of misdiagnosis of 17–19% (8). The use of Doppler echocardiography to corroborate the presence

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