Cryobiopsy for Interstitial Lung Diseases

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The term "interstitial lung diseases" (ILDs) includes a wide spectrum of heterogenous entities with different prognoses and treatment options. Because of the recent progress in the diagnostic and therapeutic landscape of ILD management, never before has the distinction between idiopathic pulmonary fibrosis, the most prevalent and severe form, and other diseases been more important.[1] However, an accurate diagnosis of idiopathic pulmonary fibrosis is a challenging process, as, according to the ATS/ERS guidelines,[2] it requires an integrated multidisciplinary approach involving pulmonologists, radiologists, and, when classic criteria are not met, also pathologists. The diagnostic workup of ILDs, indeed, includes medical history, physical examination, lung function tests, high-resolution computed tomography, bronchoalveolar lavage, and, in case of still inconclusive results, a lung tissue sample. In this context, the role of conventional transbronchial lung biopsy is limited to the exclusion of specific disorders (i.e., sarcoidosis, carcinomatous lymphangitis, organizing pneumonia), as the small sample size, the rate of crush artifacts, and the high likelihood of sampling mostly centrolobular areas do not allow to properly identify more complex and spatially heterogenous morphologic patterns.[3] This is the reason why the current guidelines recommend surgical lung biopsy (SLB) when a pathologic assessment is needed to establish a diagnosis. However, SLB is characterized by appreciable costs and risks, with a mortality rate of 2% to 4% within 90 days (mainly due to acute exacerbations), even higher (up to 15%) in patients with an underlying histologic pattern of usual interstitial pneumonia.[4] Other postoperative complications include infections, prolonged air leakage, respiratory failure, and complaint of continuing pain at 7 to 12 months at the biopsy site. Moreover, many subjects are not eligible because of a combination of advanced stage, age, comorbidities, respiratory failure, and pulmonary hypertension. Furthermore, once the surgical biopsy has been obtained, the interobserver concordance between expert pathologists is not always as high as expected, suggesting that bigger is not necessarily better, as some histologic patterns may not be clearly classified regardless of the dimension of the samples provided.[4]

More recently, a valuable alternative tool for the pathologic assessment of ILDs has come to light to support clinicians in facing the dilemma between the need of a complete clinical picture and the risks to obtain it: the transbronchial lung cryobiopsy (TBLC). Actually, the use of cryoprobes for bronchoscopic procedures was first described as early as 1977 for therapeutic purposes in case of airway occlusions. The ingenious novelty consists in using a flexible cryoprobe through a flexible bronchoscope to obtain parenchymal

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Disclosure: There is no conflict of interest or other disclosures.
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DOI: 10.1097/LBR.0000000000000260

lung tissue, as recently proposed in a number of studies worldwide reporting their successful experiences on TBLC in various populations, including patients with ILDs, those with focal opacities, and transplant recipients. Cryotechnology, composed of console, cryogen, and cryoprobe, operates by the Joule-Thomson effect, according to which a compressed gas released at high flow rapidly expands and creates very low temperature at the tip of the probe, leading to the adhesion of the tissue. Although nitric oxide may achieve lower temperatures (−80 to −89 degrees), carbon dioxide is nowadays the most commonly used cooling agent, as in the majority of countries a regulatory rule hampers the use of the first one in endoscopic suites. The probe may have 2 different diameters (1.9 and 2.4 mm); the freezing time ranges from 3 to 6 seconds, the optimal distance of the tip from the pleura is approximately 10 to 20 mm, and the number of biopsies, obtained by pulling the cryoprobe together with the bronchoscope, is usually 3 to 6.[5,6] To date, the main debate on procedural aspects refers to the type of sedation and airways control, as the procedure may be performed under either deep sedation in "intubated" patients (with an endotracheal tube or a rigid tracheoscope) or just conscious sedation. From the data published so far, a higher size of probe, a longer activation time, and carrying out the procedure under deep sedation with airways control positively correlate with a larger sample size.[6]

Overall, in most of the studies the diagnostic yield was superior or equal to 0.70, regardless of the criteria used for defining diagnostic samples (either the identification of a specified histologic pattern or the final multidisciplinary diagnosis), and the safety profile was characterized by a mortality rate at the very least negligible (0.1%).[4,6] Pneumothorax and mild-to-moderate bleeding were the main adverse events.[7–9] Pneumothorax rate was highly variable among studies, ranging from 0% to 20%, likely reflecting the proportion of baseline clinical risk factors for its onset (i.e., underlying usual interstitial pneumonia, pattern, the fibrosis severity at high-resolution computed tomography), the distance from the pleura, and the operator skills. A chest tube drainage was required in more than half of the cases.

No episode of severe bleeding (defined as causing hemodynamic or respiratory instability, requiring tamponade or other surgical interventions, transfusions, or admission to the intensive care unit) was reported. However, moderate bleeding was commonly observed, although its definition among studies was hugely different, making difficult a reliable summary of data. Anyhow, in the study by Casoni et al,[7] in which a bronchial blocker, such as Fogarty balloon, was prophylactically placed in the lobar bronchus near the biopsy segment and inflated immediately after the sampling, no moderate bleeding occurred. This underlies that the routine use of preventive bronchial blockers and an effective airways control under deep sedation are highly recommended to reduce and manage such a complication, suggesting also that the procedure should be performed in centers with experience in the field of interventional pulmonology.

In conclusion, current data suggest that TBLC may play a major role in the diagnostic workup of DPLDs, as it offers significant advantages in terms of safety compared with SLB, guaranteeing an excellent diagnostic profile. However, the absence of clinical trials directly comparing the 2 procedures, because of ethical reasons, makes difficult to completely elucidate the relative risks and benefits. In this context, it would be limiting to necessarily consider TBLC and SLB as competitors, as they could be integrated in a complementary diagnostic algorithm, with TBLC as the first diagnostic approach, reserving the more invasive surgical procedure in case of inadequate or inconclusive results. However, further prospective studies are needed to better define relevant technical aspects of TBLC, such as the optimal number of biopsies to be obtained and the utility of sampling different segments or even different lobes, to standardize the procedure as much as possible.[6]

Only 50 years have passed from the first transbronchial lung biopsy performed by Andersen et al[10] in 1965. Since then, interventional pulmonology has experienced an incessant, outstanding evolution, which has led to increasingly broaden pulmonologists' horizons and enrich their armamentarium. TBLC, this exciting innovative tool, represents a further step in such a process, as it confers a significant role on interventional pulmonologists in the diagnostic landscape of parenchymal lung diseases.

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