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EDITORIAL

The role of transbronchial biopsy in the diagnosis of diffuse parenchymal lung diseases: *Con*

O papel da biopsia transbrônquica no diagnóstico das doenças difusas do parênquima pulmonar: *Contra*

In order to engage in a focused pro/con debate, it is useful to summarize key points of agreement, before reviewing areas that remain contentious. It would be folly to deny that in certain scenarios in diffuse parenchymal lung disease (DPLD), the transbronchial biopsy (TBLB) has an invaluable diagnostic role. In DPLD, histological support for a specific diagnosis can be obtained using TBLB in 29–79% of cases.[1] This wide range reflects the multiplicity of factors influencing the yield of the procedure, including the distribution of the lesion (focal or diffuse), status of the immune system of the patient, small size of the obtained samples, confounding due to crush artifacts and failure to penetrate beyond the peribronchial sheath.[2,3] Despite these limitations, we can all agree, based on diagnostic yields of 65–90% in selected conditions,[1] that TBLB is an appropriate first biopsy procedure in many patients in whom bronchocentric DPLDs are suspected, especially sarcoidosis and lympangitis carcinomatosis. In other disorders, TBLB appearances are not diagnostically definitive in isolation but allow the formulation of a confident diagnosis when integrated with clinical data (including bronchoalveolar lavage) and radiologic findings: this applies especially to cryptogenic organizing pneumonia[4] and, less often, to hypersensitivity pneumonitis. However, when it comes to the diagnosis of individual idiopathic interstitial pneumonias (IIPs), a very different consensus emerges. In the recently published guidelines for the diagnosis of idiopathic pulmonary fibrosis (IPF)[5] it was unanimously concluded that TBLB should not be used to provide histologic support for a diagnosis of IPF. We explore the rationale behind this recommendation, which is diametrically opposed to the ''pro'' view in these paired editorials.

The practical value of making a confident diagnosis is to provide accurate information on the likely natural history and/or treated course of disease in an individual patient. Essentially, it can be argued that in DPLD, ''diagnosis is prognosis''. No diagnostic test has consistent value in suspected IIP unless it helps materially in the identification of IPF, the most prevalent IIP. A diagnosis of IPF has vital prognostic significance as the other IIPs have, on average, a much better treated outcome.[5] At present, it is accepted that the diagnosis of IPF can be based on typical HRCT appearances and a compatible clinical picture in at least 50% of IPF cases.[1] In the remaining cases, histolgical confirmation of a pattern of usual interstitial pneumonia (UIP) is required, with the final diagnosis made by consensus between histopathologists, radiologists and clinicians.[5] The histological pattern of UIP is characterized by subpleural predominance of disease, temporal heterogeneity (i.e. areas of established fibrosis juxtaposed with areas of active fibrosis and normal lung) and the presence of fibroblastic foci.[5] But which type of biopsy provides sufficiently accurate information for the formulation of a diagnosis of IPF?

Until recently, it was viewed as axiomatic that a surgical lung biopsy (SLB) was the 'gold standard' diagnostic procedure in DPLD. With the development of a multidisciplinary approach to diagnosis, it is now acknowledged that histologic information must be reconciled with clinical and radiologic data, but the central role of a diagnostic SLB in selected patients has not been seriously questioned. None the less, the limitations of SLB should be acknowledged. SLB cannot be performed in many patients because often advanced age, severity of the disease and presence of co-morbidities are major constraints. Moreover, the interpretation of SLB is subject to significant interobserver variation. In a study undertaken by pathologists with specialist expertise in the field of DPLD, the level of agreement on the first choice diagnosis was at the lower limit of what would be accepted as clinically useful, as judged by the kappa coefficient of agreement.[6] Lastly, there is the problem of ''sampling error'', consisting of the identification of a histologic pattern that is not representative of the predominant process.[7,8] In IPF, areas of fibrotic non specific interstitial pneumonia (NSIP) often exist and if captured at

SLB, an incorrect final diagnosis of NSIP may be made with adverse effects on the accuracy of prognostication, selection of appropriate therapy and planning of transplantation.

Plainly, an alternative mode of biopsy that overcomes these problems with substantial loss of diagnostic accuracy would be invaluable and it is this unmet need that justifies reappraisal of the role of TBLB. But is TBLB intrinsically reliable in the diagnosis of IPF and other IIPs, and does it address the limitations of SLB listed above? It is our contention that the answer to both questions is resoundingly negative.

In reality, it is difficult to make definitive statements on the accuracy of TBLB in the IIPs because of the lack of a properly conducted diagnostic study, reflecting the widespread view that IPF cannot be diagnosed with confidence using small TBLB samples. This perception is pivotal because a tentative diagnosis, however accurate, is of little value in the formulation of a logical plan. As long as this view remains prevalent, TBLB simply cannot provide the same diagnostic weight as SLB. However, it is worth considering the study of Berbescu et al., if only to make the point that this most insubstantial of ''diagnostic studies'' cannot be used to argue for a diagnostic role for TBLB in IPF.[9] The authors retrospectively evaluated TBLB from 21 patients with surgical biopsy proven UIP and from 1 patient with clinical and radiological findings of IPF/UIP. They concluded that 7 of 22 patients had features ''diagnostic'' of UIP such as patchy interstitial fibrosis along with fibroblastic foci and/or honeycomb change, a rather miserable yield of approximately 30%. From this small study, they reach the inexplicable conclusion that TBLB may be useful in confirming the diagnosis of UIP. The flaw in the logic is that the only patients included in this study had a final histologic diagnosis of UIP without ancillary SLB features suggestive of HP or alternative disorders such as connective tissue diseases. The authors are aware of patients ultimately proven histologically to have sarcoidosis, in which TBLB findings of honeycombing and temporal heterogeneity were ''strongly suggestive of UIP'' (as described above). Such patients could not, by definition, have been included in the study of Berbescu. A UIP pattern is not infrequent in hypersensitivity pneumonitis (HP) but the presence of areas of bronchocentric inflammation and/or poorly formed granulomata (which are often sparse in large SLB samples) are key diagnostic features which would, once again, have excluded these cases from the study discussed above. A TBLB pattern ''compatible with UIP'' will be actively misleading if additional features indicative of HP, sarcoidosis or other DPLDs are missed in small TBLB samples. In essence, the statement that TBLB appearances were indicative of UIP in cases proven by SLB to have UIP has negligeable diagnostic value. The pivotal problem of false positive diagnosis is not acknowledged in the study of Berbescu, which cannot be considered as a true diagnostic study. Indeed, the participating histopathologists were not blinded to the diagnosis of UIP prior to reviewing the TBLB samples!

Thus, no data exist to suggest that TBLB might provide useful support for a diagnosis of IPF but does this diagnostic modality address the limitations of SLB? On the face of it, TBLB is a safer procedure as it does not require general anesthesia, has an overall mortality of 0.1% which is lower than that of SLB (approximately 1%) and can be performed as an outpatient procedure.[10–12] TBLB can be performed in some patients not fit for SLB due to disease severity and presence of co-morbidities. However, even this apparent advantage can be questioned as inaccurate diagnoses carry their own dangers. Moreover, the other limitations of SLB – diagnostic interobserver variation and sampling error – are present to a much greater extent with the interpretation of TBLB samples.

In the current literature, there are no studies of observer variation in the histologic interpretation of TBLB samples. However, the level of agreement between expert pulmonary pathologists is only moderate with regard to the interpretation of SLB samples[6,13] and must necessarily be more problematic for TBLB. The small size of the TBLB and the need to integrate TBLB appearances from several biopsies into an overall histologic pattern carries its own variability, which must be added to the overall variability of histologic interpretation. The problem of discordance between observers is compounded by the fact that small TBLB samples do not allow an assessment of the extent and distribution of fibrosis within the biopsied lobe. These limitations can only be more problematic for less experienced histopathologists, seeking to make a confident diagnosis of UIP using TBLB samples, applying the criteria proposed by Berbescu et al.[9]

Similarly, the problem of ''sampling error'' can only be increased with the diagnostic use of TBLB. In IPF, it is now well recognized that in many patients, there are areas of NSIP-like change. The finding of NSIP in one lobe and UIP in another lobe is not infrequent. Attempts to synthesize a histologic diagnosis from TBLB, taken from only one lobe, cannot properly address this problem. Furthermore, a histologic pattern of UIP may also be present in chronic hypersensitivity pneumonitis or rheumatoid lung. Ancillary features suggestive of these disorders are often very limited in extent and are unlikely to be detected in a TBLB specimen. For example, the diagnosis of hypersensitivity pneumonitis will be strongly suspected when a UIP pattern is bronchocentric in distribution and there are occasional poorly formed granulomas, which will often be detected only with the examination of multiple biopsy fields. Similarly, in rheumatoid lung, the suggestive observation that lymphoid follicles are unusually prominent requires examination of suitably extensive biopsy tissue. Whether or not these key features are captured by TBLB can only be a matter of chance. The conclusion is inescapable: whatever ''sampling error'' exists with the performance of a single SLB specimen can only be amplified by the diagnostic use of TBLB.

In an attempt to overcome these limitations, it has been proposed that the use of larger forceps via rigid bronchoscope would increase the diagnostic yield of TBLB[14] and avoid crush artifacts. In a keynote series, the authors observed that in 74 out of 95 patients with DPLD, a diagnosis was made with the use of large forceps, compared to 62 out of 95 with the use of smaller forceps. However, there was one major limitation. In the 74 patients in whom the large biopsy technique was considered to be successful, the underlying diagnoses were forms of inflammatory DPLD. By contrast, in the 21 undiagnosed cases in this series, the most frequent diagnosis at SLB was UIP/IPF, followed by fibrotic NSIP and chronic hypersensitivity pneumonitis. Thus, although undoubtedly promising, this method

is yet to be validated in the diagnosis of IPF or the other IIPs.

In the field of DPLDs, the accurate identification of IPF remains the cardinal diagnostic challenge. In other disorders, anti-inflammatory treatment is often successful. In IPF, long-term stabilization of disease is not a realistic goal and enrolment in trials of novel therapeutic agents is strongly recommended in recent guideline statements. This crucial treatment dichotomy should not be based on biopsy samples which are small in size and must necessarily be associated with major interobserver variation and sampling error. At present, TBLB samples, although useful in other contexts, are patently inadequate for this purpose.

Conflicts of interest

The authors have no conflicts of interest to declare.

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