Diffuse parenchymal lung disease: a different perspective

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The preceding article by S. MUKHERJEE and colleagues amounts, essentially, to a strong plea that the number of diagnostic surgical biopsies performed in diffuse lung disease should be increased. The authors cite statements by expert groups, including a joint ATS/ERS committee and the BTS, arguing that in DPLD, diagnostic biopsies should be performed unless they are contraindicated or highly unlikely to change management. They then cite data published in the last century suggesting that prior to the mid-1990s, the frequency of transbronchial and surgical biopsy in IPF was too low.

We do not take issue with the view that failure to obtain a histological diagnosis seriously compromises management in some patients. It also appears likely that the historical rates of diagnostic biopsy in the UK were too low. However, a note of caution needs to be sounded, because the advantages of a histological diagnosis need to be balanced against the limitations of the procedure in a risk/benefit decision. In the article of MUKHERJEE and colleagues, the advantages offered by a diagnosis are stressed, but the reader is left with the distinct impression that most patients with DPLD should undergo a diagnostic surgical biopsy. The limitations of a histological diagnosis should also be acknowledged.

The 20th-century view that a histological diagnosis is the diagnostic reference standard in DPLD is increasingly difficult to sustain. In the multidisciplinary study of FLAHERTY *et al*. the histological diagnosis differed from the final consensus diagnosis in 25% of the large subgroup of patients who did not have typical clinical and radiological features of IPF. Diagnosis in DPLD is less straightforward than was once the case. The views that: a) all patients should have a histological diagnosis; b) all patients with idiopathic disease should be labelled as having 'cryptogenic fibrosing alveolitis' without a biopsy procedure; and c) HRCT appearances are almost always a reliable guide and make a histological diagnosis redundant, are equally two-dimensional. In difficult cases, histological information is often pivotal to management. However, the view that almost all patients should be biopsied should be strenuously resisted because it is not supported by recent data.

First, histological information is sometimes inconclusive: a first-choice diagnosis cannot be stated with confidence in up to 20% of samples. It should be acknowledged that clinical and radiological information often clears up diagnostic dilemmas posed by histological appearances. Secondly, concerns about 'sampling error' (divergent histopathological diagnoses in separate biopsy sites) can be addressed by ensuring that at least two biopsies are taken, and that the full spectrum of morphological abnormalities is sampled, based upon pre-operative HRCT evaluation. However, inter-observer variation between histopathologists is a third crucial consideration. In a recent study of observations on 133 biopsies, NICHOLSON *et al*. documented major variation between 10 experienced specialist thoracic histopathologists was found, with observer agreement (κ coefficient of agreement ~0.40) barely clinically acceptable. It should be stressed that in this report, histological appearances were definitive in the majority of cases. Furthermore, diagnostic disquiet expressed by an experienced histopathologist can be weighted appropriately by clinical colleagues. The key point is that the histological diagnosis is not a diagnostic 'gold standard' and this means that the decision to biopsy requires a clear perception that there is a realistic possibility that histological information will change management.

In theory, it may seem that histological information will often change managment when the differential diagnosis lies between IPF and fibrotic NSIP. A recent consensus statement has proposed that IIPs be divided into histopathological subsets that differ in prognosis and response to therapy and include UIP (the pattern seen in IPF), NSIP, respiratory bronchiolitis interstitial lung disease (RBILD), desquamative interstitial pneumonia and others. It is important to diagnose IPF accurately because it is easily the most common of the IIPs and has easily the worst prognosis. It can be argued that a firm diagnosis of IPF allows the avoidance of inappropriate high-dose corticosteroid or immunosuppressive therapy, rationalisation of transplantation and the enrolment of IPF patients in trials of novel therapies.

All of the above goals are worthy, but do they truly require a histological diagnosis in most

cases? Exactly what proportion of patients with underlying IPF should be biopsied? MUKHERJEE and colleagues acknowledge that in ≥50% of IPF patients, HRCT appearances are typical of the disease. Indeed, the figure is closer to 60% based upon accumulated evidence and it is increasingly clear that in this context, histological information adds little or nothing. But what about the remaining 40% of cases? The IPF population is an elderly population, with the peak disease prevalence occurring at the end of the seventh decade. Patient frailty and comorbidity are often strong contraindications to a diagnostic surgical procedure. In other cases, patients present with disease that is too severe to allow diagnostic biopsy. Other patients have an aversion to a surgical diagnostic procedure. Given the advanced age of the population, this leaves, at most, 20–25% of patients in whom a biopsy procedure may seem to be appropriate. However, even this is an overstatement. In more severe disease (*e.g.* $D_{L,CO}$ levels 25–35%), in which a biopsy can be performed with some increase in risk, prognostic distinctions between IPF and NSIP diminish markedly and therefore the value added by the histological information is minimal. Finally, many patients are evaluated after an initial period of treatment. It has now been shown clearly that once changes in lung function are known during a 6–12-month period of treatment, outcome distinctions between IPF and NSIP are linked solely to lung function trends, with histological information being prognostically irrelevant.

An 8–12% rate of surgical biopsy in IPF is, indeed, probably too low, but in reality, this figure may not be very distant from the 'ideal' rate of biopsy, in older IPF populations outside referral centres. The decision to proceed to a surgical procedure is a risk/benefit decision, and in summary, this should be heavily influenced by patient comorbidity, general patient frailty and awareness that histological evaluation is merely one of several tests and is sometimes fallible, although often highly useful. Above all, the decision is utterly dependent upon optimal HRCT interpretation, because in the majority of IPF patients, HRCT appearances should obviate biopsy. MUKHERJEE and colleagues highlight the fact that 'the sensitivity and specificity of HRCT scans for the diagnosis of IPF vary depending on... the skill of the individual interpreting the image.' However, this does not justify the routine performance of surgical biopsy but, rather, the routine referral of DPLD patients to regional groups such as that of MUKHERJEE and colleagues, with access to expert radiological advice.

A histological diagnosis is often invaluable in DPLD. However, despite the many insightful points made in the excellent article of MUKHERJEE and colleagues, this commentator believes that, based on careful risk/benefit evaluation, a surgical diagnostic procedure is warranted in the minority of DPLD patients, in whom histological information is likely to change management.

Recommended reading

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