Topic for debate

Diffuse parenchymal lung disease: a practical overview
Is a lung biopsy necessary for management?

Educational aims

- To describe the different aspects of lung biopsy.
- To discuss the role of lung biopsy in the management of diffuse parenchymal lung disease.

Summary

More than 200 entities comprise the diffuse parenchymal lung diseases (DPLDs), which include a wide spectrum of conditions, many uncommon and many of unknown aetiology. Although lung biopsies are considered as an essential tool for diagnosis in most cases of DPLDs, they are not frequently obtained from patients presenting with clinical evidence of DPLDs. Lung biopsy is an essential tool for diagnosis, assessment and determining prognosis in different types of DPLD. The morbidity associated with different types of lung biopsy appears to be relatively low and therefore it should be used early, preferably before starting any empirical treatment.

Diffuse parenchymal lung diseases (DPLDs) comprise >200 entities and include a wide spectrum of diseases, many uncommon and many of unknown aetiology [1]. Although lung biopsies are considered an essential tool for diagnosis in most cases of DPLD, they are not frequently obtained from patients presenting with clinical evidence of DPLD [2–6]. Furthermore, there is a lack of confidence in the diagnostic and predictive value of pathology, leading to a view that knowledge of the pathological findings does not alter the treatment approaches. Therefore, clinicians have commonly preferred to rely on a trial of therapy as a predictor of clinical course and prognosis, rather than subject the patient to a lung biopsy [5, 6]. As the histological patterns seen by pathologists usually allow for better separation of these entities than the imaging patterns seen by radiologists, the joint statement of the American Thoracic Society (ATS) and European Respiratory Society (ERS) advises surgical lung biopsy, particularly for the diagnosis of idiopathic interstitial pneumonias (IIPs), unless contraindicated. The new classification from the same group defines a set of histological patterns that provide the basis for a final clinical/pathological diagnosis [7]. The British Thoracic Society (BTS) guidelines suggest that it should be standard practice to take lung biopsy samples in DPLD when the diagnosis remains uncertain after clinical and radiological assessment, unless there are patient contraindications or when the samples...
are very unlikely to contribute to management [8]. With this background, this review discusses the different aspects of lung biopsy and its pivotal role in the management of DPLDs with some real-life cases from DPLD clinics.

Although, ideally, histological examination should be performed in DPLD to assist diagnosis, in two UK studies of idiopathic pulmonary fibrosis (IPF), transbronchial lung biopsy (TBLB) or open lung biopsy (OLB) samples were obtained in only 28–33% and 8–12% of patients, respectively [2, 3]. In the USA, a questionnaire survey suggested that most physicians try to obtain a tissue diagnosis in DPLD [9]; however, an epidemiological survey found that an OLB sample had only been taken in a small proportion (11%) of patients with IPF [10]. Biopsy procedures were more likely to be performed in younger patients, those with better lung function and those with a history of asbestos exposure. OLB was more commonly performed when thoracic surgical facilities were available on site [2].

Review of available biopsy procedures

The decision as to the type, size and site of a biopsy sample is determined by the level of pre-biopsy diagnostic certainty, the suspected nature, distribution and extent of the DPLD and the patient’s performance status. Optimising the diagnostic specificity and contribution of the lung biopsy with a multidisciplinary diagnostic approach requires taking adequate material from sites of disease activity while avoiding areas of end-stage lung fibrosis. Where feasible, biopsies from at least two different sites are recommended, in order to avoid the pitfalls of misclassification or nonspecific findings as a result of the overlapping histological features often seen in different disease patterns. Local expertise may dictate the availability of adequate biopsy samples for diagnosis.

Transbronchial lung biopsy

TBLB achieves a high diagnostic yield in DPLDs with centrilobular accentuation, such as granulomatous and metastatic diseases, infection, alveolar proteinosis and eosinophilic pneumonias [11–14].

Problems with TBLB include sampling errors and small specimen size [15, 16], making it difficult to distinguish different patterns of DPLD with overlapping histological features. Crushing of the specimen and failure to penetrate beyond the peribronchial sheath may also preclude histological assessment. Overall, the diagnostic rate is ~38–79% [11–13, 15–18]. In patients with IIP, the TBLB specimens are too small and nonrepresentative to allow either a reliable diagnosis or determination of the relative degree of cellularity and fibrosis [15, 16] and, therefore, one is unable to diagnose the principal patterns, such as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP) and desquamative interstitial pneumonia (DIP).

Pneumothorax has been reported in ≤10% of cases (generally 0.7–2%) with about half of these requiring tube drainage [11, 13, 19–22]. Bleeding occurs in 9% of cases but this only exceeds 50 mL in ~1% [11, 20, 22]. Mortality is ~0.1% with haemorrhage the main cause of death [19]. Coagulation screening prior to TBLB is a necessary practice [19, 23].

Open lung biopsy

OLB by limited thoracotomy provides larger specimens than TBLB. In a large number of series [16, 24–27], the diagnostic yield of OLB was 94% compared with 72% with TBLB, 72% with drill, and 63% with needle biopsy [16]. Mortality due to the procedure was <1% [16, 24]. Although conventionally more than one sample has been taken [25], a recent study concluded that a single biopsy sample from an apparently inflamed and least fibrotic area of the most involved lobe, as determined radiographically, achieves the highest diagnostic yield [28]. High-resolution computed tomography (HRCT) scanning is useful to guide the selection of the biopsy site. OLB is preferred for patients with extreme hypoxia, prior pleural disease or pulmonary hypertension and those who require high airway pressures or are at greater risk of haemorrhage [27].

Video-assisted thoracoscopic (VATS) lung biopsy

VATS is carried out under general anaesthesia. Biopsy specimens are the same size as those obtained with OLB and the diagnostic accuracy is comparable (86–95% with VATS compared with 93–100% with OLB) [28, 29]. Perioperative morbidity, postoperative pleural drainage and length of hospital stay appear to be lower with VATS. It has been suggested that the lingula or middle lobe (easily accessible surgically) should be avoided because biopsy samples often show nonspecific fibrosis and vascular changes not seen elsewhere in the lungs [25, 30–33]. However, in more recent studies of DPLD, both in immunocompromised and nonimmunocompromised
patients, the lingula and right middle lobe have given similar histological results to those obtained at other sites [28, 36, 37]. Required mechanical ventilation or immunosuppression are both associated with an increased risk for death following surgical lung biopsy [38].

**Percutaneous biopsy**

Percutaneous techniques have been used to obtain lung biopsy samples and diagnosis can be obtained in >78% of cases [37]. The major causes of morbidity are pneumothorax (≤50%) [37-42]. Air embolism and haemorrhage are less common sequelae but are more likely to be fatal with an overall mortality of 0.1-3.1% [40, 43-46].

**Handling of biopsy samples**

TBLB samples should be obtained with minimal trauma and handling, and placed without delay into buffered formalin [13, 49]. Open biopsy samples and those obtained by VATS should be ≥4 cm in maximum diameter when inflated and include a depth of ≥1-1.5 cm. The biopsy sample should be gently inflated with formalin in the laboratory [49]. Frozen sections are only of value in suspected malignancy. Small pieces can be used for microbiology/virology as required and pieces can be frozen for immunofluorescence. Immunohistochemical techniques, in situ hybridisation and PCR can all be applied to maximise the diagnostic yields [48-50].

**Diagnostic utility of lung biopsy**

**Diagnosis of IIP**

There is a heterogenous group of non-neoplastic DPLDs resulting from lung parenchymal damage secondary to varying patterns of inflammation and fibrosis. They comprise a number of clinicopathological entities, which are sufficiently different from one another to be designated as separate disease entities. These histopathological patterns have a definite relationship to the patient’s clinical course and responsiveness to treatment [51]. However, clinicians have commonly applied a single term that included several different pathological patterns; for example, the term IPF has been applied to patients with interstitial lung diseases of unknown cause characterised pathologically by several different histological patterns, including DIP, UIP and NSIP. The ATS/ERS consensus [7] has classified these DPLDs based on a set of histological patterns (figure 1) that provide the basis for a final clinicoradiological-pathological diagnosis. Therefore, there is now less confusion in terminology and the primary role of surgical lung biopsy is to allow for better separation of these entities than is provided by the imaging patterns seen by radiologists, thereby establishing the firm diagnosis. Other equally important information includes an indication of disease activity and the relative amounts of acute, potentially reversible injury versus unresponsive scarring, which may not be apparent from the clinical findings.

The practice of observing clinical and radiological deterioration before obtaining a biopsy is not helpful because it delays diagnosis, reduces the likelihood that the disease will be correctly identified and, not infrequently, results in patients receiving unnecessary or inadequate treatment. For the same reasons, trials of therapy should be discouraged until a concerted effort has been made to establish a firm diagnosis based on this integrated approach. In >50% of cases suspected to be IPF/UIP, the presence of typical clinical and HRCT features of UIP when identified by expert clinicians and radiologists, is sufficiently characteristic to allow a confident diagnosis and eliminate the need for surgical lung biopsy [52, 53]. Therefore, the primary role of HRCT is to separate patients with UIP from those with non-UIP lesions or those with less specific findings associated with other IIPs (NSIP, respiratory bronchiolitis interstitial lung disease, DIP, and acute interstitial pneumonia). However, the sensitivity and specificity of HRCT scans for the diagnosis of IPF vary depending on the population studied and the skill of the individual interpreting the image [54, 55].

Figure 1

Classification of IIPs. HK: histocytosis X.
Diagnosis of other DPLDs
The role of lung biopsy can be pivotal for confirmation or exclusion of an alternative diagnosis such as sarcoidosis, hypersensitivity pneumonitis, lymphangioleiomyomatosis (LAM), lymphangitic carcinoma, or the presence of an occupational disease, such as hard metal disease. Certain DPLDs, such as Langerhans’ cell histiocytosis, LAM, vasculitis and lymphoma, cannot be reliably diagnosed with TBLB and, therefore, OLB or VATS biopsy samples are necessary. Coexistence of multiple histological patterns can be rarely identified; subsequently diagnosis can change depending on clinical and radiological findings to determine the major/predominant lesion.

Case history 1

Figure 2
Langerhans’ cell histiocytosis: a cellular infiltrate of Langerhans’ cells displaying the characteristic nuclear morphology with nuclear grooves. The accompanying eosinophils are typical.

A 35-year-old male presented with sensory symptoms in his hand, which remitted, followed by diplopia and visual blurring a year later. A magnetic resonance imaging scan suggested demyelinating lesions in a periventricular distribution and chest radiograph showed bilateral miliary mottling in both upper and midzones. HRCT of the chest showed presence of thin-walled air-filled cysts and scattered pulmonary nodules suggestive of Langerhans’ cell histiocytosis which was confirmed on lung biopsy (figure 2). On the balance of probability, it was likely that the patient’s pulmonary histiocytosis (which was an incidental radiological finding) was present within the setting of a multisystem disorder and was expressed clinically and predominantly within the central nervous system.

Prognostic implications of lung biopsies in IIP

Significance of histological patterns (UIP versus NSIP)
The assignment of a histological pattern of interstitial pneumonia provides significant prognostic and diagnostic data in patients undergoing biopsy [51, 56, 57]. Lone IPF is a progressive interstitial lung disease, with a median survival of 3-6 yrs from the onset of dyspnoea. Lung biopsy helps to classify IPF into prognostically significant histopathological patterns, including UIP and NSIP; the former being the most common. A diagnosis of IPF with an NSIP pattern carries a significantly better prognosis (relating to response to treatment as well as survival) than a UIP pattern alone [58].

Significance of cellular and fibrosing NSIP
The original subdivision of NSIP by Katzenstein and Fiorelli [59] was based on the pattern of interstitial inflammation and fibrosis and recognised three groups. Group 1: primarily interstitial inflammation; group 2: both interstitial inflammation and fibrosis; and group 3: primarily fibrosis. However, a subsequent publication [60] separated NSIP into cellular (corresponding to groups 1 and 2) and fibrosing (corresponding to group 3) patterns. This separation of cellular from fibrosing patterns is important due to the significantly better prognosis of the former pattern (figure 3).

Concordant and discordant NSIPs
In their study, Flaherty et al. [61] described concordant and discordant NSIPs as follows. Concordant UIP: where a pattern of UIP is present in all biopsies; discordant UIP-NSIP: where a pattern of UIP is present in at least one biopsy and an NSIP pattern is present in at least one biopsy (intrapatient histological variability); and
concordant NSIP: where a pattern of NSIP is present in all biopsies. There was a 12% incidence of discordant UIP-NSIP in biopsies performed at multiple sites as part of diagnostic workup of patients with suspected IPF. The discordant UIP group had survival, clinical and physiological features similar to those of the concordant UIP group, and prognosis in both the concordant and discordant UIP groups was significantly worse than that of the concordant NSIP group. This study implied that multiple biopsy sites should be considered in patients requiring a surgical lung biopsy for investigation of IIPs, provided they have sufficient lung function to tolerate the procedure, in order to improve prognostic information. The study emphasises that the practice of performing multiple biopsies at different sites is preferable to single biopsies, as a pattern of UIP is not uniformly present throughout the involved lung parenchyma. A significant number of patients with IPF may otherwise be inappropriately investigated as a result of being classified as NSIP on the basis of a single biopsy. It also provides evidence that a histological pattern of NSIP is consistent with the clinicopathological entity of IPF, if all other clinical data are consistent with the diagnosis [61].

UIP: the relationship between histopathological features, mortality and disease progression

Careful analysis and quantification of the specific histopathological features found in UIP can be useful in defining the prognosis of patients with IPF. The specific histopathological features that predicted survival were the degree of alveolar space granulation tissue deposition and extent of young connective tissue present within the fibroblastic foci (FF; figure 4), rather than the extent and severity of interstitial cellularity or fibrosis. The extent and severity of interstitial cellularity, alveolar space cellularity, or fibrosis did not predict survival [62].

Medico-legal issues

Detection of fibrotic processes related to specific exposures can have important compensation implications for the patient and important public health consequences for the community; for...
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Educational questions
1. What other conditions may have similar appearances to UIP due to IPF on HRCT?
2. What features on HRCT, in a case of suspected UIP, would suggest an alternative diagnosis?
3. What is the characteristic histological pattern in DIP?

Example, cases of asbestosis and UIP may look similar but have significant medico-legal implications.

Research aspects
There are still many areas of uncertainty regarding the pathogenesis of interstitial pneumonias and other DPLDs. Lung biopsies, by providing histology, can provide a detailed direction of the basic biomolecular and cellular processes driving the entire histopathological pattern and disease outcome. They can also provide new insights for novel targeted treatment. Surgical lung biopsy is also required for clinical trials to ensure that disease is comparable among study groups and provides a way to describe new disease patterns and prognostic parameters.

Conclusion
Lung biopsy is an essential tool for diagnosis, assessment and determining prognosis in different types of DPLDs. It can help to understand which subgroup of patients could benefit from current immunosuppressive treatment. Furthermore, it can be used for assessment for suitability for lung transplant. The morbidity associated with different types of lung biopsies appears to be relatively low and therefore it should be used early preferably before starting any empirical treatment.

References:
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46. McKenna RJ Jr, Savidge or smooth muscle proliferation. Characteristically there is mild-to-moderate fibrotic thickening of alveolar septa with accumulation of alveolar macrophages rather than desquamation of epithelial cells. There is absence of extensive fibrosis or smooth muscle proliferation.

Suggested answers
1. The HRCT pattern of UIP due to IPF can be distinguishable from that found in UIP due to asbestosis, collagen vascular disease. Pleural plaques or diffuse pleural thickening help to distinguish asbestosis from IPF. Sometimes patients with chronic hypersensitivity pneumonitis or with end-stage sarcoidosis show a HRCT pattern similar to that of UIP.

2. Features on HRCT that are atypical of UIP are: confluent alveolar opacities; pleural changes; and lymphadenopathy.

3. Uniform involvement of lung parenchyma with accumulation of alveolar macrophages rather than desquamation of epithelial cells. There is mild-to-moderate fibrotic thickening of alveolar septa with mild interstitial chronic inflammation. Characteristically, there is absence of extensive fibrosis or smooth muscle proliferation.