Idiopathic Interstitial Pneumonias and the Concept of the Trump Card

Over the last several years, the clinical-radiologic-pathologic classification of idiopathic interstitial pneumonias (IIPs) has undergone fine-tuning and some remodeling to define discrete identities for these diseases. Publication in 2002 of the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification scheme1 represented an important milestone in this process. In this scheme, provisional criteria for diagnosis of idiopathic nonspecific interstitial pneumonia (NSIP) were provided, with recognition that additional investigation was necessary to solidly establish the characteristics of this process and its relationships to other IIPs. At about the same time, the existence of a relationship between NSIP and usual interstitial pneumonia (UIP) was suggested by Flaherty et al.2 These investigators discovered that 26% of patients receiving multilobar surgical lung biopsy for suspected idiopathic pulmonary fibrosis (IPF) had “discordant UIP” (NSIP in at least one lobe and UIP in at least one lobe), and that patients with a discordant UIP pattern had survival more closely resembling concordant UIP (UIP pattern in all lobes) than concordant NSIP (NSIP pattern in all lobes). Although survival for the discordant UIP group was slightly better than that of the concordant UIP group for the first 5 years, the survival curves intersected between 5 years and 6 years.

In this issue, the article by Monaghan and colleagues (see page 522) confirms these findings and further emphasizes the advantages of obtaining surgical lung biopsy samples from multiple sites. In this retrospective analysis of a cohort of 64 patients undergoing multiple biopsies of single or multiple lobes for suspected idiopathic pulmonary fibrosis (IPF) had “discordant UIP” (NSIP in at least one lobe and UIP in at least one lobe), and that patients with a discordant UIP pattern had survival more closely resembling concordant UIP (UIP pattern in all lobes) than concordant NSIP (NSIP pattern in all lobes). Although survival for the discordant UIP group was slightly better than that of the concordant UIP group for the first 5 years, the survival curves intersected between 5 years and 6 years.

In this issue, the article by Monaghan and colleagues (see page 522) confirms these findings and further emphasizes the advantages of obtaining surgical lung biopsy samples from multiple sites. In this retrospective analysis of a cohort of 64 patients undergoing multiple biopsies of single or multiple lobes for suspected idiopathic pulmonary fibrosis (IPF), which were histologically reclassified using the methods of Flaherty et al.,2 25 patients showed concordant UIP, 8 patients showed discordant UIP, and 31 patients showed concordant NSIP. At 5 years after biopsy, survival rates for the concordant NSIP, discordant UIP, and concordant UIP groups were 75%, 37%, and 17%, respectively, and the survival difference between the NSIP and UIP groups remained significant after controlling for all other variables assessed. These results agree with those of other studies3-7 that have documented superior survival for NSIP as compared to UIP. Monaghan et al also show differences in mean patient age between groups, with discordant UIP occupying the intermediate position between concordant UIP and concordant NSIP, as was also noted by Flaherty et al.2

These findings raise interesting questions about the natural history and independence vs relatedness of these IIP patterns although, histologically, patterns of UIP and NSIP are generally distinct and identifiable. UIP demonstrates patchy, temporally heterogeneous lung involvement by dense fibrosis and mild or moderate interstitial lymphoplasmacytic infiltrates, architectural remodeling, honeycomb change, and fibroblastic foci.1 Fibroblastic foci are a key feature of UIP and are believed to represent zones of disease activity whose extensiveness has been linked to survival.8,9 NSIP includes a spectrum from cellular to fibrosing patterns.1 While distinguishing the cellular NSIP pattern from UIP is usually straightforward, separation of the fibrosing pattern of NSIP from UIP can be more challenging. Fibrosing NSIP demonstrates dense or loose interstitial fibrosis that is temporally homogeneous, may have a more diffuse distribution histologically, and usually lacks the more prominent fibroblastic foci, architectural remodeling, and honeycomb change characteristic of UIP.1,10 Occasional cases with overlapping features occur and can be difficult to classify.

In patients with clinical features of CFA/IPF, it has been suggested that NSIP may represent an early phase of the disease process that is followed later by UIP,2 and that NSIP may represent relatively “inactive” disease in CFA/IPF.11 A histologic study10 of surgical lung biopsy and subsequent lung explant specimens confirms the high frequency of NSIP-like areas in UIP, but includes several cases with NSIP-like areas in explants but not in the earlier biopsies showing UIP, interpreted by the authors as...
evidence against an evolution from NSIP to UIP. Nonetheless, the results of Katzenstein et al.10 correlate well with those of Flaherty et al2 and Monaghan et al, and indicate that the range of histologic manifestations acceptable in UIP can be expanded to allow for NSIP-like areas, provided that other diagnostic features of UIP are present.

Although numerous unanswered questions remain regarding the pathogenesis of the IIPs, these articles have implications for the evaluation of patients with IIPs. As summarized by Dr. Tom Colby, Mayo Clinic, at the Third Biennial Summer Symposium of the Pulmonary Pathology Society: in the realm of IIPs, UIP is the default pattern of significance. When it is present, it determines prognosis, regardless of whether or not another pattern (ie, NSIP) is also identified. As the studies by Monaghan et al. and Flaherty et al.2 illustrate, in patients with suspected CFA/IPF the practice of sampling multiple areas of lung enhances detection of histologic UIP, and histologic UIP determines survival even if accompanied by another biopsy showing an NSIP pattern. Interestingly, another recent study12 suggests that the combination of biopsy and high-resolution CT (HRCT) may offer further enhanced capacity to separate patients into prognostic groups. Classifying patients into combined HRCT/histologic diagnosis groups produced stratification of the groups by survival, with the lowest survival in the HRCT-UIP/histology-UIP group, intermediate survival in the HRCT-indeterminate or NSIP/histology-UIP group, and best survival for the HRCT-indeterminate or NSIP/histology-NSIP group.

The importance of the clinical-radiologic-pathologic diagnosis (“the disease”) is now emphasized beyond that of the histologic diagnosis alone in the management of patients with IIPs. In some cases, clinical and HRCT data may take precedence over histologic pattern. A scenario in which the clinical and HRCT features favor IPF and the biopsy shows an NSIP pattern represents one example in which the clinical and radiologic findings can “trump” the histologic findings. Intrapatient histologic variability and sampling issues represent two important sources of inconsistencies between clinical, radiologic, and pathologic diagnoses. Accurate pathologic diagnosis is dependent on tissue representation of the disease, so sampling of nondiagnostic areas may interfere with classification of the IIP. Ideally, the lung biopsy tissues should include the spectrum of gross and/or HRCT abnormalities, so that areas of varying disease severity and morphology are represented. More is often better, within the limitations imposed by other coexisting constraints. Although we know this intuitively and from our training, the article by Monaghan and colleagues describes a thoughtful extension of this principle with utility for predicting prognosis in some types of IIPs.

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REFERENCES