When is NSIP an appropriate final diagnosis in current practice?

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Nonspecific interstitial pneumonia/fibrosis (NSIP) was proposed in 1994 as a form of chronic interstitial pneumonia characterized by relatively uniform expansion of alveolar septa by inflammation and/or fibrosis without the geographic and temporal heterogeneity of UIP. As the term implies, the histologic findings in NSIP are not specific. Findings indistinguishable from NSIP can occur focally in other conditions, most importantly UIP. The findings are also nonspecific from a clinical perspective given that identical changes can occur in surgical lung biopsies from patients with a variety of underlying causes or associations, including hypersensitivity pneumonia and various systemic connective tissue diseases. Recognizing idiopathic NSIP as a discrete entity is therefore a process of exclusion that requires careful correlation with clinical and radiological information. Given the difficulty in identifying patients with idiopathic NSIP, the consensus classification for the idiopathic interstitial pneumonias originally published in 2002 suggested that NSIP be considered “a provisional diagnosis until there is further clarity on the nature of the corresponding clinical condition.” In a revised classification that will soon be published, however, the authors advocate that NSIP be viewed as a distinct entity.

Clinical features
NSIP is the second most common idiopathic interstitial pneumonia, accounting for as many as a third of patients undergoing surgical lung biopsy in retrospective series. NSIP fails to show the gender predilection for men seen in UIP, and in some series is more common in women. NSIP also differs from UIP in that it tends to affect younger patients, with an average age at diagnosis of around 50 years. Shortness of breath and dry cough are the most common complaints, often developing in an insidious fashion indistinguishable from that described for UIP. Pulmonary function studies show restricted lung volumes and abnormalities of oxygenation, although the degree of abnormality tends to be less severe compared to patients with UIP. high resolution computed tomography (HRCT) scans show a nonspecific combination of ground glass opacities, irregular lines, and traction bronchiectasis occasionally with subpleural sparing. The radiologic findings, although frequently characteristic, cannot reliably distinguish patients with NSIP from those with early or radiologically atypical UIP or from certain other interstitial lung diseases.

Multiple studies have now confirmed the survival advantage associated with a diagnosis of NSIP compared to UIP. Median survival for all NSIP cases is over 9 years, with the best prognosis occurring in patients with minimal fibrosis (cellular variant, see later on). Most patients with cellular NSIP survive but about half have persistent stable disease. Patients in whom fibrosis predominates in surgical lung biopsies do worse than those with more cellular lesions, although still better than UIP. Mortality rates for patients with fibrotic NSIP vary widely, ranging from 11% to 68% in various studies (mean ± STD, 30.4% ± 18.9%). Reported 5 year survivals of such patients are about 76% compared to about 45% for UIP. Survivors typically have persistent lung disease. To some extent variation in mortality rates reported for patients with fibrotic NSIP reflects differences in histologic definitions and the difficulty in separating...
fibrotic NSIP from UIP. Corticosteroids have not been prospectively evaluated in a randomized fashion but may be effective in a subset of patients, especially those with minimal associated fibrosis.

**Pathologic Features**

A diagnosis of NSIP in surgical lung biopsies requires the presence of a chronic interstitial pneumonia without findings to prompt diagnosis of a more specific pathologic process. Unlike UIP, NSIP is in many respects a diagnosis of exclusion. Defined in this way NSIP spans a range of histologic abnormalities ranging from a predominantly cellular process (i.e. cellular NSIP) to paucicellular lung fibrosis (i.e. fibrotic or fibrosing NSIP). The most cellular forms are characterized by an alveolar septal infiltrate of mononuclear cells that may be patchy or diffuse. Whether patchy or diffuse, the qualitative features of the interstitial abnormalities remain constant without the geographic and temporal heterogeneity associated with UIP. The inflammatory infiltrate consists of lymphocytes and variable numbers of admixed plasma cells. Neutrophils, eosinophils, and histiocytes are relatively inconspicuous.

The relative frequency of fibrosis in NSIP is variable. Patients with fibrotic NSIP outnumber patients with cellular NSIP by a ratio of nearly 4-to-1 in published studies, but this may reflect selection bias in that most reports are from tertiary referral centers where patients with fibrotic interstitial lung disease may be over-represented. In addition there are no clearly articulated criteria for separating cellular from fibrotic NSIP. The term fibrotic NSIP should be limited to those patients in whom paucicellular fibrosis with minimal or mild inflammation is the predominant feature. Defined in this way the extent of interstitial fibrosis is variable. Fibrosis takes the form of uniform collagen accumulation resulting in expansion of alveolar septa and peribronchiolar interstitium without the patchwork distribution characteristic of UIP. Interlobular septa and visceral pleura may also be involved. Pathology reports should comment on the presence and extent of interstitial fibrosis, since it is associated with significantly increased risk for disease specific mortality. Associated smooth muscle hyperplasia tends to be less extensive than that seen in UIP. Fibroblast foci should be absent or at most rare and inconspicuous. Honeycomb change and broad zones of scarring should be absent, an important feature in distinguishing fibrotic NSIP from UIP. Patchy intraluminal fibrosis resembling organizing pneumonia is common but should be a focal and relatively inconspicuous finding that is overshadowed by the interstitial changes.

**Distinguishing fibrotic NSIP from UIP**

Separating fibrotic NSIP from UIP is perhaps the greatest challenge when it comes to making meaningful distinctions between the idiopathic interstitial pneumonias. Separating fibrotic NSIP from UIP hinges on recognition of the patchwork distribution, fibroblast foci and honeycomb change typical of UIP. Recognition of any one of these features in a biopsy for which a diagnosis of fibrotic NSIP is being contemplated is reason for caution. In this circumstance correlation with other clinical data, especially the findings on HRCT scans, may be helpful. Unfortunately even the most rigorous of multidisciplinary review cannot always reliably separate patients with fibrotic NSIP from patients with UIP because HRCT scans accurately identify only about half of patients with UIP while the others frequently show findings indistinguishable from NSIP. For that reason there are patients with UIP in whom neither HRCT nor surgical lung biopsies are diagnostic resulting in a mistaken diagnosis of idiopathic NSIP.
This persistent diagnostic challenge complicates interpretation of a retrospective review of five patients for whom a follow-up surgical lung specimen showed UIP 3-9.5 years after an original diagnosis of fibrotic NSIP. Schneider and colleagues concluded that fibrotic NSIP may precede the development of UIP, but in three of their five patients only a single site was biopsied and in two it was an upper lobe. To date the evidence that fibrotic NSIP is a precursor of UIP is weak at best. It seems at least equally likely that a subset of patients mistakenly thought to have fibrotic NSIP will ultimately prove to have UIP.

The primary problem is that areas typical of NSIP can occur focally in other conditions making sampling bias a potential barrier to accurate diagnosis. In a review of 20 explanted lungs with UIP, all but 3 showed isolated areas that were indistinguishable from NSIP (“NSIP-like areas”). Other studies showed that the presence of UIP in even a single piece of tissue defined a survival curve typical of IPF in patients from whom surgical lung biopsies taken from more than one site demonstrated both UIP and NSIP (“discordant UIP”). For these reasons establishing a diagnosis of idiopathic NSIP requires the absence of clinical, radiological or pathological findings to suggest an alternative as well as generous sampling of multiple sites for surgical lung biopsy. For example, a biopsy diagnosis of fibrotic NSIP in a patient with bibasilar honeycomb change on HRCT is almost certainly a sampling error in a patient with UIP.

Recognition of unclassifiable lesions in patients suspected of having idiopathic interstitial pneumonias

Occasionally lung biopsies show a fibrotic lesion in a clinical context strongly suggesting an idiopathic interstitial pneumonia but without sufficiently distinctive radiological or histologic findings to allow confident diagnosis of a specific entity. Typically these biopsies show fibrosis but with neither the combination of a patchwork distribution, fibroblast foci and honeycomb change diagnostic of UIP nor the uniform parenchymal involvement required for a diagnosis of NSIP. In other cases a portion of the biopsy may show a lesion unusually cellular for UIP but with other areas in which the degree of honeycomb change precludes a diagnosis of NSIP. The recently revised consensus classification proposes the term unclassifiable idiopathic interstitial pneumonia for those patients in whom no clear diagnosis can be made, suggesting that “management should be based on the most probable diagnosis after MDD and consideration of the expected disease behavior”. The frequency and significance of this nebulous and likely heterogeneous group of patients is largely unknown.

References