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Nonspecific interstitial pneumonia: pathologic features and clinical implications

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Nonspecific interstitial pneumonia (NSIP) is a form of chronic interstitial pneumonia that should be separated from the other idiopathic interstitial pneumonias, including most importantly, usual interstitial pneumonia (UIP). Diagnosis is predicated on identification of characteristic findings in a surgical lung biopsy in the appropriate clinical and radiological context. Affected patients may have a variety of underlying or associated conditions, although most have a form of idiopathic lung disease associated with a more favorable prognosis than UIP/idiopathic pulmonary fibrosis (IPF). Keys to distinguishing NSIP from UIP include absence of heterogeneous lung involvement, architectural distortion in the form of fibrotic scarring and/or honeycomb change, and fibroblast foci in NSIP.

The idiopathic interstitial pneumonias are a subset of diffuse parenchymal lung diseases in which inflammation and variable degrees of concomitant fibrosis expand and occasionally distort the interstitial compartment (ie, that portion of the lung parenchyma sandwiched between epithelial and endothelial basement membranes). Affected patients typically complain of nonproductive cough and/or shortness of breath accompanied by abnormal pulmonary function studies and diffuse radiological abnormalities.

Histopathologic classification plays a key role in separating idiopathic interstitial pneumonia into clinically meaningful categories (Table 1).[1-5] Usual interstitial pneumonia (UIP) is the most common and has distinctive morphologic features that allow precise histological diagnosis in most cases (Figure 1). Biopsy diagnosis is predicated on a combination of findings that includes: (1) a heterogeneous ("patchwork") distribution of abnormalities in which fibrosis predominates, (2) architectural distortion in the form of fibrotic scarring and/or honeycomb change, and (3) temporal heterogeneity resulting from juxtaposition of collagenous scarring and small subepithelial foci of proliferating fibroblasts and myofibroblasts termed "fibroblast foci."[2,3,6] None of these findings taken individually is specific, but taken together the combination is pathognomonic. Lung biopsy findings in other idiopathic interstitial pneumonias, such as desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), acute interstitial pneumonia (AIP), and nonspecific interstitial pneumonia (NSIP), are less specific and must be correlated with clinical and radiologic information to establish a clinicopathologic diagnosis.

In 1994 Dr. Katzenstein proposed the term *nonspecific interstitial pneumonia/fibrosis* (NSIP) for a lesion "characterized by an interstitial inflammatory or fibrosing process or both . . . [that] appeared temporally uniform within each case."[7] In other words, NSIP was defined as a form of chronic interstitial pneumonia in which there is relatively uniform expansion of alveolar septa by inflammation and/or fibrosis without the degree of heterogeneity that defines UIP. As the term implies, NSIP is not a stand-alone histologic diagnosis in that it occurs in a variety of clinical contexts, including patients with underlying systemic connective tissue dis-

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Table 1 Classification of idiopathic interstitial pneumonias

	International Classification[4]	
Katzenstein & Myers[5]	Clinical diagnosis	Pathologic pattern
Usual interstitial pneumonia (UIP)	Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP)
Desquamative interstitial pneumonia (DIP)/Respiratory bronchiolitis interstitial lung disease (RBILD)	Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
	Respiratory bronchiolitis interstitial lung disease (RBILD)	Respiratory bronchiolitis interstitial lung disease (RBILD)
Acute interstitial pneumonia (AIP)	Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)
Nonspecific interstitial pneumonia (NSIP)	Nonspecific interstitial pneumonia (NSIP)	Nonspecific interstitial pneumonia (NSIP)
	Cryptogenic organizing pneumonia (COP)	Organizing pneumonia (OP)
	Lymphoid interstitial pneumonia (LIP)	Lymphoid interstitial pneumonia (LIP)

Adapted from Travis et al.,[4] and Katzenstein & Myers.[5]

eases, hypersensitivity pneumonia (extrinsic allergic alveolitis), drug-induced lung disease, and chronic interstitial lung disease complicating diffuse alveolar damage. In addition, histopathologic findings indistinguishable from NSIP can occur focally in other conditions, most importantly UIP.[6,8,9] Given the relatively nonspecific nature of this pattern of interstitial pneumonia, recognition of NSIP as a distinct clinicopathologic syndrome requires a process of exclusion. Carefully defined, however, NSIP is an important form of idiopathic interstitial pneumonia.

Clinical features

NSIP is the second most common idiopathic interstitial pneumonia, accounting for 14% to 35% of patients undergoing surgical lung biopsy in retrospective series.[10-12] NSIP affects men and women equally with an average age at diagnosis of 48 years compared with 59 years for UIP.[7,10-18] Unlike UIP, NSIP occurs in children.[7,19] Shortness of breath and dry cough are the most common complaints, often presenting in an insidious fashion indistinguishable from that described for UIP. Occasional patients have a more rapid, subacute onset. Symptoms are present an average of 14 months before diagnosis, ranging from 3 months to over 3.5 years in various studies. Fever and weight loss are uncommon. Physical findings include inspiratory crackles in nearly all patients. Finger clubbing occurs in about 25% of patients.[10,14,16,18] Pulmonary function studies show restricted lung volumes and abnormalities of oxygenation, although the degree of abnormality tends to be less severe compared with patients with UIP. Conventional chest radiographs are abnormal at presentation in most patients. CT scans show a nonspecific combination of ground glass opacities, consolidation, and irregular lines, usually in a peripheral subpleural distribution with a predilection for lower lung zones.[4,17,20-24] The radiologic findings, although frequently characteristic, cannot reliably distinguish patients with NSIP from those with early or radiologically atypical UIP.[20,25,26]

Multiple studies have now confirmed the survival advantage associated with a diagnosis of NSIP compared with UIP.[25] Average disease-specific mortality in reported series is around 20% with mean or median survivals ranging from 1.3 to nearly 15 years.[7,10,18] Mortality rates vary widely, however, reflecting differences in case definitions and patient selection criteria. Patients in whom fibrosis predominates in surgical lung biopsies do worse than those with more cellular lesions (see below).[7,8,11,12] Corticosteroids have proven effective in at least a subset of NSIP 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. Defined in this way, NSIP spans a spectrum of interstitial pneumonias ranging from a predominantly cellular process (ie, cellular NSIP) to paucicellular lung fibrosis (ie, fibrotic NSIP).

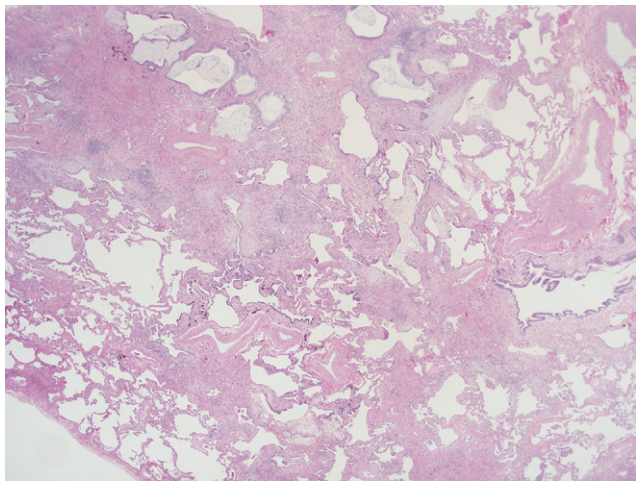

Figure 1 Low-magnification photomicrograph showing usual interstitial pneumonia (UIP) in a surgical lung biopsy. There are alternating areas of relatively unaffected lung and areas of dense scarring and honeycomb change (upper left) resulting in a characteristic "patchwork" appearance. Small interstitial zones of pallor represent fibroblast foci (original magnification 20×).