Radiology

Collaborative Radiologic and Histopathologic Assessment of Fibrotic Lung Disease[1]

Jeffrey R. Galvin, MD
Aletta Ann Frazier, MD
Teri J. Franks, MD

The idiopathic interstitial pneumonias (IIPs) are a seemingly disconnected collection of diseases usually associated with the presence of pulmonary fibrosis. Categorization of the IIPs continues to be problematic despite recent attempts to refine the diagnostic criteria and suggests that rather than separate diseases, these pneumonias represent a spectrum of injury and abnormal repair of the alveolar wall. Although the initiating injury or injuries are unknown, the IIPs share a restricted number of final common abnormal pathways that lead to volume loss and lung distortion. The pathways include *(a)* alveolar collapse, *(b)* incorporation of fibroblastic material into alveolar walls, and *(c)* cigarette smoke–related inflammation and fibrosis. A collaborative diagnostic process in which data from radiologic and histologic assessments are combined allows a more reliable identification of the predominant pathways leading to pulmonary fibrosis. This approach has implications for therapy and the future direction of research.

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[1] From the Departments of Radiologic Pathology (J.R.G., A.A.F.) and Pulmonary and Mediastinal Pathology (T.J.F.), Armed Forces Institute of Pathology, 6825 16th St NW, Bldg 54, Room M133B, Washington, DC 20306-6000; and Department of Diagnostic Radiology (J.R.G., A.A.F.) and Department of Internal Medicine, Division of Pulmonary/Critical Care Medicine (J.R.G.), University of Maryland School of Medicine, Baltimore, Md. Received May 3, 2009; revision requested June 16; revision received July 28; accepted September 30; final version accepted October 15. **Address correspondence to** J.R.G. (e-mail: *jgalvin@mac.com*).

Diffuse pulmonary fibrosis is the primary diagnostic consideration in patients with shortness of breath and restrictive pulmonary physiology. A combined American Thoracic Society (ATS) and European Respiratory Society (ERS) committee was convened to clarify the diagnostic categories that comprise the idiopathic interstitial pneumonias (IIPs). However, categorization of the fibrosis in patients with these diseases continues to be problematic for clinicians, radiologists, and pathologists alike (1,2). Patients often do not fit neatly into the currently accepted ATS/ERS categories, and our approach, which is focused to a greater degree on pathways of injury, differs in some aspects from the ATS/ERS approach and is a response to the difficulties in the ATS/ERS classification. In our scheme, the nonspecific interstitial pneumonia (NSIP) pattern of fibrosis is rarely a distinct entity and is usually associated with organizing pneumonia, smoking-related lung injury, or idiopathic pulmonary fibrosis (IPF) (Fig 1).

One of the key contributions of the 2002 consensus statement (3) was the recognition of a collaborative diagnostic process in patients with interstitial pneumonias. The executive summary of that publication recommends that "the final diagnosis should be rendered only after the pulmonologist, radiologist, and pathologist have reviewed all of the clinical, radiological and pathologic data obtained from the patient" (3). This recommendation implies that lung biopsy alone may not be the "gold standard" for evaluation of fibrotic lung disease (2). Subsequent scientific study results have confirmed that a collaborative process, including clinical data evaluation, high-spatial-resolution chest computed tomography (CT), and lung biopsy, is associated with a substantial increase in diagnostic reproducibility and the confidence level when assessing patients with diffuse pulmonary fibrosis (4). This approach also ameliorates the diagnostic inaccuracies related to biopsy sampling error and improves the low to moderate levels of interobserver agreement affecting radiologists and pathologists, especially when fibrotic NSIP is part of the differential diagnosis (5–7). This article is focused on the interaction between the pathologist and the radiologist. The approach to rendering a combined radiologic-histopathologic diagnosis is illustrated through multiple examples and accompanying detailed figure legends. The interaction with the clinician, although crucial, is beyond the scope of this discussion.

During the past 5 years, we have rendered a collaborative radiologic-histopathologic diagnosis in more than 1000 cases of chronic infiltrative lung disease referred for second-opinion consultation. The radiologic images and histologic specimens were read separately; this was then followed by a collaborative review in which the original findings were combined into a final diagnosis. The completed report included the original radiologic and histologic assessments along with a third section entitled "Radiologic-Pathologic Correlation," which clarified the meaning of the discrepancies, when they were present, and included a discussion of the diagnostic confidence level. The juxtaposition of all three sections has allowed a more transparent assessment of how the final collaborative diagnosis is reached. This approach yields a confident final diagnosis when the radiologic and histologic patterns agree or a suggested path for continued workup, depending on the nature of the discrepancy identified.

The process has been most effective when it was conducted in the form of a face-to-face meeting that enabled simultaneous review of the radiologic and histologic data. We have made extensive use of the secure Web-conferencing software Adobe Connect (Adobe Systems, San Jose, Calif) to hold collaborative "virtual case" conferences (Fig 2). This has improved efficiency and enabled collaborative consultation between individuals at distant institutions. Web conferencing has had other benefits, including the ability to communicate with the referring clinician during radiologic-histologic correlation conferences, and enabled these sessions to be recorded for later review. The sessions have provided an excellent platform for teaching both radiology and pathology residents, who can log in remotely to observe the diagnostic process and how uncertainties associated with difficult cases are addressed. A video podcast (Movie [online]) that includes a consultation case from our archive is available at the *Radiology* Web site under the "See How It's Done" section.

Essentials

- Patients with diffuse pulmonary fibrosis are difficult to characterize and require assessment at varying scales of magnification, in which the distribution of disease determined with chest CT is combined with findings derived from microscopy to make a consistent and reliable diagnosis.
- The distribution of opacities and cystic spaces displayed at chest CT is key to determining the mechanism of diffuse injury and preventing errors in categorization.
- Results of electron microscopy and quantitative assessment of histologic lung findings support the concept that the lower-lobe cystic spaces in idiopathic pulmonary fibrosis (IPF) are related to the collapse of alveoli around alveolar ducts rather than the deposition of fibrous tissue.
- The nonspecific interstitial pneumonia pattern of fibrosis may be associated with IPF, the fibrotic phase of organizing pneumonia, and cigarette smoke–related injury.

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Abbreviations:
AIP = acute interstitial pneumonia
ATS = American Thoracic Society
DAD = diffuse alveolar damage
ERS = European Respiratory Society
IIP = idiopathic interstitial pneumonia
IPF = idiopathic pulmonary fibrosis
NSIP = nonspecific interstitial pneumonia
UIP = usual interstitial pneumonia

Authors stated no financial relationship to disclose.

Figure 1

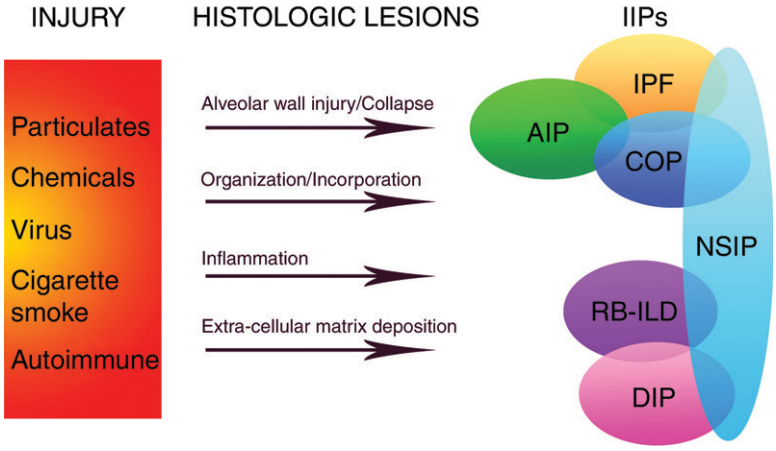
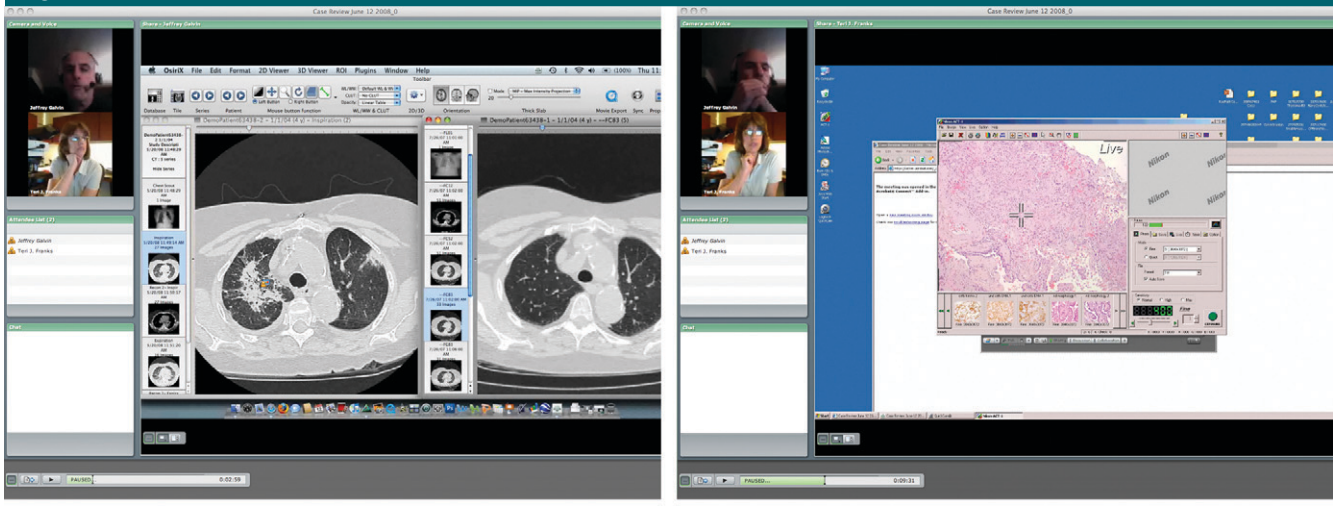


Figure 1: Overview of the IIPs, which typically have been classified as separate diseases (1). We currently use an approach that recognizes frequent overlap among the IIPs and suggest that multiple histologic lesions may be identified in individual cases. The NSIP pattern of fibrosis can be found in patients with IPF, cryptogenic organizing pneumonia *(COP),* cigarette smoke–related respiratory bronchiolitis–interstitial lung disease *(RB-ILD),* and desquamative interstitial pneumonia *(DIP). AIP* = acute interstitial pneumonia.

Figure 2



a. **b.**

Figure 2: Web-based collaboration. Screen captures of **(a)** radiologic images and **(b)** histologic specimens demonstrate real-time collaborative diagnosis rendered by using the Adobe Connect Web-based application (Movie [online]).

Legacy Terminology

The current ATS/ERS classification of the IIPs is focused on the creation of categories with clear divisions (3) and retained legacy terminology in a well-intentioned attempt to reduce confusion. However, many of the ATS/ERS terms used to categorize the IIPs, including IPF, usual interstitial pneumonia (UIP), and desquamative interstitial pneumonia, were derived from publications that are more than 3 decades old (8–10). UIP now represents a histologic pattern that is entirely different from that originally described, and desquamative interstitial pneumonia is no longer considered the result of desquamating type II pneumocytes. In addition, a focus on strict categorization diverts attention from the pathogenesis and obscures the continuity between entities in the list of IIPs (1).

To lessen the restrictive effect of legacy terminology, we started each case with a simple description of the radiologic and histologic findings, without an initial attempt to place these findings in an ATS/ERS diagnostic category. For the radiologist, this consisted of identifying the following set of parenchymal and airway abnormalities and defining their locations: low attenuation, low attenuation with walls (cysts), consolidation, ground-glass opacity, reticulation, airway distortion, and traction bronchiectasis. The pathologist also uses a restricted set of findings for the initial description of the histologic entities: cystic spaces, alveolar wall fibrosis, intraalveolar organization, interstitial incorporation of organization, inflammation, edema, hyaline membranes, and emphysema.

Table 1

Key Features of IIPs as Defined according to ATS/ERS Consensus Classification

Characteristic	IPF	NSIP	COP	AIP	RB-ILD	DIP
Mean age at onset (y)	60–65	40–50	55	50	40–50	40–50
Onset	Gradual	Gradual	Subacute	Acute	Gradual	Gradual
Chest CT distribution	Peripheral, subpleural, basal	Peripheral, subpleural, basal, symmetric	Subpleural, peribronchial	Diffuse	Diffuse	Lower lobe, mainly peripheral
Chest CT findings	Reticulation, honeycombing, traction bronchiectasis, ground-glass opacity	Ground-glass opacity, reticulation, consolidation	Consolidation and/or nodules	Consolidation, ground-glass opacity (often focal sparing), traction bronchiectasis later	Bronchial wall thickening, centrilobular nodules, ground-glass opacity	Ground-glass opacity, reticulation
Corresponding histologic diagnosis	UIP	NSIP	OP	DAD	RB	DIP
Histologic findings	Patchy, subpleural, and paraseptal dense fibrosis; honeycombing; fibroblast foci	Temporally uniform interstitial fibrosis, mild or moderate interstitial chronic inflammation	Patchy, temporally uniform intraluminal organization	Temporally uniform alveolar wall thickening, airspace organization, hyaline membranes, organization, fibrosis later	Bronchiolocentric pigmented alveolar macrophages, mild bronchiolar fibrosis, chronic interstitial inflammation	Uniform pigmented alveolar macrophages, mild to moderate interstitial fibrosis, chronic inflammation
Prognosis	Poor	Intermediate	Good	Very poor	Good	Good

Source.—Reference 3.

Note.—COP = cryptogenic organizing pneumonia, DAD = diffuse alveolar damage, DIP = desquamative interstitial pneumonia, ILD = interstitial lung disease, OP = organizing pneumonia, RB = respiratory bronchiolitis.

Distribution of Cysts

In many patients with pulmonary fibrosis, we have identified a combination of radiologic and histologic findings that matched the diagnostic criteria for a published category in the ATS/ERS classification of the IIPs (Table 1). In these cases, the distribution of cystic spaces, as determined by using high-spatial-resolution CT, has been particularly helpful in separating cases into diagnostic categories. This is especially important if only transbronchial biopsy or single-lobe biopsy is possible. We avoid using the term *honeycombing*, despite its common use in both radiologic and histopathologic studies, as the definition is not standardized and is currently a focus of study by the Fleischner Society. The following distribution of cystic spaces has been useful for categorizing the IIPs: *(a)* peripheral and lower-lobe cysts in UIP-IPF (Fig 3), *(b)* diffuse cysts in the organizing phase of AIP (Fig 4), *(c)* traction bronchiectasis or bronchioloectasis with peripheral sparing in patients with the fibrotic phase of organizing pneumonia (Fig 5), and *(d)* preexisting upper-lobe emphysematous spaces with fibrotic walls in smoking-related interstitial lung disease (Fig 6).

However, in most consultation cases, we have observed a spectrum of radiologic and histologic findings that spanned across multiple categories in the ATS/ERS classification. If one focuses on similarities rather than differences in the categorization of the IIPs, three mechanisms of injury stand out: *(a)* alveolar collapse, *(b)* incorporation of intraalveolar fibroblastic material into the alveolar wall, and *(c)* smoking-related lung injury (Table 2). The following section is organized according to spectrum of injury. Cases that fit in the categories described in the ATS/ERS classification, as well as the bridging fibrotic lesions that are not easily classified into these categories, are highlighted. We have also included in the figures examples that demonstrate approaches to managing the inevitable uncertainty in diagnosis that accompanies some cases. The reader will note that lymphoid interstitial pneumonia is not included in this discussion because we

Figure 3

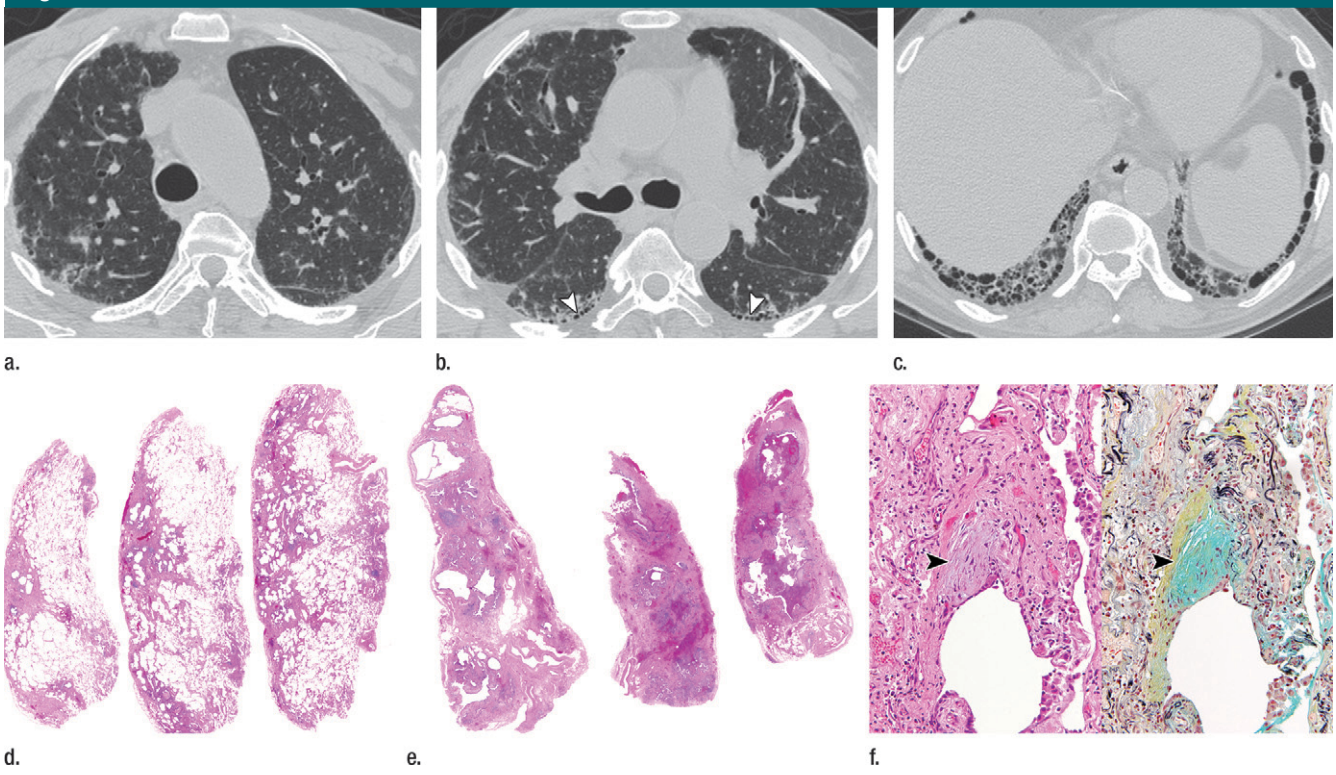


Figure 3: UIP-IPF in 60-year-old man. **(a–c)** Axial high-spatial-resolution CT images at **(a)** aortic arch, **(b)** carina, and **(c)** posterior costophrenic angles demonstrate strikingly peripheral areas of opacity. There is reticulation in upper lobes with progressively severe cystic change in middle and lower lung zones. Cysts are contiguous with pleural surface (arrowheads in **b**), and the most involved section is at the lung base in the posterior costophrenic angles. **(d)** Lung biopsy specimens from upper lobe show subpleural and paraseptal accentuation of fibrous tissue and gradient of increasing fibrosis from upper-lobe (**d**) to lower-lobe (**e**) sections; subpleural cysts are also evident in **e**. (Hematoxylin-eosin stain; original magnification, ×1.) In **d**, geographic heterogeneity is characterized by involved parenchyma alternating with areas of uninvolved or less involved parenchyma. **(f)** Lung biopsy specimens show fibroblast foci (arrowheads) in cyst walls. (Left: hematoxylin-eosin stain; original magnification, ×100; right: Movat pentachrome stain; original magnification, ×100.) There is excellent correlation between CT and histologic findings: Both are compatible with UIP-IPF. When imaging and histologic findings are diagnostic, prognosis is uniformly poor.

consider this a part of the spectrum of primary lymphoid abnormalities in the chest, which range from inflammatory to malignant entities.

IIPs Viewed as a Spectrum of Injury and Abnormal Repair

Alveolar Collapse and Incorporation of Fibroblastic Material: IPF, AIP, and Organizing Pneumonia

Patients with UIP-IPF, AIP, and organizing pneumonia demonstrate a variable combination of alveolar collapse and incorporation of fibroblastic material. UIP-IPF and AIP are diffuse processes that are differentiated primarily by the severity of injury and the pace of progression. Organizing pneumonia is a more focal, peribronchiolar process in which incorporation of fibroblastic material into alveolar walls is the dominant process that can lead to an NSIP pattern of fibrosis.

IPF.—In the latest ATS/ERS consensus statement, UIP-IPF is defined as a "specific form of chronic fibrosing interstitial pneumonia… associated with the histological appearance of usual interstitial pneumonia (UIP)" (3). Pathologists use the term *UIP* when making the histologic diagnosis, while IPF encompasses the entire clinical syndrome and is a term used by clinicians (Table 1).

Patients with UIP-IPF rarely undergo biopsy. The combination of a typical presentation and a confident radiologic diagnosis (Fig 3) is considered sufficient (11,12). Imaging that has a central role in the diagnosis of this devastating disease requires a thorough understanding of the criteria that lead to a confident radiologic diagnosis of UIP-IPF. Alveolar collapse is the principal pathophysiologic entity responsible for the progression of UIP-IPF (13–15) and by extension the radiologic appearance (16). UIP-IPF is believed to be the result of a widespread low-level injury to the alveolar wall (Fig 7). The exudation of fluid and protein from damaged alveoli (17), and alterations in pulmonary surfactant (18) result in increased surface tension that leads to the collapse of small alveoli onto larger alveolar ducts (Fig 8) owing to the Laplace relationship:

Figure 4

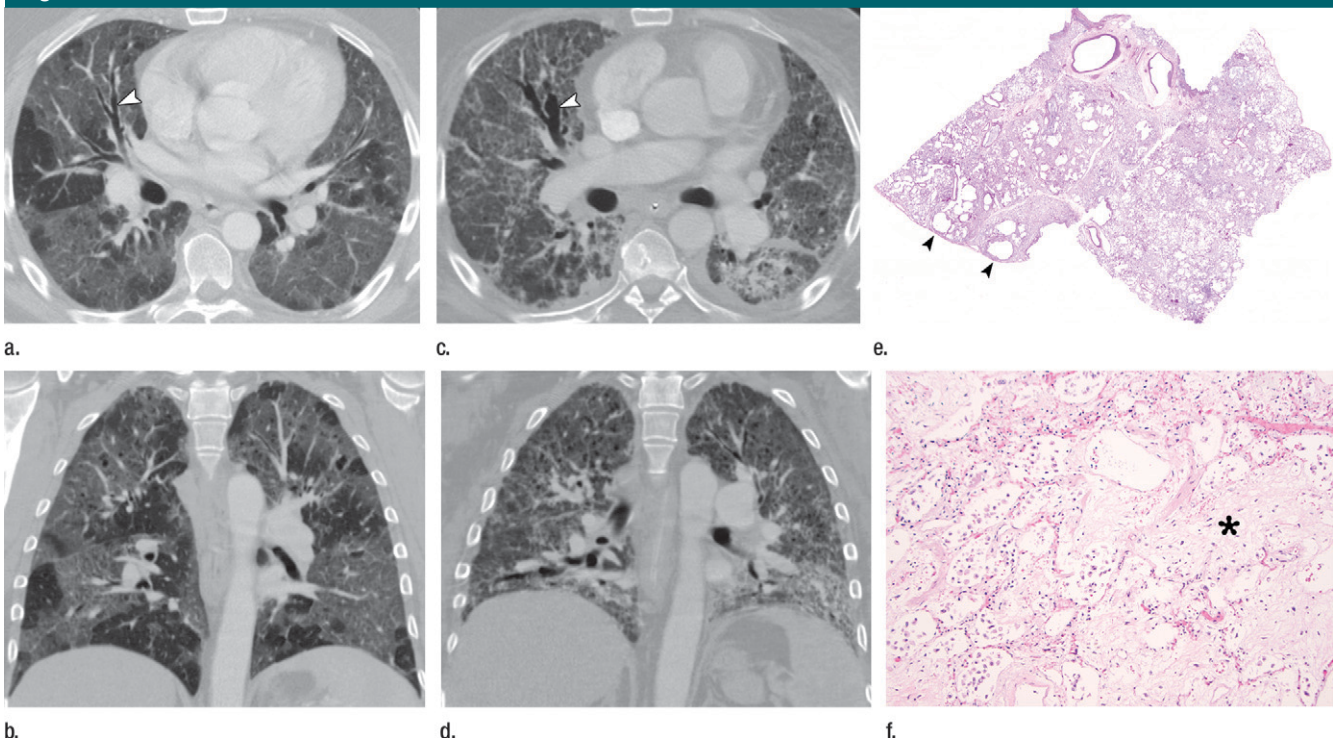


Figure 4: Organizing and fibrosing phase DAD in 56-year-old man with rapidly progressive dyspnea. **(a)** Axial and **(b)** coronal reconstruction high-spatial-resolution CT images acquired during acute phase of DAD show widespread areas of ground-glass opacity with focal areas of sparing. Note normal caliber of medial segment of middle-lobe bronchus (arrowhead in **a**). **(c, d)** Corresponding CT images acquired 2 weeks later at similar levels during organizing and fibrosing phase of DAD show diffuse reticulation with small cysts, traction bronchiectasis (arrowhead in **c**), and elevated hemidiaphragms consistent with volume loss. Note reduction in lung volumes between **b** and **d**. **(e)** Lung biopsy specimen acquired when **c** and **d** were obtained shows diffuse parenchymal injury with formation of cysts (arrowheads). (Hematoxylin-eosin stain; original magnification, ×1.) **(f)** Higher-magnification lung biopsy specimen shows intraalveolar and interstitial organization and fibrosis (*). (Hematoxylin-eosin stain; original magnification, ×100.)

Figure 5

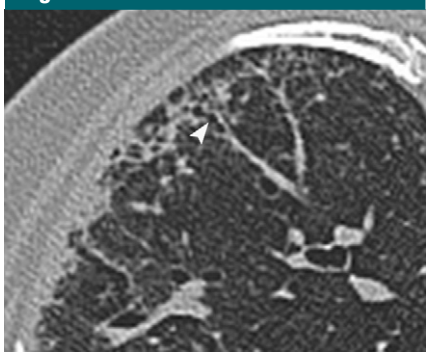
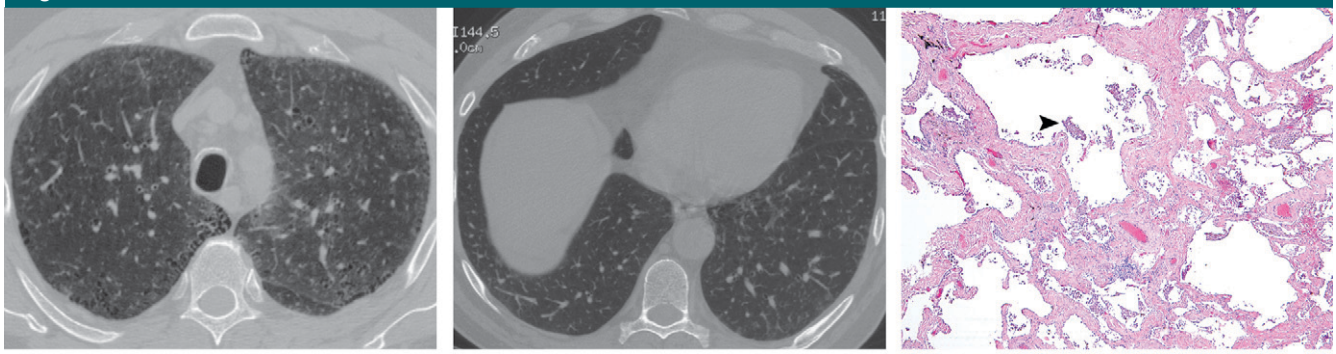


Figure 5: Organizing pneumonia with progression to NSIP in 68-year-old woman with shortness of breath. Prone high-spatial-resolution CT image obtained through lower lobe shows band of reticulation, with sparing of absolute periphery of lung associated with traction bronchioloectasis (arrowhead). Image highlights different location of cysts in organizing pneumonia as compared with UIP.

Structures with a smaller radius of curvature and subsequent increased surface tension are unstable and thus more likely to collapse (13–15,19). Once initiated, the process, powered by the increasing disparity between the enlarging alveolar ducts and the collapsing small alveoli that surround them, is more likely to continue. The denuded alveolar walls, once collapsed, become permanently apposed or molded together. This sequence of self-perpetuating collapse results in peripheral lower-lobe cysts, which we believe are the mechanism for the development of true honeycombing. This distribution of cysts is associated with clinical evidence of progression (20), profound volume loss, low-diffusing capacity, and a substantially worse prognosis (21–24). The importance of progressive collapse as the driving pathophysiologic mechanism causing alveolar wall thickening in UIP-IPF was confirmed by Coxson et al (16), who convincingly demonstrated normal amounts of fibrous lung tissue in patients with UIP-IPF, as compared with control subjects with normal pulmonary function and imaging findings.

A lower-lobe predominance of peripheral cysts has been shown to be the most important radiologic feature in the diagnosis of UIP-IPF (11,12). The posterior basal segments should be the most severely involved, as these alveoli are the smallest in the upright and supine positions and therefore are more likely to collapse (Fig 9). The cysts are also strikingly subpleural. It is this distribution of subpleural lower-lobe cysts and a gradient of reticulation that starts in the upper lobes and increases

Figure 6



a. b. c.

Figure 6: NSIP in 65-year-old man with 75-pack-year smoking history and cough. **(a)** Axial high-spatial-resolution CT image obtained through upper lobes shows focal areas of low attenuation and cysts distributed predominantly in periphery but also in central lung zones. Nodular areas of ground-glass opacity are seen throughout both lungs, with central airway thickening. **(b)** Axial high-spatial-resolution CT image obtained through lower lobes is nearly normal, with minimal patchy areas of ground-glass opacity in dependent portion of left lower lobe. **(c)** Lung biopsy specimen from right upper lobe shows temporally uniform, diffuse interstitial fibrosis surrounding emphysematous spaces, which contain smoker's macrophages (arrowhead). (Hematoxylin-eosin stain; original magnification, ×40.) There is excellent correlation between imaging and histologic findings. Upper lobe cysts identified at CT correlate with diffuse interstitial fibrosis surrounding emphysematous spaces seen with histologic analysis, at which the fibrosis is categorized as NSIP. Decreasing gradient of cysts from upper to lower lobe at imaging is consistent with smoking-related lung injury and inconsistent with IPF.

Table 2

Pathways to Pulmonary Fibrosis

ATS/ERS Classification	Pathway to Injury	Distribution of Cysts
AIP	Collapse and organization	Diffuse
IPF	Collapse and organization	Lower lobe, juxtapleural
COP	Organization and variable collapse	Peribronchiolar, subpleural sparing
RB-ILD	Cigarette smoke	Upper lobe
DIP	Cigarette smoke	Emphysema distribution

COP = cryptogenic organizing pneumonia, DIP = desquamative interstitial pneumonia, RB-ILD = respiratory bronchiolitis–interstitial lung disease.

toward the bases that enable a confident diagnosis of UIP-IPF at high-spatial-resolution CT (Fig 3). A confident radiologic diagnosis of UIP-IPF that meets the described criteria obviates biopsy unless there is strong clinical suspicion of another form of chronic infiltrative lung disease.

Distinguishing UIP-IPF from severely fibrotic NSIP poses a major problem for clinicians, radiologists, and pathologists, suggesting that these two entities represent the same disease process at different stages (1,2,5–7,25). This concept is supported by the marked histologic heterogeneity in patients with UIP-IPF when multiple lung biopsy samples are acquired (26). Patients whose histologic samples demonstrate both UIP and NSIP at multiple biopsies have a poor prognosis, similar to patients in whom all biopsies reveal UIP (27,28). They also have a substantially worse prognosis than do patients with histologic findings of NSIP at all biopsies.

The typical high-spatial-resolution CT findings of UIP-IPF are accurate predictors of the histologic pattern of UIP (21). In addition, the high-spatial-resolution CT pattern of UIP-IPF is an independent variable that adds prognostic information to the histologic diagnosis of UIP (20–24,29). Patients with high-spatial-resolution CT and histologic findings of UIP have a shorter survival (median survival, 2.8 years) than do those with indeterminate imaging and histologic findings of UIP (median survival, 5.7 years) (Fig 10) (21). When the high-spatial-resolution CT findings are not diagnostic of UIP-IPF—for example, they are minimal and lack the typical distribution of peripheral lower-lobe cysts—the prognosis is less certain. Progression from an NSIP to a UIP-IPF pattern at imaging is not uncommon and supports the concept that these are not separate diseases (30).

AIP.—AIP is the term applied to a rapidly progressive form of IIP that was originally described by Hamman and Rich (31). AIP is associated with the histologic diagnosis of DAD and the clinical manifestations of acute

Figure 7

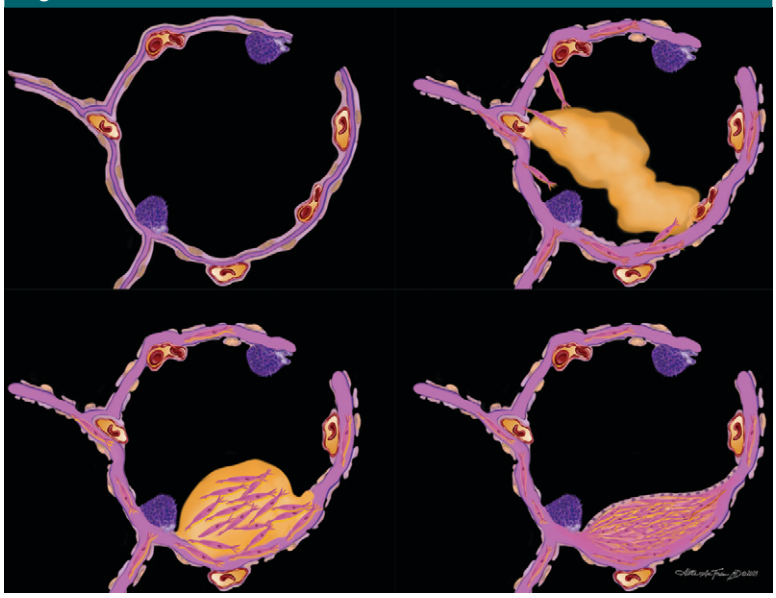


Figure 7: Proposed alveolar injury sequence in IPF (17). Top left: Normal alveolus has supporting interstitium (dark purple line) covered on both sides by cytoplasmic process of type I cell. Top right: Multiple microinjuries result in fragmented type I cells associated with disruption of basement membrane, promoting creation of wound clot and migration of fibroblasts. An abnormal sequence of wound healing leads to incorporation of organized intraalveolar exudates and fibroblasts, resulting in thickened alveolar wall (bottom left) and partial reepithelialization (bottom right).

Figure 8

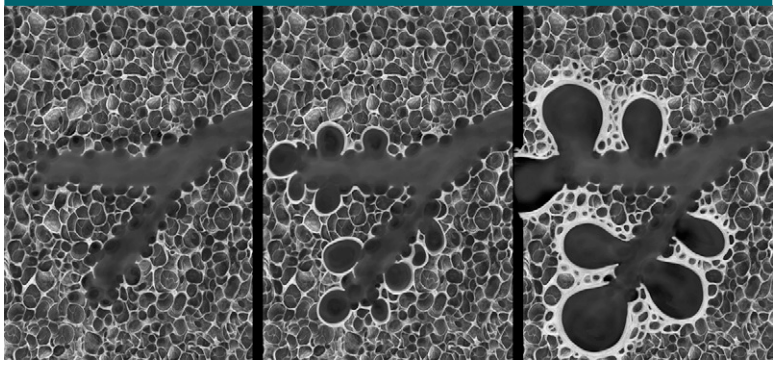


Figure 8: Illustrations of lung parenchyma at the level of the alveolar duct show collapse after alveolar injury sequence (16,19). Left: Normal central alveolar duct with surrounding small alveoli. Middle: After diffuse injury, the small alveoli surrounding the alveolar duct become unstable and collapse, enlarging the alveolar duct. Right: Thickened wall of the alveolar duct is composed of numerous collapsed alveoli and mimics fibrosis.

respiratory distress syndrome (32,33). The process begins with severe alveolar wall injury that results in widespread sloughing of type I epithelial cells and edema of the alveolar walls. Disruption of the alveolar epithelium is rapidly followed by alveolar filling with edema fluid and cellular debris. There is also widespread alveolar collapse (Fig 11) that leads to severe hypoxemia and respiratory failure. A second phase that consists of organization and incorporation of intraalveolar exudate, cellular debris, and fibroblasts into the alveolar walls contributes to further alveolar wall thickening. Traction bronchiectasis results from contraction of the fibroblastic material and is associated with increased mortality (34). Cystic spaces that appear during the organizing phase of DAD are distributed throughout the lung and are commonly associated with the radiologic findings of diffuse ground-glass opacity, reticulation, and volume loss (Fig 4) (35).

Although UIP-IPF and AIP traditionally have been considered different diseases, both demonstrate alveolar collapse, incorporation of intraalveolar debris into the alveolar walls, and increased neutrophils at bronchoalveolar lavage, suggesting a similar disease process (8,9,13–15,36,37). Compared with patients who have AIP, patients with disease at the UIP-IPF end of the spectrum have less severe injury and a more chronic course. There is a clinical spectrum in patients with the histologic findings of DAD. We have reviewed DAD cases in which the patients required only supplemental oxygen for support, while in more severe cases, patients are intubated and require mechanical ventilation with positive end-expiratory pressure.

Acute exacerbations occur in up to 18% of patients with UIP-IPF, supporting the concept of UIP-IPF and AIP as points on a continuous spectrum of injury (38). Almost all of these exacerbations are idiopathic, and the majority of them have the typical histologic finding of DAD superimposed on a background of UIP-IFP (39,40). It is interesting that Averill Liebow in his original description of the interstitial pneumonias used the term *acute UIP* when referring to the histologic findings of DAD (8,9). After 30 years, there is now evidence that supports his original observation (1). Images acquired during an acute exacerbation of IPF demonstrate diffuse areas of bilateral ground-glass opacity superimposed on peripheral reticulation and cystic spaces (Fig 12). The availability of imaging examinations that document a previous pattern of UIP-IPF can be helpful in identifying this complication. Interestingly, the surgical procedure for lung biopsy in patients with UIP-IPF is associated with episodes of acute exacerbation that often result in death (41). Low lung volumes that accompany anesthesia may initiate widespread alveolar collapse that

Figure 9

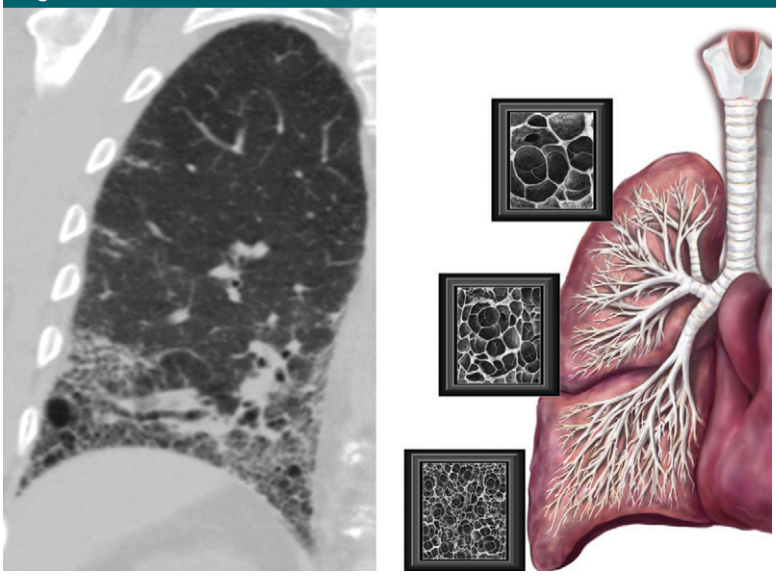


Figure 9: UIP-IPF in 77-year-old man. Lower-lobe peripheral distribution of typical reticulation and cyst formation is more readily evident on coronal reconstruction of axial CT data (left) than on source data. Right: Distribution of lower-lobe cysts in UIP-IPF follows normal distribution of alveolar size when patient is upright. Small basal and dependent alveoli are more likely to collapse than large upper-lobe alveoli and remain closed after diffuse lung injury.

Figure 10

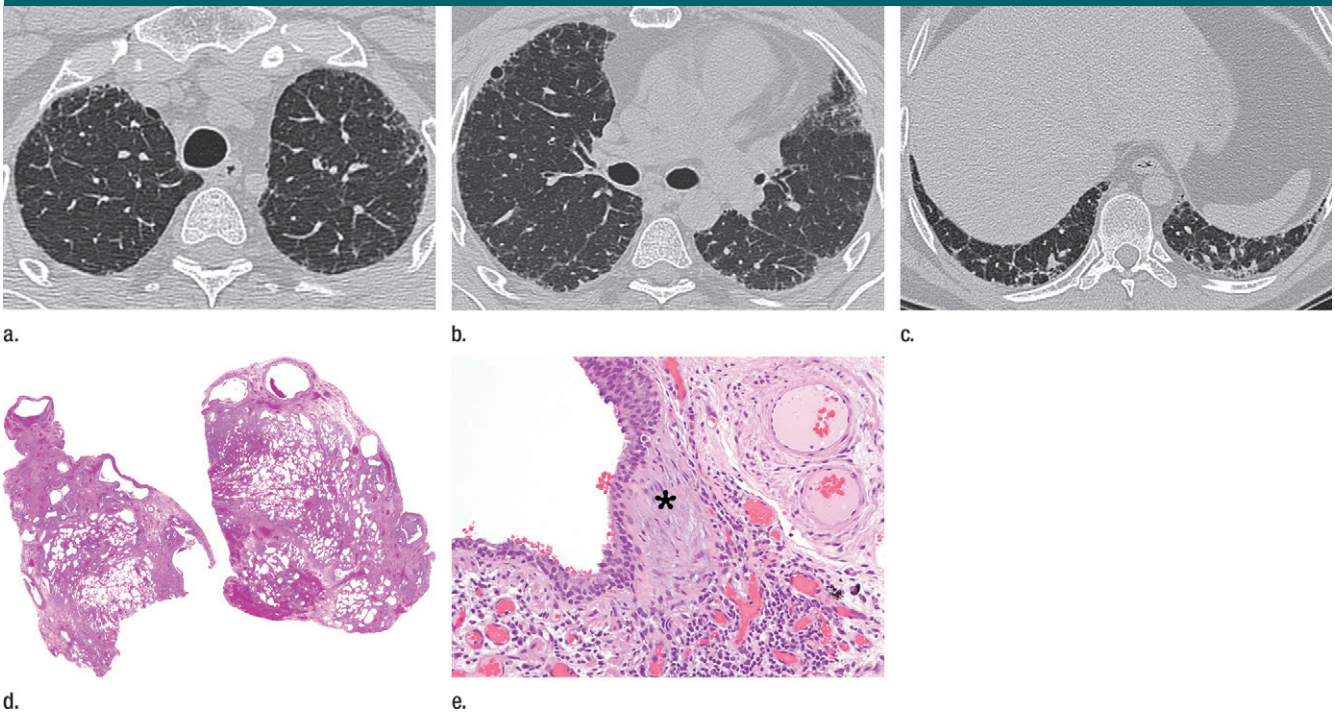


Figure 10: UIP-IPF in 44-year-old man. Axial high-spatial-resolution CT images obtained **(a)** through upper lobes, **(b)** just below carina, and **(c)** at posterior costophrenic angles show minimal peripheral reticulation, with rare small cysts similarly involving the three levels. **(d, e)** Histologic lung sections show typical findings of UIP, including subpleural fibrosis with peripheral cysts (**d**) and fibroblast foci (∗) in cyst walls (**e**). (Hematoxylin-eosin stain; original magnification, ×1 [**d**] and ×200 [**e**].) Imaging findings are consistent with UIP-IPF; however, minimal involvement and lack of lower-lobe gradient preclude confident diagnosis based on imaging findings alone. Diagnostic histologic findings with compatible but nondiagnostic imaging findings portend poor prognosis but not as poor as that for patients with concordant histologic and radiologic findings of definite UIP. However, histologic diagnosis of UIP does not equal clinical diagnosis of IPF. Histologic findings of UIP can also be seen in association with collagen vascular disease, asbestosis, fibrosing-phase hypersensitivity pneumonitis, radiation pneumonitis, and Hermansky-Pudlak syndrome.

Figure 11

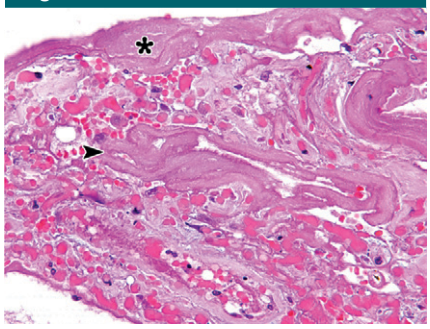


Figure 11: Alveolar collapse in DAD. High-power magnification lung tissue specimen shows edematous alveolar wall covered by hyaline membranes (*) along one surface. Centrally, hyaline membranes line a collapsed alveolar space (arrowhead). (Hematoxylin-eosin stain; original magnification, ×400.)

Figure 12

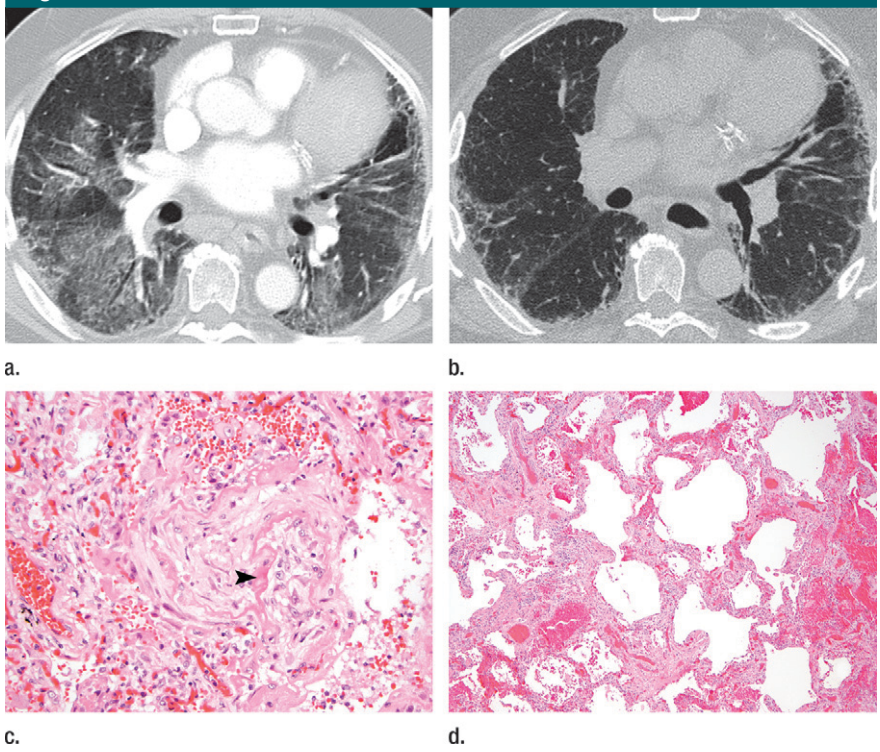


Figure 12: Accelerated-phase UIP-IPF in 56-year-old man. **(a)** Axial high-spatial-resolution CT image acquired during accelerated phase of clinical deterioration shows geographic areas of ground-glass opacity and reticulation superimposed on peripheral reticulation. **(b)** Findings on corresponding CT image acquired 6 months previously during quiescent period of UIP-IPF confirm findings in **a**. **(c, d)** Lung biopsy specimens acquired when **a** was obtained show intraalveolar organization engulfing hyaline membranes (arrowhead) (**c**) and interstitial organization (**d**), consistent with acute and organizing-phase DAD. (Hematoxylin-eosin stain; original magnification, ×200 [**c**] and ×40 [**d**]). There is excellent correlation between histologic and concurrent imaging findings: Both are consistent with DAD. However, findings in **b** provide vital information because they confirm presence of preexisting UIP-IPF. Overall, case is consistent with diagnosis of accelerated-phase UIP-IPF.

cannot be reversed because of preexisting diffuse alveolar wall injury.

Organizing pneumonia.—The histologic finding of organizing pneumonia (ie, Masson bodies) is seen in a variety of conditions including bacterial pneumonia, toxin or fume exposure, irradiation, drug reaction, and connective tissue disease. However, in the majority of cases, no etiology is identified and the process is clinically labeled cryptogenic organizing pneumonia. First described by Liebow (8,9), the concept of organizing pneumonia was not widely appreciated until the 1980s (42,43). The majority of patients with this disease respond to steroids; however, a substantial number of patients do not recover completely, and there is a consistent 3%–4% mortality rate in most series (43–45).

Organizing pneumonia is a relatively focal process and involves the peribronchiolar region of the lung, with areas of consolidation on high-spatial-resolution CT images. These areas tend to spare the absolute periphery of the lung and gradually disappear (Fig 13). In our experience, some patients with organizing pneumonia do not fully recover: They develop pulmonary fibrosis, which may not respond to steroids. The histologic pattern of the fibrosis is that of fibrotic NSIP; however, careful inspection often reveals plugs of organized material in various stages of incorporation into the alveolar wall (Fig 14). Contraction of the fibroblastic material in these thickened alveolar walls distorts nearby airways (46). At imaging, the progression, commonly observed over months, mirrors this process. Areas of peribronchiolar consolidation are gradually replaced by a mixture of reticulation and ground-glass opacity that surrounds bronchiectatic and distorted airways (Figs 15 and 16). Cysts are identified 5–10 mm from the pleura in the region of the terminal bronchioles (Fig 5). These cysts represent small dilated airways associated with variable amounts of organization and fibrosis.

A substantial number of organizing pneumonia cases referred for second-opinion consultation are mistakenly diagnosed as UIP-IPF on the basis of the presence of incorporated fibroblastic material (Fig 17) (47). This is due to a remarkable similarity in histologic appearance between the fibroblast foci of UIP (Fig 3) and the Masson bodies seen in organization (Fig 14). Detailed investigation of the fibroblastic material in IPF-UIP and organizing pneumonia suggests that they are highly related, if not identical, processes (46). High-spatial-resolution CT images obtained at multiple time points are often crucial for differentiating these two processes.

Smoking-related Interstitial Lung Disease: Inflammation and Fibrosis

Variable degrees of emphysema and alveolar wall fibrosis are commonly observed in the histopathologic specimens obtained from cigarette smokers (48–52).

Figure 13

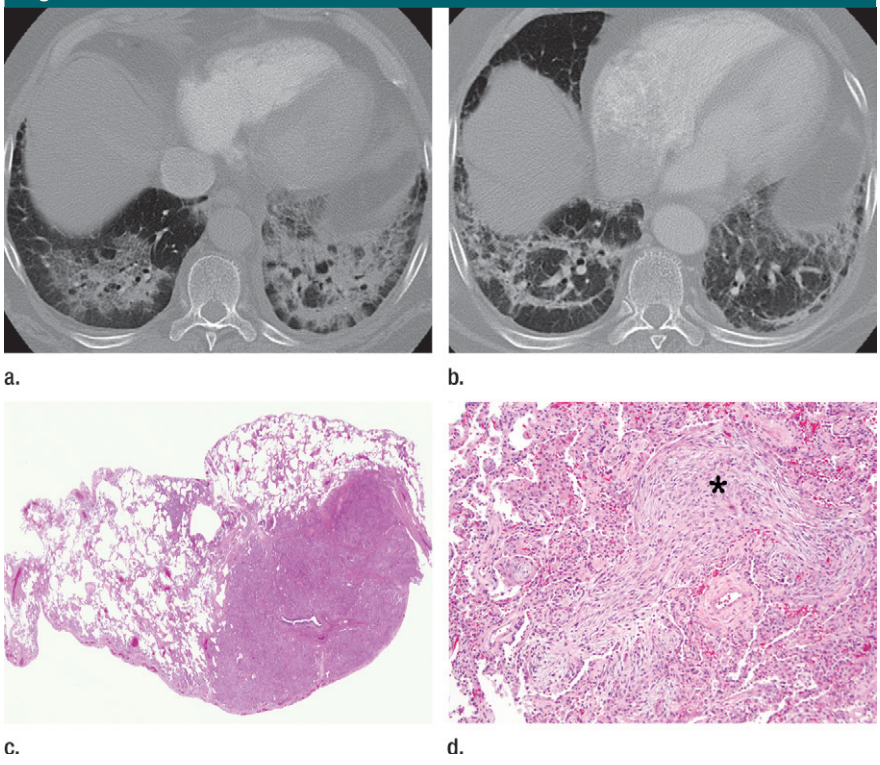


Figure 13: Organizing pneumonia in febrile 70-year-old man. **(a)** Axial high-spatial-resolution CT image obtained through lower lobes shows peribronchiolar consolidation with peripheral sparing. **(b)** Corresponding CT image acquired 6 weeks later shows residual bands of consolidation. **(c, d)** Lung biopsy specimens obtained when **b** was acquired show bronchiolocentric nodule (**c**), which correlates with bands of peripheral consolidation seen at CT; **d** shows nodule is composed of intraalveolar plugs of loose fibroblastic tissue (*), diagnostic of organizing pneumonia. (Hematoxylin-eosin stain; original magnification, ×1 [**c**] and ×100 [**d**].)

Extensive research conducted in humans and animals supports the concept that both emphysema and fibrosis can be divergent responses to a common injury—in this case, that induced by cigarette smoke (49,50,53–57). The fibrosis in these patients fits the pattern of fibrotic NSIP (52). The fibrosis is relatively uniform, with a lack of the broad scars and the architectural distortion commonly found with UIP-IPF (Fig 6) (52). The lack of heterogeneity and fibroblast foci in smoking-related fibrosis suggests that neither alveolar collapse nor incorporation of fibroblastic material is involved in the pathogenesis. The typical imaging findings also differ considerably from those of UIP-IPF, AIP, and organizing pneumonia. In smoking-related fibrosis, cystic spaces predominate in the upper lung fields (Fig 6). These cysts have the size and distribution of emphysema, unlike the strikingly peripheral lower-lobe cysts in UIP-IPF. Variable combinations of temporally uniform fibrosis, smoker's macrophages, and emphysema are common findings in dyspneic patients who eventually undergo open lung biopsy. The combination of emphysema and fibrosis results in relatively normal air flow and lung volume at pulmonary function testing, with a severely depressed diffusing capacity

Figure 14

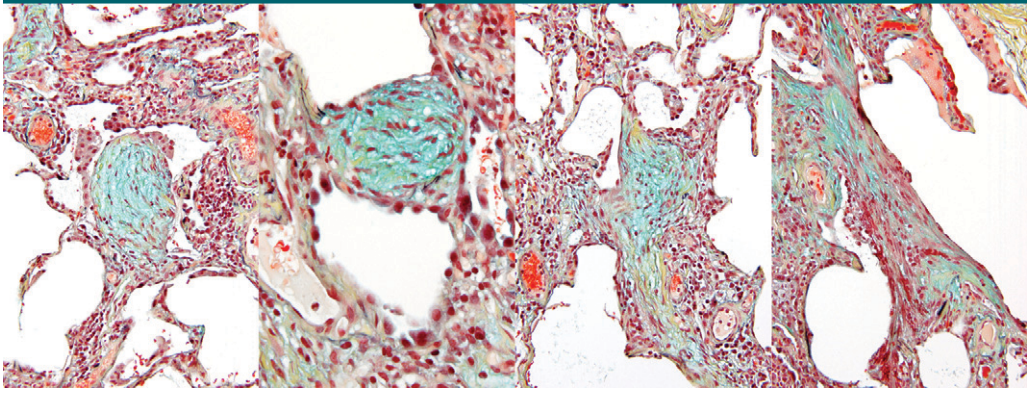


Figure 14: Incorporation of intraalveolar organization. Alveolar exudates and cellular debris from injury are cleared from alveolar spaces in process termed *organizing pneumonia,* or Masson bodies. Organizing pneumonia is evidenced by intraalveolar plugs of fibroblastic tissue, which is stained green on this collage of four histologic specimens. (Movat pentachrome stain; original magnifications, from left to right: ×10, ×20, ×10, and ×10, respectively.) Far left: Initially, organizing pneumonia appears as rounded plugs within alveolar spaces. Second from left: As clearance begins, plugs butt up against alveolar walls and become epithelialized by overgrowth of type II pneumocytes. Third from left: Plugs are then incorporated into alveolar walls. Far right: Over time, plugs become relatively flattened and collagenized but result in thickened alveolar walls.

Radiology

Figure 15

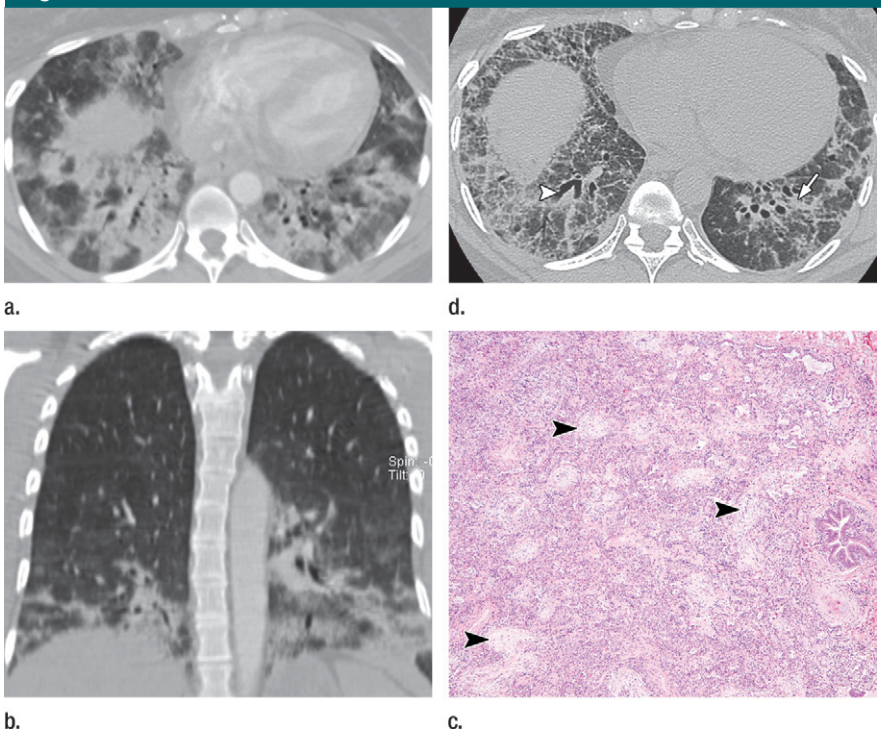


Figure 15: Organizing pneumonia with progression to fibrosis in 50-year-old woman with 1-month history of hypoxia and dyspnea. **(a)** Axial chest CT image obtained through lower lobes and **(b)** coronal reconstruction of axial CT data show peribronchiolar consolidation primarily in lower lung fields. **(c)** Lung biopsy specimen acquired at the time **a** and **b** were acquired shows intraalveolar plugs of loose fibroblastic tissue (arrowheads), diagnostic of organizing pneumonia. (Hematoxylin-eosin stain; original magnification, ×40.) **(d)** Axial high-spatial-resolution CT image acquired 8 months later shows residual areas of peribronchiolar consolidation (arrow) and new findings of widespread reticulation and traction bronchiectasis (arrowhead), consistent with diffuse fibrosis. There is excellent correlation between initial imaging (**a**) and histologic (**c**) findings: Both are compatible with organizing pneumonia. However, **d** shows diffuse pulmonary fibrosis, a potential complication that we have observed in a minority of patients with organizing pneumonia. Combined imaging features are not consistent with diagnosis of IPF.

Figure 16

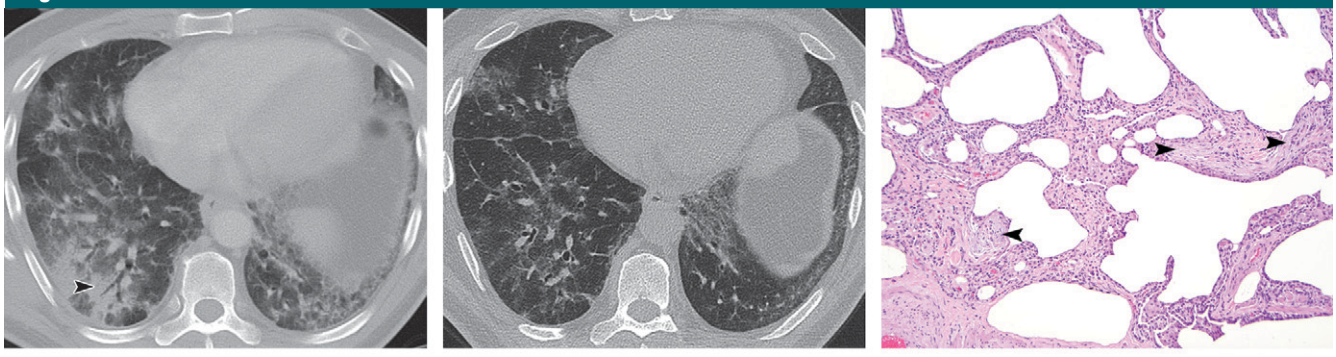


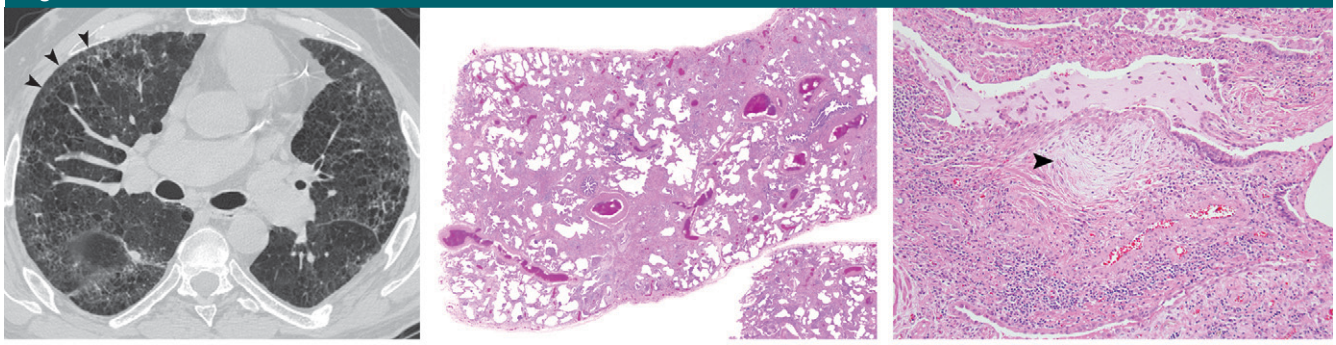
Figure 16: Organizing pneumonia with progression to NSIP in 59-year-old man. **(a)** Axial chest CT image obtained through lower lobes shows peribronchiolar areas of consolidation (arrowhead) associated with diffuse areas of ground-glass opacity. **(b)** Axial high-spatial-resolution CT image acquired 6 months later shows geographic ground-glass opacity with subtle reticulation, small cysts, and mild traction bronchiectasis, consistent with diffuse fibrosis. **(c)** Lung biopsy specimen obtained when **b** was acquired shows diffuse interstitial widening due to incorporation of organizing fibroblastic tissue (arrowheads). (Hematoxylin-eosin stain; original magnification, ×100.) There is excellent correlation between findings in **b** and **c**: Both indicate diffuse fibrosis, which corresponds to a histologic diagnosis of NSIP. Overall, the two CT images were interpreted as showing progression of organizing pneumonia to NSIP.

and marked dyspnea. This confusing constellation of findings suggests the need for tissue biopsy (58).

The legacy terminology associated with smoking-related lung injury is particularly problematic because the amount of fibrosis that is acceptable in respiratory bronchiolitis–interstitial lung disease and desquamative interstitial pneumonia is arbitrary and not well defined. Pathologists sometimes combine the diagnosis of respiratory bronchiolitis or desquamative interstitial pneumonia with NSIP if the amount of alveolar wall fibrosis is considered to be unusually large (52). However, the reliability of this assessment has not been demonstrated.

In most cases referred for consultation at our institution, the NSIP pattern of fibrosis is associated with UIP-IPF, organizing pneumonia, or smoking-related

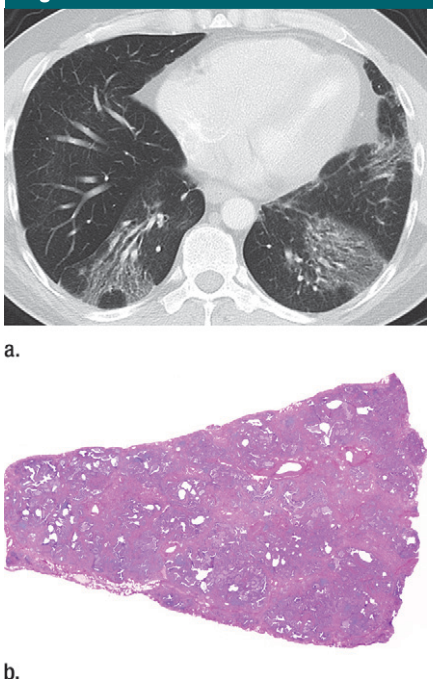
Figure 17



a. b. c.

Figure 17: Severely fibrotic NSIP with organizing pneumonia in 66-year-old man with 150-pack-year smoking history. **(a)** Axial high-spatial-resolution CT image obtained just below carina shows widespread cysts and low-attenuating areas. There is peripheral band of increased attenuation and reticulation in right lung that spares absolute lung periphery (arrowheads). Lung biopsy specimens from right lower lobe show **(b)** diffuse but geographically variable interstitial fibrosis (hematoxylin-eosin stain; original magnification, ×1), with **(c)** foci of organizing fibroblastic tissue (arrowhead) incorporated into interstitium (hematoxylin-eosin stain; original magnification, ×100). Histologic findings enable difficult differentiation between severely fibrotic NSIP and UIP. Geographic heterogeneity of interstitial fibrosis and incorporated organizing fibroblastic tissue suggest UIP. However, incorporated organizing fibroblastic tissue can also be seen in latter phases of organizing pneumonia. Lack of convincing architectural remodeling with cyst formation militates against diagnosis of UIP. Peripheral band of attenuation and reticulation with sparing of absolute lung periphery follows typical distribution of organizing pneumonia. At CT, cystic spaces are consistent with emphysema and not the typical peripheral distribution of cysts in UIP. Imaging results influence interpretation of histologic findings, suggesting organizing fibroblastic tissue is more likely a manifestation of organizing pneumonia than UIP.

Figure 18



a.

b.

Figure 18: Idiopathic NSIP in 47-year-old man. **(a)** Axial high-spatial-resolution CT image obtained through lower lung fields shows areas of ground-glass opacity and reticulation superimposed on distorted airways. Posterior displacement of major fissure on right side is consistent with volume loss. **(b)** Lung biopsy specimen from lower lobe shows diffuse interstitial fibrosis, which lacks geographic heterogeneity. Given the degree of fibrosis, cystic change is minimal and no fibroblast foci are identified. There is excellent correlation between CT and histologic findings, which when considered together meet the criteria for idiopathic NSIP.

injury with emphysema. The radiologic pattern plays an important role in differentiating these three possibilities. Imaging is especially helpful when studies obtained at multiple time points provide clear evidence of either organizing pneumonia gradually transitioning to fibrosis (Fig 16) or a stable pattern of upper-lobe cystic change associated with emphysema (Fig 6). Areas of NSIP-type fibrosis are commonly identified in patients with UIP-IPF, given the well-documented variability of the histologic findings of UIP-IPF—especially when multiple biopsy sites are examined (Fig 3). In a recent publication sponsored by the ATS, the existence of idiopathic NSIP as a distinct entity is postulated (59). Images typically demonstrate a lower-lobe predominance of diffuse or peribronchiolar reticular opacity (Fig 18). Traction bronchiectasis and lower-lobe volume loss are common associations (60). It is important to remember, however, that the NSIP pattern of fibrosis is seen in many clinical settings, including those of UIP-IPF, organizing pneumonia, hypersensitivity pneumonitis, collagen vascular disease, and cigarette smoke exposure.

Conclusion

Averill Liebow, who described the interstitial pneumonias more than 40 years ago, recognized that the IIPs "are types of tissue response, and that no implication is intended that any is pathognomonic for a specific etiologic factor. Nevertheless, histologic characteristics may provide clues both to etiology and to pathogenesis and certainly to natural history and prognosis" (8).

A multitude of normal processes must interact with precision to maintain and repair the lung when it is injured. Absence, imbalance, or exaggeration of any one of these processes leads to disease. Identification of the dominant histopathologic process combined with the distribution as assessed

with radiologic imaging provides important information regarding the likely etiology, especially in cigarette smokers, in whom there is often a combination of cystic change related to emphysema and associated fibrosis.

References

1. Maher TM, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? Eur Respir J 2007;30(5):835–839.
2. Wells AU. Histopathologic diagnosis in diffuse lung disease: an ailing gold standard. Am J Respir Crit Care Med 2004;170(8):828–829.
3. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias: this joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165(2):277–304.
4. Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004;170(8):904–910.
5. Aziz ZA, Wells AU, Hansell DM, et al. HRCT diagnosis of diffuse parenchymal lung disease: interobserver variation. Thorax 2004;59(6):506–511.
6. Nicholson AG, Addis BJ, Bharucha H, et al. Inter-observer variation between pathologists in diffuse parenchymal lung disease. Thorax 2004;59(6):500–505.
7. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 2000;162(6):2213–2217.
8. Liebow AA. Definition and classification of interstitial pneumonias in human pathology. Prog Respir Res 1975;8(1–33.
9. Liebow AA, Carrington CB. The interstitial pneumonias. New York, NY: Grune & Stratton, 1969.
10. Liebow AA, Steer A, Billingsley JG. Desquamative interstitial pneumonia. Am J Med 1965;39:369–404.
11. Hunninghake GW, Lynch DA, Galvin JR, et al. Radiologic findings are strongly associated with a pathologic diagnosis of usual interstitial pneumonia. Chest 2003;124(4):1215–1223.
12. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2001;164(2):193–196.
13. Burkhardt A. Alveolitis and collapse in the pathogenesis of pulmonary fibrosis. Am Rev Respir Dis 1989;140(2):513–524.
14. Crouch E. Pathobiology of pulmonary fibrosis. Am J Physiol 1990;259(4 pt 1):L159–L184.
15. Myers JL, Katzenstein AL. Epithelial necrosis and alveolar collapse in the pathogenesis of usual interstitial pneumonia. Chest 1988;94(6):1309–1311.
16. Coxson HO, Hogg JC, Mayo JR, et al. Quantification of idiopathic pulmonary fibrosis using computed tomography and histology. Am J Respir Crit Care Med 1997;155(5):1649–1656.
17. Selman M, King TE, Pardo A; American Thoracic Society; European Respiratory Society; American College of Chest Physicians. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med 2001;134(2):136–151.
18. Schmidt R, Meier U, Markart P, et al. Altered fatty acid composition of lung surfactant phospholipids in interstitial lung disease. Am J Physiol Lung Cell Mol Physiol 2002;283(5):L1079–L1085.
19. Hogg JC. Benjamin Felson lecture: chronic interstitial lung disease of unknown cause—a new classification based on pathogenesis. AJR Am J Roentgenol 1991;156(2):225–233.
20. Akira M, Sakatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. Radiology 1993;189(3):687–691.
21. Flaherty KR, Thwaite EL, Kazerooni EA, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003;58(2):143–148.
22. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med 1998;157(4 pt 1):1063–1072.
23. Jeong YJ, Lee KS, Müller NL, et al. Usual interstitial pneumonia and non-specific interstitial pneumonia: serial thin-section CT findings correlated with pulmonary function. Korean J Radiol 2005;6(3):143–152.
24. Nagao T, Nagai S, Hiramoto Y, et al. Serial evaluation of high-resolution computed tomography findings in patients with idiopathic pulmonary fibrosis in usual interstitial pneumonia. Respiration 2002;69(5):413–419.
25. Nicholson AG, Wells AU. Nonspecific interstitial pneumonia: nobody said it's perfect. Am J Respir Crit Care Med 2001;164(9):1553–1554.
26. Katzenstein AL, Zisman DA, Litzky LA, Nguyen BT, Kotloff RM. Usual interstitial pneumonia: histologic study of biopsy and explant specimens. Am J Surg Pathol 2002;26(12):1567–1577.
27. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med 2001;164(9):1722–1727.
28. Monaghan H, Wells AU, Colby TV, du Bois RM, Hansell DM, Nicholson AG. Prognostic implications of histologic patterns in multiple surgical lung biopsies from patients with idiopathic interstitial pneumonias. Chest 2004;125(2):522–526.
29. Shin KM, Lee KS, Chung MP, et al. Prognostic determinants among clinical, thin-section CT, and histopathologic findings for fibrotic idiopathic interstitial pneumonias: tertiary hospital study. Radiology 2008;249(1):328–337.
30. Silva CI, Müller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. Radiology 2008;247(1):251–259.
31. Olson J, Colby TV, Elliott CG. Hamman-Rich syndrome revisited. Mayo Clin Proc 1990;65(12):1538–1548.
32. Greene R. Adult respiratory distress syndrome: acute alveolar damage. Radiology 1987;163(1):57–66.
33. Piantadosi CA, Schwartz DA. The acute respiratory distress syndrome. Ann Intern Med 2004;141(6):460–470.
34. Ichikado K, Suga M, Müller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002;165(11):1551–1556.
35. Johkoh T, Müller NL, Taniguchi H, et al. Acute interstitial pneumonia: thin-section CT findings in 36 patients. Radiology 1999;211(3):859–863.
36. Katzenstein AL. Pathogenesis of "fibrosis" in interstitial pneumonia: an electron microscopic study. Hum Pathol 1985;16(10):1015–1024.
37. Rinaldo JE, Rogers RM. Adult respiratory-distress syndrome: changing concepts of

lung injury and repair. N Engl J Med 1982; 306(15):900–909.

38. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J 2006;27(1):143–150.
39. Akira M, Hamada H, Sakatani M, Kobayashi C, Nishioka M, Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. AJR Am J Roentgenol 1997;168(1):79–83.
40. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis: analysis of clinical and pathologic findings in three cases. Chest 1993;103(6):1808–1812.
41. Utz JP, Ryu JH, Douglas WW, et al. High short-term mortality following lung biopsy for usual interstitial pneumonia. Eur Respir J 2001;17(2):175–179.
42. Davison AG, Heard BE, McAllister WA, Turner-Warwick ME. Cryptogenic organizing pneumonitis. Q J Med 1983;52(207):382–394.
43. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. N Engl J Med 1985; 312(3):152–158.
44. Cordier JF. Bronchiolitis obliterans organizing pneumonia. Semin Respir Crit Care Med 2000;21(2):135–146.
45. Izumi T, Kitaichi M, Nishimura K, Nagai S. Bronchiolitis obliterans organizing pneumonia: clinical features and differential diagnosis. Chest 1992;102(3):715–719.
46. Kuhn C, McDonald JA. The roles of the myofibroblast in idiopathic pulmonary fibrosis: ultrastructural and immunohistochemical features of sites of active extracellular matrix synthesis. Am J Pathol 1991;138(5):1257–1265.
47. Mark EJ, Ruangchira-urai R. Bronchiolitis interstitial pneumonitis: a pathologic study of 31 lung biopsies with features intermediate between bronchiolitis obliterans organizing pneumonia and usual interstitial pneumonitis, with clinical correlation. Ann Diagn Pathol 2008;12(3):171–180.
48. Grubstein A, Bendayan D, Schactman I, Cohen M, Shitrit D, Kramer MR. Concomitant upper-lobe bullous emphysema, lower-lobe interstitial fibrosis and pulmonary hypertension in heavy smokers: report of eight cases and review of the literature. Respir Med 2005;99(8):948–954.
49. Lang MR, Fiaux GW, Gillooly M, Stewart JA, Hulmes DJ, Lamb D. Collagen content of alveolar wall tissue in emphysematous and non-emphysematous lungs. Thorax 1994; 49(4):319–326.
50. Nagai A, Thurlbeck WM. Scanning electron microscopic observations of emphysema in humans: a descriptive study. Am Rev Respir Dis 1991;144(4):901–908.
51. Tonelli M, Stern EJ, Glenny RW. HRCT evident fibrosis in isolated pulmonary emphysema. J Comput Assist Tomogr 1997;21(2):322–323.
52. Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease with fibrosis is a lesion distinct from fibrotic nonspecific interstitial pneumonia: a proposal. Mod Pathol 2006;19(11):1474–1479.
53. Auerbach O, Stout AP, Hammond EC, Garfinkel L. Smoking habits and age in relation to pulmonary changes: rupture of alveolar septums, fibrosis and thickening of walls of small arteries and arterioles. N Engl J Med 1963;269:1045–1054.
54. Frasca JM, Auerbach O, Carter HW, Parks VR. Morphologic alterations induced by short-term cigarette smoking. Am J Pathol 1983;111(1):11–20.
55. Hammond EC, Auerbach O, Kirman D, Garfinkel L. Effects of cigarette smoking on dogs. Arch Environ Health 1970;21(6): 740–753.
56. Niewoehner DE, Hoidal JR. Lung fibrosis and emphysema: divergent responses to a common injury? Science 1982;217(4557): 359–360.
57. Snider GL, Lucey EC, Faris B, Jung-Legg Y, Stone PJ, Franzblau C. Cadmium-chloride-induced air-space enlargement with interstitial pulmonary fibrosis is not associated with destruction of lung elastin: implications for the pathogenesis of human emphysema. Am Rev Respir Dis 1988;137(4):918–923.
58. Akira M, Inoue Y, Kitaichi M, Yamamoto S, Arai T, Toyokawa K. Usual interstitial pneumonia and nonspecific interstitial pneumonia with and without concurrent emphysema: thin-section CT findings. Radiology 2009;251(1):271–279.
59. Travis WD, Hunninghake G, King TE Jr, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 2008; 177(12):1338–1347.
60. Kligerman SJ, Groshong S, Brown KK, Lynch DA. Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations. RadioGraphics 2009;29(1):73–87