

PILOT™

Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment

SUMMER 2004

PILOT™ MISSION STATEMENT

PILOT™ is a national education initiative designed to provide physicians with a comprehensive continuing medical education program that focuses on the early and accurate diagnosis of idiopathic pulmonary fibrosis (IPF), while addressing educational objectives critical to optimizing disease intervention and management.



KEVIN O. LESLIE, MD

THE PATHOLOGIST'S APPROACH TO THE DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS (IPF)

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MAYO CLINIC SCOTTSDALE - SCOTTSDALE, AZ

Introduction

Usual interstitial pneumonia (UIP) is now recognized as the pathologic corollary of clinical idiopathic pulmonary fibrosis (IPF).^{1,2} The diagnostic features of this chronic interstitial lung disease remain essentially unchanged since first described by Liebow in the 1960s. For Liebow, UIP described a pattern of diffuse lung fibrosis that was idiopathic in about half of the patients originally studied, the other half were described as "heterogeneous in terms of structure and causation."³

Pathology of IPF

UIP is best characterized as a smoldering lung injury of unknown cause, attended by microscopic foci of fibroblastic proliferation, resembling minute healing wounds (so-called "fibroblast, or fibroblastic foci"). This injury-repair sequence culminates in the progressive accrual of dense scar and "honeycomb" cystic lung remodeling. The disease begins at the periphery of the pulmonary lobule (Figure 1) and has a

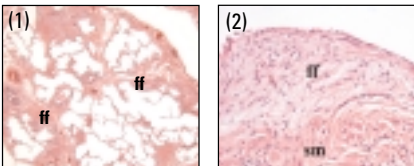


Figure 1: Peripheral lobular accentuation is characteristic of UIP: note the central sparing in the lobules. Fibroblast foci (ff) are even evident at this low magnification.

Figure 2: Transitions from fibrosis to normal lung are characteristic of UIP: fibroblastic foci appear as a "bulge" of immature fibroblasts. Note the bundles of smooth muscle (sm) subjacent to the pleura.

clear tendency to leave fibrosis and honeycomb remodeling in its wake. At the interface between peripheral fibrosis and more normal centrilobular lung tissue, tiny discrete foci of fibroblastic proliferation can be seen (Figure 2). These focal areas of injury are felt to be the critical site of injury in IPF. Distinctive smooth muscle hyperplasia (Figure 3) is often present within subpleural fibrosis (Figure 4), and this phenomenon is responsible for early descriptions of end-stage IPF as "muscular cirrhosis of the lung." Microscopic honeycomb remodeling (Figure 3) is a constant feature of UIP in the context of IPF, even

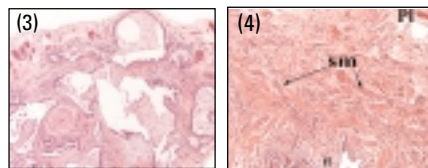


Figure 3: Microscopic honeycombing: note the small mucous-filled cystic spaces and mild chronic inflammation. This is the early microscopic corollary of gross and radiological honeycombing. These changes would not be visible radiologically.

Figure 4: Another case of UIP with prominent smooth muscle (sm) proliferation in subpleural (PI) fibrosis. This is a very common and distinctive finding in UIP of IPF. Note the characteristic fibroblast focus.

before "honeycomb cysts" are evident on CT scans. The individual components of the process are not specific, but their physical arrangement in the surgical biopsy can be relatively compelling in the right clinical and radiological context.⁴ Contrasting pathologic features of UIP and NSIP are listed in Table 1.

Table 1: Contrasting Pathologic Features of UIP and NSIP.

Features	UIP	NSIP
"Temporal" appearance	Variigated (heterogeneous)	Uniform (homogenous)
Interstitial inflammation	Scant, often around microscopic honeycombing	Prominent
Interstitial fibrosis (collagen)	Patchy	Diffuse, variable
Organizing pneumonia pattern	Focal, except during exacerbation	Focal, should not exceed 10%
Fibroblast foci	Typical	Focal, rare
Microscopic honeycomb areas	Typical, even early in disease	Rare
Smooth muscle proliferation in subpleural fibrosis	Typical, sometimes extensive	Rare

Data from *Atlas of Nontumor Pathology*, Vol. 2, p 939. Washington, DC, American Registry of Pathology, Armed Forces Institute of Pathology, 2002, and Katzenstein AL, et al. *Am J Surg Pathol*. 1994;18:136-47.

Differential Diagnosis

The differential diagnosis of UIP, clinically, radiologically, and pathologically includes chronic lung manifestations of a number of systemic

connective tissue diseases, hypersensitivity pneumonitis, certain pneumoconioses, so-called "fibrotic NSIP," and even some drug reactions. The morphologic patterns of these are often discernable in surgical lung biopsies. Some overlap occurs, but this is often resolvable with the addition of radiologic studies and/or clinical/serologic information.

Nonspecific Interstitial Pneumonia (NSIP)

In 1994, Katzenstein and Fiorelli presented 64 patients with "difficult to classify" ILD, and referred to the corresponding lung pathology as "nonspecific interstitial pneumonia" or "NSIP."⁵ The survival data for these 64 patients were significantly better than those of patients with IPF. Three separate groups were identified initially (Figures 5-7) based on the presence



Figure 5: Nonspecific interstitial pneumonia (NSIP), Katzenstein group 1: predominately chronic inflammation involving alveolar walls.

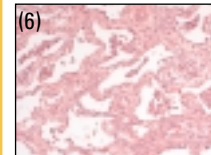


Figure 6: Nonspecific interstitial pneumonia, Katzenstein group 2: mixed chronic inflammation and mild diffuse interstitial fibrosis.

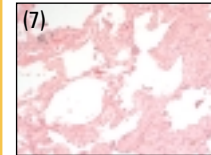


Figure 7: Nonspecific interstitial pneumonia, Katzenstein group 3: predominately interstitial fibrosis.

of diffuse chronic inflammation alone (cellular NSIP), chronic inflammation and fibrosis together, or fibrosis alone (fibrotic NSIP). The latter form of NSIP mimics IPF and, despite a 5-year mortality approaching 40%,⁶ is still associated with a significantly better survival than that observed in patients with IPF.

Acute Exacerbation of IPF

The majority of patients with IPF will die within 5 years of diagnosis as a consequence of chronic respiratory failure, comorbid cardiac disease, or lung cancer,⁷ while about 15% will die from fulminant respiratory failure. A recently completed large, randomized, placebo controlled, 48-week clinical trial in IPF provided direct evidence of this with the occurrence

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of unexpected, predominately respiratory, death in 44 of 330 patients—all of whom had relatively early disease (FVC > 50% of predicted at study enrollment).⁸ Acute exacerbation of IPF occurs typically in patients with IPF who suddenly develop acute and fulminant respiratory failure, often accompanied by fever, elevation of the sedimentation rate, marked increase in dyspnea, and new infiltrates that often have an "alveolar" character radiologically. In some patients, acute exacerbation may be the presenting manifestation of the disease. For many years this acute exacerbation was thought to be infectious pneumonia superimposed on a fibrotic lung with marginal reserve. The fact that the cases are sufficiently common, organisms are rarely identified, and a small percentage of patients respond to pulse systemic corticosteroid therapy, has lead a number of investigators to now consider such exacerbation to be a form of fulminant progression of the disease. Overall, acute exacerbation of IPF has a very poor prognosis, and death within one week is not unusual.^{9,10} Pathologically, acute lung injury resembling DAD and/or organizing pneumonia is superimposed on a background UIP with honeycombing and fibrosis (Figure 8).

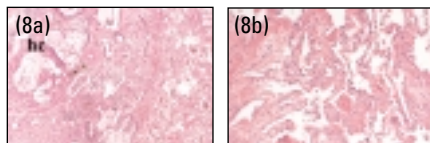


Figure 8: (8a) Acute exacerbation of UIP/IPF showing features of diffuse alveolar damage (DAD). Note the microscopic honeycomb focus (hc), attesting to chronicity. (8b) A higher magnification view of 8a, showing all of the alveolar walls affected by acute injury, with focal hyaline membranes and alveolar space fibrin. Depending on the timing of biopsy in this setting, more or less "organizing pneumonia pattern" may be present, sometimes referred to as "BOOP" pathologically.

The Role of HRCT

High resolution CT scans have emerged as a relative gold standard for diagnosis in expert hands, exceeding the predictive value of surgical biopsy for survival in some studies.¹¹ Flaherty and colleagues found that survival is decreased in patients with a typical HRCT appearance of UIP, and that a surgical lung biopsy is only necessary when the HRCT is not consistent with UIP.¹¹ Additionally, Hunninghake and colleagues determined that HRCT findings of lower-lobe honeycombing and upper-lung irregular lines are most consistent with a pathologic diagnosis of UIP.¹²

The Surgical Lung Biopsy in IPF

In those patients who have atypical clinical or HRCT findings, surgical lung biopsy may be required (transbronchial biopsies are of no use in confirming the diagnosis of IPF). Two or more surgical wedge lung biopsies are ideal for optimum diagnostic accuracy. Today these are usually obtained by video-assisted thoracoscopy (VATS). A recent study by Flaherty et al¹³ nicely illustrated the danger of relying on a single wedge biopsy, with divergent patterns sometimes seen in the same patient (eg, NSIP in one

lobe and UIP in another). Importantly, in their study, the presence of the UIP pattern in even one biopsy was predictive of poor clinical outcome. Biopsies taken from the most advanced areas of radiologic or surgically palpable abnormalities are often of little value and may contribute to increased surgical morbidity. Biopsy samples should measure 3–5 cm in surface length and 2–3 cm in depth. For optimal processing, surgical staples should be removed and the intact biopsy vigorously agitated in formalin fixative (preferred over other fixatives) in a container sealed with parafilm. "Agitation fixation" obviates the need for injection fixation and also reduces processing artifacts. Once fixed for 1–2 hours, 5 mm sections can be made for embedment without risk of compression artifacts.

Summary

Our concept of IPF/UIP has evolved to encompass that which Liebow initially recognized—chronic fibrosis and lung remodeling in UIP is the result of recurrent, often silent, episodes of focal acute lung injury. Pathologists must be cognizant of the critical importance of a multidisciplinary approach to the diagnosis. Guidelines for the use of diagnostic terminology may be helpful to pathologists as they manage uncertainty in this regard (Table 2).

Table 2

Definite UIP

Chronic fibrosing interstitial pneumonia with peripheral lobular accentuation, fibroblastic foci, smooth muscle proliferation in subpleural fibrosis, and microscopic honeycombing. Normal or nearly uninvolved lung tissue is present at the center of lobules.

Probable UIP

Advanced fibrosis with honeycomb remodeling only. Correlation with clinical and radiologic findings required for accurate diagnosis.

Chronic fibrosing interstitial pneumonia, pathologically unclassifiable

Fibrosis and remodeling but without a characteristic distribution (clinically occult chronic hypersensitivity, drug reaction, advanced connective tissue disease manifesting in the lung, pneumoconiosis, or fibrotic NSIP).

Not a fibrosing interstitial pneumonia

Variable chronic inflammatory infiltration without significant fibrosis—with or without granulomas, with or without eosinophils, with or without hemosiderosis/vasculitis (subacute hypersensitivity to inhaled or ingested antigen, eosinophilic pneumonia, smoker's ILD, NSIP-cellular, hot tub lung, constrictive small airways disease, diffuse alveolar hemorrhage/vasculitis).

Through such an approach, histopathological mimics of UIP that may result from diverse injury and repair mechanisms (such as NSIP), can be excluded.

We do not yet know why episodes of injury occur in UIP, the underlying target of the injury, or the specific mechanisms involved. However, we have now defined the problem sufficiently well that therapeutic advances are beginning to target more specific control pathways. Such targeted therapies may benefit patients in the short run, while further clarifying the required next steps in addressing this disease.

Concluding Points

1. The pathologic corollary of clinical idiopathic pulm-

onary fibrosis (IPF) is usual interstitial pneumonia (UIP).

2. UIP is a diffuse lung disease with a clear tendency to produce lung fibrosis with a consistently peripheral lobular and subpleural distribution. Late fibrosis in UIP is attended by microscopic honeycombing and eventually grossly visible honeycomb cysts.

3. The pathology underlying UIP may be one of repeated microscopic episodes of acute injury occurring over time, with repair by fibrosis. The microscopic hallmark of the acute episode is the fibroblastic focus.

4. A subset of patients with IPF will develop sudden fulminate respiratory failure, with a high mortality rate. This "acute exacerbation of IPF" may occur at any time in the disease, even as the initial presentation.

5. HRCT has emerged as a relative gold standard in the diagnosis of IPF.

6. If biopsy is required for diagnosis, two or more surgical lung biopsies, preferably from more than one lobe, are ideal. Areas of advanced fibrosis are of limited diagnostic value and add to surgical morbidity.

7. A multidisciplinary approach is an absolute requirement for an accurate diagnosis of UIP.

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HIGH-RESOLUTION CT (HRCT) DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS

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High-resolution CT (HRCT) is very important in the diagnosis of idiopathic pulmonary fibrosis (IPF). A joint statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS)¹ proposes that, in the absence of open-lung biopsy, a diagnosis of IPF may be considered likely in the presence of four major criteria and three of four minor criteria. Major criteria are (i) exclusion of known causes of infiltrative lung disease, such as exposures, drugs, and connective tissue disease, (ii) abnormal pulmonary function tests with evidence of restriction and impaired gas exchange, (iii), HRCT findings of bibasilar reticulation with minimal ground-glass opacity, and (iv) transbronchial lung biopsy or bronchoalveolar lavage showing no evidence of another disease. Minor criteria for diagnosis are (i) age more than 50 years, (ii) insidious onset of otherwise unexplained dyspnea on exertion, (iii) duration of illness of 3 months or more, and (iv) bibasilar inspiratory crackles.¹

The diagnosis of IPF is limited to patients with histologic findings of usual interstitial pneumonia (UIP).² Histologically, UIP is characterized by a patchy, heterogeneous pattern with foci of normal lung, interstitial inflammation, fibroblastic proliferation, interstitial fibrosis, and honeycombing, a heterogeneity that is best seen at low power magnification.^{2,3} The fibrosis and honeycombing predominantly involve the subpleural and paraseptal lung regions. Lack of subpleural honeycombing on open-lung biopsy should suggest an alternative diagnosis.

HRCT Findings in IPF

On HRCT, IPF is characterized by the presence of reticular opacities, which correspond to areas of irregular fibrosis and reflect the typical pathologic features of UIP.^{2,4} The predominant HRCT features of IPF include honeycombing, traction bronchiectasis, intralobular interstitial thickening, and irregular reticular opacities. Ground-glass opacity may also be seen but is much less conspicuous and is uncommonly seen in isolation.

In many cases of IPF, findings of honeycombing are visible, and this finding is most helpful in distinguishing UIP/IPF from other diffuse lung diseases. On HRCT, honeycomb cysts usually range from 2 to 20 mm in diameter, but can be larger.⁵ They are characterized by clearly definable walls one to three mm in thickness.^{6,7} The cysts are air-filled and appear very

lucent (ie, black) on HRCT in comparison to normal lung parenchyma (Figure 1).

Honeycombing has been reported on HRCT in 24% to 90% of patients with IPF,^{8,9} and the frequency of this finding varies with the severity or stage of disease. In patients with early honeycombing, a few scattered subpleural honeycomb cysts may be visible. With disease progression, the cysts form a single layer of

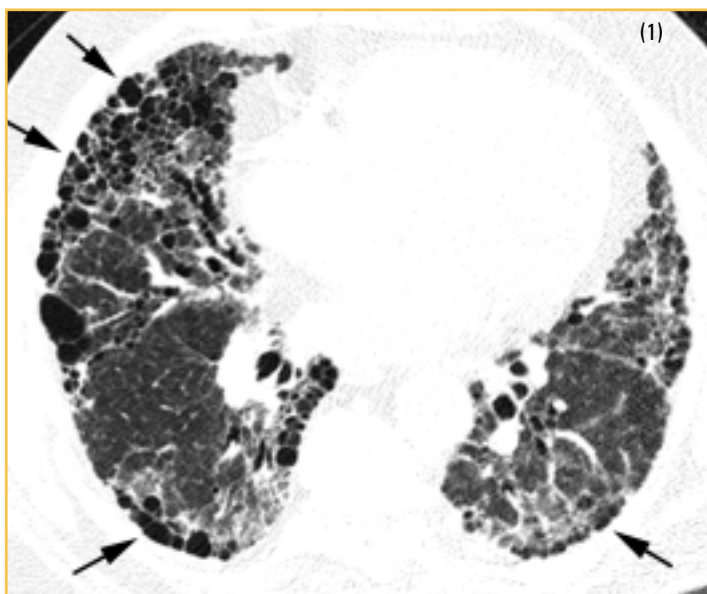


Figure 1: Honeycombing in IPF. Black, air-containing cysts (arrows) are visible in a subpleural location. In some regions, cysts are seen in multiple layers. This appearance and distribution is typical of IPF.

cysts in the subpleural lung. In severe disease, multiple layers of cysts are seen at the pleural surface, with adjacent cysts sharing walls. Honeycombing may be seen in diseases other than UIP/IPF. For example, honeycombing is visible in up to 20% of patients with

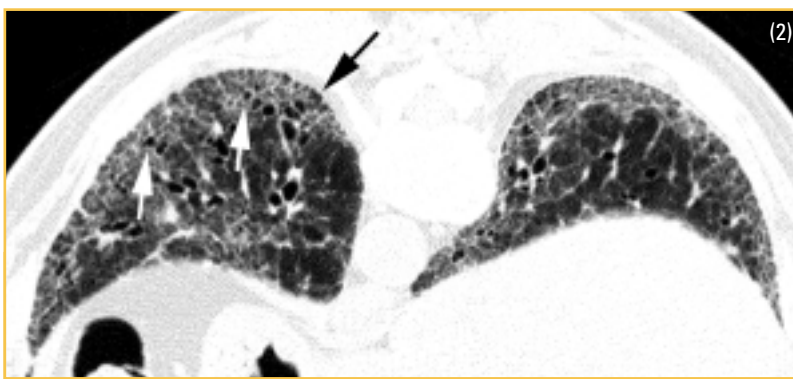


Figure 2: Reticulation and traction bronchiolectasis in IPF. A prone scan through the posterior lung bases shows a reticular pattern due to intralobular interstitial thickening. Traction bronchiolectasis (white arrows) does not involve the immediate subpleural lung but is visible about 1 cm from the pleural surface. Minimal honeycombing (black arrow) is also seen. Prone scans are valuable in diagnosing early disease.

nonspecific interstitial pneumonia (NSIP).¹⁰ However, in NSIP, it tends to be inconspicuous and of minimal extent compared to patients with UIP/IPF.

In patients with lung fibrosis, traction by fibrous tissue on the bronchial walls results in bronchial dilatation, known as *traction bronchioectasis*. It typically results in irregular bronchial dilatation that appears varicose or cork-screwed on HRCT.^{7,11} Traction bronchioectasis usually involves the segmental and subsegmental bronchi, and is most commonly visible in the perihilar regions.^{12,13} Fibrosis occurring in relation to peripheral bronchioles results in *traction bronchiolectasis* (Figure 2). Although traction bronchiolectasis may mimic honeycombing, these two entities can usually be distinguished. Unlike honeycombing, traction bronchiolectasis does not involve the immediate subpleural lung (Figure 2). Traction bronchioectasis and bronchiolectasis are common findings in IPF, but are less specific than honeycombing, and can be seen in a number of fibrotic lung diseases.

Intralobular interstitial thickening is often visible on HRCT in patients with IPF, resulting in a reticular pattern, which may predominate in some patients with this disease;^{7,9} it is often associated with traction bronchiolectasis (Figure 2).

Irregular reticular opacities are often seen on HRCT in patients with IPF in less abnormal lung regions, often the upper lobes.¹⁴ These may correspond to irregularly thickened interlobular septa or fibrosis involving the periphery of lobules. They predominate in the subpleural lung and usually appear perpendicular to the pleural surface.

Ground-glass opacity may be visible on HRCT in some patients with IPF, but it is uncommonly seen in isolation. More often, ground-glass opacity is seen in conjunction with intralobular interstitial thickening or traction bronchioectasis, reflecting the presence of fibrosis below the resolution of HRCT.^{15,16} The presence of ground-glass opacity as an isolated finding or as a predominant abnormality is much more typical of other interstitial pneumonias, such as NSIP, desquamative interstitial pneumonia (DIP), or hypersensitivity pneumonitis.

A hallmark of IPF on HRCT is its patchy distribution. Areas of mild and severe fibrosis, mild and marked inflammatory

activity, and normal lung are often present in the same patient, in the same lung, and in the same lobe. Also, and most important diagnostically, is that findings of IPF often predominate in the peripheral, subpleural regions, and in the lung bases (Figure 1). This subpleural predominance is evident on HRCT in 80% to 95% of patients.^{3,17} In approximately 70% of patients, the fibrosis is most severe in the lower lung zones, in about 20% of patients all zones are involved to a similar degree, and in about 10% of patients mainly the middle or upper lung zones are involved.^{17,18} Honeycombing and fibrosis are most often symmetrical, but asymmetry may be present.

In the vast majority of patients with IPF, serial HRCT scans show an increase in the extent of reticulation and honeycombing.¹⁹⁻²¹ This progression usually occurs gradually over several months or years. Occasionally patients develop a fulminant and often-fatal acute exacerbation.^{22,23} HRCT findings consist of extensive multifocal, peripheral or diffuse ground-glass opacity superimposed on a background of interstitial fibrosis.^{24,25} This appearance correlates with the presence of diffuse alveolar damage on lung biopsy.^{24,25}

Utility of HRCT in the Diagnosis of IPF

HRCT findings have been shown to be accurate in making a diagnosis of UIP and IPF and correlate with symptoms and pulmonary function abnormalities.²⁶ For example, Hunninghake et al²⁷ performed a prospective study of 91 patients with suspected idiopathic interstitial pneumonia (54 had a pathologic diagnosis of UIP on lung biopsy). The positive predictive value of a confident (certain) clinical diagnosis of IPF by a core of expert pulmonologists was 87%, while core radiologists reviewing HRCT had a positive predictive value of 96%. Multivariate analysis of specific clinical and HRCT features showed that lower-lung honeycombing (odds ratio, 5.36) and upper-lung irregular lines (odds ratio, 6.28) were the only independent predictors of UIP on biopsy.²⁸ Using only these two factors, a diagnosis of UIP could be established with a sensitivity of 74%, a specificity of 81%, and a positive predictive value of 85%.

Conclusions

On HRCT, the presence of basal and subpleural honeycombing strongly suggests the diagnosis of UIP and IPF, but other diseases may also show this finding. Generally a lung biopsy will not be performed if obvious honeycombing is visible. Traction bronchiolectasis may mimic honeycombing, and care

should be taken not to confuse these findings; traction bronchiolectasis is much less specific in making the diagnosis of UIP/IPF. Ground-glass opacity occurring in isolation or as a predominant finding suggests an alternative diagnosis.

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UPCOMING CME EVENTS

PILOT™ CME DINNER MEETINGS: UPDATE ON IDIOPATHIC PULMONARY FIBROSIS: A Case-Study Approach to Early and Accurate Diagnosis

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PILOT™ RESOURCE HUB

Procedure

Bronchoalveolar Lavage (BAL)

Transbronchial Biopsy (TBB)

Video-assisted Thoracoscopic Biopsy (VATS)

Role

- May rule out alternative diagnoses but not diagnostic of IPF

- May rule out alternate diagnoses but not diagnostic of IPF

- Often abnormal in IPF but does not confirm diagnosis

- Preferred technique

- Provides best tissue samples

- Excludes other processes that mimic IPF

- Biopsies should be obtained from more than one lobe of the lung

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med.* 2000; 161:646-664; 2002;165:277-304.

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