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Histopathologic Assessment of Suspected Idiopathic Pulmonary Fibrosis

Where We Are and Where We Need to Go

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• Context.—Accurate diagnosis of idiopathic pulmonary fibrosis (IPF) requires multidisciplinary diagnosis that includes clinical, radiologic, and often pathologic assessment. In 2018, the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society (ATS/ERS/IRS/ALAT) and the Fleischner Society each published guidelines for the diagnosis of IPF, which include criteria for 4 categories of confidence of a histologic usual interstitial pneumonia (UIP) pattern.

Objective.—To (1) identify the role of the guidelines in pathologic assessment of UIP; (2) analyze the 4 guideline categories, including potential areas of difficulty; and (3) determine steps the Pulmonary Pathology Society and the greater pulmonary pathology community can take to improve current guideline criteria and histopathologic diagnosis of interstitial lung disease.

Data Sources.—Data were derived from the guidelines, published literature, and clinical experience.

Conclusions.—Both guidelines provide pathologists with a tool to relay to the clinician the likelihood that a biopsy represents UIP, and serve as an adjunct, not a replacement, for traditional histologic diagnosis. There are multiple challenges with implementing the guidelines, including (1) lack of clarity on the quantity and quality of histologic findings required, (2) lack of recognition that histologic features cannot be assessed independently, and (3) lack of guidance on how pathologists should incorporate clinical and radiographic information. Current criteria for “probable UIP” and “indeterminate for UIP” hinder accurate reflection of the likelihood of IPF. These challenges highlight the need for further morphologic-based investigations in the field of pulmonary pathology.

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Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial lung disease (ILD) associated with a histologic and/or radiographic pattern of usual interstitial pneumonia (UIP) and a prognosis similar to or worse than that of many malignancies. Clinical characteristics of IPF include older age, male predominance, and a history of smoking. Accurate classification of ILDs is essential to clinical management, prognosis, and therapeutic decision-making. There has been enhanced focus on accurate classification of the UIP pattern given its poor prognosis and new therapeutic options for IPF. Multidisciplinary diagnosis (MDD) is the current gold standard in ILD
Two sets of guidelines have been published that are intended as a guide for the clinician in the clinical setting of suspicion for possible IPF. These guidelines provide criteria for classification into categories based on the degree of confidence that the radiologic or histologic findings represent a UIP pattern supporting a diagnosis of IPF, or a different pattern that would support an alternative, non-IPF diagnosis. In 2011, the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society (ATS/ERS/JRS/ALAT) published their first evidence-based guideline for diagnosis and management of IPF. The guideline was updated in 2018 to reflect new literature in the field and further clarify challenging areas of clinical, radiologic, and pathology practice. Nearly concurrently, the Fleischner Society, an international, multidisciplinary medical society for thoracic radiology dedicated to diseases of the chest, published their own evidence-based guideline for IPF diagnosis. Both guidelines include sections on the clinical, radiologic, and histologic classification of UIP as well as MDD assessment involving all 3 specialties, which together provide a cumulative likelihood of IPF.

A major goal of the 2018 ATS and Fleischner Society guidelines is to standardize category reporting within each specialty and to provide a common language for use amongst all physicians across ILD specialties. The Fleischner guideline was primarily directed at refining the criteria for radiologic UIP, but both guidelines include a schema of histologic categorization of fibrosis into 4 categories. The histologic categories are intended as a method for pathologists to communicate their confidence level that the microscopic features seen in surgical lung biopsy samples are compatible with the UIP pattern, which in the appropriate setting may be compatible with clinical IPF. It is important to understand that these categorizations are not meant as a replacement for traditional histologic diagnosis. Guideline categorization serves as a complementary adjunct to traditional diagnosis and can be included with the accompanying descriptive comments in a note.

It has been documented in the literature that there is sizable interobserver variability in all aspects of MDD assessment of the UIP pattern and IPF (and even more so for other diseases), including diagnostic interpretation of radiology and histopathology as well as amongst different MDD groups. Through more standardized categorization and criteria, the 2018 guidelines have improved the language pathologists can use to communicate confidence about whether a given histopathology is compatible with UIP. However, some key issues remain that allow for continued interobserver variability to occur, even amongst experienced ILD pathologists, both in guideline categorization and in aspects of traditional histologic diagnosis. The Pulmonary Pathology Society (PPS) Council published a Perspective discussing the impact of the 2018 guidelines on pathology practice for the ILD community. The PPS Council also acknowledged a need for a pathology-focused, in-depth analysis of the 2018 guidelines. In this effort, we aim to (1) discuss the role of the guidelines in the overall pathologic assessment of UIP, including an analysis of the similarities and differences between the 2018 ATS/ERS/JRS/ALAT and the Fleischner guidelines; (2) provide a detailed analysis of the 4 ATS/ERS/JRS/ALAT categories, including the guideline criteria for each category and potential areas of difficulty with implementation, reproducibility, and/or interobserver variability; and (3) initiate a dialogue on what steps the community of ILD pathologists can take to improve current guideline criteria, reduce interobserver variability, and enhance our practice in the assessment of UIP and other fibrotic patterns to support the clinical diagnosis of IPF and other ILDs.

THE DEFINITION OF UIP

The definition and concept of UIP has changed significantly since its introduction more than 50 years ago. Of the 5 diffuse interstitial pneumonias described by Liebow, the "undifferentiated" or "usual" pattern was termed usual interstitial pneumonia, based on the frequency of the lesion. The original histologic description included a wide spectrum of histologic injury ranging from diffuse alveolar damage to fibroplasia, and eventually end-stage lung fibrosis. Over the years the definition of UIP was refined, eliminating the diffuse alveolar damage component and introducing the concepts of geographic and temporal heterogeneity. Eventually, the distribution of the fibrosis in the periphery of the lobules (subpleural and paraseptal) was recognized as an important discriminator from other patterns of pulmonary fibrosis. The 2002 and 2013 classification of idiopathic ILD closely linked histopathologic UIP with the clinical syndrome of IPF. However, it is well recognized that histologic UIP may be seen in the setting of other fibrosing ILDs (pneumoconiosis, chronic hypersensitivity pneumonitis, and connective tissue disease-associated ILD in particular) and clinical and radiologic correlation is required to exclude other possibilities before assigning a diagnosis of IPF. In this article, references to UIP imply the histopathologic UIP pattern of fibrosis (and not the clinical syndrome IPF) unless otherwise noted.

THE 2018 ATS/ERS/JRS/ALAT and FLEISCHNER SOCIETY HISTOPATHOLOGIC GUIDELINE CATEGORIES

Both the ATS/ERS/JRS/ALAT and the Fleischner Society guidelines are intended to be used in the clinical setting of suspicion for IPF. Limiting use to this clinical scenario will avoid categorization of UIP in the setting of localized scarring (postobstructive/infectious/inflammatory), which may show some histologic features reminiscent of the pathology encountered in IPF, or in other scenarios where the clinician is suspecting a disorder other than IPF. While this clinical setting should be supplied by the submitting clinician, it is frequently missing. In this setting, if considering a UIP diagnosis, the pathologist is encouraged to seek out additional clinical and radiologic details.

The 2018 ATS/ERS/JRS/ALAT guideline outlines categories of confidence for the histopathologic classification of UIP, including the following: UIP, probable UIP, indeterminate for UIP, and alternative diagnosis. In a similar fashion, the Fleischner Society guideline outlines 4 histopathologic categories of diagnostic confidence, with some minor differences. Table 1 compares the histopathologic categories from the 2018 ATS/ERS/JRS/ALAT and the Fleischner guidelines. Both guidelines take a similar approach and provide 4 categories relaying a likelihood of UIP in the clinical setting of IPF, based on histologic features. The Fleischner guideline has added “IPF” to the
category headers (eg, probable UIP-IPF) to emphasize that the goal of the histologic guideline is to identify patients with histology compatible with IPF (in distinction from other conditions with a UIP pattern). There is significant overlap amongst the criteria in each category in both guidelines. One major difference is in the categorization of cases of secondary UIP (UIP pattern fibrosis with histology suggesting a secondary cause). The Fleischner guideline assigns an alternative diagnosis in this setting, while the ATS/ERS/JRS/ALAT leave the case as indeterminate for UIP.

Owing to the high similarities and overlap between the 2018 ATS/ERS/JRS/ALAT and the Fleischner guidelines, our review of the specific histologic categories will focus on the 2018 ATS/ERS/JRS/ALAT guideline.15 Below we review the existing guideline definitions for each category and provide examples of pathologic entities that may be assigned to the various categories.

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### Table 1. Comparison of the 2018 ATS/ERS/JRS/ALAT and Fleischner Society Guidelines for Histopathologic Diagnosis of Idiopathic Pulmonary Fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Column 1: UIP</th>
<th>Column 2: Probable UIP</th>
<th>Column 3: Indeterminate for UIP</th>
<th>Column 4: Alternative Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2018 ATS/ERS/ JRS/ALAT Guideline</strong></td>
<td>Dense fibrosis with architectural distortion (ie, destructive scarring and/or honeycombing)</td>
<td>Some histologic features from Column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF</td>
<td>Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause</td>
<td>Features of other histologic patterns of IIPs (eg, absence of FF or loose fibrosis) in all biopsies</td>
</tr>
<tr>
<td></td>
<td>Predominant subpleural and/or paraseptal distribution of fibrosis</td>
<td>AND Absence of features to suggest an alternative diagnosis</td>
<td>Some histologic features from Column 1, but with other features suggesting an alternative diagnosis</td>
<td>Histologic findings indicative of other diseases (eg, hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)</td>
</tr>
<tr>
<td></td>
<td>Patchy involvement of lung parenchyma by fibrosis Fibroblast foci Absence of features to suggest an alternative diagnosis</td>
<td>OR Honeycombing only</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fleischner Society</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dense fibrosis causing architectural remodeling with frequent honeycombing</td>
<td>Not all 4 criteria from Column 1 present</td>
<td>Less compelling histologic changes than those classified by the final column</td>
<td>Non-UIP pattern: features of other fibrotic disorders</td>
</tr>
<tr>
<td></td>
<td>Patchy lung involvement by fibrosis</td>
<td>Honeycomb fibrosis only, or:</td>
<td>For example, occasional foci of centrilobular injury or scarring, rare granulomas or giant cells, only a minor degree of lymphoid hyperplasia or diffuse inflammation, or diffuse homogeneous fibrosis favoring fNSIP</td>
<td>UIP pattern with ancillary features strongly suggesting an alternative diagnosis</td>
</tr>
<tr>
<td></td>
<td>Subpleural and/or paraseptal distribution</td>
<td>Dense fibrosis causing architectural remodeling with frequent honeycombing; FF at the edge of dense scars</td>
<td>FF at the edge of dense scars may or may not be present</td>
<td>Biopsy specimens with secondary UIP are assigned “indeterminate for UIP” by ATS/ERS/ALAT/JRS</td>
</tr>
<tr>
<td></td>
<td>FF at the edge of dense scars</td>
<td>Patchy lung involvement by fibrosis</td>
<td></td>
<td>Biopsy specimens with secondary UIP are assigned “alternative diagnosis” by Fleischner</td>
</tr>
<tr>
<td></td>
<td>Absence of features that might suggest an alternative diagnosis</td>
<td>FF at the edge of dense scars</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Identical</td>
<td>Nearly identical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ATS/ERS/JRS/ALAT, American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society; FF, fibroblast foci; fNSIP, fibrotic nonspecific interstitial pneumonia; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; UIP, usual interstitial pneumonia.

Data derived from Raghu et al7 and Lynch et al.9

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Histopathologic Assessment of IPF—Smith et al  3
Usual Interstitial Pneumonia

Histopathologic UIP is defined as having dense fibrosis with architectural distortion, present in a subpleural and/or paraseptal distribution, with patchy involvement of the lung, fibroblastic foci, and an absence of features to suggest an alternative diagnosis. Features suggesting an alternative diagnosis include granulomas, hyaline membranes, prominent airway-centered changes, areas of interstitial inflammation lacking fibrosis, marked chronic fibrous pleuritis, and organizing pneumonia (Table 2). Hyaline membranes and organizing pneumonia are specifically called out as features that would normally suggest an alternative diagnosis but may be seen in the clinical setting of acute exacerbation of IPF. This distinction requires the pathologist to have knowledge of the clinical presentation.

Biopsy samples meeting all features of UIP will likely be the least challenging to classify, but are seen less frequently owing to the radiologic diagnosis of UIP, which obviates the need for biopsy. From scanning magnification, these biopsy samples should show patchwork areas of advanced fibrosis alternating with areas of normal-appearing alveolar parenchyma (Figure 1, A). The areas of dense fibrosis should show a subpleural and/or paraseptal distribution. The demarcation between regions of advanced fibrosis and preserved parenchyma should be fairly sharp with areas of active fibroplasia in the form of fibroblastic foci at the interface zone (Figure 1, B). These biopsy specimens should not have significant interstitial inflammatory cell infiltrates or areas of extensive peribronchiolar metaplasia, especially away from the areas of fibrosis. In addition, rare multinucleated giant cells in air spaces and/or embedded deep within destructive fibrosis, particularly if associated with cholesterol clefts, may be considered compatible with a UIP designation, but how many of these foci should be allowed in cases assigned to this category has not been specified. If there are vague granulomatous inflammation (small rounded clusters of epithelioid histiocytes) and/or giant cells in the nonfibrotic interstitium or in a peribronchiolar distribution, consideration should be given to “indeterminate for UIP” or an “alternative diagnosis” designation (discussed in detail below).

Table 2. Pathologic Features Suggesting an Alternative Diagnosis or Favoring Usual Interstitial Pneumonia Secondary to Another Cause

| Hypersensitivity pneumonitis                  |
| Lymphocyte-rich bronchiolitis                |
| Extensive peribronchiolar metaplasia         |
| Poorly formed nonnecrotizing granulomas in a centrilobular distribution |
| Distinctly bronchiolocentric distribution    |
| Acute lung injury                            |
| Hyaline membranes                            |
| Organizing pneumonia with fibrosis           |
| Polyps of organizing pneumonia               |
| Pneumococcosis                               |
| Asbestos bodies                              |
| Prominent dust macules                       |
| Silicotic nodules                             |
| Sarcoidosis                                  |
| Prominent well-formed nonnecrotizing granulomas in a lymphangitic distribution |
| Smoking-related interstitial fibrosis        |
| Extensive respiratory bronchiolitis          |
| Exquisitely subpleural and/or peribronchiolar paucicellular densely eosinophilic collagen |
| Pleuroparenchymal fibroelastosis             |
| Prominent subpleural intraalveolar fibrosis and elastosis |
| Upper lobe predominance                     |
| Connective tissue disease–associated interstitial lung disease |
| Cellular inflammatory infiltrate away from areas of honeycombing |
| Prominent lymphoid hyperplasia including secondary germinal centers |
| Areas of interstitial inflammation lacking associated fibrosis |
| Marked chronic fibrous pleuritis             |

Data derived from Hariri et al.11

Figure 1. Histology of usual interstitial pneumonia. A, Dense fibrosis creating architectural distortion in a subpleural and paraseptal distribution. B, Active fibroplasia in the form of fibroblastic foci at the interface between advanced fibrosis and normal lung (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).
ATS/ERS/JRS/ALAT Column 2: Probable Usual Interstitial Pneumonia

Probable UIP is defined as having (1) some of the histologic features of UIP, but lacking either 1 or more required features or of insufficient extent for a definitive diagnosis of UIP; and (2) an absence of histologic features that suggest an alternative diagnosis. In the “probable UIP” category, the guideline does not allow for the presence of features suggesting an alternative diagnosis. Some biopsy samples show a distribution of fibrosis that would be typically characteristic of UIP (peripheral, subpleural, and paraseptal) but either (1) do not show the associated degree of architectural distortion in the form of destructive fibrosis and/or honeycombing (Figure 2, A) or (2) do not show any evidence of active fibroplasia in the form of fibroblastic foci (Figure 2, B). The former case (insufficient amounts of architectural distortion) may be encountered in patients with early stage or subclinical IPF. The latter case of absent fibroblastic foci is a relatively rare occurrence on surgical wedge biopsies; however, smaller biopsy samples may lack this feature.

Biopsy specimens showing only honeycomb remodeling, characterized by advanced fibrosis lacking spatial heterogeneity, with cystic dilated spaces lined by respiratory epithelium and (often) filled with mucous and inflammatory debris, are explicitly defined as probable UIP per the guideline (Figure 3, A through C). It is important to note that honeycomb lung represents a common end-stage result of many fibrosing ILDs. Therefore, even in the setting of microscopic honeycombing only, it is important to search for histologic features that suggest an alternative diagnosis, even if they are frequently absent.

ATS/ERS/JRS/ALAT Column 3: Indeterminate for Usual Interstitial Pneumonia

The guideline provides 2 criteria for indeterminate for UIP: (1) the presence of fibrosis, with or without architectural distortion, with features favoring a pattern other than UIP (ie, nonspecific interstitial pneumonia [NSIP] or airway-centered fibrosis); or (2) features favoring UIP secondary to another cause. The second criterion includes some histologic features from Column 1, but with other features suggesting an alternative diagnosis. The intent of the “indeterminate for UIP” category is to allow a mixture of some UIP features and features suggesting an alternative diagnosis, but overall, a definitive alternative diagnosis cannot be rendered. In combination, the “indeterminate for UIP” category allows for inclusion of a wide variety of cases, such as classic UIP appearance with the addition of occasional granulomas suggesting chronic hypersensitivity pneumonitis (Figure 4, A and B) and cases that are suggestive but not diagnostic of an NSIP pattern of fibrosis (Figure 4, C), airway-centered fibrosis (Figure 4, D), and connective tissue disease–associated ILD (Figure 4, E).

ATS/ERS/JRS/ALAT Column 4: Alternative Diagnosis

Biopsy samples designated “alternative diagnosis” show either (1) clear histologic features of secondary causes of UIP (chronic hypersensitivity pneumonitis (Figure 5, A and B), or (2) clear histologic features diagnostic of other patterns of idiopathic interstitial pneumonias (eg, NSIP [Figure 5, C] or desquamative interstitial pneumonia). Pathologists should be aware that the pathologic designation of alternative diagnosis excludes IPF as an overall MDD diagnosis according to the rubric in the 2018 ATS/ERS/JRS/ALAT guideline.7

CHALLENGES AND LIMITATIONS OF THE GUIDELINE

There are several challenges and limitations associated with the use of the guideline in pathology practice. These include (1) lack of specifications regarding the quantity and quality of histologic findings required, (2) limitations on the utilization of the “probable UIP” category for cases with classic UIP and the presence of minimal histologic feature(s) suggestive of an alternative diagnosis, (3) inclusion of a wide variety of pathologic patterns in “indeterminate for UIP,” (4) clear overlap of the “indeterminate” and “alternative diagnosis” categories, (5) inadequate guidance on how to manage histologic interpretation of surgical lung biopsy samples as a whole rather than as the sum of individual features within category criteria, and (6) lack of guidance on incorporation of clinical and radiographic information available at the time of pathologic assessment.

Figure 2. Probable usual interstitial pneumonia features. A, Peripheral fibrosis without honeycomb cyst formation or significant architectural distortion. B, Advanced fibrosis and architectural distortion without any fibroblast foci (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).
A major limitation of the histologic guideline is the lack of clarity on the quantity and quality of histologic findings required to meet the stated criteria and the overlap of the histologic descriptions. This creates the opportunity for significant variability between pathologists, even amongst pulmonary pathologists experienced with ILD. Features that are likely to cause confusion and/or disagreement include (extent of/number of) dense fibrosis/destructive scarring, fibroblast foci, granulomas, hyaline membranes/organizing pneumonia, prominent airway-centered changes, interstitial inflammation away from fibrosis/lymphoid hyperplasia, and chronic fibrous pleuritis. This level of detail may be outside the scope of the 2018 ATS/ERS/JRS/ALAT and Fleischner guidelines, but nonetheless affects diagnostic reproducibility.

**Fibrosis**

Threshold criteria for what constitutes dense fibrosis with architectural distortion may vary amongst individual pathologists. Figure 6, A through C, demonstrates 3 examples of fibrotic lung disease with varying levels of “destruction” and not every pathologist will agree which ones meet the threshold for dense fibrosis with architectural distortion. While most pathologists agree that microscopic honeycombing is advanced scarring, there is no consensus on the diagnostic and etiologic importance of microscopic bronchiolectasis or indeed how to recognize it given the frequency with which radiologists report on it. Conversely, it is also important to note that other non-ILD processes may cause destructive scarring, such as middle lobe syndrome and focal nonspecific scarring at the distal tip of the lung. Fibrosis relegated to the extreme distal portion of the lung is nonspecific and it alone should not be used to suggest a diffuse fibrosing lung disease. Another point that requires further study is whether advanced fibrosis should be an absolute requirement for a UIP designation, and more importantly, what histologic features could enable recognition of IPF at an earlier stage in the absence of advanced scarring, the stage at which therapeutic intervention is more likely to be effective.16,17

**Fibroblastic Foci**

Fibroblast foci are considered a hallmark of UIP, yet the number of fibroblastic foci in cases of UIP can vary greatly and there is no defined threshold for the number or density of fibroblastic foci required for a UIP or probable UIP designation. Furthermore, the guideline does not address the location of the fibroblast focus (centrilobular versus at the interface between advanced scarring and normal lung), which may have diagnostic significance. Fibroblast foci are also not specific to UIP and may be seen in a variety of other diseases thus limiting their diagnostic utility.18,19 Fibroblast foci may be encountered in all 4 guideline categories. Differentiating fibroblast foci from polyps of organizing pneumonia can also be a histologic challenge particularly since the former may derive from the latter. Because fibroblast foci are the hallmark of active injury and fibrosis in IPF it is logical that the number of fibroblast foci may have prognostic benefit, although the literature is mixed.20–22

**Granulomas**

In general, the presence of loose granulomatous inflammation in a background of UIP suggests UIP of a secondary cause and therefore should be classified as indeterminate for UIP. However, the number, size, location and character (well formed versus not) play a key role in a pathologist’s suspicion and confidence level for UIP versus an alternative...
diagnosis. For example, in a background of otherwise perfect UIP, a single poorly formed interstitial granuloma adjacent to an airway may be more suggestive of chronic hypersensitivity pneumonitis than several foci of giant cells in air spaces or deeply embedded within fibrosis, which can be acceptable in UIP (Figure 7, A through C).23,24 The presence of granulomas/giant cells may also suggest chronic aspiration or infection, which could be subclinical. Chronic

Figure 4. Indeterminate for usual interstitial pneumonia. A and B, Usual interstitial pneumonia–like fibrosis with foci of poorly formed interstitial granulomas suggesting usual interstitial pneumonia secondary to chronic hypersensitivity pneumonitis. C, A case with more diffuse fibrosis, without significant alteration of architecture, is reminiscent of fibrotic nonspecific interstitial pneumonia or smoking-related pathology and may be best classified as “indeterminate for usual interstitial pneumonia.” D, Airway-centered fibrosis but without granulomas, preventing a definitive diagnosis of chronic hypersensitivity pneumonitis. E, Biopsy specimen showing significant fibrosis with prominent lymphoplasmacytic infiltrates, follicles with germinal centers, and chronic fibrotic pleuritis suggesting a nonidiopathic pulmonary fibrosis etiology—in this case connective tissue disease–associated interstitial lung disease (hematoxylin-eosin, original magnifications ×12.5 [A, D, and E], ×400 [B], and ×20 [C]).
aspiration is strongly associated with IPF and it is not surprising that some patients with IPF show typical UIP features with superimposed granulomas of aspiration.25 Aside from identifying food particles, it may be very difficult to distinguish UIP with superimposed chronic aspiration from chronic hypersensitivity pneumonitis. The guideline does not address the pathologic setting of a patient with IPF and superimposed aspiration.

Figure 5. Alternative diagnosis. A and B, A biopsy specimen showing a distinct airway-centered fibrosing process with scattered poorly formed interstitial granulomas compatible with chronic hypersensitivity pneumonitis. C, Pathologic features meeting criteria for nonspecific interstitial pneumonia (hematoxylin-eosin, original magnifications ×20 [A], ×200 [B], and ×12.5 [C]).

Figure 6. Degrees of fibrosis. A, While most would agree this image represents destructive fibrosis distorting the architecture, others may not. B, In contrast, this image is more likely to be seen as not-yet-advanced fibrosis. C, Not all destructive fibrosis indicates usual interstitial pneumonia of idiopathic pulmonary fibrosis. This is honeycomb fibrosis limited to the extreme distal tip of a lobectomy specimen done for tumor in a patient without clinical or radiologic evidence of interstitial lung disease (hematoxylin-eosin, original magnification ×20 [A through C]).
Organizing Pneumonia and Hyaline Membranes

Although the guideline indicates that the presence of organizing pneumonia and hyaline membranes should suggest an alternative diagnosis, it is important to recognize that organizing pneumonia and hyaline membranes are often seen in the setting of acute exacerbation of IPF (Figure 8, A through C). While knowledge of the clinical presentation could help in making this distinction, this information...
may not always be available to the pathologist at the time of histologic assessment. Furthermore, the guideline is unclear on how pathologists should incorporate this clinical information into their histologic classification.

**Airway-Centered Disease**

Prominent airway-centered changes suggest a chronic inhalational disease such as chronic hypersensitivity pneumonitis, chronic aspiration, or smoking. These features include airway-centered fibrosis, mucocystosis, and extensive peribronchiolar metaplasia (Figure 9, A through C). How much of these changes can be seen in the setting of UIP versus other entities and how extensive the findings must be to assign one diagnostic category over another has not been established. Bridging fibrosis (fibrosis from one centrilobular region to another) has been proposed as an additional finding suggesting chronic inhalational injury. However, the specificity and reproducibility of bridging fibrosis are to be determined and require further investigation. A recent study showed that the presence of peribronchiolar metaplasia around more than half of the bronchioles supports a diagnosis of chronic hypersensitivity pneumonitis, while a separate study found that bronchiolocentric fibrosis could be identified in about a third of UIP cases, but the presence of bronchiolocentric fibrosis favored an alternative diagnosis with an odds ratio of 3.7. This is a major point of contention amongst pathologists in the field and as a result, individual pathologists use different threshold cutoffs.

**Inflammation**

Interstitial inflammation away from fibrosis, lymphoid hyperplasia, and chronic fibrous pleuritis are all features that suggest a UIP pattern secondary to connective tissue disease or an ILD other than IPF, and by the guideline, the presence of these features warrants an “indeterminate for UIP” designation (Figure 10, A through C). As with the other features, no further guidance is available and pathologists are left to rely on their own training and experience to determine their individual thresholds. For example, it is uncertain if the images in Figure 10, A through C, are sufficient to reassign a case with all required features of UIP into an “indeterminate for UIP” category owing to the lymphoid infiltrates and chronic pleuritis.

**Interpreting Histologic Features as an Amalgam**

Complicating the issues above regarding individual histologic features is the fact that histologic features cannot be evaluated in a vacuum independently of one other. Pathology practice relies on the recognition of the presence or absence of a variety of different histologic features that are incorporated into a final assessment for a comprehensive histologic diagnosis (a gestalt impression that is greater than a simple sum of individual components). The significance of a single particular finding is judged in relation to all other features present or absent in the biopsy sample. For example, a case with both borderlne airway-centricity and a few scattered giant cells is far more concerning for chronic hypersensitivity pneumonitis than if only one of the above features is encountered. This exponentially increases the challenge of reproducibility in a system that focuses primarily on assessment of individual features.

**Limitations of Probable UIP and Indeterminate for UIP**

Presently, the guideline does not allow any histologic features suggesting an alternative diagnosis to be present in either the UIP or probable UIP categories. While this might increase the specificity of these designations, it essentially relegates most cases with anything other than a perfect or near perfect UIP to the “indeterminate for UIP” category. Because patients with classic clinical and radiographic findings of IPF are not undergoing surgical lung biopsy, it is likely that the frequency of encountering these alternative features will increase. Furthermore, the histologic designation of indeterminate for UIP is the least helpful in the guideline rubric as it does not provide pathologic support for either IPF or an alternative diagnosis, which was the goal of the biopsy in the first place. The result will be a cohort of patients with quite disparate histology, all being lumped into a single category of indeterminate for UIP, for whom the pathologic assessment is clinically uninformative. Efforts should be undertaken to improve the ability to further classify biopsies as favoring IPF or favoring an alternative diagnosis, as this is likely to be more helpful in the MDD classification of patients.

**Clinical and Radiologic Information in Pathology Assessment**

The guideline implies an independent clinical, radiographic, and pathologic approach to the assessment followed by a multidisciplinary discussion to arrive at a definitive diagnosis. While this approach may work in the setting of clinical trials, it is not uncommon (and in fact is highly desirable) to have radiographic and or clinical data at the time of pathologic interpretation. Having this information available could impact the final pathology designation. For example, if it is known that the patient has exposure to an organic antigen and has upper lobe–predominant disease on imaging studies, should a biopsy still be designated as indeterminate for UIP when it is clearly airway centered but contains only a few scattered foci of multinucleated giant cells and granulomatous inflammation? Clearly the patient in this scenario most likely has chronic hypersensitivity pneumonitis and the most accurate designation would be an alternative diagnosis. However, the pathologic features alone justify only an “indeterminate for UIP” designation. A similar scenario may occur in middle-aged female patients with serologic evidence of autoimmune disease. In such circumstances, we suggest issuing a descriptive diagnosis with the favored etiology and in the comment mentioning the 2018 ATS/ERS/JRS/ALAT guideline category based on the histologic features alone (indeterminate for UIP in these scenarios). It may also be prudent to document the clinical and/or radiologic information taken into consideration during pathology interpretation in the note. Of course, the ideal scenario is to have a pathologist play an active role in institutional multidisciplinary discussions if possible.

**POTENTIAL IMPACT OF THE GUIDELINES ON PATHOLOGY PRACTICE**

The guidelines for the diagnosis of IPF impact pathologists in multiple ways. One of the largest impacts on pathologists is the recommendation that a clinical diagnosis of IPF can be made without a lung biopsy in the correct clinical and radiologic setting. This change in clinical practice appears to have already resulted in a decrease in the frequency of classic UIP biopsies encountered by surgical pathologists, which may decrease pathologists’ familiarity with classic UIP histology. From a practical perspective this means that pathologists will increasingly
Figure 9. Airway-centered pathology suggesting chronic inhalational injury. A, Marked peribronchiolar metaplasia out of proportion to the amount of fibrosis. B, Bridging fibrosis from one centrilobular region to an adjacent centrilobular region with sparing of the subpleural parenchyma. C, Airway-centered fibrosis accentuated in the centrilobular region and sparing the periphery of the lobule (hematoxylin-eosin, original magnifications ×40 [A] and ×20 [B and C]).

Figure 10. Histology that may suggest an inflammatory etiology for fibrotic lung disease (most likely connective tissue disease–associated interstitial lung disease). Not everyone will agree these findings are sufficient for an alternative diagnosis. A, Medium-powered field with lymphoplasmacytic infiltrates expanding the interstitium, reminiscent of cellular nonspecific interstitial pneumonia. B, Lymphoid hyperplasia including germinal centers in a case of fibrotic lung disease. C, Fibrotic pleural thickening with focal inflammation (hematoxylin-eosin, original magnifications ×200 [A and C] and ×100 [B]).
see biopsy samples from patients with ambiguous clinical and radiographic presentations, which may lead to diagnostic drift over time. Furthermore, the pretest probability for IPF may be much lower than it was in the past and UIP may be unexpected from the clinician’s perspective if there are clinical and/or radiographic imaging features that are unusual and have led to a surgical lung biopsy.

As clinicians have become more focused on the guideline designation, there may be a tendency for pathologists to also focus more on the guideline designation rather than a clinically useful and complete diagnosis that addresses the pathologic diagnosis as a whole rather than terms based on the sum of features identified. To reiterate statements above, the guidelines are to be used as an adjunct to a complete morphologic evaluation and clinicopathologic diagnosis.

Transbronchial cryobiopsy has received considerable attention recently as a potential alternative to surgical lung biopsy for the diagnosis of ILD. Studies regarding diagnostic yield and potential complications have been conflicting.33,34 In particular, 2 studies that performed paired cryobiopsy and surgical lung biopsy in the same patients came to opposite conclusions with one finding a poor correlation between the 2 techniques,32 while a second reported high levels of agreement.31 However, the guidelines were developed as based on surgical lung biopsy samples, and smaller cryobiopsy specimens mostly showed probable UIP in MDD/surgical lung biopsy–confirmed cases of IPF in the study of Troy et al.35 The 2018 guideline suggests that there was insufficient evidence at the time to recommend cryobiopsy in the formal diagnostic workup of patients with potential IPF. We agree with this perspective but do share enthusiasm for the potential of transbronchial cryobiopsy, particularly in experienced operator hands. Further study of appropriate guidelines in this setting is suggested.

**FUTURE STEPS IN PATHOLOGY ASSESSMENT OF FIBROTIC LUNG DISEASES**

The 2018 ATS/ERS/JRS/ALAT and Fleischner guidelines and the preceding discussion raise several future investigative opportunities. Clearly, reproducibility and outcome studies, along with improved definitions, are required for the categories in order to refine criteria and reduce interobserver variability. This includes studies investigating the quantity and quality of the various ILD features described in the guidelines, with comparisons to outcome-based measures that may include MDD diagnosis as well as follow-up clinical outcome and MDD reassessment. Future iterations of guideline criteria should include a reassessment of histologic criteria for probable UIP and indeterminate for UIP to realign each category with the intended confidence level that the histologic features seen in a biopsy specimen may be compatible with IPF. Future guideline criteria may also incorporate both quality and quantity of specific histologic features, as well as incorporation of overall pattern with respect to individual features in order to make use of the global pathologic assessment of overall histologic patterns.

There are also opportunities to incorporate new assessment methods for the diagnosis of ILD. As image analysis and augmented morphologic approaches become more common, fibrosis patterns may be an area ripe for morphologic-based image analysis studies. Unbiased deep learning algorithms paired with robust MDD and outcome data have the potential to reveal important histologic clues to etiology and prognosis that we have not yet recognized. The field of fibrotic lung disease would also greatly benefit from new biomarkers to aid in the histologic assessment and diagnosis of IPF and other ILDs, which may be either serum or tissue based.10,33–37 Indeed, a molecular classifier has shown encouraging preliminary results in identifying UIP on transbronchial biopsy specimens.38

This effort will require the community of pathologists with interest and experience in ILD to work together to achieve these goals. The PPS urges the pulmonary pathology community to (1) reach consensus on aspects of the IPF histologic guidelines where there is practice variability; (2) conduct necessary multicenter studies to assess reproducibility and outcome studies in order to develop further evidence-based guidelines for diagnosis of UIP and other ILDs, including criteria for diagnosis of early stages of IPF and other ILDs; (3) conduct and/or participate in studies investigating new methods of ILD assessment, including deep learning image analysis and biomarker studies; and (4) work together with our ILD pulmonologist and radiologist colleagues to create more robust, reproducible criteria for the MDD diagnosis of IPF and other ILDs.

**References**


