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Usual Interstitial Pneumonia in Contemporary Surgical Pathology Practice

Impact of International Consensus Guidelines for Idiopathic Pulmonary Fibrosis on Pathologists

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Context.—Idiopathic pulmonary fibrosis is a clinical syndrome characterized by the presence of usual interstitial pneumonia (UIP) radiologically and pathologically. Per consensus criteria adopted in 2011, diagnosis of idiopathic pulmonary fibrosis no longer requires a biopsy in an appropriate context if UIP is seen on imaging. As a result, lung biopsies are now typically reserved for patients having indeterminate clinical or imaging findings or suspicion for alternative diagnoses, but the impact of updated guidelines on pathology practice remains unclear.

Objective.—To determine the frequency of histologic UIP before and after 2011.

Design.—Surgical lung biopsies from adults were studied within two 4-year periods: July 1, 2006, through June 30, 2010, and January 1, 2012, through December 31, 2015. Pathology slides were reviewed in a fashion blinded to clinical information and were classified using current guidelines.

Results.—Biopsies from 177 and 86 patients (mean [SD] age, 62 [12] and 59 [14] years; 50.3% [89 of 177] and 48.8% [42 of 86] men) before and after 2011, respectively, were reviewed. Probable UIP or UIP was less-frequently encountered after 2011 in all patients with fibrosis (9 of 54 [16.7%] versus 41 of 119 [34.5%] before 2011, \( P = .02 \)) and also in patients 50 years old and older (8 of 46 [17.4%] versus 39 of 109 [35.8%] before 2011, \( P = .02 \)), with a concomitant rise in cases indeterminate for UIP or showing alternative diagnoses.

Conclusions.—Histology for UIP is less frequently encountered in our contemporary practice compared with the historic era. The pretest probability of a non-UIP diagnosis is now high, even in elderly patients, underscoring the need for pathologists to be familiar with the histologic features of alternative diagnoses.

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idiopathic pulmonary fibrosis (IPF) is a relentlessly progressive chronic fibrosing interstitial pneumonia of unknown cause, usually occurring in adults older than 50 years, with a poor prognosis and a median survival of less than 3 years. Idiopathic pulmonary fibrosis is defined by the presence of the “usual interstitial pneumonia” (UIP) histologic pattern of lung fibrosis, a pattern that is recapitulated on the macroscopic scale and readily and reliably identified by high-resolution computed tomography imaging of the chest in a significant proportion of cases.

Indeed, the positive predictive value for a radiologic diagnosis of UIP by high-resolution computed tomography for a pathologic diagnosis of UIP is reported to exceed 90% in multiple studies,\(^1,5\) but not all patients with pathologic UIP will meet high-resolution computed tomography criteria,\(^1,2,4,6\) and pathologists have an important role in the diagnosis of those patients requiring a lung biopsy.\(^7\)

Although characteristic of IPF, UIP is not specific for IPF and may be seen with systemic connective tissue diseases, chronic hypersensitivity pneumonitis, adverse drug reactions, and familial forms of interstitial lung disease. As an idiopathic disorder, IPF is a diagnosis of exclusion by definition, which requires a negative clinical, imaging, and laboratory workup for other potential causes of lung fibrosis. Treatment of IPF has rapidly evolved in recent years with the advent of antifibrotic therapy,\(^8,9\) and recommendations to avoid immunosuppression,\(^10\) and the distinction between IPF and other chronic fibrosing interstitial pneumonias has been a key component of the clinical workup with therapeutic implications. Recent data suggest that antifibrotic therapy may have a role in other progressive fibrosing interstitial pneumonias and not solely IPF,\(^11\) and it is certainly possible that this distinction may become less

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important over time, with a diminishing role for pathologic assessment. Nevertheless, it should still be remembered that histologic findings can provide clues to the underlying etiology and pathologists may still be asked to evaluate lung biopsies in more-unusual situations or when clinical uncertainty mandates additional input.

In an effort to standardize terminology and diagnostic criteria for IPF, the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) issued consensus guidelines for IPF in 2011.12 These guidelines include several recommendations that directly affect pathologists. Chief among these was the creation of 4 categories of certainty for histology (UIP, probable UIP, possible UIP, and not UIP), each with specific criteria to inform the multidisciplinary diagnosis of IPF. Perhaps less recognized by pathologists but equally important was the recommendation that IPF can be diagnosed confidently without a surgical lung biopsy in an appropriate clinical setting if the high-resolution computed tomography scan shows UIP radiologically. That concept was reemphasized when these guidelines were updated in 2018.7 In the same year, the Fleischner Society proposed its own updated terminology and recommendations for the diagnosis of IPF.13 Differences between these 2 documents in 2018 are minor and have been reviewed elsewhere.14 For pathologists, key changes (common to both documents) include renaming the possible UIP and not UIP categories as indeterminate for UIP and alternative diagnosis, respectively, to better reflect their use in clinical practice as indicators of the likelihood of IPF, because the underlying etiology ultimately drives clinical management. Both documents continue to strongly recommend against obtaining a lung biopsy if UIP is seen radiologically, but the Fleischner Society went one step further by proposing that a diagnosis of IPF can also be made without a biopsy if probable UIP is encountered radiologically, based on data supporting that notion.15 This latter proposal remains controversial, but the 2011 guidelines certainly prompted a fundamental shift in clinical practice, even before the 2018 revision, whereby lung biopsies are now primarily reserved for those patients having ambiguous clinical or imaging findings or for whom there is suspicion for an alternative etiology besides IPF.

Based on our anecdotal experience in a high-volume pulmonary pathology practice, we suspected that the 2011 consensus guidelines and recommendations to avoid biopsies in patients with clinically and radiologically straightforward IPF may have altered the frequency of fibrotic interstitial lung disease patterns encountered by surgical pathologists. We hypothesized that biopsies showing UIP histology may be less common in the current era, but to our knowledge, the true impact of the 2011 IPF guidelines on surgical pathology practice has not been systematically evaluated.

MATERIALS AND METHODS

This study was approved by the appropriate institutional review board at the Mayo Clinic (protocol 17-002763). The laboratory databases at 2 Mayo Clinic sites (in Rochester, Minnesota, and Scottsdale, Arizona) were searched for surgical lung biopsies obtained from adults older than 18 years for two 4-year periods: July 1, 2006, through June 30, 2010 (pre-2011 cohort) and January 1, 2012, through December 31, 2015 (post-2011 cohort). These times were selected to flank the time of publication of the ATS/ERS/JRS/ALAT guidelines in March 2011, with an additional buffer period of approximately 9 months before and after publication of the guidelines to account for possible differences in adoption and implementation thereof by individual practitioners across our multisite practice. Search terms included lung, wedge biopsy/biopsies, and VATS biopsy/biopsies. Cases of resected tumors or other localized processes were excluded. To avoid referral bias inherent to pathology consultation practice, extramural consultation cases were also excluded from review, and only in-house biopsies obtained at the 2 participating Mayo Clinic sites were included in the study.

Pathology slides from each case were retrieved from the pathology archives at each participating site and reviewed at a multiheaded microscope by 2 authors (B.T.L. and J.M.E.), in a fashion blinded to the patient age, sex, imaging findings, and all other clinical information, to avoid biasing the histopathologic assessment. This review was also blinded to the original pathologic diagnoses rendered at the time of biopsy. This approach was chosen rather than simply reviewing old reports to avoid a number of potentially confounding factors because the original diagnoses were rendered by many pathologists with varying expertise, some of whom were experts in pulmonary pathology and others who were general pathologists without specialty expertise in pulmonary pathology, across our multisite practice. In addition, these original pathologists varied over the years with a number of new hires and also retirements. By reviewing all slides in a completely blinded fashion rather than simply reviewing old reports, we aimed to assess the histopathology of all cases in a uniform manner using the same diagnostic criteria and thresholds, maintaining as much objectivity as possible without those additional confounding factors, but also recognizing the somewhat subjective nature of histopathologic assessment of lung biopsies in general and the lack of specific thresholds and guidance for pathologists in current international consensus criteria.16

The number of lobes sampled and the number of slides evaluated were tallied in each case. All existing hematoxylin–eosin–stained slides from each case were evaluated for the presence or absence of fibrosis, irrespective of the original diagnoses rendered at the time of biopsy. Cases with fibrosis were classified using the 2018 ATS/ERS/JRS/ALAT histologic criteria and assigned to 1 of the 4 categories: UIP, probable UIP, indeterminate for UIP, and alternative diagnosis, with no attention given to the original diagnosis made at the time of biopsy. It should be remembered that this guideline-based categorization is somewhat artificial, and these categories are infrequently used by pathologists as a true “diagnosis” in routine clinical practice, but we chose to use these categories to serve the purpose of this study to gauge the spectrum and distribution of histopathology encountered in the 2 periods of interest in our practice. Although all biopsies were obtained prior to 2018, the updated 2018 criteria and categories were used, rather than their 2011 counterparts, to provide data most relevant to current practice. When other patterns of fibrosis were encountered, they were also recorded and included fibrotic nonspecific interstitial pneumonia, airway-centered fibrosis, or mixed or unclassifiable patterns of fibrosis.

All cases were assessed for other histologic features including prominent poorly formed nonnecrotizing granulomas, well-formed nonnecrotizing (“sarcoidlike”) granulomas, necrotizing granulomas, prominent peribronchiolar metaplasia, chronic bronchiolitis, follicular bronchiolitis, lymphoid hyperplasia, prominent chronic inflammatory infiltrates away from areas of honeycombing, organizing pneumonia, acute fibrinous lung injury or diffuse alveolar damage, evidence of pleural disease (pleuritis and/or pleural fibrosis), evidence of pneumonia, and smoking-related interstitial lung disease (including patterns of “desquamative interstitial pneumonia,” subpleural hylalinized smoking-related interstitial fibrosis, airway-centered stellate scars of pulmonary Langerhans cell histiocytosis, and their various combinations; this term [smoking-related interstitial lung disease] was only assigned in those cases in which the smoking-related changes appeared to represent the dominant pathology and no concomitant UIP or other fibrosing interstitial pneumonias were seen). Essentially all of...
these additional histologic features can coexist with UIP and their presence does not necessarily preclude a diagnosis of UIP, but when they are a prominent or dominant finding they should raise suspicion for a non-UIP diagnosis, particularly when several are seen in combination. Unfortunately, this widely accepted general concept can be difficult to apply in practice, and there remain a number of significant problems with current international consensus guidelines with implications for pathologists. Because no guidance from current international consensus criteria or published data exist to indicate the threshold at which granulomas become significant, we made the arbitrary decision to consider granulomas significant for the purpose of category designation only when they were numerous (present in at least one-half of the available slides), predominantly centered on bronchioles within nonfibrotic areas, well-formed (resembling sarcoidosis), and/or necrotizing. This arbitrary decision was based largely on the principle of avoiding overinterpretation of the importance of a rare incidental granuloma, and it should be recognized that this approach is not founded on current consensus guidelines which fail to address this problem. Recognizing that organizing pneumonia, acute fibrous lung injury, and diffuse alveolar damage may be seen in the setting of an acute exacerbation of IPF,7,12 these patterns were only considered significant for the purpose of category designation when found in a fibrotic background that otherwise appeared inconsistent with UIP because of an incompatible distribution pattern; the lack of architectural distortion, the lack of honeycombing, and/or the lack of heterogeneity; or when these patterns significantly obscured the fibrotic background to the point that the architecture of fibrosis could not be determined. As with granulomas and other histologic subcharacteristics, no guidance from current international consensus criteria exists to indicate the threshold at which peribronchiolar metaplasia becomes significant, and we made the arbitrary decision to consider peribronchiolar metaplasia significant for the purpose of category designation only when extensive (involving a majority of bronchioles [>50%] or extending at least one-half of the distance between an affected airway and the nearest interlobular septum or pleura) or when occurring in a setting in which airway-centered fibrosis or other airway-centered changes also predominated, an approach similar to that used by others.17 but we also recognized that this feature has not been validated as a robust discriminatory marker in this context. For a more thorough review of the current limitations of the international consensus guidelines relating to pathology practice, the reader is referred to a recent editorial perspective on the topic from the leadership of the Pulmonary Pathology Society.16

After completion of the blinded review of slides and the classification of histopathologic findings, patient age and sex information was accessed and linked to the pathology data for analysis. Other elements of the clinical history (besides age and sex) were not accessed at any point, nor were any imaging findings, and they were not included in the data analysis. Statistical analysis was performed using R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version

| Characteristics                              | Pre-2011, No. (%), n = 177 | Post-2011, No. (%), n = 86 | Total, No. (%), n = 263 | P Value |
|---------------------------------------------|-----------------------------|-----------------------------|--------------------------|---------|
| Institutional site                          |                             |                             |                          |         |
| Mayo Clinic, Rochester, Minnesota          | 59 (33.3)                   | 35 (40.7)                   | 94 (35.7)                |         |
| Mayo Clinic, Scottsdale, Arizona           | 118 (66.7)                  | 51 (59.3)                   | 169 (64.3)               |         |
| Age, y                                      |                             |                             |                          |         |
| Mean (SD)                                   | 62.2 (12.4)                 | 58.9 (14.0)                 | 61.1 (13.0)              | .049b   |
| Median (Q1, Q3)                             | 64 (56, 71)                 | 61 (50, 69)                 | 63 (54, 70)              |         |
| Range                                       | 20–87                       | 19–87                       | 19–87                    |         |
| Sex                                         |                             |                             |                          | .89a    |
| Men                                         | 89 (50.3)                   | 42 (48.8)                   | 131 (49.8)               |         |
| Women                                        | 88 (49.7)                   | 44 (51.2)                   | 132 (50.2)               |         |
| No. of slides available                     |                             |                             |                          | .02b    |
| Mean (SD)                                   | 8.6 (4.5)                   | 10.1 (5.8)                  | 9.1 (5.0)                |         |
| Median (Q1, Q3)                             | 8 (5, 11)                   | 9 (5, 14)                   | 8 (5, 12)                |         |
| Range                                       | 1–29                        | 2–27                        | 1–29                     |         |
| No. of lobes sampled                        |                             |                             |                          | .09a    |
| 1                                           | 66 (37.3)                   | 23 (26.7)                   | 89 (33.8)                |         |
| >1                                          | 111 (62.7)                  | 63 (73.3)                   | 174 (66.2)               |         |
| Fibrosis observed                           |                             |                             |                          | .48a    |
| Yes                                         | 119 (67.2)                  | 54 (62.8)                   | 173 (65.8)               |         |
| No                                          | 58 (32.8)                   | 32 (37.2)                   | 90 (34.2)                |         |
| Fibrotic pattern, all ages                  |                             |                             |                          | .06a    |
| UIP                                         | 25 (21.0)                   | 3 (5.6)                     | 28 (16.2)                |         |
| Probable UIP                                | 16 (13.4)                   | 6 (11.1)                    | 22 (12.7)                |         |
| Indeterminate for UIP                       | 15 (12.6)                   | 9 (16.7)                    | 24 (13.9)                |         |
| Alternative diagnosis                       | 63 (52.9)                   | 36 (66.7)                   | 99 (57.2)                |         |
| Fibrotic group, all ages                    |                             |                             |                          | .02a    |
| Favor IPF (UIP or probable UIP)             | 41 (34.5)                   | 9 (16.7)                    | 50 (28.9)                |         |
| Favor non-IPF (indeterminate or alternative diagnosis) | 78 (65.5) | 45 (83.3) | 123 (71.1) |         |

Abbreviations: IPF, idiopathic pulmonary fibrosis; Q1/Q3, first or third quartiles; UIP, usual interstitial pneumonia.

a Determined by the χ² test.
b Determined by analysis of variance.
Table 2. Characteristics and Comparison of Patients 50 Years and Older in Each Cohort

| Characteristics                  | Pre-2011, No. (%), n = 150 | Post-2011, No. (%), n = 65 | Total, No. (%), n = 215 | P Value |
|----------------------------------|-----------------------------|-----------------------------|-------------------------|---------|
| **Institutional site**           |                             |                             |                         |         |
| Mayo Clinic, Rochester, Minnesota| 44 (29.3)                   | 26 (40.0)                   | 70 (32.6)               | .12*    |
| Mayo Clinic, Scottsdale, Arizona  | 106 (70.7)                  | 39 (60.0)                   | 145 (67.4)              |         |
| **Age, y**                       |                             |                             |                         | .48*    |
| Mean (SD)                        | 66.1 (8.3)                  | 65.3 (7.8)                  | 65.9 (8.1)              |         |
| Median (Q1, Q3)                  | 65 (60, 73)                 | 65 (59, 71)                 | 65 (60, 72)             |         |
| **Sex**                          |                             |                             |                         | .87*    |
| Men                              | 72 (48.0)                   | 32 (49.2)                   | 104 (48.4)              |         |
| Women                            | 78 (52.0)                   | 33 (50.8)                   | 111 (51.6)              |         |
| **No. of slides available**      |                             |                             |                         | .01*    |
| Mean (SD)                        | 8.4 (4.4)                   | 10.2 (5.9)                  | 9.0 (5.0)               |         |
| Median (Q1, Q3)                  | 8 (5, 10)                   | 9 (6, 12)                   | 8 (6, 11)               |         |
| **No. of lobes sampled**         |                             |                             |                         | .08*    |
| 1                                | 55 (36.7)                   | 16 (24.6)                   | 71 (33.0)               |         |
| >1                               | 95 (63.3)                   | 49 (75.4)                   | 144 (67.0)              |         |
| **Fibrosis observed**            |                             |                             |                         | .78*    |
| Yes                              | 109 (72.7)                  | 46 (70.8)                   | 155 (72.1)              |         |
| No                               | 41 (27.3)                   | 19 (29.2)                   | 60 (27.9)               |         |
| **Fibrotic pattern**             |                             |                             |                         | .10*    |
| UIP n = 109                      | 23 (21.1)                   | 3 (6.5)                     | 26 (16.8)               |         |
| Probable UIP                     | 16 (14.7)                   | 5 (10.9)                    | 21 (13.5)               |         |
| Indeterminate for UIP            | 14 (12.8)                   | 9 (19.6)                    | 23 (14.8)               |         |
| Alternative diagnosis            | 56 (51.4)                   | 29 (63.0)                   | 85 (54.8)               |         |
| **Fibrotic group**               |                             |                             |                         | .02*    |
| Favor IPF (UIP or probable UIP)   | 39 (35.8)                   | 8 (17.4)                    | 47 (30.3)               |         |
| Favor non-IPF (indeterminate or alternative diagnosis) | 70 (64.2) | 38 (82.6) | 108 (69.7) |

Abbreviations: IPF, idiopathic pulmonary fibrosis; Q1/Q3, first or third quartiles; UIP, usual interstitial pneumonia.

*a Determined by the χ² test.

*b Determined by analysis of variance.

RESULTS

General Characteristics and Demographics

A total of 263 patients from both institutional sites met inclusion criteria, including 169 cases (64.3%) at Mayo Clinic in Scottsdale, Arizona, and 94 cases (35.7%) at Mayo Clinic in Rochester, Minnesota. General characteristics and patient demographics for each time cohort are summarized in Table 1, and characteristics of the subset of patients 50 years and older are summarized in Table 2. Fewer biopsies were obtained after 2011, with the total number of patients declining after 2011 (86 cases compared with 177 cases before 2011, a reduction of 51.4%), and the number of patients at least 50 years old fell after 2011 (65 cases compared with 150 cases before 2011, a reduction of 56.7%). A significant difference in patient age was observed between the pre-2011 and post-2011 cohorts, with the mean age at the time of diagnosis being 3.3 years younger after 2011 (mean [SD] = 58.9 [14.0] versus 62.2 [12.4] years before 2011, P = .049). Interestingly, a significant increase was observed in the number of available slides per patient after 2011 (10.1 [5.8] versus 8.6 [4.5] before 2011, P = .02), and a similar increase in the number of available slides was also observed in the subset of patients 50 years and older (10.2 [5.9] versus 8.4 [4.4] before 2011, P = .01). No significant differences were observed in the proportion of cases obtained across participating sites, patient gender, or number of lobes sampled before versus after 2011.

Histopathologic Features

Cases were initially subdivided based on the presence or absence of fibrosis, without regard to other histologic
findings. A total of 173 cases showed fibrosis, representing 65.8% of all 263 cases; the remaining cases showed a variety of other findings (e.g., acute lung injury, diffuse alveolar damage, organizing pneumonia, vasculitis, or other inflammatory or infectious processes) but no fibrosis and were excluded from further study. No significant change was observed in the proportion of total cases showing fibrosis or in the proportion of patients 50 years or older showing fibrosis after 2011.

Cases showing fibrosis were then classified by 2018 ATS/ERS/JRS/ALAT consensus criteria and terminology. Representative examples of cases in each diagnostic category are illustrated with UIP shown in Figure 1, probable UIP shown in Figure 2, indeterminate for UIP shown in Figure 3, and alternative diagnosis shown in Figure 4. Distributions of diagnoses by patient age in the pre-2011 and post-2011 cohorts are illustrated in Figure 5. Histologic features prompting a designation as indeterminate for UIP or alternative diagnosis are summarized in Table 3. Common alternative diagnoses included nonspecific interstitial pneumonia, airway-centered fibrosis, and mixed or unclassifiable fibrotic patterns, as well as prominent granulomas, lymphoid hyperplasia, smoking-related pathology, and various patterns of acute lung injury (organizing pneumonia, diffuse alveolar damage, etc). Other features suggesting a non-UIP diagnosis included pleuritis or pleural fibrosis, prominent peribronchiolar metaplasia, diffuse alveolar hemorrhage, follicular bronchiolitis, and features of pneumoconiosis, but most of these latter features were uncommon.

After completion of the blinded slide review, patient age and sex information were accessed and linked with histology data for analysis. To determine whether the frequency of cases with histology favoring a final multidisciplinary diagnosis of IPF had changed after 2011, we combined the UIP and probable UIP cases (the 2 categories most likely to support a final multidisciplinary diagnosis of IPF; hereafter, termed the favor IPF group), and also combined the indeterminate for UIP and alternative diagnosis cases (the 2 categories most likely to suggest a non-IPF multidisciplinary diagnosis; hereafter, termed the favor non-IPF group) and subjected these composite groups to further analysis. A comparison of these 2 composite groups (Table

**Figure 1.** Usual interstitial pneumonia (UIP). Representative photomicrographs of surgical lung biopsies showing definite UIP, as defined by current international consensus criteria, from 2 different patients (A and B, and C and D, respectively). A and C. At scanning magnification, the biopsies show dense, patchy, peripherally accentuated fibrosis, sharply demarcated from adjacent uninvolved parenchyma, with areas of architectural distortion and honeycombing. B and D. Higher magnification shows fibroblast foci at the interface between fibrosis and uninvolved parenchyma, as well as smooth muscle metaplasia in areas of old dense scar. In an appropriate clinical setting, this histology would support a clinical diagnosis of the syndrome idiopathic pulmonary fibrosis (hematoxylin-eosin, original magnifications ×20 [A], ×100 [B and D], and ×12.5 [C]).

Arch Pathol Lab Med

**UIP Disappearing From Current Pathology Practice—Eldersveld et al**

5
4) revealed a significantly higher proportion of men in the favor IPF group and a trend toward older age in the favor IPF group, although the latter did not reach statistical significance. These differences mirror well-known epidemiologic differences between IPF and other fibrosing interstitial pneumonias. Further analysis revealed a significantly lower percentage of cases with favor IPF histology after 2011 (16.7% versus 34.5% before 2011, \( P = 0.02 \)) (composite data in Table 1, and data displayed by age groups in Figure 6). A similar reduction was also observed when only those patients 50 years and older were included (17.4% versus 35.8% before 2011, \( P = .02 \)) (Table 2). No site-specific differences were observed between the 2 composite groups nor were there differences in the number of available slides or the number of sampled lobes between the 2 composite groups overall nor in the subset of patients 50 years and older in these 2 composite groups, despite a general increase in the number of slides after 2011.

**DISCUSSION**

Diagnostic and treatment approaches for IPF have rapidly evolved in the past decade, driven in part by advances in imaging technology and also by data from recent clinical trials and the advent of targeted antifibrotic agents for IPF. This evolution has occurred despite these agents being expensive and having significant side effects and despite only modestly slowing the progression of IPF with no effect on the mortality from this incurable disease. Consensus guidelines for IPF in 2011 caused a paradigm shift in pulmonary medicine for patients with fibrotic interstitial lung disease, with lung biopsies now primarily reserved for those patients with clinically and radiologically indeterminate disease. Consequently, it is not surprising that the frequency of fibrotic patterns encountered in lung biopsies had changed in our practice between the 2 periods of interest, with UIP becoming less frequent after 2011. To our knowledge, this study provides the first direct evidence supporting that notion and data on the magnitude of that shift in at least one surgical pathology practice.

**Figure 2.** Probable usual interstitial pneumonia (UIP). Representative photomicrographs of sections of surgical lung biopsies showing probable UIP as defined by current international consensus criteria. Biopsies from one patient display end-stage fibrosis with honeycombing only (A), including smooth muscle metaplasia surrounding mucus-filled honeycomb cysts (B), but no less-involved or preserved parenchyma is present for evaluation. Biopsies from another patient demonstrate patchy, peripherally accentuated fibrosis sharply demarcated from the spared parenchyma, along with early honeycombing (C), but also conspicuous absence of fibroblast foci (D). In an appropriate clinical setting, this histology would also support a clinical diagnosis of the syndrome idiopathic pulmonary fibrosis, although the biopsies lack at least one required histologic feature of UIP (hematoxylin-eosin, original magnifications \( \times 12.5 \) [A and C], \( \times 100 \) [B], and \( \times 40 \) [D]).
Although older data from the 1990s suggests that UIP was the most common or “usual” fibrotic pattern encountered in surgical lung biopsies from patients with fibrotic interstitial lung disease, this was not our observation in the present study, even in the pre-2011 cohort. This was somewhat unexpected. It is certainly possible that this could reflect a more gradual shift in our institution’s practice that predated 2011 guidelines, with fewer biopsies being obtained from patients with radiologic UIP and suspected IPF even before these guidelines were issued. Indeed, several physicians from our institution had an integral role in the formulation of the 2011 guidelines. Alternatively, this could reflect a shift in pulmonary pathology practice and a more nuanced and detailed approach to evaluating lung fibrosis, driven by changes in treatment paradigms and an increased emphasis on identifying histologic features that argue for or against a clinical diagnosis of IPF, likely driven at least in part by current consensus guidelines. Interestingly, a careful review of the data from the recent COLDICE trial (Cryobiopsy Versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease Alliance; ACTRN 12615000718549, UTN U1111-1171-6880) reveals an intriguing difference in blinded diagnoses made by 3 expert pulmonary pathologists using 2 different methods, including (1) a conventional approach to assign a “specific” histopathologic diagnosis, and (2) an approach using international consensus guidelines. In that trial, simple assignment of a histopathologic diagnosis by conventional criteria resulted in 60% of surgical lung biopsies being classified as UIP consistent with IPF, yet only 27% were designated as UIP and 6% as probable UIP by these same pathologists when current international guideline categories were used, with the remainder falling into indeterminate for UIP or alternative diagnosis categories for unstated reasons but presumably because of other histologic findings seen. This difference has important implications for the clinical diagnosis of IPF and other interstitial lung diseases and highlights the profound impact of the guidelines on pathology practice. Our data mirror the lower

![Figure 3. Fibrosis indeterminate for usual interstitial pneumonia (UIP). Representative photomicrographs of sections of surgical lung biopsies showing fibrosis with histology falling into the indeterminate for UIP category, as defined by current international consensus criteria. Biopsies from one patient show a mixed fibrotic pattern that is challenging to classify, with patchy UIP-like areas of dense fibrosis with microscopic honeycombing (A), merging with nonspecific interstitial pneumonia-like areas of uniform interstitial fibrosis with chronic inflammation and lymphoid aggregates (B). C and D, Biopsies from another patient display patchy interstitial fibrosis at an earlier stage with indeterminate distribution, including both subpleural/paraseptal and centrilobular disease and prominent peribronchiolar metaplasia. Rare fibroblast foci are present, but honeycombing, granulomas, lymphoid hyperplasia, and other features enabling a more refined diagnosis are absent. This histology does not rule out the clinical syndrome idiopathic pulmonary fibrosis but could also represent an alternative etiology (hematoxylin-eosin, original magnification ×20 [A through D]).](image-url)
frequency of UIP seen in the COLDICE study when guideline criteria were used.

We acknowledge that we may have a higher threshold for diagnosing UIP compared with others, which could explain the lower frequency of UIP observed, and the high interobserver variability and only moderate reproducibility of a histologic diagnosis of UIP are well recognized. Even if it is the case that our threshold for diagnosing UIP is higher than that of others, it would fail to explain the differences observed between the 2 time periods in our study because all cases were rereviewed in a blinded fashion and subjected to the same diagnostic criteria. Regardless of the reasons for differences from other published data, our study suggests that a true shift has occurred in the frequency of fibrotic patterns encountered at the microscope since 2011 in our practice, even after accounting for a lower-than-expected frequency of UIP observed before 2011. Whether this trend has also occurred at other institutions or different practice settings remains unknown and warrants further study.

Interestingly, we also observed an increase in the mean number of slides per case since 2011. The reasons for that increase remain unknown but may reflect changes in surgical sampling, surgeon awareness of guidelines, communication between the surgeon and pulmonologist, pathology sampling, increased diagnostic uncertainty, increased expectations for more-precise classifications, and/or other factors. However, it is also notable that no difference in the mean number of slides was observed between cases classified as either UIP or probable UIP (histology favoring IPF), and cases classified as indeterminate for UIP or alternative diagnosis (histology favoring a non-IPF diagnosis), suggesting that assignment of a diagnostic category favoring or opposing an IPF diagnosis was not influenced by the number of tissue blocks submitted for evaluation.

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guidelines, an ongoing challenge in the field remains the lack of specific guidance for how much or how many features must be encountered to warrant an *indeterminate for UIP* or *alternative diagnosis* designation. For example, should one rare granuloma in 10 slides with otherwise classic and straightforward features of UIP dissuade the pathologist from assigning a diagnosis of UIP when IPF is clinically suspected? How many giant cells should one allow in cases of suspected IPF? When granulomas become numerous, their potential diagnostic significance becomes greater, but interpretation of their ultimate significance is subjective and also depends on their morphologic features, distribution, and the larger histologic context. No single feature can be interpreted in a vacuum without taking other features into consideration, but consensus criteria offer little guidance on the more nuanced and integrated histologic assessment that is inherent to the diagnostic process. Current guidelines simply state that *indeterminate for UIP*

**Figure 5.** Frequency of histologic categories of lung fibrosis before and after 2011. Comparison of the frequency of histologic categories of fibrosis observed in surgical lung biopsies obtained from patients before and after 2011 and the relationship of those categories with patient age. Fewer biopsies were obtained from patients after 2011, particularly from older adults, the age when histologic usual interstitial pneumonia (UIP) and the clinical syndrome idiopathic pulmonary fibrosis are most likely to occur. A marked reduction in absolute numbers of cases showing either UIP or probable UIP by current international consensus criteria was also observed after 2011, particularly among older adults.

| Features                                      | Pre-2011, No. (%) | Post-2011, No. (%) |
|-----------------------------------------------|------------------|-------------------|
| Other fibrotic patterns                       |                  |                   |
| NSIP                                          | 20 (26)          | 16 (36)           |
| Airway-centered fibrosis                      | 13 (17)          | 6 (13)            |
| Mixed or unclassifiable fibrosis              | 10 (13)          | 12 (27)           |
| Granulomas                                    |                  |                   |
| Poorly formed, non-necrotizing                | 13 (17)          | 9 (20)            |
| Well-formed, non-necrotizing (sarcoid-like)   | 2 (3)            | 4 (9)             |
| Necrotizing                                   | 2 (3)            | 0 (0)             |
| Organizing pneumoniaa                         | 10 (13)          | 12 (27)           |
| Smoking-related interstitial lung diseaseb    | 12 (15)          | 5 (11)            |
| Lymphoid hyperplasia or prominent chronic inflammation | 12 (15) | 7 (16) |
| Acute fibrinous lung injury or diffuse alveolar damagec | 10 (13) | 7 (16) |
| Pleural disease (pleuritis and/or pleural fibrosis) | 10 (13) | 6 (13) |
| Peribronchiolar metaplasiaa                    | 7 (9)            | 8 (18)            |
| Diffuse alveolar hemorrhage                   | 3 (4)            | 0 (0)             |
| Follicular bronchiolitis                     | 1 (1)            | 3 (7)             |
| Silicosis                                     | 1 (1)            | 0 (0)             |

Abbreviation: NSIP, nonspecific interstitial pneumonia

*a* Organizing pneumonia, acute fibrinous lung injury, diffuse alveolar damage, and peribronchiolar metaplasia noted only when prominent; for specific criteria, see Materials and Methods.

*b* Smoking-related interstitial lung disease includes cases with various combinations of desquamative interstitial pneumonia, respiratory bronchiolitis, emphysema or airway enlargement with smoking-related interstitial fibrosis, and/or pulmonary Langerhans cell histiocytosis, but no features of concomitant usual interstitial pneumonia or other fibrotic patterns suggesting the presence of an additional disorder not directly related to smoking.
alternative diagnosis designations should be used when there are ‘‘features favoring either a pattern other than UIP or features favoring UIP secondary to another cause’’ or when there are ‘‘features suggesting an alternative diagnosis,’’ respectively, but these ambiguous statements may be challenging to apply in practice. That ambiguity has only modestly improved with the updated 2018 guidelines, and there continues to be strong emphasis on multidisciplinary discussion as the gold standard for diagnosis of fibrotic lung diseases, despite the imperfect nature of multidisciplinary discussion as a diagnostic standard, but investigative efforts to discover better biomarkers tied to disease etiology, biology, and/or treatment responses could offer hope for improving the multidisciplinary assessment of patients with interstitial lung disease.16

Study Limitations

This study has several limitations, in addition to those already discussed. First, these cases represent the experience of a single institution only, albeit at 2 widely separated geographic sites. These sites have different clinicians and serve patient populations that are demographically quite different. Even so, our findings may not be generalizable to all practice settings because the case mix encountered by surgical pathologists is dependent upon the prevalence of UIP in the patient population served and subjected to biopsy.
and also by the preferences of local clinicians and surgeons and geographic differences in clinical practice. Second, this study only included surgical lung biopsies, and the potential effect of adoption of the transbronchial cryobiopsy as an alternative to the surgical lung biopsy was not assessed in this study. It is possible that the increasing use of the transbronchial cryobiopsy in our practice may explain the reduction in surgical lung biopsies from older patients and the shift in histologic patterns encountered after 2011, at least in part, although that technique was not adopted in our practice until 2013. Third, the pathologic review of the study cases was performed in a fashion blinded to all clinical information, which does not fully reflect best practice in surgical pathology, wherein clinical history, imaging, and serological and other findings are considered by the pathologist in the context of multidisciplinary discussions.20

The final multidisciplinary diagnoses in the study cases remain unknown. Admittedly, our blinded approach is somewhat artificial in that sense, but it offers the benefit of an unbiased assessment and strict application of 2018 consensus criteria to the extent possible, without being influenced by clinical information or multidisciplinary input. Despite that important limitation, it could also be argued that this approach mirrors less-ideal practice settings, at least in part, in which pathologists must evaluate lung biopsies with limited or no clinical information, which is an unfortunate practical reality in some settings (eg, large reference laboratories or consultation practices). Fourth, it is widely recognized that the histologic diagnosis of UIP and other fibrotic patterns is problematic with high interobserver variability and only moderate reproducibility,22–24 and only 2 pathologists reviewed these study cases. Consequently, future studies will be required to validate these observations, using more pathologists and/or more cases.

CONCLUSIONS

The frequency of fibrotic patterns of interstitial lung disease encountered by surgical pathologists may have shifted in recent years, after adoption of 2011 IPF guidelines, with fewer biopsies showing UIP in our contemporary practice and a concomitant rise in other fibrotic patterns. This shift may, at least in part, be a result of guidelines that strongly recommend avoiding lung biopsies in patients with clinical suspicion for IPF who have UIP by imaging.7,12,13 This shift may be further driven by increased recognition of risks of surgical lung biopsies and a trend toward avoiding surgical lung biopsies from older adults in the current era, the group of patients in whom IPF is most likely to occur and in whom UIP is most likely to be encountered. Regardless of the underlying factor(s) driving this change, our data suggest that the pretest probability of encountering histology in a surgical lung biopsy suggesting a non-UIP diagnosis is now high, even in elderly patients, and it would behove pathologists to be familiar with histologic features suggesting alternative etiologies. Nevertheless, our data also indicate that histologic UIP is still encountered in some cases, even in the current era and despite advances in imaging technology, and the pathologist should not hesitate to diagnose UIP when diagnostic features thereof are encountered.

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