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Transbronchial Biopsy in Usual Interstitial Pneumonia*

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Abstract

Background—Usual interstitial pneumonia (UIP) is a slowly progressive, usually fatal form of idiopathic interstitial pneumonia for which there is no effective treatment. Transbronchial biopsy (TBB) has been utilized only to exclude other diseases such as sarcoidosis, lymphangitic carcinoma, and infection, for example, but TBB is generally considered to have little role in confirming UIP.

Objective—To determine whether diagnostic changes of UIP can be appreciated on TBB specimens.

Design—Retrospective analysis of TBB specimens from patients with proven UIP.

Setting—Two study sites in the United States.

Participants—Twenty-one patients with UIP confirmed by surgical lung biopsy and/or lung explant, and 1 patient with UIP confirmed by clinical and radiographic findings along with follow-up information.

Measurements and results—Adequate tissue for diagnosis was available in 18 cases; in 7 cases (32% overall), there were varying combinations of interstitial fibrosis in a patchwork pattern along with fibroblast foci and/or honeycomb change. These features were considered diagnostic of UIP. Interstitial fibrosis along with fibroblast foci or honeycomb change were seen in two other cases, but the fibrosis lacked a patchwork pattern, and these features were considered consistent with UIP. Nonspecific interstitial fibrosis alone was found in nine cases.

Conclusions—In summary, characteristic histologic features of UIP can be identified on TBB specimens more often than previously appreciated. TBB may be more useful in confirming UIP than previously recognized.

Keywords

diagnosis; interstitial lung disease; pulmonary fibrosis; transbronchial biopsy; usual interstitial pneumonia

Usual interstitial pneumonia (UIP), the most common idiopathic interstitial pneumonia, is a slowly progressive, usually fatal disease that shows little, if any, response to therapy.^{1–3} It is important to separate UIP from other histologic subsets of idiopathic interstitial pneumonia and from other interstitial lung diseases that have a more favorable response to therapy and better prognosis.¹ Traditionally, surgical lung biopsy (SLB), either open thoracotomy or, more

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recently, video-assisted thoracoscopy, has been advocated for diagnosis in patients with atypical high-resolution CT (HRCT) findings, although it is not without significant morbidity and mortality in these patients.^{4,5} For example, in one study,⁴ the 30-day mortality following SLB was 17%. Transbronchial biopsy (TBB) has been utilized only to exclude other diseases such as sarcoidosis, lymphangitic carcinoma, and infection, for example, but TBB is generally considered to have little role in confirming UIP.¹ We undertook this study to examine whether diagnostic features of UIP could be found in TBB samples, and whether this procedure might yield sufficient information to support a diagnosis of UIP.

Materials and methods

Written informed consent was obtained from each patient or guardian. The protocol was approved by the local Institutional Review Board or Ethics Committee at each institution, and was in accordance with the recommendations found in the Helsinki Declaration of 1975.

Twenty-two patients with UIP who underwent TBB were identified. In 21 patients, the diagnosis was confirmed by SLB and/or explant specimens (19 by SLB, 2 by explant specimens). The histologic diagnosis of UIP was based on accepted criteria, including patchy interstitial fibrosis alternating with normal lung, fibroblast foci, and honeycomb areas.^{3,6} In one case with typical clinical and radiologic findings (subpleural honeycombing on HRCT),^{7,8} additional tissue specimens were considered unnecessary.

Sixteen patients were identified in the files of the Lung Transplant Service of the University of Pennsylvania School of Medicine between May 1993 and September 2000. Open-lung biopsy was undertaken in 14 patients, while 2 patients underwent explant at the time of lung transplantation. All patients were evaluated at the University of Pennsylvania for lung transplantation, but the diagnostic SLBs were performed at outlying hospitals.

Six patients were identified in the files of the Pathology Department at Upstate Medical University, Syracuse, between January 1990 and May 2003. Five patients underwent subsequent SLB; in one patient, TBB findings along with clinical and radiographic findings were considered diagnostic.

From one to six (mean, 2.5) hematoxylin-eosin–stained slides were available in each case. In three cases, there was also one Trichrome-stained slide. The number of pieces of alveolated lung parenchyma and bronchial wall were recorded, and the following pathologic features were evaluated: interstitial fibrosis, a patchwork pattern to the fibrosis characterized by juxtaposition of interstitial fibrosis and normal lung without transition zones, fibroblast foci, and honeycomb change. The findings were considered diagnostic of UIP if there was patchwork interstitial fibrosis along with fibroblast foci or honeycomb change, or both; findings were consistent with UIP if there was interstitial fibrosis lacking a patchwork pattern with either fibroblast foci or honeycomb change; findings were nonspecific if there was only interstitial fibrosis; and findings were insufficient if only bronchial wall was present.

Results

Clinical Features

There were 9 men and 13 women (age range, 31 to 83 years; mean, 51 years). All patients had dyspnea at presentation, and it had been present from 1 to 60 months (mean, 16 months) in 19 patients in whom this information was known. One patient (case 9) was discovered incidentally during a testicular cancer workup to have interstitial lung infiltrates on chest radiographs, and then retrospectively noted that shortness of breath had been present for 6 months. Two patients (cases 11 and 20) had a family history of pulmonary fibrosis. Radiographic studies in all

patients showed bilateral interstitial infiltrates, and HRCT results in four of five patients were typical of UIP. Pulmonary function studies showed a restrictive pattern. Prednisone therapy was initiated in 19 patients without improvement. SLB was undertaken in 19 patients from 2 weeks to 17 months (mean, 4 months) following TBB, while 2 patients underwent lung transplantation 3 years after TBB with no SLB. Five patients eventually underwent lung transplantation after an interval of 2 to 5 years (mean, 3.2 years).

Additional biopsy specimens were not obtained after TBB in one patient in whom the clinical and radiographic findings were considered typical of UIP. This patient (case 22) had a 1-year history of worsening dyspnea and pulmonary function test results along with HRCT showing extensive interstitial scarring and peripheral honeycomb change.

Pathologic Findings

Two pathologists (E.A.B., A.L.K.) reviewed the TBB specimens jointly. The pathologic findings (TBB) are summarized in Table 1. Eighteen specimens were considered adequate, containing at least one fragment of alveolated lung parenchyma (mean, 2.5; range, 1 to 5), while 4 specimens contained only bronchial wall and were considered insufficient for diagnosis.

Specimens in seven cases contained features considered diagnostic of UIP. In one patient (case 2), there was a combination of focal interstitial fibrosis with a patchwork pattern, fibroblast foci, and areas of honeycomb change, a combination of features that would be diagnostic even without clinical information (Fig 1). The patchwork pattern was characterized by the juxtaposition of foci of collagen-type interstitial fibrosis next to relatively normal lung with no intervening transition zones (Fig 1, *left, A*). The honeycomb change was characterized by enlarged, restructured air spaces surrounded by fibrosis (Fig 1, *center, B*). The enlarged airspaces were lined by cuboidal epithelium and filled with mucus containing inflammatory cells and macrophages. Fibroblast foci appeared as small aggregates of spindle-shaped cells embedded in a lightly stained, myxoid stroma (Fig 1, *right, C*). Six other cases showed features considered diagnostic of UIP in the setting of a patient with chronic interstitial lung disease. The typical patchwork pattern of interstitial fibrosis with alternating areas of interstitial fibrosis and normal alveolar septa was present in all (Fig 2, *left, A*). Fibroblast foci were additionally found in five cases (Fig 2, *right, B*), while areas of honeycomb change were present in one case (Fig 3). In two patients (cases 16 and 22), the fibroblast foci were especially numerous and easily identified at low magnification (Fig 4), while in other cases the fibroblast foci were present in atelectatic, fibrotic lung parenchyma, making their recognition difficult at low magnification. However, the lightly stained nature of the myxoid matrix containing the spindle-shaped myofibroblasts contrasted with the surrounding collagen fibrosis and helped in their identification.

Two cases were considered consistent with UIP. They showed a combination of collagen-type fibrosis with either fibroblast foci or honeycomb change, but they lacked the characteristic patchwork pattern to the fibrosis.

Nine patients had only interstitial fibrosis and mild chronic inflammation. Although a patchwork pattern to the fibrosis was noted in two cases, fibroblast foci and honeycomb change were not identified. These findings were considered nonspecific.

The number of alveolated lung fragments sampled was slightly greater in the nine diagnostic and consistent cases (mean, 3.1; range, 2 to 5) than in the nine nonspecific cases (mean, 2.1; range 1 to 4), although this difference was not significant. Similarly, the difference was not significant when comparing patients with diagnostic biopsy findings (mean, 3.3; range, 2 to 5) to those with either consistent with (mean, 2.5; range, 2 to 3) or nonspecific findings (mean,

2.1; range, 1 to 4). Diagnostic changes were noted with as few as two lung fragments, although one case with four fragments showed only nonspecific changes.

Discussion

Our findings suggest that TBB may be more useful than previously recognized in confirming UIP. The fact that 7 of our 22 cases showed changes considered diagnostic of UIP and an additional 2 cases were considered consistent with UIP indicates that significant changes can be recognized even in these small samples. It should be remembered, however, that all patients had clinical and radiographic features compatible with UIP, including chronic dyspnea, restrictive pulmonary function, interstitial infiltrates on chest radiographs, and subpleural honeycombing on HRCT. Because of the small size of TBB specimen, the pathologic findings on TBB must be correlated with the clinical and radiographic findings before making a diagnosis in cases of chronic interstitial lung disease. If the clinical and or radiographic features do not fit, consideration should be given to a larger biopsy specimen.

Because UIP is characterized by chronic inflammation and fibrosis and these features are common nonspecific findings in peribronchial parenchyma, it has generally been assumed that TBB cannot be utilized in diagnosing UIP.¹ Our study, however, shows that certain characteristic features of UIP, including patchwork pattern of involvement by fibrosis and temporal variability with fibroblast foci, collagen, and honeycomb change, previously thought to be recognizable only on SLB specimens, can sometimes be seen on TBB specimens. The patchwork pattern is characterized by areas of interstitial fibrosis juxtaposed to areas of relatively normal lung. Its presence helps to distinguish the changes from nonspecific peribronchial fibrosis in which there is a gradual transition from abnormal to normal. Likewise, evidence of temporal heterogeneity characterized by a mixture of fibroblast foci and inactive-appearing collagen fibrosis would be an unusual nonspecific finding in peribronchial parenchyma. Fibroblast foci appear as small aggregates of spindle-shaped cells within a myxoid matrix. They are localized in the interstitium beneath the alveolar epithelium, and the long axis of the component spindle-shaped cells runs parallel to the alveolar lining. Although fibroblast foci are not specific for UIP, their presence in the right clinical and pathological setting supports the diagnosis.

Honeycomb change is recognized by enlarged, sometimes irregularly shaped airspaces that often contain inspissated mucin, macrophages, and other inflammatory cells. The airspaces are usually lined by bronchiolar type epithelium but may sometimes be lined by low cuboidal or flattened alveolar epithelium. When lined by bronchial epithelium, the spaces are distinguished from bronchioles by the absence of smooth-muscle bundles in their walls. Sometimes, the epithelial lining is absent and pools of inspissated mucus within fibrotic parenchyma comprise the main finding.

The small size of the specimens obtained by TBB has been considered to be a major impediment to the successful use of TBB for diagnosing interstitial lung disease.¹ Not surprisingly, diagnostic biopsies in our study tended to contain more alveolated lung fragments than biopsies showing only nonspecific findings, although the difference was not important. Diagnostic changes of UIP, however, were found in cases with as few as two pieces of alveolated parenchyma and, conversely, one case with four pieces showed only nonspecific changes. Clearly, the bronchoscopist should take as many pieces as safely possible, although the diagnosis is sometimes possible with minimal tissue.

A common problem encountered in interpreting TBB specimens is the frequent presence of artifactual atelectasis that may both obscure diagnostic features and also be interpreted incorrectly as interstitial fibrosis.² Since alveolar epithelial hyperplasia accompanies most

forms of interstitial lung disease, identification of these cells in difficult cases helps confirm interstitial fibrosis rather than atelectasis. The presence of atelectasis can also cause difficulty in distinguishing fibroblast foci from intraluminal fibroblast plugs of bronchiolitis obliterans-organizing pneumonia (BOOP). The fibroblast plugs of BOOP are usually larger than fibroblast foci and often have elongated or branching shapes. The presence of smooth-muscle bundles in the surrounding interstitium indicating the wall of an alveolar duct or respiratory bronchiole is also helpful in indicating BOOP rather than fibroblast foci. In difficult cases, the finding elsewhere of interstitial collagen-type fibrosis and/or honeycomb change favors UIP and thus fibroblast foci, since BOOP is usually unassociated with chronic lung scarring. The radiographic findings can also be extremely helpful in difficult cases.

Recently, HRCT has been shown to be diagnostic of UIP in approximately one half of cases, and biopsy specimens therefore may not always be necessary.^{7,8} HRCT is most valuable in academic settings, however, and SLB is still widely utilized in community hospitals. Since many patients are elderly and severely ill, it is important for the pathologist to carefully examine TBB specimens to identify features supportive of UIP that can potentially obviate a subsequent more invasive procedure since SLB is not without adverse effects in these patients.

Our study is limited in that we approached the cases with the clear understanding that a diagnosis of UIP was ensured. Whether the histologic criteria proposed can successfully separate patients with UIP from those with other forms of diffuse lung disease when applied in a “blinded” and prospective fashion is beyond the scope of the current study. We demonstrate the potential sensitivity of this diagnostic technique in patients proven to have idiopathic pulmonary fibrosis, but the study design precludes speculation regarding specificity of the proposed histologic criteria in a more heterogeneous group of patients with other forms of diffuse lung disease.

Summary

Characteristic histologic features of UIP can be identified on TBB specimens more often than previously appreciated. Interstitial fibrosis with a patchwork pattern along with fibroblast foci and/or honeycomb change on TBB further support the diagnosis of UIP in the appropriate clinical and radiographic setting.

Acknowledgements

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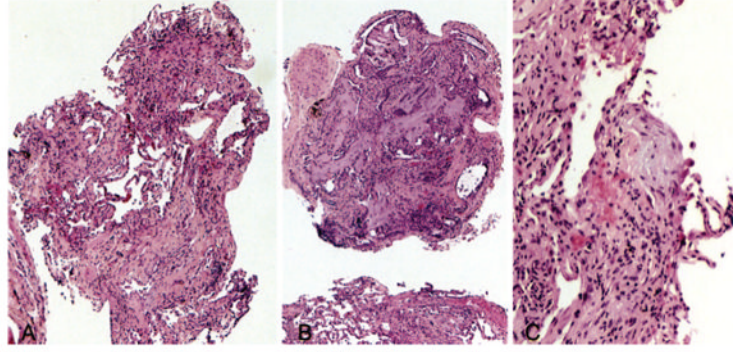
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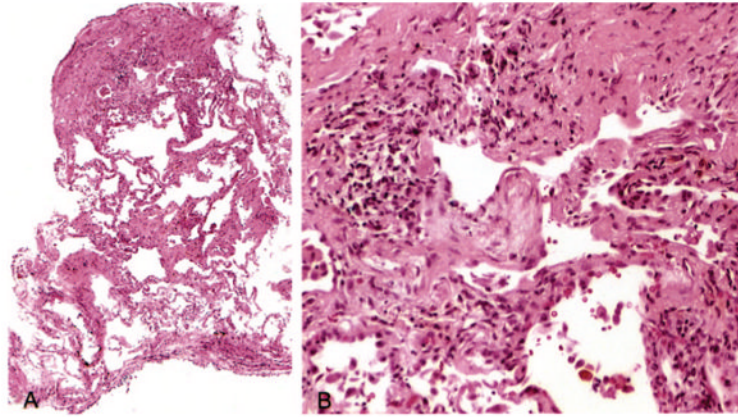
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Abbreviations

BOOP	bronchiolitis obliterans organizing pneumonia
HRCT	high-resolution CT
SLB	surgical lung biopsy
TBB	transbronchial lung biopsy
UIP	usual interstitial pneumonia

**FIGURE 1.**

Case 2. *Left, A:* Low-magnification photomicrograph showing the characteristic patchwork pattern of fibrosis in UIP. Note the relatively normal lung in the center adjacent to marked interstitial fibrosis in surrounding parenchyma (hematoxylin-eosin, original $\times 10$). *Center, B:* Low-magnification view showing honeycomb change in another fragment characterized by enlarged, irregular air spaces filled with mucin (hematoxylin-eosin, original $\times 10$). *Right, C:* Higher-magnification view showing a fibroblast focus. Note the interstitial location of spindle-shaped cells embedded in a myxoid background. The surrounding lung parenchyma shows collagen-type fibrosis and mild chronic inflammation (hematoxylin-eosin, original $\times 20$).

**FIGURE 2.**

Case 22. *Left, A:* Low-magnification photomicrograph showing variegated fibrosis (hematoxylin-eosin, original $\times 10$). Note the patchwork pattern of involvement with areas of interstitial fibrosis alternating with normal lung. *Right, B:* Higher-magnification view of a fibroblast focus present in the central upper portion on *left, A*, showing interstitial location and characteristic lightly stained myxoid stroma containing spindle-shaped cells (hematoxylin-eosin, original $\times 20$).

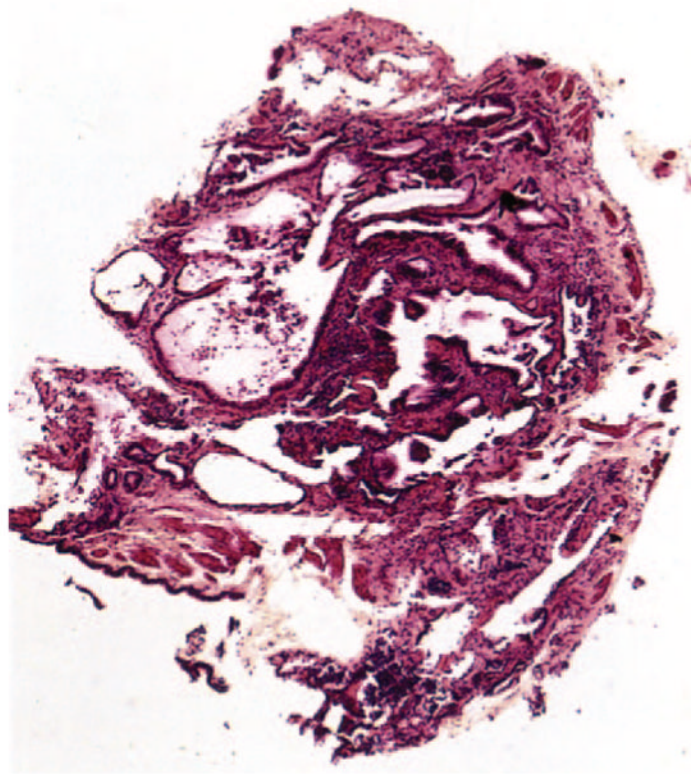


FIGURE 3. Case 14. Low-magnification photomicrograph of honeycomb change. The airspaces are enlarged, deformed, irregularly shaped, and lined by bronchial type epithelium (hematoxylin-eosin, original $\times 10$).

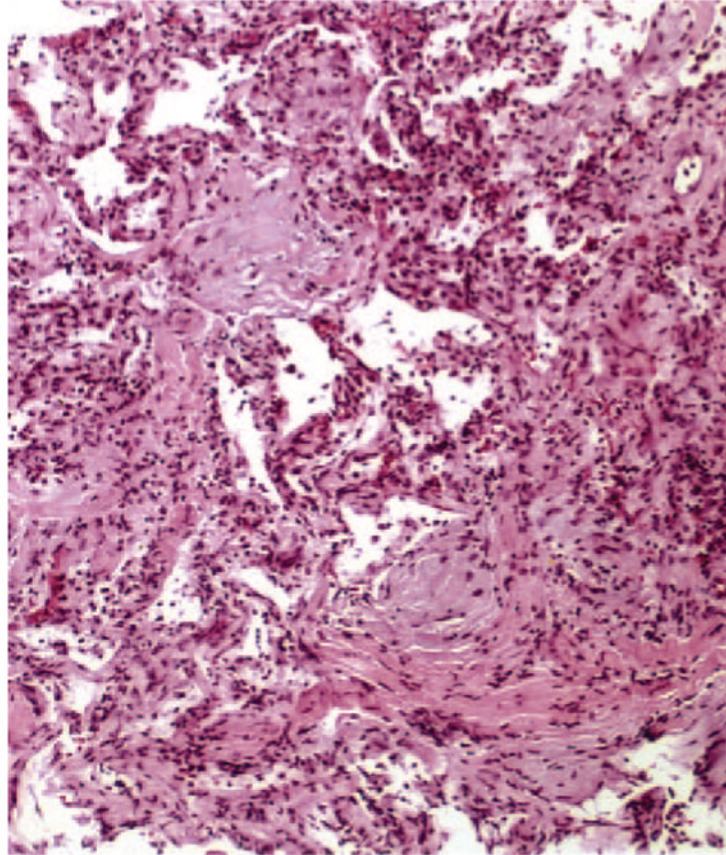


FIGURE 4.
Case 16. Prominent fibroblast foci in a background of interstitial collagen-type fibrosis. Fibroblast foci are recognized by their myxoid appearance, with spindle-shaped cells arranged parallel to the alveolar lining (hematoxylin-eosin, original $\times 10$).

Table 1

Pathologic Findings on TBB in UIP Patients

Case No.	Site of TBB	No. of Pieces of Alveolated Parenchyma	No. of Pieces of Bronchial Wall	Pathologic Findings	Pathologic Diagnosis
2	RLL	5	1	Patchwork fibrosis, ff, HCC	UIP
3	na	3	1	Patchwork fibrosis, ff	UIP
4	RLL	3	1	Patchwork fibrosis, ff	UIP
10	RLL and RUL	3	3	Patchwork fibrosis, HCC	UIP
16	na	2	4	Patchwork fibrosis, ff	UIP
17	LUL	5	1	Patchwork fibrosis, ff	UIP
22	na	2	2	Patchwork fibrosis, ff	UIP
13	RUL	3	0	Fibrosis, ff	Consistent with UIP
14	RLL	2	1	Fibrosis, HCC	Consistent with UIP
1	RLL	1	0	Fibrosis	Nonspecific
5	LRL	2	1	Patchwork fibrosis	Nonspecific
7	LRL	2	6	Fibrosis	Nonspecific
9	RLL	2	0	Fibrosis	Nonspecific
11	na	2	0	Fibrosis	Nonspecific
12	RUL	1	2	Patchwork fibrosis	Nonspecific
15	na	2	0	Fibrosis	Nonspecific
18	LRL	4	2	Patchwork fibrosis	Nonspecific
19	Left lung	3	0	Fibrosis	Nonspecific
6	RML	0	4	Only bronchial wall	Insufficient
8	RLL	0	5	Only bronchial wall	Insufficient
20	na	0	5	Only bronchial wall	Insufficient
21	RLL	0	3	Only bronchial wall	Insufficient

* ff = fibroblast foci; HCC = honeycomb change; RLL = right lower lobe; RUL = right upper lobe; RML = right middle lobe; LUL = left upper lobe; LLL = left lower lobe; na = not available.