Fibroblastic Foci in Usual Interstitial Pneumonia

Idiopathic versus Collagen Vascular Disease

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A histologic feature of usual interstitial pneumonia is the presence of fibroblastic foci. As some patients with usual interstitial pneumonia and an underlying collagen vascular disease have a better prognosis, we hypothesized that they would have fewer fibroblastic foci. Pathologists reviewed surgical lung biopsies from 108 patients with usual interstitial pneumonia (nine with collagen vascular disease) and assigned a score (absent 0, mild 1, moderate 2, and marked 3) for fibroblastic foci. Patients with idiopathic usual interstitial pneumonia had a higher median profusion of fibroblastic foci (1.75 vs. 1.0, p = 0.003). Baseline characteristics were similar, although patients with a collagen vascular disease were younger, had a shorter duration of symptoms, and had a higher percentage of predicted total lung capacity. Profusion of fibroblastic foci was the most discriminative feature for separating idiopathic from collagen vascular disease–associated usual interstitial pneumonia (odds ratio 8.31; 95% confidence interval, 1.98, 59.42; p = 0.002 for a one-unit increase in fibroblastic foci score). No deaths were noted in the collagen vascular disease–associated usual interstitial pneumonia group; 52 deaths occurred in the idiopathic usual interstitial pneumonia group (log rank; p = 0.005). We conclude that patients with collagen vascular disease–associated usual interstitial pneumonia have fewer fibroblastic foci and improved survival.

Keywords: idiopathic pulmonary fibrosis; usual interstitial pneumonia; nonspecific interstitial pneumonia; fibroblastic focus

Patients with pulmonary fibrosis associated with a collagen vascular disease (CVD) have an improved prognosis compared with patients with idiopathic pulmonary fibrosis (IPF) (1, 2). Recently, an American Thoracic Society statement concluded that IPF should reflect only the histologic picture of usual interstitial pneumonia (UIP) and exclude patients with associated CVD, thus making IPF a more homogeneous group with a worse prognosis than previously described (3, 4). Histologic patterns other than UIP have been noted with greater frequency in CVD-associated interstitial lung disease (5–10). As such, the improved prognosis for patients with CVD-associated interstitial lung disease has been felt, potentially, to relate to an increased frequency of alternative histologic categories.

Recent studies have emphasized the importance of the fibroblastic focus, a manifestation of ongoing lung injury in patients with established fibrosis (EF) (11–20). Some investigators have noted a prognostic value of quantifying fibroblastic foci (FF) in patients with idiopathic interstitial pneumonia (19, 20). Furthermore, several groups have suggested differences in the alveolar microenvironment and fibroblast phenotype between patients with idiopathic and collagen-vascular associated pulmonary fibrosis (21–24). We hypothesized that patients with CVD-associated UIP would have an improved survival compared with patients with idiopathic UIP and that this improved survival would correlate with the profusion of FF.

METHODS

Patient Recruitment and Therapy

This study used information from the University of Michigan Specialized Center of Research in the Pathobiology of Fibrotic Lung Disease database. Patients were referred for enrollment in study protocols for suspected IPF and underwent surgical lung biopsy between October 1989 and February 2000. In these patients, a suspicion of IPF was based on symptoms, physiologic abnormalities, and radiographic findings (3). Patients were excluded if they were found to have a disease other than IPF during the enrollment evaluation. Diseases that were exclusionary included pneumoconiosis, sarcoidosis, carcinoma, lymphoma, Langerhan's cell histiocytosis, and lymphangioleiomyomatosis. The study was approved by the institutional review board at the University of Michigan.

Pathologic Assessment

Two pathologists (T.V.C. and W.D.T.) reviewed surgical lung biopsy slides during three review sessions between March 1999 and February 2000. The pathologists assigned a diagnosis of UIP, nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis interstitial lung disease/desquamative interstitial pneumonia, or other (4, 11, 25). Only patients with UIP were included in this study. The profusion of FF for each lobe was scored semiquantitatively as 0–3 (absent 0, mild 1, moderate 2, and marked 3) by each pathologist (Figures 1A–1C). A mean FF score for each patient was calculated by averaging the FF score from each lobe. A maximal FF score was recorded as the highest FF score for any lobe. The mean FF score for patients with idiopathic discordant UIP versus idiopathic concordant UIP (26) was compared. Few patients with CVD had a biopsy in multiple lobes, which precluded the evaluation of histologic variability in this group of patients. Pathologic scores were also evaluated (T.V.C.) using other published scoring systems for FF (20, 27), interstitial mononuclear cell infiltrate (MC), EF, and intra-alveolar macrophages (20).

Physiologic Assessment

Physiologic assessment was performed before surgical lung biopsy and before the initiation of therapy. Pulmonary function tests, including spirometry, lung volumes, and diffusion capacity for carbon monoxide, were performed (28).

High-Resolution Computed Tomography Protocol

High-resolution computed tomography (HRCT) examinations were performed with 1.0- or 1.5-mm thick sections taken at 1-cm intervals throughout the entire lungs during inspiration in the supine position and through the caudal 10 cm of the lungs at 2- to 3-cm increments in the prone position. Two thoracic radiologists (E.A.K. and B.H.G.)

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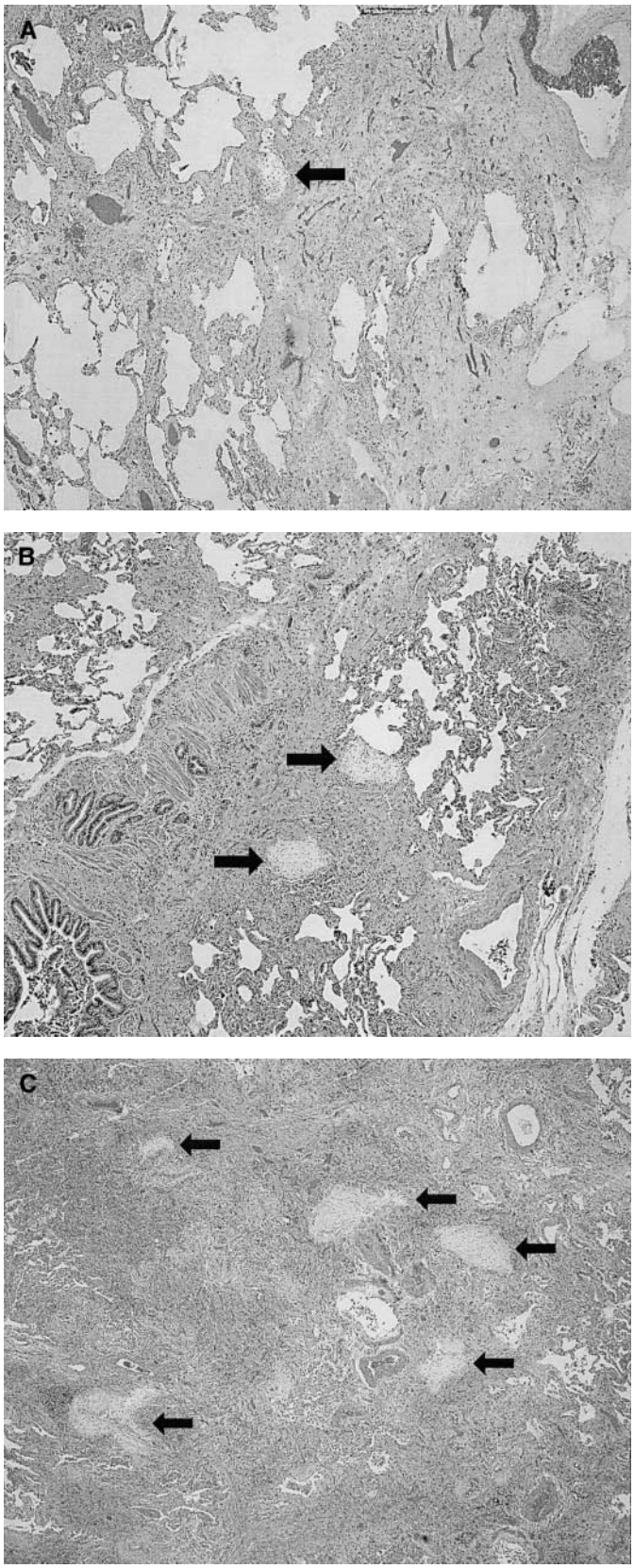

Figure 1. (*A–C*) Representative photomicrographs from histopathologic sections of surgical lung biopsy specimens from patients with a FF score of 1 (mild, *A*), 2 (moderate, *B*), and 3 (marked, *C*).

prospectively and independently scored all lobes on HRCT for ground glass opacity (CT-alv) and interstitial opacity (CT-fib) on a scale of 0–5 as described previously (28, 29). The radiologists were also asked to give an HRCT diagnosis of UIP, indeterminate (equal probability of UIP and NSIP), or NSIP (30). The radiologists were unaware of the histologic diagnosis at the time of interpretation.

Statistical Analysis

Categorical data were compared between patients with idiopathic UIP and CVD-associated UIP using Fisher's exact tests (31), and continuous data were compared using Wilcoxon rank-sum tests (32). Nonparametric tests were used because of the small number of patients in the CVD-associated UIP group. Because the Wilcoxon rank-sum test is designed to detect median differences, continuous baseline characteristics are summarized using median values with ranges. The overall survival experience for each group of patients was estimated using Kaplan–Meier curves (33). The lack of deaths in the CVD-associated UIP group precluded the use of Cox regression analysis to evaluate the potential impact of baseline factors on survival in this group (34). To evaluate whether baseline differences between patients with idiopathic UIP and CVD-associated UIP accounted for differences in survival, stratified log-rank analyses were performed across variables that were different at baseline. Tertiles were used to stratify on age and percentage predicted total lung capacity (TLC); the median time before biopsy was used as a cutoff for the strata of onset of symptoms. Stuart's Tau-c statistics were used to compare the different scoring systems of FF. In addition, logistic regression was used to examine relationships between the presence/absence of CVD and other variables (35).

RESULTS

Patient Population

During the study period, 99 patients with idiopathic UIP and 9 with CVD-associated UIP were identified. Five additional patients with histologic NSIP in combination with CVD that are not included in this research were evaluated during the same time period. The associated diagnoses in the CVD-associated UIP patients were rheumatoid arthritis (n = 4), polymyositis (n = 2), mixed connective tissue disease (n = 1), systemic lupus erythematosis (n = 1), and systemic sclerosis (n = 1).

Baseline Characteristics

Patients with idiopathic UIP had a higher profusion of FF compared with patients with UIP associated with CVD (Figure 2 and Table 1) when either the mean FF profusion ($p = 0.003$) or maximal FF profusion was examined ($p = 0.0004$). The level of agreement for FF scores between pathologists was excellent, with κ statistics ranging from 0.81–1.0 within each lobe. Baseline demographic, physiologic, and HRCT characteristics were similar, although patients with CVD-associated UIP were younger, had a shorter duration of symptoms, and had a higher percentage of predicted TLC (Table 1). In patients with CVD-associated UIP, the HRCT diagnosis was compatible with NSIP in 67% of the patients compared with UIP in 33%. There were no other unique/discriminatory findings noted on the HRCT scans from the patients with CVD-associated UIP. Patients with idiopathic discordant UIP had a lower median profusion of FF compared with patients with idiopathic concordant UIP (1.3 [0.3, 2.5] versus 2 [0.5, 3.0], $p = 0.0005$, Wilcoxon rank sum test). A lack of multiple lobe biopsies for patients with CVD-associated UIP precluded a similar analysis in these patients.

Associations Between Scoring Systems

Associations between the three pathologic scoring systems for FF were positive for each two-way comparison. A positive relationship was found in the comparison of the Brompton FF method (20) and our method (0.56, 95% confidence interval [CI], 0.46–0.67), the Denver FF method (27) and our method

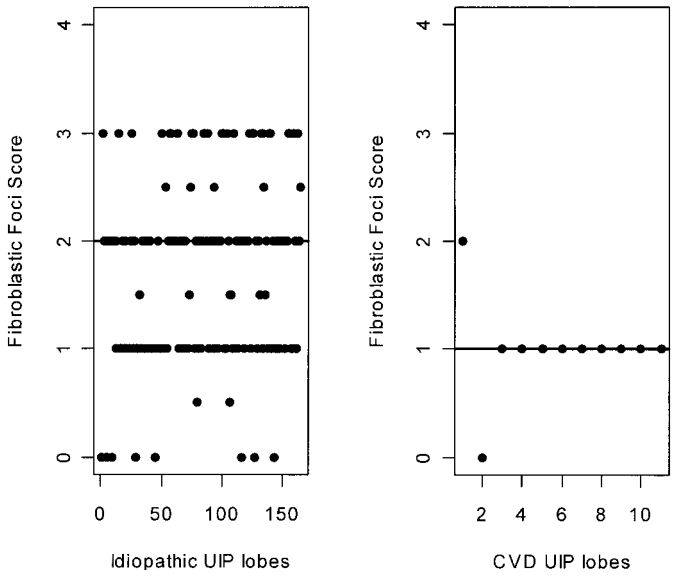

Figure 2. Dot plots showing the mean FF score for each lobe evaluated from patients with idiopathic UIP or CVD- associated UIP. The median profusion of FF was greater in the lobes from patients with idiopathic UIP compared with those with CVD-associated UIP (median [range] 2 [0, 3] versus 1 [0, 2]; p = 0.003; Wilcoxon rank sum test).

(0.55, 95% CI, 0.43–0.66), and the Brompton FF and Denver FF methods (0.48, 95% CI, 0.36–0.60).

Association of Baseline Characteristics With CVD

The mean FF and max FF were the most discriminative baseline features for separating idiopathic UIP from CVD-associated UIP. In univariate analysis (Table 2), the odds ratio of having idiopathic UIP compared with UIP associated with a CVD was 8.31 for a unit increase in mean FF score (95% CI, 1.98, 59.42; p = 0.002) and 16.99 higher for a unit increase in max FF score (95% CI, 3.28, 316; p < 0.0001). The results were similar for the Brompton FF method (odds ratio 3.23; 95% CI 1.17, 15.4; p = 0.02) and the Denver FF method (odds ratio 1.87; 95% CI, 0.89, 5.03; p = 0.10), although these associations were less extreme in magnitude and statistical significance. Mean FF remained significant or marginally significant when added to a model containing age at biopsy (likelihood ratio p value = 0.005) or onset of symptoms (likelihood ratio p value = 0.065) or TLC percentage predicted (likelihood ratio p value = 0.003). Models, including other pathologic features (MC, EF, intra-alveolar macrophages), FEV_1, FVC, diffusion capacity for carbon monoxide, and HRCT interstitial or alveolar values, were not statistically significant.

Survival

Patients with CVD-associated UIP had an improved survival compared with patients with idiopathic UIP (Figure 3). No deaths were noted in the CVD-associated UIP group during a median follow-up of 3.5 years (95% CI 2.5, ∞). This survival advantage was in marked contrast to the 52 deaths (53%) in the idiopathic

TABLE 1. BASELINE CHARACTERISTICS FOR PATIENTS WITH IDIOPATHIC USUAL INTERSTITIAL PNEUMONIA AND PATIENTS WITH COLLAGEN VASCULAR DISEASE–ASSOCIATED USUAL INTERSTITIAL PNEUMONIA

Characteristic	Idiopathic UIP Median (Range)	CVD UIP Median (Range)	p Value Fisher's Exact
Sex, male/female	46/53	6/3	0.31
Age at biopsy, yr	62 (26, 78)	54 (34, 71)	0.02
Symptom onset, yr	2.0 (0.1, 20.0)	0.5 (0.3, 2.0)	0.01
Packs per day × years (pack-years)	10 (0, 100)	0 (0, 50)	0.30
Fibroblastic foci			
Mean of lobes	1.75 (0.3, 3.0)	1.0 (0.7, 2)	0.003
Max in any lobe	2 (1, 3)	1 (1, 2)	0.0004
BFF	2.3 (1, 6)	1.3 (1, 3)	0.02
DFF	2.1 (0, 7)	1.3 (0,3)	0.17
Other pathologic features			
Established fibrosis (20)	3.7 (1.3, 5)	2.7 (2, 4)	0.10
Mononuclear cell infiltrate (20)	2.5 (0.5, 6)	2.8 (2, 4)	0.12
Intra-alveolar macrophages (20)	2.3 (1, 5.3)	1.5 (1, 5.3)	0.35
Spirometry			
FVC, L	2.18 (0.81, 5.57)	2.35 (1.46, 5.05)	0.39
FVC, percentage predicted	61 (23, 114)	68 (39, 109)	0.20
FEV_1, L	1.76 (0.71, 4.37)	2.01 (1.18, 3.09)	0.51
FEV_1, % predicted	68 (26, 131)	73 (41, 94)	0.78
Lung volume			
TLC, L	3.65 (2.12, 7.80)	4.52 (3.32, 9.12)	0.08
TLC, % predicted	72 (42, 121)	92 (69, 135)	0.04
Gas exchange			
D_{LCO}, ml/min/mm Hg	11.3 (3.42, 25.9)	13.29 (6.97, 19.33)	0.11
D_{LCO}, % predicted	45 (13, 89)	61 (29,66)	0.14
HRCT			
Alveolar (CT-Alv)	1.65 (0.5, 4.2)	1.75 (0.8, 3.2)	1.0
Interstitial (CT-Fib)	1.9 (0, 3.6)	1.65 (0.7, 3.6)	0.68

Definition of abbreviations: BFF = Brompton fibroblastic foci scoring method (20); CVD = collagen vascular disease; DFF = Denver fibroblastic foci scoring method (27); D_{LCO} = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography; TLC = total lung capacity; UIP = usual interstitial pneumonia.

TABLE 2. UNIVARIATE LOGISTIC REGRESSION PREDICTING THE PRESENCE OF IDIOPATHIC USUAL INTERSTITIAL PNEUMONIA COMPARED WITH COLLAGEN VASCULAR DISEASE–ASSOCIATED USUAL INTERSTITIAL PNEUMONIA

Predictor	Odds Ratio	95% CI*	p Value*
Age at biopsy, yr	1.06	(1.00, 1.12)	0.048
Mean fibroblastic foci score of lobes	8.31	(1.98, 59.42)	0.002
Max fibroblastic foci score of lobes	16.99	(3.28, 316)	< 0.0001
Symptom onset, years	2.9	(1.3, 11.9)	0.004
TLC, % predicted	0.95	(0.90, 0.99)	0.011
DFF	1.87	(0.89, 5.03)	0.10
BFF	3.23	(1.17, 15.4)	0.02
Mononuclear cell infiltrate†	0.53	(0.21, 1.20)	0.12
Established fibrosis†	2.03	(0.83, 5.6)	0.12
Intra-alveolar macrophages†	1.18	(0.56, 3.01)	0.68

Definition of abbreviations: BFF = Brompton fibroblastic foci scoring system (20); CI = confidence interval; DFF = Denver fibroblastic foci scoring system (27); TLC = total lung capacity.

* Confidence intervals and p values based on likelihood ratio test.

† As described by Nicholson and colleagues (20).

TABLE 3. UNIVARIATE COX PROPORTIONAL HAZARD MODELS EXAMINING THE EFFECT OF PATHOLOGIC FEATURES ON SURVIVAL

Predictor	HR (*95% CI*)	p Value
All patients		
Mean fibroblastic foci*	1.62 (1.08, 2.44)	0.02
Max fibroblastic foci*	1.61 (1.05, 2.47)	0.03
DFF	1.21 (0.97, 1.51)	0.09
BFF	1.31 (1.04, 1.66)	0.02
Mononuclear cell infiltrate†	0.90 (0.63, 1.28)	0.06
Established fibrosis†	1.54 (1.04, 2.28)	0.03
Intra-alveolar macrophages†	1.01 (0.77, 1.33)	0.93
Only idiopathic UIP patients		
Mean fibroblastic foci*	1.33 (0.86, 2.05)	0.20
Max fibroblastic foci*	1.23 (0.78, 1.94)	0.38
DFF	1.11 (0.87, 1.41)	0.39
BFF	1.21 (0.95, 1.54)	0.13
Mononuclear cell infiltrate†	0.97 (0.69, 1.37)	0.87
Established fibrosis†	1.3 (0.88, 1.93)	0.19
Intra-alveolar macrophages†	1.02 (0.76, 1.35)	0.91

Definition of abbreviations: BFF = brompton fibroblastic foci scoring system (20); CI = confidence interval; DFF = Denver fibroblastic foci scoring system (27); HR = hazard ratio; UIP = usual interstitial pneumonia.

* Fibroblastic foci score as described in METHODS.

† As described by Nicholson and colleagues (20).

UIP group (log rank p = 0.005), where the median survival was 2.7 years (95% CI, 2.4, 5.1). To account for baseline differences in age, percentage predicted TLC and onset of symptoms stratified log-rank analyses were used to compare survival between the two disease groups. Improved survival for patients with CVD-associated UIP was confirmed in all stratified analyses, with p values of 0.006, 0.05, and 0.04 for age, percentage predicted TLC, and onset of symptoms, respectively. When all patients were analyzed as a group in univariate models, the profusion of FF and the amount of EF were associated with survival (Table 3). This may be a consequence of FF acting as a surrogate for the presence/absence of CVD; when only idiopathic UIP patients were evaluated, no pathologic feature was associated with survival. The lack of deaths in the CVD-associated UIP group precluded the analysis of this group independently.

DISCUSSION

In this study, we identified a lower profusion of FF in patients with CVD-associated UIP compared with patients with idiopathic UIP. We also confirm an improved survival for patients with CVD-associated UIP.

A novel feature of this study is the marked difference in the profusion of FF between patients with idiopathic UIP and CVD-associated UIP. In fact, the profusion of FF was the most discriminative baseline feature between idiopathic and CVD-associated UIP, as identified by logistic regression. The magnitude of this difference persisted even when accounting for demographic, physiologic, and radiographic features. This is contrast to the results of others (24) and may reflect differences in the patient population, histopathologic classification, or the scoring systems used for profusion of FF. Several patients previously classified as UIP have been reclassified as NSIP after another review using the latest histopathologic criteria (4, 11, 25). Recent data suggests that a histologic picture of NSIP is frequently identified in patients with CVD (5–10). In addition, NSIP appears to be associated with an improved prognosis (7, 26, 36–40). To ensure accurate histopathologic classification, the histologic samples from each or our patients were felt to represent the histologic pattern of UIP when reviewed independently by two expert pulmonary pathologists (W.T. and T.C.) using the latest diagnostic criteria (4, 11, 25).

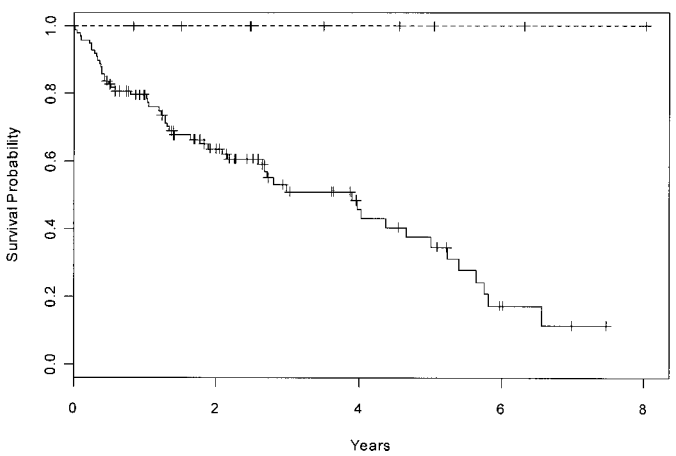

Figure 3. Kaplan-Meier survival curves in patients with CVD UIP (*dashed line*) and idiopathic UIP (*solid line*; log-rank test, p = 0.005).

The differential profusion of FF despite a similar amount of fibrosis on HRCT suggests that the underlying pathogenesis of fibrosis in these diseases may be distinctly different. Idiopathic UIP is a disease that is localized to the lung parenchyma. This observation has led to the suggestion that the etiologic agent in UIP might represent an unidentified inhaled antigen. CVDs are systemic illnesses that are characterized by the involvement of multiple organ systems suggesting that the etiologic agent might represent a circulating "autoantigen." Thus, one might speculate that the formation of FF in UIP is promoted by initial injury to the alveolar epithelium versus the vascular endothelium. Indeed, UIP has been recently characterized as an "epithelial-fibroblastic disease" in which inflammation plays only a minor role (41).

Improved survival was noted for patients with CVD-associated UIP compared with patients with idiopathic UIP. The improved survival for patients with CVD-associated UIP may be related to either the decreased profusion, or perhaps differential function, of the FF. Morphologic studies have suggested fibroblasts play an active role in the remodeling of the lung in pulmonary fibrosis (13, 16), and increasing data suggest that

the fibroblastic focus represents a site of active, ongoing injury adding to the EF (11, 13–17, 38, 41). Several authors have suggested that differences in fibroblast function and cytokine profiles exist in patients with CVD (22, 23, 42–44). Although our study did not directly address the phenotype of the fibroblasts contained in FF, it clearly demonstrates that increased profusion of FF in idiopathic UIP is associated with a poorer prognosis when compared with CVD-associated UIP.

Several scoring systems for FF have been described (19, 20). We demonstrate a moderate correlation between these methods. Unlike other reports (19, 20), we did not find the profusion of FF, by any method, to be a significant predictor of survival for patients with idiopathic UIP. This may reflect subtle differences in inclusion criteria. A differential application of the scoring systems is also possible but seems less likely given that the same pathologist (T.V.C.) participated in all studies. Further studies are needed to define the importance of and optimal way to score the profusion of FF.

Patients with CVD-associated UIP were younger than patients with idiopathic UIP. It is conceivable that response to injury, and in particular fibroblast phenotype, may be influenced by the age of the patient. A recent study using microarray analysis in fibroblasts undergoing replicative senescence, a commonly used model to study the aging process, demonstrated that the senescent state mimics inflammatory wound repair and suggested that senescent cells may contribute to chronic wound pathologies (45). Further study of the effect of age on fibroblastic function in patients with idiopathic and CVD-associated UIP is needed to explore this hypothesis further.

In addition to being younger, patients with CVD-associated UIP also had a higher percentage predicted TLC and a shorter duration of symptoms. This finding contrasts previous data that showed a shorter duration of symptoms for patients with idiopathic IPF (1). It is possible that the improved survival for patients with CVD-associated UIP was confounded by lead-time bias. The similar radiographic characteristics, in addition to a persistent benefit during stratified analyses, argue against this bias. However, the presence of any baseline difference highlights the importance and need for future prospective studies.

The qualitative appearance of the HRCT scans for the CVD-associated UIP patients in this study were compatible with NSIP in 67% of the cases and UIP in 33% of the cases. Recently published data for 73 patients with idiopathic UIP demonstrated that the HRCT appearance was felt to be NSIP in 36%, indeterminate in 27%, and UIP in 37% of the cases (30). Comparing studies, the proportion of HRCT scans with a NSIP appearance was higher for patients with CVD-associated UIP compared with patients with idiopathic UIP, although this was not statistically significant (Fisher's exact; $p = 0.23$). These data highlight the need for an interaction between clinicians, radiologists, and pathologists to come to an accurate diagnosis, as was recently recommended by the American Thoracic and European Respiratory Societies (4).

Patients with idiopathic and CVD-associated UIP in our study demonstrated a similar amount of radiographic fibrosis. Previous studies comparing IPF to CVD-associated pulmonary fibrosis noted a male predominance, older age, and increased radiographic fibrosis for patients with IPF (1, 46). These studies may have included patients with histologic patterns other than UIP. As such, we demonstrate that a histologic picture of UIP for patients with an associated CVD is associated with improved survival despite similar spirometry, gas exchange, and HRCT features to idiopathic UIP. Although it has been previously suggested that FF reflect the underlying histologic picture of UIP (25), our data suggest that the profusion of FF may have additional prognostic value.

A limitation of this study is the small number of patients with CVD-associated UIP. This may be due to more patients with CVD having other histologic patterns such as NSIP (5–10) or a decreased tendency to perform a surgical lung biopsy in these patients. The overall similarity of physiologic and radiographic characteristics for the patients in this study argues against a significant selection bias in selecting patients for biopsy. The striking results, even with a small sample size, also argue that genuine differences exist for patients with a histologic pattern of UIP with, versus without, an associated CVD. Future studies are required to clarify the role of FF in the pathogenesis of UIP.

In summary, we have shown that patients with CVD-associated UIP have a markedly improved survival compared with patients with idiopathic UIP. Furthermore, patients with CVD-associated UIP have a decreased profusion of FF compared with patients with idiopathic UIP.

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