CT Features of the Usual Interstitial Pneumonia Pattern: Differentiating Connective Tissue Disease–Associated Interstitial Lung Disease From Idiopathic Pulmonary Fibrosis

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OBJECTIVE. A substantial proportion of cases of usual interstitial pneumonia (UIP) are due to connective tissue disease (CTD)-associated interstitial lung disease (ILD). The purpose of this study was to determine whether specific CT findings can help differentiate a UIP pattern of CTD-ILD from a UIP pattern of idiopathic pulmonary fibrosis (IPF) and whether these signs are associated with survival.

MATERIALS AND METHODS. Adults visiting an ILD clinic from 2006 to 2015 enrolled in a research registry with a multidisciplinary diagnosis of CTD-ILD or IPF and a UIP pattern at high-resolution CT were included in the study. In these subjects with CT findings of UIP due to either IPF or CTD-ILD, three CT findings anecdotally associated with CTD-ILD were assessed for diagnostic accuracy: the "straight-edge" sign, the "exuberant honeycombing" sign, and the "anterior upper lobe" sign. Survival assessments were performed with univariate and multivariable techniques.

RESULTS. The subjects included 63 patients who had CTD-ILD and 133 patients who had IPF with a UIP pattern at CT. All three CT signs were significantly more common in subjects with CTD-ILD than those with IPF (prevalence, 22.2–25.4% for CTD-ILD, 6.0–12.8% for IPF; $p = 0.028$ to < 0.001). The highest specificity (94.0%) and sensitivity (25.4%) were seen for the straight-edge sign. No CT sign was associated with survival in multivariable analysis.

CONCLUSION. Although UIP is usually associated with IPF, the index of suspicion for CTD-ILD should be raised in the care of patients with any of the three CT signs. A thorough workup for CTD-ILD should be pursued, including referral to the rheumatology department.

A usual interstitial pneumonia (UIP) pattern on chest CT scans is highly suggestive of UIP pathologic findings; the most common cause of UIP is idiopathic pulmonary fibrosis (IPF) [1–5]. Under current guidelines, a UIP pattern on CT images is specific for IPF after a thorough clinical and serologic workup has excluded other causes of interstitial lung disease (ILD) [5]. Antifibrotic agents have been found to slow progression of IPF and possibly improve survival [6–8]. However, connective tissue disease (CTD)-associated ILD can also commonly present with a UIP pattern in a chest CT examination, especially in patients with rheumatoid arthritis [9, 10]. Current understanding is that the pattern of fibrosis in UIP related to CTD is similar to that in IPF [11]. However, we have anecdotally noticed specific CT signs that are more common in UIP associated with CTD-ILD than in UIP associated with IPF.

The specific CT findings we have identified include concentration of fibrosis within the anterior aspect of the upper lobes (with relative sparing of the other aspects of the upper lobes) and concomitant lower lobe involvement ("anterior upper lobe" sign) (Figs. 1 and 2); exuberant honeycomb-like cyst formation within the lungs constituting greater than 70% of fibrotic portions of lung ("exuberant honeycombing" sign) (Figs. 3 and 4); and isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane without substantial extension along the lateral margins of the lungs on coronal images ("straight-edge" sign) (Figs. 5 and 6).

The diagnostic accuracy of these specific CT findings in differentiating CTD UIP and IPF UIP is not yet known. The main purpose of this study was to evaluate the diagnostic value of each of these findings in differentiating CTD UIP and IPF UIP. We hypothesized that each of these specific CT findings would be more common in CTD-ILD

than in IPF and that the presence of multiple CT findings would be further supportive of CTD-ILD rather than IPF. We presumed that each of these CT findings would have high specificity for CTD-ILD but only modest sensitivity. A secondary goal of this study was to determine whether any of the proposed CT findings were associated with survival and whether patients with CTD UIP have longer survival than those with IPF UIP.

Materials and Methods

Subjects and Clinical Data

This HIPAA-compliant study received institutional review board approval. All patients visiting the ILD clinic at the study institution (University of Chicago) undergo an evaluation for CTD, including comprehensive serologic testing, regardless of referring diagnosis. All patients are also offered the opportunity to participate in a research registry. Adults in the registry who initially visited the clinic between 2006 and 2015 and had a UIP pattern on a diagnostic-quality CT study and a multidisciplinary diagnosis of CTD-ILD or IPF were included in the study. CT patterns were previously determined and included in the research registry as part of an ongoing study on the natural history of ILD. Patients who met the criteria for interstitial pneumonia with autoimmune features were excluded. Follow-up time was censored on January 1, 2016. Of the 1250 patients in the ILD registry, 196 had a UIP CT pattern based on a diagnostic-quality study and had a diagnosis of CTD-ILD or IPF. We extracted clinical data from the initial clinic visit, including demographics, smoking history, and pulmonary function test results. Survival was defined as time from diagnostic test (CT or surgical lung biopsy) to death, lung transplant, or censoring date.

CT Assessment

The first chest CT scan of diagnostic quality for each subject was reviewed. CT scans from outside hospital studies were considered for scoring if the image quality was considered diagnostic (28 of 196 CT scans). CT scans were considered of diagnostic quality if they included thin acquisition or reconstruction intervals (< 2.0 mm), were through the whole thorax, and were free of motion artifact that prevented visualization of high detail within the lung parenchyma. Chest CT scans were obtained with various scanners (16- to 64-MDCT, Brilliance, Philips Healthcare; 256-MDCT, Brilliance iCT, Philips Healthcare). A supine helical CT acquisition was performed during full inspiration at 120 kVp, 220 mAs, 512 × 512 pixel image reconstruction matrix. Axial images were reconstructed contiguously at 1- and 3-mm slice thickness with a lung algorithm. Coronal and sagittal images were generated (2.5-mm thickness).

Chest CT scans were scored by two thoracic radiologists (12 and 33 years of thoracic imaging experience) in consensus. They were blinded to all other clinical data. The following three specific CT signs were scored. The anterior upper lobe sign was concentration of fibrosis within the anterior aspect of the upper lobes (with relative sparing of the other aspects of the upper lobes) and concomitant lower lobe involvement (Figs. 1 and 2). The exuberant honeycombing sign consisted of extensive honeycomb-like cyst formation within the lungs comprising greater than 70% of the fibrotic portions of lung (Figs. 3 and 4). The straight-edge sign consisted of isolation of fibrosis to the lung bases without substantial extension along the lateral margins of the lungs on coronal images (Figs. 5 and 6).

Statistical Analysis

We evaluated the prevalence, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for the anterior upper lobe sign, exuberant honeycombing sign, and the straight-edge sign in CTD UIP and IPF UIP. Continuous variables are presented as mean and SD for normally distributed data or as median and interquartile range for skewed data. Categoric variables are presented as counts and percentages. Continuous variables were compared by two-tailed *t* test (parametric) or Mann-Whitney *U* test (nonparametric). Categoric variables were compared by chi-square test or Fisher exact test, as appropriate. Survival analysis was performed by univariate log-rank testing and univariate and multivariable Cox proportional hazards regression. Survival was displayed graphically with the Kaplan-Meier survival estimator and was defined as time from diagnosis to lung transplant, death, or censoring date. All statistical studies were performed with Wizard Pro software (version 1.8.28, Evan Miller).

TABLE 1: Demographics and Clinical Information

Characteristic	Idiopathic Pulmonary Fibrosis (*n* = 133)	Connective Tissue Disease–Associated Interstitial Lung Disease (*n* = 63)	*p*
Mean age (y)	69.1 (8.5)	61.5 (12.8)	< 0.001[a]
Sex (%)			
Female	15.0	73.0	< 0.001[a]
Male	85.0	27.0	
Race (%)			
White	88.7	55.6	< 0.001[a]
Black	4.5	30.2	
Hispanic	6.8	7.9	
Asian	0.0	6.3	
Smoking history (median pack-years)	20 (27)	0 (22)	< 0.001[a]
Median survival period (d)	895 (1051)	977 (1511)	0.572
Mean predicted forced vital capacity (%)	65.0 (3.4)	61.3 (4.4)	0.192
Mean predicted D_{LCO} (%)	44.8 (3.4)	44.2 (5.1)	0.840

Note—Parenthetic data are SD for mean values and interquartile range for median values. D_{LCO} = diffusing capacity of the lung for carbon monoxide.
[a]Statistically significant.

Results

Demographics

Of the 196 subjects included in the study, 63 had CTD-ILD and 133 had IPF. Subjects with IPF were older than those with CTD-ILD (Table 1). Most of the subjects with IPF were men, and most of those with CTD-ILD were women. Though the majority of subjects with both IPF and CTD-ILD were white, there was a significant difference in race distribution, with a substantial minority of subjects with CTD-ILD being black. Subjects with CTD-ILD had smoked less (fewer pack-years) than the subjects with IPF. In the CTD-ILD group, subjects with rheumatoid arthritis were most commonly represented (41.3% [26/63]) followed by those with systemic sclerosis (19.0% [12/63]) (Table 2). The median survival periods were 895 days (interquartile range, 1051 days) for subjects with IPF and 977 days (interquartile range, 1511 days) for those with CTD-ILD (Table 1).

TABLE 2: Proportion of Specific Types of Connective Tissue Disease-Associated Interstitial Lung Disease (CTD-ILD) in Cohort (*n* = 63)

Subtype of CTD-ILD	Count	Percentage
Rheumatoid arthritis	26	41.3
Systemic sclerosis	12	19.0
Myositis	9	14.3
Mixed CTD	9	14.3
Sjögren syndrome	7	11.1

Performance of CT Signs in Differentiation of Idiopathic Pulmonary Fibrosis From Connective Tissue Disease–Associated Interstitial Lung Disease in Patients With CT Findings of Usual Interstitial Pneumonia

All three evaluated signs were significantly more common in CTD UIP than in IPF UIP (Table 3). The sensitivity of any single CT sign in detecting CTD UIP was low (22.2–25.4%), though specificity was high (87.2–94.0%). The highest specificity values were for the exuberant honeycombing and straight-edge signs. The highest positive likelihood ratio was seen for the straight-edge sign (4.22) (Table 3). In cases in which more than one CT sign was present, there was a small decrease in sensitivity with a slight increase in specificity and a positive likelihood ratio of 5.28.

Survival

CTD UIP was associated with longer survival than was IPF UIP ($p = 0.016$) (Fig. 7). Similar proportions of subjects with CTD UIP and IPF UIP reached the endpoint of transplant as opposed to death (9.5% [6/63] versus 10.3% [14/133]; $p = 0.826$). In univariate analysis, only the anterior upper lobe sign was associated with longer survival, though this was likely due to the collinearity of the CT sign with CTD UIP, because the result did not persist in multivariable analysis. Among subjects with IPF UIP, those with the straight-edge sign tended to live longer than those without the straight-edge sign, but the difference was not statistically significant ($p = 0.067$). The survival periods of subjects with IPF UIP who had the straight-edge sign were not have significantly different from those of all CTD UIP subjects ($p = 0.975$). However, IPF UIP subjects without the straight-edge sign had significantly shorter survival than all CTD UIP subjects ($p = 0.011$). None of the CT signs were associated with survival in multivariable analysis (Table 4). Age, sex, and diffusing capacity of the lung for carbon monoxide were associated with survival in multivariable analysis.

Discussion

The main goal of the study was to determine whether chest CT findings anecdotally associated with CTD-ILD can help differentiate UIP in CTD-ILD as opposed to IPF and whether any of these signs is associated with survival. Our main findings were as follows: the exuberant honeycombing sign, the anterior upper lobe sign, and the straight-edge sign have high specificity but modest sensitivity in suggesting that UIP on CT images is due to CTD-ILD rather than IPF, and the absence of the straight-edge sign confers worse survival in IPF UIP than in CTD UIP.

Although many cases of CTD-ILD are diagnosed in patients who have a rheumatologic diagnosis of a well-defined CTD, a substantial minority of patients, including those with UIP, present with ILD first, and CTD is diagnosed at a later date [12–17]. Moreover, a substantial number of patients with ILD have clinical and serologic features suggestive of an underlying autoimmune disease but do not meet strict criteria for a specific CTD [18–22]. In addition, radiologists often interpret chest CT scans without access to the patient's clinical record and may not be aware that a patient has a diagnosis of CTD. The specific CT signs evaluated in this study are additional tools that the radiologist or pulmonologist can use to help differentiate CTD-ILD from IPF in patients who have a CT UIP pattern.

The imaging patterns of ILD in CTD have been described according to the radiologic and pathologic classification of the idiopathic interstitial pneumonias [11]. Although not formally tested, in many cases, this classification is appropriate and affords accurate characterization of CTD-related ILD. One of the idiopathic interstitial pneumonias, nonspecific interstitial pneumonia (NSIP) is more commonly due to CTD than it is idiopathic IPF [23]. Extensive literature details the patterns of ILD and specific CTDs [10, 24–27]. The most common CTDs to cause ILD are rheumatoid arthritis, systemic sclerosis, and the idiopathic inflammatory myopathies (dermatomyositis, polymyositis, and antisynthetase syndrome). The most common pattern of lung fibrosis in rheumatoid arthritis is UIP followed by NSIP [10, 15]. This is in contrast to systemic sclerosis, most cases of which have an NSIP pattern [24, 28, 29]. UIP is much less common in systemic sclerosis than in rheumatoid arthritis. Myositis often presents with a pattern of combined NSIP and organizing pneumonia [26, 30, 31].

TABLE 3: Performance of Specific CT Signs in Differentiation of Connective Tissue Disease–Associated Interstitial Lung Disease (CTD-ILD) From Idiopathic Pulmonary Fibrosis (IPF) in Patients With Usual Interstitial Pneumonia CT Pattern

CT Sign	Percentage of Patients With IPF With CT Sign (*n* = 133)	Percentage of Patients With CTD-ILD With CT Sign (*n* = 63)	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	*p*
Anterior upper lobe	12.8 (17)	25.4 (16)	25.4	87.2	1.99	0.86	0.028[a]
Exuberant honeycombing	6.0 (8)	22.2 (14)	22.2	94.0	3.69	0.83	< 0.001[a]
Straight edge	6.0 (8)	25.4 (16)	25.4	94.0	4.22	0.79	< 0.001[a]
More than one sign	4.5 (6)	23.8 (15)	23.8	95.5	5.28	0.80	< 0.001[a]
Any CT sign	19.5 (26)	42.9 (27)	42.9	80.5	2.19	0.71	< 0.001

Note—Values in parentheses are number of subjects.
[a]Statistically significant.

TABLE 4: Cox Unadjusted and Adjusted Models of Survival of Patients With Connective Tissue Disease and Idiopathic Pulmonary Fibrosis with a Usual Interstitial Pneumonia CT Pattern

Variable	Unadjusted			Adjusted		
	Hazard Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Age	1.019	1.006–1.032	0.005[a]	1.022	1.006–1.038	0.007[a]
Male sex	1.64	1.199–2.253	0.002[a]	1.555	1.053–2.297	0.027[a]
Smoking history (pack-years)	1.007	1.002–1.012	0.010[a]	1.002	0.996–1.009	0.428
Forced vital capacity	0.987	0.979–0.995	0.003[a]	0.99	0.979–1.000	0.065
D_{LCO}	0.984	0.977–0.991	< 0.001[a]	0.988	0.978–0.998	0.015[a]
CTD-ILD	0.675	0.489–0.932	0.017[a]	1.117	0.773–1.703	0.606
CT signs						
Anterior upper lobe	0.654	0.445–0.961	0.031[a]	0.82	0.522–1.289	0.390
Exuberant honeycombing	0.792	0.496–1.264	0.329	0.98	0.582–1.65	0.938
Straight edge	0.684	0.442–1.057	0.087	0.872	0.547–1.391	0.566

Note—CTD-ILD = connective tissue disease–associated interstitial lung disease, D_{LCO} = diffusing capacity of the lung for carbon monoxide.
[a]Statistically significant.

Classically, the consolidation from organizing pneumonia rapidly resolves with corticosteroid therapy, leaving patients with CT patterns consistent with NSIP. This typical evolution of CT findings is highly suggestive of myositis.

To our knowledge, no systematic studies have assessed whether any specific CT signs can be used to differentiate CTD UIP from IPF UIP. Our descriptions of CT signs in CTD-ILD have not been described in the literature previously. Currently, CT is central to the diagnosis in patients with suspected IPF. A confidently identified UIP pattern on CT images is thought to be so highly suggestive of a pathologic finding of UIP that biopsy is obviated according to current guidelines, and most of these patients have IPF. However, our study results suggest that even in patients with a high-confidence UIP pattern, there are specific CT findings that should make one strongly consider a CTD-ILD diagnosis. In these patients, a more thorough clinical and serologic workup for underlying CTD may be necessary, especially in younger patients, black patients, and women. Many patients with CTD may have no symptoms from a musculoskeletal standpoint, and the ILD may be the initial manifestation that leads to the eventual diagnosis [15, 32]. In addition, as aforementioned, other patients may present with seemingly idiopathic ILD at initial evaluation but then have full-blown CTD at a later point in the disease course [12–17].

The results of this study support the framework of the current IPF guidelines requiring exclusion of other known causes of ILD to diagnose IPF even when one is confident about the UIP pattern [5]. In clinical practice, however, a UIP pattern at CT is often equated with IPF. Recognition that a substantial minority of cases of UIP are secondary to an underlying disease or exposure is critical for accurate diagnosis [5]. Radiologists are encouraged to define imaging patterns mirroring pathologic diagnosis given that ultimately the goal of imaging is to reflect the pathologic finding as closely as possible. However, in patients with ILD, neither pathologic examination, clinical workup, nor imaging is the reference standard in diagnosis. Multidisciplinary diagnosis including radiologists, pathologists, and clinicians is the reference standard for achieving accurate diagnosis of ILD. Our findings suggest that in addition to defining the CT pattern as a representation of the likely underlying pathologic pattern (if biopsy were to be performed) as suggested in current guidelines, inclusion of the best clinical diagnosis (if possible) should also be made to ensure that a UIP pattern at chest CT is not automatically deemed IPF by the referring clinician.

The straight-edge sign in IPF augmented survival such that it was similar to that of CTD-ILD. Patients with CTD UIP have longer survival than do patients with IPF [33–35]; therefore, the presence of the straight-edge sign may be indicative of occult CTD-ILD in these patients who do not meet criteria for CTD or interstitial pneumonia with autoimmune features at initial evaluation. Such patients may eventually have overt CTD and need further investigation. Alternatively, this sign may be predictive of a more indolent disease course in patients with IPF, similar to that of CTD UIP. Validation of this result is necessary, preferably by means of studies designed to decipher the fundamental cause of this phenomenon.

We believe that the signs we studied may at least in some cases represent the natural evolution of some cases of NSIP into a UIP pattern. This phenomenon has been previously described [3] and is not rare in clinical practice when patients are evaluated longitudinally, but it was not optimally studied in the current study. The CT signs may reflect the natural history of the NSIP to UIP progression. For example, the exuberant honeycombing sign may arise from the homogeneous nature of NSIP as opposed to the more temporal and spatially heterogeneous nature of UIP in IPF. The affected portions of lung in NSIP may worsen uniformly over time, giving rise to the florid honeycombing pattern of end-stage disease. The straight-edge sign may be related to the peribronchovascular axial distribution of many NSIP cases; as disease extent increases, fibrosis may then extend out to the lateral margins of the lung, producing the straight-edge sign. Most cases of UIP start in the lung periphery and progress superiorly and centripetally, developing the straight-edge appearance less often.

Our study was limited by its retrospective design and the limited number of subjects, though the size of this cohort is similar to or greater than that in other single-center studies of chest CT features of ILD. In addition, a minority of CT scans were not obtained at the hospital at which the study was

performed, which introduced heterogeneity into the quality and appearance of CT scans. However, all CT scans scored for this study were of diagnostic quality as specified in our inclusion criteria. The CT scans were scored by consensus; therefore, interreader variation could not be determined. In addition, we did not compare CTD UIP and IPF UIP with respect to disease severity at CT, though we did include pulmonary function in the adjusted survival analysis. Finally, our study was performed at a tertiary referral center for ILD, and, hence, our results may not be generalizable to all clinical settings.

Our study showed that the straight-edge sign, anterior upper lobe sign, and exuberant honeycombing sign are much more common in and highly specific for CTD UIP than for IPF UIP. Our results also suggest that the straight-edge sign confers a survival advantage to patients with IPF and a UIP pattern on CT images. Given that the current study was performed at a single center, validation of these results in additional cohorts is mandatory before alteration in standard clinical practice is considered. A study evaluating whether the three signs are markers of UIP patterns that have evolved from a NSIP pattern would be useful.

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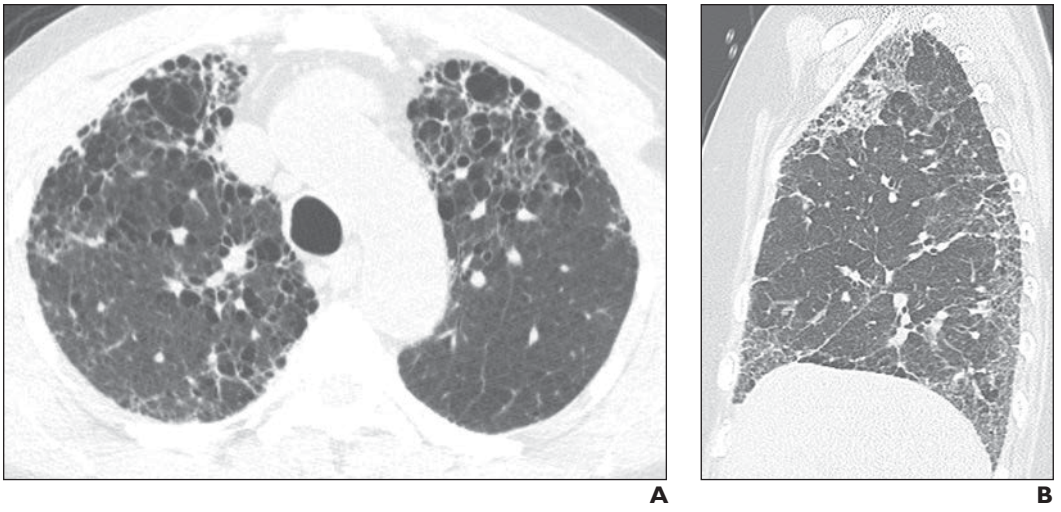

Fig. 1—65-year-old woman with connective tissue disease. **A** and **B,** Axial (**A**) and sagittal (**B**) unenhanced chest CT images show substantial degree of reticulation, traction bronchiectasis and bronchiolectasis, and honeycombing within upper lobes, mostly concentrated in anterior aspect consistent with anterior upper lobe sign.

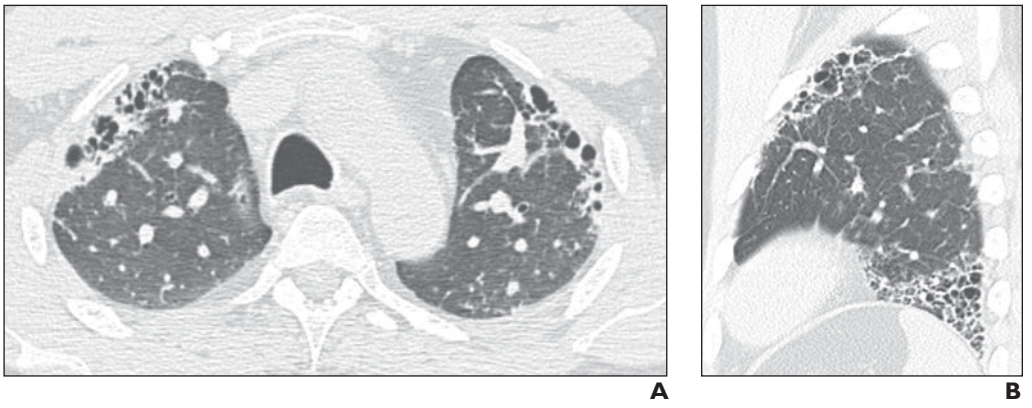

Fig. 2—52-year-old man with connective tissue disease. **A** and **B,** Axial (**A**) and sagittal (**B**) unenhanced chest CT images show substantial degree of reticulation and subpleural honeycombing within upper lobes, mostly concentrated in anterior aspect consistent with anterior upper lobe sign.

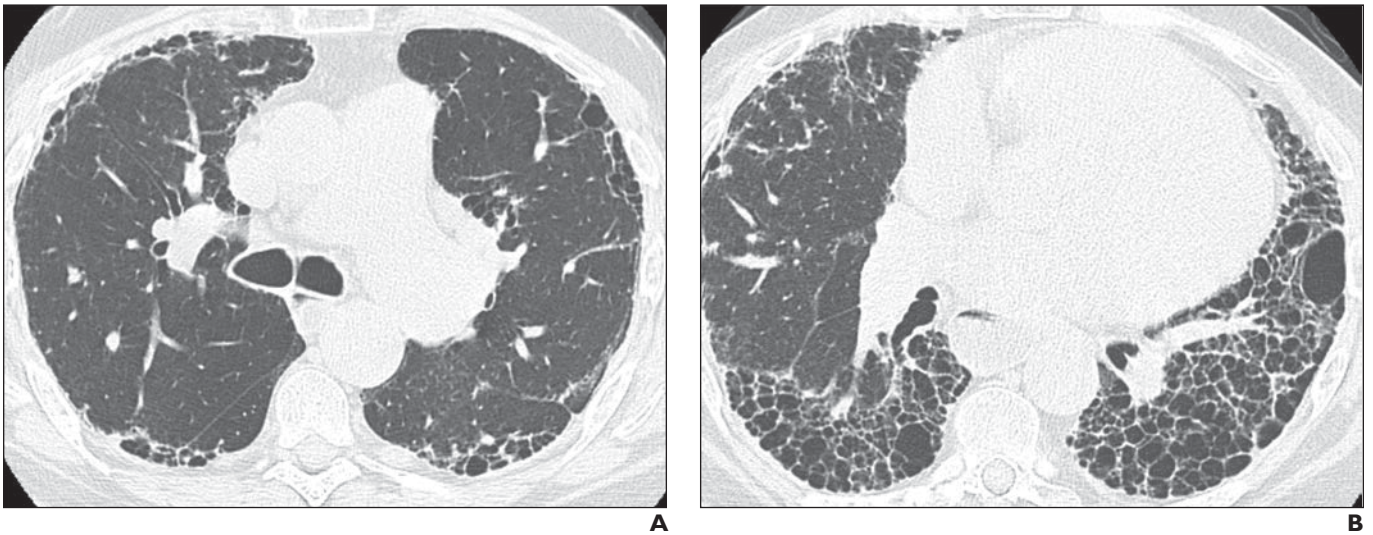

Fig. 3—61-year-old woman with known connective tissue disease. **A** and **B,** Axial unenhanced chest CT images show peripheral- and basilar-predominant pulmonary fibrosis pattern characterized primarily by florid honeycombing consistent with exuberant honeycombing sign.

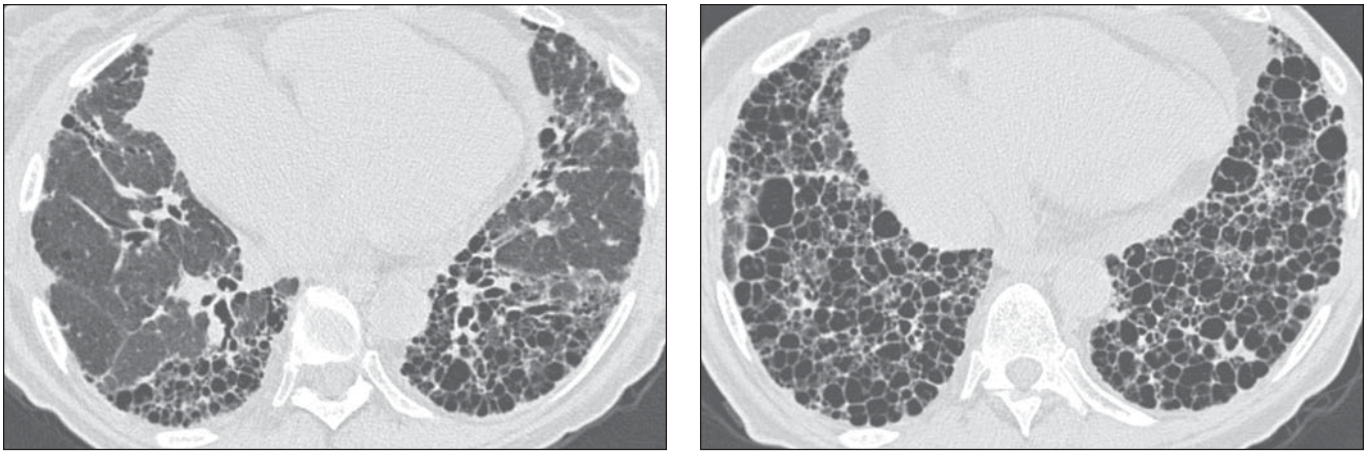

Fig. 4—57-year-old woman with known connective tissue disease.
A and **B,** Axial unenhanced chest CT images show peripheral- and basilar-predominant pulmonary fibrosis pattern characterized primarily by florid honeycombing consistent with exuberant honeycombing sign.

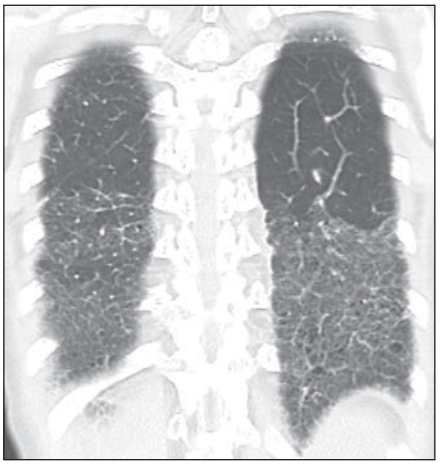

Fig. 5—49-year-old woman with connective tissue disease. Coronal unenhanced chest CT image shows basilar-preponderant pulmonary fibrosis characterized by ground-glass opacity and reticulation and traction bronchiolectasis. Along lateral aspect of lungs, fibrosis does not extend superiorly along chest wall but rather forms fairly straight interface between fibrosis and normal lung orthogonal to lateral chest wall surface, consistent with straight-edge sign.

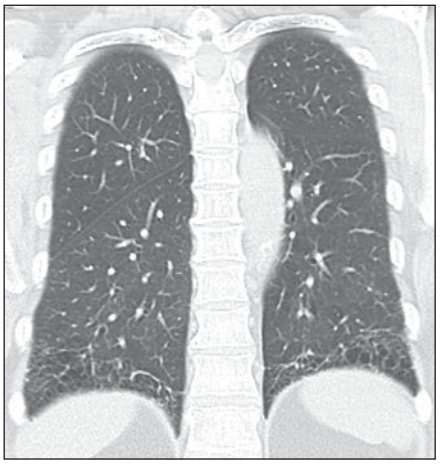

Fig. 6—31-year-old man with connective tissue disease. Coronal unenhanced chest CT image shows basilar-preponderant pulmonary fibrosis characterized mainly by large degree of honeycombing (exuberant-honeycombing sign). Along lateral aspect of lungs, fibrosis does not extend superiorly along chest wall but rather forms fairly straight interface between fibrosis and normal lung orthogonal to lateral chest wall surface, consistent with straight-edge sign.

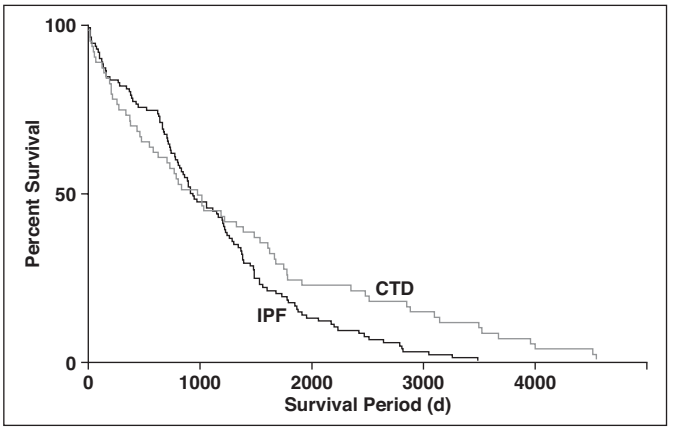

Fig. 7—Kaplan-Meier survival curves for connective tissue disease (CTD) and idiopathic pulmonary fibrosis (IPF) ($p = 0.016$).

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