






Importance of chest HRCT in the diagnostic evaluation of fibrosing interstitial lung diseases

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ABSTRACT

Many conditions result in chronic interstitial lung disease (ILD), being classified as fibrosing ILDs, including idiopathic pulmonary fibrosis, connective tissue diseases, sarcoidosis, and fibrotic hypersensitivity pneumonitis. HRCT plays an important role in the clinical evaluation of fibrosing ILDs. Current treatment perspectives are encouraging and reinforce the need for HRCT scans of adequate technical quality for early detection of fibrosing ILD. Despite efforts in this regard, the significance and management of imaging findings of early interstitial lung abnormalities have yet to be clarified. After identification of CT findings consistent with fibrosing ILD, radiologists must be able to identify characteristic morphological patterns and, in some cases, features of specific clinical entities. In cases in which HRCT features are not sufficiently specific for a definitive diagnosis, HRCT can aid in selecting the best site for surgical lung biopsy. CT follow-up is useful for identifying progressive fibrosing ILDs and detecting complications unrelated to the underlying disease, including infections, acute exacerbations, and neoplasms. Automated quantification tools have clinical applicability and are likely to be available for use in imaging analysis in the near future. In addition, incorporation of CT evaluation into scoring systems based on clinical and functional parameters for staging fibrosing disease is likely to become valuable in determining prognosis. Knowledge of the clinical applications of CT evaluation is essential for specialists managing patients with fibrosing ILD and can have a positive impact on the clinical course of the disease.

Keywords: Tomography, X-ray computed; Diagnostic imaging; Pulmonary fibrosis.

INTRODUCTION

Fibrosis is the final consequence of cell injury, matrix injury, or both by a variety of mechanisms, including trauma, thermal injury, chemical injury, hypoxia, and immune-mediated injury.⁽¹⁾ In the lung parenchyma, repeated alveolar injury leads to fibrosing interstitial lung diseases (ILDs), including idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD)-associated fibrosing ILD (CTD-fILD), and fibrotic hypersensitivity pneumonitis (HP), as well as less common diseases such as idiopathic nonspecific interstitial pneumonia (NSIP), Langerhans cell histiocytosis, tobacco-related diseases, sarcoidosis, Erdheim-Chester disease, Hermansky-Pudlak syndrome, asbestosis, silicosis, drug reactions, and IgG4-related sclerosing disease.^(1,2) Some patients develop a progressive phenotype characterized by self-sustaining fibrosis, decline in lung function, worsening quality of life, and, ultimately, early mortality, being designated progressive fibrosing ILD.⁽²⁾

The differential diagnosis of fibrosing ILDs is difficult because clinical, radiological, and pathological characteristics often overlap, a multidisciplinary approach therefore being required.⁽³⁻⁵⁾ In this context, it is essential to establish a definitive diagnosis

because nonpharmacological and pharmacological treatment approaches (including corticosteroids, immunosuppressants, and, more recently, antifibrotic agents) are disease-specific.⁽⁶⁻⁸⁾

The role of imaging in the diagnosis of fibrosing ILDs has evolved in recent decades, and HRCT currently plays an essential role in the diagnostic evaluation of fibrosing ILDs, being useful in the initial evaluation of fibrosing ILDs, in making a decision regarding the use of invasive diagnostic procedures, and in patient follow-up. The objective of the present study was to review the role of HRCT in the diagnostic evaluation of fibrosing ILDs.

DIAGNOSIS OF FIBROSING DISEASE

Technical parameters of CT examinations

CT scans of adequate technical quality are essential for accurate interpretation of ILD findings, low-quality CT images leading to misses and misinterpretations.⁽⁹⁾ For volumetric image acquisition, the following parameters should be used: a) submillimetric collimation; b) thin-slice reconstructions (≤ 1.5 mm) with the use of a high-resolution filter; c) shortest rotation time and

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highest pitch, in order to reduce image acquisition time and movement artifacts; and d) use of tools for optimizing/reducing radiation dose.^(10,11)

The first acquisition is obtained at maximal inspiration, volumetric CT acquisition being preferred because it allows multiplanar image reconstruction in the post-processing stage, clarifying disease distribution, facilitating differentiation between honeycombing and traction bronchiolectasis, and optimizing comparison with follow-up images.⁽¹⁰⁻¹²⁾ The technical staff should be trained in providing patients with simple, clear respiratory instructions for chest CT examinations, the voice of the technician being preferred to the automatic instructions from the machine because submaximal inspiratory maneuvers can lead to misinterpretation of ground-glass attenuation and reticulation.^(9,10) The second acquisition is obtained at end-expiration and is useful for identifying mosaic attenuation, which is an important finding in the diagnosis of fibrotic HP.⁽¹⁰⁾ A third acquisition can be obtained with the patient in the prone position; it can be sequential or volumetric and can be limited to the lower lobes.⁽¹¹⁾ Prone CT imaging is useful in patients with clinical suspicion of fibrosing disease and only minor lung involvement, with normal or minimally abnormal chest X-rays, and particularly for distinguishing between position-induced changes and initial interstitial changes (Figure 1).⁽¹⁰⁾

CT findings

Common HRCT findings of fibrosing disease include reticular opacities, ground-glass opacities, traction bronchiolectasis, and honeycombing, the proportion and distribution of which vary.^(10,11) Traction bronchiolectasis is an important finding for the diagnosis of fibrosing ILD and often overlaps with reticular or ground-glass opacities in patients with fibrosing lung disease. It is difficult to distinguish between traction bronchiolectasis and honeycombing in some cases, with significant interobserver variation (Figure 2).⁽¹³⁾ The term honeycombing refers to clustered cystic airspaces of typically 3-10 mm in diameter with thick, well-defined

walls.^(14,15) Although honeycombing typically presents as multiple layers of cysts, a single layer of two or three cysts is enough for a diagnosis of honeycombing.⁽¹⁰⁾ Ground-glass attenuation superimposed on reticular opacities or traction bronchiolectasis can be seen in patients with fibrosing ILD.⁽¹⁰⁾ However, the presence of "pure" ground-glass attenuation (i.e., without reticular opacities) might be related to inflammatory activity, and the presence of new bilateral ground-glass opacities in a patient with fibrosing ILD should raise the possibility of an acute exacerbation.⁽¹⁶⁾ A crazy-paving pattern, micronodules, consolidations, and cysts are encountered in specific entities.

Interstitial lung abnormalities and difficulties in early diagnosis

The widespread use of HRCT as a diagnostic tool has increased the detection of interstitial lung abnormalities (ILAs), which are incidental findings potentially consistent with ILD in individuals who are not clinically suspected of having ILD and who may or may not have clinical symptoms and functional limitations.^(17,18) ILAs represent early stages of fibrosing ILD in some cases and are of particular interest because antifibrotic therapy has been shown to slow the progression of IPF even in individuals with less extensive disease.⁽¹⁹⁾

ILAs are nondependent HRCT abnormalities affecting more than 5% of any lung zone (upper, middle, and lower lung zones being demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein). CT findings in patients with ILAs include ground-glass opacities, reticular opacities, architectural distortion, traction bronchiolectasis, honeycombing, and nonemphysematous cysts.⁽¹⁸⁾ Morphological findings unrelated to ILAs include dependent lung atelectasis, focal paraspinal fibrosis in close contact with thoracic spine osteophytes, smoking-related centrilobular opacities in the absence of other findings, mild focal or unilateral opacities, interstitial edema (associated with congestive heart failure), and findings

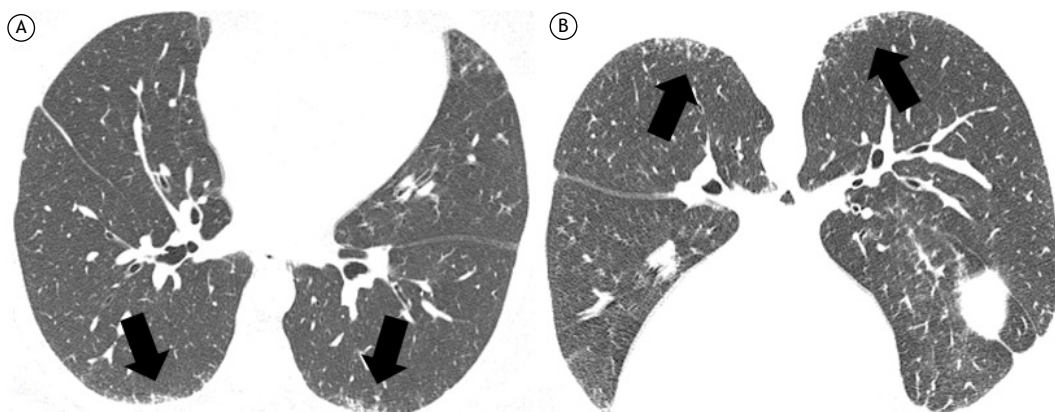


Figure 1. Axial HRCT scans with lung window settings. Note diffuse peripheral lower lobe reticular opacities (arrows in A) that are also seen on prone CT images (arrows in B), characterizing incipient interstitial lung disease.

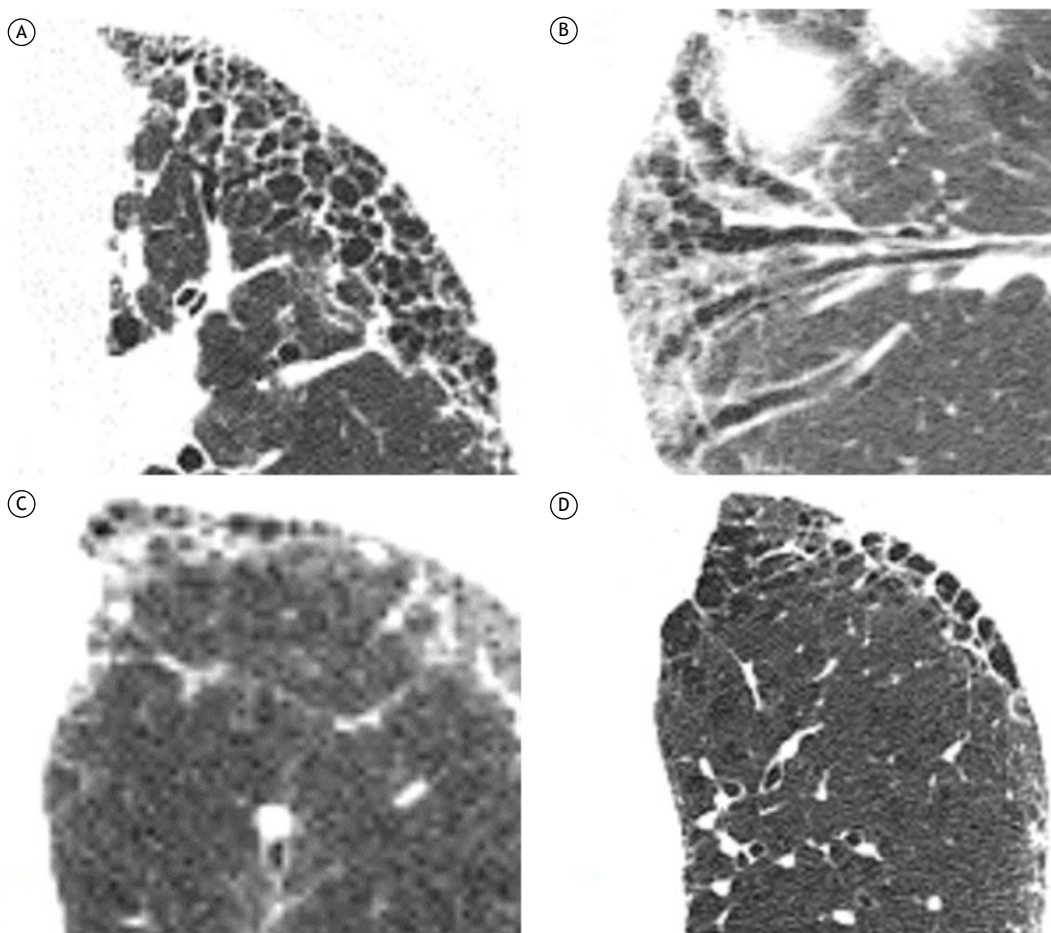


Figure 2. Axial HRCT scans with lung window settings, showing fibrosing interstitial lung disease in different patients. In A, typical honeycombing, presenting as multiple layers of cysts. In B, traction bronchiectasis in an oblique coronal plane. Note the usefulness of multiplanar reconstruction in differentiating between traction bronchiectasis and honeycombing. In C, early honeycombing, presenting as a single layer of cysts. In D, note the difficulty in differentiating between honeycombing and paraseptal emphysema.

of aspiration (patchy ground-glass opacities and a tree-in-bud pattern).⁽¹⁸⁾ ILAs are classified as follows: a) nonsubpleural; b) subpleural nonfibrotic (without architectural distortion, traction bronchiectasis, or honeycombing); and c) subpleural fibrotic (with architectural distortion and traction bronchiectasis, honeycombing, or both).⁽¹⁸⁾

In patients with ILAs, risk factors for progression to ILD include clinical risk factors (smoking, other inhalational exposures, medications, radiation therapy, previous thoracic surgery, and changes in pulmonary function tests) and specific radiological features. In a study by Putman et al.,⁽²⁰⁾ the presence of subpleural reticular opacities in the lower lobes and traction bronchiectasis significantly increased the likelihood of ILA progression, and all of the cases in which honeycombing was present progressed to ILD over the course of 5 years. Specific recommendations regarding management and follow-up have been published elsewhere.⁽¹⁸⁾

DIFFERENTIAL DIAGNOSIS BASED ON CT FINDINGS: MORPHOLOGICAL PATTERNS AND SPECIFIC CLINICAL ENTITIES

After identification of CT findings consistent with fibrosing ILD, HRCT has an important role in narrowing diagnostic possibilities by identifying characteristic morphological patterns or, in some cases, indicating specific clinical entities (such as HP, sarcoidosis, and asbestosis). HRCT findings should be interpreted in the context of an integrated multidisciplinary approach, allowing a definitive diagnosis based on clinical and radiological findings in some cases and reinforcing the need for invasive diagnostic procedures in less typical cases.^(3,4) After morphological evaluation by HRCT or surgical biopsy, potential causative factors such as environmental exposures, CTDs, and use of medications should be evaluated clinically.⁽⁴⁾ In some cases, a final diagnosis will not be achieved for a number of reasons, including inadequate clinical, radiological, or pathological data and major discordance between clinical, radiological, and pathological findings; such

cases should be classified under the category of “unclassifiable” idiopathic interstitial pneumonia.⁽⁴⁾

Major morphological patterns of fibrosing ILD

Usual interstitial pneumonia

One of the key roles that HRCT plays in the diagnostic evaluation of fibrosing ILDs is determining the likelihood of a usual interstitial pneumonia (UIP) pattern.^(3,4,10,11) A histopathological pattern of UIP is associated with multiple diagnoses, including drug-induced lung diseases, occupational diseases, CTDs, HP, and IPF.^(3,21)

An official American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and *Asociación Latinoamericana de Tórax* (ALAT, Latin American Thoracic Association) clinical practice guideline recommends that, in patients with clinical suspicion of IPF, HRCT features of the UIP pattern be categorized as follows (Figure 3):

a) UIP pattern—the typical UIP HRCT pattern, with reticular opacities, traction bronchiolectasis, and honeycombing with peripheral distribution and basal predominance. There is high concordance between an HRCT pattern of UIP and a histopathological pattern of UIP.^(10,11)

b) probable UIP pattern—an HRCT pattern with reticular opacities and traction bronchiolectasis with peripheral distribution and an apicobasal gradient, without honeycombing. Studies have shown a high correlation between an HRCT pattern of probable UIP and a histopathological pattern of UIP.^(10,11)

c) indeterminate-for-UIP pattern—HRCT patterns that do not meet the criteria for a UIP or probable UIP pattern and that are not sufficiently characteristic to suggest a specific diagnosis. An HRCT pattern indeterminate for UIP includes mild ground-glass opacities that are not clearly more extensive than and are dissociated from reticular opacities, as well as ill-defined areas of mosaic attenuation or diffuse axial/zonal distribution.^(22,23) Patients with evident but mild fibrosing disease, presumably related to early fibrosing changes, should also be included in this category, prone CT imaging being recommended to differentiate between dependent opacities and initial interstitial changes.

d) HRCT pattern suggestive of an alternative diagnosis—HRCT findings suggestive of diagnoses other than UIP/IPF, including atypical findings (including consolidation, extensive ground-glass attenuation in the absence of an exacerbation, well-defined mosaic attenuation, nodules, and cysts), atypical distribution (including upper-/mid-lung predominance, peribronchovascular involvement, and subpleural sparing), and other findings (including pleural plaques, pleural effusion, esophageal dilation, and extensive lymph node enlargement).

In specific contexts, a diagnosis of IPF can be made on the basis of clinical-radiological correlations; in

other contexts, it can be made by correlating HRCT and biopsy findings.^(10,11)

NSIP

The NSIP pattern is associated with several diseases, including CTD-FILD, HP, drug-induced lung disease, infections, immunodeficiencies, and idiopathic ILD.⁽³⁾ HRCT features suggestive of NSIP include ground-glass attenuation, reticular opacities, and traction bronchiolectasis in a predominantly basal and peripheral or diffuse distribution (Figure 4). Honeycombing is an uncommon finding, seen only in advanced cases.^(3,24,25) Findings of NSIP and UIP overlap in some patients, subpleural sparing being suggestive of an NSIP pattern on HRCT.^(24,25)

Other morphological patterns of fibrosing ILD

There are several other morphological patterns of fibrosing ILD. Pleuroparenchymal fibroelastosis is a recently described rare fibrosing disease that can be idiopathic or associated with a variety of conditions, including complications of bone marrow or lung transplantation, autoimmune diseases, CTDs, infections (with *Aspergillus* spp. or nontuberculous mycobacteria), use of cancer treatment drugs, and occupational exposures. Typical HRCT findings include pleural thickening and subpleural consolidations with traction bronchiectasis, architectural distortion, and volume loss, typically in the upper lobes (Figure 4). Pneumothorax and recurrent infections are common in patients with pleuroparenchymal fibroelastosis, with disease progression occurring in most cases (60%).^(4,26)

Despite being classified as an acute/subacute interstitial pneumonia and the fact that the majority of patients recover completely with oral corticosteroids, organizing pneumonia can progress to residual or progressive interstitial fibrosis.⁽⁴⁾ It is likely that some patients with fibrotic NSIP fall into this subgroup of patients. A mixed pattern of NSIP and organizing pneumonia can be seen in patients with antisynthetase syndrome-associated myositis.^(4,27,28) Fibrotic patterns can also be observed in patients surviving episodes of (idiopathic or secondary) late-stage diffuse alveolar damage; architectural distortion, traction bronchiectasis, and cysts can occur in such patients, predominantly in nondependent lung regions.^(3,4)

Morphological patterns such as lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, and smoking-related changes (airspace enlargement with fibrosis) can also be related to fibrotic HRCT features.^(3,4)

Specific clinical entities

Fibrotic HP

Fibrotic HP is a fibrosing ILD resulting from chronic exposure to specific antigens, the definitive diagnosis of which depends on a multidisciplinary approach. HRCT plays a central role in various algorithms for

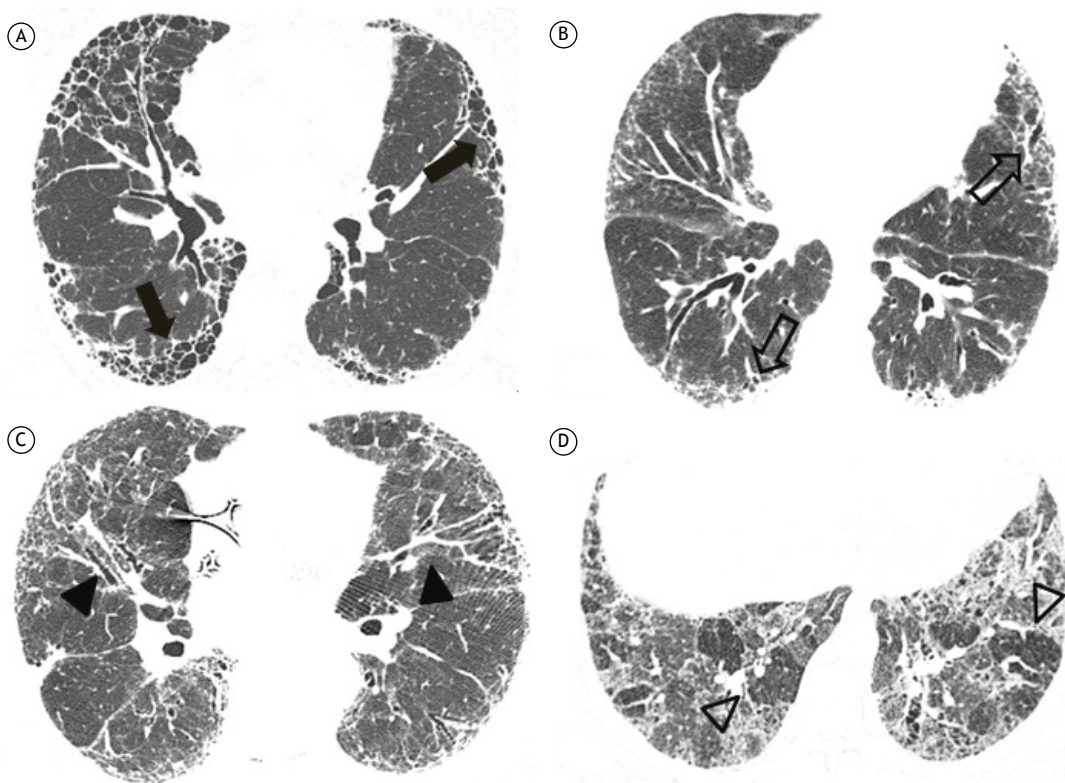


Figure 3. Axial HRCT scans with lung window settings, showing fibrosing interstitial lung disease in patients suspected of having idiopathic pulmonary fibrosis and presenting with different HRCT features of the usual interstitial pneumonia (UIP) pattern. In A, UIP pattern, with extensive honeycombing (arrows), peripheral distribution, and basal predominance. In B, probable UIP pattern, with peripheral reticular opacities and traction bronchiolectasis (open arrows), without honeycombing. In C, indeterminate-for-UIP pattern, with diffuse axial distribution and central involvement (arrowheads), as well as areas of ground-glass opacity, together with reticular opacities. In D, a pattern suggestive of an alternative diagnosis, with extensive areas of ground-glass opacity and a mosaic pattern of lung attenuation (open arrowheads).

the diagnosis of fibrotic HP,⁽²⁹⁻³²⁾ as well as in an official ATS/JRS/ALAT clinical practice guideline⁽³³⁾ for the diagnosis of fibrotic HP in adults. An HRCT pattern of fibrosing ILD and evidence of small airway disease are suggestive of a diagnosis of fibrotic HP.⁽³³⁾ Fibrosis is most severe in the mid or mid and lower lung zones or equally distributed in the three lung zones with relative basal sparing; on axial images, there is often no central or peripheral predominance of lung fibrosis.⁽³³⁾ Honeycombing can be present in a subpleural or peribronchovascular distribution and, less frequently, with a basal predominance.⁽²⁴⁾ HRCT features of small airway disease include centrilobular opacities, mosaic attenuation, air trapping, and the “three-density pattern” (formerly known as the “headcheese sign,” a combination of three attenuations on inspiratory CT images, i.e., areas of normal lung parenchyma, areas of ground-glass attenuation, and areas of hyperlucency, indicating an association between infiltrative lung disease and airway obstruction).^(33,34) Mosaic attenuation has a high diagnostic value, particularly in pulmonary parenchymal segments without overt fibrosis.^(10,24,29-32) One recent study showed that the three-density pattern is specific for fibrotic HP, highlighting that

areas of decreased attenuation can be seen in cases of IPF as well.⁽³⁵⁾ Other morphological patterns can be seen, including typical UIP and NSIP.⁽³⁶⁾ According to current guidelines, HRCT features in patients suspected of having fibrotic HP should be categorized as follows (Figure 5):

a) typical HP pattern—diffuse interstitial fibrosis with middle lung predominance or basal sparing, as well as abnormalities indicative of small airway disease.

b) compatible-with-HP pattern—variant patterns of interstitial fibrosis (UIP pattern and extensive ground-glass opacities with incipient fibrosis), peribronchovascular distribution with subpleural areas axially and upper lung predominance craniocaudally, as well as abnormalities indicative of small airway disease.

c) indeterminate-for-HP pattern—lone patterns (i.e., not accompanied by other findings suggestive of HP), including UIP pattern, probable UIP pattern, indeterminate pattern for UIP, fibrotic NSIP pattern, organizing pneumonia-like pattern, and truly indeterminate HRCT patterns.

Ancillary diagnostic tests such as bronchoalveolar lavage and surgical biopsy can be performed when

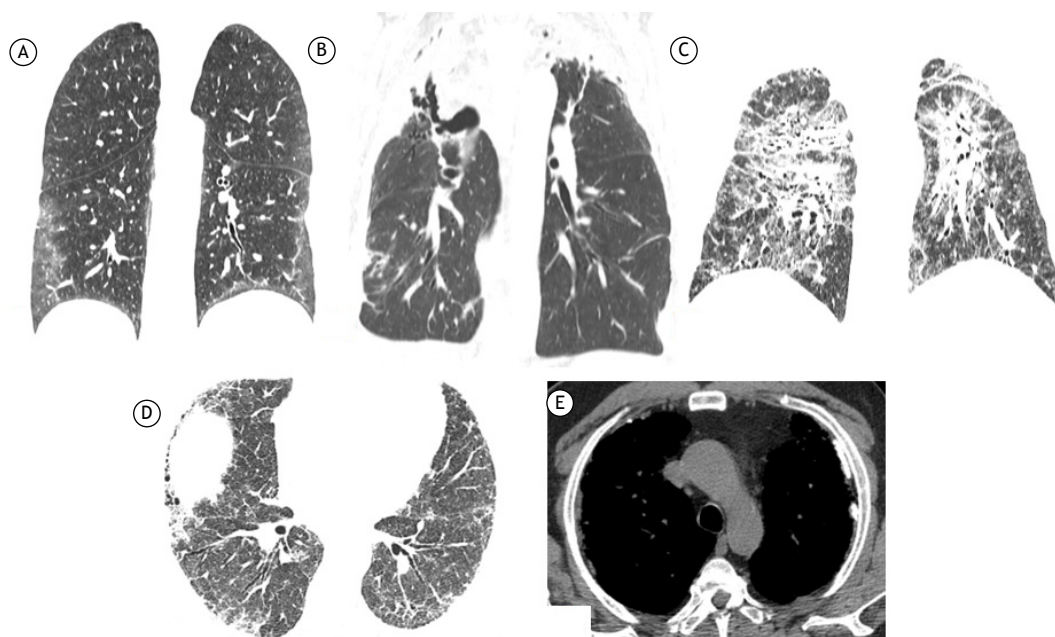


Figure 4. Axial HRCT scans of the chest showing features related to different fibrosing diseases. In A, features suggestive of nonspecific interstitial pneumonia, with a predominance of ground-glass opacities. In B, features of pleuroparenchymal fibroelastosis confirmed by histopathology showing predominantly apical fibrosing disease with upper lobe volume loss and upward hilar retraction. In C, scan of a patient with sarcoidosis, showing fibrosing disease with an upper-lobe predominance. In D and E, scans of a patient with fibrosing lung disease caused by exposure to asbestos. Note the presence of pleural plaques (arrows in E).

a reliable diagnosis cannot be made on the basis of clinical and radiological analysis.^(30,33)

CTD-fILD

ILDs are associated with multiple CTDs, with varying prevalence across diseases. The estimated prevalence of HRCT findings consistent with ILD is 70-90% in systemic sclerosis, 15-70% in inflammatory myopathies (being more common in patients with antisynthetase antibodies), 4-68% in rheumatoid arthritis, 20-85% in mixed CTD, 10-30% in Sjögren's syndrome, and up to 30% in systemic lupus erythematosus.⁽³⁷⁾ Although the patterns of fibrosis in CTD-fILD and other fibrosing ILDs are similar, Chung et al.⁽³⁸⁾ identified specific CT signs that are more common in the former than in the latter: the "anterior upper lobe" sign—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; the "exuberant honeycombing" sign—extensive honeycomb-like cyst formation within the lungs constituting greater than 70% of the fibrotic portions of lung; and the "straight-edge" sign—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 (Figure 6). The authors⁽³⁸⁾ compared patients with UIP associated with IPF and patients with UIP associated with CTD-fILD (rheumatoid arthritis or systemic sclerosis in most cases). The positive predictive values of the anterior upper lobe,

exuberant honeycombing, and straight-edge signs were 1.99 ($p = 0.028$), 3.69 ($p < 0.001$), and 4.22 ($p < 0.001$), respectively, and the signs were most common in patients with systemic sclerosis. Similarly, Walkoff et al.⁽³⁹⁾ evaluated the specificity of the "four corners" sign—pulmonary inflammation and/or fibrosis focally or disproportionately involving the bilateral anterolateral upper lobes and posterosuperior lower lobes—in a sample of patients with IPF and systemic sclerosis, and found a significant association between a confidently present four corners sign and a diagnosis of systemic sclerosis.

Sarcoidosis

Approximately 20% of patients with sarcoidosis will develop fibrosing ILD over the course of the disease, with fibrocystic changes, including honeycombing. Typical fibrotic HRCT features include upper lobe and peribronchovascular fibrosis, as well as posterior retraction of the hila, together with mediastinal lymph node enlargement (Figure 4).^(11,40)

Asbestosis

Asbestos-related fibrosing ILD usually occurs 20 years or more after exposure. The changes of asbestosis are more pronounced in the lower lobes and subpleurally, and honeycombing can occur, albeit only in advance cases; imaging findings of asbestosis can be indistinguishable from those of various clinical entities, including IPF.^(41,42) Akira et al.⁽⁴²⁾ studied HRCT

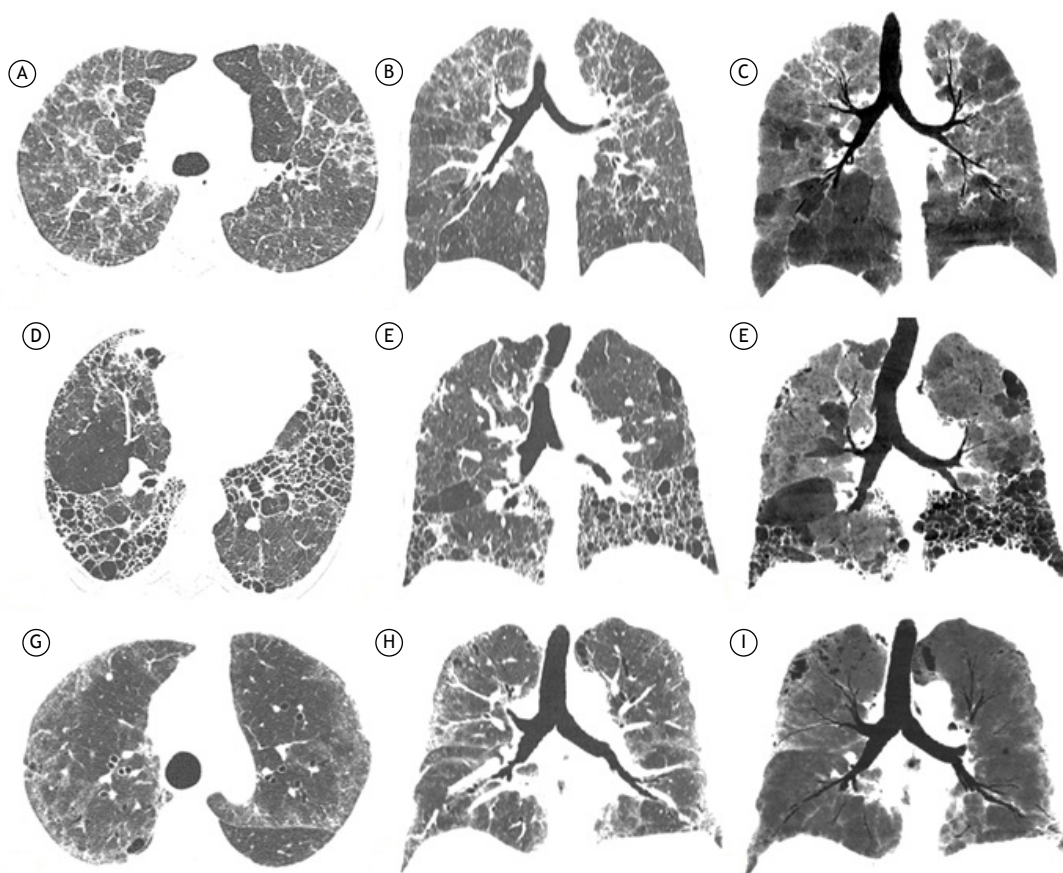


Figure 5. Axial HRCT scans with lung window settings (in A, D, and G), coronal reconstructions (in B, E, and H), and coronal minimum intensity projection reformatted images (in C, F, and I) for three patients with fibrotic hypersensitivity pneumonitis (HP). In A, B, and C, a typical HP pattern, with diffuse interstitial fibrosis axially and relatively spared lower lung zones, as well as marked mosaic attenuation in a predominantly caudal distribution, indicating small airway disease (in C). In D, E, and F, a compatible-with-HP pattern, with predominantly peripheral, basal interstitial fibrosis and extensive honeycombing (characteristic of usual interstitial pneumonia), as well as scattered areas of mosaic attenuation, constituting evidence of small airway disease (in F). In G, H, and I, an indeterminate-for-HP pattern, with areas of ground-glass opacity, reticular opacities, and traction bronchiectasis in a diffuse axial/cranio-caudal distribution, as well as no evidence of small airway disease.

scans of patients with asbestosis or IPF and concluded that subpleural dot-like or branching opacities, subpleural curvilinear lines, mosaic attenuation, and parenchymal bands are significantly more common in the former than in the latter. Although the parenchymal abnormalities found in patients with asbestosis can also be found in patients with other diseases, pleural plaques are characteristic of exposure to asbestos, being found in up to 80% of patients with asbestosis on radiographic studies (Figure 4).⁽⁴¹⁾ The diagnosis of asbestosis is based on a thorough clinical and occupational history.

ROLE OF HRCT IN SELECTING THE BEST SITE FOR SURGICAL LUNG BIOPSY

The decision to perform a surgical lung biopsy must be made by a multidisciplinary team with experience in ILDs. In the diagnosis of IPF in particular, current guidelines recommend that surgical lung biopsy be performed in newly diagnosed ILD patients who have

an HRCT pattern indeterminate for UIP or suggestive of an alternative diagnosis, conditional recommendations being made for performing surgical lung biopsy in those with a pattern of probable UIP.^(10,11,43)

When surgical lung biopsy is indicated, multiple biopsies should be obtained from two to three lobes, because the histological patterns on specimens obtained from different segments can be discordant.^(10,11) HRCT is useful for prebiopsy evaluation and selection of the best sampling sites. In order to avoid the possibility that a biopsy specimen was taken from an area not representative of the predominant disease process, biopsy specimens should be obtained from areas that reflect the full spectrum of disease patterns as guided by HRCT evaluation or intraoperative inspection of the lung surface. Areas of honeycombing should be avoided because they show end-stage disease and are likely to be of little use when establishing a diagnosis. Areas that show intermediate or relatively preserved lung parenchyma, or areas of ground-glass

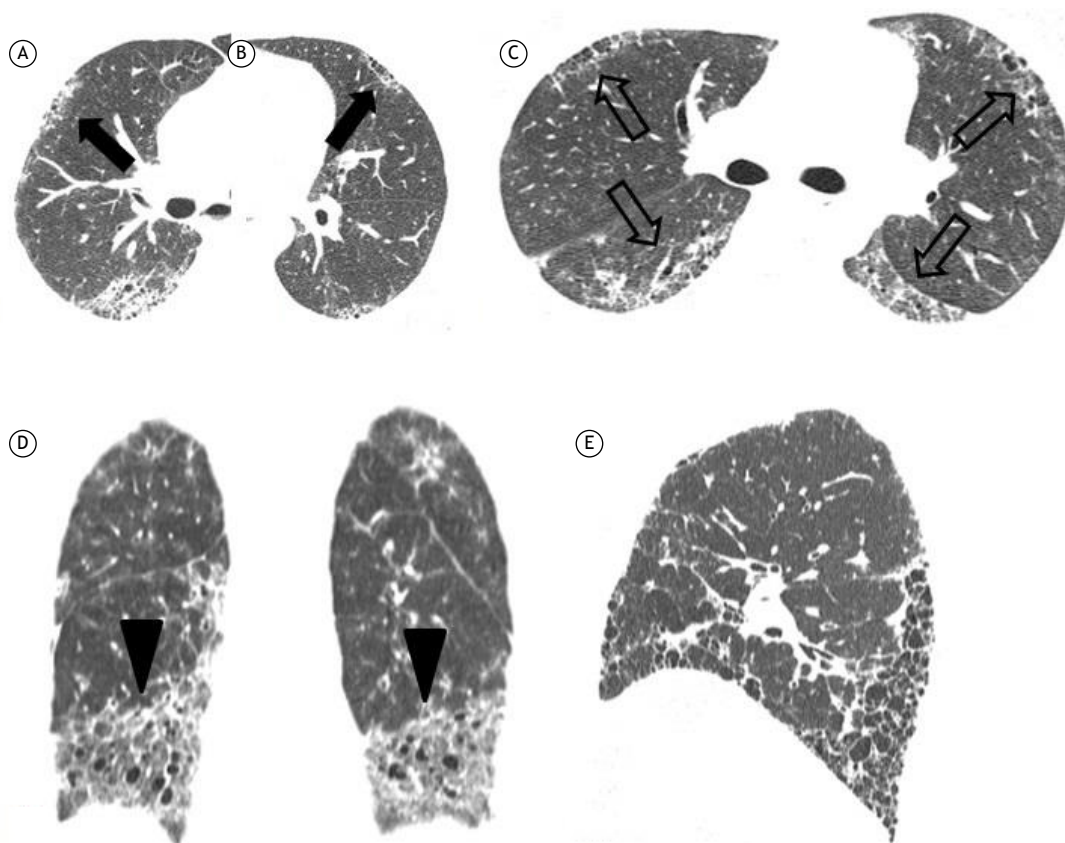


Figure 6. Specific CT signs of fibrosis in connective tissue disease-associated fibrosing interstitial lung disease. In A and B, the “anterior upper lobe” sign (arrows) in a patient with rheumatoid arthritis. In C, the “four corners” sign (open arrows)—fibrosis focally involving the bilateral anterolateral upper lobes and posterosuperior lower lobes—in a patient with systemic sclerosis. In D, the “straight-edge” sign (arrowheads)—isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane. In E, the “exuberant honeycombing” sign—extensive honeycombing constituting most of the fibrotic portions of lung.

opacity should ideally be selected for biopsy because the lung specimen must have fibrotic lung adjacent to normal lung for the pathologist to identify the UIP pattern.^(10,44,45) Flaherty et al.⁽⁴⁵⁾ specifically addressed the role of histopathological sampling in differentiating between UIP and NSIP, demonstrating histological variability in surgical lung biopsy specimens from multiple lobes and reinforcing the need for having multiple lobes biopsied. Given that the prognosis is worse for UIP than for NSIP, sampling should be optimized so as not to miss areas most likely to demonstrate the histological pattern of UIP.⁽⁴⁵⁾

DISEASE SEVERITY ASSESSMENT, QUANTIFICATION, AND FOLLOW-UP

Disease severity assessment

Given that several fibrosing ILDs have an unpredictable natural history, staging systems can be useful in estimating prognosis and guiding management decisions (e.g., timing of pharmacological treatment and lung transplantation). The most widely used model for assessing chronic fibrosing diseases is a scoring

system based on clinical and functional parameters (gender, age, FVC, and DLCO); the GAP model (**G**ender, **A**ge, and lung **P**hysiology) is most commonly used in patients with IPF and has been shown to be accurate in predicting survival.^(46,47) Adaptations of this model have recently been tested to include HRCT. Ley et al.⁽⁴⁸⁾ replaced DLCO with a visual semiquantitative HRCT score and reported that the resulting model had a performance that was comparable to that of the original GAP model. Chahal et al.⁽⁴⁹⁾ evaluated the impact of adding a visual semiquantitative fibrotic score above or below 25% to the GAP model and found that the resulting model shows improved correlation with survival, especially in patients with mild disease. Other multidimensional indices including functional variables and CT evaluation have been proposed to stage systemic sclerosis-related fibrosing ILD, sarcoidosis, and other ILDs.^(50,51)

Quantification

Qualitative (visual) and semiquantitative imaging techniques can be used in order to assess ILDs in general and correlate with outcomes in a number of ILDs; however, they are highly dependent on visual

analysis and are of limited use in detecting subtle changes in disease progression. Quantitative imaging, including histogram analysis and textural-based analysis coupled to machine learning, is a new and promising approach, allowing quantification of patterns such as ground-glass opacification, reticulation, and honeycombing.⁽⁵²⁾ In addition to quantification, automated analysis is useful for interpreting CT patterns, as demonstrated in a study by Walsh et al.,⁽⁵²⁾ in which a deep learning algorithm had a performance comparable to that of thoracic radiologists in determining the likelihood of UIP in accordance with criteria specified in the 2011 ATS/ERS/JRS/ALAT guidelines.⁽⁵³⁾ A combination of automated and visual analysis is likely to be the optimal approach to disease staging and outcome prediction in fibrosing ILDs.

Follow-up

Serial CT can reveal changes in the extent of reticulation, traction bronchiectasis, and honeycombing, allowing identification of progressive fibrosing ILDs, which are associated with a worse prognosis.⁽⁵²⁾ However, the optimum time interval for CT follow-up has yet to be established, and currently there are no formal recommendations to sequential HRCT follow-up in clinically stable patients.⁽⁵¹⁾ Given that patients with various fibrosing ILDs have a slow disease progression, the longitudinal behavior of fibrosing ILDs can be more easily detected by comparing follow-up CT scans with initial CT scans rather than by comparing follow-up CT scans only (Figure 7). HRCT evaluation of disease progression is one of the recently proposed criteria for the definition of progressive fibrosing ILD.⁽⁵⁴⁾ Patients are required to meet at least one of the following criteria for progression of fibrosing ILD within 24 months: a reduction in FVC of at least 10% of the predicted value; a reduction in FVC of 5-10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on HRCT; or worsening of respiratory symptoms and an increased extent of fibrosis on HRCT. It is important to define progressive fibrosing ILD because recent evidence shows a reduction in the rate of decline in FVC in non-IPF progressive fibrosing ILD patients undergoing treatment with nintedanib.⁽⁵⁴⁾

In addition to determining disease behavior, CT follow-up plays an important role in detecting complications such as pulmonary hypertension, pulmonary embolism, neoplasms, and coronary artery disease, all of which can have an impact on survival (Figure 8).⁽⁵¹⁾

ACUTE EXACERBATION OF FIBROSING ILD

Acute exacerbation of fibrosing ILD is defined in accordance with current criteria for IPF: an acute, clinically significant respiratory deterioration, typically less than 1 month in duration, categorized as pulmonary or extrapulmonary (pulmonary embolism, pneumothorax, pleural effusion, or any combination of the three). HRCT plays a major role in the diagnosis of acute exacerbations. In patients with episodes of inflammatory exacerbation, noninvasive criteria include HRCT findings of bilateral ground-glass opacities, consolidations, or a combination of the two superimposed on a background pattern consistent with fibrosing ILD but that are not explained by hydrostatic edema, regardless of whether the condition is idiopathic or caused by any other factor, including infection (Figure 8). CT angiography plays an important role in detecting episodes of acute exacerbation caused by pulmonary thromboembolism.^(16,55)

FINAL CONSIDERATIONS

The management of patients with fibrosing ILD is complex. In a multidisciplinary approach, CT evaluation is important at various stages of patient management, including early diagnosis, narrowing of the diagnostic possibilities (definition of morphological patterns and, eventually, pointing toward specific clinical entities), disease severity assessment, prognosis, and follow-up, as well as in identifying complications such as infections, neoplasms, and acute exacerbations. Many issues have yet to be resolved, including interobserver variation in the interpretation of scans, the optimum time interval for CT follow-up, and the significance of subclinical ILAs. New approaches involving automated techniques and machine learning can be useful at various stages, and their significance should be investigated in future studies.

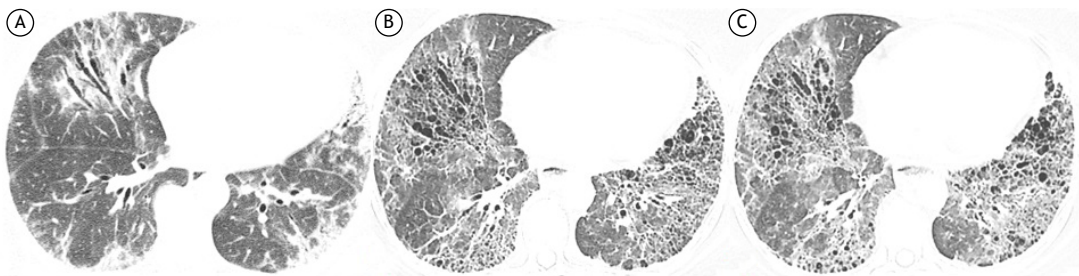


Figure 7. Axial HRCT scans. Initial CT scan (in A) and follow-up CT scans at six years (in B) and six and a half years (in C) in a patient with systemic sclerosis-related fibrosing interstitial lung disease. Although the follow-up scans apparently show no changes in disease progression, a comparison between the initial and follow-up scans reveals a progressive disease phenotype, underscoring the importance of comparing follow-up CT findings with initial CT findings.



Figure 8. Coronal reconstructions of HRCT scans showing complications of fibrosing interstitial lung disease in two patients. In A and B, scans of a patient with progressive idiopathic pulmonary fibrosis. Initial CT scan (in A) and follow-up CT scan at seven years and ten months (in B), showing disease progression and an irregular subpleural expansile neoplastic lesion in the right lower lobe, diagnosed as adenocarcinoma (arrow in B). In C and D, scans of a patient with progressive idiopathic pulmonary fibrosis. Initial CT scan (in C) and follow-up CT scan at 15 months (in D), showing disease progression and new bilateral ground-glass opacities, characterizing acute exacerbation of idiopathic pulmonary fibrosis.

AUTHOR CONTRIBUTIONS

PPTST, MFR, and EM conceived and planned the study; interpreted the data; drafted, reviewed, and

revised the manuscript; and approved the final version. MACM, DLE, and GSPM drafted, reviewed, and revised the manuscript; and approved the final version.

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