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Probable UIP: What is the Evidence that Compels this Classification and How is it Different from the Indeterminate Category?

Jonathan H. Chung, MD and Luis Landeras, MD

Background on Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is an irreversible pulmonary condition, which causes progressive lung fibrosis and scarring. It is the most common and most fatal of the idiopathic interstitial pneumonias (IIPs) and has an unpredictable as well as variable clinical course. Prognosis is typically very poor with median survival of 2-5 years.[1-3] More than 100,000 individuals in the United States are affected by IPF; IPF has an estimated prevalence of up to 4.0-42.7 per 100,000 persons.[4] Recent evidence suggests that the incidence of and mortality from IPF may be increasing.[5,6]

The diagnosis of IPF and its mimics is quite complex and still evolving. Evidence-based guidelines on the diagnosis and management of IPF were released in 2011.[7] In 2013, the American Thoracic Society (ATS) and European Respiratory Society released a multidisciplinary update on the classification of the IIPs, which draws on the multitude of studies about IIPs which were published since release of the previous classification system in 2002.[8] Recently, the Fleischner Society published an updated approach to IPF diagnosis based on advances in the field.[9] In this white paper, 2 major alterations to the usual interstitial pneumonia (UIP) classification system on CT are the introductions of the probable UIP and indeterminate for UIP categories. The ATS, European Respiratory Society, Japanese Respiratory Society, and Latin ATS subsequently in their updated guidelines published similar, or rather identical, categories with minor inconsequential differences.[10] The purposes of this review paper are first to review these changes, to provide a background on the imaging of IPF to date, and, finally, to address some nuances and shortcomings of the current state of imaging in IPF.

Department of Radiology, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL.

Address reprint requests to Jonathan H. Chung, MD, Department of Radiology, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637. E-mail: JChung@radiology.bsd.uchicago.edu

Importance of Imaging in Pulmonary Fibrosis

As opposed to the vast majority of other disease processes, diagnosis in pulmonary fibrosis does not rely solely on pathology as the gold standard. Multidisciplinary correlation of available clinical, functional, pathological, and imaging information is considered the gold standard in diagnosis rather than reliance on any single set of data.[11] In 1 study, radiologists, pathologists, and clinicians were asked to diagnose subjects with IIPs first in isolation and then collaboratively. Surprisingly, in 1 of 5 of cases pathologists changed their original diagnosis.[12] As one of the pillars of diagnosis in the setting of IPF and the IIPs, accurate interpretation of high resolution chest CT (HRCT) is paramount. A high confidence diagnosis of a usual interstitial pneumonia UIP pattern on HRCT obviates biopsy, given that it is 95% accurate in the diagnosis of IPF.[7] About half of cases of IPF can be confidently diagnosed on HRCT.[13] Patients without a typical UIP pattern on HRCT may require further evaluation with biopsy. Therefore, accurate imaging diagnosis is now even more important to avoid unnecessary lung biopsy, especially in patients with pulmonary fibrosis given that surgical biopsy is a risk factor in development of acute exacerbation.[14-16]

HRCT is central to diagnosis of interstitial lung diseases (ILDs), particularly IPF. However, HRCT is a challenging topic for many radiologists, and it has been shown that community radiologists (as well as community pathologists and pulmonologists) may not be well-versed in ILD HRCT diagnosis.[17] With development of promising treatments for IPF, the precise diagnosis of UIP/IPF is becoming even more important, and, therefore, adequate understanding of the most up-to-date imaging recommendations is mandatory.

Imaging of IPF

The first step to achieve accurate diagnosis in the setting of ILD is to ensure that HRCT scans are performed adequately. Though the line between a standard chest CT and HRCT

https://doi.org/10.1053/j.ro.2018.12.006
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continues to blur, there are differences between the 2 CT protocols that must be adhered to. The first and most important difference between HRCT and standard chest CT is reconstruction or acquisition slice thickness. Typically, standard chest CT images are reconstructed at 2.5-3 mm slice thickness in the axial plane after a standard volumetric inspiratory supine CT acquisition. However, reconstruction or acquisition of axial images in the range of 1 mm slice thickness is necessary in the setting of HRCT (Fig. 1). At some centers, even standard chest CT studies are reconstructed at near 1 mm slice thickness. As in standard chest CT, the supine inspiratory phase of a HRCT study would be reconstructed using a high spatial frequency algorithm with the field of view generally limited to the lung parenchyma. Intravenous contrast is unnecessary and, therefore, should not be used except if clinically indicated for other reasons. In HRCT, expiratory as well as prone images should also be acquired though these need not be volumetric acquisitions.

Imaging, in and of itself, cannot diagnose IPF. As suggested by its name, IPF is a diagnosis of exclusion. A detailed history and physical examination is necessary to exclude a known cause for pulmonary fibrosis. In the absence of known cause of pulmonary fibrosis, a UIP pattern is diagnostic of IPF as UIP is the imaging and histological correlate of IPF. From a practical standpoint, all cases of IPF have an imaging and/or histological diagnosis of UIP, though not all cases of UIP are IPF. As imagers, radiologists are most helpful to clinicians when they can identify a UIP pattern of pulmonary fibrosis on CT as this obviates biopsy, as aforementioned. To achieve a high diagnostic accuracy of UIP on CT, there must be a specific constellation of findings: peripheral and basal predominant reticulation with or without associated traction bronchiectasis as well as presence of subpleural honeycombing (Fig. 2). Also, there should be no other findings that are suggestive of an alternative diagnosis such as significant air trapping, significant ground glass opacity or pulmonary consolidation, diffuse nodularity, or cystic lung disease. If the pattern of pulmonary fibrosis is not UIP, diagnostic accuracy falls and surgical lung biopsy must be considered to achieve a high confidence diagnosis.

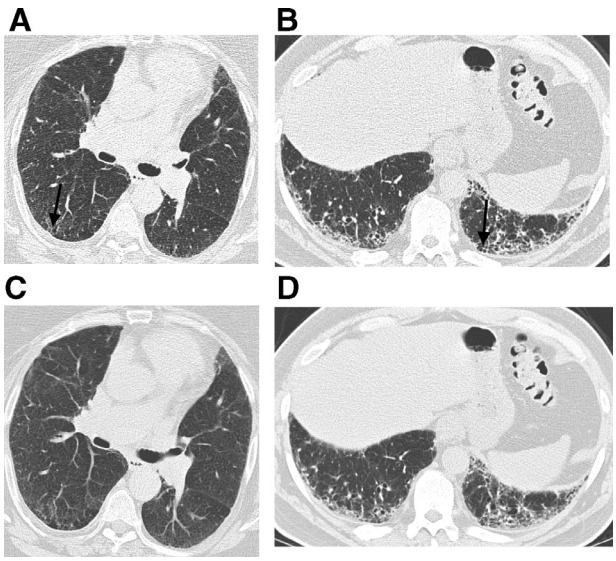

Figure 1 Thin (1 mm) thick axial images (A, B) reconstructed from HRCT demonstrate mild peripheral reticulation and mild subpleural honeycombing (arrows). Honeycombing is obscured by volume averaging on thicker (3 mm) reconstructed images (C, D).

Previous and New Guidelines

The 2011 guidelines for IPF diagnosis supported a 3-tiered approach to the imaging classification of HRCT scans in suspected pulmonary fibrosis: UIP (described above), possible UIP, and inconsistent with UIP. The possible UIP pattern on CT was identical to the UIP pattern except for absence of subpleural honeycombing. The inconsistent with UIP pattern was much more heterogeneous. This imaging pattern was actually 7 separate CT findings that were suggestive of alternative diagnoses:

1. upper/mid distribution (Fig. 3)
2. peribronchovascular distribution (Fig. 4)
3. extensive ground-glass opacity (Fig. 5)
4. significant consolidation
5. discrete cysts (not honeycombing)
6. extensive mosaic attenuation/air-trapping (Fig. 3-5)
7. profuse micronodules

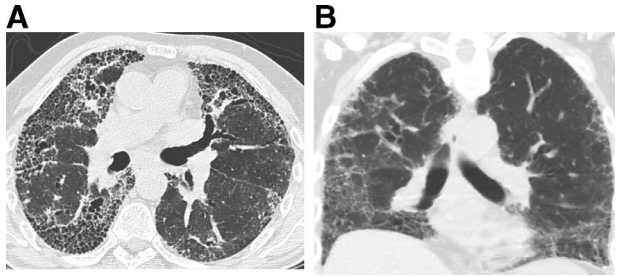

Figure 2 Axial (A) and coronal (B) images from HRCT demonstrate peripheral and basilar predominant reticulation, traction bronchiectasis, and subpleural honeycombing consistent with UIP, obviating open lung biopsy given this CT pattern's high positive predictive value for UIP on pathology.

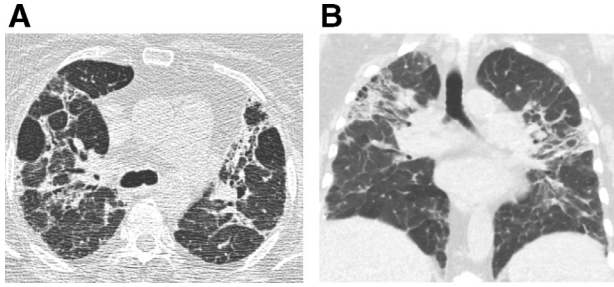

Figure 3 Axial (A) and coronal (B) images from HRCT demonstrate axially diffuse and mid/upper lung predominant reticulation, traction bronchiectasis, architectural distortion, and extensive mosaic attenuation, most consistent with a non-IPF diagnosis (formerly inconsistent with UIP). Overall, findings are highly suggestive of HP, which was the eventual multidisciplinary diagnosis.

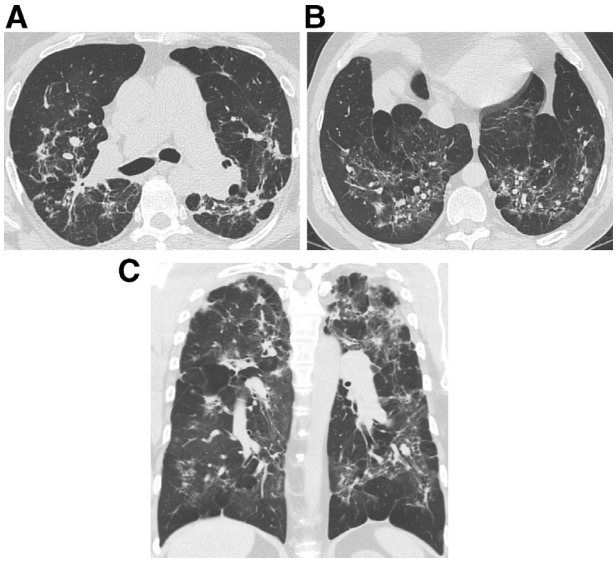

Figure 4 Axial (A, B) and coronal (C) images from HRCT demonstrate axially peribronchovascular and upper lung predominant reticulation, traction bronchiectasis, architectural distortion, and mosaic attenuation, most consistent with a non-IPF diagnosis (formerly inconsistent with UIP). Overall, findings are most consistent with fibrotic sarcoidosis, which was proven on pathology.

If any 1 of these 7 findings was present, then the CT was categorized as inconsistent with UIP.

In late 2017, the Fleischner Society released a white paper introducing a new imaging classification in suspected IPF. Highlights of this new classification system include:

1. Changing the category of "possible UIP" to "probable UIP" (Fig. 6).
2. Relaxation of biopsy recommendation in those who have a "probable UIP" pattern on CT.
3. Introduction of the "indeterminate for UIP" category (Figs. 7 and 8).
4. Inclusion of zonally diffuse cases into the typical UIP pattern.
5. Renaming of the inconsistent with UIP category to "CT features most consistent with non-IPF diagnosis."

The rationale for the change in nomenclature from possible UIP to probable UIP is based on multiple studies that have shown that this CT pattern is highly associated with UIP pathology. Data from a large genome-wide association study including a heterogeneous collection of ILD subtypes showed that a possible UIP pattern on CT had pathology similar to UIP on CT and significantly different from inconsistent with UIP on CT.[18] Yagihashi et al. showed that in a cohort of IPF subjects, nearly all patients with a possible UIP pattern on CT had UIP on pathology.[19] Interestingly, these researchers also found that a very high proportion of their subjects with an inconsistent with UIP pattern also had UIP on pathology, which emphasizes the importance of disease prevalence in determining the performance imaging results. Another radiology-pathology study showed that the proportion of UIP and possible UIP cases on CT showing a UIP

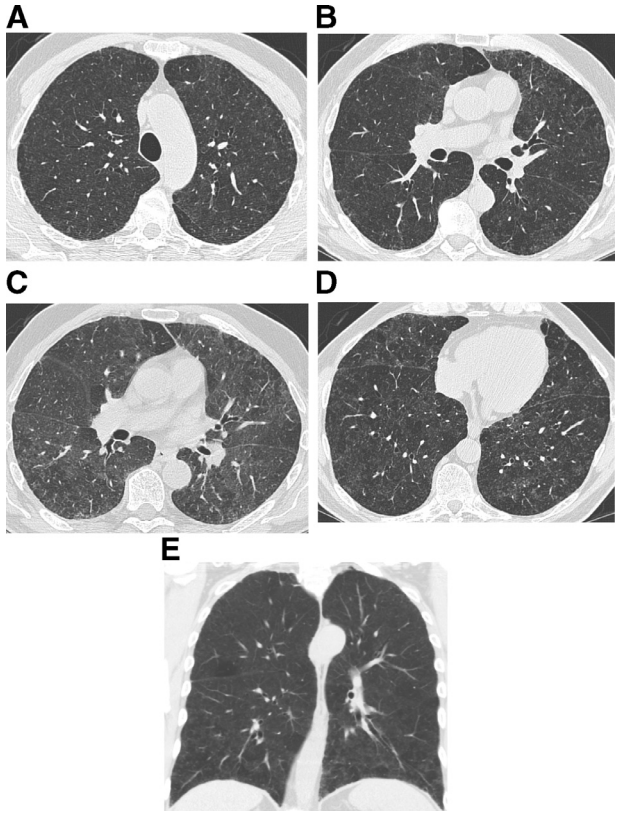

Figure 5 Axial (A-D) and coronal (E) images from HRCT demonstrate diffuse ground glass opacity in a centrilobular configuration and basilar mosaic attenuation, consistent with a non-IPF diagnosis (formerly inconsistent with UIP). The constellation of findings is highly suggestive of HP.

pattern on pathology were similar (~8% difference). Moreover, in subset analysis of subjects who were older than 60 years of age, the proportion of UIP cases on pathology were nearly identical (~2% difference).[20,21]

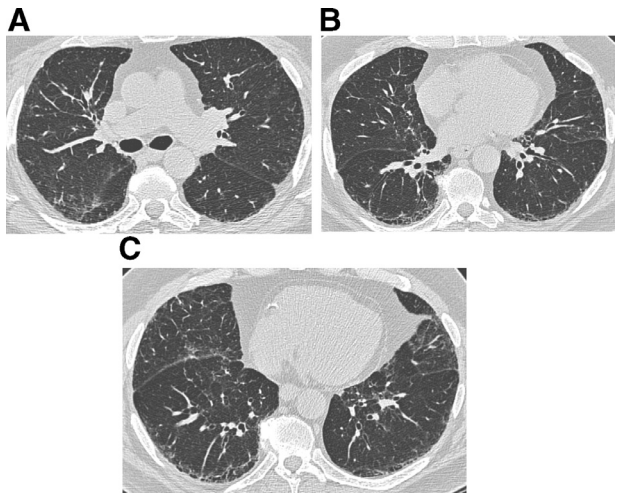

Figure 6 Axial (A-C) images from HRCT demonstrate peripheral and basilar predominant reticulation, and traction bronchiectasis, without subpleural honeycombing consistent with probable UIP (possible UIP).

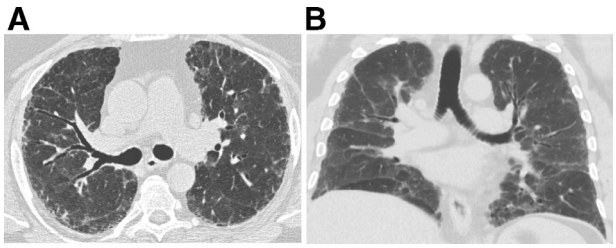

Figure 7 Axial (A) and coronal (B) images from HRCT demonstrate peripheral and basilar predominant reticulation, ground glass opacity, and traction bronchiectasis, without subpleural honeycombing categorized as indeterminate for UIP. Given the modest degree of ground glass opacity, the pattern on CT was thought not to be consistent with a non-IPF diagnosis, but not confidently a probable UIP, either. A multidisciplinary diagnosis of HP was made based on suggestive pathological findings and history of chronic mold exposure.

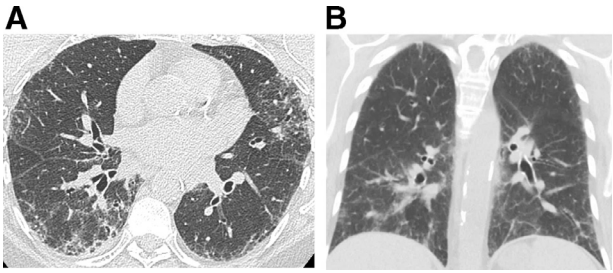

Figure 8 Axial (A) and coronal (B) images from HRCT demonstrate peripheral and basilar predominant reticulation, mild patchy ground glass opacity, and traction bronchiectasis, without subpleural honeycombing categorized as indeterminate for UIP. Pathology demonstrated a UIP pattern.

Brownell et al., demonstrated the importance of considering pretest probability in the setting of UIP diagnosis.[22] Depending on the prevalence of UIP on pathology (gold standard), the positive predictive value (PPV) of a possible UIP pattern on CT was widely divergent (62.5% [29% prevalence of UIP on pathology] vs 94.4% [67% prevalence of UIP on pathology]). When restricting analysis to subjects with more severe fibrosis on CT, males, and age greater than 60 years; PPV increased substantially in the lower pathological UIP prevalence group (increase from 62.5%-95.0%). Salisbury et al., also showed that in subjects without honeycombing on CT, age and extent of lung reticulation was highly specific (96%) for a multidisciplinary diagnosis of IPF and could have obviated biopsy in 16% of cases.[23] Raghu et al., showed that IPF patients with or without honeycombing on CT (essentially those with a UIP pattern or possible UIP pattern on CT) had similar decline rates when treated with nintedanib and when not treated with nintedanib, which further supports diagnosing patients with a possible UIP pattern on CT with a working label of IPF.[24]

Based on this large amount of evidence, the Fleischner Society white paper on diagnostic criteria for IPF supports presumptive diagnosis of IPF in the setting of a probable (previously possible) UIP pattern in the patients with high pre-CT probability of having IPF. That is, patients older than 60 years, without clinically significant environmental or medication exposure, and with no evidence of connective tissue disease. Surgical lung biopsy would be considered when the CT pattern is either indeterminate or suggestive of an alternative diagnosis to IPF.

The previous classification forced one to categorize a CT pattern into a defined group even in cases, which could not be confidently performed. Though there is sparse data on what proportion of cases could not be confidently categorized, limited data suggests that 10%-30% of cases have a pattern not well-categorized using previous UIP CT classification system.[18,20] Given human nature, many of these cases were categorized as possible UIP even though they were better fits for either a definitive UIP or an inconsistent with UIP pattern. For eg, a CT scan demonstrating peripheral and basilar predominant fibrosis with subpleural honeycombing and mild to moderate degree of air trapping should be either labeled UIP or inconsistent with UIP depending on whether the degree of air trapping was determined to be great enough to suggest an alternative diagnosis (bilateral and greater than 3 lobe involvement). Anecdotally, there was a tendency to categorize these cases as possible UIP to avoid either extreme in classification. However, current data suggests that these indeterminate for UIP cases have a divergent histological pattern as compared to possible UIP CT cases.[18,20] Indeed, if anything, these indeterminate for UIP cases would be best categorized as inconsistent with UIP using previous nomenclature. The new classification system specifically addresses this issue by introducing the indeterminate for UIP CT category. This imaging pattern was most often invoked in cases of mild ground-glass opacity or air-trapping not confidently meeting criteria to achieve an inconsistent for UIP (known as most consistent with a non-IPF diagnosis in the current classification system) or a diffuse distribution of pulmonary fibrosis.[18,20] Surgical lung biopsy should be strongly considered in this setting given the high likelihood of a non-IPF clinical diagnosis.

Distribution

UIP can be diagnosed confidently on CT if there is diffuse zonal distribution as long as the other findings of UIP are present. It has long been known that a minority of UIP cases have a diffuse zonal distribution, ranging from 10%-15% of pathologically proven UIP cases.[18,25,26] Of the 3 most common patterns of fibrosis identified on chest imaging (UIP, nonspecific interstitial pneumonitis , and hypersensitivity pneumonitis [HP]), nonspecific interstitial pneumoniti is most reliably basilar predominant (~90% of cases) while fibrotic HP is basilar predominant in 1/3-1/2 of cases.[18,25,27] However, data suggests that zonal distribution may not be as reliably predictive of pathological diagnosis as axial distribution. In a retrospective radiology-pathology correlation study, researchers found that the zonal distributions of pulmonary fibrosis of pathological UIP and non-UIP patterns were not significantly different. In both groups, lower lung predominant disease was present in around 80% of cases. However, they did find that axial distribution on CT was

significantly different in those with UIP than those without UIP on pathology ($P < 0.001$).[18] This data, however, must be considered in the light of a high proportion of pathological UIP cases in this study (over 70%), which is higher than other similar studies in the literature.

Issues With the Classification System

Honeycombing

Given recent evidence, identification of CT honeycombing has decreased in its overall importance from a diagnostic standpoint as previously discussed, especially in cases of high pretest probability for IPF. This is especially true given the aforementioned evidence suggesting that presence or absence of CT honeycombing does not alter the rate of functional decline in IPF.[24] Moreover, there is early data which suggest that though CT honeycombing is important in predicting prognosis in patients with non IPF-ILD, it does not predict survival in patients with IPF.[28] However, definitive diagnosis of UIP on imaging (regardless of the pretest probability of IPF) still requires identification of honeycombing on CT.

Although a seemingly straightforward task, differentiation of CT honeycombing from traction bronchiolectasis and paraseptal emphysema can be quite difficult. Agreement for honeycombing on CT between 5 diagnostic radiologists specialized in diffuse lung disease with greater than 130 cumulative years of experience in chest CT interpretation was only moderate to substantial (kappa value between 0.45 and 0.67).[29] Moreover, agreement between nonexperts was far lower, demonstrating how difficult identification of CT honeycombing can be. Though reliable differentiation of CT honeycombing from paraseptal emphysema may be impossible in all cases, it is helpful to recall that paraseptal emphysema is usually an apical process while honeycombing is usually mid and lower lung preponderant. Moreover, honeycombing nearly always occurs in the setting of adjacent reticulation while paraseptal emphysema is usually free of substantial adjacent reticulation. Differentiation of CT honeycombing from traction bronchiolectasis can be more problematic. However, a general rule in differentiating CT honeycombing from traction bronchiolectasis is to limit diagnosis of CT honeycombing to cases in which subpleural cystic lesions lineup in rows (even 2 cysts) without any intervening lung parenchyma or in cases where cysts stack upon each other. It is important to also limit diagnosis of CT honeycombing to cases in which cysts emanate from the subpleural lung. That being said, there are cases of bronchovascular predominant pulmonary fibrosis in which cystic lesions coalesce centrally rather than peripherally in the lung; these cystic areas likely represent a similar point of end-stage fibrosis as in typical CT honeycombing.

Ground Glass Opacity

A common issue with the "CT features most consistent with non-IPF diagnosis" category is ground glass opacity. Ground glass opacity must be greater than the degree of associated reticulation in order to be significant. However, this is a very subjective determination. Those without a large amount of experience in characterization of diffuse lung disease on CT often struggle in determining whether ground glass is extensive enough and or free of substantial reticulation "pure." This is further complicated by differences in CT chest protocols across different medical centers and different vendor scanners. Indeed, even severe reticulation may be relatively subtle with thicker slice reconstruction; mild but significant reticulation made manifest as simple ground glass opacity due to volume averaging with adjacent lung. Therefore, thin cut reconstruction requisition is essential in accurate characterization of ground glass opacity vs reticulation. In addition, a very sharp reconstruction kernel may also falsely give the appearance of reticulation within the lung parenchyma even in case of pure ground glass opacity.

Mosaic Attenuation/Air-trapping

The presence of significant air-trapping on HRCT is suggestive of HP rather than UIP/IPF. In the setting of diffuse lung disease, extensive mosaic attenuation is presumptively considered air-trapping. However, mosaic attenuation can be also due to small vessel disease (chronic pulmonary hypertension) or lobular sparing of diffuse lung disease—both not uncommon in ILD. This is why the expiratory series is essential in a HRCT protocol, at least on initial assessment of ILD, as it will definitively differentiate air-trapping from its mimics. Another issue with air-trapping is that it can be found in IPF and even in normal patients.[30] Some air-trapping in IPF is not uncommon, occurring in up to 72% of cases in 1 series.[19] Greater than 50% of subjects with normal pulmonary function tests demonstrated substantial air-trapping on CT; extensive air-trapping was even present in normal nonsmoking subjects.[31] So, the question becomes how much air-trapping is "marked" enough such that it would suggest an alternative diagnosis to UIP in IPF? Unfortunately, this threshold has yet to be defined and may require the aid of quantitative analysis or correlation with functional parameters.

Conclusion

CT is central to the accurate diagnosis of pulmonary fibrosis in suspected IPF. Recent changes to the UIP imaging classification system have addressed many of the shortcomings of the previous system. The most notable changes include introduction of the probable UIP and indeterminate for UIP patterns on CT. Understanding of the new classification system is imperative to accurately communicate imaging findings of pulmonary fibrosis with clinicians.

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