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Seminars in
ROENTGENOLOGY

Advances in CT Diagnosis of UIP and IPF

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What Is IPF/UIP?

Interstitial lung disease (ILD) encompasses a large, complex, and heterogeneous group of non-neoplastic pulmonary disorders. Although diverse, they often share clinical, diagnostic, physiologic, and/or pathologic features.[1] Idiopathic pulmonary fibrosis (IPF), the most common idiopathic interstitial pneumonia, has been defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause which occurs primarily in older male adults and in those with a history of smoking, and is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).[2,3] IPF has the poorest prognosis of the chronic interstitial pneumonias and although characterized by worsening dyspnea and progressive loss of lung function which proves fatal for most patients within 5 years, there is significant phenotypic heterogeneity resulting in variability in the temporal course of disease progression and mortality.[4-6] Some progress rapidly, some relatively slowly, and others experience acute deteriorations in respiratory function that are associated with high morbidity and mortality.[7-10] A decline in forced vital capacity (FVC) has been shown to correspond with disease progression and be predictive of mortality.[11] The clinical course remains difficult to predict as is dependent on multiple factors including severity of disease at diagnosis, comorbidities, and individual patient variables.[12]

UIP is the pattern of interstitial pneumonia seen in IPF.[13] It is not a specific diagnosis but a radiologic and pathologic pattern, requiring a clinical context to define a specific diagnosis. Therefore, although high-resolution computed tomography (HRCT) interpretation plays a critical role in the IPF diagnostic pathway, neither CT nor histopathologic analysis alone can make the diagnosis of IPF. Rather, IPF is the clinical diagnosis in patients with a radiologic and/or histopathologic UIP pattern for whom other potential causes of this pattern have been excluded. Specifically, an IPF diagnosis requires the exclusion of other entities that may be associated with a UIP pattern, including environmental or occupational exposures, medication, or systemic disease.[2,14] The majority of patients with radiologic UIP are found to have a clinical diagnosis of IPF[15]; therefore, it is imperative to have a robust and systematic approach to CT of the chest to accurately interpret and ascribe a UIP pattern. Diagnostic accuracy for IPF improves and is best facilitated in the setting of effective communication and collaboration of pulmonary medicine physicians, thoracic radiologists, and pathologists.[14]

Until recently, no effective therapies were available for IPF; however, a number of landmark clinical trials[16-19] have shown that new therapies slow disease progression and functional decline and are now conditionally recommended according to the Official ATS/ERS/JRS/ALAT Clinical Practice Guideline of 2015.[20] The availability of these new treatments adds further importance to the early and accurate diagnosis of IPF, and there is indirect evidence that early intervention may improve survival.[21-23] The focus of this paper is to highlight recent advances in understanding of IPF that in turn aids diagnosis and serves to inform the most recent IPF diagnostic criteria.

CT Technique

As CT has a central role in the assessment and diagnosis of patients with ILD, high-quality CT images are imperative to facilitate accurate image interpretation. CT scans obtained for characterization of ILD should be noncontrast, thin slice (1-1.5 mm), and obtained in full inspiration, without respiratory motion. Thin section improves resolution and reduces partial volume averaging effects. A moderately high spatial frequency reconstruction algorithm (eg, GE bone algorithm, Siemens B45, Philips D or YB, Toshiba Lung Std.) allows visualization of the fine detail of the lung; however, use of highly edge enhancing algorithms (eg, GE Lung algorithm, Siemens B70) results in increased image noise, and may impair evaluation of the lungs. Contiguous (volumetric) imaging is preferred, as it allows detection of focal abnormalities such as cancer and infection, enables identification of bronchial disease, and facilitates coronal and sagittal reformats, which are helpful for assessing disease distribution and aid in the differentiation of traction bronchiectasis from honeycombing.

Expiratory scans are recommended to confirm or exclude lobular air trapping suggestive of a non-IPF diagnosis, such as hypersensitivity pneumonitis.[24] These are performed as

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https://doi.org/10.1053/j.ro.2018.12.001

noncontiguous scans at 2 cm intervals and must be directly compared with the inspiratory CT to determine the degree of change in lung density. Heterogeneous lung emptying does not always indicate air trapping. Prone scans (noncontiguous) are indicated in suspected disease with a (near) normal chest X-ray (CXR) or when dependent opacity is present on the supine CT[25] in order to differentiate atelectasis from true abnormality. They can be useful if pleural fluid is present and sometimes show honeycombing more clearly, reducing interobserver variability.[26] Ideally, they should be performed routinely unless the technologist is confident there is no dependent opacity. Both the expiratory and prone acquisitions can be performed at lower doses than the inspiratory CT scan.[25] Acceptable CT scans can be obtained with a reduced-dose technique by use of automatic tube current modulation, optimization of tube potential, beam-shaping filters, or dynamic z-axis collimators. Reduced-dose CT scans reconstructed with iterative algorithms can allow the detection of subtle interstitial abnormalities, and can be compared with standard-dose CT images.

Guidelines for Diagnosis of UIP/IPF

The diagnostic criteria for IPF published in 2011 by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT)[2] include the following: (1) exclusion of other known causes of ILD (eg, domestic and occupational environmental exposures, connective tissue disease (CTD), and drug toxicity), (2) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (SLB), and (3) specific combinations of HRCT and SLB pattern in patients subjected to SLB.

In the 2011 guidelines, a UIP pattern on HRCT required 4 criteria: (1) subpleural basal predominance, (2) reticular abnormality, (3) honeycombing with or without traction bronchiectasis, and (4) absence of features listed as inconsistent with UIP pattern. The above radiologic features in the absence of honeycombing constituted the "possible UIP" pattern. A pattern inconsistent with UIP was defined when any of the following 7 HRCT features was present: (1) upper or mid-lung predominance, (2) peribronchovascular predominance, (3) extensive ground glass abnormality (extent > reticular abnormality), (4) profuse micronodules (bilateral, predominantly upper lobes), (5) discrete cysts (multiple, bilateral, away from areas of honeycombing), (6) diffuse mosaic attenuation/air-trapping (bilateral, in 3 or more lobes), and (7) consolidation in bronchopulmonary segment (s)/lobe(s).

The 2011 guidelines indicated that in the appropriate clinical setting in patients with a UIP pattern on HRCT, the diagnosis of IPF could be established without the need for SLB, but SLB was recommended for diagnosis in all cases with CT patterns of possible UIP or inconsistent with UIP. In a patient subjected to SLB, the following specific combinations of HRCT and SLB were recommended for unequivocal diagnosis of IPF following multidisciplinary discussion (MDD): (1) any histopathologic pattern with a CT UIP pattern or (2) histopathologic UIP or probable UIP combined with a CT possible UIP pattern. Those with histopathologic possible UIP or nonclassifiable fibrosis combined with a possible UIP CT pattern may reach a probable IPF diagnosis following MDD, while those with a histopathologic UIP pattern combined with an inconsistent with UIP CT pattern could be diagnosed with possible IPF following MDD. All other combinations of radiologic and histopathologic patterns could not result in an IPF diagnosis under these guidelines.

Rationale for Change in Diagnostic Criteria

Landmark clinical trials of treatment of IPF with pirfenidone or nintedanib[16-19] demonstrated significant impact on slowing disease progression and functional decline in patients with IPF, and appeared particularly effective in patients with mild-to-moderate lung function impairment.[27] At present, robust data to support/recommend use of nintedanib or pirfenidone in the various non-IPF fibrotic ILDs are lacking.[1] In light of these findings, in 2015 the ATS published an official update to the 2011 Clinical Practice Guideline for the treatment of IPF and gave a conditional recommendation to treat IPF with nintedanib and pirfenidone.[20] These advances in treatment led to the realization of the need for a more robust diagnostic pathway to diagnose and treat IPF.

The 2011 IPF diagnostic guidelines[2] and their subsequent application into clinical practice were pivotal in facilitating prospective clinical trials that have resulted in greater clinical, radiologic, and histologic understanding of IPF. These trials in turn have subsequently highlighted some limitations in the current guidelines.

HRCT is integral to IPF diagnosis[2] as its interpretation significantly influences subsequent diagnostic/management decisions. Multiple studies have convincingly shown the accuracy of a CT UIP pattern for a UIP pathologic diagnosis,[28-30] and in the correct clinical context, an IPF diagnosis is established. However, honeycombing as a requirement for CT UIP pattern in the 2011 guidelines has proven problematic for several reasons. There is contention as to its precise definition, and significant interobserver variability as to its presence or absence even among experienced thoracic radiologists. The modest level of agreement is mainly a consequence of the misclassification of emphysema and difficulty in distinguishing between peripheral traction bronchiectasis and honeycombing.[31] Reasonable levels of interobserver agreement are a requisite for diagnostic criteria to be clinically useful, and as up to two-thirds of patients with IPF/UIP are diagnosed solely by CT, the issue of radiologic interobserver agreement for this diagnosis is relevant.[32] Honeycombing represents end-stage cystic destruction of the lung parenchyma and may indicate more advanced disease. In some, but not all studies, its presence is linked to a poor prognosis.[8] The evidence supporting currently recommended IPF therapies as per the 2015 ATS/ERS/RS/ALAT

guidelines,[20] focused on patients with mild-to-moderate PFT impairment.[27,9] Reliance on a CT feature signifying advanced disease may result in missing a therapeutic window in those with milder disease who could benefit from therapy.

An increasing number of studies have shown that in the correct clinical context, a possible UIP HRCT pattern has a sufficiently high positive predictive value to warrant an IPF diagnosis in the absence of SLB. This has led to the recognition of a category of probable UIP, which is further discussed by Dr Chung in a separate chapter in this edition.

Integration of HRCT and histopathologic findings is often helpful in assigning a likelihood of IPF diagnosis and is emphasized by the 2011 ATS/ERS/JRS/ALAT guidelines. However, this proves problematic when the clinical setting and histopathologic findings are concordant with a UIP/IPF pattern/diagnosis but the HRCT pattern is inconsistent with UIP. In this scenario, current guidelines only allow for a possible IPF diagnosis at best.

The term "inconsistent with UIP" used in the 2011 guidelines is now known to be a misnomer, as a substantial proportion of cases with this pattern has UIP on SLB. A study by Svezerllati et al. showed that CT appearances in patients with biopsy-proven IPF are often atypical and overlap with those of other chronic ILDs. Of 55 patients with biopsy proven UIP, 62% had low probability features of UIP and expert readers favored alternate CT diagnoses, such as nonspecific interstitial pneumonia (NSIP), chronic (fibrotic) hypersensitivity pneumonitis (CHP/FHP), and sarcoid.[33] Silva et al. found that in 21.4% of CT chest interpretations with biopsy proven UIP, either CHP/FHP or NSIP were favored by chest radiologists.[34] In another study, NSIP was the preferred CT diagnosis in 36% of biopsy-proven UIP.[35] In a selected population of subjects enrolled in a clinical trial of IPF, a study by Raghu et al.[36] demonstrated 82% of 120 patients with an inconsistent with UIP radiologic pattern demonstrated either UIP or probable UIP on SLB. Similarly, in a population of subjects enrolled in 3 different IPF clinical trials, Yagahashi et al.[29] documented that 94.7% of those with "inconsistent" HRCT features had histologically definite or probable UIP; there were no major pathologic differences between radiology−pathology-concordant and -discordant groups. One must be cautious in equating pathologic results with diagnosis in the setting of ILD.[13] However, the salient point is that an "inconsistent with UIP" radiologic pattern does not rule out the diagnosis of IPF but mandates histologic confirmation regardless of patient pretest probability[37] and MDD.

In this scenario or in others where IPF is suspected but diagnosis cannot be reached according to guidelines,[2] the idea of considering disease behavior has been suggested to assist in formulating a diagnosis.[5] If a patient's fibrosing lung disease is not easily stratified on HRCT or appearances are discordant with clinical and/or histopathologic findings, but significantly worsens over a relatively short interval (less than a year), there is a high probability of an accurate IPF diagnosis, irrespective of initial HRCT classification.[15]

The category of "inconsistent with UIP" is complex, with 7 unique CT findings and given the expansive and heterogeneous inclusion criteria, this category may be susceptible to false-positives and false-negatives. Not many studies have addressed this potential problem. Chung et al.[13] assessed the diagnostic significance of each of the specific findings and found that ground glass opacity (GGO), air trapping, consolidation, and diffuse axial distribution were associated with a non-UIP pathologic diagnosis; however, there was no significant association with zonal distribution or diffuse nodularity, although admittedly the latter may be secondary to low prevalence.

A small but substantial proportion of patients with fibrosis have CT scans that do not fulfill the criteria for UIP or possible UIP but lack the criteria to be classified as inconsistent with UIP. These may be classified as indeterminate. Chung et al.[28] showed that the positive predictive value of a probable UIP pattern was different from indeterminate UIP pattern (defined as imaging findings not sufficiently characteristic to reach a definite, probable, or inconsistent with UIP level) for histopathologic UIP (82% vs 55%, respectively).

Under the 2011 criteria, patients with nondiagnostic CT scans must proceed to SLB or be exiled from current IPF diagnostic guidelines.[38] Patients typically investigated for IPF are elderly, have several comorbidities, and/or severe physiologic impairment, making SLB risky.[39,5] The diagnostic fate of and management recommendations for those who elect not or cannot undergo SLB in this setting are not adequately addressed in these criteria.[2]

The accessibility and/or outcome of histopathologic interpretation are pivotal for patients being investigated for IPF without a UIP HRCT pattern. Its analysis effectively regulates whether or not an IPF diagnosis can be conferred. Many similarities can be drawn between HRCT interpretation limitations and those encountered with histopathologic assessment. As with HRCT, the interpretation of histologic findings is subject to difficult distinctions between entities and interobserver variability, the latter of which is magnified between thoracic and general pathologists.[40] As with HRCT, distinction between NSIP and UIP is particularly challenging and further complicated by the fact that NSIP and UIP are often found in one specimen. This highlights the potential impact of sampling error that may lead to incorrect diagnosis/classification.[41-43] Recall also, as with HRCT, patterns in ILDs are not ascribed to specific diseases but can correspond to many. UIP is not unequivocally IPF but can be seen in hypersensitivity pneumonitis, CTD, pneumoconiosis and be secondary to some pernicious effects of drugs.[44]

Updated Criteria for Diagnosis of IPF

Recognizing the need for refinement of the IPF diagnostic algorithm in light of recent research, both the Fleischner Society and the ATS/ERS/JRS/ALAT have recently published updated IPF diagnostic criteria[25,45] addressing and incorporating the aforementioned observations. Both sets of criteria continue to emphasize the importance of multidisciplinary diagnosis in establishing the diagnosis of IPF. Salient changes from the 2011 criteria will be discussed below.

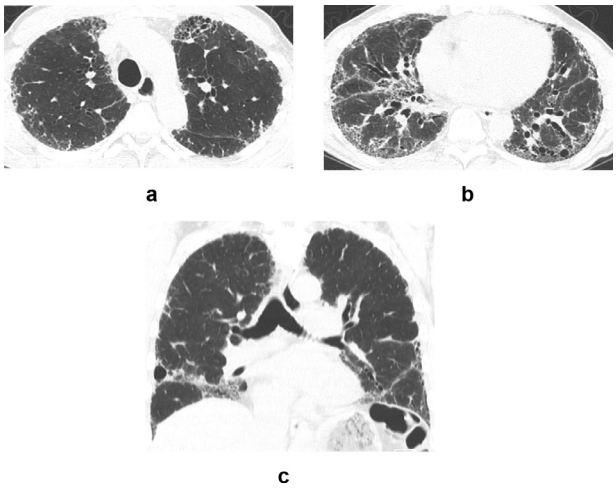

Figure 1 Usual interstitial pneumonia (UIP) pattern. High-resolution computed tomography (CT) images (A-B) transverse section and (C) coronal reconstruction illustrate reticular abnormality with traction bronchiectasis and honeycombing, with a subpleural and basal predominance.

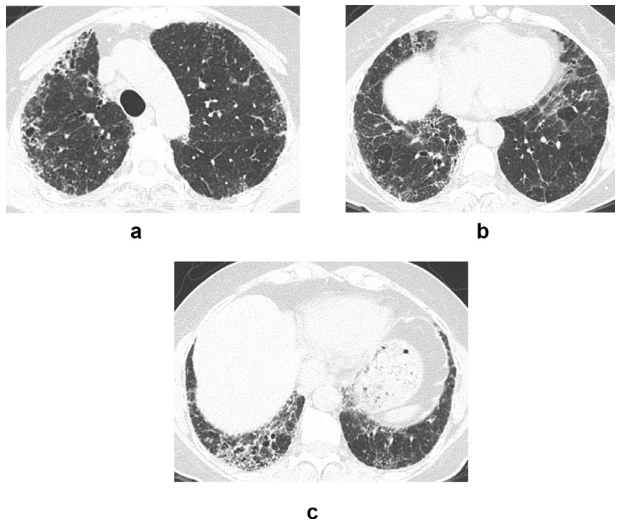

Figure 3 Indeterminate for usual interstitial pneumonia (UIP) pattern. High-resolution computed tomography (CT) transverse images (A-C) illustrate subpleural reticulation and traction bronchiolectasis without distinct basal predominance. Minor mosaic attenuation at the lung bases excludes it from the "definite UIP" and "probable UIP" categories but is not marked enough to be classified as "consistent with a non-idiopathic fibrosis (IPF) diagnosis".

In both sets of criteria, 4, instead of 3, diagnostic categories based on CT appearance are defined in the evaluation of IPF: (1) typical UIP CT pattern (Fig. 1), (2) probable UIP CT pattern (Fig. 2), (3) CT pattern indeterminate for UIP (Fig. 3), and (4) CT features most consistent with, or suggestive of, a non-IPF/alternative diagnosis (Fig. 4). The definitions of these categories in each guideline are essentially the same. Both sets of definitions recognize the presence and severity of traction bronchiectasis as a significant predictive marker of poor patient outcome.[46] The addition of the new category of indeterminate for UIP acknowledges, although less likely, that UIP can still be present in the absence of typical or probable UIP patterns. This category also addresses the fact that a reasonable number of CTs encountered in clinical practice do not accurately fit into possible UIP and yet also do not have features warranting an inconsistent with UIP stratification based on old classification. Allowance has also been

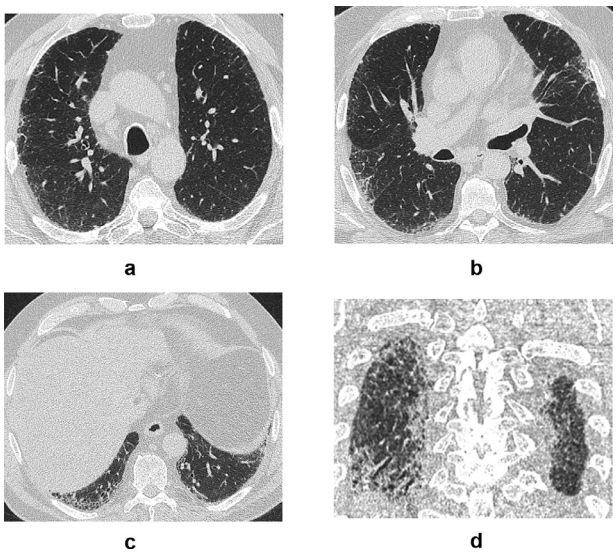

Figure 2 Probable usual interstitial pneumonia (UIP) pattern. High-resolution computed tomography (CT) transverse images in the upper, mid and lower zones (A-C) demonstrate subpleural and basal predominant reticulation and traction bronchiolectasis. Note the absence of honeycombing. The coronal reconstruction (D) confirms that the peripheral cystic change on the transverse images represents dilated airways rather than honeycombing.

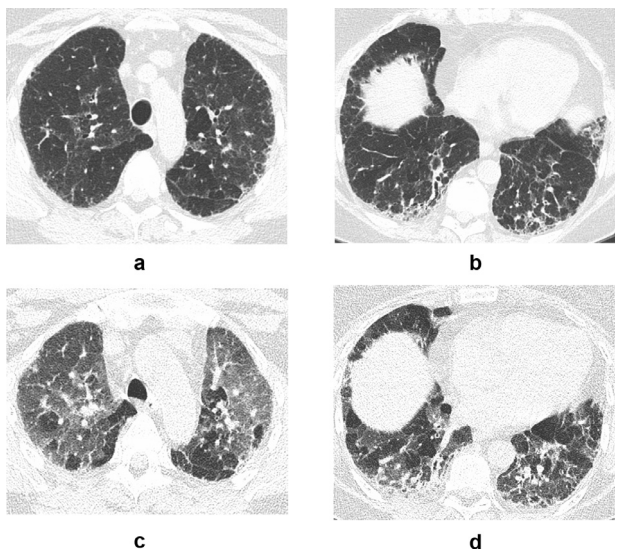

Figure 4 Most consistent with a non-idiopathic pulmonary fibrosis (IPF) diagnosis. High-resolution computed tomography (CT) transverse images in full inspiration (A-B) demonstrate reticulation and traction bronchiolectasis in addition to ground glass opacity and moderately extensive mosaic attenuation. (C-D) Corresponding CT images at end expiration confirming lobular gas-trapping, highly suggestive of hypersensitivity pneumonitis.

made here for variable or diffuse distribution of abnormality. The previously complex and confusing "inconsistent with UIP" category has been renamed "features most consistent with a non-IPF diagnosis" in the Fleischner White Paper, and "findings suggestive of an alternative diagnosis" in the updated ATS/ERS/JRS/ALAT guidelines, recognizing that histologic UIP can still be encountered in patients with these appearances. In the Fleischner paper, subpleural sparing was added as a distribution feature suggestive of a non-IPF diagnosis, since this finding is highly suggestive of NSIP. In the ATS/ERS/JRS/ALAT paper, perilymphatic distribution, pleural plaques, dilated esophagus, distal clavicular erosions, extensive lymph node enlargement, and pleural abnormality were included as features suggestive of alternative diagnosis.

The primary difference between the 2018 ATS/ERS/JRS/ALAT and Fleischner criteria lies in the diagnostic recommendations. The Fleischner recommendations indicated that a confident diagnosis of IPF could be made in the absence of a SLB in both the UIP and probable UIP CT categories, in the correct clinical context (age >60 years, absence of clinically significant environmental or medication exposure, and no evidence of CTD). This acknowledges evidence confirming that histopathologic UIP is likely even in the absence of honeycombing, particularly in those with high pretest probability of the disease. This approach may improve sensitivity of a confident CT diagnosis and may facilitate earlier diagnosis and access to therapy. The Fleischner paper recommends SLB for confirmation of a UIP histologic pattern in an indeterminate clinical context or when the CT pattern is not in keeping with either typical or probable UIP. In these circumstances, a confident diagnosis of IPF could then be made following MDD. Both the Fleischner and the ATS/ERS/JRS/ALAT papers acknowledge that IPF should not be unequivocally excluded in settings where the CT pattern is more suggestive of another ILD, as histopathologic UIP does not always have a correlative UIP CT pattern. In contrast to the Fleischner recommendations, the 2018 ATS/ERS/JRS/ALAT guidelines do not consider age as a stratification variable, do not differentiate between probable UIP and less specific CT categories, and suggest (but do not mandate) SLB for diagnosis of IPF in all subjects who do not have typical UIP on CT, only after an MDD by expert clinicians.

A second difference between these publications is that the Fleischner paper addressed the challenge of patients with a progressive fibrosing interstitial pneumonia in the absence of an alternative explanation, in whom an SLB could not be obtained or is not available. In these subjects, the concept of a working diagnosis of IPF was introduced as a pragmatic management solution. A working diagnosis should incorporate an assessment of pretest clinical probability and disease behavior, should be assigned by a multidisciplinary team, and should be reviewed at regular intervals as it may change over time. The ATS/ERS/JRS/ALAT document does not specifically address this issue, probably because of the lack of hard evidence for this concept.

In summary, the Fleischner diagnostic criteria allow for a confident diagnosis of IPF in a patient with a typical clinical context of IPF and a CT pattern of typical or probable UIP. In all other situations, multidisciplinary diagnosis is appropriate to direct the decision to proceed with biopsy or other diagnostic assessments. Multidisciplinary assessment can yield a working diagnosis of IPF in some situations where diagnostic criteria are partially met, particularly if diagnostic tissue is not available. A working diagnosis may change over time—for example, if a CTD becomes apparent, or a previously unrecognized exposure is identified and therefore should be rereviewed at multidisciplinary conference. The ATS/ERS/JRS/ALAT criteria suggest (but do not require) biopsy in all subjects without a typical CT pattern of UIP.

Differential Diagnosis

Although CT imaging can accurately characterize disease patterns, due to overlapping radiologic appearances even experienced chest radiologists frequently struggle with differential diagnosis.[47] As mentioned previously, imaging contribution to the diagnosis of IPF is complicated by 2 factors. First, biopsy-proven UIP may mimic other interstitial disease on HRCT including: NSIP, CHP/FHP, and sarcoidosis.[48] Second, the UIP pattern is not unique to IPF but also seen secondary to causes like CHP/FHP, familial fibrosis, CTD, asbestosis, and vasculitis.[49]

Current guidelines include a category "most consistent with a non-IPF diagnosis," or "findings suggestive of an alternative diagnosis" listing HRCT features to assist in differentiating between the main potential diagnoses. The most challenging distinction is often between UIP and NSIP. Relative subpleural sparing (not usually present in patients with UIP but seen in up to 60% of patients with NSIP in some series),[25] basal predominant GGO and lack of honeycombing[34] are the HRCT features that best distinguish NSIP from UIP. Although in the correct clinical setting, a confident diagnosis of CHP/FHP can be made when profuse and poorly defined centrilobular nodules, mosaic attenuation and lobular air trapping, or a mid to upper lung distribution of fibrosis is present, in more advanced cases of CHP/FHP, where honeycombing is quite common, the HRCT pattern may mimic that of UIP.[50] Mosaic attenuation and air trapping are more decisive in distinguishing HP from UIP in nonfibrotic areas of lung (eg, diagnostic confidence of air trapping goes down in areas of fibrosis).[25]

CTD-associated ILD can commonly present with a UIP pattern on HRCT, especially in patients with rheumatoid arthritis. In patients with a UIP pattern on HRCT, the possibility of an underlying CTD should be considered in younger patients, in those with signs and symptoms of systemic disease, and in the presence of a pleural effusion, esophageal dilatation, or pericardial abnormality.[25,50] Chung et al. have described specific CT signs that are more common in UIP associated with CTD-ILD than in UIP associated with IPF. These 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 or the "four-corner" sign), exuberant honeycomb-like cyst formation within the lungs constituting greater than 70% of fibrotic portions of

lung ("exuberant honeycombing" sign) 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). High specificity (94.0%) and low sensitivity (25.4%) were seen for the straight-edge sign.[49]

Complications of IPF

Acute Exacerbation

The natural history of IPF is typically a steady deterioration in symptoms and lung function. However, many conditions can complicate its course, resulting in a more acute deterioration in symptoms and pulmonary function. Acute respiratory worsening is said to occur in a small minority of patients with IPF annually (approximately 5%-10%) and may be secondary to common conditions such as pneumonia, pulmonary embolism, pneumothorax, or cardiac failure. When a cause cannot be identified for acute (less than 30 days) clinically significant respiratory decline, the term acute exacerbation of IPF has been used.[2,10] Bilateral GGO, superimposed on a background of fibrosis,[2] is almost invariably found on HRCT in such cases, and must be distinguished clinically from infection, edema, or poor inspiration (Fig. 5). Acute exacerbation can occur at any point during IPF, occasionally as its presenting manifestation, but is more likely to occur in patients with extensive fibrosis and occurs more frequently in patients with IPF than other forms of fibrotic lung disease. The most common histologic pattern of lung injury associated with acute exacerbation is diffuse alveolar damage, followed by organizing pneumonia. Distribution of new GGO/consolidation is classified as diffuse, patchy, or peripheral, with the peripheral distribution offering the best prognosis. Overall, its prognosis is poor, with the majority of patients requiring mechanical ventilatory support and dying within weeks to months after acute presentation.[50,51]

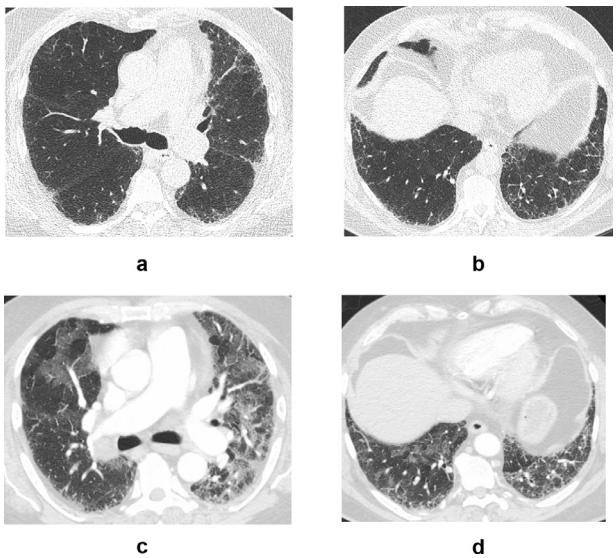

Figure 5 Acute exacerbation of idiopathic pulmonary fibrosis (IPF). (A-B) Baseline high-resolution computed tomography (CT) images obtained in the mid and lower zones show subpleural, lower lung predominant, reticular abnormality with traction bronchiectasis, indicating a probable UIP pattern. (C-D) CT images obtained a few months later when the patient became acutely hypoxic show extensive superimposed ground glass opacity, suggesting acute exacerbation (though infection would need to be excluded).

Lung Cancer

Several studies have reported an increased risk of lung cancer in patients with IPF, particularly in older males who are current or former smokers, with a prevalence of up to 15%. In a large cohort studied by Hubbard et al.,[52] there was a 5-fold increase in incidence of lung cancer in patients with IPF compared with the general population control cohort. The increased risk of lung cancer in patients appeared to change little following adjustment for the effect of smoking status, suggesting the increase in the prevalence of lung cancer in IPF is independent of smoking. As with the general population, adenocarcinoma is the most common histopathologic type of lung cancer associated with IPF, followed by squamous cell carcinoma.[50] Likewise, the most common HRCT appearance of lung cancer associated with IPF is an ill-defined or well-defined nodule or mass (Fig. 6). However, in contrast to lung cancer in the general population, lung cancer associated with IPF occurs more frequently in the lower lobes[53,54] and/or with equal distribution between upper and lower lobes,[55,56] with an increase in synchronous tumors, occurring in up to 15% of patients with IPF.[57] Cancers most commonly develop in the peripheral lung in areas of severe fibrosis or at the junction of fibrotic and normal lung, increasing the likelihood of a delay in diagnosis and making comparison with previous imaging essential.[50]

Infection

As with other structural lung diseases, patients with IPF are at increased risk of a range of pulmonary infections, particularly those caused by *Aspergillus* species (most commonly aspergilloma formation in a pre-existing cavity) and *Mycobacterium* species (note the radiologic manifestations of pulmonary TB in patients with IPF may be atypical), as well as a number of opportunistic infections, importantly Pneumocystis jiroveci pneumonia. In contrast to patients with other chronic lung diseases, patients with IPF do not seem more

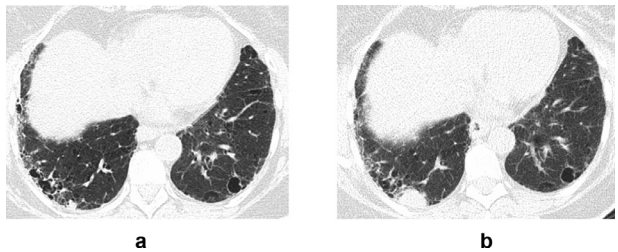

Figure 6 High-resolution computed tomography (CT) images show primary lung cancer and usual interstitial pneumonia (UIP). (A) Transverse section CT showing a small nodule peripherally in the right lower lobe, with (B) interval growth demonstrated 5 months later.

susceptible to infection with nontuberculous mycobacterial species than the general population. As pre-existing pulmonary abnormality may mask the typical radiographic appearances of these infections, HRCT can be valuable. However, the imaging appearance of infections, especially Pneumocystis jiroveci pneumonia, may be indistinguishable from that of acute exacerbation of IPF.[10]

Other

Spontaneous pneumothorax and pneumomediastinum occur in up to 12% of patients with IPF, usually associated with mild/no symptoms and of uncertain clinical significance. Nearly half the patients with IPF referred for lung transplantation have pulmonary hypertension, which is associated with decreased survival. The relationship between the 2 is not fully explained, as a large number of patients have discordance between the degree of fibrosis or oxygen saturation and pulmonary arterial pressures.[50] Patients with IPF have an increased prevalence of ischemic heart disease, and cardiogenic pulmonary edema is a common cause of acute deterioration, suggested on imaging by the presence of profuse septal thickening, patchy GGO, and pleural effusions.[10]

Interstitial Lung Abnormality in Subclinical ILD

The extensive use of HRCT in clinical and research settings has increased the detection of interstitial lung abnormalities (ILA). ILA can be defined as subclinical ILD with specific radiologic, physiologic, and sometimes histologic abnormalities in asymptomatic individuals or in those with symptoms that have been ascribed to other causes.[58] The prevalence of ILA in the general population has been reported as around 7%, substantially higher than the prevalence of IPF (≈0.002%-0.04%).[59] Similar clinical associations have been noted for both ILA and IPF (age, smoking status, and level of tobacco exposure)[23] and subclinical ILD is associated with reduced total lung capacity, reduced 6-minute walk, a genetic profile similar to that of IPF, increased risk of postoperative acute respiratory distress syndrome (ARDS) and increased mortality.[58] CT features of ILA are consistent with, but subtler than those observed in patients with established clinical ILD[58] and are further divided into fibrotic and nonfibrotic. Features of nonfibrotic ILA include nondependent GGO that affects >5% of any lung zone and diffuse centrilobular nodularity with GGO, often due to respiratory bronchiolitis (in smokers) or aspiration, and frequently resolve at follow-up imaging. Fibrotic ILA features include nondependent reticular abnormality, honeycombing, traction bronchiectasis, and subpleural irregularity; most likely representing some form of idiopathic interstitial pneumonia (NSIP or UIP) (Fig. 7). Classifying ILA as fibrotic or nonfibrotic has prognostic implications. In a study on ILA prevalence and progression over 2 years in a national lung cancer screening population, ILA was found in about 10% (86 of 884) of participants. Nonfibrotic ILA, found in about 6% (52 of 884) of participants, improved in about 50% (23 of 47), and progressed in 11% (5 of 47) of cases at the 2-year follow-up CT. Fibrotic ILA, found in about 2% (19 of 884), did not improve and progressed in about 37% (7 of 19) at 2-year follow-up CT.[60] It remains unclear whether, with sufficient time, all fibrotic ILA would eventually progress to IPF, or if only a small subgroup of fibrotic ILA represents subclinical IPF with the remainder due to "benign" age-related change. Recent analyses have demonstrated benefits of antifibrotic agents in mild disease[19,61] and Araki et al. noted that ILA progression was predictive of a 4-fold increase in the risk of death.[62] It would be beneficial to prospectively identify the subgroup of ILA that represents subclinical IPF, to facilitate earlier diagnosis and treatment. The appropriate management of incidentally detected fibrotic ILA remains unclear. Possible management option would include baseline pulmonary function tests, review for an underlying cause, and follow-up CT scans at an appropriate interval (perhaps 1-2 years). Further longitudinal studies are required to better define the natural history of subclinical ILD; this will allow us to identify which patients will go on to develop clinically significant ILD, and to conclusively demonstrate that subclinical ILD indeed precedes the development of pulmonary fibrosis in at-risk populations.

Figure 7 Early interstitial lung abnormalities with progression. (A) Prone axial CT in a 73-year old man shows mild subpleural irregularity, septal thickening and ground glass abnormality, with a few subpleural cysts on the right. (B) CT obtained 6 years later shows increase in extent of abnormality, particularly in the right lung.

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