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HRCT of fibrosing lung disease

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ABSTRACT

The use of high-resolution computed tomography (HRCT) has brought increased diagnostic discrimination to the evaluation of lung disease, particularly fibrosing lung diseases. Once the presence of a predominantly fibrosing lung disease has been established on evaluation of a HRCT, a stepwise approach is proposed that can refine the potential HRCT diagnoses from a list of over 100 different interstitial lung diseases to one of only five fibrosing lung diseases. Within the category of the fibrosing lung diseases, the recognition of idiopathic pulmonary fibrosis (IPF) is key. IPF is the most prevalent idiopathic interstitial pneumonia and has a mortality greater than any of the other diffuse lung diseases. Several diagnostic dilemmas are explored including challenges with the recent IPF diagnosis and management guidelines (2011), as well as with the 'difficult to characterize' fibrosing diseases such as smoking-related lung fibrosis, unclassifiable disease and acute exacerbations of fibrosing lung disease.

Key words: computed tomography, fibrosis, idiopathic interstitial pneumonia, lung, prognosis.

Abbreviations: ATS/ERS/JRS/ALAT, American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (Asociación Latinoamericana de Tórax); CPFE, combined fibrosis and emphysema; CT, computed tomography; CTD, connective tissue disease; CTPA, computed tomography pulmonary angiogram; DIP, desquamative interstitial pneumonia; FLD, fibrosing lung disease; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; MDT, multidisciplinary team; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

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INTRODUCTION

High-resolution computed tomography (HRCT) has revolutionized the diagnosis of diffuse lung disease. In particular, the recognition of the HRCT signs of fibrosing lung disease (FLD) allows the list of potential diagnoses of interstitial lung disease to be narrowed down from over a hundred disorders to just five diseases.

Of the FLD, the recognition of a usual interstitial pneumonia (UIP) pattern is key, as it has the worst prognosis of all the fibrosing interstitial lung diseases. The advent of new treatments that slow disease progression in idiopathic pulmonary fibrosis (IPF) and the increasing number of drug trials in the future has accentuated the importance of accurate diagnosis. A step-by-step approach to the interpretation of a HRCT can simplify the recognition of a UIP pattern and help in the identification of its mimics.

Several of the pertinent challenges in the HRCT diagnosis of a UIP pattern are discussed. Specifically, difficulties that relate to the recent IPF diagnostic and management guidelines, particularly concerning cases of non-classical UIP/IPF are considered. Furthermore, fibrosing entities that are hard to define are discussed, including cigarette smoking-related FLD and those cases that do not exhibit a clear HRCT morphology and are consequently deemed unclassifiable.

HRCT FEATURES OF FLD

A simple stepwise approach can aid HRCT interpretation and is especially applicable to FLD (Fig. 1). The first step is to decide whether a computed tomography (CT) is normal or abnormal. If abnormal, deciding whether the disease is predominantly airway or interstitial in nature is the next step (Fig. 1). If the airways appear normal, then the penultimate step concerns the discrimination between a predominantly FLD and a non-fibrotic disease; one of the reasons that this is such a crucial point is that the

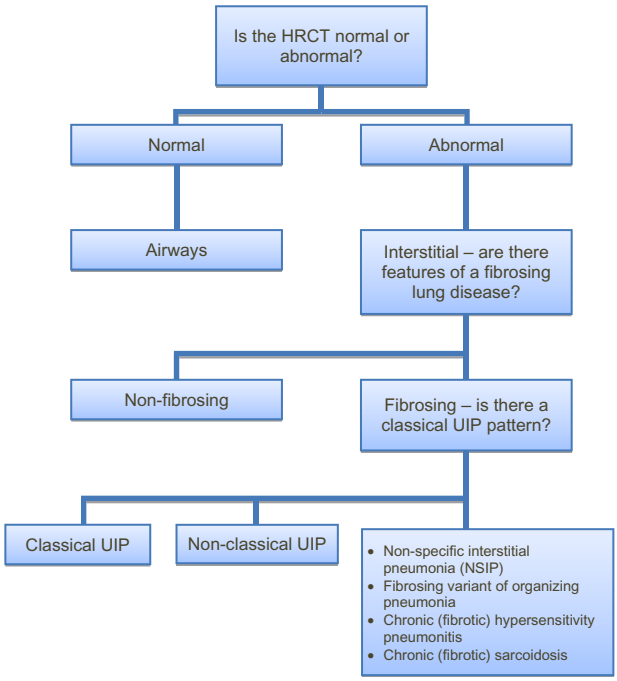

Figure 1 High-resolution computed tomography (HRCT) interpretation algorithm for fibrosing lung disease. UIP, usual interstitial pneumonia.

differential diagnosis of FLD is short ($n = 5$) c.f. non-FLD ($n > 150$). To make this distinction requires the recognition of the three cardinal CT signs of fibrosis: honeycomb cysts, traction bronchiectasis and volume loss (these are considered in more detail in the next section). The three signs are not of equal weight; lobar volume loss for example, when present without the other two signs has limited diagnostic value. However when all three signs are present, the presence of a predominantly FLD is certain. The last step of this simple algorithm is the decision about which of the limited choices of FLD the HRCT findings most likely represent.

Key signs of lung fibrosis

Honeycomb pattern

The first mention of honeycombing related to pulmonary fibrosis in the English literature appeared in the mid-20th century.[1] Recent pathological definitions of honeycombing are variable but include: 'enlarged airspaces lined by bronchiolar epithelium and often filled by mucin and variable numbers of inflammatory cells. They are surrounded by dense collagen and variable amounts of inflammation. . . . Scars are characterized by irregular, thick areas of collagen deposition that obliterate alveoli'.[2]

By contrast, honeycombing on HRCT has been defined as clustered, thick-walled, cystic spaces of similar diameters, measuring between 3–10 mm, but up to 25 mm in size.[3] Honeycomb cysts are characteristic of a UIP pattern of fibrosis and typically occur in a peripheral, basal, subpleural distribution. Although often cited as being layered in the literature, a single layer of subpleural cysts is also a manifestation of honeycombing. In practice, however, honeycomb cysts in a single layer are often found adjacent to areas of layered cysts.

The honeycomb cysts identified on HRCT correspond only to cysts on a gross pathological specimen that remain visible to the naked eye. Smaller cysts, identified on pathological samples and termed 'microscopic honeycombing', may represent dilated bronchioles measuring 1–2 mm surrounded by fibrotic lung.[4] As microscopic honeycombing identified on histology is beyond the limits of resolution of HRCT, there is no clear HRCT correlate of this pathologic finding.[5]

When honeycombing is present in a characteristic distribution (that is, subpleural and basal) on HRCT, it has been shown to have a positive predictive value of 90–100% for a histological diagnosis of UIP.[6] However, the identification of honeycombing can, on occasion, be difficult. The relatively modest level of agreement, even amongst experienced thoracic radiologists for the identification of honeycombing, is mainly a consequence of the misclassification of emphysema and traction bronchiectasis.[7]

Areas of centrilobular or paraseptal emphysema that are superimposed on the fine interstitial fibrosis pattern can appear very similar to honeycombing (Fig. 2a). Obvious paraseptal emphysema in the upper lobes may indicate that the cystic appearances in the lower lobes are, in fact, likely to represent emphysema admixed with fibrosis, which is not necessarily UIP (Fig. 2b). Similarly, severe traction bronchiectasis can resemble honeycombing, and to distinguish this, coronal images should be interrogated to identify 'honeycomb cysts' that join up as a distorted tube, thus representing traction bronchiectasis (Fig. 3).[7] Differentiation of these features from honeycombing is important for diagnostic and prognostic considerations as outlined below.

Traction bronchiectasis

As defined in the Fleischner Society, glossary of terms for thoracic imaging, traction bronchiectasis and bronchiolectasis represent irregular bronchial and bronchiolar dilatation caused by surrounding retractile fibrosis.[3] To distinguish traction bronchiectasis from the so-called 'freestanding' bronchiectasis, that is airway dilatation that occurs unrelated to fibrosis, the signs of underlying fibrosis must be present. Background fibrosis around tractionally dilated bronchi is identified on HRCT as reticulation and/or ground glass opacification through which the irregular distorted airway can be seen to course. Traction bronchiectasis is predominantly seen in the periphery of the lungs, where bronchi contain less supportive cartilage and are thus more prone to retraction and distortion, and typically demonstrate a varicose 'beaded' appearance (Fig. 4a).

Several recent studies analyzing prognostic markers in various fibrosing interstitial lung diseases have identified the presence and severity of traction bronchiectasis as being the most predictive marker of

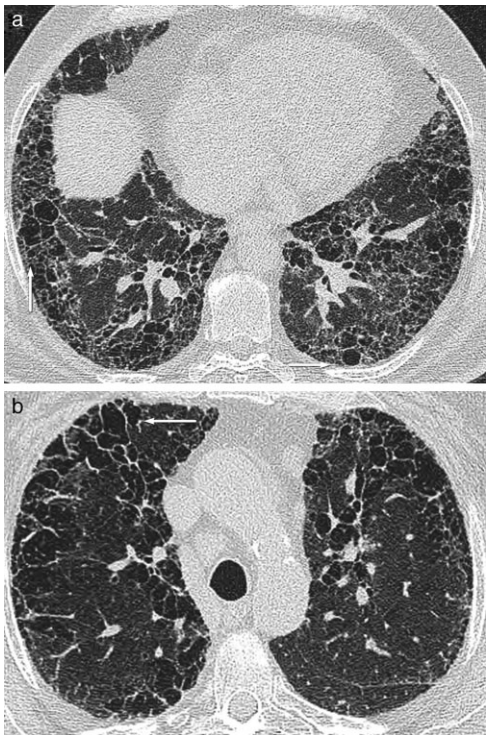

Figure 2 Emphysema mimicking honeycombing in a 69-year-old smoker. (a) At the lungs bases, there is the suggestion of honeycombing (arrows) in a peripheral distribution. (b) Scrutiny of the upper lobes shows destructive emphysema, with a mainly paraseptal distribution (arrow), making the identification of honeycombing less secure.

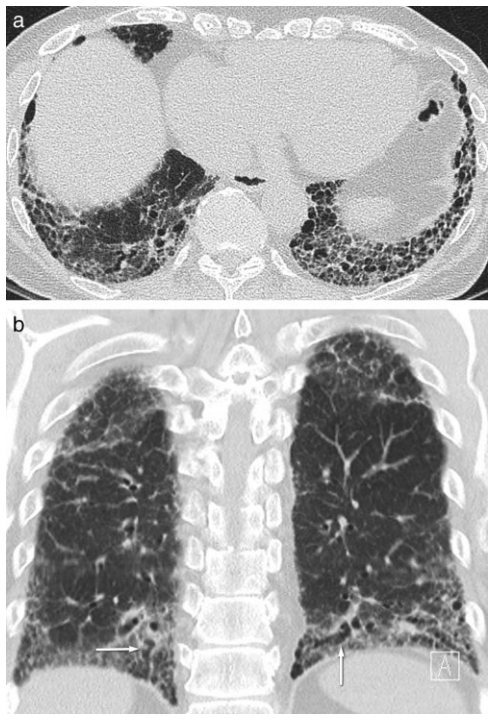

Figure 3 Traction bronchiectasis in a 64-year-old male patient with biopsy confirmed idiopathic pulmonary fibrosis. (a) The peripheral, basal, subpleural cystic spaces, surrounded by reticulation and ground glass opacification suggest honeycombing. (b) However, coronal reformats show that the cystic spaces join up with one another (arrows) and therefore represent dilated airways. When dilated airways are superimposed on areas of reticulation and/or ground glass opacification reflecting interstitial fibrosis, the bronchial dilatation is termed traction bronchiectasis.

a poor patient outcome, often more so than honeycombing.[8–11] A study by Sumikawa *et al.* reported good inter-observer variation for the identification of traction bronchiectasis.[8] The inter-observer agreement and prognostic strength of traction bronchiectasis in the study by Walsh *et al.* investigating patients with connective tissue disease (CTD)-related interstitial lung disease (ILD) was shown even when a binary score simply indicating the presence or absence of traction bronchiectasis was used.[10] The same studies found that the identification of traction bronchiectasis was associated with less observer variation than honeycombing.[8,10]

When traction bronchiectasis is misclassified, it is usually in one of three situations. First, as described above, it may in fact represent honeycomb cysts. Second, when ground glass opacification is widespread, the conspicuity of airways is increased, giving an illusion of dilatation when they may in fact be of normal diameter (Fig. 4b). Lastly, in acute and subacute inflammatory diseases, such as diffuse alveolar damage and organizing pneumonia (OP), bronchi may become dilated and distorted, and this appears to be a reversible phenomenon in some cases[12] (Fig. 5).

Volume loss

Volume loss, although the least specific of the three HRCT signs of FLD, can, on occasion, be a very useful indicator of fibrosis. It is of most value in corroborating the presence of FLD when honeycombing is absent and traction bronchiectasis is equivocal. The loss of lung volume in the lower lobes is inferred from the position of the oblique fissures on axial HRCT imaging. In health, the oblique fissure originates posteriorly, at the level of the aortic arch, and nearly touches the anterior chest wall when it reaches the diaphragm (Fig. 6a). Volume loss in the upper lobes elevates the position of the oblique fissure so that it lies above the level of the aortic arch at its superior aspect (Fig. 6b). When fibrosing disease is asymmetrical, as is often the case with IPF, recognition of volume loss is more straightforward because of the discrepancy of the positions of the two oblique fissures (Fig. 6b).

Ancillary features of fibrosis

HRCT signs such as reticulation and ground glass opacification are seen in many conditions other than FLD; nevertheless, they can be helpful as they are commonly associated with fibrosis. Interestingly, although reticulation is defined by small linear opacities that represent thickened intralobular or interlobular septa,[3] thickening of the latter is not,

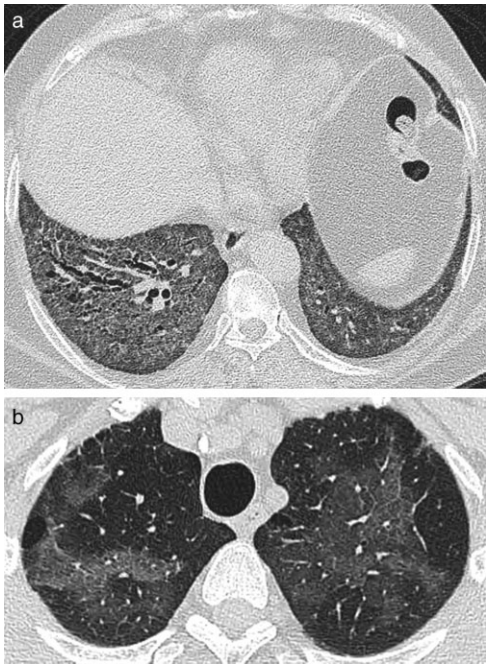

Figure 4 (a) A typical appearance of traction bronchiectasis in a 66-year-old male patient with connective tissue disease-related NSIP. The airways running lengthways in the right lower lobe are distorted and dilated and run through areas of fine reticulation and ground glass opacification. (b) The airways that run through the areas of diffuse ground glass opacification in the upper lobes appear conspicuous as the black air within them contrasts with the surrounding grey lung. On closer scrutiny, however, the airways are not dilated when compared with the accompanying vessels. The patient was diagnosed with a lipoid pneumonia.

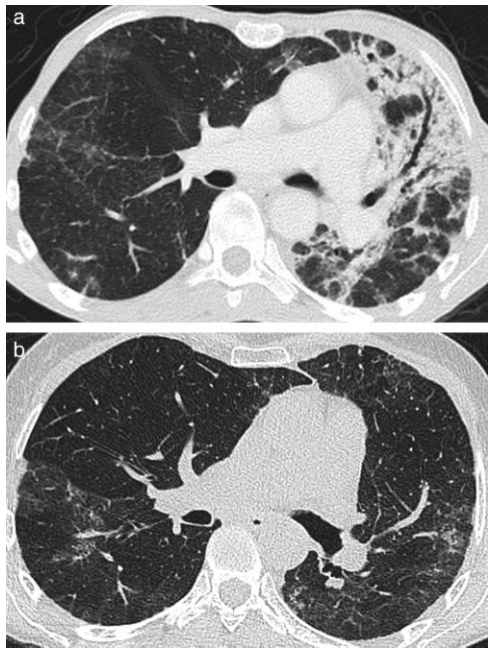

Figure 5 (a) The diffuse consolidation within the left lung contains dilated, varicose appearing airways, reminiscent of traction bronchiectasis. At first glance, the appearances suggest irreversible fibrosis, but airway dilatation may be reversible when secondary to inflammatory causes. (b) Ten months later, the consolidation has resolved and the dilated airways have reverted to their original normal calibre. The patient was diagnosed with a combination of aspiration and organizing pneumonia.

contrary to expectation, an important or common sign of interstitial fibrosis. The presence of conspicuous interlobular septal thickening can therefore suggest the possibility of diseases other than the common FLD.

Ground glass opacification, when it is seen in the context of FLD most frequently represents very fine fibrosis. When it occurs in conjunction with other features of fibrosis such as a coarse reticular pattern and areas of traction bronchiectasis, the ground glass opacification may take on a somewhat a granular appearance (Fig. 4a). Occasionally, ground glass opacification can represent coexistent viral pneumonitis, pulmonary oedema or, importantly, an acute exacerbation of disease in patients with interstitial fibrosis.

HRCT CHARACTERISTICS OF FIBROSING INTERSTITIAL PNEUMONIAS

Once the existence of a predominantly FLD on a HRCT has been established, the final stage in interpretation is to assign the pattern and distribution to one of five differential diagnoses, namely: three of the idiopathic pneumonias—UIP, non-specific interstitial pneumonia (NSIP) and the fibrosing variant of OP, and two granulomatous FLD—chronic hypersensitivity pneumonitis (HP) and fibrotic sarcoidosis.

With this scheme, there is no attempt to necessarily identify a specific disease, for example CTD-related FLD *per se* (because NSIP,[13,14] UIP[15] and the fibrosing variant of OP may occur in CTD). The diagnosis of CTD-related FLD, drug-induced and most occupational FLD requires clinical information and/or multidisciplinary discussion.

In most cases, after analysis of the HRCT, the differential can usually be narrowed down to one or two of the morphological patterns. At this point, with the aid of clinical information or histology, in a multidisciplinary team (MDT) setting, the diagnosis can almost invariably be further refined.[16]

Classical and non-classical UIP

Classical UIP

The importance of identifying UIP reflects the fact that the majority of patients with UIP are clinically diagnosed with IPF. Of all the idiopathic interstitial pneumonias, IPF is the most common and has by far the worst prognosis of any FLD[17] with a quoted survival of only 43% at 5 years in one early study.[18] More recent trial data have suggested that in IPF patients with relatively preserved lung function, survival may be better than previously thought.[19–21] The accurate

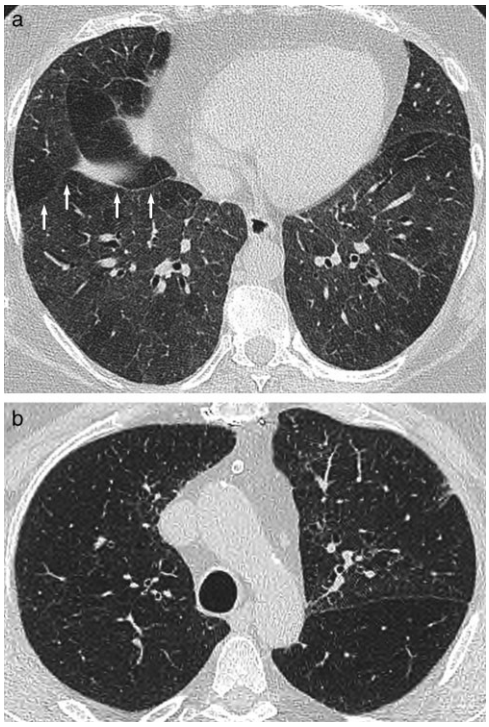

Figure 6 Examples of lobar volume loss in two cases of hypersensitivity pneumonitis. (a) Mosaic attenuation of the lungs is present, and there is lower lobe volume loss as evidenced by the relatively posterior position of the right oblique fissure (arrows) at the level of the hemidiaphragm, whereas in health, at the point of contact with the hemidiaphragm, the fissures should nearly reach the anterior chest wall. (b) Asymmetrical left upper lobe volume loss secondary to fibrosis in a 70-year-old male patient with chronic hypersensitivity pneumonitis. The left oblique fissure is visible in the mid-lung at the level of the aortic arch. In health, the oblique fissure should arise from the posterior chest wall at approximately the level of the aortic arch.

identification of IPF is clearly crucial to give a patient a realistic impression of their likely prognosis and potentially enrol them in a drug trial or to institute licensed drug therapy.[22,23]

The first American Thoracic Society and European Respiratory Society consensus for the idiopathic interstitial pneumonias (IIP) in 2002 stipulated that the identification of UIP on HRCT required the identification of bilateral, subpleural, basal (lower zone) reticulation with honeycombing and/or traction bronchiectasis.[24] Over time, the importance of honeycombing to diagnose a UIP pattern has been emphasized so that in the recent joint American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (Asociación Latinoamericana de Tórax) (ATS/ERS/JRS/ALAT) IPF diagnosis and management guidelines, the presence of honeycombing has become central to the confident HRCT diagnosis of UIP.[25] The HRCT findings of subpleural, basal honeycombing is now considered a classical or definite UIP pattern (Fig. 7).

Most cases of FLD that do not show a classical UIP pattern on HRCT will be one of five alternative diagnoses: UIP non-classical HRCT pattern, fibrotic NSIP,

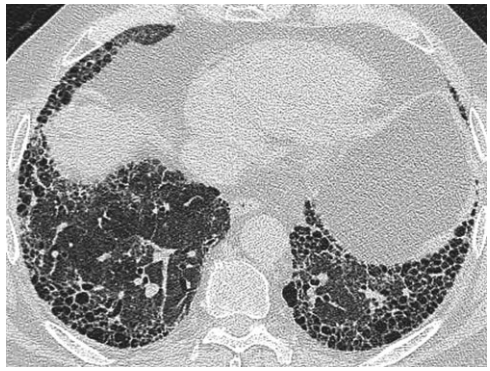

Figure 7 Classical usual interstitial pneumonia pattern on high-resolution computed tomography. Extensive honeycombing and reticulation is present throughout the lower zones of the lungs of 66-year-old male smoker. Only a small volume of architecturally normal lung parenchyma remains in the left lower lobe. The normal parenchyma appears increased in density, consequent to the physiological redistribution of blood preferentially towards areas of normal parenchyma.

a fibrosing variant of OP, chronic HP or sarcoidosis. The distinction between these entities, particularly UIP and chronic HP can prove elusive and is the basis of the most difficult of MDT discussions.

Non-classical UIP

Non- classical UIP (analogous to the term 'possible UIP' used in the ATS/ERS 2011 Guidelines) on HRCT includes those cases in which there are signs of a FLD, without honeycombing, and no features to suggest a FLD pattern other than UIP (discussed below) (Fig. 8).

The question of what proportion of cases of UIP on HRCT are non-classical (i.e. without honeycombing) is not easy to answer. In early reports in which all cases of UIP were pathologically proven, studies based on relatively small patient numbers quoted the frequency of honeycombing on HRCT as 60–80%.[17,26,27] Over time, with the increased recognition of IPF with a non-classical pattern, a 60–80% prevalence of honeycombing in UIP appears to be a considerable overestimate. A recent drug trial in which 432 IPF patients were recruited reported that only 33% of patients with a MDT diagnosis of IPF showed honeycombing on HRCT.[28]

An interesting finding from a recent study that analyzed the HRCT appearances of patients with biopsy-proven UIP in whom HRCT did not demonstrate honeycombing was that the greatest predictor of a UIP diagnosis was a patient's age.[29] In the study by Fell *et al.*, an age greater than 75 years in a patient with at least moderately extensive reticular abnormalities was associated with a 100% positive predictive value of UIP on surgical lung biopsy. This reduced to a positive predictive value of 91 when the patients were 65 years old. Although a single centre study, its findings have led to a patient's age often being factored in when assessing the likelihood of a diagnosis of IPF.

Fibrotic non-specific interstitial pneumonia

Understanding the HRCT features of NSIP has become refined over time. Many cases that might

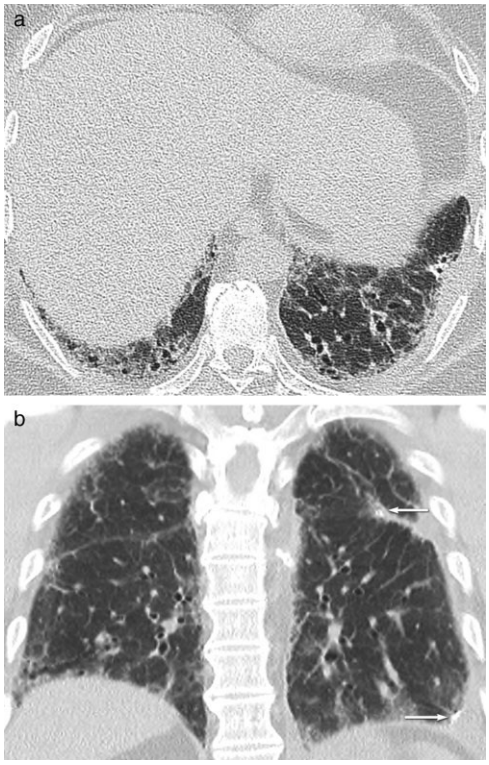

Figure 8 Non-classical usual interstitial pneumonia. (a) The absence of honeycombing is conspicuous in an 80-year-old patient with biopsy-proven idiopathic pulmonary fibrosis. At the extremes bases of the lower lobes, there is reticulation, ground glass opacification and traction bronchiectasis indicating fibrosis. (b) The predominantly lower zone distribution of fibrosis is conformed on coronal reformat high-resolution computed tomography, and again highlight the absence of any honeycombing. Surgical biopsy staples are visible in the left upper and lower lobes (arrows).

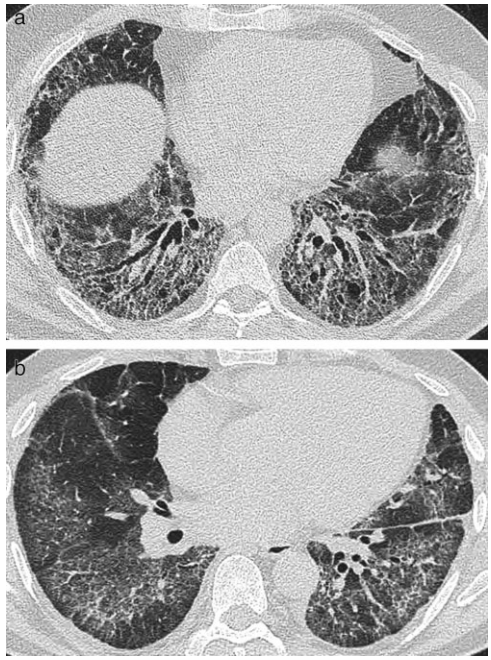

Figure 9 NSIP. (a) Ground glass opacification, fine reticulation and traction bronchiectasis in a basal distribution in a patient with fibrotic NSIP. The 50-year-old male patient had an underlying connective tissue disease. No honeycombing is evident, but there is overlap with the HRCT appearances of non-classical usual interstitial pneumonia. (b) HRCT of a 63-year-old male patient with idiopathic NSIP. Subpleural sparing characterized by a narrow zone of peripheral relatively normal lung is an occasional feature of NSIP, but is of limited discriminatory value. HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia.

previously have been labelled as NSIP fulfil criteria now considered to be 'possible UIP' on HRCT.[30] The HRCT appearances of fibrotic NSIP are usually those of fibrosis in a lower zone distribution in which ground glass opacification predominates over reticulation, with minimal or no honeycombing (Fig. 9a). There may be subpleural sparing (Fig. 9b); over time, the fine ground glass pattern may be replaced by coarser reticulation (Fig. 10), and ultimately some honeycomb destruction.

The appearances of fibrotic NSIP overlap with non-classical UIP and when considering the diagnosis of NSIP, two factors require consideration: the first, as previously mentioned, is the patient's age—IPF becomes a more likely prospect as the patient's age increases. The second factor is whether or not there is the clinical possibility of a background CTD. Should a patient be elderly with no clinical signs of a CTD, the diagnosis of IPF should be strongly considered.

Fibrosing variant of OP

Organizing pneumonia has numerous causes and associations, including CTD (when it may coexist with NSIP); and as a consequence of various forms of transplantation.[31] Although OP is characterized by consolidation on HRCT (the usual, but not only sign), in some cases, the loose granulation tissue that characterizes OP can become incorporated into alveolar walls as established fibrosis (usually NSIP). This may occur over a prolonged period and so when fibrosis develops, the preceding OP consolidation may only be evident on review of previous CT scans.

The typical manifestations of OP include perilobular opacification (Fig. 11a), consolidation with or without air bronchograms, peribronchovascular consolidation (Fig. 11b) and rarely the so-called reverse halo or atoll sign. When fibrosis supervenes in OP, it often demonstrates a bronchocentric distribution, particularly in patients with anti-synthetase disorder(s).[32,33]

Chronic HP

The HRCT appearances of chronic fibrotic HP have been extensively documented.[34–36] Central to the diagnosis of chronic HP identification is the distribution of fibrosis and the presence of certain ancillary findings. Fibrosis in HP may be concentrated in the upper or lower lobes, or may in fact be randomly distributed with no zonal predilection (Fig. 12).[35] Although this may at first glance appear to offer no discriminatory

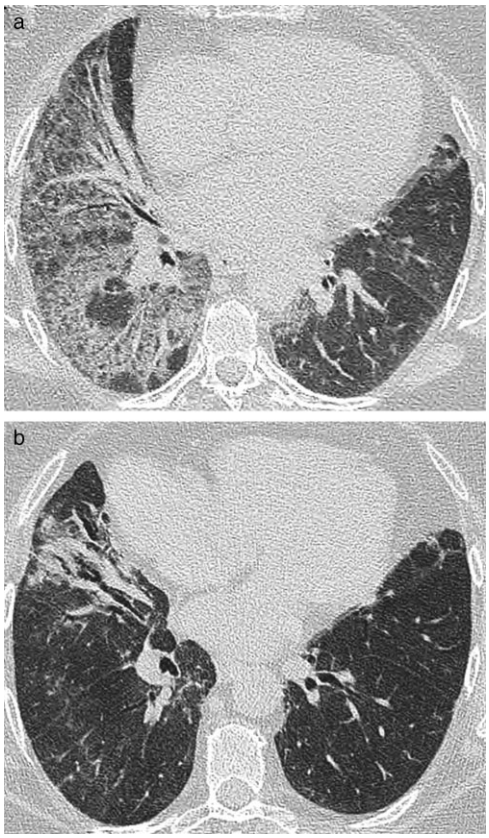

Figure 10 Progression of NSIP fibrosing lung disease in a 64-year-old female patient with symptoms suggestive but not diagnostic of a connective tissue disease. (a) In the right middle and lower lobes, relatively asymmetrical ground glass opacification and reticulation indicating a mixed fibrotic and cellular NSIP predominate with some subpleural sparing. No honeycombing or traction bronchiectasis is present. (b) Two and a half years later, the ground glass opacification and reticulation within the right lower lobe has resolved. In the middle lobe, there are signs of increasing fibrosis with traction bronchiectasis, coarse reticulation and volume lobar loss. NSIP, non-specific interstitial pneumonia.

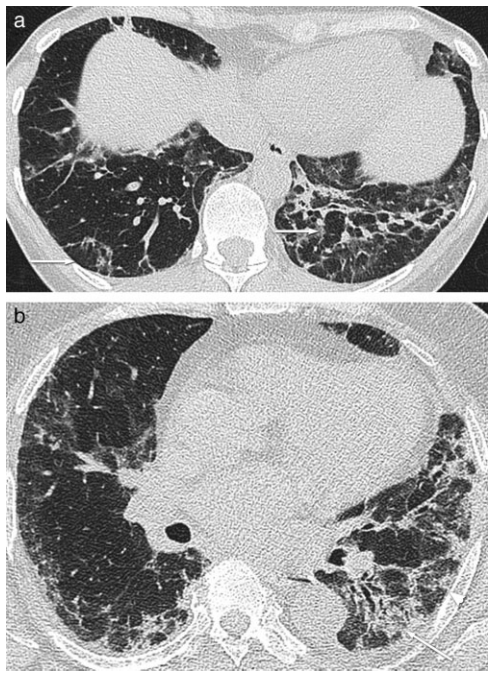

Figure 11 (a) Organizing pneumonia and NSIP in a 42-year-old female patient with polymyositis. A perilobular pattern is visible in both lower lobes representing organizing pneumonia (arrows). Subtle traction bronchiectasis in the left lower lobe with reticulation and ground glass opacification indicates a component of fibrotic NSIP. (b) Peribronchiolar consolidation (arrow) in the left lower lobe in a patient with organizing pneumonia. There is evidence of traction bronchiectasis indicating fibrosis as well as a perilobular pattern (arrowhead). NSIP, non-specific interstitial pneumonia.

value, in cases where the fibrosis is diffuse, with no particular zonal distribution, the possibility of chronic HP should always be considered.

Cases of chronic HP with predominantly basal fibrosis may be difficult, or impossible, to distinguish from classical UIP, particularly as a honeycomb pattern has been reported as being present in up to 60% of patients with chronic fibrotic HP (Fig. 13).[36]

When trying to differentiate between a UIP pattern and HP, four ancillary features can be helpful. The most important is the presence of lobules of decreased attenuation, specifically within the spared, non-fibrotic lung (Fig. 14a). The localized air trapping that this lobular pattern represents is the result of small airways obliteration, a pathological feature of HP. The importance of the identification of lobules of decreased attenuation within spared lung in chronic HP rests on the fact that such lobules are often also seen in areas of established fibrosis, especially in cases of UIP. Specifically, the presence of lobular air trapping in more than four lobes has been reported to identify chronic HP as the most likely diagnosis in a case of FLD.[37]

Within the upper lobes, in chronic HP, there may be a vague, subtle bronchocentricity to the fibrosis, but to a much lesser extent that the marked perihilar and bronchocentric fibrosis encountered in sarcoidosis (Fig. 14b). Furthermore, some thickened interlobular septa with no zonal predilection may also be evident, a finding that is not a particularly prominent feature of UIP or NSIP. Finally, the features of subacute HP may coexist with those of chronic HP (Fig. 14c). Subtle, indistinct ground glass centrilobular nodules and areas of ground glass opacification may be evident, intermingled among areas of fibrosis, although the conjunction of both forms of disease on HRCT is relatively uncommon.

Fibrotic sarcoidosis

Sarcoidosis when fibrotic, predominantly results in fibrosis that radiates off the hila and tends to involve the posterior segments of the upper lobes (Fig. 15a).[38] Such a striking upper zone distribution of disease is in stark contrast to a classical UIP pattern. Nevertheless, the features of chronic fibrotic sarcoidosis may mimic those of chronic HP quite closely. Less frequently, fibrotic sarcoidosis can manifest as one of two basal

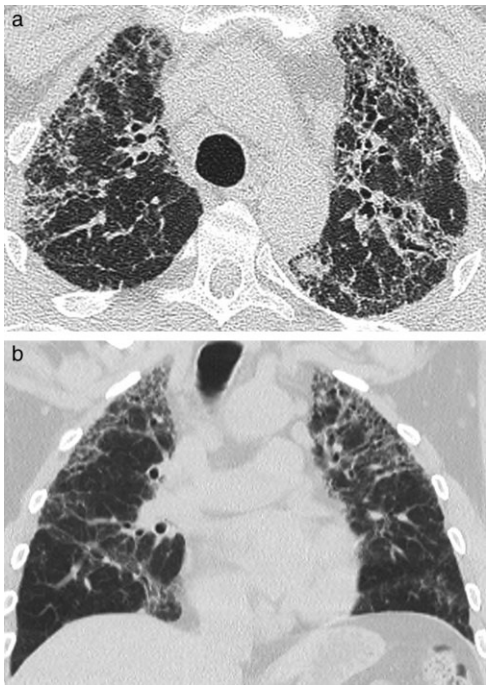

Figure 12 Chronic hypersensitivity pneumonitis. (a) A diffuse distribution of fibrosis involving both upper and lower lobes, emphasized on coronal imaging (b) is suggestive of hypersensitivity pneumonitis.

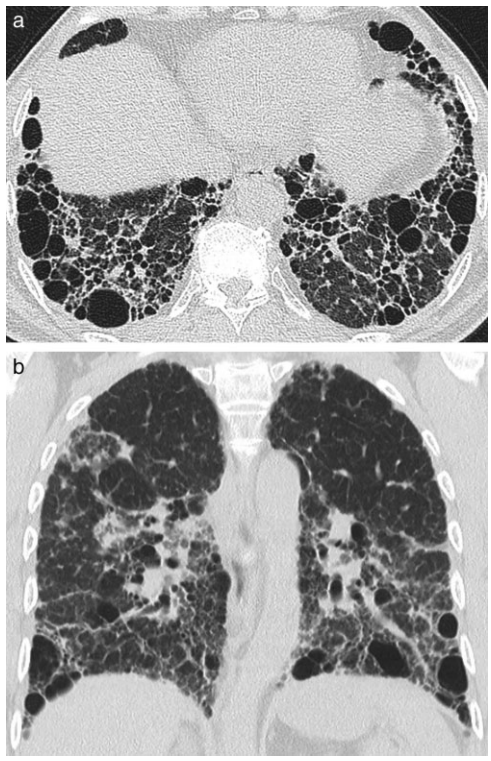

Figure 13 Chronic hypersensitivity pneumonitis in a 61-year-old male pigeon breeder with a 6-year history of shortness of breath. (a,b) Axial and coronal high-resolution computed tomography images show diffuse fibrosis with honeycomb cysts in the lower zones. The patient was too unwell to undergo a surgical lung biopsy.

predominant fibrotic patterns, one of which is characterized by some honeycombing. When honeycombing is evident in sarcoidosis, a distinguishing feature from UIP is that the honeycombing is not confined to the lung bases. Honeycomb cysts are admixed with emphysematoid bullae resulting in a destructive 'fibrobullous' pattern (Fig. 15b).[39] The other basal fibrotic pattern of sarcoidosis consists of reticulation representing nodular thickening of the interlobular septa within the middle and lower zones.[38]

PITFALLS AND CHALLENGES

'Possible UIP' conundrum

The 2011 ATS/ERS/JRS/ALAT statement on the diagnosis and management of IPF has clarified many aspects of IPF but at the same time has caused some confusion. In practice, the majority of patients with IPF do not show honeycombing on HRCT,[28] and according to the 2011 IPF statement, patients falling into this category of 'possible UIP', based on HRCT findings, should be further characterized by histopathological findings on surgical lung biopsy.

In reality, only a small proportion of these 'possible' IPF patients, either chose or are fit enough to undergo a surgical lung biopsy; these particular patients are often elderly and may already suffer from severe pulmonary disease, not to mention numerous pre-existing medical comorbidities. Without histopathological confirmation of UIP, strict adherence to the guidelines would mean that these patients cannot be given the diagnosis of IPF. Given that other similar appearing patterns on HRCT, including some cases of HP or NSIP, may not be readily excluded, patients with a possible UIP appearance on HRCT may therefore have a final disease designation of 'unclassifiable'.

A further contentious issue in the ATS/ERS/JRS/ALAT 2011 IPF guidelines also arises when HRCT appearances are inconsistent with UIP (the use of this category is highly experience dependent). Should the patient, as recommended by the guidelines undergo a surgical lung biopsy, and the resulting biopsy show a histological diagnosis of UIP, multidisciplinary discussion is required to determine whether the patient can be considered to have IPF or be categorized as unclassifiable.

The two situations outlined above are problematic for two reasons. Although the lack of a clear diagnosis and a resultant prognosis are likely to be a matter of consternation to the patient, just as importantly, the inability to provide a definite or probable IPF diagnosis leaves the patient without knowledge of appropriate drug therapies and/or complicates potential inclusion into clinical trials.

There are two further diagnostic determinants, which are likely to have an influence on the diagnosis of IPF. A patient's age should probably, but not definitively, influence the assignation of a definite, probable

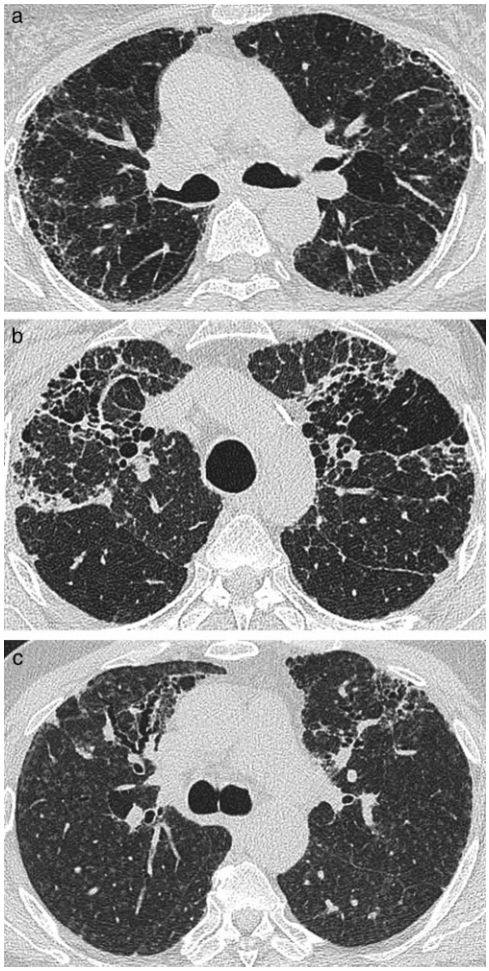

Figure 14 Additional features of chronic hypersensitivity pneumonitis are (a) sparing of secondary pulmonary lobules in non-fibrotic lung and (b) a relative bronchocentric distribution of fibrosis in the upper lobes. (c) Although often described as a characteristic finding, the centrilobular nodules of subacute hypersensitivity pneumonitis are an uncommon high-resolution computed tomography finding in the setting of chronic hypersensitivity pneumonitis.

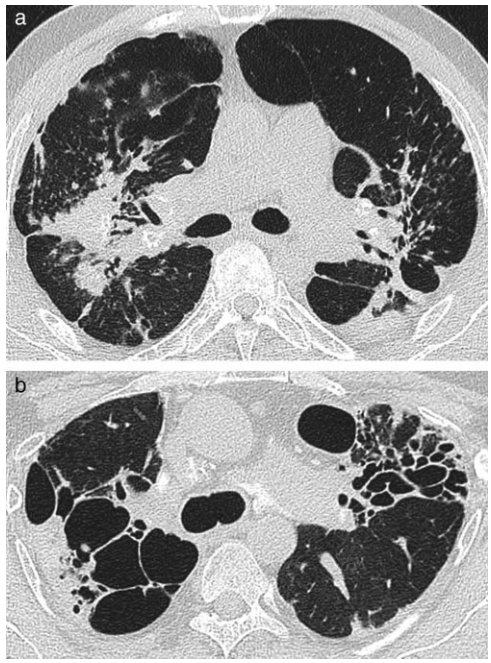

Figure 15 Fibrotic sarcoidosis. (a) Typical upper lobe perihilar distribution. Conglomerate masses surrounding calcified hilar nodes are composed of aggregations of granulomatous nodules. The dilated pulmonary artery, wider in diameter than the ascending aorta, indicates supervening pulmonary hypertension, a recognized complication of sarcoidosis. (b) Occasionally emphysematoid destruction of the lung can occur alongside fibrosis. This again primarily involves the upper lobes and the fibrobullous cavities can become colonized with aspergillus.

or possible IPF diagnosis, according to the findings of Fell *et al.*[29] Second, the idea of considering disease behaviour when formulating a FLD diagnosis is a recent concept.[30,40] If a patient's FLD is not easily categorized on HRCT but shows a marked worsening in extent over a relatively short interval (less than a year), there is a high probability that the disease is IPF, whatever the HRCT findings (hence the maxim 'if it behaves like IPF it probably is IPF'). Until large studies are performed that determine what proportion of possible UIP patients does indeed have IPF, disease behaviour will be a useful diagnostic pointer. A recent study looking at an IPF drug trial cohort attempted to answer this question, but the exclusion of all patients that did not have IPF on histology limited the applicability of this study to a wider population of patients with FLD.[41]

Unrecognized chronic HP with a UIP pattern

Most cases of FLD that demonstrate honeycombing in a typical subpleural and basal distribution on HRCT are found to have no cause and are therefore likely to represent IPF. In cases of fibrotic lung disease in which there is a clear cause, honeycombing on HRCT may reflect chronic HP, fibrosing sarcoidosis or one of the CTD. Although these conditions tend not to have a distribution of disease that is typically subpleural and basal on HRCT, on occasion, appearances are identical to a classical UIP pattern making the HRCT differentiation impossible.

Chronic HP is underdiagnozed in patients with a predominant honeycomb pattern on HRCT and the importance of eliciting a detailed clinical history of antigen exposure was emphasized in a recent study that re-evaluated 46 patients diagnosed as definite IPF using the 2011 IPF guidelines.[42] Although the study used non-traditional diagnostic criterion to classify patients as HP, 20 of the 46 patients had their initial IPF diagnosis altered to chronic HP.[42] Nevertheless, one of the most common diagnostic dilemmas in a MDT discussion results from a UIP pattern on HRCT that could represent either chronic HP or IPF, where neither the previously mentioned ancillary HRCT signs suggesting an HP diagnosis or a clear exposure history are available.

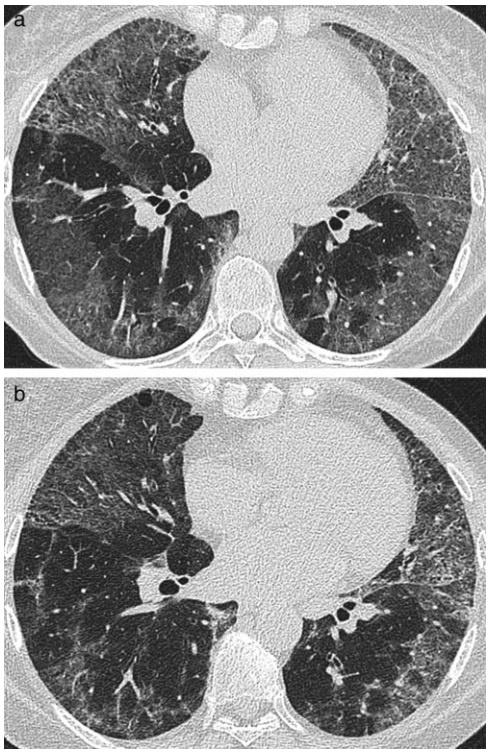

Figure 16 Desquamative interstitial pneumonia developing into fibrotic NSIP in a 63-year-old female smoker. (a) Initial HRCT where a predominant ground glass pattern can be seen, particularly in the left lung. At this time, a biopsy of the left lower lobe and lingula was performed and a diagnosis of DIP was made, although the pathological sample demonstrated some established uniform fibrosis in alveolar walls. (b) HRCT 6 years after the biopsy and initial HRCT shows a subtle but definite increase in the degree of reticulation, more in keeping with a fibrotic NSIP phenotype. DIP, desquamative interstitial pneumonia; HRCT, high-resolution computed tomography; NSIP, non-specific interstitial pneumonia.

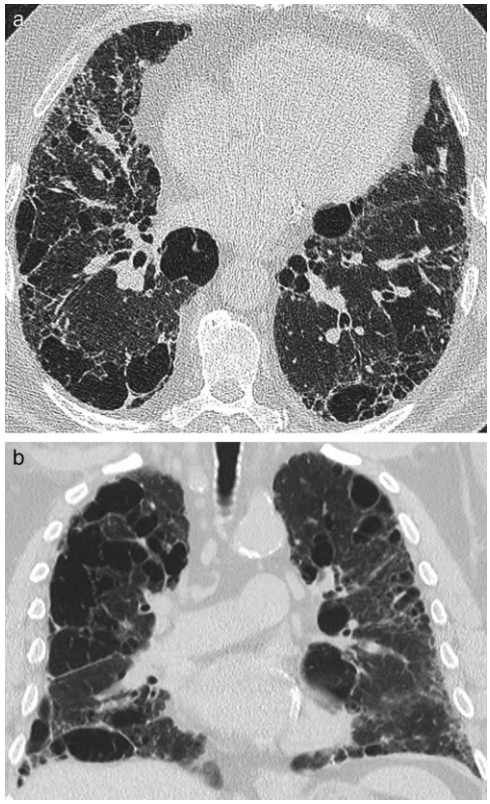

Figure 17 Combined pulmonary fibrosis and emphysema. (a,b) There are large areas of coalescent destructive paraseptal emphysema peripherally. Reticulation and traction bronchiectasis adjacent to the emphysema indicates coexistent fibrosis. The subpleural distribution of emphysema confounds the basal peripheral reticulation and identification of subpleural sparing, therefore making the radiological distinction between NSIP and UIP difficult. The patient was unable to undergo a surgical lung biopsy secondary to comorbidities. NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

FLD associated with smoking

A complex relationship that has yet to be fully elucidated exists between the effects of cigarette smoking and interstitial lung fibrosis. Desquamative interstitial pneumonia (DIP), a histological and HRCT pattern that had previously been considered a purely inflammatory manifestation of smoking-related disease, is now known to be associated with limited fibrosis on HRCT.[43–45] Whether the fibrosis evident on HRCT represents DIP evolving into fibrosis or there is co-development of DIP and NSIP is unclear (Fig. 16).[44]

The question of whether there is a direct link between cigarette smoking and NSIP and UIP is more complex. Studies on patients with IPF have found an increased risk of IPF in current or former smokers when compared with non-smokers with an odds ratio varying from 1.57 to 2.9.[46,47] When families with familial IPF have been studied, symptomatic and asymptomatic patients with HRCT appearances of early ILD had a significantly higher prevalence of smoking compared with patients with no HRCT evidence of ILD (67% and 45% respectively).[48]

A seemingly contradictory effect has been reported in current smokers with IPF, in whom mortality appears to be reduced when compared with ex-smokers.[49] However, the apparently reduced mortality in current smokers is thought to represent bias secondary to the fact that smokers with bad disease quit smoking, whereas those with less severe disease continue to smoke: the so-called 'healthy smoker effect'.[50]

Patients with emphysema and IPF have an increased mortality when compared with IPF patients without emphysema,[51] a finding thought to be related in part to the development of pulmonary hypertension.[52,53] In IPF, a significant proportion of patients have concurrent emphysema, constituting an entity for which the term combined fibrosis and emphysema (CPFE) has been coined.[51] When emphysema coexists with fibrosis on a HRCT, the exact extent of the two individual pathologies can be hard to discern because they are often admixed (Fig. 17).

Traction bronchiectasis has been shown to be reduced in severity in the presence of emphysema.[54] The small airways are attached to the alveoli by radially arranged fibres, and the contraction of these fibres, occurring as a consequence of interstitial fibrosis, is thought to result in the pulling apart of airways,

visible on HRCT as traction bronchiectasis.[54] Emphysema however destroys alveolar walls and disrupts the radially arranged alveolar attachments of the small airways inhibiting the development of traction bronchiectasis. Nevertheless, on occasions when traction bronchiectasis is visible, interspersed among emphysema, it has been shown to be useful in confirming the presence of fibrosis.[55]

A further diagnostic challenge in the interpretation of a HRCT of a patient with CPFE lies in differentiating whether the CT appearances represent a UIP pattern of fibrosis or NSIP coexisting with paraseptal emphysema. As mentioned previously, studies have shown that the inter-observer agreement for honeycombing is perturbed by coexisting paraseptal emphysema and is moderate at best,[7] thus a definite UIP diagnosis on HRCT can be difficult when emphysema is present. Emphysema can also interfere with some of the HRCT appearances that help distinguish an NSIP pattern from a UIP pattern, such as subpleural sparing and fine reticulation. Again, the clinical picture, disease behaviour and an MDT discussion become central in resolving such difficulties.

Unclassifiable FLD

Despite guidance from the IIP consensus classification,[30] it has been shown in a study by Ryerson *et al*. that (at least) 10% of cases of ILD remain unclassifiable following assessment of clinical, radiological and pathological data.[56] Concluding that a disease is unclassifiable ILD is particularly likely in cases of end-stage fibrotic disease in which histopathological features are entirely non-specific or encompass a variety of patterns (Fig. 18).

The cases selected in the study by Ryerson *et al*.[56] were evaluated in an era when a surgical biopsy was the gold standard for ILD diagnosis. Therefore, the majority of patients whose disease was deemed unclassifiable were those in whom a biopsy was contraindicated due to patient co-morbidity, age or patient preference. The recognized mortality associated with surgical biopsy and use of a MDT as a new diagnostic standard in ILD have both reduced the number of patients in whom pathological tissue is now available, or necessary, for diagnosis. In addition, in up to 18% of cases, the pathological diagnosis itself may be made with a low level of confidence from the histopathologist's point of view.[57] Considering these factors, it is likely that a figure of 10% is a marked underestimate for the frequency of unclassifiable ILD in practice today.

Nevertheless, some valuable information can be gleaned from the study of Ryerson *et al*.[54] It was found that 17% of patients with unclassifiable disease demonstrated a UIP pattern on HRCT according to the 2011 IPF guidelines,[25] whereas 50% of patients had a possible UIP pattern; interestingly, 50% of the entire unclassifiable cohort was found to have honeycombing on their HRCT.[56] The most frequent differential diagnoses were HP (68%), IPF (64%), NSIP (41%), CT-ILD (32%), drug-induced ILD (9%) and sarcoidosis (8%).[56] Those cases with a HRCT diagnosis of UIP or possible UIP were found to have a prognosis similar to IPF.[56]

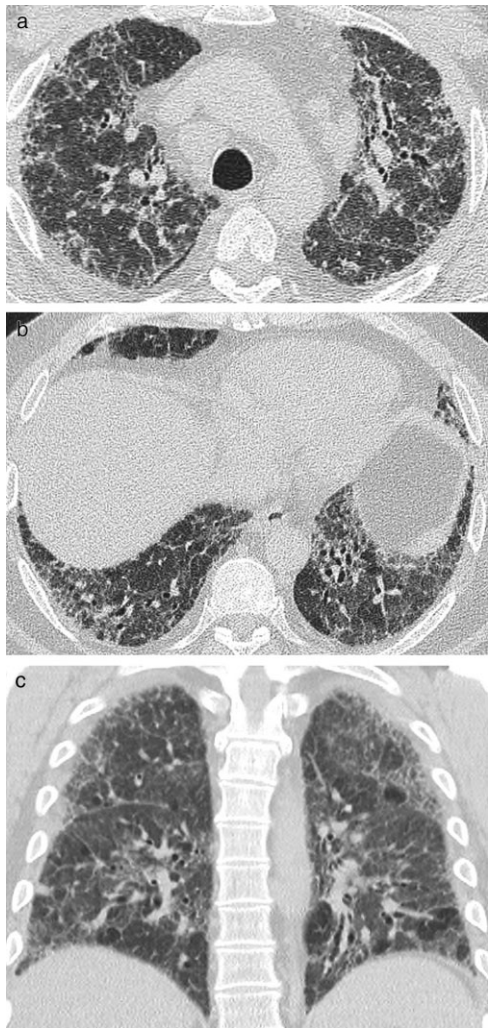

Figure 18 Unclassifiable fibrosing lung disease. (a,b) A relatively diffuse distribution of fibrotic disease with no zonal predominance. The lack of honeycombing precludes a diagnosis of classical UIP, and the differential remains between non-classical UIP, chronic HP and NSIP. (c) Pulmonary lobules, on the coronal reformat HRCT are identifiable, but within fibrotic areas of lung parenchyma and therefore do not necessarily imply chronic HP. Further MDT discussion is required for this type of case with clinical information and/or pathology being assimilated to reach either a final diagnosis or the assignation 'unclassifiable'. HP, hypersensitivity pneumonitis; MDT, multidisciplinary team; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

Although a well-versed MDT forum may refine and reduce the proportion of patients that are considered unclassifiable, it is clear that a significant proportion of patients does and will remain unclassifiable. A management conundrum arises with regard to unclassifiable ILD patients, as they have no diagnosis with which to base treatment strategies. A recently published clinical classification of disease behaviour goes some ways to addressing this management issue.[30] The classification considers the temporal stability or progression of a patient's disease and allocates a patient a specific management strategy. In so doing, it may obviate the need for a formal clinical

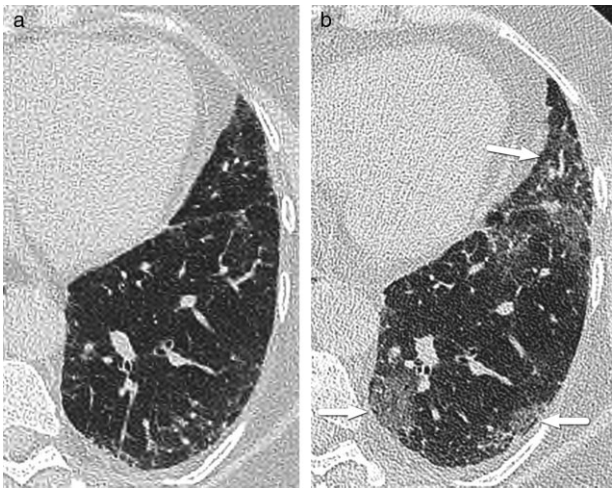

Figure 19 An acute exacerbation of interstitial lung disease. (a) An initial hypersensitivity pneumonitis (HRCT) in a 53-year-old patient diagnosed with chronic hypersensitivity pneumonitis demonstrates a minor degree of subpleural reticulation within the left lower lobe. (b) A subsequent HRCT scan 11 months later, obtained during an acute deterioration in symptoms demonstrates new foci of ground glass opacification within the left lung (arrows). There was no evidence of infection and an echocardiogram demonstrated normal ventricular function. The appearances are in keeping with an acute exacerbation of interstitial disease; the patient died less than 2 weeks after the HRCT was performed.

diagnosis before appropriate management and monitoring can be instituted.[30]

Imaging of acute exacerbation of FLD

An acute exacerbation of interstitial disease has been defined as an episode of unexplained new or worsening shortness of breath that has developed within the previous 30 days and is characterized by ground glass opacification (representing diffuse alveolar damage and generalized leakage) on HRCT superimposed on a background of fibrosis (Fig. 19).[58] Acute exacerbations are seen in a variety of FLD, but most frequently IPF,[59–61] and can dramatically alter the trajectory of a patient's clinical course with previously indolent disease progressing rapidly to death.

Although an acute exacerbation may be the presenting feature of IPF,[62] evidence suggests that it is more likely to complicate patients with more extensive baseline fibrosis.[63] In a recent 10-year follow-up of the prognosis of acute exacerbations in IPF, the hospital mortality rate was 56.9%. The 3-month mortality in this cohort was 80.6% in those with more extensive stage disease (abnormal lung >50% on HRCT), but 54.5% in those with limited stage disease (HRCT abnormal lung <50%).[63]

The lack of specific imaging characteristics (essentially the rapid development of ground glass opacification on a background of FLD) requires that an acute exacerbation is essentially a diagnosis of exclusion. Differential diagnoses include concomitant infection (such as *Pneumocystis* pneumonia or cytomegalovirus infection) and pulmonary oedema due to left ventricular failure.

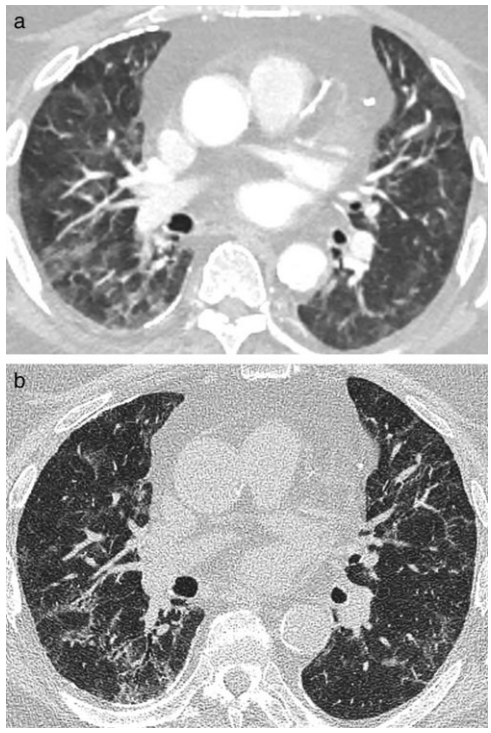

Figure 20 Effect of contrast enhancement as part of a computed tomography pulmonary angiogram (CTPA). (a) A CTPA was performed to identify the cause of an acute deterioration in a 76-year-old patient with organizing pneumonia. The administration of intravenous contrast results in an increase in density within areas of lung parenchyma, visible as foci of ground glass opacification. If not recognized as artefactual, the ground glass opacities may be thought to represent early acute exacerbation of interstitial lung disease. (b) A concurrent interspaced HRCT taken prior to the CTPA shows that the increased pulmonary parenchymal density is due to contrast medium and not generalized parenchymal disease.

When excluding the diagnosis of pulmonary embolus with a CT pulmonary angiogram (CTPA), intravenous contrast enhancement unpredictably increases the attenuation of the background lung parenchyma, which can complicate the evaluation of whether the lungs are of abnormally increased attenuation (i.e. ground glass opacification) (Fig. 20). To circumvent this problem, interspaced HRCT sections should ideally be obtained prior to the acquisition of the contrast- enhanced CTPA, thereby allowing the background lung to be satisfactorily evaluated for the sometimes subtle increase in density of the lung parenchyma, which heralds a full-blown acute exacerbation.

CONCLUSION

The HRCT evaluation of FLD is best accomplished using a stepwise approach. HRCT phenotypes of this small group of diseases usually fit into one or two out of five potential differential diagnoses. The diagnosis

can then be further refined following discussion in a MDT setting. Nevertheless, difficulties remain, particularly with regard to the separation of chronic HP from IPF; the evaluation of parenchymal patterns of smoking-related lung disease; and unclassifiable FLD.

There is a need for greater clarity in the diagnosis and management of patients with a 'possible UIP' pattern who do not undergo a surgical lung biopsy. Consideration of disease behaviour as well as patient age are increasingly being explored to refine the diagnosis of HRCT identified FLD.

Acknowledgement

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