Plain Film and HRCT Diagnosis of Interstitial Lung Disease

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Learning Objectives

- To learn how to systematically approach HRCTs of interstitial lung diseases.
- To become familiar with the most important interstitial lung diseases.

There is little doubt that imaging tests have a central role in the investigation of patients with suspected and established diffuse interstitial lung diseases (DILD). In most cases, physicians who manage patients with DILD will request a plain chest radiograph. However, high-resolution computed tomography (HRCT) is usually indicated, particularly at the initial review. HRCT, for a variety of reasons discussed below, is superior to plain radiography. In many cases where, historically, biopsy might have been considered mandatory, there has been a paradigm shift because of HRCT. For example, in some patients with idiopathic pulmonary fibrosis (characterized by the histological pattern of usual interstitial pneumonia), the HRCT appearance may be characteristic enough to render biopsy unnecessary [4, 22, 58]. In instances where a radiological diagnosis is not possible, HRCT may provide guidance as to the best site for surgical biopsy. More recently, HRCT has moved into the realms of prognostic evaluation and disease staging [11, 16, 56, 59].

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4.1 The HRCT Technique

In the era of multi-detector row CT machines, a brief reminder of the HRCT technique is pertinent. The two technical features that differentiate HRCT imaging from conventional CT are, first, the narrow x-ray beam collimation that significantly improves spatial resolution and, second, the use of a dedicated reconstruction algorithm [35]. The "high-frequency" algorithm effectively exaggerates the naturally high-contrast milieu of the lungs (i.e., aerated lung versus more solid elements) [35]. The conspicuity of vessels, small bronchi, and interlobular septa is increased compared to conventional (thick-section) CT images [38]. An important downside of high-frequency algorithms is the increased visibility of image noise, although, in practice, this generally does not hamper radiological interpretation.

4.2 HRCT in Diffuse Interstitial Lung Disease

The term DILD is a convenient "catch-all" for a heterogeneous group of disorders (Table 4.1) [4]. The DILDs have been subcategorized as follows: (a) DILDs that have a known etiology (e.g., secondary to exposure to certain drugs or a connective tissue disorder); (b) the idiopathic interstitial pneumonias (which themselves have undergone classification [5] and a more recent update [52]); (c) the granulomatous DILDs; and (d) a group of diffuse lung diseases that include Langerhans cell histiocytosis and lymphangioleiomyomatosis.

In patients with established diffuse lung disease, HRCT will not only detect but also characterize parenchymal abnormalities with greater accuracy than plain chest radiography. One important caveat is that in patients with nodular infiltrates, traditional "interspaced" HRCT images may mislead; on thin-section images, the dimensions of nodules and pulmonary vessels may be comparable, which makes distinction difficult [47]. This is unlikely to be an issue on thin-section

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Table 4.1 Classification of diffuse interstitial lung diseases (DILD)

DILD with known cause
• Connective tissue disorders
• Rheumatoid arthritis
• Asbestosis
• Hypersensitivity pneumonitis
• Others
Idiopathic interstitial pneumonias
• Idiopathic pulmonary fibrosis
• Idiopathic non-specific interstitial pneumonia
• Respiratory bronchiolitis interstitial lung disease
• Desquamative interstitial pneumonia
• Acute interstitial pneumonia
• Pleuroparenchymal fibroelastosis
Granulomatous DILD
• Sarcoidosis
• Silicosis
• Hypersensitivity pneumonia
• Drug-induced DILD
• Combined variable immune deficiency syndrome
• Others
Other DILD
• Langerhans cell histiocytosis
• Lymphangioleiomyomatosis
• Lymphoid interstitial pneumonia
• Birt-Hogg-Dubé syndrome
• Alveolar proteinosis
• Others

volumetric acquisitions. In practice, the range of CT features that commonly indicate the presence of ILD is relatively limited. Thus, radiologists will typically encounter some combination of reticulation, ground-glass opacification, honeycombing, dilatation of airways in regions of reticulation and ground-glass opacification ('traction bronchiectasis'), nodules, and thickening of the interlobular septa [17].

Findings at HRCT generally reflect the *macroscopic* abnormalities seen by the pathologist. This was elegantly demonstrated in the very early days of HRCT by Müller and colleagues who showed that morphologic features in patients with idiopathic pulmonary fibrosis—at that time still known by the moniker "cryptogenic fibrosing alveolitis"—reflected the histopathological changes [37]. A reticular pattern was seen in seven of nine patients and corresponded to areas of irregular fibrosis at microscopy.

Not surprisingly, because there is no anatomical superimposition, the sensitivity of HRCT is better than that of chest radiography. However, a more important issue than sensitivity is the confidence and accuracy with which a diagnosis can be made. In the oft-quoted landmark study by Mathieson and colleagues, experienced chest radiologists were asked to independently indicate up to three diagnoses, on chest radiographs and CT, in 118 patients with a variety of biopsy-confirmed ILDs [34]. Importantly, for the first-choice diagnosis, readers were asked to assign a level of confidence. The first important finding of this study (which effectively put HRCT on the map), was that, compared with chest radiography, a confident diagnosis was made nearly *twice* as often with HRCT. The second, and perhaps more striking, message was that when experienced radiologists were confident of the diagnosis on HRCT, they were almost always correct [34]; by contrast, a confident diagnosis on chest x-ray (which, incidentally, was offered in only one-quarter of cases) was associated with a significantly lower rate of correct diagnoses.

The results of subsequent studies have not always mirrored those of the initial study by Mathieson [34, 42]. However, because of study design, the majority of the comparative studies in HRCT likely undervalued its true utility [58]: first, there was no recourse to pretest probabilities for observers in early series, and, therefore, these do not accurately reflect clinical practice. Second, radiologists (and specifically those with an interest in thoracic disease) have become increasingly familiar with the spectrum of HRCT patterns and disease. This, almost certainly, would be associated with a proportionate increase in the confidence of *experienced* observers in making HRCT diagnoses, were such a study to be repeated today. Some justification for this last statement comes from a study that addressed the clinically vexing issue of "end-stage" lung disease [43], in which two experienced thoracic radiologists independently made correct first-choice diagnoses in just under 90% of cases with nearly two-thirds being made with high confidence. On first inspection, these data seem less than impressive. However, the results of open lung biopsy (the supposed "gold-standard" for the diagnosis of DILD) are often inconclusive, in part, no doubt, relating to the degree of observer variability between pathologists [39].

Key Point

- HRCT is the modality of choice for the investigation of patients with a suspected DILD.

4.3 An Approach to HRCT Diagnoses

It may come as some comfort to delegates that HRCT interpretation can be difficult, even for trained thoracic radiologists! This is not surprising given the sheer numbers of documented DILDs. This wide spectrum of disorders manifests with a relatively small number of histopathological patterns (e.g., fibrosis, consolidation, intra-alveolar hemorrhage), which, in turn, are reflected by a similarly select group of HRCT features (i.e., reticulation, ground-glass opacification, nodularity, thickening of interlobular septa). However, with a

systematic approach to HRCT interpretation, the observer should, in time, be able to offer a sensible (and manageably short) list of differential diagnoses. To this end, a proposed schema, presented in the form of questions that the observer should ask (in roughly the order given), is provided as follows.

4.3.1 Is There a "Real" Abnormality?

This is a crucial first question: the radiologist must first determine whether what is shown on HRCT represents real disease. CT features attributable to technical factors/normal variation (for instance, caused by a poor inspiratory effort, inadequate mAs, regions of physiologically dependent atelectasis) must not be overinterpreted and reported as "disease." Making the distinction between normality and abnormality can also be difficult when there is apparently minimal disease or, conversely, when there is diffuse abnormality (e.g., subtle but widespread decreased [mosaicism] or increased [ground-glass opacity] attenuation).

4.3.2 If There Is An Abnormality, What Is/Are the Predominant HRCT Pattern(s)?

Having decided that there is a definite abnormality on HRCT, the observer should attempt to identify the dominant pattern(s) using only the standard radiological terms [17]. The use of nonstandard terminology (e.g., patchy opacification, parenchymal opacities), or descriptive terms in which there is an implied pathology (e.g., interstitial pattern or alveolitis) is misleading and best avoided.

4.3.3 What Is the Distribution of Disease?

Many DILDs have a predilection for certain zones. Therefore, an evaluation of dominant distribution is of diagnostic value. For instance, it is known that, in the majority of patients with idiopathic pulmonary fibrosis (IPF), disease tends to be most obvious in the mid- to lower zones. This contrasts with fibrosis in patients with sarcoidosis, which typically has a predilection for the upper lobes. In addition to this, the radiologist should take note of the axial distribution (i.e., central versus peripheral), which, in contrast to CXR, can readily be made on HRCT, is of potential value. Using the example of IPF and sarcoidosis again, the former is commonly peripheral (subpleural), whereas, in the latter, disease tends to be central (and bronchocentric). A final example is seen in patients with organizing pneumonia where consolidation may have a striking perilobular predilection [53].

Table 4.2 Differential diagnosis of micronodular diseases based on the distribution type

Centrilobular distribution
• Bronchial diseases
– Infections
– Hypersensitivity pneumonia
– Respiratory bronchiolitis
– Follicular bronchiolitis
• Vascular diseases
– Pulmonary edema
– Vasculitis
– Pulmonary hypertension
– Metastatic calcification
Perilymphatic distribution
• Sarcoidosis
• Lymphangitic carcinomatosis
• Pneumoconiosis
Random distribution
• Miliary TB
• Viral infections
• Metastases

In addition to zonal distribution, the distribution on the level of the secondary pulmonary nodule can also be of diagnostic value. This is particularly true for micronodular diseases in which the allocation of nodules to one of the three distribution types (centrilobular, perilymphatic, random) is of use to narrow the differential diagnosis (Table 4.2).

4.3.4 Are There Any Ancillary Findings?

Ancillary HRCT features may suggest or, indeed, exclude certain diagnoses. Thus, the presence or absence of the following may be of diagnostic value in specific cases:

1. *Pleural thickening/effusions/plaques (± calcification)*—may suggest asbestos-related lung disease as opposed to IPF as a possible cause of lung fibrosis.
2. *Lymph node enlargement (hilar/mediastinal)*—reactive intrathoracic nodal enlargement is a recognized "normal" in fibrotic DILDs. However, symmetrical hilar nodal enlargement may suggest a diagnosis of sarcoidosis or occupational lung disease. Intrathoracic nodal enlargement is uncommon in pulmonary vasculitis (e.g., Wegener's granulomatosis).
3. *Bronchiectasis*—coexistent suppurative airway disease in a patient who has established pulmonary fibrosis may point to a diagnosis of an underlying connective tissue disease, such as rheumatoid arthritis.
4. *A dilatation of the esophagus in a patient with CT findings suggesting a non*-specific interstitial pneumonia points toward scleroderma as the underlying disease.

4.3.5 What Is the Likely Pathology?

A knowledge of the relationships between HRCT appearance and the possible histopathological correlates is crucial. Thus, in a patient with predominant consolidation, it is reasonable to conclude that the dominant pathology involves the air spaces, whereas, with reticulation, the pathological process likely affects the interstitium.

4.3.6 What Is the Clinical Background?

Clinical data must always be integrated when formulating a radiological opinion. However, it is often advisable to review the clinical information *after* the evaluation of radiological features. This is particularly true at the very start of HRCT interpretation when the radiologist is deciding whether or not there is a "real" abnormality (see above). Specific clinical features that may be of importance in HRCT interpretation include basic demographic data (age, gender, ethnicity), potential exposures (smoking history, contact with animals, occupation), the time course of the illness (i.e., have symptoms developed over hours and days or weeks and months?), and any relevant past medical history.

4.4 HRCT Appearances in Select DILDs

A working knowledge of the relationship between histopathological changes and HRCT patterns and the typical appearance of common DILDs is of value in day-to-day practice. The following section briefly considers the HRCT appearance in a few DILDs.

4.4.1 Usual Interstitial Pneumonia/Idiopathic Pulmonary Fibrosis

Usual interstitial pneumonia (UIP) is the most common form of chronic fibrosing lung diseases. At low-power microscopy, there is temporally heterogeneous fibrosis admixed with areas of unaffected lung [4]. In areas of fibrosis, there will be characteristic honeycombing. The disease has a striking basal and subpleural predilection. UIP can be caused by a variety of diseases, including connective tissue diseases, chronic hypersensitivity pneumonia, pneumoconiosis, and, in rare cases, also by sarcoidosis. The most common cause of UIP, however, is idiopathic pulmonary fibrosis (IPF), in which no underlying diseases can be diagnosed [45]. IPF is the most common IIP, and, with a median survival from time-to-diagnosis between 2 and 3 years, the one with the worst prognosis [45]. As current treatments are considered to prolong survival, a timely and confident diagnosis of IPF is of paramount importance.

To make a diagnosis of a 'UIP pattern' on HRCT, the radiologist must, therefore, look for the following: i) a reticular pattern; ii) honeycombing (with or without traction bronchiectasis); and iii) a subpleural, basal distribution of disease [45]. The radiologist must also ensure that there are no changes to suggest other diagnoses (i.e., mid/upper zone predominance, a peribronchovascular predominance with subpleural sparing, extensive pure ground-glass, widespread micronodularity, multiple cysts [away from areas of honeycombing], and extensive mosaic attenuation with extensive sharply defined lobular air-trapping on expiration and consolidation) [31] (Fig. 4.1). In the absence of honeycombing (but with the other features listed above), an HRCT diagnosis of 'probable UIP' can be made.

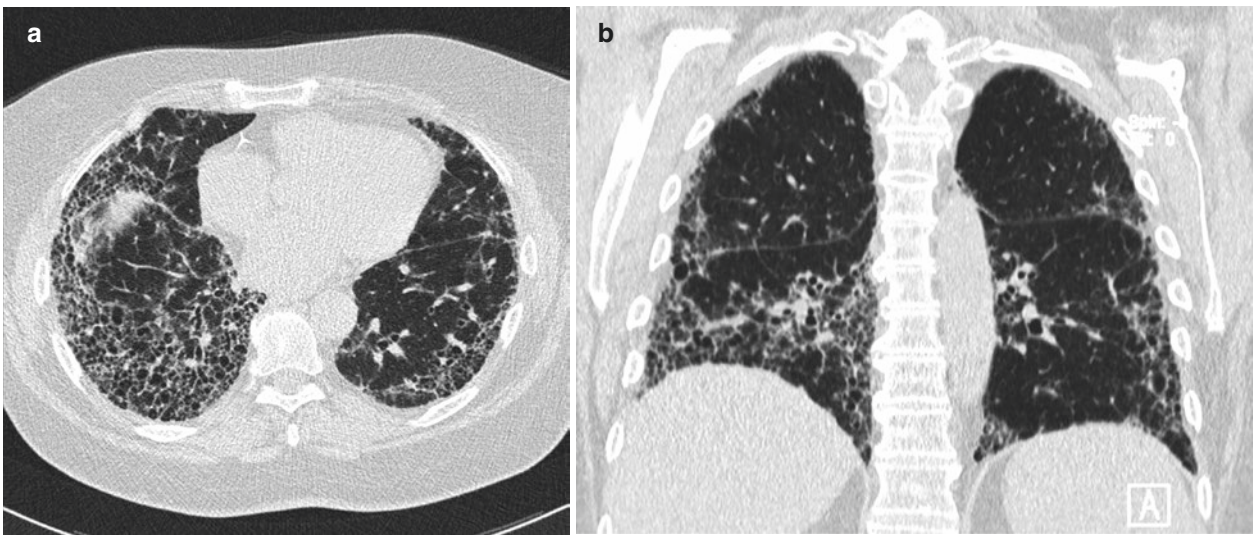

Fig. 4.1 Axial (**a**) and coronal (**b**) reformations of a 72-year-old female patient with progressive dyspnea on exertion. There are reticular abnormalities and honeycombing with basal and subpleural abnormalities. As there are no changes to suggest other diagnoses, the diagnosis of UIP can be made without histological confirmation

The presence of a UIP pattern on HRCT is accurate and obviates histologic confirmation [22, 31, 44, 46]. In patients with a CT pattern of a "probable UIP" and a high clinical likelihood of IPF (age >60 years, current or former smoker, no other potential causes of fibrosis), a confident diagnosis of IPF can be made without a biopsy [31]. However, atypical appearances may be present in over half of patients with biopsy-proven disease [13, 50].

Key Point

- Idiopathic pulmonary fibrosis is the most common IIP and a specific chronic, progressive, fibrosing interstitial pneumonia.

4.4.2 (Cryptogenic) Organizing Pneumonia

Organization is a common response to lung injury and is part of the normal process of lung repair. It is represented on histology by plugs of fibroblastic tissue that fill the alveolar spaces. This same fibroblastic tissue may be identified in respiratory and terminal bronchioles, explaining the use of the older term "bronchiolitis obliterans organizing pneumonia" (BOOP), but which has been replaced by organizing pneumonia (OP) [5]. Organizing pneumonia was first recognized in 1923 as a response to unresolved pneumonia [51]. Most cases are likely to be post-infectious; however, the pathogen is rarely recovered. The OP pattern is also a common feature in a wide range of other diseases including collagen vascular disease, hypersensitivity pneumonitis, chronic eosinophilic pneumonia, drug reaction, and radiation-induced lung injury. The appearance of OP on imaging is highly variable depending on the prior injury and the stage at which it is imaged [26]. A minority of cases present as solitary pulmonary nodules or focal areas of consolidation. However, the dominant finding in OP is bilateral consolidation that is peripheral, often with sparing of the subpleural portion of the lung (Fig. 4.2). Opacities are often perilobular and may be associated with septal lines. In some patients, OP may progress to an NSIP pattern of fibrosis. Although many patients with OP will clear with steroids, a substantial minority are left with significant disability due to pulmonary fibrosis [3, 26, 29].

Most cases of OP respond quite rapidly to steroid treatment. Recurrences are frequently observed, particularly in patients subsequent to a too-short steroid treatment.

Key Point

- Organizing pneumonia is a non-specific response to lung injury and is characterized by a filling of the alveolar space with fibroblastic tissue.

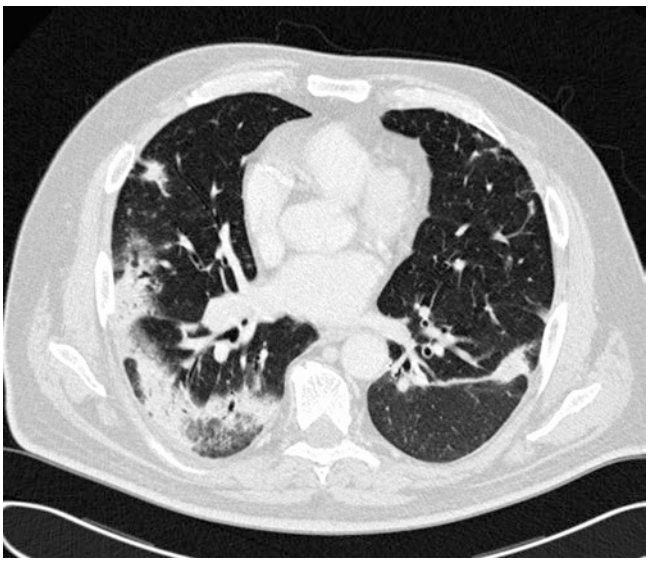

Fig. 4.2 Axial CT scan of a 64-year-old male patient with a treatment-resistant pneumonia. The CT scan shows bilateral peripheral consolidation, with sparing of the subpleural portion of the lung. The findings are suggestive of an organizing pneumonia

4.4.3 Non-specific Interstitial Pneumonia

After UIP, non-specific interstitial pneumonia (NSIP) is the most common pattern of idiopathic interstitial pneumonias (IIP) and is associated with a better rate of survival [12, 13, 52]. This pattern of IIP may be idiopathic but, more commonly, is seen in a variety of clinical contexts, including connective tissue disorders (especially systemic sclerosis) and as a consequence of drug-related toxicity. At a histologic level, there are varying amounts of interstitial inflammation and fibrosis, which, in stark contrast to what is seen in UIP, have a temporally and spatially uniform appearance.

On HRCT, one of the key findings is ground-glass opacification, which is typically bilateral and symmetrically distributed in the lower zones [12, 33] (Fig. 4.3). A (relative) sparing of the subpleural space is seen in up to 43% of the cases [49]. In some patients, over time, the extent of ground-glass may decrease and become replaced by reticulation (i.e., with UIP-like features) [49]. Reticulation (generally without significant honeycombing) is usually also present.

Key Point

- NSIP is most commonly seen in patients with connective tissue disorders and, on HRCT, is characterized by symmetrical, bilateral ground-glass opacification with a basal predominance.

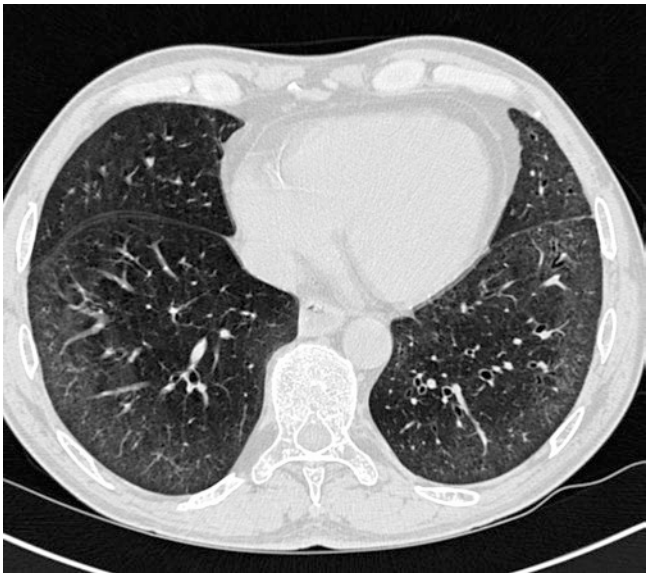

Fig. 4.3 Axial CT scan of a 61-year-old female patient with known scleroderma. The CT scan shows symmetrical, peripheral, extensive ground-glass opacities, with a relative sparing of the subpleural space. The findings are highly suggestive of a non-specific interstitial pneumonia (NSIP)

4.4.4 Smoking-Related Lung Diseases

Respiratory bronchiolitis (RB), of variable severity, is an almost invariable pathologic finding in all smokers [41]. Importantly, this pathologic lesion is asymptomatic and not associated with physiologic impairment in the vast majority of cases. However, in a small minority of cases, there will be the clinical manifestations of an interstitial lung disease—it is this clinico-pathologic/radiologic entity that has been called respiratory bronchiolitis interstitial lung disease (RBILD). The cardinal HRCT signs of RB/RBILD include "soft" centrilobular nodules, ground-glass opacification, smooth thickening of the interlobular septa, and lobular foci of decreased attenuation [10, 21, 36].

Desquamative interstitial pneumonia (DIP) was first described by Liebow in 1965. Dyspneic patients with DIP were found to have numerous inflammatory cells in the alveolar spaces [30]. The cells were thought to be desquamated pneumocytes but are now recognized as the same macrophages identified in patients with RB and RB-ILD; the majority of patients with DIP are heavy smokers, and it is now considered part of the spectrum of inflammatory lung disease related to the inhalation of cigarette smoke [21]. Patients with DIP suffer an increased incidence of pulmonary fibrosis that fits the histologic pattern of NSIP [9, 60]. Imaging in patients with DIP is typified by homogeneous or patchy areas of ground-glass opacity in the mid and lower lung zones [9, 20].

In adults, Langerhans cell histiocytosis (LCH) is isolated to the lungs in approximately 90% of cases. Although the pathogenesis is unknown, almost all of the patients are cigarette smokers. PLCH is characterized by bronchiocentric collections of Langerhans cells admixed with a variety of other inflammatory cells, forming a stellate nodule [55]. Over time, infiltration of the airway wall results in damage to the airway wall and subsequent dilatation of the airway [23]. In the late stage of PLCH, small stellate scars are surrounded by emphysematous spaces. The imaging reflects the histologic progression with early bronchiocentric nodules in the upper lobes, progressing to a combination of bizarre-shaped cysts and nodules [1, 28] (Fig. 4.4). In the final stages, the appearance may be indistinguishable from severe bullous emphysema.

It is important to recognize that findings of RB, DIP, pulmonary LCH, and the NSIP pattern of fibrosis commonly coexist in biopsies of dyspneic smokers. Some of the histologic changes are reflected on imaging, while others are below the resolution of chest computed tomography.

The relationship between cigarette smoke and fibrosis remains contentious [8, 10, 15, 24, 25, 61, 62]. Niewoehner's original description of RB did not include fibrosis of the alveolar wall [41]. However, there is substantial support for a relationship between cigarette smoke exposure and a pattern of alveolar wall fibrosis other than UIP [2, 6, 14, 24, 27, 40, 57]. In our experience, there is a group of dyspneic cigarette smokers who present with a combination of well-formed cystic spaces on computed tomography that follow the typical, upper lobe-predominant distribution of smoking-related emphysema, with variable surrounding ground-glass opacity and reticulation that may extend into the lower lung zones [15]. The patients commonly present with strikingly normal flows and volumes on pulmonary function testing and a low diffusing capacity. The unexpectedly normal flows and volumes are the result of the opposing effects of emphysema and fibrosis [57].

4.4.5 Sarcoidosis

Noncaseating, epithelioid cell granulomata are the histopathological hallmark of sarcoidosis. Granulomata distribute along the lymphatics. Thus, the lymphatic pathways that surround the axial interstitium, which invests bronchovascular structures, and those that exist subpleurally (including the subpleural lymphatics along the fissures) are typically involved (Fig. 4.4). Not surprisingly, a nodular infiltrate (presumably reflecting conglomerate granulomata) with a propensity to involve the bronchovascular elements is a characteristic CT finding [7, 32]. Subpleural nodularity is also commonly seen. In the later stages of the disease, there

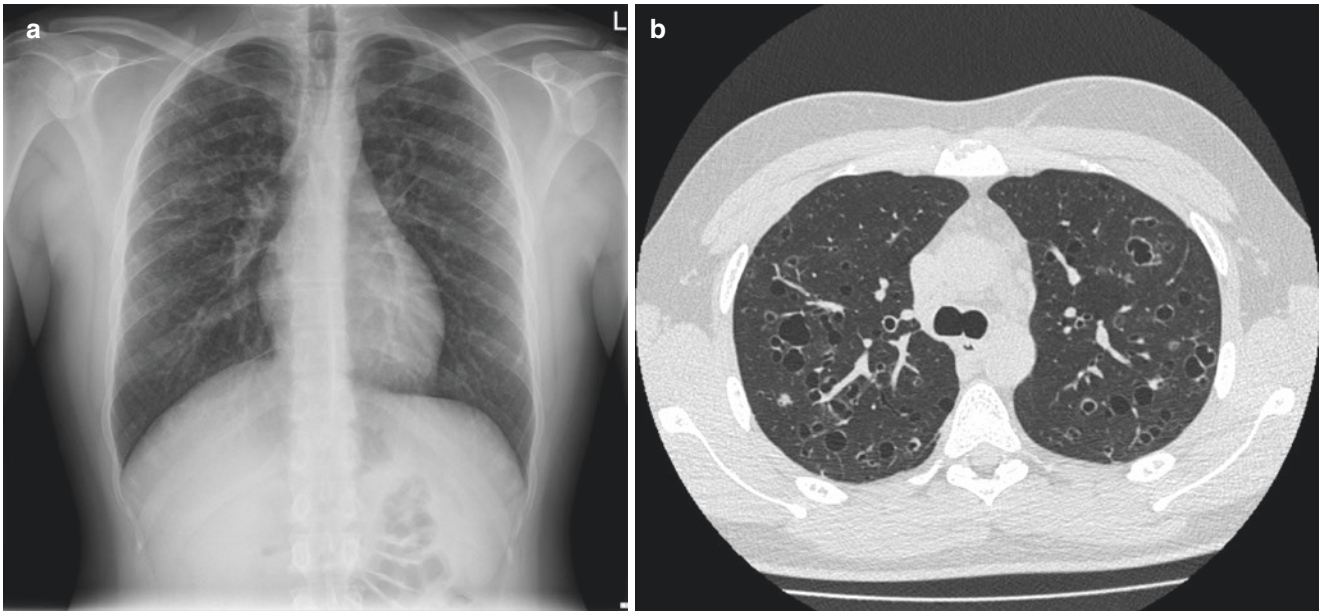

Fig. 4.4 Chest radiograph (**a**) and axial CT scan (**b**) of a 23-year-old male patient with coughing and dyspnea on exertion, which shows thin- and thick-walled cysts with an upper lobe predominance. In addition to the cysts, the CT scans also show some ill-defined nodules. The findings are highly suggestive of a Langerhans cell histiocytosis (LCH)

may be obvious signs of established lung fibrosis with upper zone volume loss, parenchymal distortion, and traction bronchiectasis. Because of the bronchocentric nature of the disease, signs of small airways disease are seen at CT in some patients with sarcoidosis [18].

Key Point

- Sarcoidosis is a systemic granulomatous disease that most frequently manifests in the chest. Granulomata in sarcoidosis tend to follow a perilymphatic distribution pattern, with a predominance in the upper lung zones.

4.4.6 Hypersensitivity Pneumonitis

Exposure to a range of organic antigens will cause lung disease in some patients, probably due to an immunologically mediated response. In the subacute stage, there is an interstitial infiltrate comprising lymphocytes and plasma cells, with a propensity for small airways (bronchioles) involvement. Scattered noncaseating granulomata may be seen. Predictably, at CT, there is diffuse ground-glass opacification, ill-defined centrilobular nodules and lobular areas of decreased attenuation on images performed at end-expiration [19, 48] (Fig. 4.5). The CT appearance in subacute hypersensitivity pneumonitis may be identical to that

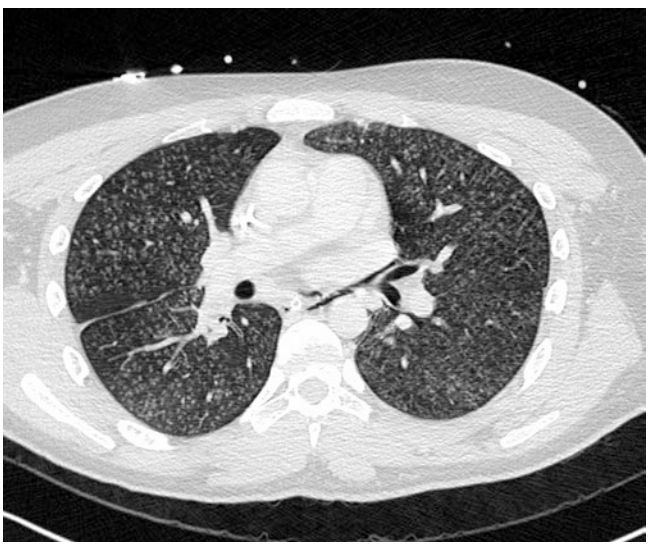

Fig. 4.5 Axial CT scan of a 19-year-old male patient with flu-like symptoms for some weeks. The CT scan shows countless ill-defined centrilobular nodules. The suspicion of an acute hypersensitivity pneumonia could be confirmed by a high lymphocyte count at bronchoscopy and by the history of exposure to mold

in patients with respiratory bronchiolitis-associated interstitial lung disease (RBILD) [10]. However, consideration of the smoking history may help in differentiation: a history of smoking is the norm in the vast majority of patients with RBILD, whereas cigarette smoke appears to lead to a relative protection against the development of hypersensitivity pneumonitis.

Chronic hypersensitivity pneumonia (CHP) is the consequence of a prolonged or repetitive course of acute HP and is characterized by fibrotic changes on HRCT and/or histology [54]. On HRCT, CHP is characterized by the presence of reticular abnormalities and traction bronchiectasis, with a predominance in the upper and middle lung fields, and frequently shows a peribronchovascular accentuation with subpleural sparing [54]. Honeycombing is observed in up to 69% of the cases [54]. Centrilobular nodules, air trapping, and/or a mosaic pattern in a patient with a fibrosing lung disease is a good clue to the diagnosis of CHP.

4.5 Concluding Remarks

HRCT plays a central role in the differential diagnosis of DILD. The final diagnosis requires a combination of radiological, clinical, and serological information, which is best accomplished in an interdisciplinary discussion. In many cases, the diagnosis achieved in this way is so confident that a histopathological confirmation is not necessary.

Take-Home Messages

- DILDs require a systematic analysis of the HRCT.
- The HRCT differential diagnosis of DILD is based on a systematic analysis of the predominant CT pattern, the ancillary CT findings, and the distribution of the findings.
- The final diagnosis of DILDs should be made in an interdisciplinary discussion.

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