# Idiopathic Interstitial Pneumonias

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Paul J. Lee and Jeffrey P. Kanne

**Abstract**

The idiopathic interstitial pneumonias are a distinct group of clinicopathologic entities. High-resolution computed tomography (HRCT) plays a critical role in the evaluation and management of patients. In the appropriate clinical setting, characteristic HRCT findings may be diagnostic, obviating the need for open lung biopsy. In more challenging or complicated cases, consensus among the clinician, radiologist, and pathologist may be required. This chapter describes and depicts the characteristic HRCT features of usual interstitial pneumonia, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, respiratory bronchiolitis, respiratory bronchiolitis associated interstitial lung disease, desquamative interstitial pneumonia, and lymphoid interstitial pneumonia.

**Keywords**

Interstitial lung disease (ILD) · High-resolution computed tomography (HRCT) · Usual interstitial pneumonia (UIP) · Nonspecific interstitial pneumonia (NSIP) · Cryptogenic organizing pneumonia (COP) · Respiratory bronchiolitis (RB) · Respiratory bronchiolitis–interstitial lung disease (RB-ILD) · Desquamative interstitial pneumonia (DIP) · Lymphoid interstitial pneumonia (LIP)

## Introduction

Over 200 causes of interstitial lung disease have been described. Environmental and occupational exposures, systemic diseases, and genetic causes can all result in a variety of interstitial lung diseases. The idiopathic interstitial pneumonias (IIP) refer to a group of distinct clinicopathologic entities without known causes [1]. Classification of IIP has undergone several iterations as understanding of these entities evolves [2–4].

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The most common IIP is idiopathic pulmonary fibrosis (IPF), which accounts for approximately 40% of all idiopathic interstitial lung disease [5]. While idiopathic forms do exist, the other IIPs more commonly result from exposures, such as tobacco smoke or connective tissue disease.

High-resolution computed tomography (HRCT) plays a key role in assessing the patient with known or suspected interstitial lung disease. While the primary function of HRCT is to distinguish patients with usual interstitial pneumonia (UIP), which is associated with IPF, from those without UIP, HRCT findings can often suggest other causes of diffuse lung disease. Although surgical biopsy is advocated in patients with suspected IIP who do not have a definite UIP pattern on HRCT, consensus between clinicians and radiologists with expertise in interstitial lung disease may suffice to establish a diagnosis.

## Usual Interstitial Pneumonia

IPF is uncommon with an incidence of 6.8–16.3 per 100,000 persons in the USA [6]. Men are affected twice as often as women, and the incidence increases with increasing age. While the exact cause of IPF remains unknown, environmental factors such as occupational dusts and fumes [7], cigarette smoke [8], and Epstein-Barr virus infection [9] may be contributory. Prognosis remains poor with fewer than 50% of patients surviving 5 years following diagnosis [10].

IPF is characterized histologically by UIP. The UIP pattern on HRCT consists of reticular opacities, traction bronchiectasis, and architectural distortion in a patchy subpleural and bibasilar distribution (Fig. 12.1) [11, 12]. These findings may be asymmetric but not unilateral. Honeycombing is a critical component of a confident, radiologic diagnosis of UIP (Figs. 12.2, 12.3). Honeycombing consists of clustered cystic spaces stacked upon a subpleural base. These cystic spaces have well-defined walls and typically range from 3 to 10 mm in size but may extend up to 2.5 cm in diameter [1, 5, 13]. Centrilobular and paraseptal emphysema may coexist with CT findings of UIP and should not be mistaken for honeycombing (Fig. 12.4) [8, 14–18]. Mild mediastinal lymphadenopathy is also common, typically involving the right paratracheal and subcarinal stations. The degree of lymphadenopathy typically correlates with the extent of parenchymal reticulation, although short axis lymph node measurements rarely exceed 1.5–2.0 cm in the absence of another superimposed cause [19, 20]. Ground-glass opacities can be associated with areas of fibrosis and may even represent regions of fibrosis. However, ground-glass opacities should account for a relatively minor component of parenchymal abnormality.

Studies have shown that the positive predictive value of a confident CT diagnosis of UIP by expert pulmonary radiologists ranges from 90 to

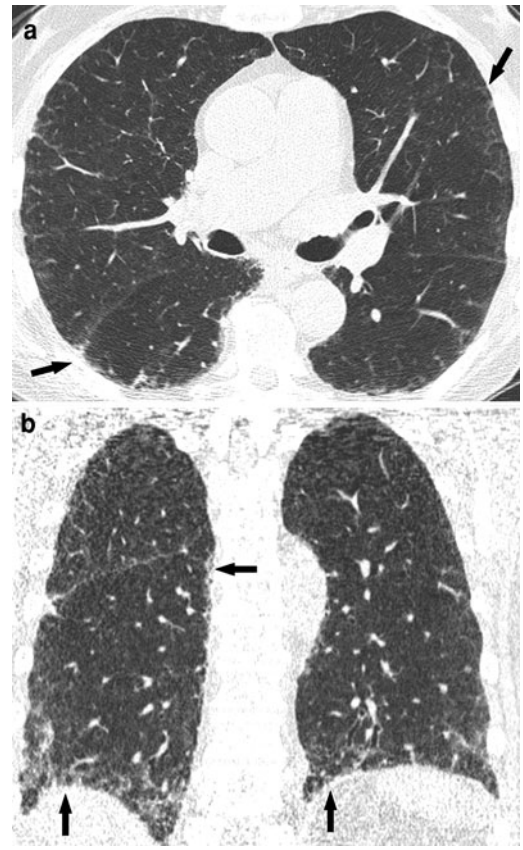


**Fig. 12.1** Usual interstitial pneumonia. Transverse (**a**) and coronal reformatted (**b**) low-dose HRCT images show subpleural and basal reticulation (*arrows*)

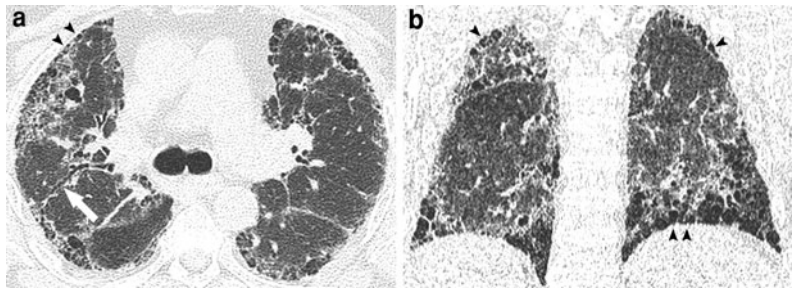


**Fig. 12.2** Usual interstitial pneumonia. Transverse (**a**) and coronal reformatted (**b**) low-dose HRCT images show subpleural and basal predominant reticulation with subpleural honeycombing (*arrowheads*)

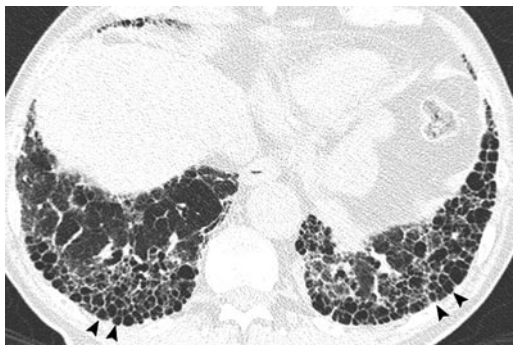

**Fig. 12.3** Usual interstitial pneumonia. Transverse HRCT image shows extensive, symmetric honeycombing (*arrowheads*) in the lung bases

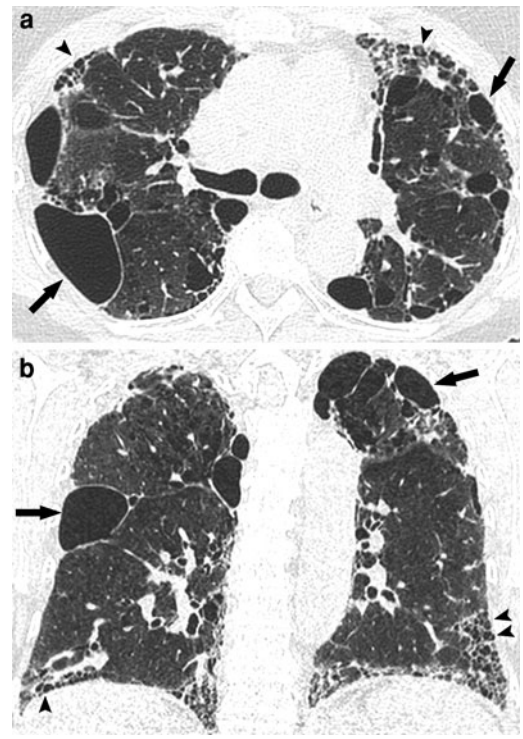


**Fig. 12.4** Combined pulmonary fibrosis and emphysema. Transverse (**a**) and coronal reformatted (**b**) HRCT images show upper lobe predominant bullous emphysema (*arrows*) and basal predominant subpleural honeycombing (*arrowheads*)

100%. However, these studies also show that a confidant diagnosis is not made in 25–50% of histologically proven cases of UIP [21–27]. Silva et al. demonstrated that the findings of basal honeycombing, the absence of subpleural sparing, and the absence of centrilobular nodules best distinguish UIP from chronic hypersensitivity pneumonitis and nonspecific interstitial pneumonia (NSIP) [28]. CT findings that should suggest alternative etiologies include micronodules; air trapping; non-honeycomb cysts; consolidation; a peribronchovascular distribution of fibrosis, and significant pleural calcifications, plaques, or effusion [5].

Complications associated with IPF include acute exacerbation (Fig. 12.5), pulmonary hypertension [29–31], pulmonary thromboembolism, coronary artery disease, bronchogenic carcinoma (Fig. 12.6), pneumothorax (Fig. 12.7), pneumomediastinum, and infection. Opportunistic organisms in this setting include *Mycobacteria*, *Pneumocystis jiroveci*, and *Aspergillus* species [32, 33]. Acute exacerbation occurs in approximately 5–10% of patients on an annual basis. Associated CT findings include new ground-glass opacities and consolidation in a peripheral, diffuse, or multifocal random

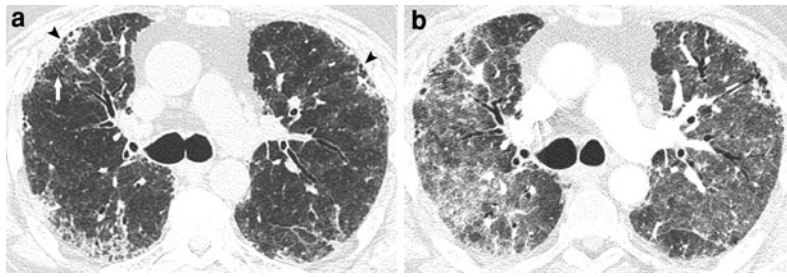


**Fig. 12.5** Acute exacerbation of UIP. **a** HRCT image shows subpleural predominant reticulation with mild traction bronchiectasis (*arrows*) and bronchiolectasis (*arrowheads*). A small amount of ground-glass opacity is present. **b** HRCT 9 days later shows development of extensive ground-glass opacity

distribution (Fig. 12.8). It is unclear whether these acute exacerbations represent rapid advancement of the primary disease or superimposed infection, infarction, or other pathology difficult to separate from the primary process [34–39]. Pulmonary hypertension is commonly associated with IPF, although CT-derived vascular measurements may be of limited predictive value [40]. Bronchogenic carcinoma (Fig. 12.9) develops in approximately 10–15% of those with relatively longstanding IPF and usually manifests as new focal consolidation or nodule in a region of severe fibrosis [41]. The appropriate role of routine screening for these complications has not been defined [5].

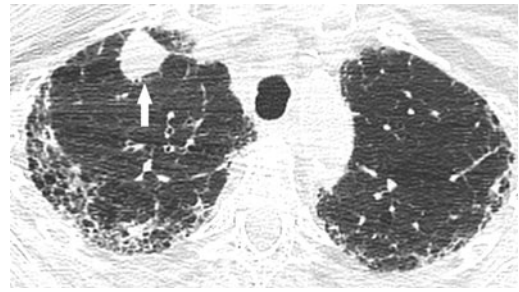

**Fig. 12.6** UIP with bronchogenic carcinoma. HRCT image shows a large nodule (*arrow*) on a background of subpleural reticulation and honeycombing. Transthoracic needle biopsy showed non-small cell lung carcinoma

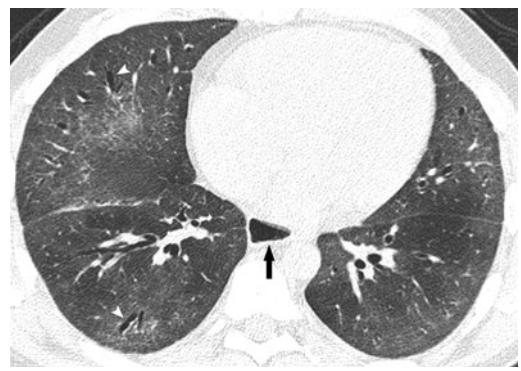

**Fig. 12.7** NSIP associated with systemic sclerosis. HRCT image shows extensive ground-glass opacity. There is mild bronchial dilation (*arrowheads*). Note the patulous and fluid-filled esophagus (*arrow*)

## Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) was first used to classify patients with interstitial lung disease and surgical biopsies not fitting into any well-defined histologic pattern [3]. Currently, idiopathic NSIP is recognized as a distinct clinicopathologic entity associated with a better prognosis than IPF. Patients with idiopathic NSIP tend to be lifetime non-smoking females of Asian ethnicity [42]. However, NSIP is most commonly associated with connective tissue disease such as systemic sclerosis or may be the sequela of a drug reaction.

While the HRCT findings of NSIP have proven to be more variable than was initially suggested [43–46], the majority of cases have ground-glass opacities and findings of fibrosis including fine reticulation, traction bronchiectasis, and volume loss in a symmetric mid to lower lung distribution (Figs. 12.7, 12.8) [47, 48]. The severity and distribution of these parenchymal abnormalities are more uniform than in UIP.

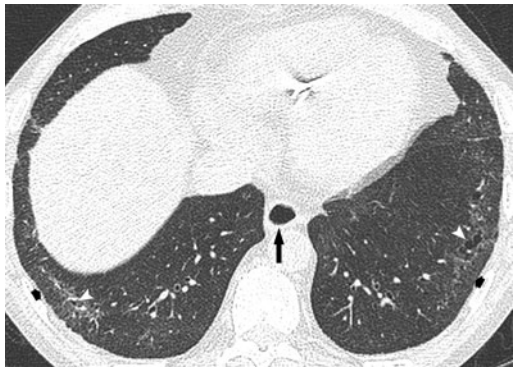

**Fig. 12.8** NSIP associated with mixed connective tissue disease. HRCT image shows mild ground-glass opacity and reticulation in the lower lobes associated with mild traction bronchiectasis (*arrowheads*). Note the patulous esophagus (*thin arrow*). Mild subpleural sparing is evident (*wide arrows*)

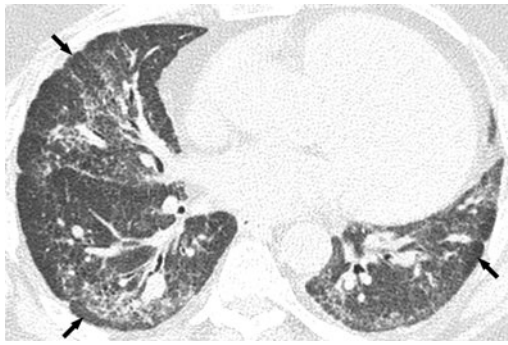

**Fig. 12.9** NSIP associated with undefined connective tissue disease. HRCT image shows ground-glass opacity with reticulation in the lower lungs. Note the rim of relative subpleural sparing (*arrows*)

Distribution along the axial plane may be peripheral, peribronchovascular, or diffuse. When present and in the appropriate setting, a thin rim of subpleural sparing is a rather specific finding for NSIP and should heighten diagnostic confidence (Fig. 12.9) [43]. As with IPF, mild mediastinal lymphadenopathy is common, particularly at the right paratracheal and subcarinal stations, and correlates with the degree of parenchymal involvement. Given the high association of NSIP with underlying collagen vascular diseases and other disorders,

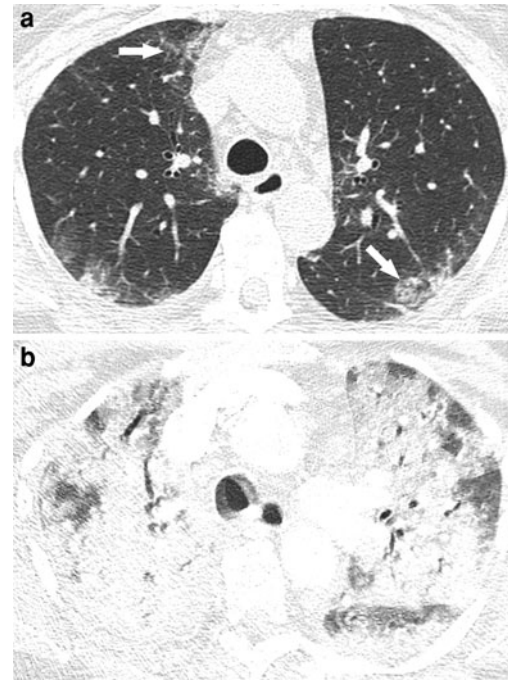


**Fig. 12.10** Acute exacerbation of NSIP. **a** HRCT image shows multiple foci of peripheral ground-glass opacity (*arrows*). **b** HRCT image one month later shows extensive consolidation in both lungs. The patient presented with acute hypoxia and dyspnea

associated abnormalities may be sought on available imaging studies.

Although NSIP is characterized by two histologic subtypes, cellular and fibrotic, there are generally no imaging features to reliably distinguish between the two. As would be expected, reticulation is more commonly seen with fibrotic subtype, although the cellular subtype may also demonstrate fine reticulation. In our experience, a posterior basilar and anterior apical distribution of reticulation, when present in the appropriate setting, is relatively specific for the fibrotic subtype. However, with regard to the extent of ground-glass opacity, consolidation, or traction bronchiectasis, there is no reliable separation in CT findings between the two subtypes [10, 49–51].

Additional findings on HRCT tend to be nonspecific or should suggest alternative etiologies. Relatively mild honeycombing may be seen in NSIP, but significant honeycombing is more

commonly associated with a histologic diagnosis of UIP. The reported prevalence of consolidation in NSIP varies widely and may often represent superimposed infection or organizing pneumonia [10, 44, 48, 49, 51–57]. New consolidation or ground-glass opacities in an acutely ill patient with NSIP may represent an acute exacerbation (Fig. 12.10). While such exacerbations occur less commonly than in patients with IPF, the annual incidence of NSIP acute exacerbations may approach 5% [58]. With appropriate treatment, some findings of NSIP may be reversible on follow-up examination [59].

## Cryptogenic Organizing Pneumonia

Organizing pneumonia (OP) refers to the histologic pattern described as polypoid plugs of loose organizing connective tissue within the alveoli. This pattern may be idiopathic but is more commonly associated with one of numerous underlying etiologies, including connective tissue disease and drug reaction. Formerly termed bronchiolitis obliterans organizing pneumonia (BOOP), cryptogenic OP (COP) refers to an idiopathic clinical syndrome characterized by organizing pneumonia. The newer terminology reflects the primary histologic features while avoiding confusion with small airways disease (bronchiolitis). Patients with COP are often initially diagnosed with community acquired pneumonia, and further workup is often pursued after failure of antibiotic treatment.

Characteristic HRCT findings of OP include unilateral or, more commonly, bilateral, patchy areas of consolidation, characteristically involving the lower lobes. Consolidation is present on HRCT in at least 90% of patients and follows a subpleural or peribronchovascular distribution in approximately 50% of patients (Fig. 12.11) [60, 61]. Foci of consolidation may be migratory on serial imaging. Common associated findings include ground-glass opacities in a random distribution (60%) (Fig. 12.12), air bronchograms (Fig. 12.13), and mild bronchial dilation. Lung volumes are typically preserved, and architectural distortion is generally absent.

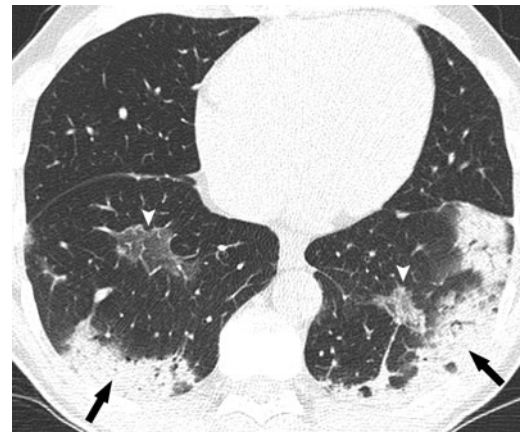

**Fig. 12.11** Cryptogenic organizing pneumonia. HRCT image shows peripheral consolidation (*arrows*) in the lower lobes with a few foci of ground-glass opacity (*arrowheads*)

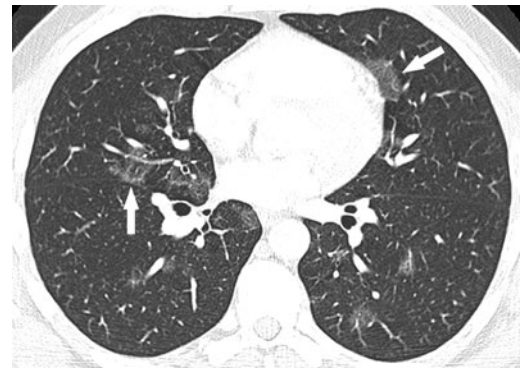

**Fig. 12.12** Cryptogenic organizing pneumonia. HRCT image shows scattered foci of ground-glass opacity (*arrows*) in both lungs. Consolidation is more common than ground-glass opacity in COP

Small pleural effusions may occur in a small minority of patients. The reverse-halo sign (Fig. 12.14) was first described in the setting of OP as a relatively specific finding. This sign refers to a central region of ground-glass opacity surrounded by a $> 2$ mm crescent or ring of denser consolidation. Kim et al. reported the reverse-halo sign in 19% of biopsy proven cases of OP [62]. However, a reverse halo sign has since been reported in numerous separate entities [62]. Reticulation and honeycombing are uncommon to rare but when present are associated with an increased risk of progressive disease [63–65].

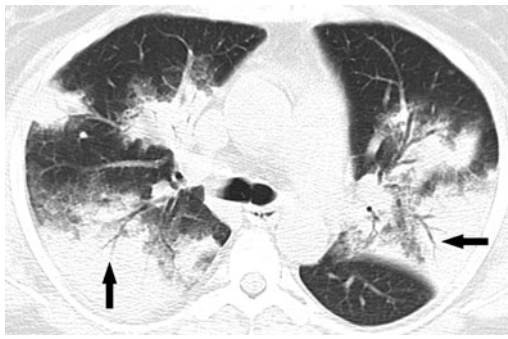

**Fig. 12.13** Cryptogenic organizing pneumonia. HRCT image shows multiple foci of peripheral and peribronchial consolidation with air bronchograms (*arrows*)

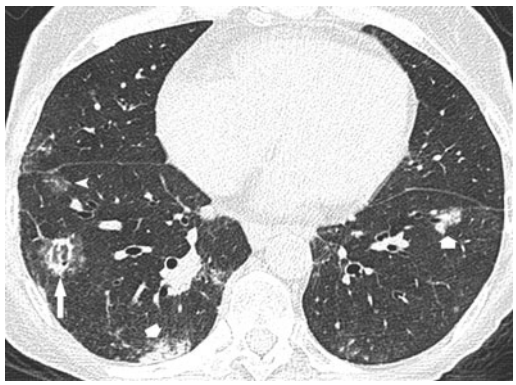

**Fig. 12.14** Cryptogenic organizing pneumonia. HRCT image shows foci of consolidation (*wide arrows*) and ground-glass opacity (*arrowhead*) and a reverse halo sign (*thin arrow*), the latter characterized by central ground-glass opacity and a rim of consolidation

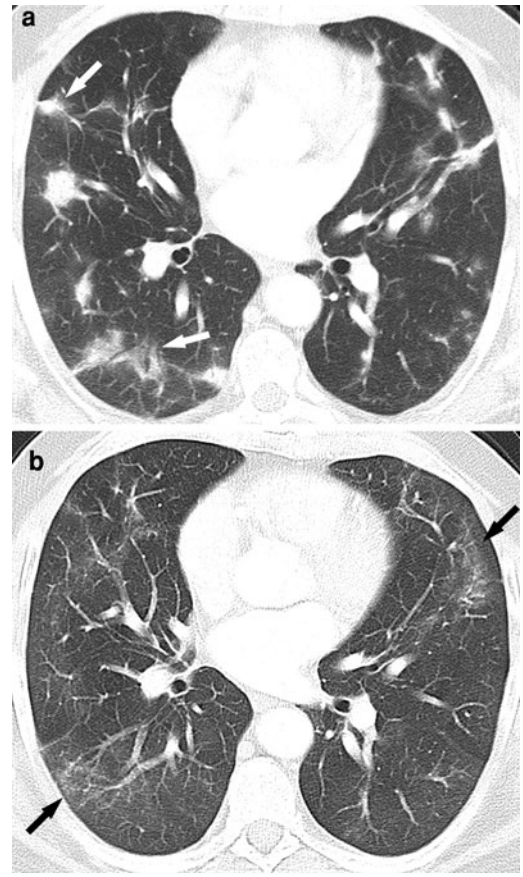


**Fig. 12.15** Resolving cryptogenic organizing pneumonia. **a** HRCT image shows scattered of lung consolidation (*arrows*) in a peripheral and peribronchial distribution. **b** HRCT image obtained 2 weeks later shows patchy ground-glass opacity (*arrows*) where consolidation once was

With treatment, clinical and radiologic response is often striking. Symptomatic improvement may be expected within 1–2 days, while radiologic resolution occurs over several weeks (Fig. 12.15) [66]. Although relapse is not common, it does not worsen the long-term prognosis.

## Respiratory Bronchiolitis, Respiratory Bronchiolitis–Interstitial Lung Disease, and Desquamative Interstitial Pneumonia

Respiratory bronchiolitis (RB), RB-associated interstitial lung disease (RB-ILD), and desquamative interstitial pneumonia (DIP) are included in the most recent IIP classification despite being almost invariably associated with cigarette smoking. RB, RB-ILD, and DIP represent a spectrum of smoking-related interstitial lung disease characterized by the accumulation of pigmented macrophages in the respiratory bronchioles and alveoli [67]. With RB, pigmented macrophages are limited primarily to the respiratory bronchioles whereas macrophage accumulation is more extensive with RB-ILD and diffuse in DIP. By definition, patients with RB are asymptomatic while those with RB-ILD and DIP may present with dyspnea, cough, and abnormal pulmonary function tests [68].

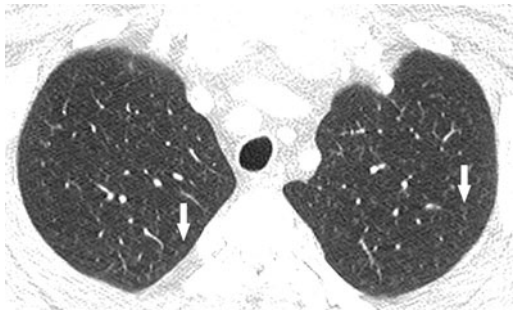

**Fig. 12.16** Respiratory bronchiolitis. HRCT image shows scattered, poorly defined ground-glass attenuation nodules (*arrows*) in the upper lobes of this cigarette smoker

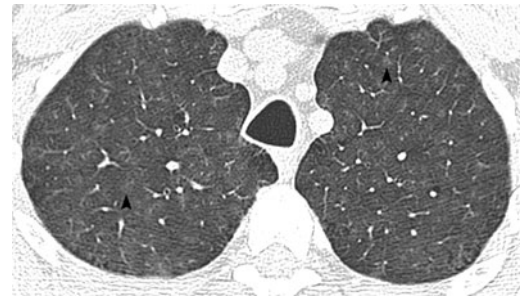

**Fig. 12.17** RB-ILD. HRCT image shows diffuse, poorly defined centrilobular nodules (*arrowheads)* in the upper lobes of this heavy cigarette smoker who presented with dyspnea and cough

Characteristic HRCT findings of RB include mild, poorly defined centrilobular nodules in a mid and upper lung distribution (Fig. 12.16) with scattered, patchy ground-glass opacities [69]. Associated findings include occasional lobular air trapping and emphysema. With RB-ILD, the extent of poorly defined centrilobular nodules is greater (Fig. 12.17), and more extensive patchy ground-glass opacity may be present (Fig. 12.18) [70]. With smoking cessation, these parenchymal abnormalities are reversible to some degree [71].

DIP is rare and associated with more severe and diffuse parenchymal abnormality [72]. HRCT findings consist of diffuse ground-glass opacities with peripheral and lower lung predominance (Fig. 12.19) [12]. Reticular opacities are common but are often relatively mild and limited to a bibasilar distribution (Fig. 12.20). Small well-defined cysts may occur in areas of ground-glass opacity [73]. Centrilobular nodules are uncommon, while CT findings of respiratory bronchiolitis tend to be less severe than in RB-ILD [74]. DIP on CT may be indistinguishable from NSIP, acute or subacute hypersensitivity pneumonitis, and infections such as *Pneumocystis jiroveci* [67].

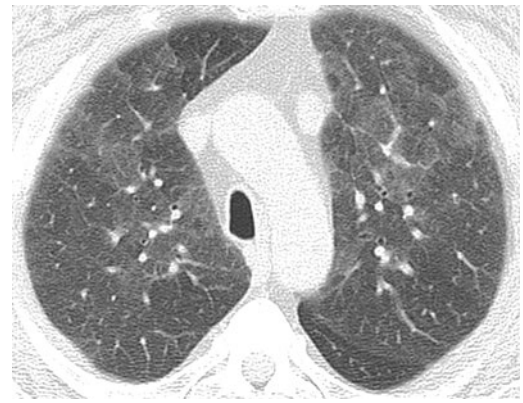

**Fig. 12.18** RB-ILD. HRCT image shows patchy ground-glass opacities in the upper lobes of this heavy cigarette smoker who presented with dyspnea

## Acute Interstitial Pneumonia

Acute interstitial pneumonia (AIP) is diagnostically reserved for diffuse alveolar damage of unknown origin. Histologically, AIP is indistinguishable from acute respiratory distress syndrome (ARDS) secondary to shock or sepsis. CT findings in the early exudative phase include dependent, subpleural consolidation and ground-glass opacities in a geographic, patchy, symmetric, and bilateral distribution (Fig. 12.21). Multiple foci of lobular sparing contribute to a geographic pattern. Greater than 50% of the lung parenchyma is typically involved [75].

In the subacute, organizing stage, traction bronchiectasis and architectural distortion progress with the duration of illness (Fig. 12.22). These findings are characteristically prominent relative to any degree of reticulation or honeycombing [76]. Pleural effusions are found in approximately 30%. While typically indistinguishable from ARDS, AIP is more commonly

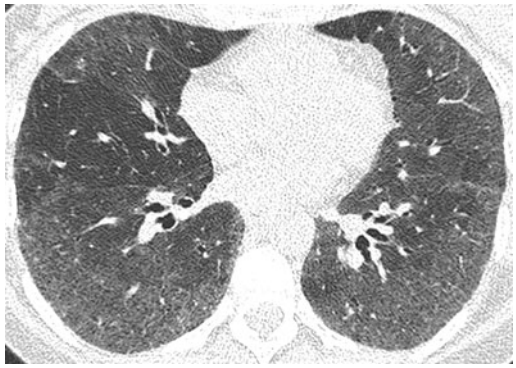

**Fig. 12.19** Desquamative interstitial pneumonia in a heavy smoker. Low-dose HRCT shows extensive ground-glass opacity in the periphery of the lung bases. The HRCT findings of DIP can overlap those of NSIP

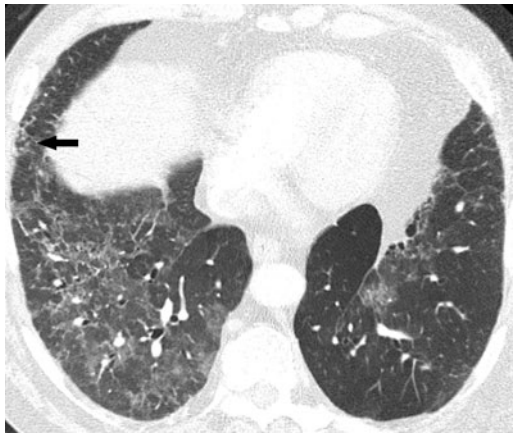

**Fig. 12.20** Desquamative interstitial pneumonia in a heavy smoker. HRCT image shows patchy ground-glass opacity in the lower lobes. Mild subpleural reticulation (*arrow*) is present

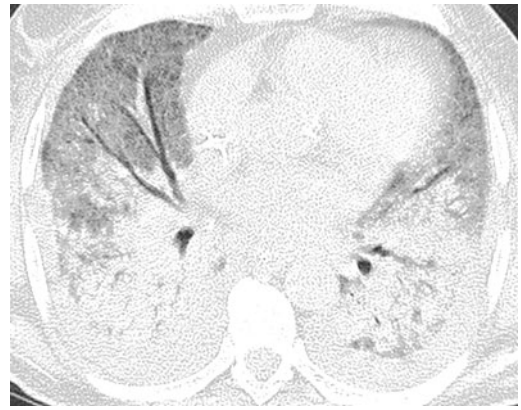

**Fig. 12.21** Acute interstitial pneumonia. Low-dose HRCT image shows diffuse ground-glass opacity with superimposed septal thickening in the anterior lungs and consolidation in the dependent lungs

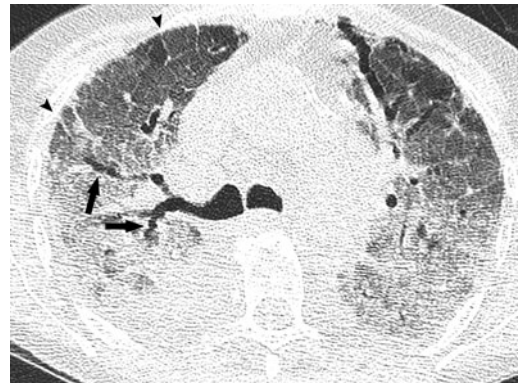

**Fig. 12.22** Organizing phase of acute interstitial pneumonia. HRCT image shows ground-glass opacity and septal thickening (*arrowheads*) with dependent consolidation. Traction bronchiectasis (*arrows*) suggests developing fibrosis, although this is sometimes reversible

lower lobe predominant in distribution with a greater prevalence of fibrotic changes [77, 78]. As with UIP and NSIP, the degree of fibrotic changes positively correlates with a worsened prognosis. ARDS, conversely, is more commonly associated with interlobular septal thickening. Differential considerations for an AIP/ARDS pattern include pulmonary edema, widespread infection, pulmonary hemorrhage, and acute eosinophilic pneumonia [67, 76, 79].

If a patient with AIP recovers, consolidation and ground-glass opacities typically clear in a progressive fashion, while residual areas of reticulation and hypoattenuation remain, particularly in the nondependent lung [76].

## Lymphoid Interstitial Pneumonia

Lymphoid interstitial pneumonia (LIP) is a rare diagnosis most commonly seen in patients with Sjögren syndrome. Additional associations include other connective tissue and autoimmune diseases as well as AIDS, the latter particularly in children. Despite being a lymphoproliferative

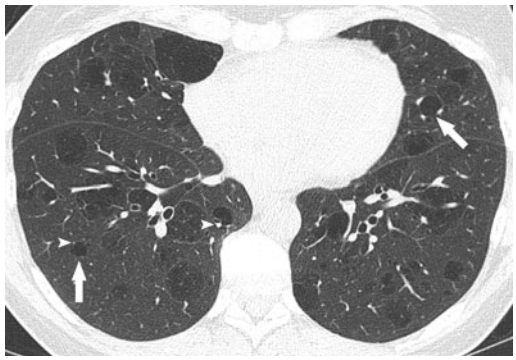

**Fig. 12.23** Lymphoid interstitial pneumonia and Sjögren syndrome. HRCT image shows numerous thin-walled cysts (*arrows*) with adjacent vessels (*arrowheads*)

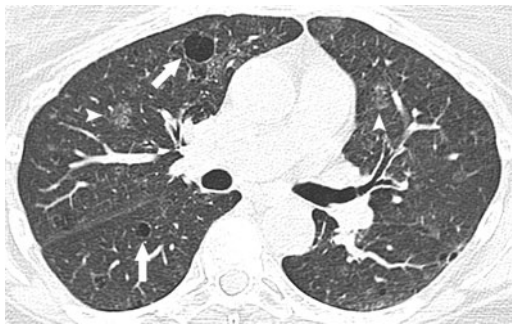

**Fig. 12.24** Lymphoid interstitial pneumonia and Sjögren syndrome. HRCT image shows scattered thin-walled cysts (*arrows*) and scattered ground-glass attenuation opacities (*arrowheads*)

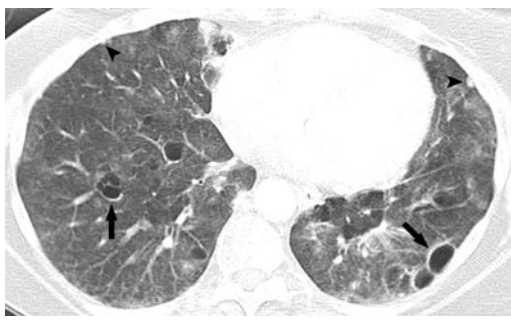

**Fig. 12.25** Lymphoid interstitial pneumonia and Sjögren syndrome. HRCT image shows extensive ground-glass opacity, subpleural nodules (*arrowheads*), and scattered thin-walled cysts

disorder, LIP is included in the most recent classification system as an interstitial lung disease, given its inclusion in associated differential diagnoses of diffuse lung disease and its histologic pattern, which is characterized by a polyclonal lymphocytic and plasma cell infiltration of the alveolar septum [1].

The common HRCT findings of LIP include bilateral ground-glass opacity, thin-walled perivascular cysts located predominantly within the lower lobes, and poorly defined centrilobular nodules (Figs. 12.23, 12.24, 12.25). The cysts tend to range from 1 mm to 30 mm in diameter and are typically fewer in number compared with lymphangioleiomyomatosis. Less common findings include perilymphatic nodules and septal and bronchovascular thickening [67, 80–82]. Nodules or calcifications may develop in cysts, reflecting amyloid deposition.

## Conclusion

In summary, HRCT is critical to evaluating patients with known or suspected diffuse lung disease. In patients with the appropriate clinical presentation, a highly confident diagnosis of UIP on HRCT is sufficient to establish a diagnosis of IPF. HRCT may also suggest the presence of other interstitial or diffuse lung diseases. Finally, consensus among the clinician, radiologist, and pathologist may be required to establish a diagnosis when the pieces of the diagnostic puzzle are not straightforward.

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