

# Smoking-related Interstitial Lung Disease: Radiologic-Clinical-Pathologic Correlation<sup>1</sup>

## TEACHING POINTS

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## ONLINE-ONLY CME

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## LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- Describe the spectrum of radiologic findings in smoking-related interstitial lung diseases with emphasis on the high-resolution CT findings.
- List the corresponding clinical features, pulmonary function test results, and histopathologic findings.
- Discuss the evolving relationship between smoking and interstitial lung disease.

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Cigarette smoking is a recognized risk factor for development of interstitial lung disease (ILD). There is strong evidence supporting a causal role for cigarette smoking in development of respiratory bronchiolitis ILD (RB-ILD), desquamative interstitial pneumonitis (DIP), and pulmonary Langerhans cell histiocytosis (PLCH). In addition, former and current smokers may be at increased risk for developing idiopathic pulmonary fibrosis (IPF). The combination of lower lung fibrosis and upper lung emphysema is being increasingly recognized as a distinct clinical entity in smokers. High-resolution computed tomography is sensitive for detection and characterization of ILD and may allow recognition and classification of the smoking-related ILDs (SR-ILDs) into distinct individual entities. However, the clinical, radiologic, and histologic features overlap among the different SR-ILDs, and mixed patterns of disease frequently coexist in the same patient. The overlap is most significant between RB-ILD and DIP. Macrophage accumulation is bronchiolocentric in RB-ILD, producing centrilobular ground-glass opacity, and more diffuse in DIP, producing widespread ground-glass changes. The coexistence of upper lung nodules and cysts in a smoker allows confident diagnosis of PLCH. Final diagnosis of an SR-ILD and identification of the specific entity can be achieved with certainty only after the pulmonologist, radiologist, and pathologist have reviewed all of the clinical, radiologic, and pathologic data.

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**Abbreviations:** CPFE = combined pulmonary fibrosis with emphysema, DIP = desquamative interstitial pneumonitis, DLCO = diffusing capacity of the lung for carbon monoxide, IIP = idiopathic interstitial pneumonia, ILD = interstitial lung disease, IPF = idiopathic pulmonary fibrosis, NSIP = non-specific interstitial pneumonitis, PFT = pulmonary function test, PLCH = pulmonary Langerhans cell histiocytosis, RB-ILD = respiratory bronchiolitis ILD, SR-ILD = smoking-related ILD, UIP = usual interstitial pneumonia

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See the commentary by Ketai following this article.

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## Teaching Point

## Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders of known or unknown etiology, characterized by dyspnea, diffuse parenchymal lung abnormalities, restrictive pulmonary function, and impaired gas exchange (1).

Cigarette smoking is related to the development of several ILDs, including respiratory bronchiolitis ILD (RB-ILD), desquamate interstitial pneumonitis (DIP), pulmonary Langerhans cell histiocytosis (PLCH), and idiopathic pulmonary fibrosis (IPF) (Table 1). The smoking-related ILDs (SR-ILDs) are overlapping clinicopathologic entities that frequently coexist in the same patient. The recent refinement of the classification of the idiopathic interstitial pneumonias (IIPs) and the increasing use of high-resolution computed tomography (CT) to characterize the ILDs (1,2) have led to increased recognition and understanding of the SR-ILDs.

In this article, we discuss and illustrate the clinical features, high-resolution CT findings, and pathologic findings of the SR-ILDs. The diagnostic approach to patients with SR-ILD is discussed, emphasizing the need for integration of the radiologic-clinical-pathologic data in order to achieve an accurate diagnosis.

## Respiratory Bronchiolitis ILD

Respiratory bronchiolitis is a histopathologic lesion found in the lungs of virtually all cigarette smokers. It is usually asymptomatic and of little clinical significance (3). Much less often, patients who are heavy smokers develop RB-ILD, a clinicopathologic entity characterized by pulmonary symptoms, abnormal pulmonary function test (PFT) results, and imaging abnormalities, with respiratory bronchiolitis being the histologic lesion at surgical lung biopsy (4).

## Epidemiologic and Clinical Features

RB-ILD usually affects current smokers 30–40 years of age with a 30 pack-year or greater history of cigarette smoking. There is a slight male predominance. Mild cough and dyspnea are the most common presenting symptoms. Inspiratory crackles are present in one-half of patients, and digital clubbing is rare (5). PFT results may be normal or show a mixed obstructive-restrictive pattern with reduced diffusing capacity (5).

**Table 1**  
**Smoking-related ILDs**

Respiratory bronchiolitis ILD
Desquamate interstitial pneumonitis
Pulmonary Langerhans cell histiocytosis
Idiopathic pulmonary fibrosis, including UIP and CPFE

Note.—CPFE = combined pulmonary fibrosis with emphysema, UIP = usual interstitial pneumonia.

**Table 2**  
**High-Resolution CT Findings of RB-ILD**

Centrilobular nodular opacities
Patchy ground-glass opacity
Bronchial wall thickening
Upper lobe predominance
Associated centrilobular emphysema
Air trapping at expiration
Findings of fibrosis absent

## Radiologic Findings

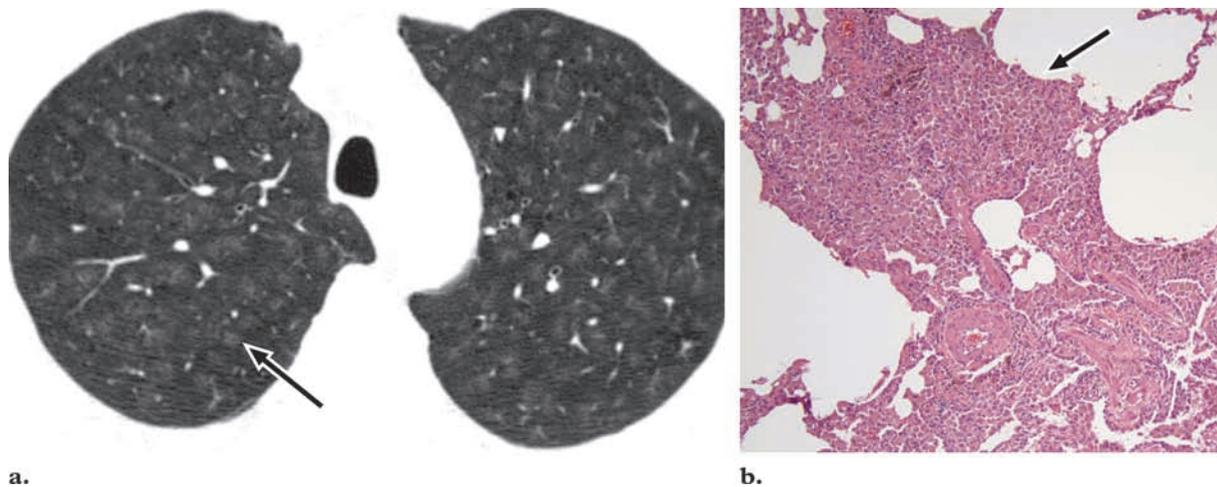
Chest radiographs often appear normal, but they commonly show nonspecific thickening of the central and peripheral bronchial walls as fine bilateral reticulonodular opacities, typically upper lung or diffuse in distribution. The high-resolution CT findings are summarized in Table 2.

The most common high-resolution CT findings in RB-ILD are centrilobular nodules, ground-glass opacities, and thickening of the bronchial walls, which predominate in the upper lobes (Fig 1a). Upper lobe emphysema is also commonly present. A small percentage of patients have a reticular pattern due to fibrosis in the absence of honeycombing and traction bronchiectasis (6–8). The differential diagnosis of RB-ILD includes acute hypersensitivity pneumonitis, DIP, and nonspecific interstitial pneumonitis (NSIP).

## Histopathologic Findings

RB-ILD is characterized by pigmented macrophages and mild interstitial inflammatory changes centering on respiratory bronchioles and neighboring alveoli (Fig 1b). The alveolar septa in the peribronchial regions may be mildly thickened but without significant fibrosis (4,9).

## Teaching Point



**Figure 1.** RB-ILD in a 32-year-old man with a 17 pack-year history of smoking who presented with a cough, restrictive PFT results, and reduced diffusion capacity. **(a)** High-resolution CT image obtained through the upper lungs shows bilateral centrilobular ground-glass nodules (arrow). **(b)** Photomicrograph of a surgical lung biopsy specimen shows a bronchiolocentric collection of pigmented macrophages (arrow).

**Table 3**  
**High-Resolution CT Findings of DIP**

Bilateral patchy ground-glass opacity
Reticular opacities
Subpleural and basal predominance
Honeycombing uncommon
Associated centrilobular emphysema

### Treatment and Outcome

Patients with RB-ILD generally have a good prognosis. The condition of most patients remains stable or improves, and no deaths have been attributed to RB-ILD, to our knowledge. Progressive fibrotic lung disease does not occur. Smoking cessation is the most important treatment of RB-ILD. Corticosteroids have little role in most cases, although beneficial results have been reported in anecdotal symptomatic cases (5).

### Desquamative Interstitial Pneumonitis

Although the term *desquamative interstitial pneumonitis* has been retained in the consensus classification of IIPs, it is considered a misnomer, as the predominant pathologic feature is the intraalveolar accumulation of pigmented macrophages and not desquamation of epithelial cells as previously thought. The condition represents the end spectrum of RB-ILD with similar pathologic findings and an almost invariable association with smoking.

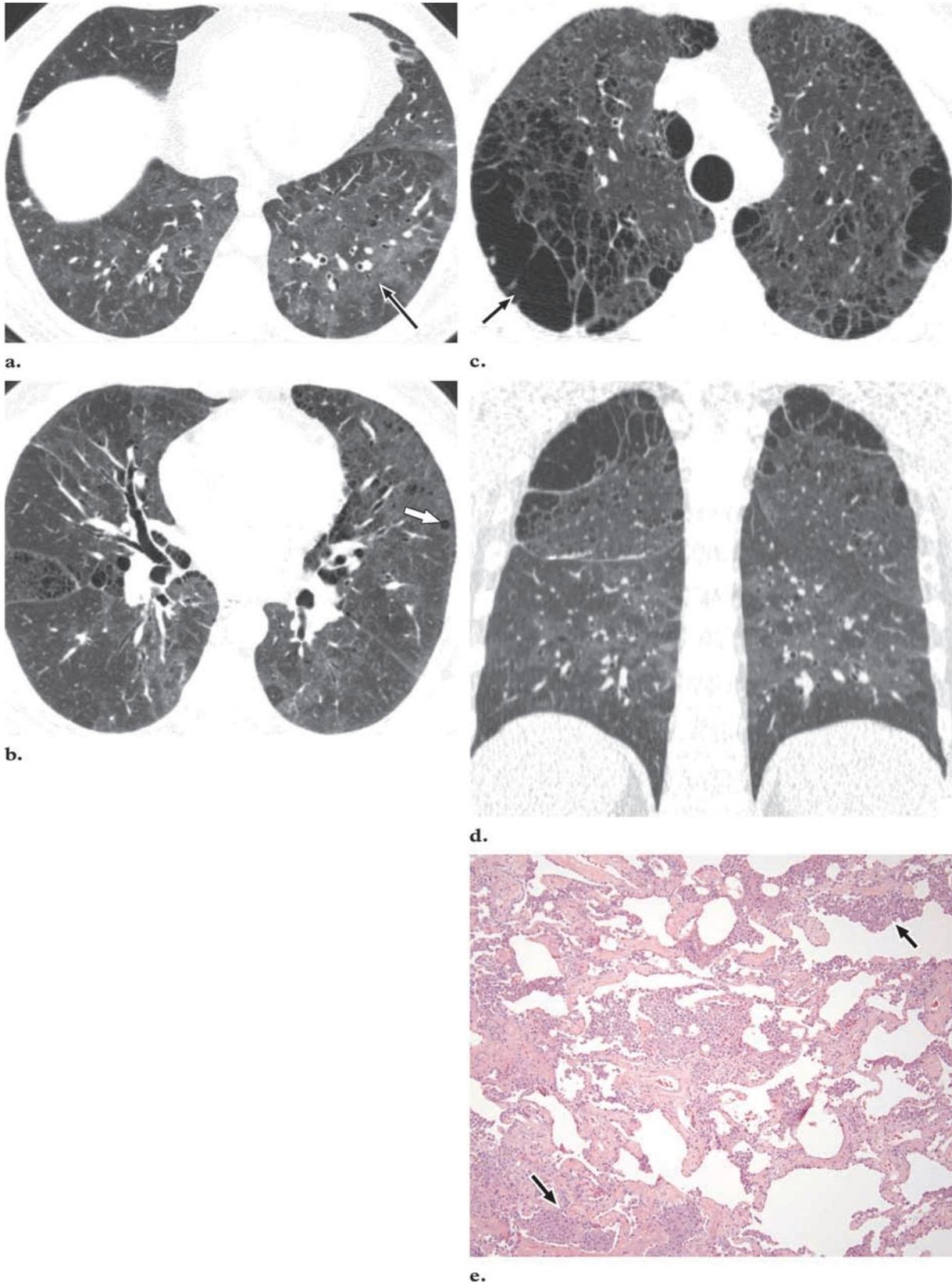
### Epidemiologic and Clinical Features

DIP is an uncommon form of IIP that primarily affects cigarette smokers in their 4th or 5th decades. Males are affected nearly twice as often as females. Approximately 90% of patients with DIP are smokers. DIP can occasionally be seen in nonsmokers in association with systemic disorders, infections, and exposure to occupational or environmental agents or drugs (9–11). Dyspnea and dry cough are the most common presenting symptoms, and the onset is usually insidious. Inspiratory crackles are heard in 60% of patients, and digital clubbing occurs in nearly one-half of patients (5). The most common and striking PFT abnormality is marked reduction in diffusing capacity, with reductions of 50% or more being common (5). Restrictive defects are also common. Patients with advanced disease may have hypoxemia at rest or with exertion.

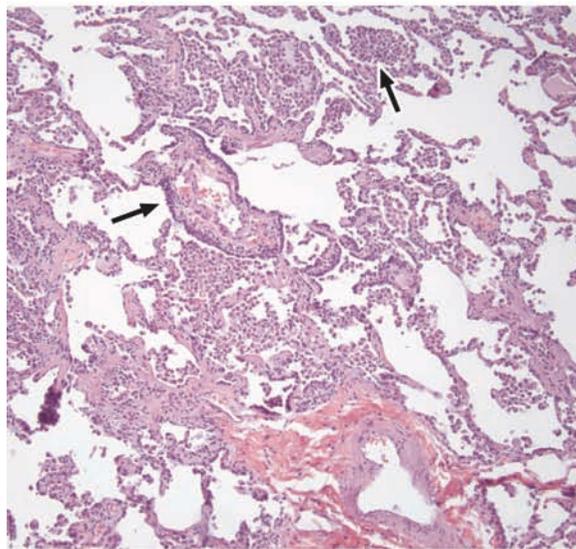
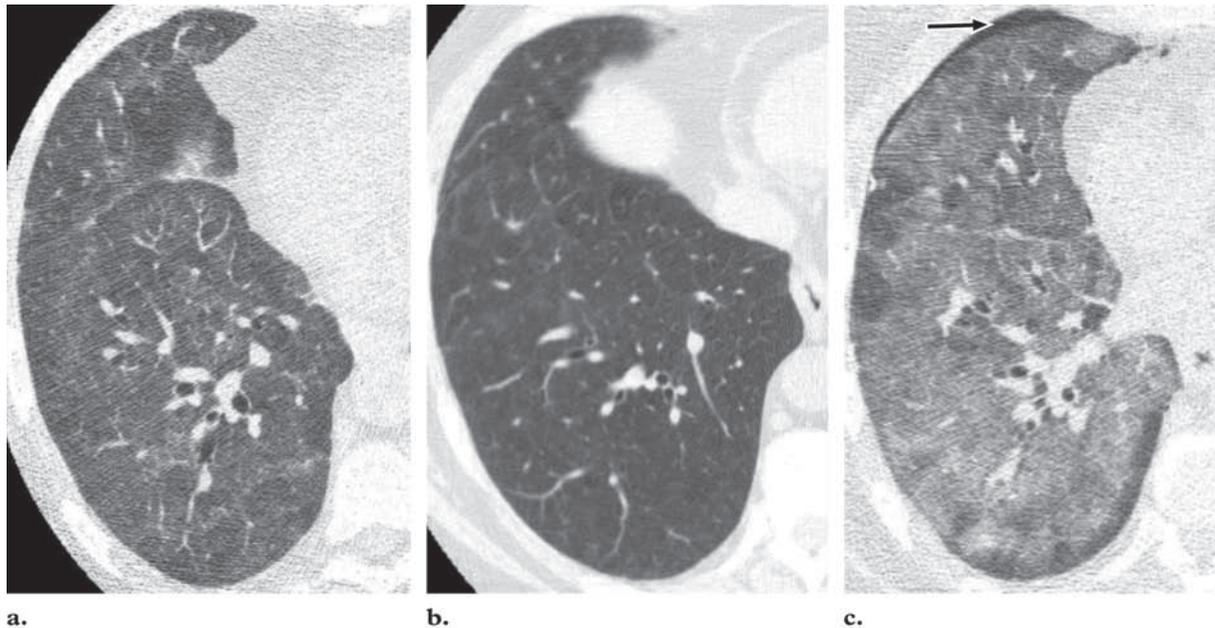
### Radiologic Findings

Chest radiographs are insensitive for detection of DIP and are reported to be normal in 3%–22% of biopsy-proved cases (1). The radiologic patterns are nonspecific and include patchy ground-glass opacities with a lower lung and peripheral predominance. The high-resolution CT findings

**Figure 2.** DIP and emphysema in a 48-year-old man with a 30 pack-year history of smoking who presented with a cough, gradually increasing shortness of breath, and mild restriction at pulmonary function testing, with diffusing capacity of the lung for carbon monoxide (DLCO) 50% of the predicted. **(a)** High-resolution CT image obtained through the lower lungs shows bilateral diffuse ground-glass opacity (arrow). **(b)** High-resolution CT image obtained through the mid lungs shows diffuse ground-glass opacity, peripheral reticulation, and small cysts (arrow). **(c)** High-resolution CT image obtained through the upper lungs shows paraseptal (arrow) and centrilobular emphysema. **(d)** Coronal reformatted image shows the basilar predominant distribution of the ground-glass opacity and the apical emphysema. **(e)** Photomicrograph of a surgical lung biopsy specimen shows widespread intraalveolar accumulation of pigmented macrophages (arrows).



**Figure 3.** DIP in a 50-year-old woman with a 25 pack-year history of smoking. Smoking continued after diagnosis. Corticosteroid therapy was started. (a) High-resolution CT image obtained through the right lower lung at initial diagnosis shows diffuse ground-glass opacity. (b) High-resolution CT image obtained through the right lower lung 3 years later shows near-complete resolution of the ground-glass opacity. (c) High-resolution CT image obtained 6 months later shows exacerbation of the DIP with new dense ground-glass opacity. Arrow = small right pneumothorax. (d) Photomicrograph of a surgical lung biopsy specimen shows diffuse interstitial chronic inflammation and pigmented macrophages within the alveoli and around bronchioles (arrows).



d.

may show partial or complete resolution (13,14) (Fig 3a–3c). Small cystic spaces may develop within the areas of ground-glass opacity (Fig 2b), although progression to reticular abnormality and honeycombing is unusual. The differential diagnosis includes RB-ILD, hypersensitivity pneumonitis, NSIP, and atypical infections such as *Pneumocystis carinii* pneumonia.

### Histopathologic Findings

The most striking finding in DIP is an increased number of pigmented macrophages evenly dispersed within the alveolar spaces (5) (Figs 2e, 3d). Alveolar septa are thickened to a variable degree by diffuse fibrosis and mild interstitial inflammation. The overall alveolar architecture is usually well maintained, and honeycombing is minimal or absent. The histologic features overlap with those of RB-ILD, and the key feature to differentiate the two disorders is the distribution and extent of lesions: bronchiolocentric in RB-ILD and diffuse in DIP.

of DIP are summarized in Table 3. The predominant abnormality at high-resolution CT in patients with DIP is ground-glass opacity, which may be peripheral, patchy, or diffuse in distribution (8,12). A peripheral subpleural and basal predominance of ground-glass opacity is most commonly seen (Fig 2a–2d). Honeycombing is uncommon. Coexistent emphysema may be present. At follow-up high-resolution CT of patients receiving treatment, the ground-glass opacity

### Teaching Point

## Treatment and Outcome

Smoking cessation is the primary treatment for DIP and may lead to disease regression. Most patients with DIP receive oral corticosteroids. Although no randomized trials have demonstrated the efficacy of this therapy, it is generally recommended for patients with significant symptoms, PFT abnormalities, and progressive disease. A higher percentage of patients with DIP respond to corticosteroid therapy than do patients with UIP; approximately two-thirds of DIP patients show stabilization or improvement of symptoms, and complete recovery is possible. The response to corticosteroids is not uniform, as approximately 25% of patients may continue to progress despite treatment (5). The role of cytotoxic and other immunosuppressive agents remains undefined. The 5- and 10-year survival rates are 95.2% and 69.6%, respectively (10). Late relapse and recurrence in a transplanted lung have been reported (5).

## Pulmonary Langerhans Cell Histiocytosis

The term *Langerhans cell histiocytosis* refers to a group of diseases of unknown etiology often recognized in childhood, in which Langerhans cell accumulations involve one or more body systems, including bone, lung, pituitary gland, mucous membranes, skin, lymph nodes, and liver. This disease is also referred to as histiocytosis X or eosinophilic granuloma. The term *pulmonary Langerhans cell histiocytosis* refers to disease in adults that affects the lung, usually in isolation and less commonly in addition to other organ systems (15).

## Epidemiologic and Clinical Features

Ninety percent to 100% of adults with PLCH are current or former smokers (16). The condition is uncommon, with a prevalence of 3.4% in a series of 502 patients undergoing surgical lung biopsy for chronic diffuse infiltrative lung disease (17). The peak occurrence is at 20–40 years of age. Men and women are equally affected (15). PLCH is more common in white patients. Up to 25% of patients are asymptomatic, with the disease discovered incidentally during radiologic studies. The most common presenting symptoms are nonproductive cough and dyspnea. Constitutional symptoms, such as weight loss, fever, night sweats, and anorexia, occur in up to one-third of patients. In 10% of patients, PLCH manifests as spontaneous pneumothorax.

**Table 4**  
**High-Resolution CT Findings of PLCH**

Thin-walled cysts, some confluent or with bizarre shapes
Thick-walled cysts
Nodules, usually 1–5 mm, centrilobular or peribronchial, may be cavitory, and seen in association with cysts
Progression from three to two to one
Upper lobe predominance of nodules and cysts, costophrenic angles spared
Fine reticular opacities
Ground-glass opacities

PLCH in adults is usually isolated to the lungs. Extrapulmonary manifestations may occur in 5%–15% of patients and include bone lesions, diabetes insipidus, and skin lesions (15). Crackles and wheezes may occasionally be heard, and in advanced cases breath sounds are decreased. Clubbing is rare. At the time of presentation, PFTs show normal results or demonstrate mild obstructive, restrictive, or mixed abnormalities; however, the most frequent PFT abnormality is a reduction in diffusion capacity in 60%–90% of patients (15). The prevalence and severity of pulmonary hypertension in advanced PLCH are much greater than in other chronic lung diseases and appear to be at least in part independent of chronic hypoxemia and abnormal pulmonary mechanics. Intrinsic pulmonary vascular disease characterized by a severe diffuse pulmonary vasculopathy involving the pulmonary muscular arteries and interlobar veins is likely to be responsible (18).

## Radiologic Findings

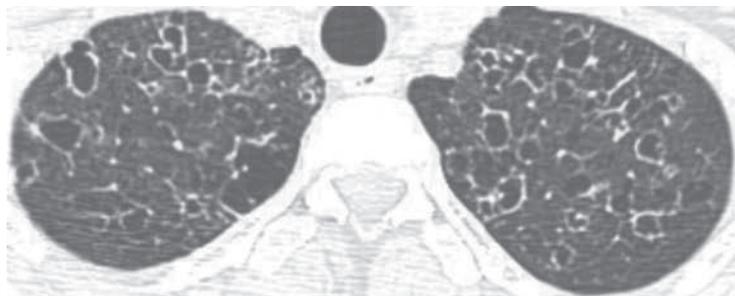
Chest radiographs demonstrate nodular or reticulonodular opacities predominantly in the upper lungs (19). There is usually sparing of the costophrenic angles. Lung volumes are preserved. As the disease advances, cystic changes and bullae appear in the upper lungs and lung volumes increase.

The high-resolution CT findings of PLCH are summarized in Table 4. **High-resolution CT is sensitive and specific for the diagnosis of PLCH, the characteristic finding being a combination of nodules and cysts predominating in the upper and mid lungs, sparing the bases (Fig 4).** Early in the disease, nodules with irregular borders predominate, mainly in a peribronchiolar distribution. As the disease evolves, thick- or thin-walled cysts predominate and are often irregular (Figs 5a, 5b, 6a, 6b). Longitudinal studies with high-resolution CT show that the solid

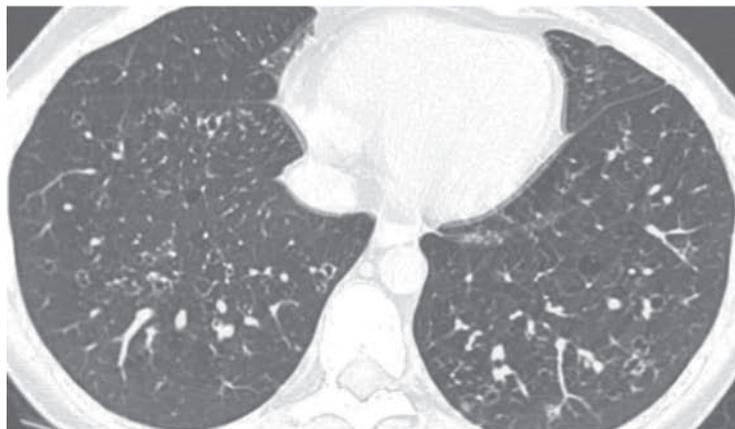
**Teaching Point**



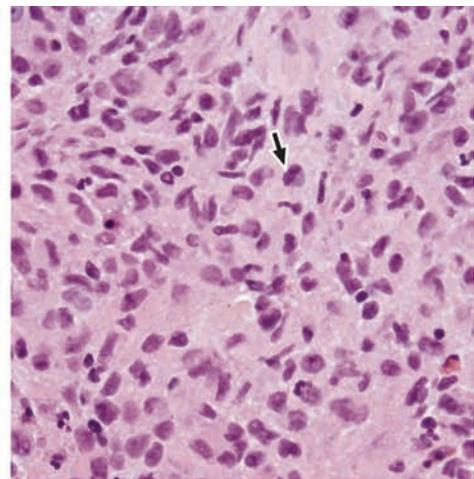
**Figure 4.** Biopsy-proved PLCH with nodules and cysts in a smoker. High-resolution CT image obtained through the upper lungs shows a combination of nodules and cysts. Such a pattern in a smoker makes the diagnosis almost certain. Some nodules are cavitating (arrow).



a.

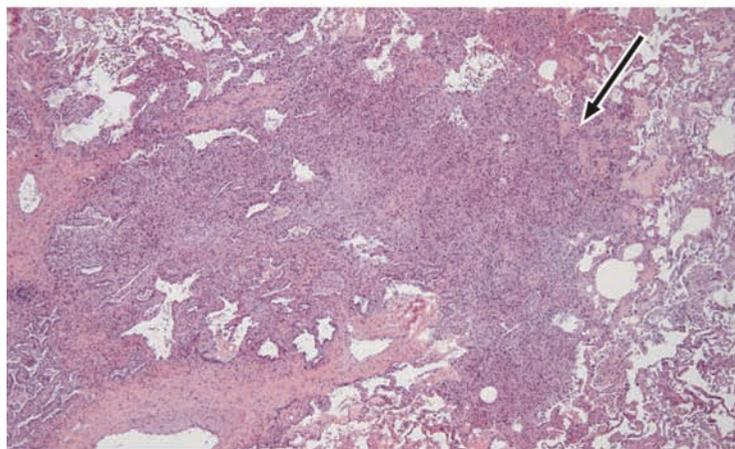


b.

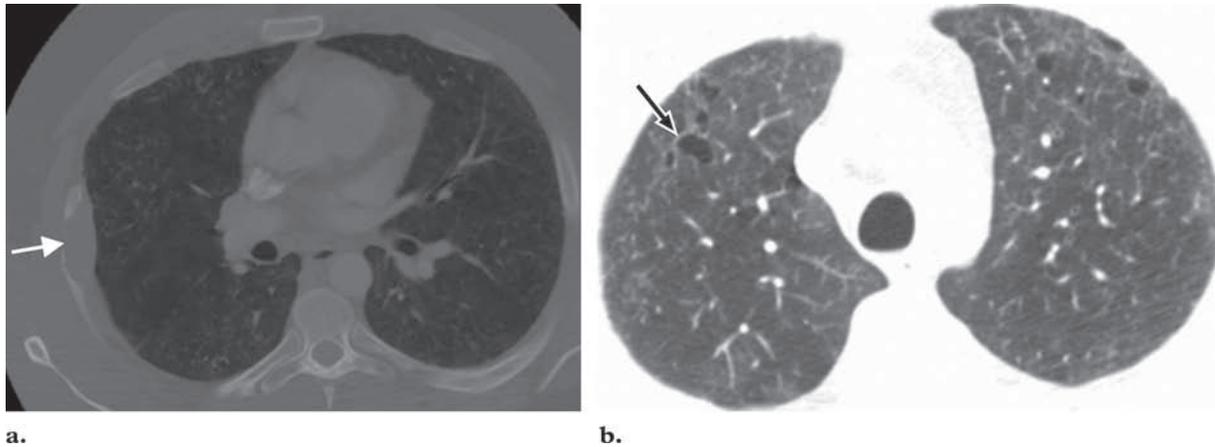


d.

**Figure 5.** PLCH in a 42-year-old woman with a 40 pack-year history of smoking who presented with a cough and dyspnea, a DLCO 45% of the predicted, and restrictive PFT results. (a, b) High-resolution CT images obtained through the upper (a) and lower (b) lungs show bilateral irregular cysts with an upper lung predominance. (c, d) Low-power (c) and high-power (d) photomicrographs of a surgical lung biopsy specimen show stellate peribronchiolar nodules (arrow in c) containing Langerhans cells (arrow in d).



c.



**Figure 6.** PLCH with bone involvement in a 29-year-old male smoker with rib pain and a cough. **(a)** High-resolution CT image (bone window) shows a lucent cystic lesion in the right fifth rib (arrow). A biopsy specimen from the rib was diagnostic for eosinophilic granuloma, which was confirmed with immunohistochemical staining. **(b)** High-resolution CT image obtained through the upper lungs shows irregular cysts (arrow) and reticular opacities.

nodules progress to cavitary nodules, then thick-walled cysts, and finally thin-walled cysts (20).

In the appropriate clinical context, high-resolution CT findings are highly specific and obviate further testing (15,21). In patients with only nodules at high-resolution CT, the differential diagnosis is extensive and includes sarcoidosis, silicosis, metastatic disease, and tuberculosis. The distribution in the upper and mid lungs and the centrilobular nature of the nodules in PLCH are helpful differentiating features. Cystic disease in PLCH should be distinguished from lymphangiomyomatosis, emphysema, and IPF.

### Histopathologic Findings

A key histologic feature is the presence of cellular peribronchiolar nodules containing Langerhans cells and inflammatory cells in the early stages (15). Langerhans cells stain positive for S100, CD1a, and human leukocyte antigen-DR at immunohistochemical analysis. With time, there is a progression from cellular nodules to cellular and fibrotic nodules to entirely fibrotic nodules forming stellate peribronchiolar scars (22). At microscopic analysis, there are discrete bronchiolocentric, stellate interstitial nodules separated by relatively normal or somewhat distorted lung tissue (Fig 5c). At high power, Langerhans cells are distinguished by a moderate amount of light eosinophilic cytoplasm and a single nucleus with an indented cerebriform outline and a finely dispersed chromatin pattern (Fig 5d). Varying degrees of respiratory bronchiolitis- or DIP-like changes are exceedingly com-

**Table 5**  
**High-Resolution CT Findings of IPF**

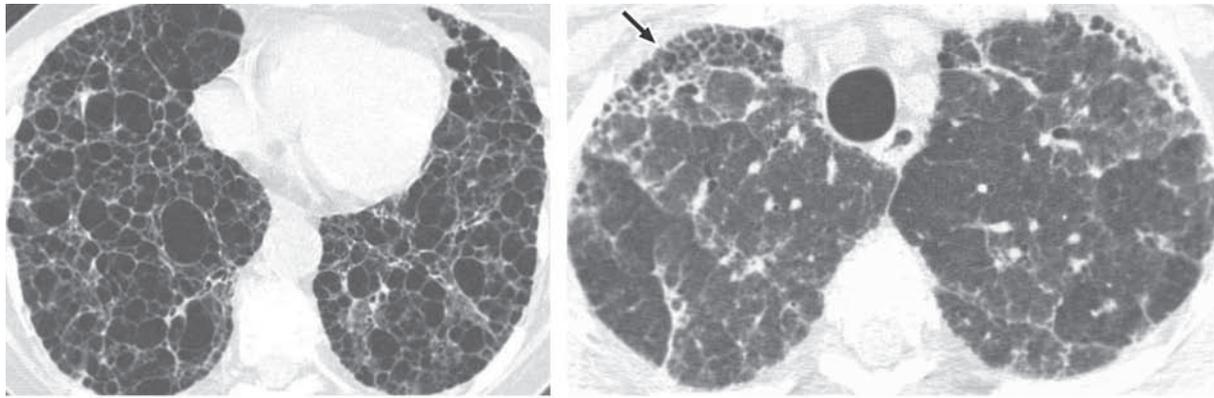
Irregular septal thickening
Honeycombing
Traction bronchiectasis
Ground-glass opacity in areas of fibrosis
Lower-lung subpleural and peripheral predominance

mon at histologic analysis in PLCH, away from the nodular lesions (23).

### Treatment and Outcome

Smoking cessation is essential and leads to stabilization of symptoms in most patients. In a substantial proportion, this may be the only intervention required (15). Corticosteroids are the mainstay of medical therapy for PLCH. Chemotherapeutic agents such as vinblastine, methotrexate, cyclophosphamide, etoposide, and cladribine have been used in patients with progressive disease unresponsive to corticosteroids or with multiorgan involvement (15). Lung transplantation is considered for patients with advanced PLCH associated with severe respiratory impairment and limited life expectancy.

The natural history is variable and unpredictable in an individual patient (16). Approximately 50% of patients experience a favorable outcome with partial or complete clearing of radiologic abnormalities and symptom resolution. In 30%–40% of patients, symptoms of variable severity persist; in 10%–20%, recurrent pneumothorax or progressive respiratory failure with cor pulmonale occurs. A few cases of recurrence despite smoking cessation have been reported.



**Figure 7.** Advanced IPF in a 69-year-old former smoker with severe hypoxemia at rest. **(a)** CT image shows extensive honeycombing in the lower lungs. **(b)** High-resolution CT image obtained through the upper lungs shows peripheral honeycombing and reticulation (arrow).

### Idiopathic Pulmonary Fibrosis

IPF is a distinctive pattern of chronic IIP of unknown cause limited to the lungs and associated with a surgical lung biopsy specimen showing UIP (1).

### Relationship of IPF to Smoking

A relationship between cigarette smoking and IPF has been recognized for many years. Alveolar wall fibrosis in addition to coexistent emphysema was demonstrated at histopathologic analysis in early autopsy studies of smokers dying from emphysema (24). A high prevalence of current or former smokers is noted in series of IPF patients, varying from 41%–83% (5). In a multicenter case-control study, a history of smoking was associated with an increased risk of developing IPF, with an odds ratio of 1.6 (25). In a recent meta-analysis of observational studies examining environmental and occupational risk factors for IPF, statistically significant increased risk for IPF was associated with cigarette smoking and exposures (26). The overall odds ratio for smoking as a risk factor for IPF was 1.58. There is an independent strong association between smoking and the development of familial interstitial pneumonia of various subtypes including UIP (odds ratio, 3.6; 95% confidence interval, 1.3–9.8) (27).

Recent work suggests that smoking may have a detrimental effect on IPF survival, with survival and severity-adjusted survival being higher in nonsmokers than in former smokers or in a combined group of former and current smokers (28).

### Epidemiologic and Clinical Features

IPF is the most common form of idiopathic ILD, manifesting in the 6th–7th decades with a slight male predominance. Clinical features include gradually progressing dyspnea, chronic cough,

and bibasilar inspiratory crackles (29). Digital clubbing is seen in approximately two-thirds of patients. PFTs usually demonstrate a restrictive defect with reduced lung volumes and diffusing capacity.

### Radiologic Findings

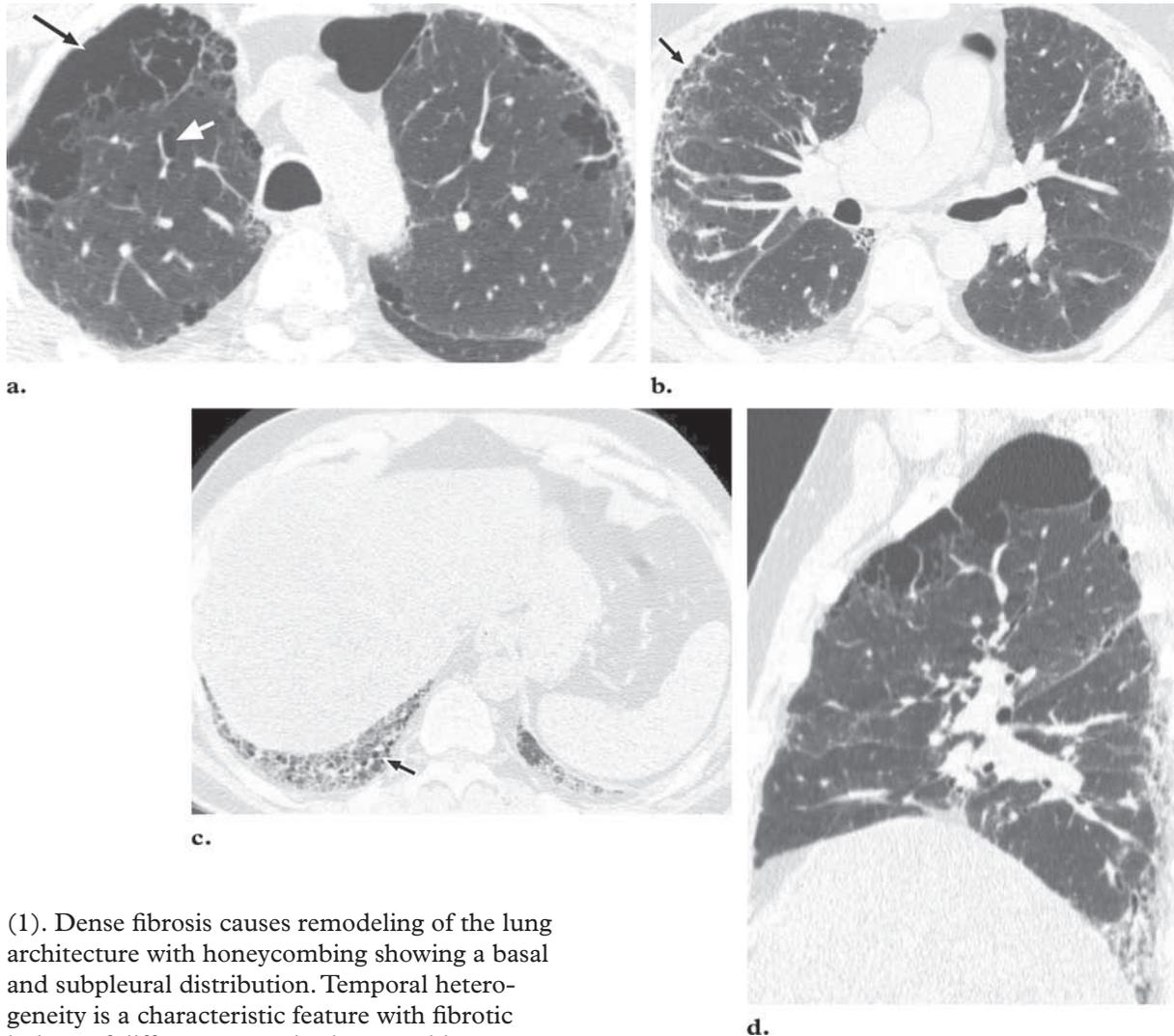
The typical chest radiograph in IPF shows bilateral basal and peripheral reticular opacities. Progressive fibrosis leads to a reduction in lung volumes and honeycombing. The high-resolution CT findings are summarized in Table 5. Typical high-resolution CT features allowing confident diagnosis are irregular reticular opacities, traction bronchiectasis, and honeycombing in a basal peripheral and subpleural distribution (Fig 7). In particular, honeycombing is a core finding in UIP that usually facilitates distinction from other types of chronic IIPs at high-resolution CT.

High-resolution CT has been shown to be a highly accurate tool for diagnosis of UIP, with a positive predictive value of 95%–100% (30). However, some cases of UIP are difficult to differentiate from fibrotic NSIP, which may exhibit honeycombing. The most useful finding when differentiating between NSIP and UIP at high-resolution CT is the greater extent of honeycombing in cases of UIP (31). The high-resolution CT differential diagnosis of IPF includes pulmonary fibrosis related to connective tissue disease and asbestosis, hypersensitivity pneumonitis, and drug toxicity.

### Histopathologic Findings

Key features of UIP are fibroblastic foci consisting of a cluster of fibroblasts and immature connective tissue within the pulmonary interstitium

**Figure 8.** CPFE in a 58-year-old male smoker with cough, dyspnea, and clubbing; a DLCO 35% of the predicted; and a family history of IPF (his mother and a brother). **(a)** High-resolution CT image obtained through the upper lungs shows paraseptal (black arrow) and centrilobular (white arrow) emphysema. **(b)** High-resolution CT image obtained through the mid lungs shows peripheral honeycombing and reticulation (arrow). **(c)** CT image shows traction bronchiectasis (arrow), reticular opacity, and ground-glass opacity in an area of the lower lung. **(d)** Sagittal reformatted image shows the upper lung apical distribution of the emphysema and the lower lung distribution of the fibrosis.



(1). Dense fibrosis causes remodeling of the lung architecture with honeycombing showing a basal and subpleural distribution. Temporal heterogeneity is a characteristic feature with fibrotic lesions of different stages in the same biopsy specimen (fibroblastic foci, mature fibrosis, and honeycombing). The histologic abnormality is spatially heterogeneous, with patchy lung involvement and normal lung adjacent to severely fibrotic lung.

### Treatment and Outcome

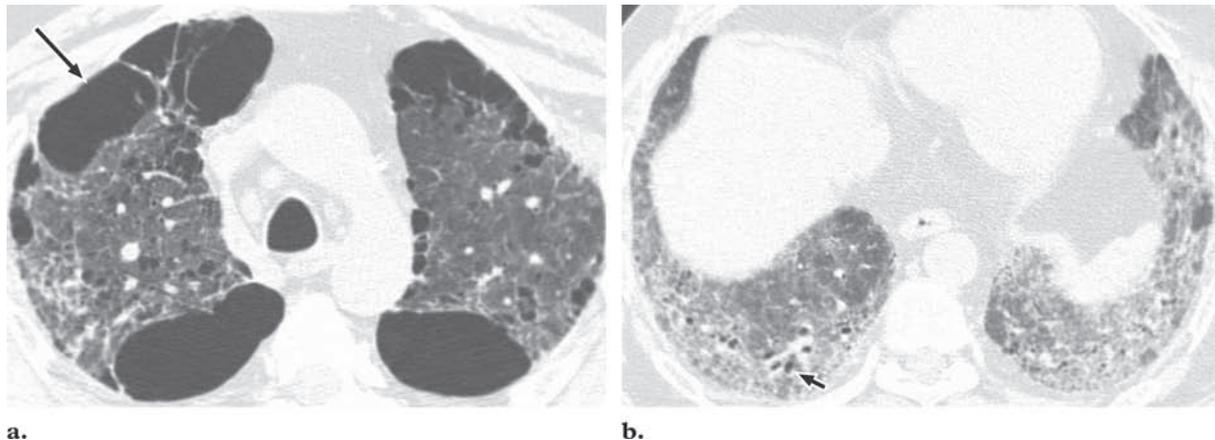
The clinical course is gradual deterioration with a median survival of 2.5–3.5 years (32). Treatment remains largely supportive; the response to steroids is poor, and no drug therapy has clearly

demonstrated a survival benefit. A number of novel investigational agents are being studied, and lung transplantation is an option (33).

### Combined Pulmonary Fibrosis and Emphysema

The combination of emphysema in the upper lobes and fibrosis in the lower lobes (CPFE) is being increasingly recognized as a distinct entity in smokers (34,35). Patients are almost exclusively men in their 6th and 7th decades. Lung volumes are relatively preserved despite markedly

**Figure 9.** CPFE (NSIP pattern) in a 54-year-old man with an 80 pack-year history of smoking, resting hypoxemia, and a DLCO 19% of the predicted. **(a)** High-resolution CT image obtained through the upper lungs shows paraseptal emphysema (arrow). **(b)** High-resolution CT image obtained through the lower lungs shows bilateral ground-glass opacity with septal thickening and traction bronchiectasis (arrow); there is no honeycombing.



**Table 6**  
**Distinctive Features of CPFE**

Emphysema in the upper lungs and fibrosis in the lower lungs at high-resolution CT
Severe reduction in diffusion capacity
Relatively preserved lung volumes
High prevalence of pulmonary arterial hypertension

impaired diffusion capacity and hypoxemia during exercise. Honeycombing, reticular opacities, and traction bronchiectasis are the most frequent findings at high-resolution CT in the lower lungs, while the upper lungs exhibit paraseptal and centrilobular emphysema (Fig 8).

The high-resolution CT patterns are usually typical of IPF, though in some series a greater prevalence of ground-glass opacity with a pattern resembling fibrosing NSIP has been reported (35). Surgical lung biopsy usually reveals a pattern of UIP, though the coexistent presence of pigmented alveolar macrophages in a pattern resembling RB-ILD or DIP may be found in areas. A histologic pattern of NSIP has also been recognized in some patients with CPFE with ground-glass opacities in isolated cases (36) (Fig 9).

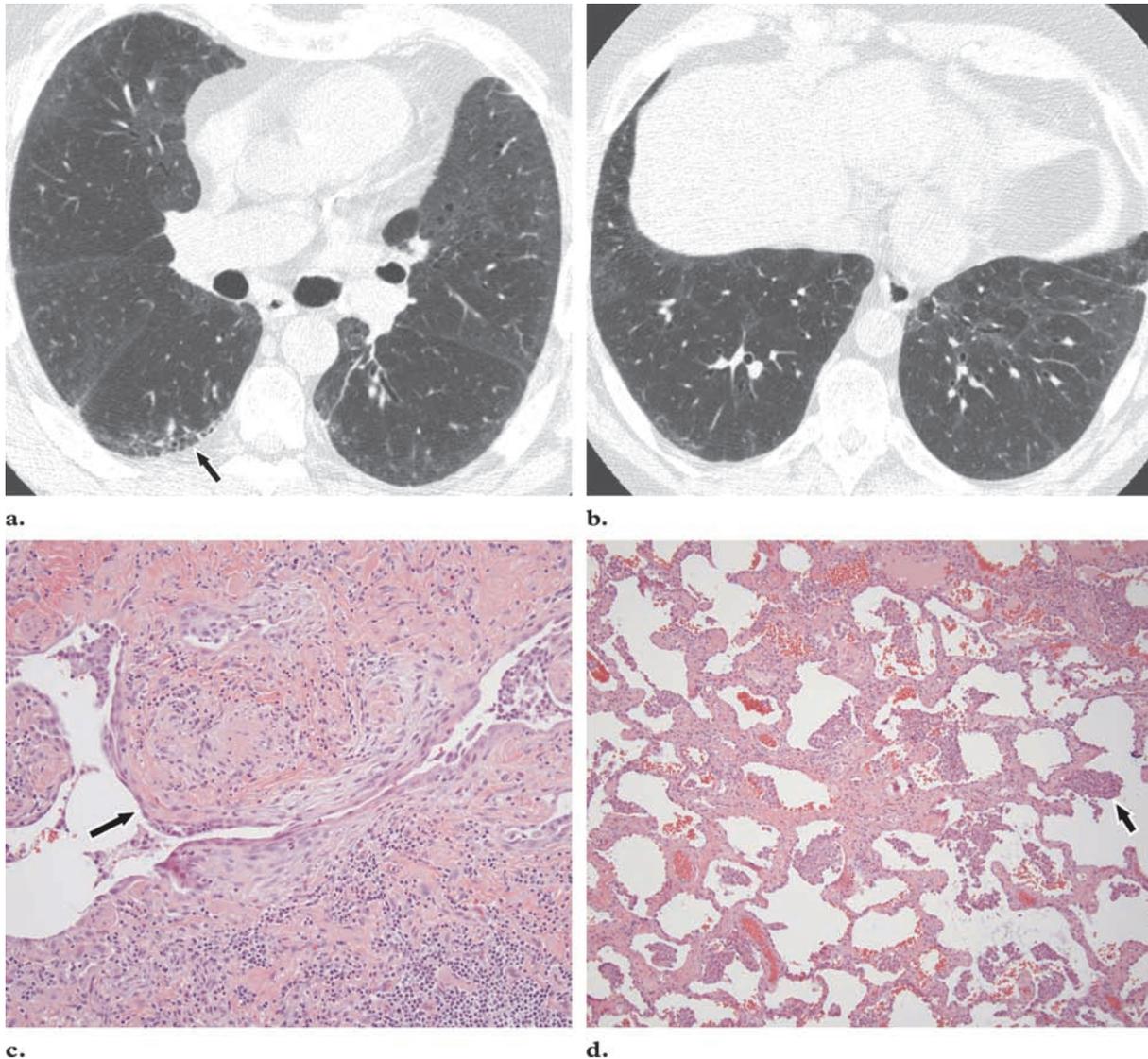
In some cases of CPFE, emphysema and fibrosis may co-occur in the same area of the lung (35). The resultant low-attenuation emphysematous foci may have apparent walls due to thickening of the adjacent interlobular septa. Such a

high-resolution CT pattern may be confused with other cystic lung disease such as lymphangioleiomyomatosis and PLCH. Clinical correlation and attention to other imaging features such as nodules in PLCH and diffuse cystic change in lymphangioleiomyomatosis may be helpful.

There is a high prevalence of pulmonary hypertension in CPFE, and this is a critical determinant of prognosis. Median survival is reported to be 6.1 years, better than in patients with IPF alone but worse than expected for emphysema in the absence of fibrosis. Distinctive features of the CPFE syndrome are summarized in Table 6.

### Overlap and Relationship between the Different SR-ILDs

The clinical, radiologic, and histologic features overlap among the different SR-ILDs. The overlap is most significant between RB-ILD and DIP. They may be different components of the same histopathologic disease spectrum, representing diverse degrees of severity of the same process caused by chronic smoking. Respiratory bronchiolitis or DIP changes at histologic analysis are very common in patients with PLCH, correlating with the cumulative exposure to cigarette smoke, and are often accompanied by significant ground-glass attenuation at high-resolution CT (23). Smokers who develop IPF often have RB-ILD and DIP changes at high-resolution CT and histopathologic



**Figure 10.** Mixed pattern of UIP and DIP in a 53-year-old man with a 30 pack-year history of smoking, restrictive PFT results, and a reduced DLCO. **(a)** High-resolution CT image obtained through the mid lungs shows diffuse ground-glass opacity with peripheral reticulation and mild honeycombing posteriorly (arrow). **(b)** CT image obtained through the lower lungs shows diffuse ground-glass opacity. **(c, d)** Photomicrographs of a surgical lung biopsy specimen show temporally heterogeneous fibrosis (arrow in **c**) (UIP) and interstitial inflammation with intraalveolar macrophages (arrow in **d**) (DIP).

analysis (Fig 10), and patients with DIP may develop a high-resolution CT pattern of fibrotic NSIP over time (37). A combination of SR-ILD–related high-resolution CT findings, such as ground-glass opacities, cysts, micronodules, septal thickening, and honeycombing, can be seen in the same patient, confounding radiologic classification into a discrete smoking-related entity.

### Diagnostic Approach to Patients with SR-ILDs

An integrated clinical, radiologic, and pathologic approach to the diagnosis of SR-ILD is recommended, as with other diffuse parenchymal lung diseases (1). The diagnostic process begins with

a clinical evaluation that includes history, physical examination, chest radiography, and pulmonary function tests. High-resolution CT plays an integral role in evaluation. In the appropriate clinical context, the presence of typical changes at high-resolution CT, such as nodules and cysts in PLCH and honeycombing and emphysema in smoking-related IPF, renders the diagnosis almost certain and may obviate further testing. Surgical lung biopsy is indicated when the findings at high-resolution CT are relatively nonspecific, as in RB-ILD and DIP, or when a confident definitive diagnosis is needed.

A final diagnosis of an SR-ILD and identification of the specific entity can be made with certainty only after the pulmonologist, radiologist, and pathologist have reviewed all of the clinical, radiologic, and pathologic data. Distinction of SR-ILD from other forms of diffuse parenchymal lung disease and recognition of the specific pattern of SR-ILD, in particular the separation of RB-ILD, DIP, and PLCH from IPF, have important clinical implications. Smoking cessation is an important component in the management of SR-ILD, though the natural history of SR-ILD and the influence of smoking on the clinical course of these patients have not been fully delineated. Smoking cessation may lead to improvement in many patients with RB-ILD and general stabilization or improvement in DIP and PLCH. In general, the prognosis for RB-ILD, DIP, and PLCH is significantly better than that for IPF.

### Conclusions

The variety of ILDs associated with cigarette smoking is wider than generally appreciated, and many forms often coexist. Although key high-resolution CT findings of SR-ILDs can be recognized, mixed patterns of disease associated with cigarette smoking may be confusing at high-resolution CT, particularly when combined with an interstitial pneumonitis such as NSIP. An integrated clinical, radiologic, and pathologic approach is necessary for accurate diagnosis of the SR-ILDs.

### References

1. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277–304.
2. Mueller-Mang C, Grosse C, Schmid K, Stiebellehner L, Bankier AA. What every radiologist should know about idiopathic interstitial pneumonias. *RadioGraphics* 2007;27:595–615.
3. Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. *N Engl J Med* 1974;291:755–758.
4. Myers JL, Veal CF Jr, Shin MS, Katzenstein AL. Respiratory bronchiolitis causing interstitial lung disease: a clinicopathologic study of six cases. *Am Rev Respir Dis* 1987;135:880–884.
5. Ryu JH, Colby TV, Hartman TE, Vassallo R. Smoking-related interstitial lung diseases: a concise review. *Eur Respir J* 2001;17:122–132.
6. Moon J, du Bois RM, Colby TV, Hansell DM, Nicholson AG. Clinical significance of respiratory bronchiolitis on open lung biopsy and its relationship to smoking related interstitial lung disease. *Thorax* 1999;54:1009–1014.
7. Holt RM, Schmidt RA, Godwin JD, Raghu G. High resolution CT in respiratory bronchiolitis-associated interstitial lung disease. *J Comput Assist Tomogr* 1993;17:46–50.
8. Heyneman LE, Ward S, Lynch DA, Remy-Jardin M, Johkoh T, Muller NL. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? *AJR Am J Roentgenol* 1999;173:1617–1622.
9. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. *Mayo Clin Proc* 1989;64:1373–1380.
10. Carrington CB, Gaensler EA, Coutu RE, FitzGerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978;298:801–809.
11. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 1998;157:1301–1315.
12. Hartman TE, Primack SL, Swensen SJ, Hansell D, McGuinness G, Muller NL. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. *Radiology* 1993;187:787–790.
13. Akira M, Yamamoto S, Hara H, Sakatani M, Ueda E. Serial computed tomographic evaluation in desquamative interstitial pneumonia. *Thorax* 1997;52:333–337.
14. Hartman TE, Primack SL, Kang EY, et al. Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia: assessment with serial CT. *Chest* 1996;110:378–382.
15. Vassallo R, Ryu JH, Colby TV, Hartman T, Limper AH. Pulmonary Langerhans'-cell histiocytosis. *N Engl J Med* 2000;342:1969–1978.
16. Tazi A. Adult pulmonary Langerhans' cell histiocytosis. *Eur Respir J* 2006;27:1272–1285.
17. Gaensler EA, Carrington CB. Open biopsy for chronic diffuse infiltrative lung disease: clinical, roentgenographic, and physiological correlations in 502 patients. *Ann Thorac Surg* 1980;30:411–426.
18. Fartoukh M, Humbert M, Capron F, et al. Severe pulmonary hypertension in histiocytosis X. *Am J Respir Crit Care Med* 2000;161:216–223.
19. Lacroix J, Roth C, Battesti JP, Basset F, Chretien J. Chest radiological features of pulmonary histiocytosis X: a report based on 50 adult cases. *Thorax* 1982;37:104–109.
20. Brauner MW, Grenier P, Tijani K, Battesti JP, Valeyre D. Pulmonary Langerhans cell histiocytosis: evolution of lesions on CT scans. *Radiology* 1997;204:497–502.
21. Bonelli FS, Hartman TE, Swensen SJ, Sherrick A. Accuracy of high-resolution CT in diagnosing lung diseases. *AJR Am J Roentgenol* 1998;170:1507–1512.
22. Caminati A, Harari S. Smoking-related interstitial pneumonias and pulmonary Langerhans cell histiocytosis. *Proc Am Thorac Soc* 2006;3:299–306.

23. Vassallo R, Jensen EA, Colby TV, et al. The overlap between respiratory bronchiolitis and desquamative interstitial pneumonia in pulmonary Langerhans cell histiocytosis: high-resolution CT, histologic, and functional correlations. *Chest* 2003;124:1199–1205.
24. Weiss W. Cigarette smoking and diffuse pulmonary fibrosis. *Am Rev Respir Dis* 1969;99:67–72.
25. Baumgartner KB, Samet JM, Coultas DB, et al. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. *Collaborating Centers. Am J Epidemiol* 2000;152:307–315.
26. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proc Am Thorac Soc* 2006;3:293–298.
27. Steele MP, Speer MC, Loyd JE, et al. Clinical and pathologic features of familial interstitial pneumonia. *Am J Respir Crit Care Med* 2005;172:1146–1152.
28. Antoniou KM, Hansell DM, Rubens MB, et al. Idiopathic pulmonary fibrosis: outcome in relation to smoking status. *Am J Respir Crit Care Med* 2008;177:190–194.
29. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. *N Engl J Med* 2001;345:517–525.
30. Hunninghake GW, Lynch DA, Galvin JR, et al. Radiologic findings are strongly associated with a pathologic diagnosis of usual interstitial pneumonia. *Chest* 2003;124:1215–1223.
31. Sumikawa H, Johkoh T, Ichikado K, et al. Usual interstitial pneumonia and chronic idiopathic interstitial pneumonia: analysis of CT appearance in 92 patients. *Radiology* 2006;241:258–266.
32. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199–203.
33. Martinez FJ. Idiopathic interstitial pneumonias: usual interstitial pneumonia versus nonspecific interstitial pneumonia. *Proc Am Thorac Soc* 2006;3:81–95.
34. Grubstein A, Bendayan D, Schactman I, Cohen M, Shitrit D, Kramer MR. Concomitant upper-lobe bullous emphysema, lower-lobe interstitial fibrosis and pulmonary hypertension in heavy smokers: report of eight cases and review of the literature. *Respir Med* 2005;99:948–954.
35. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J* 2005;26:586–593.
36. Hansell DM, Nicholson AG. Smoking-related diffuse parenchymal lung disease: HRCT-pathologic correlation. *Semin Respir Crit Care Med* 2003;24:377–392.
37. Craig PJ, Wells AU, Doffman S, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. *Histopathology* 2004;45:275–282.

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## Smoking-related Interstitial Lung Disease: Radiologic-Clinical-Pathologic Correlation

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Cigarette smoking is related to the development of several ILDs, including respiratory bronchiolitis ILD (RB-ILD), desquamative interstitial pneumonitis (DIP), pulmonary Langerhans cell histiocytosis (PLCH), and idiopathic pulmonary fibrosis (IPF) (Table 1).

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The most common high-resolution CT findings in RB-ILD are centrilobular nodules, ground-glass opacities, and thickening of the bronchial walls, which predominate in the upper lobes (Fig 1a).

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The predominant abnormality at high-resolution CT in patients with DIP is ground-glass opacity, which may be peripheral, patchy, or diffuse in distribution (8,12). A peripheral subpleural and basal predominance of ground-glass opacity is most commonly seen (Fig 2a–2d). Honeycombing is uncommon.

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High-resolution CT is sensitive and specific for the diagnosis of PLCH, the characteristic finding being a combination of nodules and cysts predominating in the upper and mid lungs, sparing the bases (Fig 4).

### Page 1394

An integrated clinical, radiologic, and pathologic approach to the diagnosis of SR-ILD is recommended, as with other diffuse parenchymal lung diseases (1).