Histologic Findings Lung biopsy shows granulation tissue within small airways, alveolar ducts, and airspaces, with chronic inflammation in the surrounding alveoli. Foci of organizing pneumonia are a nonspecific reaction to lung injury found adjacent to other pathologic processes or as a component of other primary pulmonary disorders (e.g., cryptococcosis, granulomatosis with polyangiitis [Wegener], lymphoma, hypersensitivity pneumonitis, and eosinophilic pneumonia). Consequently, the clinician must carefully reevaluate any patient found to have this histopathologic lesion to rule out these possibilities.

Treatment Glucocorticoid therapy induces clinical recovery in two-thirds of patients. A few patients have rapidly progressive courses with fatal outcomes despite glucocorticoids.

ILD ASSOCIATED WITH CIGARETTE SMOKING

Desquamative Interstitial Pneumonia • *CLINICAL MANIFESTATIONS* DIP is a rare but distinct clinical and pathologic entity found almost exclusively in cigarette smokers. The histologic hallmark is the extensive accumulation of macrophages in intraalveolar spaces with minimal interstitial fibrosis. The peak incidence is in the fourth and fifth decades. Most patients present with dyspnea and cough. Lung function testing shows a restrictive pattern with reduced D_{LCO} and arterial hypoxemia. The chest x-ray and HRCT scans usually show diffuse hazy opacities.

HISTOLOGIC FINDINGS A diffuse and uniform accumulation of macrophages in the alveolar spaces is the hallmark of DIP. The macrophages contain golden, brown, or black pigment of tobacco smoke. There may be mild thickening of the alveolar walls by fibrosis and scanty inflammatory cell infiltration.

TREATMENT Clinical recognition of DIP is important because the process is associated with a better prognosis (10-year survival rate is ~70%) in response to smoking cessation. There are no clear data showing that systemic glucocorticoids are effective in DIP.

Respiratory Bronchiolitis–Associated ILD • *CLINICAL MANIFESTATIONS* Respiratory bronchiolitis–associated ILD (RB-ILD) is considered to be a subset of DIP and is characterized by the accumulation of macrophages in peribronchial alveoli. The clinical presentation is similar to that of DIP. Crackles are often heard on chest examination and occur throughout inspiration; sometimes they continue into expiration. The process is best seen on HRCT lung scanning, which shows bronchial wall thickening, centrilobular nodules, ground-glass opacity, and emphysema with air trapping. There is a spectrum of CT features in asymptomatic smokers (and elderly asymptomatic individuals) that may not necessarily represent clinically relevant disease.

HISTOLOGIC FINDINGS The histologic findings in RB-ILD include alveolar macrophage accumulation in respiratory bronchioles, with a variable chronic inflammatory cell infiltrate in bronchiolar and surrounding alveolar walls and occasional peribronchial alveolar septal fibrosis. The pulmonary parenchyma may show presence of smoking-related emphysema.

TREATMENT RB-ILD appears to resolve in most patients after smoking cessation alone.

Pulmonary Langerhans Cell Histiocytosis • *CLINICAL MANIFESTATIONS* This is a rare, smoking-related, diffuse lung disease that primarily affects men between the ages of 20 and 40 years. The clinical presentation varies from an asymptomatic state to a rapidly progressive condition. The most common clinical manifestations at presentation are cough, dyspnea, chest pain, weight loss, and fever. Pneumothorax occurs in ~25% of patients. Hemoptysis and diabetes insipidus are rare manifestations. The radiographic features vary with the stage of the disease. The combination of ill-defined or stellate nodules (2–10 mm in diameter), reticular or nodular opacities, bizarre-shaped upper zone cysts, preservation of lung volume, and sparing of the costophrenic angles are characteristics of PLCH. HRCT that reveals a combination of nodules and thin-walled cysts is virtually diagnostic of PLCH. The most common pulmonary function abnormality is a markedly reduced D_{LCO}, although varying degrees of restrictive disease, airflow limitation, and diminished exercise capacity may occur.

HISTOLOGIC FINDINGS The characteristic histopathologic finding in PLCH is the presence of nodular sclerosing lesions that contain Langerhans cells accompanied by mixed cellular infiltrates. The nodular lesions are poorly defined and are distributed in a bronchiolocentric fashion with intervening normal lung parenchyma. As the disease advances, fibrosis progresses to involve adjacent lung tissue, leading to pericicatricial air space enlargement, which accounts for the concomitant cystic changes.

TREATMENT Discontinuance of smoking is the key treatment, resulting in clinical improvement in one-third of patients. Most patients with PLCH experience persistent or progressive disease. Death due to respiratory failure occurs in ~10% of patients.

ILD ASSOCIATED WITH CONNECTIVE TISSUE DISORDERS

Clinical findings suggestive of a CTD (musculoskeletal pain, weakness, fatigue, fever, joint pain or swelling, photosensitivity, Raynaud's phenomenon, pleuritis, dry eyes, dry mouth) should be sought in any patient with ILD. The CTDs may be difficult to rule out since the pulmonary manifestations occasionally precede the more typical systemic manifestations by months or years. The most common form of pulmonary involvement is the nonspecific interstitial pneumonia histopathologic pattern. However, determining the precise nature of lung involvement in most of the CTDs is difficult due to the high incidence of lung involvement caused by disease-associated complications of esophageal dysfunction (predisposing to aspiration and secondary infections), respiratory muscle weakness (atelectasis and secondary infections), complications of therapy (opportunistic infections), and associated malignancies. For the majority of CTDs, with the exception of progressive system sclerosis, recommended initial treatment for ILD includes oral glucocorticoids often in association with an immunosuppressive agent (usually oral or intravenous cyclophosphamide or oral azathioprine) or mycophenolate mofetil.

Progressive Systemic Sclerosis (PSS) • *CLINICAL MANIFESTATIONS* (See also Chap. 382) Clinical evidence of ILD is present in about one-half of patients with PSS, and pathologic evidence in three-quarters. Pulmonary function tests show a restrictive pattern and impaired diffusing capacity, often before any clinical or radiographic evidence of lung disease appears. The HRCT features of lung disease in PSS range from predominant ground-glass attenuation to a predominant reticular pattern and are mostly similar to idiopathic NSIP.

HISTOLOGIC FINDINGS NSIP is the histopathologic pattern in most patients (~75%); the UIP pattern is rare (<10%).

TREATMENT Therapy is similar to that in idiopathic NSIP. UIP in PSS has a better outcome than IPF. The most widely used initial treatment regimen is low-dose glucocorticoid therapy and an immunosuppressive agent, usually oral or pulse cyclophosphamide. There are no convincing data showing this regime to be efficacious, and there is concern that the risk of renal crisis rises substantially with corticosteroids. Pulmonary vascular disease alone or in association with pulmonary fibrosis, pleuritis, or recurrent aspiration pneumonitis is strikingly resistant to current modes of therapy.

Rheumatoid Arthritis • *CLINICAL MANIFESTATIONS* (See also Chap. 380) ILD associated with RA is more common in men. Pulmonary manifestations of RA include pleurisy with or without effusion, ILD in up to 20% of cases, necrobiotic nodules (nonpneumoconiotic intrapulmonary rheumatoid nodules) with or without cavities, Caplan syndrome (rheumatoid pneumoconiosis), pulmonary hypertension secondary to rheumatoid pulmonary vasculitis, organized pneumonia, and upper airway obstruction due to cricoarytenoid arthritis.

HISTOLOGIC FINDINGS There are two primary histopathologic patterns of ILD that are observed in patients with ILD associated with RA: NSIP pattern and UIP pattern.