Chapter 287: Interstitial Lung Disease

INTRODUCTION

Diffuse parenchymal lung diseases include a large number (>200) of heterogeneous conditions that affect the lung parenchyma with varying degrees of inflammation and fibrosis. While remodeling of the interstitial space, the region between the epithelium and endothelium, tends to be the dominant site of involvement for most of the interstitial lung diseases (ILDs), it is important to recognize the prominent role of the alveolar epithelium and endothelial cells (including both airways and vessels) in the pathogenesis of these interstitial lung disorders.

Despite the diverse array of conditions, most patients ultimately diagnosed with an ILD will come to medical attention with reports of progressive exertional dyspnea or a persistent dry cough. However, because some ILDs are part of multisystem disorders, some patients will be identified based on non-respiratory symptomatology (e.g., skin thickening in the setting of systemic sclerosis, Chap. 353) or physical examination findings (e.g., ulnar deviation of the fingers in the setting of rheumatoid arthritis [RA], Chap. 351). Additionally, ILDs can also be identified incidentally based on the results of abnormal pulmonary function tests, chest x-rays (CXRs), computed tomography (CT) studies of both the chest and abdomen (which can both visualize, at least a portion, of the lung parenchyma), and positron emission tomography (PET) scans. It is important to remember that ILDs can be associated with high rates of morbidity and mortality, and although prognosis depends on both disease extent and specificity, this fact makes these important disorders to recognize in a timely manner.

Owing to a variety of clinical presentations, as well as overlapping imaging and histopathologic findings (Table 287-1), ILDs can be difficult to diagnose. A generally accepted central tenet of ILD diagnosis is that the combined weight of clinical data, laboratory studies, pulmonary function testing, imaging findings, and histopathology (if obtained) are jointly required to make a confident diagnosis. No single piece of data confers a diagnosis alone. For example, a lung biopsy demonstrating a usual interstitial pneumonia (UIP) pattern is helpful in diagnosing a patient with idiopathic pulmonary fibrosis (IPF) but can also be present in some connective tissue diseases (CTDs) (e.g., RA-associated ILD, Chap. 351). In light of this challenge, most ILD centers recommend a multidisciplinary approach to the diagnosis (and in some cases the management) of ILDs. An example of a multidisciplinary approach might include a conference attended by pulmonologists, rheumatologists, radiologists, and pathologists where all of the data generated on a patient can be discussed and reviewed jointly by those with unique sets of expertise in the care of patients with ILD.

TABLE 287-1

Common Interstitial Lung Disease Findings

	IPF	Nonspecific Interstitial Pneumonia	Respiratory Bronchiolitis Associated ILD	Systemic Sclerosis Associated ILD	Sarcoidosis
Clinical symptoms	Gradual onset of SOB, dry cough. Unusual in younger adults.	Subacute onset of SOB, dry cough. Frequently associated with other conditions.	Can be asymptomatic, or have SOB, and cough.	Gradual onset of SOB, dry cough. Fatigue, tightening of skin, exaggerated cold response, reflux, and difficulty swallowing.	Can be asymptomatic, or have SOB, and cough. Can also have fatigue, palpitations, eye, skin, and joint findings.
Physical examination findings	Frequent rales at lung bases, digital clubbing is common.	Frequent rales. Clubbing is less common.	Rales common. Clubbing is rare.	Can have rales in isolation. Also skin thickening, joint swelling, and telangiectasias.	Can be normal, rales may be present. Can have skin findings, joint pain, and enlarged lymph nodes.
Exposures	Idiopathic but many exposed to smoke. Genetic findings may explain >1/3 of the risk of the disease.	Can be idiopathic but should prompt consideration for associated conditions.	Strong association with smoking.	Mostly unknown, some debate about solvent and silicate exposures.	Mostly unknown, although silicate dusts thought to play a role in some cases.

	IPF	Nonspecific Interstitial Pneumonia	Respiratory Bronchiolitis Associated ILD	Systemic Sclerosis Associated ILD	Sarcoidosis
HRCT findings	Bilateral subpleural reticular changes most prominent in lower, posterior lung zones. Traction bronchiectasis and honeycombing common. Classic UIP pattern is considered diagnostic.	Peripheral subpleural ground glass and reticular patterns. Traction bronchiectasis is common but honeycombing is rare. HRCT not diagnostic.	Diffuse patchy centrilobular ground glass nodules.	Can have UIP or NSIP patterns, also dilated esophagus, occasional mediastinal calcifications, and pulmonary vascular enlargement.	Can have mediastinal and hilar lymphadenopathy. Peribronchovascular reticular-nodular findings.
Histopathology	UIP pattern including fibroblastic foci, temporal and spatial heterogeneity, honeycombing.	Cellular or fibrotic pattern of NSIP. More uniform than a UIP pattern.	Respiratory bronchiolitis with adjacent inflammatory and fibrosing changes. Pigment laden macrophages.	Both UIP or NSIP patterns can occur.	Non-caseating granulomas.
Clinical course	50% 3–5 year mortality.	18% 5-year mortality.	25% 7-year mortality.	20–30% 10-year mortality.	Generally low but varies by state.

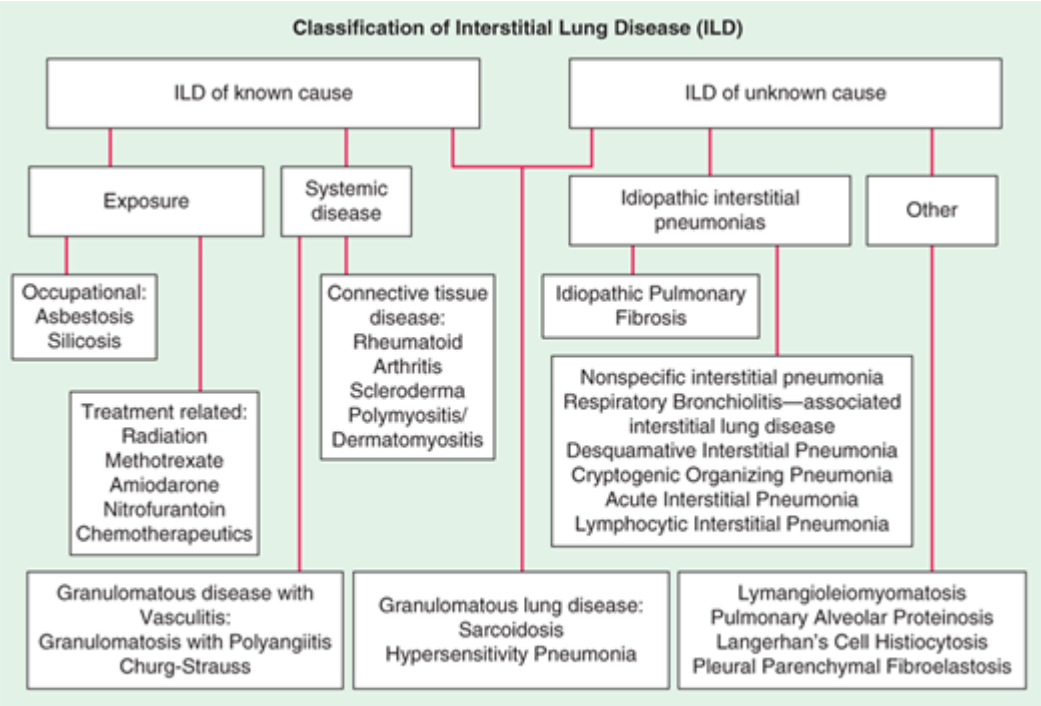
Abbreviations: HRCT, high resolution chest CT; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; SOB, shortness of breath; UIP, usual interstitial pneumonia

While there are numerous ways to categorize the ILDs, one classic approach is to divide the ILDs into those of known and unknown causes **(Fig. 287-1)**. Although even this approach has limitations (e.g., genetic studies demonstrate that a significant portion of familial and IPF [classically described as a diseases of unknown cause] may be explained, in part, by genetic factors), it is a useful place to start. Known causes of ILD include

occupational exposures (e.g., asbestosis), medications (e.g., nitrofurantoin), and those related to an underlying systemic disease (e.g., cryptogenic organizing pneumonia [COP] in the setting of polymyositis). Unknown causes of ILD include groups of rare disorders often with classic presentations (e.g., a spontaneous pneumothorax in a young female with diffuse cystic changes on a chest CT might suggest lymphangioleiomyomatosis [LAM]) and the most common group of ILDs, the idiopathic interstitial pneumonias (IIPs). Granulomatous lung diseases straddle both known (e.g., hypersensitivity pneumonitis (HP) due to chronic bird exposure, Chap. 282), and unknown (e.g., sarcoidosis, Chap. 360) causes and are often separated due to their unique presentations, imaging findings, and diagnostic evaluation. Equally important to knowledge of disease classification is knowledge of disease prevalence. Although there is variability within different demographic groups, most studies demonstrate that IPF, sarcoidosis (Chap. 360), and ILDs related to CTDs (Chap. 406) as a group are among the most common forms of ILD.

Figure 287-1

Classification of interstitial lung disease. This algorithm represents a common approach to sub-classifying the interstitial lung diseases. It is typical to divide the interstitial lung diseases into those of known and unknown causes (although it is important to note that genetic studies demonstrate that a significant portion of familial and idiopathic pulmonary fibrosis [classically described as diseases of unknown cause] may be explained, in part, by genetic factors). The idiopathic interstitial pneumonias were more precisely defined by a 2002 study as described in Am J Respir Crit Care Med 165:277, 2002, referenced in the Further Reading list.



DIAGNOSTIC APPROACH

The initial diagnostic approach to diffuse parenchymal lung disease is often broader than a focus on ILD and should include an evaluation for alternate causes including cardiovascular disease (e.g., heart failure, Chap.

253), diffuse infections (e.g., *pneumocystis* pneumonia, Chap. 215), and malignancy (e.g., bronchoalveolar cell carcinoma, Chap. 315 in HPIM 19e). This chapter will focus on the diagnostic evaluation that helps to distinguish among the various forms of ILD.

HISTORY

Age

Age at presentation has a strong influence on the pretest probability that IPF, in particular, is present. For example, IPF occurs most commonly in patients aged >60 and is quite rare among patients aged <50. In fact, in patients aged >65 without strong evidence for an alternate diagnosis, atypical chest CT findings are still more likely to result in a histopathologic diagnosis of UIP (a pathologic hallmark of IPF) than they are to result in an alternate IIP diagnosis. Other common ILDs such as sarcoidosis, CTD associated ILD, and less common ILDs such as LAM, pulmonary Langerhans cell histiocytosis (PLCH) tend to present between the ages of 20 and 40.

Sex

Although less influential than age, sex has some influence on likelihood of various ILDs. LAM (and related disorder tuberous sclerosis) (see Chap. 315 in HPIM 19e) is a disorder that is frequently diagnosed in young women. Many CTD-associated ILDs are more common among women, with the exception of RA associated ILD which is more common among men. IPF and occupational/exposure-related ILDs (likely due to work related exposures that tend to differ between men and women) are more common among men.

Duration of Symptoms

Acute presentations (*days to weeks*) of ILD are unusual and are commonly misdiagnosed as more common diseases such as pneumonia, a COPD exacerbation, or heart failure. ILDs that can present acutely include eosinophilic pneumonia, acute interstitial pneumonia (AIP), HP, and granulomatosis with polyangiitis (GPA). An acute exacerbation of IPF as the initial presentation of this disease should also be a consideration given its prevalence. ILDs most commonly have a chronic indolent presentation (*months to years*) typified by IPF. However subacute presentations (*weeks to months*) can occur in most of the ILDs, but in the right context could suggest sarcoidosis, CTD associated ILD, drug-induced ILD, or COP.

Respiratory Symptoms

Progressive dyspnea, most frequently noted with exertion, is the most common complaint in patients presenting with an ILD. Despite this fact, both research studies of general population samples and clinical experiences of asymptomatic patient referrals with abnormal chest CT imaging patterns have also demonstrated that some patients, even those with more extensive disease, may not report dyspnea. Cough, particularly a dry cough, is also common, and can be the most prominent symptom in patients with IPF. Cough is often reported in other ILDs, particularly those that have prominent airway involvement including

sarcoidosis and HP. Cough with hemoptysis is rare and could suggest an ILD associated with diffuse alveolar hemorrhage (DAH) (e.g., Goodpasture's syndrome), GPA, or LAM. Cough with hemoptysis could also suggest a secondary pulmonary infection that can be seen in patients with traction bronchiectasis and in those receiving immunosuppressive therapy. Chest pain is rare in most of the ILDs with the exception of sarcoidosis where chest discomfort is not uncommon. Fatigue is common to all of the ILDs.

Past Medical History

The most pertinent history includes a personal history of a CTD or a history of symptoms commonly associated with a CTD (e.g., Raynaud's phenomena). It is also important to remember that ILD associated with a CTD can be the initial presenting symptom of the disease and can precede the development of additional symptomatology by many years. A history of malignancy is important; as some malignancies can be associated with dermatomyositis associated COP and sarcoid-like reactions. A history of asthma and allergic rhinitis might suggest a diagnosis of eosinophilic GPA.

Medications

Many medications have been associated with ILD and to complicate matters further, many medications commonly used to treat inflammatory and granulomatous lung disease are also associated with ILD development (e.g., methotrexate, azathioprine, rituximab, and the tumor-necrosis factor-alpha blocking agents). Specific medications in many classes are also known to cause ILD, including antibiotics (e.g., nitrofurantoin), anti-arrhythmics (e.g., amiodarone) and many of the anti-neoplastic agents (e.g., bleomycin).

Family History

A family history of ILD (of almost any type) is important to ascertain. The percentage of pulmonary fibrosis that is familial, as opposed to idiopathic, varies by study, with estimates ranging from <5% to as high as 20%. Despite this variability, most agree that the presence of a close relative with an IIP is among the strongest risk factors for IPF. Family studies have consistently noted familial aggregation of diverse forms of IIP (such as IPF, non-specific interstitial pneumonia [NSIP], and DIP running in the same family) and in some cases other forms of ILD. To date, the most well replicated genetic factors for pulmonary fibrosis (a promoter variant of a mucin gene [*MUC5B*]) and various genetic determinants known to influence telomere length (e.g., variants in the telomerase reverse transcriptase gene [*TERT*]) appear to be associated with both familial and idiopathic forms of pulmonary fibrosis similarly.

Social History

A history of smoking is nearly always present in some forms of ILD (e.g., respiratory bronchiolitis and desquamative interstitial pneumonia [DIP]—sometimes referred by pathologists jointly as smoking related—ILD) where it is felt to be causative. A history of smoking is also noted in approximately three-quarters of IPF patients. Occupational and environmental exposure histories are also important to obtain as they might

identify exposures known to cause pulmonary fibrosis (e.g., significant asbestos exposure) or HP (pigeon breeder's lung).

PHYSICAL EXAMINATION

End-inspiratory fine crackles, or rales, noted at the lung bases are found in most patients with IPF and may be one of the earliest signs of the disease. However, rales are nonspecific and can be found in many forms of ILD and other disorders. Wheezing is uncommon in most forms of ILD but can be present in some disorders, such as sarcoidosis, HP, and eosinophilic GPA. Signs of advanced disease include cyanosis, digital clubbing, and cor pulmonale.

LABORATORY STUDIES

Laboratory studies can be particularly helpful in the workup for an underlying CTD-associated ILD. As noted previously, these tests can reveal the presence of an underlying CTD as the cause of an ILD (e.g., a positive anti-cyclic citrullinated peptide [anti-CCP] antibody for RA) even when no other symptomatology or physical examination findings suggestive of the disorder are present. However, the cost-effectiveness and the extent of laboratory testing that should be ordered in various clinical contexts have yet to be determined (as there is a relatively long list of auto-antibody tests that could be ordered).

PULMONARY FUNCTION TESTS

Most forms of ILD will eventually result in a restrictive deficit on pulmonary function testing. A restrictive deficit is typified by a reduced total lung capacity (TLC), and symmetrically reduced measures of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). A reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) is also common and may precede a reduction in lung volumes; however, there is more measurement variability in DLCO measurement and the test is less specific for ILD. A reduced FEV1 to FVC ratio, which is diagnostic of airway obstruction, is unusual in many forms of ILD but can be present as an isolated finding, or in conjunction with an additional restrictive deficit, in ILDs involving the airways such as sarcoidosis, HP, and LAM. Although pulmonary function testing is rarely diagnostic, reductions in lung function help to characterize the extent of disease, and evidence for decline in repeated measures of pulmonary function (e.g., FVC) have been correlated with an elevated rate of mortality.

CHEST IMAGING STUDIES

Chest X-Ray

Findings on CXR can be the first clinical indication that an ILD might be present. For example, enlarged hilar lymph nodes and a pattern of central nodular opacities in the mid to upper lung zones can suggest sarcoidosis. A basilar reticular pattern, with small cystic spaces, in the absence of clinical evidence for heart failure, might suggest IPF. With a few exceptions, CXR alone rarely leads to a specific diagnosis.

Chest CT

High resolution chest CT (HRCT) imaging is now considered to be standard of care in the initial evaluation of a patient with a suspected ILD. HRCT can be diagnostic for some ILDs (e.g., IPF) in right clinical context and may preclude the need for, and spare the patient the risk of, a lung biopsy. HRCT also helps to define the extent of the ILD, the presence of more concerning features suggestive of advanced disease (e.g., honeycombing), can provide information on coexisting diseases (e.g., emphysema and lung cancer), and when not diagnostic, can help to provide the most useful locations for obtaining lung biopsy specimens.

LUNG BIOPSY

Fiberoptic Bronchscopy

Bronchoscopy can be helpful in establishing a specific ILD diagnosis, and can help to establish an alternate diagnosis, in select cases. Examination of serial lavage fluid can be helpful in establishing DAH which can be present in ILDs with vasculitis (e.g., GPA), and in some cases, cellular examination can suggest a specific diagnosis (eosinophilia >25% in chronic eosinophilic pneumonia or fat globules in macrophages in lipoid pneumonia). Trans-bronchial lung biopsies and lymph node biopsies (in sarcoidosis in particular) can lead to a confident diagnosis in patients with likely granulomatous lung disease (e.g., sarcoidosis and HP). However, in general, bronchoscopically obtained tissue samples are often felt to be insufficient to diagnose most of the IIPs. There is some preliminary evidence that bronchoscopically obtained cryobiopsies, which can result in yields larger than those obtained by transbronchial forceps biopsies, could improve the diagnostic yield of bronchoscopy; however, the precise role cryobiopsies in the diagnostic workup of ILD has yet to be clarified.

Surgical Lung Biopsy

A surgically obtained lung biopsy specimen can help solidify the diagnosis of ILD. In many cases these are now obtained through a video-assisted thoracoscopic (VATS) approach (as compared to an open thoracotomy), which tends to reduce the length of operative times and hospital stays. The diagnostic yield of biopsies tends to be higher if obtained prior to treatment. The desire to obtain a surgical lung biopsy should be weighed against the risks which can include a short-term mortality rate of as high as 5%. These risks are reported to be higher in biopsies of patients ultimately diagnosed with IPF, and in those presenting acutely.

INDIVIDUAL FORMS OF ILD

The ILDs include a diverse group of lung pathologies that can be subclassified into those disorders of unknown cause (e.g., IIPs), and those of known cause (e.g., sometimes referred to as secondary interstitial pneumonias [connective tissue disease-associated ILDs]) (see Fig. 287-1). Although this remains a useful approach to classifying this diverse group of disorders it is important to recognize that genetic studies are challenging this classic categorization. For example, numerous ILDs commonly listed as having an “unknown cause” have been determined to have significant genetic underpinnings (e.g., IPF and LAM), while the pathophysiologic processes that result in ILDs of “known cause” (e.g., connective tissue disease) remain incompletely understood. Diagnosis is based on combined information obtained from a patient’s clinical presentation, measures of pulmonary function, imaging, immune serologies, and histopathology. It is

important to remember that prognosis and treatment vary widely by disorder (and disease extent). In some cases, medical therapy that is felt to be effective for some ILDs has been proven to be harmful for others. Medical treatments range from immune modulators to anti-fibrotic medications while lung transplantation remains the standard of care for those with advanced and rapidly progressive ILDs.

IDIOPATHIC INTERSTITIAL PNEUMONIAS

IDIOPATHIC PULMONARY FIBROSIS

Clinical Manifestations

IPF is the most common ILD of unknown cause. Prevalence increases with age and is estimated at 50–200:100,000. IPF is commonly diagnosed in the fifth or sixth decade in life, affects men more than women, and is frequently associated with a history of smoking or other environmental exposures. IPF is a variably progressive disease that carries a poor prognosis with an estimated 50% 3–5-year survival.

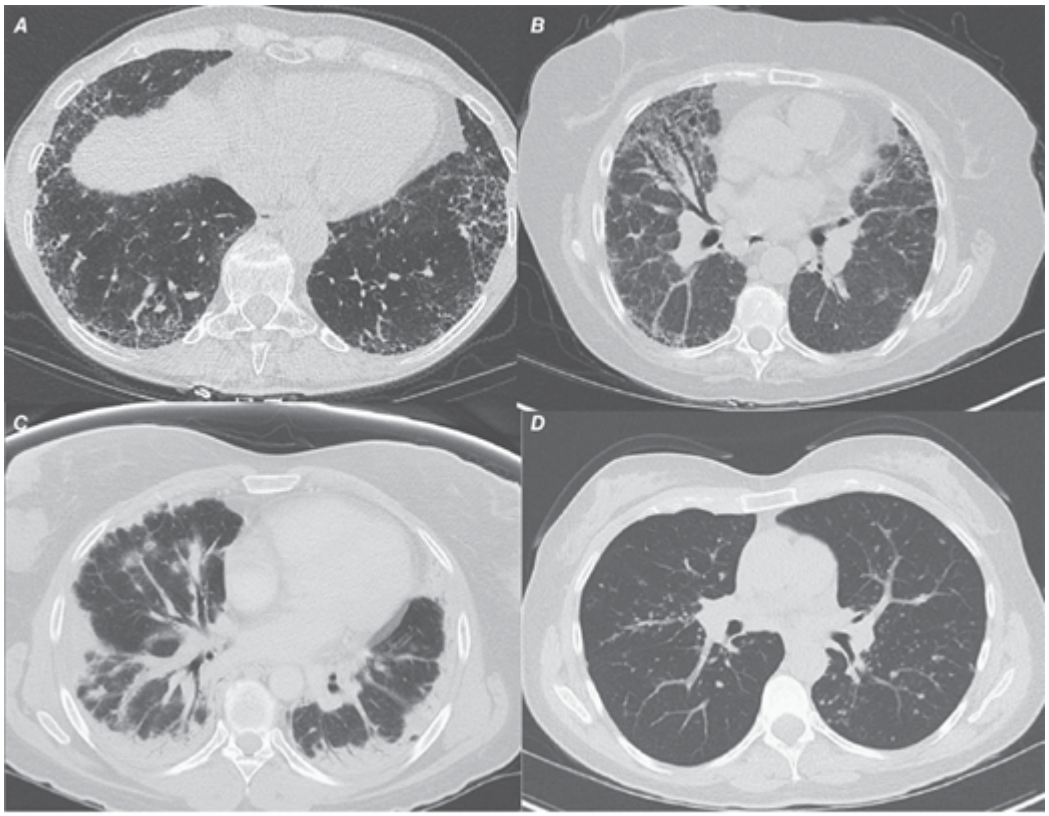
HRCT Image Findings

Chest CT findings include subpleural reticulation with a posterior basal predominance usually including more advanced fibrotic features, such as honeycombing and traction bronchiectasis. Collectively these imaging findings are referred to as a UIP pattern. The presence of extensive ground glass opacities, bronchovascular changes, micronodules, mosaic attenuation, or an upper lung predominance should raise suspicion for an alternative diagnosis (Fig. 287-2).

Figure 287-2

Chest CT imaging and interstitial lung disease. ***A***. Idiopathic pulmonary fibrosis (IPF): Classic findings of IPF (apparent on this image) include a posterior, basilar predominance of subpleural reticular markings and more advanced features of pulmonary fibrosis including traction bronchiectasis and honeycombing. This constellation of findings is often referred to as a usual interstitial pneumonia (UIP) pattern. ***B***. Non-specific interstitial pneumonia (NSIP): Chest CT findings of NSIP can overlap with those of a UIP pattern but tend to include a bilateral, symmetric pattern that presents with a greater percentage of ground-glass opacities than is apparent in a UIP pattern. Additional unique findings include more diffuse imaging abnormalities with a predominance not limited to the lung bases, imaging abnormalities that spare the subpleural regions, and thickening of the bronchovascular bundles (as is apparent in the right mid lung zone on this image). ***C***. Cryptogenic organizing pneumonia: Chest CT findings include patchy, sometimes migratory, subpleural consolidative opacities (as is apparent on this image) often with associated ground-glass opacities. Peribronchiolar, or perilobar opacities can be present and sometimes a rim of subpleural sparing (often referred to as a reversed halo or atoll sign) can be seen which can help to aid in the diagnosis. ***D***. Sarcoidosis: Sarcoidosis can present with varied imaging abnormalities but a pattern of mediastinal and hilar lymphadenopathy with a pattern of reticular-nodular opacities involving the bronchovascular bundles (apparent in this image) are common features. Additional findings can include diffuse small nodules in a

miliary pattern, larger nodular opacities, extensive ground glass infiltrates and, mosaic attenuation suggestive of small airways involvement, and in more advanced cases, signs of pulmonary fibrosis.



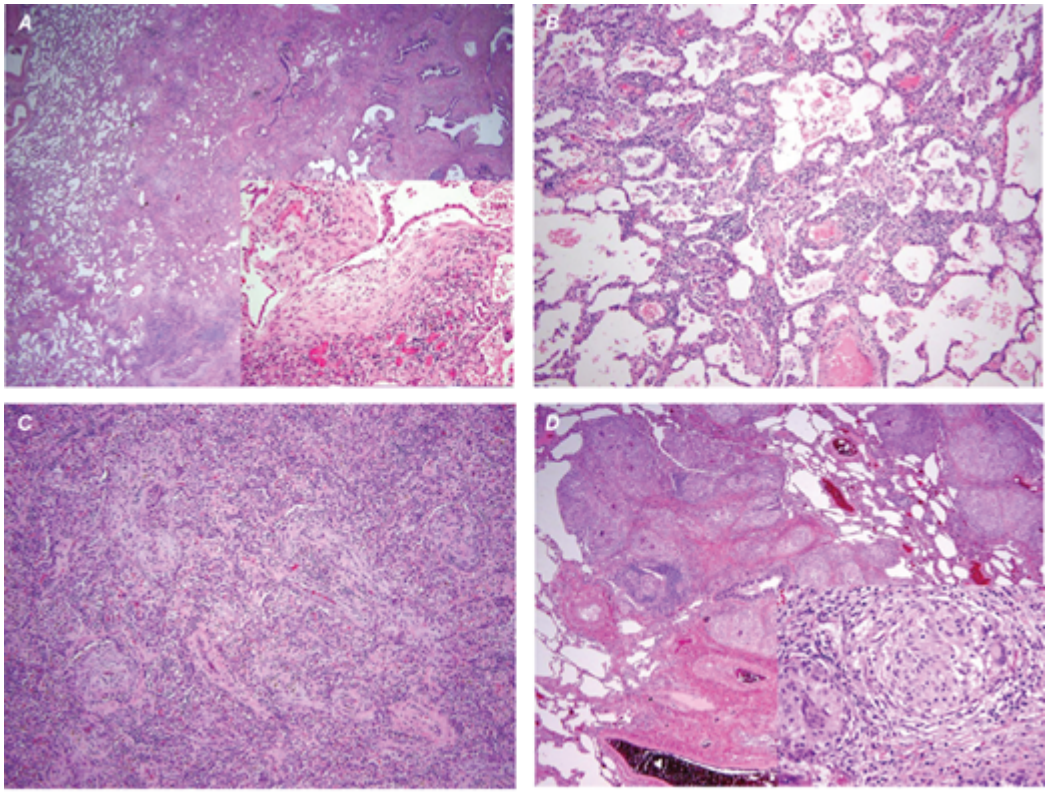
Histopathology

Diagnostic VATS biopsy findings include subpleural reticulation associated with honeycomb changes and fibroblast foci (subepithelial collections of myofibroblasts and collagen). These fibrotic changes alternate with areas of preserved normal alveolar architecture consistent with temporal and spatial heterogeneity **(Fig. 287-3)**. Collectively, these pathologic findings are referred to as UIP.

Figure 287-3

Histopathology of interstitial lung disease. ***A***. Idiopathic pulmonary fibrosis (IPF): Histopathologic findings include subpleural reticulation associated with honeycomb changes alternating with areas of preserved normal lung architecture referred to as temporal and spatial heterogeneity (as is apparent in the low power image above). Additional important diagnostic findings include fibroblast foci, which are subepithelial collections of myofibroblasts and collagen (as is apparent in the higher powered inset of this image). Collectively these pathologic findings are referred to as usual interstitial pneumonia (UIP). ***B***. Non-specific interstitial pneumonia (NSIP): Histopathologic findings of NSIP include varying amounts of interstitial inflammation and fibrosis with a uniform appearance (as is apparent in this image). Honeycomb changes are usually absent and fibroblast foci are rare. NSIP is often referred to histopathologically as being either predominantly cellular or fibrotic. ***C***. Cryptogenic organizing pneumonia (COP): Histopathologic findings of COP include patchy regions of organizing pneumonia with granulation tissue that commonly involves the

small airways, alveolar ducts, and alveoli with surrounding inflammation that can involve the alveolar walls (as is apparent in this image). ***D***. Sarcoidosis: The hallmark histopathologic feature of sarcoidosis is presence of granulomas (as are apparent numerously in the low powered image and more closely visualized in the higher powered inset image). Typically these are referred to as non-caseating which suggests the absence of necrosis. Caseating granulomas are rare in sarcoid and should prompt additional evaluation for an underlying infection. Because malignancy can result in a granulomatous reaction it is important to closely survey biopsy specimens with granulomatous involvement for additional signs of malignancy.



Treatment

Historically, IPF was felt to be refractory to medical therapy with lung transplantation the only viable therapeutic option. This dogma changed in 2014 with large clinical trials that demonstrated that antifibrotic therapy (pirfenidone and nintedanib) can slow decline of lung function in IPF patients. Further meta-analyses have suggested that anti-fibrotic therapy may also improve survival. In contrast, treatment with immunosuppression, which had been commonly prescribed to many IPF patients, has now been demonstrated (in some cases) to be associated with increased morbidity and mortality. Physical therapy and supplemental oxygen, when indicated, can improve exercise tolerance and reduce likelihood of developing pulmonary hypertension. Lung transplantation can extend survival and improve the quality of life in a subset of IPF patients who meet criteria to undergo transplant.

NON-SPECIFIC INTERSTITIAL PNEUMONIA

Clinical Manifestations

Idiopathic NSIP is a distinct clinical entity with characteristic clinical, radiologic, and pathologic features; however, NSIP is also commonly observed in patients with connective tissue disease and less frequently with familial interstitial pneumonia, drug toxicity, and infection. Although the prevalence of NSIP is not well established, it is commonly diagnosed in non-smoking females in their fifth decade of life. Positive serologic tests for connective tissue disease are frequently observed. Idiopathic NSIP has a relatively good prognosis, with a 5-year survival >80%; patients with a predominant cellular NSIP pattern have a more favorable prognosis than those with a fibrosing NSIP pattern.

HRCT Image Findings

Diffuse subpleural, symmetric, ground glass, and reticular opacities are common. Volume loss and traction bronchiectasis involving the lower lung zones can also be found. Occasionally subpleural sparing is noted, while peribronchiolar thickening and honeycombing are uncommon.

Histopathology

Diagnostic lung biopsy findings include varying amounts of interstitial inflammation and fibrosis with a uniform appearance. Honeycomb changes are usually absent and fibroblast foci are rare. NSIP is often referred to histopathologically as being either predominantly cellular (and potentially more responsive to medical therapy) or fibrotic (and potentially less likely to resolve with medical therapy).

Treatment

Pulmonary fibrosis associated with connective tissue disease is commonly treated with immunosuppression despite the paucity of randomized clinical trials to demonstrate efficacy. Idiopathic NSIP is often treated with oral steroids (prednisone), cytotoxic agents (mycophenolate, azathioprine, and cyclophosphamide), or biologics (rituximab). Oxygen therapy, pulmonary rehabilitation, and lung transplantation may be required in patients with progressive disease.

SMOKING-RELATED ILD

Although smoking-related ILDs including respiratory bronchiolitis with interstitial lung disease (RB-ILD), and DIP are frequently subclassified with the IIPs, these disorders (along with PLCH, an ILD with unique clinical, imaging and histopathologic manifestations) are commonly felt to be the result of active or prior tobacco smoke exposure. DIP has also been known to occur in children with familial pulmonary fibrosis (FPF). Smokers, particularly elderly smokers, frequently have radiologic (centrilobular) interstitial abnormalities. These interstitial abnormalities are often incidentally found on routine CXR or chest CT studies in asymptomatic, or minimally symptomatic individuals. Respiratory bronchiolitis is felt to correlate histopathologically with these imaging findings. However, in some cases these imaging findings can progress to more advanced radiologic changes where more diffuse signs of interstitial pneumonia tend to be present.

Clinical Manifestations

These disorders predominantly occur in active, and in many cases heavy, smokers who are typically between 40 and 50 years of age. In those ultimately diagnosed with RB-ILD or DIP, dyspnea and cough are relatively common and symptomatic wheezing is not rare. The prevalence of smoking-related ILDs is not well understood, but they are generally felt to account for <10% of the IIPs. While there is minimal data on the natural histories and prognoses of these conditions, prolonged survival can be expected in most patients with RB-ILD and death secondary to progressive ILD is felt to be rare.

HRCT Image Findings

Prominent and common findings in RB-ILD include central bronchial wall thickening, peripheral bronchial wall thickening, centrilobular nodules, and ground-glass opacities. Septal lines and a reticular pattern are also not uncommon. Honeycombing is generally felt to be rare (and indicates a worse prognosis). Similar findings are noted in patients with DIP where diffuse (or patchy) bilateral symmetric ground-glass opacities tend to be even more prominent.

Histopathology

Common features of RB-ILD include the accumulation of pigmented macrophages within the lumens of respiratory bronchioles and alveolar ducts, accompanied by chronic inflammation of the respiratory bronchiolar walls and both bronchiolar and peribronchiolar alveolar fibrosis causing architectural distortion. These features are patchy and confined to the peribronchiolar region. DIP tends to include similar changes but they have a more diffuse pattern characterized by pigmented macrophage accumulation, pneumocyte hyperplasia, and prominent interstitial thickening.

Treatment

All patients with smoking-related ILD should be counseled to discontinue smoking and/or encouraged to enroll in a formal smoking cessation program. Small studies have evaluated, and patients are often treated with immunosuppressive (e.g., prednisone) and cytotoxic (e.g., azathioprine, and cyclophosphamide) agents and in some cases with bronchodilators. To date there is no strong evidence that these therapies result in significant improvements symptoms, measures of pulmonary function, or if they prevent clinical deterioration.

CRYPTOGENIC ORGANIZING PNEUMONIA

Clinical Manifestations

COP typically involves patients in their 50–60s and often presents as a subacute flu-like illness, with cough, dyspnea, fever, and fatigue. Inspiratory rales are often present on examination and most patients are noted to have restrictive lung deficits on pulmonary function testing with hypoxemia. It is commonly mistaken for pneumonia. It is important to note that this syndrome can occur in isolation or can be secondary to an underlying connective tissue disease (e.g., polymyositis), medications, or can result from an underlying

malignancy. Laboratory testing for various connective tissue diseases is helpful as they can both be diagnostic and suggest the need for prolonged medical therapy.

HRCT Image Findings

The most common imaging findings include patchy, sometimes migratory, subpleural consolidative opacities often with associated ground-glass opacities. Peribronchiolar, or perilobar opacities can be present and sometimes a rim of subpleural sparing (often referred to as a reversed halo or atoll sign) can be seen which can aid in the diagnosis.

Histopathology

Surgical lung biopsy specimens tend to reveal patchy regions of organizing pneumonia with granulation tissue that commonly involves the small airways, alveolar ducts, and alveoli with surrounding inflammation that can involve the alveolar walls (Fig. 287-2).

Treatment

Corticosteroids can result in substantial clinical improvement in many patients but usually need to be continued for at least 6 months as relapse rates are high. Evidence is growing that alternate cytotoxic (e.g., mycophenolate, cyclophosphamide) or biologic (e.g., rituximab) therapies can be helpful in both treating the disease and reducing the need for steroids. In some patients with secondary forms of the disease, long-term therapy may be needed.

ACUTE OR SUBACUTE IIPS

ACUTE INTERSTITIAL PNEUMONIA (HAMMAN-RICH SYNDROME)

Clinical Manifestations

AIP is a rare and often fatal lung disorder that is characterized by an acute onset of respiratory distress and hypoxemia. A prodromal period of symptoms consistent with an acute upper respiratory infection is common. The mortality rate within 6 months of presentation can be quite high (>50%) and recurrences are common. In those that recover, lung function improvement can be substantial. AIP can be difficult to distinguish from acute respiratory distress syndrome (ARDS) and an acute exacerbation of an unsuspected underlying pulmonary fibrotic process.

HRCT Image Findings

The most common imaging findings are patchy bilateral ground-glass opacities. Dependent regions of air-space consolidation are also common.

Histopathology

Similar to ARDS and acute exacerbations of underlying pulmonary fibrosis, AIP presents histopathologically as diffuse alveolar damage (DAD) demonstrated on a surgical lung biopsy.

Treatment

Treatment is mostly supportive and often includes mechanical ventilation. There is no proven drug therapy for AIP. Glucocorticoids are often given but they are not clearly effective and have been demonstrated not to be beneficial in other forms of DAD (e.g., ARDS).

ACUTE EXACERBATIONS OF IIPS

Clinical Manifestations

Acute exacerbations are not separate disorders, but rather an accelerated phase of lung injury that can occur in any ILD resulting in pulmonary fibrosis. Acute exacerbations are most commonly described, and most severe in, patients with known IPF. Acute exacerbations are characterized by an acute onset (<30 days) of respiratory distress and hypoxemia occurring in a patient with underlying pulmonary fibrosis not explained by an alternate cause (e.g., pneumonia, left heart failure). Reported mortality rates are very high (>85%) and mean survival periods range from as little as days to months.

HRCT Image Findings

The most common imaging findings include patchy bilateral ground-glass opacities and dependent regions of air-space consolidation. Sometimes these new changes can be appreciated on the background of the imaging findings typified by the underlying IIP, although sometimes they obscure the preceding imaging findings.

Histopathology

Acute exacerbations of underlying pulmonary fibrosis present histopathologically as DAD, although sometimes organizing pneumonia can also be demonstrated on a surgical lung biopsy.

Treatment

Treatment is mostly supportive. Mechanical ventilation, when not being used as a bridge to lung transplantation, is controversial as the survival rate in these patients tends to be poor. There is some evidence that drug therapy (e.g., Nintedanib) may reduce the rate of acute exacerbations in patients with IPF. Drug therapy, in the context of an acute exacerbation is also controversial. Immunosuppressive (e.g., prednisone) and cytotoxic (e.g., cyclophosphamide) therapies are commonly used without proven benefit.

ILD ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

ILD is a common disease manifestation of many connective tissue diseases. Disease progression, response to therapy and survival is variable and associated with specific radiologic and histopathologic patterns. ILD occurs most commonly in patients with scleroderma (systemic sclerosis form, or SSc), RA, polymyositis/dermatomyositis, and less frequently Sjögren syndrome and systemic lupus erythematosus (SLE). ILD may precede the development of extrapulmonary manifestations of a specific connective tissue disease or may present as part of a poorly defined connective tissue disease. In rare cases, lung manifestations may be the sole feature of the patient's clinical presentation.

SYSTEMIC SCLEROSIS

Clinical Manifestations

ILD is the most common pulmonary manifestation of SSc **(Chap. 353)**. ILD occurs in about 50% of SSc patients with diffuse disease and in about 30% of patients with limited disease. Pulmonary hypertension can occur separately or concomitantly with ILD and is more frequent in patients with limited SSc.

HRCT Image Findings

Similar imaging findings noted in both patients with NSIP and IPF can be present, although findings consistent with COP and DAD may also be present. Additional HRCT findings may include a dilated esophagus and pulmonary artery enlargement.

Histopathology

Comparable to the imaging overlap, histopathologic changes commonly noted in patients with NSIP and IPF are frequently identified. Additionally, aspiration related to esophageal dysmotility is common in SSc, in these patients histopathologic findings consistent with COP and DAD may be observed.

Treatment

Cyclophosphamide has a modest benefit in preservation of lung function and is associated with significant toxicity. Mycophenolate has recently been shown to have similar efficacy and improved tolerability. Clinical trials testing antifibrotic therapies (pirfenidone and nintedanib) are presently being conducted. Minimizing the risk of reflux by using high-dose proton pump inhibitors or antireflux surgery should be considered in SSc with progressive ILD. Lung transplantation can potentially be offered to select patients without significant aspiration or chest wall restriction.

RHEUMATOID ARTHRITIS

Clinical Manifestations

A common extraarticular complication of RA is ILD **(Chap. 351)**. Although RA is more common in females, RA-ILD is more frequent in males and in patients with a history of tobacco exposure. In a small subset of patients,

ILD is the first disease manifestation of RA. Clinically evident disease RA-ILD occurs in nearly 10% of the RA population; however, up to 40–50% of subjects have radiologic abnormalities on chest CT suggesting ILD in the context of RA may be under-diagnosed.

HRCT Image Findings

The most common imaging pattern of ILD in patients with RA is a UIP pattern, although NSIP patterns are not uncommon. There is evidence that survival in patients with RA is decreased in those with a UIP pattern and among those with more extensive fibrosis in general.

Histopathology

Histopathologic findings of UIP and NSIP are most common. Some studies suggest that UIP in the context of RA (as compared to IPF) may present with a reduced number of fibroblastic foci and an increased amount of germinal centers. Comparable to the imaging findings, UIP (and DAD) patterns in patients with RA are associated with reduced survival.

Treatment

In contrast with SSc, there are no randomized clinical trials testing the role of immune suppression in RA-ILD. Extrapolating from the scleroderma experience, immunosuppresive (e.g., prednisone) and cytotoxic (e.g., mycophenolate, azathioprine, cyclophosphamide, and calcineurin inhibitors) agents have been used with variable success. Clinical trials testing antifibrotic therapies (pirfenidone and nintedanib) are presently being conducted. Lung transplantation is a viable therapeutic approach for eligible patients with progressive disease that is not responsive to medical therapy.

DERMATOMYOSITIS/POLYMYOSITIS

Clinical Manifestations

The idiopathic inflammatory myopathies are disorders characterized by immune-mediated destruction and dysfunction of muscle, however this disorder can affect the skin, joints, cardiovascular system and lung (Chap. 358). The prevalence of ILD associated with inflammatory myopathy varies by report, however ILD is present in up to 45% of patients with positive anti-synthetase antibodies. The anti-synthetase syndrome is characterized by positive anti-synthetase antibodies, myositis, fever, Raynaud phenomenon, mechanic's hands, arthritis, and progressive ILD. There is a subset of anti–Jo-1 antibody–positive individuals who can develop a rapidly progressive form of ILD consistent with an acute exacerbation. Some studies have suggested that ILD may be even more common in those with other antibodies (e.g., anti-PL-12). Dermatomyositis/polymyositis can occur as an isolated connective tissue disease or as a process associated with an underlying malignancy.

HRCT Image Findings

Common imaging patterns of ILD in patients with dermatomyositis/polymyositis include those consistent with NSIP with or without evidence for COP. A UIP pattern can also occur. Some studies have suggested that a UIP pattern may be more common among those with anti-PL-12 antibodies.

Histopathology

The antisynthetase syndrome is associated with multiple histopathologic subtypes including NSIP, COP, and UIP. DAD, a histopathologic pattern observed in AIP and acute exacerbations, is associated with rapidly progressive ILD in myositis patients.

Treatment

Immunosuppresive (e.g., prednisone) and cytotoxic (e.g., mycophenolate, azathioprine, cyclophosphamide, and calcineurin inhibitors) agents are often used in patients with progressive ILD. Some patients (particularly those with less fibrosis) have been noted to improve or resolve their ILD in response to medical therapy. In small studies relapses have been more common in patients treated with prednisone alone. Patients who fail immune suppressive therapy can benefit from lung transplantation.

GRANULOMATOUS ILDS

The most common granulomatous ILD is sarcoidosis, a multisystem disorder of unknown cause where lung involvement is often the most dominant feature, will be discussed in Chap. 360. HP, a granulomatous reaction due to inhalation of organic (e.g., bird fancier's lung secondary to exposure to bird feathers) and inorganic (e.g., coal worker's pneumoconiosis secondary to exposure to coal dusts) dusts, is also an important and common cause of ILD and is discussed in Chap. 282.

Granulomatous Vasculitides

These disorders are characterized by blood vessels with inflammatory infiltrates associated granulomatous lesions with or without the presence of tissue necrosis (See Chap. 60). The lungs are commonly involved and a unique feature of these disorders is that hemoptysis can be a presenting symptom. Although laboratory testing is often helpful and can provide specific information, biopsies of involved tissue can be essential for making the diagnosis. Many of these disorders include additional systemic manifestations. GPA, also referred to as Wegener's disease, is an example of a granulomatous vasculitis that commonly affects the lung (including inflammatory infiltrates in small to medium sized vessels), the ears, nose, throat, and kidney (resulting in glomerulonephritis). Common imaging abnormalities of GPA include nodules, patchy ground glass, and consolidative opacities that can be migratory, and hilar lymphadenopathy. Eosinophilic GPA (EG, also referred to as Churg-Strauss syndrome) is another example of a granulomatous vasculitis that affects the lung (including eosinophilic infiltrates in small to medium sized vessels) that can result in numerous clinical manifestations but frequently includes chronic sinusitis, asthma, and peripheral blood eosinophilia. Common imaging abnormalities of EG include peripheral consolidative opacities that can be migratory and small pleural effusions.

GENETICS AND ILD

Studies of genetic epidemiology have led to important insights in our understanding of ILD. First, studies of families with FPF have demonstrated that unique IIPs can cosegregate with specific genetic variants known to be associated with IPF. This suggests that many genetic variants appear to predispose to interstitial lung injury patterns more broadly than to unique diagnoses specifically. Second, most of the genetic variants known to be associated with FPF are also associated with more sporadic forms of the disease. Third, at least one of the genetic factors most strongly associated with FPF and IPF is both common and confers a large increase in the risk of these diseases. At least one copy of a mucin 5B (*MUC5B*) promoter variant is present in ~20% of Caucasian populations and 35–45% of patients with IPF and confers and approximate sixfold increase in the risk of this disease. Fourth, studies of general population samples demonstrate that imaging abnormalities suggestive of an early stage of pulmonary fibrosis in research participants without known ILD are not uncommon (occurring in ~7–9% of adults) and are also associated with the same genetic variants known to be associated with IPF (e.g., the *MUC5B* promoter variant). This latter finding suggests a path forward towards an early detection of IPF. Additional genetic findings demonstrating replicable associations with pulmonary fibrosis include numerous genetic variants in, and adjacent to, genes known to be involved in the regulation of telomere length (e.g., the *TERT* gene, the telomerase RNA component [*TERC*] gene, and the regulator of telomere elongation helicase 1 [*RTEL1*] gene) and surfactant protein genes (e.g., surfactant protein A2 [*SFTPA2*] gene).

Genetic studies have also provided some insights into other forms of ILD. Genome-wide association studies of sarcoidosis have demonstrated numerous variants in genes, and in genomic regions, that are associated with the disease. Some of these disease associated variants in sarcoidosis fall in human leukocyte antigen (*HLA*) regions, in regions of genes involved in immune regulation (e.g., interleukin 12B [*IL12B*]) in regions of genes that are less well understood (butroyrophilin-like 2 [*BTNL2*]) but also appear to be involved in T-cell activation. LAM is often associated with genetic variants in the tuberous sclerosis complex genes (e.g., *TSC1* and *TSC2*), consistent with the known evidence that this disease can occur in isolation but also in patients with known tuberous sclerosis. Many genetic factors for rare diseases such as Hermansky-Pudlak syndrome (a rare autosomal recessive disorder that results in pulmonary fibrosis but also includes oculocutaneous albinism, bleeding diatheses, and horizontal nystagmus) have also been discovered (e.g., *HSP1*, and *HSP3-7*).

GLOBAL CONSIDERATIONS

 The prevalence, clinical presentation, and natural history of most ILDs in European countries resemble that described in the United States. However, as expected, there is growing evidence for racial differences in clinical (rate of acute exacerbations) or genetic (*MUC5B*) attributes between Caucasian and Asian populations. To date there are limited data on the prevalence of ILD in Hispanics, subjects of African descent and many other ethnic groups.

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