Diagnosis

Few patients with CF are diagnosed as adults. Adults diagnosed with CF most often present with pulmonary or gastrointestinal symptoms. Pulmonary manifestations often include chronic productive cough, recurrent sinusitis, and recurrent pulmonary infections requiring several courses of antibiotics. For those with gastrointestinal symptoms, loose and frequent stools with abdominal pain are the most common. Pancreatic insufficiency (either endocrine or exocrine) may occur but is less common. Chronic, persistent pulmonary or gastrointestinal symptoms requiring repetitive treatment should raise suspicion for CF. Radiographic findings of upper lobe–predominant with mucoid impaction may be present.

Often the greatest challenge to making the diagnosis is failing to include CF in the differential diagnosis. A family history of CF can be quite helpful in this regard. Sweat chloride testing is the initial test for CF, although it is less sensitive in adults. Abnormal results on repeat testing are diagnostic of CF. DNA testing confirms the diagnosis and helps with prognosis. A negative sweat chloride test in an adult patient does not rule out disease. Therefore, if the clinical suspicion remains high after negative repeat sweat chloride testing, consideration for referral to a center with expertise in CF or genetic testing is appropriate.

KEY POINTS

- Adults diagnosed with cystic fibrosis most often present with pulmonary or gastrointestinal symptoms; pulmonary manifestations often include chronic productive cough, recurrent sinusitis, and recurrent pulmonary infections requiring several courses of antibiotics.
- A negative sweat chloride test in a patient who presents as an adult should not rule out cystic fibrosis.

Treatment

The pillars of CF management are airway clearance, antibiotic therapy, nutritional support, and psychosocial support. The primary objectives of CF treatment are maintaining lung health and controlling/minimizing the impact of CF-affected organ disease. The Cystic Fibrosis Foundation practice guidelines recommend use of chronic medications to improve lung function and reduce exacerbations. These medications include mucolytics, hydrating agents, inhaled antibiotics, oral macrolide antibiotics, and *CFTR* potentiators. The treatment of CF lung disease is experiencing a period of rapid evolution, and management is suboptimal unless it involves a multidisciplinary approach best provided at a CF care center.

Diffuse Parenchymal Lung Disease

Diffuse parenchymal lung diseases (DPLDs) are a group of disorders based on similar clinical, radiographic, physiologic, and pathologic changes that affect the alveolar walls and often the related small airways and distal pulmonary vasculature. Like other lung diseases, these disorders present primarily with shortness of breath. Imaging studies will typically demonstrate bilateral rather than unilateral lung disease. Although COPD and pulmonary hypertension affect the distal airways and vasculature, these are excluded from the category of DPLD.

Classification and Epidemiology

Although there are hundreds of disorders that can present with diffuse parenchymal lung disease, they are typically divided into those with a known cause or those which are idiopathic (**Table 12**). The updated classification of idiopathic interstitial pneumonia will be discussed below. A thorough history that defines the time course is a critical first step in making the diagnosis.

DPLD is uncommon, compared to other pulmonary diseases such as asthma or COPD. The true prevalence of DPLDs is unknown; however, the literature estimates the prevalence at approximately 70 per 100,000 persons, with idiopathic cause accounting for 30% to 40% of disease in these patients.

Diagnostic Approach and Evaluation

Nonproductive cough and dyspnea are the most common presenting symptoms of a DPLD. Dyspnea that comes on suddenly and is of short duration is more likely due to respiratory infection, asthma, pulmonary embolism, or heart failure than DPLD. In contrast, patients presenting with subacute or chronic dyspnea lasting weeks to months without response to treatment should be evaluated for DPLD. As opposed to the typical nonproductive cough of DPLD, a long history of cough with sputum production can suggest an underlying chronic infection, airways inflammation such as chronic bronchitis, or bronchiectasis.

When DPLD is suspected, questions should focus on determining the onset of symptoms, the disease course (improving or worsening), medications, and exposures. The most common identifiable etiologies of DPLDs are those associated with exposures, and the history should include a thorough review of occupations, home environment, hobbies, and other activities. Medication review should include current medications as well as those taken before the onset of symptoms.

Connective tissue diseases can lead to the development of DPLD; therefore, the review of systems should assess for symptoms of arthralgia, myalgia, arthritis, tenosynovitis, dry eyes, dry mouth, dysphagia, gastroesophageal reflux, and unexplained rash. A family history of DPLD due to connective tissue disease should substantially increase clinical suspicion.

Physical examination findings differ depending on the underlying cause of DPLD. In patients with connective tissue disorders, findings may include Raynaud phenomenon, skin

TABLE 12. Classification and Distinguishing Features of Select Forms of Diffuse Parenchymal Lung Disease

Known Causes	
Drug-induced	Examples: amiodarone, methotrexate, nitrofurantoin, chemotherapeutic agents (see www.pneumotox.com for a complete listing).
Smoking-related	"Smokers'" respiratory bronchiolitis characterized by gradual onset of persistent cough and dyspnea. Radiograph shows ground-glass opacities and thickened interstitium. Smoking cessation improves prognosis.
	Desquamative interstitial pneumonitis and pulmonary Langerhans cell histiocytosis are other histopathologic patterns associated with smoking and DPLD.
Radiation	May occur 6 weeks to months following radiation therapy.
Chronic aspiration	Aspiration is often subclinical and may exacerbate other forms of DPLD.
Pneumoconioses	Asbestosis, silicosis, berylliosis.
Connective tissue diseases	
Rheumatoid arthritis	May affect the pleura (pleuritis and pleural effusion), parenchyma, airways (bronchitis, bronchiectasis), and vasculature. The parenchymal disease can range from nodules to organizing pneumonia to usual interstitial pneumonia.
Systemic sclerosis	Nonspecific interstitial pneumonia pathology is most common; may be exacerbated by aspiration due to esophageal involvement; antibody to Scl-70 or pulmonary hypertension portends a poor prognosis. Monitoring of diffusing capacity for early detection is warranted.
Polymyositis/dermatomyositis	Many different types of histology; poor prognosis.
Other connective tissue diseases	Varying degrees of lung involvement and pathology can be seen in other forms of connective tissue disease.
Hypersensitivity pneumonitis	Immune reaction to an inhaled antigen; may be acute, subacute, or chronic. Noncaseating granulomas are seen.
Unknown Causes	
Idiopathic interstitial pneumonias	
Idiopathic pulmonary fibrosis	Chronic, insidious onset of cough and dyspnea, usually in a patient aged >50 years. Usual interstitial pneumonia pathology (honeycombing, bibasilar infiltrates with fibrosis). Diagnosis of exclusion.
Acute interstitial pneumonia	Dense bilateral acute lung injury similar to acute respiratory distress syndrome; 50% mortality rate.
Cryptogenic organizing pneumonia	May be preceded by flu-like illness. Radiograph shows focal areas of consolidation that may mimic infectious pneumonia or may migrate from one location to another.
Sarcoidosis	Variable clinical presentation, ranging from asymptomatic to multiorgan involvement. Stage 1: hilar lymphadenopathy. Stage 2: hilar lymphadenopathy plus interstitial lung disease. Stage 3: interstitial lung disease. Stage 4: fibrosis. Noncaseating granulomas are hallmark.
Rare DPLD with Well-Defined Features	
Lymphangioleiomyomatosis	Affects women in their 30s and 40s. Associated with spontaneous pneumothorax and chylous effusions. Chest CT shows cystic disease.
Chronic eosinophilic pneumonia	Chest radiograph shows "radiographic negative" heart failure, with peripheral alveolar infiltrates predominating. Other findings may include peripheral blood eosinophilia and eosinophilia on bronchoalveolar lavage.
Pulmonary alveolar proteinosis	Median age of 39 years, and males predominate among smokers but not in nonsmokers. Diagnosed using bronchoalveolar lavage, which shows proteinaceous material in and around alveolar macrophages. Chest CT shows "crazy paving" pattern.

DPLD = diffuse parenchymal lung disease.

thickening, sclerodactyly, malar rash, inflammatory arthritis, or tenosynovitis. Lung examination findings are variable and may be normal. This is more likely early in disease or in those with imaging findings of ground-glass opacity or micronodules. Decreased breath sounds and dullness to percussion may suggest a pleural effusion, which is atypical for many DPLDs. Wheezes may suggest small airways disease, while inspiratory dry "Velcro" crackles are more suggestive of fibrosis. In more severe disease there may be right heart strain on electrocardiography or evidence of right-sided heart failure with findings of jugular venous distention, peripheral edema, a pronounced pulmonic second sound, and an S_3. These findings are also suggestive of more long-standing disease.

The physical examination should include resting and exertional pulse oximetry. It is common for patients with DPLD to have normal resting pulse oximetry. However, because of reductions in the functional pulmonary capillary bed, individuals with DPLD will often demonstrate desaturation when ambulating. The desaturation may not require supplemental oxygen; however, desaturation of greater than 4% while ambulating is consistent with a diffusion limitation, which is a hallmark of interstitial lung disease.

Patients with a clinical suspicion of DPLD should undergo full pulmonary function testing, including lung volumes and DLCO. The vast majority of DPLDs have restrictive physiology. However, there are a few diseases that have obstruction or exhibit a combined obstructive and restrictive deficit. Simple spirometry has a limited role because it can only identify obstruction and may be normal in the setting of restriction or reduced DLCO.

Plain chest radiography is an appropriate initial test for the evaluation of dyspnea and cough in patients suspected of having DPLD. Chest radiography may show various findings in patients with DPLD, including diffuse reticular and reticulonodular patterns, increased septal line thickening, consolidation, pleural effusions with or without pleural calcification, bronchiectasis, and hilar or mediastinal lymphadenopathy. The chest radiograph can be normal in patients with minimal disease, and a normal chest radiograph does not rule out DPLD.

KEY POINTS

- Patients presenting with subacute or chronic symptoms of dyspnea lasting weeks to months without response to treatments should be evaluated for diffuse parenchymal lung disease.
- Patients with a clinical suspicion of diffuse parenchymal lung disease should undergo full pulmonary function testing, including lung volumes and DLCO.
- A normal chest radiograph does not rule out diffuse parenchymal lung disease.

High-Resolution CT Scanning

High-resolution CT (HRCT) scan of the chest (slice thickness 1-2 mm) is the best imaging study to identify abnormalities that can help diagnose the underlying disease (**Table 13**). When disease of the small airways is suspected, HRCT imaging should be obtained both on inspiration and on expiration to accentuate air trapping. Prone images may be helpful if there is subtle septal thickening posteriorly that can be difficult to

TABLE 13. Patterns of Disease Associated with a Diagnosis of Diffuse Parenchymal Lung Disease

Lung Disease	Imaging	Comments
Acute interstitial pneumonia	Diffuse ground glass with consolidation	Indistinguishable from ARDS but without a risk factor for ARDS
Organizing pneumonia	Patchy ground glass, alveolar consolidation, peripheral and basal predominance	Connective tissue diseases, infections, drug-related, or idiopathic
Idiopathic pulmonary fibrosis/usual interstitial pneumonia	Basal-predominant and peripheral-predominant septal line thickening with traction bronchiectasis and honeycomb changes	The usual interstitial pneumonia pattern can be seen in connective tissue disease, asbestosis, and chronic hypersensitivity pneumonitis; idiopathic pulmonary fibrosis is a diagnosis of exclusion
Nonspecific interstitial pneumonia	Ground glass, basal predominance	Idiopathic and common finding in connective tissue disease
Respiratory bronchiolitis	Centrilobular nodules and ground-glass opacity in an upper-lung predominant distribution	May be an asymptomatic finding in an active smoker
Desquamative interstitial pneumonia	Basal-predominant and peripheral-predominant ground-glass opacity with occasional cysts	
Hypersensitivity pneumonitis	Acute: ground-glass opacification; centrilobular micronodules that are upper- and mid-lung predominant	Acute: associated with flulike illness
	Chronic: mid- and upper-lung predominant septal lung thickening with traction bronchiectasis; usual interstitial pneumonia pattern may be seen	Chronic: often cannot identify a causative antigen
Sarcoidosis	Upper lobe-predominant; mediastinal and hilar lymphadenopathy; cystic changes including development of aspergilloma; small nodules oriented along bronchovascular bundles	Findings for sarcoidosis are often not specific; DPLD with diffuse mediastinal and hilar lymphadenopathy greater than 2 cm in size should raise suspicion

ARDS = acute respiratory distress syndrome; DPLD = diffuse parenchymal lung disease.

distinguish from dependent atelectasis. The findings on HRCT highly correlate with the histopathology identified on open lung biopsy. In fact, most of the time the diagnosis of idiopathic pulmonary fibrosis can be made without lung biopsy based on the results of HRCT.

Serologic Testing

Although the American Thoracic Society guidelines recommend screening all patients with DPLD with an antinuclear antibody (ANA), rheumatoid factor, and anti-cyclic citrullinated peptide antibodies, it is most appropriate in younger patients, in particular those younger than 40 years of age, patients with symptoms of an underlying rheumatologic disorder, and patients with a family history of autoimmune or rheumatologic disease. Standard serological testing for individuals who have no clinical evidence of autoimmune disease remains controversial. Additional serologic tests for connective tissue and vascular diseases should be based on history and physical examination. See MKSAP 18 Rheumatology for further discussion of testing for connective tissue disease.

Lung Biopsy

When pulmonary function tests and HRCT are insufficient for making the diagnosis, the physician must consider the risks and benefits of either a bronchoscopic or surgical lung biopsy, including the patient's general health and risk of intervention. Careful assessment of risk factors, alternate diagnostic strategies, and impact of the results of lung biopsy on treatment should be discussed within a multi-disciplinary team, including a thoracic radiologist, thoracic surgeon, and pulmonary specialist with expertise in DPLD. Although a bronchoscopic biopsy provides much less tissue than a surgical lung biopsy, it has a high yield for making a diagnosis of sarcoidosis and is typically performed as an outpatient procedure. Overall in-hospital mortality associated with a surgical lung biopsy (either thoracoscopic or open biopsy) for DPLD remains low for scheduled cases (1.7%), but is much higher for emergency cases (16%).

KEY POINTS

HVC

- The diagnosis of diffuse parenchymal lung disease can often be made based on high-resolution CT without a lung biopsy.
- Serologic testing for diffuse parenchymal lung disease is most appropriate in young patients, those with symptoms of rheumatologic disease, or those with a family history of rheumatologic conditions.

Diffuse Parenchymal Lung Diseases with a Known Cause

Smoking-Related Diffuse Parenchymal Lung Disease

There are several DPLDs that occur almost exclusively in individuals who are current smokers. Examples include respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and pulmonary Langerhans cell histiocytosis (PLCH). A history of smoking is also believed to be a risk factor for the development of idiopathic pulmonary fibrosis.

RB-ILD is the histopathologic diagnosis associated with the HRCT finding of centrilobular micronodular disease in current smokers. This diagnosis may incidentally be made in asymptomatic smokers undergoing low-dose CT lung cancer screening. DIP is characterized by alveolar filling with macrophages and is associated with ground-glass opacities on CT imaging, although this imaging finding is not specific for DIP. Patients with DIP typically are symptomatic with a dry cough and dyspnea.

PLCH, on the other hand, has diffuse thin walled cysts and several pulmonary nodules that are mid- and upper lung zone predominant on HRCT. PLCH can also be associated with the development of pulmonary hypertension. Demonstrating the presence of Langerhans cells with S100 or CD1a staining of tissue obtained by either transbronchial or open lung biopsy confirms the diagnosis.

On physiologic testing, RB-ILD may have combined restriction and obstruction, whereas DIP typically is associated with pure restrictive disease. PLCH often produces restrictive disease, but may have preserved total lung capacity and evidence of obstruction when significant cystic disease is present. DLCO is reduced in all of these conditions.

For all smoking-related DPLDs, the primary management is smoking cessation. The use of glucocorticoids for those with more severe smoking-related DPLD or who have quit smoking and have persistent symptoms is often attempted, but has uncertain treatment effect.

KEY POINTS

- Respiratory bronchiolitis-associated interstitial lung disease may be diagnosed in asymptomatic smokers based on high-resolution CT findings and pulmonary function testing.
- The primary management of all smoking-related diffuse parenchymal lung diseases is smoking cessation.

Connective Tissue Diseases

Individuals younger than 40 years of age who present with DPLD have a high prevalence of connective tissue disease (CTD). The review of systems should include a thorough review of rheumatologic symptoms. Signs and symptoms of CTD warrant serologic evaluation based on the most likely disorder. Ruling out this potential cause for DPLD is very important even in the older population, despite the lower prevalence of CTD, because of the implications for treatment with immunomodulating agents. Pulmonary abnormalities are extremely common in patients with rheumatoid arthritis and include bronchiolitis, organizing pneumonia, rheumatoid nodules, nonspecific interstitial

pneumonia (NSIP), and usual interstitial pneumonia (the same pathology that is seen with idiopathic pulmonary fibrosis). Furthermore, patients with rheumatoid arthritis treated with methotrexate are also at risk for possible drug-induced DPLD.

Patients with systemic sclerosis are at high risk for the development of lung disease, which is the leading cause of death in these patients. NSIP is the most common histopathologic diagnosis on lung biopsy, and HRCT imaging typically demonstrates findings of bilateral lower lobe ground-glass opacities with or without septal line thickening and traction bronchiectasis. The pathologic pattern of NSIP can occasionally be diagnosed in a patient before the development of systemic disease. Although cyclophosphamide has been shown to be of modest benefit, it has high toxicity and has been replaced by mycophenolate mofetil, which has similar efficacy and is better tolerated with decreased side effects. As a result, mycophenolate mofetil is considered first-line therapy for those with progressive DPLD and systemic sclerosis. For patients thought to have idiopathic NSIP, rheumatology consultation and evaluation for immunosuppressive treatment is appropriate.

KEY POINTS

- Pulmonary abnormalities are extremely common in patients with rheumatoid arthritis and can include bronchiolitis, organizing pneumonia, rheumatoid nodules, nonspecific interstitial pneumonia, and usual interstitial pneumonia.
- Patients with systemic sclerosis are at high risk for the development of lung disease, which is the leading cause of death in these patients.

Hypersensitivity Pneumonitis

Repetitive inhalation of antigens in a sensitized patient can result in hypersensitivity pneumonitis (HP), an immunologic response that results in noncaseating granulomas and peribronchial mononuclear cell infiltration with giant cells. The antigens are typically complex proteins, which can come from several sources including agricultural dusts, thermophilic fungi, and bacteria, but can also be some small-molecular-weight chemical compounds. There are three forms of HP, and they each present differently. The acute form, which is most easily identified, results after a large exposure to an inciting antigen. The patient will develop fevers, cough, and fatigue, typically within 12 hours of exposure. Chest radiography can demonstrate diffuse micronodular disease but may be normal. Physical examination will reveal inspiratory crackles. If a HRCT scan is performed, it will demonstrate diffuse centrilobular micronodules and ground-glass opacities (**Figure 5**). After removal from the offending antigen, symptoms will resolve within approximately 48 hours. The recurrence of symptoms if the patient is rechallenged is the hallmark of the disease.

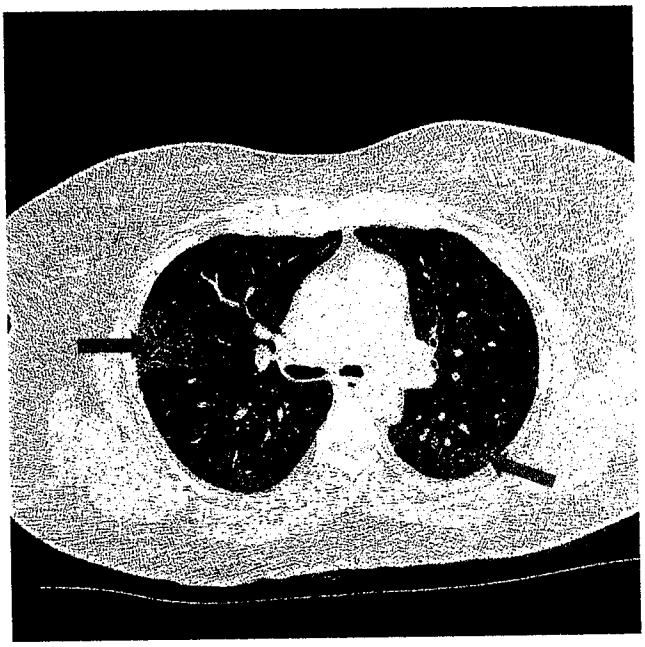

FIGURE 5. Chest CT scan demonstrating hypersensitivity pneumonitis with patchy, bilateral ground-glass opacities (*red arrow*) and centrilobular micronodules (*blue arrow*) in the mid-lung section.

Subacute and chronic forms of HP likely occur after more prolonged lower-level antigen exposure. Bird fanciers disease is an example of a chronic disorder. These patients have a chronic low-level exposure to avian antigens within the home and will ultimately experience cough, fatigue, weight loss, and shortness of breath. Similar to the acute form, the HRCT will show micronodules and ground-glass opacities, but there is also evidence of septal line thickening and fibrosis. In its most severe and chronic form, significant traction bronchiectasis and honeycomb changes will be evident. Evidence of severe fibrosis on CT imaging significantly increases the risk for progression of disease and death.

Removal of exposure to the offending antigen is essential in the treatment of HP. To identify potential antigens, careful history is vital, as serologic testing is often limited and may not include antibodies to the responsible antigen. Glucocorticoids are often used for those with more severe symptoms. Response to this therapy is variable. Prolonged glucocorticoid use is associated with significant side effects, and should be avoided without clear objective evidence of improved pulmonary function.

KEY POINTS

- The acute form of hypersensitivity pneumonitis is characterized by fever, cough, and fatigue within 12 hours of a major exposure to an inciting antigen; recurrence of symptoms with rechallenge is the hallmark of acute hypersensitivity pneumonitis.
- Removal of exposure to the offending antigen is essential in treatment of hypersensitivity pneumonitis.

Drug-Induced Diffuse Parenchymal Lung Disease

Many medications have been implicated in the development of DPLD (**Table 14**). A review of medications should include those that are new and those taken for prolonged periods because the duration of exposure to the development of disease can vary, even for the same agent. For instance, amiodarone lung toxicity has an acute form consistent with acute lung injury/acute respiratory distress syndrome, and a chronic indolent form with reticular abnormalities and subpleural nodules. Prompt treatment by removal of the offending agent is important for resolution of symptoms. For those with more severe symptoms, glucocorticoids may have some benefit, although data are anecdotal.

Radiation Pneumonitis

Radiation pneumonitis typically occurs 4 to 12 weeks after initial radiation exposure. Patients present with cough, shortness of breath, and a new radiographic infiltrate. Fever, pleuritic chest pain, fatigue, and weight loss are accompanying nonspecific symptoms. Differential diagnosis often includes infection and drug-induced lung injury. HRCT will demonstrate ground-glass opacities, usually within the field of

TABLE 14. Select Drug-Induced Parenchymal Lung Diseases

Drug	Clinical Points	Radiographic Findings and Treatment
Amiodarone	More common in: Older patients Increased dosage and higher cumulative dose First year of therapy (but can occur late)	Multiple radiographic presentations possible, including ground-glass opacities, subpleural nodules, and reticular abnormalities Very long half-life prevents clearance from the pulmonary parenchyma: Rare improvement with discontinuation of the drug alone High risk of recurrence with tapering of glucocorticoids
Methotrexate	Occurs in less than 5% of treated patients Unpredictable time to presentation No clear correlation between dose and disease severity	Diffuse reticular and ground-glass attenuation Patients generally do well after stopping medication. Glucocorticoids are often given and duration is based on response.
Nitrofurantoin	Acute (more common): Fevers, chills, cough, shortness of breath, chest pain; rash can occur in 10%-20% of patients. Peripheral eosinophilia common Chronic: Distinct from the acute form Onset months to years after prolonged exposure	Acute: Faint bilateral lower lobe septal lines; moderate pleural effusions may be present. Treatment: Often will resolve with discontinuation but will recur with repeat exposure. Chronic: Reticular opacities with subpleural lines and thickened peri-bronchovascular areas. Treatment: Possible benefit of glucocorticoids from anecdotal reports.
Busulfan	Occurs in less than 8% of treated patients. Currently used solely as a conditioning regimen for HSCT; often combined with other agents associated with pulmonary toxicity. Injury typically occurs 30 days to 1 year after exposure.	Multiple patterns including: ground glass opacities, reticulation, bibasilar septal lines, asymmetric peripheral and peribronchial consolidation, centrilobular nodules, and dependent consolidation Optimal treatment unknown and is often supportive. Glucocorticoids may be used for more progressive disease.
Bleomycin	Risk significantly increases with cumulative dose. Increased age, renal insufficiency, concomitant chemotherapy and/or radiation also increases risk of toxicity. Typically subacute presentation 1-6 months after exposure; may resemble hypersensitivity pneumonitis but with more rapid onset and progressive course.	Imaging patterns suggest the multiple possible pathologic findings seen: Consolidation with ground glass (diffuse alveolar damage) Septal line thickening, traction bronchiectasis, and honeycomb change (end-stage fibrosis) Patchy ground glass with subpleural consolidation or peribronchial consolidation (organizing pneumonia) Diffuse ground glass with centrilobular micronodules (hypersensitivity pneumonitis) Glucocorticoids are used for more severe disease and disease may recur with tapering of steroids.

HSCT = hematopoietic stem cell transplantation.

radiation exposure. A well-defined nonanatomic demarcation between normal and abnormal lung consistent with the radiation field is pathognomonic but not always present. Radiographic abnormalities, such as organizing pneumonia, may also be seen outside the field of exposure and can be nodular or alveolar. Treatment of radiation pneumonitis is typically glucocorticoids for severe disease with more extensive abnormalities on imaging, respiratory symptoms, or with hypoxemia. Observation may be appropriate for those with mild disease. From 6 to 12 months after radiation exposure, additional findings on HRCT may develop, including septal line thickening, traction bronchiectasis, and volume loss more consistent with chronic fibrosis. In addition, individuals exposed to radiation are at risk for the development of radiation-recall pneumonitis, which can occur when exposed to select chemotherapy agents including adriamycin, etoposide, gemcitabine, paclitaxel, and pemetrexed.

KEY POINTS

- Radiation pneumonitis typically presents 4 to 12 weeks after initial radiation exposure, with cough, shortness of breath, and a new radiographic infiltrate.
- Treatment of severe forms of radiation pneumonitis typically is glucocorticoids, whereas observation may be appropriate for those with mild disease.

Diffuse Parenchymal Lung Diseases with an Unknown Cause

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), which is associated with the histopathologic appearance of usual interstitial pneumonia (UIP), is the most common idiopathic form of DPLD. It typically presents in patients between 50 and 70 years of age who have a greater than 6-month duration of a dry cough and dyspnea on exertion. History will reveal no potential cause for the development of fibrosis, and lung examination is notable for Velcro inspiratory crackles that are predominant at the bases and may be subtle in early disease. Clubbing is present in up to 50% of patients and should raise suspicion for IPF. The diagnosis of IPF is challenging because it is uncommon and indolent. Because smoking is a risk factor, patients are often treated for COPD without significant improvement. Similarly, crackles on examination may lead to management for presumed heart failure. Chest radiographs may demonstrate bibasilar septal line thickening with reticular changes, and volume loss and bronchiectasis when the disease is more severe. The best diagnostic test is HRCT, which may show abnormalities, such as bilateral, peripheral, and basal predominant septal line thickening with honeycomb changes, when the chest radiograph is normal (**Figure 6**). When HRCT is consistent with UIP, lung biopsy may not be necessary for diagnosis.

IPF is progressive, with a median survival of 3 to 5 years after diagnosis. The progression of disease, however, is variable

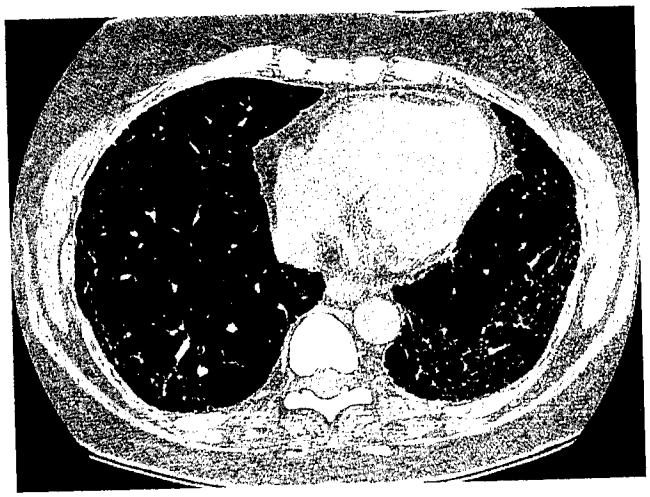

FIGURE 6. High-resolution chest CT demonstrating the typical findings in idiopathic pulmonary fibrosis, including increased reticular changes that are predominantly peripheral and basilar in distribution, honeycombing (at the left base), and absence of significant ground-glass opacification.

and may be associated with periods of stability with intermittent periods of acute decline. A subset of patients develop an acute exacerbation with a worsening of symptoms, typically of less than 1 month's duration, and associated new findings on chest CT of bilateral ground-glass opacities after having relatively stable disease over time. These events can be "triggered" by an inciting event such as an infection or may be "idiopathic." Heart failure and volume overload should be excluded as causes of the radiographic changes or clinical decompensation.

An important aspect of treatment of IPF includes optimum management of comorbidities such as obesity, heart failure, and deconditioning. Sleep-disordered breathing is common in this population due to nocturnal hypoxemia and increased prevalence of obstructive sleep apnea. Treatment of hypoxemia includes supplemental oxygen with exertion and at rest as needed based on pulse oximetry testing. For those with deconditioning, pulmonary rehabilitation has demonstrated benefits in exercise tolerance and quality of life in several small studies. In progressive and severe disease, pulmonary hypertension and right-sided heart failure are commonly observed. One preliminary study suggesting improvement in quality of life with sildenafil needs further study before recommending its use in this population.

In 2014, two FDA-approved therapies, nintedanib and pirfenidone, became available. Both therapies target the fibroblast, which is considered central in the progression of fibrosis. Although the mechanisms of these two medications differ, clinical response is quite similar, with both demonstrating a decline in the rate of progression of disease. Although these medications delay IPF progression, they are not curative. Referral to a pulmonologist or interstitial lung disease (ILD) center may be appropriate before initiating treatment with these medications.

H CONT. Lung transplantation is a life-prolonging therapy for those without comorbidities that may otherwise limit life expectancy. Typically, transplant centers exclude those with untreatable end-organ damage outside the lungs. Early referral of eligible patients to a transplant center is appropriate given the unpredictability of disease progression.

The most common cause of death in patients with IPF is respiratory failure. In patients with respiratory failure, the need for mechanical ventilation portends an extremely poor prognosis. As a result, consensus-based guidelines recommend against mechanical ventilation for IPF patients if lung transplantation is not an option. Palliative care consultation to establish advanced care plans should be considered for patients with IPF who are not candidates for lung transplantation and who have a severe exacerbation and poor performance status. Ideally, advance care planning, including end-of-life goals of care and palliative strategies, should be decided before urgently facing the decision of whether to begin mechanical ventilation in the setting of respiratory failure. H

KEY POINTS

- FDA-approved therapy with nintedanib and pirfenidone decreases the rate of progression of idiopathic pulmonary fibrosis but is not curative.
- HVC Consensus-based guidelines recommend against mechanical ventilation for patients with idiopathic pulmonary fibrosis if lung transplantation is not an option.

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is the most common DLPD associated with autoimmune disorders, but it can occasionally be idiopathic and not associated with an underlying connective tissue disease. There are two forms of NSIP: cellular and fibrotic. The fibrotic form has a worse prognosis and is poorly responsive to treatment. The cellular form has a better prognosis and will typically respond to immunosuppressive treatments. Although the overall prognosis is better than for IPF, the 5-year mortality of idiopathic NSIP remains approximately 15% to 25%. Individuals with progressive decline in pulmonary function are at increased risk of death regardless of the underlying pathology. Similar to IPF, select patients may benefit from lung transplantation. NSIP affects a younger population than IPF. HRCT will demonstrate bilateral lower-lobe reticular changes and an absence of honeycombing, but can also demonstrate areas of ground-glass opacification. These findings on HRCT have been associated with systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, and polymyositis, as well as undifferentiated connective tissue disease. Because idiopathic NSIP is rare, a thorough investigation for an underlying autoimmune disorder is essential. NSIP was common in patients with AIDS in the pre-antiretroviral therapy era; however, it is much less common since the advent of antiretroviral therapy.

KEY POINTS

- Nonspecific interstitial pneumonia is the most common diffuse parenchymal lung disease associated with autoimmune disorders.
- Bilateral lower-lobe reticular changes and an absence of honeycombing on high-resolution CT scan, often accompanied by areas of ground-glass opacification, have been associated with systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, and polymyositis, as well as undifferentiated connective tissue disease.

Cryptogenic Organizing Pneumonia

Organizing pneumonia is defined by histopathologic findings of patchy proliferation of granulation tissue that affects the terminal bronchiole, and alveolar ducts and spaces, and is associated with surrounding inflammation. This pattern often follows or is associated with various types of injury to the lung, including acute infection, radiation exposure, drug-induced pneumonitis, and autoimmune diseases. In patients in whom no cause is identified, the diagnosis is termed cryptogenic organizing pneumonia (COP).

Patients with COP typically present with cough, fever, and malaise for 6 to 8 weeks. Initial chest radiographs will demonstrate patchy opacities that mimic pneumonia and, as a result, patients are often initially misdiagnosed with community-acquired pneumonia and treated with standard antibiotics (**Figure 7**). However, nonresolving symptoms and failure to respond to antibiotics should raise suspicion for organizing pneumonia or COP. HRCT imaging will demonstrate ground-glass opacities or areas of alveolar consolidation resembling an infectious pneumonia, but findings can include peripheral nodules and nodules along the bronchovascular bundle. The diagnosis may not require lung biopsy if the clinical presentation and HRCT findings are consistent with COP. For cases with atypical presentation, lung biopsy may be necessary to make the diagnosis. H H

Patients with COP typically respond to glucocorticoid therapy. In organizing pneumonia associated with an autoimmune disorder, treatment should focus on the autoimmune condition. Relapses of COP with tapering of glucocorticoids are common, and therefore a long taper of glucocorticoids or transition to alternate immunosuppressive therapy should be considered.

KEY POINTS

- Patients with cryptogenic organizing pneumonia typically present with complaints of cough, fever, and malaise for 6 to 8 weeks, which may mimic community-acquired pneumonia.

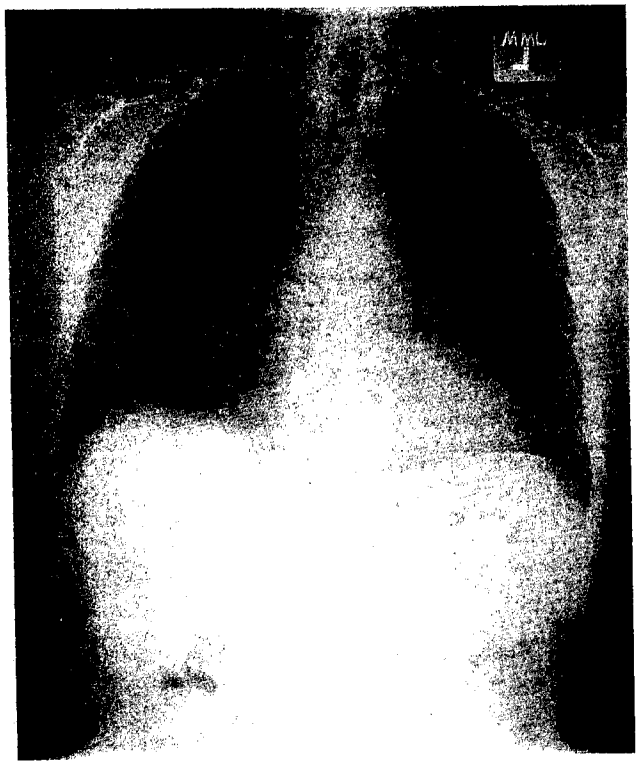

FIGURE 7. Chest radiograph showing cryptogenic organizing pneumonia, demonstrating multiple patchy bilateral alveolar opacities that are nonspecific and may be difficult to distinguish from more typical infectious pneumonia. Infiltrates may be migratory, with resolution of established opacities as new areas appear on serial imaging. Imaging may also be nonspecific, showing interstitial infiltrates and alveolar opacification or one or more rounded nodules that may be interpreted as malignancy.

Acute Interstitial Pneumonia

Acute interstitial pneumonia develops rapidly during days to weeks, resulting in acute respiratory failure with bilateral alveolar opacities on HRCT of the chest consistent with pulmonary edema. The pathologic findings on open lung biopsy are those of diffuse alveolar damage. This process is clinically, radiographically, and pathologically indistinguishable from acute respiratory distress syndrome. The differentiating factor is the lack of risk factors for the development of acute respiratory distress syndrome. The history should carefully assess any history of aspiration, sepsis, or inhalational exposure that could result in acute lung injury.

Management includes supportive care, as for other patients with acute lung injury or acute respiratory distress syndrome. This includes low tidal volume ventilation if required and critical care management to avoid complications of illness. Although glucocorticoids are often used, there is little evidence other than case reports of improvement with their use. Mortality remains high (approximately 50%), and those who recover from the initial illness often have complications, are at risk for the development of chronic lung disease, and may have a relapse. Long-term management of these patients includes consideration of immunosuppression; however, there are limited data to guide therapy.

- Acute interstitial pneumonia is clinically, radiographically, and pathologically indistinguishable from acute respiratory distress syndrome; the differentiating point is the lack of risk factors for the development of acute respiratory distress syndrome.

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown cause that can affect several organ systems. Greater than 90% of patients with sarcoidosis have lung involvement. The prevalence of sarcoidosis is approximately 10 to 20 per 100,000 individuals. Sarcoidosis affects blacks more frequently than whites and typically occurs in younger patients. Many patients are asymptomatic, and lung involvement is incidentally found on chest radiography done for other reasons (**Figure 8**). Findings from chest radiography can help predict the probability of spontaneous resolution (**Table 15**). CT scanning can show pulmonary parenchymal disease or intrathoracic lymphadenopathy, either alone or in combination. Although there are various appearances of sarcoidosis on chest CT scanning, a particularly characteristic finding is the presence of small nodules alongside bronchovascular bundles.

Pulmonary function testing is typically abnormal and findings can be obstructive, restrictive, or both. Sarcoidosis is a diagnosis of exclusion. Diagnosis, with a few exceptions (**Table 16**), typically requires bronchoscopic biopsy, with tissue obtained from a lymph node or from the pulmonary

FIGURE 8. Chest radiograph showing stage I pulmonary sarcoidosis with hilar lymphadenopathy and normal lung parenchyma.

TABLE 15. Chest Radiograph Staging of Pulmonary Sarcoidosis

Stage	Radiographic Pattern	Clinical Course and Comments
0	Normal	
I	Hilar lymphadenopathy with normal lung parenchyma	>90% will have spontaneous resolution without treatment
II	Hilar lymphadenopathy with abnormal lung parenchyma	Approximately 50% rate of spontaneous improvement without treatment
III	No lymphadenopathy with abnormal lung parenchyma	Approximately 20% rate of spontaneous improvement without treatment
IV	Parenchymal changes with fibrosis and architectural distortion	

TABLE 16. Clinical Presentations of Sarcoidosis that Do Not Require a Biopsy

Syndrome	Additional Findings/Symptoms
Asymptomatic bilateral hilar lymphadenopathy	No evidence of fevers, malaise, or night sweats to suggest a malignancy
Löfgren syndrome	Bilateral hilar lymphadenopathy, migratory polyarthralgia, erythema nodosum, and fever
Heerfordt syndrome	Anterior uveitis, parotiditis, fever (uveoparotid fever), and facial nerve palsy

H CONT.

parenchyma. The diagnosis is made by the finding of noncaseating granulomas with exclusion of potential mimicking infections (mycobacteria, fungi), exclusion of other systemic granulomatous diseases, and ideally with involvement of more than one organ system.

Pulmonary hypertension may develop through several different mechanisms, including chronic hypoxemia, destruction of the capillary bed resulting in severely reduced capillary surface area, granulomatous inflammation of the pulmonary arteries, compression of pulmonary arteries secondary to contiguous lymphadenopathy, pulmonary veno-occlusion from granulomatous inflammation, and left ventricular dysfunction from cardiac involvement. Development of pulmonary arterial hypertension is a poor prognostic indicator, with a median survival of approximately 3 years.

The primary treatment of sarcoidosis is glucocorticoids, although many patients do not need to be treated. In addition, spontaneous resolution without treatment is common and related to the radiographic stage of disease (see Table 15). The decision to treat and assessment of response should be based on symptoms and organ dysfunction, not radiographic findings. For those without symptoms or organ dysfunction, observation is appropriate. If treatment is required, low- to medium-dose glucocorticoid therapy, often on alternate days, is appropriate. Short-term symptomatic benefit is clear from retrospective study data; however, long-term benefits remain less clear. For patients with more severe or prolonged symptoms, side effects from chronic glucocorticoids should be considered. In this setting, adjunctive glucocorticoid-sparing therapies are often used. Pulmonary consultation should be considered for management of persistent disease. For patients with pulmonary hypertension or severe disease with significant activity limitation due to lung disease, evaluation for lung transplantation is appropriate. C

KEY POINTS

- Greater than 90% of patients with sarcoidosis have lung involvement; radiographic staging can predict the probability of spontaneous resolution.
- The primary treatment of symptomatic sarcoidosis is glucocorticoids.

Occupational Lung Disease

When to Suspect an Occupational Lung Disease

Occupational lung disease can affect any part of the respiratory tract, including sinuses, airways, the lung parenchyma, and the surrounding pleura. As a result, signs and symptoms associated with occupational exposure include rhinitis, reactive airways disease, COPD, pleural disease, diffuse parenchymal lung disease, and malignancy. Occupational lung diseases can present acutely, subacutely, or slowly after many years of exposure. As a result, these diseases require that clinicians maintain suspicion for and obtain a careful history of occupational exposures. Clinical presentations related to silica and asbestos exposures are well characterized and recognized. However, new agents that may lead to respiratory diseases are frequently introduced in industry. Factors suggesting an underlying occupational lung disease include patient concerns about an exposure, a temporal association with an exposure, unexplained signs or symptoms, and evidence of coworkers with similar symptoms (**Table 17**). In addition, patients may experience relief of symptoms when away from the work environment and recurrence of symptoms upon their return. For the patient with occupational lung disease, similar to diffuse parenchymal lung disease, cough and dyspnea on exertion are common.