

V CHRONIC DIFFUSE INFILTRATIVE LUNG DISEASE

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Chronic diffuse infiltrative lung disease encompasses a wide variety of disorders that primarily affect the alveoli and lung interstitium; involvement of the airways and the pulmonary vasculature is secondary to the interstitial process.

Chronic diffuse infiltrative lung disease affects a surprisingly large proportion of the population. A study from New Mexico suggests a prevalence of 81 cases per 100,000 in males and 67 cases per 100,000 in females. Pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF) are the most common diagnoses.¹ In the United States, some of these disorders are more common in ethnic minorities, though data are incomplete.²

Pathogenesis

Certain pathogenetic mechanisms of lung injury may affect the development of diffuse infiltrative lung disease. In animal studies, several causative agents (e.g., bleomycin, paraquat, radiation, and cyclophosphamide) have been shown to produce a pattern of injury that resembles common idiopathic varieties of the disorder.³ In these models, there is initial damage to type I epithelial and capillary endothelial cells. After a phase of edema and mild hemorrhage, sometimes with extravascular fibrin accumulation, there is an influx of neutrophils. Newly recruited lymphocytes and macrophages appear a few days later. Under the influence of various growth factors, the type II cells replicate and spread out, replacing the damaged type I epithelial cells. Within 2 weeks, collagen, elastin, and other extracellular matrix components are present, and eventually, extensive lung fibrosis becomes evident. A combination of environmental exposures and genetic susceptibility may play a significant role in the pathogenesis of the disease.⁴ Variations in this common pathway lead to the specific diseases discussed in this subsection.

Approach to the Patient with Suspected Chronic Diffuse Infiltrative Lung Disease

Although more than 100 causes of diffuse infiltrative lung disease have been described, a smaller group of causes accounts for the vast majority of cases. Given the nonspecificity of the clinical, radiographic, and sometimes even pathologic features, the differential diagnosis should be approached carefully.⁵ In all cases, a history and physical examination should be performed, a chest radiograph should be taken, and pulmonary function should be evaluated. Although such measures often do not lead to a definitive diagnosis, they help determine the likeliest causes in a given case and thus serve to markedly limit the diagnostic possibilities, thereby reducing costs and effort of further studies.

PRESENTING SYMPTOMS AND PATIENT HISTORY

The most common presenting complaints in diffuse infiltrative lung disease are dyspnea of gradual onset—initially with extreme exertion—and nonproductive cough. Chest pain and hemoptysis are uncommon except in specific disorders.

The history should include careful questioning as to the duration of symptoms—usually cough or dyspnea. Often, symptoms have been present for many months or even years, which would render an infectious cause very unlikely. In contrast, a more rapidly evolving course, over days to weeks, increases concern about infection. Exclusion of infection as the cause of diffuse infiltrative lung disease is of paramount importance because of the need for specific antimicrobial therapy and because many noninfectious causes of this disorder are treated with glucocorticoids. Fever may be observed in several noninfectious types of diffuse infiltrative lung disease (e.g., sarcoidosis, hypersensitivity pneumonitis, collagen vascular disease, and drug-induced disease), but its presence should always alert the clinician to the possibility of infection. Infectious diffuse infiltrative lung disease that evolves subacutely over weeks to months is rarely caused by common viral or bacterial organisms. On the other hand, mycobacterial and pathogenic fungal infections (e.g., histoplasmosis, coccidioidomycosis, and blastomycosis) can present subacutely and are usually associated with fever. Perhaps the most common infectious cause is *Pneumocystis carinii* pneumonia (PCP) in a patient with AIDS. AIDS-related PCP may present as dyspnea that evolves slowly over many weeks, occasionally without fever or other evidence of systemic toxicity; this pattern may resemble that of common noninfectious causes of diffuse infiltrative lung disease. A careful history regarding risk factors for HIV infection is a critical part of the evaluation of all patients with recent-onset diffuse infiltrative lung disease.

In addition to establishing the duration of illness and the presence or absence of fever and other systemic complaints, the history should focus on the patient's occupation and medications. Many different occupational exposures can lead to diffuse infiltrative lung disease, but most are rarely encountered in clinical practice. Occupation-related varieties are caused by exposure to the inorganic dusts, such as asbestos and silica, or to organic dusts that cause hypersensitivity pneumonitis. Asbestosis typically becomes evident many years after exposure, so in taking the history, it is important to note the patient's prior occupations. The most common cause of occupation-related hypersensitivity pneumonitis is farmer's lung, which primarily affects dairy farmers. A farmer should be questioned carefully about any relation between respiratory or systemic symptoms and exposure to organic material (moldy hay or grain) that may contain thermophilic actinomycetes. The history should also include questions about possible exposure to pigeons or pet birds and to humidifiers, because such exposure can result in hypersensitivity pneumonitis [see Table 1].

Many drugs have been reported to cause diffuse infiltrative lung disease. A history should focus on both prescribed and over-the-counter medications and should include questions about medications taken during the preceding weeks or months [see Table 2].

Finally, the history should seek to determine whether there have been symptoms that indicate the presence of an underlying collagen vascular disease or vasculitis. A history that reveals the prior occurrence of Raynaud phenomenon, photosensitivity, skin rashes, or arthritis carries great diagnostic relevance.

Table 1 Common Causes of Hypersensitivity Pneumonitis

<i>Disease</i>	<i>Antigen Source</i>	<i>Probable Antigen(s)</i>
Farmer's lung	Moldy hay	Thermophilic actinomycetes, <i>Micropolyspora faeni</i> , <i>Thermoactinomyces vulgaris</i>
Bagassosis	Moldy pressed sugarcane (Bagasse)	Thermophilic actinomycetes, <i>T. sacchari</i> , <i>T. vulgaris</i>
Multiple bird handler's diseases	Bird droppings, products, and feathers	Bird proteins
Laboratory worker's lung	Rat fur	Rat urine proteins
Diisocyanates and trimellitic anhydrides	Chemical exposures	Altered proteins
Ventilator lung	Contaminated humidifiers, dehumidifiers, air conditioners, and heating systems	Thermophilic actinomycetes, <i>T. candidus</i> , <i>T. vulgaris</i> , <i>Penicillium</i> species, <i>Amoeba</i> species, <i>Klebsiella</i> species, and <i>Candida</i> species

PHYSICAL EXAMINATION

The physical examination has less diagnostic utility than the history but is important nonetheless. Collagen vascular disorders may be suggested by detection of synovitis, telangiectasia, sclerodactyly, or a malar rash. Sarcoidosis also involves extrapulmonary organs and should be suspected if uveitis, erythema nodosum, or plaque-like skin lesions consistent with cutaneous sarcoidosis are detected. Malignant diffuse infiltrative lung disease (i.e., lymphangitic spread) may be associated with findings relevant to the primary tumor, such as an abdominal or breast mass, hepatomegaly, or guaiac-positive stools. Finally, cardiovascular examination is very important because on occasion, chronic pulmonary venous congestion resulting from occult mitral stenosis or left ventricular failure may present as diffuse infiltrative lung disease.

LABORATORY EXAMINATION

The laboratory examination comprises studies that are more or less routine (e.g., complete blood count, biochemical screening) and those that are more specialized. Sarcoidosis may be suggested by cytopenias if the bone marrow is involved or by the presence of hypercalcemia or elevated serum liver enzyme levels. Collagen vascular disease and malignancy may also result in cytopenias. Peripheral eosinophilia would suggest chronic eosinophilic pneumonia. Uncommonly, eosinophilic granuloma pre-

sents as a diffuse pulmonary disorder together with laboratory evidence of diabetes insipidus.

Additional laboratory tests, such as autoimmune serology and determination of angiotensin-converting enzyme (ACE) level, may prove useful, depending on the clinical and radiographic features in a given case. Antinuclear antibodies or rheumatoid factor is usually present in the serum of patients with collagen vascular disorders, but it is also found in low titer in up to 50% of patients with IPF. Increased serum levels of ACE are suggestive of sarcoidosis, but ACE can also be elevated in miliary tuberculosis, berylliosis, asbestosis, and silicosis. Hypersensitivity pneumonitis is nearly always associated with the presence of serum antibody against the offending antigen. However, the presence of antibody against one of the causative agents of hypersensitivity pneumonitis in serum does not prove that hypersensitivity pneumonitis is the cause of diffuse infiltrative lung disease but only that there has been sufficient exposure to the antigen to elicit an immunologic response. Resolution of pneumonitis with disappearance of antibody after stopping the exposure provides a more conclusive association.

CHEST RADIOGRAPHY

Radiographic features are for the most part nonspecific. Diffuse infiltrative lung disease may be characterized by bilaterally

Table 2 Drugs That Commonly Induce Chronic Parenchymal Lung Disease

<i>Category</i>	<i>Drugs</i>	<i>Notes</i>
Chemotherapeutic agents	Bleomycin Busulfan Cyclophosphamide Vinblastine Nitrosoureas	Dose related, worse with O ₂ Induces pulmonary fibrosis, with high mortality and occasionally alveolar proteinosis Variable onset and course Synergistic with mitomycin-C Dose related, delayed onset
Cardiovascular drugs	Amiodarone Hydralazine, others	Long half-life, induces ARDS after procedures Induce SLE
Anti-inflammatory drugs	Methotrexate Penicillamine Gold	Produces granulomas, as found on biopsy Induces Goodpasture-like syndrome, SLE, bronchiolitis obliterans Injectable only; induces BAL lymphocytosis
Antibiotics	Nitrofurantoin Sulfasalazine	Induces acute and chronic parenchymal lung disease BOOP, PIE, or pulmonary fibrosis
Illicit drugs	Methylphenidate Cocaine	I.V. injection produces talc granulomas Induces BOOP, alveolar hemorrhage

ARDS—acute respiratory distress syndrome BAL—bronchoalveolar lavage BOOP—bronchiolitis obliterans organizing pneumonia PIE—peripheral eosinophilia

symmetrical interstitial, alveolar, or mixed alveolar-interstitial radiographic patterns. In some cases, the lung fields appear completely normal on the chest radiograph despite the presence of significant clinical and physiologic abnormalities. There are certain ancillary radiographic clues that, if present, may help in making the differential diagnosis and in narrowing the list of possible causes [see Table 3].

HIGH-RESOLUTION COMPUTED TOMOGRAPHY

The use of high-resolution computed tomography (HRCT) represents a significant advance in the evaluation of diffuse parenchymal lung disease. With the use of HRCT, the extent, location, and pattern of lung involvement can be determined with great accuracy [see Figure 1]. HRCT can often detect abnormalities in patients who have symptoms of interstitial lung disease but whose chest radiographs are normal. When combined with clinical data and chest radiography, HRCT of the chest can lead to a specific diagnosis in 60% to 80% of cases.⁶ When HRCT indicates a specific diagnosis (e.g., eosinophilic granuloma), the need for a lung biopsy is eliminated.⁵

PULMONARY FUNCTION TESTING

Pulmonary function testing provides diagnostic clues to the presence of diffuse infiltrative lung disease and is useful during the course of the disease. The hallmarks of the disorder include a restrictive ventilatory pattern (reduced lung volume), a normal or increased ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC), a reduction in the diffusing capacity of the lung for carbon monoxide (DL_{CO}), and a reduction in arterial oxygen tension (P_aO_2) associated with normal or reduced arterial carbon dioxide tension (P_aCO_2). In addition, there is usually significant exercise limitation resulting from a fall in P_aO_2 , abnormalities in respiratory mechanics, associated pulmonary vascular disease, or a combination of these factors.

BRONCHOALVEOLAR LAVAGE

In most cases, the cause of lung disease remains uncertain despite careful clinical, radiographic, laboratory, and physiologic evaluation. The next step is usually to perform bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsy. Certain causes can be diagnosed solely by BAL, others only by biopsy, and some by either technique. BAL is most useful for diagnosing infectious causes, especially PCP. The diagnostic sensitivity of this procedure for AIDS-related PCP is approximately 90% to 95%. Thus, it is the procedure of choice for diagnosing the 20% to 50% of cases of AIDS-related PCP that cannot be diagnosed

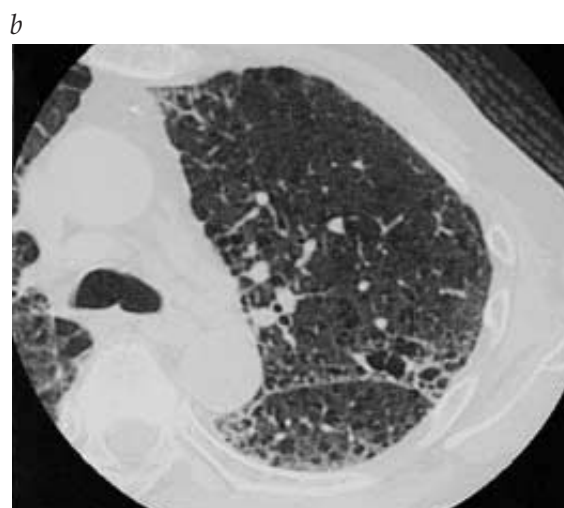


Figure 1 High-resolution computed tomography (HRCT) in patients with chronic diffuse interstitial lung disease can occasionally suggest a specific diagnosis. (a) Posteroanterior radiography demonstrates a diffuse interstitial process, but differential diagnosis is lengthy. (b) HRCT shows a combined interstitial and cystic process that is virtually diagnostic of eosinophilic granuloma of the lung.

Table 3 Radiographic Clues to Diagnosis of Diffuse Infiltrative Lung Disease

Associated Radiographic Finding	Primary Diagnostic Considerations
Hilar adenopathy	Sarcoidosis, lymphoma, carcinoma, granulomatous infection
Pleural effusion	Collagen vascular disease, asbestosis, lymphangiomatosis (chylous), tuberculosis
Pneumothorax	Eosinophilic granuloma, <i>Pneumocystis carinii</i> pneumonia, lymphangiomatosis
Upper lung zone predominance	Silicosis, eosinophilic granuloma, sarcoidosis
Peripheral predominance	Eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia, drug-induced injury

by induced sputum examination. Other opportunistic infections, such as cytomegalovirus pneumonia and disseminated fungal or tuberculous infection, can also be diagnosed by BAL. Noninfectious causes that can be diagnosed by this technique include alveolar proteinosis, lymphangitic carcinomatosis, and alveolar cell carcinoma. In addition, BAL may provide helpful information by revealing one of the following changes: (1) increased numbers of eosinophils in chronic eosinophilic pneumonia, (2) asbestos bodies in asbestosis, (3) so-called foamy cells with lamellar inclusions in amiodarone-induced disease, (4) hyperplastic and atypical type II pneumocytes in cytotoxic drug-induced lung injury, (5) Langerhans cells in eosinophilic granuloma, and (6) a bloody effluent with abundant hemosiderin in alveolar macrophages in diffuse alveolar hemorrhage. Quantitating the number and distribution of inflammatory cells (e.g., macrophages, lymphocytes, and neutrophils) may suggest a specific diagnosis.⁷ The alveolar lavage

Table 4 Diagnostic Efficacy of Transbronchial Lung Biopsy

Diseases Frequently Diagnosed by TLB Findings

Infectious diffuse infiltrative lung disease
Sarcoidosis
Lymphangitic carcinoma
Alveolar cell carcinoma
Talc-induced diffuse infiltrative lung disease

Diseases Suggested by TLB Findings

Cytotoxic-induced disease
Bronchiolitis obliterans organizing pneumonia (occasionally)
Eosinophilic pneumonia
Hypersensitivity pneumonitis

Not Diagnosable by TLB Findings

Idiopathic pulmonary fibrosis
Diseases commonly misdiagnosed as idiopathic pulmonary fibrosis
Eosinophilic granuloma
Lymphangiomyomatosis
Bronchiolitis obliterans organizing pneumonia
Hypersensitivity pneumonitis
Sarcoidosis (occasional cases)
Lymphangitic carcinoma (occasional cases)

TLB—transbronchial lung biopsy

case, the impact that a more precise diagnosis would have on therapy, and an assessment of the risk of open lung biopsy in a given case⁵ [see Figure 2]. The frequency with which open lung biopsy is performed to better define the histopathologic features of noninfectious forms of the disease varies greatly among different centers. Use of video-assisted thoracoscopy rather than open lung biopsy has not resulted in the anticipated decrease in morbidity and cost.⁸

TREATMENT

The treatment recommendations in this subsection are based on small, nonrandomized series (often without control groups), case reports, and clinical experience. There are very few randomized controlled trials of treatment for these diseases.

Even before a specific diagnosis is known, preventive measures can be initiated. Immunization against pneumococcal antigens (every 5 years) and yearly immunizations against influenza are indicated. Patients who have a reversible obstructive defect may benefit from bronchodilators. Supplemental oxygen given at rest and with exercise will often improve patients' tolerance of activities of daily living.⁹ Pulmonary hypertension and cor pulmonale occurring in patients with far advanced disease can be improved with appropriate treatment [see 14:XI *Pulmonary Hypertension, Cor Pulmonale, and Primary Pulmonary Vascular Diseases*].

Chronic Diffuse Infiltrative Lung Disease of Known Etiology

DRUG-INDUCED DISEASE

Many different drugs have been reported to cause diffuse infiltrative lung disease [see Table 2].¹⁰ Estimates are that drug-induced lung disease affects several hundred thousand patients each year. To minimize the morbidity and mortality of drug-induced disease, early recognition is critical. Discontinuance of the offending agent is often followed by spontaneous improvement, whereas failure to appreciate the causal relation between the drug and the pulmonary disease can lead to irreversible lung injury. Unfortunately, certain aspects of drug-induced disease can hinder the recognition of this cause-and-effect relation. First, the drugs that cause diffuse infiltrative lung disease are numerous, and drug-induced lung disease usually occurs in only a small fraction of patients who receive such drugs. Second, the onset of the pulmonary disease may occur weeks to months after the drug is begun. In the case of cytotoxic drug-induced disease, the onset of respiratory symptoms can occur many weeks after the last exposure to the offending agent. Finally, the drugs that cause diffuse infiltrative lung disease are often prescribed for conditions that are themselves associated with an increased risk of the disease. For example, a patient who receives an anticancer chemotherapeutic agent is at risk for infection and tumor infiltration of the lung. Similarly, the anti-inflammatory drugs that cause parenchymal lung disease are often prescribed for one of the collagen vascular disorders that can have diffuse infiltrative lung disease as one of its features. For all these reasons, the physician must have a heightened awareness of the possibility of a drug-induced etiology in patients with diffuse infiltrative lung disease.

Disease Induced by Cytotoxic Drugs

Diffuse infiltrative lung disease is a major cause of morbidity and mortality in patients undergoing treatment for an underlying malignancy.¹⁰ In some cases, the drug used to treat the malignancy is the direct cause of the pulmonary lesions. Some patients die

liquid of healthy nonsmokers typically contains 84% to 99% macrophages, 1% to 14% lymphocytes, and 0% to 1% neutrophils. The common causes of nongranulomatous diffuse infiltrative lung disease (e.g., IPF, some of the collagen vascular disorders, and asbestosis) are often characterized by a neutrophilic alveolitis, whereas sarcoidosis and hypersensitivity pneumonitis are associated with increases in lymphocytes. However, overlap exists (e.g., IPF with an increased number of lymphocytes or sarcoidosis with a normal number of lymphocytes).

LUNG BIOPSY

In many cases, the diagnosis remains unknown until a lung biopsy is obtained. Pathologically, these disorders may be characterized by variable degrees of involvement of alveolar septa or alveoli by inflammatory cells, mesenchymal cells, fibrosis, granuloma, or neoplastic cells. In rare instances, the abnormal substance that accumulates in the lung parenchyma is blood, proteinaceous material (alveolar proteinosis), amyloid, smooth muscle (lymphangiomyomatosis or tuberous sclerosis), or an abnormal material that is deposited as a result of an inherited storage disorder (Gaucher disease, Niemann-Pick disease, or Hermansky-Pudlak syndrome).

Lung tissue may be obtained either by transbronchial lung biopsy during bronchoscopy [see Table 4] or by one of two open biopsy techniques: traditional open lung biopsy or video-assisted thoracoscopy. Transbronchial lung biopsy is most useful in diagnosing infectious diffuse infiltrative lung disease and sarcoidosis. Noncaseating granulomas can be demonstrated on transbronchial lung biopsy specimens in 70% to 90% of patients with sarcoidosis. The diagnostic yield is highest (approximately 90%) in patients with radiographically apparent lung disease (stages II and III) and lowest (approximately 70%) in patients with hilar adenopathy alone (stage I). Whether one proceeds to open lung biopsy after obtaining a nonspecific transbronchial lung biopsy depends on the specific clinical and radiographic features in an individual

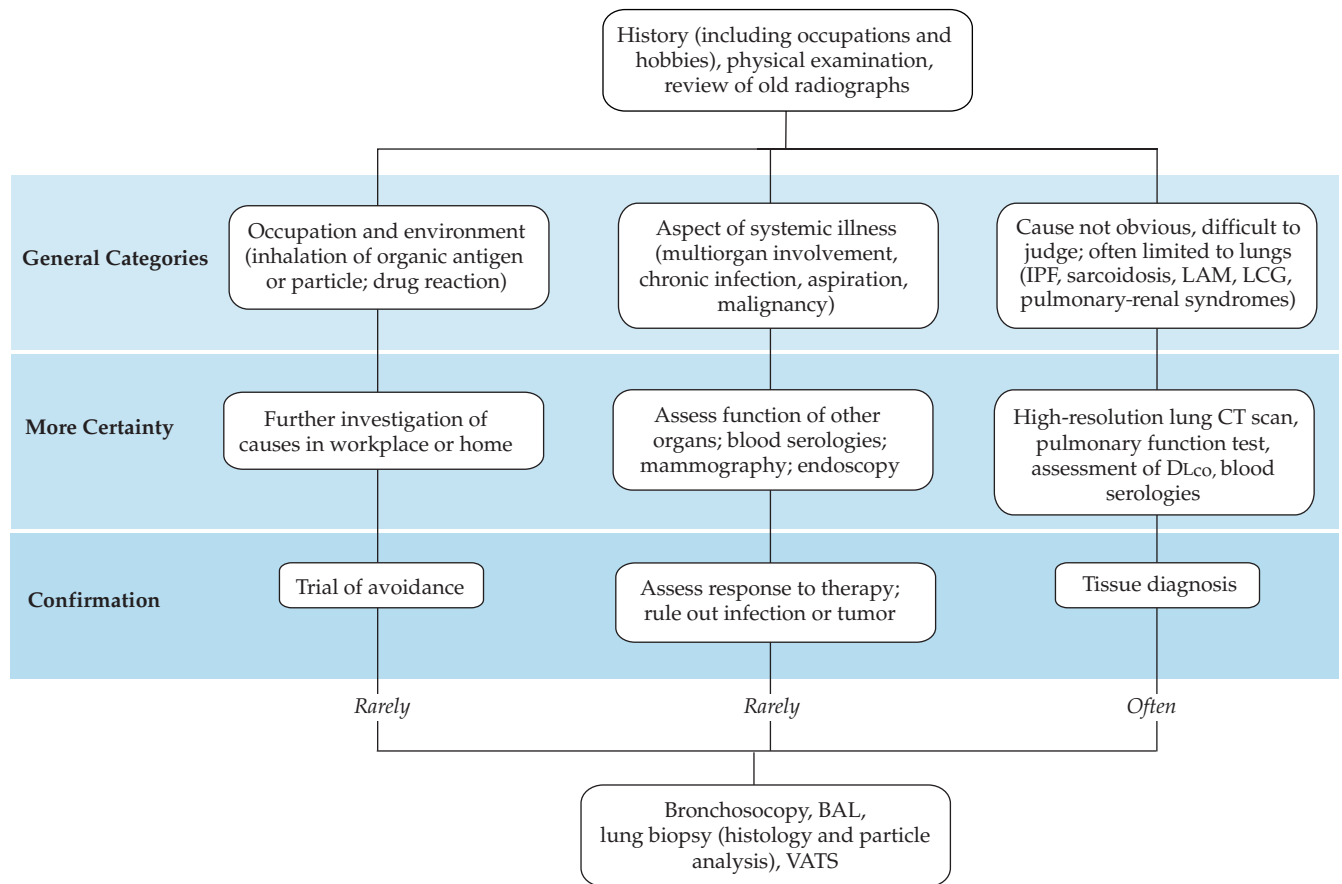


Figure 2 Algorithm for the evaluation of diffuse interstitial lung disease.⁵ (BAL—bronchoalveolar lavage; IPF—idiopathic pulmonary fibrosis; LAM—lymphangioleiomyomatosis; LCG—Langerhans cell granulomatosis; DL_{co}—diffusing capacity of the lung for carbon monoxide; VATS—video-assisted thoracoscopic surgery).

of cytotoxic drug-induced pulmonary toxicity, and others experience permanent impairment of lung function irrespective of being cured of their malignancy. Most of the drugs used in the treatment of malignancy have the potential to cause diffuse infiltrative lung disease. The major offending agents are bleomycin, cyclophosphamide, methotrexate, and the nitrosoureas. Cyclophosphamide and methotrexate are also being used increasingly in the management of nonmalignant conditions, though they are administered at much lower doses in the treatment of these disorders than in the treatment of malignancy. Drug-induced pulmonary disease occurs less frequently at these lower doses, but it can occur.

Clinical manifestations The clinical features of cytotoxic drug-induced disease are nonspecific. Cough and dyspnea are often prominent, and fever is not uncommon. The chest radiograph usually reveals bilateral and symmetrical interstitial infiltrates, though asymmetry may be seen early in the course of disease. The pace of the disease, both clinically and radiologically, is variable. Most often the onset is subacute, with cough and dyspnea occurring over several weeks. A more explosive onset, with features of acute respiratory distress syndrome (ARDS) and an urgent need for mechanical ventilatory support, can also be seen. Lung fibrosis resulting from therapy with bleomycin and other agents can occur insidiously over many months.

Pathologic features The pathologic features of cytotoxic drug-induced disease are distinctive but not pathognomonic. In-

terstitial inflammatory cell infiltration and fibrosis may be observed. However, the most characteristic finding of cytotoxic drug-induced disease is an increase in type II pneumocytes that show marked atypia. This pathologic feature is highly suggestive of cytotoxic drug-induced disease, but similar changes in type II cells can be seen with severe viral infections and during the reparative phase of ARDS.

A somewhat different pathologic picture is seen with disease induced by cytarabine or methotrexate. Cytarabine has been associated with an often fatal form of noncardiac pulmonary edema. Methotrexate-induced disease has been associated with granulomas, lymphocytic alveolitis, and a significant increase in helper T cells.

Diagnosis Diagnosis of cytotoxic drug-induced lung disease is established by defining a previous exposure to the offending agent, excluding infection as the cause of the lung damage, and demonstrating pathologic features that are consistent with drug-induced injury. The temporal relation between drug exposure and the onset of lung disease is variable. An interval of a few weeks between the last exposure to the drug and the onset of symptoms is not unusual; in rare cases, this interval can be as long as several months. The clinical and radiographic features of lung disease induced by a cytotoxic drug are indistinguishable from those caused by opportunistic infection. Thus, an aggressive approach to diagnosis is required. Failure to detect an infectious etiology by bronchoscopy increases the likelihood of drug-induced disease, espe-

cially if the characteristic type II cell changes are observed in a transbronchial lung biopsy specimen. However, open lung biopsy may be required to confidently exclude infection and to better define the histopathologic features of cytotoxic drug-induced injury. Even with open lung biopsy, the diagnosis of cytotoxic drug-induced disease remains inferential because there are no pathognomonic criteria on which to base a diagnosis.

Treatment Elimination of further drug exposure is essential in managing cytotoxic drug-induced lung disease. Anecdotal reports indicate that glucocorticoid therapy has been associated with rapid improvement in gas exchange and reversal of chest radiograph abnormalities. If the cytotoxic drug-induced disease is very severe or appears to progress despite elimination of further drug exposure, an empirical course of glucocorticoids is advisable.

Prevention Cytotoxic drug-induced lung disease is not easily prevented, because these drugs are often necessary for optimal treatment of an underlying potentially fatal malignancy. For patients with testicular carcinoma who receive bleomycin, the risk of pulmonary lesions appears to be dose related. Monitoring of the DL_{CO} and spirometry during therapy may in some cases permit detection of lung injury early enough to allow discontinuance of further drug exposure and lessen the likelihood of permanent and severe lung impairment. However, therapy for non-Hodgkin lymphoma with bleomycin in combination with doxorubicin, cyclophosphamide, vincristine, and prednisone causes diffuse infiltrative lung disease in a non-dose-dependent fashion, thereby impeding efforts to prevent it. Perhaps the most effective strategy to reduce morbidity and mortality from cytotoxic drug-induced disease is not to prevent it altogether but rather to diagnose it as early as possible; further drug exposure can then be avoided by switching to alternative chemotherapy regimens whenever feasible.

Noncytotoxic Drugs That May Cause Disease

Diffuse infiltrative lung disease may result from exposure to a variety of noncytotoxic agents, including antibiotics, anti-inflammatory agents, antiarrhythmics, and illicit drugs.¹⁰ In addition, this disorder may be one of the manifestations of drug-induced systemic lupus erythematosus (SLE).

Nitrofurantoin Nitrofurantoin, an antibacterial agent used primarily for the treatment of urinary tract infection, is one of the most common causes of drug-induced lung disease.¹⁰

Both acute and chronic pulmonary toxicity can occur, but the acute syndrome is much more common. The acute pleuropulmonary reaction begins 2 to 10 days after initial drug exposure and is manifested by dyspnea, cough, and often fever. Pleurisy occurs in one third of patients. The chest radiograph shows a pattern of alveolar or interstitial infiltrates, sometimes accompanied by a pleural effusion. Peripheral blood eosinophilia may be observed. The disorder is diagnosed on the basis of a history of recent exposure to nitrofurantoin and spontaneous resolution of the clinical and radiographic changes 1 to 4 days after discontinuance of the drug. This rate of resolution is much faster than would occur with infection and serves to establish the diagnosis with a high degree of certainty. Chronic toxicity is not associated with systemic symptoms and has a clinical and radiographic picture that is indistinguishable from that of IPF. If there is no improvement within 2 to 3 months after withdrawal of the drug, corticosteroid therapy is indicated.

Amiodarone Amiodarone is an antiarrhythmic agent that is used most often in the treatment of refractory ventricular tachyarrhythmia. This drug is associated with a variety of dose-dependent toxic effects on different organs, but the major limitation to its use is pulmonary toxicity, which occurs in 5% to 7% of cases. Amiodarone-induced pulmonary toxicity is usually heralded by the onset of cough and dyspnea that may initially be attributed to congestive heart failure. Systemic symptoms, including low-grade fever, are not uncommon. The chest radiograph may show a bilateral, symmetrical interstitial process similar to that observed in other types of diffuse infiltrative lung disease. However, more unusual radiographic patterns are not uncommon and include unilateral disease and isolated upper lobe disease; the latter finding may suggest tuberculosis. Pleural effusion occurs occasionally.

A diagnosis of amiodarone-induced lung disease is established primarily by excluding other likely causes of the pulmonary disorder, especially infection and heart failure. Bronchoscopy with BAL and biopsy helps exclude infection and reveals the presence of so-called foamy macrophages with lamellar inclusions (visualized by electron microscopy). These changes within macrophages are indicative of exposure to amiodarone but do not prove that the drug is the cause of the pulmonary process, because similar changes are seen in asymptomatic persons who are receiving the drug.

Withdrawal of the drug is the cornerstone of management, but glucocorticoids seem to be useful in more severe or persistent cases. Interestingly, there have been several reports of acute amiodarone-induced lung disease in patients who have undergone relatively minor surgical procedures, such as placement of an automatic defibrillator, or in those who have undergone pulmonary angiography, possibly as a consequence of oxygen supplementation during the procedure. Often, the disease follows a fulminant course, and sometimes the outcome is fatal. Because the half-life of the drug is several weeks, patients who undergo these procedures are still at risk for acute lung injury if the drug was discontinued 1 to 2 months before the procedure.

Gold and penicillamine Gold and penicillamine, used primarily for the management of rheumatoid arthritis and other collagen vascular disorders, can lead to diffuse infiltrative lung disease. It may be difficult to determine whether the pulmonary damage is caused by the therapeutic agent or by the underlying disorder, even with an open lung biopsy. Discontinuance of the drug, along with empirical corticosteroid therapy if symptoms are severe, is advisable. Penicillamine has also been implicated in cases of diffuse alveolar hemorrhage with glomerulonephritis, drug-induced SLE, and panbronchiolitis with severe airflow obstruction.

Illicit drugs Illicit drugs can also cause diffuse infiltrative lung disease. Talc-induced granulomatosis and pulmonary fibrosis can result from injection of crushed and dissolved amphetamines or narcotic pills that have talc as the filler. The disease can progress years after the last exposure, because the talc persists in the lungs and continues to elicit an inflammatory response. Open lung or transbronchial lung biopsy reveals a granulomatous inflammation with abundant talc particles, which can be visualized with polarizing microscopy. Failure to evaluate granulomas with the polarizing microscope may lead to an erroneous diagnosis of sarcoidosis. The diagnosis can also be made by detecting talc in the retina. Heroin use can lead to acute pulmonary edema but does not in itself cause a chronic diffuse infiltrative lung disease. Cocaine has been associated with acute pulmonary edema and has been reported to cause

diffuse alveolar hemorrhage and a syndrome of pulmonary infiltrates with eosinophilia. Cocaine-related pulmonary reactions do not lead to chronic lung lesions.

PNEUMOCONIOSES

Environmental or occupational exposure to particulate matter can cause several pneumoconioses that manifest as asthma, chronic bronchitis, or diffuse parenchymal (mostly interstitial) disease. Representative pneumoconioses include asbestosis, silicosis, coal worker's pneumoconiosis (CWP), and berylliosis.

Asbestosis

Exposure to asbestos, a silicate used in insulation, in friction-bearing surfaces, and to strengthen materials, is associated with the development of pleural changes (plaques and effusions), an increased incidence of malignancy (bronchogenic carcinoma and mesothelioma), and diffuse interstitial fibrosis. Only diffuse interstitial fibrosis is called asbestosis.¹¹

Asbestosis is characterized by the gradual onset of dyspnea 20 to 30 years after exposure to asbestos. Cough is usually present but is nonproductive unless the patient has been a smoker and has complicating chronic bronchitis. Fine end-inspiratory rales can be heard before the chest radiograph becomes abnormal, and digital clubbing is common. In the late stages of asbestosis, signs of cor pulmonale may develop.

Early in the course of disease, the chest radiograph may be normal, but small, irregular linear shadows gradually develop in the lower lung zones. Pulmonary function tests may show restriction, decreased DL_{CO} , and exercise-induced hypoxemia. Diagnosis of asbestosis is made when a patient has a history of exposure to asbestos, pleural plaques (an objective indicator of exposure), and, in uncertain cases, excess asbestos in specimens obtained from the lung (by BAL, transbronchial lung biopsy, or open lung biopsy).

There is no specific treatment for patients with asbestosis.¹¹

Silicosis

Silicosis is a chronic fibrotic lung disease caused by exposure to crystalline free silica.¹¹ The occupational settings in which significant free-silica exposure may occur include certain types of mining; the cutting, polishing, and carving of stone; foundry work; and abrasive cleaning (sandblasting). Exposure of approximately 5 years' duration is usually required for the development of silicosis unless the exposure is very heavy. There are two forms of silicosis: simple nodular silicosis, in which many patients are asymptomatic or suffer only from chronic bronchitis secondary to tobacco use, and progressive massive fibrosis (PMF), in which patients may develop disabling dyspnea.

Physical findings are often absent. Radiographically, simple nodular silicosis is characterized by diffuse, small, rounded opacities that tend to be more prominent in the upper lobes. Hilar node enlargement may be seen, sometimes with concentric (egg-shell) calcifications. In patients with PMF, the opacities coalesce into large, irregularly shaped masses. In patients with simple nodular silicosis, pulmonary function may be normal or may exhibit a mixed pattern of obstruction and restriction. Severe restriction and hypoxemia, as well as pulmonary hypertension, develop in patients who have PMF.

Diagnosis of silicosis can usually be made if a patient has a history of exposure and if the chest radiograph is consistent with silicosis (see above). In atypical cases, the presence of silica in BAL liquid or in lung biopsy specimens (often guided by CT scan of

the chest) can establish the diagnosis and exclude tuberculosis and carcinoma.

Tuberculosis and infection with atypical mycobacteria occur with increased frequency in patients with silicosis and may be confused with the progression of the silicosis, making conclusive diagnosis difficult. Because cell-mediated immunity appears to be normal in patients with silicosis, the tuberculin skin test can be helpful in identifying patients in whom diagnosis of tuberculosis should be explored.

Silicosis has been thought to be an untreatable disease,¹¹ though one report suggests that oral glucocorticoids reduce lung inflammation and improve lung function.¹² Prevention of further exposure to silica and prevention and treatment of active tuberculosis are important aspects of care.

Coal Worker's Pneumoconiosis

CWP is an uncommon cause of pulmonary fibrosis in workers who are exposed to coal dust and graphite. Most of these patients are miners.

Many patients with CWP have a chronic cough that is sometimes productive of gray or black sputum, which may be caused by chronic bronchitis that is related to tobacco use or exposure to coal dust. Much like silicosis, CWP comprises simple CWP and PMF. PMF is characterized by severe dyspnea, whereas simple CWP is not associated with an increased incidence of dyspnea. The radiographic changes characteristic of simple CWP are small, rounded opacities; opacities that are larger than 1 cm are arbitrarily classified as PMF. Simple CWP does not progress if dust exposure is eliminated, whereas PMF can progress after exposure has stopped.

There is no specific treatment for either form of disease.

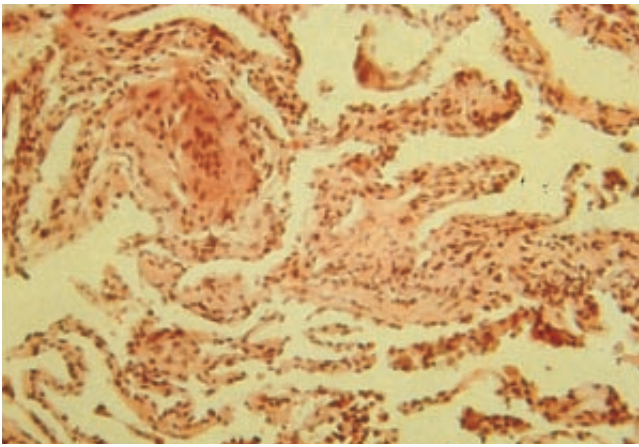
Berylliosis

Beryllium is a metal that is used in modern high-technology industries. High-intensity exposure to beryllium can cause an acute chemical bronchitis and pneumonitis, which is very rare today because of strict environmental controls. However, chronic berylliosis is still frequently seen. Chronic berylliosis is characterized by multisystemic granulomatous disease that has many similarities to sarcoidosis and that occurs months to years after exposure. The number of chronic cases appears to be decreasing, probably because of increased awareness of the disease and environmental controls. Beryllium is thought to bind to host proteins that are carried throughout the body. These beryllium-protein complexes stimulate a delayed hypersensitivity response, which produces granulomatous inflammation at the sites of disease activity.

The symptoms of berylliosis are dyspnea, cough, chest pain, fatigue, weight loss, and arthralgia. Rales are not an early feature. The radiographic findings, which may precede clinical symptoms, include ill-defined nodular and irregular opacities that are sometimes associated with hilar adenopathy. As the disease progresses, the lungs become smaller and areas of honeycombing develop. Pulmonary function tests may be normal; more often, however, they are characterized by a low DL_{CO} with or without restriction, or they demonstrate mild obstruction. Other abnormalities include hyperuricemia, hypercalcemia, hypercalciuria, and elevated serum levels of ACE.

The criteria for diagnosis include a well-documented history of exposure or a demonstration of excess beryllium in patient specimens; objective evidence on radiography and pulmonary function testing for the presence of lower respiratory tract disease that is consistent with berylliosis; and demonstration of granulo-

a



b

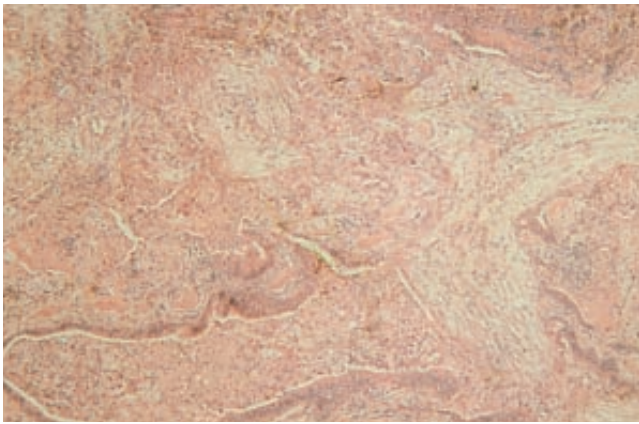


Figure 3 Open-lung biopsy specimen from a patient with hypersensitivity pneumonitis (farmer's lung disease) shows characteristic features of (a) scattered granulomas and (b) bronchiolitis obliterans.

matous inflammation in the lung, lymph nodes, or other sites of disease activity.

Differentiating berylliosis from sarcoidosis may be difficult. A diagnosis of sarcoidosis is suggested by the presence of uveitis and erythema nodosum, the presence of hilar adenopathy without parenchymal infiltrates, or improvement after short-term administration of steroids. A diagnosis of berylliosis is suggested by lymphocyte transformation in response to beryllium compounds performed on lymphocytes obtained from blood or BAL.

The most important step in the management of berylliosis is prevention of further exposure. Glucocorticoids may improve the course of the disease, but these agents may have to be given for the rest of the patient's life.¹³

HYPERSENSITIVITY PNEUMONITIS

The term hypersensitivity pneumonitis (allergic alveolitis) refers to interstitial lung disease that results from inhalation of organic antigens.¹⁴ Several organic antigens cause this syndrome [see Table 1], but the most common form of hypersensitivity pneumonitis, called farmer's lung, is caused by inhalation of proteins from thermophilic *Actinomyces* organisms present in moldy hay and grain. Other relatively common causes of hypersensitivity pneumonitis include pigeon breeder's disease and bird fancier's disease, in which inhaled proteins from pigeons or pet birds in-

duce the syndrome. Humidifier lung disease is a type of hypersensitivity pneumonitis that results from exposure to contaminated forced-air systems. The responsible antigens in such cases are *Actinomyces* organisms, as in farmer's lung, but also can include *Aureobasidium* organisms and various amoebae. Forms of hypersensitivity pneumonitis other than farmer's lung, pigeon breeder's disease, bird fancier's disease, and humidifier lung disease are rare and generally result from exposure to antigens in rather arcane occupations (e.g., paprika slicing and mummy wrapping).

Pathogenesis and Pathology

The pathogenesis of hypersensitivity pneumonitis is not fully understood. The current hypothesis is that inhaled material causes direct activation of the alternative complement pathway, leading to the formation of chemotactic factors for neutrophils and in turn to acute neutrophilic alveolitis. The products of complement activation also stimulate the alveolar macrophages to produce monokines, causing a sequence of events that results in granuloma formation.

The pathologic changes in hypersensitivity pneumonitis have been well defined by examination of open lung biopsy specimens of a large number of patients with farmer's lung disease. All patients have an interstitial pneumonitis, and two thirds have scattered granulomas. Fibrosis may occur in more chronic forms of the disease, and as many as 50% of patients may have bronchiolitis obliterans. The pathologic picture of lymphocytic interstitial pneumonitis with granuloma formation and bronchiolitis obliterans is characteristic of hypersensitivity pneumonitis [see Figure 3]. BAL studies have examined the nature of the lymphocyte population in the lung and have demonstrated that the lymphocytes are predominantly of the suppressor-cytotoxic T cell subclass. This inversion of the ratio of helper T cells to suppressor-cytotoxic T cells in hypersensitivity pneumonitis contrasts with the predominance of helper T cells in patients with sarcoidosis. The finding of an intense lymphocytic alveolitis with inversion of the ratio of helper T cells to suppressor-cytotoxic T cells suggests hypersensitivity pneumonitis, but this pattern cannot be considered specific, because a similar lavage profile may be seen in other disorders (e.g., IPF associated with a lymphocytic alveolitis).

Clinical Manifestations

Hypersensitivity pneumonitis exists in two basic clinical forms: acute and chronic.

Acute hypersensitivity pneumonitis Acute hypersensitivity pneumonitis is characterized by fever, chills, cough, dyspnea, and malaise that typically occur 4 to 8 hours after antigenic exposure. Most patients with acute hypersensitivity pneumonitis improve spontaneously after exposure to the antigen ceases. Occasionally, patients experience a more severe episode characterized by hypoxemia and by considerable respiratory distress and require hospitalization. Because of the prominence of systemic symptoms during the acute episode, the patient may be erroneously diagnosed as having a respiratory infection. With continuing exposure to the inhaled antigen—as may occur in people living on a farm, for example—the patient may have daily episodes of acute hypersensitivity pneumonitis that blend into each other. If this pattern occurs, the patient may complain of having a flulike illness for many weeks. Respiratory symptoms, such as cough and wheezing, that occur immediately after exposure to an organic material should not be attributed to hypersensitivity pneumonitis but rather to an irritant response within the airways.

Chronic hypersensitivity pneumonitis In chronic hypersensitivity pneumonitis, there are usually no systemic symptoms; rather, the symptom complex is marked by chronic dyspnea and cough on exertion. The clinical presentation is that of interstitial lung disease of uncertain etiology.

Diagnosis

There is no single diagnostic test that can be used to establish an unequivocal diagnosis of hypersensitivity pneumonitis. Therefore, one must rely on a combination of history, radiography, serologic study, and exclusion of other possible causes. A history of previous episodes of acute hypersensitivity pneumonitis is of great diagnostic value. In taking the history, the clinician should focus on establishing whether a relevant antigenic exposure has occurred and, if so, try to determine whether this exposure caused typical acute symptoms to occur several hours later. Such a history is more likely to be obtained in cases of heavy exposure (e.g., to moldy hay or a pigeon coop) than in cases of low-level exposure (e.g., to a humidifier or a single bird). In the latter circumstance, the exposure is more or less continuous, and it is much more difficult to establish a causal relation between antigenic exposure and symptoms. Patients should be questioned carefully as to their occupations and hobbies and whether symptoms resolve when they are on vacation or at other times when they are away from the putative source of illness. At least 50% of patients who present with the chronic form of the disease deny having a history of an acute episode. Such acute episodes may well have occurred, but the patient may have attributed the symptoms to respiratory tract infections. The patient may spontaneously improve on hospitalization for evaluation of a respiratory illness, only to experience a recurrence of symptoms soon after returning home. Such a history should always raise suspicion about hypersensitivity pneumonitis as a cause of the respiratory illness.

Chest radiography The chest radiographs of patients with acute hypersensitivity pneumonitis may vary from demonstrating no changes to demonstrating alveolar, nonlobar infiltrates. As chronic disease develops, a reticular, nodular, or combined infiltrate evolves, and fibrosis may become evident during continued antigenic exposure. HRCT can be very useful in suggesting the diagnosis and differentiating hypersensitivity pneumonitis from IPF.¹⁵

Serologic study Serologic study is useful primarily in establishing that there has been exposure to a specific antigen. Nearly all patients with farmer's lung and pigeon breeder's disease have antibodies to thermophilic *Actinomyces* organisms and pigeon serum, respectively. However, these antibodies may also be present in the serum of a significant percentage of asymptomatic persons. Hence, the presence of antibody in serum does not establish a diagnosis of hypersensitivity pneumonitis but demonstrates that there has been significant exposure to the antigen.

Bronchoscopy Patients who present with subacute to chronic hypersensitivity pneumonitis should undergo diagnostic bronchoscopy with BAL and transbronchial biopsy. The lavage fluid in hypersensitivity pneumonitis typically shows an intense lymphocytosis, often with more than 50% lymphocytes. As noted earlier, these are primarily suppressor-cytotoxic T cells. As time elapses since the last exposure to antigen, BAL tends to normalize.¹⁶

Lung biopsy Transbronchial lung biopsy would be expected to show a nonspecific interstitial pneumonitis in most patients

and may show evidence of granuloma or bronchiolitis obliterans. Even in the two thirds of cases in which granulomas are present, these lesions are more scattered than sarcoid granulomas and are therefore not as likely to be demonstrated by transbronchial biopsy. Open lung biopsy is usually reserved for especially difficult and confusing cases in which a diagnosis cannot be established by a combination of history, radiography, serologic study, and bronchoscopy. Few patients who have hypersensitivity pneumonitis require open lung biopsy for diagnosis.

Treatment

Treatment of hypersensitivity pneumonitis primarily involves stopping the exposure to the causative antigen. This step may be accomplished rather early in the case of humidifier lung disease or bird fancier's disease but is somewhat more difficult to accomplish in patients with farmer's lung. Sometimes, the dairy farmer is able to have another person do the work that involves exposure to the moldy hay. High-efficiency masks may help reduce the number of spores the patient inhales. Improvement in farming practices, including better ventilation and other steps to reduce the moisture content of hay, may significantly lessen the antigenic load. Referral of the patient to a center that deals with agricultural lung disease is appropriate.

Glucocorticoids are used primarily for acute hypersensitivity pneumonitis characterized by severe systemic symptoms and gas exchange abnormalities. Patients with subacute to chronic hypersensitivity pneumonitis may also improve more rapidly if they are given a course of glucocorticoids for several weeks. Elimination of further antigen exposure is essential when glucocorticoids are administered. Otherwise, the symptoms may be masked by use of the glucocorticoids, and continued exposure to the antigen could result in further lung damage. When antigenic exposure ceases, most patients undergo spontaneous improvement. Patients who have entered a fibrotic phase of the disease may not show substantial improvement, and there is a small subset of patients who seem to deteriorate even though antigenic exposure has apparently been eliminated. In the latter group, it may be beneficial to follow the serum antibody level; with lack of further exposure, the titer will gradually fall. An unchanging or rising titer would suggest continuing antigenic exposure.

MALIGNANT DIFFUSE INFILTRATIVE LUNG DISEASE

Diffuse involvement of the lung by malignancy occurs with lymphangitic carcinomatosis, alveolar cell carcinoma, lymphoma, and leukemia.

Disease Caused by Pulmonary Lymphangitic Carcinomatosis

Pulmonary lymphangitic carcinomatosis most often results from adenocarcinomas. The adenocarcinomas usually originate in the breast, gastrointestinal tract, or lung. The symptoms referable to lymphangitic tumor—that is, cough and dyspnea—are the same as those of nonmalignant diffuse infiltrative lung disease. However, lymphangitic carcinomatosis generally progresses much faster than other interstitial lung diseases; survival beyond 3 to 6 months is unusual. The chest radiograph shows bilateral reticular or reticulonodular infiltrates and, often, Kerley B lines. The latter finding should, in the absence of heart failure, raise suspicion that malignancy is responsible for the pulmonary disorder. Pleural effusions and hilar adenopathy may also be observed. Less often, lymphangitic carcinomatosis presents as unilateral involvement, or the patient has an entirely normal chest radiograph

Table 5 Chronic Diffuse Parenchymal Lung Diseases of Unknown Cause*

<i>Entity</i>	<i>Clinical and Laboratory Clues</i>	<i>Radiographic Clues</i>	<i>Pulmonary Function</i>	<i>Associated Diseases, Exposures, Risk Factors</i>
Sarcoidosis	Young African-American, females; minimal symptoms; skin lesions; increased SACE activity	BHA; upper lung field infiltrates; bronchovascular bundle nodularity on HRCT	Restriction with decreased DL _{CO} ; some have obstruction	Familial incidence sometimes
Idiopathic pulmonary fibrosis (IPF)	Older men; slowly progressive dyspnea; dry end-inspiratory rales; clubbing of digits	Sometimes normal initially; bibasilar reticular infiltrates; peripheral fibrotic changes with subpleural honeycombing on HRCT	Diffusion decreased more than lung volumes	Familial IPF, cigarette smoking, chronic aspiration, ? viral infections
Desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease (DIP/RBILD)	Middle-aged men; slowly progressive dyspnea; clubbing of digits	Bibasilar hazy opacities; ground-glass changes with some linear and reticulonodular infiltrates on HRCT	Restrictive defects less severe than in IPF	Highly associated with cigarette smoking
Acute interstitial pneumonia (AIP)	Rapid onset of dyspnea, cough, fever evolving to respiratory failure	Diffuse bilateral airspace opacities; areas of ground-glass changes and consolidation on HRCT	Rapidly progressive restrictive defect with hypoxemia	Viral prodrome
Lymphocytic interstitial pneumonia (LIP)	Older women more than men; associated disorder may dominate clinical picture	Reticulonodular infiltrates	Restrictive defect with decreased DL _{CO}	Autoimmune disorders (Sjögren syndrome), dysproteinemias, viral infections (HIV), bone marrow transplantation
Nonspecific interstitial pneumonia and fibrosis (NSIP/F)	Middle-aged; women slightly greater than men; dyspnea and cough; often with fever	Bilateral hazy opacities; bilateral patchy ground-glass changes on HRCT	Restrictive defect with decreased DL _{CO}	Collagen vascular disorders, exposures to agents known to cause hypersensitivity pneumonitis, other environmental exposures, drugs
Bronchiolitis obliterans organizing pneumonia (BOOP)	Idiopathic BOOP seen in older patients; abrupt onset of cough, dyspnea, fever; rales and wheezes	Some have solitary focal infiltrates; bilateral patchy alveolar or ground-glass infiltrates; bilateral areas of consolidation on HRCT	Mixed restriction and obstruction	Many idiopathic but some associated with infections, collagen vascular disorders, aspiration, transplantation, inhaled toxins
Collagen vascular disease	Often asymptomatic; progressive dyspnea, cough, sometimes with chest pain, hemoptysis; positive serologies	Usually have bilateral diffuse or patchy infiltrates; on HRCT, may be ground-glass, fibrotic, or combination	Restrictive defect with decreased DL _{CO}	Rheumatoid arthritis, SLE, PSS, Sjögren syndrome, MCTD, PM/DM
Eosinophilic granuloma	Age 20–50 years; sometimes asymptomatic; cough and dyspnea	Pneumothorax common, sometimes at presentation; nodules and cysts seen on chest radiograph and HRCT	Mixed restriction and obstruction with decreased DL _{CO}	Cigarette smoking
Alveolar proteinosis	Abnormal radiograph, acute complicating infection, or progressive cough and dyspnea; increased LDH	Bilateral alveolar filling that looks like pulmonary edema without signs of congestion	Restrictive defect with decreased DL _{CO} ; increased shunt fraction	Most cases idiopathic; associated with acute silica exposure, several hematologic malignancies, busulfan
Chronic eosinophilic pneumonia (CEP)	Middle-aged women; productive cough, dyspnea, fever, wheezing; eosinophilia	Bilateral peripheral; often upper lung field infiltrates very suggestive	Restrictive and obstructive defects	None
Anti-glomerular basement membrane (anti-GBM)	Young male cigarette smokers; most have hemoptysis; drop in hemoglobin, hematuria, iron deficiency; positive anti-GBM antibody	Fluffy perihilar acinar shadows; alveolar filling on HRCT	Restrictive pattern that improves with clinical resolution; DL _{CO} increased with bleeding	Cigarette smoking, hydrocarbon exposure
Lymphangio-myomatosis	Women in childbearing years; dyspnea, hemoptysis, pneumothorax, chylothorax	Diffuse, thin-walled cysts on HRCT	Obstruction with increased lung volumes; DL _{CO} decreased	Tuberous sclerosis produces identical radiographic picture

*After ruling out infections, drugs, and inhalants (organic and inorganic).

ARDS—acute respiratory distress syndrome BHA—bilateral hilar adenopathy DAD—diffuse alveolar damage DL_{CO}—diffusing capacity of the lung for carbon monoxide
 HRCT—high-resolution computed tomography LDH—lactate dehydrogenase LIP—lymphocytic infiltrative pneumonia MCTD—mixed connective tissue disease
 PM/DM—polymyositis/dermatomyositis PSS—progressive systemic sclerosis SACE—serum angiotensin-converting enzyme SLE—systemic lupus erythematosus
 UIP—usual interstitial pneumonia

Table 5 Chronic Diffuse Parenchymal Lung Diseases of Unknown Cause (continued)

<i>Extrathoracic Manifestations</i>	<i>Histopathology</i>	<i>Therapy</i>	<i>Prognosis</i>
Neurologic, eye, skin, heart, liver, hypercalcemia, joints	Noncaseous granulomas; must exclude granulomatous infection, berylliosis	For many—none; when indicated, steroids, antimalarials, methotrexate	Excellent
Arthralgias; cor pulmonale late in disease	UIP; fibrosis with widening of the alveolar septa; fibroblastic foci of varying age; minimal inflammation	A minority respond to steroids; cytotoxic therapy with cyclophosphamide, azathioprine; in unresponsive patients, colchicine	Complete recovery not possible; mortality 68%; median survival 2–3 yr
None	Homogeneous filling of air spaces, especially in the peribronchiolar areas	Good response to discontinuance of smoking; good response to steroids	Complete recovery possible; mortality 27%; mean survival 12 yr
None	Diffuse alveolar damage; cannot be differentiated from ARDS pathologically	Supportive care with oxygen, mechanical ventilation; not clear whether steroids of any benefit	Mortality 78%; survival often less than 6 mo
Depends on associated disorder	Lymphocytic infiltrate of alveolar walls and alveoli that must be distinguished from lymphoma	Treatment of underlying disorder; some respond to steroids, others require immunosuppressive agents	Depends on underlying disorder; can be progressive
None	Often confused with UIP; temporally uniform mixture of alveolar wall inflammation (mostly lymphocytes and plasma cells and fibrosis)	Good response to steroids	Complete recovery possible; median survival 13.5 yr; survival worse with increased fibrosis
Depends on associated disorder	Intraluminal plugs of connective tissue in the bronchioles, alveolar ducts, and alveolar spaces	Focal infiltrates do not require therapy; for others, steroids are successful with high incidence of relapse	Patients with focal BOOP have no increased mortality; those with diffuse disease have a good prognosis with steroids
Arthritis, skin rash or thickening, dysphagia, serositis, dry eyes/mouth, myositis, pulmonary hypertension	Some have UIP pattern, but NSIP/E, LIP, BOOP, DAD also seen	In some, steroids useful (PM/DM, Sjögren syndrome); in others, cytotoxic therapy indicated	Depends on the associated process, response to therapy
Bone lesions, diabetes insipidus	Nodular lesions containing Langerhans cells with Birbeck granules	Smoking cessation; steroids not clearly of benefit	Median survival 6 yr; older age, airflow obstruction, hyperinflation—poor prognosis
None	Granular, eosinophilic material within alveolar spaces that stains positively with the periodic acid–Schiff staining	Some patients require no therapy; whole lung lavage is treatment of choice	Some patients will undergo spontaneous remission; excellent response to whole lung lavage
None	Massive, mixed interstitial and alveolar inflammatory infiltrates that have a high eosinophil content	Steroids are effective, producing rapid response; relapse common	Spontaneous remissions in 10%; many require long-term steroids; with steroids, death uncommon from CEP
Glomerulonephritis	Alveolar hemorrhage, sometimes with linear immunofluorescent staining; kidney biopsy shows crescentic glomerulonephritis and linear immunofluorescent staining	Immunosuppressive agents, glucocorticoids, plasmapheresis	50% mortality; dialysis needed after 2 yr
Renal angiomyolipomas	Diffuse proliferation of smooth muscle cells in the lung and visceral pleura, with cyst formation	Oophorectomy, progesterone treatment, or a combination of the two; lung transplantation for end-stage disease	25% mortality at 8 yr

despite severe dyspnea and hypoxemia. In patients with lymphangitic carcinomatosis and a normal chest radiograph, tumor cells are often found in abundance in small pulmonary vessels, occasionally resulting in severe pulmonary hypertension (tumor em-

bolism syndrome). Diagnosis is generally made by bronchoscopy, either by BAL alone or by transbronchial biopsy. An alternative means of establishing the diagnosis is by microvascular cytologic examination of blood aspirated through a wedged pulmonary

arterial catheter. This technique may be considered in the very breathless patient in whom right heart catheterization may be better tolerated than bronchoscopy. Open lung biopsy is only occasionally required to diagnose lymphangitic carcinomatosis.

Disease Caused by Alveolar Cell Carcinoma

Alveolar cell carcinoma may present as a simple nodule or mass, as multiple nodules, or with air-space disease that can be focal, multifocal, or quite diffuse.¹⁷ When the tumor presents as diffuse disease, the differential diagnosis includes nonmalignant causes of diffuse alveolar filling, such as pulmonary edema, alveolar proteinosis, alveolar sarcoidosis, and alveolar hemorrhage. Diagnosis of alveolar cell carcinoma is usually established fairly easily by bronchoscopy with BAL and transbronchial biopsy.

Disease Caused by Lymphoma or Leukemia

Lymphoma and leukemia may cause diffuse infiltrative lung disease. Lymphomatous involvement of the lung parenchyma is usually seen in association with mediastinal lymphadenopathy and evidence of extrathoracic lymphoma.¹⁸ On occasion, isolated pulmonary disease is the presenting manifestation of lymphoma. When the underlying leukemia is poorly controlled, leukemic infiltration of the lung is usually seen and may contribute to death by causing respiratory failure. Diagnosis of leukemic or lymphomatous infiltration of the lung may require open lung biopsy to adequately characterize the nature of the infiltrating process and to completely exclude infection. However, in some cases, bronchoscopy may suffice for making the diagnosis.

Chronic Diffuse Infiltrative Lung Disease of Unknown Etiology

An overview of diagnosis and treatment for chronic diffuse infiltrative lung disease of unknown etiology is presented [see Table 5].

SARCOIDOSIS

Sarcoidosis is a multisystem disease of unknown etiology that is characterized pathologically by the presence of noncaseating granulomas in various tissues.¹⁹ Any organ system may be affected. Most patients are asymptomatic and seek medical attention because of unrelated respiratory symptoms; most of those patients who are asymptomatic are first recognized through a chest radiograph abnormality. Fewer than 5% of patients with sarcoidosis have a normal chest radiograph. Further, the morbidity and mortality that are associated with sarcoidosis result most often from pulmonary involvement. Thus, it is appropriate to think of sarcoidosis as primarily a respiratory tract disorder that may also have features of extrapulmonary disease.

Many infectious and noninfectious conditions are associated with granuloma formation and a histopathologic picture indistinguishable from that of sarcoidosis. Thus, diagnosis of sarcoidosis requires the exclusion of other causes of granuloma formation. Berylliosis and histoplasmosis, for example, can have clinicopathologic features identical to those of sarcoidosis [see Approach to the Patient with Suspected Chronic Diffuse Infiltrative Lung Disease, *above*].

Epidemiology

Sarcoidosis occurs worldwide, in all ethnic groups, but there are striking regional and ethnic differences in its incidence and prevalence. For example, in the United States, sarcoidosis is 10

times more common in blacks than in whites and tends to be more severe in black patients. However, this increased prevalence is not observed in blacks in Europe. It has been estimated that the prevalence of sarcoidosis in the United States is between one in 10,000 and one in 2,500. Persons 20 to 40 years of age are most often affected, but the disease can present in children and the elderly. Males and females are affected almost equally, with the prevalence of sarcoidosis being only slightly higher in females. Familial sarcoidosis has been reported in a number of kindreds; less commonly, sarcoidosis has been diagnosed in both a husband and a wife, which would suggest a common environmental factor.

Pathogenesis

A specific sequence of events leads to granuloma formation in sarcoidosis²⁰ [see Figure 4]. Expansion of the helper T cell population in the lungs likely occurs through the activation of T cells by macrophages via interleukin-1 (IL-1) and the subsequent release of IL-2 (also termed T cell growth factor) by the helper T cell. IL-2 causes self-replication of the existing T cell population. This population of helper T cells (dominantly of the Th1-type), which are greatly increased in number and in degree of activity, recruits monocytes from peripheral blood into the lung by releasing monocyte chemotactic factor and colony-stimulating factors and thereby participates in the formation of granulomas. The monocytes become tissue macrophages and, ultimately, the epithelioid cells and multinucleated giant cells that form the core of the granuloma. Monocyte- and macrophage-derived fibroblast growth factors may, in some patients, lead to the development of fibrosis. Another effect of the expanded and activated helper T cell population at sites of disease activity is local stimulation of B cells to produce immunoglobulin, which accounts for the hypergammaglobulinemia that is often seen in this disorder.

Clinical Manifestations of Intrathoracic Sarcoidosis

The most common manifestations of intrathoracic sarcoidosis are bilateral hilar lymphadenopathy and diffuse infiltrative lung disease. A staging system has been created on the basis of the presence or absence of these two manifestations on radiography: stage I, bilateral hilar lymphadenopathy alone; stage II, bilateral hilar lymphadenopathy and diffuse infiltrative lung disease; and stage III, diffuse infiltrative lung disease alone [see Figure 5].

Symptoms resulting from parenchymal lung involvement include dyspnea and cough. Pulmonary function abnormalities are found in nearly all symptomatic patients and in some patients who are asymptomatic. Physiologic abnormalities in patients with symptomatic sarcoidosis typically consist of a reduction in DL_{CO} and vital capacity without airflow obstruction. The DL_{CO} typically becomes abnormal before the vital capacity, but both are usually affected in persons with moderate to severe symptoms. Airflow obstruction is relatively uncommon except in patients with advanced disease or with endobronchial involvement of larger airways. In rare instances, diffuse endobronchial granulomas in small airways lead to a predominantly obstructive abnormality in patients who present with stage I disease.

Most patients with stage I sarcoidosis are asymptomatic, and the abnormality is detected on a routine chest radiograph. When stage I disease is symptomatic, the symptoms are nonpulmonary in nature and consist of systemic complaints of fever, malaise, arthralgia, or erythema nodosum. The presence of fever, bilateral hilar lymphadenopathy, arthralgia or arthritis, and erythema nodosum is known as Löfgren syndrome.²¹ Approximately 10% of patients who have stage I disease display evidence of extrapul-

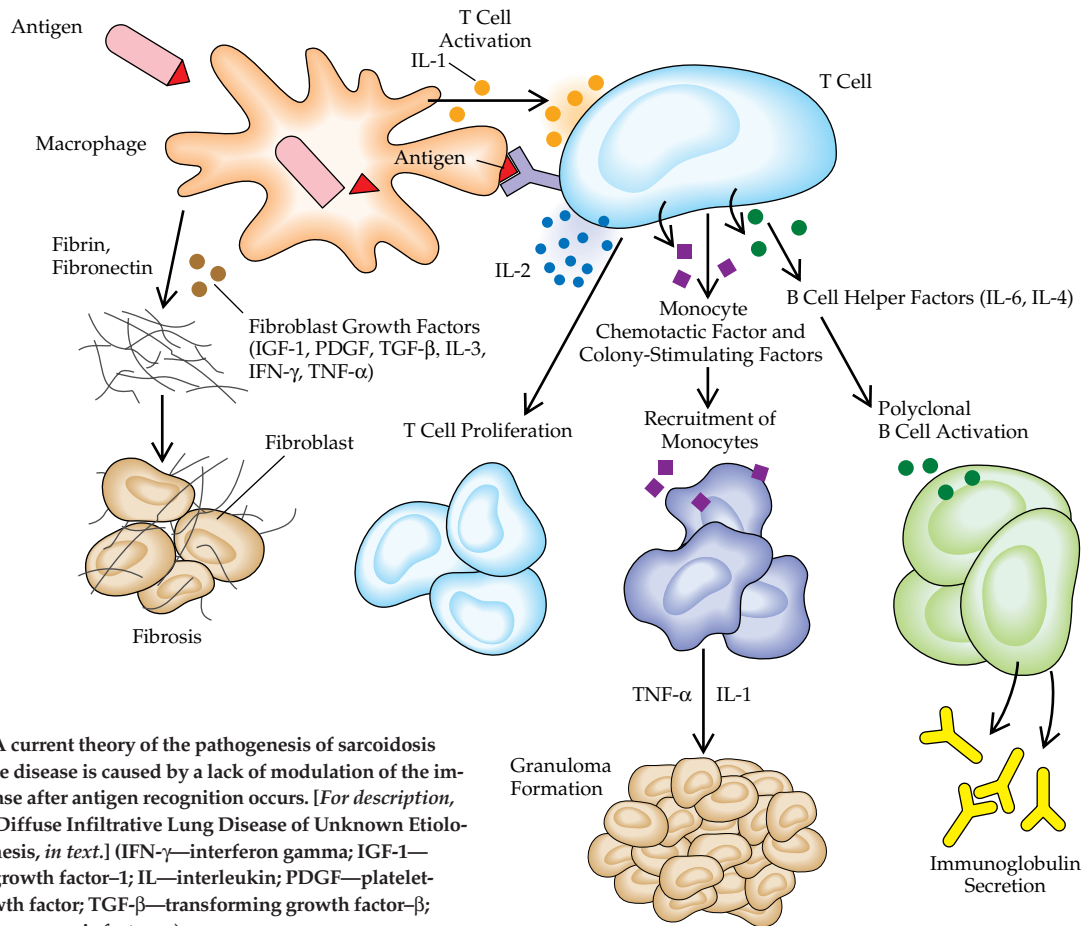


Figure 4 A current theory of the pathogenesis of sarcoidosis holds that the disease is caused by a lack of modulation of the immune response after antigen recognition occurs. [For description, see *Chronic Diffuse Infiltrative Lung Disease of Unknown Etiology, Pathogenesis, in text.*] (IFN- γ —interferon gamma; IGF-1—insulinlike growth factor-1; IL—interleukin; PDGF—platelet-derived growth factor; TGF- β —transforming growth factor- β ; TNF- α —tumor necrosis factor- α).

monary organ involvement (e.g., involvement of the eyes, nervous system, or lacrimal glands). Approximately 75% of patients who have stage I sarcoidosis will undergo spontaneous remission within 2 years after presentation. Erythema nodosum at initial presentation increases the likelihood of spontaneous remission. Those patients in whom bilateral hilar lymphadenopathy fails to remit within 2 years may remain stable, may undergo spontaneous remission at a later time, or may develop progressive pulmonary disease. No more than 10% to 15% of patients develop progressive pulmonary disease.

The frequency of symptoms is higher in patients with stage II sarcoidosis, but asymptomatic cases are not unusual. Symptoms may be primarily systemic, as in stage I disease, or may arise from pulmonary involvement. A presentation of extensive radiographic abnormalities associated with only minimal respiratory symptoms is not uncommon. Roughly 50% of patients with stage II sarcoidosis will be in remission 2 years after presentation. Stage II disease is more likely to be progressive and to follow a chronic symptomatic course than stage I disease.

Stage III disease is found at presentation in 5% to 15% of patients. Respiratory symptoms are common, but as in stage II disease, the chest radiograph may make the patient appear much worse than is actually the case. Only one third of patients with stage III sarcoidosis will be in remission 2 years after presentation. The disease commonly takes a chronic course that eventually leads to lung fibrosis. Certain extrapulmonary manifestations of chronic sarcoidosis, such as infiltrative skin disease, occur much

more often in patients with stage III disease than in patients with stage I or stage II disease. This chronic course of stage III disease is not surprising, because patients who are diagnosed at this point in the disease process may represent those persons who earlier had bilateral hilar lymphadenopathy (stages I and II) and failed to undergo spontaneous remission.

Unusual manifestations of intrathoracic sarcoidosis include pleural effusion, alveolar infiltrates, large nodular opacities, cavitation, atelectasis, and calcification. Pleural involvement occurs in 1% to 4% of patients and consists of pleural effusion or thickening of the visceral and parietal pleurae. Effusions are rarely large, and they typically contain a high percentage of lymphocytes. Pleural biopsy reveals granulomas, and the major differential diagnosis to consider in patients with pleural sarcoidosis is tuberculosis. Alveolar sarcoidosis has variable presentations, ranging from patchy infiltrates in asymptomatic patients to rather extensive air-space consolidation in patients with respiratory failure. Nodules of 2 to 10 cm in diameter occur and rarely cavitate. The differential diagnosis of nodular sarcoidosis includes fungal infection, tuberculous infection, and, especially, metastatic tumor. Atelectasis can be caused by endobronchial sarcoidosis. Calcification in lymph nodes is a late manifestation of disease and is seen in 5% of patients.

Necrotizing sarcoid granulomatosis, characterized by masses of confluent granulomas with some degree of vasculitis, is probably a variant of sarcoidosis. The two disorders have many features in common, including hilar lymphadenopathy and extrapulmonary granulomatous inflammation.

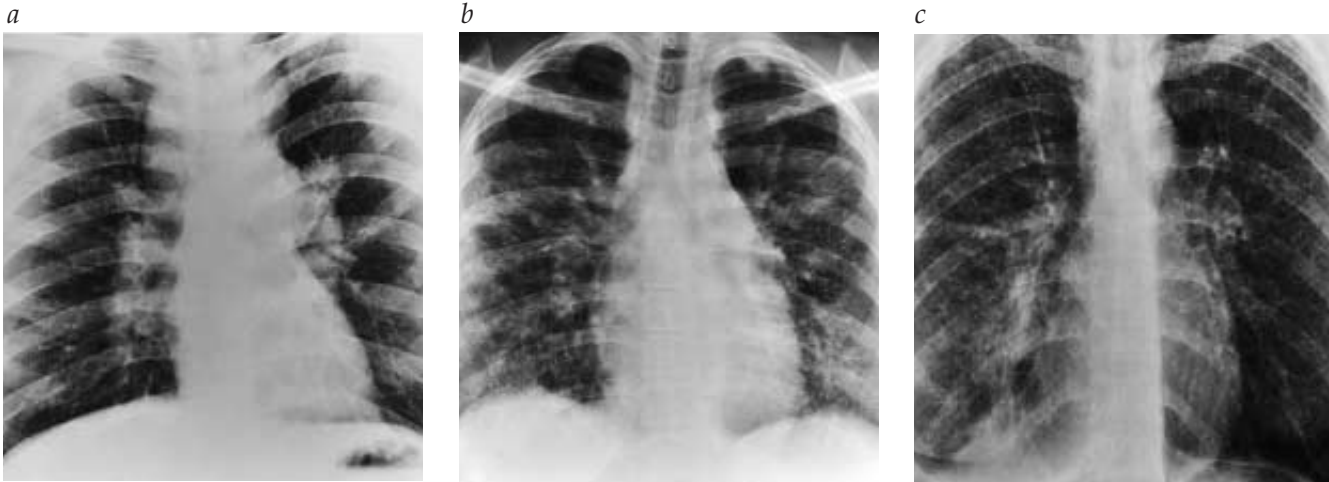


Figure 5 (a) In stage I sarcoidosis, the chest radiograph reveals bilateral hilar and right paratracheal adenopathy with normal lung parenchyma. (b) In stage II sarcoidosis, adenopathy and parenchymal infiltration are apparent on the radiograph. (c) Stage III sarcoidosis is characterized by parenchymal infiltration, without definite adenopathy.

Clinical Manifestations of Extrathoracic Sarcoidosis

Although extrathoracic sarcoidosis is a much less common cause of morbidity than intrathoracic disease, it can dominate the clinical picture in some patients.

Erythema nodosum, a nongranulomatous panniculitis, is the most common cutaneous manifestation of sarcoidosis. More than 90% of patients with sarcoidosis who develop erythema nodosum have a stage I radiograph; the other 10% have stage II radiographs. Granulomatous skin lesions occur in 10% to 30% of patients and are especially common in African Americans. Lupus pernio is a bluish-purple swollen lesion on the nose, cheeks, earlobes, fingers and toes, lips, or knees that may become disfiguring. Skin plaques tend to be violaceous, angular, and flat with a raised edge. Psoriasislike plaques may also be seen. Nodules may be elevated or may arise in the subcutaneous tissue. As a rule, these granulomatous skin manifestations of sarcoidosis are seen with chronic and persistent stage III pulmonary disease.

Ocular involvement occurs in about 25% of patients with sarcoidosis. The uveal tract is most often affected; sarcoidosis is responsible for 2% to 4% of all cases of uveitis. Anterior uveal tract disease with iridocyclitis usually presents as tearing and photophobia with little or no pain. Heerfordt syndrome, or uveoparotid fever, is an uncommon manifestation of sarcoidosis that consists of uveitis, parotid enlargement, cranial nerve palsies, subacute meningitis, and systemic symptoms. Posterior uveitis (chorioretinitis) causes blurring of vision, or patients may be asymptomatic. Chorioretinitis may be difficult to detect when anterior uveitis is present.

The nervous system is affected in fewer than 5% of patients with sarcoidosis. Central nervous system manifestations include chronic meningitis, encephalopathy, hypothalamic lesions, cranial nerve involvement, and seizures. Peripheral sensory and motor neuropathy may be seen. Chronic meningitis in sarcoidosis may be difficult to distinguish from tuberculous or fungal meningitis and is typically associated with cerebrospinal fluid lymphocytosis, increased CSF protein levels, and, sometimes, low CSF glucose levels. Sarcoidosis can give rise to space-occupying lesions in various locations, resulting in diverse neurologic abnormalities.

Evidence of cardiac sarcoidosis is seen much more often at autopsy than would be suspected on the basis of clinical manifestations. Rhythm disturbances are the most common manifestations

of cardiac sarcoidosis. Both ventricular tachyarrhythmias and complete heart block can occur and can lead to sudden death. Other, less common features of cardiac sarcoidosis include heart failure, pericardial disease, papillary muscle dysfunction, and ventricular aneurysm in the absence of coronary artery disease. Echocardiography, Holter monitoring, and thallium-201 scanning may show abnormalities but do not necessarily indicate that granulomas are in the myocardium. Age, comorbidities, and the types of abnormalities must be taken into account to assess the probability of myocardial sarcoidosis.

Bone or joint involvement is observed in 1% to 10% of patients. Bone disease is characterized by cystic lesions and tends to be restricted to the fingers and toes. Swollen digits may be seen. Synovial sarcoidosis can present as monoarticular or polyarticular chronic arthritis.

Patients with sarcoidosis often have liver and spleen granulomas, but liver dysfunction or massive splenomegaly is unusual. In rare cases, sarcoidosis leads to cirrhosis and portal hypertension. Upper respiratory tract involvement is usually manifested by nasal or laryngeal symptoms. Epistaxis and nasal congestion, which may be mistaken for allergic or vasomotor rhinitis, are common symptoms. Sarcoidosis should be considered when nasal obstruction is refractory to conventional therapy. Laryngeal sarcoidosis involves the supraglottic structures and, on occasion, the vocal cords. Hoarseness is the most common symptom, but upper airway obstruction can occur.

Endocrine abnormalities in sarcoidosis include hypercalcemia and pituitary dysfunction, which may present as diabetes insipidus. Hypercalcemia is seen much less often than hypercalciuria. Hypercalcemia and hypercalciuria in sarcoidosis are caused by the unregulated, increased synthesis of 1,25-dihydroxyvitamin D by activated macrophages in the granulomas, resulting in an increase in calcium absorption in the gut.

Diagnosis

The diagnosis of sarcoidosis is established by demonstration of noncaseating granulomas in tissue [see Figure 6] and exclusion of other causes of granulomas. Intrathoracic sarcoidosis is diagnosed most easily by bronchoscopy with transbronchial lung biopsy. The yield of transbronchial lung biopsy depends on the radiographic stage. In patients with pulmonary infiltrates (stages II and

III), transbronchial lung biopsy demonstrates noncaseating granulomas in approximately 90% of cases. In stage I disease, the yield is 60% to 70%. If a diagnosis is not established by transbronchial lung biopsy, mediastinoscopy is indicated and will provide a diagnosis in over 95% of cases. Biopsy of extrapulmonary tissues can be used for diagnosis when clinically indicated (e.g., in patients with peripheral lymph node enlargement or skin lesions).

When noncaseating granulomas are found in tissue, possible causes of granuloma formation other than sarcoidosis must always be excluded. Occasionally, lymphoma or carcinoma is associated with granulomatous inflammation in local lymph nodes. Infectious causes of granulomas in the lungs and mediastinal lymph nodes, particularly tuberculosis and histoplasmosis, should be ruled out. A tuberculin skin test, fungal serologic studies, and the use of special stains on tissue biopsy specimens are necessary. For example, such findings as hilar lymphadenopathy, pulmonary infiltrates, and noncaseating granulomas in tissue may prompt the physician to make a presumptive diagnosis of sarcoidosis while these special studies are pending. If a high complement fixation titer for histoplasmosis were detected, the diagnosis would be changed to histoplasmosis.

At the time of bronchoscopy, BAL is usually performed in addition to biopsy. In active sarcoidosis, the lavage fluid usually shows increased numbers of lymphocytes, and the ratio of helper T cells to suppressor-cytotoxic T cells is elevated. Because other pulmonary disorders, both infectious and noninfectious, may be associated with lymphocytosis, this finding lacks diagnostic specificity. Hypersensitivity pneumonitis may be confused with sarcoidosis because both disorders are associated with lavage fluid lymphocytosis and noncaseating granulomas in tissue. However, an inverted ratio of helper T cells to suppressor-cytotoxic T cells is typically seen in hypersensitivity pneumonitis. Levels of ACE are usually elevated in active sarcoidosis. Therefore, the measurement of ACE levels may aid in the diagnosis of sarcoidosis. However, it is not clear whether this test has much diagnostic value beyond satisfying essential pathologic criteria. Diagnosis of sarcoidosis on the basis of an elevated ACE level alone, without confirmation of the diagnosis by demonstration of noncaseating granulomas in tissue, is not recommended. Elevated ACE levels have also been detected in miliary tuberculosis, leprosy, biliary cirrhosis, silicosis, and asbestosis. With the exception of miliary tuberculosis, it is not

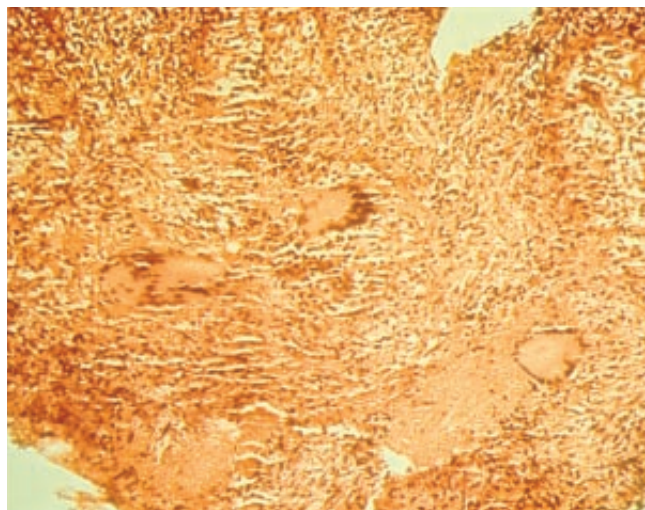


Figure 6 Noncaseating granulomas can be seen in this tissue biopsy specimen from a patient with sarcoidosis.

likely that these diseases would be clinically confused with sarcoidosis. When the ACE level is elevated, repeated ACE measurements during treatment of sarcoidosis may be helpful because the ACE level often correlates with disease activity.

Differential Diagnosis

The differential diagnosis of stage I sarcoidosis primarily includes lymphoma and granulomatous infections such as tuberculosis and histoplasmosis. More infrequent causes of bilateral hilar lymphadenopathy include metastatic carcinoma (especially renal cell carcinoma) and amyloidosis. Most patients who have lymphoma that manifests as bilateral hilar lymphadenopathy have peripheral lymphadenopathy, splenomegaly, or systemic symptoms such as fever, weight loss, and night sweats. Young adults who present with asymptomatic bilateral hilar adenopathy but neither peripheral lymphadenopathy nor splenomegaly are very unlikely to have lymphoma. It is therefore reasonable to make a presumptive diagnosis of stage I sarcoidosis in such patients without confirming the diagnosis by examination of a tissue specimen. However, a tuberculin skin test and fungal serologic studies should be performed, and clinical and radiographic follow-up is required to ensure that there is no evidence of progression of the disease. If disease progression is observed, it is imperative to perform a tissue biopsy to establish the diagnosis.

Treatment

Glucocorticoids are standard therapy for symptomatic sarcoidosis, though there is no definitive proof that they influence long-term outcome. Most patients respond very well to therapy, and often, low dosages of prednisone (e.g., 15 mg every other day) may be effective in suppressing disease activity. A higher dosage (e.g., 40 to 60 mg/day) is usually given for a few weeks to induce regression of disease activity. The primary indication for glucocorticoids is symptomatic pulmonary involvement. Other indications include significant systemic symptoms (e.g., fever or weight loss), hypercalcemia, and involvement of extrapulmonary tissues that leads to established functional impairment or a risk of organ dysfunction. The required duration of therapy is uncertain. It is common practice to treat pulmonary sarcoidosis with prednisone for 1 year, then to withdraw the drug to see whether the disease is in remission. Relapses of the disease are treated in a similar fashion, with higher initial dosages of prednisone that are tapered to a low dosage for maintenance. Some patients relapse repeatedly as prednisone is withdrawn and require low-dose suppressive therapy indefinitely.

If the use of steroids is strictly contraindicated or if the patient does not respond to steroid therapy, methotrexate²² or chlorambucil may be tried. Chloroquine is often useful in patients with skin disease.

Lung transplantation in sarcoidosis has been associated with histologic evidence of recurrence in the transplanted lung, but the survival of these patients has been comparable to the survival of patients undergoing lung transplantation for other indications.²³

IDIOPATHIC PULMONARY FIBROSIS

IPF, also known as fibrosing alveolitis, is one of the most common causes of chronic diffuse infiltrative lung disease.²⁴ Although this disorder has characteristic clinical, radiographic, physiologic, and histopathologic features, none of these features is pathognomonic. Therefore, a diagnosis of IPF requires not only a compatible clinicopathologic picture but also the exclusion of all other causes of diffuse disease. For example, the pul-

monary manifestations of IPF may be indistinguishable from diffuse disease associated with collagen vascular disorders; asbestosis; chemotherapy-induced lung fibrosis and several closely associated disorders; bronchiolitis obliterans organizing pneumonia (BOOP); lymphocytic interstitial pneumonia (LIP); desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease (DIP/RBILD); acute interstitial pneumonia (AIP); and nonspecific interstitial pneumonia/fibrosis (NSIP/F).²⁴

Pathogenesis

The pathogenesis of IPF is not well understood. A viral trigger has been suspected of playing a role in certain instances because a substantial minority of patients date the onset of their respiratory symptoms to a flulike illness. Cigarette smoking, chronic aspiration, exposure to various environmental factors, and use of antidepressant drugs have been suggested as risk factors.²⁴ A genetic susceptibility may also be important. It may be that IPF results when a genetically susceptible person is exposed to a viral or environmental agent that triggers a set of events leading to a cascade of inflammatory, immune, and fibrotic processes in the lung.

The alveolitis of early IPF is characterized by an increase in the number of activated neutrophils and the presence of activated macrophages in the BAL specimen. Neutrophils may be attracted to the lung by an imbalance between macrophage-derived chemoattractant substances (e.g., tumor necrosis factor- α [TNF- α] and IL-8) and anti-inflammatory substances (e.g., interferon gamma and IL-10).²⁵ In some cases, the chemoattractants will be released in response to local immune complexes. Immune complexes have been detected in lung tissue, lavage liquid, and blood of patients with high-intensity neutrophilic alveolitis. Once in the lung, the neutrophils may cause local tissue injury by releasing various potentially toxic substances, such as oxygen radicals and proteolytic enzymes. Lung inflammation may eventually be followed by extensive fibrosis. It is possible that the chronic neutrophilic inflammation of IPF plays a role in the development of lung fibrosis. However, the fibrogenic process probably results in large part from the activity of lung macrophages. Macrophages from patients with IPF spontaneously release growth factors for fibroblasts, such as transforming growth factor- β , causing an increase in fibroblasts in the lung.³ The macrophages in this disease also release fibronectin, a substance that promotes binding and migration of fibroblasts. These macrophages spontaneously release fibroblast stimulatory factors, such as IL-1 β and TNF- α , that cause fibroblasts to secrete increased amounts of the constituents of the extracellular matrix. Thus, alveolar macrophages appear to play a critical role in the development of IPF.

Clinical Manifestations

As with other types of diffuse infiltrative lung disease, dyspnea on exertion and cough are the most prominent symptoms. Physical examination typically reveals fine dry inspiratory rales. Cyanosis may be noted when hypoxemia is severe, and features of cor pulmonale (e.g., elevated jugular venous pressure, edema, and a prominent pulmonic second heart sound) indicate advanced disease. Clubbing of the digits is noted in 25% to 50% of cases but is often absent early in the course of the disease. There are no other extrathoracic manifestations of disease. Clinical evidence of extrapulmonary disease (e.g., arthritis, skin disease, or serositis) suggests a systemic disorder, such as sarcoidosis or one of the collagen vascular diseases, rather than IPF.

Diagnosis

A diagnosis of IPF is established by correlating histopathologic and clinical findings. Clinically, IPF is suspected when a diffuse infiltrative lung disease occurs with no involvement of other organ systems and there is no apparent relation to infection, environmental exposure, or drugs. The chest radiograph shows no evidence of hilar adenopathy or pleural effusion. Laboratory tests in IPF are generally unrevealing, except for the presence of a positive antinuclear antibody or positive rheumatoid factor in up to 50% of cases. Thus, serum antinuclear antibody and rheumatoid factor cannot be relied on to differentiate IPF from diffuse infiltrative lung disease associated with collagen vascular disorders.

The initial approach to diagnosing IPF is to exclude as many causes of diffuse infiltrative lung disease as possible by a combination of history and clinical examination. However, a number of causes remain that cannot be reliably identified without a lung biopsy. Such causes include stage III sarcoidosis, lymphangitic carcinomatosis, lymphangioleiomyomatosis, eosinophilic granuloma, DIP/RBILD, NSIP/F, LIP, AIP, and the more diffuse forms of BOOP.

Imaging studies The radiographic features are nonspecific and most often consist of a bilateral reticular or reticulonodular pattern that typically appears in the lower lung fields; if cor pulmonale develops, enlargement of the pulmonary arteries and heart occurs. In as many as 10% of patients with symptomatic IPF, the chest radiograph may be entirely normal. Radiographic findings in patients with IPF are limited to the lung fields. Hilar lymphadenopathy or pleural effusion suggests a different cause of diffuse infiltrative lung disease.

HRCT may be helpful at this stage of the evaluation because the pattern of abnormalities seen in IPF is specific, and many of these other causes have characteristic and very different patterns.²⁶ Also, it is likely that HRCT would reveal abnormalities in cases in which the chest radiograph is normal.

The HRCT pattern in IPF includes patchy, peripheral, subpleural, bibasal reticular abnormalities with minimal ground-glass opacity. With advanced disease, honeycomb lung and traction bronchiectasis/bronchiolectasis, indicating end-stage lung fibrosis, are seen. Extensive areas of ground-glass haziness, indicating an acinar filling process, are not characteristic of IPF and may be seen in AIP, LIP, DIP/RBILD, and NSIP/F.

Pulmonary function testing The physiologic abnormalities of IPF are basically the same as those described for diffuse infiltrative lung disease. The classic composite physiologic picture of IPF is reduced DL_{CO}, restriction of lung volume, exercise-induced oxygen desaturation, and absence of airflow obstruction. Some of the alterations correlate with the pathologic findings.²⁷

Histopathologic features The histopathologic features of IPF are nonspecific. Similar histopathologic findings are observed in diffuse infiltrative lung disease associated with collagen vascular disease, various types of drug-induced diffuse disease, and other disorders. Chronic fibrosis and a scant inflammatory cell infiltrate, the essential pathologic features of IPF, are common reactions to a variety of agents.

The histopathologic picture in IPF is termed usual interstitial pneumonitis (UIP) and is characterized by minimal interstitial inflammatory round cell infiltrate, widening of alveolar septa, and fibrosis with fibroblastic foci²⁸ [see Figure 7]. The distribution of the

lesion is irregular: areas of intense fibrosis can coexist with areas of near-normal lung in the same open lung biopsy specimen.

UIP must be differentiated from DIP/RBILD, AIP, LIP, NSIP/F, and BOOP, because of different prognoses²⁹ and treatment approaches (see below).

Lung biopsy Transbronchial lung biopsy is a sensitive tool for diagnosing sarcoidosis and lymphangitic cancer and may reveal pathologic features suggestive of IPF (i.e., fibrosis and widened alveolar septa with scant inflammatory cell infiltrate). Open lung biopsy is needed to exclude other causes of diffuse disease. It is up to the clinician to decide whether to proceed to open lung biopsy when clinical evaluation and transbronchial lung biopsy are highly suggestive of IPF. Open lung biopsy is advisable when there is any doubt about whether there is an infectious cause. Open lung biopsy should usually be performed in younger patients to establish the diagnosis of the underlying disorder with a reasonable degree of certainty.⁵ Older patients with typical clinical features and a compatible transbronchial lung biopsy result may be reasonably spared the morbidity associated with open lung biopsy. In certain cases, it may be reasonable to diagnose IPF without any tissue biopsy. For example, a tissue biopsy may not be needed to diagnose IPF in an elderly patient who has had progressive dyspnea on exertion for many months to years and who has fine, end-inspiratory crackles and clubbing of the digits on examination, bilateral coarse interstitial infiltrates, low-titer serum antinuclear antibody, and no evidence of an environmental or a drug-related disorder.

Prognosis and Treatment

The median survival for patients with newly diagnosed IPF is 2 to 3 years.³⁰ Most deaths result from progressive pulmonary impairment.

Prednisone is used to treat progressive disease, and about 20% to 30% of patients receiving prednisone show symptomatic, radiographic, and functional improvement.²⁴ However, even those who respond usually do not show dramatic improvement, unlike patients with symptomatic sarcoidosis who are treated with glucocorticoids. The response to prednisone is better if fibrosis is less prominent than inflammation on open lung biopsy; response is typically poorer if fibrosis predominates.³¹ However, because lung involvement is heterogeneous, the histopathologic features may vary in different regions of the lungs. Thus, open lung biopsy is not indicated for the purpose of deciding whether to treat symptomatic patients with glucocorticoids. Studies of the relation between HRCT results and improvement in pulmonary function suggest that the extent of the ground-glass pattern of attenuation correlates with responsiveness to glucocorticoids.³¹ One of the best predictors of long-term outcome is a short-term (6 to 12 weeks) response to prednisone, with responders having a better prognosis.³¹

Cyclophosphamide or azathioprine has also been used in conjunction with prednisone, usually when prednisone alone has proved to be unsuccessful.²⁴ Predictors of a beneficial response to cytotoxic therapy include short duration of symptoms and a good transient response to glucocorticoid therapy.³² Occasionally, patients who fail to respond to prednisone therapy show improvement with combined immunosuppressive therapy or with colchicine.³³ Single-lung transplantation has also been used successfully for end-stage lung fibrosis.³⁴

Several new, innovative therapies for IPF are being assessed.³⁵ In a recently published randomized controlled trial, a combination of interferon gamma-1b and low-dose prednisolone given to

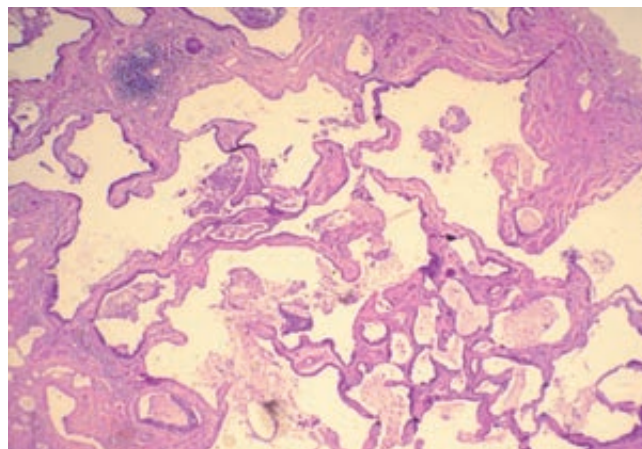


Figure 7 Usual interstitial pneumonia is characterized by alveolar septal thickening, caused by fibrosis; minimal inflammatory cell infiltrate; honeycombing; and irregular involvement from one region to the next.

IPF patients unresponsive to steroids or other immunosuppressive agents led to greater improvement in lung function over 12 months than was seen with prednisolone alone.³⁶

DESQUAMATIVE INTERSTITIAL PNEUMONIA/RESPIRATORY BRONCHIOLITIS INTERSTITIAL LUNG DISEASE

Patients with DIP/RBILD present with cough and dyspnea of insidious onset.²⁸ Clubbing of digits is present in about 50% of cases. The average age at onset of symptoms is the early to middle 40s, which is significantly younger than the age at onset of IPF symptoms. Men are affected twice as often as women. Almost all of these patients are cigarette smokers, and many investigators feel that the disease is caused by tobacco use.

The chest radiograph typically shows vague, bibasilar opacities that correlate with ground-glass densities on HRCT. Some studies have found more reticulonodular and linear changes.²⁸

The lung biopsy specimen in DIP/RBILD is characterized by a fairly homogeneous pattern in which alveolar spaces are filled with pigmented alveolar macrophages. These accumulations of macrophages are often accentuated in peribronchiolar air spaces, sparing the more distal air spaces²⁸ [see Figure 8].

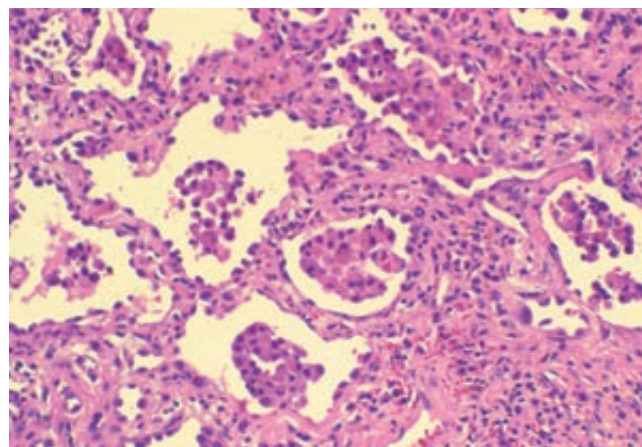


Figure 8 Desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease. The alveoli and septal walls are filled with macrophages, and no fibrosis is apparent.

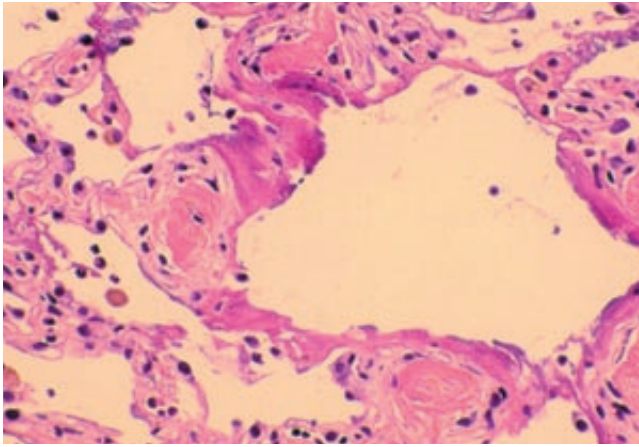


Figure 9 Acute interstitial pneumonia. The biopsy specimen shows diffuse alveolar damage.

Discontinuance of smoking has been associated with improvement of symptoms. In some series, many patients improve without therapy, and steroids have been associated with a beneficial response in about 60%. The mortality is 20% to 30%, and the mean survival is 12 years.

ACUTE INTERSTITIAL PNEUMONIA

Acute interstitial pneumonia is a distinct idiopathic condition that produces respiratory failure of rapid onset.³⁷ AIP is also known as Hamman-Rich syndrome.

The clinical presentation of patients with AIP is similar to that of patients with ARDS except that, in AIP patients, no predisposing factor can be identified. Patients often have had a viral prodrome before onset. Over a period of less than 30 days, symptoms of dyspnea, cough with mucoid sputum, and fever evolve into respiratory failure. Imaging studies by routine chest radiograph or HRCT show diffuse pulmonary infiltrates with ground-glass changes and consolidation.

The diagnosis is made by the recognition of a clinical illness compatible with ARDS in the absence of a predisposing factor after the exclusion of other alveolar-filling diseases such as infectious pneumonia (especially PCP), alveolar hemorrhage, and eosinophilic pneumonia. The diagnosis is usually made through bronchoscopy with bronchoalveolar lavage.

AIP is characterized pathologically by the findings of diffuse alveolar damage. It cannot be differentiated from ARDS caused by sepsis, toxins, or shock [see Figure 9]. AIP evolves through the same sequence of pathologic patterns as ARDS [see 14:X Pulmonary Edema].

Treatment is largely supportive through use of oxygen with either noninvasive or invasive mechanical ventilation. Steroids are advocated, but their use is not supported by controlled trials.

The mean 6-month mortality is 78%.

LYMPHOCYTIC INTERSTITIAL PNEUMONIA

LIP is an interstitial lung disease characterized by diffuse or localized lymphocytic infiltration of the alveolar and interstitial areas of the lung. This disorder can occur in association with a number of autoimmune processes (especially Sjögren syndrome), dysproteinemias, viral infections (HIV), bone marrow transplantation, or as an idiopathic process.

LIP occurs more often in women than men. The mean age of onset is 56 years. Patients present with dyspnea and cough, but

the associated disorder may dominate the clinical picture. Rales and lymphadenopathy are common physical findings.

Imaging studies typically show reticulonodular infiltrates. The presence of hilar or mediastinal adenopathy or pleural effusion suggests lymphoma. HRCT will usually show a mixture of interstitial and alveolar (ground-glass) changes.

Bronchoscopic specimens can be useful, showing a striking lymphocytosis on BAL and revealing lymphocytic infiltration on transbronchial lung biopsy [see Figure 10]. The pathologist will often need to use special studies to differentiate LIP from neoplastic forms of lymphocytic infiltration of the lung.

Patients with LIP should be treated for their underlying disorder, if present. Some patients respond to steroids, though many require immunosuppressive agents.

NONSPECIFIC INTERSTITIAL PNEUMONIA/FIBROSIS

NSIP/F has often been confused with IPF. In one retrospective analysis of patients that had been diagnosed with IPF, 14% were found to have NSIP/F and were noted to have a better prognosis than patients with IPF.²⁹

NSIP/F occurs in middle-aged adults, with a mean age of onset of 49 years, but it can also affect children and older adults. There is a slight female predominance. Although some cases are idiopathic, many of the patients have collagen vascular diseases, and some have a history of environmental or therapeutic drug exposures. A few of the patients have a history of an acute lung injury, such as that caused by pneumonia, ARDS, or surgery.

Dyspnea, cough, and sometimes fever are the dominant clinical features, with imaging studies showing bilateral interstitial infiltrates. HRCT scanning demonstrates bilateral, patchy areas of ground-glass abnormality.

NSIP/F can only be diagnosed by lung biopsy. As with IPF, transbronchial lung biopsy is not likely to produce an adequate specimen, and therefore open biopsy is required. Pathologically, NSIP/F is characterized by a temporally uniform mixture of alveolar wall inflammation (mostly lymphocytes and plasma cells) and fibrosis [see Figure 11].

Steroids provide improvement in more than half of the patients with NSIP/F, and the prognosis for patients with NSIP/F is significantly better than that for patients with IPF.³⁸

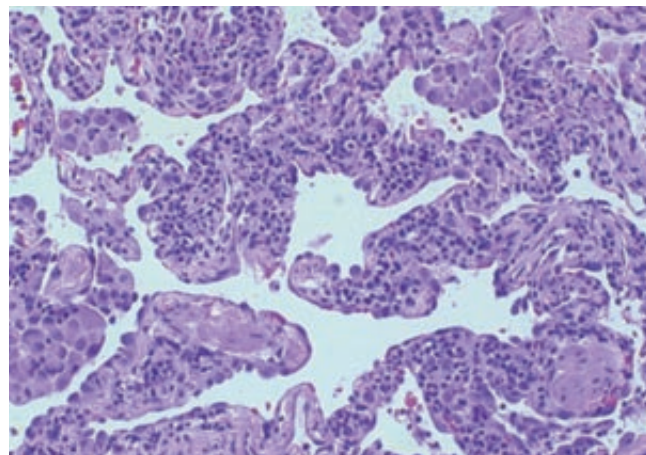


Figure 10 Lymphocytic interstitial pneumonia. The biopsy specimen shows infiltration of the alveolar walls and alveoli with mature lymphocytes.

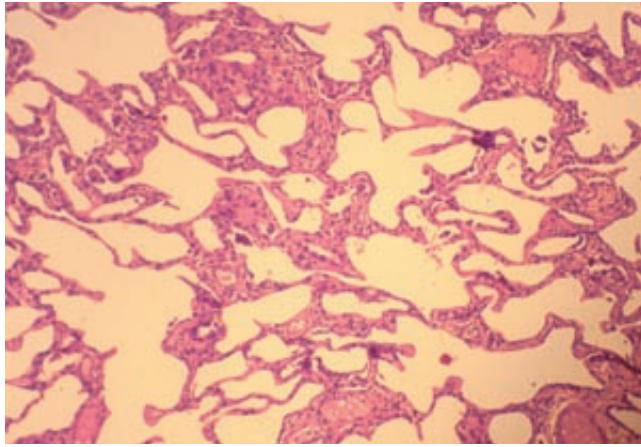


Figure 11 Nonspecific interstitial pneumonia/fibrosis. The biopsy specimen shows a temporally uniform mixture of alveolar wall inflammation (mostly lymphocytes and plasma cells and fibrosis).

BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA

BOOP [see 14:IV *Focal and Multifocal Lung Disease*], also called cryptogenic organizing pneumonitis,³⁹ occurs partly in the interstitium, partly within the alveoli, and partly in the small airways. BOOP is another disorder sometimes incorrectly diagnosed as IPF. The disease may result from any number of secondary causes, including inhalation of toxic fumes (e.g., oxides of nitrogen), viral infections, aspiration, lung transplantation, collagen vascular disorders, and other lung diseases, such as IPF and hypersensitivity pneumonitis.

Clinical Manifestations

BOOP occurs in three clinical patterns: symptomatic idiopathic, secondary, and focal asymptomatic.⁴⁰ Although a thorough history sometimes identifies one of the secondary causes mentioned above, in some patients with idiopathic BOOP, an open lung biopsy is required to distinguish the disease from other diffuse parenchymal processes.

Patients with BOOP are usually 50 to 60 years of age. The illness frequently begins abruptly and is characterized by dry cough and dyspnea; fever, malaise, and fatigue are more common in patients with BOOP than in those with IPF. Physical examination sometimes discloses rales that are often associated with wheezes. Clubbing of the digits, which is common in IPF, is absent.

Diagnosis

The diagnosis of BOOP is made by the correlation of the clinical findings with the results of imaging studies, particularly HRCT. Lung biopsy is often required in those patients with idiopathic BOOP.

The chest radiograph typically shows bilateral patchy alveolar or ground-glass infiltrates, in contrast to the interstitial infiltrates that occur in IPF. HRCT often shows bilateral areas of consolidation involving mainly the subpleural region or peribronchovascular region, or both, that are quite suggestive of the diagnosis.⁴¹ Pulmonary function tests demonstrate obstruction, restriction, or a mixed pattern with decreased diffusing capacity and hypoxemia.

The lung biopsy in BOOP is characterized by the presence of intraluminal plugs of connective tissue in the bronchioles, alveolar ducts, and alveolar spaces [see *Figure 12*].

Treatment

Treatment with glucocorticoids has been quite successful, and many patients respond dramatically within days of starting therapy. When glucocorticoids are withdrawn, however, many patients relapse and experience recurrent systemic symptoms, infiltrates, and hypoxemia. Patients with focal asymptomatic BOOP do not require therapy.

COLLAGEN VASCULAR DISEASES WITH ASSOCIATED PULMONARY INVOLVEMENT

Collagen vascular diseases commonly affect the lung. As many as two thirds of patients have clinical evidence of pleuropulmonary involvement, and nearly all have abnormal findings at autopsy. The immune mechanism is thought to be immune complex deposition, but the evidence that this mechanism is at work is more convincing in some collagen vascular disorders than in others. Pulmonary function tests in patients with interstitial infiltrates and fibrosis show restriction, small airway obstruction, and reduced DL_{CO} with hypoxemia at rest, which worsens with exercise. HRCT of the chest often detects subtle interstitial disease that cannot be seen by routine chest radiography. Although the chronic interstitial disease seen in some of these disorders is pathologically indistinguishable from IPF, patients with a collagen vascular disease seem to have a better prognosis than those with IPF⁴²; this is true even for those patients in whom collagen vascular disease develops after IPF.⁴³ Other patients with collagen vascular disease will have a pathologic pattern consistent with one of the other IPF-like disorders such as NSIP/F or BOOP.

Systemic Lupus Erythematosus

SLE is one of the most prevalent of the collagen vascular diseases, especially in African-American women of childbearing age; however, as many as 18% of cases occur after the fifth decade of life. Drug-induced SLE is a common clinical problem, especially in elderly patients with heart disease. Drugs that commonly cause SLE include hydralazine, procainamide, isoniazid, phenytoin, quinidine, methyl dopa, and several of the beta-blocking agents. A few other drugs have been implicated, but the evidence is less strong.

Pleuropulmonary complications of SLE occur frequently (in 38% to 89% of cases) and often must be differentiated from infec-

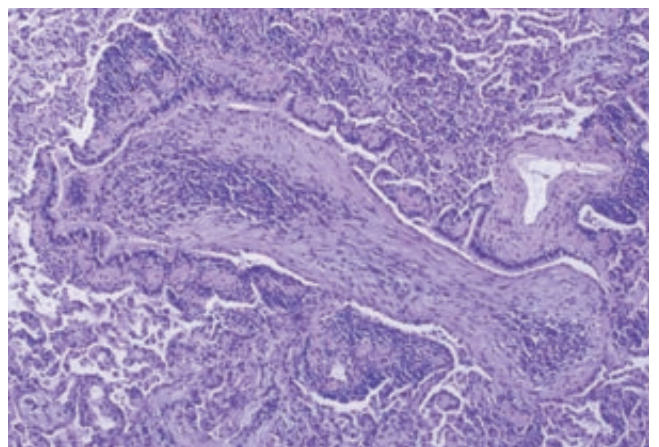


Figure 12 Bronchiolitis obliterans organizing pneumonia. The biopsy specimen shows intraluminal plugs of connective tissue in the bronchioles, alveolar ducts, and alveolar spaces.

tions.⁴⁴ Pleural disease, atelectasis, acute lupus pneumonitis, and chronic interstitial pneumonitis are the most common clinical problems. Less commonly, alveolar hemorrhage or pulmonary vascular disease (acute reversible hypoxemia syndrome, vasculitis, or thromboembolism) may occur. Pleuropulmonary disease is frequently the presentation of patients with drug-induced SLE.

Acute lupus pneumonitis initially presents as sudden onset of cough and dyspnea. Radiographically, it appears as patchy basilar opacities. Occasionally, radiography shows only horizontal linear shadows that have been attributed to small areas of atelectasis; patients in whom this occurs usually respond well to glucocorticoids.

Chronic interstitial pneumonitis occurs as a complication in about 10% of patients with SLE. Many of the patients with chronic interstitial pneumonitis have mild, often asymptomatic disease detectable only by lung function testing and HRCT. Some cases are the result of prior episodes of acute lupus pneumonitis. Pathologically, most of these cases are similar to cases of NSIP/F. Rarely, chronic interstitial pneumonitis evolves into severe pulmonary fibrosis. Steroids and other immunosuppressive agents may be beneficial, but no trials have been performed to investigate this.

Patients with SLE may present with overwhelming alveolar hemorrhage or have occult hemorrhage during the course of their disease. Severe alveolar hemorrhage in SLE is associated with a 70% mortality. The symptoms are cough and dyspnea with or without hemoptysis; chest radiographs show fluffy alveolar infiltrates that may be patchy or confluent. Treatment is similar to that of Goodpasture syndrome and includes plasmapheresis and immunosuppressive therapy [see 10:V *Glomerular Diseases*].

Rheumatoid Arthritis

Although the incidence of rheumatoid arthritis is higher in women than in men, pleuropulmonary complications occur more frequently in men.⁴⁵ Pleuropulmonary complications are clinically apparent in up to 14% of patients within 2 years of presentation⁴⁶ and in approximately 50% of patients over the course of the illness; a much higher percentage have pathologic involvement. In occasional cases, thoracic involvement becomes apparent before the articular disease, making diagnosis difficult.

The most frequent pleuropulmonary problems are interstitial lung disease, bronchiolitis, pleural disease, and parenchymal rheumatoid nodules. Less common problems include chronic airflow obstruction, bronchiectasis, BOOP, bronchiolitis obliterans, and pulmonary vasculopathy. These problems are usually associated with active arthritis, high titers of rheumatoid factor, circulating immune complexes, and cryoglobulinemia.

Diffuse interstitial pneumonitis with fibrosis is the most common and serious pulmonary problem in patients with rheumatoid arthritis. Dyspnea, sometimes with cough, is the symptom that occurs most frequently. Clubbing of the fingers may be present. The chest radiograph evolves from fine nodularity to coarse reticulation and finally to a honeycomb pattern. Results of BAL may be abnormal, demonstrating increased numbers of lymphocytes, neutrophils, eosinophils, or all three; this variability has not been shown to have a bearing on management. In patients with interstitial disease that is characterized by increased cellularity in lung biopsy specimens or the presence of progressive symptoms, glucocorticoids should be administered.

Rheumatoid (necrobiotic) nodules may be found in many tissues, including the lung parenchyma, endobronchial mucosa, and pleurae; in any of these locations, the nodules may cavitate. These lesions have a characteristic histopathologic appearance on

microscopic examination; unless percutaneous transthoracic needle biopsy or open lung biopsy is performed, such lesions can be difficult to differentiate from those of malignancy or tuberculosis. Most rheumatoid nodules do not cause symptoms, and treatment is rarely necessary once a diagnosis is established.

Progressive Systemic Sclerosis

Progressive systemic sclerosis (PSS), also called scleroderma, is a disorder that predominantly affects women in the fourth to sixth decades of life. The prognosis is unfavorable, especially in African Americans, men, and patients with pulmonary disease.

Pulmonary complications, particularly interstitial lung disease, frequently develop, occurring in as many as 90% of confirmed cases of PSS.⁴⁷ Interstitial lung disease in PSS is characterized by basilar reticular or reticulonodular fine infiltrates that become coarser as the disease progresses. In addition, radiography may show a loss of volume over time, and pneumothorax may occur. Evidence of pulmonary hypertension may be greater than would be expected from the degree of radiographic abnormality or pulmonary function disturbance, especially when Raynaud phenomenon is part of the clinical syndrome.

Glucocorticoids are not useful as therapy for interstitial lung disease associated with PSS; cyclophosphamide may be effective in patients who are shown by BAL to have active alveolitis.⁴⁷ As a result of esophageal motility disturbance, aspiration of gastric and esophageal contents often occurs; aspiration occurs more frequently when patients are in the recumbent position. Aspiration can be prevented by elevating the upper body to the near-upright position.

CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) is a variant of PSS. Patients with CREST syndrome have prominent pulmonary vascular disease. This pulmonary hypertension may be associated with interstitial fibrosis, as is seen in PSS, or it may occur as an isolated finding [see 15:V *Scleroderma and Related Diseases*].

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are autoimmune disorders that are characterized by weakness and occasionally by pain in proximal limb and neck muscles, skin rash (dermatomyositis), and neoplasm. The most frequent pulmonary complications of polymyositis and dermatomyositis are respiratory failure caused by respiratory muscle weakness, aspiration secondary to posterior pharyngeal and proximal esophageal weakness, and interstitial lung disease.⁴⁸

Interstitial lung disease is seen in a minority of patients and may be associated with anti-Jo-1 antibody, an autoantibody that is specific to the cellular enzyme histidyl-tRNA synthetase. These patients may have BOOP, pulmonary fibrosis, or diffuse alveolar damage. In contrast to the interstitial disease associated with many of the other connective tissue disorders, that associated with polymyositis and dermatomyositis responds well to glucocorticoid therapy.

Sjögren Syndrome

Sjögren syndrome comprises the triad of keratoconjunctivitis sicca, xerostomia, and recurrent swelling of the parotid glands and is often (in 60% of cases) associated with other collagen vascular diseases. Sjögren syndrome frequently includes pleuropulmonary problems, but in many cases, these problems are secondary to the underlying connective tissue disease. Thoracic complications that may be directly related to Sjögren syndrome include interstitial

infiltrates, often lymphocytic in nature (LIP); pleurisy with or without effusion; follicular bronchiolitis; and desiccation of the tracheobronchial tree, producing bronchiectasis and recurrent bronchitis or pneumonitis.⁴⁹

Dyspnea is the primary symptom of the interstitial disease associated with Sjögren syndrome, whereas hoarseness and cough that is productive of thick, tenacious sputum are symptoms of laryngeal and tracheobronchial involvement. Chest radiography may show interstitial infiltrates with a prominent nodular component. These infiltrates have a lymphoplasmacytic histology that can be difficult to differentiate from that seen in patients with lymphoma. Results of pulmonary function tests demonstrate restrictive, obstructive, or mixed patterns. The lymphocytic interstitial pneumonitis and bronchiolitis associated with Sjögren syndrome respond to glucocorticoid treatment or immunosuppressive therapy.

Mixed Connective Tissue Disease

Several reports have described patients who have features of SLE, PSS, and polymyositis, often with associated pulmonary disease.⁵⁰ A hallmark of such mixed connective tissue disease is the presence of high titers of antibodies to extractable nuclear ribonucleoprotein (anti-nRNP). This syndrome is usually a relatively benign disease that responds well to glucocorticoids, although some cases display a less benign course that is associated with fatal diffuse interstitial lung disease or pulmonary hypertension.

EOSINOPHILIC GRANULOMA OF THE LUNG

Eosinophilic granuloma of the lung, or pulmonary histiocytosis X, is an uncommon cause of diffuse infiltrative lung disease that primarily affects persons who are 20 to 50 years of age.⁵¹ The disease is uncommon in African Americans and extraordinarily rare in Asians. The etiology of eosinophilic granuloma is unknown, but there is a strong association with cigarette smoking. In children and young adults, eosinophilic granuloma is a systemic disease with a similar histologic appearance, and either diabetes insipidus resulting from pituitary involvement or eosinophilic granuloma of bone may be seen in 15% to 20% of patients.

Clinical Manifestations

Most patients with pulmonary eosinophilic granuloma have cough or dyspnea, but as many as 25% of affected persons have only radiographic abnormalities and no symptoms. Between 10% and 20% of patients develop pneumothoraces, and a spontaneous pneumothorax may be the initial manifestation of the disease. The association of spontaneous pneumothorax with radiographic evidence of diffuse interstitial infiltrates suggests a diagnosis of eosinophilic granuloma or AIDS-related PCP.

The patterns seen on chest radiographs and HRCT in eosinophilic granuloma are variable. Nodular and ground-glass opacities with thick-walled cysts are typically present early in the course of the disease. Later, thin-walled cysts, linear opacities, and emphysematous lesions are seen.

Eosinophilic granuloma often causes a reduction in DL_{CO} and vital capacity. However, unlike most other types of diffuse infiltrative lung disease, airflow obstruction is a characteristic feature, particularly in the later stages of the disease. The high incidence of airflow obstruction in eosinophilic granuloma may result from bronchiolar involvement in earlier stages of the disease and from bullae in late-stage disease. Smoking may also be a contributing factor in the high frequency of airflow obstruction in this disorder. Significant impairment of exercise performance is frequent

and is greater than might be expected from the degree of volume restriction. Increasing wasted ventilation ratio (V_D/V_T) and falling P_{aO_2} with exercise result in poor exercise performance in patients with pulmonary vascular abnormalities.⁵²

Histopathologic Features

The histopathologic features of eosinophilic granuloma are unique and include the presence of cells that resemble Langerhans cells in the skin. These cells stain positively with anti-CD1a monoclonal antibody and are shown by electron microscopy to contain characteristic inclusions termed X bodies, or Birbeck granules.⁵¹ These cells can be seen in other types of diffuse infiltrative lung disease, but their numbers are much greater in eosinophilic granuloma. In patients with eosinophilic granuloma, $CD4^+$ T cells are in apposition to Langerhans cells, and there are increased numbers of neuroendocrine cells.⁵³ Granulocyte-macrophage colony-stimulating factor and TGF- β are found in the lesions, suggesting that these factors are potential mediators of the stimulation of Langerhans cells and fibroblasts, respectively. These findings suggest that the pathogenesis of eosinophilic granuloma involves interactions among these cells that result in fibroblast stimulation and fibrosis.

Diagnosis

The diagnosis of eosinophilic granuloma can be made most confidently by open lung biopsy. However, it has been suggested that the finding of more than 5% $CD1a^+$ cells in BAL fluid, along with an appropriate clinical and radiographic picture, may suffice for diagnosis.⁵¹ HRCT may prove to be a useful noninvasive technique for diagnosing eosinophilic granuloma.

Prognosis and Treatment

Patients with eosinophilic granuloma have a median survival of 6 years after diagnosis. Increased age, airflow obstruction, and hyperinflation are predictors of a poor prognosis.

Patients with eosinophilic granuloma have shown improvement after smoking cessation, and treatment with glucocorticoids has been reported to be effective, though no therapy has been sufficiently studied or has produced sufficiently convincing evidence of clinical benefit to justify a definitive recommendation.

ALVEOLAR PROTEINOSIS

Alveolar proteinosis is a rare disease of unknown etiology characterized by the intra-alveolar accumulation of a cellular lipoproteinaceous material that resembles surfactant.⁵⁴ The accumulation of surfactant-like material may result from increased production or decreased degradation of surfactant by macrophages. It has been proposed that underutilization of surfactant, with decreased return from alveoli to type II cells, may overwhelm the normal macrophage's ability to clear this substance. In addition, the lipoproteinaceous material may inhibit the macrophage's defense against infection, thereby producing the increased incidence of infection with intracellular pathogens that has been observed in patients with alveolar proteinosis. A disorder that is clinically similar to idiopathic alveolar proteinosis occurs in persons with acute silica exposure (usually sandblasters) and in patients with any of several hematologic disorders.

Clinical Manifestations

Patients with alveolar proteinosis present in one of three ways: (1) without symptoms but with an abnormal chest radiograph; (2) with abrupt onset of cough, fever, and chest pain caused by the disease and complicated by opportunistic infection (with *Nocar-*

dia species, fungi, or *Mycobacterium* species); and (3) with dyspnea and cough (sometimes productive) of gradual onset. Physical findings are often minimal. The chest radiograph or HRCT usually shows a bilateral alveolar filling process mimicking pulmonary edema but without Kerley B lines, pleural effusions, or enlargement of the central vasculature. In later stages of the disease, coarse interstitial markings resulting from superimposed fibrosis can be seen. An elevated serum lactate dehydrogenase level without elevation of other serum enzyme levels may help the physician make the diagnosis.

Histopathologic Features

The histopathologic changes in alveolar proteinosis include the presence of a granular, eosinophilic material within alveolar spaces that stains positively with the periodic acid-Schiff (PAS) reagent [see Figure 13]. Inflammation and fibrosis have been detected in some cases but are usually not prominent features. Electron microscopy reveals that the intra-alveolar substance contains numerous lamellar bodies, similar to those found in type II epithelial cells.

Diagnosis

Diagnosis of pulmonary alveolar proteinosis is made most conveniently by BAL. The effluent appears grossly turbid, and staining reveals large amounts of the PAS-positive material [see Figure 13]. PCP causes accumulation of a similar intra-alveolar substance, and this infection must be excluded by special stains. The lavage liquid should be cultured for *Nocardia* species, fungi, and *Mycobacterium* species.

Treatment

Treatment of alveolar proteinosis is indicated if significant dyspnea is present at the time of diagnosis or if lesser symptoms fail to remit spontaneously after an observation period of several months. Because some patients undergo spontaneous remission, it is preferable to wait several months whenever possible before instituting treatment. Therapy for pulmonary alveolar proteinosis consists of whole lung lavage with sterile saline. The non-lavaged lung is protected by a double-lumen endotracheal tube. Most patients improve substantially after removal of the alveolar

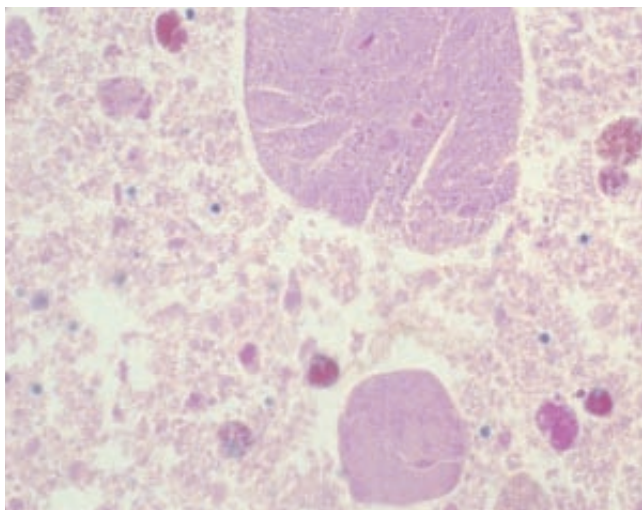


Figure 13 Bronchoalveolar lavage effluent reveals distinctive periodic acid-Schiff-positive material that is diagnostic of alveolar proteinosis.

material by lavage, and the contralateral lung can be lavaged at a later date.

EOSINOPHILIC PNEUMONIA

Pulmonary infiltrates with peripheral eosinophilia (PIE), occasionally with bronchospasm, are most often the result of acute hypersensitivity.⁵⁵ PIE comprises five syndromes: (1) simple pulmonary eosinophilia (Löffler syndrome); (2) prolonged pulmonary eosinophilia without asthma; (3) pulmonary eosinophilia with asthma [see 14:II *Asthma*]; (4) tropical pulmonary eosinophilia; and (5) pulmonary vasculitis (allergic granulomatosis and angiitis) [see 14:IV *Focal and Multifocal Lung Disease*]. In many of these disorders, substances secreted by eosinophils may help cause injury to the lung parenchyma, airways, or both. Although hypereosinophilic syndrome is not included in this classification, it too is occasionally associated with pulmonary infiltrates [see 14:VII *Disorders of the Chest Wall*]. A new disorder, acute eosinophilic pneumonia, has been described. Miscellaneous disorders that may also cause pulmonary infiltrates with blood eosinophilia include infections (e.g., tuberculosis, brucellosis, and fungal diseases), neoplastic diseases (e.g., bronchogenic carcinoma, Hodgkin disease, and immunoblastic lymphadenopathy), and immune processes (e.g., rheumatoid lung disease and sarcoidosis).

Simple Pulmonary Eosinophilia (Löffler Syndrome)

Löffler syndrome is characterized by transient and sometimes migratory infiltrates and by mild symptoms lasting less than 1 month. The infiltrates are usually homogeneous in density; either a single infiltrate or multiple infiltrates may occur. Symptoms may be absent, or dyspnea and dry cough may develop. Pathologic examination reveals interstitial and intra-alveolar accumulation of eosinophils, macrophages, and fluid. Löffler syndrome may be idiopathic or may be caused by parasitic infestation (e.g., with *Ascaris* or *Strongyloides*) or a drug (e.g., nitrofurantoin or penicillin). Therapy consists of removing the offending drug or treating the parasitic infestation; in most cases, no other therapy is required. Occasionally, patients with very symptomatic idiopathic disease require glucocorticoid therapy.

Prolonged Pulmonary Eosinophilia without Asthma

Prolonged pulmonary eosinophilia (chronic eosinophilic pneumonia) is an idiopathic disease that predominantly affects middle-aged women. It is characterized by productive cough, dyspnea, malaise, weight loss, night sweats, and fever associated with progressive peripheral pulmonary infiltrates. Hemoptysis and wheezing may be present, which may lead to confusion with other causes of PIE. Pulmonary function test results may be normal or may show either restriction or obstruction.⁵⁶ Open lung biopsy specimens show massive, mixed inflammatory infiltrates that have a high eosinophil content. Some pulmonary vessels may contain a few inflammatory cells, but true vasculitis is not present.

Diagnosis is based on the clinical syndrome, chest radiography, and whether or not blood eosinophilia is present. If results of chest radiography show typical dense peripheral infiltrates with central sparing, the diagnosis can be made without tissue examination. Usually, confirmatory information can be easily obtained by BAL and transbronchial lung biopsy.

Spontaneous remissions occur in as many as 10% of cases, but respiratory failure can also occur. Treatment with glucocorticoids is rapidly effective. Because relapses are frequent, the need to continue therapy for as long as 5 years is common.

Pulmonary Eosinophilia with Asthma

Allergic bronchopulmonary aspergillosis can cause pulmonary infiltrates in a patient with asthma [see 14:II *Asthma*].

Tropical Pulmonary Eosinophilia

The diagnosis of tropical pulmonary eosinophilia is suggested by the onset of asthma, fever, and marked blood eosinophilia and the presence of basilar mixed reticulonodular and alveolar infiltrates in a person who has recently traveled to the Far East.⁵⁷ This disease probably represents a form of filariasis (caused by *Wuchereria bancrofti* or other organisms). Despite therapy with diethylcarbamazine, many patients with this disorder have persistent inflammation and develop chronic interstitial disease.

Pulmonary Vasculitis (Allergic Granulomatosis and Angiitis)

Allergic granulomatosis and angiitis is a multisystem disorder characterized by vasculitis and necrotizing granulomatous inflammation that involve the lungs, nervous system, and skin.⁵⁸ Although the kidneys, heart, spleen, and GI tract are much less commonly affected, any organ or tissue may be involved. The prominence of eosinophilia and elevated IgE levels suggest that immediate hypersensitivity mechanisms may play an important role in pathogenesis [see 14:IV *Focal and Multifocal Lung Disease*].

Hypereosinophilic Syndrome

Hypereosinophilic syndrome is characterized by a wide range of clinical manifestations that occur when mature eosinophils infiltrate organs [see 5:VII *Nonmalignant Disorders of Leukocytes*].

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia is characterized by the acute onset of cough, dyspnea, fever, tachypnea, and rales; patients frequently require mechanical ventilation.⁵⁹ There is no clear association with cigarette smoking, environmental exposures, or drug intake, and patients tend to be young. Blood eosinophilia is not seen in most cases and is therefore not useful in diagnosing this disorder. Chest radiography and CT scanning show nonspecific combinations of alveolar (ground-glass) infiltrates and mixed alveolar-interstitial infiltrates that are sometimes associated with pleural effusions. The diagnosis can be made by bronchoalveolar lavage, which shows dramatic increases in the percentage of eosinophils, often to greater than 20% (the normal count is less than 1%). The administration of corticosteroids leads to rapid improvement, and relapses after steroid withdrawal are rare.

DIFFUSE ALVEOLAR HEMORRHAGE

Alveolar hemorrhage syndromes are characterized by diffuse parenchymal bleeding in the absence of blood aspiration, coagulopathy, elevation of pulmonary venous pressure, or an identifiable local cause (e.g., pulmonary emboli, cancer, or bronchitis). Frequently, diffuse alveolar hemorrhage is immunologically mediated and is often associated with glomerulonephritis.

The diseases that cause this syndrome are anti-glomerular basement membrane (anti-GBM) antibody disease (Goodpasture syndrome), idiopathic and rapidly progressive glomerulonephritis with or without immune complexes, vasculitis (e.g., Wegener granulomatosis), SLE, and idiopathic pulmonary hemosiderosis.⁶⁰ Although each of these disorders has suggestive clinical characteristics, in many cases the diagnosis cannot be made on clinical grounds. In addition, many patients with diffuse alveolar hemor-

rhage are acutely ill, making a rapid and specific evaluation necessary. A suggested diagnostic approach to such a patient consists of the following steps:

1. Obtain serum to test for anti-GBM antibody, antinuclear and anti-DNA antibody, antineutrophil cytoplasmic antibody, complement levels, and immune complexes.
2. Perform bronchoalveolar lavage with an iron stain of the obtained specimen. If hemosiderin-laden macrophages are present in large numbers, the diagnosis of alveolar hemorrhage is confirmed.
3. If step 1 fails to confirm a diagnosis or the results are not rapidly available, a biopsy of the kidney, lung, or another involved site should be performed. Immunofluorescence and electron microscopy with routine tissue examination should be included.

Almost all cases of alveolar hemorrhage can be rapidly diagnosed if the physician follows this approach. Treatment with high doses of intravenous glucocorticoids should be started while the evaluation is in progress, because alveolar hemorrhage can rapidly become life threatening.

Anti-GBM Antibody Disease

Anti-GBM antibody disease occurs in young men who smoke cigarettes. It is characterized by glomerulonephritis and diffuse alveolar hemorrhage⁶¹ and is caused by cytotoxic antibody against the $\alpha 3$ chain of type IV collagen in glomerular and alveolar basement membranes.

Many patients present with hemoptysis, which can be massive; however, some episodes of hemorrhage occur without hemoptysis. Most patients complain of dyspnea, and gross hematuria is common. Iron deficiency anemia is present in nearly all patients, and renal failure is present initially in 50% of cases.

Chest radiography initially shows fluffy perihilar acinar shadows; later, interstitial changes are seen. Pulmonary function tests demonstrate a restrictive pattern that improves with clinical resolution. DL_{CO} may be increased because of carbon monoxide uptake by extravascular hemoglobin. As the disease becomes chronic, interstitial radiographic changes and restrictive pulmonary function abnormalities may persist.

The diagnosis is confirmed when circulating anti-GBM antibody is detected (95% of patients have anti-GBM antibody) or linear deposits of IgG (occasionally IgA) are demonstrated on the glomerular or alveolar basement membrane. Anti-GBM antibody can also be eluted from the involved tissue.

Current recommendations for treatment include immunosuppressive agents, glucocorticoids, and plasmapheresis. Despite this aggressive therapy, 50% of patients die or require long-term dialysis after 2 years. Death is often caused by massive alveolar hemorrhage that is frequently precipitated by infection.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis, a disorder characterized by recurrent alveolar hemorrhage, occurs primarily in children (usually younger than 10 years of age) and young adults. When it occurs in adults, men are more often affected than women. Presentation of the disease is similar to that of Goodpasture syndrome except for the absence of renal involvement. Recurrent episodes of clinical and subclinical hemorrhage occur over time, resulting in lung damage that may be obstructive or restrictive in nature. Lung tissue shows changes of acute and chronic hemor-

rhage, but no vasculitis, immune complexes, or linear-staining deposits are found.

Patients with idiopathic pulmonary hemosiderosis are treated with glucocorticoids. Anecdotal evidence supports the use of immunosuppressive agents and plasmapheresis. Mean survival is 3 to 5 years, but spontaneous remissions and long-term survival do occur.

LYMPHANGIOLEIOMYOMATOSIS

The onset of lymphangioleiomyomatosis, which affects women of childbearing age almost exclusively, is often heralded by some combination of hemoptysis, pneumothorax, and chylothorax.⁶² At the onset of symptoms, there may be no diffuse radiographic abnormality, though a fine reticulonodular process, predominating at the lung bases, may be seen. Occasionally, there is a diffuse interstitial pattern in association with hyperinflation. In contrast to most diffuse infiltrative lung diseases, this disorder is often characterized by obstructive physiology with increased lung volumes, which has been attributed to peribronchial smooth muscle hypertrophy. In addition, DL_{CO} is usually decreased.

The diagnosis may be strongly suspected in a young non-smoking woman with chylothorax, fixed airway obstruction, and a diffuse interstitial radiographic pattern.⁶³ HRCT that shows diffuse, thin-walled cysts is diagnostic. These findings are identical to those of tuberous sclerosis. Open lung biopsy reveals diffuse proliferation of smooth muscle cells in the lung and visceral pleura, with cyst formation possibly secondary to bronchiolar obstruction. Approximately 50% of patients also have renal angiomyolipomas as an associated finding, often first identified on CT scanning. More than 75% of patients survive longer than 8 years.⁶⁴ There is some evidence that disease progression is hormone dependent, and some slowing of progression has been reported with oophorectomy, progesterone treatment, or a combination of the two. Lung transplantation may be considered for end-stage disease. Although transplantation may be lifesaving, there have been cases of recurrence in the transplanted lung, emphasizing the systemic nature of the disorder.

MICROLITHIASIS

Microolithiasis is an exceedingly rare, sometimes familial disorder that is most often diagnosed in an asymptomatic patient by a routine chest radiograph. The chest radiograph reveals a strikingly distinct and diffuse scattering of small calcified nodules that, on histopathologic examination, are seen to be calcified spheres that occupy the alveolar space.⁶⁵ This condition may progress to respiratory failure. A possible response to treatment with disodium etidronate, a diphosphonate, has been reported in a single patient.⁶⁶

Gerald W. Staton, Jr., M.D., participates in the speakers' bureaus of Glaxo-SmithKline and Intermune Pharmaceuticals, Inc.; Roland H. Ingram, Jr., M.D., has no commercial relationships with manufacturers of products or providers of services discussed in this subsection.

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Acknowledgments

Figure 1 Courtesy of Dr. Sam Aguayo, Veterans Affairs Medical Center, Decatur, Georgia.

Figure 4 Andy Christie.

Figures 7 through 12 Courtesy of Dr. Anthony Gal, Emory University Hospital, Decatur, Georgia.