TABLE 25. Clinical Presentations of Sarcoidosis that Do Not Warrant a Biopsy

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

H CONT.

Glucocorticoids are the mainstay of therapy. Treatment is usually limited to those with evidence of clinical symptoms from organ dysfunction. Because there is a high rate of spontaneous remission and stability, most treatment protocols favor a period of observation without therapy. The decision to initiate glucocorticoid therapy for sarcoidosis should be based on symptoms or physiologic impairment that is attributable to sarcoid disease. There is a paucity of randomized controlled trials to provide guidance regarding whether glucocorticoid therapy will provide definitive benefit. Retrospective data suggest that treatment with glucocorticoids may have short-term symptomatic benefit but does not clearly affect long-term disease outcomes. If glucocorticoids are used for treatment of sarcoidosis, studies suggest that low-dose or alternate-day treatment strategies are as efficacious as higher-dose strategies and appear to have fewer side effects. Studies also show that once glucocorticoid therapy has begun, many patients will remain on this therapy for prolonged periods. Tapering regimens are often prolonged and should be based on clear, attributable symptoms or physiologic metrics in conjunction with careful and frequent follow-up.

Pulmonary hypertension may develop in some individuals with sarcoidosis owing to multiple physiologic reasons, including DPLD, pulmonary vascular disease, pulmonary artery compression from significant lymphadenopathy, left ventricular dysfunction, and pulmonary venous occlusion. For individuals who develop pulmonary hypertension without evidence of left ventricular dysfunction, mortality is significantly higher, with a median survival of approximately 3 years. For this group of patients, as well as individuals with significant limitations due to pulmonary disease, lung transplantation is a viable therapeutic option.

For a discussion of the musculoskeletal manifestations of sarcoidosis, see MKSAP 17 Rheumatology. H

KEY POINTS

- Pulmonary involvement occurs in more than 90% of patients with sarcoidosis, but is often asymptomatic.
- Glucocorticoids are the mainstay of therapy for symptomatic pulmonary sarcoidosis.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a rare disorder that occurs sporadically in women or in association with tuberous sclerosis. It manifests as a diffuse cystic lung disease due to infiltration of smooth muscle cells into the pulmonary parenchyma. Genetic mutations within the cells lead to activation of the mammalian target of rapamycin (mTOR) pathway. Diagnosis is based on imaging studies with diffuse thin-walled cysts (**Figure 11**) as well as spontaneous pneumothorax, angiomyolipomas, and elevated vascular endothelial growth factor-D (VEGF-D). Hormonal therapy, which was used in the past, is not effective in altering the disease course. Immunosuppression with sirolimus has demonstrated promise in limiting progression of pulmonary disease in patients with lymphangioleiomyomatosis.

Occupational Lung Disease

When to Suspect an Occupational Lung Disease

Occupational lung diseases affect all aspects of the respiratory tract, from the upper airways to the lower airways and interstitium. Clinical manifestations may include rhinitis, asthma, COPD, constrictive bronchiolitis, and restrictive diseases. Symptom onset following exposure can be acute (reactive airways disease/small airways dysfunction as occurs in acute chlorine gas exposure) as well as prolonged or subacute with a significant latent period (as with asbestosis). Because the clinical presentation of occupational lung disease is highly variable and dependent on the particular exposure, a high index of suspicion is necessary to identify this disorder.

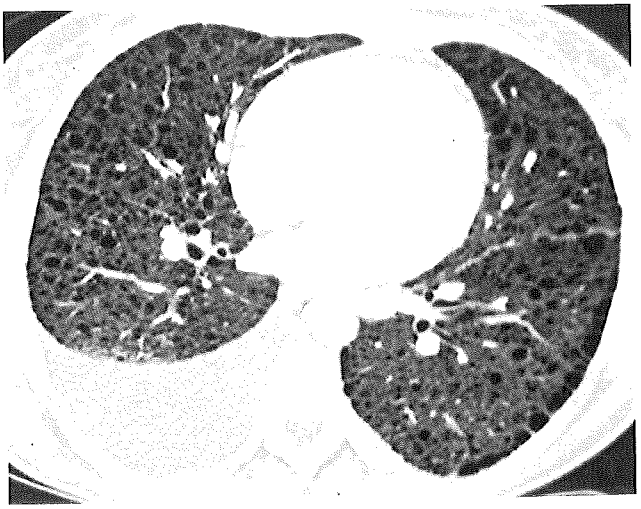

FIGURE 11. CT image of a patient with lymphangioleiomyomatosis showing diffuse thin-walled cysts and a right chylothorax.

Key Elements of the Exposure History

Factors that should raise the index of suspicion for an occupational-associated lung disease are shown in **Table 26**. Careful attention to historical details and a comprehensive occupational history are often crucial to identification of these disorders. In addition to identification of specific exposures, the duration and concentrations of exposures should be elicited. Owing to the variable time of onset of symptoms, the history should include exposures that date back many years. Furthermore, the interviewer should inquire about any potential additional exposures outside the work environment that may affect respiratory health (**Table 27**).

For individuals who work with potentially harmful substances, the U.S. Occupational Safety and Health Administration (OSHA) requires that employers maintain Material Safety Data Sheets (MSDS). These documents outline chemical properties of substances and the known potential health risks. OSHA requires that employers provide the MSDS upon request. These documents may be helpful in determining the risk of lung disease associated with a particular exposure.

When concern for an occupational disease persists but the history is unrevealing, referral to an occupational/environmental lung disease specialist is appropriate.

KEY POINT

- Careful attention to historical details and a comprehensive occupational history are often crucial to identification of occupational lung disease; in addition to identification of specific exposures, the duration and concentrations of exposures should be elicited.

TABLE 26. Conditions that Should Increase Clinical Suspicion of Occupational Lung Disease

The patient raises a concern about possible exposures at work
There is a temporal relationship to clinical symptoms and work:
Symptoms worsen during or after work
Symptoms abate or improve with time off or away from the workplace
Coworkers are affected with similar symptoms
There are known respiratory hazards at work (these can be identified by Material Safety Data Sheets [MSDS] from the workplace)
Failure to respond to initial therapy or symptoms that are further exacerbated upon returning to work
Onset of a respiratory disorder without typical risk factors
Clustering of disease in one geographic area

TABLE 27. Elements of a Thorough Patient History for Suspected Occupational Lung Disease

Understand the Occupation
What tasks do you perform at your current job?
How long have you been working at your current job?
What other jobs have you had in the past and for how long?
Understand the Type and Extent of Exposure
Are you exposed to vapors, gases, dust, or fumes in your work?
Do you know the amount and type of chemicals used?
Do you have Material Safety Data Sheets (MSDS) from your workplace?
Is your work environment well ventilated?
Does your employer require you to wear protective equipment? Do you wear it for the full duration of your exposure?
Is there visible dust in the air or on surrounding equipment?
Understand the Temporal Relationship of Symptoms to the Work Environment
Were there any changes to your work process prior to the onset of symptoms?
Do symptoms improve when you are away from the work environment? With vacation?
Understand Other Relevant Exposures
What are your hobbies?
Do you have pets in the home?
What is your travel history?

Management

The overriding principle in management of occupational lung disease is prevention. This includes interventions in the workplace to avoid exposures as well as early identification of coworkers who may also be at risk. For those who are affected, removal of the offending agent is essential. Symptomatic management often includes pharmacologic interventions.

Workers' compensation issues may require an assessment of the extent to which symptoms and physiologic impairment are directly attributable to a work exposure. These assessments are challenging, and referral to a specialist may be most appropriate.

KEY POINT

- The overriding principle in management of occupational lung disease is prevention, consisting of interventions in the workplace to avoid exposures as well as early identification of coworkers who may also be at risk. HVC

Surveillance

When primary prevention fails or when a new potential threat is identified, surveillance programs including health screening and serial pulmonary function testing are appropriate. A recent example is the assessment of returning war veterans from Afghanistan and Iraq. Sentinel cases of constrictive

bronchiolitis have identified multiple potential exposures (open fire pits, diesel exhaust, particulate matter from sand storms, and exposure to rocket fuel) that may result in lung disease. Because of this, a thorough assessment of war veterans for possible evidence of lung disease is recommended and should include symptom review and serial pulmonary function tests for those who are symptomatic. Identification of patients with mild or early disease allows for earlier intervention and counseling.

Asbestos-Related Lung Disease

Asbestos is a silicate mineral fiber previously used as an insulating material that is a major cause of lung disease. Although asbestos use in the United States has been virtually eliminated since its peak in the 1980s, asbestos-related diseases will persist well into this century owing to the long latency period between exposure and disease development (15-35 years). Although developed nations have nearly eliminated its use, asbestos inhalation remains at roughly 2 million metric tons per year worldwide. The result is that asbestos-related diseases will continue to be a major public health concern in the developing world for many years. Currently, approximately 107,000 people die each year owing to asbestos-related mesothelioma, lung cancer, and interstitial lung disease (asbestosis).

Risk Factors

The extent of asbestos exposure correlates with risk for disease, with the most common occupational exposures occurring in the construction, automotive servicing, and shipbuilding industries. Asbestos-related diseases are also commonly found in mining workers and in areas where manufacturing of asbestos has led to contamination of the environment. In this instance, individuals will not have an occupational exposure history.

KEY POINT

- Asbestos exposures are most commonly associated with the construction, automotive servicing, shipbuilding, and mining industries.

Pathophysiology

Asbestos fibers are inhaled and are deposited at the level of airway bifurcations and the alveolus. The lung may clear fibers (typically shorter fibers), whereas others are transported to the interstitium or via the lymphatics to the pleura. Parietal plaques are the most common finding, and the mechanism by which fibers transmigrate and develop plaques remains unclear. Diffuse parenchymal lung disease due to asbestos (asbestosis) is secondary to the extent of the fiber burden. The initial process begins with an alveolitis. If the fiber burden is low, this can resolve spontaneously. With a higher burden, proinflammatory and cytotoxic agents are released by macrophages with resultant recruitment of fibroblasts. If the process is sustained, collagen deposition leads to irreversible chronic fibrosis.

Asbestos-Related Pleural Diseases

Asbestos is associated with multiple forms of pleural disease. Pleural plaques are the most common form of disease and are characterized by smooth, white, raised, irregular lesions affecting predominantly the parietal and, very rarely, the visceral pleura (**Figure 12**). Pleural plaques are asymptomatic in the absence of parenchymal disease and are typically incidentally identified on routine chest radiograph.

Pleural fibrosis is a visceroparietal pleural reaction that may be either localized or diffuse. When the process is diffuse, it can lead to symptomatic restrictive disease. Treatment options for this are limited, and there is little benefit to surgical removal of the pleural layer (decortication) in this cohort. Pleural fibrosis may also lead to the development of rounded atelectasis (**Figure 13**). This is a process in which the lung becomes atelectatic in the region of the pleural fibrosis. The area forms a mass-like lesion that includes bronchi and vessels. These are often asymptomatic but may lead to respiratory impairment if they become large enough. Although these lesions may be concerning for a possible malignancy, they are often distinguished radiographically by a thoracic radiologist as benign.

Benign asbestos pleural effusion may occur either early or late after asbestos exposure. It may be asymptomatic or associated with chest pain. The pleural fluid analysis will be exudative and is often hemorrhagic. Further, eosinophils are present in nearly one third of patients. Benign asbestos pleural effusion is diagnosed only after exclusion of infection, pulmonary

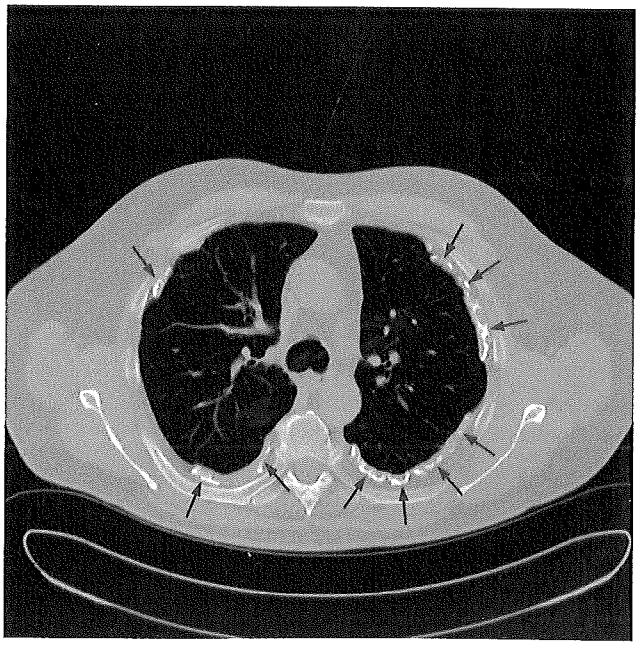

FIGURE 12. Chest CT showing extensive calcified pleural plaques (*arrows*) associated with asbestos exposure.

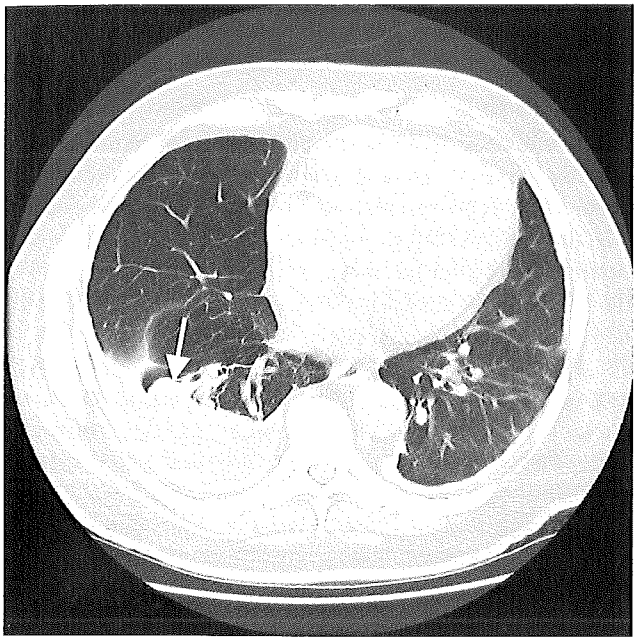

FIGURE 13. Chest CT showing rounded atelectasis (*arrow*) with its typical findings of a round area of lung parenchyma associated with a pleural abnormality and a comet tail that extends into the lung parenchyma.

embolism, and malignancy. Exclusion of mesothelioma is difficult owing to the low sensitivity of cytology and the presence of "reactive" mesothelial cells. Clinicians should have a low threshold to refer for consideration of pleuroscopy for these patients. An experienced thoracic surgeon or interventional pulmonologist can often discern mesothelioma on direct inspection. See Lung Tumors for a discussion of mesothelioma.

Asbestos exposure significantly increases the risk of lung cancer. In a recent report, 19% of patients with extensive asbestos exposure died secondary to lung cancer. For those that were nonsmokers, the risk of lung cancer mortality was 3.6-fold higher than controls. For those with a combined history of smoking and asbestos exposure, the risk of lung cancer mortality was 14.4 times higher than controls. For patients with a history of asbestosis, however, the additional risk of smoking was supra-additive (36.8 times higher than controls). The risk of developing cancer was mitigated by discontinuing smoking at any point. This new information further encourages smoking cessation and highlights the potential importance of lung cancer screening in those with the combined risk factors of smoking and asbestosis.

KEY POINTS

- Asbestos exposure is associated with multiple forms of pleural disease, including pleural plaques, pleural fibrosis, benign asbestos pleural effusion, and mesothelioma.
- Asbestos exposure significantly increases the risk of lung cancer and lung cancer mortality, particularly when combined with smoking.

Silicosis

Silicosis is a spectrum of fibrotic lung diseases related to the inhalation of silica dust. The most common form of silica is quartz, and any occupation that disturbs the earth's crust involves potential risk. Workers in industries that process silica-containing rock or sand are also at risk. Simple silicosis is marked by profusion of small rounded nodules that are upper-lobe predominant. The disease course may be accelerated (3-10 years after exposure) or latent (>10 years after exposure). The lesions may become confluent and lead to progressive massive fibrosis. Although individuals with simple silicosis may be asymptomatic, those with progressive massive fibrosis develop symptomatic shortness of breath.

The incidence of tuberculosis is increased in those with silicosis, and symptoms should prompt an evaluation for possible infection. In addition, altered cellular immunity may account for the increased prevalence of connective tissue disease in those with silicosis. Mine workers are often exposed to multiple dusts and radon, and they have high rates of tobacco use; however, the development of silicosis is also an independent risk factor for the development of lung cancer.

Once fibrotic disease develops, there are no clear therapeutic interventions to alter the disease course. Individuals with continued exposure to silica dust should change to a silica-free environment. Because airways disease and cancer are also associated with silica exposure, smoking cessation is always an appropriate recommendation. Symptomatic treatment includes inhaled bronchodilators, antibiotics for infections, and supplemental oxygen for hypoxemia. For individuals with progressive disease, consideration of lung transplantation referral is appropriate.

KEY POINT

- The incidence of tuberculosis is increased in patients with silicosis, and symptoms should prompt an evaluation for possible infection.

Pleural Disease

There are two main types of abnormalities that affect the pleura: increased fluid (pleural effusion) and air (pneumothorax) in the pleural space.

Pleural Effusion

Pleural effusion is the most common disorder affecting the pleura, with approximately 1.5 million pleural effusions diagnosed each year. These occur as a result of increased fluid formation and/or decreased fluid resorption in the pleural space. There are over 50 known causes and the pathophysiology varies depending on the cause. The vast majority of pleural effusions in the United States are the result of heart failure, pneumonia, or malignancy. A systematic approach to diagnosis is necessary based on the clinical presentation of the patient.