31. INTERSTITIAL LUNG DISEASES

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1. What is interstitial lung disease (ILD)?

Interstitial lung disease encompasses a large group of entities characterized by involvement of the interstitial space of the lung, which is the space in the walls of the alveoli between the basement membrane of the alveolar epithelium and the basement membrane of the capillary endothelium. It contains fibroblasts, macrophages, and collagen and noncollagen proteins. The interstitial space is the gas exchange surface of the lung; in some forms of ILD, alterations in the small airways, alveolar ducts, respiratory bronchioles and terminal bronchioles also may be seen.

2. What is meant by pulmonary fibrosis?

Pulmonary fibrosis is the pathologic end-result of the various chronic disease processes involved in ILD. Fibrosis begins with the development of an initial alveolar injury after inhalation of a gas, fume, or dust. This initial insult is followed by a cascade of protective responses characterized by tissue inflammation. If inflammation becomes chronic or recurrent, proliferation of smooth muscle, fibroblasts, and collagen ensues with accompanying architectural distortion. Fibrosis is a process of progressive scarring with associated distortion.

3. How common is ILD?

Current estimates for the annual incidence of ILD are of 40–80 cases per 100,000 in the general population. Occupational exposures are believed to cause 25–50% of cases (20 cases in 100,000 in males and 0.6 cases in 100,000 in females). However, this percentage may be an underestimate because of difficulties in making a conclusive diagnosis of ILD and in tracing workplace exposures over the entire working life of patients.

4. What are the causes of ILD?

ILD in immunocompetent hosts may be grouped according to cause or syndrome:

Inhalation causes (occupational and environmental): inorganic dusts leading to asbestosis, silicosis; organic dusts or aerosols leading to hypersensitivity pneumonitis, as in machine workers, farmers, pigeon breeders.

Idiopathic disease: sarcoidosis, histiocytosis X, idiopathic pulmonary fibrosis.

Inherited causes: familial idiopathic pulmonary fibrosis, tuberous sclerosis, neurofibromatosis.

Collagen vascular disease/pulmonary renal syndromes: pneumonitis with systemic lupus erythematosus, ILD with rheumatoid arthritis, Wegener's granulomatosis, Goodpasture's syndrome.

Other specific entities: bronchiolitis obliterans, lymphangioleiomyomatosis, eosinophilic pneumonia.

5. What exposures may result in occupational interstitial lung disease (O-ILD)?

Exposures to inorganic dusts in the workplace may result in ILD. Examples are free silica, asbestos, coal, beryllium, and hard metal (tungsten carbide with cobalt). Less common causes include exposures to tin, aluminum, or iron. Exposure to organic dusts or aerosols (thermophilic bacteria, fungi, animal proteins) may result in hypersensitivity pneumonitis. ILD also may result from toxic pneumonitis due to chemical or gas exposure. Industries in which such exposures occur and the disease outcomes are listed in the table below.

Occupational Interstitial Lung Diseases

INDUSTRY	DISEASE	AGENT
Mining	Coal worker's pneumoconiosis, silicosis	Coal dust, silica
Insulating, ship-working, steam-fitting, plumbing	Asbestosis	Asbestos
Airplane, spacecraft manufacture	Chronic beryllium disease	Beryllium particulate
Machine working	Hypersensitivity pneumonitis	Metal-working fluids
Machining, sawing, filing,	Hard metal disease: interstitial pneumonitis and hypersensitivity pneumonitis	Cobalt
Farmwork, silo work	Farmer's lung	Bacterial and fungal proteins in moldy hay or grain

6. What are the symptoms of O-ILD?

Most patients with O-ILD report some level of dyspnea, initially with exertion and in later stages with minimal activity. Some patients complain of tiredness or fatigue and inability to accomplish tasks that they previously performed. Initially they may attribute their limitations to normal aging. Cough is a common symptom: usually it is not accompanied by phlegm unless a component of bronchitis is involved. Chest pain may occur in patients with accompanying pleural disease. Although hemoptysis may occur in cases of ILD associated with vasculitis or diffuse alveolar hemorrhage syndrome, it is not a usual feature of uncomplicated O-ILD and should prompt an evaluation for carcinoma, tuberculosis, or other complications.

7. How can patients with O-ILD be identified?

Patients with O-ILD may present with dyspnea and cough. Others may be identified through changes on chest radiograph (see question 11) without symptoms or with impairment that they attribute to aging or other causes. For some patients the first finding may be an abnormality on spirometry, such as a reduction in vital capacity.

8. What are common findings on physical examination of a worker with O-ILD?

Early and even advanced ILD may be unremarkable on physical exam. More commonly, however, physical findings include bibasilar end-inspiratory crackles (Velcro rales) on lung auscultation. In addition, the patient may be tachypneic or tachycardic, at rest or with mild exertion; patients in later stages may show signs of cor pulmonale and pulmonary hypertension. Examination also should be made for findings that accompany nonoccupational ILD, including skin, joint, and ocular findings associated with connective tissue disease, vasculitis, or sarcoidosis. In rare cases of advanced ILD, clubbing of the digits may be seen.

9. What are the usual findings of pulmonary function testing?

Lung volume measurements, such as vital capacity, residual volume, functional residual capacity, and total lung capacity, are reduced in ILD. Air flow rates, such as the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC), are usually normal because the FEV_1 is reduced in proportion to reduction of vital capacity. This pattern, termed restrictive disease, is classic for ILD. A mixed pattern of restriction and obstruction or a pattern primarily of obstruction (FEV^1 and FEV_1/FVC ratio reduced) is frequently seen in workers with ILD as a result of occupational dust exposure or smoking on the airways. Reduction in carbon monoxide diffusion in the lung (DL_{CO}) is common because of loss of gas exchange units and ventilation-perfusion mismatch. However, the level of reduction in DL_{CO} does not match the severity of disease.

10. What are the findings of arterial blood gas (ABG) measurements?

ABG measurements at rest may reveal no abnormalities or hypoxemia (decreased partial oxygen pressure [PO_2]); partial pressure of carbon dioxide (PCO_2) may be normal or decreased. A

normal resting PO_2 should prompt a check for hypoxemia during exertion or sleep. One of the best ways to follow disease progression in ILD is to assess resting and exercise gas (O_2) over time.

11. What are the expected findings of chest radiography?

Up to 20% of patients with asbestosis or coal worker's pneumoconiosis and up to 10% of patients with hypersensitivity pneumonitis may appear to have a normal chest radiograph. Therefore, patients with symptoms or abnormal pulmonary function tests (PFTs) should be evaluated completely despite a normal initial radiograph. In patients with radiographic abnormality a high-quality film reveals common patterns of specific occupational ILDs (see below). A common feature of late-stage disease is honeycombing, which represents fibrous change in the lung parenchyma.

Silicosis: diffuse rounded reticulonodular densities with upper zone predominance; irregular opacities, possibly massive fibrosis with advanced disease; eggshell calcification of hilar nodes unusual.

Coal worker's pneumoconiosis: diffuse reticulonodular densities; large opacities.

Asbestosis: diffuse densities of irregular shape with lower zone predominance; pleural findings may accompany parenchymal asbestosis; pleural plaques, diffuse pleural thickening, pleural effusions.

12. What is the ILO system for classifying chest radiographs in workers with O-ILD?

Chest radiographs in workers with pneumoconiosis (silicosis, coal worker's pneumoconiosis, and asbestosis) are categorized using a standard method devised by the International Labour Organisation (ILO). The system, called the International Classification of Radiographs of Pneumoconioses, consists of 22 standard radiographs that illustrate the parenchymal opacities and pleural changes associated with pneumoconiosis. These radiographs are used to classify the size, shape, profusion (concentration or density), and extent of parenchymal opacities and pleural changes on posteroanterior (PA) radiographs. The classification is not designed to correlate with the pathologic severity of disease. The system, last updated in 1980, is currently undergoing revision; an updated classification scheme should be released in early 1999.

13. What is the utility of computed tomography (CT) in ILD?

Both conventional CT (resolution of 8–10 mm of lung tissue per slice) and high-resolution CT (HRCT, in which the images resolve tissue slices 1–3 mm in thickness) may be used to evaluate the interstitium, pleura, and airways in O-ILD. Conventional CT has been found to be superior to chest radiography for evaluation of pulmonary masses and pleural plaques (due to asbestos exposure). HRCT allows better identification of thickened lobular interfaces, nodular abnormalities, and loss of volume associated with pulmonary fibrosis. In addition, HRCT is useful for selecting the appropriate area for biopsy. However, CT scanning is not necessary for the evaluation of O-ILD in a patient with a history of exposure and consistent chest radiographic findings. Furthermore, there is no widely accepted standardized method for categorization of O-ILD using CT.

14. What blood tests may be helpful in evaluating O-ILD?

Blood tests are usually nonspecific in O-ILD and are best used for excluding nonoccupational causes of ILD, such as a connective tissue disorder. Potentially useful tests for evaluating the presence of nonoccupational causes of ILD include immunoglobulin levels, rheumatoid factor, antinuclear antibodies, and erythrocyte sedimentation rate. An exception to the above generalization is beryllium-related disease, in which a specific peripheral lymphocyte transformation response helps to detect workers who have developed an immune response to beryllium after exposure. Blood tests also may play a role in evaluating hypersensitivity pneumonitis in which the presence of serum precipitins (IgG antibodies) denotes exposure to a specific antigen.

15. How is lung tissue obtained for pathologic examination?

Various microscopic and staining techniques are used to examine lung architecture, cellular components, and foreign inhaled bodies (ferruginous bodies). Bulk analysis, in which the tissue is digested, is used to analyze the mineral and dust content of the tissue. Open lung biopsy,

video-assisted thoracoscopic biopsy, and transbronchial biopsy are the three ways to obtain tissue for examination. Open lung biopsy and video-assisted thoracoscopic biopsy require surgery and inpatient stays. Transbronchial biopsy obtains specimens through a bronchoscope and is less invasive but provides a smaller sample that may not reveal tissue architecture, which may be useful for making a specific diagnosis.

Tissue biopsy is not routinely needed for the diagnosis of O-ILD if the clinical and radiologic patterns are consistent with a history of exposure to a known etiologic agent. However, biopsy has a role in excluding neoplastic or infectious processes and allows assessment of disease severity and response to treatment.

16. What histologic patterns are commonly found in O-ILD?

The histologic patterns typically associated with particular exposures are listed below.

Granulomatous lesions: beryllium, organic dusts
Diffuse fibrosis (usually interstitial pneumonitis): asbestos, hard metal
Macules: coal, tin, aluminum
Nodular fibrosis: coal, silica
Bronchiolitis obliterans: fumes and gases

17. What is the role of bronchoscopy in the diagnosis of ILD?

Bronchoscopy is usually an outpatient procedure during which a fiberoptic scope is introduced into the trachea and main airways through the nose or mouth. It is used for visualizing the airways, taking transbronchial biopsies (TBB), and obtaining lavage fluids (washings). Lavage fluid has been used for cellular immunophenotyping to determine the diagnosis, course, and prognosis of disease, but this use remains controversial. The small tissue samples procured through TBB are most helpful in the diagnosis of granulomatous interstitial processes in which abnormal tissue is found in the peribronchiolar region (e.g., sarcoidosis, beryllium disease, hypersensitivity pneumonitis). Many cases of O-ILD can be diagnosed by history, radiograph, and PFT findings; bronchoscopy should be used as needed for clarification or confirmation.

18. What is the recommended diagnostic pathway for ILD?

Although the approach to diagnosis of ILD varies on a case-by-case basis, the path starts with history, physical exam, chest radiograph, and PFTs to establish that ILD is in the differential diagnosis. These evaluations should be followed by an in-depth assessment of environmental or occupational exposures and exclusion of systemic connective tissue disease, pulmonary renal syndromes, and vasculitis. If the diagnosis remains in question, bronchoalveolar lavage and transbronchial biopsy may be helpful. If neither is diagnostic, open biopsy or thoracoscopic biopsy guided by HRCT should follow.

19. What are the complications of ILD?

Many but not all types of ILD are chronic with progressive loss of lung function and disability. Progressive hypoxemia may require chronic oxygen supplementation. ILD (more specifically, fibrosis) has been found to increase the risk for development of lung cancer independently of the risk conferred by exposure to agents such as asbestos or silica.

20. What is the prognosis of ILD?

ILD related to asbestos, coal, or silica exposure is generally slowly progressive and irreversible, eventually leading to disability and sometimes death. Disease often progresses even after cessation of exposure. In some cases the disease is more rapidly progressive (e.g., acute silicosis, which has a fatal course in a short period). Other types of ILD, such as hypersensitivity pneumonitis, may stabilize or improve after removal from exposure to the offending agent.

21. When should a worker be evaluated for ILD?

All workers exposed to agents known to cause an ILD are candidates for evaluation. Exposed workers who are healthy should be enrolled in surveillance programs in which lung function and

radiographs are monitored regularly for changes over time. Many ILDs, including asbestosis, silicosis, and coal worker's pneumoconiosis, involve long latency periods between first exposure and appearance of detectable signs of disease. Workers may not show signs of disease until after discontinuation of exposure; therefore, it is important to evaluate workers with a history of exposure. The latency period between exposure and disease (which ranges from months to 20 or more years) makes it necessary to continue to monitor the health of retired workers. In addition, latency is important to keep in mind in evaluating the current health of workers at a particular workplace. Although the current worker group may appear to be free of disease, current exposures may still be hazardous, causing disease that will not become apparent for years to come. Current healthy workers must be protected from excessive exposure to prevent future disease. Guidelines for determining whether exposures are excessive include the permissible exposure limits (PELs) enforced by the Occupational Safety and Health Administration (OSHA), the recommended exposure limits (RELs) published by National Institute for Occupational Safety and Health (NIOSH,) and the threshold limit values (TLV's) published by the American Conference of Governmental Industrial Hygienists.

22. How is O-ILD managed?

A primary focus of management is removal of the offending exposure in the work or home environment. Treatment of hypoxemia, preventive care with influenza and pneumococcal vaccinations, screening for mycobacterial infection with purified protein derivative (PPD) testing, early treatment of infections, counseling for smoking cessation, and patient and family education about self-care strategies are important components of care for patients with chronic and progressive pulmonary disease such as asbestosis or silicosis. Prevention is critical because the disease is irreversible. In cases of O-ILD with evidence of ongoing inflammation and alveolitis, such as hypersensitivity pneumonitis, a course of corticosteroids and cytotoxic drugs may slow disease progression.

23. How can O-ILD be prevented?

Prevention of ILD in the workplace begins with recognition of the hazardous exposure. **Primary prevention**, which reduces the occurrence of disease, is achieved by eliminating excessive exposure to the hazardous agent. The agent may have to be eliminated entirely and an appropriate replacement found. For example, crystalline quartz (sand) must be eliminated and replaced in abrasive blasting because of the high risk to workers. If an agent cannot be eliminated entirely, exposure in the workplace must be minimized with engineering changes such as ventilation and confinement. To supplement engineering controls and to protect against intermittent high-exposure events, workers may be further protected by educational programs and use of respiratory protective equipment.

Secondary prevention involves methods of early detection and benefits affected workers by reducing the risk of progression. Examples include screening of exposed workers with PFTs or chest radiographs on a regular basis. Screening tests must be accompanied by an ongoing monitoring program to identify workers who exhibit early signs of disease or ill effects due to exposure. Effective interventions must be included.

Physicians evaluating a patient with O-ILD have a role in preventing future cases by reporting the case and ensuring proper workplace evaluation and follow-up. Many state health departments or departments of labor provide this service, as do OSHA and the Mine Safety and Health Administration (MSHA) for workplaces under their jurisdiction. Occupational health professionals or government public health offices are good sources of information for a physician attempting to develop a follow-up plan for a patient with suspected disease and excessive exposure in the workplace.

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