INTERSTITIAL LUNG DISEASE: CAUSES, TREATMENT, AND PREVENTION

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The interstitial lung diseases (ILD) are a diverse group of lung disorders that involve primarily the parenchyma of the lung. Whether idiopathic or secondary to systemic disorders, inhaling exposures, or drugs, they inflame and scar the interstitium of the lungs and obliterate alveoli and capillary units. The scarring or fibrosis produces restrictive lung impairment while destruction of the alveoli, interstitium, and capillaries results in severe gas exchange abnormalities. Clinically, the ILD present subtly with progressive dyspnea on exertion and a dry cough. Rales or crackles on examination prompt chest radiography that may reveal bilateral infiltrates. These infiltrates are often treated as atypical pneumonias that fail to respond to antimicrobial therapy over weeks to months. Because of this and their infrequent presentation in the primary care setting, the diagnosis of ILD is commonly delayed. This paper highlights the natural history of the ILD in general, gives a broad overview of the pathophysiology in these diseases, and encourages greater awareness for the detection of ILD in primary care. (*Ethn Dis*. 2005;15[suppl 2]: S2-45–S2-48)

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INTRODUCTION

The interstitial lung diseases (ILD) are a diverse group of diffuse inflammatory and fibrotic afflictions of the lung parenchyma.[1] Though the term ILD implies that the space between the alveoli and capillaries, or interstitium, is the site of these diseases, the air spaces, bronchioles, and the pulmonary vasculature may also be affected. Thus, many diffuse lung diseases such as idiopathic pulmonary fibrosis (IPF), which affects the interstitium, bronchiolitis obliterans with organizing pneumonia (BOOP), which involves the air spaces, and Wegener's granulomatosis, which produces a pulmonary vasculitis, are all considered ILD. They share several important features. Principally, both lungs are involved, since the ILD appear to be the result of systemic pathologic immune responses, whether or not the underlying cause is known. For example, rheumatoid arthritis and systemic lupus erythematosus (SLE) are frequently accompanied by bilateral pneumonitis and lung fibrosis. Another important feature is that ILD are not infectious diseases. Infectious lung diseases such as community-acquired pneumonias (CAP) tend to be mainly unilobar or discretely multilobar. Atypical pneumonias are bilateral in a diffuse pattern like the ILD, but as in CAP, are self-limited and typically resolve with appropriate antibiotic therapy. The ILD are indolent and chronic with variable flare-ups despite monitoring and therapy. Many progress to irreversible lung fibrosis, respiratory insufficiency, and eventually, respiratory failure.

Classification of ILD into granulomatous and non-granulomatous forms of known or unknown origin is a simple, useful way to classify the most common ILD encountered in practice. Sarcoidosis and hypersensitivity pneumonitis are the prototypical granulomatous ILD of unknown and known etiologies, respectively. Sarcoidosis afflicts African Americans with a prevalence of 36 per 100,000 compared to 11 per 100,000 for Caucasians.[2] The disease tends to be more severe in African Americans as well.[3] Hypersensitivity pneumonitis is an alveolitis produced by >100 known organic "dusts" or antigens that may lead to irreversible fibrosis after continuous exposure to the offending antigen. Idiopathic pulmonary fibrosis is the most common non-granulomatous ILD encountered.[4] The etiology remains elusive, and no effective therapy exists for this uniformly fatal disease. The most common non-granulomatous ILD with known etiologies are associated with autoimmune diseases, most notably, rheumatoid arthritis, scleroderma, and SLE. Several occupational exposures involving asbestos, silica, and metals may produce chronic interstitial diseases. Finally, various drugs can produce interstitial pneumonias and fibrosis. Methotrexate may cause a granulomatous pneumonitis while nitrofurantoin can produce a non-granulomatous lung inflammation and fibrosis.

PRESENTATION AND NATURAL HISTORY

Because of their relatively low prevalence and subtle early symptoms, the diagnosis of many ILD is delayed. On

average, IPF is diagnosed 6 months after the initial presentation to the clinician.[4] In some cases where previous chest films are available, faint evidence of fibrosis can be detected even years before clinical presentation.

Symptoms in ILD are non-specific. Dyspnea on exertion and a dry cough are the most common complaints.[1] Dyspnea is a normal response with heavy exercise, but it suggests pulmonary pathology when it develops during performance of normal activities of daily living. Key in the differential diagnosis for dyspnea is conditions producing cardiac insufficiency and chronic diseases associated with cardiopulmonary deconditioning. Dyspnea at rest occurs late in the disease course, by which time a diagnosis of a specific ILD usually has been made. Cough is nonproductive, and sputum production likely indicates a concomitant infection. Cough associated with ILD is intermittent and occasionally paroxysmal with exercise or deep breathing. Cough commonly interrupts pulmonary function testing.

Interstitial lung diseases associated with other systemic pathology may be diagnosed on the basis of the underlying disease. Thus, dyspnea and cough in a patient with joint stiffness and tenderness in the mornings may portend rheumatoid pneumonitis. Notably, ILD associated with autoimmune diseases presents well after the specific disease is established. However, pulmonary involvement may occasionally precede the more common manifestations of entities like SLE and rheumatoid arthritis.

A host of environmental and occupational exposures can cause ILD. This fact underscores the necessity of taking a comprehensive work and exposure history at the initial patient encounter. Detailed current and remote information about hobbies, travel, and pets is a must. For example, hypersensitivity pneumonitis produced by avian antigens can be seen in persons who are in contact with chickens, pigeons, and exotic birds.

DIAGNOSTICS IN ILD

Physical Examination

The lungs are clearly the focus of the examination in ILD. The classical finding is inspiratory rales or "crackles." Crackles may be faint in early disease or in disease of any duration where the lung function happens to be well preserved. Eventually, the crackles become coarser and loud and are often described as "velcro crackles." Wheezing may be heard in ILD that involve the airways, especially sarcoidosis. One should also remember that a significant number of patients with ILD are former or current smokers and wheezing may result from concomitant obstructive lung disease.

The rest of the physical examination can give clues to the underlying cause of the ILD. Examination of the head may be especially revealing. Conjunctivitis and the purple, rolled-up lesions of lupus pernio on the face are suggestive of sarcoidosis. A malar rash points to SLE, while the distinctive heliotropic rash indicates dermatomyositis/polymyositis. Keratoconjunctivitis and swollen parotid glands suggest Sjogren's syndrome. A thorough musculoskeletal exam may reveal the small joint deformities and nodules of rheumatoid arthritis. Clubbing of the fingers is not specific but is common in the late stages of IPF. Red, scaly, atrophic rashes on the extensor surfaces of the extremities, including the fingers, are very consistent with dermatomyositis.

Radiology

The standard posteroanterior and lateral chest radiograph confirms the clinical suspicion of ILD and the distribution of the infiltrates is helpful in the classification of the disease.[5] Non-granulomatous diseases predominate in the lower lobes bilaterally. The appearance ranges from "soft, fluffy" patchy or contiguous infiltrates to dense reticular infiltrates suggestive of advanced fibrosis. Lung volumes appear reduced in the latter case, where the increased elastic recoil produced by fibrosis reduces lung capacities. Predominantly upper lobe involvement occurs in only a few ILD. One of the most common ILD, sarcoidosis, tends to exhibit infiltrates mainly in the upper lobes. Sarcoidosis is also unique in that the radiographic stage of the disease roughly correlates with disease progression and outcome. Stage one disease demonstrates only bilateral hilar adenopathy with or without paratracheal adenopathy. The disease will resolve in approximately two thirds of persons with this stage. Stage two disease includes bilateral lung infiltrates along with the adenopathy and predicts disease resolution in roughly one half of those with sarcoidosis. Stage three disease reveals expanded bilateral infiltrates with no adenopathy and resolves in approximately one third of subjects. Stage four disease demonstrates diffuse fibrosis and fibrocystic changes that indicates advanced, irreversible lung injury. Silicosis and the uncommon eosinophilic granulomatosis and lung involvement in ankylosing spondylitis are the other entities with upper lobe predominance.

The advent of high resolution computerized tomography (HRCT) of the lung, which allows more precise examination of lung pathological derangements, has revolutionized diagnostics and monitoring in ILD. The finding of bibasilar honeycombing and so-called traction bronchiectasis strongly supports IPF in the appropriate clinical setting and can thus avoid open lung biopsy in many cases. The accuracy of the diagnosis in eosinophilic granuloma of the lung and lymphangiomyomatosis is greatly enhanced by HRCT.

Pulmonary Function Testing

With few exceptions, ILD typically result in restrictive or lower-than-normal lung volumes that are readily detected by pulmonary function testing.[1] Spirometric testing reveals a parallel drop in forced expiratory volume in one

second (FEV_1) and forced vital capacity (FVC) such that the FEV_1/FVC is normal. However, to truly confirm the restrictive lung impairment of ILD, lung volume testing must be performed. Total lung capacity, functional residual capacity, and residual volume will be decreased. As the disease and the attendant fibrosis progress, the increase in elastic recoil of the lung tissues worsens the restrictive impairment. The individual with ILD has more difficulty increasing tidal volumes with exertion, which creates tachypnea and an increased work of breathing. Exercise limitation is a major problem for patients with moderate-to-severe lung restriction.

Gas transfer or, more specifically, movement of oxygen across the alveolar-capillary membrane per unit time is diminished in ILD. The diffusing capacity for carbon monoxide (DLCO) is used to measure gas transfer. The decrease in alveolar surface area, increases in the thickness of the interstitium, and primarily, destruction of alveolar-capillary units contribute to the drop in DLCO found in ILD. A drop in DLCO may, in fact, be detected or worsen before the derangements in spirometry and lung volumes. Diffusing capacity of the lung should always be included when pulmonary function tests are obtained to assess or monitor the progression of ILD for this reason.

Interstitial lung diseases that tend to involve the airways will sometimes produce an obstructive impairment that accompanies the restrictive defect on lung function testing. A drop in the FEV_1/FVC typically detects this pattern. Most notable of these ILD is sarcoidosis, where almost one half of individuals demonstrate lower than normal FEV_1/FVC.[6]

Serology and Tissue Examination

Serology is used mainly to assess secondary ILD caused by specific autoimmune disorders.[1] Tests for anti-nuclear antibodies (ANA) and rheumatoid factor (RF) are standard in the initial screening of ILD. Caution is indicated in their interpretation since slightly elevated levels of ANA and RF can be detected in the idiopathic pneumonias such as IPF. Several-fold higher levels of ANA and RF would suggest SLE and rheumatoid arthritis, respectively, as the underlying causes of the ILD. Panels of serum precipitin tests for antigens causing hypersensitivity pneumonitis are occasionally used when the evidence of a specific exposure is questionable. However, precipitins merely indicate exposure to a given antigen and do not specify that the antigen caused the disease.

Primary ILD frequently requires tissue diagnosis for accurate diagnosis.[1] Bronchoscopy with transbronchial biopsy is usually adequate to make a diagnosis in the granulomatous ILD such as sarcoidosis and, with less accuracy, in hypersensitivity pneumonitis. Transbronchial biopsies are also useful in the detection of lymphangitic carcinomatosis to the lungs that may be confused for ILD. Most primary ILD, however, require centimeter-sized lung samples for accurate diagnosis. This requirement is especially true for the non-granulomatous ILD, where large areas of preserved architecture provide a context to distinguish the various idiopathic pneumonias. Large lung samples can only be obtained by open lung biopsy or, increasingly, by visually assisted thoracoscopic (VAT) biopsy. Both require general anesthesia and pose more risk than transbronchial biopsy. An ideal biopsy contains normal or near-normal tissue adjacent to cellular pathology and fibrosis. Heterogeneous patches of thickened interstitium with numerous fibroblastic foci are typical of usual interstitial pneumonitis (UIP) that in current classification is the clinical entity IPF. A uniform pattern of interstitial thickening with prominent inflammation is consistent with non-specific interstitial pneumonitis (NSIP). Alveolar ducts and respiratory bronchioles filled with collagenous matrix implicate BOOP.

TREAMENT AND PREVENTION

Drug Treatment Strategies

Treatment of ILD, in general, has been less than adequate. Where the underlying cause is known, treatment of that cause should be pursued. Until recently, the initiation and progression of the ILD were thought to be driven almost exclusively by derangements in the body's cell-mediated and humoral inflammatory responses. More specifically, they were seen as hyperimmune abnormalities, and therapies were directed at suppressing the immune response. Systemic steroids were the "workhorses" of these therapies, but drugs like azathioprine, cyclophosphamide, and methotrexate, alone or as adjuncts to steroid therapy, were the mainstay. These drugs are still important today. For example, the combination of prednisone and cyclophosphamide has dramatically increased survival in the once-fatal Wegener's granulomatosis. Steroids also have a large role in the management of sarcoidosis.

Pathologic evidence over the years has shown that inflammation and fibrosis coexist in many of the ILD. Fibrosis may actually be the most prominent finding in some ILD such as IPF. Clinical and basic research now shows that mediators regulating collagen deposition are expressed abnormally in several of the ILD. Consequently, new therapies are being developed with the aim of blunting the fibrotic response. One of the best-studied agents is interferon-γ 1β that down-regulates the powerful pro-fibrotic cytokines transforming growth factor and connective tissue growth factor in the lung cells of patients with IPF.[7] Interferon and other anti-fibrotic agents, perhaps in combination with potent immunosuppres-

sives, may soon produce better outcomes in the treatment of ILD.

Preventable ILD

A number of ILD result from inhaling exposures.[1] Already mentioned are hypersensitivity pneumonitis and silicosis. Exposure to respirable asbestos and inorganic dusts generated in several industrial settings produces indolent fibrosis in susceptible individuals. Patients who present with unexplained dyspnea should be asked about their workplace and other environmental exposures. Removing the exposure may be the difference between healthy lungs and development of ILD with irreversible fibrosis.

Many common drugs have been associated with ILD. Notable examples include the anti-arrhythmic amiodarone, nilutimide used to treat prostate cancer, and a host of antibiotics and anti-cancer drugs. A thorough drug history is paramount in the workup of unexplained dyspnea. The presence of crackles on lung exam, even with a clear chest film, should prompt a search on which drug has the potential to induce pneumonitis/fibrosis. That drug should be stopped or replaced and the patient sent for evaluation by a specialist.

SUMMARY

Interstitial lung diseases are less common than the more prevalent and easily recognizable lung diseases, such as asthma and chronic obstructive pulmonary disease. The incidence of ILD is even less than that of lung cancer, yet the morbidity and mortality approach those of lung cancer for some of the ILD. The onset of symptoms is typically very subtle, and a high index of suspicion by the clinician is important to avoid long delays in diagnosis and management. Nevertheless, the initial workup for ILD is straightforward: plain chest radiography supports impressions gathered during the history and physical and justifies examination by computerized tomography and pulmonary function testing. Computerized tomography should include high-resolution images, and pulmonary function testing should be complete, including lung volume and diffusing capacity measurements. The patient should then be referred to a specialist or center with experience in ILD. In many cases, the main function of the specialist is to obtain lung tissue to confirm the diagnosis of ILD and to assist with therapy and management of the affected individual.

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