The keys to diagnosing interstitial lung disease: Part 3

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Abstract: Important components of the workup for interstitial lung disease (ILD) include the history and physical examination, chest radiography, high-resolution CT (HRCT), pulmonary function testing and, in some cases, bronchoalveolar lavage (BAL) and/or biopsy. Pulmonary function tests usually show a restrictive ventilatory impairment. However, some patients have a mixed restrictive/obstructive pattern: in fact, almost 50% of patients with sarcoidosis have airflow obstruction at presentation. HRCT has an increasingly important role in the assessment of ILD. In some cases, the results may obviate the need for biopsy. BAL can help confirm the diagnosis of ILD; it also can identify conditions such as infection or hemorrhage or suggest an alternative diagnosis. Surgical lung biopsy has the advantage of yielding samples of lung tissue that are usually diagnostic, especially if HRCT is used to target lung regions. (J Respir Dis. 2005;26(11):466-478)

The interstitial lung diseases (ILDs) represent a unique group of diseases that present clinicians with the challenge of integrating the art of medicine with the technology of medicine. The diagnosis requires both an adept history taking and appropriate use of a variety of tests. In some ways, the evaluation may involve a "Sherlock Holmes" approach. Clues that may seem minor to the history taker or insignificant to the patient must be fit into a larger puzzle, and the clinician must integrate each piece of the puzzle to reach the diagnosis.

Osler's statement that "the practice of medicine is an art based on science" certainly applies to both the diagnosis and management of ILD. Indiscriminate use of tests may waste resources and confuse the clinical diagnosis, whereas inadequate use of tests may lead to underdiagnosis. Thus, striking a balance between art and technology is the key.

In the September and October 2005 issues of The Journal of Respiratory Diseases, we reviewed the different types of ILDs. In this article, we will present our approach to the diagnosis.

**DIAGNOSTIC TOOLS**

**History and physical examination**

Findings from the history and physical examination, while not diagnostic, can strongly suggest or support a specific diagnosis and can influence the differential diagnosis and subsequent testing. Key clinical features include the occupational history, drug use history, smoking history, presence of systemic signs or symptoms, onset of symptoms, and findings from the physical examination. Table 1 summarizes the findings that strongly implicate specific causes of ILD.

During the interview, direct the patient toward recollecting key exposures. For example, be sure to ask about exposure to birds or grains, which may suggest hypersensitivity pneumonitis, and about occupations that may involve exposure to asbestos or silica. Key drug exposures to ask about include nitrofurantoin, amiodarone, methotrexate, and bleomycin.

A relatively rapid onset and progression of symptoms such as dyspnea and cough may point to an infectious, inflammatory (collagen vascular disease), or granulomatous (sarcoidosis) disorder. Inflammatory and granulomatous disorders are particularly likely if prominent extrapulmonary manifestations, such as joint or skin findings, are present.

Physical findings that suggest sarcoidosis include lymphadenopathy, uveitis, erythema nodosum, ankle arthritis, parotiditis, and lupus pernio. The lung examination is usually unremarkable in patients with sarcoidosis unless late-stage fibrosis has developed, in which case crackles can be heard on auscultation. The crackles associated with idiopathic pulmonary fibrosis (IPF) and usual interstitial pneumonia (UIP) are characteristically Velcro™-like and are heard in the lower lung zones. In patients with fibrotic sarcoidosis, crackles may be heard in the upper lung zones because these are areas of greater disease activity. In addition, many patients with sarcoidosis have evidence of airway obstruction; these patients may have wheezing on examination and may respond to inhaled bronchodilators.

Patients who have IPF or asbestosis typically have digital clubbing, which is rarely found in patients who have sarcoidosis. Clues that suggest other types of ILD include a malar rash in systemic lupus erythematosus (SLE), saddle nose deformity in Wegener granulomatosis, and dry eyes and dry mouth in Sjögren syndrome.

**Pulmonary function testing**
Resting and exercise lung function tests can provide useful insights into the diagnosis and prognosis of ILDs. Static pulmonary function tests usually demonstrate a restrictive ventilatory impairment, with reduced lung volumes and reduced carbon monoxide-diffusing capacity (DlCO). While these are the classic resting abnormalities seen in most ILDs, variation exists. For example, patients with UIP and IPF who are smokers have higher-than-expected vital capacity and total lung capacity, probably as a result of coexistent emphysema. Patients with lymphangioleiomyomatosis (LAM) or pulmonary Langerhans cell histiocytosis may also have preserved lung volumes or hyperinflation.

Some ILDs are associated with airflow obstruction, yielding a mixed restrictive/obstructive pattern on pulmonary function tests. These include rheumatoid arthritis (if the patient has bronchiectasis or upper airway involvement, such as cricoarytenoiditis), sarcoidosis, pulmonary Langerhans cell histiocytosis, LAM, and bronchiolitis obliterans. In fact, almost 50% of patients with sarcoidosis have airflow obstruction at presentation. Most of these patients have radiographic stage I disease. Important differences exist between UIP/IPF and some of the other ILDs. Because of the greater degree of lung fibrosis in UIP/IPF, lung elastance is increased relative to other ILDs. This increased elastance leads to lower lung volumes, particularly residual volume, than those seen with hypersensitivity pneumonitis, asbestosis, and silicosis.

In addition, a greater reduction in DlCO is seen in UIP/IPF than in other ILDs, such as sarcoidosis. Thus, while pulmonary function tests do not confirm the diagnosis of ILD, when considered in the clinical context, they can contribute significantly to the diagnosis. Exercise testing

Cardiopulmonary exercise testing (CPET) can also be useful if the cause of the patient's dyspnea is not clearly explained by the results of resting pulmonary function tests or chest radiography. Classically, CPET demonstrates a decreased exercise capacity; decreased anaerobic threshold; and abnormal gas exchange, such as exercise hypoxemia and increased dead space fraction.

In addition, an abnormal ventilatory response is often seen, with a marked elevation in respiration rate early in exercise. This early, rapid rise in respiration rate is the result of the impaired ability to increase tidal volume associated with lung parenchymal restriction. The pattern of rapid shallow breathing, which may be present at rest, becomes very pronounced during exercise. If pulmonary hypertension is present, the exercise-induced hypoxemia may be more severe; if right-sided heart failure is also present, cardiac performance may be diminished (decreased heart rate reserve, decreased oxygen pulse).

The 6-minute walk test has been shown to have prognostic value in patients with IPF and nonspecific interstitial pneumonia (NSIP). In one study, patients whose oxygen saturation fell below 88% for 1 minute had a 35% 4-year survival, compared with 69% among those who did not have oxygen desaturation. Compared with results of static pulmonary function tests, such as repeated forced vital capacity, an abnormal 6-minute walk test result is more strongly associated with a poor prognosis, demonstrating a 10% drop over 6 months.

In patients with NSIP, desaturation during the 6-minute walk is less common but has been associated with a reduction in 4-year survival from 100% to 66%. In other ILDs, such as sarcoidosis, the relationship between sequential static lung functions and 6-minute walk is not clear. However, CPET may detect lung disease earlier in sarcoidosis than will static pulmonary function tests; it may also detect cardiac causes of dyspnea earlier.

Radiographic imaging

Although nearly 10% of biopsy-proven ILDs have been shown to be missed on the plain chest radiograph, many diagnostic clues can be obtained from routine posteroanterior and lateral chest radiographs (Table 2). The chest radiograph typically shows interstitial markings that are more often prominent at the lung bases. Prominent markings in the lower lung zones suggest entities such as IPF, chronic hypersensitivity pneumonitis, fibrotic NSIP, and asbestosis.

Prominent upper lung zone markings suggest the possibility of sarcoidosis, silicosis, acute hypersensitivity pneumonitis, chronic beryllium disease, and pulmonary Langerhans cell histiocytosis. Other clues include calcified pleural plaques (asbestosis), hilar adenopathy (sarcoidosis), and pneumothorax (pulmonary Langerhans cell histiocytosis or LAM). Every effort should be made to obtain the patient's previous chest radiographs to ascertain the time of disease onset and rate of progression.

High-resolution CT (HRCT), which has become widely used over the past decade, represents an extremely important addition to the diagnostic armamentarium for ILD. By allowing for ultrathin cuts of lung tissue (1- to 2-mm collimation), HRCT defines structures frequently involved in ILD, such as the bronchioles, interlobular septa and, most importantly, the secondary pulmonary lobule. The secondary pulmonary lobule is the smallest unit of lung tissue that is marginated by connective tissue septae. It is a polyhedral structure that has a core of bronchiolo, artery, and lymphatics.
surrounded by alveoli. The borders are the interlobular septae, which contain venous drainage channels and lymphatics. Each ILD involves some or all of these structures in different patterns that are important to recognize (Table 3).

HRCT has assumed a prominent role in the evaluation of ILD. However, it still suffers from many limitations. These include the variable experience of the radiologist; less-than-optimal sensitivity in UIP/IPF; and poor ability to discriminate ILD mimics, such as diffuse infection, heart failure, and malignancy.

Despite these limitations, HRCT has an excellent ability to predict the histopathology. In UIP/IPF, sarcoidosis, LAM, and pulmonary Langerhans cell histiocytosis, a confident diagnosis on the basis of HRCT patterns predicts the correct pathology in more than 90% of cases. Thus, HRCT findings may obviate the need for histologic sampling if they are consistent with the clinical picture.

**Bronchoalveolar lavage**

This is one of the most commonly performed bronchoscopic procedures. In evaluating patients in whom ILD is suspected, bronchoalveolar lavage (BAL) can identify conditions such as infection or hemorrhage, help confirm the clinical diagnosis, or suggest an alternative diagnosis. The BAL profile of inflammatory cells, inflammatory cell ratios, and pathogenic features (atypical cells, protein, organisms) can be fairly specific for some disease processes. In conjunction with a compatible clinical-radiographic picture, BAL can be diagnostic in pulmonary alveolar proteinosis (PAP), eosinophilic pneumonia, Langerhans cell histiocytosis, pulmonary hemosiderosis, infections that can mimic ILD (pneumonia caused by *Pneumocystis*, nontuberculous mycobacteria, or endemic mycoses), and hypersensitivity pneumonitis (Table 4).

BAL findings are highly suggestive—but not necessarily diagnostic—in sarcoidosis, desquamative interstitial pneumonia, respiratory bronchiolitis with ILD, drug-induced lung disease, and the pneumoconioses. Normal BAL findings virtually exclude PAP, alveolar hemorrhage syndromes, eosinophilic pneumonia, hypersensitivity pneumonitis, and active sarcoidosis. Some experts have considered BAL to have a role in prognostication. Patients with IPF who are found to have a high number of lymphocytes in BAL fluid appear to have a more favorable outcome, while an increased number of eosinophils in BAL fluid appears to identify those with a more rapidly progressive disease. However, the linkage of BAL lymphocytosis to better outcome is based on older studies that classified patients with NSIP or UIP/IPF as having IPF and did not distinguish NSIP from IPF. Patients with NSIP frequently have BAL lymphocytosis and a more favorable clinical course than those with IPF. Thus, the presence of BAL lymphocytosis in a patient with a clinical and radiographic picture suggestive of IPF may be consistent with NSIP.

In sarcoidosis, BAL neutrophilia may portend a more progressive disease that responds poorly to therapy, while a high CD4:CD8 ratio has been associated with a more favorable course. However, it is not clear whether BAL lymphocytosis and CD4:CD8 ratios are particularly useful in predicting the clinical course of sarcoidosis.

The main role of BAL in patients with ILD is to identify or exclude diseases for which treatment is available or to provide additional support for a diagnosis that is strongly supported by clinical and radiographic findings. **Lung biopsy**

Transbronchial lung biopsy is less invasive and safer than surgical lung biopsy and can be performed with BAL. Although it frequently can retrieve lung tissue that is diagnostic of many forms of ILD, such as sarcoidosis, transbronchial lung biopsy has limitations. Tissue sampling may be inadequate or nondiagnostic. However, the risk of complications, although somewhat higher than with bronchoscopy and BAL alone, remains lower than the risk with surgical lung biopsy. The advantage of surgical lung biopsy is that one can sample lung tissue that is nearly always diagnostic, especially if HRCT is used to target lung regions that are most likely to yield diagnostic tissue. However, the risk of complications—which include death—is not negligible and the decision to perform lung biopsy should be made thoughtfully.

It is now clear that patients with clinical and HRCT findings that are typical for IPF do not need a "gold standard" surgical lung biopsy for a reasonably confident diagnosis to be made. However, many ILD experts recommend surgical lung biopsy for patients who do not have such typical findings and do not have contraindications for thoracic surgery, especially if they are young and otherwise healthy. **A DIAGNOSTIC APPROACH**

The diagnostic approach to ILD must integrate the clinical data, radiographic findings and, if needed, the histopathologic appearance (Figure). As noted above, the history taking should include specific questions about potential exposures and the physical examination should include a search for signs of associated conditions, such as collagen vascular disease.

An HRCT scan should be obtained if the diagnosis is not evident from the routine chest radiograph.
and clinical data. It should be scrutinized for features of fibrosis, such as honeycombing, reticular lines, and traction bronchiectasis. These features are consistent with UIP. Clinicians can frequently use clinical and imaging data to differentiate IPF from other forms of ILD (Table 5). If the fibrotic changes are atypical for UIP, consider other causes, such as non-IPF idiopathic interstitial pneumonia, sarcoidosis, or hypersensitivity pneumonitis. Other HRCT findings that may assist in the diagnosis include a dilated esophagus (suggesting limited scleroderma), pleural effusion (LAM, rheumatoid arthritis, or SLE), mediastinal/hilar adenopathy (sarcoidosis, lymphangitic carcinomatosis, or silicosis), and pneumothorax (LAM or pulmonary Langerhans cell histiocytosis).

Once these features have been integrated with clinical findings, a decision about tissue sampling must be made. If the clinical scenario is classic for a specific disorder (for example, a premenopausal woman with diffuse cystic lung disease and pneumothorax or an older person with chronic dyspnea, clubbing, and subpleural/basilar honeycombing) and the radiologist and clinician can make a confident diagnosis, a lung biopsy is not necessary. However, if diagnostic uncertainty exists, invasive procedures, including bronchoscopy (with BAL and/or transbronchial lung biopsy) or surgical lung biopsy, must be considered, to make an accurate diagnosis and to determine optimal therapy. Whenever possible, the clinician, radiologist, and pathologist should review the data and arrive at a consensus. Such a multidisciplinary approach has been shown to optimize diagnostic accuracy.

This paradigm does not apply to patients with end-stage lung disease who are transplant candidates for whom a histopathologic diagnosis is needed. Invasive procedures are unlikely to benefit patients with end-stage lung disease who have diffuse honeycomb change on HRCT and severe pulmonary dysfunction.

References: REFERENCES
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