in contrast to the responses of mature SMCs, which, in general, dedifferentiate before they exhibit marked changes in proliferative or migratory behavior.

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Overview of Pulmonary Fibrosis*

Francis H.Y. Green, MD

Pulmonary fibrosis is a component of over 200 interstitial lung diseases. Some have known etiologies, however, for many diseases, the etiology remains unknown or obscure. This brief review examines the prevalence and classification of these diseases, the approach to be taken for the investigation of a patient suspected of having pulmonary fibrosis, the implications for the performance of lung biopsy, and

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Remodeling and Repair in Respiratory Diseases
current thoughts concerning the pathogenesis of the idiopathic forms of fibrotic lung disease. A brief review of established and emerging therapeutic strategies is included.

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Key words: classification; idiopathic pulmonary fibrosis; pathogenesis; review

Abbreviations: COP = cryptogenic organizing pneumonia; CXR = chest radiograph; DIP = desquamative interstitial pneumonia; DLCO = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution CT; IFN = interferon; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; RB = respiratory bronchiolitis; SP-C = surfactant protein C; TGF = transforming growth factor; UIP = usual interstitial pneumonia

Interstitial lung diseases (ILDs) are a diverse group of lung diseases that are characterized by chronic inflammation and progressive fibrosis of the pulmonary interstitium. The interstitium is defined as the alveolar walls (including epithelial cells and capillaries), septae, and the perivascular, perilymphatic, and peribronchiolar connective tissues.

There are over 200 ILDs (Fig 1). They can be broadly classified into the following categories: ILDs with a known etiology, such as those due to occupational/environmental factors, drugs, hypersensitivity reactions and infections; ILDs associated with systemic disorders, such as sarcoidosis and collagen vascular disorders; and rare miscellaneous conditions, such as eosinophilic granuloma and the idiopathic interstitial pneumonias (IIPs). The fibrosing ILDs have certain clinical and pathologic features in common. The common clinical features include the following:

- progressive dyspnea on exertion;
- nonproductive paroxysmal cough;
- abnormal breath sounds on auscultation;
- abnormal findings on chest radiograph (CXR) or high-resolution CT (HRCT) scan; and
- restrictive pulmonary physiology with decreased vital capacity and diffusing capacity of the lung for carbon monoxide (DLCO) and widened alveolar-arterial oxygen pressure difference.

The common pathologic features include the following:

- fibrosis of the interstitium, involving collagen, elastic and smooth muscle elements;
- architectural remodeling of the interstitium;
- chronic inflammation of the interstitium (ie, variable increases in lymphocytes, plasma cells, macrophages, eosinophils, and mast cells);
- hyperplasia of type II cells; and
- hyperplasia of endothelial cells.

Data on the prevalence of ILD is scant, and death certificate-based mortality data are neither sensitive nor accurate for describing the occurrence of ILDs. The prevalence in New Mexico for all types of ILD was estimated at 509 cases per 100,000 population for men and 622 cases per 100,000 population for women. The incidence of ILD was estimated at 31.5 per 100,000 persons per year for men and 26.1 per 100,000 persons per year for women. Idiopathic pulmonary fibrosis (IPF) accounted for 46.2% of all ILD diagnoses in men, and
44.2% in women. Despite the poor quality of the data and the changes in diagnostic criteria/classification (ie, diagnostic transfer), there is evidence that IPF is increasing in many Western nations. By contrast, asbestosis, one of the more common occupationally induced ILDs, accounts for approximately 7 deaths per million in the US population.

**Evaluation of a Patient With Pulmonary Fibrosis**

A complete patient evaluation would include the following: history; physical examination; laboratory investigations; lung function tests; CXR and HRCT scanning; and lung biopsy.

**History and Physical Examination**

It is necessary to establish whether the disease is acute, episodic, or chronic, and whether it is associated with a systemic illness. It is also essential to establish a lifetime exposure history, including a complete list of occupations, drug use, hobbies, pets, travel, potential immunosuppression, and smoking history.

**Laboratory Investigations**

The minimum initial investigations should include urinalysis, full blood count, and differential blood count, measurements of urea, electrolyte, and creatinine levels, liver function tests, and autoantibody tests [ie, antinuclear factor (ANF) and rheumatoid factor (RF)]. If vasculitis is suspected, antineutrophil cytoplasmic and antibasement membrane antibodies also should be measured.

**Lung Function Tests**

Although a restrictive pattern of lung function is probably the most common symptom, a proportion of patients have preserved lung volumes or airflow obstruction in the initial stages of the disease. The most appropriate and simplest tests are for vital capacity and Dlco, and these tests are the most useful for monitoring the progression of the disease.

**Imaging Techniques**

CXRs and HRCT scans are essential for the evaluation of a patient with ILD. HRCT scanning helps to narrow the differential diagnosis, allows earlier diagnosis, is useful for assessing disease extent, and can detect confounding diseases, such as emphysema. A correct diagnosis can be made using HRCT scanning on 61 to 80% of patients. In a recent study, the correlation between the findings of HRCT scanning and tissue diagnosis in IPF was found to be good for the presence of honeycombing, the extent of normal tissue, and vessel changes. However, there was a poor correlation between ground-glass appearance and the histologic findings.

**Lung Biopsy and BAL**

Lung biopsy may be valuable for diagnosis and for measuring disease activity, progression, and response to treatment. Transbronchial lung biopsy is diagnostically useful in 38 to 79% of patients, particularly those with specific entities, such as infections or sarcoidosis. Open-lung biopsy may not be required for the evaluation of a patient with suspected ILD as many of the diseases have sufficiently characteristic clinical, radiologic, and laboratory features to establish the diagnosis. The diagnostic yield is approximately 90%. Open-lung biopsy should include at least two biopsy sites, the choice of which should be based on the HRCT results. Areas of honeycomb fibrosis should be avoided, as these reveal nonspecific end-stage changes that are of no diagnostic usefulness. The performance of a biopsy early in the course of the disease and prior to treatment is also recommended.

BAL is a useful technique that may play a role in the diagnosis of inorganic dust diseases, opportunistic infections, suspected malignancy, some hematologic diseases, transplantation-related and drug-induced diseases, and alveolar proteinosis. BAL is of value in research studies of IIP but is of limited use diagnostically, except when used to exclude alternative diagnoses.

**The IIPs**

The classification and diagnostic criteria for the IIPs were recently reviewed by an international multidisciplinary panel that was jointly convened by the American Thoracic Society and the European Respiratory Society. The panel included clinicians, radiologists, and pathologists who were experts in adult pulmonary diseases. In all, the panel identified seven conditions that were considered sufficiently different from one another to be designated as separate disease entities (Table 1). The most important of these conditions was IPF, also known as usual interstitial pneumonia (UIP). The committee stressed the need for the diagnosis to be made in a dynamic manner requiring close communication among clinician, radiologist, and pathologist. Other recommendations of the committee included that the term nonspecific interstitial pneumonia (NSIP) be considered a provisional diagnosis until there is further clarity on the nature of the conditions and the spectrum of clinical entities associated with this pathology. The committee recommended that, in the absence of contrary indications, the performance of a surgical lung biopsy may be valuable for diagnosis and for measuring disease activity, progression, and response to treatment.
lymphocytic interstitial pneumonia (LIP).11,12 These entiti-
pathic bronchiolitis obliterans-organizing pneumonia and
organizing pneumonia (COP), which also is known as idio-
acute interstitial pneumonia, NSIP, and cryptogenic orga-
from IPF/UIP are desquamative interstitial pneumonia

The six categories of IIP that need to be distinguished
from IPF/UIP are desquamative interstitial pneumonia
(DIP), respiratory bronchiolitis (RB)-associated ILD, acute interstitial pneumonia, NSIP, and cryptogenic organ-
izing pneumonia (COP), which also is known as idio-
patic bronchiolitis obliterans-organizing pneumonia and
lymphocytic interstitial pneumonia (LIP).11,12 These enti-
tes have distinct pathologic and clinical features, and
markedly different outcomes in response to corticosteroid
therapy.3 The major purpose of a histologic examination is
to distinguish IPF/UIP from the other histologic subsets of
IIP. The contrasting pathologic features for four of the IIP
subsets are shown in Table 2. DIP, LIP, and COP are
more distinct pathologically and rarely cause diagnostic
confusion. Many of the pathologic features associated with
IIP are seen in patients with connective tissue disorders.
Their prognosis, however, is related to that for patients
with the underlying disease, and their condition should be
classified as IIP associated with a specific connective
tissue disorder.13

Patients with IPF/UIP have a poor prognosis, with a
median survival time of 28.2 months.14 The survival time for
patients with IPF/UIP is considerably worse than that
for the other categories of IIP.15,16 The risk factors for
progressive disease include the following: male gender
(age > 50 years); moderate dyspnea on exertion; history of
cigarette smoking17; moderate to severe loss of lung
function; neutrophilia or eosinophilia at presentation in
BAL fluid; reticular opacities or honeycomb changes
found on HRCT scans; poor response to corticosteroid
therapy; and fibroblastic foci found on lung pathology.
Patients with IPF are at greater risk for lung cancer, which
accounts for 10% of all deaths.16

<table>
<thead>
<tr>
<th>Feature</th>
<th>UIP</th>
<th>DIP/RB-ILD</th>
<th>AIP</th>
<th>NSIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal appearance</td>
<td>Variegated</td>
<td>Uniform</td>
<td>Uniform</td>
<td>Uniform</td>
</tr>
<tr>
<td>Interstitial inflammation</td>
<td>Scant</td>
<td>Scant</td>
<td>Scant</td>
<td>Usually prominent</td>
</tr>
<tr>
<td>Collagen fibrosis</td>
<td>Patchy</td>
<td>Variable, diffuse in DIP; focal, mild in RB-ILD</td>
<td>No</td>
<td>Variable, diffuse</td>
</tr>
<tr>
<td>Fibroblast proliferation</td>
<td>Fibroblastic foci</td>
<td>No</td>
<td>Diffuse</td>
<td>Occasional, diffuse, or rare fibroblastic foci</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Honeycomb changes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Intra-alveolar macrophage</td>
<td>Occasional, focal</td>
<td>Diffuse in DIP; peribronchiolar in RB-ILD</td>
<td>No</td>
<td>Occasional, patchy</td>
</tr>
<tr>
<td>accumulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaline membranes</td>
<td>No</td>
<td>No</td>
<td>Occasional, focal</td>
<td>No</td>
</tr>
</tbody>
</table>

**AIP = acute interstitial pneumonia. Adapted from Katzenstein et al.12**

**Therapeutic Approaches to IPF/UIP**

Since lung fibrosis is currently considered to be irre-
versible, the management principles for IPF/UIP and
other chronic fibrosing lung diseases are as follows:
(1) early identification and aggressive treatment; (2) per-
manent removal of offending agents; and (3) palliation of
complications.

Although corticosteroid therapy is commonly used for
treatment of IPF/UIP, there have been no placebo-
controlled clinical trials performed.19 Approximately 20% of
patients will respond positively. Unfortunately, in many
studies diagnoses were not based on the findings of lung
biopsies or were not classified by current pathologic
criteria, thus, there is doubt as to the nature of the disease
being treated. Newer agents, such as interferon (IFN)-
gamma, show considerable promise for treatment of the dis-
 ease.11,20 Other nonsteroidal agents that have been tried in
initial clinical trials or are under consideration are shown in
Table 3.

**Prognostic and Predictive Factors**

The relationship between individual histologic features
disease progression in patients with IPF/UIP was
recently addressed using biopsy materials from the Royal
Brompton Hospital (London, UK).13 Four histologic fea-
tures (ie, fibroblastic foci, interstitial mononuclear cell
infiltrates, established fibrosis, and intra-alveolar macro-
phages) were evaluated for prognostic significance. Fibro-
blastic foci were linked to increased mortality, low DLCO,
and declines in FVC at 6 and 12 months. Increased levels
of interstitial mononuclear cell infiltrates were also inde-
dependently linked to functional decline, but only at 6
months. The other histologic features had no prognostic
value. These data suggest that disease progression can be
predicted by lung biopsy findings. Similar findings have
been reported by Bjoraker et al16 from the Mayo Clinic.
The differential cell count from samples of BAL fluid21
has been used with limited success to monitor the progress-
on of IPF.5 The use of serum markers looks to be more
promising. The presence of serum surfactant proteins has
been shown to have predictive value for disease progres-
sion in patients with IPF/UIP and pulmonary fibrosis associated with scleroderma. Plasma α-defensins, and serum type I and type II procollagen also have been suggested for use as prognostic markers.

Pathogenesis of Pulmonary Fibrosis

The pathogenesis of IPF/UIP is poorly understood. Genetic and environmental factors play a role. Inherited abnormalities of surfactant proteins are associated with IPF. Recently, cases of IPF/UIP and NSIP have been found in one family that were associated with a mutation in the surfactant protein C (SP-C) gene. SP-C-deficient (−/−) mice also developed severe ILD. The finding that both IPF/UIP and NSIP were associated with the SP-C gene in this kindred is of interest as it suggests that the two entities are closely linked. Environmental factors also play a role. IPF is more likely to occur in certain occupations in which there is exposure to dust, raising the possibility that environmental factors contribute to the pathogenesis of IPF/UIP.

With regard to the underlying pathogenesis, it is not known whether the disease is caused by a persistent inflammatory stimulus or an abnormal response to shear forces, or whether it represents abnormal repair and remodeling in response to patchy foci of injury. Numerous cytokines and fibrogenic factors are up-regulated or down-regulated in pulmonary fibrosis, including transforming growth factor (TGF-β), endothelin-1, insulin-like growth factor-1, tumor necrosis factor-α, and platelet-derived growth factor. Changes in matrix metalloproteinases and their inhibitors, apoptosis, the presence of cell adhesion molecules, the presence of myofibroblasts, changes in mast cell function, excessive procollagen activity, diminished vascularity, and abnormal epithelial cell function have been described in patients with IPF/UIP. All of these studies offer promising opportunities for therapeutic interventions. The early indications that IFN-γ may be beneficial in the treatment of patients with IPF may be due to the known interactions of this cytokine with several pathways that are implicated in its pathogenesis. IFN-γ down-regulates the cytokines TGF-β and interleukin-4, inhibits myofibroblast apoptosis, suppresses the myofibroblast phenotype, and increases the activity of matrix metalloproteinases.

Future Directions

Major unanswered questions concerning the pathogenesis of IPF/UIP remain. What is the continuing stimulus for the inflammatory-fibrotic process in IPF/UIP? Is IPF/UIP primarily a disorder of the repair process? What are the mechanical and structural changes involved in the remodeling of the lung? What is the significance of the fibroblastic foci? What is the role of the alveolar epithelium? What interventions are most likely to succeed in mitigating the fibrosis? At this time, no one approach or theory is preeminent. Research should continue on as many fronts as possible. Recently, a working group of the National Heart, Lung, and Blood Institute met to discuss potential directions for future research. Because the occurrence of IPF/UIP is relatively rare in the general population, many of the recommendations concerned the requirement to create regional centers of excellence that would be able to conduct clinical trials and develop innovative diagnostic techniques, and new drug delivery systems.

References


Table 3—Nonsteroidal Therapeutic Approaches to Lung Fibrosis

<table>
<thead>
<tr>
<th>Types of Agents</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic</td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
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<tr>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Blockers of collagen synthesis or fibrosis</td>
<td>Prolyl hydroxylase</td>
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<tr>
<td></td>
<td>Colchicine</td>
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<tr>
<td></td>
<td>D-penicillamine</td>
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<tr>
<td></td>
<td>IFN-γ</td>
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<tr>
<td></td>
<td>IFN-β</td>
</tr>
<tr>
<td></td>
<td>Pirfenidone</td>
</tr>
<tr>
<td>Increase of matrix reabsorption</td>
<td>IFN-β</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Glutathione</td>
</tr>
<tr>
<td></td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Arachidonic acid metabolite modifiers</td>
<td>Leukotriene B4</td>
</tr>
<tr>
<td>Blockers of neutrophil adhesion molecules</td>
<td>Prostaglandin E2</td>
</tr>
<tr>
<td>Inhibitors of specific fibrogenic cytokines and growth factors</td>
<td>TGF-β</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Urokinase</td>
</tr>
</tbody>
</table>

*From the American Thoracic Society and Crystal et al.


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