Idiopathic Pulmonary Fibrosis

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Table of Contents

Introduction ........................................... 2
Clinical Presentation ................................. 3
Diagnostic Evaluation ............................... 5
Pathologic Analysis of Lung Tissue ............ 7
Treatment ............................................. 8
Prognosis ............................................. 10
Board Review Questions ........................... 10
Answers .............................................. 11
References ........................................... 11
Suggested Reading ................................. 11

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Idiopathic Pulmonary Fibrosis

I. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease of unknown etiology. In the past, the medical literature has been confusing because of the various names that have been used to describe IPF. These include cryptogenic fibrosing alveolitis, Hamman-Rich syndrome, diffuse interstitial fibrosis, idiopathic interstitial pneumonia, honeycomb lung, fibrosing alveolitis, and usual interstitial pneumonia (UIP). The 2 most commonly used terms are IPF and cryptogenic fibrosing alveolitis. The primary distinction between IPF and cryptogenic fibrosing alveolitis is that cryptogenic fibrosing alveolitis includes patients with well-defined connective tissue diseases. By definition, IPF is idiopathic and thus has no clear association with any underlying disease, drug, or occupational or environmental factor known to cause pulmonary fibrosis.

The prevalence of IPF in the general population is difficult to determine. Open lung biopsy has been considered the gold standard for the diagnosis of IPF but has not been examined in large population-based studies. Tertiary care centers have reported prevalence rates of 3 to 6 cases per 100,000. An epidemiologic study from a county in New Mexico found a prevalence of approximately 30 cases per 100,000. Most IPF patients present after age 50 years, with a peak incidence of presentation after age 70 years. Up to 70% of patients with IPF are current or former smokers.

There are clear cases of familial IPF, which tends to manifest itself at an earlier age (20–40 years) and to have a more rapidly progressive course. The genetics of familial IPF have yet to be confirmed, but it is thought
to be an autosomal dominant disorder with variable penetrance. Although the role of genetics in IPF has not been established, there are clearly inherited diseases with features similar to IPF, such as Hermansky-Pudlak syndrome, neurofibromatosis, and tuberous sclerosis. Perhaps as the genetic defects of these diseases become more established, they will shed insight into the mechanisms of IPF.

As is the case with many idiopathic diseases, it is postulated that a genetic predisposition to environmental or infectious agents initiates an inflammatory and immune response. Exposure to metal dusts such as steel, brass, lead, cobalt, aluminum, zinc, cadmium, and mercury are associated with pulmonary fibrosis. Pulmonary fibrosis has also been documented to occur after infection with adenovirus, Epstein-Barr virus, and hepatitis C. Some patients with IPF date the onset of symptoms to a flu-like illness associated with respiratory symptoms. However, it is also possible that there was preexisting progressive fibrosis and that a viral respiratory tract infection simply tipped the patient over into the symptomatic range.

The differential diagnosis of patients presenting with interstitial lung disease is extensive (Table 1) and emphasizes the importance of taking a detailed history and performing a thorough physical examination. Because IPF is a diagnosis of exclusion, a careful, detailed occupational and environmental history is mandatory. If no underlying disease, occupational exposure, drug use or abuse, or environmental factor associated with pulmonary fibrosis can be identified, then IPF can be diagnosed.

II. CLINICAL PRESENTATION

CASE PRESENTATION

A 55-year-old woman presents to a pulmonologist with symptoms of fatigue, weight loss, and a gradual reduction in her activity. She used to be very active, playing tennis and horseback riding, but she gave up those activities approximately 4 months ago. She says that she has become “out of shape” and cannot do the things she used to be able to do. Her symptoms began about 9 months ago, when she developed an upper respiratory tract infection. Since that time, she has had a dry, nonproductive cough, which has been progressively worsening. She denies experiencing fevers, chills, night sweats, joint pains, or skin changes. She has not worked outside of the home and has 3 children, all of whom are healthy. She has never been hospitalized, has no underlying medical conditions, and is on no medications. No other family members have been ill, and family history is unremarkable.

On physical examination she is noted to have rapid shallow breathing. Her respiratory rate is 28 breaths/min, pulse rate is 110 bpm, blood pressure is 120/84 mm Hg, and she is afebrile. There is no evidence of peripheral cyanosis, digital clubbing, or pitting edema of the lower extremities. Cardiac examination shows normal heart sounds but tachycardia. Auscultation of her lungs reveals fine inspiratory crackles at both bases, extending halfway up her back. When she lies flat on her left side, there are rales at the base of her left lung and the right lung is clear. When she turns onto her right side, rales are over her right lung and the left side is clear (ie, gravitational dependence of rales).

- What aspects of this patient’s presentation point to a diagnosis of IPF?
- What diagnostic tests are appropriate at this point?

DISCUSSION

The gradual onset and progressive worsening of a nonproductive cough and dyspnea are the hallmarks of IPF. A persistent nonproductive cough that is unresponsive to antitussive medication may be the primary patient complaint. Seventy-five percent of patients with IPF have cough at their initial presentation. Although some patients present with cough alone, with time, all patients develop dyspnea on exertion.

The insidious onset and progression of dyspnea is harder to detect. The lung has a large reserve; even after a pneumonectomy, dyspnea on exertion does not occur if the remaining lung is normal. Fibrosis must therefore be substantial before symptoms develop. In addition, patients have a tendency to reduce their activity, so they don’t perceive their dyspnea. Thus it is important to discuss with the patient his or her current level of activity as compared with 6 months to 1 year ago. With careful questioning, 10% of patients presenting with IPF deny dyspnea on exertion, 32% are short of breath going up a hill, 22% get dyspneic walking on level ground, and 36% are severely disabled, complaining of dyspnea at rest or after walking less than 100 yards.

Physical Examination

On physical examination, the characteristic finding (>80% of patients) is the presence of gravity-dependent, late, fine inspiratory crackles (“Velcro rales”) predominately at the lung bases. As the disease progresses, crackles may extend into the apices and lose their gravitational dependence. Digital clubbing is present in 25% to
### Idiopathic Pulmonary Fibrosis

**Table 1. Clinical Classification of Interstitial Lung Disease**

<table>
<thead>
<tr>
<th><strong>Collagen vascular disease-associated</strong></th>
<th>Fluoxetine</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>Phenylephrine</td>
<td>BCG vaccine</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td>Polymyositis-dermatomyositis</td>
<td></td>
<td>Oxygen (100%)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
<td>Radiation</td>
</tr>
<tr>
<td>Scleroderma</td>
<td></td>
<td></td>
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<tr>
<td>Sjögren’s syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Systemic lupus erythematosus</td>
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</tr>
</tbody>
</table>

**Drug- or treatment-induced**

<table>
<thead>
<tr>
<th>Antiarrhythmic</th>
<th>Adenocortical steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>β-Blocking agents</td>
<td></td>
</tr>
<tr>
<td>Tocainide</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Bone marrow transplantation</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>Eosinophilic granuloma</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Gaucher’s disease</td>
</tr>
<tr>
<td>Nifurbutarol</td>
<td>Hermansky-Pudlak syndrome</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Interstitial cardiogenic edema</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Lymphangioloeyiomymatosis</td>
</tr>
<tr>
<td>Gold</td>
<td>Lymphangitic carcinomatosis</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Nebruforminosis</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Niemann-Pick disease</td>
</tr>
<tr>
<td>Chemotherapeutic</td>
<td>Postinfection</td>
</tr>
<tr>
<td>α-Interferon</td>
<td>Pulmonary vasculitis</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Respiratory bronchiolitis</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Occipital or environmental exposure-related</td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>Aluminum oxide fibrosis</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Antimony pneumoconiosis</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Asbestosis</td>
</tr>
<tr>
<td>Cytoxane arabinoside</td>
<td>Bagassism (sugar cane)</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>Baritis (barium)</td>
</tr>
<tr>
<td>Lomustine (CNU)</td>
<td>Berylliosis</td>
</tr>
<tr>
<td>l-Tryptophan</td>
<td>Bird breeder’s lung</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Ceramic tile worker’s pneumoconiosis</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Cheese worker’s lung</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>Chicken handler’s lung</td>
</tr>
<tr>
<td>N ilutamide</td>
<td>Coal worker’s pneumoconiosis</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Coffee worker’s lung</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Compost lung</td>
</tr>
<tr>
<td>Neurotropic and psychotropic</td>
<td>Diatomaceous earth pneumoconiosis</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Dove handler’s lung</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Duck fever</td>
</tr>
<tr>
<td></td>
<td>Farmer’s lung</td>
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<tr>
<td></td>
<td>Fishmeal worker’s lung</td>
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</tbody>
</table>

**Primary or unclassified disease-related**

| Adult respiratory distress syndrome     | Furrer’s lung          |
| AIDS                                    | Goose-down hypersensitivity pneumonia |
| Amyloidosis                             | Hard metal fibrosis    |
| Bone marrow transplantation             | Humidifier lung        |
| Eosinophilic granuloma                  | Kaolin pneumoconiosis  |
| Gaucher’s disease                       | Machine operator’s lung|
| Hermansky-Pudlak syndrome               | Malt worker’s lung     |
| Interstitial cardiogenic edema          | Maple bark-stripper’s lung |
| Lymphangioloeyiomymatosis               | Meat worker’s lung     |
| Lymphangitic carcinomatosis             | Miller’s lung (wheat flour) |
| Nebruforminosis                         | Mushroom worker’s lung |
| Niemann-Pick disease                    | Paprika splitter’s lung|
| Postinfection                           | Paragaut toxicity      |
| Pulmonary vasculitis                    | Polyvinyl chloride pneumoconiosis |
| Respiratory bronchiolitis               | Sauna-taker’s lung     |
| Sarcoidosis                             | Shale pneumoconiosis   |
| Tuberous sclerosis                      | Siderosis (arc-welder’s lung) |
| Occupational or environmental exposure-related |
| Aluminum oxide fibrosis                 | Silicone pneumonitis   |
| Antimony pneumoconiosis                 | Silicosiderosis (iron oxide) |
| Asbestosis                              | Silicosis              |
| Bagassism (sugar cane)                  | Stannosis (tin)        |
| Baritis (barium)                        | Suberosis (cork)       |
| Berylliosis                             | Talc pneumoconiosis    |
| Bird breeder’s lung                     | Tea grower’s lung      |
| Ceramic tile worker’s pneumoconiosis    | Textile worker’s pneumonitis |
| Cheese worker’s lung                    | Tobacco grower’s lung  |
| Chicken handler’s lung                  | Toluene disococanate hypersensitivity pneumonitis |
| Coal worker’s pneumoconiosis            | Wood-burning interstitial fibrosis |
| Coffee worker’s lung                    | Woodworker’s disease   |

**Idiopathic fibrotic disorders**

| Acute interstitial pneumonia            | Furrer’s lung          |
| Autoimmune hemolytic anemia             | Goose-down hypersensitivity pneumonia |
| Bronchiolitis obliterans- organizing pneumonia |
| Celiac disease                          | Hard metal fibrosis    |
| Chronic active hepatitis                 | Humidifier lung        |
| Cryoglobulinemia                         | Kaolin pneumoconiosis  |
| Cryptogenic cirrhosis                    | Machine operator’s lung|
| Desquamatative interstitial pneumonia   | Malt worker’s lung     |
| Familial idiopathic pulmonary fibrosis  | Maple bark-stripper’s lung |
| Idiopathic pulmonary fibrosis           | Meat worker’s lung     |
| Idiopathic thrombocytopenic purpura     | Miller’s lung (wheat flour) |
| Inflammatory bowel disease               | Mushroom worker’s lung |
| Lymphocytic interstitial pneumonias     | Paprika splitter’s lung|
| Nonspecific interstitial pneumonia      | Paragaut toxicity      |
| Primary biliary cirrhosis               | Polyvinyl chloride pneumoconiosis |


50% of the patients and tends to occur later in the dis-
ease. If the disease is moderate to severe, evidence of pul-
monary hypertension (ie, right ventricular S3 with an 
increased P2, right ventricular lift) or cor pulmonale may 
be present. Cyanosis is a late manifestation of the disease. 
Extrapulmonary manifestations do not occur except as 
above. Weight loss, fatigue, and malaise may be present. 
Fever is uncommon and suggests an alternative diagno-
sis or a complicating infectious process. Spontaneous 
pneumothorax may occur late in the disease but is much 
less common than in eosinophilic granuloma or lympho-
angioleiomyomatosis.

III. DIAGNOSTIC EVALUATION

DIAGNOSIS AND EVALUATION OF CASE PATIENT

A chest radiograph (Figure 1) and a high-resolution 
computed tomographic (HRCT) scan of the chest 
(Figure 2) are ordered for the case patient. The chest 
radiograph shows bilateral reticular opacities and loss 
of lung volume. The HRCT scan of the chest shows 
patchy subpleural areas of ground-glass opacities and 
reticular opacities, as well as some cystic structures 
greater than 5 mm (consistent with honeycombing). 
Intervening areas of normal lung are visible.

Routine laboratory testing, including hemoglobin 
level, leukocyte count and differential, and blood 
chemistries, are normal. Tests for antinuclear antibody 
and rheumatoid factor are negative. Her erythrocyte 
sedimentation rate is slightly elevated (30 mm/h).

Pulmonary function studies are performed with the 
following results: forced vital capacity (FVC), 60% of 
predicted; forced expiratory volume in 1 second (FEV1), 
65%; total lung capacity (TLC), 55% of predicted; dif-
fusion capacity, 45% of predicted. These changes are 
consistent with moderate restrictive lung disease.

Results of an arterial blood gas analysis on room air 
are as follows: pH, 7.36; PCO2, 34 mm Hg; PaO2, 65 mm 
Hg. With exercise, her oxygen saturation level decreas-
es to 87%.

- What is the advantage of HRCT for diagnosis of 
  interstitial lung diseases?
- What pulmonary function test findings are typical 
  for IPF?

LABORATORY TESTING

Laboratory testing cannot be used to confirm a diag-
osis of IPF but may be useful in eliminating other 
known causes of interstitial lung disease. Erythrocyte 
sedimentation rate and autoimmune profiles help to 
establish the diagnosis of connective tissue diseases, 
thus supporting a diagnosis of cryptogenic fibrosing 
alveolitis. Ten percent to twenty percent of patients with 
IPF test positive for antinuclear antibody and rheuma-
toid factor, and 50% have circulating immune com-
exes. These tests do not correlate with the extent or 
activity of disease, however, and do not predict response 
to therapy. Serum lactate dehydrogenase may be ele-
vated, especially in patients with rapidly deteriorating 
lung function.

CHEST RADIOGRAPH

The chest radiograph is usually the test that points to 
the presence of interstitial lung disease. It is abnormal 
in 90% to 95% of patients with IPF. Reports do exist of 
normal chest radiographs from patients with biopsy-
proven interstitial lung disease, but this is rare in IPF.

The most common radiographic findings are the 
presence of reticular (ie, net-like) and fine nodular pat-
terns. The nodular pattern is the result of overlapping 
of the linear reticular changes. Because of the increased 
thickness of the lungs at their bases, radiographic 
changes are more prominent at the lung bases. The lung 
volume also appears to be reduced. Honeycombing (a 
coarse reticular pattern with cystic lucencies) is a late 
manifestation of IPF and portends a poor prognosis. 
Pleural involvement and the presence of mediastinal 
adenoapthy are uncommon and suggest an alternative 
diagnosis.
Although chest radiographs are usually abnormal in patients with IPF, they lack sensitivity and specificity. HRCT scans of the chest provide far more information concerning the pulmonary parenchyma and are more sensitive and specific for the diagnosis of IPF.

**HIGH-RESOLUTION COMPUTED TOMOGRAPHY**

Because HRCT scans 1- to 2-mm sections of lung parenchyma, it is more sensitive for the detection of IPF than conventional chest radiography. The characteristic features of HRCT in patients with IPF are the presence of patchy heterogeneous ground-glass opacities, reticular densities, and honeycomb cysts in a subpleural location.

The HRCT abnormalities correlate with histopathology. The ground-glass opacities correlate with the presence of active cellular alveolitis. The reticular pattern reflects fibrosis. Honeycombing corresponds to cystic lesions greater than 5 mm in diameter. HRCT findings predict the likelihood of response to therapy. The presence of mostly ground-glass opacities with little honeycombing portends a favorable response to therapy, whereas the presence of extensive honeycombing without ground-glass opacities portends a poor response to therapy. Serial HRCT scans in patients being treated for IPF show that the ground-glass opacities either resolve (responsive to therapy) or progress to a reticular pattern (unresponsive to therapy). Few patients with just a reticular pattern on HRCT will respond to therapy.

Substantial variability exists both within and between institutions with regard to the ability of HRCT to provide a specific diagnosis. In some types of interstitial lung disease (eg, lymphangioleiomyomatosis) the HRCT findings, interpreted together with the proper clinical information, are sufficiently diagnostic that open lung biopsy is not required.

**PULMONARY FUNCTION TESTING**

Pulmonary function testing results typical of IPF show restriction as manifested by the presence of a reduced TLC. The functional residual capacity (FRC) and residual volume (RV) are also reduced. The diffusion capacity of the lung for carbon monoxide (DLco) is also frequently reduced and may precede reductions in lung volume. The FEV1 and FVC are proportionally reduced, thus preserving the FEV1:FVC ratio. Because of increased static elastic recoil, flow rates for a given lung volume may be increased, and thus the FEV1:FVC ratio may be elevated.

Resting arterial blood gases may be normal or may show hypoxemia with a respiratory alkalosis, depending on the severity of the disease. The hypoxemia at rest is caused by ventilation and perfusion mismatch and not by diffusion limitation. Some patients with normal oxygenation at rest develop exercise-induced desaturation. Exercise testing is more sensitive than resting physiologic testing in detecting abnormalities in oxygen transfer and is a good parameter for following the clinical course of patients with IPF. During exercise, patients with IPF increase their minute ventilation by increasing their respiratory rate, rather than by increasing their tidal volume. In the early stage of IPF, there is seldom pulmonary hypertension at rest; however, pulmonary hypertension may develop during exercise. When the vital capacity falls below 50% of predicted or the DLco falls below 45% of predicted, there is frequently resting pulmonary hypertension. Late in the course of IPF, patients may develop carbon dioxide retention and evidence of chronic respiratory failure.

**RADIONUCLIDE IMAGING**

Gallium Ga 67 citrate has been used to assess the presence of pulmonary inflammation. However, because gallium scans are difficult to quantitate, are expensive, are inconvenient for the patient, and do not predict response to therapy or the patient’s clinical course, gallium scans have no role in staging or monitoring disease activity in patients with IPF.

**LUNG BIOPSY**

Although the histologic changes revealed by lung biopsy are diagnostic, a flexible approach in the use of lung biopsy is appropriate. In an elderly patient with findings typical for IPF (ie, gravitational dependence of...
crackles on physical examination, a restrictive defect as evidenced by pulmonary function tests, and characteristic HRCT findings, a biopsy may not be justified or necessary. On the other hand, young patients with constitutional symptoms (eg, fever and sweats), atypical changes on HRCT, or with rapidly deteriorating lung function should undergo an open biopsy procedure.

The preferred surgical approach is video-assisted thoracoscopic lung biopsy or an open lung biopsy performed through a mini-thoracotomy. Bronchoscopy with transbronchial biopsy is simple and safe and can be performed as an outpatient procedure; however, the small tissue samples and the peripheral and patchy nature of IPF make transbronchial biopsies less useful in patients with IPF except to help exclude other diseases. If sarcoidosis, malignancy, infection, hypersensitivity pneumonitis, or alveolar proteinosis is a likely consideration for the patient, then bronchoscopy with transbronchial biopsy might be helpful by obviating an open biopsy procedure.

If an open biopsy is performed, 2 to 3 samples from different areas of both the upper and lower lobes should be obtained. The tip of the lingula and right middle lobe should be avoided because scarring and nonspecific inflammation unrelated to the underlying disease process are often present in these areas.

IV. PATHOLOGIC ANALYSIS OF LUNG TISSUE

RESULTS OF CASE PATIENT’S BIOPSY

The patient undergoes a video-assisted thoracotomy with multiple biopsies from both the left upper and lower lobes. Figure 3 shows the lung biopsies stained with hematoxylin and eosin on the left and trichrome stain (collagen stain) on the right.

- What is the diagnosis based on this patient's histologic findings?

HISTOLOGIC SUBTYPES OF IDIOPATHIC PULMONARY FIBROSIS

IPF can be classified by histologic appearance into 4 distinct forms: UIP, desquamative interstitial pneumonia (DIP) (also known as respiratory bronchiolitis interstitial lung disease), acute interstitial pneumonia (AIP), and nonspecific interstitial pneumonia (NSIP).

Usual Interstitial Pneumonia

Patients with “classic” findings for IPF, as described in the case presented, typically have UIP on biopsy (Figure 3). UIP is characterized by a patchy, nonuniform subpleural distribution of interstitial changes. Histologic variation from one low-magnification field to another exhibits alternating zones of interstitial fibrosis, inflammation, honeycombing, and normal lung tissue. A small amount of lymphocytic inflammation may be present in areas of collagen deposition or honeycombing, but significant inflammatory changes suggest another diagnosis.

Desquamative Interstitial Pneumonia

The most striking histologic finding in DIP is the presence of increased numbers of macrophages within the alveolar spaces. These macrophages have abundant cytoplasm containing finely granular yellow-brown pigment. These cells were originally thought to be desquamated epithelial cells, hence the misnomer of DIP. Fibroblastic foci and honeycombing are not present, and the overall appearance on low magnification is one of monotonous uniformity from one field to another, contrasting sharply with the heterogeneity of UIP. In one series, 90% of patients with DIP had a history of smoking cigarettes.

Acute Interstitial Pneumonia

AIP, also called Hamman-Rich syndrome, is characterized by diffuse interstitial fibrosis. AIP is different from UIP in that there is active fibrosis consisting of proliferating fibroblasts and myofibroblasts with minimal collagen deposition. The changes are temporally uniform and appear to be relatively acute, reflecting a reaction to lung injury that occurred several weeks previously. The histologic changes are similar to those of UIP except that the process is diffuse rather than patchy. The appearance of AIP is similar to that of the organizing phase of diffuse alveolar damage that occurs after a variety of noxious lung insults. If the process continues for more than a month, enlarged restructured air spaces can be formed that resemble the honeycomb changes of UIP. Other manifestations of acute lung injury, such as remnants of hyaline membranes within alveolar spaces, may be present. AIP carries a relatively poor prognosis.

Nonspecific Interstitial Pneumonia

NSIP is characterized by the presence of varying degrees of inflammation and fibrosis within the alveolar walls, but it lacks the more specific changes used to diagnose UIP, AIP, or DIP. Generally, there are areas of inflammation with minimal fibrosis or a mixture of inflammation and fibrosis. The process may be patchy with intervening areas of normal lung tissue similar to UIP, but the changes appear temporally uniform, which contrasts with the temporal heterogeneity of UIP.
Because the HRCT of the case patient’s chest shows areas of ground-glass opacities and the biopsy shows some inflammation, it is decided to give her a trial of steroid therapy. She is treated with prednisone 60 mg per day for 1 month and then the dosage is decreased to 40 mg per day. Despite therapy, she develops increasing dyspnea both at rest and with exertion. Three months after initiation of therapy, repeated pulmonary function studies show progressive reduction in her DLCO and TLC. On physical examination, more crackles are noted in her lungs. Cardiac examination reveals an increased P2. Because of her rapid deterioration, the patient is admitted to the hospital and given intravenous steroids and cyclophosphamide.

**How effective is pharmacologic therapy for IPF?**

**Are there alternatives to pharmacologic treatment for IPF?**

**DISCUSSION**

The main goal of treatment for IPF is to suppress inflammation and thereby prevent progression to irreversible fibrosis. However, no clear data exist showing that suppression of inflammation actually prevents the subsequent development of fibrosis. There is evidence that the disease is more responsive to treatment if inflammation rather than fibrosis is present. Early diagnosis...
therefore appears to be important. Once the diagnosis is made and the level of clinical severity is determined, most patients receive therapy because this is a potentially fatal disease.

**PHARMACOLOGIC TREATMENT**

Corticosteroids are the mainstay for the treatment of IPF, but a favorable clinical response occurs in only 20% to 30% of patients. Different subtypes of IPF respond differently to steroid therapy. U1P and A1P generally have a poor response to steroid therapy whereas D1P and bronchiolitis obliterans with organizing pneumonia have a favorable response.3,5,6 There are no prospective studies assessing the optimal dosage or duration of therapy. Many clinicians prescribe 60 mg of prednisone per day, with tapering after 4 to 6 weeks, but others recommend an initial dosage of 1.5 mg/kg body weight of prednisone per day up to a maximum daily dose of 100 mg. This dose of prednisone is continued for 4 to 6 weeks and is then decreased to 40 mg/day or 1 mg/kg per day for another 4 to 6 weeks, and is then decreased to 0.5 mg/kg per day. The patient should be reevaluated at the end of 3 months. If there is objective improvement, the prednisone is decreased to a maintenance dosage of 20 mg/day or 0.25 mg/kg per day. Most investigators believe that daily treatment is necessary and advise against changing to alternate-day therapy.

Relapse or deterioration requires an increase in the dosage of prednisone or the addition of another cytotoxic agent (eg, azathioprine or cyclophosphamide). Cyclophosphamide is frequently used as second-line drug therapy for patients who have failed steroid therapy because of either the progression of disease or the development of side effects. The recommended dose of cyclophosphamide is 2 mg/kg body weight per day given orally as a single dose, prescribed along with prednisone 0.25 mg/kg body weight per day.

Most patients tolerate 100 to 125 mg of cyclophosphamide. Cyclophosphamide therapy is initiated at a dosage of 25 to 50 mg per day, and is gradually increased in 25-mg increments, with a goal of reducing the leukocyte count to between 4000 and 7000/mm³. The leukocyte count needs to be monitored twice a week for the first 3 months of therapy. In patients with rapidly progressing disease, high-dose intravenous methylprednisolone 250 mg every 6 hours and intravenous cyclophosphamide 1.5 mg/kg body weight are administered.

**Adverse Effects of Medications**

Because most patients with IPF are elderly, the frequency of complications and side effects of therapy are significant. In fact, one abstract that reported results of 16 patients treated with prednisone concluded that prednisone treatment may increase rather than decrease mortality in patients with IPF.7 Because of the high incidence of side effects, investigators at the Mayo Clinic have studied the use of colchicine in the treatment of patients with IPF.8 This prospective study found no difference in the clinical course of patients treated with prednisone versus colchicine. The patients treated with colchicine had a few minor side effects, whereas those patients treated with prednisone had serious side effects that were not always reversible with cessation of therapy. For patients who develop complications from prednisone therapy or in whom the clinician feels the risk of side effects outweighs the possible benefits, colchicine could be considered.

**Evaluating Response to Treatment**

Pharmacologic therapy for IPF must continue for 3 to 6 months before its effectiveness can be assessed. Only 10% to 30% of patients have objective improvement in their physiologic or radiographic abnormalities in response to therapy. Subjective improvement occurs frequently. Those patients who do respond to therapy usually have only a partial and transient response. Treatment responders generally will relapse, suggesting that prolonged (probably lifelong) treatment is required.

Sustained and complete remissions occur in fewer than 5% of IPF patients. Changes in pulmonary function and HRCT are used to distinguish responders from nonresponders; however, no clear guidelines exist for defining a response. An improvement of 10% to 15% in a single pulmonary function parameter (eg, vital capacity or DLco) or 6-minute walk distance has been considered evidence of a response. If the patient has had deteriorating lung function, even the lack of further deterioration (stabilization) could be considered a response. The majority of patients continue to experience deterioration of their lung function.

**LUNG TRANSPLANTATION**

Lung transplantation is an important option to consider for patients with IPF. Lung transplantation is the only treatment that has the potential to restore significant functional improvement in patients with IPF. After lung transplantation, patients frequently no longer need supplemental oxygen, and there is reversal of their pulmonary hypertension and right ventricular dysfunction. The 1-year and 2-year survival rates after single lung transplantation for patients with IPF range from 57% to 73%.7 Patients with a vital capacity or TLC that is lower than 60% of predicted or a DLco less than 40% of predicted...
have a 2-year mortality rate of greater than 50%. Because there can be up to a 2-year waiting time before a lung becomes available, it is important to consider transplantation at the time of initial diagnosis with referral to an appropriate center. Many patients die of respiratory failure while waiting for transplantation. Contraindications to lung transplantation include age greater than 60 to 65 years; inadequate psychosocial profile; significant renal, hepatic, or cardiovascular disease; previous major cardiothoracic surgery; morbid obesity; and current administration of high-dose prednisone.

VI. PROGNOSIS

The natural history of IPF has not been well defined, but it is characterized by a gradual but inexorable loss of lung function over months to years. Data derived from several reports suggest that the median survival time after diagnosis, with or without treatment, is less than 5 years. The 5-year mortality rate is greater than 40%. The major cause of death is respiratory failure. Approximately 10% of patients with IPF develop lung cancer. In rare cases the course of the disease is fulminating, progressing to fatal respiratory failure within 6 to 12 months. Occasionally, after an initial period of decline, the disease process stabilizes. Spontaneous resolution is very rare. Patients who present with a significant amount of honeycombing demonstrated on chest radiograph have a poor prognosis.

OUTCOME OF CASE PATIENT

Lung transplant evaluation of the case patient is undertaken and she is considered to be a good candidate. She improves somewhat on intravenous therapy and is sent home on prednisone 60 mg/day and cyclophosphamide 2 mg/kg body weight per day orally. Her lung function continues to deteriorate. She develops respiratory failure and dies 2 years after being placed on the lung transplant waiting list.

BOARD REVIEW QUESTIONS

Choose the single best answer for each question.

1. A 60-year-old woman presents with a chief complaint of dyspnea on exertion. The patient states that she has experienced shortness of breath for 6 months, but in retrospect, she has noticed problems with her breathing ever since she had “the flu” about 2 years ago. On physical examination you find bilateral crackles at both lung bases. A chest radiograph shows bilateral increased reticular opacities. All of the following conditions would be included in the differential diagnosis of this patient EXCEPT:
   A) Usual interstitial pneumonia (UIP)
   B) Bronchiolitis obliterans with organizing pneumonia
   C) α1-Antitrypsin deficiency
   D) Desquamative interstitial pneumonia

2. Which one of the following choices describes findings on high-resolution computed tomography (HRCT) of the chest that, in the proper clinical setting, would be diagnostic of UIP?
   A) Diffuse reticular opacities throughout both lungs with evidence of hyperinflation
   B) Patchy subpleural areas of reticular and ground-glass opacities with some honeycombing and intervening areas of normal lung
   C) Diffuse ground-glass opacities throughout both lungs
   D) Traction bronchiectases with 5-mm cystic structures

3. Which one of the following techniques is the best method of establishing a diagnosis of UIP?
   A) Transbronchial lung biopsy
   B) Mediastinoscopy
   C) Positive emission tomography
   D) Gallium scan
   E) Open lung biopsy

4. An 85-year-old man presents with a 2-year history of progressively increasing shortness of breath, with dyspnea on exertion. Physical examination reveals bilateral, gravity-dependent crackles and digital clubbing. Pulmonary function studies show a total lung capacity (TLC) of 45% of predicted and a diffusion capacity for carbon monoxide (DLco) of 25% of predicted. An arterial blood gas analysis shows a pH of 7.42, Pco2 of 36 mm Hg, and Po2 of 60 mm Hg. A computed tomographic scan of the chest shows subpleural reticular and ground-glass opacities and honeycombing with intervening areas of normal lung. Which one of the following diagnostic tests should be performed next?
   A) Transbronchial lung biopsy
   B) Cardiopulmonary exercise test
   C) Open lung biopsy
   D) Gallium scan
5. A 60-year-old woman has just been diagnosed with biopsy-proven UIP. Over the past year she had increasing dyspnea on exertion, and she now experiences shortness of breath walking from her bed to the bathroom. Her TLC is 40% of predicted with a DLco of 25% of predicted. Her PaO2 at rest is 55 mm Hg, and it falls to 45 mm Hg with minimal exertion. You start the patient on home oxygen therapy, and after a discussion of risks and benefits of pharmacologic therapy, she decides that she wants to receive treatment for her lung disease. Which one of the following is an appropriate drug regimen for this patient?  
A) 1.5 mg prednisone/kg of body weight per day for 6 weeks  
B) 0.5 mg prednisone/kg of body weight per day for 3 months  
C) 2 mg prednisone/kg of body weight on alternate days for 2 months  
D) 0.5 mg prednisone/kg of body weight on alternate days for 3 months

6. A 50-year-old man presents with a 2-year history of dyspnea on exertion. Physical examination reveals bilateral gravity-dependent crackles. The chest radiograph is read as normal. Pulmonary function testing shows normal TLC, normal diffusion capacity, and normal expiratory flow rates. Arterial blood gases on room air show a pH of 7.42, PCO2 of 34 mm Hg, and PO2 of 60 mm Hg. Which one of the following diagnostic tests should be performed next?  
A) Gallium scan  
B) Open lung biopsy  
C) HRCT scan of the chest  
D) Transbronchial lung biopsy

7. A 60-year-old man with a recent diagnosis of UIP (biopsy-proven) has been treated with 1.5 mg prednisone/kg of body weight for the past 6 weeks. Despite treatment, the patient is complaining of progressive dyspnea on exertion. Pulmonary function tests show a fall in TLC from 60% to 50% of predicted, and the PaO2 has decreased from 63 to 55 mm Hg. It is your assessment that there has been no response to the prednisone treatment. At this time, which one of the following is an appropriate recommendation?  
A) Admit to the hospital for intravenous high-dose (250 mg every 6 hours) methylprednisolone  
B) Add cyclophosphamide, increasing the dosage incrementally until 2 mg/kg of body weight is reached, and decrease the prednisone dosage  
C) Refer the patient for lung transplant evaluation  
D) Taper and discontinue the prednisone  
E) All of the above may be appropriate

ANSWERS
1. C  
2. B  
3. E  
4. B  
5. A  
6. C  
7. E

REFERENCES

SUGGESTED READING