A primary care approach to interstitial lung disease
When to suspect idiopathic pulmonary fibrosis

Jonathan Ilowite, MD
The diagnosis of interstitial lung disease (ILD) can be a daunting task. With hundreds of possibilities for diagnosis—and a confusing classification scheme that seems to keep changing—it is not surprising that many specialists and primary care clinicians are uncomfortable when they see a patient in whom they suspect ILD. Studies suggest that many patients wait years after symptoms develop and see multiple physicians before they receive a proper diagnosis.

This review is not meant to be all-encompassing or particularly scholarly. Rather, it describes an approach to guide the primary care clinician when faced with a patient with possible ILD.

When should I suspect ILD?

Patients with the insidious onset of chronic cough and worsening dyspnea should set off the alarm for possible ILD. Of course, common entities such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) can also present with those symptoms. Here are 3 items that might clue you in that ILD is a stronger possibility.

1. Crackles: Listen closely for crackles. I have received several referrals from primary care physicians this year, and this was the only sign that the patient had fibrosis. Of course, CHF also can present with crackles, but this can easily be distinguished from ILD with appropriate studies, such as a brain natriuretic peptide (BNP) or 2D-echocardiogram.

2. Desaturation: I believe every clinician should have an oximeter in the office. Patients with ILD typically will desaturate with minimal exercise, more so than with CHF or COPD. Walk them around the office and observe.

3. Examine the hands: Look for evidence of arthritis, clubbing, vasculitis, and other systemic conditions that might clue you into a particular systemic disease associated with ILD. (See section on Autoimmune Disease for more information on pages 3-4.)

What should I do next if I suspect ILD?

Get full pulmonary function testing and order a high-resolution CT (HRCT) scan of the chest. Unfortunately, different facilities may interpret that order differently. Ideally, the facility will do thin cuts (2 mm or less), prone and supine views, inspiratory and expiratory views, and sagittal and coronal reconstructions.
What should I do to determine the type of ILD?
At this point, it would be perfectly okay to refer the patient to your community pulmonologist—preferably one with a special interest in ILD. But if you want to go further, the next step is to determine if there is a known cause or association with the ILD, or whether it is idiopathic.

Here are the 5 major categories of known causes:

1. Medications or toxins
2. Occupational exposure
3. Autoimmune disease
4. Hypersensitivity pneumonitis
5. Radiation pneumonitis

Let’s discuss these in more detail.

1. Medications
Many medications have been implicated in ILD. The best compendium of these can be found at www.pneumotox.com. However, some medications are more common than others and should be specifically asked about.

_Amiodarone_. Patients should be asked about this medication, and more generally about any medications they may have taken in the past or currently to control their heart rate.

_Nitrofurantoin_. Ask too about this medication, in all its forms (Macrobid, Macrobid) and frequency of its use. I worry that with concern over side effects with quinolones and emerging resistance to Bactrim, the use of this class of medications is going to rapidly increase, and therefore the incidence of ILD as well.

_Chemotherapy_. Methotrexate, busulfan, bleomycin, and other traditional chemotherapy agents have been associated with ILD. In addition, many of the newer immunomodulatory agents used to treat common cancers, such as breast and lung, have also been implicated in lung toxicity.

2. Occupational Exposure
Common causes of pneumoconiosis include silicosis, coal workers’ pneumoconiosis, and asbestosis. Sometimes the occupational history is straightforward (eg, coal miner). However, it can be challenging. I had a patient who worked as a dental technician and developed silicosis grinding tooth implants. Asbestos, although no longer used in construction, is still present in abundance in older buildings. Many technical professions—plumbers, electricians, and contractors (as well as automechanics and brake technicians) are therefore at risk for significant exposure. Asbestos was also plentiful in older ships, so asbestosis is also commonly seen in older patients who worked aboard naval vessels.

3. Autoimmune Diseases
A number of collagen vascular diseases and

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vasculitides are commonly associated with ILD. Probably the most common are scleroderma, polymyositis and dermatomyositis, rheumatoid arthritis, and Sjögren’s syndrome. That is why I talked about the importance of a careful examination of the hands earlier in this report, as many of these conditions will present with a telltale rash, deformity, or swelling of the joint that can be seen on close scrutiny. A careful history with attention to morning stiffness, joint swelling, pleuritic pain, dysphagia, Raynaud’s, dry eyes and mouth, and/or muscle pain may point you to a specific diagnosis.

However, just to make life more difficult, often patients can present with ILD months or years before other clinical manifestations of their rheumatological disease. Thus, many pulmonologists will send off a battery of lab tests for the more common rheumatological entities, even in the absence of extrapulmonary findings.

4. Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is an ILD caused by an allergic reaction in the lung to exposure to specific antigenic proteins. If you practice in a rural area, the most common of these antigens are present in mold spores found in silos. In suburban and urban practices, the most common entity we see is in relation to indoor birds. Many patients do not consider these birds pets and need to be specifically asked if they have any indoor birds. I had one patient who kept a garage full of homing pigeons. Unfortunately, this hobby was destroying the patient’s lungs.

Mold in the home is another common cause of HP. Ask patients about leaky pipes, smelly basements or bathrooms, humidification systems, or flooding in the home. If necessary, an industrial hygienist can be hired to evaluate the home. The physical exam may often reveal an inspiratory squeak in addition to crackles of the lung, and labs (HP panel) can be ordered for antibodies to common allergens to help with this diagnosis.

5. Radiation

Radiation to the chest or nearby organs, such as for lung cancer, breast cancer, or lymphoma, can cause ILD. Early radiation pneumonitis usually occurs 4 to 12 weeks after radiation exposure: it is a subacute illness, often with fevers, cough, dyspnea, malaise, and chest pain. A more fibrotic, chronic phase can develop, usually 6 to 12 months after exposure.

Idiopathic

Once you have ruled out the common, known causes or associations of ILD, you are left with the idiopathic causes, which have an alphabet soup of names. . . IPF, NSIP, RB-ILD, COP, DIP, and AIP, LIP, and IPPFE. A detailed discussion is beyond the scope of this article. However, by far the most common is IPF (idiopathic pulmonary fibrosis). It commonly presents as an insidious-onset nonproductive cough and dyspnea in an elderly patient (occurring more commonly in men than women). Extrapulmonary signs and symptoms are usually absent, and the HRCT scan will often show a particular pattern called UIP (usual interstitial pneumonia) which has a peripheral basilar predominance consisting of reticular abnormalities and possibly honeycombing. Nodules, ground glass opacities, or air trapping are generally inconsistent with a UIP pattern. It is now extremely important to make this diagnosis as early as possible, as the earlier a diagnosis is made, the earlier a treatment regimen can be started.

The Bottom Line

ILD is a challenging group of heterogeneous diseases and entities of known and unknown causes.

I hope this report can help you organize your thoughts in the approach to and diagnosis of ILD. ■

Acknowledgment

I would like to acknowledge Dr. David Lederer, a world expert on ILD who practices at Columbia University, and whose lectures and writings have formed the framework for this discussion.
Idiopathic Pulmonary Fibrosis (IPF) is one of a heterogeneous group of diseases known as the idiopathic interstitial pneumonias. It is the most common of these disorders; as many as 132,000 patients have IPF, with an estimated 50,000 new cases diagnosed each year. (Raghu and colleagues note that by extrapolating rates to the overall US population, prevalence is estimated to be 42.7 per 100,000 [incidence, 16.3 per 100,000]). The disease carries a terrible prognosis, and most patients will live for only 3 to 5 years after diagnosis. This report will highlight some of the challenges primary care physicians face in diagnosing and treating this rare and ultimately fatal disorder.

What is IPF—and who gets it?
IPF is a progressive, debilitating lung disease characterized by progressive fibrosis of the lung parenchyma. This fibrotic process is mediated through fibroblast proliferation, which in turn lays down collagen. This results in the loss of lung function over time and impairment of gas exchange. Clinical symptoms include progressive dyspnea, worsening cough, and fatigue.

In general, this disease affects older patients. The disease is rarely diagnosed in patients younger than age 50. It seems to affect males more than females. Though it is idiopathic, there does seem to be some familial clustering and genetic predilection. Furthermore, it does seem to be more common in patients with a history of smoking, and may be associated with GERD.

When should I suspect IPF?
This is a vitally important question. Studies suggest that the diagnosis of IPF can often take 1 to 2 years. Patients often report having seen multiple physicians and years of delay before receiving an accurate diagnosis. Bronchitis, asthma, COPD, emphysema, or heart disease are often considered first, as the history of insidious onset of cough and dyspnea in an elderly patient is very nonspecific, and often leads to a presumptive diagnosis of one of the much more common aforementioned conditions.

What can I do to recognize this disease earlier in its course?

1. Read the chest X-ray (CXR) report carefully. If a CXR is ordered for someone...
with progressive dyspnea and cough, there may be clues on the CXR that are easily overlooked. Radiologists may report “old scarring,” or nonspecific fibrotic changes buried in the body of the report that might be easily overlooked if you are not suspicious of this disease.

2. Listen for crackles. This may be the only sign on a physical exam. Although crackles can also be heard in congestive heart failure and many other pulmonary conditions, it is not typically observed in asthma or COPD. The crackles characteristic of IPF mimic the sound of Velcro. These crackles are softer, higher in pitch, and shorter in duration than course crackles.

3. Walk the patient with oximetry. This is often the best clue that a patient may be suffering from IPF. Patients with IPF will often desaturate markedly, with minimal ambulation. This desaturation will occur earlier, and be more marked, than with other entities such as CHF and COPD.

4. Examine the hands. Patients with IPF often have clubbing present on their digits, which would not be seen in CHF or COPD. Furthermore, other causes of interstitial lung disease often will show telltale signs if the hands are examined.

What’s the next step?
If you suspect IPF after history and physical exam, the next step should be to order a full battery of pulmonary function tests and a high-resolution chest CT (HRCT) scan. Pulmonary function tests (PFTs) should show a restrictive pattern. FVC will be reduced; however, the ratio of FEV₁/FVC will be normal or high. Lung volumes will all be symmetrically reduced. Finally, the diffusing capacity will be low.

When performing an HRCT scan in patients with suspected IPF, images should be no more than 2 mm thick on axial reconstruction. In addition, prone and supine views, inspiratory and expiratory scans, and coronal and sagittal reconstructions are recommended. The HRCT pattern required for IPF is called UIP (usual interstitial pneumonia). The typical pattern consists of a subpleural, basal predominance, reticular abnormalities, and honeycombing. Features such as peribronchovascular predominance, extensive ground glass abnormalities, profuse micronodules, discrete cysts, diffuse mosaic attenuation, or consolidation abnormalities should be absent or minimal. A lack of honeycombing does not rule out the possibility of IPF; however, the classification would change to possible UIP.

Is anything else necessary for the diagnosis? Unfortunately, yes. IPF is a diagnosis of exclusion, determined when other causes of interstitial lung disease have been ruled out. Autoimmune disease, hypersensitivity pneumonitis, occupational lung disease, radiation fibrosis, medications and chemotherapy—to name a few—can all cause fibrotic changes in the lung. In some cases, the history, HRCT scan, and laboratory testing will be enough to make the diagnosis. However, sometimes a surgical lung biopsy is necessary.

For many cases, a multidisciplinary discussion among the patient’s pulmonologist, radiologist, and pathologist is employed to reach a diagnosis.

What is the natural history of IPF?
As stated, the general trend of this disease is an inexorable decline in lung function, leading to death within a few years. However, there is wide variability in this decline. Some patients decline slowly over time, while others decline rapidly. In either progression, instances of acute exacerbation of IPF (AE-IPF) significantly impact lung function and disease prognosis. Occurrences of AE-IPF may occur at any time during the course of the disease and
rapidly accelerate disease progression. Studies have shown that mortality rates for AE-IPF hospitalizations may be as high as 50%, increasing to 60% within 3 months. One of the best predictors of disease progression is the forced vital capacity (FVC), and it is recommended that lung function be monitored periodically in all patients with IPF.

What are the management strategies for patients with IPF?

Many strategies are needed for a comprehensive approach to treatment for patients with IPF. These fall into disease-centered, symptom-centered, and support-centered categories:

- Smokers should be encouraged to stop smoking.

- Comorbidities such as gastroesophageal reflux disease, obstructive sleep apnea, congestive heart failure, pulmonary hypertension, emphysema, and depression should be evaluated and treated.

- Pulmonary rehabilitation should be considered for all patients.

- Oxygen should be prescribed if there is resting or exertional hypoxemia.

- Treatment with FDA-approved pharmacologic therapies that slow the progression of IPF should be considered.

- Patients may want to consider enrolling in a clinical trial.

- All patients should have pneumonia, flu, and other age-appropriate vaccinations.

- Early referral for consideration for lung transplantation should be considered.

- Patients should be encouraged to join support or advocacy groups.

- Palliative care and end-of-life issues should be discussed as well.

Take Home Points

IPF is a progressive, debilitating, and ultimately fatal lung disease. It is vitally important that this disease is recognized in its early stages. This article has summarized several key features to help the primary care physician recognize this disease.
A Case of Worsening Dyspnea and Cough

Bob, a 72-year-old man with a 40-pack-year smoking history, presents with progressive dyspnea and non-productive cough. He quit smoking approximately 8 years ago, after being diagnosed with severe COPD. Until last year, he had been relatively stable, other than an occasional instance of “bronchitis,” usually treated with an antibiotic and/or steroids. He takes a corticosteroid and a long-acting β₂-adrenergic agonist to manage his COPD. Over the past year or so, however, his lung function has progressively declined. He no longer can walk up the steps in his house without stopping and gasping for breath. He also notes that getting the paper in the morning from the driveway has become a chore, particularly when he bends over. His cough has gotten markedly worse and is described as hacking and nonproductive.

Question:
1. What could cause the subacute worsening of Bob’s symptoms?

The differential is large, as almost all pulmonary and many non-pulmonary diseases present with the insidious onset of dyspnea and cough. The important teaching point is that patients with COPD, particularly those who had a relatively stable course, may have other etiologies for worsening symptoms than just progression of their COPD. A good clinician will delve further into the history to find a clue.

Bob denies taking up tobacco again, and claims to have no chest pain. He recently had a cardiac stress test and echocardiogram and was told that the results were unremarkable. He does not have any new hobbies or pets. He has travelled to Florida and Europe during the past 2 years. Most of his leisure time now is spent watching television or reading in the house. He does not have any symptoms of arthritis. He notes no mold problems in the home.

**Physical Exam**
- Temperature: 98.6°F; Pulse: 89; Respirations: 20
- Blood Pressure: 135/85; O₂ Saturation: 94%
- General appearance: Slightly anxious, mild respiratory distress
- Head, Ears, Eyes, Nose, and Throat: Unremarkable
- Skin: Numerous actinic keratoses, age-related changes
- Lungs: Decreased breath sounds, prolonged expiratory phase, bibasilar crackles
- Heart: Normal rhythm
- Abdomen: Normal
Extremities: Normal pulses, clubbing, no cyanosis, edema  
Neurology: Grossly intact  

**Question:**  
2. What are the abnormal findings? Does this help narrow the differential? What are the next steps?  

Abnormal findings include low oxygen saturation, and the presence of “crackles” and clubbing on physical examination. Although low oxygen saturation is common in COPD, crackles and clubbing are not signs of this disease. Clubbing can be seen in many chronic pulmonary and extrapulmonary diseases—including pulmonary malignancy, interstitial lung disease, bronchiectasis, and inflammatory bowel disease.15  

The patient was sent for a high-resolution CT scan of the chest (Figures 1, 2, and 3) as well as pulmonary function testing (Table).  

**Interpretation**  
Pulmonary function testing showed evidence of moderate obstruction. Lung volumes are normal. Carbon monoxide diffusing capacity is severely reduced. The PFTs, in the absence of additional clinical information, might be interpreted as consistent with COPD; however, the marked reduction of DL_{CO}—which is way out of proportion to the reduction in flows, suggests the possibility of a mixed defect. In this patient, both the severe emphysema and the pulmonary fibrosis seen on the
CT scan are negatively affecting the lungs’ ability to diffuse CO into the bloodstream, which accounts for the severe reduction in diffusing capacity. Interestingly, fibrosis and COPD actually counteract each other in flows and volume. Pulmonary fibrosis will increase the lung compliance, while COPD will reduce it. Alternatively, pulmonary fibrosis typically reduces lung volumes symmetrically, while COPD can raise total lung capacity (TLC) and functional residual capacity (FRC) because of hyperinflation. Thus, when patients have combined pulmonary fibrosis and COPD, lung volumes and flows are often relatively preserved; however, CO diffusing capacity is markedly decreased, as seen in this patient.

Clinical Course
The primary care physician made a tentative diagnosis of pulmonary fibrosis and referred the patient to a pulmonologist who specialized in interstitial lung disease. The pulmonologist confirmed the history, obtained a careful occupational and exposure history, and sent off screening labs for collagen vascular disease and hypersensitivity pneumonitis. These assays were negative, other than an ANA that was mildly elevated at 1:40, with a speckled pattern. The patient was discussed in a multidisciplinary conference that included a radiologist, pulmonologist, rheumatologist, and pathologist.

Following the multidisciplinary discussion, Bob was given the diagnosis of idiopathic pulmonary fibrosis (IPF).

The patient was enrolled in a pulmonary rehabilitation program. During his screening 6-minute walk and also during exercise at rehabilitation, he was noted to have severe oxygen desaturation (74%) during exercise. The use of a portable oxygen concentrator for exercise and sleep was recommended. The patient was then instructed to see his pulmonologist every 6 months.

Idiopathic Pulmonary Fibrosis
IPF is a fatal disease of the lung, causing progressive fibrosis that leads to worsening dyspnea and cough over time. The course can be unpredictable and variable in an individual patient, but on average, patients die of this disease within 3 years of diagnosis. Exacerbations can occur at any time and are particularly severe, often leading to death within a few months.

The disease is predominantly one of the elderly, and men are affected more than women. The cause is unknown, but it is important to rule out other causes of interstitial lung disease, such as collagen vascular disease, medications or toxins, and hypersensitivity pneumonitis.

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11 Take Home Facts and Tips on IPF

1. IPF is a fatal lung disease. Patients usually succumb within 3 years of diagnosis. This is worse than most common cancers, including breast, colon, and ovarian cancer.

2. There are as many as 132,000 people in the US with IPF, and about 50,000 new cases are diagnosed each year. The incidence and prevalence are on the rise.

3. IPF is initially misdiagnosed in as many as 50% of patients, and 38% of patients report needing to see 3 or more physicians before receiving a diagnosis of IPF. The diagnostic process can take an average of 1 to 2 years from symptom onset to final diagnosis, as patients are often misdiagnosed with bronchitis, asthma, COPD, emphysema, or heart disease.

4. IPF is more common in men than women, and many patients with IPF have a history of cigarette smoking.

5. IPF can run in families.

6. The clinical presentation of IPF may include:
   a. Velcro-like crackles at the base of the lungs
   b. Digital clubbing
   c. Desaturation with exercise
   d. Dry, nonproductive cough

7. The clinical course of IPF is variable. Lung function may decline slowly or rapidly, and the disease course may be accelerated by acute exacerbations.

8. Exacerbations can occur in anyone and at any time, and are often fatal.

9. Chest x-rays can rule out other causes of dyspnea; however, a diagnosis of IPF requires a high resolution CT scan.

10. A multidisciplinary approach, including a pulmonologist, pathologist, and radiologist, is recommended when approaching suspected cases of IPF.

11. Treatment and management of patients with IPF require disease-centered, symptom-centered, and support-centered strategies.
REFERENCES