Diagnosis and Management of Idiopathic Pulmonary Fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. Its signs and symptoms are relatively non-specific, and patients often present with chronic cough, progressive dyspnea, resting or exertional hypoxemia, and inspiratory crackles on lung auscultation. Definitive diagnosis requires the exclusion of known causes of pulmonary fibrosis and identification of the usual interstitial pneumonia (UIP) pattern of disease either on high-resolution computed tomography (HRCT) scan of the chest or on surgical lung biopsy. Multidisciplinary discussion involving pulmonologists, radiologists, and pathologists with expertise in the diagnosis of IPF and other forms of interstitial lung disease is recommended and often required. Management focuses on anti-fibrotic therapy and early referral to lung transplant centers for those who are candidates. This review will discuss the current recommendations for the diagnosis, prognostication, and management of patients with IPF.

KEYWORDS: idiopathic pulmonary fibrosis (IPF), cryptogenic fibrosing alveolitis, usual interstitial pneumonia (UIP), interstitial lung disease (ILD), idiopathic interstitial pneumonia (IIP), diffuse parenchymal lung diseases (DPLD)

INTRODUCTION

History, Epidemiology, and Pathogenesis

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing interstitial lung disease of an uncertain etiology and a poorly understood pathogenesis.[1] It is the most common of the idiopathic interstitial pneumonias (IIPs) and accounts for 20% of all interstitial lung disease (ILD).[2,3] IPF was first described in the modern literature in 1935 as "fulminating diffuse interstitial fibrosis of the lungs" by Louis Hamman and Arnold Rich and was subsequently coined "Hamman-Rich Syndrome."[4] By the 1960s the term IPF was increasingly being used, but it was not until 1998 when Katzenstein and Myers proposed a classification scheme of IIPs that the diagnosis of IPF was exclusively reserved for those individuals with the usual interstitial pneumonia (UIP) pattern on lung biopsy.[5] This classification scheme was formally adopted by international societies in 1999, resulting in publication of the first international consensus statement on the diagnosis and management of IPF.[6]

Precise estimates of the incidence and prevalence of IPF are difficult to determine, but appear to vary considerably between countries and regions for reasons that remain unclear.[1,7] In the U.S., recent estimates suggest an incidence of 7–17 per 100,000 person years and incidence and mortality rates appear to be increasing over time worldwide.[7,8]

IPF is more common in men, current or former cigarette smokers, and in occupations with a high level of inorganic dust exposure.[1,8] Aging, however, is by far the greatest risk factor.[8] Although some individuals can be diagnosed as young as 50 years old, the median age at the time of diagnosis is 66 years old and incidence, prevalence, and mortality all increase with increasing age.[7-9] Genetic factors also appear to play an important role, as both common and rare genetic variants have been associated with the development of IPF, and up to 20% of cases may in fact be familial.[10] Indeed, IPF is increasingly thought of as the result of a complex interplay between aging, host susceptibility (i.e. genetics and epigenetics), and environmental factors.[11] The specific relationships between these factors have not been fully elucidated, but the end result appears to be the development of an aberrant, or over-exuberant, wound healing response to repetitive microscopic lung injuries.[12,13] Many possible causes of microscopic injury have been theorized and include viral infections, gastroesophageal reflux, inhaled particulates, or other environmental exposures.[12,13]

DIAGNOSIS

The presentation of patients with IPF is relatively non-specific with insidious onset of dyspnea on exertion, non-productive cough, and inspiratory crackles on lung exam.[2,12,14] Systemic symptoms that would indicate a multisystem disease are not common and if present should raise suspicion for an alternative diagnosis.[15] Clubbing may be present but has only been reported in 25–50% of patients.[2,12] On pulmonary function testing patients are most commonly found to have restriction with a reduced diffusion capacity, but these changes can at times be mild, particularly in early disease.[1] In contrast, virtually all patients have abnormal chest

imaging on presentation.[15] Conventional chest x-ray (CXR) shows reticulonodular opacities that are typically bilateral, symmetric, and lower lung zone predominant. Occasionally the disease can be asymmetric or unilateral or can lack the typical apico-basilar gradient.[15]

Definitive diagnosis first requires the exclusion of any known causes of ILD such as connective tissue disease, drug toxicity, or environmental exposures.[14] Careful history taking is critical with special attention paid to exposures, co-morbidities, medication use, environmental exposures, and family history in order to exclude other etiologies as mentioned above.[1,15] Laboratory findings are generally non-specific, but can be helpful in ruling out alternative diagnoses such as connective tissue diseases.[15] High resolution computed tomography (HRCT) of the chest plays a central role in the diagnosis of IPF. The characteristic pattern on HRCT consists of bilateral, lower lung zone predominant reticular opacities and honeycombing.[1] Honeycombing refers to aggregates of subpleural, thick-walled cysts typically <1 cm in diameter.[1,14] Architectural distortion with traction bronchiectasis and bronchiolectasis is also frequently seen.[14] When this typical pattern is seen on HRCT it is 90–100% specific for histologic UIP and in these cases a lung biopsy is generally not required to confirm the diagnosis.[14] However, in cases where the HRCT lacks honeycombing and/or contains features that are not characteristic of UIP, a histologic diagnosis may be required. A surgical lung biopsy – either via thoracotomy or, more commonly, video-assisted thoracoscopic surgery (VATS) – has historically been required for a histologic diagnosis. Bronchoscopic transbronchial forceps biopsies are currently not recommended because the small size of tissue samples obtained does not allow for adequate assessment of the heterogenous changes seen in UIP.[2,15] The emerging technique of bronchoscopic cryobiopsy may provide a diagnosis of UIP in some cases, but the exact role of this technique in the diagnostic algorithm for IPF remains unclear.[16] If a biopsy is obtained, the typical UIP pattern consists of patchy fibrosis in a predominantly subpleural/paraseptal distribution along with areas of microscopic honeycombing and fibroblastic foci.[14] Fibroblastic foci are aggregates of proliferating fibroblasts and active myofibroblasts which are felt to be indicative of ongoing lung injury and repair that represent the "leading edge" of fibrosis development.[14] Just as with HRCT, lung biopsy specimens may not show all of the typical features of UIP and/or may show features suggestive of an alternative diagnosis. Accordingly, multidisciplinary discussion is recommended between pulmonologists, radiologists, and pathologists to determine whether or not a diagnosis of IPF can be confirmed based on the combination of clinical features, HRCT, and lung biopsy findings if obtained.[1,14]

PROGNOSIS

IPF is a progressive disease characterized by gradually worsening shortness of breath and, in most cases, the eventual development of respiratory failure.[1] The average survival is only 3–5 years following diagnosis.[13,17,18] At the same time, it is a clinically heterogenous disease process with considerable variability in the pace of disease progression between both different individuals with the disease and within any given individual over time.[19] Some patients suffer from rapidly progressive disease with a precipitous decline in lung function, while others may experience only slow, steady decline over many years.[20] Accordingly, predicting disease progression can be challenging and there is great interest in identifying characteristics that can predict an individual's disease course.[19] Although some imaging findings, such as presence of traction bronchiectasis, have been found to independently predict mortality, changes in pulmonary function tests over time have been found to be among the most robust predictors.[2] A decline as small as 5% in percent predicted FVC over the course of 6 months was found to be associated with more than a two-fold increase in risk of death over the subsequent 12 months.[19] Not surprisingly, older age and recent respiratory hospitalizations, including acute exacerbations of IPF, have also been found to portend poorer outcomes.[19]

Acute exacerbations of IPF (AE-IPF) can occur and often lead to hospitalization for respiratory failure with a precipitous decline in lung function. The proposed definition of AE-IPF requires: 1) a preexisting or concurrent diagnosis of IPF, 2) acute worsening of symptoms (typically <1 month), 3) imaging findings of bilateral ground-glass opacification and/or consolidation superimposed on a background pattern consistent with UIP, and 4) determination that the deterioration is not fully explained by congestive heart failure or volume overload.[21] On histology, although biopsy is not required for diagnosis, a pattern of diffuse alveolar damage or organizing pneumonia can be seen superimposed on a background of UIP.[1] The mortality of hospitalized cases of AE-IPF is approximately 50%.[2,22] Even patients who survive hospitalization for AE-IPF continue to have a poor prognosis, and approximately half of all IPF related mortality occurs after a nonelective respiratory hospitalization.[19] Currently there are no known risk factors for the development of acute exacerbations, other than lower FVC and DLCO at baseline, and these events can occur at any point in the disease course regardless of underlying disease severity.[2,21] Unfortunately, there are no effective treatments for AE-IPF other than supportive care.[21] High-dose steroids are currently recommended and are commonly prescribed for AE-IPF, but there have been no randomized controlled trials performed to support this practice.[1]

TREATMENT

Initially, therapeutics for IPF were focused on modulating the inflammatory response on the supposition that fibrosis was the end stage manifestation of chronic inflammation in the lung. However, over the last decade this treatment paradigm has shifted due to several studies that demonstrated not only a lack of benefit with immunosuppression, but also the possibility for harm.[23,24] The most notable of these was the PANTHER study published in 2012, which was a randomized, placebo-controlled trial of combination therapy with prednisone, azathioprine, and N-acetylcysteine (NAC) for the treatment of IPF.[23] This study was halted early due to an increase in all-cause mortality, hospitalizations, and treatment-related serious adverse events.[23] It has been hypothesized that prior observational data supporting the use of immunosuppression for IPF may have been skewed by the inclusion of other forms of IIPs that respond more favorably to anti-inflammatory therapy and have more favorable prognoses.[15]

Along with the recognition that anti-inflammatory therapy was ineffective in IPF, there was also growing acceptance that IPF was a disease characterized by abnormal wound healing responses in the lung.[12] Therefore, more recent clinical trials have focused on drugs that target these wound healing responses rather than inflammation. In 2014 the U.S. Food and Drug Administration (FDA) approved two antifibrotic medications, nintedanib and pirfenidone, for the treatment of IPF based on large clinical trials showing that both agents slow the decline in lung function by about 50% per year.[25,26] Pirfenidone is a pyridine molecule with an unknown mechanism of action, but that is thought to have a multitude of anti-fibrotic, anti-inflammatory, and anti-oxidant effects.[15] It has been shown *in vitro* to block growth factor simulated collagen synthesis, extracellular matrix (ECM) secretion, and fibroblast proliferation.[13,15] Nintedanib is a small molecule inhibitor of several receptor tyrosine kinases, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) receptors, and it also appears to inhibit fibroblast activation and ECM synthesis.[13] Although neither of these drugs are curative for IPF, nor have they definitively been shown to prolong survival, they are the first therapies that have been shown to impact the course of this disease. Furthermore, there are a multitude of additional drugs currently being investigated in late phase clinical trials that provide further hope that more effective treatment options are on the horizon.[27]

Non-pharmacologic therapy for IPF patients consists of supplemental oxygen administration for those who suffer from clinically significant resting or exertional hypoxemia and pulmonary rehabilitation to help preserve and even improve exercise tolerance.[1] Lung transplantation is the only treatment option that offers IPF patients with advanced disease the opportunity for prolonged survival, as it has been shown to reduce the risk of death at 5 years.[1,28] Referral for lung transplant evaluation should be considered in all patients with IPF. Unfortunately, many IPF patients are ineligible for lung transplant due to advanced age and/or co-morbid conditions at the time of presentation.[15]

CONCLUSION

IPF is a chronic lung disease characterized by the progressive accumulation of scar tissue (fibrosis) in the lungs, leading to impaired gas exchange, difficulty breathing, and eventually death. IPF symptoms are non-specific and generally consist of insidious onset of dyspnea on exertion and chronic coughing. The diagnosis requires the identification of a UIP pattern of disease on HRCT scan and/or surgical lung biopsy and the exclusion of known causes of pulmonary fibrosis. Anti-fibrotic medications, namely pirfenidone and nintedanib, have been shown to slow disease progression in IPF and are now the mainstays of treatment along with nonpharmacologic therapies such as supplemental oxygen and pulmonary rehabilitation. Lung transplantation is the only intervention that has been shown to reduce mortality in IPF, but unfortunately many patients are ineligible due to advanced age and co-morbidities.

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