Mini-Review

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Diagnosis of idiopathic pulmonary fibrosis: Current issues

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Summary **Idiopathic pulmonary fibrosis (IPF) accounts for the majority of lung diseases classified as idiopathic interstitial pneumonia (IIP). It is considered to be lethal because prognosis is very poor and far worse than other types of IIP. An early and accurate diagnosis of IPF is critical. The diagnostic process is complex and requires a multidisciplinary approach involving a pulmonologist, radiologist and pathologist.**

Keywords: Idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, diagnosis

1. Introduction

Idiopathic interstitial pneumonia (IIP) makes up a heterogeneous group of diseases. The most common and most lethal type of IIP is idiopathic pulmonary fibrosis (IPF) that accounts for 55% of lung diseases classified as IIP (*1-3*). Louis Hamman and Arnold Rich published a paper describing diffuse interstitial fibrosis of the lung in 1944 (*4*). They described thickening of the alveolar interstitium and an area of dense fibrotic scar tissue within the lung. Liebow and Carrington heralded the modern era of interstitial lung disease histo-pathology with the notion that IIP could be split into separate pathological subtypes in 1969 (*5*). In 2002, a panel of experts sponsored jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) released an official statement for the purpose of providing a new and comprehensive classification of IIP that considered all clinical, radiographic and pathological features (*1*). In the recent revision of the IIP classification, IPF is classified under major IIP and has been sub-categorized under chronic fibrosing interstitial pneumonias. The alternative terminology "cryptogenic fibrosing alveolitis" has been eliminated, leaving IPF as the sole clinical term for this diagnosis (*6*). The prognosis for individuals with IPF is poor, far worse than nonspecific interstitial pneumonia and other IIP, with a 5 years survival rate that is worse than several types of cancer (*7,8*). An early and accurate diagnosis of IPF is critical. Diagnosis of IPF requires precision and a multidisciplinary approach involving pulmonologists, radiologists and pathologists (*2*). This article aims to review the current issues in the diagnosis of IPF.

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2. Definition

IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia characterized by idiopathic origin, occurrence primarily in older adults, exclusively pulmonary involvement and pattern of Usual Interstitial Pneumonia (UIP) proven by histopathology and/or radiology. The confirmation of diagnosis of IPF requires the exclusion of other idiopathic interstitial pneumonias (IIP's) and interstitial lung disease associated with environment exposure, drugs, or systemic disease (*9-11*).

3. Diagnosis

3.1. *Clinical Features*

The diagnosis of IPF should be suspected in those adult patients with older age typically in the sixth and seventh decades. Its occurrence is rare in less than fifty years of age provided there could be manifestation of overt features of an underlying connective tissue disease that was sub-clinical at the time of IPF diagnosis. (*18,19*). The clinical features commonly associated with IPF are unexplained chronic exertional dyspnea, dry cough, bibasilar end-inspiratory crackles also known as Velcro crackles, and finger clubbing (found in 60% of cases).

(*12-17*). IPF is more common in men than women and the majority of patients have a history of cigarette smoking (*10-15*).

3.2. *Radiological Features*

The revised guidelines identify the high-resolution computed tomography (HRCT) features of IPF as UIP, possible UIP and inconsistent with UIP patterns (*2*). The features of a classical UIP pattern on HRCT require *i*) the presence of sub-pleural abnormalities with lower lobe predominance *ii*) reticular abnormality, *iii*) honeycombing with or without traction bronchiectasis and *iv*) exclusion of other features inconsistent with UIP pattern (upper or middle lobe predominance, peribronchovascular involvement, extensive ground glass abnormality, profuse micronodules, discrete multiple cysts other than honeycombing, extensive mosaic pattern and/or air trapping, or sub-pleural or basal consolidation (*20-22*). The presence of honeycombing with or without traction bronchiectasis can make then the diagnosis difficult using HRCT alone. Further workup is required for diagnosis if HRCT scan is showing features of possible and/or inconsistent UIP patterns (*2*). The revised IPF guidelines emphasize the analysis of HRCT. However, the major problem in clinical practice is the classification of patients with a predominantly basal and sub-pleural distribution of reticular abnormalities typical of IPF, but without honeycombing on HRCT. The current guidelines have been unfortunate in categorizing those patients with IPF having traction bronchiectasis, co-existing emphysema and fibrosis (*23*), and/or those above 60 years of age (*24*). Further expertise is needed in distinguishing typical and atypical HRCT appearances of IPF, as there is significant inter-observer variation among clinicians (*25*). Expert interpretation of HRCT data and the identification of honeycombing are important landmarks for radiological diagnosis of IPF (*26*).

3.3. *Histopathological features*

The diagnosis of definite IPF is uncertain in at least one-third of cases by HRCT thorax alone (*27,28*). It is recommended currently that a surgical lung biopsy should be performed when the diagnosis of definite IPF is uncertain even with HRCT thorax (*2*). The histopathological pattern of UIP is characteristically inhomogeneous, bilateral, involving lower lobes, predominantly sub-pleural occurrence and patchy in appearance (*2*). For the definitive diagnosis of UIP, features are *i*) marked fibrosis with or without honeycombing in a predominantly sub-pleural/ paraseptal distribution, *ii*) patchy parenchymal fibrosis and *iii*) presence of fibroblast foci. Probable UIP pattern includes *i*) evidence of marked fibrosis with or without honeycombing, *ii*) absence of either patchy involvement or fibroblastic foci, but not both *iii*) absence of features against a diagnosis of UIP suggesting an alternative diagnosis *iv*) honeycombing changes only. Criteria for possible UIP pattern are *i*) patchy or diffuse parenchymal fibrosis with or without interstitial inflammation, *ii*) absence of other criteria for UIP, *iii*) absence of features against a diagnosis of UIP. Features not supporting UIP pattern are *i*) hyaline membrane, *ii*) organizing pneumonia, *iii*) granulomas, *iv*) marked interstitial inflammatory cells, *v*) predominantly airway centered changes, *vi*) other features suggestive of an alternative diagnosis.

3.4. *Other investigations*

3.4.1. *Bronchoalveolar lavage (BAL)*

The most important application of BAL is to increase the index of suspicion for alternative disorders in patients with suspected IPF. When evaluating such individuals, BAL is useful in excluding other conditions, especially Chronic Hypersensitivity Pneumonitis (HP), for which a diagnosis is suggested by lymphocytosis > 40% (*2*). Current evidence recommends that BAL cellular analysis should not be performed routinely in the diagnostic evaluation of a majority of patients with IPF as there is unclear evidence regarding diagnostic specificity (2).

3.4.2. *Transbronchial lung biopsy (TBB)*

Transbronchial lung biopsy (TBB) has been shown to be useful in establishment of diagnosis of diseases with predominantly bronchocentric involvement such as sarcoidosis that can mimic IPF by having a UIP pattern on HRCT in rare instances (*26,29-30*). The sensitivity and specificity are unknown for TBB in diagnosis of IPF even when the UIP pattern is demonstrated in biopsy material (*2,31*). Therefore, TBB is recommended in a minority of individuals (*2*).

3.4.3. *Serology*

Serological testing for connective tissues diseases is now considered to be part of routine diagnostic workup of IPF in most patients whether manifestation of connective tissue disorders exist or not. Serological evaluation includes predominantly rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) and anti-nuclear antibody titer (ANA) but other serological tests such as anti-synthetase antibodies (*e.g*. Jo-1), creatine kinase and aldolase, Sjogren's antibodies (SS-A, SS-B), and scleroderma antibodies (Scl-70, PM-1) can be indicated in appropriate clinical cases. Careful screening is required for exclusion of other connective tissues disorders with these clinical features such as arthritis, Raynaud's phenomenon, skin changes, abnormal

esophageal motility before commitment of diagnosis of IPF as few patients can have mildly positive antinuclear antibody titer and/or rheumatoid factor levels without any other clinical features of connective tissue. In the absence of additional serologic or clinical evidence to support a connective tissue diagnosis, the diagnosis of IPF is appropriate. Serial serologic and clinical evaluation monitoring is essential for subsequently confirming the development of a connective tissue disease associated ILD thereby requiring revision of the diagnosis (*2*).

3.4.4. *Biomarkers*

Identification of biomarkers has been an area of new research interest for diagnosis of IPF. They may be useful to identify patients at high risk of progression of disease apart from diagnosis. These biomarkers are estimated in serum as well as BAL. High levels of epithelial or macrophage-related proteins such as SP-A, SP-D, KL-6 (Krebs von den Lungen-6), CCL18 (chemokine ligand-18), and MMP-7 (matrix metalloproteinase-7) are found in IPF patients distinguishing from other IIP's (*32-37*). Further validation is required for their associations in the near future.

4. Evolution of diagnosis of IPF over the years

The diagnosis of IPF was established on the basis of the presence of all four major criteria and three out of four minor criteria over the decade that was the era before surgical lung biopsy (SLB) gained much importance (*1,9*). The four major criteria were *i*) exclusion of other known cause of ILD, such as medication exposure, environmental or occupational exposure and connective tissue disorders; *ii*) abnormal spirometric findings such as reduced forced vital capacity, with an increased ratio of forced expiratory volume in 1 second/forced vital capacity (evidence of restrictive pattern) and impaired gas exchange parameters including increased alveolar-arterial oxygen tension difference with rest or exercise or decreased diffusing capacity of the lung for carbon monoxide; *iii*) Bilateral reticular abnormalities with basal predominance and minimal ground glassing on HRCT thorax scan; and *iv*) TBB or BAL showing inconclusive findings to support diagnosis. The four minor criteria were *i*) age of onset more than 50 years, *ii*) insidious onset of otherwise unexplained dyspnea, *iii*) duration of illness of more than 3 months, and *iv*) dry or "velcro" bibasilar, inspiratory crackle. However, this set of framed criteria is observed to have significant limitations particularly concerning the four minor criteria. The early diagnosis of IPF can be missed in that subset of patients less than 50 years. Further, some IPF patients may initially present with acute symptomatic exacerbations rather than having insidious onset. Moreover, occurrence of co-morbid factors such as pre-existing pulmonary fibrosis and/or smoking related lung damage can make diagnosis of IPF difficult in patients with disease duration of ≥ 3 months. Similarly, the presence of crackles may not be evident for establishment of diagnosis of IPF.

The diagnostic guideline published in 2000 for IPF was later updated in 2011 by an international collaboration of the ATS and ERS, as well as the Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT) in view of consideration of these limitations and recently gained importance of the multi-disciplinary approach of radiology and pathology subsets. (*2*) The diagnostic criteria were revised and are summarized: *i*) Exclusion of other known causes of ILD (domestic and occupational environmental exposure, connective tissue disease and drug toxicities) as mentioned before; *ii*) the presence of a definite UIP pattern on the HRCT scans in individuals not requiring further confirmation of diagnosis by SLB; and *iii*) the lack of definite UIP pattern and presence of other patterns on the HRCT scan requiring further confirmation by SLB. It can be stated that the presence of a classical UIP pattern on the HRCT scans is sufficient for the diagnosis of IPF in an appropriate clinical setting without SLB.

5. Conclusion

An early and accurate diagnosis of IPF is critical. The clinician has to rely on clinical, laboratory, radiologic, and/or pathologic data for establishment of diagnosis of this disease. An adult with unexplained exertional dyspnea with cough, bibasilar inspiratory crackles and clubbing in the presence of classical UIP pattern on HRCT is sufficient for the diagnosis of IPF. Other investigation like BAL, TBB and serological study should not be performed in the diagnostic evaluation of IPF in the majority of individuals but may be appropriate for a minority. A multidisciplinary approach is the mainstay to improve the diagnostic yield of IPF early and accurately.

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