Literature Review

Early Diagnosis of Interstitial Lung Disease

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Abstract

Interstitial Lung Disease (ILD) includes more than 200 diseases that involve the interstitial lung. The diagnosis of ILD depends on the onset of symptoms, causes, and clinical manifestations. An anamnesis comprehensive and physical examination are essential in diagnosing ILD. In addition, laboratory tests are carried out in certain clinical conditions. The analysis of biomarkers in ILD is helpful for diagnosis, disease monitoring, and prediction of prognosis. Pulmonary function studies support the diagnosis of ILD and as a predictor of prognosis. High-resolution Computed Tomography (HRCT) is the main diagnostic procedure in ILD patients. In certain conditions, a lung biopsy may be considered. Multidisciplinary discussion (MDD) enhances accurate diagnosis. An accurate early diagnosis of ILD is necessary to ensure that patients receive optimal management, reduce the risk of developing pulmonary fibrosis and reduce the risk of death. Early diagnosis of ILD define as early identification of symptoms, laboratory and radiological findings at the early stage of the disease

Keywords: early diagnosis, fibrosis, high resolution CT, interstitial lung disease

INTRODUCTION

Interstitial lung disease (ILD) is a large group of diseases that includes more than 200 interstitial lung diseases. Most ILDs are classified as rare diseases and are associated with high morbidity and mortality rates in all age groups.[1,2] The interstitial space is the space between the capillary endothelium and the alveolar epithelium. However, this disease also involves surrounding areas such as the periphery of the airways and blood vessels.[1]

Idiopathic pulmonary fibrosis (IPF) is the most common form of ILD in older adults and has a poor prognosis. Sarcoidosis is more common in young adults and generally has a good prognosis.[1] Some patients with ILD may develop a progressive fibrotic phenotype. Progressive fibrosis is associated with worsening respiratory symptoms, decreased lung function, and a limited response to immunomodulatory therapy. Hence, there is a decrease in quality of life and worse prognosis in this phenotype.[2]

The clinical course of ILD is highly variable and is determined by the underlying cause.[1] The cause of ILD is often unknown. The most common symptoms are cough without phlegm, shortness of breath, and those associated with certain systemic diseases.[3,4] Some

forms of ILD respond well to treatment, but others are untreatable.

Early diagnosis of ILD define as early identification of symptoms, laboratory and radiological findings at the early stage of the disease. Therefore, a quick and accurate diagnosis is essential. This is to ensure that patients receive optimal management and prevent the development of pulmonary fibrosis.[1]

ILD CLASSIFICATION

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) changed the classification of ILD in 2013 based on the etiology and characteristic features of the disease. In this classification, ILD is divided into four groups: ILD with a known cause, Idiophatic Interstitial Pneumonia (IIP), granulomatous ILD, and other forms of ILD.[5] Group IIP is a term used to describe various ILDs with characteristic clinical, radiological, and pathological features.[2] The IIP group is divided into 3 parts, namely major, rare and unclassified. The major group is the most common in IIP and is divided into the chronic fibrosis group, associated with smoking and the onset of acute or subacute disease.[5] The IPF group is the most common type of IIP, accounting for 50% of all IIPs (Figure 1).[2]

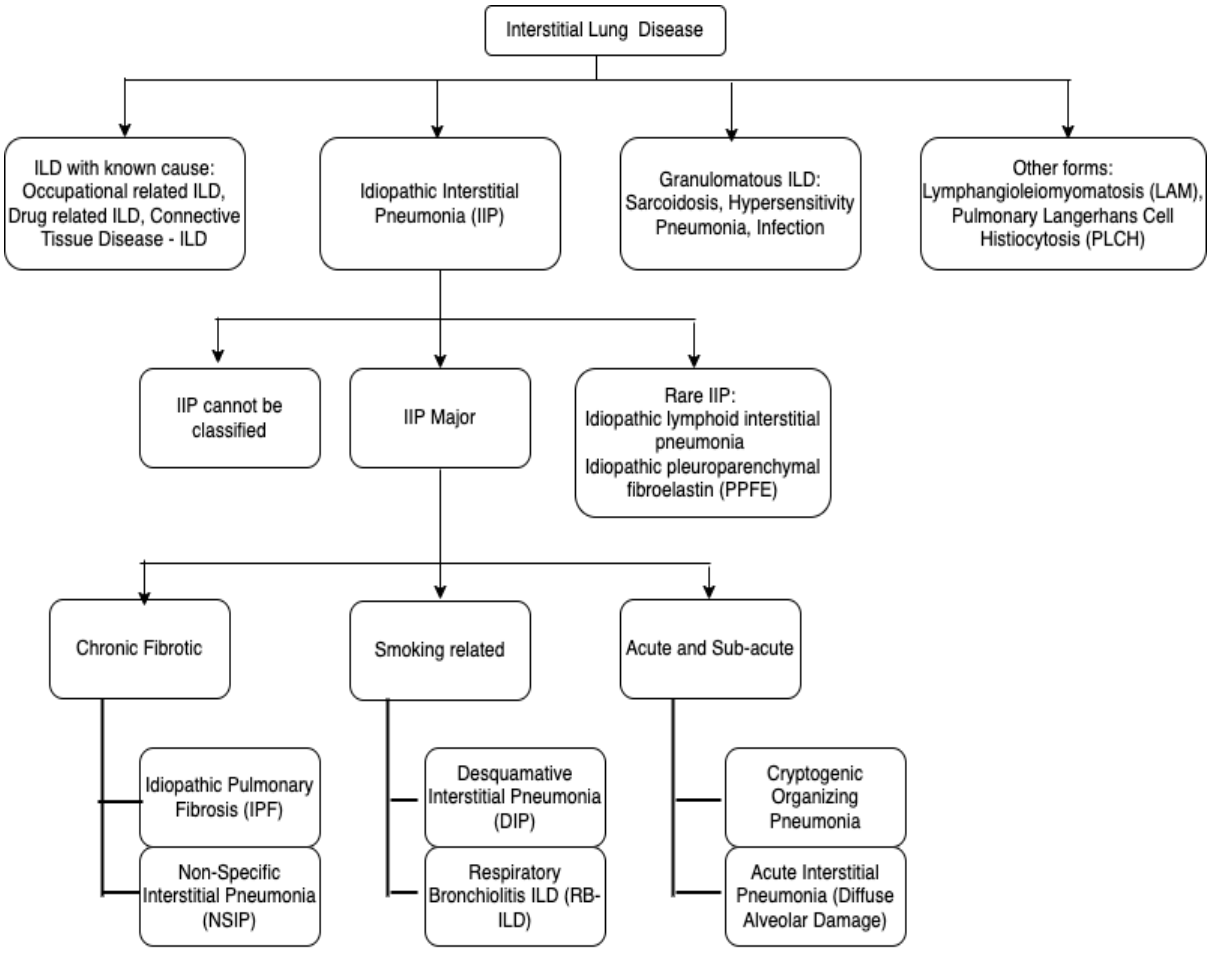

Figure 1. Interstitial Lung Disease Classification[2]

RISK FACTOR

Several risk factors for the incidence of ILD include demographics, genetics, occupational exposures, hobbies, the environment, drugs, microbes, and a history of smoking. Idiopathic pulmonary fibrosis is common in men aged 50-60 years. Sarcoidosis is more common in young people and their 40s, although it can manifest in older age.[3]

Familial interstitial pneumonia (FIP) is identified when two or more family members are diagnosed with ILD. Therefore, family history is essential in identifying patients with inherited ILD. The IIP group accounted for 2-20% of FIP.[6] A family history can be found in 1-3% of IPF patients and 6-19% of sarcoidosis patients.[3]

Occupations at risk include miners (pneumoconiosis), granite workers, welders, shipyard workers, plumbers, electricians, car mechanics, poultry farmers, bird farmers, mushroom farmers, workers in the computer, and electronics industry, nuclear industry, and related jobs. Exposure to hobbies such as bird fancier, cultivating mushrooms, or woodworking. Another risk factor of ILD is using drugs such as methotrexate, amiodarone, bleomycin, busulfan, chemotherapy, cytotoxic drugs, and narcotics. Microbial agents such as viruses, fungi, and bacteria also play an important role in developing IPF disease.[3] A history of smoking is associated with the risk of developing IPF and other pulmonary fibrotic diseases.[7,8]

DIAGNOSIS

Diagnosis of ILD depends on several categories such as the onset of symptoms (acute, subacute, chronic), etiology of the disease (known and unknown), and the clinical manifestations of the underlying systemic or extrapulmonary disease. The approach to the diagnosis of ILD is adapted to different clinical scenarios. Patients may present with specific clinical symptoms such as dry cough and shortness of breath. Patients can also be at risk for ILD because there is a history of exposure such as amiodarone, asbestos, or certain diseases in the family.[9]

Patients may also present without symptoms but have abnormalities on chest X-ray or computed tomography (CT) scans, or there are findings on pulmonary function examinations such as restriction abnormalities or impaired gas exchange on analysis of the pulmonary diffusion capacity for carbon monoxide or diffusing capacity of the lung for carbon monoxide (DLCO).[9]

Anamnesis

A comprehensive anamnesis is very important in diagnosing ILD, especially regarding the onset of respiratory symptoms, the history of the disease, the history of known exposures that can cause ILD, the history of previous systemic diseases, and the severity of the disease. The severity of the disease is known by accurately assessing the level of limitation of physical activity with the degree of perceived shortness.[9]

The most common symptoms are shortness of breath and a dry cough. Extrapulmonary symptoms include gastroesophageal reflux disease (GERD) symptoms, joint swelling or pain in rheumatoid arthritis (RA), skin thickening, Raynaud's phenomenon, and dysphagia in systemic sclerosis.[9]

Physical Examination

On physical examination, thickening of the skin and acral necrosis of scleroderma and clubbing can be seen in 40% of ILD patients to 66% of IPF patients. In addition, there may also be Livedo Racemosa in SLE patients, the vasculitis in patients with Churg Strauss syndrome, and cyanotic edematous skin in dermatomyositis. On auscultation of the lungs, 90% of IPF patients and 60% of CTD-ILD can hear a crackling sound on inspiration or called a "Velcro" sound.[9] The Velcro sound is produced by abnormal airflow into the pulmonary fibrosis tissue and can be heard in the early stages of the fibrosis process.[10]

Laboratory Tests

Laboratory tests can also be a useful adjunct when used in certain clinical conditions. Laboratory tests include complete peripheral blood, kidney function, liver function, electrolyte levels, including calcium. In addition, certain serum antibodies can also be tested to evaluate CTD-ILD and certain systemic diseases such as antinuclear antibodies (ANA) and rheumatoid factor (RF).[9]

Increased levels of matrix metalloproteinases (MMP), both serum MMP1 and MMP7, bronchoalveolar lavage (BAL) fluid and sputum, serum levels of insulin-like growth factor-binding protein (IGFBP) 2 serum levels of the chemokine CXCL13 are diagnostic biomarkers in IPF patients. In addition, elevated levels of Krebs von de Lungen (KL) 6 serum and BAL fluid were found in patients with IIP, hypersensitivity pneumonitis, sarcoidosis, asbestosis, and CTD-ILD.[11]

Pulmonary Function

Pulmonary function examination is needed to evaluate patients suspected of having ILD, which consists of blood gas analysis, spirometry, body plethysmograph, DLCO, and oximetry both at rest and activity. Examination of lung function, in general, cannot support the diagnosis of specific ILD but is needed to assess respiratory limitations, assess disease severity, monitor disease progression and response to therapy, and as a predictor of disease prognosis. Restriction abnormalities, decreased lung volume and reduced diffusion capacity are common outcomes in ILD patients.[1,3,9,12]

Radiological Examination

The chest X-ray was the first radiological examination performed but has limited sensitivity and specificity in ILD.[1] The most frequently findings on chest radiographs of ILD patients include diffuse reticulonodular, ground-glass opacities (GGO), or both. High-resolution computed tomography (HRCT) has a greater accuracy

value than chest X-ray and is the main diagnostic procedure in ILD patients.[9] We can find several typical patterns on HCRT namely reticular patterns, nodular patterns, alveolar patterns, and cystic pattern.[12]

The reticular pattern is characterized by linear opacity, forming a web-like braid, resulting from thickening of the interlobular and intralobular septa, interconnected with each other, located in the periphery and basal areas of the lung and is common in IPF patients. The nodular pattern is around discrete opacity and varies in size from a few millimetres to 3 cm, commonly found in sarcoidosis. The alveolar way is an opacity that arises due to alveolar filling consisting of GGO, consolidation and tree in the bud. A cystic way is an enlarged air space surrounded by walls of varying thickness and composition. This pattern is found in LAM and PLCH.[12,13]

Based on HRCT images, there are four categories of IPF diagnosis, namely the usual interstitial pneumonia (UIP) pattern, probable UIP, indeterminate UIP and alternative diagnoses. The UIP image is a typical IPF image (Table 1).[14] Figure 2 shows common typical pattern on HRCT of ILD patients.[15]

Table 1. Patterns of HRCT images on IPF[14]

UIP	Probable UIP	Indeterminate UIP	Alternative diagnosis
Predominant in subpleura and basal, heterogeneous distribution	Predominant in subpleura and basal, heterogeneous distribution	Predominant in subpleura and basal	The findings lead to other diagnoses namely: CT image: - Cystic - Mosaic Attenuation - Dominant GGO - Lots of micronodules - Centrilobular nodules - Nodules - Consolidation
Honeycombing with or without traction bronchiectasis/bronchiectasis in the periphery	Reticular pattern with traction bronchiectasis/bronchiolectasis in the periphery	Mild reticulation, may be accompanied by mild ARF (early UIP pattern)	Dominant distribution: - Peribronchovascular - Perilymphatic - Upper or middle lung
	May be accompanied by mild GGO	CT images or distribution of pulmonary fibrosis that do not point to a specific cause (indeterminate UIP)	Other: - Pleural plaque (leading to asbestosis) - Esophageal dilation - Erosion of the distal clavicle (leading to RA) - Enlarged lymph nodes (leads to other causes) - Pleural effusion, pleural thickening (leading to CTD/drug-induced)

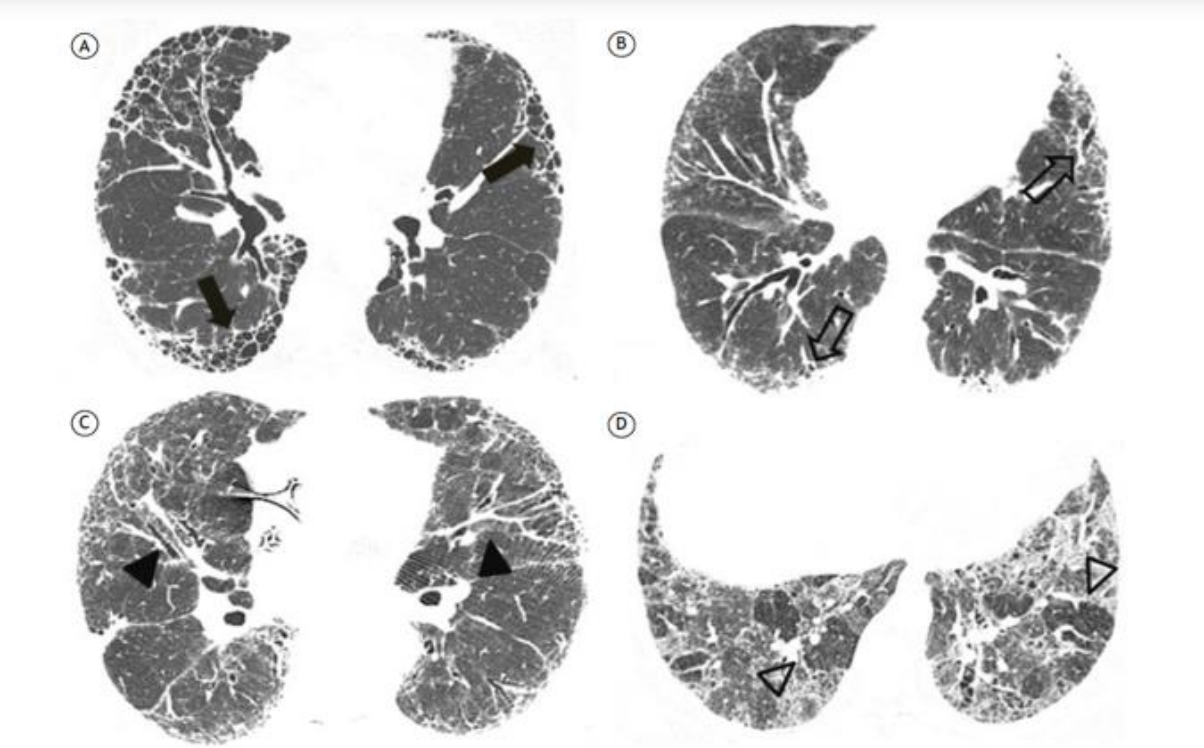

Figure 2. High-resolution CT image of IPF. A. UIP pattern: broad honeycombing in the subpleural and dominant in the basal (arrows). B. Probable UIP: reticular opacity and traction bronchiectasis (arrows) without honeycombing. C. Indeterminate UIP: central and diffuse regional abnormalities (arrows), GGO and reticular opacity. D. Alternative diagnosis: Extensive ARF and mosaic attenuation pattern (arrow).[15]

Bronchoscopy and Lung Biopsy

A lung biopsy is usually not required if a specific diagnosis can be made by history, physical examination, laboratory studies, and HRCT. However, if a specific diagnosis has not been reached, a lung biopsy may be considered. In addition to establishing a particular diagnosis, lung biopsy can also help assess prognosis and guide treatment. Furthermore, it can be determined whether lung biopsy by bronchoscopy or by surgical biopsy.[12]

Bronchoscopy can also obtain microbiological material, cytology with bronchoalveolar lavage (BAL) technique so that it can provide sufficient evidence to diagnose sarcoidosis, hypersensitivity pneumonitis, PLCH, DIP, lymphocytic interstitial pneumonia, LAM and pulmonary alveolar proteinosis (PAP). Histopathological diagnosis has an accuracy value of 90%.[12]

In IPF, histopathological examination is no longer the gold standard for diagnosis because sampling errors can occur, and there is uniformity of disease patterns in patients with advanced disease. Multidisciplinary discussion (MDD) involving pulmonologists, radiologists and anatomical pathologists has become the gold standard in diagnosing IPF. Multidisciplinary discussion is also an appropriate approach for the diagnosis of most ILD patients and holds the most promise for achieving diagnostic confidence.[9] Adequate case presentation and discussion of clinical and radiological data are essential for an accurate diagnosis.[5]

EARLY DIAGNOSIS OF ILD

Some ILDs are characterized by progressive fibrosis so that they have progressive symptoms, decreased quality of life, decreased lung function, poor response to treatment, are fatal and reach death an average of 3 years after diagnosis. IPF is the most common form of ILD and is more severe. IPF patients initially experience non-typical clinical symptoms such as dry cough and shortness of breath when active, so they are often misdiagnosed until pulmonary function examinations and radiological examinations show ILD.[16,17]

Determining the diagnosis of ILD with confidence is a big challenge because of the heterogeneous variety of diseases that often experience delays in diagnosis.[18] A cohort study of delayed diagnosis of ILD in 129 patients who met the IPF criteria according to the ATS found an average delay of diagnosis of 2.2 years with a range of 1.0-3.8 years. The delay in diagnosing ILD was defined from the onset of symptoms until a tertiary health centre visit. Delay in diagnosis is associated with an increased risk of death.[16] On the other hand, an accurate early diagnosis will have significant implications for treatment and prognosis and reduce death risk.[16,17]

The delay in diagnosing ILD can be caused by several factors, such as atypical symptoms causing patients to arrive late to health facilities. In addition, it can also be caused by a misdiagnosis by clinicians in the community so that they are late in referring to a tertiary health centre. Therefore, it is hoped that primary health services and pulmonary doctors can consider the diagnosis of ILD in patients with symptoms of shortness of breath of unknown cause and then involve other expertise in diagnosing and managing ILD early in the course of the disease.[16,19]

Currently, screening for ILD is limited to patients with known risk factors for ILD or a history of familial IPF. Another factor is the delay in obtaining a final diagnosis at a tertiary health centre. All of these contribute to the delay in the diagnosis of ILD. Research on biomarkers and quantitative imaging methods currently being developed can be the key to identifying ILD as early as possible.[16,19]

Screening for ILD in patients with systemic sclerosis with HRCT shows that 60% of whom has normal lung function. In this case, pulmonary function examination alone performs less well than HRCT in detecting ILD. High-resolution CT analysis and concurrent and serial lung function studies have shown that screening with HRCT as a baseline for predicting the risk of developing pulmonary fibrosis, the rate of fibrosis progression and lung function decline.[20]

Further studies on the examination of biomarkers such as CCL18 and non-radiative pulmonary imaging modalities such as ultrasonography (USG) and magnetic resonance imaging (MRI) are expected to serve as a support for the early detection of ILD.[20]

The American Thoracic Society and emergency response system (ERS) emphasize the need for a dynamic

integrated diagnostic process among pulmonologists, radiologists and pathologists, by exchanging information in determining the diagnosis in patients with suspected ILD. A study examining the importance of MDD shows that MDD improves accurate diagnosis because more data are available. The patient may be decided not to have a lung biopsy based on clinical symptoms and high-resolution CT results that are convincing for the diagnosis of IPF. In addition, for ILD patients other than IPF, it can be agreed to perform a lung biopsy as a final diagnosis.[21]

CONCLUSION

The diagnosis of ILD depends on several categories such as the onset of symptoms, the cause of the disease and the clinical manifestations of the underlying disease. A comprehensive history and physical examination are very important in diagnosing ILD. Laboratory tests are needed as support in certain clinical conditions. Analysis of biomarkers in ILD is useful for diagnosis, disease monitoring and prediction of prognosis.

Examination of lung function can support the diagnosis of ILD and also as a predictor of disease prognosis. High-resolution computed tomography is the main diagnostic procedure in ILD patients. Multidisciplinary discussion (MDD) enhances accurate diagnosis. A real early diagnosis of ILD is necessary to ensure that patients receive optimal management, reduce the risk of developing pulmonary fibrosis and reduce the risk of death.

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