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Review Article

Management of Interstitial Lung Diseases: Does the Stage at Diagnosis Influence the Outcome?

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Abstract

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse lung diseases of known and unknown causes and pose diagnostic and therapeutic challenges to the clinician. Treating ILD is always like reaching a certain point in the uphill and looking at the unconquered domain. Living with interstitial lung disease (ILD), also presents many challenges. Patients often express feelings of isolation, due to the absence of emotional support provided by their healthcare team at the time of diagnosis. A proactive approach to the diagnosis and management of patients with ILD and comprehensive medical care can result in improved quality of life and survival. Identifying the disease type, that too, at the early stages and initiating treatment appropriate to the stage brings satisfactory outcome. This review is based on an analysis of current literature and clinical experience.

Keywords: *Interstitial Lung Diseases; Multidisciplinary Team; Alveolitis; End Stage Lung Disease*

Abbreviations

ILD: Interstitial Lung Disease; SLB: Surgical Lung Biopsy; MDT-Multidisciplinary Team; HRCT: High Resolution Computerized Tomography; CTD: Connective Tissue Diseases; HP: Hypersensitivity Pneumonitis; IPF: Idiopathic Pulmonary Fibrosis; DIP: Desquamative Interstitial Pneumonia; COP: Cryptogenic Organizing Pneumonia; NSIP: Nonspecific Interstitial Pneumonia; iNSIP: Idiopathic Nonspecific Interstitial Pneumonia; ESLD: End Stage Lung Disease; SSc ILD: Systemic Sclerosis Related ILD; MTXP: Methotrexate pneumonitis; MMF: Mycophenolate Mofetil; FVC: Forced Vital Capacity; LT: Lung Transplantation

Introduction

Interstitial lung diseases consisting of many unrelated conditions of known and unknown causes pose diagnostic and therapeutic challenges to the treating physician. Many practitioners have a fatalistic view about ILD, believing that a specific diagnosis and prompt management is of limited importance since prognosis and treatment response is universally poor. As a result, many patients receive a delayed diagnosis and are not referred to appropriate specialists. It is always painful to understand that there is no ideal drug till date to treat ILD. Clinicians and patients confronted with ILD are understandably frustrated as there is no cause or cure for most of the ILDs [1]. A conservative approach to the diagnosis and management is mostly followed in India because of the lack of resources and standardized approach to diagnosis of ILD. There is apparent phobia, reluctance, hesitancy, and/or uncertainty on the part of patients also when services like surgical lung biopsy (SLB) are offered to them [1]. Centers of excellence for diagnosis and management of ILD, with expertise in pulmonology, radiology, thoracic surgery, and pathology are needed to enhance the accuracy of diagnosis of ILD and its management.

Living with ILD

Living with interstitial lung disease (ILD), presents many challenges. The type, severity, symptoms and progression varies from person to person. Many people living with interstitial lung disease are told that there is not much to attain with treatment. This leads to feelings of isolation, especially with the absence of emotional support provided by their healthcare team at the time of diagnosis. Psychological and social support is often neglected early in the course of the disease, and patients and caregivers are left to cope without a social worker or a therapist.

There is a dearth of accurate information about interstitial lung diseases. Not only do we need high-quality disease-specific information, but we must also do a better job of directing patients to this information when it exists. A proactive approach to the diagnosis and management of patients with ILD and comprehensive medical care can result in improved quality of life and survival. Pulmonary rehabilitation provides a unique opportunity to implement an in-person, educational program tailored to patients with ILD [2]. Health care providers should participate and support the integration of group discussions in a pulmonary rehabilitation program.

Outline of management

The diagnosis and management of ILD is complex and requires the expertise of pulmonologists, radiologists and pathologists. For a better management outcome in ILD, it is essential that an early diagnosis should be established. Once diagnosed typing is to be done using multidisciplinary team (MDT) approach or by lung biopsy. Prognosis, identification of extra-pulmonary manifestations and comorbidities, choice of medication and consideration for transplant all depend on an accurate diagnosis and staging of the disease.

The clinical points which may help in identifying ILD are progressive dyspnea, clubbing, bibasilar crackles and suggestive findings and patterns in X-Rays/HRCT. ILD are to be differentiated from common conditions such as chronic pulmonary edema, atypical pneumonia, aspiration syndromes and drug induced lung diseases. Once diagnosed categorization of ILD are essential for choosing the appropriate management strategy. Clinical signs of systemic diseases like connective tissue diseases (CTD), extra pulmonary manifestations of sarcoidosis, HRCT findings such as zonal distribution of lesions and patterns are useful information to type the disease. This can be further refined by MDT discussions and histopathological examination of biopsy specimens. Bronchoalveolar lavage studies and transbronchial lung biopsy are recently being increasingly used for confirmatory diagnosis in certain types of ILDs such as sarcoidosis and HP.

Stage of the disease at Diagnosis

Stage of the disease at diagnosis is important because different stages represent different pathological process in the evolution of the disease. It leads to a final end stage lung disease with extensive fibrosis where any form of treatment is not going to reverse the pathology.

Stage-1: Alveolitis

The disease start as inflammation of the alveolar cells (alveolitis). This is an immunological inflammation to an offending antigen which reaches the alveoli through blood (angiocentric) or through bronchi (bronchocentric). This stage is represented in the HRCT as ground glass opacities (Figure A). Histopathological features include chronic inflammation of interstitium with mild to moderate loss of alveolar architecture. Since this is a stage where intensive immune inflammation takes place, anti-inflammatory drugs (corticosteroid) or immune-suppressants (e.g. Azathioprine) are the effective agents for treatment. This stage can be considered as stage-1 in the pathogenesis of ILD.

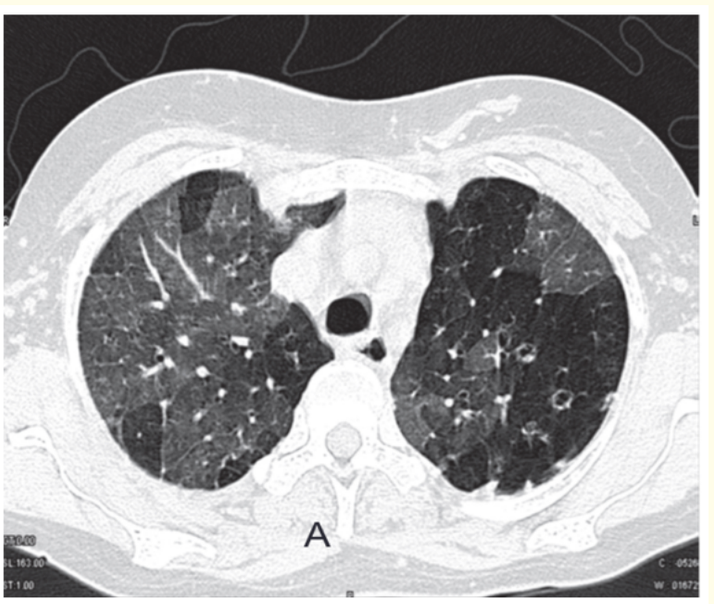

Figure A: *HRCT showing stage-1 disease with diffuse ground glass pattern.*

Stage-2: Interstitial thickening

In this stage the inflammation progresses with more and more inflammatory cells infiltrating the site with interstitial edema. Alveolar wall and interstitium thickens and there is immune complex deposition in the alveoli, interstitium and peri-bronchovascular region. This stage of disease corresponds to reticular shadows and nodular shadows in the HRCT (Figure B). Alveolar walls and interstitium are prominently visualized in HRCT as interlobular septal thickening. Since this is the stage of early fibrosis, treatment should be with antifibrotic drugs. Immunosuppressants also help in this stage to suppress the intense inflammation.

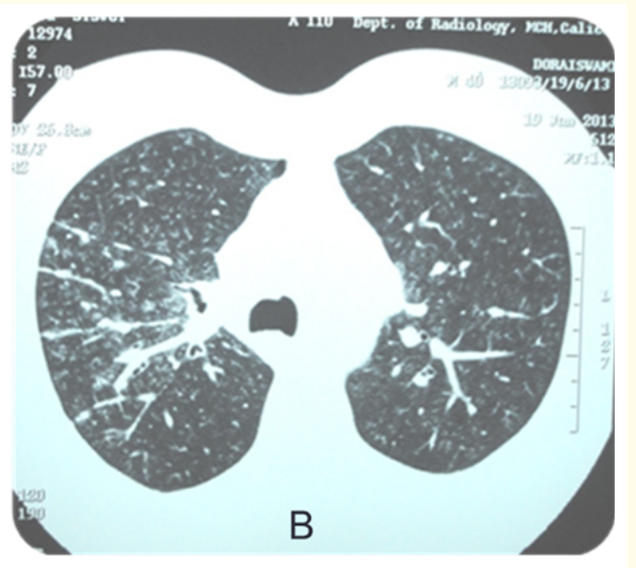

Figure B: *Stage-2 disease with reticular shadows, peri-bronchovascular thickening and nodules.*

Stage-3: Interstitial fibrosis:

This is the stage where there is extensive repair process with diffuse pattern of interstitial fibrosis. Alveolar walls are thickened with deposition of fibrous tissue in the interstitium. The alveoli become small and are well delineated by the fibrosis. Fibrosis exerts traction on the small airways (bronchiolectasis) and medium sized airways (bronchiectasis). This stage is represented in the HRCT by honey combing and traction bronchiectasis (Figure C). Since the fibrosis at this stage is irreversible no drugs are effective. In conditions such as IPF where honey comb lesions are predominantly seen, there are always multiple crops of lesions at different stages of evolution (temporal heterogeneity). Antifibrotics may be tried at this stage with the hope of preventing fibrosis of areas having early lesions.

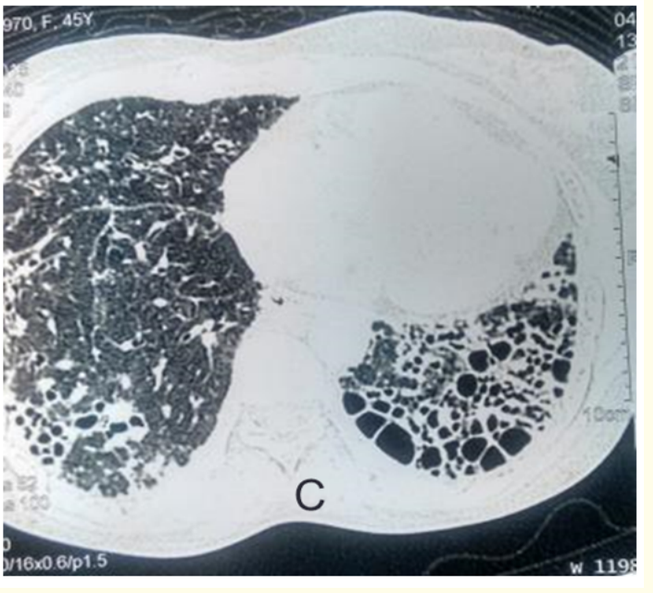

Figure C: *Stage 3 disease with honey combing and traction bronchiectasis.*

Stage-4: End stage lung disease

This stage denotes diffuse involvement of both lungs with honey combing and traction bronchiectasis (Figure D). The alveolar architecture is increasingly lost with eventual formation of cysts separated by bands of fibrosis which corresponds to the honeycombing pattern seen on imaging studies. Lung volume gets reduced and pulmonary function is grossly affected. Patients presents with severe exercise intolerance and hypoxemic respiratory failure. Lung transplantation is the only treatment option at this stage.

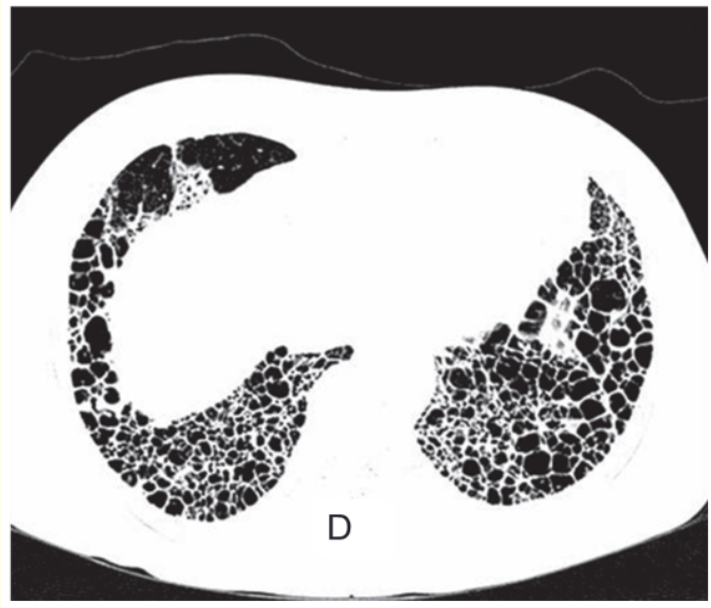

Figure D: *Stage 4 disease showing diffuse honey combing.*

Management based on stage

Interstitial lung diseases still remains a difficult disease to treat mainly because of its heterogeneity, non-availability of an ideal drug and lack of proper understanding of the different diseases by the treating physician. Once diagnosed, an alert of poor prognosis is conveyed to the patient. This leads to poor compliance to treatment and follow up. At the same time many ILDs responds to treatment if started at an early stage making the patient lead a symptom free life. In others progression of disease to unaffected area may be prevented so that patient can lead a relatively independent life. The most important factor is to diagnose and type the disease early and select the drug appropriate for the stage.

Drugs used in ILD are 1) Anti-inflammatory drugs, such as corticosteroid (e.g. Prednisolone) which reduces active inflammation in the lungs, 2) Immune-suppressing drugs, such as Azathioprine, Cyclophosphamide, and Mycophenolate mofetil, which act by suppressing the immune mediated inflammatory damage and 3) Antifibrotic drugs such as Pirfenidone and Nintedanib which are capable of preventing fibrosis and scarring in the lungs.

Corticosteroids

Corticosteroids still remains an important component of ILD management. When the disease is diagnosed at stage-1 with alveolitis as the main pathology and HRCT showing ground glass shadows, steroids acts well to contain the inflammation. There are few ILDs where steroid is the drug of choice. They are desquamative interstitial pneumonitis (DIP), acute hypersensitivity pneumonitis (HP), cryptogenic

organizing pneumonia (COP) and early sarcoidosis. Early stages of nonspecific interstitial pneumonitis (NSIP) and idiopathic pulmonary fibrosis (IPF) steroids are effective along with cytotoxic drugs or antifibrotic drugs. Since there are no international recommendations for steroid use in IPF, many clinicians are reluctant to use this important drug. In a retrospective series where 23 IPF patients are treated with steroid alone and 36 IPF patients are treated with steroid and azathioprine, it is found that 81.6% and 86.1% had a favorable or static response in each group respectively [3]. It is also reported that adding azathioprine to steroid in this cohort did not yield any additional benefit in clinical response and survival. Adverse events with corticosteroids are a concern, especially in elderly patients with multiple co morbidities. Correct dosing schedule and regular monitoring will help in reducing the long term side effects.

In a prospective study, 261 patients with idiopathic nonspecific interstitial pneumonitis (iNSIP) were enrolled, and 95 patients were followed-up for more than 1 year. Corticosteroid treatment was performed in 86 patients. The treatment group showed a significant improvement in lung function after 1-year: A shorter duration of respiratory symptoms at diagnosis was significantly associated with a good response to treatment ($p = 0.018$) [4].

Immunosuppressants

Drugs mainly used for ILD from this group are azathioprine, Cyclophosphamide, Methotrexate and Mycophenolate mofetil. Azathioprine is a preferred drug in few ILDs such as systemic sclerosis ILD (SSc ILD), NSIP and Granulomatosis with polyangiitis (Wegener's granulomatosis). This drug is well tolerated and with very few side effects. This may be used along with steroids. Many patients with end stage lung diseases (ESLD) are treated with azathioprine giving no benefit to the patient. It is to be strictly followed that azathioprine may be given only in satge-1 and stage-2 disease along with other anti-inflammatory drugs.

Cyclophosphamide is another immunosuppressant widely used in connective tissue associated ILD (CTD-ILD) especially SSc-ILD and Granulomatosis with polyangiitis. This is also well tolerated with fewer side effects if used in optimal doses. This can be administered as oral or intravenous in a daily/Pulse therapy schedule. Methotrexate is another immunosuppressant which is used widely in CTD-ILD and the response is variable. It is to be noted that dosing schedule of methotrexate is convenient to the patient. It has the potential to induce methotrexate pneumonitis (MTXP) and drug induced interstitial lung disease.

Mycophenolate Mofetil is another immunosuppressant which is safe to use in IPF, Chronic HP, SSc ILD and Patients with ILD waiting for lung transplantation. In a large diverse cohort of CTD-ILD, MMF was well tolerated and had a low rate of discontinuation. Treatment with MMF was associated with either stable or improved pulmonary physiology over a median 2.5 years of follow up [5].

Antifibrotics

Drugs approved for treating IPF in this group are Pirfenidone and Nintedanib. Pirfenidone is to be used in high doses at the range of 2.4 gm/day and it is costly too. Usual side effects are gastrointestinal symptoms. Since it is widely recommended in IPF, most clinicians prefer to use this drugs in all ILDs without reaching a definite diagnosis of IPF. Another problem noticed is that it is used in sub therapeutic doses that too in end stage lung diseases. Nintedanib is a new tyrosine kinase inhibitor widely recommended for IPF. Dosing schedule is convenient but it has severe gastrointestinal side effects including diarrhoea.

Analysis of data from three phase 3 trials demonstrated that treatment with pirfenidone for 1 year resulted in clinically meaningful reductions in disease progression in patients with IPF [6]. In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression. Nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients [7].

Lung transplantation

Lung transplantation (LT) can be a lifesaving therapy for patients suffering from advanced lung disease due to interstitial lung diseases. Candidates with IPF derive significant survival benefit from lung transplantation. But they experience high mortality on the waiting list. The proportion of IPF patients who died while awaiting transplantation ranged from 14% to 67% [8]. Recurrence is reported for several interstitial lung diseases after lung transplantation. In a recent registry report worldwide, 23% of all lung transplant recipients had a diagnosis of idiopathic pulmonary fibrosis [9].

Summary

Most clinicians, who diagnose ILD, consider it as a single disease. This results in most patients receiving treatment as IPF. More over delay in diagnosis and failure to type the disease leads to poor treatment outcome and high mortality. There are many types of ILDs which responds to treatment if initiated early and patients can lead a disease free life. Diagnosis at stage-1 and stage-2 and treating them with drugs appropriate to the stage and type is important for a better outcome. Treating advanced ILD especially IPF (Stage-4) with potentially toxic and costly drugs will only add to the sufferings of the patient. A good rehabilitation program and discussion between patient and care givers on the natural course of the disease will instill confidence in the patient.

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