Interstitial Lung Diseases

Interstitial Lung Diseases:

A Guide to State-of-the-Art Diagnosis and Treatment

Edited by

Ravindran Chetambath

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I dedicate this book to my beloved grandchildren, Parvathy and Rishan. I hope these pages may guide and inspire them as they grow, explore the world, and always let them know how deeply loved and cherished they both were.

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PREFACE

The field of interstitial lung diseases (ILDs) has seen remarkable advances over the past few decades. Our evolving understanding of the pathophysiology and genetic background of these conditions has led to the development of new diagnostic tools and therapeutic approaches, transforming the outlook of ILD management. This book, "Interstitial Lung Diseases: A Guide to State-of-the-Art Diagnosis and Treatment," aims to serve as a comprehensive resource for clinicians, researchers, and students who are dedicated to the care and study of patients with ILDs.

Working on this book, I have drawn upon the expertise of leading authorities in pulmonology, radiology, rheumatology, and other relevant fields. Our goal is to provide a detailed and up-to-date guide that reflects the current best practices and emerging trends in the diagnosis and management of ILDs. Each chapter deals with critical aspects of ILD care, from the initial clinical evaluation and diagnostic workup to the latest therapeutic strategies and approaches to patient management.

The authors recognize that the diagnosis and treatment of ILDs can be complex and challenging. Therefore, focus is given to presenting the material in a clear and accessible manner, with practical insights and illustrations that underscore key points. The integration of multidisciplinary perspectives ensures that readers gain a holistic understanding of ILD management, which is essential for optimizing patient outcomes.

This book also addresses the ongoing challenges and future directions in ILD research and care. The authors explore the impact of new technologies in imaging and biomarker discovery and the importance of patient-centered approaches in managing chronic lung diseases. By highlighting these areas, we hope to inspire continued innovation and collaboration in the field.

As you read through this book, we encourage you to consider how the guidelines and recommendations presented can be applied in your practice. Our ultimate aim is to empower healthcare professionals with the knowledge and tools needed to improve the lives of patients with interstitial

lung diseases. I am confident that this book will be a valuable addition to your professional library and a reliable reference for years to come.

I extend my deepest gratitude to all the contributors who have shared their expertise and insights, and to the patients whose experiences have informed and inspired this work. *I* hope that this book will serve as a beacon of knowledge and a catalyst for ongoing advancements in the field of ILD.

Sincerely,

Ravindran Chetambath,
Professor & Senior Consultant in Pulmonology,
Editor, "Interstitial Lung Diseases: A Guide to State-of-the-Art Diagnosis and Treatment"

CHAPTER 1

INTERSTITIAL LUNG DISEASES: AN OVERVIEW AND CURRENT CLASSIFICATION

RAVINDRAN CHETAMBATH MD, FRCP,
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Introduction

Interstitial lung diseases (ILD) are a group of diffuse parenchymal lung disorders characterized by damage to the lung parenchyma due to inflammation and fibrosis. Even though the interstitium is primarily affected, the airspaces, peripheral airways, and vessels are also involved in certain clinical entities.[1] International Consensus Statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) suggested the term Diffuse parenchymal lung diseases (DPLD)[2]. New insight into the pathogenesis and high-resolution computed tomography (HRCT) evaluation, led to a better understanding of these diseases. ILD comprises more than 200 entities of known and unknown causes. Our understanding of the underlying mechanisms of specific ILDs has grown substantially over the last few years. This has helped to evolve effective therapies. Management of ILD is always a challenge, but early diagnosis, appropriate treatment, and a balanced prognostic evaluation are always rewarding.

Classification

In 2002, the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus classification of the ILDs[2] was published. This was necessary because high-resolution computed tomography and the multidisciplinary team approach has revolutionized the diagnosis

of ILD. This has helped to include patients who did not have a diagnosis by lung biopsy due to obvious reasons. This was a more realistic classification, depicting the clinical, radiological, and pathological characteristics of various ILDs. Since this classification was formulated almost two decades ago, it needed revision to include many new entities.

In 2013, a revision was proposed for the 2002 IIP classification, based on experiences gained from the previous decade[3]. The seven main disease entities in that group were preserved. Idiopathic NSIP was considered as a distinct clinical entity. Regrouping of a few entities was suggested emphasizing some important disease characteristics, i.e., chronic fibrosing IIPs (IPF, NSIP), smoking-related conditions (RB-ILD, DIP), and acute/subacute IIPs (cryptogenic organizing pneumonia (COP) and acute interstitial pneumonia (AIP)). The newly reported rare histologic patterns such as acute fibrinous and organizing pneumonia (AFOP) and interstitial pneumonia with a bronchiolo-centric distribution were included. Idiopathic pleuro-parenchymal fibroelastosis and unclassifiable idiopathic interstitial pneumonia were also added as a separate group. In 2018, Cottin and coworkers proposed a new classification (Figure 1.1) by relocating or regrouping all clinical entities identified and described since 2002[4].

ILD as a broad term, comprises idiopathic interstitial pneumonia (IIPs), autoimmune ILDs (CTD-ILD), hypersensitivity pneumonitis, sarcoidosis, and other rare ILDs. Idiopathic interstitial pneumonias (IIPs) are now subdivided into idiopathic pulmonary fibrosis (IPF) and non-IPF IIPs. Idiopathic pulmonary fibrosis is regarded as a prototype for progressive-fibrosing ILDs. IPF is both diagnostically and prognostically distinct from non-IPF IIPs. The IPF, the most common of the IIPs[2], typically occurs in people aged greater than or equal to 50 years. It has an insidious onset characterized by unexplained dyspnoea, especially on exertion, and a non-productive cough that develops for 3 months [5,6]. In most patients, IPF follows a progressive course, eventually leading to hypoxemia and right heart failure. With 5-year mortality approaching 70%, the prognosis is worse than any other ILDs[7]. Prognosis is inferior in patients with pre-existing IPF who develop an acute exacerbation over a very short period of time[7]. A proportion of patients with interstitial lung diseases (ILDs) are identified as progressive-fibrosing phenotypes. Progressive fibrosis is characterized by worsening symptoms, decline in lung function, poor response to immunomodulatory drugs, poor quality of life, and, early death.

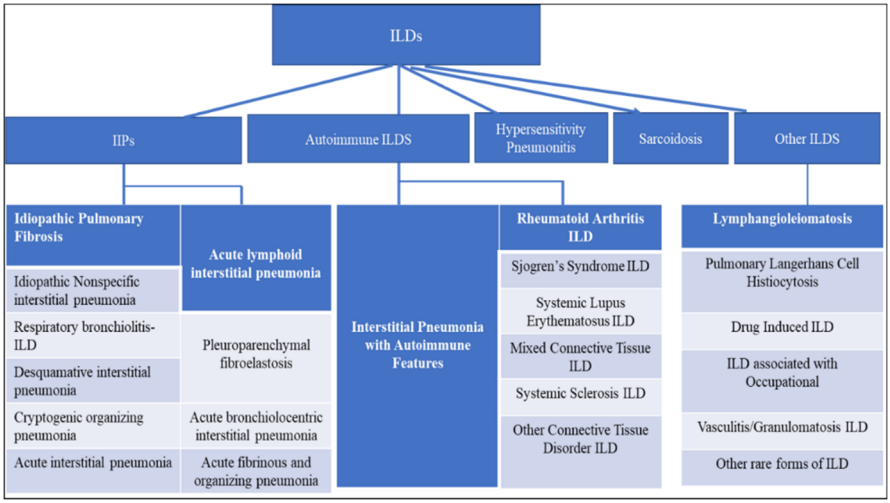

Figure 1.1: Classification of ILD adapted from Cottin V, et al. (2018)[4]

As earlier believed, IPF is not a systemic disorder but a distinctive type of progressive fibrosing interstitial pathology without any obvious etiology and associated with a histological pattern of UIP[2]. The ATS/ERS classification emphasizes the distinction between the UIP of IPF, from other potential causes of the UIP pattern such as collagen vascular disease and hypersensitivity pneumonitis. Gribbin et al[8]. demonstrated a change in incidence from 27.3 to 67.8 cases per million from 1991 to 2003. Whether this increase in incidence is due to early detection of the disease or due to changing environmental factors is to be further studied.

The IIPs other than IPF have six distinct entities separated each other by clinical, radiological, and histopathological features (Figure 1.2). The non-IPF IIPs cover a spectrum of disorders that include desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), acute interstitial pneumonia (AIP), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP) and nonspecific interstitial pneumonia (NSIP)[9]. Many cases of NSIP are likely to be due to or associated with etiologies such as collagen vascular diseases, hypersensitivity pneumonitis, and drug-induced lung disease. Truly idiopathic cases are relatively rare[10]. Its presence in the classification scheme is justified by the fact that NSIP has a favorable prognosis when compared to IPF[10]. Patients with NSIP are often responsive to corticosteroid treatment, unlike their IPF counterparts[10]. For the first time, the grading of

disease behaviour and the heterogeneity of the natural progression of IIPs were considered (Figure 1.3). Non-IPF IIPs also include rare clinical forms like pleuro-parenchymal fibroelastosis, idiopathic bronchiolo-centric interstitial pneumonia, and acute fibrinous and organizing pneumonia.

Categorization of Major idiopathic interstitial pneumonias

Category	Clinical-radiological- pathologic diagnoses	Associated radiology and /or pathologic-morphologic patterns
Chronic fibrosing IP	Idiopathic pulmonary fibrosis Idiopathic nonspecific interstitial pneumonia	Usual interstitial pneumonia nonspecific interstitial pneumonia
Smoking-related IP	Respiratory bronchiolitis interstitial lung disease Desquamative interstitial pneumonia	Respiratory bronchiolitis Desquamative interstitial pneumonia
Acute/subacute IP	Cryptogenic organizing pneumonia Acute interstitial pneumonia	organizing pneumonia Diffuse alveolar damage
Abbreviations: IP- interstitial pneumonia		

Figure 1.2: Subcategorization of idiopathic interstitial pneumonia

Idiopathic Interstitial Pneumonias
Classification according to the Disease Behavior

Clinical Behavior	Treatment Goal	Monitoring strategy
Reversible and self limited (RBILD)	Remove possible cause	Short term (3-6 months) observation to confirm disease regression
Reversible disease with risk of progression (Cellular NSIP, COP, DIP)	Initially achieve response and then rationalize long term therapy	Short term observation to confirm response. Long term observation to ensure that gains are preserved
Stable with residual disease (Fibrotic NSIP)	Maintain status	Long term observation to assess disease course
Progressive irreversible disease with potential for stabilization (Some fibrotic NSIP)	Stabilize	Long term observation to assess disease course
Progressive irreversible disease despite therapy (IPF, Some fibrotic NSIP)	Slow progression	Long term observation to assess disease course and need for transplant or effective palliation
Abbreviations: COP- cryptogenic organizing pneumonia, DIP- desquamative interstitial pneumonia, IPF- idiopathic pulmonary fibrosis, NSIP- nonspecific interstitial pneumonia, RBILD- respiratory bronchiolitis interstitial pneumonia		

Figure 1.3: Classification of idiopathic interstitial pneumonia based on disease behavior

The next important group of ILDs are those associated with connective tissue diseases (CTD). Most of the connective tissue diseases develop ILD during the disease course. Connective tissue disease-interstitial lung disease (CTD-ILD) has various manifestations. however, the most frequent patterns seen are NSIP or UIP. Diagnosis of CTD-ILD should be considered if it is detected in younger women who are never smokers and there is involvement of pleura, airways, or vessels.[11] Manifestations of ILD develop in rheumatoid arthritis, polymyositis/dermatomyositis, systemic sclerosis, Sjogren's syndrome, mixed connective tissue diseases, systemic lupus erythematosus, and ankylosing spondylitis. A subset of patients who do not satisfy the American College of Rheumatology (ACR) criteria for the diagnosis of connective tissue disease if present with symptoms and autoantibodies suggestive of an autoimmune condition are grouped into undifferentiated connective tissue disease (UCTD).[12] These patients are considered to be having interstitial pneumonia with autoimmune features (IPAF).

Hypersensitivity pneumonitis (HP) is another important class of interstitial lung disease that is characterized by a complex immunological reaction of the lung parenchyma in response to repetitive inhalation of a sensitized allergen. The inflammation in HP involves not only the interstitium but also the small airways. The severity of the disease and clinical presentation varies depending on the inhaled antigen and its quantity. The initial classification into acute, subacute, and chronic is not in use now and HP is broadly divided based on the presence of fibrosis or no fibrosis [13] (Fibrotic HP or Non-fibrotic HP) (Table 1.1).

Hypersensitivity Pneumonitis (HP)	
Non-fibrotic HP	Fibrotic HP

Table 1.1: Classification of hypersensitivity pneumonitis

Sarcoidosis is a multisystem inflammatory disease of unknown etiology that predominantly affects the lungs and intrathoracic lymph nodes. Sarcoidosis is manifested by noncaseating granulomas (NCGs) in affected organ tissues. In the lungs, sarcoidosis manifests as diffuse parenchymal lung disease with or without mediastinal lymphadenopathy.

The staging of sarcoidosis is as follows (Table 1.2):

Stages	Radiographic findings
Stage 0	Normal chest radiographic findings
Stage I	Bilateral hilar lymphadenopathy
Stage II	Bilateral hilar lymphadenopathy and infiltrates
Stage III	Infiltrates alone
Stage IV	Fibrosis

Table 1.2: Staging of Sarcoidosis

Other ILDs include rare forms such as Lymphangioleiomyomatosis, Pulmonary Langerhans Cell Histiocytosis, Drug-induced ILD, ILD associated with occupational exposure, and ILD due to vasculitis or granulomatosis.

Epidemiology

Interstitial lung diseases (ILDs) are known to cause disability and death across the globe. Incidence and prevalence rates of ILDs have not been precisely estimated due to difficulties in ascertaining a specific diagnosis of a specific disease. The crude annual incidence of ILDs ranges from 1 to 70.1 per 100,000 population worldwide, as reported by various studies, while the prevalence lies between 6.27 and 97.9 per 100,000 population[14]. In a study undertaken by Coultas DB et al.[14], data from a dedicated ILD registry estimated the incidence at 30/1,00,000 per year with at least one-third in the idiopathic pulmonary fibrosis category. The estimated incidence was higher for men than women. The prevalence of ILDs was 20% higher in males (80.9 per 100,000) than in females (67.2 per 100,000). In Japan, the prevalence is 4.1/1,00,000, and in Finland, it is estimated to be 7-12/1,00,000. When data from different periods were evaluated, it is suggested that the rates are increasing from 3.5/1,00,000 in 1984 to 30/1,00,000 in 1994. Idiopathic pulmonary fibrosis (IPF) accounts for 20% of all ILDs in clinical practice, with an incidence ranging from 0.9 to 14 cases/100.000/year worldwide.[3]

The incidence and prevalence of ILDs vary among studies, which is likely due to differences in design and difficulty in differential recognition[16,17,18]. There may also be geographic differences in disease burden. Based on a

study in India, various ILDs diagnosed are HP (47.3%), CTD-ILD (13.9%), IPF (13.7%), idiopathic nonspecific interstitial pneumonia (8.5%), sarcoidosis (7.8%), pneumoconiosis (3%), and other ILDs (5.7%).[19] In 2019 a study from the United States showed the crude prevalence of ILDs per 100000 as 179.7 in males and 218.9 in females[17]. The age-standardized prevalence of ILDs per 100,000 was 121.3 (95% UI 105.7–136.5) in males and 131.4 (95% UI 114.8–148.3) in females. According to the same study, crude and age-standardized case fatality rates in males were 4.0% (95% UI 2.6–4.4) and 3.8% (95% UI 2.4–4.2), respectively. In females, the crude and age-standardized case fatality rates were 2.7% (95% UI 1.5–3.0) and 2.2% (95% UI 1.3–2.5), respectively[17]. ILD was ranked 30th among causes of death in 2019, compared to 32nd in 2010 and 41st in 1990.[18]

Pathogenesis

Pathogenesis of ILD comprises 4 steps: (1) triggering of T cells by antigen-presenting cells, represented by alveolar macrophages and dendritic cells; (2) release of cytokines and chemokines by macrophages, activated lymphocytes, dendritic cells, and polymorphonuclear cells. Cytokines and chemokines attract and retain immune-inflammatory cell populations in the lung inducing their survival and in situ proliferation at the site of ongoing inflammation; (3) stable and dynamic accumulation of immunocompetent cells and the formation of organized structure of granuloma and (4) granuloma formation which generally ends in fibrosis. Cell lines involved in the pathogenesis of diffuse fibrosis are T lymphocytes, macrophages, dendritic cells, and polymorphonuclear cells. Fibrosis is induced by the activation, proliferation, and migration of fibroblasts into the site of injury and deposition of matrix proteins. Fibroblasts are key players in the pathogenesis of IPF and systemic sclerosis-ILD (SSc-ILD). Recently, Hsu et al.[20] compared gene expression of lung fibroblasts of patients affected by SSc-associated pulmonary fibrosis (SSc-PF). Various cytokines and chemokines attracted at the site of inflammation play a significant role in the formation of fibrosis. They include: interleukin-1, interleukin-2, interleukin-4, interleukin-6, interleukin-10, interleukin-12, interleukin-13, interleukin-15, interleukin-17, interleukin-18, interleukin-23, GM-CSF, Tumour necrosis factor-á, interferon-ã and chemoattractant proteins like CCR1, CCR2 and CCR5.

Familial cases of interstitial pneumonia (FIP) are inherited as an autosomal dominant trait with variable penetrance and account for 2% to 20% of the

overall cases of idiopathic interstitial pneumonia[21]. Rare genetic variants have also been reported by different studies performed on large populations of FIP[22,23]. These variants are those implicated in the maintenance of telomere length and surfactant function. Two large genome-wide association studies (GWAS) have identified common genetic variants, crucial for epithelial integrity, as risk factors of IPF [24,25]. These studies identified the potential importance of telomere biology, host defense, and cellular barrier function for the development of the disease.

Pathology

Pathological changes in the lung in ILD depend on the site of involvement, the extent of damage, and repair. Advances in the understanding of the pathogenic mechanisms are rapidly progressing and new morphologic and molecular markers are under investigation that could contribute to a more accurate diagnosis. A pattern is defined based on a variety of morphologic features including the distribution of tissue changes, the amount of architectural distortion, the presence, type, and location of fibrosis, and repair processes. The quantitative evaluation of different inflammatory cells also helps in defining the pathology.

IPF, the prototype of ILDs is associated with the histological pattern of usual interstitial pneumonia (UIP). UIP is not unique to IPF but may also occur in connective tissue diseases, asbestosis, drug toxicity, pulmonary Langerhans cell histiocytosis (PLCH), and hypersensitivity pneumonitis (HP). In UIP, the characteristic pathological feature in low-power examination (Figure 1.4A) shows fibrotic areas of dense collagen with a typically subpleural and para-septal distribution. There is a sharp demarcation between normal and abnormal lungs. There is comparatively little nonspecific chronic inflammation when compared with other IIPs[2]. On higher magnification (Figure 1.4B), varying numbers of fibroblastic foci are evident. There are areas of loose fibroblastic proliferation that are highly interconnected (Figure 1.5A). Fibrosis in UIP must be temporarily and spatially heterogeneous. The fibroblastic foci are of lower vascularity than that seen in organizing pneumonia. Inflammatory cells are typically seen in areas of established fibrosis rather than the fibroblastic areas. These findings suggest that, although inflammation has a role in the pathogenesis, there may be significant epithelial-mesenchymal interaction (cross talk) in UIP as a response to frequent alveolar epithelial injury and an altered alveolar microenvironment. Bronchiolar scarring and prominent smooth muscle hyperplasia are common. Honeycombing is a major feature

of UIP and histologically three different types of honeycombing can be recognized: (1) those formed by large emphysematous spaces surrounded by dense collagen scarring; (2) cysts formed by large dilated bronchiolar structures and (3) areas of dense fibrosis including irregular bronchiolar structures.

NSIP, the histopathologic pattern first reported by Katzenstein and Fiorelli,[26] is characterized by diffuse involvement of inflammation and/or fibrosis. The relevant feature is the uniformity of inflammatory and fibrosing changes observed in the alveolar septa. Histologically, the fibrosis seen in NSIP is diffuse as against the patchy involvement seen in UIP and there is little fibroblastic foci[2,9].

Cryptogenic organizing Pneumonia (COP) formerly termed bronchiolitis obliterans organizing pneumonia (BOOP), histologically shows intra-alveolar polypoid buds of granulation tissue, which are typical of greater vascularity than the fibrotic foci seen in UIP. The OP pattern is produced by the reparative accumulation of granulation tissue within affected alveoli following widespread subacute injury and focal signs of alveolar damage.

In sarcoidosis, non-necrotizing granulomas localize in interstitial spaces following lymphatic routes in intralobular septa, bronchovascular bundles, and the pleural base. Granulomas are formed by collections of epithelioid cells, macrophages, multinucleated giant cells, and lymphocytes mostly exhibiting the CD3+, and CD4+ helper/inducer immunophenotype. Hypersensitivity pneumonitis is characterized by a chronic inflammatory infiltration of the alveolar septa, typically exhibiting centrilobular accentuation and bronchiolar involvement. The inflammatory cells are mainly T lymphocytes exhibiting the CD8+ phenotype. Small non-necrotizing granulomas and isolated giant cells are also featured.

In RB-ILD a mild chronic inflammation is found in the wall of the respiratory and terminal bronchioles associated with slight fibrosis and thickening of adjacent alveolar walls. The most characteristic feature is the accumulation of pigmented macrophages in the lumen of respiratory bronchioles and alveoli.

Pulmonary Langerhans cell histiocytosis (PLCH) is characterized by the abnormal accumulation of Langerhans cells (LC) along with a variable number of eosinophils. In the cellular phase of the disease, there will be a centrilobular accumulation of LC. Cystic lesions are produced by the central splitting of large nodules and by dense fibrosis surrounding alveolar

spaces. In chronic cases, the fibrosis and structural remodelling are too severe to give a pattern similar to UIP.

In lymphangioleiomyomatosis (LAM), there will be an accumulation of LAM cells. These are perivascular epithelioid cells which appear as plump spindle-shaped eosinophilic cells forming sheets and nodules around the bronchioles which are often dilated and appearing as small cysts. In pulmonary alveolar proteinosis, the characteristic feature is the filling of alveoli with PAS-positive material (Figure 1.5B).

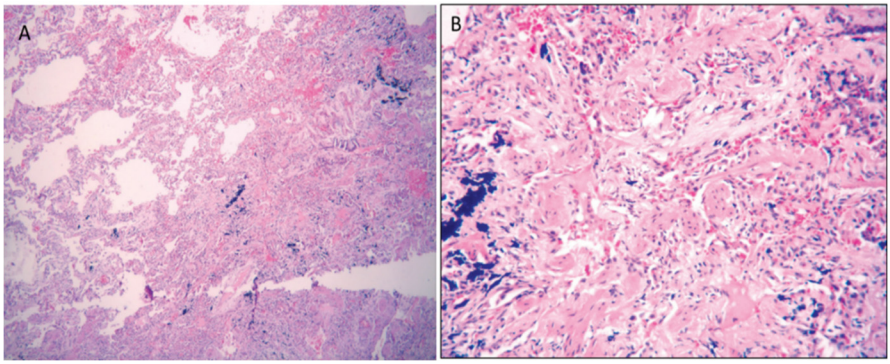

Figure 1.4: Histopathology of UIP- A: Low power magnification illustrating patchwork pattern of lung involvement with interstitial fibrosis and inflammation (right half) and normal lung (left half). B: High power magnification showing interstitial fibrosis and minimal inflammation

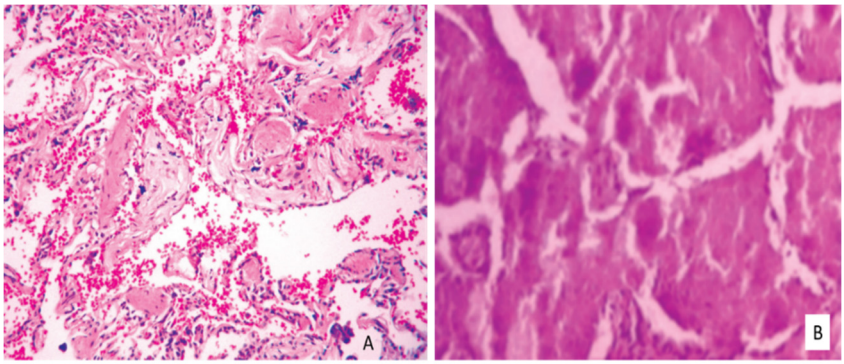

Figure 1.5: A Lung biopsy specimen showing fibroblast foci in UIP pattern. B: Lung biopsy specimen showing PAS-positive alveolar filling pattern in pulmonary alveolar proteinosis

Clinical Symptoms

As part of clinical evaluation, a thorough history should be elicited from all patients for an accurate diagnosis. It should begin with the onset, duration, and rate of progression of symptoms. Predominant symptoms with which most ILDs present are progressive shortness of breath and dry cough. History should focus on extra-thoracic manifestations and constitutional symptoms. Acute symptoms usually suggest infections, drug-induced lung injury, non-fibrotic (acute) hypersensitivity pneumonitis, or acute interstitial pneumonia (AIP). The subacute presentation suggests cryptogenic organizing pneumonia (COP), non-fibrotic (subacute) HP, eosinophilic pneumonia, or connective tissue diseases. Chronic presentation usually indicates IPF, NSIP, asbestosis, CTD-associated ILD, chronic sarcoidosis, and fibrotic (Chronic) HP. The presence of cough raises the possibility of coexisting airway involvement as in RB-ILD, Sarcoidosis, and hypersensitivity pneumonitis (HP). The presence of hemoptysis is suggestive of alveolar hemorrhage syndromes such as Wegener's granulomatosis or Good-pasture syndrome. Pleuritic chest pain raises the possibility of pneumothorax in LAM, PLCH, and neurofibromatosis or pleurisy associated with CTD such as RA, and SLE. Extrapulmonary symptoms, if any, may pinpoint a definitive diagnosis such as joint symptoms in CTD, dysphagia and aspiration in scleroderma, skin lesions in sarcoidosis, neurofibromatosis or Hermansky Pudlak syndrome, and hematuria in pulmonary renal syndromes. A detailed environmental and occupational history is essential for identifying the cause of ILD. At-risk occupations are miners, sandblasters, shipyard workers, pipe fitters and electricians, workers in aerospace and electronics industries, farm workers, and bird fanciers. Several drugs are well known to cause ILD[27]. These include cytotoxic agents, antibiotics, amiodarone, methotrexate, and penicillamine to list a few.

Physical Signs

The most consistent pulmonary sign is the bibasilar end-inspiratory 'Velcro 'crackles and is detected in more than 80% of patients with ILD[6]. In the early stage of the disease, these crackles are gravity-dependent. As the fibrosis progresses and traction bronchiectasis settles crackles may be coarser and fixed. Mid-inspiratory high-pitched squeaks are observed in ILD with associated bronchiolitis. Clubbing and tachypnoea are frequently seen in IPF. Clubbing is also seen in asbestosis and DIP. Exercise-induced hypoxia may be demonstrated in early stages but resting hypoxia and

pulmonary hypertension develop as the disease progresses. Skin lesions, peripheral lymphadenopathy, and hepatosplenomegaly are associated with sarcoidosis. Characteristic skin lesions and joint deformities are features of CTD. Sclerodactyly, telangiectasia, and Raynaud's phenomenon are characteristic features of scleroderma. Oculocutaneous albinism raises the possibility of ILD associated with Hermansky-Pudlak syndrome.

Investigations

Routine Blood Examinations

Routine blood testing is rarely supportive but can be strongly suggestive in an appropriate clinical setting. Routine blood tests include complete blood count, differential count, platelet count, ESR, blood sugar, blood urea nitrogen, creatinine, liver function tests, and calcium.

Serology

Serological tests are more useful than routine blood examinations. In the setting of CTD, antinuclear antibody, rheumatoid factor, ds DNA, and ANA profile will help in establishing an etiological diagnosis. An elevated level of angiotensin-converting enzyme, even though insensitive and nonspecific, may be seen with sarcoidosis. If pulmonary vasculitis or DAH is suspected, anti-neutrophil cytoplasmic antibody (C-ANCA, P-ANCA), anti-glomerular basement membrane antibody, and antinuclear antibody (ANA) should be checked. In suspected cases of polymyositis measurement of aldolase, creatine kinase, and anti-Jo-1 antibody may be of help.

Pulmonary Function Studies

Spirometry

Typical spirometric abnormality is a restrictive pattern wherein the FEV1 is reduced, FVC is reduced and the FEV1/ FVC ratio is normal or elevated. Coexisting obstructive airflow patterns are seen in patients with ILD and emphysema or DPLDs where there is airway involvement such as RB-ILD, HP, PLCH, LAM, or Sarcoidosis. In obliterative bronchiolitis obstructive defect alone is noticed without significant restrictive abnormality.

Lung Volumes

Spirometric findings if suggestive of ILD, lung volume measurement using body plethysmography may be useful to confirm diffuse parenchymal involvement. The ILDs are characterized by symmetrically decreased lung volumes, i.e. decreased total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV).

Diffusion Capacity

The ILDs are characterized by decreased diffusion capacity (DLCO). This is expected as alveolar wall thickening and interstitial fibrosis are leading to a situation of 'alveolo-capillary block'. A DLCO that is decreased out of proportion to other tests may suggest concomitant pulmonary vascular diseases such as scleroderma, pulmonary veno-occlusive disease, and rarely pulmonary alveolar proteinosis. The DLCO may be raised in diffuse alveolar haemorrhage syndrome.

Arterial Blood Gas Analysis

Arterial blood gas analysis may show normal values in the early stages of the disease. However, there may be exercise-induced hypoxemia even when X-ray or HRCT are within normal limits. As the parenchymal involvement progresses ABG analysis may show decreased PaO2 and normal PaCO2 even at rest.

Exercise Testing

Occasionally PFT and resting arterial blood gas analysis may be entirely normal in the early stages of ILD. However, ABG sampling done during exercise may show decreased PaO2 and widening of P(A-a) O2. Hence pulse oximetry at rest and during exercise (6-minute walk test) should be initially performed in all ILDs. A formal cardiopulmonary exercise testing allows measurement of peak oxygen consumption, exercise gas exchange, and dead space ventilation in patients with early ILD.

Chest Radiograph

Chest radiographs may demonstrate some useful diagnostic patterns in ILD. Characteristic lesions are reticular, nodular, reticulonodular, and cystic lesions (Figures 1.6A, 1.6B). The distribution, location, and overall appearance of these lesions vary depending on the disease (Figure 1.7A,1.7B). In general, the majority of conditions are characterized by reduced lung volume (Figure 1.7A). In conditions like PLCH, ILD on preexisting COPD, LAM, RB-ILD, etc., lung volumes are fairly preserved (Figure 1.7B). The predominant distribution of lesions in the upper zone suggests a diagnosis of silicosis, sarcoidosis, PLCH, or fibrotic HP. If the lesions are mainly in the midzone, it could be PAP, pneumocystis infection, or pulmonary edema (Figure 1.8A, 1.8B). A predominant lower zone pattern is characteristically seen in IPF, CTD-associated ILD, asbestosis, and DIP. At least 10% of patients found to have diffuse disease at biopsy will have a normal chest X-ray[28]. Chest radiographs may be normal in ILD. However, the presence of reduced lung volume, reticular opacities, and honeycombing are highly suggestive of interstitial involvement. If there is radiographic evidence of confluent alveolar opacities, pleural disease, or significant mediastinal lymphadenopathy IPF is least likely.

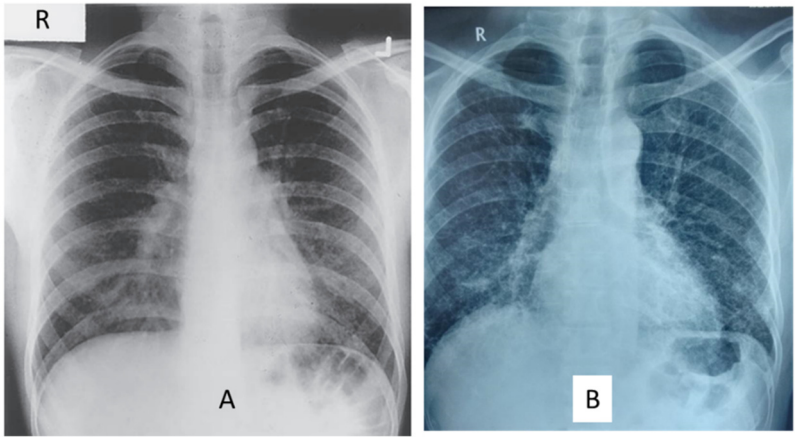

Figure 1.6: X-ray Chest PA view showing reticular and nodular opacities confined to lower zones (A) and similar opacities involving all the lung zones except apical areas (B).

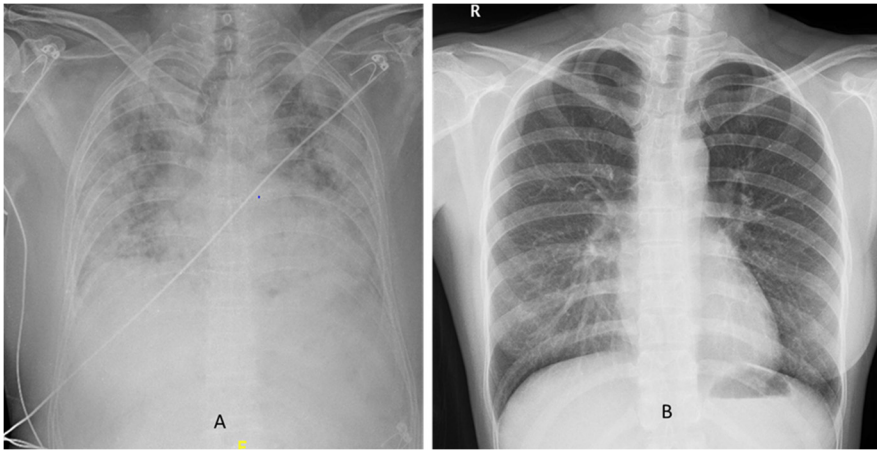

Figure 1.7: X-ray Chest showing interstitial shadows with reduced lung volume (A) and preserved lung volume (B)

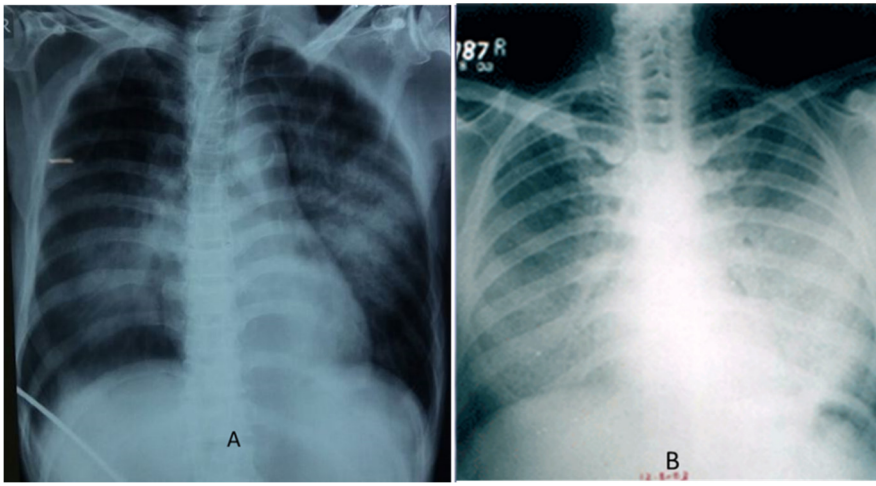

Figure 1.8: X-ray Chest showing midzone predominant interstitial opacities-bilateral perihilar shadows in pulmonary edema (A) and Pulmonary alveolar Proteinosis (B)

HRCT Thorax

The HRCT is now the gold standard diagnostic tool for ILD. It is a more sensitive test than a plain chest radiograph (sensitivity > 90%) and the image pattern on HRCT often suggests a particular set of diagnostic possibilities. The HRCT is the standard diagnostic test in all cases of suspected ILDs, except for a small proportion of patients for whom chest radiograph findings are definitive. HRCT may eliminate the need for lung biopsy in as many as 50% of patients with IIP[29,30]. At the same time, histological diagnosis is the definitive procedure for excluding other disease processes that can mimic IPF, particularly hypersensitivity pneumonitis. The HRCT also identifies mixed patterns of disease like ILD and emphysema or coexisting pleural, hilar, or mediastinal abnormalities. It is also useful in guiding the site for BAL or lung biopsy. The typical HRCT patterns will include ground-glass opacity and reticular abnormality, characterized by a fine, lace-like network of lines. This is often accompanied by subpleural irregularity, architectural distortion, traction bronchiectasis, and honeycombing. Ground-glass opacity, the early abnormality in ILD indicates an inflammatory state, which is a potentially treatment-responsive condition, as seen in hypersensitivity pneumonitis, DIP, or respiratory bronchiolitis. If the ground-glass opacity is accompanied by a fine reticular abnormality or traction bronchiectasis, it is suggestive of fibrosis as seen in NSIP or UIP.

Imaging criteria for the diagnosis of UIP on HRCT include the presence of a bilateral, predominantly basal, subpleural reticular abnormality with a craniocaudal gradient. Subpleural honeycombing is a specific feature of UIP (Figure 1.9A). Other important criteria for the diagnosis of UIP include the absence or very little ground-glass opacities, nodules, consolidation, and pleural involvement. The presence of lobular mosaic attenuation or air trapping suggests the diagnosis of fibrotic (chronic) hypersensitivity pneumonitis rather than IPF. In approximately one-third of patients with IPF, the characteristic HRCT pattern of UIP is not present.[29,30]

In NSIP there is a variable mixture of ground glass attenuation and a reticular pattern with minimal honeycombing (Figure 1.9B). To a large extent, HRCT features overlap with that of UIP (Figure 1.10A). The HRCT in RB-ILD shows ground glass infiltrate of variable intensity and distribution. Superimposed on this pattern, there may be more ill-defined centrilobular nodules and a few secondary lobules of decreased attenuation