Review Article

Systematic Pathological Approach in the Evaluation of Interstitial Lung Diseases: An Overview

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Abstract

Interstitial lung disease (ILD) constitutes a heterogeneous group of non-neoplastic conditions characterised clinically by restrictive lung function, radiologically by reticulonodular type of infiltrates and pathologically by inflammation, alveolare-damage and fibrosis, predominantly involving the alveolar interstitium. Definitive categorisation of sub-types of ILDs is important as the prognosis and treatment is different in each case. Pathologist and radiologist play a major and equal role in the proper diagnosis of each case. Hence, multi-disciplinary team approach including respiratory clinician, surgeon, radiologist and pathologist is a must in all cases, as non-specific histopathological diagnosis can become a specific diagnosis on clinical-pathological and radiological discussion.

[Indian J Chest Dis Allied Sci 2017;59:23-32]

Key words: Interstitial lung disease, Bronchoalveolar lavage, Lung biopsy.

Introduction

Interstitial lung disease (ILD) constitutes a heterogeneous group of non-neoplastic conditions characterised clinically by restrictive lung function, radiologically by reticulonodular type of infiltrate and pathologically by inflammation, damage and fibrosis, predominantly involving the alveolar interstitium and to a lesser extent alveolar air spaces and peripheral airways. As majority of these lesions involve the air spaces, blood vessels and small airways, the term diffuse parenchymal lung disease (DPLD) is a better term.[1] Pulmonary fibrosis is an important global public health problem with increase in incidence and mortality as treatment protocols and disease-free survival have revealed largely disappointing results. ILDs have diverse aetiology but identifying the exact cause in majority of the individuals is extremely difficult. Definitive categorisation of the ILD is important because each subtype has different prognosis and overall survival when compared to others. Although histopathology is considered to be the "gold standard" in defining the type, activity and pattern of the disease process, multi-disciplinary team approach in each case is necessary for the proper diagnosis and management.[2] The present review highlights the pattern based approach for the histopathologist in evaluating a clinically suspected case of ILD along with the main clinical and radiological features.

Clinical Presentation

Most of the patients with ILD have similar clinical signs and symptoms with varying degree of severity. Common presentation includes gradual onset of exertional breathlessness which may or may not be associated with non-productive cough.[3,4] Detail history of the clinical presentation and duration of symptoms are very important to understand the progression and prognosis of the disease process.[3,5] Depending upon the duration of symptoms, the disease process may be classified as: (i) acute (few days to a week); (ii) sub-acute (few weeks to months); and (iii) chronic (few months to years).[3-5] Initial clinical evaluation should always include history of smoking habits, occupation, hobbies, recent travel, drug and treatment.[3,6] Family history should also be taken to exclude the hereditary nature of the disease.[5] Physical examination of patients with ILD usually reveals bilateral basal crepitations, varying degree of hypoxaemia with or without pulmonary arterial hypertension (PAH).[5] A thorough systemic examination in each case is always required to rule out secondary lung involvement in other systemic/ autoimmune diseases. Table 1 shows categorisation of ILDs depending upon the disease duration.[6] Routine blood analysis and serum biochemistry are generally not helpful in arriving the specific diagnosis[3] but in suspected cases, relevant serological tests should be carried out to exclude lung involvement in conditions, like systemic lupus erythematosus (SLE),

[Received: February 13, 2017; accepted: March 01, 2017]

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rheumatologic diseases and autoimmune vasculitic diseases.[5] Culture studies are helpful in identifying the infective aetiology.

Table 1. Clinical categorisation of interstitial lung disease

Acute	Sub-acute	Chronic
Infections	Hypersensitivity pneumonitis	Pneumoconiosis
Diffuse alveolar damage	Sarcoidosis	Drugs
Acute lung injury	Smoking	Smoking
Acute interstitial pneumonia	Drugs and infections	Alveolar proteinosis
Diffuse alveolar haemorrhage	Cryptogenic organising pneumonia	Usual interstitial pneumonia
	Non-specific interstitial pneumonia	Non-specific interstitial pneumonia
	Lymphoid interstitial pneumonia	Sarcoidosis

Pulmonary function tests

Lung physiology in patients with ILD reveal restrictive lung features with ventilatory deficit, reduced compliance and impaired gas exchange resulting in hypoxaemia. Severity of these findings reflects the degree and amount of interstitial inflammation and fibrosis. Pulmonary function tests (PFTs) reflects the severity of the disease more accurately than chest radiography.[1] PFTs reveal reduced forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC), however, FEV_1/FVC ratio is usually preserved. PFTs, in general, are not helpful in the definitive diagnosis of ILDs,[3,5] but these are of help in the assessment of respiratory limitation, monitoring the disease progression and follow-up.[7]

Aetiopathogenesis

There are numerous known and unknown agents those elicit histopathological and radiological features of ILDs but only few cases will develop classical clinical signs and symptoms. The disease process mainly depends on the host susceptibility, genetic and multi-factorial environmental factors. Pathogenetic mechanism involved is almost similar in majority of the cases. Inhalation of known and unknown agents cause injury to the alveolar epithelial lining followed by recruitment of inflammatory cells which produces variety of cytokines, ultimately resulting in fibroblastic proliferation. Aetiology and pathogenesis of idiopathic pulmonary fibrosis (IPF) is highly complex.[8] In autoimmune diseases, alveolar injury is caused by circulating auto-antibodies. The cellular inflammatory response depends on the nature of injury and duration. In hereditary cases, presence of sporadic mutation causes development of the ILD. Various studies have shown that there are no consistent genetic factors associated with ILDs; however, familiar interstitial pneumonias show heterogeneous mutations in surfactant associate protein C (SFTPC), surfactant protein A 2 (SFTPA2), telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) in approximately 20% of the cases.[2]

Classification

There are about more than 300-400 different factors that are known to cause ILDs. Of these, a majority are environmental, occupational and radiation exposures, systemic autoimmune diseases, infections and drugs.[5] For clinical and treatment purposes, ILDs of unknown cause are categorised as idiopathic interstitial pneumonias (IIPs).[8,9] Table 2 shows recent American Thoracic Society (ATS)/European Respiratory Society (ERS) classification of interstitial pneumonias.[2,4,10]

Table 2. Revised American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonias: multi-disciplinary diagnoses

Major ILDs of Known Aetiology
Pneumoconiosis (e.g., asbestosis, berylliosis, etc)
Hypersensitivity pneumonitis
Drug and radiation induced ILD
Post infectious ILD
ILD with systemic autoimmune diseases (e.g., rheumatoid arthritis and SLE)
Major Idiopathic Interstitial Pneumonias
Idiopathic pulmonary fibrosis
Idiopathic non-specific interstitial pneumonia
Respiratory bronchiolitis–ILD
Desquamative interstitial pneumonia
Cryptogenic organising pneumonia
Acute interstitial pneumonia
Rare Idiopathic Interstitial Pneumonias
Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias

Definition of abbreviations: ILD=Interstitial lung disease; SLE=Systemic lupus erythematosus

Radiology

Radiologist plays a key role in the evaluation of patients who suspected to have ILD clinically. High resolution computed tomography (HRCT) has become the standard radiological test which is very helpful and gives greatest diagnostic accuracy than routine chest x-ray in identifying and typing of ILDs.[9,11] HRCT in ILD usually reveals the following patterns: (i) increased attenuation (ground-glass opacity); (ii) reticulo-nodular opacities; (iii) cyst formation; and (iv) fibrosis.[6] Complete lack of pulmonary parenchymal changes on HRCT imaging virtually excludes the diagnosis of ILD.[8] Recently multi-detector computed tomography (MDCT) has been introduced that can image the entire thorax with a single breath-hold manoeuvre and allow even better results.[8] For the pathologist, HRCT findings simulate the gross pathology of the whole lung parenchyma and will be of great help in evaluating the surgical lung biopsy samples of ILDs. To determine the disease progression and severity, radiologists/clinician should evaluate the detailed past history and critically review all the previous imaging findings.[1] The primary role of HRCT is to separate patients with typical findings of IPF from those with the less-specific findings associated with other IIPs.[12] Some classical HRCT features of ILDs are mentioned in table 3.

Idiopathic interstitial pneumonia

Idiopathic interstitial pneumonia is a distinctive type of chronic ILD with unknown aetiology and poor prognosis.[2] The disease process is entirely limited to the lungs. Characteristic radiological features include basal and peripheral predominant reticular opacities, focal ground-glass appearance with honey-combing fibrosis and traction bronchiectasis (Figure 1A). Histopathology shows characteristic spatial and temporal heterogeneity, patchy fibrosis, and moderate interstitial cellular infiltrate with an intervening uninvolved normal lung parenchyma (Figure 1B). These findings are typically present in the sub-pleural and para-septal distribution. Fibroblastic foci are scattered at the periphery with destructive lung fibrosis. Fibroblasts in fibroblastic foci characteristically show parallel alignment to the long axis of alveolar septum.[13] Smooth muscle metaplasia in the interstitium may be seen (Figures 1 C and D). Similar histopathological findings may be sometimes also seen in collagen vascular disease, drug toxicity, fibrosing chronic hypersensitivity pneumonitis, radiation pneumonitis and occupational exposures like asbestosis.[13] Bronchoalveolar lavage (BAL) fluid cytology usually reveals variable cellular yield with mild excess of neutrophils and eosinophilic series of cells. Amount of cellularity does not correlate with the severity of the diseases. However, excess eosinophils (≥20%) should raise the diagnosis of eosinophilic ILD and lymphocyte count greater that 15% should raise the alternative diagnosis. Finally, multi-disciplinary team discussion with relevant supportive tests is a must for the definitive diagnosis of IIP and to exclude other ILDs of known cause.

Non-specific interstitial pneumonia

These are the group of ILDs with favourable prognosis. Radiology reveals bilateral symmetrical reticulo-nodular and ground-glass opacities in the lung fields.

Table 3. Common typical radiological (HRCT) features of ILD include

Histological Pattern	Typical CT Distribution	Typical CT Findings
IPF/UIP	Peripheral, sub-pleural, basal	Reticular; honey-combing; Traction bronchiectasis/ bronchiectasis; Architectural distortion; Focal ground-glass attenuation
NSIP	Peripheral, sub-pleural, basal, symmetric	Ground-glass attenuation; Irregular lines; Consolidation
OP	Sub-pleural/peribronchial	Patchy consolidation and/or nodules
DAD	Diffuse parenchymal	Consolidation and ground-glass opacity often with lobular sparing; Traction bronchiectasis later
DIP	Lower zone, peripheral predominance	Ground-glass attenuation; Reticular lines
RB-ILD	Diffuse	Bronchial wall thickening; Centrilobular nodules; Patchy ground-glass opacity
LIP	Diffuse	Centrilobular nodules; Ground-glass attenuation; Septal and bronchovascular thickening; Thin-walled cysts

Definition of abbreviations: HRCT=High resolution computed tomopgraphy; ILD=Interstitial lung disease; IPF=Interstitial pulmonary fibrosis; UIP=Usual interstitial pneumonia; NSIP=Non-specific interstitial pneumonia; OP=Organising pneumonia; DAD=Diffuse alveolar damage; DIP=Desquamative interstitial pneumonia; RB-ILD=Respiratory bronchiolitis-interstitial lung disease; LIP=Lymphoid interstitial pneumonia

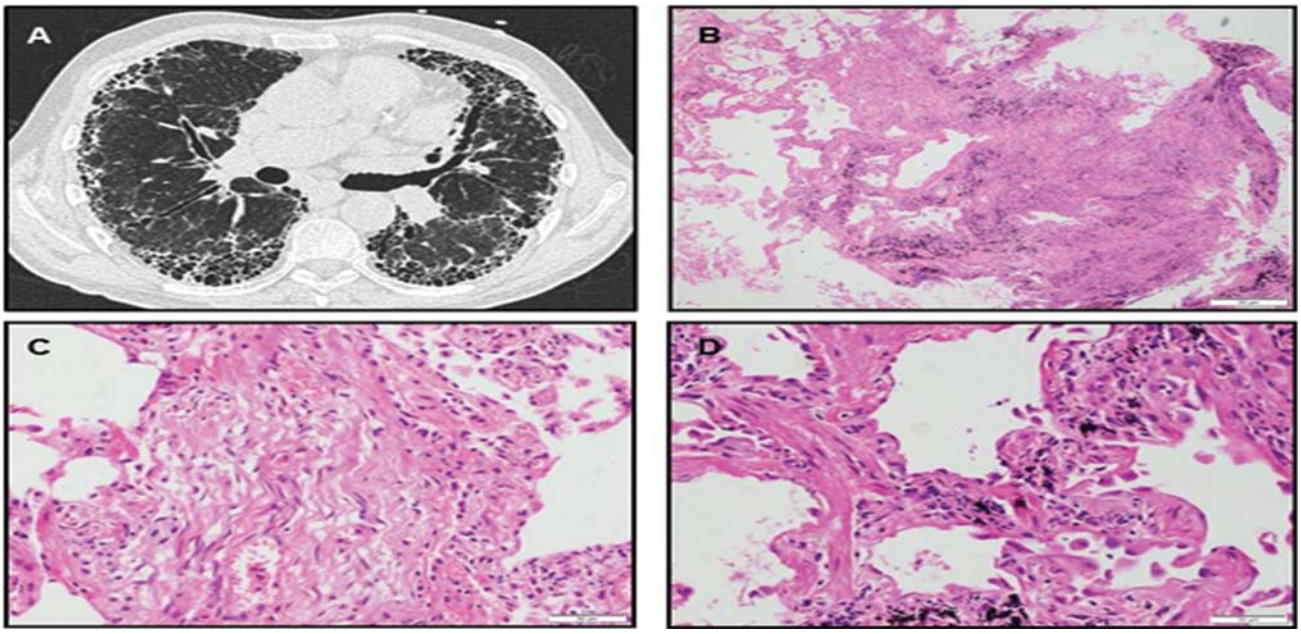

Figure 1. Usual interstitial pneumonia/idiopathic pulmonary fibrosis: (A) radiology shows basal and peripheral predominant reticular opacity, focal ground-glass appearance and honey-comb fibrosis; (B) histology reveals patchy fibro-cellular interstitial inflammation with intervening normal lung parenchyma (Haematoxylin and Eosin × 40); (C) parallel alignment of fibroblastic cells (Haematoxylin and Eosin × 40) and (D) prominent type II pneumocytes with smooth muscle metaplasia (Haematoxylin and Eosin × 40).

Features of traction bronchiectasis and honey-combing are frequently not seen (Figure 2A). Histopathological feature consists of two phases: (i) cellular phase and (ii) fibrotic phase. Cellular phase is characterised by mild to moderate diffuse chronic interstitial inflammation consisting of lymphocytes and plasma cells without any evidence of fibrosis (Figure 2B). Alveolar lining epithelium shows hyperplasia of type II pneumocytes. BAL fluid cytology in this phase usually reveals increase number of lymphocytes. While evaluating cellular phase of non-specific interstitial pneumonia (NSIP) one should always exclude the possibility of acute lung injury (ALI) patterns like hyaline membrane disease, dense eosinophilic infiltrate, presence of granulomas or infections and viral inclusions. Presence of the above-mentioned findings will change the diagnosis of NSIP. Fibrotic phase is characterised by loose or dense interstitial fibrosis which lack the temporal or spatial heterogeneity which is characteristically seen in IPF/UIP (usual interstitial pneumonia).[1,2] As NSIP is a diffuse process, intervening normal lung parenchyma is not seen. Architecture of the lung appears to be preserved. Interstitial inflammation will be minimal.[13] Alveolar wall is thickened by inflammation and fibrosis but fibroblastic foci are usually not seen. BAL fluid cytology in fibrotic phase reveals low cellular yield with very few lymphocytes.

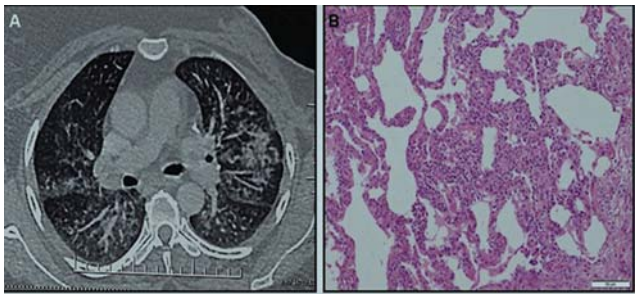

Figure 2. Cellular phase of NSIP: (A) radiology shows bilateral symmetrical ground-glass opacities in the lung fields and (B) histology reveals predominant interstitial chronic inflammatory cell infiltrate without any intervening normal lung parenchyma (Haematoxylin and Eosin × 10).

Definition of abbreviations: NSIP=Non-specific interstitial pneumonia

Cryptogenic organising pneumonia

Cryptogenic organising pneumonia (COP) is also known as bronchiolitis obliterans organising pneumonia (BOOP).[1] Classical radiology reveals presence of single or multi-focal sub-pleural consolidation with the presence of air-bronchogram (Figure 3A). Microscopy reveals patchy involvement with preservation of the lung parenchyma. Histology shows features of organising pneumonia with the presence of fibroblastic plug (Masson body) within the alveolar duct, alveoli (Figure 3B) and in the bronchioles.[13] Interstitium shows mild interstitial chronic inflammation.[2] Similar type of microscopic features can also be seen in organising phase of aspiration pneumonia, organising diffuse alveolar damage, organising drug reactions, collagen vascular diseases, hypersensitivity pneumonitis, eosinophilic pneumonia, inflammatory diseases and graft *versus* host diseases.

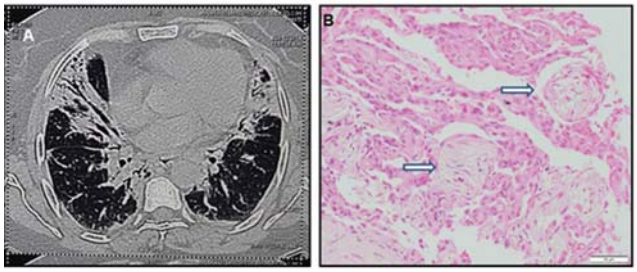

Figure 3. Organising pneumonia: (A) radiology shows sub-pleural predominant lung consolidation with the presence of air-bronchogram and (B) histology reveals many classical fibroblastic plugs (Masson bodies—arrow) within the alveolar air spaces (Haematoxylin and Eosin × 20).

Points which are against BOOP include presence of neutrophilic abscess, hyaline membrane in the alveolar lumen, prominent interstitial fibrosis, granulomas, vasculitis or dense eosinophilic infiltration. Identification of any of the above-mentioned findings will render the possibility of alternative diagnosis. Definitive diagnosis of this entity is very important as majority of patients will recover completely after the treatment with corticosteroids.[2] BAL fluid analysis will reveal increase in total cellular count with lymphocytic predominance. Mild increase in neutrophils and eosinophils may be seen. The CD4+ to CD8+ T-lymphocyte ratio will be decreased.

Acute interstitial pneumonia

Acute interstitial pneumonia (AIP) is characterised by a rapidly progressive hypoxaemia with histologically distinct form of interstitial pneumonia. Mortality rate is approximately 50% or more. Survivors will have good long-term prognosis.[2] The term AIP should be reserved for the conditions with unknown aetiology. Radiological findings include geographic distribution of ground-glass opacities, consolidation with presence of air-bronchogram. Consolidation is predominantly located in the basal dependent regions of the lungs. Histology reveals features of diffuse alveolar damage[13] (DAD) which is characterised by diffuse uniform distribution, alveolar septal thickening and organisation with presence of focal or diffuse hyaline membranes (Figure 4A).[13] These features are indistinguishable from acute respiratory distress syndrome caused by sepsis and shock. Small microvascular thrombi may be seen in the septal capillaries. In due course, lung may resolve completely or progress to end-stage fibrosis. Exudative phase will show prominent hyaline membrane with interstitial oedema and mild inflammation whereas resolving organising phase will show proliferating loose fibroblastic connective tissue with hyperplasia of the type II pneumocytes. Adjacent alveoli may be compressed to become slit like spaces. Squamous metaplasia can be seen and it should not be mistaken for a malignant process. DAD pattern has many differentials like drugs, Collagen vascular diseases, shock, toxic inhalation, trauma, uraemia, transfusions and infections.[13] Detail history, special histochemical stains and culture studies are helpful in the proper evaluation of the case. BAL fluid analysis will reveal increased total cell count with neutrophils and hemosiderin laden macrophages. Reactive pneumocytes and fragments of hyaline membrane can also sometimes be identified.

Respiratory bronchiolitis interstitial pneumonia

Respiratory bronchiolitis interstitial pneumonia is commonly seen in smokers with microscopy revealing accumulation of pigmented dusty macrophages in the lumen of respiratory bronchioles. Iron stain reveals few pigmented haemosiderin laden macrophages. Radiology shows centrilobular nodules with patchy ground-glass appearance.[2] BAL fluid cytology usually reveals increased number of pigmented alveolar macrophages (Figure 4B) with few neutrophils.[2] Chronic cases may show peribronchiolar fibrosis. Significant interstitial and honey-comb fibrosis is usually not seen.[1] These patients are rarely symptomatic and usually associated with minor airways. This condition completely resolves after the cessation of smoking.[1]

Desquamative interstitial pneumonia

Desquamative interstitial pneumonia (DIP) is considered to be the end spectrum of respiratory bronchiolitis-ILD. Its name is misnomer as it is characterised by accumulation of intra-alveolar dusty macrophages (Figure 4C) rather than desquamation of the epithelial cells. It is commonly seen in smokers and people with environmental inhalation exposure. Radiology reveals ground-glass opacities in majority of the cases.[1] BAL fluid analysis will show increased number of pigmented alveolar macrophages. It has good prognosis and it improves after cessation of smoking.[1] Special stain (perls Prussian blue stain) may show focal positivity for iron. Chronic cases may reveal mild to moderate interstitial thickening with chronic inflammation. Significant interstitial or honey-comb fibrosis is usually not seen.

Lymphoid interstitial pneumonia

Lymphoid interstitial pneumonia is usually associated with systemic or autoimmune diseases. Detection of pulmonary involvement is usually incidental or sometimes presents with dyspnoea and cough. This may occasionally resolve or progresses to develop diffuse pulmonary fibrosis. Radiology reveals ground-glass opacities with cyst formation.[1]

BAL fluid cytology reveals many lymphocytes. Histopathology is characterised by diffuse and nodular infiltration of polymorphous population of lymphocytes, histiocytes and plasma cells predominantly in the alveolar septa (Figure 4D), rarely this condition may evolve into lymphoma involving the mucosa associated lymphoid tissue (MALT). Differential diagnosis that should be considered is low-grade lymphoma, cellular NSIP, hypersensitivity pneumonitis, infections and drug induced changes.[1]

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis is also known as extrinsic allergic alveolitis. It is a complex syndrome with variable clinical presentation and disease course. It is caused by hypersensitivity reactions to various airborne antigens. Pathophysiology involves repeated antigenic exposure, development of T-cell mediated immune response (Type III and IV hypersensitivity) resulting in fibrosis. It has good prognosis and responds to steroids and improves on removal of the antigenic stimulus. Radiology reveals diffuse patchy bronchiolocentric reticular type of infiltrate with ground-glass opacities, predominantly seen in the bilateral basal region.[1] BAL fluid cytology reveals mainly lymphocytes. Histology characteristically shows bronchiolocentric distribution of inflammatory cells with involvement of the adjacent alveoli. Inflammatory infiltrate predominantly consists of lymphocytes, plasma cells and histiocytes which are mainly seen in the peribronchiolar area and in the adjacent alveolar interstitium. Identification of poorly formed epithelioid cell granulomas or multinucleate giant cells in the interstitium, if present, will be an important helpful finding in the diagnosis of hypersensitivity pneumonitis in difficult cases. Foamy histiocytic collections and multinucleate giant cells may also be seen in the alveolar lumen. Occasionally giant cells may also show presence of cholesterol clefts in their cytoplasm. In chronic phase interstitium shows fibroblastic proliferation with less inflammatory cells. In the end-stage disease it leads to pulmonary interstitial fibrosis which is

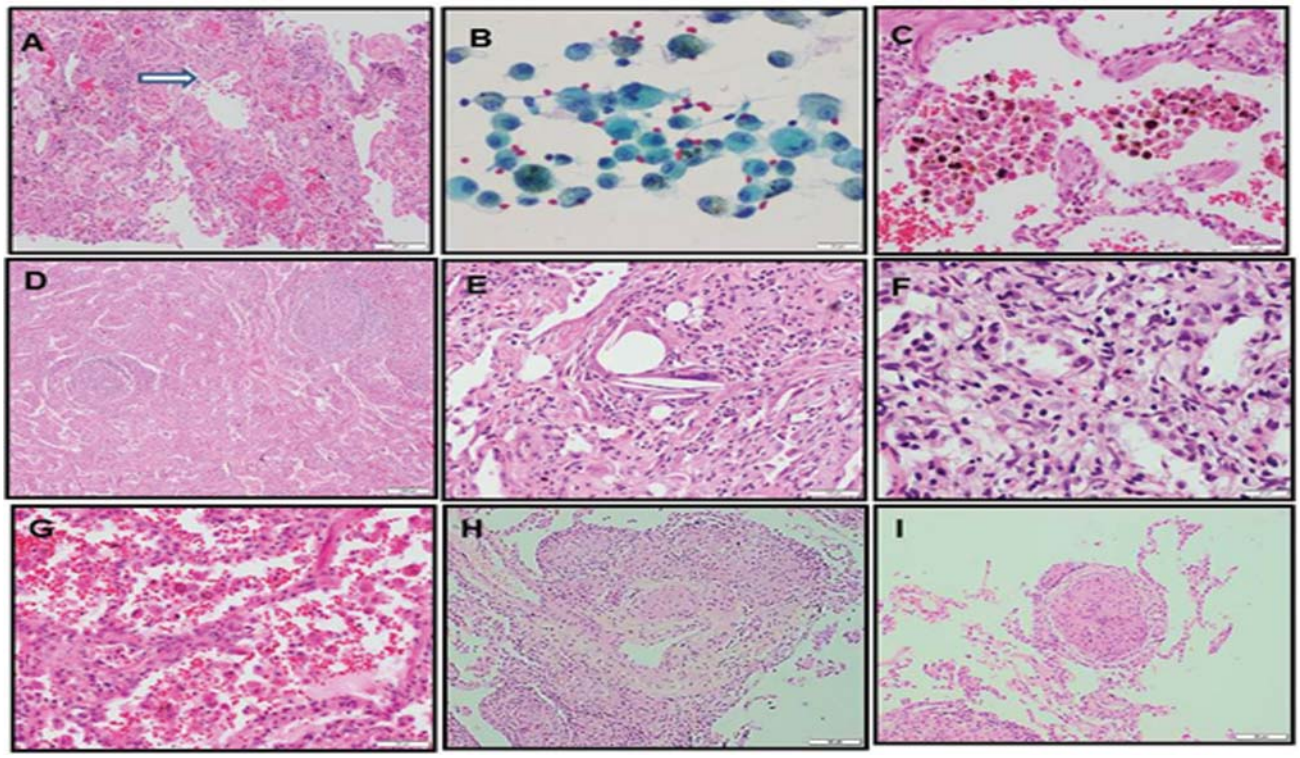

Figure 4. Photomicrograph showing important histological findings: (A) acute interstitial pneumonia showing hyaline membrane (arrow) (Haematoxylin and Eosin × 10); (B) BAL fluid showing many pigmented alveolar macrophages (Papanicolaou stain × 40); (C) dusky pigmented (Smoky) macrophages in the alveolar lumen in DIP (Haematoxylin and Eosin × 20); (D) prominent lymphoid follicles in LIP (Haematoxylin and Eosin × 10); (E) ill-formed granuloma and giant cell in HP (Haematoxylin and Eosin × 40); (F) interstitial eosinophilic infiltration in eosinophilic pneumonia (Haematoxylin and Eosin × 40); (G) fresh haemorrhage in the alveolar lumen (Haematoxylin and Eosin × 20) and (H and I) characteristic perivascular and interstitial location of granulomas in sarcoidosis (H— Haematoxylin and Eosin × 40 and I— Haematoxylin and Eosin × 10).

***Definition of abbreviations*: BAL=Bronchoalveolar lavage; DIP=Desquamative interstitial pneumonia; LIP=Lymphoid interstitial pneumonia and HP=Hypersensitivity pneumonitis**

difficult to differentiate from other end-stage fibrotic lung diseases. Proper treatment intervention along with removal of antigenic stimuli at the early stage of the disease has an excellent prognosis (Figure 4E).

Eosinophilic interstitial pneumonia

The term eosinophilic interstitial pneumonia refers to a heterogeneous group of disorders characterised by the presence of predominant interstitial eosinophilic infiltration (Figure 4F) with or without peripheral eosinophilia. Main differential diagnosis that should be considered are: parasitic infections, drugs, allergic bronchopulmonary aspergillosis, tropical eosinophilia and vasculitic disorders. Radiology reveals bilateral, patchy peripheral infiltrate with sparing of hilar region.[14] Treatment depends on identifying the cause and idiopathic cases will respond well to corticosteroid treatment. Around one-third of the treated cases may relapse. BAL fluid cytology reveals many eosinophilic series of cells.

Diffuse alveolar haemorrhage

Diffuse alveolar haemorrhage (DAH) is characterised by the accumulation of fresh and old haemorrhage in the alveolar lumen. Fresh haemorrhage shows presence of intact red blood cells (Figure 4G), whereas old haemorrhage shows presence of numerous hemosiderin laden macrophages with mild fibrosis and features of organisation. Identifying the capillaritis, if present, is of medical emergency.

Pulmonary alveolar proteinosis

Exact cause of pulmonary alveolar proteinosis (PAP) is not known. Pathophysiology reveals imbalance between surfactant production and inadequate clearance by macrophages. BAL fluid analysis reveals increased granulocyte monocyte-colony stimulating factor (GM-CSF) antibody. Radiologically it shows ground-glass appearance with thickening of the interlobar septae (crazy pavement appearance) (Figure 5A). BAL is both therapeutic and diagnostic in these cases. Histology shows presence of homogeneous granular periodic-acid-Schiff (PAS) positive material in the alveolar lumen (Figure 5B). Electron microscopy of the fluid will reveal presence of numerous lamellar bodies.[15]

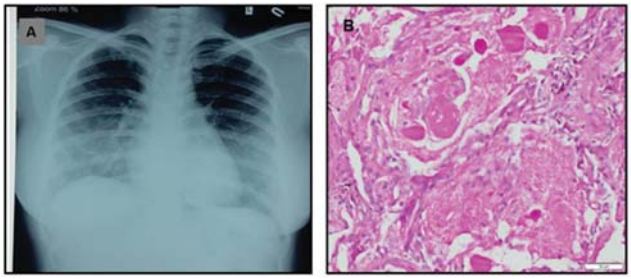

Figure 5. Pulmonary alveolar poteinosis: (A) radiology shows bilateral dependent ground-glass (Crazy pavement) opacities in the lung parenchyma and (B) histology reveals granular periodic-acid-Schiff (PAS) positive proteinaceous material in the alveoli (PAS stain × 20).

Idiopathic pleuroparenchymal fibroelastosis

Idiopathic pleuroparenchymal fibroelastosis is a recently recognised unusual form of fibrosing interstitial pneumonia. Radiology reveals sub-pleural reticulonodular opacities in the upper lung fields revealing pleural fibrosis with linear extension in the lobular septa. Traction bronchiectasis and honey-comb fibrosis may be sometimes seen. Histopathology shows dense sub-pleural and subjacent lung parenchymal fibroelastosis. Parenchyma distant from the lesion will be spared. Interstitium may show mild patchy interstitial type of inflammation. This is also known as idiopathic upper lobe fibrosis. It should be distinguished from other fibrotic lung diseases because it is highly progressive.[2,16-18]

Unclassifiable idiopathic interstitial pneumonias

According to the ATS/ERS classification all the cases of ILD in which final diagnosis is not made even after extensive clinico-pathological evaluation and multi-disciplinary discussions should be categorised as unclassifiable IIP.[2,10]

Bronchoalveolar Lavage

Importance of cellular analysis in BAL fluid for diagnostic and prognostic purpose in ILD patients remains controversial. In the appropriate clinical and radiological setting, BAL will be of diagnostic value in certain diseases, like alveolar proteinosis, pulmonary Langerhans cell histiocytosis and infections.[8] Although BAL is non diagnostic in majority of the cases, it will definitely contribute some message in the difficult scenario.[1,7] Identification of numerous haemosiderin-laden macrophages suggests haemorrhagic diseases which will help the clinician to investigate in that direction. BAL features in different subtypes of ILDs are mentioned in the respective sub-headings. Best regions for lavage in diffuse parenchymal diseases are right middle lobe or left lingular lobe with areas of ground-glass opacification.[8]

Lung Biopsy

A thorough clinico-radiological evaluation along with supportive laboratory tests will solve the diagnosis in majority of the cases of ILD; hence, these cases do not require lung biopsy. In symptomatic and/or functionally impaired patients with unexplained physiologic and radiologic features of ILD, surgical lung biopsy should be carried out to arrive at the specific diagnosis.[8]

Following are the basic requirements to carry out the biopsy: (i) relatively younger patients (<65 years of age); (ii) history of fever, weight loss, night sweats, haemoptysis; (iii) family history of ILD; (iv) patients with symptoms and signs of peripheral vasculitis; (v) atypical radiological features; (vi) symptomatic patients with a normal chest radiograph; (vii) unexplained extra-pulmonary manifestations (with negative serology, negative antinuclear cytoplasmic antibody (ANCA), negative glomerular basement membrane antibody in the appropriate clinical setting); (viii) unexplained pulmonary hypertension; (ix) rapidly progressive disease; and (x) rapid deterioration/new symptom with new radiologic abnormalities in long-standing stable ILD.[7]

Transbronchial lung biopsy (TBLB) has less mortality and morbidity but is likely to be non diagnostic in majority of the cases of ILDs.[3] In few conditions, like DAD/AIP, sarcoidosis, HP, haemorrhagic disorders and occasionally organising pneumonia /COP, adequately taken TBLB provides specific diagnosis. The primary role of transbronchial biopsies is to exclude sarcoidosis and other infectious aetiologies.[7] Surgical lung biopsy (SLB) obtained via video-assisted thoracic surgery (VATS) or open lung biopsy has more risks but it is necessary for the proper evaluation and definitive diagnosis of the ILD cases.[3] Open lung biopsy should be avoided especially in frail elderly patients, patients with ventilatory support, patients with moderate to severe pulmonary hypertension, or patients with multiple co-morbidities.[3] For good histopathological interpretation lung biopsy should always be taken in consultation with the pulmonologist, radiologist and the surgeon. Few important points that should be conveyed to the clinician/surgeon before the biopsy procedures are: (i) biopsy should be obtained early in the course of the disease, prior to the treatment by immunosuppressive and immunomodulant therapy; (ii) it is almost impossible to identify the disease pattern in a biopsy obtained later; (iii) biopsy should be HRCT guided as selection of the site is very important; and (iv) at least three good biopsies should be taken from extensively involved area; less involved areas; and also from radiologically normal lung.

After biopsy, the lung specimen should be stored in 10% buffered formalin and should be inflated properly by shaking and swirling movements to inflate the alveoli. Tissue should not be crushed at any given point of time.[7] Routine haematoxylin and eosin staining is a must for the diagnosis and depending on the histological features further special histochemical stains, like Masson trichrome (to identify fibrosis), elastic van Geison (to identify vessel), silver methanamine (to identify fungi), Gram's stain (to identify bacteria), acid-fast stain (to identify acid-fast bacilli) should be done. When sarcoidosis is suspected multiple level cuts should be done to identifying the granulomas (Figure 4 H and I).

Pattern-based Approach for Pathologist

Many diffuse parenchymal lung diseases share a common disease pattern. Pathologists should obtain detail clinical history along with HRCT findings before evaluating the biopsy sample. Clinical history gives the course and severity of the disease while HRCT give the gross morphology of the lungs. The main role of histopathologist is to provide critical information like aetiology, disease activity, duration, reversibility and prognosis of the disease process in a given case of ILD, hence, pattern-based approach is most important and helpful in identification and categorisation of the disease. In chronic conditions, presence of microscopic honey-combing fibrosis, distortion of the lung parenchyma and cyst formation reveals chronic process; however, presence of loose fibroblastic foci reveals the activity of the disease. Main histopathological features that should be commented while reporting are: (i) features of acute lung injury; (ii) degree of interstitial fibrosis; (iii) amount and type of interstitial inflammation; (iv) features and type of alveolar filling; (v) presence of granuloma; (vi) features of infectious aetiology; (vii) evidence of vasculitis (Figure 6 A and B); (viii) identification of any foreign material (occupational exposure diseases like asbestosis etc); and (ix) any unusual histological findings.[13]

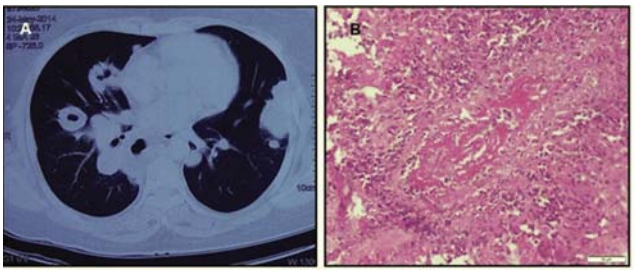

Figure 6. Wegener's granulomatous vasculitis: (A) radiology shows multiple pulmonary nodules with cavitatory lung lesions and interstitial fibrosis and (B) histology reveals features of vasculitis with palisading histiocytes (Haematoxylin and Eosin × 10).

Sometimes presence of secondary infections and mixed aetiology will be difficult in the biopsy interpretation. Few histological features of acute injury are DAD, diffuse alveolar haemorrhage, hyaline membrane and tissue necrosis. Chronic disease shows fibrosis with tissue remodelling. Acute lung injury in the background of fibrosis reveals acute on chronic disease. Presence of numerous tissue eosinophils should be labeled as acute eosinophilic pneumonia. In occasional end stage disease process where the lung biopsy shows only fibrosis without any other histological findings, should be labeled as chronic fibrosis lung disease (Figures 7 and 8).

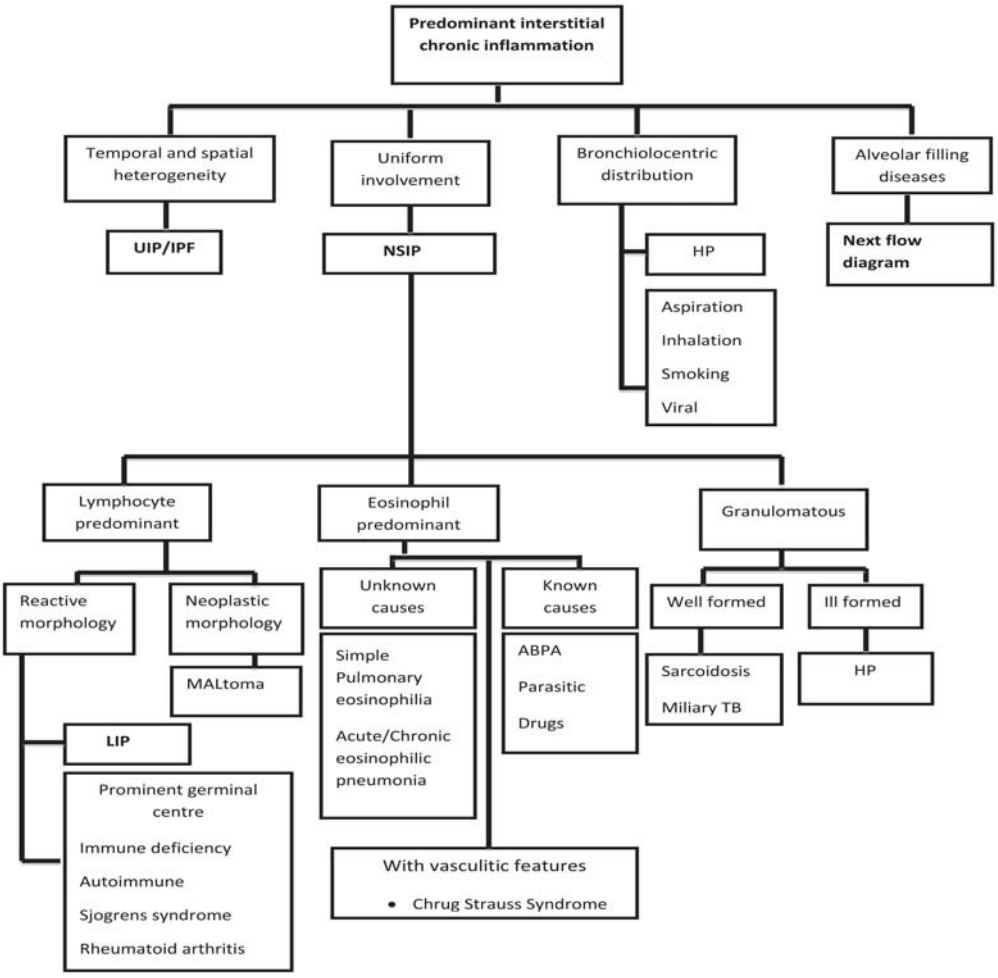

Figure 7. Flow diagram showing the histopathological approach in interstitial lung disease.

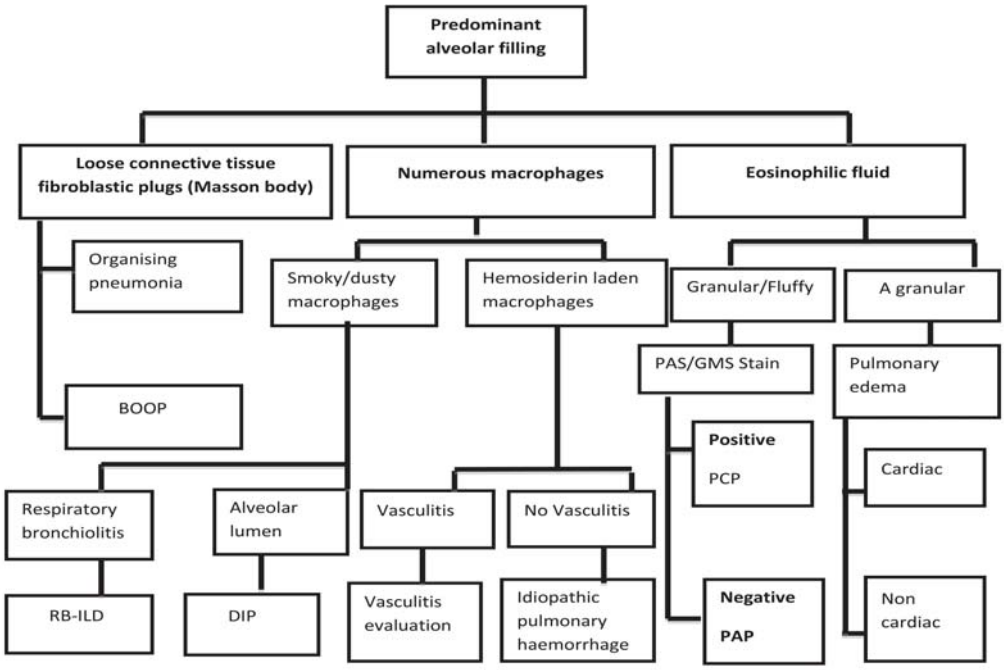

Figure 8. Flow diagram showing the histopathological approach in alveolar filling diseases.

Biomarkers

Many researchers have made an effort to identify the reliable biomarker to predict the prognosis in ILDs. But none of them are truly reliable. Serum lactate dehydrogenase activity may be of little help in predicting the prognosis in IPF patients. Sarcoidosis patients are monitored by serum angiotensin converting enzyme activity and serum interleukin-2 receptor levels. Other markers of help are Mucin-1 mucin, surfactant proteins A and D, matrix metalloproteinases.[3,5] However, none of them are recommended for routine monitoring and follow-up in patients with ILD.

Sub-clinical Cases in Elderly Individuals

Routine radiological screening of chest in elderly patients done for evaluating other diseases revealed presence of ILD-like findings in more than half of the patients without any clinical signs and symptoms of restrictive lung findings. Majority of these patients were found to be smokers. These findings were not seen in younger individuals. Lung findings in these cases will resolve completely after the cessation of smoking and it will worsen if the individual continue to smoke. Hence, these features should be kept in mind while reporting lung biopsy, especially in elderly individuals.

Treatment and Prognosis

Management decisions include improving the health status, improving exercise tolerance, preventing and treating the exacerbations and preventing the disease progression.[8] Administration of corticosteroids will improve the disease particularly in COP, eosinophilic pneumonia, sarcoidosis and cellular NSIP. Therapy will be less effective when there is significant fibrosis. Patients with IPF are treated with immunosuppressive and antifibrotic therapies.[8] Anti-inflammatory/immunosuppressive therapy has very limited role in the treatment of IPF. End-stage lung should be treated with lung transplantation.

Cause of Death

Common cause of death in ILD is due to respiratory causes, like acute exacerbation, progressive fibrosis, associated pneumonia and occurrence of cor-pulmonale. Non respiratory causes of death include cardiac failure and sepsis.

Conclusions

Interstitial lung disease and lung fibrosis are increasing public health problems. Proper clinical evaluation including detail history and HRCT scan is must before evaluating the biopsy specimen. Definitive identification and sub categorisation of ILDs are important as some ILDs have excellent prognosis and completely curable where as IPF has bad prognosis and it is difficult to treat. Multi-disciplinary team approach is must in all individual cases as non-specific histopathological diagnosis can become a specific diagnosis on discussion.

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