Classification of Interstitial Lung Disease

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ABSTRACT

Interstitial lung diseases, also known as diffuse parenchymal lung diseases (DPLD), are a group of disorders involving the distal lung parenchyma. Diffuse parenchymal lung diseases are classified into four main groups, of which idiopathic interstitial pneumonias (IIP) are an important group of diseases. The terminology of idiopathic interstitial pneumonia is often confusing and it is called idiopathic pulmonary fibrosis (IPF) in the United States, cryptogenic fibrosing alveolitis (CFA) in the United Kingdom or idiopathic interstitial pneumonia in Japan. The landmark classification of chronic interstitial pneumonia was proposed by Leibow and Carrington in 1969. The new classification proposed by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) has seven histological patterns: (i) usual interstitial pneumonia (UIP); (ii) non-specific interstitial pneumonia (NSIP); (iii) organizing pneumonia (OP); (iv) diffuse alveolar damage (DAD); (v) respiratory bronchiolitis (RB); (vi) desquamative interstitial pneumonia (DIP) and (vii) lymphoid interstitial pneumonia (LIP). The histological pattern of usual interstitial pneumonia is now reserved for the entity that is described as idiopathic interstitial pneumonia or cryptogenic fibrosing alveolitis. Idiopathic pulmonary fibrosis or cryptogenic fibrosing alveolitis is a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs in which a surgical lung biopsy shows a histological pattern of UIP. All other patterns proposed by the ATS/ERS are considered as separate entities.

INTRODUCTION

Interstitial lung diseases, also known as diffuse parenchymal lung diseases (DPLD) are a group of disorders involving the distal lung parenchyma.[1,2] Hamman and Rich in 1944 described several cases of "diffuse interstitial fibrosis of the lungs" which were rapidly progressive and fatal within a few weeks or months.[3] Many cases of diffuse pulmonary fibrosis with a chronic course were then described. These cases were thought to be the chronic stage of Hamman–Rich syndrome and were termed as "idiopathic pulmonary fibrosis". Subsequent studies had shown that Hamman–Rich syndrome had no chronic stage and the condition similar to this is now termed as acute interstitial pneumonia (AIP). There are more than 200 diseases with lung interstitial involvement with similar clinical, physiologic and radiographic manifestations.[4,5] The important causes/categories of interstitial lung diseases are listed in Table 1.[4] These disorders affect not only the interstitium, but also the airspaces, peripheral airways and vessels along with their respective epithelial and endothelial linings. Diffuse parenchymal lung diseases (DPLD) are classified into four groups:[6] (1) DPLD of known causes; (2) idiopathic interstitial pneumonias (IIP); (3) granulomatous DPLD and (4) DPLD with well defined clinicopathologic features (Table 2).

IDIOPATHIC INTERSTITIAL PNEUMONIAS

The terminology of idiopathic interstitial pneumonias (IIP) varies from country to country and is often confusing. It is called idiopathic pulmonary fibrosis (IPF) in the United States,[7] cryptogenic fibrosing alveolitis (CFA) in the United Kingdom[8] or idiopathic interstitial pneumonia in Japan.[9] In our country, it is termed either as IPF or CFA.

The landmark classification of chronic interstitial pneumonia was proposed by Leibow and Carrington in 1969.[10] They described five types of chronic interstitial pneumonias: (i) usual interstitial pneumonia (UIP), (ii) bronchiolitis obliterans with interstitial pneumonia (BIP), (iii) desquamative interstitial pneumonia (DIP), (iv) lymphoid interstitial pneumonia (LIP) and (v) giant cell interstitial pneumonia (GIP). Subsequently, Katzenstein[11] and Muller and Colby[12] provided classifications that retained UIP and DIP as distinct entities and added new entities such as respiratory bronchiolitis associated interstitial lung disease (RB–ILD), bronchiolitis obliterance organizing pneumonia (BOOP), acute interstitial pneumonia (AIP), and non-specific interstitial pneumonia (NSIP). The terms GIP and LIP were omitted from their classifications because GIP was found to be associated with hard metal pneumoconiosis and LIP was found to develop into

Table 1: Potential Causes/Categories of Interstitial Lung Disease

- Inhaled Agents
- Inorganic:
  - Silica
  - Asbestos
  - Beryllium
- Organic:
  - Animal/bird antigens
  - Farm antigens
- **Drug-Induced**
- Antibiotics
- Antiarrhythmics
- Anti-inflammatory agents
- Chemotherapeutic agents
- Antidepressants
- Radiation
- Oxygen
- **Connective Tissue Disease**
- Scleroderma
- Polymyositis/dermatomyositis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease
- Ankylosing spondylitis
- Primary Sjogren's syndrome
- Behcet's syndrome
- **Infections**
- Atypical pneumonias
- *Pneumocystis carinii pneumonia*
- Tuberculosis
- **Idiopathic**
- Sarcoidosis
- Eosinophilic granuloma
- Bronchiolitis obliterans organizing pneumonia
- Lymphocytic interstitial pneumonia
- Lymphangioleiomyomatosis
- Usual interstitial pneumonia
- Nonspecific interstitial pneumonia
- Desquamative interstitial pneumonia
- Respiratory bronchiolitis with interstitial lung disease
- Acute interstitial pneumonia
- **Malignant**
- Lymphangitic carcinomatosis
- Bronchoalveolar cell carcinoma

lymphomas. Classifications of idiopathic interstitial pneumonias by these investigators are presented in Table 3.

In order to avoid confusion in the terminology of IIPs, a new comprehensive clinical-radiographic and pathologic classification is provided by the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[6] The classification proposed by the ATS/ERS has seven histological patterns: (i) usual interstitial pneumonia (UIP); (ii) non-specific interstitial pneumonia (NSIP); (iii) organizing pneumonia (OP); (iv) diffuse alveolar damage (DAD); (v) respiratory bronchiolitis (RB); (vi) desquamative interstitial pneumonia (DIP) and (vii) lymphoid interstitial pneumonia (LIP). The histological patterns that conform to the final clinico-radiologic-pathologic diagnosis are provided in Table 4. The term UIP is generally reserved for

Table 2: Diffuse Parenchymal Lung Diseases (DPLD)

1. DPLD of known cause (eg: drugs, associated with collagen vascular diseases, environmental exposures etc.)
2. Idiopathic interstitial pneumonias
   a. Idiopathic pulmonary fibrosis (Histological pattern: Usual Interstitial pneumonia-UIP)
   b. Interstitial pneumonias other than IPF
      i. Non-specific interstitial pneumonia (Provisional) (NSIP)
      ii. Cryptogenic organizing pneumonia (COP)
      iii. Respiratory bronchiolitis interstitial lung disease (RB-ILD)
      iv. Desquamative interstitial pneumonia (DIP)
      v. Lymphoid interstitial pneumonia (LIP)
      vi. Acute interstitial pneumonia (AIP)
3. Granulomatous DPLD (e.g.: Sarcoidosis)
4. Other forms of DPLD (e.g.: lymphangioleiomyomatosis, pulmonary Langerhan's histiocytosis, pulmonary alveolar proteinosis, eosinophilic pneumonia etc.).

Table 3: Previous classifications of idiopathic interstitial pneumonia

I. Classification by Leibow and Carrington[10]
   i. Usual interstitial pneumonia
   ii. Desquamative interstitial pneumonia
   iii. Bronchiolitis obliterans interstitial pneumonia
   iv. Lymphoid interstitial pneumonia
   v. Giant cell interstitial pneumonia

II. Classification by Katzenstein[11]
   i. Usual interstitial pneumonia
   ii. Desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease.
   iii. Acute interstitial pneumonia
   iv. Non-specific interstitial pneumonia

III. Classification by Muller and Colby[12]
   i. Usual interstitial pneumonia
   ii. Desquamative interstitial pneumonia
   iii. Bronchiolitis obliterans organizing pneumonia
   iv. Acute interstitial pneumonia
   v. Non-Specific interstitial pneumonia

Table 4: New Classification of Idiopathic Interstitial Pneumonias*

Histologic pattern	Clinical-Radiologic-Pathologic diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/ cryptogenic fibrosing alveolitis
Non-specific interstitial pneumonia	Non-specific interstitial pneumonia (provisional)
Organising pneumonia	Cryptogenic organising pneumonia
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia	Lymphoid interstitial pneumonia

(*ATS/ERS International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonia. *Am J Respir Crit Care Med* 2002; 165:277-304)

those patients in whom the lesion is idiopathic which is currently referred to as either IPF or CFA. Idiopathic pulmonary fibrosis or

Table 5: Pathologic Features of the Chronic Idiopathic Interstitial Pneumonias

Features	UIP	NSIP	COP	RB-ILD	DIP	LIP
Temporal appearance	Variegated	Uniform	Uniform	Uniform	Uniform	Uniform
Spatial appearance	Patchy	Uniform	Patchy	Patchy	Uniform	Patchy
Interstitial inflammation	Scant	Prominent	Mild	Mild-	Rare Moderate	Alveolar septal T-Cells
Collagen fibrosis	Always	Variable, Patchy	Occasional diffuse	Variable,	Rare peribronchiolar	Rare
Fibroblast proliferation	Prominent	Rare,	No Diffuse	No	No	No
Organizing Pneumonitis	No	Variable	Yes	No	No	No
Microscopic Honeycombing	Yes	Rare	Rare	No	No	No
Macrophage accumulation	Variable	Variable	No	Peribronchiolar,	Alveolar, pigmented	No non-pigmented

CFA is therefore a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs in which a surgical lung biopsy shows a histological pattern of UIP.[13] All other histopathologic patterns (DIP, NSIP, RB-ILD, AIP, COP, and LIP) are considered separate entities and they should not be included in the group of patients with IPF. Pathologic features of the chronic idiopathic interstitial pneumonias are given in Table 5.[14]

USUAL INTERSTITIAL PNEUMONIA (UIP)

This is characterized by marked fibrosis with insidious onset, slow progression and poor prognosis. There is patchy involvement with areas of marked fibrosis, and areas of less fibrosis and more inflammation. It often progresses to end-stage disease or "honey-comb" lung. The distribution is frequently subpleural and paraseptal. It has a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis and honeycomb change. The interstitial inflammation consists of alveolar septal infiltrate of lymphocytes, plasma cells and histiocytes and is associated with hyperplasia of Type II pneumocytes. Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change.[6]

NON-SPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

Non-specific interstitial pneumonia is characterized by the uniform appearance of interstitial inflammation mainly with lymphocytes, and rarely with plasma cells in all areas of the biopsy specimen. Two patterns of NSIP are described: cellular pattern and fibrosing pattern. Mild to moderate interstitial chronic inflammation with Type II pneumocyte hyperplasia is seen in cellular pattern. Fibrosing pattern can lead to dense or loose interstitial fibrosis that lacks the temporal patchy features of UIP. The lung architecture in fibrosing pattern may appear lost on examination of hematoxylin and eosin stained sections, but there is preservation of elastic stains.[6]

CRYPTOGENIC ORGANISING PNEUMONIA (COP)

Intraluminal organizing pneumonia in the distal air-spaces (bronchioles, alveolar ducts and alveoli) is the characteristic finding in cryptogenic organizing pneumonia. There is mild interstitial inflammation with patchy distribution and preserved lung architecture. The same entity is also referred to as bronchiolitis obliterans organizing pneumonia (BOOP). However, the term cryptogenic organizing pneumonia is preferred.[6]

RESPIRATORY BRONCHIOLITIS ASSOCIATED INTERSTITIAL LUNG DISEASE (RB-ILD)

Respiratory bronchiolitis associated interstitial lung disease is found in cigarette smokers. There is focal bronchiolar-alveolar macrophage accumulation and the macrophages are usually pigmented. The macrophages are seen within first- and second-order respiratory bronchioles. There is only mild bronchiolar fibrosis and chronic inflammation. It is rarely symptomatic and is associated with minor small airway dysfunction. It has been suggested that desquamative interstitial pneumonia is a more extensive form of RB-ILD.[11]

DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

There is only mild interstitial fibrosis and the macrophages are uniformly distributed predominantly in the alveoli. The alveolar macrophages are non-pigmented as opposed to the pigmented macrophages seen in RB-ILD. Many consider that it represents the end of a spectrum of RB-ILD because of its similar pathology and association with cigarette smoke, both active and passive.[15]

LYMPHOID INTERSTITIAL PNEUMONIA (LIP)

There is diffuse interstitial infiltration of T lymphocytes which may be grouped into germinal centers. There is predominant alveolar septal distribution.

ACUTE INTERSTITIAL PNEUMONIA (AIP)

The original description of Hamman-Rich syndrome falls in this category and it is a rare fulminant form of lung injury presenting acutely usually in a previously healthy individual. There is diffuse alveolar damage (DAD) and this is indistinguishable from acute respiratory distress syndrome (ARDS) caused by sepsis and shock. The term AIP is reserved for cases of unknown cause. Histological features reveal exudative, proliferative and/or fibrotic phases of diffuse alveolar damage. There may be patchy or diffuse airspace organization. Focal or diffuse hyaline membranes may also be seen.

A small subset of patients with interstitial pneumonia remains unclassified even after extensive clinical radiological and/or pathologic evaluation.[6]

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