Idiopathic Interstitial Pneumonia: The Importance of Histologic Pattern Analysis

Çiğdem (Ataizi) Çelikel
Marmara University School of Medicine Department of Pathology

Abstract

Idiopathic interstitial pneumonia is a subset of diffuse interstitial lung diseases. Idiopathic interstitial pneumonia is a heterogenous disorder consisting of several clinicopathological entities with differing histopathological patterns. Due to the fact that all of these entities have different clinical course, response to therapy, and prognosis, distinquishing these hisologic patterns are mandatory for the accurate determination of prognosis and optimal management in an individual patient. This review mainly concerns the pathologic descriptions of individual patterns of idiopathic interstitial pneumonia and the important features in the differential diagnosis of these patterns.

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Diffuse interstitial lung disease (ILD) is usually used in a clinicoradiological context to refer to conditions that cause diffuse parenchymal lung infiltrates, restrictive pulmonary dysfunction and impaired gas exchange(1). ILD accounts for perhaps the greatest number of difficulties in diagnostic pathology of lung diseases(2). This reflects, in part, the large number of etiologically diverse conditions included under this heading and the fact that certain morphologically similar conditions can be seperated into distinct categories only after correlation of the pathologic changes with the clinical and radiographic findings(2). But, unfortunately, clinician, radiologist, and pathologist all have different points of view and frames of reference of ILDs(2).

Idiopathic interstitial pneumonia (IIP) is a subset of diffuse ILDs which accounts for about 25 to 30 % of the cases(3). IIP represents a heterogenous group of acute, subacute, and chronic ILD with no known etiology characterized by relatively nonspesific histologic findings with variable amounts of inflammation and fibrosis(4). The clinical term idiopathic pulmonary fibrosis (IPF), which became widespread in North America during 1970's, has been traditionally used for idiopathic cases of interstitial pneumonias(5). At the same period of time, in Great Britain, the term cryptogenic fibrosing alveolitis (CFA)

Correspondence: *Çiğdem Ataizi Çelikel*
MARMARA Üniversitesi Tıp Fakültesi
Hastanesi Patoloji Anabilim Dalı, 81190
Altunizade / İSTANBUL

was established, and most investigators have considered CFA and IPF as different terms of the same entity(6). However, in recent studies, the histologic patterns have been more carefully defined and these studies suggested that patients previously diagnosed to have IPF (CFA) display a variety of histologic patterns that are associated with varying responses to therapy and prognosis(2,7,8). Currently, the use of the clinical term IPF has become more restricted and it is recommended to be used only for patients with usual interstitial pneumonia (UIP) pattern of pulmonary fibrosis(2,8).

IIPs are histologically characterized by the expansion of the interstitial compartment (lung parencyma localized between the epithelial and endothelial basement membranes in the alveolar septa) by an infiltrate of inflammatory cells which is sometimes accompanied by fibrosis, either in the form of abnormal collagen deposition or a proliferation of fibroblasts capable of collagen synthesis (2). Liebow was the first who recognized different morphologic variants of interstitial pneumonia (Table – 1) (9). He classified chronic IIPs as 1)UIP, 2) desquamative interstitial pneumonia (DIP), 3) bronchiolitis obliterans with classical interstitial pneumonia (BIP), 4) lymphoid interstitial pneumonia (LIP), and 5) giant cell interstitial pneumonia. He emphasized that each of these categories represented patterns of tissue response, and that none should be considered "pathognomonic for a spesific factor". And also, he underlined the fact that precise histologic classification of interstitial pneumonia provides "clues both to the etiology and pathogenesis and certainly to natural history and prognosis" (9). A number of observations have been made over the intervening decade which have limited the utility of Liebow's classification sheme (2,8). LIP is pathogenetically heterogenous group that includes small lymphocytic lymphomas, chronic lymphocytic leukemias, and lymphoid hyperplasia as well as inflammatory conditions (10). Patients with GIP are also a heterogenous group and most adults with this lesion appear to have a form of hard metal pneumoconiosis (10). Due to the fact that they are not idiopathic, these two disorders have been dropped from the overall group IIPs (10,11,12). BIP in Liebow's classification is totally abondened because this category comprised cases of interstitial pneumonia with BOOP pattern besides the cases of primary BOOP both of which have different prognosis limiting the utility of classification (13). During the past 10 to 15 years, the entities of nonspesific interstitial pneumonia (NSIP), AIP and BOOP have been added to the group of IIPs, although there is still ongoing debate on the inclusion of BOOP (7,14,15). Current pathologic classification of IIP patterns are given in Table -2 and major pathological and clinical features of the IIPs are contrasted in Table -3 and Table -4.

AIP is an acute, fulminant form of IIP that was initially described by Hamman and Rich in 1994, and later

Table 1. Liebow classification of interstitial pneumonia - 1975 (9)

Usual interstitial pneumonia (UIP)
Bronchiolitis obliterans with usual interstitial pneumonia (BIP)
Desquamative interstitial pneumonia (DIP)
Lymphoid interstitial pneumonia (LIP)
Giant-cell interstitial pneumonia (GIP)

Table 2. Revised classifications of histologic patterns of idiopathic interstitial pneumonias

Müller & Colby (12)	Katzenstein, 2000 (23)	Travis. 2000 (11)
Usual interstitial pneumonia	Usual interstitial pneumonia	Usual interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Bronchiolitis obliterans organizing pneumonia (BOOP)		Bronchiolitis obliterans organizing pneumonia (BOOP)
Acute interstitial pneumonia	Acute interstitial pneumonia	Acute interstitial pneumonia
Nonspesific interstitial pneumonia (NSIP)	Nonspesific interstitial pneumonia	Nonspesific interstitial pneumonia (NSIP)
	(NSIP)	Cellular
		Fibrosing

Table 3. Clinical features of Idiopathic Interstitial Pneumonias [2,7,11,18,24,26,28,29,30,31]

Features	AIP	BOOP	DIP	RBILD	UIP	NSIP-cellular	NSIP-fibrosing
Mean age, year	49	55	42	36	57	53	48
Occurrence in children	rare	rare	rare	no	no	occasional	occasional
Cigarette smoking	not related	not related	100 %	100 %	77 %	88 %	64 %
Onset	acute	subacute	insidious	insidious	insidious	subacute, insidious	subacute, insidious
Mortality rate (mean survival)	62 % (1-2 months)	< 5 %	27 % (12 year)	0 %	68 % (5-6 year)	0 % (18 months)	11 %
Response to steroids	poor	good	good	good	poor	good	good
Complete recovery	yes	yes	yes	yes	no	yes	yes

Abbreviations: AIP= Acute interstitial pneumonia, BOOP= Bronchiolitis obliterans organazing pneumonia, DIP= Desquamative interstitial pneumonia, RB-ILD= Respiratory bronchiolitis associated interstitial lung disease, UIP= Usual interstitial pneumonia, NSIP= Nonspesific interstitial pneumonia.

considered to be the early stage of UIP. AIP is analogous to adult respiratory distress syndrome (ARDS), differing only in that it is not preceded by a catastropic event, that is idiopathic (16). Hamman - Rich disease and accelerated interstitial pneumonia are the other terms that have been proposed for this clinicopathological syndrome (17). Regardless of the term used, the important point is that AIP should be distinquished from the group of subacute and chronic interstitial pneumonias because of the marked differences in natural history (2,18). Histologically, AIP is identical to the organizing or proliferative stage of diffuse alveolar damage which is the pathologic counterpart of ARDS (16). It shares many histologic features of UIP, that is why these two patterns have been traditionally lumped together under the heading of UIP in previous clinical and pathology literature (17,19). The main finding in AIP is extensive interstitial fibroblast proliferation within an edematous-appearing stroma, different from UIP in which the fibrosis is mainly inactive and composed of collagen (8). In UIP there can be microscopic foci of fibroblastic proliferation (fibroblastic foci) which is histologically identical to AIP but focal in distribution (8). The difference between AIP and UIP is due to the fact that in AIP the acute injury is massive occurring during a single period of time, whereas in UIP the acute injury is focal recurring over many years (16,20,21). Ultrastructural studies of AIP cases have confirmed the presence of acute epithelial and endothelial damage (20,21). Because of the large area of lung injured in AIP, mortality rates are high, ranging from 50 to 88 %, with most deaths occurring within 1 to 2 months (18).

BOOP is a fibrosing lung disease that differs from the other IIPs in that the fibroblast proliferation is predominantly intraluminal rather than interstitial (22). This is why Katzenstein et al excludes BOOP from their new classification (23). However, in routine practice patients with BOOP are often includede in the clinical and histologic differential diagnosis of IIPs, that is the reason why Colby (12) and Travis (11) categorizes BOOP as a subacute form of IIPs. Idiopathic BOOP, that is cryptogenic organizing pneumonia, affects males and females equally and occurs mainly in the adults with a peak incidence in the 6th decade (24). Most patients have a subacute illness and roentgenograms typically show patchy airspace opacities (24,25,26). The prognosis is excellent and steroids appear to be beneficial (27,28). Pathologically BOOP is distinguished by the presence of immature-appearing plugs of fibroblastic tissue within respiratory bronchioles, alveolar ducts, and peribronchiolar alveolar spaces. The alveolar septa within the areas of intraluminal fibrosis are usually thickened and contain an infiltrate of mononuclear inflammatory cells. The alveolar spaces contain foamy alveolar macrophageswhich reflects the presence of proximal airway obstruction (22,25,27). The different clinical manifestations and prognosis of AIP and BOOP relates to the peribronchiolar localization of the epithelial damage in BOOP compared with more diffuse involvement in AIP (22,25).

UIP is the most common pattern of IIPs acounting approximately 60 % of the cases. Patients typically present in the 5th or 6th decade complaining of the insidious onset of dyspnea and nonproductive cough

Table 4. Pathologic features of Idiopathic Interstitial Pneumonias

Features	AIP	BOOP	DIP	RBILD	UIP	NSIP-cellular	NSIP-fibrosing
Distribution	Diffuse	centrilobular	diffuse	mild, focal	patchy/subpleural	diffuse	Diffuse/periacinar
Temporal appearance	homogenous	homogenous	homogenous	homogenous	variegated	homogenous	homogenous
Septal inflammation	scant	scant	scant	none	scant, patchy	prominent	scant, diffuse
Collagen fibrosis	absent	scant	variable, diffuse	scant, patchy	characteristic, patchy	absent	diffuse
Fibroblast proliferation	diffuse,	diffuse,	absent	absent	fibroblastic	absent	rare
BOOP pattern	interstitial	intraluminal			foci prominent		fibroblastic foci
	absent	characteristic	absent	absent	absent	occasional	occasional, focal
Honeycombing	Absent	absent	absent	absent	characteristic	absent	rare
alveolar macrophage	Absent	absent	diffuse	peribronchiolar	occasional	occasional	occasional
Hyaline membranes	occasional	absent	absent	absent	absent	absent	Absent

Abbreviations: AIP= Acute interstitial pneumonia, BOOP= Bronchiolitis obliterans organazing pneumonia, DIP= Desquamative interstitial pneumonia, UIP= Usual interstitial pneumonia, NSIP= Nonspesific interstitial pneumonia.

(29,30). The disease usually follows a relentlessly progressive course with most patients dying of respiratory failure within 5 to 10 years of diagnosis (8,29,31). There are no reliable histologic predictors of outcome, although the degree of fibrosis on open lung biopsies does correlate loosely with the degree of functional and radiographic impairment (2). In a recent study by Travis et al, honeycombing and interstitial inflammation involving 60 % or more of the lung biopsy and presence of intrapleural fat correlated with a poor prognosis (11). UIP has a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change which comprises the major point for differential diagnosis (8). The fibrotic zones are composed mainly of dense acellular collagen, although scattered foci of fibroblast proliferation may also be seen (2,8,32). Areas of honeycomb change are composed of cystic fibrotic ir spaces which are frequently lined by bronchiolar epithelium and filled with mucin (2,8,11). Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change, a process referred to in the past as "muscular cirrhosis" (11).

DIP is a distinct pattern that differs substantially from UIP. It typically affects cigarette smokers in their fourth or fifth decades of life (29). Corticosteroids are beneficial in the majority of patients and the overall survival is about 70 % after 10 years (29). DIF differs histologically from UIP in that the changes tend to be much more uniform at low magnification and lack the variegated appearance typical of UIP. The alveolar septa are thickened by a sparse inflammatory infiltrate that often includes plasma cells and occasional eosinophils, and they are lined by plump cuboidal pneumocytes. The most striking feature is the presence of numerous mononuclear cells within most of the distal air spaces (8,11,23). These changes overlap with those described in respiratory bronchiolitis, a lesion of cigarette smokers in which the respiratory bronchioles and adjacent alveolar spaces are filled with lightly pigmented macrophages (33,34). Respiratory bronchiolitis can cause clinically detectable interstitial lung disease in some individuals, a condition referred to as respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), and there is some evidence to suggest that DIP and RB-ILD are related entities (33).

Table 5. Histologic patterns and etiologic possibilities in the differential diagnosis of idiopathic interstitial pneumonias		
	Histologic patterns	**Possible etiologies**
DIP pattern	UIP, NSIP-cellular-fibrozing, RB, RB-ILD	Cigarette smoking
	Eosinophilic pneumonia	Pneumoconiosis (especially asbestosis)
	Chronic hemorrhage, hemosiderosis	
	Veno-occlusive disease	
UIP pattern	AIP, DIP, NSIP-fibrozing	Collagen vascular disease
	Hypersensitivity pneumonitis pattern	Drug-induced pneumonitis
	Langerhans cell histiocytosis	Radiation pneumonitis
	Diffuse Alveolar Damage pattern	Pneumoconiosis (especially asbestosis) Hermanski-Pudlak syndrome
NSIP, cellular pattern	NSIP-fibrozing pattern, BOOP, AIP	Collagen vascular disease
	Diffuse Alveolar Damage pattern	Drug-induced pneumonitis
	Hypersensitivity pneumonitis pattern	Hypersensitivity pneumonitis
	Lymphocytic Interstitial Pneumonia pattern	Infection, Immunodeficiency, HIV infection
NSIP-fibrozing pattern	UIP, BOOP, NSIP, cellular pattern	Collagen vascular disease
	Fibrotic phase of other interstitial disorders	Hypersensitivity pneumonitis
	(e.g., Hypersensitivity pneumonitis pattern,	Drug-induced pneumonitis
	Histiocytosis X, DIP pattern, DAD)	Infection

Abbreviations: AIP= Acute interstitial pneumonia, BOOP= Bronchiolitis obliterans organazing pneumonia, DIP= Desquamative interstitial pneumonia, RB= respiratuar bronchiolitis, ILD= interstitial lung disease, DAD= diffuse alveolar damage, UIP= Usual interstitial pneumonia, NSIP= Nonspesific interstitial pneumonia.

The term NSIP has been proposed for cases that do not fit the histopathologic criteria for the other IIPs, namely DIP, UIP, BOOP, and AIP. However in 1994, Katzenstein and Fiorelli defined NSIP as a distinct pathologic pattern which has important clinical implications considering mainly the clinical outcome of the patients (7). Since 1994, additional reports concerning NSIP showed that NSIP cases can be dividede into cellular and fibrotic variants (4,7,11,23,29,30). All reported series have confirmed a better prognosis for NSIP than for UIP, but when NSIP cases are grouped into those with and without fibrosis, deaths have been reported only in the fibrotic group, ranging from 13 to 41 % (7,11,29,30). Histologically NSIP is a uniform-appearing, cellular interstitial pneumonia with or without fibrosis (7,11,29). The process may be patchy with intervening areas of normal lung, but in contrast to UIP the changes are temporally uniform, that is the entire process reflects changes occurring at a single time, either in the past or currently ongoing (11,30). UIP causes the major difficulty in the differential diagnosis of NSIP-fibrosing pattern. The most beneficial features which are used in favor of UIP are diffuse fibroblastic foci, subpleural distribution, and temporal heterogenity (11). Although in NSIP, fibrosis may be active as in AIP, hyaline membranes, thrombosis, and architectural derangement characteristic of AIP are not seen (11). Pleural fibrosis and metaplastic bone formation were found to have prognostic value in NSIP (11).

In an appropriate clinical setting, the diagnosis of IIP could be suspected on the basis of history, physical examination, chest radiography, and pulmonary function tests (36). High-resolution computed tomography (HRCT) of the chest may provide additional clues in the diagnosis and also in identifying the histopathologic lesion (36-39). However, HRCT has limited value especially in the diagnosis of IIPs with NSIP pattern with the accuracy being 9 % (38). The relatively low sensitivity and specificity of the diagnosis of IIP other than UIP has been also emphasized by Raglue et al (36). In order to identify the histologic lesion in these cases, lung biopsy is indicated (4,36). In lung biopsies, pattern analysis ccording to the distribution, intensity, and nature of

the interstitial fibrosis and inflammation is the initial step in the differential diagnosis of IIPs (2,8,11). But as Liebow mentioned, the pattern of tissue response is not specific for a certain disease and it can be encountered in other types of ILDs (9).

The exclusion of all the etiologic possibilities with individual histologic pattern of interstitial pneumonias that are summarized in Table-5 would ultimately determine the process as idiopathic. It should be kept in mind that to diagnose these entities wedge biopsy of the lung is required which can only be supplied by thoracoscopy or thoracotomy and that small biopsies such as transbronchial biopsies cannot provide sufficient tissue (4,36). Bronchoalveolar lavage (BAL) has limited diagnostic value in the diagnosis of subtypes of IIP, but could be used in patients who refuses lung biopsy as an exclusionary test (4,40).

References

1. DeRemee RA. Diffuse interstitial pulmonary disease from the perspective of the clinician. Chest 1987;92:1068-1073.
2. Ryu JH, Colby TV, Hartman TE. Idiopathic pulmonary fibrosis: current concepts. Mayo Clin Proc 1998;73:1085-1101.
3. Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung disease. Am J Respir Crit Care Med 1994:150:967-972.
4. Myers JL. NSIP, UIP, and the ABCs of idiopathic interstitial pneumonias. Eur Respir J 1998;12:1003-1004.
5. Crystal RG, Bitterman PB, Rennard SI, et al. İnterstitial lung diseases of unknown cause: disorders characterized by chronic inflammation of the lower respiratory tract. N Engl J Med 1984;310:154-166.
6. Stack BH, Choo-Kang YF, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. Thorax 1972;27:535-542.
7. Katzenstein A-LA, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis: histologic features and clinical significance. Am J Surg Pathol 1994;18(2):136-147.
8. Katzenstein A-LA, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998;157:1301-1315.
9. Liebow A. Definition and classification of interstitial pneumonias in human pathology. Prog Respir Res 1975;8:1-33.
10. Katzenstein A-LA. Katzenstein and Askin's surgical pathology of non-neoplastic lung disease. W.B. Saunders, Philadelphia;1997.
11. Travis WD, Matsui K, Moss J, et al. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns. Survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 2000; 24(1):19-33.
12. Müller NL, Colby TV. Idiopathic interstitial pneumonias: high resolution CT and histological findings. Radiographics 1996;16:1009-10033.
13. Myers JL, Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and panbronchiolitis. Clin Chest Med 1993;14:611-622.
14. Askin FB. Acute interstitial pneumonia. Radiology 1993;188(3):620-621.
15. Epler GR. Bronchiolitis obliterans organizing pneumonia: definition and clinical features. Chest 1992;102(suppl):2S-6S.
16. Katzenstein A-LA, Myers JL, Mazur M. AIP A clinicopathologic, ultrastructural, and cell kinetic study. Am J Surg Pathol 1986;10.256-267.
17. Shale DJ. The adult respiratory distress syndrome –20 years on. Thorax 1987;42:641-646.
18. Fowler AA, Hamman RF, Zerbe GE. ARDS: prognosis after onset. Am Rew Respir Dis 1985; 132:472.
19. Olson J, Colby TV, Ellott G. Hamman-Rich syndrome revisited. Mayo Clin Proc 1990;65:1538-1548.
20. Katzenstein A-LA. Pathogenesis of fibrosis in interstitial pneumonia. An electronmicroscopic study. Human Pathol 1985;16:1015-1024.
21. Kuhn C, Boldt J, King TE, et al. An immunohistochemical study of architectural remodeling and connective tissue synthesis in pulmonary fibrosis. Am Rev Respir Dis 1989;140:1693-1703.
22. Colby TV. Pathological aspects of bronchiolitis obliterans organizing pneumonia. Chest 1992;102(suppl):38S-43S.
23. Katzenstein A-LA, Myers JL. Nonspecific interstitial pneumonia and the other idiopathic interstitial pneumonias: classification and diagnostic criteria. Am J Surg Pathol 2000; 24(1):1-3.
24. Cordier JF. Cryptogenic organizing pneumonia. Clin Chest Med 1993;14:677-692.
25. Epler GR, Colby TV. The spectrum of bronchiolitis obliterans. Chest 1983;83(2):161-162.
26. Epstein DM, Bennett MR. Bronchiolitis obliterans organizing pneumonia with migratory pulmonary infiltrates. AJR 1992;158:515-517.
27. Epler GR, Colby TV, McLoud TC, et al. Bronchiolitis obliterans organizing pneumonia. N Engl J Med 1985;17:152-158.
28. Corrin B. Bronchiolitis obliterans organizing pneumonia, a British view. Chest 1992;102(suppl):7S.
29. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157:199-203.
30. Nagai S, Kitaichi M, Itoh H, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998;12:1010-1019.
31- Daniil ZD, Gilchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1999;160:899-905.
32. Colby TV, Swenson SJ. Anatomic distribution of histopathologic patterns in diffuse lung disease: correlation with HRCT. J Thorac Imaging 1996;11:1-26.
33. Heyneman LE, Ward S, Lynch DA, et al. Respiratory bronchiolitis, Respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? AJR 1999;173:1617-1622.
34. Hartman TE, Primach SL, Swenson SJ, et al. Desquamative interstitial pneumonia: thin section CT findings in 22 patients. Radiology 1993;187:787-790.
35. Cottin V, Donsbeck A-V, Revel D, et al. Nonspecific interstitial pneumonia: individualization of a clinicopathologic entity in a series of 12 patients. Am J Respir Crit Care Med 1998;158:1286-1293.
36. Joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS). Idiopathic Pulmonary Fibrosis: diagnosis and treatment (International concensus statement). Am J Respir Crit Care Med 2000:161:646-664.
37. Raghu G, Mageto YN, Lockhart D, et al. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease. Chest 1999;116:1168-1174.
38. Swenson SJ, Aughenbaugh GL, Myers JL. Diffuse lung disease:diagnostic accuracy of CT in patients undergoing surgical biopsy of the lung. Radiology 1997;205:229-234.
39. Johkoh T, Müller NL, Cartier Y, et al. Idiopathic interstitial Pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology 1999;211:555-560.
40. Du Bois RM, Wells AU. Cryptogenic fibrosing alveolitis (Idiopathic Pulmonary Fibrosis). In Grassi C, Brambilla C, Costabel U, Eds. Pulmonary Diseases. McGraw-Hill, Clinical Medicine Series;1999,p211-222.