Radiologic Findings of Idiopathic Interstitial Pneumonia

□종 설□

Jai Soung Park, M.D.
Department of Radiology, Soonchunhyang University School of Medicine

특발성 간질성 폐렴의 영상 소견

순천향대학교 의과대학 방사선과학교실
박 재 성

특발성 간질성 폐렴은 폐포보다는 폐간질을 주로 침범하는 미만성 염증성 섬유화 병변으로 병변의 분류에 임상적 및 병리학적으로 많은 혼동과 변화를 겪어왔다. 최근에는 미국흉부학회와 유럽호흡기학회의 공동 모임에서 이 질환 군에 해당되는 모든 임상과들이 모여서 7가지의 병변으로 재분류 하였는데, 이는 Idiopathic pulmonary fibrosis, Nonspecific interstitial pneumonia, Cryptogenic organizing pneumonia, Acute interstitial pneumonia, Respiratory bronchiolitis interstitial lung disease, Desquamative interstitial pneumonia, Lymphocytic interstitial pneumonia 등이다. 이에 저자는 최근 분류에 의한 특발성 간질성 폐렴의 7가지 병변을 영상 소견을 중심으로 기술하고자 한다.
(Tuberc Respir Dis 2005; 58: 330-343)

Despite the considerable progress in the classification of the idiopathic interstitial pneumonias (IIPs), the lack of an international standard has resulted in variable and confusing diagnostic criteria and terminology. The advent of high-resolution computed tomography (HRCT), the narrowed pathologic definition of usual interstitial pneumonia (UIP) and recognition of the prognostic importance of separating UIP from other IIP pattern have profoundly changed the approach to the IIPs. Idiopathic interstitial pneumonia (IIP) includes a group of nonneoplastic, noninfectious lung disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis. The term is somewhat descriptive and inaccurate, because not all diseases classified as being in this category are limited to the interstitium, nor is the etiology entirely idiopathic. However, most of the diseases have some degree of interstitial cellular infiltration and/or collagen deposition[1].

Address for correspondence : **Jai Soung Park, M.D.**
Department of Radiology Soonchunhyang University Bucheon Hospital 1174 Joong-dong, Wonmi-ku, Bucheon Kyunggi-do 420-853, Korea
Phone : 82-32-621-5851,3
Fax : 82-32-621-5874
E-mail : jspark@schbc.ac.kr

To overcome the lack of an international standard in the diagnostic criteria and terminology of IIPs, the consensus meeting sponsored by American Thoracic Society (ATS) and European Respiratory Society (ERS) was held and reported recently an international consensus statement. This statement recognized the following 7 clinco-radiologic-pathologic entities of IIPs and established uniform definition and criteria for the diagnosis of each of these IIPs[2] (Table 1). It is important to keep in mind that similar histological patterns characteristic of these disorders can be seen in association with a variety of etiologies and the final diagnosis should be rendered only after the pulmonologist, radiologist, and pathologist have reviewed all of the clinical, radiological, and pathological data obtained from the patient[2]. The word "pattern" should be added to the histopatholgic diagnosis to distinguish it from the clinico-radiologic-pathologic diagnosis[2].

HRCT is indicated for all but a small proportion of patients for whom a specific diagnosis is strongly suggested by the standard chest radiograph. The primary role of HRCT is to separate patients with typical findings of IPF/UIP from those with the less specific findings associated with other IIPs. HRCT

Table 1. Histologic and clinical classification of idiopathic interstitial pneumonias

Histologic Patterns	Clinical-Radiologic-Pathologic Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary Fibrosis / cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Organizing pneumonia	Cryptogenic organizing pneumonia
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphocytic interstitial pneumonia	Lymphocytic interstitial pneumonia

is also important in detecting clues to non-IIP disorders such as sarcoidosis, hypersensitivity pneumonitis, and eosinophilic pneumonia, and in selecting the appropriate site for the biopsy.

Idiopathic Pulmonary Fibrosis

The tem UIP and IPF have become more narrowly defined. According to the current definition, IPF is a distinctive type of chronic fibrosing intersititial pneumonia of unknown cause limited to the lungs and associated with a surgical lung biopsy showing a histologic pattern of UIP[3].

The patient's age at onset is usually greater than 50 years and IPF is slightly more common in male[4]. Onset of symptom is usually gradual, with dyspnea the most prominent and disabling symptom. In most patients, symptoms have been present for more than 6 months before presentation[4]. Most patients exhibit a restrictive pattern of ventilatory defect with a decreased in DLCo and resting hypoxemia. Median survival from time of diagnosis varies between 2.5 and 3.5 years[3,5,6]. Bronchoalveolar lavage fluid (BALF) contains an excess of neutrophils and there may also be a mild or moderate increased in the percentage of eosinophils[7,8]. Lymphocytosis is not a feature of UIP[3].

The UIP pattern is characterized by heterogeneity that includes patchy chronic inflammation (alveolitis), progressive injury (small aggregates of proliferating myofibroblasts and fibroblasts, termed "fibroblastic foci"), and fibrosis (dense collagen and honeycomb change)[10]. It has a heterogeneous appearance at low magnification. The histological changes affect the peripheral subpleural parenchyma most severely[10].

The common chest radiographic abnormality in patients with IPF is peripheral reticular opacity, most marked at the base, and often associated with honeycombing and lower lobe volume loss[11](Fig. 1A). UIP is characterized on CT by the presence of reticular opacities, often associated with traction bronchiectasis. Honeycombing and ground glass opacity is common(Fig. 1B and 1C). Architectural distortion is often prominent and lobar volume loss is seen with more advanced fibrosis. The distribution of UIP on CT is characteristically basal and peripheral, although often patchy[12,13]. On serial scans in treated patients, the areas of ground glass opacity regress, but more commonly progress to fibrosis with honeycombing[12](Fig. 2A and 2B). When ground glass opacity attenuation is associated with reticular lines, traction bronchiectasis or bronchiolectasis, it usually indicates histologic fibrosis[14]. Typical HRCT findings of UIP are found in about 50% of patients with biopsy-proven disease[15,16]. When the radiologic diagnosis of UIP is based on those typical HRCT findings, it is correct in more than 90% of cases[15,16].

Occasionally, patients with IPF develop a fulminant and often fatal acute exacerbation[17]. Patients who are biopsied during an accelerated phase of their illness may show a combination of UIP pattern and variety of acute lesions. These include infection, prominent organizing pneumonia, diffuse alveolar damage (DAD), and capillaritis. If no cause can be

determined, this may represent "accelerated decline of IPF" or "acute exacerbation of IPF"[17]. The HRCT findings consist of extensive multifocal, diffuse or, less commonly, peripheral ground glass opacity superimposed on a background of interstitial fibrosis[18] (Fig. 3A and 3B). The CT pattern of UIP due to IPF can be indistinguishable from that found in UIP due to asbestosis and to collagen vascular disease. Patients with chronic hypersensitivity pneumonitis, or with end-stage sarcoidosis, may uncommonly develop a CT pattern similar to that of UIP.

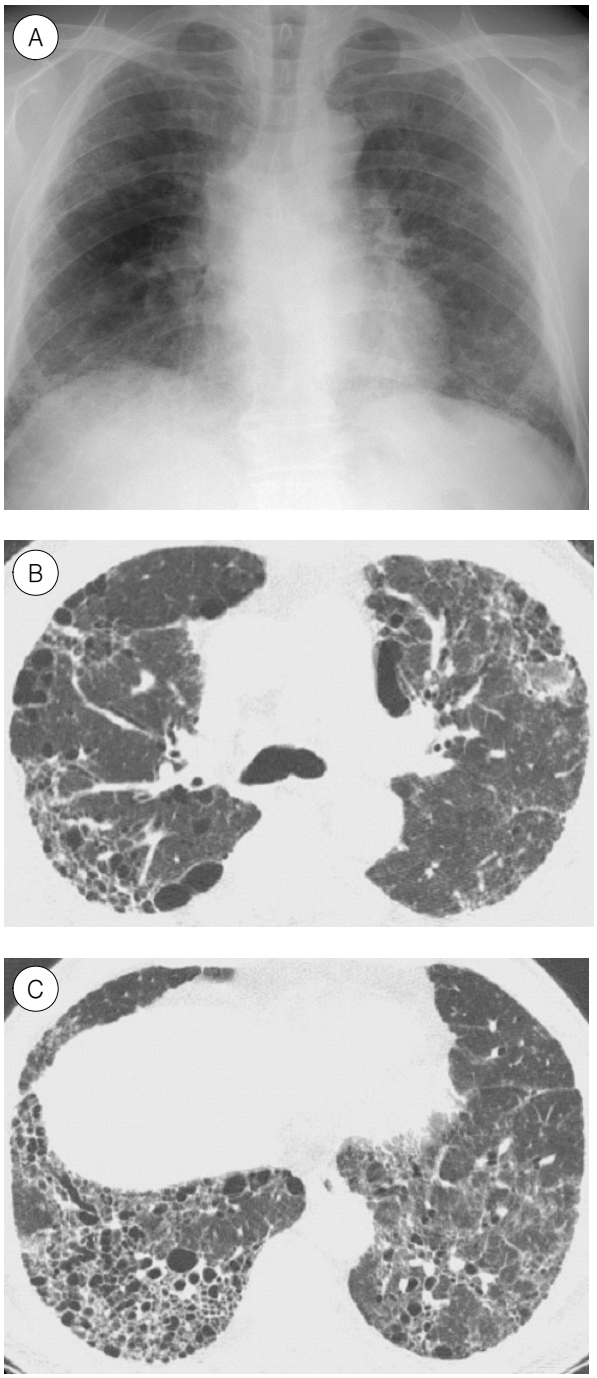

Figure 1. Idiopathic pulmonary fibrosis in a 54-year-old man. (**A**) Chest Radiograph shows peripheral reticular opacities in both middle and lower lung zones, with honeycombing. Mild volume loss of lower lobe is also noted. (**B** and **C**) HRCT scan shows basal and subpleural predominant reticular opacities with traction bronchiectasis, ground glass opacity and honeycombing.

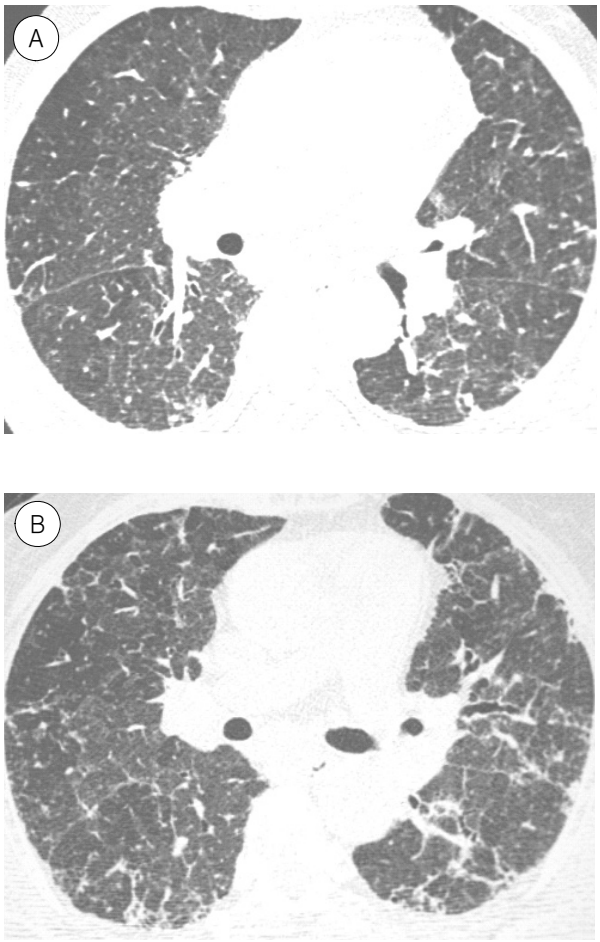

Figure 2. Idiopathic pulmonary fibrosis in a 45-year-old woman. (**A**) The initial HRCT scan obtained at level of bronchus intermedius shows subpleural reticular opacities and subtle areas of ground glass opacity or small consolidation in the periphery of both lower lobes. (**B**) After 2 years and 6 months, the follow up CT scan obtained at similar level shows progression of reticular opacities in both lower lobes. There are also seen increased extent of subpleural ground glass opacity and small consolidation.

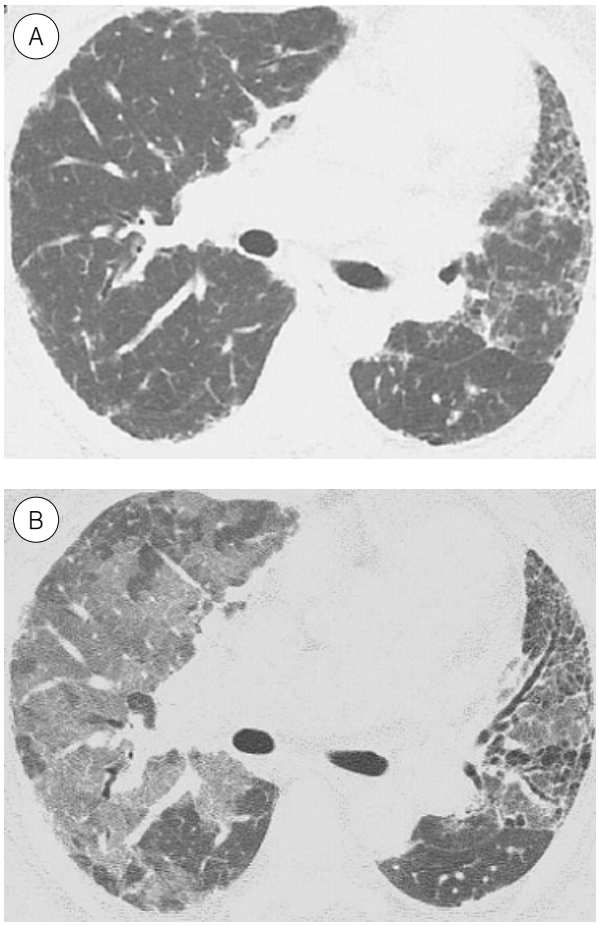

Figure 3. Acute exacerbation of IPF in a 63 year-old man. (**A**) Initial HRCT scan obtained at level of bronchus intermedius shows subpleural predominant reticular opacities, honeycombing and subtle areas of ground glass opacity, typical of IPF. (**B**) After 7 months, the follow up CT scan obtained at similar level shows extensive multifocal areas of groud glass opacity, superimposed on a background of IPF.

Nonspecific Interstitial Pneumonia

The recognition that lung biopsy samples from some patients with idiopathic interstitial disease do not fit into any well-defined histologic patterns of IIP led to proposals of the terms "unclassified interstitial pneumonia" by Kitaichi in 1990[19] and nonspecific interstitial pneumonia (NSIP) by Katzenstein and Fiorelli in 1994[20]. Katzenstein and Fiorelli divided NSIP into three major subgroups based on the amount of inflammation and/or fibrosis in the lung biopsies. Improved prognosis has been observed in several studies and appears to correlate with differences in the dominant pathology, whether a cellular or fibrotic pattern of NSIP is present and dominates. At present, the term is recommended to identify a distinct idiopathic form of IIP with a more favorable prognosis than IPF. Other clinical conditions associated with NSIP pattern on histopathology include collagen vascular diseases, hypersensitivity pneumonitis, certain infection, and potential exposures[20].

The mean age of patients at onset of NSIP is a decade or more younger than patients with IPF. There is neither sexual predominance nor association with cigarette smoking[20,21]. The illness is less chronic with compared with IPF, with the duration spanning months to years, and it has a more favorable prognosis than IPF[10,20-22]. The mortality rate is 15% to 20% in 5 years[1-20]. On BALF, unlike in UIP, increases in the percentages of lymphocytes occur in about 50% of cases, and similar proportions also have increased numbers of neutrophils and/or eosinophils[23].

The NSIP pattern encompasses a broad spectrum of histologic features with varying degrees of alveolar wall inflammation or fibrosis[20]. The most important difference between the fibrosing pattern of NSIP and UIP patterns is the temporal uniformity of the former, which contrasts with the variegated appearance of the connective tissue in the UIP pattern.

NSIP typically shows bilateral pulmonary infiltrates and the lower lung zones are more frequently involved[20,21](Fig. 4A). On HRCT, ground glass opacity is the predominant finding in the majority of cases and is most commonly bilateral and symmetrical with subpleural predominance(Fig. 4B and 4C). Irregular linear or reticular opacities are seen in approximately half of all cases, and may associated with traction bronchiectasis[22,24](Fig. 5A, 5B and 5C). Honeycombing and consolidation are relatively infrequent[20-22,24]. Fibrosing

NSIP may be associated with HRCT evidence of honeycombing[24,25]. The CT differential diagnosis of patients with the pathologic pattern of NSIP depends on the dominant CT pattern exhibited and includes UIP, hypersensitivity pneumonitis, cryptogenic organizing pneumonia[24,25].

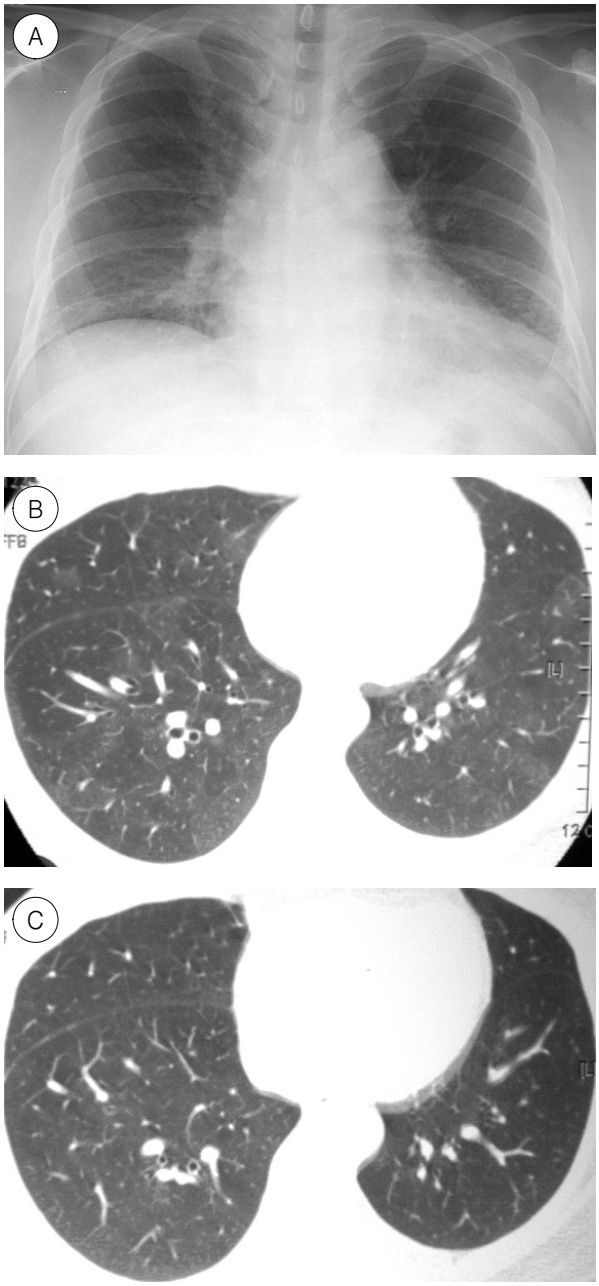

Figure 4. Nonspecific interstitial pneumonia (group 1, cellular pattern) in a 48-year-old woman. (**A**) Initial chest radiograph shows peripheral increased opacities in both lower lung zones. (**B**) Initial HRCT scan obtained at level of basal segmental bronchi shows diffuse areas of ground glass opacity in both lower lobes. (**C**) After 4 months, the follow up CT scan obtained at similar level shows almost decreased areas of ground glass opacity in both lungs.

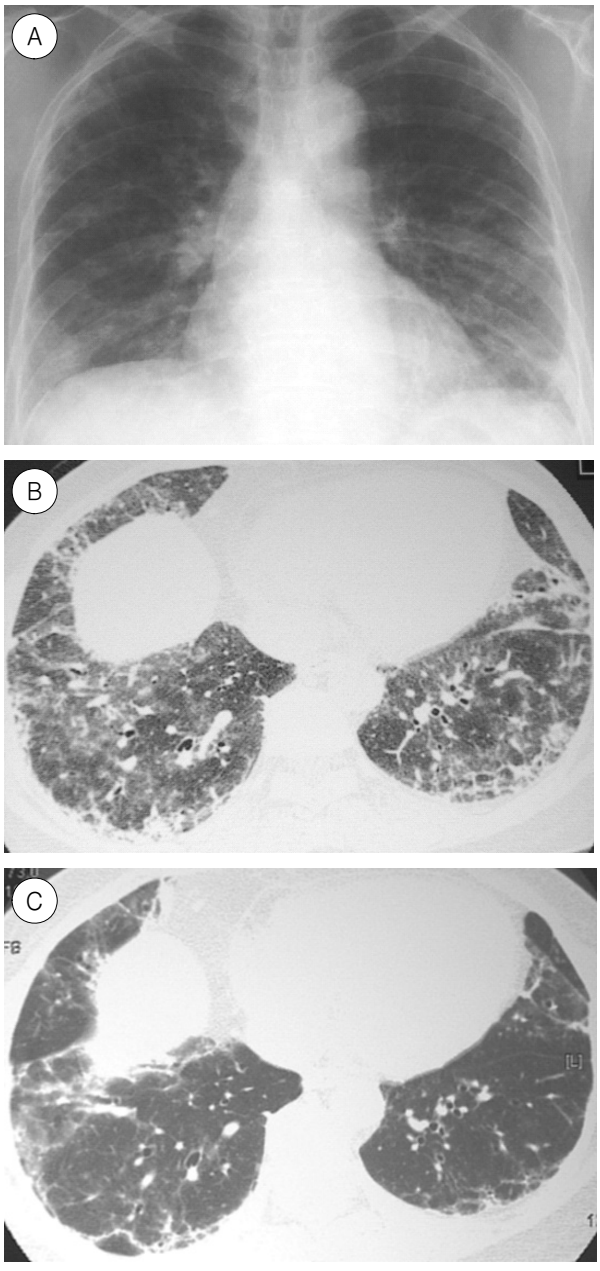

Figure 5. Nonspecific interstitial pneumonia (group 2, fibrtic pattern) in a 52-year-old man. (**A**) Initial chest radiograph shows subpleural and basal predominant increased opacities in both middle and lower lung zones. (**B**) Initial HRCT scan obtained at level of liver dome shows patchy distribution of ground glass opacity containing reticular opacities in both lower lobes. (**C**) After 6 months, the follow up CT scan obtained at similar level shows much decreased areas of ground glass opacity without interval change of reticular opacities.

Cryptogenic Organizing Pneumonia

Cryptogenic organizing pneumonia (COP) has also been known as bronchiolitis obliterans organizing pneumonia (BOOP) and the latter term came into common usage. The etiology is unknown in most cases (idiopathic COP).

There is an equal sex distribution. Mean age of onset is 55 years. Patient typically present with an illness of relatively short duration (median, less than 3 months) with variable degrees of cough and dyspnea[26,27]. Symptoms usually follow a suspected but unconfirmed lower respiratory tract infection. Pulmonary function test (PFT) confirm a restrictive ventilatory pattern with a moderately reduced DLCo[26]. The majority of the patients recover completely on administration of oral corticosteroids but a significant number relapse within 1 to 3 months when the corticosteroids are reduced[26]. A small proportion of patients recover spontaneously[27]. BALF contains increases in the total number and proportion of lymphocytes. The ratio of CD4+ to CD8+ cells is decreased, and the proportion of neutrophils (particularly in the early stages) and of eosinophils is also frequently increased[26,28].

Pathologically, the organizing pneumonia pattern is a patchy process characterized primarily by organizing pneumonia involving alveolar ducts and alveoli with or without bronchiolar intraluminal polyps[27]. The histologic pattern can be seen in association with pulmonary infection, organizing DAD, drug reaction, collagen vascular diseases, hypersensitivity pneumonitis, and toxic fume inhalation[27].

The most common radiographic findings in COP are bilateral or unilateral areas of consolidation[29]. The distribution is usually patchy but may be confined to the subpleural region in a minority of cases[30]. Small nodular opacities are seen in 10-50% of cases[31,32](Fig. 6A). The chest CT scan reveals areas of airspace consolidation in 90% of the patients with COP, which frequently shows a subpleural or peribronchial distribution[31,32](Fig. 6B). The lower lung zones are more frequently involved. Small nodules are evident in 50% of cases, usually seen along bronchovascular bundles, and are centrilobular. The airspace consolidation correspond histologically to the regions of lung parenchyma that show airspace fibrosis and the small nodules are related to foci of organizing pneumonia limited to the peribronchial region and/or to fibroblastic tissue plugs within the bronchiolar lumen. Ground glass opacity is present in about 60%

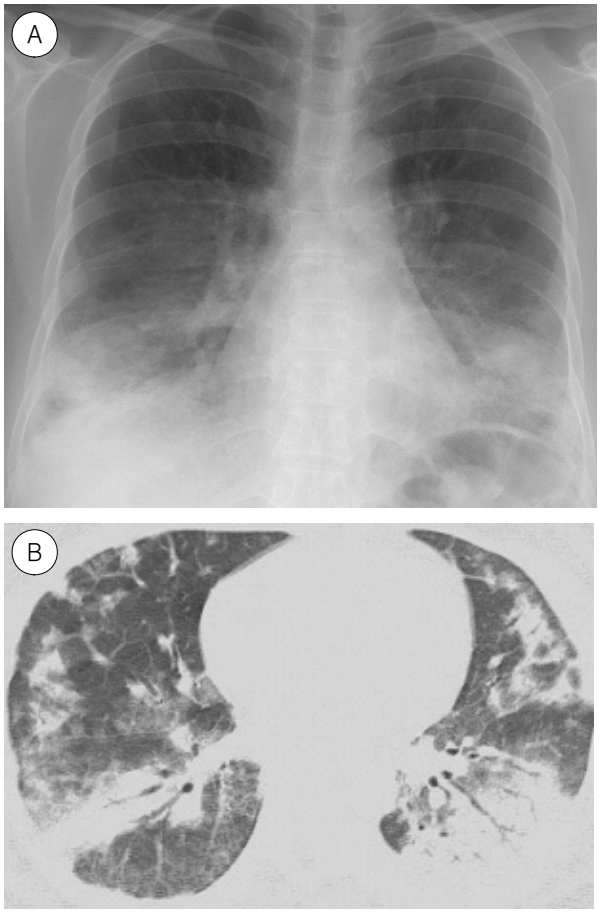

Figure 6. Cryptogenic organizing pneumonia in a 36-year-old man. (**A**) Chest radiograph shows patchy consolidation in both lower lung zones. (**B**) HRCT scan obtained at level of inferior pulmonary vein shows peribronchovascular and subpleural distribution of consolidation. Also note ground glass opacity and large nodules in both lungs.

of cases, usually associated with consolidation or nodules[31,32]. The ground glass opacity correlate with areas of alveolar septal inflammation and minimal airspace fibrosis[33]. Approximately 15% of patients with COP present with multiple large nodules[34]. The majority of patients with COP demonstrate radiographic improvement with treatment. However, the parenchymal abnormality may regress or change in one area and even emerge in new locations without treatment[29-32]. If reticular opacities are present on the chest radiograph or HRCT with COP, the patient less likely respond to steroid and may progress to lung fibrosis[30](Fig 7A and 7B). The radiographic differential diagnosis of COP in patients with areas of consolidation includes bronchioloalveolar cell carcinoma, lymphoma, vasculitis, sarcoidosis, and infection (particularly tuberculosis or nontuberculous mycobacterial infection). When the consolidation is subpleural, then the diagnosis of chronic eosinophilic pneumonia should be considered. Those patients who present with multiple large masses have a differential diagnosis that includes metastatic lung tumor, lymphoma, and pulmonary infection including septic emboli.

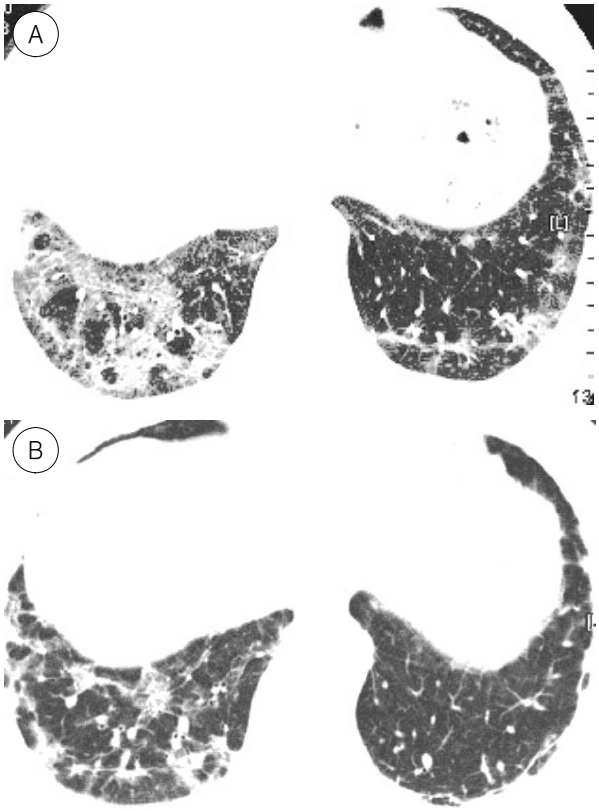

Figure 7. Cryptogenic organizing pneumonia in a 42-year-old woman. (**A**) Initial HRCT scan at level of liver dome shows patchy areas of ground glass opacity with inner reticular opacities in both lower lobes. (**B**) After 8 months, the follow up CT scan obtained at similar level shows much decreased areas of ground glass opacity in both lungs. But increased extent of reticular opacities of fibrosis is revealed.

Acute Interstitial Pnemonia

AIP is an entity that is also referred to as idiopathic diffuse alveolar damage (DAD) and was formerly called Hamman-Rich syndrome[35]. AIP is a rapidly progressive process with an acute (2-3 weeks) presentation in previously healthy individuals[35,36]. AIP occurs over a wide age range. Patients often have a prior illness suggestive of a viral upper respiratory infection with constitutional symptoms. Severe exertional dyspnea develops over a few days[35,36]. PFT shows a restrictive pattern with reduced diffusing capacity[35]. The majority of patients fulfill the diagnostic clinical criteria for ARDS[35]. AIP needs to be distinguished from DAD superimposed on UIP (accelerated decline of UIP), DAD in patients with collagen vascular diseases, ARDS with known cause, infection, drug-induced pneumonitis, hypersensitivity pneumonitis, and acute eosinophilic pneumonia[2]. Mortality rates are high (50% or more) and most deaths occur between 1 and 2 months from onset[36]. BALF contains increased total cells, hemorrhage, neutrophils, and occasionally increased lymphocytes[2].

Lung biopsies from patients with AIP show histologic features of the acute and/or organizing phases of DAD[35,36]. The lung biopsy typically shows diffuse involvement. The exudative phase shows edema, hyaline membranes in alveoli and interstitial acute inflammation. The organizing phase shows loose

organizing fibrosis, mostly within alveolar septa and type II pneumocyte hyperplasia[35,36].

The chest radiograph reveals bilateral airspace opacification with air-bronchograms(Fig. 8A). The distribution is often patchy, with sparing of the costophrenic angles[37]. The cardiac silhouette and vascular pedicle are normal, and interstitial abnormalities such as septal lines and peribronchial cuffing are usually absent. Pleural effusions are uncommon. As the disease progresses the lungs tend to become diffusely consolidated. As AIP moves from the exudative to the organizing stage the radiograph shows less consolidation and presents a ground glass appearance with reticular opacities[37]. The most common findings on CT are areas of ground glass opacity, bronchial dilatation, and architectural distortion[38](Fig. 8B). In the early exudative phase, the lung shows areas of ground glass opacity that are most often bilateral and patchy with areas of focal sparing giving a geographic appearance[37]. Consolidation is seen in the majority of cases but is not as common as ground glass opacity. The distribution is most often basilar but can occasionally be diffuse or rarely have upper lobe predominance[37]. The later organizing stage of AIP is associated with distortion of bronchovascular bundles and traction bronchiectasis. The areas of consolidation tend to be replaced by ground glass opacity. Cysts and other lucent areas of lung become more common in the late stages of AIP[37-39]. The most common residual HRCT findings are areas of hypoattenuation, lung cysts, reticular abnormality and associated parenchymal distortion occurring mainly in the nondependent lung[37,38]. The radiologic differential diagnoses of AIP depends on the stage and include widespread infection, hydrostatic edema, hemorrhage, alveolar proteinosis, bronchioloalveolar cell carcinoma, and DIP.

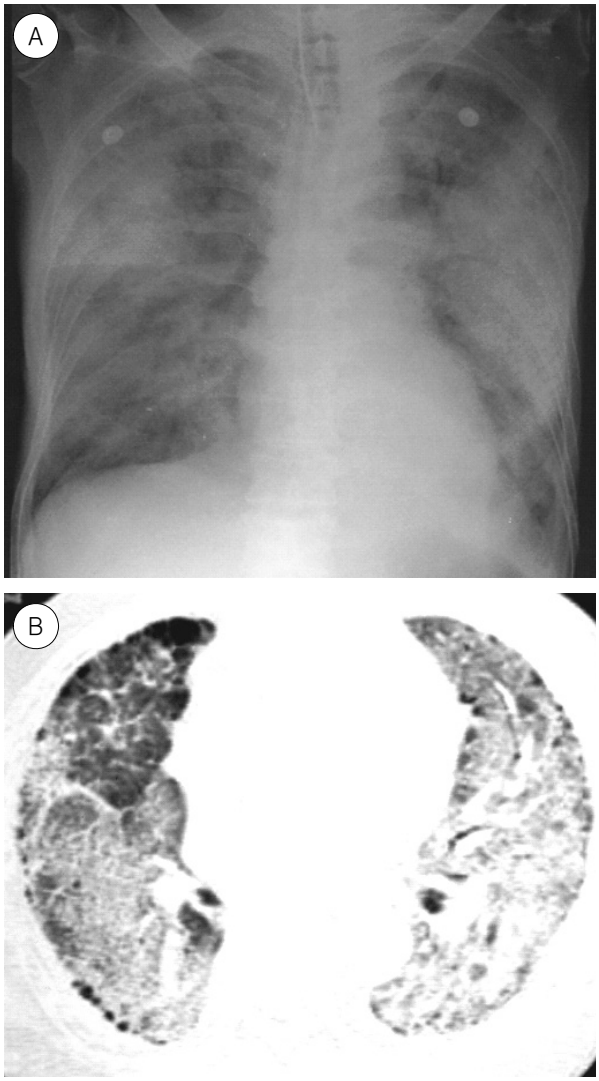

Figure 8. Acute interstitial pneumonia in a 57-year-old woman. (**A**) Chest radiograph shows extensive and patchy areas of consolidation in both lungs. (**B**) HRCT scan obtained at level of right inferior pulmonary vein shows mixed consolidation and ground glass opacity with minute reticular opacities in both lungs. Also note subpleural distribution of paraseptal emphysema.

Repiratory Bronchiolitis-associated Interstitial Lung Disease

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is the clinical manifestation of interstitial lung disease associated with the pathologic lesion of respiratory bronchiolitis[40-42]. RB-ILD and DIP are regarded as a spectrum of smoking-related fibrotic and inflammatory reactions[43,44]. RB is a

histopathologic lesion found in cigarette smokers and is characterized by the presence of pigmented intraluminal macrophages within first- and second-order respiratory bronchioles[40,41,43]. It is rarely symptomatic and is usually associated with no more than minor small airway dysfunction[40,41,43]. However, in rare cases, the condition presents as a form of interstitial lung disease with significant pulmonary symptoms, abnormal pulmonary function, and imaging abnormalities. It is then described as RB-ILD. DIP is considered to be a more extensive form of RB-ILD in which the pigmented macrophages fill alveolar spaces diffusely throughout larger areas of the lung, although there are differences in the clinical presentation, imaging findings, and prognosis between the two patterns[43,44].

Patients with RB-ILD rarely have symptoms. However, the lung disease in some patients is associated with significant dyspnea and hypoxemia, a new or changed cough[40]. It usually affects current smokers in the fourth and fifth decades of life with a history of 30 pack-years of cigarette smoking[40,41,43]. Men are more often affected than women by a ratio of almost 2:1. In patients with minimal symptoms, PFT typically reveals a mild to moderate reduction in DLCo. In more established cases, features of both airway obstruction and restriction, or occasionally an isolated increase in residual volume, may be found[40]. BALF contains alveolar macrophages with varying golden, brown, or black-pigmented inclusions characteristic and indistinguishable from those observed in normal smokers[38]. Modest increased neutrophils may also be present[40].

In RB, the changes are patchy at low magnification and have a bronchiolocentric distribution. There are pigmented macrophages within the lumen of respiratory bronchioles, alveolar ducts, and peribronchial alveoli. There are submucosal and peribronchiolar lympho-histiocytic cellular infiltrations, mild peribronchiolar fibrosis, hyperplasia of type II pneumocytes, and bronchialization of alveoli[40,41,43].

The most common chest radiographic abnormality in RB-ILD is thickening of the wall of central or peripheral bronchi, seen in about 75-90% of patient[41,43]. Ground glass opacity is seen in about 60-70%. It may be normal in up to 14%. The HRCT findings include centrilobular nodules, patchy ground glass opacity, and thickening of the walls of central and peripheral airways[42,43] (Fig. 9A and 9B). Upper lobe

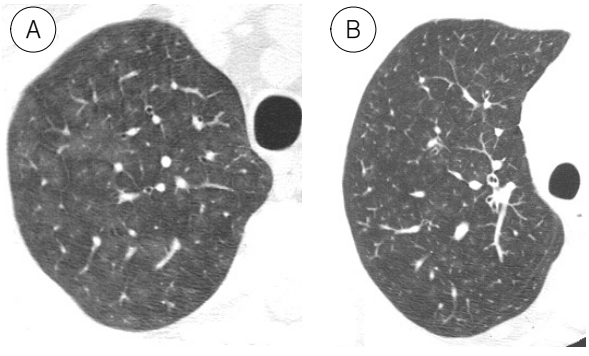

Figure 9. Respiratory bronchiolitis-associated interstitial lung disease in a 32-year-old man. HRCT scan shows upper lung predominant patchy areas of ground glass opaciy (**A**), centrilobular nodules (**B**) and bronchial wall thickening in right lung.

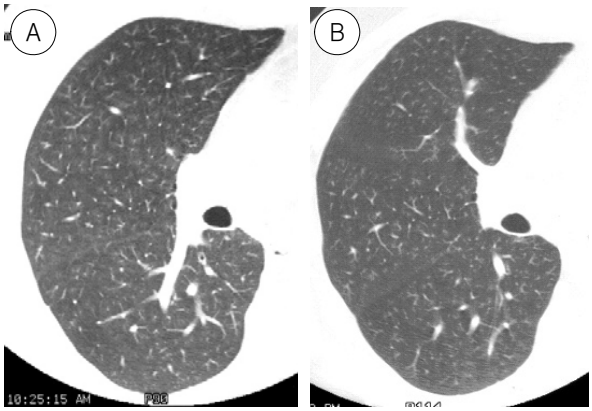

Figure 10. Respiratory bronchiolitis-associated interstitial lung disease in a 43-year-old woman. (**A**) Initial HRCT scan at level of bronchus intermedius shows extensive ground glass opacity and centrilobular nodules with bronchial wall thickening. (**B**) After 5 months of cessation of smoking, the follow up CT scan at similar level shows much decreased extent of ground glass opacity and centrilobular nodules.

centrilobular emphysema is common but not severe[41,43]. The extent of centrilobular nodules on CT correlates with the degree of macrophage accumulation and chronic inflammation in respiratory bronchioles[41]. Ground glass opacity correlates with macrophage accumulation in the alveolar spaces and alveolar ducts[41]. Many patients improve after cessation of smoking[40,41,43](Fig. 10A and 10B). The CT features of RB-ILD overlap with those of hypersensitivity pneumonitis, DIP, and NSIP.

Desquamative Interstitial Pneumonia

The name of DIP originally described by Liebow and Carrington from the belief that dominant histologic feature was desquamation of epithelial cells[44]. However this is now recognized to be intra-alveolar macrophage accumulation[45] rather than desquamation of epithelial cells. The condition is considered by many to represent the end of a spectrum of RB-ILD in view of is similar pathology and almost invariable association with cigarette smoke[2].

DIP affects primarily cigarette smokers in their fourth or fifth decades of life[44]. DIP is more common in men than in women by a ratio of 2:1[44,46]. Insidious onset of dyspnea and dry cough over weeks or months is usual and patients may progress to respiratory failure[46]. Lung physiology confirms normal lung volumes or a mild restrictive abnormality, and the DLCo is moderately decreased[10]. The prognosis of DIP is generally good[44]. Most patients improve with smoking cessation and corticosteroids[46]. The long-term survival rate is about 70% over 10 years[10,46]. BALF invariably contains increased numbers of alveolar macrophages, a large proportion of which have granules of "smoker's pigment"[40]. Increases in neutrophils, eosinophils, and lymphocytes may also be found[40].

The DIP pattern is characterized by diffuse involvement of the lung by numerous macrophage accumulations within most of the distal airspaces ("alveolar macrophage pneumonitis")[47]. There is little alveolar wall thickening, with scant infiltration of plasma cells, occasional eosinophils, and almost no fibrosis. Emphysema is often present[44,46]. The main feature that distinguishes DIP from RB is that DIP affects the lung in a uniform diffuse manner and lacks the bronchiolocentric distribution seen in RB[47]. A focal nonspecific "DIP-like" reaction is an expected consequence of cigarette smoking in a number of interstitial lung diseases[2]. This pattern often overlies the histologic

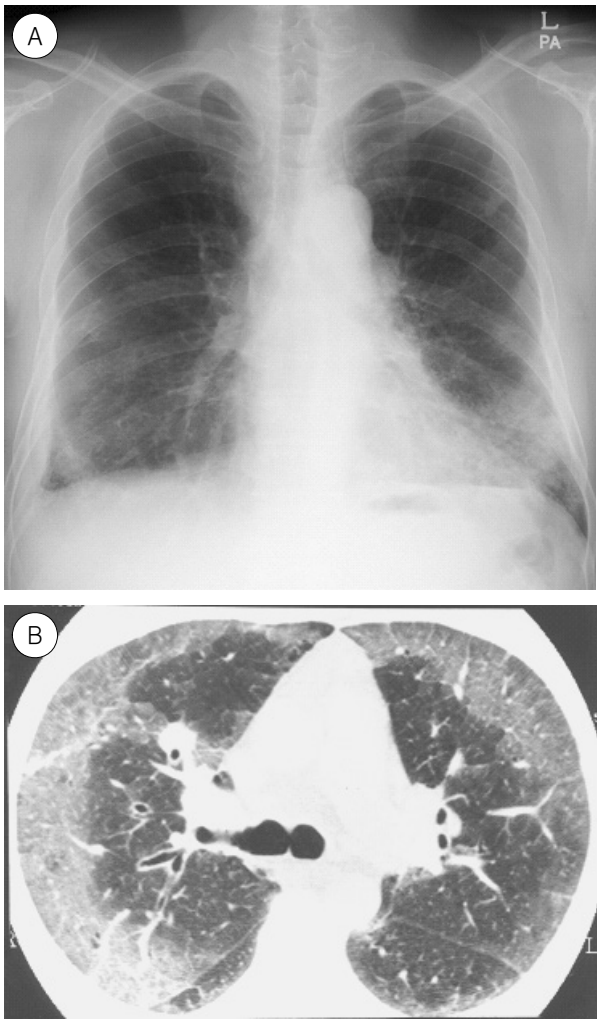

Figure 11. Desquamative interstitial pneumonia in a 52-year-man. (**A**) Chest radiograph shows peripheral increased opacities in both middle and lower lung zones. Note pleural thickening at right lower hemithorax. (**B**) HRCT scan at level of carina shows subpleural distribution of ground glass opacity with inner minute reticular opacities in both lungs.

patterns of UIP, RB, NSIP, eosinophilic pneumonia, chronic hemorrhage or hemosiderosis, and venoocculusive disease.

The chest radiograph is relatively insensitive for detection of DIP and has been reported to be normal in 3-22% of biopsy-proven cases[44,46]. Reported radiographic signs of DIP include widespread patchy ground glass appearance with a lower zone predilection and sometimes a peripheral predominance[48](Fig. 11A). Ground glass opacity is present on CT in all cases of DIP[49](Fig. 11B). This has a lower zone distribution in the majority of cases, a peripheral distribution in 59% of cases, and is patchy in 23%. The distribution is diffuse and uniform in 18%. Irregular linear or reticular opacities are frequent (59%) but limited in extent and usually confined to the lung bases. Honeycombing is seen in less than one-third of cases, and is usually peripheral and limited in extent. On follow-up HRCT, patients receiving treatment can be expected to show partial or near complete resolution of areas of ground glass opacity[50]. Progression of ground glass opacity to a reticular pattern occurs infrequently (less than 20%). The ground glass opacity, which is the hallmark of this disease, is presumed to be due to a combination of diffuse intra-alveolar cells and diffuse mild septal fibrosis. Irregular linear opacities and honeycombing are presumed to correlate with evidence of lung fibrosis[49,50]. Radiologic differential diagnoses include RB-ILD, acute or subacute hypersensitivity pneumonitis, sarcoidosis, and infections such as pneumocystis carinii pneumonia.

Lymphoid interstitial pneumonia

The term lymphoid interstitial pneumonia (LIP) was introduced by Liebow and Carrington to describe a diffuse lymphocytic interstitial infiltrate that was distinct form other patterns of interstitial pneumonitis[51]. However, it was changed with advances in understanding the nature of pulmonary lymphoid infiltrates and many groups prefer to classify LIP under the heading of pulmonary lymphoproliferative disorders. LIP is therefore considered to be preneoplastic, and only a small number of cases found to actually undergo malignant transformation[52]. With regard to histogenesis, LIP is perhaps best regarded as a histologic variant of diffuse pulmonary lymphoid hyperplasia with predominantly interstitial changes[52,53].

The clinical presentation of LIP is not well defined. It is more common in women, and although it may present at any age, is most typically diagnosed in the fifth decade[54]. Patients present with insidious onset of cough and dyspnea over the course of 3 or more years. There may be associated fever, weight loss, arthralgia, and mild anemia. Lymphadenopathy is present in some cases, but is more common in the presence of Sjögren's syndrome[54]. The presentation of LIP is usually that of the underlying systemic or autoimmune disorder such as rheumatoid arthritis, Sjögren's syndrome, Hashimoto's disease, pernicious anemia, chronic active hepatitis, systemic lupus erythematosus, autoimmune hemolytic anemia, primary biliary cirrhosis, myasthenia gravis, hypogammaglobulinemia, and severe combined immunodeficiency, particularly in children with AIDS[54]. Clinically, cases of LIP must be thoroughly investigated for any known cause or associations, such as collagen vascular diseases and immunodeficiency. There has reported good response to corticosteroid treatment in large proportion of patients. However, more than one-third progress to diffuse fibrosis[54]. The BALF shows many lymphocytes and immunophenotyping of these cells should not reveal any clonality[54-56].

LIP is defined as a dense interstitial lymphoid infiltrate, including lymphocytes, plasma cells, and histiocytes with associated type II cell hyperplasia[54,55]. The alveolar septa should be extensively infiltrated. Lymphoid follicles, including follicles with germinal

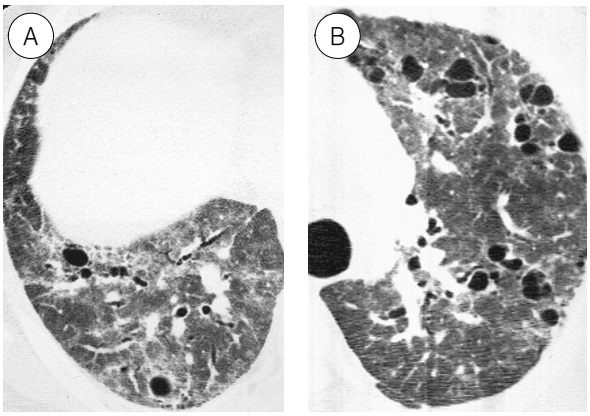

Figure 12. Lymphocytic interstitial pneumonia in a 28-year-old woman. (**A**) HRCT scan at level of liver dome shows patchy distribution of ground glass opacity, centrilobular ndules and reticular opacities in right lung. (**B**) At level of aortic arch HRCT scan shows perivascular cysts and subpleural nodules in left lung.

centers, are often present, usually in the distribution of pulmonary lymphatics .

Two chest radiographic patterns for LIP have been described: basilar with an alveolar component and diffuse with associated honeycombing[55,56]. The dominant CT finding is usually ground glass opacity[55,56] (Fig. 12A and 12B). Poorly defined centrilobular or subpleural micronodules can be seen[56]. Perivascular cysts or honeycombing also can be seen[57]. Reticular abnormality is seen in about 50% of patients. Lung nodules and widespread consolidation may occur[55,56].

References

1. Groskin S. Chronic interstitial lung disease. In: *Heitzmans' the lung: radiologic-pathologic correlation*. St Louis: Mosby-Year Book; 1983. p. 235-359.
2. American Thoracic Society, European Respiratory Society. American Thoracic Society and the European Respiratory Society International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonia. Am J Respir Crit Care Med 2002;165: 277-304.
3. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. Am J Respir Crit Care Med 2000;161:646-64.
4. Turner-Warwick M. Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. Thorax 1980;35:171-80.
5. Nagai S, Kitaichi M, Hamada K, Nagao T, Hoshino Y, Miki H, et al. Hospital-based historical cohort study of 234 histologically proven Japanese patients with IPF. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16:209-14.
6. Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med 2001;134:136-51.
7. Wells AU, Hansell DM, Rubens MB, Cullinan P, Haslam PL, Black CM, et al. Fibrosing alveolitis in systemic sclerosis: bronchoalveolar lavage findings in relation to computed tomographic appearance. Am J Repir Crit Care Med 1994;150:462-8.
8. Cushley MJ, Davison AG, du Bois RM, Egan J, Flower CD, Gibson GJ, et al. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. Thorax 1999;54:S1-14.
9. The BAL Cooperative Group Steering Committee. Bronchoalveolar lavage constituents in healthy Individuals, idiopathic pulmonary fibrosis, and selected comparison groups. Am Rev Respir Dis 190;141: S169-202.
10. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998;157:1301-15.
11. Staples CA, Müller NL, Vedal S, Abboud R, Ostrow D, Miller RR. Usual interstitial pneumonia: correlation of CT with clinical, functional, and radiologic findings, Radiology 1987;162:377-81.
12. Akira M, Sakatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. Radiology 1993;189:687-91.
13. Müller NL, Miller RR, Webb WR, Evans KG, Ostrow DN. Fibrosing alveolitis: CT-pathologic correlaton. Radiology 1986;160:585-8.
14. Nishimura K, Kitaichi M, Izumi T, Nagai S, Kanaoka M, Itoh H. Usual interstitial pneumonia: histologic correlation with high-resolution CT. Radiology 1992; 182-337-42.
15. Hunninghake GW, Zimmerman MB, Schwarts DA, King TE Jr, Lynch D, Hegele R, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2001:164: 193-6.
16. Raghu G, Mageto YN, Lockhart D, Scmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. Chest 1999:116:1168-74.
17. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki

K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis: analysis of clinical and pathologic findings in three cases. Chest 1993;103:1808-12.
18. Akira M, Hamada H, Sakatani M, Kobayashi C, Nishioka M, Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. Am J Roentgenol 1997;168:79-83.
19. Kitaichi M. Pathologic features and the classification of interstitial pneumonia of unknown etiology. Bull Chest Dis Res Inst Kyoto Univ 1990;23:1-18.
20. Katsenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis: histologic features and clinical significance. Am J Surg Pathol 1994;18:136-47.
21. Park JS, Lee KS, Kim JS, Park CS, Choi DL, Kim KJ, et al. Nonspecific interstitial pneumonia with fibrosis: radiographic and CT findings in seven patients. Radiology 1995;195:645-8.
22. Kim TS, Lee KS, Chung MP, Park JS, Hwang JH, Kwon OJ, et al. Nonspecific interstitial pneumonia with fibrosis: high-resolution CT and pathologic findings. Am J Roentgenol 1998;171:1645-50.
23. Park CS, Chung SW, Lim GI, Uh ST, Kim YH, Park JS, et al. Increased levels of interleukin-6 are associated with lymphocytosis in bronchoalveolar lavage fluids of idiopathic nonspecific interstitial pneumonia. Am J Respir Crit Care Med 2000:162: 1162-8.
24. Hartman TE, Swensen SJ, Hansell DM, Colby TV, Myers JL, Tazelaar HD, et al. Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. Radiology 2000;217:701-5.
25. MacDonald SL, Rubens MB, Hansell DM, Colby TV, du Bois RM, Nicholson AG, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances and diagnostic accuracy of high-resolution computed tomography. Radiology 2001;221:600-5.
26. King TE Jr, Mortenson RL. Cryptogenic organizing pneumonitis. Chest 1992;102:8S-13S.
27. Izumi T, Kitaichi M, Nishimura K, Nagai S. Bronchiolitis obliterans organizing pneumonia. Chest 1992;102: 715-9.
28. Costabel U, Teschler H, Guzman J. Bronchiolitis obliterans organizing pneumonia (BOOP): the cytological and immunocytologic profile of bronchoalveolar lavage. Eur Respir J 1992;5:791-7.
29. Müller NL, Guerry-Force ML, Staples CA, Wright JL, Wiggs B, Coppin C, et al. Differential diagnosis of bronchilitis obliterans with organizing pneumonia and usual interstitial pneumonia: clinical, functional and radiologic findings. Radiology 1987;162:151-6.
30. Cordier JF, Loire R, Brune J. Idiopathic bronchiolitis obliterans organizing pneumonia: definition of characteristic clinical profiles in a series of 16 patients. Chest 1989;96:999-1004.
31. Lee KS, Kulling P, Hartman TE, Müller NL. Cryptogenic organizing pneumonia: CT findings in 43 patients. Am J Roentgenol 1994;162:543-6.
32. Müller NL, Staples CA, Miller RR. Bronchiolitis obliterans organizing pneumonia: CT features in 14 patients. Am J Roentgenol 1990;154:983-7.
33. Nishimura K, Itoh H. High-resolution computed tomographic features of bronchiolitis obliterans organizing pneumonia. Chest 1992;102:26S-31S.
34. Akira M, Yamamoto S, Sakatani M. Bronchiolitis obliterans organizing pneumonia manifesting as multiple large nodules or masses. Am J Roentgenol 1998;170:291-5.
35. Olson J, Colby TV, Elliott CG. Hamman-Rich syndrome revisited. Mayo Clin Proc 1990;65:1538-48.
36. Katzenstein AL, Myers JL, Mazur MT. Acute interstitial pneumonia: a clinicopathlogic, ultrastructural, and cell kinetic study. Am J Surg Pathol 1986;10:256-67.
37. Primack SL, Hartman TE, Ikezoe J, Akira M, Sakatani M, Müller NL. Acute interstitial pneumonia: radiographic and CT findings in nine patients. Radiology 1993;188:817-20.
38. Primack SL, Hartman TE, Ikezoe J, Akira M, Sakatani M, Müller NL. Acute interstitial pneumonia: radiographic and CT findings in nine patients. Radiology 1993;188:817-20.
39. Desai SR, Wells AU, Rubens MB, Evans TW, Hansell DM. Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. Radiology 1999; 210:29-35.
40. King TE Jr. Respiratory bronchiolitis-associated interstitial lung disease. Clin Chest Med 1993;14:693-8.
41. Heyneman LE, Ward S, Lynch DA, Remy-Jardin M, Johkoh T, Müller NL. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? Am J Roentgenol 1999;173:1617-22.
42. Gruden JF, Webb WR. CT findings in a proved case of respiratory bronchiolitis. Am J Roentgenol 1993; 161:44-6.
43. Park JS, Brown KK, Tuder RM, Hale VA, King TE Jr, Lynch DA. Respiratory bronchiolitis-associated interstitial lung disease: radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 2002;26:13-20.
44. Liebow AA, Steer A, Billingsley JG. Desquamative interstitial pneumonia. Am J Med 1965;39:369-404.

45. Tubbs RR, Benjamin SP, Reich NE, McCormack LJ, van Ordstrand HS. Desquamative interstitial pneumonitis: cellular phase of fibrosing alveolitis. Chest 1977;72:159-65.
46. Carrington CB, Gaensler EA, Coutu RE, FitzGerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 1978;298:801-9.
47. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989;64:1373-80.
48. Feigin DS, Friedman PJ. Chest radiography in desquamative interstitial pneumonitis: a review of 37 patients. Am J Roentgenol 1980;134:91-9.
49. Hartman TE, Primack SL, Swensen SJ, Hansell D, McGuinness G, Muller NL. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1993;187:787-90.
50. Hartman TE, Primack SL, Kang EY, Swensen SJ, Hansell DM, McGuinness G, et al. Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia: assessment with serial CT. Chest 1996;110:378-82.
51. Liebow AA, Carrington CB. The interstitial pneumonias. In: Simon M, Potchen EJ, LeMay M, editors. Frontiers of pulmonary radiology, 1st ed. New York: Grune & Stratton; 1969. p. 102-41.
52. Kradin RL, Young RH, Kradin LA, Mark EJ. Immunoblastic lymphoma arising in chronic lymphoid hyperplasia of the pulmonary interstitium. Cancer 1982;50:1339-43.
53. Yousem SA, Colby TV, Carrington CB. Follicular bronchiolitis/bronchiolitis. Hum Pathol 1985;16:700-6.
54. Strimlan CV, Rosenow EC 3rd, Weiland LH, Brown LR. Lymphocytic interstitial pneumonitis: review of 13 cases. Ann Intern Med 1978;88:616-21.
55. Julsrud PR, Brown LR, Li CY, Rosenow EC 3rd, Crowe JK. Pulmonary processes of mature-appearing lymphocytes: pseudolymphoma, well-differentiated lymphocytic lymphoma, and lymphocytic interstitial pneumonitis. Radiology 1978;127:289-96.
56. Johkoh T, Müller NL, Pickford HA, Hartman TE, Ichikado K, Akira M, et al. Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1999;212:567-72.
57. Ichikawa Y, Kinoshita M, Koga T, Oizumi K, Fujimoto K, Hayabuchi N. Lung cyst formation in lymphocytic interstitial pneumonia: CT features. J Comput Assist Tomogr 1994;18:745-8.