J Korean Med Sci 1999; 14: 113-27
ISSN 1011-8934

■ REVIEW ■

Idiopathic Interstitial Pneumonias: Clinical Findings, Pathogenesis, Pathology and Radiologic Findings

Idiopathic interstitial pneumonias are currently classified into four categories: usual interstitial pneumonia, nonspecific interstitial pneumonia with fibrosis, acute interstitial pneumonia and desquamative interstitial pneumonia. The fibrotic process in interstitial pneumonias appears to result from a complex interaction between fibroblasts, other lung parenchymal cells and macrophages. The complex relationship between the local release of growth-promoting cytokines by alveolar macrophages and resident fibroblasts represents a necessary step for fibrosis or remodeling after lung injury. Injury to the epithelium and basement membranes is likely necessary for the fibrotic process to occur. Usual interstitial pneumonia, most frequent among interstitial pneumonias and has a poor prognosis, appears on high-resolution CT as patchy subpleural areas of ground-glass attenuation, irregular linear opacity, and honeycombing. Nonspecific interstitial pneumonia with fibrosis, the second most frequent and has a better prognosis than usual interstitial pnemonia, appears as subpleural patchy areas of ground-glass attenuation with associated areas of irregular linear opacity on CT. Acute interstitial pneumonia with high mortality rate presents as extensive bilateral airspace consolidation and patchy or diffuse bilateral areas of ground-glass attenuation. Desquamative interstitial pneumonia with good prognosis presents as patchy subpleural areas of ground-glass attenuation in middle and lower lung zones.

Key Words : *Lung; Fibrosis; Lung disease, interstitial; Pneumonia*

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Received : 17 March 1999
Accepted : 24 March 1999

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INTRODUCTION

Idiopathic interstitial pneumonias (IIPs) are a heterogeneous group of inflammatory and fibrosing lesions that manifest as infiltrative lung disease (1). According to differences in histologic appearances, they were initially classified by Liebow (2) into five types: usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP), giant cell interstitial pneumonia (GIP), and bronchiolitis with interstitial pneumonia (BIP). It has since been shown that GIP is a kind of pneumoconiosis, being found almost exclusively in workers exposed to cobalt, primarily in the form of hard metal, which contains alloys of tungsten carbide and cobalt. LIP includes cases of diffuse interstitial infiltrate of polyclonal lymphocytes and plasma cells, as well as cases of diffuse lymphoid hyperplasia in the lung. Many cases of LIP have been reclassified as lymphomas. LIP and related entities are therefore better classified as lymphoproliferative disorders rather than being included in chronic interstitial pneumonia (1, 3). The term bronchiolitis obliterans with interstitial pneumonia has been replaced by idiopathic bronchiolitis obliterans organizing pneumonia (BOOP). We have excluded it from the idiopathic interstitial pneumonias, because of the airspace involved in this entity (4, 5).

Recently, two other forms of idiopathic interstitial pneumonia have been described: acute interstitial pneumonia (AIP) and nonspecific interstitial pneumonia with fibrosis (NSIP) (also called nonclassifiable interstitial pneumonia [NCIP]) (1, 3, 6 - 8). AIP corresponds closest to Hamman-Rich syndrome (1, 3). And NSIP has been proposed for those cases in which the classic features of UIP, DIP, or AIP are not present (7). Therefore, idiopathic interstitial pneumonias currently consist of four clinicopathologic entities: UIP, DIP, AIP and NSIP.

In this article, the authors review clinical findings, pathogenesis, pathology, and radiologic findings of the four kinds of idiopathic interstitial pneumonias.

CLINICAL FINDINGS

Common clinical findings of IIP are as follows: (a) Chief complaints are cough and/or dyspnea. (b) Fine inspiratory

crackle, typically "Velcro rale", is heard in the bilateral lower lungs on auscultation of the chest. (c) Restrictive defects with a decreased diffusing capacity of the lung are commonly found on pulmonary function testing. (d) Chest radiograph shows bilateral diffuse shadows. (e) Known etiologies such as collagen vascular diseases, hypersensitivity pneumonitis, environmental or occupational exposure, drugs, viral or other infectious diseases and sarcoidosis are not identified. It is not easy to make a specific clinicopathologic diagnosis unless surgical lung biopsy is performed, because of these common clinical characteristics.

The clinical course or onset of IIP is categorized as acute (less than four weeks of symptom duration), subacute (in between acute and chronic) and chronic (more than one year of symptom duration) forms. UIP usually tends to have a chronic course, but acute exacerbation of UIP occasionally occurs (10, 11). Acute/subacute forms of IIP include AIP, DIP, and NSIP. For clinical purposes, distinuishing UIP from other forms of IIP is very important, because of marked differences in treatment response and prognosis (12). UIP (62% of biopsy-proved idiopathic pulmonary fibrosis) is the most common form of idiopathic interstitial pneumonia, followed by NSIP (14%), DIP (8%) and AIP (2%) (12).

Usual interstitial pneumonia

Usual interstitial pneumonia is the most common IIP, accounting for at least over 60% of idiopathic pulmonary fibrosis cases (12). While the term "usual interstitial pneumonia" is often used synonymously with "idiopathic pulmonary fibrosis", UIP is a histopathologic diagnosis and it may also be seen in other conditions such as collagen vascular diseases and drug reactions (13). Accordingly, when the pathologic diagnosis of UIP is made, we must search for evidence of associated collagen vascular diseases or drug exposure before UIP, as an idiopathic pulmonary fibrosis, is confirmed.

Usual interstitial pneumonia occurs predominantly in middle-aged adults (mostly 40-70 years of age), and men are affected nearly twice as often as women. The onset is usually insidious and patients have a 1-3-year history of nonproductive cough and slowly progressive exertional dyspnea (12, 13-16). An acute exacerbation of previously stable or slowly progressive UIP occasionally occurs (10, 17, 18). Systemic symptoms, including fever, malaise, joint symptoms, and weight loss, were found in nearly half of the patients (13). Clubbing is frequently encountered on physical examination, occurring in over half of the patients (13, 16). Erythrocyte sedimentation rate is increased in many patients, and rheumatoid factor and antinuclear antibodies may be positive even in patients without associated collagen vascular disease (13).

The prognosis of UIP is extremely poor, with mortality rates ranging from 59% to 70%. Among 48 patients untreated, none improved spontaneously, and 41 (85.4%) became worse during the mean observation period of 4.5 years (19). Most UIP patients are initially treated with high-dose steroids (prednisolone 1 mg/kg/day) for 4-12 weeks. Then, if there is a response, the treatment is slowly tapered off unless the patient shows deterioration. The duration of therapy needs to be adjusted for each patient. There is some evidence supporting the additional benefit of cytotoxic drug such as cyclophosphamide or azathioprine (20, 21), although cytotoxic agents are often reserved for corticosteroid failures. Favorable treatment response is observed in 10-30% of patients. The improvement is rarely dramatic and usually partial or transient. A complete remission or cure is rare. Many patients, particularly the elderly, experience substantial side effects from the drugs without improvement of pulmonary symptoms. Therefore, some investigators recommend a less toxic agent (i.e., colchicine) or supportive care only (i.e., oxygen supplementation) if the patient is over 60 years of age (22). The efficacy of colchicine, however, still needs to be confirmed (23-25). Slightly better response rates have been reported by other investigators, but their researches seemed to have several drawbacks, such as absence of adequate histologic confirmation, inclusion of cases with associated collagen vascular diseases or small number of patients (26-29). Considering the drawbacks of their studies, the results of previous UIP reports might be misleading because it had been impossible to separate true UIP from NSIP until 1994 when Katzenstein and Fiorelli (13) first described NSIP. If NSIP is properly differentiated from UIP, treatment response or mortality rate of UIP might become worse. The mean survival of UIP was 5.6 years in the report by Carrington et al. (19), but the median survival of UIP reported by Bjoraker et al. (12), who separated NSIP from UIP, was 2.8 years. Further clinical results are needed to determine whether true UIP, after excluding NSIP, is a medically treatable disease.

Nonspecific interstitial pneumonia with fibrosis

NSIP was first reported by Katzenstein and Fiorelli in 1994 (13). Similar cases, however, must have existed before 1994 and probably these cases were included under the categories of UIP or idiopathic pulmonary fibrosis. NSIP can be defined histologically because it lacks features of UIP, DIP, AIP, LIP, or GIP. Eleven (17%) of the 64 patients with NSIP in the series of Katzenstein and Fiorelli (13) had histories of exposure, either at home or through occupation, to substances that might possibly cause an interstitial pneumonia, while 10 (16%) had underlying collagen vascular disease of various sorts. Five (8%) patients had histories, suggesting antecedent acute lung injury, which raises the possibility that NSIP may represent a resolving phase of diffuse

alveolar damage. For this reason, some pathologists or clinicians still think that NSIP is essentially a histologic diagnosis of exclusion or a "wastebasket" histologic diagnosis, representing cases of idiopathic interstitial pneumonia that can not be classified into one of the above categories (30). Following reports of idiopathic NSIP (12, 31-33) including 31 patients of Nagai et al. (34) have described the different features between NSIP and UIP, both in clinical and prognostic aspects. As a result, idiopathic NSIP may become a unique clinicopathologic entity of IIP, like UIP. Treatment response or prognosis of NSIP is much better than that of UIP and is nearly comparable to BOOP (12, 34), separating NSIP from other forms of IIP, which is important clinically. The term nonclassifiable interstitial pneumonia is almost synonymous with NSIP. Nonspecific interstitial pneumonia that develops in patients with acquired immunodeficiency syndrome should be differentiated from NSIP. Nonspecific interstitial pneumonia is part of a spectrum of lymphocytic interstitial pneumonia, which is characterized pathologically by interstitial inflammation with lymphocytes and plasma cells and associated with varying degrees of edema and fibrin deposition (35, 36).

The average age at onset is 53 years (13, 31, 32, 34). The most important clinical characteristics that distinguish NSIP from UIP are the lack of strong predilection for males, a subacute (several months) rather than an insidious onset, and the relative lack of clubbing (9.7%) (34). Lymphocytosis with a decreased ratio of CD4:CD8 T-lymphocytes in bronchoalveolar lavage (BAL) cell findings is also helpful in distinguishing NSIP from UIP (34).

Nonspecific interstitial pneumonia with fibrosis has a relatively good prognosis, with most patients responding to corticosteroid treatment. Nearly half (45%) of 48 patients in a follow up by Katzenstein and Fiorelli (13) recovered completely and 42% remained stable or improved, while only 11% died of progressive lung disease. The prognosis appears to depend on the extent of fibrosis, since no deaths occurred in patients whose biopsy specimen showed pure inflammation and no fibrosis. Of 31 patients of Nagai et al. (34), 23 (74.2%) showed either improvement or remission, but 3 (20.0%) worsened and 2 (13.3%) died either of progressive disease or cytomegalovirus pneumonia as a complication of therapy. All of the patients, who suffered a more aggressive course, were in the fibrotic subset of NSIP. Similarly, the overall median survival of 14 patients with NSIP in the study of Bjoraker et al. (12) was greater than 13 years. All seven patients of Park et al. (31) and of 12 of Cottin et al. (32) were alive at follow up of 7.5 months and 50 $\pm$40 months after diagnosis, respectively.

Acute interstitial pneumonia

Acute interstitial pneumonia, also called "Hamman-Rich syndrome"(37), is characterized by respiratory failure developing over days to weeks and histopathologically characterized by organizing diffuse alveolar damage in which the etiologic agent was not identified (38-40). Although the clinical manifestation of AIP is similar to that of adult respiratory distress syndrome (ARDS) and both show the same histologic features of diffuse alveolar damage, the two should not be considered synonymous. An appropriate clinical setting or known causes such as infection, drug, trauma, shock, aspiration and others must be present in ARDS. In this context, AIP might be an idiopathic form ARDS (39). AIP, however, has several characteristics, although nonspecific, clinical features. Most patients had a prior illness with fever in nearly half at presentation, similar to a viral respiratory infection that progresses to a fulminant pneumonia. There is no apparent sex predilection for AIP. The mean age at onset of all reported cases is 49 years, but patients from 7 to 77 year old have been described. Mortality rates of AIP are high, ranging from 50% to 88% (39, 40). Despite aggressive therapy including high-dose steroid administration, all died within 6 months after the onset of symptoms. In general, the therapeutic response seems to be dependent on the stage, although no correlation has been demonstrated between the specific histopathologic feature and survival (39, 41).

Desquamative interstitial pneumonia

The average age at presentation is typically 30-50 years, about 10 years younger than patients with UIP. Men are affected nearly twice as often as women. Patients usually complain of slowly progressive dyspnea and dry cough. Clubbing is noted in nearly half of the patients. Restrictive defects on pulmonary function testing are usually less marked than observed in cases of UIP. DIP has a relatively good prognosis. In the study of Carrington et al. (19), 24/40 (60%) patients with DIP showed steroid response with complete recovery of the disease. Eleven (27.5%) of the 40 patients died after an average of 12 years. Several DIP cases of Carrington et al. (19) were corrected later into representing respiratory bronchiolitis-interstitial lung disease by Yousem et al. (42). Hartman et al. (43) also reported radiographic stabilization or improvement in most of their 11 patients with DIP as compared to the progression in most of the 12 UIP patients. Data by Akira et al. (44) were similar. Although it was once thought that DIP was an early stage of UIP, DIP does not progress to UIP on sequential CT evaluation (44).

PATHOGENESIS

Idiopathic interstitial pneumonia is a poorly understood

interstitial lung disease characterized by chronic inflammation and fibrosis of lung parenchyma. While the early studies suggested that inflammation and fibrosis are confined to the interstitium of the alveolar walls, it is now understood that most fibrotic lung disorders are "intra-alveolar" as well as "interstitial" and initial injury causes collapse of functional alveolar capillary units by intra-alveolar fibrosis (45-47). Intra-alveolar or intraluminal fibrosis appears in several forms: (a) intraluminal buds, which partially fill the alveoli, alveolar ducts, and/or distal bronchioles; (b) obliterative changes, in which loose connective tissue masses obliterate the distal airspaces; and (c) mural incorporation of previously intraluminal connective tissue masses, which fuse with the alveolar, alveolar ductal, or bronchiolar structures and frequently become reepithelialized. It is now recognized that intraluminal fibrosis is an important component in the pattern of injury and repair in an interstitial lung disorder.

As the inflammation found in lung tissue from patients with fibrotic lung disease occurs in the alveolar structure, the inflammation is referred to as an "alveolitis" (48). Evidences indicate that the alveolitis precedes the fibrosis of fibrotic lung disease. First, in the early stage of the disease, areas of alveolitis are found without evidence of derangement of the alveolar architecture (49). Second, in familial cases of idiopathic pulmonary fibrosis, the children of patients with fibrotic lung disease have alveolitis without clinical evidence of the disease, suggesting that alveolitis comes first (50). Third, in animal models of pulmonary fibrosis, induction of the alveolitis is followed by fibrotic change (51). Finally, suppression of the alveolitis is associated with a stabilization of the disease (52).

Etiology

Although remarkable advances in our understanding of the pathogenesis of interstitial lung disease have been made, the etiology that causes lung injury or inflammation in interstitial lung disease remains unknown. Inhalation of injurious agents or blood borne agents are believed to cause injury. Viral infections such as Epstein-Barr virus or adeno-virus may be implicated (53, 54), but it seems to be a coincidental finding rather than a causative agent. Environmental exposure could be relevant (55). Genetic factors may play a part (50).

Epithelial and endothelial cell injury

Irrespective of its etiology, most current theories on the pathogenesis of pulmonary fibrosis are based on the hypothesis that there is initial damage to endothelial or epithelial cells or both. Inflammatory and immune cells then move into the interstitium and alveolar spaces from the circulation and release mediators that stimulate collagen production by fibroblasts (56). Epithelial control of fibroblast proliferation has been observed in tracheal grafts. If a tracheal graft is denuded of epithelium, the lumen gradually disappears along with fibrous tissue, but this is prevented if the graft is re-epithelialized (57). Experiments using cytotoxic agents have shown that prevention of re-epithelialization similarly leads to fibrosis, but this does not occur if epithelial regeneration is allowed to take place (58). Therefore, repeated damage to alveolar epithelial cells may be an important mechanism in the development of fibrosing alveolitis. Repair of epithelial damage results in proliferation of type 2 pneumocytes, which is a prominent histological feature of idiopathic pulmonary fibrosis (59). Endothelial cells are also capable of releasing potent mediators that may play a role in tissue damage. Evidence from clinical studies and animal models suggests pulmonary vascular leakage of proteins occurs many days before lung fibrosis becomes detectable by biochemical or histologic techniques (60, 61).

Inflammatory cell infiltration

In IIP, inflammatory cells accumulate in the interstitium of the lung and alveolar spaces, leading to a disintegration of the normal alveolar architecture with subsequent fibrosis. The alveolitis of pulmonary fibrosis is dominated by alveolar macrophages, but the most striking component is the increased numbers of neutrophils. Early observation of BAL in fibrotic lung diseases also suggests an increase in the numbers of neutrophils and eosinophils in BAL fluid (62). In the normal lung, neutrophils are present but in low numbers, representing at most 1-2% of the inflammatory cells on the alveolar epithelial surface (63). In contrast, in idiopathic pulmonary fibrosis, neutrophils represent 5-20% of the inflammatory cells present on the surface (64). Considering that neutrophils have a life span of only 1-2 days (64), a fibrotic lung must contend with a chronic burden of neutrophils and a powerful array of mediators. These inflammatory cells are activated, releasing a variety of products (such as proteases and oxidants) that injure lung parenchymal cells (65). These inflammatory cells accumulate through a combination of recruitment from blood and increased proliferation in the lung parenchyma. In the lung tissue of patients with IIP, however, neutrophil accumulation is not prominent. This discrepancy remains to be clarified. The alveolar macrophage plays a central role in this process by releasing chemotactic factors for neutrophils, such as leukotriene B_4 and interleukin-8 (64). Lung parenchymal cells also release chemoattractants for leukocytes. The release of chemoattractants by lung parenchymal cells was, in part, stimulated by cytokines (interleukin-1 and tumor necrosis factor-α) generated from alveolar macrophages (65) (Fig. 1). In idiopathic forms of fibrotic lung disease, the specific factors that chronically activate the alveolar macrophages to release these

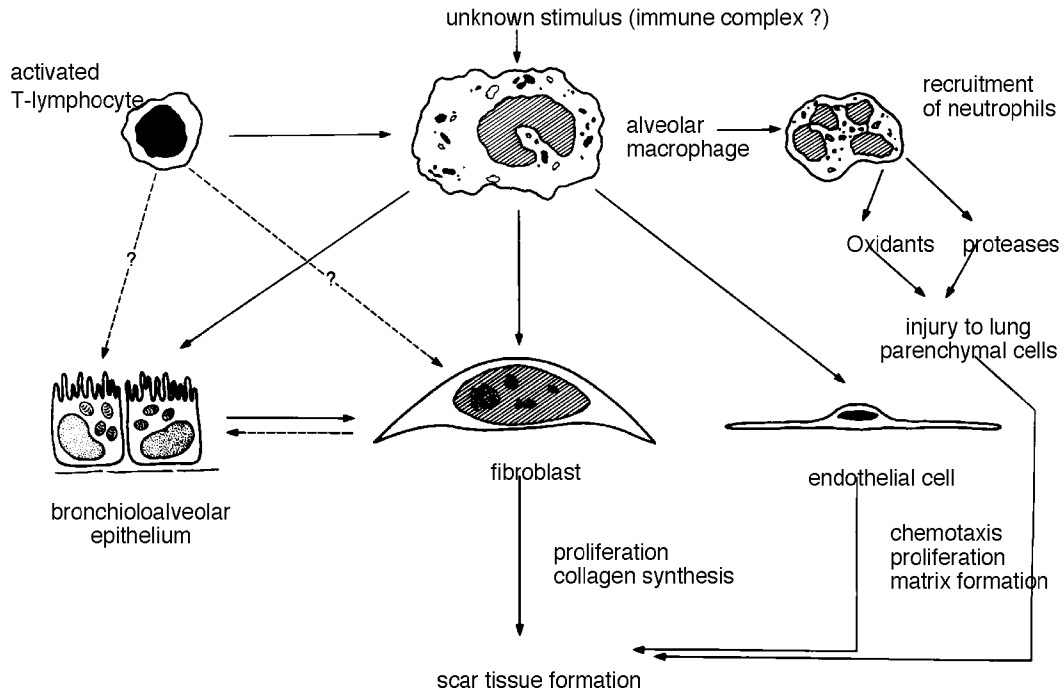

Fig. 1. Important cellular interaction related to pulmonary fibrosis.

chemoattractants and cytokines may be immune complexes (66). However, it is likely that these inflammatory processes are much more complex and involve multiple interactions among inflammatory cells, lung parenchymal cells, oxidant and antioxidants, proteases and antiproteases, adhesion molecules, and coagulation proteins.

Mechanisms of fibrosis

There is compelling evidence that the pulmonary immune system, via a complex network of cytokines and soluble molecules, may influence the fibrotic process in the lung and lung remodeling in patients with pulmonary fibrosis. The fibrotic process in the lung appears to result from a complex interaction between fibroblasts, other lung parenchymal cells, and macrophages. It should be stated that the complex relationship existing between the local release of growth-promoting cytokines [platelet-derived growth factor (PDGF), fibronectin, insulin-like growth factor-1 (IGF-1), transforming growth factor β (TGF- β)] by alveolar macrophages and resident fibroblasts represents a necessary step for fibrosis or remodeling after lung injury (67-70). The development of pulmonary fibrosis is a result of the aberrant expression of fibrogenic cytokines or dysfunctions in the regulatory mechanisms for cytokine clearance in the pulmonary microenvironment. Injury to the epithelium and basement membranes is likely necessary for the fibrotic process to occur (71). Fibroblasts migrate into areas of acute lung injury and are stimulated to secrete collagen and other matrix proteins. These cells also release various proteases that have the capacity to degrade and remodel these matrix proteins.

Transforming growth factor-β has potent stimulatory effects on the synthesis of extracellular matrix molecules (such as procollagen and fibronectin) by lung fibroblast cell lines, and this is associated with an increase in steady state levels of mRNA for these proteins (72). It also influences fibroblast proliferation. In addition, it has the potential to inhibit collagenase secretion by fibroblasts, thus decreasing degradation of extracellular collagen (73). Alveolar mac-rophages are the major source of TGF in the lower respiratory tract, but lung epithelial cells may directly propel fibroblast growth via the in situ release of members of the TGF family (74). Other macrophage-derived cytokines or molecules mediating proliferative activity of fibroblasts include PDGF, fibronectin and IGF-1, which are generated by the interactions among recruited inflammatory cells, T cells and alveolar macrophages (75). These act as growth signals for fibroblasts and epithelial cells and their receptors are abundantly expressed in lungs with pulmonary fibrosis (69, 76). It has been demonstrated that TGF-β modulates the expression of PDGF receptors on target cells and these cytokines cooperate in promoting fibroblast growth (77).

From the other point of view, as Bonner and Brody pointed out, dysfunctions in the expression of cytokine-binding pro-

teins may play a part in the pathogenesis of pulmonary fibrosis (78). In normal tissue, these proteins, which include α-macroglobulins, extracellular matrix proteins, monospecific cytokine-binding proteins, and secreted extracelluar domains of cytokine receptors, are critical avenues for the clearance of fibrogenic cytokines during physiologic repair processes. They postulated that alterations of these clearance mechanisms might lead to the local overexpression of TGF and PDGF. This hypothesis was still to be proved.

Another group of mediators involved in the evolution of fibrosis is the 5-lipoxygenase metabolites of arachidonic acid. Alveolar macrophages retrieved from the BAL fluid of patients with pulmonary fibrosis have significant amounts of leukotrienes (leukotriene B_4 and C_4) (79). In addition, lung fibroblasts isolated from patients with pulmonary fibrosis show a striking defect in their capacity to synthesize the anti-inflammatory and anti-fibrogenic molecule prostaglandin E_2 and phospholipase A_2 (80). In view of the fact that leukotriene B_4 and C_4 stimulate fibroblast proliferation and chemotaxis and favor collagen deposition, their hyperproduction and defect in prostaglandin E synthesis could be relevant in the pathogenesis of pulmonary fibrosis.

Factors and circumstances that determine whether areas of the lung heal with minimal injury or progress to irreversible injury need to be clarified. Consistent with the theory that inflammation drives the process of fibrosis, a similarity for the differences among the fibrotic lung disorders might be focused on the different types of inflammation that characterize each disorder. Even in those diseases where the cause is known (i.e., asbestosis), the factors that cause progression of fibrosis in specific areas of the lung are not defined. Therefore, effective therapy for these disorders must be given early in the natural course of the disease, prior to the development of extensive and irreversible fibrosis.

PATHOLOGY

Usual Interstitial Pneumonia

Usual interstitial pneumonia (UIP) is thought to result from repetitive episodes of lung injury, inflammation and repair. The diagnostic feature of UIP is simultaneous presence of multifocal sites of inflammation, proliferation, and fibrosis in the lung with interspersed areas of normal lung parenchyma. This feature, known as temporal variegation, is caused by multiple, ongoing, metachronous sites of lung injury (6, 8) (Fig. 2).

Most fibrosis consists of eosinophilic collagen with few associated inflammatory or stromal cells. This collagen deposition thickens alveolar septa and forms patchy scars. It also accompanies areas of honeycombing change. Although most of the fibrosis is composed of relatively old acelluar collagen bundles, small aggregates of actively proliferating fibroblast are consistently identifiable (29, 81, 82). Although fibroblast foci are not pathognomonic for UIP, they are necessary for diagnosis. They suggest the fibrosis is ongoing rather than representing the residuum of a process that occurred in the past. The presence of fibroblast foci in some places and scarring with collagen deposition or honeycombing in others comprises the essence of temporal heterogeneity of UIP and distinguishes the UIP from other idiopathic interstitial pneumonias.

Inflammation is usually mild and is composed mainly of small lymphocytes. Occasional neutrophils and eosinophils and scattered plasma cells may also be present, but not in large nubers. The inflammation occurs mainly in the areas of collagen deposition or honeycombing change and rarely in normal alveolar septa. There is no evidence that inflammation is more prominent in early disease. The presence of severe inflammation should suggest a diagnosis other than UIP.

Nonspecific interstitial pneumonia with fibrosis

Nonspecific interstitial pneumonia with fibrosis is essentially a diagnosis of exclusion, representing cases of idiopathic interstitial pneumonia that cannot be classified into one of the UIP, AIP and DIP. NSIP is characterized histopathologically by varying proportions of interstitial inflammation and fibrosis that are temporally uniform within each case (13) (Fig. 3). The process may be patchy with intervening areas of unaffected lung, but the changes are temporally uniform. In other words, they appear to have occurred over a single relatively narrow time span. In a review of 64 cases of NSIP by Katzenstein and Fiolli (13), three histologic patterns emerged: cases with cellular interstitial pneumonia and relatively little fibrosis (group 1, about 50% of cases), cases with cellular interstitial pneumonia and significant amount of admixed fibrosis (group 2, about 40%), and cases with predominant fibrosis (group 3, about 10%). Although the presence of extensive fibrosis especially in group 3 may initially suggest UIP, the uniformity of the changes and the lack of active fibrosis easily distinguishes NSIP from UIP. Foci of intraluminal organization, characteristic of bronchiolitis obliterans organizing pneumonia, are seen in nearly half of patients. However, these foci are small and inconspicuous and they constitute less than 10% of the overall changes (13).

Acute Interstitial Pneumonia

Acute interstitial pneumonia is characterized histopathologically by organizing diffuse alveolar damage in which no etiologic agent is identified. The histopathologic findings include alveolar edema, hyaline membrane formation, and extensive fibroblast proliferation but little mature collagen

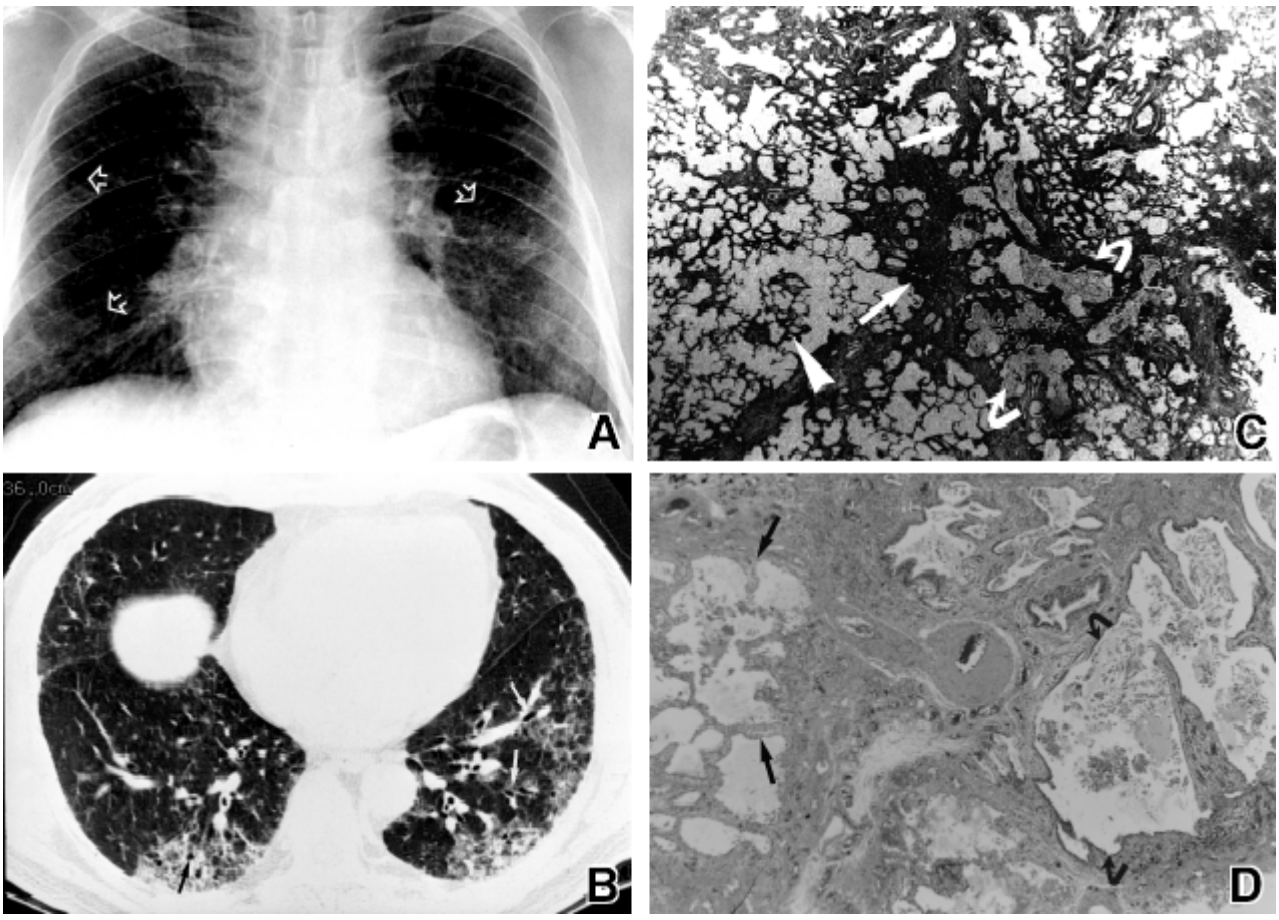

Fig. 2. Usual interstitial pneumonia in a 60-year-old man. A: Chest radiograph shows reticular lesions (open arrows) in subpleural areas of both lungs. Left lung is more extensively involved than right lung. B: High-resolution (1.0-mm collimation) CT scan obtained at level of liver dome shows patchy subpleural areas of ground-glass attenuation plus irregular linear opacity in both lungs. Bronchial dilatation (arrows) is associated. C: Low-magnification (H & E, ×40) photomicrography of biopsy specimen from left lower lobe shows characteristic variegated appearance of usual interstitial pneumonia with alternating zone of fibrosis (arrows), inflammation, honeycombing (curved arrows), and intervening residual islands of normal lung (arrowheads). D: High-magnification (H & E, ×100) photomicrography shows active interstitial inflammation (arrows) and fibrosis adjacent to honeycombing area (characterized by enlarged airspace lined by bronchiolar-type epithelium) (curved arrows).

deposition (3, 40, 41) (Fig. 4). The fibrosis in AIP differs from the other interstitial pneumonias in that the fibrosis is active and consists of proliferating fibroblasts with minimal collagen deposition. The changes are temporally uniform and appear relatively active. The appearance is identical to that of the fibroblast foci in UIP, but the pathologic process is diffuse rather than focal. If the process continues for more than a month, microscopic honeycombing change similar to UIP follows. However, the changes differ from UIP in that the walls of the airspaces of microscopic honeycombing are composed of fibroblasts as well as collagen, and are lined by alveolar rather than bronchial epithelium. The rapid development of honeycombing changes results from partial or complete collapse of some alveoli with subsequent enlargement of others (45, 83, 84).

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia is characterized histopathologically by a large number of macrophages within the airspaces, mild interstitial fibrosis, and relative histologic uniformity from field to field (3, 19, 85) (Fig. 5). Most macrophages are mononuclear, although scattered multinucleated giant cells may be observed. Minimal to moderate alveolar septal widening usually accompanies the airspace changes and is generally characterized by collagen deposition with a scant inflammatory cell infiltrate. Fibroblast foci are not a feature and honeycombing change is minimal if

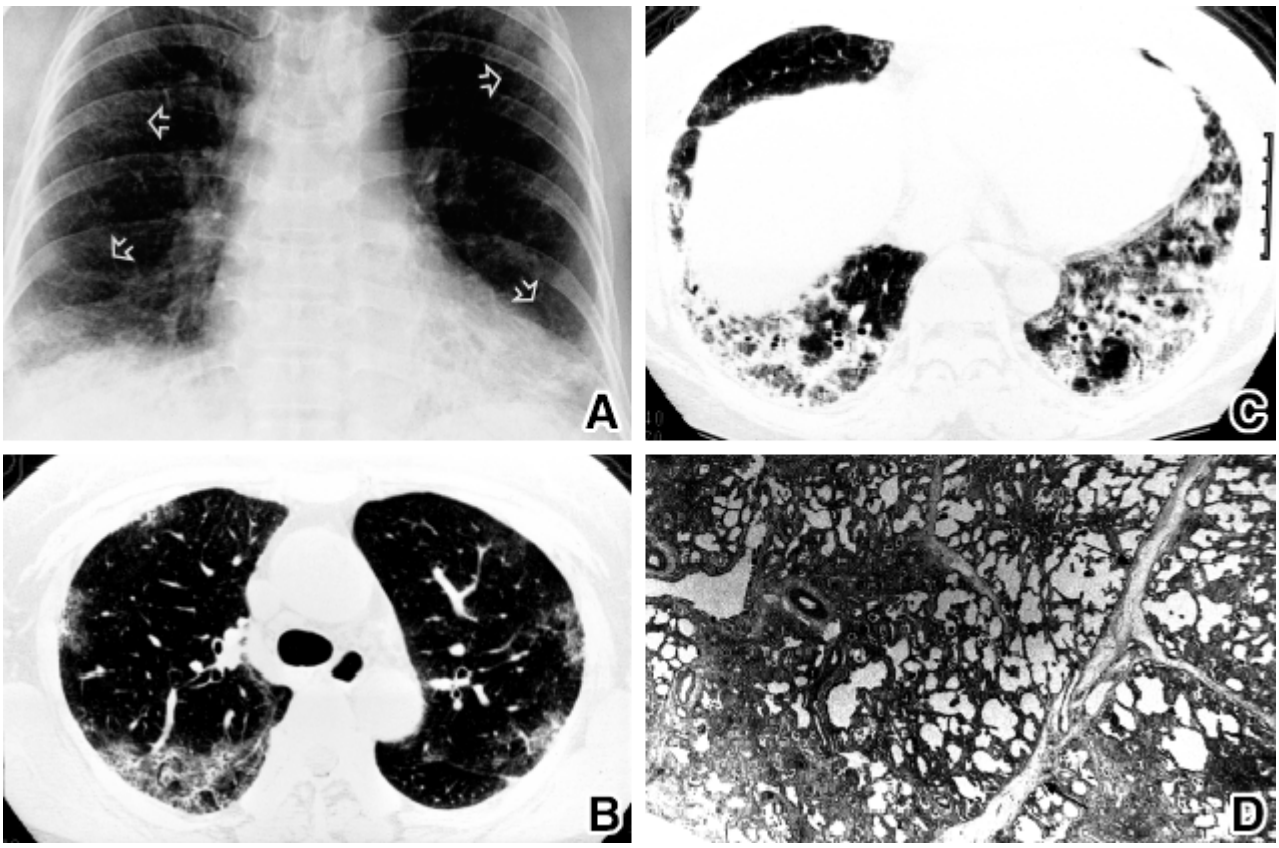

Fig. 3. Nonspecific interstitial pneumonia with fibrosis in a 51-year-old woman. A: Chest radiograph shows subtle increased opacity with fine reticular lesions (open arrows) in subpleural areas of both lungs. B: High-resolution (1.0-mm collimation) CT scan obtained at level of carina shows patchy subpleural areas of ground-glass attenuation with irregular linear opacity in both lungs. C: CT scan obtained at level of liver dome shows mixed areas of ground-glass attenuation and consolidation in both lungs. Some areas of irregular linear opacity and bronchial dilation are also seen. D: Low-magnification (H & E, x 40) photomicrography of biopsy specimen from anteromedial basal segment of left lower lobe shows temporally uniform interstitial inflammatory and fibrosing process in alveolar septa (alveoli are thickened by mixture of chronic inflammatory cells and collagen type fibrosis). Also note thickened interlobular septa (arrows).

present at all.

Macrophage accumulation in DIP is often accentuated within peribronchiolar airspaces, but when the macrophage collection is confined to the peribrochiolar areas sparing the more distal airspaces, the process is termed respiratory bronchiolitis interstitial lung disease (RBILD) (86, 87). In this condition, interstitial thickening similar to that seen in DIP accompanies the airspace changes but is confined to the peribronchiolar parenchyma (88).

RADIOLOGIC FINDINGS

Usual Interstitial Pneumonia

The most common radiographic findings of UIP are peripheral and bibasilar irregular linear opacities, subtle opacities, honeycombing, and loss of lung volume (Fig. 2). Radiographic evidence of mediastinal lymph node enlargement is rare. Chest radiographs are normal in about 5% of patients with UIP (6-8). The profusion of irregular linear opacities and the degree of volume loss and honeycombing, respectively, roughly correlate with the severity of disease, length of survival, and overall prognosis. However, correlation of radiographic findings with clinical manifestations and physiologic indexes is often poor (28, 89). In early UIP, chest radiographs typically demonstrate symmetric, peripheral and bibasilar, small- to medium-sized irregular linear or subtle opacities. The more advanced disease is characterized by coarse reticular or reticulonodular opacities. With end-stage fibrosis, distinct honeycomb cysts up to 1 cm in diameter and progressive loss of lung volume are observed.

The characteristic HRCT findings of UIP are areas of ground-glass attenuation, irregular linear opacity, and honeycombing involving predominantly the basal and subpleural lung regions (3, 34) (Fig. 2). Traction bronchiectasis is

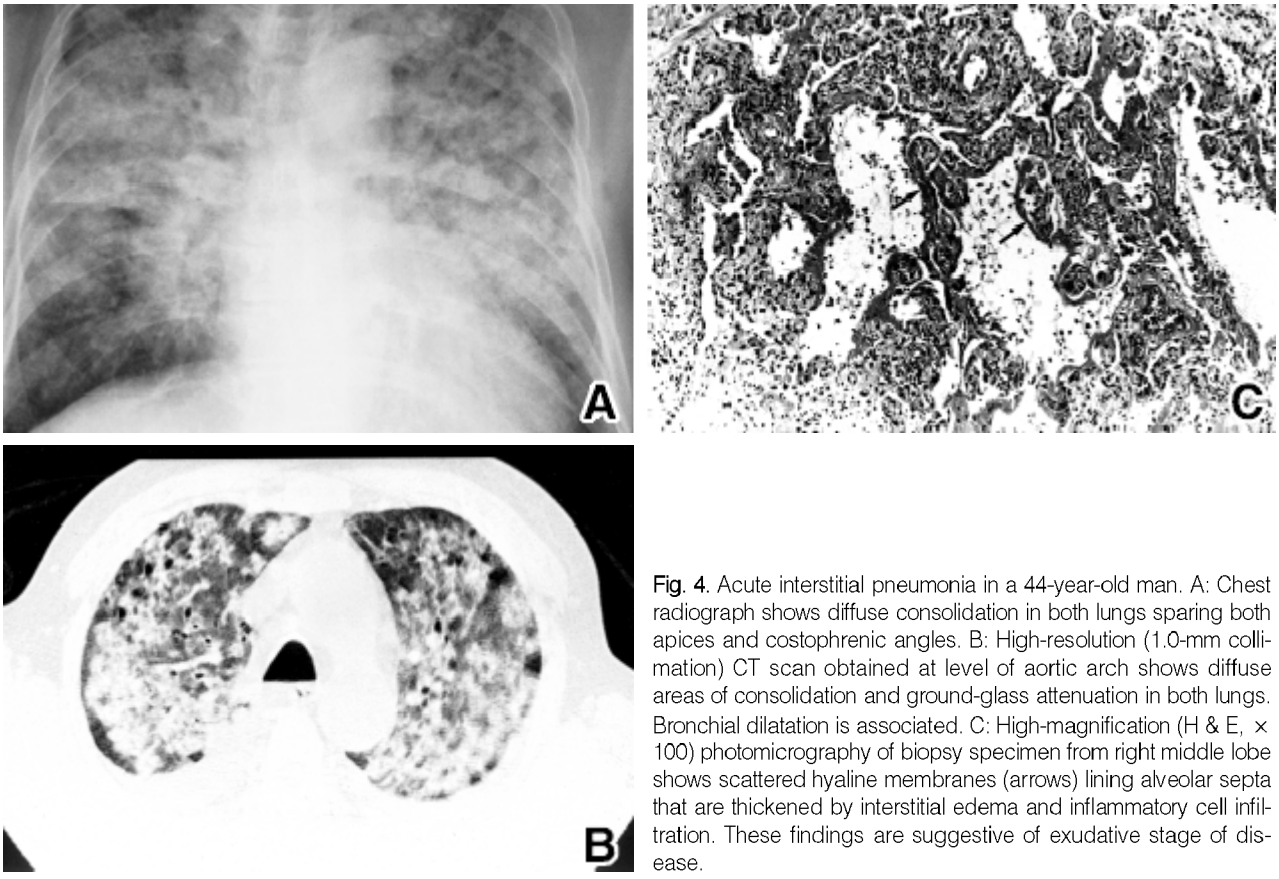

Fig. 4. Acute interstitial pneumonia in a 44-year-old man. A: Chest radiograph shows diffuse consolidation in both lungs sparing both apices and costophrenic angles. B: High-resolution (1.0-mm collimation) CT scan obtained at level of aortic arch shows diffuse areas of consolidation and ground-glass attenuation in both lungs. Bronchial dilatation is associated. C: High-magnification (H & E, × 100) photomicrography of biopsy specimen from right middle lobe shows scattered hyaline membranes (arrows) lining alveolar septa that are thickened by interstitial edema and inflammatory cell infiltration. These findings are suggestive of exudative stage of disease.

frequently associated. This pattern and distribution allow a specific diagnosis with CT in the majority of cases. Lack of subpleural honeycombing on HRCT or lung biopsy should suggest an alternative diagnosis (33). Nishimura et al. (90) correlated HRCT findings of UIP with histopathologic findings. Air bronchiolograms in the areas of intense lung attenuation (honeycombing) on HRCT scans corresponded to the dilated bronchioles (> 1 mm in diameter) with fibrosis. Irregular thickened vessels, bronchial walls and irregular pleural surfaces were a result of fibrosis in the periphery of the secondary pulmonary lobules. Areas of ground-glass attenuation on HRCT scans correlated with patchy alveolar septal fibrosis or inflammation. Akira et al. (91) evaluated the serial HRCT scans in 29 patients (12 patients received no treatment and 17 patients received corticosteroids) with UIP. Twenty-six of 29 patients showed progression of honeycombing, which was variable at CT (median, 0.4% [range, 0%-11%] per month) but not significantly different between untreated and treated patients. Areas of ground-glass attenuation on CT scans preceded and predicted the development of honeycombing in that location (Fig. 6). They concluded that low-dose therapy with corticosteroids does not suppress alveolitis sufficiently to prevent continued deterioration of the alveolar structures. Recently, Hartman et al. (43) compared the outcomes when areas of ground-glass attenuation were seen on HRCT in patients with UIP or DIP who had initial and follow-up HRCT scans (median interval, 10 months). In 9 of 12 (75%) patients with UIP, the areas of ground-glass attenuation increased in extent or progressed to fibrosis despite treatment; however, only 2 of 11 (18%) patients with DIP showed progression of disease. This would indicate that in patients with UIP, areas of ground-glass attenuation are more likely to give rise to honeycombing and irreversible lung disease than in patients with DIP. Their study also confirms the data by Carrington et al. (19) who suggested that the likelihood of response to treatment correlate not only with the extent of active alveolitis/fibrosis but also with the underlying histologic diagnosis.

Nonspecific Interstitial Pneumonia with fibrosis

The most common radiographic findings of NSIP are bibasilar and peripheral subtle opacities with or without areas of fine irregular linear opacity (Fig. 3). Normal chest radiograph may be seen in 6-14% of patients with NSIP (13, 31). Hilar nodal enlargement (6%) and pleural effusion

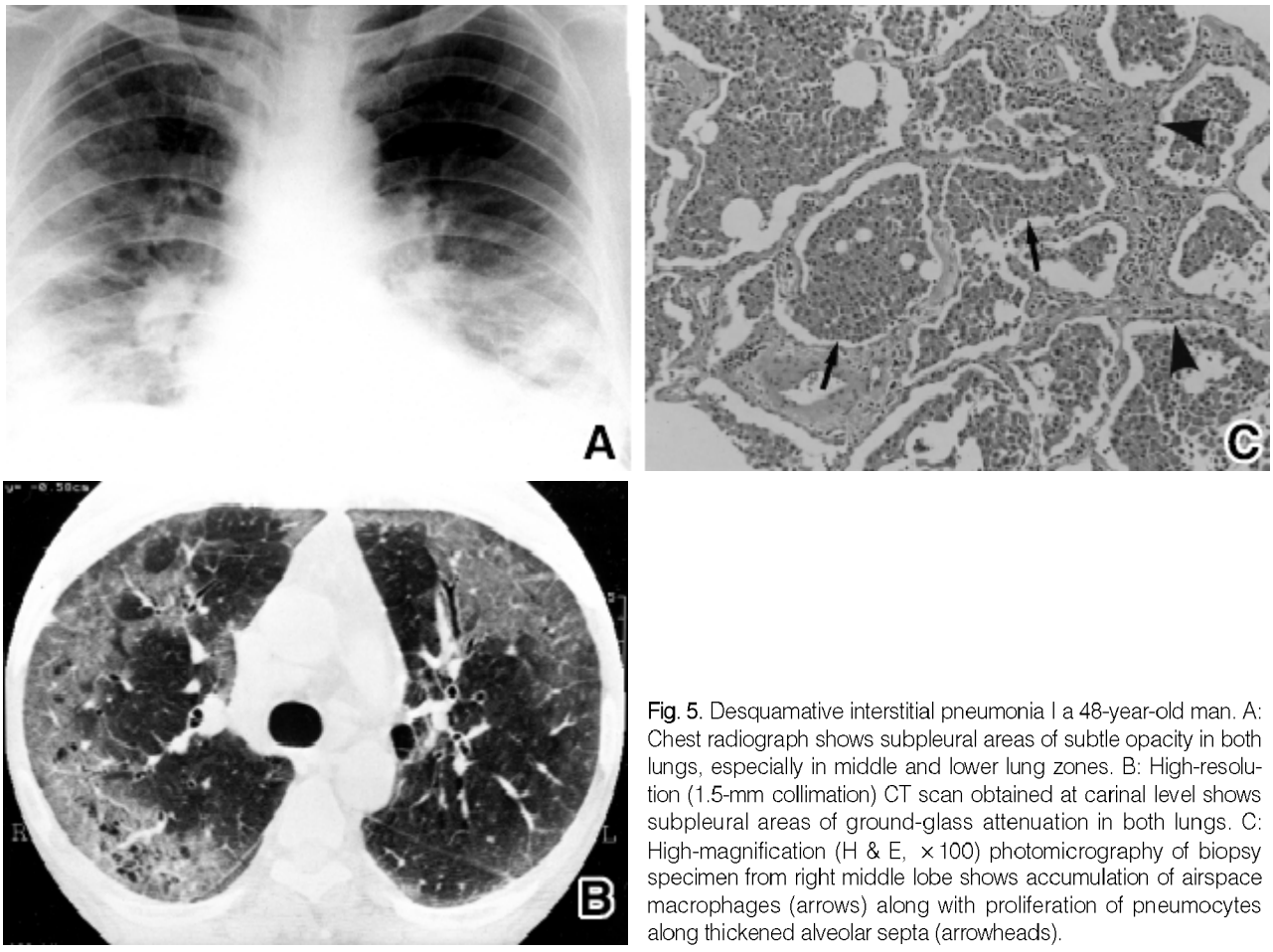

Fig. 5. Desquamative interstitial pneumonia I a 48-year-old man. A: Chest radiograph shows subpleural areas of subtle opacity in both lungs, especially in middle and lower lung zones. B: High-resolution (1.5-mm collimation) CT scan obtained at carinal level shows subpleural areas of ground-glass attenuation in both lungs. C: High-magnification (H & E, ×100) photomicrography of biopsy specimen from right middle lobe shows accumulation of airspace macrophages (arrows) along with proliferation of pneumocytes along thickened alveolar septa (arrowheads).

(5%) appear occasionally (13).

Predominant HRCT manifestations are patchy subpleural areas of ground-glass attenuation, mixed with areas of irregular linear opacity (Fig. 3). Thickening of bronchovascular bundles and bronchial dilatation are also frequently seen (31, 33). Areas of consolidation are associated in about 35% of cases especially in the lower lung zones. Honeycombing is unusual (33). On CT-pathologic correlation, areas of ground-glass attenuation with or without irregular linear opacity or bronchial dilatation on HRCT correspond pathologically to areas of interstitial thickening caused by varying degrees of interstitial inflammation and fibrosis showing temporal uniformity. Areas of consolidation represent the areas of bronchiolitis obliterans organizing pneumonia, foamy cell collections in alveolar spaces, or microscopic honeycombing with mucin stasis.

In patients with NSIP, the areas of ground-glass attenuation decrease in extent on follow up with HRCT and the extent of decrease shows significant correlation with that of functional improvement. Kim et al. (92) assessed serial changes in HRCT findings and pulmonary function in 13 patients with biopsy-proved NSIP (mean follow-up period, 11 months). On initial CT, all 13 patients with NSIP had areas of ground-glass attenuation and irregular linear opacity. With treatment, the areas of ground-glass attenuation decreased significantly in extent on follow-up CT (Fig. 7). The areas of irregular linear opacity decreased slightly in extent. Initial FVC improved significantly on follow-up examination. The decrease in the extent of ground-glass attenuation on CT showed significant correlation with changes of FVC and DLco.

Acute Interstitial Pneumonia

Acute interstitial pneumonia typically appears with progressive airspace consolidation in both lungs on chest radiograph (Fig. 4). The radiographic findings are quite similar to those of adult respiratory distress syndrome (39, 40). Primack et al. (40) reviewed the HRCT findings in 9 patients with AIP. The CT findings consisted of extensive bilateral

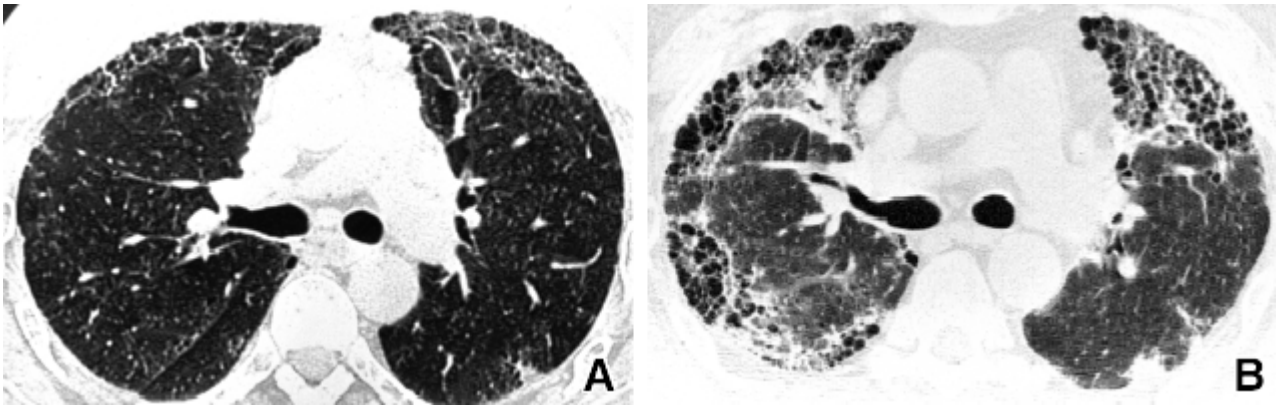

Fig. 6. Progression of disease in a 56-year-old man with usual interstitial pneumonia. A: Initial high-resolution (1.0-mm collimation) CT scan obtained at subcarinal level shows some areas of honeycombing, irregular linear opacity and ground-glass attenuation in subpleural areas of both lungs, especially in anterior aspects of both lungs. B: CT scan obtained at similar level and 28 months after A shows progression of disease with markedly increased extent of honeycombing, irregular linear opacity and ground-glass attenuation in both lungs.

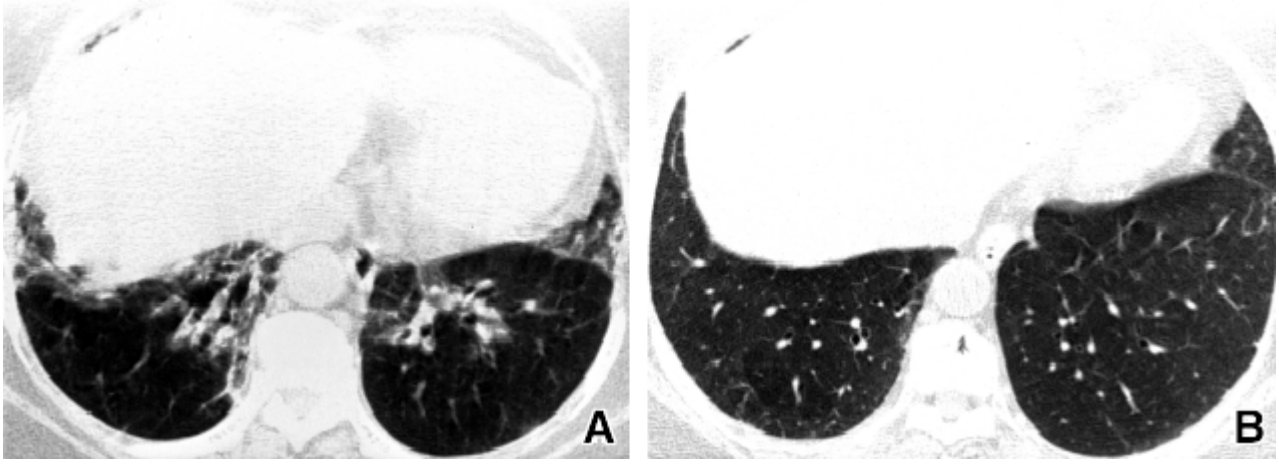

Fig. 7. Improvement of disease in a 47-year-old woman with nonspecific interstitial pneumonia with fibrosis. A: Initial high-resolution (1.0-mm collimation) CT scan obtained at level of liver dome shows patch subpleural areas of ground-glass attenuation with irregular linear opacity and bronchial dilation in both lung bases. B: Follow-up CT scan obtained at similar level and 11 months after A shows both lungs nearly normalized with disappearance of abnormal findings seen in A.

airspace consolidation (67% of cases) and patchy (67% of cases) or diffuse (33% of cases) bilateral areas of ground-glass attenuation (Fig. 4). A predominantly central or subpleural distribution was present in only 22% of cases. Recently, Ichikado et al. (41) evaluated the relation between pathologic phases and HRCT findings in 27 biopsy sites from 14 AIP patients. They found that areas of increased attenuation without traction bronchiectasis (n=9) were associated with either the exudative (n=5) (Fig. 4) or early proliferative (n=4) phase. Areas of increased attenuation with traction bronchiectasis (n=11) were associated with either the proliferative (n=4) or fibrotic (n=7) phase. Areas of honeycombing (n=1) corresponded to restructuring of distal airspaces and dense interstitial fibrosis. Spared areas (n=6) within or adjacent to areas of increased attenuation showed pathologic findings of the exudative phase. They concluded that the findings of traction bronchiectasis in areas of increased attenuation suggest the proliferative or fibrotic phase.

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia manifests with bilateral reticular lesions especially in lower lung zones with normal lung volume in 46-73% of patients (19, 93). Subtle opacities or airspace consolidation (Fig. 5), which were originally thought to be characteristic of DIP (94, 95), are seen in only 25-33% of patients. Predominant HRCT findings of DIP are bilateral areas of ground-glass attenuation that

involve mainly the middle and lower lung zones. A predominantly subpleural distribution is seen in approximately 60% of cases (Fig. 5). Irregular linear opacity, suggestive of fibrosis, is seen in approximately 50% of cases, and honeycombing is seen in 30%. The fibrosis is mild, involving mainly the subpleural regions and lung bases (85). Akira et al. (44) analyzed the sequential (mean follow-up period of 3.2 ±1.3 years, range: 1.6-6.5 years) CT findings of eight patients with DIP. They assessed the changes in pattern and extent of disease over time and also determined whether the appearances of DIP on CT scan change to those of UIP during follow-up examinations. Decrease in extent of ground-glass attenuation was seen in all patients after treatment with corticosteroids although recurrence of ground-glass attenuation was seen in only three patients. Cystic lesions, which were seen in six patients, showed no change in extent in three patients, decreased in two, and increased in one. They concluded that some of the microcysts in DIP are different from the honeycomb cysts seen in UIP, and some of the cysts seen in DIP resolve with time. DIP does not progress to UIP in the short term.

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