Usual Interstitial Pneumonia and Non-Specific Interstitial Pneumonia: Serial Thin-Section CT Findings Correlated with Pulmonary Function

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Objective: We wanted to demonstrate and compare the serial high-resolution CTs (HRCT) and the pulmonary function test (PFT) findings of the usual interstitial pneumonia (UIP) and the non-specific interstitial pneumonia (NSIP).

Materials and Methods: The serial HRCT scans and the PFT results were retrospectively analysed and compared for 35 patients having UIP without significant honeycombing (UIP-w/o hc, < 5% of honeycombing at CT), 35 patients having UIP with honeycombing (UIP-w/i hc, ≥ 5% of honeycombing), and 25 patients with NSIP. The mortality rates were also compared. Follow-up CT scans were available in 75 patients (29 UIP-w/o hc patients, 22 UIP-w/i hc patients and 24 NSIP patients) and the follow-up periods ranged from 150 to 2,370 days. The initial and follow-up PFT data were available for 71 patients.

Results: On the initial CT, significant differences were present between the UIP-w/i hc patients and both the UIP-w/o hc patients and the NSIP patients in the overall extent, ground-glass opacity (GGO) away from the reticulation, reticulation and honeycombing (all $p < 0.05$). Improvement was noticed in five (17%) of 29 UIP-w/o hc patients, none of 22 UIP-w/i hc patients, and 9 (37%) of 24 NSIP patients; deterioration was noted in six (21%) UIP-w/o hc patients, two (9%) UIP-w/i hc patients and three (13%) NSIP patients ($p = 0.044$ between UIP-w/o and UIP-w/i hc; $p = 0.637$ between UIP-w/o hc and NSIP; $p = 0.007$ between UIP-w/i hc and NSIP). The serial changes of the pulmonary function in the NSIP patients were different from those noted for the UIP-w/i hc and UIP-w/o hc patients ($p = 0.440$ between UIP-w/o and UIP-w/i hc; $p = 0.022$ between UIP-w/o hc and NSIP; $p = 0.003$ between UIP-w/i hc and NSIP). Five (14%) of the 35 patients with UIP-w/o hc, 16 (46%) of the 35 patients with UIP-w/i hc and three (12%) of the 25 patients with NSIP died ($p = 0.002$, comparison for the three groups).

Conclusion: On CT, NSIP and UIP-w/o hc patients have similar patterns of parenchymal abnormalities and a similar likelihood of change in the extent of disease on follow-up. Patients with UIP-w/i hc have distinctive features and a worst prognosis.

High-resolution CT (HRCT) plays an important role for the diagnosis and management of patients with idiopathic interstitial pneumonia (1–4). However, the ability of HRCT to distinguish usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP), the two largest subsets of idiopathic interstitial pneumonias, is controversial because there is considerable overlap in CT findings for these maladies (3, 5, 6). This distinction is important because NSIP is known to show a better prognosis than UIP (7–9).

It has been reported that there is a difference in survival between those patients having the HRCT findings typical of UIP (extensive subpleural honeycombing, reticu-

lation and minimal ground-glass opacity) and those patients without these typical features (10). The extent of honeycombing of the lung on HRCT is small (around 5%) in the patients surviving UIP (11), and this is the most probable or definite diagnostic indicator of the disease (10, 12), and the honeycombing is progressive in extent on the follow-up studies even with low-dose corticosteroid treatment (13). Therefore, patients with UIP may be subdivided into those patients having UIP without significant honeycombing (UIP-w/o hc; < 5% of honeycombing at CT) and those patients having UIP with honeycombing (UIP-w/i hc; ≥ 5% of honeycombing).

The differences in the CT patterns and for survival that are observed for the same interstitial lung disease entity in different series or from different institutions might be explained by the differences in the homogeneity of the patient population included. The aim of the current study was to demonstrate the initial and serial CT findings of the pathologically proven UIP and NSIP patients seen at a single institution, and these findings were correlated with the serial pulmonary function changes.

MATERIALS AND METHODS

Patients and Histopathologic Diagnosis

All the open and thoracoscopic lung biopsy diagnoses for the cases of idiopathic interstitial pneumonias seen in a single tertiary hospital over a nine-year period (November 1994 - October 2003) were searched for by conducting a review of the computer records. One hundred and twenty-eight patients with idiopathic interstitial pneumonias were identified. Two independent experienced lung pathologists (one with 13 years of experience from our hospital and the other with 27 years of experience from another hospital), who were blinded to the clinical and radiological features, retrospectively reviewed all the pathologic specimens from these patients. The pathologic specimens were obtained by video-assisted thoracoscopic surgery (VATS) (n=89), open lung biopsy (n=36), and lobectomy (n=3). Of the 128 patients, 29 patients were diagnosed to have idiopathic interstitial pneumonias other than UIP or NSIP. Therefore, we excluded these 29 patients from the study. Of the remaining 99 patients, three was regarded to have radiologically and clinically overt acute exacerbations of the usual interstitial pneumonias and one was regarded to have mixed *Pneumocystis carinii* and cytomegalovirus pneumonias. These four patients were also excluded from the study. We included the remaining 95 patients who were diagnosed as having had UIP or NSIP by one or two of the lung pathologists. When the two pathologists had a different opinion (n=9) regarding the diagnosis of UIP or

NSIP, an experienced chest physician with 13 years of experience made the final diagnosis in consideration of all available clinical, radiological and histopathologic data.

Clinical Features and Pulmonary Function Test

Clinical data were obtained by reviewing the patients' hospital records. These records included the duration and nature of the symptoms, the initial and follow-up PFT findings, the treatment regimens and the number and causes of death. The mean interval between the onset of clinical symptoms and the initial CT was 15 months (SD [standard deviation]; 25 months, range; 10 days to 120 months). The presenting symptoms included dyspnea in 39 patients (41%), cough in 32 (34%), cough and dyspnea in 16 (17%), chest pain in four (4%), fever in one (1%), and blood tinged sputum in one (1%). The remaining two (2%) patients were asymptomatic. The mean time interval between lung biopsy and the initial CT examination was 18 days (median; 9 days, range; 0 to 300 days). In 89 (94%) of 95 patients, the CT was performed within 60 days of biopsy. In the remaining six patients, the CT was performed within 60−300 days of biopsy. CT was performed before biopsy in 91 (95%) patients and it was obtained after biopsy in four patients.

All of the patients received no treatment before the initial CT scan. During the follow-up period between their CT scans, 47 (49%) patients received cyclosphosphamide therapy with or without corticosteroids, 24 (25%) received interferon-gamma with or without cyclosphosphamide or corticosteroids, nine (10%) received parenteral or oral corticosteroids alone, and 15 (16%) received no treatment.

The initial and follow-up pulmonary function test (PFT) data were available for 71 (75%) of 95 patients. Forced spirometry and the single-breath carbon monoxide diffusing capacity of the lung (DL_{CO}) were obtained with pulmonary function units (SensorMedics Corporation, Yorba Linda, CA, USA). The forced vital capacity (FVC) and DL_{CO} were expressed as a percentage of the predicted value based on the patients' height, age, gender and ethnic origin.

CT Interpretation

The initial HRCT scans were available for all 95 patients. The follow-up CT scans, regardless of the patients' final outcome (death), were available for 75 (79%) of 95 patients. These included all five of the deceased UIP-w/o hc patients, eight of the 16 deceased UIP-w/i hc patients, and two of the three deceased NSIP patients. In these deceased patients, the last CT scans obtained prior to the acute exacerbation of pulmonary fibrosis or prior to the appearance of the pulmonary lesions that led to the

patients' death were analyzed. The mean intervals between the initial and follow-up CTs were 711 days (SD; 551, range; 210−2,220 days) in the UIP-w/o hc patients, 484 days (SD; 366, range; 150−1,440 days) in the UIP-w/i hc patients, and 939 days (SD; 703, range; 150−2,370 days) in the NSIP patients, respectively.

The HRCT scans were performed using 1-mm collimation at 10-mm intervals from the lung apices to the lung bases at the end of inspiration. The images were reconstructed using a high spatial frequency algorithm and they were photographed on the lung window (window width; 1,500 H, level; −700 H). Two experienced chest radiologists (with two years and six years of experience, respectively), who were unaware of the clinical, lung function or pathological data, independently analyzed the CT images.

The observers made a subjective assessment of the overall extent of the pulmonary parenchymal abnormality as well as the extent of the consolidation, the total extent of the ground-glass opacity (GGO), the extent of the GGO away from the reticulation, reticulation, honeycombing and nodular opacities. Consolidation was considered present when the opacity obscured the underlying vessels. GGO was defined as an area of hazy increased attenuation without obscuration of the underlying vascular markings. Reticulation was defined as the innumerable, interlacing lines suggesting a mesh. Honeycombing was regarded as present when clustered cystic airspaces 3−10 mm in diameter with shared well-defined walls were identified with layering in the subpleural lungs. The extent of the parenchymal abnormality was scored to the nearest 5%; when less than 10% of the lung was involved, an estimate to the nearest 1% was recorded. The overall symmetry and distribution of the parenchymal abnormalities both in the transverse (central, peripheral, diffuse or random) and longitudinal planes (upper zone, lower zone, random or diffuse) were recorded. The two independent observers who initially analyzed the images from the first HRCT study were blinded to the follow-up scans. Next, the two independent observers simultaneously viewed the initial and follow-up HRCT images of each patient and they scored the overall extent and distribution of the CT abnormalities and the extent of each CT pattern on the follow-up study. These data were used to calculate the interobserver agreement and the data were used in the comparisons outlined below. Finally, a consensus reading was performed between the two observers and a third experienced chest radiologist (with 15 years of experience), in the cases where there was a discrepancy between the two observers regarding the presence or absence of individual CT patterns. These data were used solely for descriptive purposes.

Data Analysis

Interobserver variations in the specific diagnoses of idiopathic interstitial pneumonias and in distinguishing NSIP from UIP between the two lung pathologists were calculated using Kappa statistics.

The number of the deceased patients and the causes of death during the follow-up period were described and compared for the three groups, namely, the patients in UIP-w/o hc, the patients in UIP-w/i hc and the patients in NSIP. Statistical differences of the mortality rates during the follow-up period for the three different groups of interstitial pneumonia were tested for by performing Chi-square testing followed by Fisher's exact test with using the permutation method for multiple testing. The inter-observer agreement for the overall extent and presence of irregular linear opacity, honeycombing, GGO, GGO away from the reticulation, reticulation and consolidation was analyzed by calculating the intra-class correlation coefficient.

The means of both observers for the overall extent of disease and for each CT pattern were calculated for the initial and the follow-up studies. A change in the overall disease extent of 10% or greater was considered to represent disease regression or progression, while a change of less than 10% was considered insignificant and within experimental error. We correlated the changes in the extent of each parenchymal and total abnormality and the changes in the extent of the pulmonary function by using Spearman's correlation analysis.

Statistical differences for the presence of and the extent of the various patterns of parenchymal abnormalities for the three different groups were analyzed by using Kruskal-Wallis test or by one-way analysis of variance (ANOVA), and by using the least significant difference test for multiple comparisons. The statistical differences for the inter-scan HRCT changes and the pulmonary function of the three different groups were tested for by Fisher's exact test with using the permutation method and Bonferroni's correction for multiple testing. In all the statistical analyses, *p* values less than 0.05 were regarded as significant.

RESULTS

The diagnostic agreement between the two lung pathologists for the diagnosis of UIP and NSIP was 91% (86 of 95 cases) (kappa score, 0.76). Of the 95 patients included in the study, 35 patients (37%) had UIP-w/o hc, 35 patients (37%) had UIP-w/i hc and 25 patients (26%) had NSIP. During the follow-up period, five patients (14%) of the 35

UIP-w/o hc patients, 16 patients (46%) of the 35 UIP-w/i hc patients, and three patients (12%) of the 25 NSIP patients died ($p = 0.002$, comparison for the three groups was done using Chi-square testing followed by Bonferroni's correction, Table 1). The mortality rates of the patients with UIP-w/i hc were significantly different from those of the patients with UIP-w/o hc ($p = 0.014$) or NSIP ($p = 0.016$). However, the mortality rates were not significantly different between the patients with UIP-w/o hc and the patients with NSIP ($p = 1.000$). The causes of death in the five UIP-w/o hc patients were acute exacerbation of pulmonary fibrosis per se in four and lung cancer in one; the causes of death in the 16 UIP-w/i hc patients were acute exacerbation of pulmonary fibrosis per se in 10,

Table 1. Interobserver Agreements for the Mean Extent of Each Parenchymal Abnormality at the Initial High-Resolution CT

Parenchymal Abnormality	Intra-class Correlation Coefficient	95% CI for Intra-class Correlation Coefficient
Overall	0.956	(0.940, 0.969)
GGO	0.920	(0.892, 0.943)
GGO away from reticulation	0.177	(0.056, 0.306)
Consolidation	0.757	(0.683, 0.819)
Reticulation	0.519	(0.407, 0.624)
Honeycombing	0.784	(0.716, 0.840)
Nodular opacity	0.699	(0.613, 0.774)

Note.—GGO = ground-glass opacity
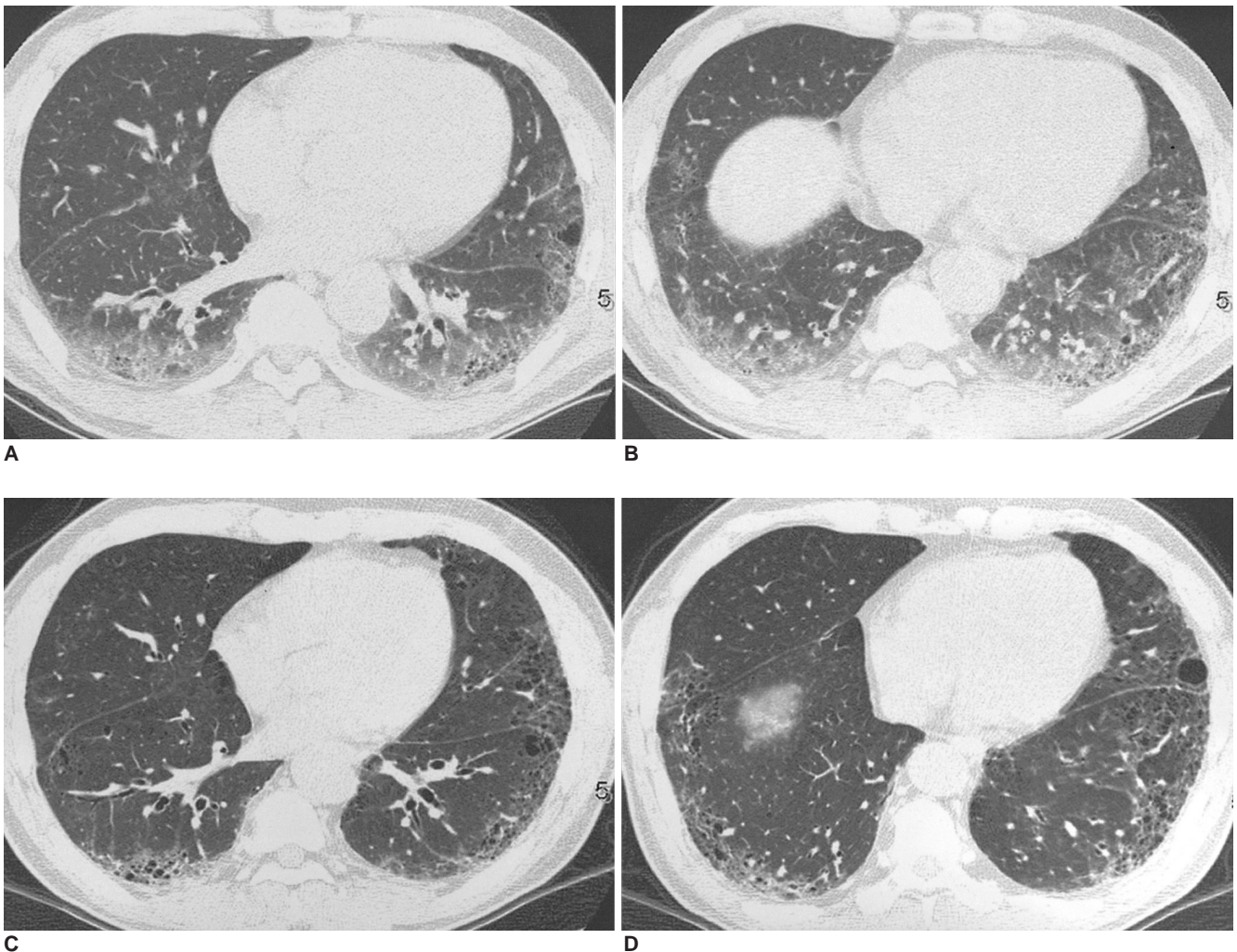

A

B

C

D

Fig. 1. Usual interstitial pneumonia without significant honeycombing in a 54-year-old man.
A, B. Lung window of the transaxial high-resolution (1.0-mm collimation) CT scans obtained at the levels of the inferior pulmonary vein (**A**) and the liver dome (**B**), respectively, show patchy ground-glass opacity, reticulation, and a little honeycombing in the subpleural areas and in the posterior aspect of both lower lobes (total extent; 34% of the lung volume, ground-glass opacity; 24%, reticulation; 8%, honeycombing; 2%).
C, D. CT scans obtained at similar levels to **A** and **B** and at four and half years later show the decreased extent of the overall parenchymal abnormalities, but the increased extent of honeycombing and reticulation (total extent; 24% of the lung volume, ground-glass opacity; 7%, reticulation; 11%, honeycombing; 6%).

pneumonia in three, lung cancer in two and adult respiratory distress syndrome triggered by interferon-gamma treatment in one; the causes of death in the three NSIP patients were sepsis, wound infection and lymphoma, respectively.

Initial HRCT Findings

There was fair to good agreement between the observers for the extent of parenchymal abnormalities except for the GGO away from the reticulation (Table 1). On the initial CT, GGO, GGO away from the reticulation, reticulation, honeycombing, consolidation and nodular opacities were present in 35 (100%), 12 (34%), 35 (100%), 22 (63%), seven (20%), and two (6%) of the 35 UIP-w/o hc patients

(Fig. 1); in 35 (100%), four (11%), 35 (100%), 35 (100%), six (17%), and one (3%) of the 35 UIP-w/i hc patients (Fig. 2); and in 25 (100%), 12 (48%), 23 (92%), 11 (44%), nine (36%), and three (12%) of the 25 NSIP patients (Fig. 3), respectively. The abnormalities were symmetrical in all the patients. On the transaxial plane, the distribution of the abnormalities was predominantly subpleural in 33 (94%) of the 35 UIP-w/o hc patients, in 34 (97%) of the 35 UIP-w/i hc patients and in 22 (88%) of the 25 NSIP patients; the distribution of the abnormalities were random in one (3%) of the 35 UIP-w/o hc patients, zero (0%) of the 35 UIP-w/i hc patients, and one (4%) of the 25 NSIP patients; and the distribution of the abnormalities was diffuse in one (3%) of the 35 UIP-w/o hc patients, in one (3%) of the 35
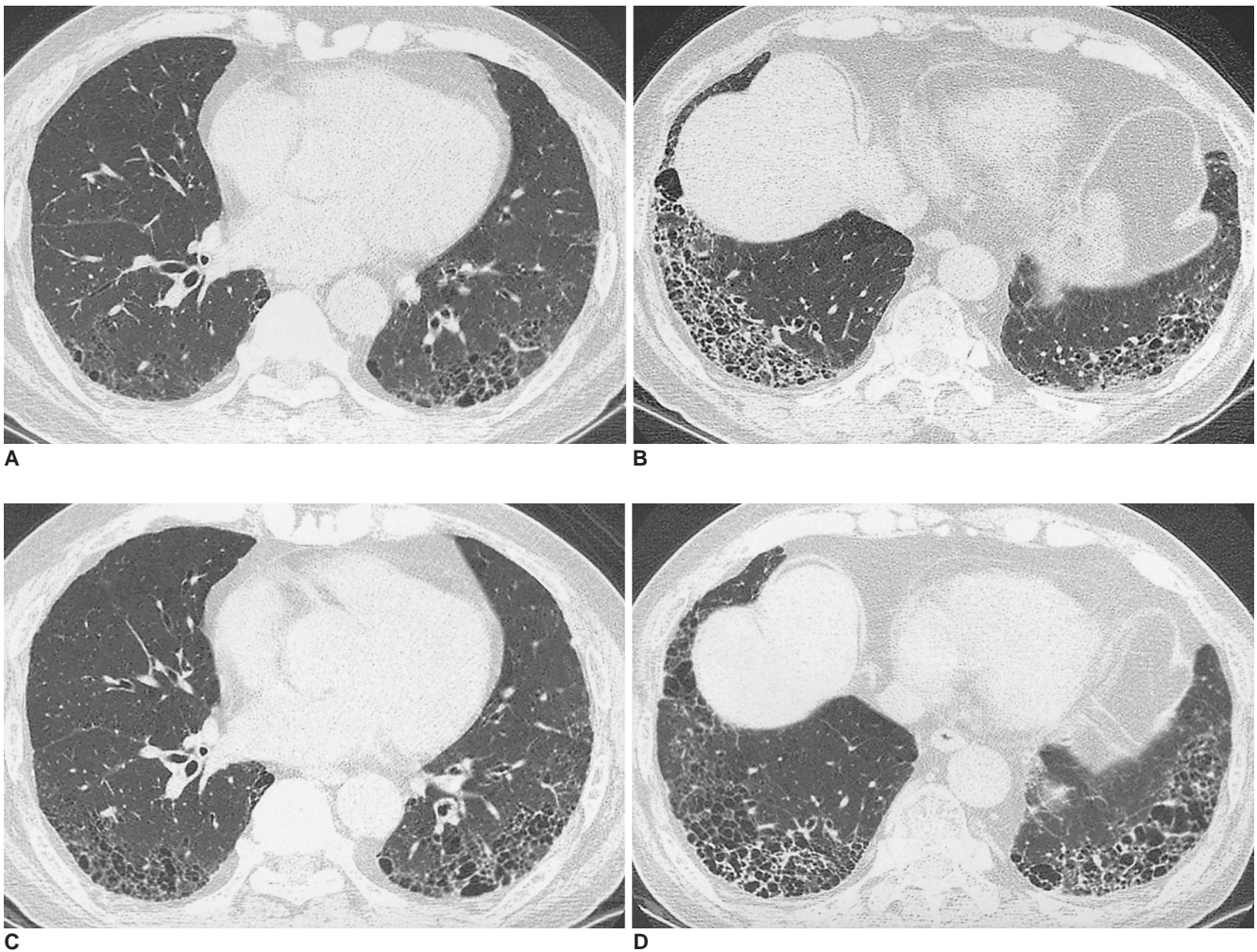

Fig. 2. Usual interstitial pneumonia with honeycombing in a 63-year-old man.
A, B. Lung window of transaxial hiph-resolution (1.0-mm collimation) CT scans obtained at the levels of inferior pulmonary vein (**A**) and the liver dome (**B**), respectively, show patchy ground-glass opacity, reticulation and honeycombing in the subpleural area and in the posterior aspect of both lower lobes (total extent; 27% of lung volume, ground-glass opacity; 10%, reticulation; 5%, honeycombing; 12%).
C, D. CT scans obtained at similar levels to **A** and **B** and four years later show little change in extent of the parenchymal abnormalities (total extent; 30% of lung volume, ground-glass opacity; 10%, reticulation; 5%, honeycombing; 15%).

UIP-w/i hc patients, and in two (8%) of the 25 NSIP patients. On the cephalo-caudal plane, the lesions were predominantly in the lower zone in 25 (71%) of the 35 UIP-w/o hc patients, in 27 (77%) of the 35 UIP-w/i hc patients and in 21 (84%) of 25 NSIP patients; the lesions were random in nine (26%) of the 35 UIP-w/o hc patients, in seven (20%) of the 35 UIP-w/i hc patients, and in three (12%) of 25 NSIP patients; and the lesions were diffuse in one (3%) of the 35 UIP-w/o hc patients, in one (3%) of the 35 UIP-w/i hc patients, and in one (4%) of the 25 NSIP patients.

The mean extents of the overall lung abnormality, GGO, GGO away from the reticulation, reticulation, honeycombing, consolidation and nodular opacities were 27%, 17%, 2%, 8%, 2%, 1% and 0% in the UIP-w/o hc patients; 43%, 19%, 0%, 11%, 13%, 0% and 0% in the UIP-w/i hc patients; and 33%, 20%, 3%, 9%, 2%, 3% and 0% in the NSIP patients, respectively (Table 2). The mean extents of overall lung abnormality, GGO away from the reticulation, reticulation and honeycombing of UIP-w/i hc patients were
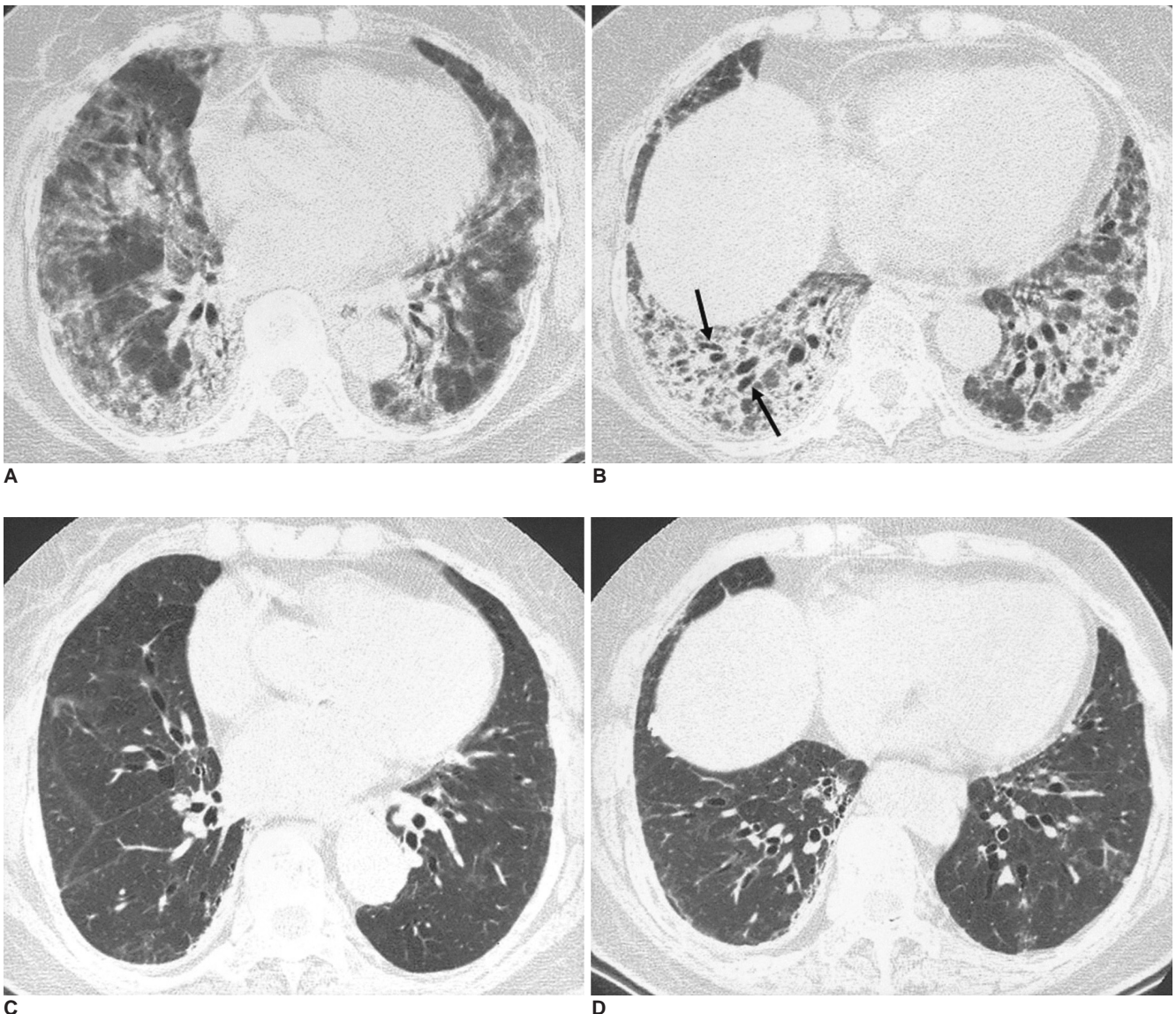
Fig. 3. Non-specific interstitial pneumonia in a 73-year-old woman.
A, B. Lung window of the transaxial hiph-resolution (1.0-mm collimation) CT scans obtained at the levels of the inferior pulmonary vein (**A**) and the liver dome (**B**), respectively, show extensive patchy ground-glass opacity, consolidation and reticulation in both lungs (total extent; 45% of lung volume, ground-glass opacity; 30%, consolidation; 7%, reticulation; 8%). Also note the traction bronchiectasis (arrows).
C, D. CT scans obtained at similar levels to **A** and **B** and five years later show the decreased extent of the parenchymal abnormalities (total extent; 20% of lung volume, ground-glass opacity; 12%, reticulation; 8%).

significantly different from those of the patients with UIP-w/o hc or NSIP (Tables 2, 3). However, the mean extent of each parenchymal abnormality was not significantly different between the patients with UIP-w/o hc and the patients with NSIP (Tables 2, 3).

Follow-up HRCT Findings

At the follow-up CT, the mean ($\pm$ SD) overall extent of

abnormal lung parenchyma was 26% ($\pm$ 16%) in the UIP-w/o hc patients, 44% ($\pm$ 18%) in the UIP-w/i hc patients, and 24% ($\pm$ 11%) in the NSIP patients. The distribution of the parenchymal abnormalities was similar to those seen at the initial CT. The mean extent of GGO, GGO away from the reticulation, reticulation, honeycombing, consolidation and nodular opacities at the follow-up CT were 13%, 0%, 10%, 2%, 1% and 0% in the UIP-w/o hc

Table 2. The Mean Extent of Parenchymal Abnormalities at the Initial High-Resolution CT

Parenchymal abnormality	Group	N	Mean	Median	SD	Range	Inter-quartile range	p-value*
Overall*	UIP-w/o hc	35	27	27.0	15.9	(5, 77)	(17, 35)	< 0.001
	UIP-w/i hc	35	43	42.0	17.6	(15, 95)	(32.0, 50.0)	
	NSIP	25	33	30.0	17.7	(8, 93)	(20, 40)	
GGO*	UIP-w/o hc	35	17	13.0	14.6	(2, 67)	(8, 22)	0.436
	UIP-w/i hc	35	19	15.0	13.3	(6, 77)	(10.0, 22.0)	
	NSIP	25	20	17.0	13.2	(5, 60)	(10, 25)	
GGO away from reticulation*	UIP-w/o hc	35	2	0	6.0	(0, 27)	(0, 1)	0.004
	UIP-w/i hc	35	0	0	0.6	(0, 3)	(0, 0)	
	NSIP	25	3	0	6.4	(0, 28)	(0, 3)	
Consolidation*	UIP-w/o hc	35	1	0	1.7	(0, 7)	(0, 0)	0.082
	UIP-w/i hc	35	0	0	1.0	(0, 5)	(0, 0)	
	NSIP	25	3	0	4.4	(0, 18)	(0, 5)	
Reticulation[†]	UIP-w/o hc	35	8	8.0	3.7	(1, 15)	(5, 10)	0.004
	UIP-w/i hc	35	11	11.0	4.5	(3, 23)	(8, 13)	
	NSIP	25	9	8.0	4.7	(0, 20)	(7, 12)	
Honeycombing*	UIP-w/o hc	35	2	2	1.4	(0, 4)	(0, 2)	< 0.001
	UIP-w/i hc	35	13	11	7.3	(5, 30)	(7, 17)	
	NSIP	25	2	0	2.7	(0, 10)	(0, 3)	
Nodular opacity*	UIP-w/o hc	35	0	0	0.4	(0, 2)	(0, 0)	0.338
	UIP-w/i hc	35	0	0	0.2	(0, 1)	(0, 0)	
	NSIP	25	0	0	0.6	(0, 2)	(0, 0)	

Note.——*Kruskal-Wallis test, [†]ANOVA test, NSIP = non-specific interstitial pneumonia, UIP-w/o hc = usual interstitial pneumonia without significant honeycombing, UIP-w/i hc = usual interstitial pneumonia with honeycombing, GGO = ground-glass opacity, N = number of patients, SD = standard deviation

Table 3. Statistical Differences of the Mean Extent of Parenchymal Abnormalities at the Initial CT in Three Different Groups of Interstitial Pneumonia

Parenchymal Abnormality	UIP-w/o hc vs. UIP-w/i hc	UIP-w/o hc vs. NSIP	UIP-w/i hc vs. NSIP
Overall*	$p < 0.001$	$p = 0.143$	$p = 0.009$
GGO away from reticulation*	$p = 0.034$	$p = 0.154$	$p = 0.001$
Reticulation[†]	$p = 0.001$	$p = 0.249$	$p = 0.056$
Honeycombing*	$p < 0.001$	$p = 0.697$	$p < 0.001$

Note.——*The least significant difference test using ranks for multiple comparisons, [†]The least significant difference test for multiple comparisons, GGO = ground-glass opacity, NSIP = non-specific interstitial pneumonia, UIP-w/o hc = usual interstitial pneumonia without significant honeycombing, UIP-w/i hc = usual interstitial pneumonia with honeycombing

Table 4. Statistical Differences of the Inter-scan Changes of the Parenchymal Abnormalities in the Three Different Groups of Interstitial Pneumonia

Inter-scan Changes	UIP-w/o hc vs. UIP-w/i hc	UIP-w/o hc vs. NSIP	UIP-w/i hc vs. NSIP
Changeable-Stable	$p = 0.044$	$p = 0.637$	$p = 0.007$
Improvement-Stable	$p = 0.167$	$p = 0.937$	$p = 0.004$
Improvement-Deterioration	$p = 1.000$	$p = 1.000$	$p = 0.392$
Stable-Deterioration	$p = 0.854$	$p = 1.000$	$p = 1.000$

Note.——Changeable = Improvement or deterioration, Improvement = $\geq$ 10% reduction, Deterioration = $\geq$ 10% increase, Stable = less than 10% of inter-scan changes, NSIP = non-specific interstitial pneumonia, UIP-w/o hc = usual interstitial pneumonia without significant honeycombing, UIP-w/i hc = usual interstitial pneumonia with honeycombing

patienta; 18%, 1%, 13%, 13%, 1% and 0% in the UIP-w/i hc patients; and 13%, 0%, 9%, 2%, 0% and 0% in the NSIP patients, respectively.

Inter-scan Changes

There was an improvement ($\geq 10\%$ reduction) in the overall disease extent in five (17%) of the 29 UIP-w/o hc patients (Fig. 1), zero (0%) of the 22 UIP-w/i hc patients and nine (37%) of the 24 NSIP patients (Fig. 3); a deterioration ($\geq 10\%$ increase) of the disease extent was noted in six (21%) of the UIP-w/o hc patients, in two (9%) of the UIP-w/i hc patients and in three (13%) of the NSIP patients. The observed changes were less than 10% in the remaining 18 (62%) UIP-w/o hc patients, in 20 (91%) of the UIP-w/i hc patients (Fig. 2), and in 12 (50%) of the NSIP patients. A statistically significant difference of the inter-scan changes was observed in the three different groups ($p = 0.044$ between the UIP-w/o and UIP-w/i hc patients, $p = 0.637$ between the UIP-w/o hc and NSIP patients, $p = 0.007$ between the UIP-w/i hc and NSIP patients, with employing Fisher's exact test and using the permutation method and Bonferroni's correction for multiple testing, Table 4).

Overall, the mean ($\pm$ SD) absolute change in the extent of the total GGO, GGO away from the reticulation, reticulation, honeycombing, consolidation and nodule in UIP-w/o hc patients was -5% (18%), -2% (7%), 2% (4%), 1% (2%), 0% (2%), and 0% (0%), where a negative change indicates a reduction. Overall, the mean ($\pm$ SD) absolute change in the extent of the total GGO, GGO away from the reticulation, reticulation, honeycombing, consolidation and nodule was 2% (7%), 1% (4%), 1% (2%), 0% (3%), 0% (2%), and 0% (0%) in the 22 UIP-w/i hc patients and -5% (10%), -2% (6%), 1% (4%), 0% (3%), -2% (4%), and 0% (1%) in the 24 NSIP patients, respectively.

Relationship between the Initial HRCT Pattern and the Changes in Pulmonary Function

The initial and follow-up PFT data were available in 71 patients (23 NSIP, 28 UIP-w/o hc and 20 UIP-w/i hc patients). There was an improvement ($\geq 15\%$ reduction) for the pulmonary function in four (14%) of the 28 UIP-w/o hc patients, in zero (0%) of the 20 UIP-w/i hc patients and in nine (39%) of the 23 NSIP patients; there was a deterioration ($\geq 15\%$ increase) in two (7%) of the UIP-w/o hc patients, in two (10%) of the UIP-w/i hc patients and in three (13%) of the NSIP patients. The observed changes were less than 15% in the remaining 22 (79%) UIP-w/o hc patients, in the remaining 18 (90%) UIP-w/i hc patients and in the remaining 11 (48%) NSIP patients. The

Table 5. Correlation between the Changes in the Extent of Parenchymal Abnormality and the Changes in the Extent of Pulmonary Function

Parenchymal Abnormality	Forced Vital Capacity	Diffusing Capacity of the Lung
Overall	$r = -0.723$, $p < 0.001$	$r = -0.236$, $p = 0.051$
GGO	$r = -0.718$, $p < 0.001$	$r = -0.196$, $p = 0.107$
GGO away from reticulation	$r = -0.401$, $p = 0.001$	$r = 0.016$, $p = 0.896$
Consolidation	$r = -0.395$, $p = 0.001$	$r = -0.045$, $p = 0.713$
Reticulation	$r = -0.514$, $p < 0.001$	$r = -0.262$, $p = 0.029$
Honeycombing	$r = -0.188$, $p = 0.122$	$r = -0.209$, $p = 0.085$
Nodular opacity	$r = 0.189$, $p = 0.120$	$r = 0.202$, $p = 0.096$

Note.— GGO = ground-glass opacity

serial changes of the pulmonary function in the NSIP patients were different from those in UIP-w/i hc and UIP-w/o hc patients ($p = 0.440$ between the UIP-w/o and UIP-w/i hc patients; $p = 0.022$ between the UIP-w/o hc and NSIP patients; $p = 0.003$ between the UIP-w/i hc and NSIP patients).

The change in the overall extent, GGO, reticulation, GGO away from the reticulation and consolidation of the parenchymal abnormalities on the HRCT showed moderate correlation with the changes in FVC, but only the change in extent of reticulation correlated with the change in the DL_{CO} (Table 5).

DISCUSSION

The initial reports on the HRCT features of NSIP suggested there was a characteristic pattern consisting of patchy bilateral, predominantly middle- and lower-zone predominant GGO with or without consolidation or reticulation, and the absence or the rarity of honeycombing (14, 15). Contrary to the relatively homogenous descriptions in these initial reports, Hartman et al. (5), in a study of 50 patients with biopsy-proven NSIP, reported a much broader spectrum of HRCT findings. In their series, only 22% of the patients had HRCT findings compatible with the previous descriptions of NSIP, while 32% of the patients' findings were considered more typical of UIP and the remainder were considered as either non-diagnostic or more compatible with other chronic infiltrative lung diseases. MacDonald et al. (6) also reported a considerable overlap between the CT findings of NSIP and those of UIP. In our study, we demonstrated that while UIP-w/i hc had the characteristic HRCT findings, the manifestations of UIP-w/o hc were similar to those of NSIP.

Previous studies have reported that the areas of GGO in

the patients with NSIP were more likely to improve with treatment than the areas of GGO in the patients with UIP (13, 16, 17). The GGO areas in NSIP patients corresponded histopathologically to the areas of interstitial thickening that are caused by various degrees of interstitial inflammation or fibrosis (15). However, in our study, the follow-up CT scans showed no significant differences in the changes of the extent and pattern of the parenchymal abnormalities between the NSIP and UIP-w/o hc patients. It should be noted, however, that the follow up period of the UIP-w/o hc patients (mean; 711 days, SD; 551) was slightly shorter than that of the NSIP patients (mean; 939, SD; 703). Our study also demonstrated that the short-term prognosis of the NSIP patients was similar to that of the UIP-w/o hc patients, but it was better than that of the UIP-w/i hc patients. During the follow-up period, 16 (46%) of the 35 patients with UIP-w/i hc died compared to three (12%) of the 25 patients with NSIP and five (14%) of the 35 patients with UIP-w/o hc.

The histological distinction between UIP and NSIP can be difficult. In our study, two expert lung pathologists disagreed on the diagnosis of UIP vs NSIP in nine of 95 (9%) patients. Furthermore, inter-lobar and intra-lobar histologic variability is known to be common in idiopathic interstitial pneumonias. Flaherty et al. (18) have found that interlobar histologic variability was seen in 26% of the patients with NSIP and UIP. The concurrent presence of the histologic UIP and NSIP patterns within the same patient also raises questions about the pathogenesis and the nosology of these two disorders. One of the possible pathogenesis is that NSIP may be an early lesion that progresses to UIP over time.

Serial changes of the pulmonary function, including the forced vital capacity and diffusing capacity for carbon monoxide, have been reported in patients with UIP and NSIP (16, 19). When comparing the extent of GGO at presentation with the improvement of the pulmonary function after corticosteroid treatment in 19 patients with idiopathic pulmonary fibrosis, Lee et al. (19) found a significant correlation with the forced vital cavity ($r = 0.70$) and the diffusing capacity for carbon monoxide ($r = 0.67$). Kim et al. (17) have also reported that the changes in the extent of the GGO at the follow-up CT correlated well with the changes in the diffusing capacity for carbon monoxide and the forced vital capacity in the patients with NSIP. In our study, the change in the overall extent, GGO, reticulation, GGO away from the reticulation and consolidation of the parenchymal abnormalities on HRCT showed a moderate correlation with the changes in the FVC. However, the change of all the parenchymal abnormalities except reticulation did not show any correlation with the changes in the

diffusing capacity of CO gas (DL_{CO}) (Table 5). In our study, the serial changes of the pulmonary function in the three different groups were different from the HRCT changes. The follow-up CT scans showed no significant differences in the changes of the extent and the pattern of parenchymal abnormalities between the NSIP and UIP-w/o hc patients. However, the serial changes of pulmonary function were different between the NSIP and UIP-w/o hc patients.

Our study has several limitations. First, our estimation of the extent of the parenchymal HRCT abnormalities was subjective. This semi-quantitative method may not have reflected the exact extent of disease. However, our study showed fair to good agreement between the observers for the extent of parenchymal abnormalities, except for GGO away from the reticulation. Second, the follow-up periods of the UIP-w/o hc patients (mean; 711 days, SD; 551) and the UIP-w/i hc patients (mean; 484 days, SD; 366) were relatively shorter than that of the NSIP patients (mean; 939 days, SD; 703). Third, the serial changes of the extent of the parenchymal HRCT abnormalities and the pulmonary function may be different between the patients with and without treatment. The current study included both the patients with and without treatment. Fourth, about 10% of the NSIP patients had a predominant interstitial inflammation histopathology; thus, these patients had a clearly better prognosis than the remaining 90% of the NSIP patients (7, 14, 20, 21). We included all the NSIP patients without considering these histopathologic or prognostic distinctions.

In conclusion, the patients with NSIP and UIP-w/o hc showed quite similar patterns of parenchymal abnormalities at the initial and follow-up CTs, and this was different from those patterns of the UIP-w/i hc patients, and they had a better prognosis than the patients with UIP-w/i hc. Changes in the overall extent, GGO, reticulation, GGO away from the reticulation and consolidation of the parenchymal HRCT abnormalities showed moderate correlation with the changes in the FVC. Long-term, prospective follow-up studies are needed on the clinical and radiologic findings of NSIP and UIP; interdisciplinary and consensus meetings on the radiologic and histopathologic diagnosis are required to document the relationship between these two disorders.

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