Comparison of Pulmonary Abnormalities on High-Resolution Computed Tomography in Patients with Early versus Longstanding Rheumatoid Arthritis

SHUNSUKE MORI, ISAMU CHO, YUKINORI KOGA, and MINEHARU SUGIMOTO

ABSTRACT. ***Objective.*** To identify the predominant radiological abnormalities in the lungs of patients with early rheumatoid arthritis (RA) and in those with longstanding RA.

Methods. We performed high-resolution computed tomography (HRCT) on a total of 126 patients with early RA (n = 65) and longstanding RA (n = 61). The most likely diagnosis for each case was made on the basis of the predominant HRCT findings and their extent in the lungs. Pulmonary function tests were done for RA patients with parenchymal abnormalities.

Results. The most frequent finding was bronchial dilatation (41.3%), followed by ground-glass attenuation (27.0%), parenchymal micronodules (15.1%), subpleural micronodules (15.1%), reticulation (11.9%), bronchial wall thickening (11.9%), nodules (10.3%), honeycombing (8.7%), and airspace consolidation (4%). Parenchymal micronodules and bronchial wall thickening, indicative of small airway diseases, were more prominent in the patients with longstanding RA. There were no significant differences in the frequency of interstitial abnormalities such as ground-glass attenuation, reticulation, honeycombing, or consolidation between the 2 groups. We identified 10 patients with bronchiolitis pattern, 11 with nonspecific interstitial pneumonia (NSIP) pattern, 2 with usual interstitial pneumonia (UIP) pattern, and 2 with organizing pneumonia (OP) pattern. Mean values of FEV_1/FVC ratio and FEV_{25-75} were lower in the patients with the bronchiolitis pattern, and DLCO was decreased in the patients with the NSIP or UIP pattern.

Conclusion. Interstitial abnormalities were frequently observed even in patients with early RA, although most of them had no respiratory symptoms. Bronchiolar abnormalities were associated with the duration of RA. (First Release June 15 2008; J Rheumatol 2008;35:1513–21)

Key Indexing Terms:
RHEUMATOID ARTHRITIS HIGH-RESOLUTION COMPUTED TOMOGRAPHY
BRONCHIOLITIS INTERSTITIAL PNEUMONIA DISEASE DURATION

Rheumatoid arthritis (RA) is a systemic inflammatory disease. The main characteristic is a persistent synovitis of multiple joints, but numerous extraarticular manifestations occur in almost all organs, including cutaneous, ocular, hematological, cardiovascular, and pulmonary lesions. In recent cohort studies, nearly 40% of patients with RA experienced some type of extraarticular manifestations[1-3]. Pulmonary involvement manifests as a variety of clinical signs such as pleural lesions, rheumatoid nodules, interstitial lung disease/restrictive disease, and airway disease/obstructive disease[4,5]. In postmortem studies on Japanese patients with RA, pulmonary involvement (mainly interstitial lung diseases and obstructive airway diseases) is the second most common cause of death, following infectious diseases[6,7]. Nevertheless, the etiology of these complications remains to be elucidated. Prevalence rates of pulmonary abnormalities in RA have been reported with wide variance, depending on criteria used to define disease, methods used to detect disease, and patient populations examined[5,8]. In some investigations, interstitial lung disease was the most common pulmonary manifestation of RA[9-14], but in others chronic airway disease was most predominant[15-20].

Based on histopathological features, Yousem, *et al* identified 5 different groups of rheumatoid lung disease: rheumatoid nodules, organizing pneumonia (OP), usual interstitial pneumonia (UIP), lymphoid hyperplasia, and cellular interstitial infiltrates, recently considered as nonspecific interstitial pneumonia (NSIP)[21]. Since these morphological changes cause significantly different prognoses during the course of RA[10,22,23], it is important to evaluate which

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pattern of abnormalities is dominant in each individual case. For establishment of a definitive diagnosis of interstitial lung diseases or airway diseases, a lung biopsy has been required. However, recent studies have confirmed that each of these entities has a characteristic histological finding and a typical radiological pattern, which correlate well with each other[24-27], although considerable overlap in radiological features exists between NSIP and UIP[9,28,29]. High-resolution computed tomography (HRCT) therefore proves useful for detection and characterization of the morphological changes in lungs of patients with RA. Most recently, Tanaka, *et al*[9] identified 4 major HRCT patterns in patients with RA-associated pulmonary complications, namely UIP, NSIP, bronchiolitis, and OP patterns. They also confirmed that the classification based on HRCT features properly reflects pathological findings in most patients.

It has been reported that RA-associated lung disease is seen more frequently in men with longstanding rheumatoid disease, in the presence of high rheumatoid factor titers, and in the setting of more severe joint involvement[4,30,31]; however, it is a subject of debate. We performed HRCT on a total of 126 patients with early or longstanding RA. Abnormalities on HRCT imaging were categorized, and the frequency of each finding and its extent in the lungs were compared between the 2 patient populations. We made an HRCT-based diagnosis and examined a possible correlation between abnormal HRCT findings, clinical characteristics, and results of pulmonary function tests (PFT).

MATERIALS AND METHODS

Patients. We prospectively examined radiological abnormalities in the lungs of a total of 126 patients with RA (65 with early RA; 61 with longstanding RA) who visited the Department of Rheumatology of Kumamoto Saishunsou National Hospital from April 2003 through April 2007. Regardless of whether they were outpatients or patients to be hospitalized, patients diagnosed with early or longstanding RA were enrolled consecutively in this study unless they met any of the following exclusion criteria: (1) a history of pulmonary diseases precluding an accurate pulmonary evaluation; (2) a history of other collagen vascular diseases/autoimmune diseases; (3) a history of exposure to dust such as asbestos or silica; or (4) a history of thoracic radiation for cancer therapy. From the initial population (n = 167), 12 patients with early RA and 19 with longstanding RA were excluded due to these criteria: tuberculosis/atypical mycobacterial disease (n = 4), chronic bronchitis (n = 3), emphysema (n = 10), fungal infection in the lungs (n = 1), Sjögren's syndrome (n = 8), systemic sclerosis (n = 1), primary biliary cirrhosis (n = 1), asbestosis (n = 1), and thoracic radiation for lung cancer (n = 2). Ten patients (3 early RA, 7 longstanding RA) refused enrollment in the study. All participants fulfilled the 1987 American College of Rheumatology criteria for diagnosis of RA[32]. Patients with early RA were defined as those who had been diagnosed within 1 year, and longstanding RA was defined as disease duration > 3 years. Our rheumatology department has been organized to serve patients with early RA; patients were not selected based on their reasons for visit, including evaluation of articular symptoms, treatment consultation, RA complications, or other reasons. No patient had received methotrexate (MTX) or anti-tumor necrosis factor-α (anti-TNF-α) agents before enrollment. Most patients (76.2%) had no complaint of any respiratory symptoms at the time of enrollment. Twenty-one patients (16.7%) were smokers or ex-smokers. The ethics committee of our hospital approved the protocol for the study.

HRCT scanning and evaluation. A Somatom Sensation 4 instrument (4DCT, Siemens, Erlangen, Germany) was used for this study. Thin-selection CT scans (120 kV, 130 mA) were obtained with 2-mm collimation at 10-mm intervals, extending from the lung apices to the diaphragm. The images were reconstructed with a high spatial-frequency algorithm. HRCT examinations were performed with patients in the supine position, at the suspended end-inspiratory volume, with imaging times of 1 second. All images were obtained at window levels appropriate for the lung parenchyma (window width 1300 to 1500 HU; window level –750 to –650 HU) and the mediastinum (window width 400 HU; window level 30–50 HU). HRCT images were reviewed in random order independently by 2 observers (IC and YK) who were blinded to the patients' clinical status and PFT results. Final decisions were made by consensus if there were disagreements.

HRCT abnormalities included the following findings: (1) bronchial dilatation (bronchiectasis), (2) bronchial wall thickening, (3) airspace consolidation, (4) nodular attenuation (including parenchymal micronodules, nodules, and subpleural micronodules), (5) ground-glass attenuation, (6) linear attenuation (reticulation, including septal lines, nonseptal lines, and subpleural lines), (7) honeycombing, and (8) architectural distortion. These abnormal findings were defined according to the criteria described by Terasaki, *et al*[15] except that nodular attenuation was subdivided into 3 groups: (a) parenchymal micronodules ≤ 3 mm diameter, (b) nodules > 3 mm diameter, and (c) subpleural micronodules ≤ 3 mm diameter. To evaluate the distribution and extent of pulmonary abnormalities, HRCT findings were separately scored as the number of pulmonary segments involved (segments 0–19). For each case, one or 2 predominant HRCT findings and their distribution and extent were evaluated. The most likely diagnosis for each case was made according to the criteria of HRCT patterns defined by Tanaka, *et al*[9], and the following 4 patterns were identified: bronchiolitis pattern, UIP pattern, NSIP pattern, and OP pattern. Twenty-six patients were diagnosed with one of these patterns, and the others were not classified into any pattern at this time.

Pulmonary function tests. PFT were performed on patients with the UIP, NSIP, or bronchiolitis pattern on HRCT imaging, using a standard protocol. Fifteen patients who had no respiratory symptoms or abnormal HRCT patterns participated voluntarily in the study. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio (a sensitive index of overall airway obstruction), and forced expiratory flow from 25% to 75% of vital capacity (FEV_{25-75}, a specific index of small-airway function) were measured by a rolling seal type of spirometer (Chestac 65V or Chestac 8800; Chest Inc., Tokyo, Japan), with subjects in the sitting position. Diffusing capacity of carbon monoxide (DLCO, an index of restrictive interstitial disease) was evaluated by the single-breath method using the same machines. Measured values were compared with normal values predicted for age, sex, and height of the individual, using data of Berglund, *et al*[33] for FEV_1, Schmidt, *et al*[34] for FEV_{25-75}, and Burrows, *et al*[35] for DLCO. Results were expressed as a ratio of measured to predicted values (percentage predicted).

Statistic analysis. Clinical characteristics and HRCT findings of patients with early RA and longstanding RA were compared using the Mann-Whitney U test and chi-square test. The Mann-Whitney U test was used to compare quantitative data not distributed normally, the chi-square test to compare frequencies. Probability values < 0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics of patients. Patients enrolled (n = 126) were predominantly female, mean age 60.0 years (Table 1). Thirty patients (23.8%) complained of cough, and 2 (1.6%) had sputum production. No patient complained of other respiratory symptoms including wheezing or dyspnea. One hundred five patients (83.3%) had never smoked, 8 (6.3%) were current smokers, and 13 (10.3%) were ex-

Table 1. Clinical characteristics of patients with RA at baseline. Data are mean ± SD or numbers of patients (%).

	RA, n = 126	Early RA, n = 65	Longstanding RA, n = 61	p
Age, yrs	60.0 ± 12.4	57.6 ± 13	62.5 ± 11.3	0.04*
Sex, M/F	26/100	17/48	9/52	0.11**
Duration from				
Joint symptoms, mo	—	7.8 ± 6.4	—	—
Diagnosis, mo	—	2.6 ± 4.5	—	—
Disease duration, yrs	—	—	11.8 ± 9.7	—
Respiratory symptom (%)	30 (23.8)	11 (16.9)	19 (31.1)	0.06**
Cough	30 (23.8)	11 (16.9)	19 (31.1)	—
Sputum	2 (1.6)	0	2 (3.3)	—
Current or former smokers (%)	21 (16.7)	13 (20.0)	8 (13.1)	0.30**
Positive RF (%)	108 (85.7)	54 (83.1)	54 (88.5)	0.38**
Positive anti-CCP antibody (%)	120 (95.2)	61 (93.8)	59 (96.7)	0.45**
CRP, mg/dl	2.7 ± 3.1 (n = 124)	1.9 ± 2.3 (n = 64)	3.5 ± 3.6 (n = 60)	0.001*
ESR, mm/h	48.9 ± 27.9 (n = 107)	46.2 ± 25.6 (n = 62)	52.7 ± 30.5 (n = 45)	0.25*
DAS28-CRP	4.7 ± 1.2 (n = 124)	4.5 ± 1.0 (n = 64)	4.9 ± 1.4 (n = 60)	0.17*

* Mann-Whitney U test; ** chi-square test. Anti-CCP: anti-cyclic citrullinated peptide; RF: rheumatoid factor; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28-CRP: Disease Activity Score for 28 joints- C-reactive protein.

smokers. Clinical characteristics of patients with early RA (n = 65) and longstanding RA (n = 61) were compared. Patients with early RA were significantly younger than those with longstanding RA. Compared with the early RA group, the longstanding RA group had increased levels of C-reactive protein (CRP). The percentage of patients with respiratory symptoms was higher in the longstanding RA group. There were no significant differences in sex or values of other disease activity measures between these patient populations.

HRCT findings. The frequency and scores of HRCT findings are summarized in Table 2. The most frequent finding was bronchial dilatation, which was observed in 52 of 126 patients with RA (41.3%). Ground-glass attenuation was the second most common abnormality (27.0%), followed by parenchymal micronodules (15.1%), subpleural micronodules (15.1%), linear attenuation (reticulation, 11.9%), bronchial wall thickening (11.9%), nodules (10.3%), honeycombing (8.7%), and airspace consolidation (4%). Architectural distortion was not found. Of note, the frequencies of parenchymal micronodules and bronchial wall thickening were significantly higher in the patients with longstanding RA compared with the early RA group. Bronchial dilatation was also seen more often in patients with longstanding RA, although this was not statistically significant. Between the 2 groups, there were no significant differences in the frequency of the interstitial abnormalities such as ground-glass attenuation, reticulation, honeycombing, or consolidation. Nodules and subpleural micronodules were also seen in both patient groups with similar frequency. The parenchymal micronodules were connected to branching linear structures, and were often seen simultane-

Table 2. Comparison of HRCT findings between early RA and longstanding RA. Data are mean ± SD or numbers of patients (%).

HRCT Findings	Numbers of Patients (%)				Score		
	RA, n = 126	Early RA, n = 65	Longstanding RA, n = 61	p**	Early RA, n = 65	Longstanding RA, n = 61	p*
Ground-glass attenuation	34 (27.0)	18 (27.7)	16 (26.2)	0.85	3.8 ± 3.5	5.7 ± 4.9	0.54
Linear attenuation (reticulation)	15 (11.9)	7 (10.8)	8 (13.1)	0.68	8.0 ± 2.6	5.9 ± 2.1	0.09
Honeycombing	11 (8.7)	5 (7.7)	6 (9.8)	0.67	7.6 ± 2.1	6.3 ± 1.7	0.31
Airspace consolidation	5 (4.0)	2 (3.1)	3 (4.9)	—	4.5	1.7	—
Bronchial dilatation	52 (41.3)	22 (33.8)	30 (49.2)	0.08	4.1 ± 2.3	5.7 ± 4.2	0.19
Bronchial wall thickening	15 (11.9)	4 (6.2)	11 (18)	0.04	8.0 ± 5.1	6.5 ± 5.0	0.51
Nodular attenuation							
Parenchymal micronodules	19 (15.1)	5 (7.7)	13 (21.3)	0.03	7.8 ± 6.4	6.8 ± 5.2	0.92
Subpleural micronodules	19 (15.1)	9 (13.8)	10 (16.4)	0.63	1.6 ± 1.0	2.2 ± 1.7	0.41
Nodules	13 (10.3)	7 (10.8)	6 (9.8)	0.86	1.7 ± 0.1	1.2 ± 0.4	0.29
Architectural distortion	0	0	0	—	0	0	—

* Mann-Whitney U test; ** chi-square test. HRCT: high-resolution computed tomography.

ously with bronchial wall thickening and bronchial dilatation. The nodules tended to be located in the periphery of the lung parenchyma, frequently just below the pleura. Neither cavity formation nor pleural effusion was observed. Traction bronchiectasis was rare.

Predominant HRCT findings and clinical characteristics. We reviewed HRCT findings of all patients and identified 4 patterns of pulmonary abnormalities based on the predominant findings and the distribution and extent of these lesions. Of the 126 RA patients studied, 25 (19.8%) were diagnosed with one of these HRCT patterns: 9 in 65 patients with early RA (13.8%) and 16 in 61 patients with longstanding RA (26.2%). The most common pattern was NSIP (11 patients, 8.7%), followed by the bronchiolitis pattern (10 patients, 7.9%), the UIP pattern (2 patients, 1.6%), and the OP pattern (2 patients, 1.6%). Table 3 summarizes the frequency of the predominant HRCT findings in patients with the bronchiolitis, NSIP, UIP, or OP pattern and Figures 1-4 show HRCT scans of patients with these patterns. Patients with the bronchiolitis pattern had parenchymal micronodules (100%), bronchial dilatation (80%), and bronchial wall thickening (80%). Branching linear attenuation connected to parenchymal micronodules was prominent. All patients with the NSIP pattern had ground-glass attenuation and reticulation. These findings were observed bilaterally with basal and peripheral predominance. All patients with the UIP pattern had reticulation, honeycombing, and bronchial dilatation. Reticulation and honeycombing were located in the basal and peripheral areas. All patients with the OP pattern showed multiple and patchy airspace consolidation with subpleural or peribronchial distribution. Some patients with the NSIP or UIP pattern showed evidence of airway disease such as bronchial wall thickening and bronchial dilatation. On the other hand, some patients with the bronchiolitis pattern showed characteristic findings of interstitial disease, such as ground-glass attenuation, reticulation, and honeycombing.

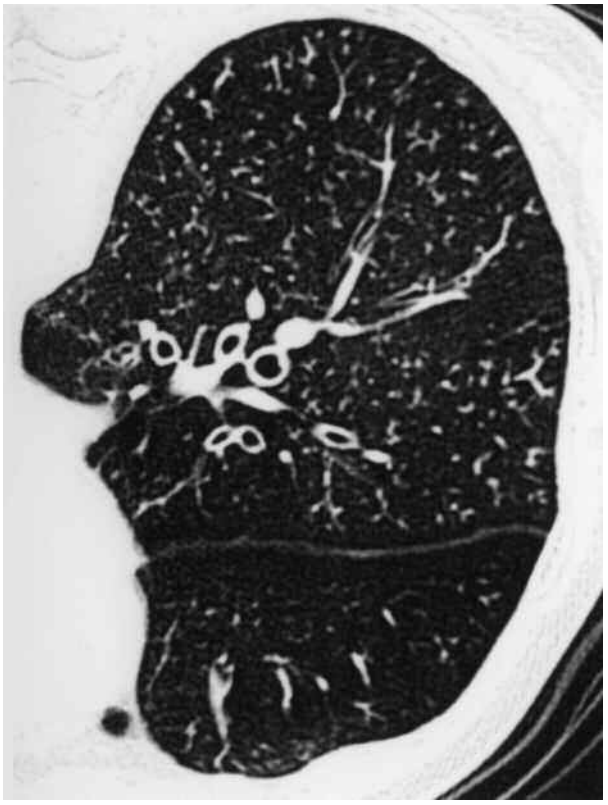

Figure 1. HRCT scan from a 72-year-old woman with the bronchiolitis pattern. Multiple parenchymal micronodules and branching linear structures are evident, suggesting the presence of bronchiolar lesions. Bronchial wall thickening and bronchial dilatation are also visible.

Table 4 shows the clinical characteristics of RA patients with each of the 4 patterns. These data were obtained at entry to the study. The bronchiolitis pattern was more frequently observed in patients with longstanding RA. The prevalence rate of the interstitial pneumonia pattern was not significantly different between patients with early RA and those with longstanding RA. Smoking or sinusitis appeared

Table 3. Predominant HRCT findings in RA patients with UIP, NSIP, OP, or bronchiolitis pattern. Data are numbers of patients (%).

HRCT Findings	UIP Pattern, n = 2	NSIP Pattern, n = 11	OP Pattern, n = 2	Bronchiolitis Pattern, n = 10
Ground-glass attenuation	1 (50)	11 (100)	1 (50)	2 (20)
Reticulation (linear attenuation)	2 (100)	11 (100)	0	1 (10)
Honeycombing	2 (100)	3 (27.3)	0	2 (20)
Airspace consolidation	0	0	2 (100)	1 (10)
Bronchial dilatation	2 (100)	5 (45.4)	0	8 (80)
Bronchial wall thickening	1 (50)	0	0	8 (80)
Nodular attenuation				
Parenchymal micronodules	0	0	0	10 (100)
Subpleural micronodules	0	0	0	3 (30)
Nodules	0	0	0	2 (20)
Architectural distortion	0	0	0	0

UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; HRCT: high-resolution computed tomography.

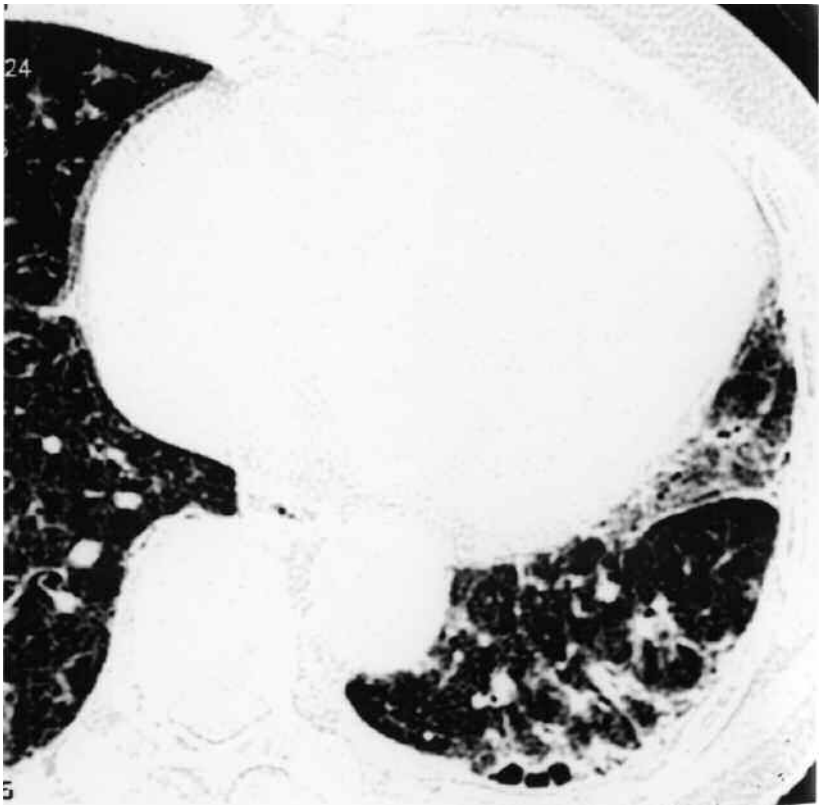

Figure 2. HRCT scan from a 67-year-old woman with the nonspecific interstitial pneumonia (NSIP) pattern. Ground-glass attenuation and reticulation are visible in the peripheral and subpleural regions.

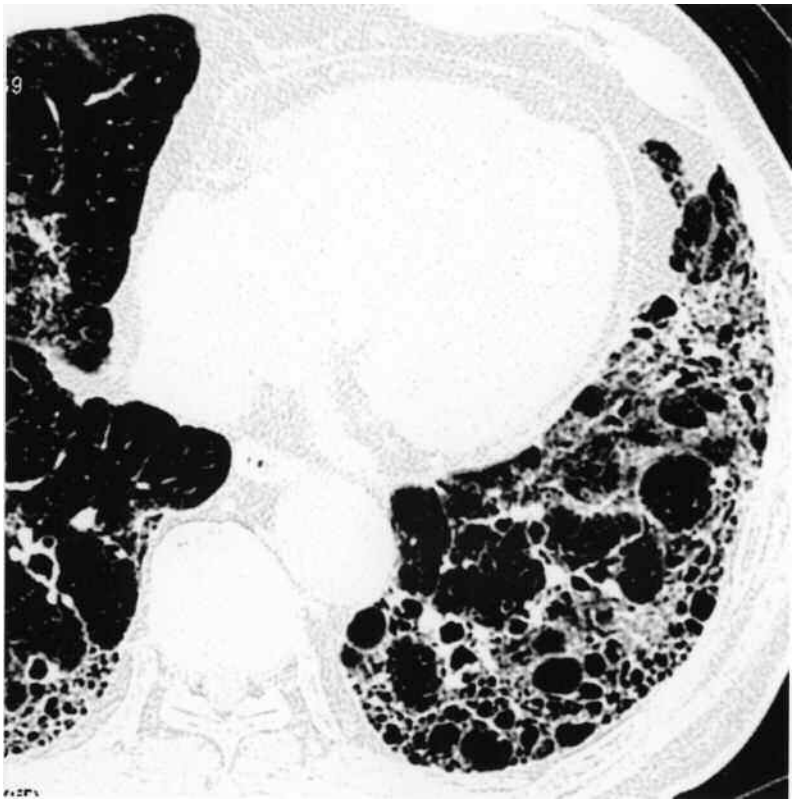

Figure 3. HRCT scan from a 71-year-old man with RA and the usual interstitial pneumonia (UIP) pattern. Reticulation and honeycombing are prominent in the peripheral and subpleural regions.

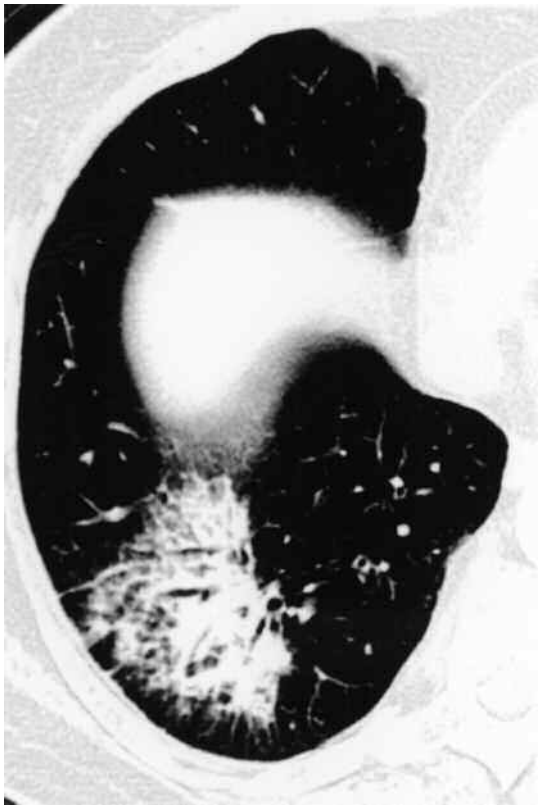

Figure 4. HRCT scan from a 79-year-old woman with RA and the organizing pneumonia (OP) pattern. Patchy airspace consolidation is seen, with peribronchial distribution.

to be unrelated to the development of these patterns. All patients with the bronchiolitis pattern had a chronic cough. Two of them were clinically diagnosed with bronchiectasis. These cases previously had had bloody phlegm, and chronic production of purulent sputum was continued. *Pseudomonas aeruginosa* was detected in cultures of their sputum. Of 11 patients with the NSIP pattern, 7 (63.6%) complained of a dry cough at the examination for this study.

Pulmonary function tests and prognosis. PFT results are shown in Table 5. The mean values of the FEV_1/FVC ratio and FEV_{25-75}, which are indices of airway obstruction, were significantly lower in patients with the bronchiolitis pattern as compared with asymptomatic controls. The mean DLCO, an index of restrictive disease, was significantly decreased in patients with the UIP or NSIP pattern.

During a followup period of 6 months through 4 years, 3 out of 8 patients with longstanding RA and the bronchiolitis pattern were hospitalized 2 or more times due to pulmonary infections, and 3 received therapy for pneumonia once or twice without hospitalization. One patient with early RA and the bronchiolitis pattern was twice treated with antibiotics for lung infection without hospitalization. One patient with early RA and the UIP pattern had pulmonary infection twice in a year. Three of 11 patients with the NSIP pattern (one early RA, 2 longstanding RA) received antibiotic therapy for pulmonary infection once or twice without hospitalization; they were successfully treated with antibiotics. With a single exception, all cases have survived until this time and have stable pulmonary function. One patient with longstanding RA and the bronchiolitis pattern died of hepatic metastasis of cancer of unknown origin.

DISCUSSION

By evaluation of the predominant HRCT findings and their distribution and extent in the lungs of RA patients, we identified 15 patients (11.9%) with an interstitial pattern (UIP, NSIP, or OP pattern) and 10 patients (7.9%) with the bronchiolitis pattern (Table 3). PFT supported the HRCT-based diagnosis; namely, the mean values of FEV_1/FVC ratio and FEV_{25-75} were significantly lower in patients with the bronchiolitis pattern. The mean DLCO was significantly decreased in patients with the NSIP or UIP pattern (Table 5). The prevalence rate of the UIP, NSIP, or OP pattern was not significantly different between the study populations with early RA and with longstanding RA. Notably, the bronchiolitis pattern was more frequently seen in the longstanding RA group (Table 4). The frequencies of parenchymal micronodules and bronchial wall thickening were significantly higher in this patient population (Table 2), and these

Table 4. Clinical characteristics of RA patients with the UIP, NSIP, OP, or bronchiolitis pattern. Data are mean ± SD or numbers of patients.

	UIP Pattern, n = 2	NSIP Pattern, n = 11	OP Pattern, n = 2	Bronchiolitis Pattern, n = 10	Total n = 25
Age, yrs	70.5	67.2 ± 2.9	61	66.8 ± 2.7	67.4 ± 1.8
Sex, M/F	1/1	2/9	0/2	0/10	3/22
Disease duration, early/longstanding	1/1	5/6	1/1	2/8*	9/16
Respiratory symptoms					
Cough	1	7	2	10	21
Sputum	0	0	0	2	2
Current or former smokers	1	2	0	0	3
Sinusitis	0	1	0	2	3

* p = 0.037, number of early RA patients versus longstanding RA patients (chi-square test). UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia.

Table 5. Pulmonary function tests in RA patients with UIP, NSIP, or bronchiolitis pattern. Data are mean ± SD.

	UIP or NSIP Pattern, n = 13	Bronchiolitis Pattern, n = 10	Asymptomatic Patients†, n = 15
FEV_1/FVC	81.1 ± 6.1	74.5 ± 5.0*	83.4 ± 4.7
FEV_1 (% predicted)	108.2 ± 17.5	83.8 ± 19.3	93.8 ± 29.9
$FEV_{25–75}$ (% predicted)	81.1 ± 19.3	50.9 ± 13.8**	90.4 ± 18.6
DLCO (% predicted)	79.7 ± 9.9**	101.6 ± 24.8	102.9 ± 11.4

* p = 0.0133, compared with asymptomatic patients; ** p = 0.0003, compared with asymptomatic patients (all Mann-Whitney U test). † Asymptomatic patients consist of RA patients who visited our hospital for routine checkup without complaint of respiratory symptoms and who had no abnormal HRCT patterns. UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; $FEV_{25–75}$: forced expiratory flow from 25% to 75% of vital capacity; DLCO: diffusing capacity of carbon monoxide.

abnormal findings are suggestive of the presence of constrictive bronchiolar disease. The established RA group appears to be predisposed to complications of small-airway disease. A high prevalence of airway abnormalities was also observed in previous HRCT studies on patient populations with relatively longer mean disease duration[15-19]. In our study, the CRP value, an indicator of disease activity, was significantly higher in patients with longstanding RA, although other disease activity measures showed similar levels in the 2 patient groups (Table 1). It is therefore not clear whether small-airway abnormality may reflect high levels of disease activity. The longstanding RA group apparently consisted of older individuals compared with the early RA group (Table 1). Recently, Svartengren, *et al*[36] showed that small-airway clearance decreases with age among healthy individuals, which may be one factor associated with the increased risk of development of bronchiolitis among the elderly.

The exact mechanism of the frequent development of small-airway disease in RA has not yet been evaluated. As shown in Tables 2 and 3, bronchiectasis was predominant even in the early RA group, and it was found in 80% of patients diagnosed as having the bronchiolitis pattern. Recently, colonization of small airways with pathogenic microorganisms in patients with bronchiectasis has been reported[37,38]. Chronic colonization, secondary recurrent inflammation, and progressive lung injury may contribute to the development of airway obstruction during the course of RA[38]. We detected *P. aeruginosa*, a marker of severe structural damage in the lung[37], in the sputum of 2 patients with the bronchiolitis pattern and clinically proven bronchiectasis. Meanwhile, Hassan, *et al*[20] showed that airflow obstruction and bronchial reactivity are both increased in unselected RA patients, and they proposed that preexisting inflammatory changes in the small airway may secondarily induce mucosal edema, which leads to bronchial narrowing and airway obstruction. In either case, continuous inflammation may modify the structural and functional features of bronchi/bronchioles. Indeed, bronchoalveolar lavage studies showed increased numbers of inflammatory cells in RA patients with bronchiolar diseases[38,39]. Further investigation of bronchial immunopathology is required to address this question.

In our study, the most common radiological change in patients with RA was bronchial dilatation (41.3%; Table 2). Bronchial dilatation is a hallmark of bronchiectasis. Clinically evident bronchiectasis is unusual in RA; however, the HRCT technique has shown that bronchiectasis is a common finding in RA. Hassan, *et al*[40] suggested that the incidence of bronchiectasis in lifelong-nonsmoking RA patients with no pulmonary symptoms is much higher (25%) than previously reported. In other studies on patients with long mean disease durations, bronchiectasis was seen on HRCT scans in about 30%, and was one of the most frequent lung manifestations[16-19]. Our data proved the high prevalence of bronchiectasis even in the patients with recent-onset RA (33.8%; Table 2). The reason for the elevated rate of bronchiectasis in RA is a matter of controversy. Shadick, *et al*[31] postulated that bronchiectasis is a common sequela of fibrotic interstitial diseases in patients with severe, longstanding disease; namely, in the fibrotic process, cicatrization may result in traction of adjacent bronchi and subsequent ectasia of the airway. However, we found early-stage development of bronchial dilatation in patients with RA. Traction bronchiectasis, which is depicted in areas of honeycombing[41], was rare in this study. Moreover, on HRCT scans the fibrotic abnormalities such as reticulation and honeycombing were less prominent compared with bronchiectasis in our patients (Table 2). Alternatively, Bamji and Cooke suggested that RA itself and the use of disease modifying antirheumatic drugs predispose to development of chronic bronchial suppuration[42]. Chronic respiratory tract infection and secondary inflammatory reactions may eventually lead to development of bronchiectasis. However, this explanation is untenable in our study since only 2 participants at the time of HRCT examination experienced chronic bronchial suppuration, and most of the patients with early RA had no respiratory symptoms. As well, McMahon, *et al*[43] showed that bronchiectasis often precedes the arthritis. Other mechanisms of the association between RA and bronchiectasis should exist for these cases. One explanation

may be that RA patients have a genetic susceptibility to development of bronchiectasis[44].

Ground-glass attenuation was the second most common HRCT finding (27.0%), and reticulation and honeycombing were seen in 11.9% and 8.7% of all participants, respectively (Table 2). These radiological abnormalities correspond to interstitial pulmonary disease, and the frequency of each finding was not significantly different between the early RA and longstanding RA groups. Our data therefore indicate that interstitial lung changes occur frequently in RA patients and they are independent of disease duration. In our study, 76.2% of patients did not complain of any respiratory symptoms (Table 1); however, interstitial changes were apparently present in a considerable number of patients even at the early stage. Gabbay, *et al* also reported that interstitial lung disease in early RA is a frequent finding on HRCT (33%)[8]. In another report, interstitial disease was seen in 28% of a patient group with a mean disease duration of 8 months, although 35% of this population had a disease duration > 10 years[13]. Several clinical studies showed that interstitial diseases sometimes start simultaneously with articular symptoms, and less frequently, precede them[45,46]. With the use of HRCT, simultaneous or even preceding pulmonary changes may be detected more often. Whether the appearance of interstitial abnormalities at the early stage of RA predicts subsequent development of respiratory diseases is unclear. We cannot exclude the possibility that an abnormality on HRCT is a benign finding in RA patients without respiratory symptoms. Its clinical significance and predictive value would be determined by longitudinal followup studies.

Concerning the interstitial pattern on HRCT, Tanaka, *et al*[9] reported that the UIP pattern exists more commonly than the NSIP pattern in RA, although the latter is dominant in other connective tissue diseases. We observed that the NSIP pattern was the most predominant interstitial pattern in the groups with both early and longstanding RA, which may be due to the high prevalence of ground-glass attenuation in our populations. Such discrepancy in classification of the interstitial pattern may also reflect difficulty in discrimination between the UIP and fibrotic NSIP patterns due to overlapping HRCT findings in some patients.

In a large number of reports, interstitial disease was the most common HRCT abnormality, although rates of occurrence of its characteristic HRCT findings vary widely[9-14]. Conversely, several groups observed a high frequency of bronchial/bronchiolar obstruction on HRCT findings and/or PFT results[15-20]. It is difficult to compare our findings with those previously published, since many of these studies consisted of RA populations with longer and greatly varying disease durations. In addition, most studies were done retrospectively; therefore, subjects were inclined to be patients who had respiratory symptoms and some cases received MTX and/or anti-TNF-α agents. Several studies were also performed on patients who had clinically proven interstitial pneumonia[11,14] or patients who were suspected of having pulmonary complications[9,10,15,16,18]. Since the participants in our study were not selected based on the reasons for their visit to hospital, they are very likely to represent the overall RA population. The study was done prospectively for 2 patient populations categorized according to duration of disease, and no patient had received MTX or anti-TNF-α agents. Thus, 2 possible factors responsible for pulmonary abnormalities in RA were excluded. In previous prospective studies on unselected RA patients, a high prevalence of airway abnormalities was observed in populations with a long mean duration of RA (30%–32%)[17,19], and interstitial lung diseases were frequent in the recent-onset groups (19%–33%)[8,13,47], in keeping with our findings.

The most common radiological change in patients with early RA and longstanding RA was bronchial dilatation. Parenchymal micronodules and bronchial wall thickening were predominantly observed in the patients with longstanding RA, which contributed to the higher incidence of the bronchiolitis pattern in this patient population. In contrast, the frequency of interstitial abnormalities was not significantly different between the 2 groups. Ground-glass attenuation, the predominant finding associated with the NSIP pattern, was the most prominent interstitial abnormality in patients with RA. Abnormal HRCT findings were frequently observed even in early RA patients, although most of them had no respiratory symptoms. It is of interest whether the presence of these abnormalities at the early stage of RA is a predictive factor for subsequent development of respiratory diseases, or simply a benign finding.

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