High Resolution Computed Tomography in Fibrosing Alveolitis Associated with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To investigate the use of high resolution computed tomography (HRCT) in diagnosis of patients with fibrosing alveolitis associated with systemic sclerosis (FA-SSc), and to determine predictors of disease progression.

Methods. We retrospectively studied 90 patients with SSc who had undergone an initial (Time 1) and followup (Time 2) clinical and HRCT evaluation, with a mean ± SD interval of 5.14 ± 2.98 years between T1 and T2.

Results. At T1, HRCT was normal in 40 patients; at T2, 34/40 (85%) continued to have a normal HRCT. For the 50 patients with FA-SSc on HRCT scan at T1, the overall disease progression comprised extension of lung changes toward the apices with worsening of lung fibrosis at T2. Among the 37 patients who had areas of isolated ground-glass opacities at T1, 25 (68%) had progression of lung fibrosis at T2. These 25 patients were mostly men, who showed a more marked decrease of diffusing capacity and a longer interval between T1 and T2.

Conclusion. The results emphasize the good longterm prognosis indicated by a normal initial HRCT in SSc. Patients with FA-SSc with abnormal HRCT experienced progressive replacement of ground-glass opacities by honeycombing and/or traction bronchiectasis/bronchiolectasis. Ground-glass opacity is probably the first step of lung fibrosis in SSc, and treatment should be discussed even at this early stage. (J Rheumatol 2006;33:1789–801)

Key Indexing Terms:
SYSTEMIC SCLEROSIS FIBROSING ALVEOLITIS LUNG DISEASE
HIGH RESOLUTION COMPUTED TOMOGRAPHY LUNG FUNCTION TESTS

Fibrosing alveolitis (FA) is a common manifestation in systemic sclerosis (SSc), ranking third behind the skin and the peripheral vasculature in the frequency of involvement[1]. Moreover, FA associated with SSc (FA-SSc) is the second most important cause of death after cardiac involvement and pulmonary hypertension[2]. FA-SSc has a better prognosis than isolated cryptogenic FA, and the condition of many patients with SSc can remain stable for years[3]. The therapeutic dilemma is whether or not to prescribe immunosuppressive agents and to know when to initiate this treatment[4]. Immunosuppressive agents can diminish or stop the fibrotic process, but the response to treatment is variable and there are troublesome side effects[5]. For proper selection of patients who may benefit from this therapeutic approach and appropriate scheduling of treatment, it is of paramount importance to accurately stage the extent of FA-SSc disease and to monitor its progression.

Similarly to its well recognized role in the detection and staging of interstitial lung disease, high resolution computed tomography (HRCT) of the chest has been found to be a sensitive and reproducible method of determining the extent and the patterns of FA-SSc[6-8], but it is also an efficient means of detecting early disease[9,10]. The main CT features of FA-SSc consist of areas of ground-glass attenuation, reticular opacities, and traction bronchiectasis and/or bronchiolectasis within areas of ground-glass opacities, in good correlation with histologic findings[11,12]. Whereas a ground-glass pattern seen as an isolated CT feature is associated with a high likelihood of cellular infiltration, i.e., inflammation[13], traction bronchiectasis and/or bronchiolectasis and reticular opacities (honeycombing pattern) are highly suggestive of underlying fibrosis. Wells, *et al* showed that the relative proportions of fibrosis and cellularity histologically observed in FA-SSc could be predicted by the appearance on CT[11]. Nevertheless, there are

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contradictory statements regarding the prognostic value of the initial CT findings. It is often admitted that ground-glass attenuation is of better prognostic value because it can be reversible with treatment[14]. Wells, *et al* observed this response only if ground-glass attenuation unequivocally exceeded the reticular pattern[15]. Followup studies have also shown that areas of ground-glass attenuation can be seen on HRCT scans before a reticular pattern becomes apparent, suggesting that inflammation precedes fibrosis in FA-SSc[16,17]. However, it is not clear why ground-glass attenuation seems to be sometimes reversible and sometimes replaced by fibrosis. Finally, if the outcome of abnormal HRCT patterns has been previously assessed, there is little information on the longterm outcome of normal HRCT scans in SSc[12]. Our aims were to evaluate longterm changes of normal and abnormal HRCT patterns in patients with SSc, and to identify the predictive factors of an unfavorable outcome.

MATERIALS AND METHODS

Population. Between January 1991 and January 2001, 156 patients with a diagnosis of SSc were evaluated in our institution. From this initial population, we selected patients who had undergone at least 2 HRCT examinations of the chest, with a minimum of 2 years between the initial CT scan (performed at Time 1, T1) and the followup CT scan (performed at T2). The final study group consisted of 90 patients, all meeting the criteria of the American College of Rheumatology for the diagnosis of SSc[18]. Among the 66 patients who were not included in the study, 19 were seen between January 2000 and January 2001 and had no followup scan. Thirteen patients were lost to followup. Six patients died (one from FA-SSc, 2 from pulmonary hypertension, one from acute renal crisis, and 2 from unknown causes). Fourteen patients had not had an initial CT scan because the chest radiograph was considered normal. Fourteen patients with a first, normal CT scan had not had a followup scan.

The institutional review board did not require approval or patients' informed consent for retrospective study of case records and CT studies.

Clinical information. We retrospectively compiled clinical assessment data on the patient's sex, smoking history, age at occurrence of the first SSc symptom (Raynaud's phenomenon in all cases), age at the time of diagnosis of SSc, and age at T1. We defined the duration of SSc as the time interval between the patient's age at the onset of Raynaud's phenomenon and his/her age at T1. Cutaneous extension was graded according to the LeRoy classification system, that is, limited (hands, forearms, face, or feet) or diffuse (truncal and acral)[19]. Dyspnea was assessed at T1 and T2 and graded according to the New York Heart Association (NYHA)[20]. We recorded the presence or absence of lung crackles at T1. Presence of esophageal involvement was assessed by esophageal manometry in 83 of the 90 patients. Investigation for sicca syndrome was undertaken in 74 patients according to the revised European criteria[21]. Eighty patients underwent echocardiography to assess systolic pulmonary arterial pressure (sPAP); sPAP > 40 mm Hg was suggestive of pulmonary hypertension. Patients were considered to have been treated between T1 and T2 if they had received cyclophosphamide intravenously (700 mg/m^2 monthly for 6 months) or orally (100 mg/day for 6 months) (n = 6) or corticosteroids (> 10 mg prednisone or equivalent) for at least 6 months (n = 22).

Biological evaluation. Hemoglobin level, erythrocyte sedimentation rate (ESR), and plasma gammaglobulin level at T1 were recorded. Antinuclear antibodies (ANA) were detected by indirect immunofluorescence either on rat liver or on HEp-2 cells. Subtypes of ANA (anticentromere, anti-Scl-70, and antinucleolar antibodies) were recorded.

Pulmonary function tests (PFT). Seventy-three patients underwent PFT at T1 and among them, 62 had a second evaluation at T2. PFT at T1 and T2 were systematically performed within 4 weeks of corresponding CT examinations, following standard protocols. Forced expiratory volume in 1 second (FEV_1) was determined using a Pneumoscreen (Jaeger, Wuerzburg, Germany). Slow inspiratory vital capacity (VC) and the ratio FEV_1/VC were also determined. Residual volume was determined with the helium dilution method. Total lung capacity (TLC) was calculated by adding residual volume to VC. The diffusing capacity for carbon monoxide (DLCO) and DLCO adjusted for alveolar volume (KCO) were calculated by the single-breath method and corrected for hemoglobin level. The predictive values for each subject, based on sex, age, and height, were obtained from standard tables[22]. KCO was obtained in 40/73 patients at T1, all of them also having a determination of KCO at T2. Data were expressed as percentages of the predicted values. Measurement of arterial blood gases was performed on air from patients at rest. The rate of change (Δ) was expressed as the percentage of change of the variable between T1 and T2. For example, ΔVC = (VC at T2 – VC at T1)*100/VC at T1. ΔVC, ΔTLC, $\Delta DLCO$, ΔKCO, ΔPaO_2, and ΔSaO_2 were calculated.

HRCT evaluation

HRCT protocol. HRCT studies were performed on an Elscint 2400 (Elscint, Hackensack, NJ, USA) or a Somatom Plus scanner (Siemens, Erlangen, Germany). In every case, the HRCT examination consisted of sequential acquisition of 1-mm scans, spaced at 10 mm, intervals extending from the lung apices to below the costophrenic angles. The scanning parameters included a 350-mm field of view, a 512 × 512 matrix of reconstruction, 130 kV, 420 mA, and a 2-second scanning time on the Elscint 2400 unit, or 137 kV, 255 mA, and 1-second scanning time on the Siemens unit. Images were reconstructed with a high spatial frequency algorithm for lung analysis and with a standard soft-tissue algorithm for mediastinal evaluation. Images were viewed at lung (window width 1600 HU, window level 600 HU) and mediastinal (window width 350 HU, window level 50 HU) window settings. Lung evaluation was performed at suspended end-inspiratory volume. HRCT examinations were carried out with patients in the prone position to avoid physiologic-dependent lung opacities in the posterior lung. No intravenous contrast material was used.

HRCT interpretation. Without knowledge of the patient's clinical condition or if a scan was T1 or T2, 2 radiologists (MRJ, IM) independently viewed HRCT scans in random order; in case of differing interpretations, final conclusions were reached by consensus. To precisely analyze lung changes over time, for each patient the second CT scan, which was either T1 or T2 scan, was read with direct comparison with the first interpreted CT scan. The radiologists determined the presence and distribution of the following CT signs suggestive of SSc involvement: (1) Areas of isolated ground-glass opacities, which were defined as hyperattenuated areas, varying from minimal to marked attenuation, in which the bronchi and vessels remained visible. This CT finding corresponded to the sole identification of areas of increased lung attenuation with no bronchial and/or bronchiolar abnormalities within the areas of ground-glass attenuation. (2) Honeycombing, defined as areas of cystic spaces with thickened walls. And (3) traction bronchiectasis and/or bronchiolectasis within areas of ground-glass opacities. Bronchiolectasis were recognized from the abnormal appearance of bronchi in peripheral locations — dilated bronchiolar divisions along their length when seen horizontally and peripheral "signet ring" signs viewed in a vertical direction.

The extent of pulmonary disease was evaluated in 3 areas of the lungs, as follows: the upper zones were defined as the areas above the level of the carina; the middle zones, between the level of carina and the level of the inferior pulmonary veins; and the lower zones, beneath the level of the inferior pulmonary veins. Each HRCT sign was separately coded as present or absent in the 6 areas. For each zone, a score was based on a visual estimation of the percentage of lung tissue demonstrating the CT sign (1: extent < 25%; 2: extent between 25% and 50%; 3: extent between 50% and 75%; and 4: extent > 75%). The global extent score of each sign was the sum of the 3 zonal scores. Three additional variables were assessed subjectively on a visual basis, that is, the anteroposterior and central-peripheral distributions. Moreover, the degree of ground-glass attenuation was determined for the entire CT scan by means of comparison with a set of standards (mild — minimal increase in

lung attenuation compared to normal lung parenchyma; moderate — higher degree of attenuation; and severe — marked increase in attenuation without vascular markings being obscured).

In order to compare overall CT findings, we used a grading system similar to that reported by Wells, *et al* to allow categorization of the respective amount of inflammatory and fibrotic changes on each CT examination, as follows: grade 1 — areas of isolated ground-glass attenuation predominate; grade 2 — areas of isolated ground-glass attenuation are equally extensive as honeycombing and/or presence of traction bronchiectasis and/or bronchiolectasis; and grade 3 — honeycombing and/or presence of traction bronchiectasis and/or bronchiolectasis predominate.

Agreement between the 2 readers was observed in all but 3 interpretations. The discordances concerned the recognition of "traction bronchiolectasis" versus microcystic "honeycombing." The consensus reading of these 3 scans classified the abnormalities as "honeycombing."

Progression of HRCT findings. To assess the sequential changes over time for each patient, the pattern, extent, and distribution of abnormal CT findings on one CT scan were examined and compared with findings in the same region on the other CT scan, without knowing which CT scan was performed at T1 or T2.

To assess the extent of FA-SSc and to identify predictive indicators of FA-SSc using CT scans, we performed the following comparisons: (1) First, we compared baseline and followup characteristics between patients with a normal CT scan at T1 and T2, and patients with a normal CT scan at T1 and an abnormal followup scan at T2. (2) Second, we studied patients with FA-SSc at T1 with < 50% of lung parenchyma affected by SSc. For each patient, we determined if FA-SSc had progressed over normal lung parenchyma at T2 (first group) or had not (second group). We compared the baseline and followup characteristics between these 2 groups. (3) Third, we focused on the the outcome of the 37 patients with areas of isolated ground-glass opacities at T1. For each patient, we determined if there was (first group) or was not (second group) an appearance or progression of honeycombing and/or traction bronchiectasis and/or bronchiolectasis replacing these areas of formerly isolated ground-glass opacities. We compared the baseline and followup characteristics between these 2 groups.

Statistical analysis. All statistical analysis was performed using SAS software (SAS Institute, Cary, NC, USA). P values < 0.05 were considered statistically significant. Results are expressed as frequencies and percentages for categorical variables and as the mean ± standard deviation (SD) for continuous data. Comparative analyses were done using the chi-square or the Fisher exact test for categorical data. For continuous data, paired comparisons were made using the paired Student t test. For unpaired comparisons, we used the Wilcoxon rank-sum test when the number of subjects in a group was less than 30 (small sample). When the size of each group was greater than 30, the assumption of equal variances was tested using the Fisher test. When this assumption was not rejected, the Student t test was used. Otherwise, we employed the test using unequal variances and the Satterthwaite approximation.

RESULTS

Initial evaluation. Baseline characteristics of the study population at T1 are summarized in Table 1. At T1, 40/90 (44.4%) patients had a normal HRCT scan, whereas 50/90 (55.6%) patients presented with HRCT features of FA-SSc. The abnormal HRCT findings at T1 included traction bronchiectasis and/or bronchiolectasis in 38/50 patients (76.0%), areas of isolated ground-glass opacities in 37/50 patients (74.0%), and/or honeycombing in 20/50 patients (40.0%). Among the 37 patients with areas of isolated ground-glass opacities at T1: 8 patients had areas of isolated ground-glass attenuation alone without honeycombing or traction bronchiectasis and/or bronchiolectasis; and 29 patients also had honeycombing and/or traction bronchiectasis and/or bronchiolectasis with variable combinations: (a) traction bronchiectasis and/or bronchiolectasis without honeycombing (n = 17 patients); (b) both honeycombing and bronchiectasis and/or bronchiolectasis (n = 11); and (c) honeycombing without traction bronchiectasis and/or bronchiolectasis (n = 1).

The cephalocaudal and transversal distributions of lung abnormalities are summarized in Table 2. The 3 HRCT features predominated in the peripheral, posterior, and lower lung zones. Areas of isolated ground-glass opacities were graded as mild in 21/37 patients (56.8%), moderate in 14/37 patients (37.8%), and severe in 2/37 patients (5.4%).

The 50 patients with an abnormal HCRT scan at T1 were classified as follows: 21 (42%) patients had a grade 1 scan; 17 (34%) had a grade 2 scan; and 12 (24%) had a grade 3 scan.

Comparison of baseline characteristics between patients with normal and abnormal HRCT scan at T1 is shown in Table 3.

Followup studies

The entire study group had a sequential CT evaluation with a mean interval between the 2 examinations of 5.14 ± 2.98 years (range 2.00–12.25 yrs).

Progression of the 40 patients with normal HRCT scan at T1. Among the 40 patients with a normal HRCT scan at T1, 34 (85.0%) patients had a normal scan at T2, whereas 6 patients (15%) showed abnormal findings on the followup CT including: (a) areas of isolated ground-glass attenuation alone in 2 patients; (b) areas of isolated ground-glass attenuation associated with honeycombing and/or traction bronchiectasis and/or bronchiolectasis in 3 patients with the following combinations: (i) bronchiectasis and/or bronchiolectasis without honeycombing (n = 2), and (ii) traction bronchiectasis and/or bronchiolectasis associated with honeycombing (n = 1); (c) traction bronchiectasis and/or bronchiolectasis alone (n = 1).

The baseline and followup characteristics of the 34 patients with a normal CT scan at T1 and T2 were compared to those of the 6 patients who showed abnormal findings on the followup CT examination (Table 4). At T1, the proportion of patients with significant dyspnea and presence of lung crackles was significantly greater in the 6 patients who showed abnormal findings on the followup CT examination (p = 0.007, p = 0.02, respectively). Despite the lack of statistically significant difference, we observed a trend toward a higher frequency of sPAP ≥ 40 mm Hg (p = 0.06) and a lower frequency of anticentromere antibodies (p = 0.09) at T1 in these 6 patients. At T1, VC, DLCO, and KCO were significantly lower in these 6 patients (p = 0.03, p = 0.02, and p = 0.04, respectively). Finally, there was a trend for dyspnea to worsen by at least one NYHA class more frequently in these 6 patients between T1 and T2 [3/6 (50%) vs 4/34 (11.8%); p = 0.06].

Progression of the 50 patients with abnormal HRCT scan at T1. 1. Changes of HRCT features between T1 and T2. Table 5 summarizes the progression between T1 and T2 of areas of

Table 1. Baseline characteristics of patients. Results are expressed as frequencies and percentages for categorical variables and as the mean ± SD for continuous data.

Characteristic	
Patients, n	90
Female, n (%)	72 (80)
Limited SSc/Diffuse SSc, n (%)	51 (56.7)/39 (43.3)
Ever smoked, n (%)	11 (12.2)
Age at occurrence of Raynaud's phenomenon, yrs, mean (SD)	40.8 (15.8)
Age at diagnosis of SSc, yrs, mean (SD)	48.2 (14.3)
Age at T1, yrs, mean (SD)	51.0 (15.4)
Duration of SSc, yrs, mean (SD)	10.0 (10.2)
Esophageal involvement, n (%)	74 (89.1)
Sicca syndrome, n (%)	15 (18.9)
Dyspnea class I/II/III/IV, n (%)	50 (55.6)/25 (27.8)/12 (13.3)/3 (3.3)
Presence of lung crackles, n (%)	34 (37.8)
Systolic pulmonary arterial pressure ≥ 40 mm Hg, n (%)	17 (21.2)
ANA: anticentromere/anti-Scl-70/antinucleolar/other, n (%)	34 (37.8)/27 (30)/8 (8.9)/17 (18.9)
Lung function at T1, %, mean (SD), n = 73	
VC	93.3 (18.8)
FEV_1	92.7 (21.3)
FEV_1/VC	78.9 (10.1)
TLC	91.3 (17.8)
DLCO	78.2 (27.9)
KCO	66.3 (15.8)
PaO_2, mm Hg	91.7 (9.8)
SaO_2	95.7 (2.0)

SSc: systemic sclerosis; T1: date of first HRCT; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; DLCO: diffusing capacity for CO; KCO: DLCO adjusted for alveolar volume.

Table 2. Distribution of pulmonary abnormalities in the 50 patients with an abnormal CT examination at T1. Results are expressed as frequencies and percentages for categorical variables and as mean ± SD for continuous data.

	Areas of Isolated Ground-glass Opacities, n = 37	Traction Bronchiectasis and/or Bronchiolectasis, n = 38	Honeycombing, n = 20
Transversal distribution, n (%)			
Central	19 (21.1)	8 (8.9)	3 (3.3)
Peripheral	37 (41.1)	37 (41.1)	20 (22.2)
Anterior	28 (31.1)	27 (30.0)	11 (12.2)
Posterior	35 (38.9)	35 (38.9)	19 (21.1)
Cephalocaudal distribution			
Upper lung zones, n (%)			
< 25%	20 (22.2)	14 (15.5)	8 (8.9)
25–50%	4 (4.4)	1 (1.1)	0 (0.0)
50–75%	0 (0.0)	0 (0.0)	0 (0.0)
> 75%	0 (0.0)	0 (0.0)	0 (0.0)
Middle lung zone, n (%)			
< 25%	15 (16.6)	18 (20.0)	10 (11.1)
25–50%	10 (11.1)	6 (6.6)	4 (4.4)
50–75%	3 (3.3)	2 (2.2)	0 (0.0)
> 75%	0 (0.0)	0 (0.0)	0 (0.0)
Lower lung zones, n (%)			
< 25%	13 (14.4)	13 (14.4)	10 (11.1)
25–50%	8 (8.9)	14 (15.5)	6 (6.6)
50–75%	5 (5.5)	7 (7.8)	2 (2.2)
> 75%	0 (0.0)	0 (0.0)	2 (2.2)
Global extent score	2.32 ± 2.15	2.28 ± 2.06	1.24 ± 1.92

Table 3. Comparison of baseline characteristics between patients with a normal CT scan and patients with an abnormal CT scan at T1. Results are expressed as frequencies and percentages for categorical variables and as the mean ± SD for continuous data.

Characteristic	Patients with Normal CT at T1, n = 40	Patients with Abnormal CT at T1, n = 50	p
Female/males, n	34/6	38/12	NS
Limited SSc/Diffuse SSc, n (%)	33 (82.5)/7 (17.5)	18 (36)/32 (64)	< 0.0001
Ever smoked, n (%)	5 (12.5)	6 (12)	NS
Age at occurrence of Raynaud's phenomenon, yrs, mean (SD)	38.0 (14.8)	42.9 (16.2)	NS
Age at HRCT1, yrs, mean (SD)	49.8 (17.1)	52.0 (14.0)	NS
Duration of SSc, yrs, mean (SD)	11.6 (11.4)	8.9 (9.1)	NS
Followup duration, yrs, mean (SD)	5.1 (2.6)	5.2 (3.3)	NS
Esophageal involvement, n (%)	28/35 (80)	46/48 (95.8)	0.03
Sicca syndrome, n (%)	8/32 (25)	8/42 (19.0)	NS
Dyspnea class I/II vs III/IV at HRCT1, n (%)	36 (90)/4 (10)	39 (78)/11 (22)	0.01
Presence of lung crackles, n (%)	2 (5)	32 (64)	< 0.0001
Systolic pulmonary arterial pressure ≥ 40 mm Hg, n (%)	3 (7.5)	14 (28)	0.02
Anticentromere, n (%)	26 (65)	7 (14)	< 0.0001
Anti-Scl-70, n (%)	5 (12.5)	22 (44)	0.001
Antinucleolar, n (%)	3 (7.5)	5 (10)	NS
Hemoglobin g/dl, mean (SD)	13.1 (1.2)	13.2 (1.4)	NS
ESR, mm, mean (SD)	14.0 (15.1)	22.0 (22.8)	0.051
Plasma gammaglobulin, g/l, mean (SD)	12.6 (5.0)	15.3 (5.4)	0.01
Lung function at T1, %, mean (SD)			
VC	99.2 (17.2)	90.0 (19.0)	0.04
FEV_1	98.6 (21.7)	89.8 (20.7)	NS
FEV_1/VC	77.2 (11.7)	79.8 (9.1)	NS
TLC	97.2 (15.3)	95.0 (16.1)	NS
DLCO	91.1 (29.3)	71.4 (24.9)	0.004
KCO	70.2 (13.4)	63.8 (16.9)	NS
PaO_2, mm Hg	94.2 (7.6)	90.4 (10.6)	NS
SaO_2	95.9 (1.2)	95.6 (2.2)	NS†

† Test using unequal variances. SSc: systemic sclerosis; T1: date of first HRCT; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; DLCO: diffusing capacity for CO; KCO: DLCO adjusted for alveolar volume; NS: nonsignificant.

isolated ground-glass opacities, honeycombing, and traction bronchiectasis and/or bronchiolectasis. The mean overall extent score was significantly higher at T2 than at T1 for honeycombing and for traction bronchiectasis and/or bronchiolectasis. The proportion of patients with traction bronchiectasis and/or bronchiolectasis was also significantly greater at T2 than at T1 [48/50 (96%) vs 38/50 (76%); p = 0.01]. The proportion of patients with areas of isolated ground-glass opacities and the mean overall extent score of isolated ground-glass opacities were lower at T2 than at T1, but the difference did not achieve statistical significance.

In addition, we studied changes of the transversal and cephalocaudal distribution of the CT signs between T1 and T2. Overall, there was progression from peripheral to central lung zones, from posterior to anterior lung zones, and from lower to the middle and upper lung zones (data not shown).

2. Spatial extension of FA-SSc over normal lung parenchyma. To assess spatial extension by FA-SSc over normal lung parenchyma, we focused on patients with FA-SSc affecting less than 50% of lung parenchyma at T1 (n = 42). For each patient, we determined if FA-SSc had progressed over normal lung parenchyma at T2 (n = 21) or had not (n = 21). We compared the baseline and followup characteristics between these 2 groups (Table 6). Very few indicators at T1 could predict which patient would experience a progression of FA-SSc over normal lung parenchyma. Dyspnea at T1 was more severe in patients experiencing progression of FA-SSc over normal lung parenchyma, whereas lung crackles tended to be less frequent [8/21 (38.1%) vs 14/21 (66.6%); p = 0.06] at T1. VC% and TLC% were higher at T1 in patients experiencing spatial progression over normal lung parenchyma, but differences were not statistically significant (p = 0.1, p = 0.08, respectively). There was a greater decrease in PaO_2, SaO_2, and DLCO between T1 and T2 in patients whose FA-SSc had progressed (p = 0.04, p = 0.04, and p = 0.08, respectively).

Figure 1 shows the changes of extent scores for ground-glass, honeycombing, and traction bronchiectasis and/or bronchiolectasis between T1 and T2 in patients experiencing a progression of FA-SSc over normal lung parenchyma. Figure 2 shows the same scoring in patients with no spatial extension of FA-SSc over normal lung parenchyma. The 2 figures show that patients with extension over normal lung parenchyma had lower extent scores for ground-glass at T1 (0.7 ± 0.9 vs 2.6 ± 1.8; p = 0.007) and experienced a significant increase of

Table 4. Comparison of baseline and followup characteristics between patients with a normal CT scan at T1 and T2 and patients with a normal CT scan at T1 and an abnormal followup CT scan at T2. Results are expressed as frequencies and percentages for categorical variables and as the mean ± SD for continuous data.

Characteristic	Patients with Normal CT at T1 and T2, n = 34	Patients with Normal CT at T1, and Abnormal CT at T2, n = 6	p
Female/male, n	30/4	4/2	NS
Limited SSc/Diffuse SSc, n (%)	28 (82.4)/6 (17.6)	5 (83.3)/1 (16.7)	NS
Ever smoked, n (%)	5 (14.7)	0 (0.0)	NS
Age at occurrence of Raynaud's phenomenon, yrs, mean (SD)	38 (14.0)	38 (23.6)	NS
Age at HRCT1, yrs, mean (SD)	50.4 (17.4)	46.3 (16.4)	NS
Duration of SSc, yrs, mean (SD)	11.8 (11.3)	9.5 (13.8)	NS
Followup duration, yrs, mean (SD)	5.0 (2.5)	5.8 (3.2)	NS
Esophageal involvement, n (%)	24/31 (77.4)	4/4 (100)	NS
Sicca syndrome, n (%)	17/33 (51.5)	1/4 (25)	NS
Dyspnea class I/II vs III/IV at HRCT1, n (%)	33/1	3/3	0.007
Presence of lung crackles, n (%)	0 (0)	2 (33.3)	0.02
Systolic pulmonary arterial pressure ≥ 40 mm hg, n (%)	1/28 (3.5)	2/5 (40)	0.06
No. of treated patients, n (%)	3 (8.8)	1 (16.7)	NS
Anticentromere, n (%)	24 (70.6)	2 (33.3)	0.09
Anti-Scl-70, n (%)	4 (11.8)	1 (16.7)	NS
Antinucleolar, n (%)	3 (8.8)	0 (0)	NS
Hemoglobin g/dl, mean (SD)	13.1 (1.2)	12.4 (0.8)	NS
ESR, mm, mean (SD)	13.4 (15.6)	17.8 (10.9)	NS
Plasma gammaglobulin, g/l, mean (SD)	12.6 (5.3)	13.2 (3.4)	NS
Lung function, %, mean (SD)			
VC at T1	101.9 (15.9)	78.7 (15.3)	0.03
FEV_1 at T1	101.8 (20.0)	66 (1.4)	0.06
FEV_1/VC at T1	77.7 (11.2)	73.3 (17.7)	NS
TLC at T1	97.2 (15.3)	95.0 (16.1)	NS
DLCO at T1	94.3 (27.8)	69.0 (35.8)	0.02
KCO at T1	72.5 (12.8)	54.5 (4.9)	0.04
PaO_2 at T1, mm Hg	95.1 (6.9)	85.5 (12.0)	NS
SaO_2 at T1	96.0 (1.3)	95.4 (0.9)	NS
Dyspnea class I/II vs III/IV at T2, n (%)	32/2	3/3	0.02
Worsening of dyspnea, yes/no	4/30	3/3	0.06

SSc: systemic sclerosis; T1: date of first HRCT; VC: vital capacity; FEV_1: forced expiratory volume in 1s; TLC: total lung capacity; DLCO: diffusing capacity for CO; KCO: DLCO adjusted for alveolar volume; NS: nonsignificant.

Table 5. Progression of isolated ground-glass opacities, traction bronchiectasis and/or bronchiolectasis, and honeycombing between T1 and T2. Results are expressed as frequencies and percentages for categorical variables and as the mean ± SD for continuous data.

	Findings at T1, n = 50	Findings at T2, n = 50	p
Areas of isolated ground-glass opacities			
Patients with the abnormal CT feature, n (%)	37 (74)	32 (64)	NS
Mean overall extent score (± SD)	2.32 ± 2.15	2.03 ± 2.83	NS
Traction bronchiectasis and/or bronchiolectasis			
Patients with the abnormal CT feature, n (%)	38 (76)	48 (96)	0.01
Mean overall extent score (± SD)	2.28 ± 2.06	3.05 ± 2.52	0.009
Honeycombing			
Patients with the abnormal CT feature, n (%)	20 (40)	27 (54)	NS
Mean overall extent score (± SD)	1.24 ± 1.92	1.69 ± 2.38	0.0004

NS: nonsignificant.

ground-glass and traction bronchiectasis and/or bronchiolectasis extent scores between T1 and T2 (p = 0.01, p = 0.0008, respectively), whereas the score for honeycombing progressed only slightly (p = nonsignificant). Conversely, patients without progression of FA-SSc over normal lung parenchyma between T1 and T2 experienced a significant decrease of the

Table 6. Comparison of patients experiencing spatial extension of FA-SSc over normal lung parenchyma and patients with unchanged parenchyma.

Characteristic	Spatial Extension over normal lung, n = 21	Unchanged lung, n = 21	p
Female/male, n	16/5	18/3	NS
Limited SSc/Diffuse SSc, n (%)	11/10	7/14	NS
Ever smoked, n (%)	1 (4.8)	2 (9.6)	NS
Age at occurrence of Raynaud's phenomenon, yrs, mean (SD)	38.4 (17.4)	42.6 (18.9)	NS
Age at T1, yrs, mean (SD)	49.2 (12.7)	49.7 (17.5)	NS
Duration of SSc, yrs, mean (SD)	11.3 (12.3)	7.1 (7.1)	0.18
Followup, yrs, mean (SD)	6.3 (3.2)	5.3 (3.3)	NS
Esophageal involvement, n (%)	19 (90.5)	19 (90.5)	NS
Sicca syndrome, n (%)	4/18 (22.2)	2/18 (11.1)	NS
Dyspnea class I/II/III/IV at T1, n (%)	5/11/5/0	14/6/1/0	0.02
Presence of lung crackles, n (%)	8 (38.1)	14 (66.6)	0.06
Systolic pulmonary arterial pressure ≥ 40 mm Hg, n (%)	7/20 (35)	3/18 (16.7)	NS
Treatment, n (%)	8 (38.1)	9 (42.8)	NS
Anticentromere, n (%)	6 (28.5)	2 (9.6)	NS
Anti-Scl-70, n (%)	9 (42.8)	10 (47.6)	NS
Antinucleolar, n (%)	1 (4.8)	3 (14.3)	NS
Hemoglobin g/dl, mean (SD)	12.7 (1.4)	13.0 (0.9)	NS
ESR, mm, mean (SD)	22.2 (28.8)	18.4 (14.2)	NS
Plasma gammaglobulin, g/l, mean (SD)	14.6 (6.5)	13.7 (3.4)	NS
Lung function, %, mean (SD)			
VC at T1	98.0 (18.8)	88.4 (15.2)	0.1
FEV_1 at T1	98.8 (22.3)	87.7 (18.4)	NS
FEV_1/VC at T1	79.2 (8.8)	80.2 (9.8)	NS
TLC at T1	97.8 (19.9)	86.6 (13.4)	0.08
DLCO at T1	79.5 (19.4)	79.8 (24.0)	NS
KCO at T1	65.7 (15.3)	66.5 (13.9)	NS
PaO_2 at T1, mm Hg	92.9 (8.0)	93.6 (7.05)	NS
SaO_2 at T1	96.4 (1.0)	96.0 (0.9)	NS
ΔVC	–7.7 (10.0)	–3.5 (13.0)	NS
ΔFEV_1	–8.2 (8.6)	–7.2 (19.5)	NS
ΔTLC	–6.55 (17.8)	1.5 (21.3)	NS
ΔDLCO	–25.7 (25.2)	–11.6 (16.3)	0.08
ΔPaO_2	–9.6 (14.0)	0.13 (8.1)	0.04
ΔSaO_2	–2.5 (2.9)	–0.75 (1.0)	0.04
Dyspnea class I/II/III/IV at T2, n (%)	1/13/6/1	5/13/3/0	NS
Worsening of dyspnea, yes/no	14/7	10/11	NS

SSc: systemic sclerosis; T1: date of first HRCT; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; DLCO: diffusing capacity for CO; KCO: DLCO adjusted for alveolar volume; NS: nonsignificant.

ground-glass extent score (p = 0.0005) and an increase in the honeycombing score (p = 0.01). For the traction bronchiectasis and/or bronchiolectasis extent score, there was an increase between T1 and T2, but the difference was not statistically significant.

3. Changes of HRCT features classified with the grading system (grade 1, 2, and 3 lesions). Results are summarized in Table 7. All patients with grade 3 lesions at T1 had grade 3 lesions at T2. For patients with grade 1 or 2 lesions at T1, 11/21 (52.4%) and 9/17 (52.9%), respectively, had progression of at least 1 grade at T2.

Progression of 37 patients with areas of isolated ground-grass opacities at T1. As the significance of areas of isolated ground-glass opacities is still a matter of debate, we focused on the outcome of the 37 patients with areas of isolated ground-glass opacities at T1. Among these 37 patients, 25 (68%) experienced appearance or progression of honeycombing and/or traction bronchiectasis and/or bronchiolectasis replacing these areas of former isolated ground-glass opacities between T1 and T2, whereas in 12 (32%) patients, honeycombing and/or traction bronchiectasis and bronchiolectasis were stable (n = 8) or were still absent (n = 4). Figures 3 and 4 show an example of the progressive replacement of ground-glass opacities by honeycombing and traction bronchiectasis and bronchiolectasis between T1 and T2. Comparison of these 2 groups (25 patients with progression of honeycombing and/or traction bronchiectasis/bronchiolectasis vs 12 patients without progression) is presented in Table 8. Significant results were a predominance of men, a longer duration between HRCT1 and HRCT2, and a greater decrease of KCO between T1 and T2 in the 25 patients with progression of honeycombing and/or traction bronchiectasis and bronchiolectasis.

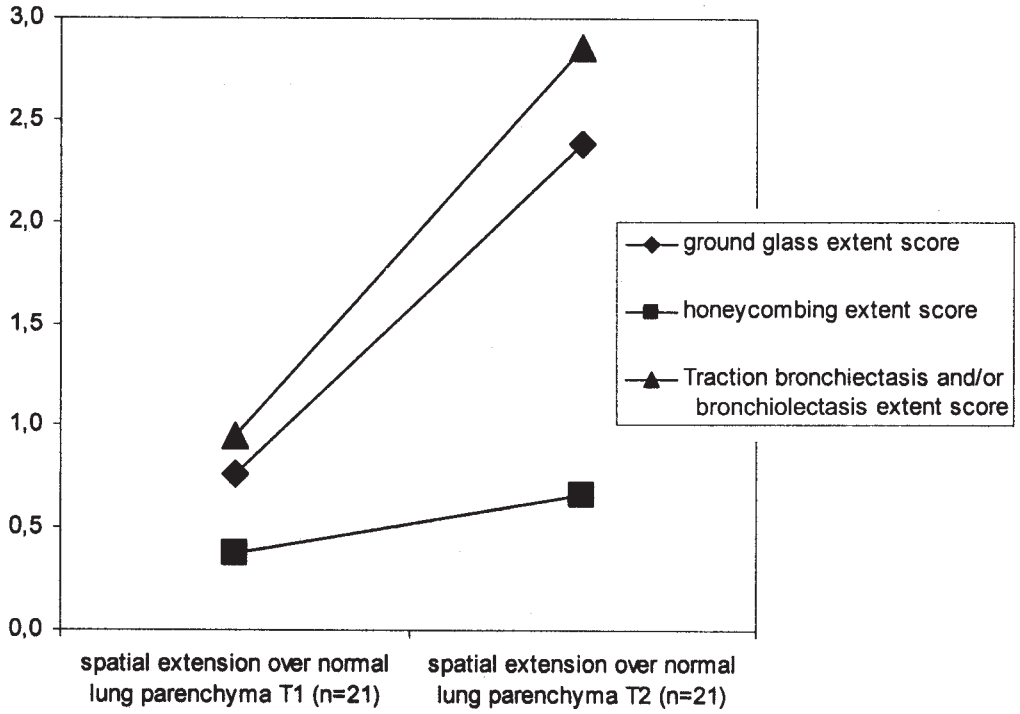

Figure 1. Scores for extent of ground-glass opacity, honeycombing, and traction bronchiectasis and/or bronchiolectasis between T1 and T2 in patients with progression of FA-SSc over normal lung parenchyma.

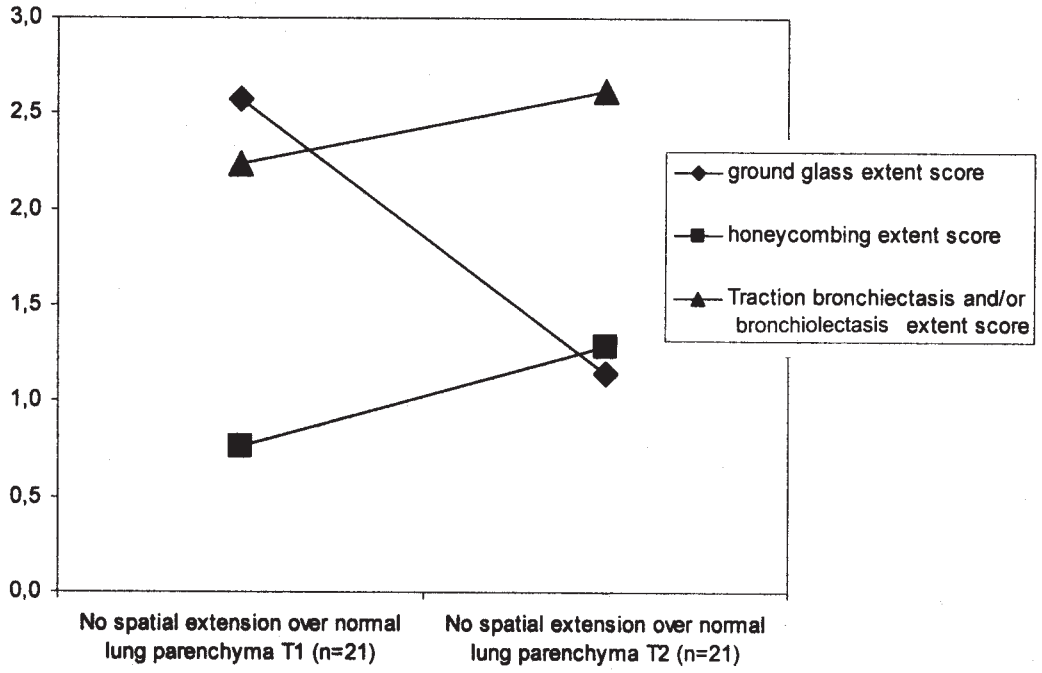

Figure 2. Scores for extent of ground-glass opacity, honeycombing, and traction bronchiectasis and/or bronchiolectasis between T1 and T2 in patients without spatial progression of FA-SSc over normal lung parenchyma.

DISCUSSION

We investigated the outcome of HRCT patterns in patients with FA-SSc during a long followup period. First, we emphasize that as a group our population had very mild lung involvement, with lung volumes over 90% of predicted and DLCO minimally depressed. Despite that, a majority of patients (50/90, 55.6%) presented with HRCT features of FA-SSc, providing an opportunity to study lung involvement ear-

Table 7. Progression of CT features (grade 1, 2, and 3 lesions).

	Grade 1 at T2, Inflammation > Fibrosis (%)	Grade 2 at T2, Inflammation = Fibrosis (%)	Grade 3 at t2, Fibrosis > Inflammation (%)
Grade 1 at T1 inflammation > Fibrosis, n = 21	10 (47.6)	7 (33.3)	4 (19.1)
Grade 2 at T1 inflammation = fibrosis, n = 17	1 (5.9)	7 (41.2)	9 (52.9)
Grade 3 at T1 fibrosis > inflammation, n = 12	—	—	12 (100)

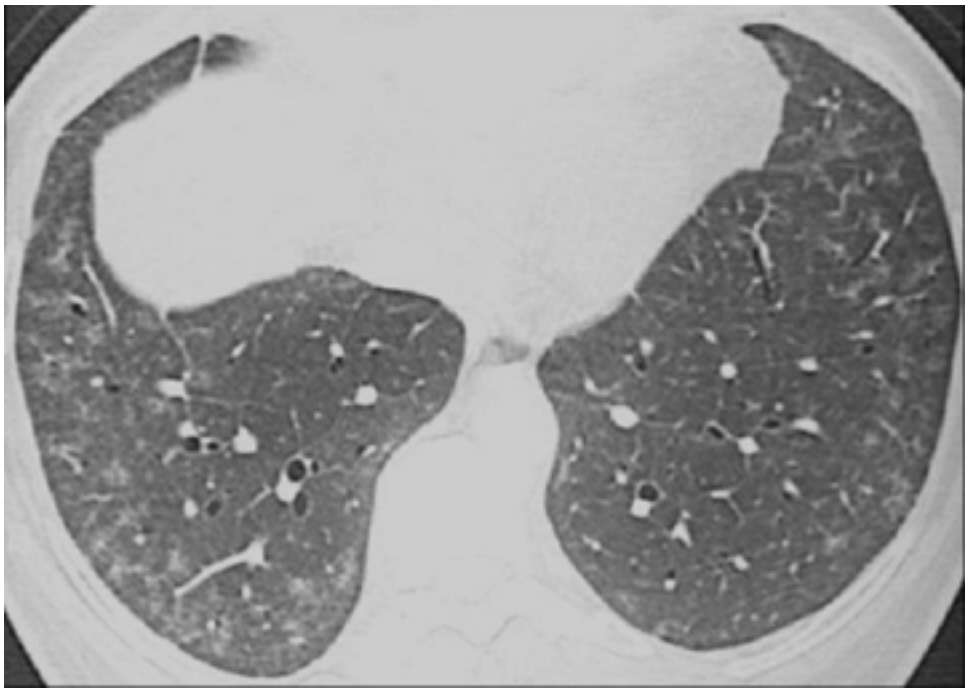

Figure 3. HRCT scan obtained at the level of the lower lobes in a 65-year-old woman, showing diffuse ground-glass attenuation on both sides. Note the ill-defined and peripheral micronodules in both lungs, predominant in the right lower lobe.

lier than is often the case in SSc, and showing that it is justified to use HRCT scan as a screening tool in FA-SSc.

When we compared the baseline characteristics of the 40 patients with a normal HRCT and the 50 patients with an abnormal HRCT at T1, we found the classical association between FA-SSc and diffuse SSc with anti-SCL-70 antibodies (Table 3). However, up to 18/51 (35.3%) patients with limited SSc and 8/34 (23.5%) patients with anticentromere antibodies had FA-SSc. In our opinion, these findings suggest that a screening CT scan is also justified in these latter patients, and we propose a screening CT scan to all our patients with SSc regardless of the subtypes of SSc and antibodies. Interestingly, we found that patients with an abnormal HRCT at T1 had higher gammaglobulin concentrations and ESR than patients with a normal HRCT. This has also been described by Yuhara, *et al*[23]. The explanation for this is not clear, but it may reflect the systemic inflammatory status, as the frequency of sicca syndrome (frequently associated with hypergammaglobulinemia) was not different between the 2 groups.

Concerning the followup study, our first finding was that 85% of patients with a normal HRCT still had a normal HRCT after a mean followup of about 5 years. Although this result may seem obvious enough, it must be emphasized that the longterm outcome of normal HRCT in SSc has been poorly studied. We found only one study, in which 5/5 (100%) patients with a normal HRCT still had a normal HRCT after a mean followup of 1.75 years[12]. Together, these results show that a normal HRCT in SSc seems to indicate good longterm prognosis for lung involvement. The 6 patients (15%) whose normal HRCT at T1 became abnormal at T2 were more dyspneic and had lung crackles more frequently at T1 than patients with a normal HRCT at T1 and T2. The presence of lung crackles may be surprising in patients with a normal HRCT. However, Arroliga, *et al* have reported the presence of lung

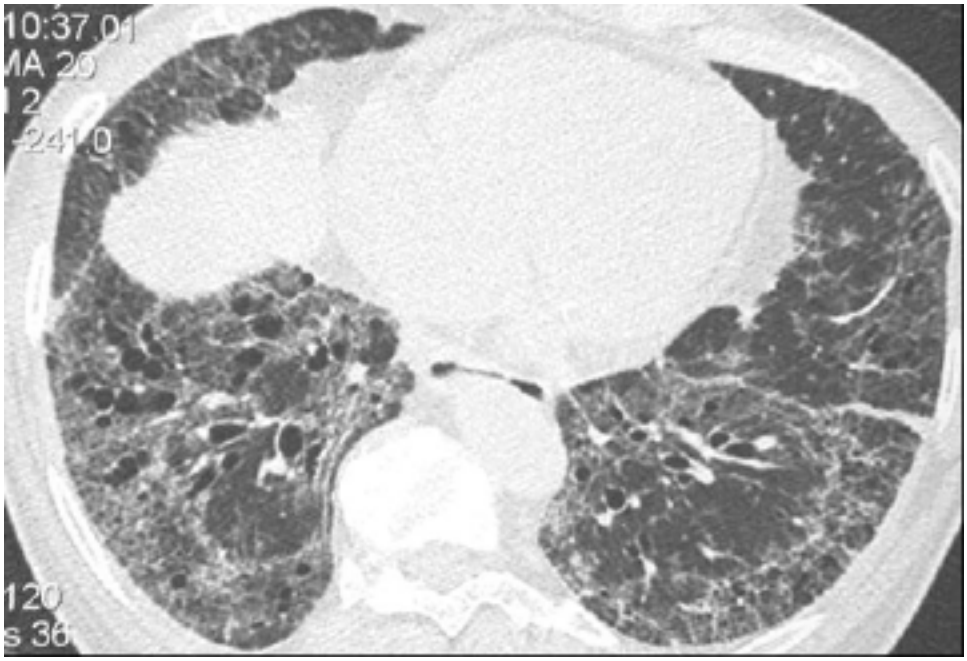

Figure 4. Followup HRCT scan 7 years later at the same level in the same patient as in Figure 3. Note areas of microcystic honeycombing, mostly peripherally located, as well as ground-glass attenuation and traction bronchiectasis, more extensive in the right lower lobe, both indicative of lung fibrosis also suggested by lung retraction. Note abnormal dilatation of the esophagus.

crackles without radiological abnormalities[1]. VC, DLCO, and KCO were significantly lower at T1 in the 6 patients. The lower DLCO and KCO could be attributed to the higher frequency of pulmonary hypertension in these patients. The presence of lung crackles and lower VC suggest that the 6 patients may have had lung involvement that was missed by HRCT at T1, emphasizing the importance of clinical examination and PFT in the initial evaluation in SSc. Anticentromere antibodies tended to be associated with lower frequency of abnormal HRCT at T2, which is in accord with the "protective" role of these antibodies, as it is well known that they are associated with a lower risk of fibrosis at initial evaluation in SSc[24]. The absence of statistical significance must be interpreted with caution because of the small number (n = 6) of patients whose followup HRCT became abnormal. Considering these results, we now propose and apply in our clinical practice that in patients with a normal initial HRCT, normal lung auscultation, and normal PFT, systematic followup HRCT may not be necessary, especially if there are anticentromere antibodies, but should be proposed only in case of worsening of the dyspnea, appearance of lung crackles, or alteration in PFT.

In cases of FA-SSc, a physician will wish to know the prognosis for extension of the FA-SSc over the normal lung parenchyma. As dilemma in treatment most often concerns patients with disease that is not too severe, we focused on patients with less than 50% of lung parenchyma affected by FA-SSc at T1, and compared those whose FA-SSc progressed over lung parenchyma (21/42, 50%) to those whose FA-SSc did not progress (21/42, 50%) between T1 and T2.

Our results showed the following:

1. There was no clear, simple baseline clinical or biological indicator that could predict patients who would experience disease progression.
2. Patients experiencing progression of FA-SSc over lung parenchyma were probably those who were less severely affected at T1, as shown by a lesser frequency of lung crackles, higher VC% and TLC% ($p = 0.1$, $p = 0.08$, respectively), a lower extent score for ground-glass opacity, traction bronchiectasis and/or bronchiolectasis and honeycombing (only statistically significant for ground-glass appearance).
3. The spatial extension over normal lung parenchyma was essentially due to progression of ground-glass opacities and traction bronchiectasis and/or bronchiolectasis and led to a greater decrease in PaO_2, SaO_2, and DLCO between T1 and T2. There was also a greater decrease in TLC, but it was not statistically significant.

In the Wells study, DLCO and also TLC showed the best association with the extent of disease[25]. These data suggest that the progression of SSc lesions throughout normal lung parenchyma is first indicated by ground-glass opacities and traction bronchiectasis and/or bronchiolectasis, and affected patients with less severe extent at baseline, whereas patients who already had a high score for ground-glass opacities tended to experience a progressive replacement of ground-glass opacity by honeycombing. The therapeutic consequences of repeating scans in patients with FA-SSc were not directly assessed in our study, and remain to be addressed in future studies. However, our results confirm that a repeated HRCT

Table 8. Comparison of baseline and followup characteristics between patients with areas of isolated ground-glass opacities at T1 (n = 37) who showed either progression (n = 25) or stability (or absence) (n = 12) of honeycombing/traction bronchiectasis and/or bronchiolectasis between T1 and T2. Results are expressed as frequencies and percentages for categorical variables and as the mean ± SD for continuous data.

Characteristic	Progression of Fibrosis, n = 25	Stability of Fibrosis, n = 12	p
Female/males, n	17/8	12/0	0.03
Limited SSc/Diffuse SSc, n (%)	9 (36)/16 (64)	4 (33.3)/8 (66.7)	NS
Ever smoked, n (%)	3 (12)	1 (8.3)	NS
Age at occurrence of Raynaud's phenomenon, yrs, mean (SD)	41.5 (17.4)	48.1 (12.2)	NS
Age at T1, yrs, mean (SD)	51.1 (14.8)	55.5 (10.8)	NS
Duration of SSc, yrs, mean (SD)	9.0 (10.8)	7.4 (8.4)	NS
Followup, yrs, mean (SD)	6.3 (3.3)	3.8 (2.7)	0.03
Esophageal involvement, n (%)	22 (88)	11 (91.7)	NS
Sicca syndrome, n (%)	1/19 (0)	3/11 (0)	NS
Dyspnea class I/II/III/IV at T1, n (%)	21/4	11/1	NS
Presence of lung crackles, n (%)	16 (64)	6 (50)	NS
Systolic pulmonary arterial pressure ≥ 40 mm Hg, n (%)	5 (20)	5 (41.7)	NS
Treatment, n (%)	16 (64.0)	2 (16.6)	0.008
Anticentromere, n (%)	4 (16)	3 (25)	NS
Anti-Scl-70, n (%)	12 (48)	5 (41.7)	NS
Antinucleolar, n (%)	2 (8)	1 (8.3)	NS
Hemoglobin g/dl, mean (SD)	13.3 (1.1)	12.6 (1.1)	NS
ESR, mm, mean (SD)	24.1 (17.6)	15.4 (16.4)	NS
Plasma gammaglobulin, g/l, mean (SD)	16.1 (5.9)	13.1 (3.3)	NS
Lung function, %, mean (SD)			
VC at T1	86.1 (17.3)	96.2 (13.2)	0.09
FEV_1 at T1	86.8 (20.8)	93.4 (17.3)	NS
FEV_1/VC at T1	81.2 (10.0)	78.4 (7.5)	NS
TLC at T1	86.8 (16.1)	94.9 (16.0)	NS
DLCO at T1	72.1 (19.7)	76.0 (22.3)	NS
KCO at T1	69.7 (10.5)	63.3 (12.5)	NS
PaO_2 at T1, mm Hg	94.1 (6.8)	89.7 (8.4)	NS
SaO_2 at T1	96.3 (1.0)	95.5 (1.0)	NS
ΔVC	–8.7 (18.1)	–4.1 (12.6)	NS
ΔFEV_1	–13.3 (20.2)	–2.86 (10.5)	NS
ΔTLC	–2.9 (21.7)	–10.1 (8.7)	NS
ΔKCO	–14.5 (20.1)	–7.5 (25.9)	0.04
ΔPaO_2	–6.45 (15.7)	–1.7 (7.2)	NS
ΔSaO_2	–2.5 (6.3)	–0.4 (1.1)	NS
Dyspnea class I/II vs III/IV at T2, n (%)	17/8	9/3	NS
Worsening of dyspnea, yes/no	14/11	4/8	NS

SSc: systemic sclerosis; T1: date of first HRCT; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; DLCO: diffusing capacity for CO; KCO: DLCO adjusted for alveolar volume; Δ: (value at T2 – value at T1)* 100/value at T1; NS: nonsignificant.

associated with PFT may be useful to follow progression of FA-SSc over time and to determine the optimal timing for treatment.

About half the patients with grade 1 lesions at T1 (areas of isolated ground-glass opacities predominating) progressed to grade 2 or grade 3 (honeycombing/traction bronchiectasis and/or bronchiolectasis predominating) at T2, and half the patients with grade 2 at T1 progressed to grade 3 lesions at T2. All patients with grade 3 lesions at T1 continued to have grade 3 lesions at T2. These results confirm that the "natural history" of about half our patients was a progressive replacement of areas of isolated ground-glass opacities by honeycombing/traction bronchiectasis and/or bronchiolectasis. This was confirmed by the significantly higher global extension score of honeycombing/ traction bronchiectasis and/or bronchiolectasis at T2, whereas the global extension score of ground-glass opacities at T2 was lower than at T1, although it did not achieve statistical significance. The extension of honeycombing/traction bronchiectasis and/or bronchiolectasis involved the middle and upper zones as well as the central and anterior areas. The diminution in overall extent score of the areas of isolated ground-glass opacities was in accord with the results reported by Wells, *et al*[15] and Terrif, *et al*[16]. Rémy-Jardin, *et al*[12] have also shown that honeycombing was seen to develop within areas of isolated ground-glass opacities on initial HRCT with concurrent disappearance of the ground-glass pattern. This probably explains some discrepancies in the literature concerning the progression of HRCT patterns over the time. In Wells' study, the most frequent change in the CT appearance associated with progression of disease was an

increase in reticular pattern, whereas in Kim, *et al*[26] the global extension score of honeycombing and ground-glass opacities both increased significantly on followup CT. As the followup periods are different in these studies and in our study and as the patient cohorts were also different (more severely affected in Wells, *et al*[15]), the results may reflect that patients were observed at different time intervals during a common natural history.

One of the main issues in FA-SSc is to identify the patient's stage in the progression of the lung disease when the first HRCT is performed[4]. The aim is to know whether lesions may be reversible or whether progression of lesions could be influenced by treatment. As honeycombing/traction bronchiectasis and/or bronchiolectasis have been shown to correlate histologically with irreversible fibrosis and ground-glass opacities with potentially reversible inflammation[27], we focused on the outcome of patients who had areas of isolated ground-glass opacities at T1 (either alone or associated with honeycombing and/or traction bronchiectasis and/or bronchiolectasis). The first result was that a majority, nearly two-thirds, of these patients demonstrated a progression or an appearance of honeycombing/traction bronchiectasis and/or bronchiolectasis at T2, regardless of treatment. Similarly, in Rémy-Jardin's study, 8/13 (61.5%) patients having ground-glass opacities experienced a progression of the fibrosis[12]. In Wells, *et al*[15], ground-glass opacities almost always regressed with treatment when it was the predominant pattern seen on the initial HRCT. When ground-glass opacities coexisted with an equally extensive honeycombing pattern, ground-glass opacities were less likely to regress and sometimes progressed. Moreover, it has been shown that very fine intralobular fibrosis, which lies beyond the limits of resolution of HRCT, would not be depicted as a reticular abnormality, but might result in an amorphous increase in lung density as a result of volume-averaging, producing a ground-glass appearance[15]. Together, these data suggest that ground-glass opacities either indicate a mild fibrosis or correspond to an inflammatory alveolitis, both progressing in the majority of patients to established lung fibrosis, and they do not always indicate a prognosis as favorable as sometimes reported[14,28]. In our study, patients with areas of isolated ground-glass opacities experiencing progression of fibrosis had a significantly longer interval between T1 and T2 than patients with no such progression. Dévényi, *et al* also found that patients with isolated ground-glass opacities had a shorter disease duration than patients with honeycombing[29]. These results are also in accord with the "natural history" of ground-glass opacities progressing over time to established lung fibrosis. It is therefore possible that our 2 groups of patients distinguished according to the stage of progression of fibrosis represent the same natural history observed at 2 different stages. Patients with progression of fibrosis were more likely to be treated with cyclophosphamide and/or corticosteroids. This reflects the usual way to treat patients and must be interpreted with caution. As our study was retrospective, it cannot be used to assess the efficacy of treatment in FA-SSc. Finally, a greater extent of fibrosis was more frequent in men and was associated with a greater decrease in KCO, emphasizing again the value of followup PFT. This is in accord with Kim's study[26], where the increase in the extent of honeycombing on CT correlated significantly with the decrease in KCO, but with neither VC nor FEV_1. Interestingly, we found no differences concerning the subtypes of SSc and ANA between the 2 groups of patients. This suggests that if FA-SSc is less frequent in patients with anticentromere antibodies and limited SSc, it is not necessarily less progressive if present.

In conclusion, a normal HRCT at the first evaluation seemed to indicate good longterm prognosis in patients with SSc. For patients with FA-SSc, there appeared to be a natural history of disease progression. Areas of isolated ground-glass opacities replaced normal lung parenchyma, and were then replaced by honeycombing and/or bronchiectasis/bronchiolectasis. Among patients with isolated ground-glass opacities on the first HRCT, about two-thirds demonstrated progression of the fibrosis on the followup HRCT, especially in male patients. This is an additional argument that isolated ground-glass opacity is probably the first step of lung fibrosis in SSc, and that treatment should be discussed at this early stage, to avoid disease progression. In our study, subtypes of SSc and antinuclear antibodies did not affect the progression of established FA-SSc.

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REFERENCES

1. Arroliga AC, Podell DN, Matthay RA. Pulmonary manifestations of scleroderma. J Thorac Imaging 1992;7:30-45.
2. Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis. Demographic, clinical and serologic features and survival in 1012 Italian patients. Medicine 2002;81:139-53.
3. Wells AU, Cullinan P, Hansell DM, et al. Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1994;149:1583-90.
4. Latsi PI, Wells AU. Evaluation and management of alveolitis and interstitial lung disease in scleroderma. Curr Opin Rheumatol 2003;15:748-55.
5. Giacomelli R, Valentini G, Salasano F, et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. J Rheumatol 2002;29:731-6.
6. Desai SR, Veeraraghavan S, Hansell DM, et al. CT features of lung disease in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. Radiology 2004;232:560-7.
7. Strickland B, Strickland NH. The value of high definition, narrow section computed tomography in fibrosing alveolitis. Clin Radiol 1988;39:589-94.
8. Muller NL, Miller RR. State of the art: computed tomography of chronic diffuse infiltrative lung disease: part 1. Am Rev Respir Dis 1990;142:1206-15.
9. Schurawitzki H, Stiglbauer R, Graninger W, et al. Interstitial lung disease in progressive systemic sclerosis: high-resolution CT versus

radiography. Radiology 1990;176:755-9.
10. Muller NL, Miller RR, Webb WR, Evans KG, Ostrow DN. Fibrosing alveolitis: CT-pathologic correlation. Radiology 1986;160:585-8.
11. Wells AU, Hansell DM, Corrin B, et al. High resolution computed tomography as a predictor of lung histology in systemic sclerosis. Thorax 1992;47:738-42.
12. Remy-Jardin M, Remy J, Wallaert B, Bataille D, Hatron PY. Pulmonary involvement in progressive systemic sclerosis: sequential evaluation with CT, pulmonary function tests, and bronchoalveolar lavage. Radiology 1993;188:499-506.
13. Muller NL, Staples CA, Miller RR, Vedal S, Thurlbeck WM, Ostrow DN. Disease activity in idiopathic pulmonary fibrosis: CT and pathologic correlation. Radiology 1987;165:731-4.
14. Lee JS, Im JG, Ahn JM, Kim YM, Han MC. Fibrosing alveolitis: prognostic implication of ground-glass attenuation at high-resolution CT. Radiology 1992;184:451-4.
15. Wells AU, Rubens MB, du Bois RM, et al. Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. AJR Am J Roentgenol 1993;161:1159-65.
16. Terrif BA, Kwan SY, Chan-Yeung MM, Muller NL. Fibrosing alveolitis: chest radiography and CT as predictors of clinical and functional impairement at follow-up in 26 patients. Radiology 1992;184:445-9.
17. Crystal RG, Gadek JE, Ferrans VJ, Fulmer JD, Line BR, Hunninghake GW. Interstitial lung disease: current concepts of pathogenesis, staging and therapy. Am J Med 1981;70:542-68.
18. Masi AT, Rodnan GP, Medsger TA Jr, et al. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.
19. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.
20. New York Heart Association Criteria Committee. Diseases of the heart and blood vessels: nomenclature and criteria for diagnosis. Boston: Little Brown & Co.; 1964.
21. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
22. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OE, Peslin R, Yernault JC. Standardization of the measurements of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5-52.
23. Yuhara T, Takemura H, Akama T, Yamane K, Sumida T. The relationship between serum immunglobulin levels and pulmonary involvement in systemic sclerosis. J Rheumatol 2000;27:1207-14.
24. Steen VD, Owens GR, Fino GJ, Rodnan GP, Medsger TA Jr. Pulmonary involvement in systemic sclerosis (scleroderma). Arthritis Rheum 1985;28:759-67.
25. Wells AU, Hansell DM, Rubens MB, et al. Fibrosing alveolitis in systemic sclerosis: indices of lung function in relation to extent of disease on computed tomography. Arthritis Rheum 1997;40:1229-36.
26. Kim EA, Johkoh T, Lee KS, et al. Interstitial pneumonia in progressive systemic sclerosis: serial high-resolution CT findings with functional correlation. J Comput Assist Tomogr 2001;25:757-63.
27. McDonald SLS, Rubens MB, Hansell DM, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. Radiology 2001;221:600-5.
28. Vedal SV, Welsh VE, Miller RR, Muller NL. Desquamative interstitial pneumonia: computed tomographic findings before and after treatment with corticosteroids. Chest 1988;93:215-7.
29. Devenyi K, Czirjak L. High resolution computed tomography for the evaluation of lung involvement in 101 patients with scleroderma. Clin Rheumatol 1995;14:633-40.