Pulmonary Manifestations in Sjögren's Syndrome: Correlation Analysis Between Chest Computed Tomographic Findings and Clinical Subsets with Poor Prognosis in 80 Patients

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ABSTRACT. ***Objective.*** Sjögren's syndrome (SS) has a varied clinical spectrum and has been associated with various chest computed tomography (CT) findings. We sought to delineate the characteristic CT features in various subsets of SS, especially poor prognosis subsets.

Methods. Retrospectively identified 80 never-smoker SS patients [56 primary SS (1-SS), 24 secondary SS (2-SS)] who underwent chest CT at our institution during a 3-year period from 2004 through 2007 were included in this study. Chest CT findings were qualitatively and semiquantitatively analyzed with comparison between 1-SS and 2-SS, and correlation with anti-SSB/La seropositivity and the presence of clonally derived lymphoproliferative disorder (cLPD), which are known to be pathognomonic and prognostic clinical features of SS patients.

Results. All patients were women with median age of 60 years. Anti-SSB/La antibodies were found in 17 primary SS patients and 4 2-SS patients. Eleven patients with cLPD were identified and all of them had 1-SS. The most frequent CT finding in both types of patients was interlobular septal thickening. Secondary SS was associated with a significantly greater frequency and extent of honeycombing versus 1-SS. Univariate and multivariate analysis showed a significant association between honeycombing and 2-SS. In patients with 1-SS and in the SS group as a whole, we observed independent and significant associations between cysts and anti-SSB/La seropositivity or cLPD.

Conclusion. Cysts are significantly associated with anti-SSB/La seropositivity and cLPD. The presence of lung cysts revealed by chest CT might be a prognostic clinical feature, a clue, or a predictor of cLPD in patients with SS. (J Rheumatol First Release Dec 15 2009; doi:10.3899/jrheum.090507)

Key Indexing Terms:
SJÖGREN'S SYNDROME COMPUTED TOMOGRAPHY LUNG CYSTS
SSB ANTIBODIES LYMPHOPROLIFERATIVE DISORDERS

Sjögren's syndrome (SS) is a chronic inflammatory and lymphoproliferative disease with autoimmune features characterized by a progressive mononuclear cell infiltration of exocrine glands, notably the lacrimal and salivary glands[1]. SS expresses a varied clinical spectrum, extending from sicca-limited disease to a systemic disease affecting various organs and can present either alone (primary SS, 1-SS) or in the context of an underlying connective tissue disease (secondary SS, 2-SS)[2,3].

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Accepted for publication August 7, 2009.

Various radiographic findings have been reported as pulmonary manifestations of 1-SS[4-6]. Computed tomography (CT) can noninvasively delineate structural abnormalities in the lungs and has proven to be a more sensitive measure compared to plain radiography, pulmonary function tests, and clinical findings[6,7]. As for studies assessing CT findings of lung involvement in SS, there have been a few reports assessing sizable numbers of patients with SS[4-6,8]. Although reports suggested that pulmonary CT findings, such as thin-walled cysts, ground-glass opacities, peribronchovascular interstitial thickening, and interlobular septal thickening, were relatively characteristic in 1-SS[4-6,8,9], discrepancy exists concerning frequency and characteristic CT features of pulmonary involvement in SS, partly due to the complexity and varying nature of the disease.

SS is also known as a lymphoproliferative disorder ranging from polyclonal lymphocytic infiltration of the salivary and lacrimal glands to oligo- or monoclonal B cell proliferation resulting in clonally derived lymphoproliferative disorders (cLPD), such as monoclonal gammopathy, light-chain amyloidosis, and malignant lymphoma[10-17]. In addi-

tion, high prevalence of cLPD is a distinct feature of SS in comparison to other connective tissue diseases[10,12,15,17-19]. Patients with SS had 16- to 44-fold increased risk of developing lymphoma, and the estimated prevalence of malignant lymphoma in SS was 4.3%, with the majority being low-grade marginal zone lymphoma, particularly of mucosa-associated lymphoid tissue (MALT) origin[12,14-16]. On the other hand, in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), the estimated prevalence of malignant lymphoma was about 9 times lower than that of SS, and associated lymphomas are predominantly of the diffuse large B cell type[18,19]. Therefore, cLPD is the consequence of the core disease process and prognostic systemic manifestation of SS.

Anti-SSA/Ro and anti-SSB/La have been widely used for the diagnosis of SS, and are disease-specific autoantibodies for SS[1-3,20,21]. These autoantibodies are probably generated very early in the disease process or even before clinical symptoms emerge, and may be constantly observed during the course of illness in the individual patient[20,21]. Anti-SSB/La is invariably accompanied by anti-SSA/Ro, and has a higher diagnostic specificity for SS than does anti-SSA/Ro alone[20,21], and the presence of anti-SSB/La antibodies is closely associated with internal organ damage and hematological abnormalities[20,21]. Moreover, determination of anti-SSB/La antibodies may prove to be a reliable prognostic factor in 1-SS[20,21]. Thus, presence of cLPD and seropositivity for anti-SSB/La are the core clinical findings of systemic involvement of SS.

To clarify characteristic and prognostic pulmonary CT findings in SS, we analyzed the frequency and extent of abnormal chest CT findings in 80 never-smoker SS patients and compared chest CT findings with various clinical subsets of SS, including primary and secondary SS, or subsets with or without specific and prognostic signs of SS, focusing on cLPD and anti-SSB/La antibodies.

MATERIALS AND METHODS

Study population. We retrospectively reviewed electronic medical records and identified 93 consecutive patients with SS who visited the Division of Rheumatology, Nagoya City University Hospital, and underwent chest CT at our hospital during a 3-year period from January 2004 through December 2007. Among them, 2 patients with extensive lung disease due to other established etiologies, 10 patients with smoking history, and 1 patient without information about smoking history were excluded. All 80 never-smoker patients selected for our study were Japanese and fulfilled the criteria defined by the 1999 Revised Japanese Criteria for diagnosis of SS[22]. According to these criteria, the diagnosis of SS can be made when a patient meets at least 2 of the following 4 items: (1) salivary or lacrimal gland histopathology demonstrating foci of lymphocytes with focus score ≥ 1; (2) abnormal findings in sialography ≥ Stage 1 according to the Rubin and Holt classification[23], or decreased saliva production (≤ 10 ml/10 min according to chewing gum test or ≤ 2 g/2 min according to Saxon test) with decreased salivary function according to salivary scintigraphy; (3) ocular signs of corneal damage due to inadequate tearing, test results indicating impaired salivary gland function, inadequate tear production (Shirmer test ≤ 5 mm/5 min) with evidences of corneal erosion (rose bengal test ≥ 3 according to van Bijsterveld score or positive fluorescein staining); (4) and the presence of autoantibodies (anti-SSA/Ro, anti-SSB/La, or both)[24]. To evaluate the correlations between clinical and chest CT findings, we categorized patients by 1-SS or 2-SS or the groups divided by presence or absence of anti-SSB/La antibodies, or cLPD during the study period. For detection of anti-SSA/Ro and anti-SSB/La antibodies, double immunodiffusion assay or enzyme linked immunosorbent (ELISA) assay (TFB, Inc., Tokyo, Japan) was used. These assays were performed by SRL, Inc. (Tokyo, Japan), which is a company that provides a comprehensive laboratory testing service in Japan. We defined anti-SSA/Ro and anti-SSB/La seropositivity by the positive result obtained by either double immunodiffusion assay or ELISA assay. Institutional review board approvals were obtained, but informed consent from patients was waived because of the retrospective analyses of this study.

CT scanning. All patients were examined with a 16-multidetector-row CT (Mx 8000 IDT 16; Philips, Brest, The Netherlands) or a 64-multidetector-row CT (SOMATOM Definition; Siemens, Forchheim, Germany). The image reconstruction was performed with 3 mm section thickness with 3 mm reconstruction interval through the whole lung. High-resolution CT scans (1 mm section thickness with 10 mm interval using a high-spiral-frequency algorithm) were also obtained. All CT scans were obtained during end-inspiratory pause. Window settings for the lung were a level of –550 HU and a width of 1500 HU.

Chest CT was interpreted independently and with random order by 2 chest radiologists (MH, TA) without knowledge of the clinical status of the patients. A decision was made by consensus if there were disagreements. These observers evaluated the presence, extent, and distribution of the following CT findings: airspace consolidation, bronchiectasis including bronchioloectasis, cysts, emphysema, ground-glass opacities, honeycombing, ill-defined centrilobular nodules, interlobular septal thickening, intralobular reticular opacities, mosaic perfusion, nonseptal linear or plate-like opacities, thickening of bronchovascular bundles, and generation of traction bronchiectasis[25]. The extent of involvement of each abnormality was assessed independently for each of 3 zones, upper, middle, and lower, of each lung. The upper lung zone consisted of the scans from the apex of the lungs to the level of the tracheal carina. The scans from the level of the tracheal carina to pulmonary venous confluence represented the middle lung zone. The scans below the venous confluence down to the diaphragm were defined as the lower lung zone. A 5 point scale was used in the individual lung zone to grade the degree of abnormalities: 0, no abnormalities; 0.25, ≤ 25% of the zone involved; 0.5, between 26% and 50% of the zone involved; 0.75, between 51% and 75% of the zone involved; 1, > 75% of the zone involved. As for cysts, the numbers, size, cephalocaudal (upper, middle, or lower), and mediolateral (inner one-third, middle one-third, or outer one-third) distributions were also assessed. The extent of each CT finding was expressed by the percentage of the summed score from 6 lung zones (the summed score was divided by 0.06) was provided for quantitative analysis of extent of various abnormalities and correlation to clinical conditions.

Statistical analysis. All statistical analyses were performed with statistical software (Dr. SPSS II; SPSS, Chicago, IL, USA). Univariate analysis was used to compare the various CT findings between 2 groups. Fisher's exact probability test and Mann-Whitney U test were used to examine differences in proportions for and the extent of each CT finding between 2 groups, respectively. Kruskal-Wallis test was used to examine differences in proportions for each CT finding among 3 cephalocaudally or mediolaterally divided lung zones. A p value of < 0.05 was considered to indicate a significant difference.

Multivariate logistic regression analysis was used to identify CT findings that differed independently between groups. The presence of all CT findings except for traction bronchiectasis was independently analyzed and included as covariates, because occurrence was secondary to interstitial inflammatory processes and the extent of traction bronchiectasis showed multicollinearity with the extent of interlobular reticular opacities and hon-

eycombing (Pearson correlation coefficient > 0.8). A backward stepwise procedure was used in the logistic regression analysis to select the variables that should have been included in the model. The removal of a variable from the model was based on the significance of the likelihood ratio criterion ($p < 0.1$). The multivariate odds ratio and 95% confidence intervals were estimated.

RESULTS

Clinical characteristics. Demographic data, clinical findings, and treatment status at the time of CT examination are presented in Table 1. All subjects were women ranging from 24 to 80 years of age (median age 60) with mean disease duration of 6 years (0 to 30). Fifty-six patients had 1-SS and the others had 2-SS in association with other rheumatic diseases: systemic sclerosis (SSc) 9, RA 5, SLE 5, polymyositis 2, mixed connective tissue disease 1, and overlap syndrome 2 (SLE + RA 1, SSc + polymyositis 1). At the time of CT examination, 40 patients had both ocular and oral sicca symptoms, 13 had oral sicca symptoms without ocular sicca, and 9 had ocular sicca symptoms without oral sicca. The other 18 patients complained of neither oral sicca nor ocular sicca symptoms. Nineteen (24%) patients had respiratory symptoms. Treatment status was as follows: the average dose of corticosteroids was 3.1 mg/day of prednisolone equivalent; 48 patients were not taking corticosteroids or immunosuppressants; and 14 patients were taking the corticosteroid equivalent to prednisolone > 5 mg/day. Forty patients had only anti-SSA/Ro antibodies, 20 patients had both anti-SSA/Ro antibodies and anti-SSB/La antibodies, and one patient had only anti-SSB/La antibodies. The other 19 patients had neither antibody. Seventeen patients with 1-SS and 4 patients with 2-SS had anti-SSB/La antibodies. Of 21 patients who had anti-SSB/La antibodies 11 were from 47 patients checked by only double immunodiffusion assay, 8 from 25 patients checked by double immunodiffusion and ELISA assays at different timepoints, and 2 from 8 patients checked by only ELISA assay. Discordant results by double immunodiffusion and ELISA assays at different timepoints were found in 4 patients (2 were positive by immunodiffusion but negative by ELISA, and 2 negative by immunodiffusion but positive by ELISA).

Twenty-nine patients had extraglandular lesions and 11 of them had cLPD. All patients with cLPD had 1-SS. Six had mucosa-associated lymphoid tissue lymphoma: 2 in salivary glands, one in lungs, one in stomach, one in thymus, and one in trachea. Two had immunoglobulin A-lambda type monoclonal gammopathy of undetermined significance. Two had light-chain amyloidosis: one had skin lesion only and one had lung amyloidosis. The remaining patient had non-Hodgkin lymphoma. We did not observe a significant association between anti-SSB/La seropositivity and cLPD (Fisher's exact probability test; $p = 0.19$).

Chest CT findings. The CT findings in 1-SS and 2-SS are summarized in Table 2. Abnormalities on chest CT were present in 72 (90%) of 80 SS patients. The frequency of abnormalities was 50 (89%) patients with 1-SS and 22 (92%) with 2-SS. Interlobular septal thickening was the most common and widespread abnormality in patients with both 1-SS and 2-SS, followed by pleural thickening, ill-

Table 1. Demographic data, clinical findings, and treatment status in the study population.

Characteristic	1-SS, n = 56	2-SS, n = 24
Median age (range), yrs	59 (24–80)	64 (33–73)
Female, %	100	100
Median disease duration (range), yrs	3 (0–29)	6 (0–30)
Sicca symptoms, oral only/ocular only/both, n	5/10/30	4/3/10
Patients with respiratory symptoms, n (%)	11 (20)	8 (33)
Patients with anti-SSA/Ro, n (%)	46 (82)	14 (58)
Patients with anti-SSB/La, n (%)	17 (30)	4 (16)
Patients with leukopenia < 3500 mm^3, n (%)	24 (43)	9 (38)
Serum IgG, mg/dl, mean ± SD	2337 ± 1109	2153 ± 754
Patients with extraglandular manifestations, n (%)	29	—
Patients with cLPD, n (%)	11	0
Associated connective tissue diseases	—	SSc 9, RA 5, SLE 5, PM 2, MCTD 1, OS 2
Corticosteroid dose, mg/day, mean (range)	2.0 (0–20)	5.8 (0–40)
Patients without corticosteroid therapy, n (%)	37 (66)	11 (46)
Patients on corticosteroid therapy, n	19	13
> 0 and ≤ 5 mg/day	14	4
> 5 and ≤ 10 mg/day	4	6
> 10 and ≤ 20 mg/day	1	2
> 20 mg/day	0	1
Patients on immunosuppressants*, n	3	4

* All patients were receiving corticosteroid therapy. cLPD: clonally derived lymphoproliferative disorder; SSc: systemic sclerosis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; PM: polymyositis; MCTD: mixed connective tissue disease; OS: overlap syndrome.

Table 2. Frequency and extent of thin-section computed tomographic findings (CT) in primary (1-SS) and secondary Sjögren's syndrome (2-SS). Data on extent of thin-section CT findings are mean ± SD of the percentage of CT scores. P values were calculated by comparing data of 1-SS versus 2-SS using Fisher's exact probability test for frequency and Mann-Whitney U test for extent of CT findings.

CT Finding	All SS, n = 80		1-SS, n = 56		2-SS, n = 24		p	
	N (%)	Extent	N (%)	Extent	N (%)	Extent	N	Extent
Airspace consolidation	13 (16)	1.6 ± 4.3	8 (14)	2.4 ± 5.9	5 (21)	3.5 ± 6.9	0.516	0.395
Bronchiectasis	18 (23)	6 ± 15.7	12 (21)	3.6 ± 6.9	6 (25)	4.2 ± 7.4	0.774	0.620
Cysts	30 (38)	6.3 ± 12.5	22 (39)	6.5 ± 8.2	8 (33)	5.6 ± 8	0.802	0.439
Emphysema	5 (6)	2.2 ± 12.5	2 (4)	0.6 ± 3.1	3 (13)	2.1 + 5.6	0.156	0.137
Ground-glass opacities	32 (40)	9.1 ± 20.3	20 (36)	6 ± 8.1	12 (50)	8.3 ± 8.5	0.320	0.103
Honeycombing	11 (14)	4.9 ± 14.7	**4 (7)**	**1.2 ± 4.3**	**7 (29)**	**4.9 ± 7.7**	**0.014**	**0.010**
Ill-defined centrilobular nodule	31 (39)	6.8 ± 11.4	20 (36)	6 ± 8.1	11 (46)	7.6 ± 8.5	0.457	0.392
Interlobular septal thickening	57 (71)	18.3 ± 20.4	38 (68)	11.3 ± 7.9	19 (79)	13.2 ± 6.9	0.421	0.112
Intralobular reticular opacities	30 (38)	7.7 ± 16.3	20 (36)	6 ± 8.1	10 (42)	6.9 ± 8.4	0.624	0.549
Mosaic perfusion	19 (24)	12.3 ± 27.0	12 (21)	3.6 ± 6.9	7 (29)	4.9 ± 7.7	0.568	0.522
Nonseptal linear or plate-like opacities	13 (16)	1.6 ± 4.2	10 (18)	3 ± 6.4	3 (13)	2.1 ± 5.6	0.745	0.447
Pleural thickening	33 (41)	7.7 ± 15.0	20 (36)	6 ± 8.1	13 (54)	9 ± 8.5	0.143	0.150
Thickening of BVB	23 (29)	8.0 ± 18.0	16 (29)	4.8 ± 7.6	7 (29)	4.9 ± 7.7	1.000	0.969
Traction bronchiectasis	14 (18)	4.4 ± 13.3	7 (13)	2.1 ± 5.6	7 (29)	4.9 ± 7.7	0.107	0.096

Data in bold type indicate significant differences between 1-SS and 2-SS. BVB: bronchovascular bundles; n: number of patients with each thin-section finding.

defined centrilobular nodule, ground-glass opacities, cysts, and intralobular reticular opacities. Distribution of these CT findings between the right and the left lung zones in the same cephalocaudal zones was not significantly different. Among the 6 most frequent CT findings in 1-SS, intralobular reticular opacities and ground-glass opacities were more predominantly observed in the lower lung zones.

In contrast, proportions of numbers of the lung zones with interlobular septal thickening, cysts, ill-defined centrilobular nodules, and pleural thickening were not significantly different among the upper, the middle, and the lower lung zones (Figure 1).

Table 3 demonstrates the frequency and the extent of various CT findings in the clinical subsets of 1-SS patients. Univariate analysis showed that 2-SS was associated with a significantly greater frequency and extent of honeycombing than 1-SS. Cysts were more frequently and extensively observed in 1-SS patients or in all SS patients with anti-SSB/La or with cLPD than in those without. Intralobular reticular opacities were more frequently observed in 1-SS patients with cLPD than those without. These associations between the CT findings and anti-SSB/La seropositivity or cLPD observed in 1-SS patients were also seen in the same analysis using data of all SS patients, except for the association between frequency of intralobular reticular opacities and cLPD (data not shown).

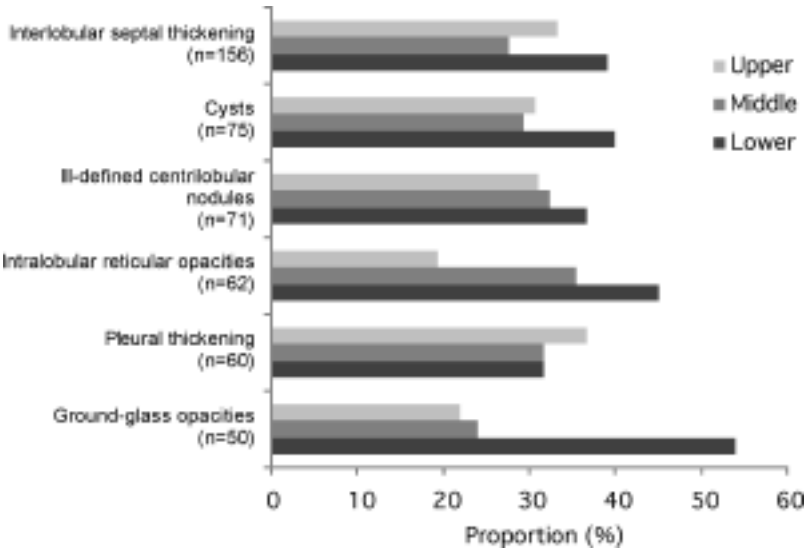

Figure 1. Cephalocaudal distributions of the 6 most frequent thin-section CT findings in primary Sjögren's syndrome. *Significant differences between groups.

Table 3. Frequency and extent of thin-section computed tomographic (CT) findings in patients with primary Sjögren's syndrome with or without clonally derived lymphoproliferative disorder or anti-SSB/La antibodies. Data on extent of thin-section CT findings are mean ± SD of percentage of CT scores. P values calculated by comparing differences between subsets with and without clonally derived lymphoproliferative disorder, or between subsets with or without anti-SSB/La antibodies using Fisher's exact probability test for frequency and Mann-Whitney U test for extent of the CT findings.

CT Findings		cLPD + (n = 11) vs cLPD– (n = 45) N (%)	p	Extent	p	Anti-SSB/La+ (n = 17) vs Anti-SSB/La– (n = 39) N (%)	p	Extent	p
Airspace consolidation	+	3 (27)	0.181	3.0 ± 5.9	0.140	4 (24)	0.228	2.5 ± 5.1	0.160
	–	5 (11)		0.7 ± 2.4		4 (10)		0.6 ± 2.2	
Bronchiectasis	+	4 (36)	0.224	8.8 ± 17.9	0.172	5 (29)	0.480	6.1 ± 14.5	0.365
	–	8 (18)		3.5 ± 10.1		7 (18)		3.9 ± 10.9	
Cysts	+	**8 (73)**	**0.017**	16.9 ± 14.7	**0.002**	**12 (71)**	**0.003**	**16.6 ± 17.9**	**< 0.001**
	–	**14 (31)**		4.5 ± 11.0		**10 (26)**		**2.7 ± 6**	
Emphysema	+	1 (9)	0.357	0.8 ± 2.5	0.290	1 (6)	0.519	5.9 ± 24.3	0.524
	–	1 (2)		2.2 ± 14.9		1 (3)		0.2 ± 1.3	
Ground-glass opacities	+	4 (36)	1.000	4.9 ± 8.5	0.885	6 (35)	1.000	7.8 + 20.1	0.901
	–	16 (36)		5.7 ± 14.2		14 (36)		4.5 ± 8.8	
Honeycombing	+	2 (18)	0.169	4.2 ± 12.5	0.139	2 (12)	0.577	3.5 ± 13.3	0.391
	–	2 (4)		2.4 ± 11.5		2 (5)		2.5 ± 10.9	
Ill-defined centrilobular nodule	+	5 (45)	0.497	10.3 ± 18.7	0.455	9 (53)	0.128	9.7 ± 15.7	0.124
	–	15 (33)		5.7 ± 10.5		11 (28)		5.3 ± 10.7	
Interlobular septal thickening	+	10 (91)	0.084	20.1 ± 13.8	0.132	14 (82)	0.213	23.5 ± 23.9	0.056
	–	28 (62)		15.3 ± 20.1		24 (62)		13 ± 15.7	
Intralobular reticular opacities	+	**7 (64)**	**0.041**	9.2 ± 9.8	0.051	4 (24)	0.242	9.6 ± 24.9	0.441
	–	**13 (29)**		6.4 ± 16.7		16 (41)		5.8 ± 9.3	
Mosaic perfusion	+	3 (27)	0.686	18.2 ± 36.9	0.556	3 (18)	0.738	10.8 ± 28.2	0.673
	–	9 (20)		10.4 ± 25.2		9 (23)		12.4 ± 27.8	
Nonseptal linear or plate-like opacities	+	4 (36)	0.093	4.2 ± 6.7	0.078	3 (18)	1.000	2.5 ± 6.4	0.957
	–	6 (13)		1.5 ± 4.3		7 (18)		1.8 ± 4.1	
Pleural thickening	+	4 (36)	1.000	6.1 ± 10.6	0.962	9 (53)	0.128	12 ± 24.3	0.121
	–	16 (36)		7.0 ± 16.5		11 (28)		4.6 ± 8.9	
Thickening of BVB	+	5 (45)	0.263	9.9 ± 17.8	0.214	5 (29)	1.000	12.1 ± 22.3	0.679
	–	11 (24)		8.1 ± 19.7		11 (28)		6.8 ± 17.8	
Traction bronchiectasis	+	2 (18)	0.614	3.4 ± 10.0	0.554	2 (12)	1.000	4.7 ± 18.2	0.914
	–	5 (11)		3.5 ± 12.5		5 (13)		3 ± 8.2	

Data in bold type indicate significant differences between groups. BVB: bronchovascular bundles.

Regression analysis for CT findings and clinical conditions. The only CT feature that distinguished 1-SS from 2-SS was the presence of honeycombing (odds ratio 0.19). By analysis using 1-SS patients or all SS patients, the presence of cysts was independently and significantly associated with seropositivity for anti-SSB/La antibodies (odds ratio 12.76 in 1-SS, 6.83 in all SS) and cLPD (odds ratio, 6.02 in 1-SS, 5.69 in all SS). Presence of intralobular reticular opacities was associated with cLPD (odds ratio 4.41), and negatively associated with anti-SSB/La seropositivity (odds ratio 0.08) by the analyses using 1-SS patients. Presence of pleural thickening was associated with anti-SSB/La seropositivity (odds ratio 4.24) by the analysis using all SS patients (Table 4).

Lung cysts and other CT findings. Lung cysts were observed in 22 patients (39%) with 1-SS and 8 patients (33%) with 2-SS. As the presence of cysts was independently and significantly associated with cLPD and anti-SSB/La seropositivity, we also assessed the characteristics of cysts and correlation between the presence of cysts and the presence and greater

Table 4. Thin-section computed tomographic (CT) findings significantly associated with clinical subsets.

Clinical Subset and CT Findings	Odds Ratio	95% CI
Primary vs secondary		
Honeycombing	0.19	0.05, 0.72
Anti-SSB/La+ vs anti-SSB/La–		
Primary SS (n = 56)		
Cysts	12.76	2.75, 59.17
Intralobular reticular opacities	0.08	0.01, 0.77
All SS (n = 80)		
Cysts	6.83	2.08, 22.38
Pleural thickening	4.24	1.29, 13.99
cLPD+ vs cLPD–		
Primary SS (n = 56)		
Cysts	6.02	1.30, 27.95
Intralobular reticular opacities	4.41	1.00, 19.46
All SS (n = 80)		
Cysts	5.69	1.38, 23.56

cLPD: clonally derived lymphoproliferative disorder; SS: Sjögren's syndrome.

extent of the other CT findings in 1-SS patients. Figures 2 to 4 show the CT scans of representative cases with lung cysts. The numbers of cysts ranged from 1 to 105 (mean = 14). Cysts were also variable in size, ranging from 3 to 52.1 mm (mean = 16 mm). The summed numbers of cysts in each cephalocaudal and mediolateral zone in all SS patients were as follows: upper 51 (18%), middle 78 (27%), lower 155 (55%), inner one-third 77 (27%), middle one-third 83 (29%), and outer one-third 124 (44%). Distribution of the numbers of cysts among 3 cephalocaudal zones or 3 mediolateral zones was not significantly different.

Univariate and multivariate analyses showed no significant associations between presence of lung cysts and presence and extent of each CT finding other than cysts in 1-SS patients (Table 5). Next, we examined these associations in a total of 336 lung zones (6 lung zones × 56 patients) of 1-SS patients to identify the associated CT abnormalities surrounding lung cysts. Frequency of the lung zones with CT findings accompanied by lung cysts in 1-SS patients is shown in Table 5. Univariate analysis showed that the presence of cysts was significantly associated with a significantly greater frequency and extent of airspace consolidation, bronchiectasis, emphysema, honeycombing, interlobular septal thickening, intralobular reticular opacities, and thickening of bronchovascular bundles. Multivariate logistic regression analysis showing the presence of cysts was independently and significantly associated with the presence of airspace consolidation (odds ratio 4.2), emphysema (odds ratio 8.1), and interlobular septal thickening (odds ratio 2.2).

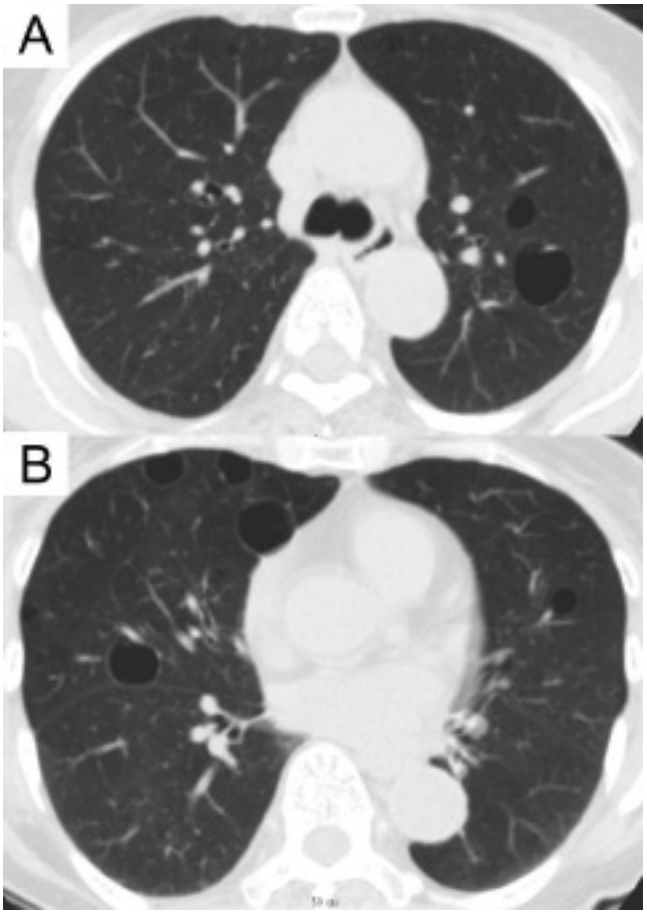

Figure 2. A 73-year-old woman with primary Sjögren's syndrome without anti-SSB/La, accompanied by mixed-type cryoglobulinemia, and mucosa-associated lymphoid tissue lymphoma in salivary glands. Thin-section CT scans at the level of carina (A) and at the level where the right inferior lobar bronchus divides into basal bronchi (B) show multiple solitary thin-walled lung cysts without surrounding abnormal findings.

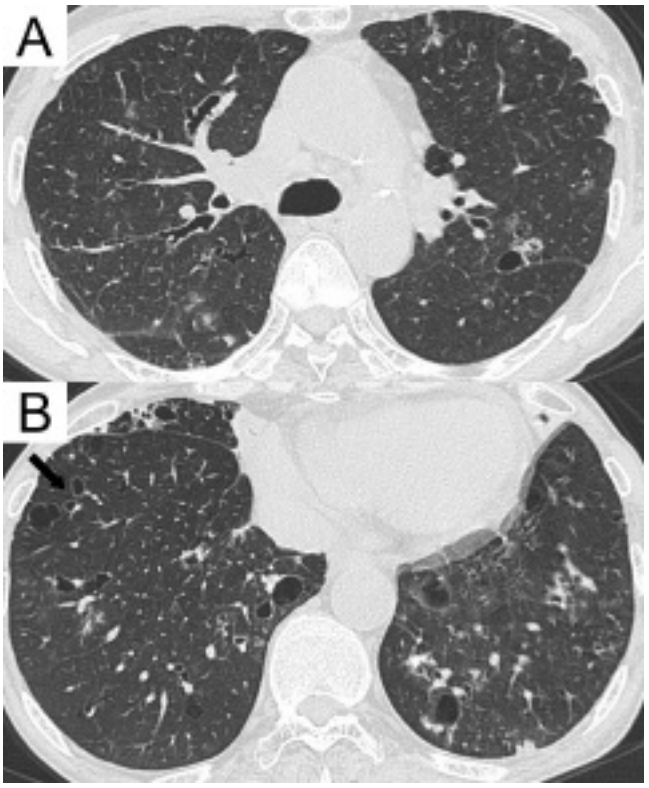

Figure 3. A 68-year-old woman with primary Sjögren's syndrome with anti-SSB/La, accompanied by mixed-type cryoglobulinemia and mucosa-associated lymphoid tissue lymphoma in the trachea. Thin-section CT scans at the level of carina (A) and 2 cm above the lung dome (B) show bronchiectasis, bronchiolectasis, thin-walled lung cysts, ill-defined centrilobular nodules, interlobular septal thickening, and patchy ground-glass opacities. Note dilated bronchioles adjacent to a cystic space (arrow).

DISCUSSION

A wide variety of chest CT abnormalities were reported in association with SS[4-6,8,9]. Although cohort studies recruiting sizable numbers of patients with 1-SS showed that clinical lung disease associated with 1-SS is estimated to be about 10%[3,26], the actual frequency of lung involvement associated with 1-SS might be higher because there are some patients without symptoms or with normal plain chest radiography who might not have undergone chest CT examination.

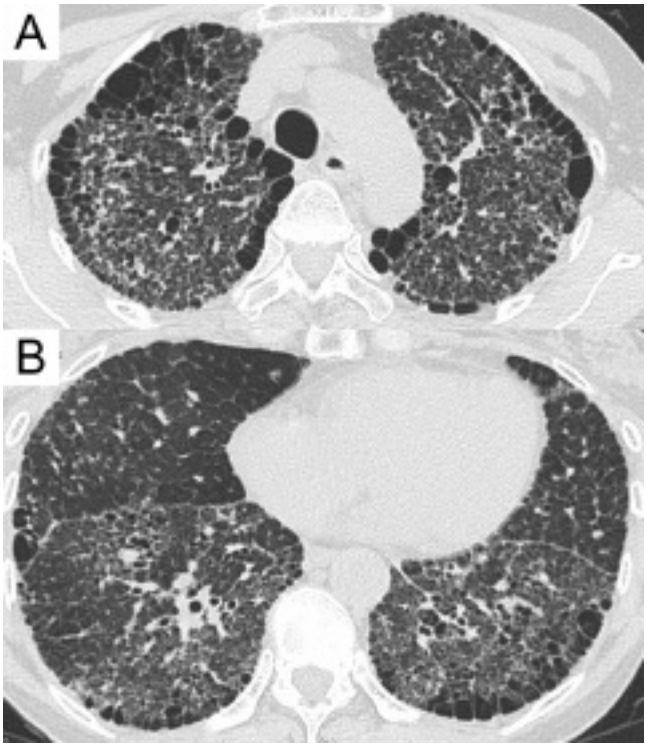

Figure 4. A 67-year-old woman with primary Sjögren's syndrome with anti-SSB/La, accompanied by interstitial pneumonia. Thin-section CT scans at the level of aortic arch (A) and 2 cm above the lung dome (B) show multiple thin-walled cysts in paraseptal distribution, bronchiectasis, bronchiolectasis, ill-defined centrilobular nodules, interlobular septal thickening, intralobular reticular opacities, ground-glass opacities, thickening of bronchovascular bundles, and traction bronchiectasis. Note that aligned multiple thin-walled cysts in paraseptal distribution are predominantly observed in the upper lung zones. In contrast, ground-glass opacities are predominantly observed in the basal lung zones.

Bronchiolar abnormalities, ground-glass opacities, and interlobular septal thickening have been reported to be the common findings seen in patients with SS[4-6,8]. Koyama, *et al* reviewed chest high-resolution CT findings of 60 patients with 1-SS and showed that the most common findings were ground-glass opacities (92%), centrilobular nodules (78%), nonseptal linear opacities (75%), interlobular septal thickening (55%), bronchiectasis (38%), and cysts (30%)[5]. Although our results differ from previous reports in the ranking of frequent CT findings, common CT findings in our study are similar to previous reports.

Matsuyama, *et al* reported that a CT pattern mainly comprising ground-glass opacities, peribronchovascular interstitial thickening, and interlobular septal thickening was exclusively observed in 1-SS, while centrilobular abnormalities were less frequent in patients with 2-SS[8]. In our cohort, presence of honeycombing was the only feature with significantly different frequency between 1-SS and 2-SS. Several previous reports regarding high-resolution CT findings in patients with 1-SS showed that about 8%–10% of studied subjects had honeycombing[4-6,8,9], which was comparable to our results (6%). As for associated connective tissue diseases, two-thirds of the patients in our 2-SS series were classified as having SSc or RA. Frequency of honeycombing has been reported to be 22% to 44.4% in SSc[26-28], 8.7% to 60% in RA[29,30], 4.8 to 20% in polymyositis[28,31], and 11.4% in mixed connective tissue disease[28], and seems to be greater than or at least equal to those reported in SS. Although lung involvement due to underlying rheumatic disorders is difficult to differentiate from changes caused by 2-SS, the more frequent presence of honeycombing in 2-SS versus 1-SS might be explained by the possibility that gen-

Table 5. Frequencies of patients and lung zones with computed tomographic (CT) findings of lung cysts in primary Sjögren's syndrome. Lung cysts were observed in 75 lung zones of 22 patients in 336 lung zones of 56 patients with primary Sjögren's syndrome. p values were calculated by comparing differences between the number of patients or lung zones with each CT finding with lung cysts and those with no lung cysts using Fisher's exact probability test.

	Patients			Lung Zones		
	Cysts+, n = 22 N (%)	Cysts–, n = 34 N (%)	p	Cysts+, n = 75 N (%)	Cysts–, n = 261 N (%)	p
Airspace consolidation	4 (18)	4 (12)	0.698	**7 (9)**	**6 (2)**	**0.011**
Bronchiectasis	5 (23)	7 (21)	1.000	**11 (15)**	**12 (5)**	**0.007**
Emphysema	2 (9)	0 (0)	0.150	**6 (8)**	**2 (1)**	**0.002**
Ground-glass opacities	7 (32)	13 (38)	0.777	15 (20)	35 (13)	0.196
Honeycombing	3 (14)	1 (3)	0.289	**8 (11)**	**9 (3)**	**0.030**
Ill-defined centrilobular nodule	10 (45)	10 (29)	0.262	21 (28)	50 (19)	0.109
Interlobular septal thickening	17 (77)	21 (62)	0.257	**49 (65)**	**107 (41)**	**0.000**
Intralobular reticular opacities	9 (41)	11 (32)	0.575	**22 (29)**	**40 (15)**	**0.010**
Mosaic perfusion	6 (27)	6 (18)	0.508	11 (15)	29 (11)	0.420
Nonseptal linear or plate-like opacities	5 (23)	5 (15)	0.491	8 (11)	17 (7)	0.221
Pleural thickening	8 (36)	12 (35)	1.000	18 (24)	42 (16)	0.125
Thickening of BVB	8 (36)	8 (24)	0.369	**19 (25)**	**32 (12)**	**0.010**
Traction bronchiectasis	4 (18)	3 (9)	0.415	8 (11)	16 (6)	0.203

Data in bold type indicate significant differences between groups. BVB: bronchovascular bundles; N: number of patients or lung zones with each thin-section finding.

eration of honeycombing is dominated more by the associated connective tissue diseases.

Our current study assesses the association between the various thin-section CT findings and prognostic clinical and serological findings of SS to delineate the characteristic CT findings of SS with poor prognosis. To our knowledge, there has been no report comparing the chest CT findings with the specific and prognostic clinical signs of SS. Univariate and multivariate analysis demonstrated that presence of cysts was significantly and independently associated with the presence of cLPD and anti-SSB/La in 1-SS. In previous reports regarding chest CT findings in SS patients, prevalence of lung cysts varies between 12% and 30%[5,6,8]. Cystic lung diseases other than honeycomb cysts have been rarely reported in association with lung involvement of connective tissue diseases other than SS[5,6,8,9,26-34]. In our study, cysts were present in 22 patients (38%) with 1-SS and 8 patients (33%) with 2-SS. Lung cysts may present without other abnormal CT findings[6] or in association with areas of ground-glass attenuation indicating lymphoid interstitial pneumonia or solid nodules[6,8,9,32-34]. SS patients with multiple thin-walled lung cysts have been reported, and some were complicated with pulmonary amyloidosis, lymphocytic interstitial pneumonia, and malignant lymphoma[34-36]. The mechanism of parenchymal cyst formation is still under debate. Some authors proposed the process of the formation of cystic lesions as a ball-valve mechanism, with stenosis of the bronchioles due to infiltration of inflammatory cells or amyloid deposits into bronchioles[32,34]. Others stressed the implication of fragility of alveolar walls due to interstitial inflammation in the generation of lung cysts by the findings that cysts were frequently observed in lymphoid interstitial pneumonia and by the absence of lung cysts in other diseases known to cause small airway obstruction[6,35,37]. In our study, cysts were the only finding in 2 of the 22 (9%) 1-SS patients with cysts, and in 14 lung zones of the 75 lung zones (19%) of 1-SS patients with cysts. In per-patient analysis, there was no significant correlation between the presence of lung cysts and presence of other CT findings. In the analysis using 336 lung zones, the presence of cysts was significantly correlated with the presence of airspace consolidation, bronchiectasis, emphysema, honeycombing, interlobular septal thickening, intralobular reticular opacities, and thickening of bronchovascular bundles. We also examined these correlations in the 242 lung zones of 1-SS patients where at least one CT finding was observed. Univariate and multivariate analyses showed emphysema was the only CT feature that was significantly associated with the presence of cysts (data not shown). Considering the possible implication of fragility of alveolar and bronchiolar walls in the generation of solitary lung cysts in patients with SS and the lack of CT-detectable interstitial inflammation in some SS patients with lung cysts, a pulmonary emphysema-like process might be implicated in the fragility of alveolar and bronchiolar walls.

Our study has several limitations mainly attributed to its retrospective design. First, the investigated cohort of patients with SS was inhomogeneous (wide range of age as well as disease duration) and rather small, especially with respect to the subgroup of patients with 2-SS (only 24 patients). Second, 2 different methods for detection of anti-SSB/La antibodies were used. Previous reports have shown that ELISA assays are more sensitive than immunodiffusion for detection of anti-SSB/La antibodies[38]; therefore, results of the 2 assays might not be directly comparable. In our study, in patients with 1-SS (51 of 56) and in the SS group as a whole (72 of 80) about 90% of patients were checked for anti-SSB/La by double immunodiffusion. Univariate and multivariate analyses using patients who were checked for anti-SSB/La by double immunodiffusion also showed significant association between presence or extent of cysts and anti-SSB/La seropositivity by double immunodiffusion. The consistency of results of our study remains to be determined when applying the anti-SSB/La ELISA assay. Third, results of pulmonary function tests were lacking. Diffuse bronchiolar air trapping due to the bronchiolar lesions can be detected by flow-volume curve analysis. Our study provides limited information about the correlation between the CT and physiological alterations of pulmonary function.

In conclusion, the presence and the greater extent of honeycombing were significantly associated with 2-SS. This might be predominantly due to the lung involvement caused by associated connective tissue diseases. Correlation analysis between the CT findings and the clinical findings demonstrated that presence of lung cysts was significantly and independently correlated with both cLPD and anti-SSB/La seropositivity, the latter being known to be highly specific for SS and closely associated with systemic involvement. Thus, the presence of lung cysts may be a clue or a predictor of systemic involvement, especially cLPD, and lung cysts may be a core pulmonary pathology and prognostic chest CT feature of patients with SS.

ACKNOWLEDGMENT

We thank our colleagues, Drs. Shogo Banno, Yoshihito Hayami, Shinji Maeda, Rei Ito, Division of Rheumatology, Nagoya City University Hospital, for providing the patient data and CT scans. We also thank Prof. Ryuzo Ueda and Associate Prof. Shinsuke Iida, Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, for general support.

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