Small airway disease associated with Sjögren's syndrome: Clinico-pathological correlations

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Summary

Background: Relationships among clinical, physiological, imaging and pathological findings of small airway disease associated with Sjögren's syndrome have remained unclear.

Subjects and methods: We retrospectively studied 14 patients who underwent surgical lung biopsy and who were diagnosed with small airway disease associated with primary or secondary Sjögren's syndrome. We compared clinical, bronchoalveolar lavage, physiological, imaging and pathological findings between primary and secondary Sjögren's syndrome. We scored HRCT and pathological abnormalities and investigated correlations among physiological, HRCT and pathological data, changes in physiological parameters and in HRCT scores after two years of treatment, as well as correlations between these values and pathological scores.

Results: Bronchoalveolar lavage fluid, physiological, imaging and pathological findings of the airways did not significantly differ between primary and secondary Sjögren's syndrome. Air trapping on HRCT negatively correlated with MEF50 and MEF25. Although lymphoid cell infiltration and peribronchiolar fibrosis were the most common pathologies, constrictive change scores correlated negatively with MEF50 and MEF25, positively with air trapping scores and negatively with improvements after therapy in MEF_{50}, MEF_{25} and air trapping.

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Conclusions: Constrictive change was the most significant determinant of physiological and imaging presentations and of changes in these factors after therapy for small airway disease associated with Sjögren's syndrome.

Introduction

Sjögren's syndrome (SjS) is an inflammatory connective tissue disorder of unknown etiology, characterized as an autoimmune exocrinopathy.[1] Various types of pulmonary involvement are associated with SjS, including interstitial pneumonia, lymphoproliferative disorders[2,3,4,5,6] and small airway disease.[2,3,7]

Sjögren's syndrome is often associated with other connective tissue disorders (CTDs), especially rheumatoid arthritis (RA). Such conditions are referred to as secondary SjS (sSjS), whereas SjS without other CTDs is termed primary SjS (pSjS).[8] Small airway disease is a frequent feature of many patients with RA and constrictive or follicular types of bronchiolitis are considered representative of the pathologies associated with RA.[9,10,11,12,13,14,15] However, the histopathological features of a case series of small airway disease associated with SjS have never been studied and differences in small airway disease between pSjS and sSjS remain unclear.

Air trapping on high-resolution CT (HRCT) is a sensitive method of detecting the early features of small airway disease.[16] However, the relationship between air-trapping and histopathological abnormalities in small airway disease associated with SjS has not been investigated. In addition, although corticosteroid is effective for treating bronchiolitis in adults with other etiologies,[17] changes in physiological impairment or in HRCT abnormalities after therapy and the relationships between these changes and pathological abnormalities in small airway disease associated with SjS have not been examined.

We retrospectively investigated various clinical aspects and histopathological findings of small airway disease associated with SjS proven by surgical lung biopsy (SLB), as well as differences in these findings between pSjS and sSjS. We also assessed whether pulmonary function test (PFT) and HRCT findings in small airway disease associated with SjS accurately reflect histopathological findings. We also examined relationships among histopathological findings, changes in pulmonary function and HRCT abnormalities.

Methods

Study design and patients

We retrospectively studied 14 patients who underwent surgical lung biopsy (SLB) and who were diagnosed with small airway disease associated with SjS between April 1999 and March 2005. Eight of them presented at our institutions with continuous respiratory symptoms and six were referred to us for detailed investigations of respiratory conditions from other institutions. None of the 14 patients had been previously diagnosed with SjS. Three patients had been diagnosed with RA at the time of presentation. All 14 were diagnosed with SjS and two patients were diagnosed as having SjS associated with RA within one month after presentation at our institution. No other connective tissue disorders (CTDs) were recognized during observation periods of over 24 months (45 ± 16 months; mean ± SD). All patients fulfilled the 2002 revised criteria for SjS defined by the European Study Group on Classification Criteria for Sjögren's syndrome.[18] Three patients without sicca symptoms were positive for at least three of the four objective criteria including histopathology of minor salivary glands. We excluded patients with findings of interstitial pneumonia or emphysema defined by HRCT, and those with lymphoma, diffuse panbronchiolitis and respiratory bronchiolitis associated with interstitial lung disease. None of the patients had received prior gold or penicillamine therapy. All of the 14 patients underwent PFT, fiberoptic bronchoscopy and HRCT one to three weeks before surgical lung biopsy. Demographic data, clinical presentation, physical findings and laboratory results were extracted from the medical records. All patients provided written, informed consent to participate in the study, which was approved by the internal review boards of our institutions.

All patients were treated and underwent annual PFT and HRCT examinations for over two years at our institutions. We analyzed HRCT abnormalities at the time of diagnosis and at two years thereafter, as well as histopathological findings of biopsy specimens. We compared initial clinical presentations, physical, laboratory, bronchoalveolar lavage fluid (BALF) findings and histopathological scores between patients with pSjS and sSjS. We also compared PFT results and HRCT scores at diagnosis and at two years later between patients with pSjS and sSjS.

Pulmonary function tests

The PFT data included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1)/FVC, residual volume (RV)/total lung capacity (TLC), diffusion capacity for carbon monoxide (DLco) and maximum expiratory flow at 25 and 50% (MEF_{25} and MEF_{50}). Observed values were compared with those predicted for the age, gender and height of each individual. The PFT results are expressed as a percentage of predicted values.

Scoring HRCT abnormalities

We scored the following findings from CT scans obtained at suspended end-inspiratory volumes: centrilobular nodules, branching linear opacity, bronchial wall thickening, bronchial dilation and interlobular septal thickening, and scored air trapping at end-expiratory volumes. Individual abnormalities on each HRCT slice were graded as 0, absent; 1, 1%—25% of the cross-sectional area of the lung affected; 2,

26%—50% affected; 3, 51%—75% affected and 4, 76%—100% affected. The extent of low attenuated areas was estimated to score air trapping as described.[16] Scores for each patient were calculated by averaging the values in all CT slices. We simply determined the presence or absence of large nodules ($\geq$7 mm) and cysts.

Histopathological findings and scores

Histopathological findings were investigated and scored by pulmonary pathologists (JF and TT) who were blinded to the clinical, physiological and HRCT findings. Findings in small airways alone were scored. Membranous (MB) and respiratory (RB) bronchioles were individually assessed. The individual features scored in MB comprised (a) peribronchiolar fibrosis, (b) mucous plugs, (c) lymphoid cell infiltration, (d) basement membrane thickening, (e) constrictive change, (f) luminal macrophages, (g) dilation, (h) eosinophils, (i) goblet cell hyperplasia and (j) neutrophils. Findings scored in RB comprised (a) peribronchiolar metaplasia, (b) peribronchiolar fibrosis, (c) mucous plugs, (d) lymphoid cell infiltration, (e) constrictive change, (f) airspace macrophages, (RB macrophages), (g) eosinophils. Each finding was graded as 0, none; 1, weak; 2, moderate and 3, marked as described.[19] The numbers of MB and RB were counted for each patient. The pathological scores for each finding were calculated as follows: the grade and number of observed bronchioles in each grade were firstly multiplied, and then the sum of all multiplied numbers in each finding was divided by the total number of bronchioles identified in the specimen. Here, pathological scores $\geq$ 1.0 were considered abnormal. Histopathological diagnoses were defined as follows. Follicular bronchiolitis comprised hyperplasia of bronchus-associated lymphoid tissue so that airways have prominent lymphoid tissue with follicles and a germinal center. Constrictive bronchiolitis was defined as bronchiolar lumens that were narrowed or obliterated by submucosal fibrous tissue. Non-specific chronic bronchiolitis was defined as bronchioles with infiltrating chronic inflammatory cells that did not conform to any specific histopathological diagnosis.

We investigated correlations among pathological scores, between initial PFT results and initial HRCT scores, between pathological scores and initial PFT results and between pathological scores and initial HRCT scores.

Correlations between pathological scores and changes in PFT results and changes in HRCT after treatments.

We summarized treatment strategies for all of the patients, and investigated the relationship between treatment and subjective/objective improvement over a period of two years. We compared PFT results and HRCT scores for all patients at the time of diagnosis and at two years later. We calculated differences between PFT results and HRCT scores at the time of diagnosis and those at two years later. We also investigated correlations between pathological scores and changes in PFT results and changes in HRCT.

Statistical analysis

Clinical, physiological, BALF, HRCT and histopathological data were compared between patients with pSjS and sSjS using Student's t test or the χ^2 test. The PFT results and HRCT scores at the time of diagnosis and at two years later were compared using a paired t test. Relationships between treatment strategies and subjective/objective improvements were investigated using the χ^2 test. Relationships among PFT results, HRCT and pathological scores, as well as correlations between pathological scores and improvements in physiological data as well as HRCT scores were investigated using Pearson's correlation coefficient.

Results

Fourteen (11 females, three males) of the patients included in this study were aged 55.8 $\pm$ 14.3 (mean $\pm$ SD; range 27—76) years. In total, 7 (50%) had never smoked and five had previously smoked and quit. All patients had cough, 5 (36%) had sputum, 7 (50%) had dyspnea on exertion and 5 (36%) had fever. Arthralgia and sicca symptoms were found in six and 11 patients, respectively. The mean interval between respiratory symptoms and SLB was 12 $\pm$ 25 (range 3—60) months. The mean interval between sicca symptoms and SLB was 7 $\pm$ 29 (range 0—69) months.

Table 1 summarizes the characteristics of patients with pSjS ($n = 9$) and with sSjS ($n = 5$). Other than symptoms and serological data associated with RA, respiratory symptoms, chest physical findings and laboratory results did not significantly differ between the two groups. The total cell count in BALF was increased in both groups. The numbers of lymphocytes or neutrophils or both in BALF increased in most patients, and BALF findings did not significantly differ between the two groups. Respiratory infections were caused by *H. influenzae* in one patient each with pSjS and with sSjS, and by *Pseudomonas* in one patient each with pSjS and sSjS.

The initial PFT results did not significantly differ between the two groups (data not shown). The RV/TLC was increased, whereas MEF_{50} and MEF_{25} were decreased in all patients. The FEV1/FVC ratio was <70% in 3 of 9 and in 2 of 5 patients with pSjS and sSjS, respectively. The initial HRCT scores also did not significantly differ between the two groups (data not shown). Centrilobular nodules, bronchial wall thickening and air trapping were evident in all patients. Because cysts and large nodules were only found in two and three patients, respectively, these features were not scored. Air trapping scores significantly correlated with RV/TLC ($r = 0.72$, $p < 0.01$), MEF_{50} ($r = -0.56$, $p < 0.05$) and MEF_{25} ($r = -0.61$, $p < 0.05$). No other significant correlations were identified between PFT results and HRCT scores. The PFT results and HRCT scores at two years after diagnosis also did not significantly differ between the two groups.

Table 2 summarizes the histological diagnosis and abnormal histological findings. The histological diagnosis was based on the most predominant histological finding in the biopsy specimen from each patient. The most common basis for a histological diagnosis of small airway disease was non-specific chronic bronchiolitis, ($n = 9$) followed by follicular and constrictive bronchiolitis ($n = 2$), follicular ($n = 2$), and constrictive ($n = 1$) bronchiolitis. The amounts of follicular and constrictive bronchiolitis were equal in two of the five patients with sSjS, and histologically confirmed

Table 1 Comparison of patients' characteristics, symptoms, laboratory data and BALF findings between pSjS and sSjS at the time of diagnosis.

	pSjS ($n = 9$)	sSjS ($n = 5$)	p value
Age (y)	57.8 ± 11.0	52.6 ± 18.2	0.58
Female gender	7	4	0.92
Current or former smoker	4	3	0.67
Cough	9	5	
Sputum	3	2	0.80
Dyspnea on exertion	5	2	0.58
Fever	3	2	0.80
Arthralgia	1	5	0.001
Sicca symptoms	7	4	0.92
Wheeze	2	2	0.48
Sinusitis	4	3	0.57
Repeated respiratory infection	3	2	0.80
PaO_2 (mmHg)	81.6 ± 8.0	82.6 ± 7.0	0.21
White blood cell count (/μL)	5803 ± 2700	7138 ± 3195	0.42
C-reactive protein (mg/dL)	1.95 ± 1.36	2.71 ± 3.08	0.53
RAPA positive	3	5	0.004
Antinuclear antibody positive	3	2	0.80
Anti-Ro antibody positive	5	2	0.58
Anti-La antibody positive	3	2	0.80
Bronchoalveolar lavage fluid findings			
Total cell count ($\times 10^3$/mL)	5.99 ± 7.47	6.98 ± 6.13	0.80
Macrophages (%)	51.0 ± 22.7	38.6 ± 25.4	0.38
Lymphocytes (%)	26.9 ± 14.2	24.0 ± 19.1	0.76
Neutrophils (%)	20.0 ± 31.3	37.8 ± 40.1	0.38
Eosinophils (%)	2.10 ± 2.23	0.6 ± 0.89	0.18
CD4/8	2.16 ± 0.87	1.38 ± 0.71	0.12
Positive bacterial cultures	2	2	0.48

Data are presented as numbers, or as means $\pm$ standard deviation.
PaO_2, arterial oxygen tension; RAPA, rheumatoid arthritis particle agglutination.

in both. Two patients had interstitial abnormalities, one of which comprised foci of mild organizing pneumonia and the other was focal and mild cellular interstitial pneumonia. Findings in both of these patients were microscopically detectable and these patients were included in the analysis. Among the 14 patients, 13 had MB and all 14 had RB in specimens. The most frequent abnormal pathological findings were lymphoid cell infiltration and peribronchiolar fibrosis in both MB and RB. Histological abnormalities found outside small airways comprised intimal fibrosis indicating vessel wall thickening and these findings were limited to those with secondary SjS.

Pathological scores for each finding in small airways did not significantly differ between patients with pSjS and sSjS (data not shown). The peribronchiolar fibrosis score significantly correlated with scores for lymphoid cell infiltration ($r = 0.74$, $p < 0.05$) and constrictive change ($r = 0.82$, $p < 0.001$) in MB. Lymphoid cell infiltration scores significantly correlated with those of constrictive change in MB ($r = 0.59$, $p < 0.05$). No other pathological scores significantly correlated. Constrictive change in MB correlated negatively with MEF$_{50}$ ($r = 0.77$, $p < 0.01$) and MEF$_{25}$ ($r = 0.74$, $p < 0.01$), and positively with RV/TLC ($r = -0.59$, $p < 0.05$) and air trapping scores ($r = 0.67$, $p < 0.01$) (Figs. 1 and 2). Other pathological scores did not

significantly correlate with either PFT results or HRCT scores.

Cough and sputum improved after treatment in 12 of 14 and in 3 of 5 patients, respectively. However, dyspnea on exertion improved in only 2 of 7 patients. Treatment was individually tailored for all patients and none of them died. Clarithromycin, inhaled corticosteroid and oral prednisolone (0.5–1 mg/kg) were administered to 11, 10 and 5 patients, respectively. Three patients with RA received methotrexate. No other immunosuppressive agents were administered. Treatment did not significantly correlate with subjective or objective improvements in symptoms.

The patients were followed up using PFT and HRCT between 23 and 25 months after diagnosis. None of the PFT results or HRCT scores had significantly changed. The MEF$_{50}$, MEF$_{25}$ and air trapping scores on HRCT tended to improve, but the difference did not reach significance (Table 3). The MEF$_{50}$ and MEF$_{25}$ scores increased and decreased in seven patients each. Air trapping scores improved and deteriorated in nine and five patients, respectively (Fig. 3). Constrictive change scores in MB negatively correlated with increased MEF$_{50}$ ($r = -0.67$, $p < 0.05$), increased MEF$_{25}$ ($r = -0.69$, $p < 0.01$) and decreased air trapping scores on HRCT ($r = 0.57$, $p < 0.05$). No other changes significantly correlated with pathological scores.

Table 2 Comparison of histopathological findings between pSjS and sSjS.

	pSjS (n = 9)	sSjS (n = 5)	p
Histological diagnosis of small airway disease			
Follicular bronchiolitis	1	3[c]	0.09
Constrictive bronchiolitis	1	2[c]	0.27
Non-specific chronic bronchiolitis	7	2	0.20
Histological findings (non airway)			
Diffuse lymphoid hyperplasia	2	0	0.40
Pleural thickening[b]	6	3	0.80
Vessel wall thickening	0	4	0.005
Emphysema[b]	3	3	0.34
Interstitial change[b]	1	1	0.60
Findings in Small Airway			
Membranous bronchioles (MB)	n = 9	n = 4[a]	
Peribronchiolar fibrosis	3	1	0.55
Mucous plug	1	1	0.60
Lymphoid cell infiltration	4	4	0.44
Basement membrane thickening	1	0	0.64
Constrictive change	1	2	0.27
Luminal macrophages	0	0	
Dilation	1	0	0.64
Tissue eosinophilia	2	1	0.73
Goblet cell hyperplasia	1	0	0.64
Neutrophils	1	0	0.64
Respiratory bronchioles (RB)	n = 9	n = 5	
Peribronchiolar metaplasia	2	1	0.73
Peribronchiolar fibrosis	2	3	0.20
Mucous plug	0	1	0.36
Lymphoid cell infiltration	4	2	0.66
Constrictive change	0	1	0.36
RB macrophages	2	1	0.73
Tissue eosinophilia	0	0	

[a] Specimen from only one patient with sSjS did not contain MB.
[b] Detectable only by microscopy.
[c] Amounts of follicular and constrictive bronchiolitis were equal in 2 of 5 patients with sSjS and histological assessment confirmed that each had both types of bronchiolitis.

Discussion

Among the various features of small airway pathology associated with SjS, lymphoid cell infiltration and peribronchiolar fibrosis were the most predominant findings. Scores for air trapping and physiological impairments in small airways significantly correlated only with constrictive changes among the various pathological findings. Furthermore, improvements in MEF_{50}, MEF_{25} and air trapping scores after treatment inversely correlated with scores for constrictive change. These data showed that pathological constrictive change is accurately reflected by small airway abnormalities in PFT and HRCT and that although less conspicuous, it is the most significant pathological determinant of clinical presentations including response to treatment.

To distinguish whether lung involvement is caused by SjS or by other CTD components is difficult in patients with sSjS accompanied by other CTDs. Our data indicated that none of respiratory symptoms, BALF findings, PFT results, HRCT abnormalities and small airway pathology significantly differs between pSjS and sSjS. However, this could be due to the small patient cohort investigated herein. Pathologies such as follicular, constrictive and lymphocytic bronchiolitis are reportedly associated with SjS.[12,13,15,20] However, the present findings indicated that most of the small airway disease associated with pSjS is non-specific chronic bronchiolitis and that follicular or constrictive bronchiolitis is also an occasional feature of pSjS. On the other hand, follicular bronchiolitis and constrictive bronchiolitis were frequent features of sSjS associated with RA. The notable finding that vessel walls were thickened only among patients with sSjS in our cohort could be a specific feature of RA.

Pathologies identified by HRCT in patients with SjS include interstitial lung diseases, lymphoproliferative disorders and small airway disease alone or in various combinations.[21,22,23,24] Although slight interstitial changes were detectable in two of 14 patients by microscopy, the HRCT findings in these patients reflected small airway disease alone and were essentially similar to those of small airway disease with other etiologies.[9,10,14,25] Therefore, small airway disease comprised the fundamental lung
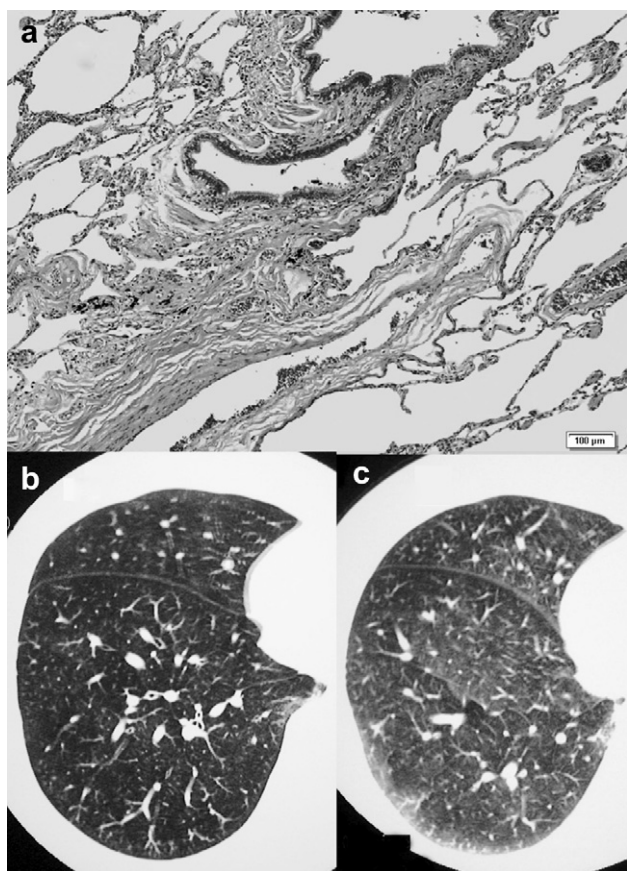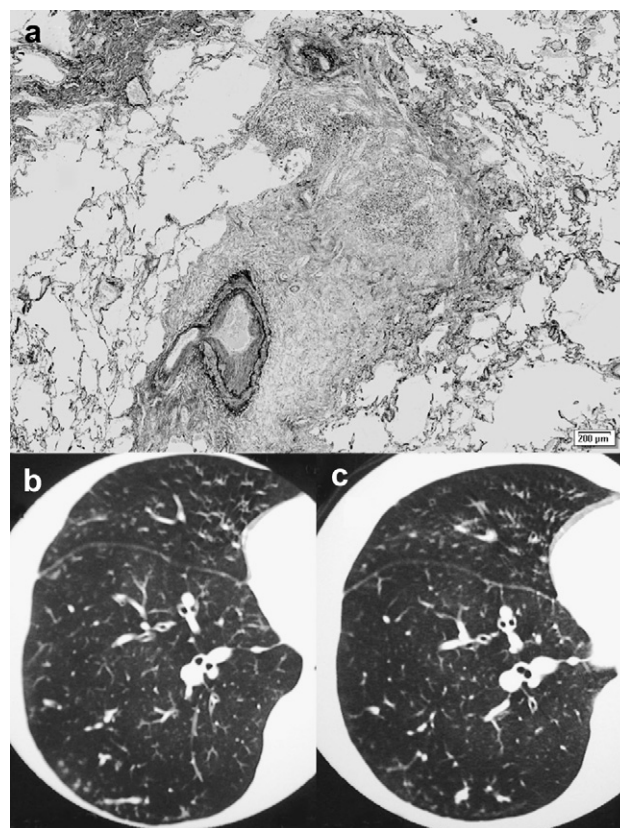
Figure 1 Pathological correlation with HRCT findings in a 64-year-old female patient with small airway disease associated with primary Sjögren's syndrome. a) Histopathological findings show mildly narrowed bronchiolar lumen as submucosal fibrosis. Constrictive change of MB was judged as grade 2. b) High-resolution CT at suspended end-inspiratory volumes shows heterogeneous lung attenuation and centrilobular nodules. c) High-resolution CT at end-expiratory volumes shows air-trapping, centrilobular nodules and clearer extent of abnormality. Air-trapping score was judged as grade 3.

involvement in these patients. Thin-walled cysts, although characteristic of SjS, are found only in a small proportion of patients.[22,23,24]

This study found a significant correlation between air-trapping on HRCT and small airway obstruction determined by PFT in small airway disease associated with SjS, although others have found a poor correlation between physiological data and air trapping on HRCT in such patients.[26,27] However, these studies included patients with interstitial pneumonia (including reticular opacities, ground glass opacities and honeycombing on HRCT, small airway disease and both).

Because scores for lymphoid cell infiltration, peribronchiolar fibrosis and constrictive change significantly correlated, these pathologies could worsen with disease progression. Our results differed from those of a study that found an inverse correlation between inflammation and fibrosis and no correlation between the degree of bronchial fibrosis and airflow limitation.[28] This can be explained by the fact that obliterative bronchiolitis in the patients

Figure 2 Pathological correlation with HRCT findings in a 46-year-old female patient with small airway disease associated with secondary Sjögren's syndrome. a) Histopathological findings show bronchiolar lumen severely narrowed by dense collagenous fibrosis and moderate lymphocytic infiltration. Constrictive change in MB was judged as grade 3 (EVG staining). b) High-resolution CT at suspended end-inspiratory volumes shows diffuse air-trapping and centrilobular nodules. c) High-resolution CT at end-expiratory volumes shows diffuse air-trapping and centrilobular nodules. Normal increase in attenuation and volume reduction were not evident in high-resolution CT even at end-expiratory volumes. Air-trapping score was judged as grade 4.

enrolled in that study was caused by various etiologies and SjS was not included.

The optimal therapy for patients with small airway disease associated with SjS remains unclear. Although physiological parameters of small airway or air trapping on HRCT after treatment did not significantly improve in our patients, over half of them experienced some improvements in symptoms. Because patients with SjS have increased bronchial responsiveness,[29] inhaled corticosteroid could be effective against small airway disease with SjS. Erythromycin might be useful for patients with small airway disease associated with RA or pSjS.[10,30] In addition, patients with small airway disease accompanied by SjS might be predisposed to upper and lower airway infection, and sinusitis or repeated respiratory infection has been identified in patients with SjS.[30,31] Such conditions could modulate bronchiolar lesions in SjS and thus treating infection would be important.

Table 3 Comparison of pulmonary function test results and HRCT scores between at diagnosis and at two years later.

	Diagnosis	Two years later	P
Pulmonary function tests			
VC (%pred)	96.8 ± 12.2	95.3 ± 11.2	0.13
FEV1/FVC (%pred)	74.6 ± 8.5	76.2 ± 8.9	0.12
RV/TLC (%pred)	41.3 ± 7.5	39.7 ± 8.4	0.09
DLco (%pred)	79.4 ± 17.3	79.0 ± 15.2	0.75
MEF_{50} (%pred)	37.3 ± 11.5	39.6 ± 13.9	0.08
MEF_{25} (%pred)	21.1 ± 6.1	23.1 ± 8.3	0.06
HRCT scores			
Centrilobular nodules	1.57 ± 0.5	1.43 ± 0.5	0.33
Branching linear opacities	0.57 ± 0.51	0.41 ± 0.5	0.12
Bronchial wall thickening	1.29 ± 0.47	1.07 ± 0.61	0.08
Bronchial dilatation	0.5 ± 0.8	0.57 ± 0.85	0.33
Interlobular septal thickening	0.64 ± 0.49	0.71 ± 0.61	0.58
Air trapping	1.84 ± 0.63	1.67 ± 0.85	0.09

Data are presented as means ± standard deviation.
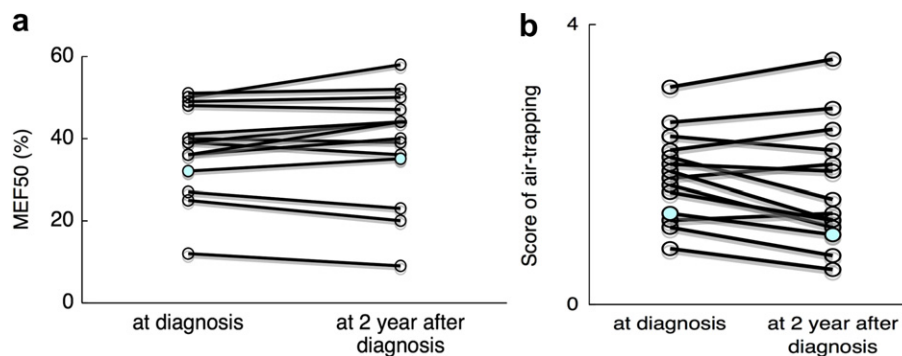
Figure 3 Changes in MEF_{50} (a) and in air trapping scores on HRCT (b) after two years of treatment.

None of these 14 patients had been previously diagnosed with SjS and therefore SjS was detected as a result of respiratory involvement and a chief complaint of respiratory symptoms. This might mean that respiratory symptoms comprise the first clinical presentation of SjS and that small airway disease associated with SjS is one of several conditions associated with respiratory symptoms such as chronic cough.

The main limitation of this study is the inherent bias associated with the small cohort of retrospectively studied patients, although surgical lung biopsies were obtained from all of them. This study could not determine the most appropriate therapy because the corresponding clinicians applied various treatment strategies. The relatively well-preserved pulmonary function in this cohort of patients could have potential implications on these results; for example, significant improvement with therapy could be obscured.

Constrictive change is considered to be the most significant determinant for clinical presentation and a treatment response in small airway disease associated with SjS. This study indicated that disease progression is associated with the progression of constrictive changes in the bronchioles and less effective or ineffective treatment. Early diagnosis and treatment is significant for small airway disease associated with SjS, and appropriate treatment should be further investigated.

Conflict of interest

None.

References

1. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med* 2004;**164**: 1275—84.
2. Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM. Respiratory manifestations in primary Sjogren's syndrome. A clinical, functional, and histologic study. *Chest* 1985;**88**: 226—9.
3. Lahdensuo A, Korpela M. Pulmonary findings in patients with primary Sjögren's syndrome. *Chest* 1995;**108**:316—9.
4. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. *Chest* 2006;**130**:1489—95.
5. Deheinzelin D, Capelozzi VL, Kairalla RA, Filho JVB, Saldiva PHN, de Carvalho CRR. Interstitial lung disease in primary Sjogren's syndrome. Clinical-pathological evaluation and response to treatment. *Am J Respir Crit Care Med* 1996; **154**:794—9.
6. Ito I, Nagai S, Kitaichi M, Nicholson AG, Johkoh T, Noma S, et al. Pulmonary manifestations of primary Sjögren syndrome: a clinical, radiologic, and pathologic study. *Am J Respir Crit Care Med* 2005;**171**:632—8.

7. Papiris SA, Maniati M, Constantopoulos SH, Roussos C, Moutsopoulos HM, Skopouli FN. Lung involvement in primary Sjögren's syndrome is mainly related to the small airway disease. *Ann Rheum Dis* 1999;**58**:61–4.

8. Moutsopoulos HM, Chused TM, Mann DL, Klippel JH, Fauci AS, Frank MM, et al. Sjögren's syndrome (sicca syndrome): current issues. *Ann Intern Med* 1980;**92**:212–26.

9. Perez H, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis. Clinical, functional, and HRCT findings. *Am J Respir Crit Care Med* 1996;**157**:1658–65.

10. Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M. Bronchiolar disease in rheumatoid arthritis. *Am J Respir Crit Care Med* 1998;**154**:1531–6.

11. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med* 2003;**168**:1277–92.

12. Yousem SA, Colby TV, Carrington CB. Follicular bronchiolitis/-bronchitis. *Hum Pathol* 1985;**16**:700–6.

13. Wells AU, du Bois RM. Bronchiolitis in association with connective tissue disorders. *Clin Chest Med* 1993;**14**:655–66.

14. Howling SJ, Hansell DM, Wells AU, Nicholson AG, Flint JDA, Müller NL. Follicular bronchiolitis: thin-section CT and histologic findings. *Radiology* 1999;**212**:637–42.

15. Fortoul TI, Cano-Valle F, Oliva E, Barrios R. Follicular bronchiolitis in association with connective tissue diseases. *Lung* 1985;**163**:305–14.

16. Arakawa H, Webb WR. Air trapping on expiratory high-resolution CT scans in the absence of inspiratory scan abnormalities: correlation with pulmonary function tests and differential diagnosis. *AJR* 1998;**170**:1349–53.

17. Kindt GC, Weiland JE, Davis WB, Gadek JE, Dorinsky PM. Bronchiolitis in adults. A reversible cause of airway obstruction associated with airway neutrophils and neutrophil products. *Am Rev Respir Dis* 1989;**140**:483–92.

18. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren syndrome: a revised version of the European criteria proposed by the American—European Consensus Group. *Ann Rheum Dis* 2002;**61**:554–8.

19. Fukuoka J, Franks TJ, Colby TV, Flaherty KR, Galvin JR, Hayden D, et al. Peribronchiolar metaplasia: a common histologic lesion in diffuse lung disease and a rare cause of interstitial lung disease: clinicopathologic features of 15 cases. *Am J Surg Pathol* 2005;**29**:948–54.

20. Aerni MR, Vassallo R, Myers JL, Lindell RM, Ryu JH. Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients. *Respir Med* 2008;**102**:307–12.

21. Franquet T, Gimenez A, Monill JM, Diaz C, Geli C. Primary Sjögren syndrome and associated lung disease: CT findings in 50 patients. *AJR* 1997;**169**:655–8.

22. Taouli B, Brauner MW, Mourey I, Lemouchi D, Grenier PA. Thin-section chest CT findings of primary Sjögren syndrome: correlation with pulmonary function. *Eur Radiol* 2002;**12**:1504–11.

23. Matsuyama N, Ashizawa K, Okimoto T, Kadota J, Amano H, Hayashi K. Pulmonary lesions associated with Sjögren syndrome: radiographic and CT findings. *Br J Radiol* 2003;**76**:880–4.

24. Lohrmann C, Uhl M, Warnatz K, Ghanem N, Kotter E, Schaefer O, et al. High-resolution CT imaging of the lung for patients with primary Sjögren Syndrome. *EJR* 2004;**52**:137–43.

25. Hansell DM, Rubens MB, Padley SPG, Wells AU. Obliterative Bronchiolitis: individual CT signs of small airways disease and functional correlation. *Radiology* 1997;**203**:721–6.

26. Franquet T, Díaz C, Domingo P, Giménez A, Geli C. Air trapping in primary Sjögren syndrome: correlation of expiratory CT with pulmonary function tests. *J Comput Assist Tomogr* 1999;**23**:169–73.

27. Uffmann M, Kiener HP, Bankier AA, Baldt MM, Zontsich T, Herold CJ. Lung manifestation in asymptomatic patients with primary Sjögren syndrome: assessment with high resolution CT and pulmonary function tests. *J Thoracic Imaging* 2001;**16**:282–9.

28. Markopoulou KD, Cool CD, Elliot TL, Lynch DA, Newell Jr JD, Hale VA, et al. Obliterative bronchiolitis: varying presentations and clinicopathological correlation. *Eur Respir J* 2002;**19**:20–30.

29. Potena A, Corte RL, Fabbri LM, Papi A, Trotta F, Ciaccia A. Increased bronchial responsiveness in primary and secondary Sjögren's syndrome. *Eur Respir J* 1990;**3**:548–53.

30. Borie R, Schneider S, Debray M-P, Adle-Biasssette H, Danel C, Bergeron A, et al. Severe chronic bronchiolitis as the presenting feature of primary Sjogren's syndrome. *Respir Med* 2011;**105**:130–6.

31. Haris SR, Mark EJ. Case records of the Massachusetts general hospital. Weekly clinicopathological exercises: case 17-2001: a 42-year-old man with multiple pulmonary cysts and recurrent respiratory infections. *N Engl L Med* 2001;**344**:1701–8.