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Clinical and Laboratory Features in Patients with Pulmonary Involvement of Primary Sjören's Syndrome

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ABSTRACT

Background : Pulmonary involvement in primary Sjören's syndrome has been the subject of various studies.

Objectives : To determine the incidence of pulmonary involvement in patients with primary Sjögren's syndrome and to clarify the clinical and laboratory features of primary Sjögren's syndrome with pulmonary manifestations.

Methods : We reviewed 91 patients with primary Sjögren's syndrome. Clinical and laboratory findings in patients with pulmonary involvement were compared with those in patients without pulmonary involvement.

Results : Sixteen patients with primary Sjögren's syndrome had radiographic evidence of pulmonary involvement including reticulonodular shadows indicative of lobular pneumonitis, cystic lesions, and honeycombing indicative of interstitial pneumonitis with fibrosis. The prevalence of serum anti-U1-RNP antibodies and serum levels of IgA were significantly higher in patients with pulmonary involvement (44% and 425±154 mg/dl) than in those without (15% and 337±139 mg/dl, both $P<0.05$). Patients with primary Sjögren's syndrome, regardless of pulmonary involvement, tended to have lower carbon monoxide diffusing capacities/VA and lower maximum expiratory flow values at 50% of vital capacity than did healthy controls. Of the 3 patients with pulmonary involvement who died, only 1 died of exacerbation of interstitial pneumonitis.

Conclusion : Clinically significant pulmonary involvement is a relatively common complication of primary Sjögren's syndrome. Positivity for serum anti-U1-RNP antibodies and high serum IgA levels of primary Sjögren's syndrome may indicate future pulmonary involvement.

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Key words : primary Sjögren's syndrome, pulmonary involvement, cystic lesion, anti-U1-RNP antibodies, serum, IgA levels

Introduction

Sjögren's syndrome is a slowly progressive inflammatory autoimmune disease characterized by lymphocyte-mediated destruction of exocrine glands[1]. Pulmonary involvement in primary Sjögren's syndrome has been the subject of various studies[2-6]. The reported frequencies of physiologic abnormalities range from 19% to 65% and depend on the criteria used to define abnormality. In this context distin-

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guishing between primary and secondary Sjögren's syndrome is important. To our knowledge, few studies have examined only respiratory problems in patients with primary Sjögren's syndrome in Japan. Constantopoulos et al[4] have reported that 75% of patients with primary Sjögren's syndrome have pulmonary involvement, of which 25% is diffuse interstitial disease.

These previous studies led us to review 91 patients with primary Sjögren's syndrome treated at the Division of Respiratory Disease of The Jikei University School of Medicine and at the Division of Connective Tissue Disease of the International Medical Center of Japan. We compared clinical and serologic findings in patients with primary Sjögren's syndrome with and without pulmonary involvement in an attempt to predict whether pulmonary involvement will develop, because worse of pulmonary involvement is important factor of life prevision. We also examined radiologic, functional, radioscopic, and bronchoalveolar lavage fluid (BALF) findings in patients with pulmonary involvement.

Patients and Methods

The study population of 91 patients with primary Sjögren's syndrome included 16 patients with dyspnea. Eight patients with primary Sjögren's syndrome were examined at the Respiratory Disease Division of the Jikei University School of Medicine because of respiratory complaints, and 8 were selected from among 83 consecutive patients with primary Sjögren's syndrome examined at the Connective Tissue Disease Division of the International Medical Center of Japan. The patients' mean age was 63 years (range, 48 to 77 years). Two patients were ex-smokers. Primary Sjögren's syndrome was diagnosed when a patient complaining of dryness of the mouth and eyes but with no evidence of other autoimmune rheumatic diseases fulfilled at least one objective criteria for xerophthalmia and one for xerostomia. Diagnostic criteria for xerophthalmia were a positive Schirmer test (<5 mm in 5 minutes), positive rose bengal staining, or both. Diagnostic criteria for xerostomia were abnormal salivary gland function on scintigraphy or sialography, lymphocytic infiltration of the salivary glands on lip biopsy, or both.

We assayed serum samples for antinuclear antibody (ANA) using immunofluorescence and anti-SS-A/anti-SS-B (anti-Ro/anti-La) by counterimmunoelectrophoresis. We also examined levels of immunoglobulin (IgG, IgM, and IgA), complement (C3 and C4), and rheumatoid factor using laser nephelometric assay.

Five pulmonologists examined chest radiographs, high-resolution computed tomography scans, or both; if at least three pulmonologists agreed, interstitial abnormalities were considered to be present. In six patients with primary Sjögren's syndrome with pulmonary involvement we studied BALF and specimens obtained with transbronchial biopsy and video-assisted thoracoscopic surgery. Pulmonary function was evaluated with a Collins Pulmonary Testing System (Warren E. Collins, Braintree, MA, USA). The physiologic evaluation included plotting flow-volume curves and determining forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), maximum expiratory flow at 50% of vital capacity (MEF_{50}), and maximum expiratory flow at 25% of vital capacity (MEF_{25}). The MEF_{50} and MEF_{25} are effort-independent measurements taken at the end of expiration and reflect the state of small peripheral airways of the lung. We also measured carbon monoxide diffusion in the lung (DLCO) by the single-breath method[7]. The results of pulmonary function tests are expressed as percentages of the predicted values[8].

Results

Sixteen patients (2 men and 14 women) had primary Sjögren's syndrome and dyspnea. Their mean age was 63 years (range, 48 to 77 years), and the mean disease duration was 10 years (range, 1 to 22 years; Table 1). Both examinations for keratoconjunctivitis sicca—the Schirmer test and rose bengal staining—were positive in 15 of the 16 patients. Xerostomia was confirmed by lip biopsy in 9 patients and by salivary-gland scintigraphy or sialography in 14. Both tests were positive in 7 patients and at least 1 was positive in the remaining 9.

Table 1. Clinical data and criteria used for diagnosing Sjogren's Syndrome in the study population

Patient No.	Age (years)	Sex	Duration (years)	KCS	Lip Biopsy	Sialography/ Scintigraphy
1	55	F	3	+	—	+
2	58	F	22	+	—	+
3	48	F	8	+	ND	+
4	56	F	1	—	+	—
5	73	F	4	+	—	+
6	66	M	5	+	+	+
7	66	M	10	+	—	+
8	70	F	10	+	ND	+
9	67	F	15	+	+	+
10	77	F	10	+	+	+
11	63	F	9	+	+	ND
12	63	F	13	+	+	+
13	68	F	12	+	+	+
14	55	F	8	+	ND	+
15	59	F	13	+	+	+
16	56	F	9	+	+	+

KCS=keratoconjunctivitis sicca ; ND=not done

Table 2. Radiographic, clinical, therapeutic and prognostic data

Patient No.	Chest X-ray	Dyspnea	Cough	Pain	Rales	Prednisolone	Immuno-suppressants	Outcome
1	IP+pleural thickening	+	+	+	+	No	No	Stable
2	cystic lesion	+	+	+	+	30 mg	No	Stable
3	IP (Honeycomb)	+	+	+	+	60 mg+pulse	CYA	Deterioration
4	IP+Consolidation	+	+	−	+	pulse	MIZ	Stable
5	IP (Honeycomb)	+	+	+	+	40 mg+pulse	CPA	Deceased
6	IP	+	+	+	+	No	No	Stable
7	IP	+	+	+	+	No	No	Stable
8	IP	+	+	−	+	No	No	Stable
9	IP	+	+	−	+	60 mg	No	Deceased
10	IP	+	+	−	+	25 mg	No	Stable
11	IP	+	+	−	+	No	No	Stable
12	IP	+	+	−	+	No	No	Stable
13	IP	+	+	−	+	No	No	Deceased
14	IP+consolidation	+	+	+	+	50 mg	No	Improved
15	cystic lesion	+	+	−	+	No	No	Stable
16	IP	+	+	−	+	15 mg	No	Stable

IP=interstitial pneumonitis ; +=present ; −=absent ; CYA=cyclosporin ; MIZ=mizoribine ; CPA=cyclophosphamide

The radiographic findings included reticulonodular shadows indicative of lobular pneumonitis ($n=12$), cystic lesions ($n=2$), and honeycombing suggestive of interstitial pneumonitis with fibrosis ($n=2$; Table 2). All 16 patients complained of dyspnea and cough, usually related to physical effort. Defined chest pain was reported by 7 patients. Rales, usually in the lower thirds of both lungs, were heard in all patients. Eight patients were treated with corticosteroids (range of maximal daily

Table 3. Clinical and laboratory data for 16 patients with primary Sjögren's syndrome with pulmonary involvement and 75 patients without pulmonary involvement

Patient No.	Raynaud's phenomenon	Arthralgia	RF	FANA	Anti-U1-RNP	Anti-SS-A	Anti-SS-B	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)
1	−	+	+	+ (Sp 640x)	+	+	−	2610	616	152
2	−	+	+	+ (Sp 640x)	−	+	−	2905	445	288
3	−	−	−	±	−	+	+	2161	473	22
4	−	+	−	+ (H 40x)	−	−	−	1080	304	59
5	−	−	+	+ (H+Sp 40x)	−	−	−	2582	487	186
6	+	−	+	+ (Sp 2560x)	+	−	−	2002	352	165
7	−	−	−	±	−	−	−	1506	356	68
8	−	+	+	+ (Sp 160x)	−	+	+	2947	764	123
9	+	+	+	+ (Sp 5120x)	+	+	+	1940	467	190
10	+	+	−	+ (Sp 2560x)	−	+	−	1230	282	57
11	+	+	+	+ (Sp 5120x)	+	−	−	2040	645	203
12	−	−	+	+ (Sp 1280x)	−	+	+	2920	411	306
13	+	−	+	+ (Sp 5120x)	+	−	−	1650	348	287
14	+	+	−	+ (Sp 320x)	−	−	−	1530	184	151
15	−	+	+	+ (Sp 320x)	+	+	+	3390	353	296
16	+	+	−	+ (Sp 5120x)	+	+	−	2102	231	150
with PD	7/16 (44%)	10/16 (63%)	10/16 (63%)	14/16 (88%)	7/16 (44%)	9/16 (56%)	5/16 (31%)	2230+848	425+154	166+74
without PD	28/75 (37%)	43/75 (57%)	50/75 (67%)	63/75 (84%)	11/75 (15%)	27/75 (36%)	13/75 (17%)	2190+660	337+139	192+159
P	NS	NS	NS	NS	<0.05	NS	NS	NS	<0.05	NS

RF=rheumatoid factor; FANA=fluorescent anti-nuclear antibody; Sp=speckled; H=homogenous; PD=pulmonary disease; NS=not significant

dose, 15 to 60 mg), and 3 of these patients received methylprednisolone pulse therapy (500 to 1,000 mg/day for 3 consecutive days) together with immunosuppressants (cyclosporin, mizoribine and cyclophosphamide; Table 2). The outcomes were generally favorable (Table 2). Of the 3 patients who died, only 1 died of an exacerbation of interstitial pneumonitis whereas 2 died of other causes (cerebrovascular accident and small cell carcinoma of the lung).

Patients who had primary Sjögren's syndrome with pulmonary involvement were significantly more likely to have serum anti-U1-RNP antibodies (7 of 16 patients, 44%) and had significantly higher serum levels of IgA (425 ± 154 mg/dl) than did patients with primary Sjögren's syndrome without pulmonary involvement (11 of 75 patients, 15%, $P<0.05$ by the Chi-square test, and 337 ± 139 mg/dl, $P<0.05$ by the Mann-Whitney U test; Table 3). However, no significant differences were found between these groups of patients in the prevalence of Raynaud's phenomenon, arthralgia, rheumatoid factor, fluorescent antinuclear antibody, anti-SS-A antibody, or anti-SS-B antibody or in levels of IgG or IgM (Table 3).

Spirometry was performed in 15 patients, and

Table 4. Functional data

Patient No.	FVC	%FVC	FEV1.0	FEV1.0%	%DLCO	DLCO/VA	MEF50	MEF25	V50/V25	FRC	RV	RV%
Normal range		≥80		≥70	≥80	≥5			<3			<30
1	1.81	76	1.21	67	91	4.69	0.96	0.3	3.20	2.97	1.93	49
2	2.56	100	1.99	78	68	3.35	3.31	0.57	5.81	2.56	1.57	36
3	0.96	37	0.83	87	ND	ND	1.81	0.5	3.62	1.08	0.76	44
4	2.91	115	2.19	75	64	3.41	2.53	0.54	4.69	2.26	1.23	28
5	1.29	62	1.20	93	60	4.02	2.75	1.03	2.67	1.53	1.14	46
6	2.69	83	1.01	38	41	1.70	0.35	0.14	2.50	3.26	2.12	44
7	2.97	89	2.46	83	82	4.70	3.55	1.00	3.55	3.20	1.60	34
8	2.19	97	1.62	77	97	2.99	1.55	0.53	2.92	2.99	2.46	53
10	1.43	52	1.21	84	33	3.13	2.21	0.59	3.74	1.07	0.82	59
11	1.78	66	1.46	82	65	ND	2.34	0.48	4.87	1.93	1.31	42
12	2.04	80	1.79	88	97	5.26	2.82	0.96	2.94	2.07	1.49	105
13	2.27	86	1.68	74	104	5.60	2.31	0.39	5.92	2.56	2.02	50
14	2.33	88	1.90	81	70	3.01	3.43	0.77	4.45	2.36	1.60	43
16	3.02	113	2.53	84	86	3.83	3.52	1.12	3.14	2.24	1.64	33
17	2.65	91	2.16	81	76	ND	3.24	0.61	5.31	2.54	1.21	30

Abnormal values are underlined

Table 5. BALF findings

Patient No.	Total cells ($\times 10^6$)	Macrophage (%)	Lymphocytes (%)	Neutrophils (%)	Eosinophils (%)
Normal range	18.6±1.9	85.2±1.6	11.8±1.1	1.6±0.07	0.2±0.06
1	1.1	19	20	58	3
2	10.4	68	22	7	3
3	24.9	84	11	3	2
4	12.8	49	51	0	0
5	32.7	35	58	5	2
8	2.2	31	62	2	5

DLCO was measured in 12 patients (Table 4). The percentage frequency of abnormal FVC (below 80% of the predicted value) was 33% (5 of 15 patients). The FEV1.0% was abnormal (less than 70% of the predicted value) in 2 (20%) of 15 patients. Diffusion capacity was abnormal (DLCO/VA less than 5.0) in 10 (83%) of 12 patients, and V50/V25 was abnormal (greater than 3.0) in 9 (60%) of 15 patients.

In 6 of the patients, BALF contained an increased total number of cells. In these patients proportions of lymphocytes or polymorphonuclear cells or both were higher than normal and proportions of macrophages were lower than normal (Table 5).

Transbronchial biopsy specimens obtained from 5 patients included bronchiolar and alveolar tissue, but in some other patients alveolar tissue was not sufficient to make a clear diagnosis. Interstitial fibrosis was noted in 4 patients, and a peribronchiolar lymphocytic infiltrate was noted in 1 patient.

Discussion

Our review of 91 patients with primary Sjögren's syndrome identified 16 patients with possible lung disease. These patients had either been referred to the pulmonary division of our hospital or visited the rheumatology department of another institution. We assessed the clinical and laboratory features of these patients, who had evidence of interstitial lung disease. Moreover, we found 2 rare cases of cystic pulmonary

lesions. To our knowledge, only 8 cases of Sjögren's syndrome complicated by cystic lung disease have been reported[9,10].

Reported frequencies of lung disease in primary Sjögren's syndrome vary widely according to the population and the methods of evaluation and are proportional to the sensitivity of the study methods. Stirimlan et al reported a 9% incidence of pulmonary involvement[11], based mostly on symptoms and radiologic findings. However, in this study, cases were not divided into primary and secondary Sjögren's syndrome. When cases are divided into primary and secondary Sjögren's syndrome and functional criteria are included, lung involvement becomes more frequent in primary Sjögren's syndrome; for example, Papathanasiou et al have reported that 37.5% of their patients had interstitial lung disease[12]. On the basis of mainly pulmonary function, Vitali et al[13] have reported that interstitial lung involvement is more frequent in primary Sjögren's syndrome but appears to be mild. Pulmonary function tests showed lung involvement in Sjögren's syndrome, either primary or secondary, in 6 of 13 patients studied by Newball and Brahim[14] and in 12 of 20 patients studied by Segal et al.[15]. In 100 patients with primary Sjögren's syndrome studied by Kelly et al., 24% had some reduction in pulmonary function[6]. In our study, V50/V25 was abnormal (greater than 3.0) in 9 of 15 patients (60%). Newball and Bramin[14] described 2 patients whose small airways were infiltrated by lymphocytes and inflammatory cells, causing edema and luminal narrowing. Gudbjornsson et al.[16] reported that patients with primary Sjögren's syndrome who had no obvious pulmonary disease on radiologic examination frequently had obstructive defects in the small airways. The high frequency of reduced diffusion capacity in our study (10 of 12 patients, 83%) might be attributed to airway obstruction induced by the uneven distribution of alveolar ventilation[17,18].

In our study, patients with primary Sjögren's syndrome and pulmonary disease had a higher prevalence of anti-U1-RNP antibodies (44%) and higher mean serum levels of IgA (425±154 mg/dl) than did patients without pulmonary disease (15%, $P<0.05$, and 337±139 mg/dl, $P<0.05$). Hatron et al.[19] have reported that patients with primary Sjögren's syndrome and BALF abnormalities had clinical and biologic findings suggesting more severe disease than did patients without BALF abnormalities, as demonstrated by higher mean levels of serum gamma globulins and a higher prevalence of antinuclear antibody. Transforming growth factor-β is thought to stimulate fibroblasts and cause pulmonary fibrosis[20]. In studies of the role of cytokines in lung disease, early research attention has focused on cytokines released by alveolar macrophages. However, both structural cells and immune-effector cells of the lung can produce and release cytokines. The cytokines that have received the most attention in relation to pulmonary diseases are platelet-derived growth factor, interleukin-1, transforming growth factor-β, tumor necrosis factor-α insulin-like growth factor 1, and, most recently, interleukin-6. Alterations in cytokine production, secretion, and action are determining forces in the destructive, inflammatory and fibrotic lung disorders. A complex and changing network of cytokines is invoked during the course of disease[20]. The prevalence of anti-U1-RNP antibodies and the mean serum levels of IgA were higher in patients who had primary Sjögren's syndrome with pulmonary involvement, although their significance remains to be established. .

Eight of the 16 patients in our study were treated with oral, parenteral corticosteroids, or both, and 3 of these 8 were treated with both immunosuppressants and corticosteroids. The other 8 patients received no medication to treat pulmonary disease. An azathioprine-based regimen has been reported to significantly increase FVC in patients with primary Sjögren's syndrome[21].

BALF abnormalities were found in 6 of our patients, all of whom had abnormally high lymphocyte counts. Three patients had high polymorphonuclear cell counts, a marker of severity in interstitial lung disease, and two patients were treated with immunosuppressants[22]. These findings may be compatible with the presence of subclinical inflammatory alveolitis[19].

Clinically significant pulmonary involvement is a relatively common complication of primary Sjögren's syndrome. The pulmonary manifestations include

interstitial pneumonitis, rare multiple cystic lesions, and small airway disease. Outcomes are good in most patients, even if the lung disease is untreated, but a few patients will require aggressive therapy with high-dose corticosteroids (including pulse therapy) and immunosuppressants. Because worse of pulmonary involvement is important factor of life prevision, predicting whether pulmonary involvement will develop is important. Our results suggest that positivity for serum anti-U1-RNP antibodies and high serum levels of IgA in primary Sjögren's syndrome indicate future pulmonary involvement.

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