Lung involvement in Sjögren's syndrome: a comparison between patients with primary and with secondary syndrome

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SUMMARY Lung function was assessed in 20 patients with primary Sjögren's syndrome (SS) and in a group of patients with SS associated with a variety of connective tissue diseases. Signs of small airway disease and of altered diffusion capacity, together with chest x-ray features of mild interstitial involvement, were the most common findings in primary SS. On the whole, lung involvement was more frequent and severe in patients with the secondary form of the syndrome. In both primary and secondary SS lung function changes did not correlate with the other clinical and serological parameters, except for a more severe impairment of diffusion capacity in patients with Raynaud's phenomenon.

Key words: lung volume measurements, airway obstruction, pulmonary diffusing capacity, pulmonary fibrosis, Raynaud's disease, antinuclear antibodies, immune complex disease.

Sjögren's syndrome (sicca syndrome) (SS) is an autoimmune disease characterised by exocrine gland involvement, particularly the lacrimal and salivary glands, sometimes associated with connective tissue diseases or immunological disorders.¹ The presence of pulmonary involvement in SS has already been described,² and a number of lung function studies have shown different patterns of respiratory impairment.^{2–6} These studies however, employed disparate techniques^{3,4} and/or took into account only isolated parameters.^{4,6} Furthermore, in many instances no distinction was made between patients with the primary or the secondary form of SS,^{2–5} and smoking was not explicitly considered.^{2–6} It is not surprising, therefore, that most of these studies have yielded different and often conflicting results.^{2,3,6} To verify the prevalence and nature of lung involvement in SS we evaluated lung function, arterial blood gases, and radiographic findings in two comparable, unselected groups of non-smokers with primary or secondary SS.

Materials and methods

PATIENTS

Forty patients with SS (all non-smoking women, aged 21–75 years, mean 45.2 years), referred to the Rheumatic Disease Unit of the University of Pisa between 1977 and 1984 were studied. Of these, 20 (aged 21–67 years, mean 44.3 years) had primary SS and 20 (aged 22–75 years, mean 45.0 years) had secondary SS (seven progressive systemic sclerosis (PSS), six rheumatoid arthritis (RA), three systemic lupus erythematosus (SLE), two essential mixed cryoglobulinaemia (EMC), and two mixed connective tissue disease (MCTD)). In both groups the diagnosis of SS was suspected from the presence of xerostomia, xerophthalmia, and parotid swelling, and established when keratoconjunctivitis sicca was shown (positive Schirmer's test or slit lamp examination after rose bengal staining, or both), and when salivary gland involvement was confirmed by sialography or lip biopsy, or both.¹

In the secondary SS group the diagnosis of the associated diseases was made on the basis of well established criteria for RA,⁷ SLE,⁸ PSS,⁹ MCTD,¹⁰ and EMC.¹¹

None of the patients studied had signs or symp-

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toms of acute respiratory disease when their lung function was investigated or previous important bronchopulmonary disorders of other aetiology.

SEROLOGICAL STUDIES

Blood samples for serological studies were obtained from all patients at the time of lung function evaluation.

The determination of cryoglobulins was made as previously described.¹¹ Circulating immune complexes (CIC) were measured by a competitive enzyme immunoassay previously developed in our laboratory.¹² Values above 35% of inhibition were considered abnormal. CH₅₀ levels were determined by the method of Kent and Fife¹³ (normal values 160–220 U/ml) and antinuclear antibodies (ANA) by indirect immunofluorescence, with mouse liver as the substrate. Anti-extractable nuclear antigen (anti-ENA) antibodies were detected by counterimmunoelectrophoresis according to the method of Bunn *et al.*¹⁴ A commercial source of rabbit thymus (Pel-Freez Biologicals Inc., Rogers, Arkansas) and human spleen extract¹⁵ was available. Reference anti-SSA (Ro), anti-SSB (La), anti-RNP, and anti-Sm sera were kindly provided by Dr M Reichlin and Dr G R V Hughes.

LUNG FUNCTION STUDIES

On the same morning, the following measurements were made in each patient: (a) static lung volumes: total lung capacity (TLC), residual volume (RV), the RV/TLC ratio, vital capacity (VC) (obtained by a computerised high power pulmonary desk system); (b) forced vital capacity (FVC) and derived indexes, according to the protocol of the CNR special project on preventive medicine (same apparatus) (unpublished data). For this study, the following parameters were recorded: maximal expiratory volume in the first second (FEV₁), the FEV₁/VC ratio, forced expiratory flow between 75 and 85% of FVC (FEF 75–85), and maximal expiratory flow at 75% of FVC (MEF 75); (c) diffusing capacity of the lung for carbon monoxide (CO) in a single breath (DLCO–SB),¹⁶ which divided by alveolar volume yields the CO coefficient of transfer (KCO)¹⁷ (Morgan Resparameter MK4); (d) the diffusing capacity of CO at the steady state: total (DLCO–SS2),¹⁸ and per unit of minute ventilation (DLCO–SS2/VE); fractional uptakes of CO (DuCO, DuaCO) were also calculated;¹⁹ and (e) arterial gases (Po₂ and Pco₂) at rest, on a blood sample withdrawn from the radial artery (IL model 213).

Lung function parameters were expressed as percentages of predicted values; the latter were derived from Goldman²⁰ for static spirometry, from

Morris²¹ and Knudson²² for flow-volume curves, from Cotes¹⁷ and Van Ganse²³ for DLCO–SB and KCO, respectively, from Bates¹⁸ and from Mastrangelo¹⁹ for DLCO–SS2 and DuCO–DuaCO, respectively.

CHEST ROENTGENOGRAMS

Chest x-ray examination was carried out in two projections: posteroanterior and lateral. Teleradiograms were all evaluated by the same physician, with a simple scoring system: 0 = no alterations; 1 = hilar blurring or bibasilar accentuation of interstitial network; 2 = diffuse interstitial thickening; 3 = presence of micronodular or linear shadows and/or ill defined cardiac borders.

STATISTICAL ANALYSIS

Mean values were compared by the Student's *t* test and the χ^2 test with Yates's correction was used to compare percentages. Simple and multiple correlations between the serological and the lung function parameters were also sought.

Results

Only a few of our patients had bronchopulmonary symptoms (see footnotes to Tables 1 and 2). Among the patients with primary SS 65% had evidence of extraglandular organ involvement. In one of these (case No. 15) a lymphosarcoma became evident a few months before the study (Table 1).

As far as serological findings are concerned rheumatoid factor (RF) and ANA were largely present in both primary and secondary SS. Anti-ENA antibodies were found in one half of the patients in both groups; however, although anti-SSA and anti-SSB antibodies accounted for nearly all the specificities observed in primary SS patients, anti-RNP and anti-SSB were the most common antibodies in secondary SS (Tables 1 and 2).

The lung function parameters most frequently impaired in patients with primary SS (Table 3) were MEF 75, KCO, and DLCO–SS2 (55% of patients), and DuCO and DuaCO (45% of patients). In contrast, lung volumes were only rarely affected in these patients. Patients with secondary SS showed a larger spectrum of lung function abnormalities. Moreover, for nearly all the parameters considered an impairment was more frequent in this group than in the patients with the sicca syndrome alone, and this difference reached statistical significance for DLCO–SB (Table 3).

Finally, when the mean values of the various parameters in the two groups were compared (Table 4) some lung function indexes (FEV₁, MEF 75, FEF 75–85) and Po₂ were significantly lower in the

Table 1 Main clinical and serological data in 20 patients with primary Sjögren's syndrome

Patient No.	Age (years)	Disease duration (years)	Main clinical manifestations*	Schirmer's test (<15 mm/5 min)	Rose bengal staining	Sialo-graphy	Lip biopsy	ANA†	Anti-ENA	RF (titre)	CH ₅₀ (U/ml)	CIC (% inhib)	Cryoglobulins
1	56	12	W,L,P,T	+	+	+	+	S	SSB	1:20	229	21	-
2	50	5	W,A	+	+	+	-	D	-	-	236	0	-
3	29	3	W,A,L	+	+	+	+	S	{SSA SSB}	1:80	137	67	-
4	27	7	W,P,R	+	+	+	-	S	SSB	1:20	194	30	-
5	36	6	W,A,R	+	+	+	+	S	SSB	-	193	ND	-
6	39	8	W,A,R	+	+	+	-	S	-	-	195	0	-
7	28	9	W,A,R	+	+	+	ND	S	-	1:80	144	58	+
8	44	12	W,A	+	+	+	ND	D	-	1:160	210	18	-
9	53	36	A,Te,R,PN,CH	+	+	+	+	S	-	1:80	114	32	+
10	42	10	W,A	+	+	+	+	-	-	1:160	292	0	-
11	46	4	W	+	+	+	+	-	-	1:160	132	51	ND
12	34	13	W,P,L	+	+	+	+	-	-	1:80	170	45	-
13	58	10	W,A,T	+	+	+	+	S	-	1:160	186	26	-
14	21	1	W,L,T	+	+	+	+	S	SSB	1:80	92	6	-
15	42	12	W,A,R,Ly	+	+	+	+	-	-	1:160	67	ND	+
16	56	19	W,A	+	+	+	ND	D	-	-	166	0	-
17	43	2	W,A	+	+	+	-	D	-	-	101	31	-
18	67	9	W,A,L,Tc,R	+	+	+	ND	S	RNP	-	192	10	-
19	58	15	W,A	+	+	+	+	S	SSA	1:40	230	22	-
20	57	13	W,A,R,T,S	+	+	+	ND	-	SSA	1:20	173	ND	-
Mean	44.3	11.3											
SD	12.5	7.8											

Note: Patients Nos 5 and 10 had non-productive cough; patients Nos 2 and 9 had mild exertional dyspnoea.
*W=weakness (subjective); L=leucopenia; P=purpura; T=thrombocytopenia; R=Raynaud's phenomenon; A=arthralgias; Te=telangiectasis; PN=peripheral neuropathy;
CH=chronic hepatitis; Ly=lymphosarcoma; S=splenomegaly.
†S=speckled pattern; D=diffuse pattern. ND=not determined. For other symbols see text.

Table 2 Main clinical and serological data in 20 patients with secondary Sjögren's syndrome

Patient No.	Age (years)	Disease duration (years)	Associated disease*	Schirmer's test (<15 mm/5 min)	Rose bengal staining	Sialography	Lip biopsy	ANAT	Anti-ENA	RF (titre)	CH ₅₀ (U/ml)	CIC (% inhib)	Cryoglobulins
21	53	7	RA	+	+	+	-	D	-	1:160	225	ND	ND
22	24	1	SLE	-	+	+	-	D	{SSB RNP	1:40	169	47	ND
23	36	8	SLE	+	+	+	+	S	RNP	1:80	107	0	-
24	44	4	MCTD	+	+	-	+	S	RNP	-	131	25	-
25	47	5	MCTD	+	+	+	-	S	RNP	-	198	27	ND
26	57	3	RA	+	+	+	+	D	-	1:80	205	21	-
27	36	6	EMC	+	+	+	ND	-	-	1:640	118	51	+
28	54	7	EMC	-	+	+	ND	-	-	-	<50	ND	+
29	34	7	PSS	+	+	+	+	S	-	1:80	172	14	-
30	61	3	PSS	+	+	+	+	D	Sm	-	238	ND	ND
31	24	3	PSS	-	+	ND	+	S	SSB	1:80	185	ND	-
32	22	2	PSS	+	-	+	ND	S	-	-	179	ND	-
33	38	5	SLE	+	-	+	+	S	{RNP SSB	1:160	238	10	-
34	75	7	PSS	+	ND	+	-	D	-	-	187	ND	-
35	52	17	RA	+	+	+	-	ND	-	1:80	ND	ND	ND
36	49	13	PSS	+	+	+	+	S	RNP	-	206	13	-
37	52	5	PSS	+	+	+	-	D	-	-	150	69	ND
38	39	13	RA	+	+	+	+	D	SSB	1:20	180	54	+
39	48	15	RA	+	+	+	+	-	-	1:40	180	ND	ND
40	56	12	RA	+	+	+	+	-	-	-	185	21	-
Mean	45.0	7.1											
SD	13.5	4.5											

Note: Patients Nos 23, 36, and 39 had non-productive cough; patients Nos 29, 30, 31, 37 had mild exertional dyspnoea.
*RA=rheumatoid arthritis, SLE=systemic lupus erythematosus, PSS=progressive systemic sclerosis, EMC=essential mixed cryoglobulinaemia; MCTD=mixed connective tissue disease.
†S=speckled pattern; D=diffuse pattern; ND=not determined.
For other symbols see text.

secondary syndrome than in the primary SS group. This finding was confirmed by chest *x*-ray evaluation: radiographic abnormalities were significantly more frequent (Table 3) and severe (Table 4) in patients with associated diseases than in those with primary SS.

Respiratory functional indexes did not differ on the average between patients with or without parotid swelling, ANA or anti-ENA antibodies, and RF, in the whole population of SS patients or in the two subgroups. None of the lung function parameters was significantly correlated with RF titre, gammaglobulins, CH₅₀, or CIC levels, in both single and multiple regression analysis, either in the whole group of patients or in the primary or secondary group. However, patients in both groups with Raynaud's phenomenon showed significantly lower DLCO-SB values as compared with those without this clinical feature (mean±SD: 77.2±17.6 v 84.7±14.6 as percentage of the predicted values, respectively; *t*=2.077, *p*<0.05).

Discussion

In this study we show that lung involvement can occur in the course of SS. In our patients lung involvement was characterised by the impairment of the tests usually considered to be indicative of small airway disease (FEF 75–85 and MEF 75),²⁴ or of the diffusion capacity parameters (DLCO, KCO, DuCO, DuaCO), or both. Finally, interstitial lung involvement was evident in some of our patients on chest *x*-ray examination. On the whole both functional and radiographic abnormalities were less frequent and severe in patients with primary SS than

in those with SS associated with other connective tissue diseases. These results are only partially in agreement with previous reports. An impaired diffusion capacity has already been found in a large percentage of 46 patients with primary SS.⁶ Impaired DLCO and restrictive ventilatory defects were also observed by Strimlan *et al.*² and by Fairfax *et al.*⁴ in two series of 18 and 17 patients with SS. In contrast, mostly obstructive defects were observed by Segal *et al.*,⁵ and Newball and Brahim,³ who studied relatively small numbers of patients with SS. In none of these reports, however, did patients with primary SS account for more than 50% of the population studied. Furthermore, the presence of small airway disease was not directly shown in these studies, although it could be suspected on the basis of some lung function and/or histological findings.^{3,4}

The lower prevalence of obstructive or restrictive defects in our patients with primary SS can be explained in two ways: first, patients with bronchopulmonary disorders, such as pleurisy, bronchitis, or pneumonitis, not necessarily related to SS, and smokers were rigidly excluded; secondly patients with primary SS were separated from those with an associated connective tissue disease, because it is known that a more or less severe pulmonary involvement is often present in the course of RA,²⁵ SLE,²⁶ PSS,²⁷ MCTD,¹⁰ and EMC.¹¹ This may also explain the more frequent and severe lung impairment observed in our patients with secondary SS.

No pathological data are available, and therefore the pathogenesis of the lung lesions observed in our patients with primary SS remains largely speculative. It has been suggested that the sicca syndrome may favour the occurrence of a chronic inflamma-

Table 3 Lung involvement in Sjögren's syndrome: a comparison of patients with primary and secondary syndrome

Parameter	Pathological limits (% of predicted)	Primary SS pathological cases		Secondary SS pathological cases		χ^2 (Yates)	<i>p</i>
		No	%	No	%		
TLC	<80 >120	0/20	0	2/19	10.5	0.583	NS†
RV	<80 >120	5/20	25	5/19	26.3	0.074	NS
FEV1	<82*	1/20	5	5/19	26.3	1.960	NS
MEF 75	<52*	11/20	55	14/19	73.7	0.778	NS
FEF 75–85	<47*	3/20	15	9/19	47.4	3.393	NS
DLCO-SB	<80	4/20	20	11/20	55	3.840	<0.05
KCO	<80	11/20	55	11/20	55	0.101	NS
DLCO-SS2	<80	11/20	55	16/20	80	1.823	NS
DuCO	<80	9/20	45	12/20	60	0.401	NS
DuaCO	<80 *	9/20	45	7/20	35	0.104	NS
Chest <i>x</i> -ray score	≥1	5/18	27.8	15/20	75	6.685	<0.01

*These figures are the normal 95th percentile, derived from an analysis of the data collected in an epidemiological survey in the North of Italy (unpublished data).

†NS=not significant.

For symbols see text.

Table 4 Lung function, arterial blood gases, and radiographic data in patients with primary and secondary Sjögren's syndrome

	X-ray score	TLC (%) [*]	RV (%)	FEV1 (%)	MEF 75 (%)	FEF 75-85 (%)	V _C (%)	FEV1/ V _C (%)	RV/ TLC (%)	DLCO -SB (%)	KCO (%)	DLCO -SS2 (%)	DuCO (%)	DuaCO (%)	Po ₂ (mmHg)	Pco ₂ (mmHg)
Primary SS patients	Mean	105	93	104	62	85	79	93	85	14	22	80	82	81	96	37
	SD	14	23	14	36	40	9	22	14	76	80	68	10	8	9	3
Secondary SS patients	Mean	101	100	92	41	50	73	95	76	17	17	29	76	82	89	36
	SD	19	20	17	20	33	9	13	17	161	0.32	1.38	11	10	7	3
	t	0.69	1.09	2.30	2.22	2.06	1.79	0.23	1.61	NS	NS	NS	1.70	0.05	2.65	0.55
	p	NS [†]	NS	>0.05	<0.05	>0.05	NS	NS	NS	NS	NS	NS	NS	NS	>0.02	NS

*Values expressed as percentage of predicted values.
†NS=not significant.
For other symbols see text.

tory process in the bronchial walls and glands and this could cause an obstructive syndrome.² However, signs and symptoms of chronic bronchial damage were very rarely encountered in our patients. On the other hand, the presence of small airway disease could be due to interstitial involvement, in a way similar to that suggested for other systemic disorders.²⁸ This hypothesis would be supported in our study by the radiographic findings and by the diffusion capacity abnormalities. The pathogenesis of the interstitial lung damage found in connective tissue diseases is still debated, but experimental²⁹ and clinical³⁰ studies support the role of immune complex deposition with subsequent local activation of an inflammatory response. CICs are frequently encountered in the course of SS, and they are commonly believed to be responsible for some of the systemic features of this disorder.³¹ In this study and a previous one⁴ CIC levels failed to correlate with lung function impairment but this does not necessarily rule out this hypothesis. It is known that CIC levels may change on follow up,³² whereas most of the lung function parameters are the result of a pathological and functional damage already established in these diseases. On the other hand, the lack of correlation between clinical features and CIC levels might be due to the fact that none of the methods employed for immune complex detection is able to determine all the immune complexes,³³ and that multiple types of complexes are likely to be present in the same serum.³²

Finally, an increased vasospasm of lung vessels ('Raynaud's phenomenon of the lung') has been observed in patients with certain connective tissue diseases, such as scleroderma,³⁴ and this finding has been postulated to have an important role in determining some lung function abnormalities.³⁵ We have no evidence that Raynaud's phenomenon of the lung was present in our patients. However, the fact that diffusion capacity was more impaired among our SS patients with Raynaud's phenomenon suggests that this mechanism might also contribute to the lung damage in SS.

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