Prevalence and spectrum of symptomatic pulmonary involvement in primary Sjögren's syndrome

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ABSTRACT

Objective. *The present cross-sectional study aimed to estimate the prevalence of chronic respiratory symptoms in primary Sjögren's syndrome (pSS) and define the clinical, functional and imaging characteristics of symptomatic pulmonary disease in pSS.*

Methods. *Four hundred and fourteen consecutive pSS patients were interviewed for the presence of chronic respiratory complaints (cough and/or dyspnea). Symptomatic pSS patients without respiratory or other comorbidities underwent further investigation with clinical evaluation and assessment with pulmonary functional testing (PFTs) and chest high resolution CT (hrCT) on inspiratory and expiratory phase. Comparison of clinical and laboratory features between symptomatic and asymptomatic pSS patients was also performed.*

Results. *Prevalence of chronic respiratory symptoms in pSS was estimated at 21.5% (89/414). Symptoms were attributed to underlying comorbidities in approximately one third of cases (30/89). Thirty nine of the remaining 59 patients were finally assessed with PFTs and hrCT. Small airway disease was diagnosed in 20 individuals with an obstructive pattern in PFTs and/or compatible radiological signs. Seven patients were diagnosed with interstitial lung disease, while in the remaining 12 pSS patients, with normal PFTs and hrCT, symptoms were attributed to xerotrachea. Raynaud's phenomenon occurred more frequently in symptomatic than asymptomatic patients (p=0.024).*

Conclusion. *Approximately one fifth of a large cohort of pSS patients presented chronic respiratory symptoms. Small airway disease was the most commonly recognised pulmonary disorder among symptomatic pSS patients, followed by xerotrachea and interstitial lung disease.*

Introduction

Sjögren's syndrome (SS) is a common, slowly progressive autoimmune disease, encompassing a wide range of organ-specific or systemic manifestations. It is characterised by B-cell hyperactivity and lymphocytic infiltration of exocrine glands and other target organs. Oral dryness and keratoconjunctivitis sicca as a result of diminished lacrimal and salivary gland function are the most prevalent symptoms of the syndrome, while extraglandular (or systemic) manifestations occur in around one third of patients. SS may occur alone (primary SS or pSS) or in association with an established connective tissue disease (1).

Pulmonary manifestations are among the most frequent extraglandular manifestations in pSS. The exact prevalence of clinically significant respiratory disease in pSS varies across studies at a range of 9 to 24% (2-4). Differences in the classification criteria for SS proposed over time, the functional and imaging methods used to diagnose respiratory disease and the characteristics of studied populations might account for this variability. Of note, up to 75% of pSS patients without respiratory symptoms may present abnormal patterns of pulmonary function testing, bronchoalveolar lavage (BAL) and/or chest computed tomography (CT) (5, 6). Xerotrachea (7), small airway disease (SAD) due to follicular or lymphocytic bronchiolitis (6) and interstitial lung disease (ILD), mainly lymphocytic and non-specific interstitial pneumonia (8, 9) (LIP and NSIP, respectively), and less frequently of the type of usual interstitial pneumonia and organising pneumonia (UIP and OP, respectively), are among the most common respiratory manifestations. BALT type non-Hodgkin's lymphoma (10), pulmonary amyloidosis, pleural effusion and pul-

monary hypertension are, by far, rare pulmonary complications of pSS (11). The aim of the present cross-sectional study is to estimate the prevalence of chronic respiratory symptoms in a cohort of well-characterised pSS patients and define the underlying abnormalities using functional and imaging modalities. Additionally, we wish to investigate possible associations of respiratory complaints with clinical and laboratory characteristics of pSS.

Material and methods

Study cohort

Our initial cohort included 723 patients with pSS derived from the Department of Pathophysiology (Medical School, University of Athens), a patient collection diagnosed and followed-up by HMM, and the Rheumatology Department of General Hospital "G. Gennimatas". All patients fulfilled the European/American International classification criteria for pSS (12) and were recruited from 1993 to 2016. Four hundred and fourteen patients finally underwent a structured clinical interview (from 06/2015 to 05/2016), for the presence of chronic respiratory symptoms such as cough and/or dyspnea lasting for at least three consecutive months. The remaining 309 patients had either been lost to follow-up or died at the beginning of the present study.

Patients with chronic cough and/or dyspnea prior to pSS onset, attributed to underlying aetiology [chronic obstructive pulmonary disease (COPD), bronchial asthma, postinfectious bronchiectases, chronic pulmonary infections (tuberculosis, pulmonary abscess), chronic thromboembolic disease, gastroesophageal reflux (GERD), upper airway cough syndrome, congestive heart failure (CHF) or chronic medication use (*e.g.* agiotensin-converting-enzyme inhibitor)], were excluded from further investigation (13). The remaining patients were asked to provide informed consent for participating in a comprehensive assessment with pulmonary function tests and computed tomography scan, as described in the sections below. The present clinical research study was conducted according to the principles of the Declaration of Helsinki (1975/83) and received approval from the research ethics board of "Laiko" General Hospital, Athens, Greece (Approval number: 4311).

Clinical and laboratory characteristics of pSS

Demographic, clinical and laboratory characteristics were recorded from all participating pSS patients after thorough chart review. In detail, age, sex, date of SS diagnosis, oral, ocular, or skin dryness, history of salivary gland enlargement (SGE), results of Schirmer's test (abnormal test ≤5mm/5min), ocular staining (abnormal score by Rose Bengal ≥4) and unstimulated sialometry (abnormal salivary flow ≤1.5 ml/15 min), liver involvement (primary biliary cirrhosis or autoimmune hepatitis), interstitial renal disease, lymphadenopathy, splenomegaly, presence of myalgias, arthralgias, arthritis, chronic fatigue, Raynaud's phenomenon, palpable purpura, glomerulonephritis, peripheral or central nervous system (PNS or CNS) involvement and previous diagnosis of lymphoma. Laboratory parameters including full blood count, abnormal γ-globulins levels, monoclonal gammopathy, C4 complement protein levels (mg/dl), cryoglobulins and autoantibodies like antinuclear (ANA) (positive titres equal or higher than 1:320), anti-Ro/SSA or/and anti-La/SSB antibodies, anti-mitochondrial antibodies (AMA), anti-centromere antibodies (ACA) and rheumatoid factor (RF) (positivity defined as levels >20 IU/ml), were also recorded. The extent of lymphocytic infiltration of salivary glands was evaluated by minor salivary gland biopsy, using focus and Tarpley scores (12).

Pulmonary function testing (PFTs)

PFTs included pre- and post-bronchodilator spirometry, static lung volumes and diffusion capacity for carbon monoxide (CO). Flow-volume loops, forced expiratory volume in the 1st second (FEV_1), forced vital capacity (FVC), forced expiratory flow 25%-75% ($FEF_{25\%-75\%}$), all expressed as percentage of predicted normal values (% pred.), and absolute value of FEV_1 to FVC ratio (FEV_1/FVC) were determined. Post-brochodilator response was considered significant, when an increase in FEV_1 or FVC of at least 12% and 200 mL from baseline was observed. Total lung capacity (TLC) and RV to TLC ratio (RV/TLC) (both % pred.) were measured by the single-breath helium dilution method, while the single-breath diffusion technique was used for measuring the diffusion capacity for CO, corrected for haemoglobin, ($DLCO_{SB}$) (% pred.) (*JAEGER MS Diffusion PFT Unit*). An obstructive defect was defined as an absolute value of FEV_1/FVC less than 0.7, while isolated SAD was functionally diagnosed on the basis of an abnormal measurement of $FEF_{25\%-75\%}$ (<60% pred.) (14–16) despite normal FEV_1, FVC (>80% pred.) and FEV1/FVC ratio (>0.7). A restrictive defect was defined when a normal FEV_1/FVC ratio was combined with TLC lower than 80% pred.

CT imaging

High resolution CT (hrCT) scan of the lungs was performed in all patients at the day of pulmonary function testing. Thin-section CT images (1mm slice thickness) with a high spatial frequency reconstruction algorithm were acquired at full inspiration and end-tidal expiration (Siemens Somatom Definition 128 slice CT system). Abnormal hrCT findings were classified into four major categories: reticular (septal thickening, honeycombing), nodular (multiple large or small nodules), high attenuation (consolidation, ground glass opacities) and low attenuation (air trapping, lung cysts) pattern. Among the radiological findings, those directly (peripheral airway wall thickening, bronchiectasis or bronchiolectasis, centrilobular nodules, "tree-in-bud" opacities) or indirectly (air trapping on expiratory phase, subsegmental atelectasis) related to SAD (17), or those compatible with ILD (18, 19) were also recognised. CT images were independently evaluated by two experienced radiologists.

Statistical analysis

Continuous and categorical clinical and laboratory parameters of pSS were

compared between symptomatic and asymptomatic patients with *t*-test or Mann-Whitney test, where appropriate, and chi-square or Fisher's exact test, respectively. Within the group of symptomatic patients who had a complete assessment with PFTs and CT scan, Mann-Whitney and Fisher's exact test were implemented for the comparison of the above characteristics between patients with ILD and other type of pulmonary involvement. The level of statistical significance was set at 0.05.

Results

Prevalence of chronic respiratory symptoms - Association with clinical and laboratory features

Approximately one-fifth (89/414) of interviewed pSS patients reported chronic respiratory complaints.Among them, thirty individuals had significant underlying respiratory disease or related comorbidities prior to pSS onset. Fifteen were heavy smokers and had COPD, nine patients had bronchial asthma, three had CHF, two had chronic upper airway cough syndrome and one had obesity and unilateral diaphragmatic paralysis after thoracic radiotherapy for ispilateral breast cancer. Among the remaining symptomatic (n=59) patients, 17 complained for cough, 19 had dyspnea and 23 reported both cough and dyspnea. Their clinical, laboratory and treatment characteristics at the time of the pulmonary interview were compared to those of asymptomatic patients (n=325), as shown in Tables I and II. With the exception of Raynaud's phenomenon, which was more frequently encountered in patients with chronic respiratory symptoms (37.3% vs 23.4%, p=0.024), there were no statistically significant differences (p values >0.05 in all comparisons) between these two groups of patients. Presence of positive autoantibodies, hypocomplementaemia and serum electrophoresis abnormalities were also equally distributed between the two groups (Table II). Individuals with respiratory symptoms had a higher median MSG biopsy focus (2 *vs* 1.49) and Tarpley score (3 *vs* 2), differences which did not reach statistical significance (p=0.091 and 0.090, respectively, by Mann-Whitney test). Biopsy-proven lymphoproliferative disease, mainly arising from salivary glands, was diagnosed in almost one sixth of either symptomatic or asymptomatic patients. Mucosa-associated lymphoid tissue (MALT) - type lymphoma was the most common histopathological diagnosis (54 out of 65 total cases of lymphoma), followed by diffuse large B-cell lymphoma (7/65).

Table I. Comparison of clinical characteristics between pSS patients with and without chronic respiratory symptoms.

Patient characteristic	Asymptomatic n=325	Symptomatic n=59	Total n=384	*p*-value
Gender (female), n (%)	305 (93.8)	58 (98.3)	363 (94.5)	0.222*
Current age (years) (mean ± SD)	63.1 ± 12.8	61.2 ± 11.9	62.8 ± 12.6	0.206
Clinical characteristics specific for SS				
Disease duration (years) (mean ± SD)	11.9 ± 6.3	11.4 ± 6.8	11.9 ± 2.1	0.553
Glandular manifestations, n (%)				
Oral dryness	289 (88.9)	56 (94.9)	345 (89.8)	0.161
Ocular dryness	295 (90.8)	55 (93.2)	350 (91.1)	0.542
Skin dryness	16 (4.9)	7 (11.9)	23 (6)	0.066*
History of SGE	90 (27.7)	19 (32.2)	109 (28.4)	0.480
Abnormal Schirmer's test	194/244 (79.5)	27/36 (75)	221/280 (78.9)	0.536
Abnormal Bengal stain	86/186 (46.2)	7/23 (30.4)	93/209 (44.5)	0.150
Extraglandular (systemic) manifestations, n (%)				
Easy fatigue	82 (25.2)	17 (28.8)	99 (25.8)	0.563
Arthralgias/myalgias	224 (68.9)	39 (66.1)	263 (68.5)	0.668
Arthritis	70 (21.5)	14 (23.7)	84 (21.9)	0.708
Raynaud's phenomenon	76 (23.4)	22 (37.3)	98 (25.5)	0.024
Palpable purpura	40 (12.3)	9 (15.3)	49 (12.8)	0.533
Vasculitic ulcer	1 (0.3)	0 (0)	1 (0.3)	1*
Myositis	4 (1.2)	1 (1.7)	5 (1.3)	0.568*
PNS involvement	12 (3.7)	2 (3.4)	14 (3.6)	1*
CNS involvement	12 (3.7)	2 (3.4)	14 (3.6)	1*
Lymphadenopathy	46 (14.2)	9 (15.3)	55 (14.3)	0.824
Splenomegaly	9 (2.8)	1 (1.7)	10 (2.6)	1*
Liver involvement	13 (4.0)	2 (3.4)	15 (3.9)	1*
Interstitial renal disease	5 (1.5)	0 (0)	5 (1.3)	1*
Glomerulonephritis	10 (3.1)	0 (0)	10 (2.6)	0.372*
Treatment				
Pilocarpine hydrochloride	100 (30.8)	27 (45.8)	127 (33.1)	0.024
Systemic steroids	87 (26.8)	22 (37.3)	109 (28.4)	0.099
Hydroxychloroquine	122 (37.5)	28 (47.5)	150 (39.1)	0.151
Immunosuppression**	64 (19.7)	14 (23.7)	78 (20.3)	0.478

pSS: primary Sjögren's syndrome; SGE: salivary gland enlargement; PNS: peripheral nervous system; CNS: central nervous system. All clinical and therapeutic features were collected at the time of pulmonary interview.
*denotes Fisher's exact test, **_e.g._ systemic corticosteroids, methotrexate, azathioprine, cyclophosphamide, rituximab or chemotherapy regimens for lymphoma.

Further diagnostic work-up in pSS patients with respiratory symptoms - Clinical evaluation-PFTs findings

Thirty nine of the 59 pSS patients finally provided consent for further diagnostic work-up with clinical evaluation, spirometry, static lung volumes and diffusion capacity, as depicted in Table III. Most of the 39 patients (n=24) reported concomitantly complaints of cough and dyspnea. Dyspnea was mild to moderate (modified MRC scale: 0-2) in more than 90% of patients. Median disease (pSS) duration at the onset of respiratory symptoms was 5 years (range: 0-17 years). In the majority of cases, arterial oxygen saturation ($SatO_2$), as measured by pulse oximetry, was normal at rest and insignificantly decreased on effort (median $SatO_2$: 97% and 95%, respectively). Thirty four of the 39 patients were never smokers, three of them were ex-smokers (all of them long-term quitters), and two of them were active (light to moderate) smokers (less than 20 cigarettes/day). In 38.5% (15/39) a significant reduction in $FEF_{25\%-75\%}$ (<60% pred.) was

Table II. Comparison of haematological, serological and histopathological characteristics between pSS patients with and without chronic respiratory symptoms.

Patient characteristic	Patient group		Total	*p*-value
	Asymptomatic	Symptomatic		
Haematological and serological characteristics				
Leukocytopenia n (%)	13/325 (4.0)	1/59 (1.7)	14/384 (3.6)	0.705*
Hypergammaglobulinaemia n (%)	166/303 (54.8)	27/56 (48.2)	193/359 (53.8)	0.446
Monoclonal gammopathy n (%)	24/303 (7.9)	3/56 (5.4)	27/359 (7.5)	0.782*
RF positivity n (%)**	159/294 (54.1)	34/56 (60.7)	193/350 (55.1)	0.360
ANA positivity n (%)***	235/313 (75.1)	49/58 (84.5)	284/371 (76.5)	0.121
Anti-Ro positivity n (%)	229/311 (73.6)	39/55 (70.9)	268/366 (73.2)	0.674
Anti-La positivity n (%)	122/307 (39.7)	16/53 (30.2)	138/360 (38.3)	0.187
AMA positivity n (%)	11/206 (5.3)	4/42 (9.5)	15/248 (6.0)	0.293*
ACA positivity n (%)	12/313 (3.8)	4/58 (6.9)	16/371 (4.3)	0.291*
Cryoglobulinaemia n (%)	30/237 (12.7)	3/51 (5.9)	33/288 (11.5)	0.168
C4 complement protein levels [median (range)]	18.0 (0-46.7)	19.0 (1.4-96.0)	19.0 (0-96.0)	0.684
Lymphoproliferative disease n (%)	55/325 (16.9)	10/59 (16.9)	65/384 (16.9)	0.996
Histopathological characteristics				
MSG biopsy focus score [median (range)]	1.49 (0-12)	2 (0-12)	1.6 (0-12)	0.091
MSG biopsy Tarpley score [median (range)]	2 (0-4)	3 (0-4)	2 (0-5)	0.090

pSS: primary Sjögren's syndrome; RF: rheumatoid factor; ANA: antinuclear antibodies; AMA: antimitochondrial antibodies; MSG: minor salivary gland; ACA: anti-centromere antibodies.
*denotes Fisher's exact test; **positive RF >20 IU/ml; ***positive for ANA titres ≥1:320.

Table III. Characteristics of chronic respiratory symptoms and pulmonary function test results in symptomatic pSS patients.

		n=39
Clinical characteristics, n (%)		
Chronic cough		28 (71.8)
	Dry	16 (41.0)
	Productive	12 (30.8)
Dyspnea		35 (89.7)
Modified MRC scale	0	2 (5.1)
	1	12 (30.8)
	2	18 (46.1)
	3	2 (5.1)
	4	1 (2.6)
Oxygen pulse oximetry (%) [median (min-max)]	At rest	97 (87-99)
	On effort	95 (80-98)
Spirometry		
Pre bronchodilation (% pred.) (mean ± SD)	FEV_1	99.28 ± 25.40
	FVC	105.72 ± 22.49
	FEV_1 to FVC ratio	0.78 ± 0.10
	$FEF_{25\%-75\%}$	71.39 ± 31.18
Post bronchodilation (% pred.) (mean ± SD)	FEV_1	101.81 ± 24.68
	FVC	106.69 ± 21.83
	FEV_1 to FVC ratio	0.79 ± 0.09
	$FEF_{25\%-75\%}$	77.86 ± 34.80
Change (%)(mean ± SD)	ΔFEV_1	3.29 ± 9.12
	ΔFVC	0.25 ± 8.87
	$\Delta FEF_{25\%-75\%}$	17.36 ± 27.33
Static lung volumes (% pred.) (mean ± SD)	TLC	93.92 ± 14.88
	RV/TLC	97.87 ± 16.98
Diffusion capacity (% pred.) (mean ± SD)	$DLCO_{SB}$	81.74 ± 17.38

observed, while four of these patients had more severe obstruction with low FEV_1/FVC ratio (<0.7) and moderate to severe decrease in FEV_1 (<80% pred.). Post-bronchodilator response was significant in only two cases. Three additional patients had a moderate restrictive pattern (TLC: 60-70% pred.) with reduced $DLCO_{SB}$ (<80% pred.). On the other hand, spirometric parameters, TLC and $DLCO_{SB}$ were within normal limits in approximately half (21/39) of the patients tested.

CT findings

As shown in Table IV, the most common hrCT finding was expiratory air trapping in 12/39 patients (30.8%), followed by linear atelectatic lesions in 8/39 (20.5%) and reticular pattern due to septal thickening in 6/39 (15.4%). Direct and/or indirect CT signs of SAD was observed in 15/39 patients (38.5%), while signs compatible with ILD at various stages of severity were the predominant CT imaging feature in 7 patients (17.9%) (Fig. 1, Panels a to d). CT imaging was normal or with non-specific findings in 17 individuals (43.6%). Ten patients had CT and PFT findings both compatible with SAD, while diagnosis of SAD was based on either PFTs or CT scan in other 10 patients (5 for each category). In the 12 remaining patients with a normal CT scan and PFTs, symptoms were attributed to xerotrachea.

Only one of the 7 patients with a radiological pattern compatible with ILD had biopsy-proven LIP. Another one had a possible UIP pattern but suffered from severe respiratory failure at initial presentation and was clinically unfit for surgical biopsy, two others had a typical UIP pattern, while the remaining three had findings inconsistent with UIP pattern but refused to undergo surgical biopsy.

Comparison of clinical and laboratory characteristics between patients with ILD and other non-ILD diagnosis

The only statistical significant difference derived from the comparison of clinical and laboratory findings of patients with ILD (n=7) and patients with another non-ILD diagnosis (either xerotrachea or SAD) (n=32) was the

Table IV. Distribution of chest hrCT findings in symptomatic patients with pSS.

Classification of hrCT findings	Distribution of findings						
	Unilateral n (%)	Bilateral n (%)	Upper lung field(s) n (%)	Middle lung field(s) n (%)	Lower lung field(s) n (%)	More than one lung field(s) n (%)	Total n (%)
Reticular pattern							
Septal thickening	2 (5.1)	4 (10.3)	1 (2.6)	0	2 (5.1)	3 (7.7)	6 (15.4)
Honeycombing	0	3 (7.7)	0	1 (2.6)	0	2 (5.1)	3 (7.7)
Nodular pattern							
Multiple large nodules (> 1cm)	0	1 (2.6)	0	0	0	1 (2.6)	1 (2.6)
Multiple small nodules (< 1cm)	1 (2.6)	2 (5.1)	1 (2.6)	0	0	2 (5.1)	3 (7.7)
Perilymphatic	0	0	0	0	0	0	0
Centrilobular	1 (2.6)	2 (5.1)	1 (2.6)	0	0	2 (5.1)	3 (7.7)
Random	0	0	0	0	0	0	0
High attenuation pattern							
Ground glass opacity	0	1 (2.6)	0	0	0	1 (2.6)	1 (2.6)
Consolidation	0	0	0	0	0	0	0
Low attenuation pattern							
Air trapping	1 (2.6)	11 (28.2)	0	0	4 (10.3)	8 (20.5)	12 (30.8)
Lung cysts	0	3 (7.7)	0	0	2 (5.1)	1 (2.6)	3 (7.7)
Other findings							
Bronchiectases	0	1 (2.6)	0	0	1 (2.6)	0	1 (2.6)
Pleural effusion	0	0	N/A	N/A	N/A	N/A	0
Pleural thickening	0	1 (2.6)	N/A	N/A	N/A	N/A	1 (2.6)
Hilar/mediastinal lymhadenopathy	0	1 (2.6)	N/A	N/A	N/A	N/A	1 (2.6)
Bronchial wall thickening	0	4 (10.3)	N/A	N/A	N/A	N/A	4 (10.3)
Traction bronchiectases	1 (2.6)	2 (5.1)	0	1 (2.6)	1 (2.6)	1 (2.6)	3 (7.7)
Linear atelectatic lesions	5 (12.8)	3 (7.7)	1 (2.6)	2 (5.1)	2 (5.1)	3 (7.7)	8 (20.5)

hrCT: high resolution computed tomography; N/A: non applicable.

higher prevalence of monoclonal gammopathy in the ILD group (29% or 2/7 *vs* 0% or 0/32, p=0.033, Fisher's exact test). Lymphoproliferative disease was also more frequently diagnosed in patients with ILD (43% or 3/7 *vs* 9% or 3/32), but the difference was marginally insignificant, p=0.059, Fisher's exact test). Five out of the 6 patients with lymphoproliferative disease had biopsy-proven mucosa-associated lymphoid tissue (MALT) - type lymphoma arising from salivary glands. Five patients with ILD were treated with azathioprine and/or oral steroids, while the remaining two received rituximab as a component of chemotherapy regimens for concomitant lymphoma.

Pulmonary involvement in pSS patients positive for ACA [ACA(+)]

Compared to ACA (-) pSS population, ACA (+) pSS patients displayed increased rates of Raynaud's phenomenon, lower rates of anti-Ro/SSA and anti-La/SSB antibodies as well as higher median MSG focus scores (81% or 13/16 *vs*. 24% or 84/355, p<0.001/44% or 7/16 *vs*. 75% or 255/340, p=0.016 and 6% or 1/16 *vs*. 40% or 133/334, p=0.007/2.7 *vs*. 1.5, p=0.009, respectively). No statistically significant differences in chronic respiratory symptoms were detected between the two subgroups. ACA positivity was detected in only 3 out of 39 (8%) symptomatic patients assessed with PFTs and thoracic hrCT. SAD and xerotrachea were the main pathologies which seem to account for the presence of clinical symptomatology in these patients.

Discussion

To the best of our knowledge, this is one of the largest studies so far estimating the prevalence of chronic respiratory symptoms in consecutive pSS patients and evaluating clinical, laboratory and functional features of symptomatic pulmonary disease in pSS (4, 8). In the current study we sought to clarify: 1) the prevalence of chronic respiratory complaints in pSS, 2) possible associations of complaints with clinical and laboratory parameters, 3) the predominant pattern of lung abnormality and 4) whether clinical and laboratory parameters differ between patients with ILD and other non-ILD pulmonary disease. According to our data, about one fifth of pSS patients had clinically significant symptoms (cough and/or dyspnea), but, in approximately one third of these cases, the symptomatology was attributed to established chronic respiratory disease or comorbidities preceding the onset of pSS. Among patients without any other evident cause of respiratory symptoms, SAD and xerotrachea were the most frequent respiratory complications, as pointed out long ago by our previous studies (6, 7). We also found that Raynaud's phenomenon occurred more frequently in symptomatic than asymptomatic patients and that monoclonal gammopathy was more prevalent in symptomatic patients with ILD than symptomatic patients with another non-ILD diagnosis.

Several previous studies have shown that ILD and SAD are among the most common pulmonary manifestations in pSS. However, these studies were heterogenous in terms of diagnostic methods [utilisation of hrCT imaging (20-22), pulmonary function testing or both

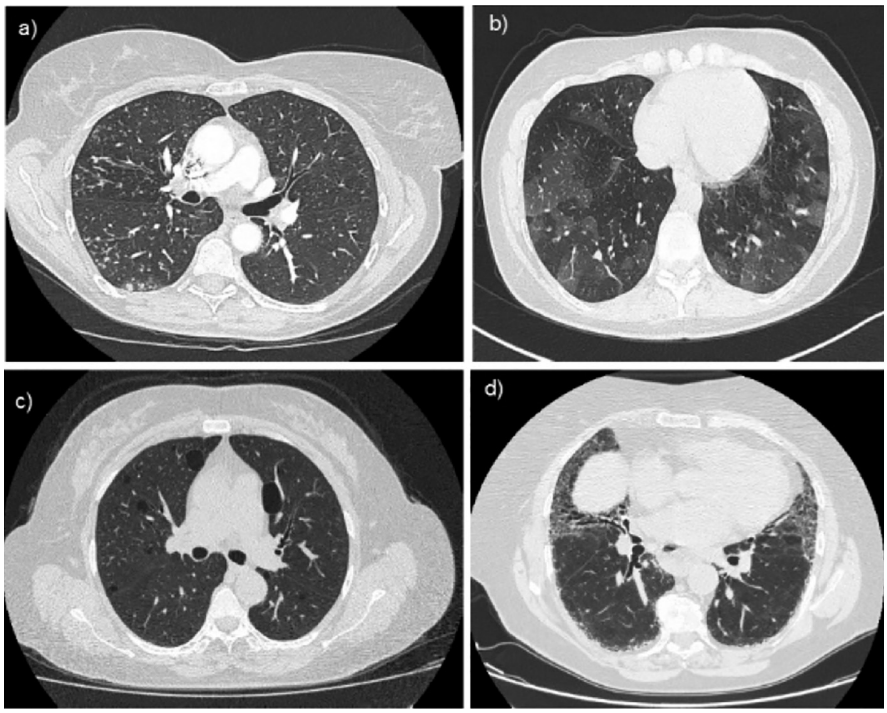

Fig. 1. Characteristic findings of chest computed tomography (CT) in symptomatic patients with primary Sjögren's syndrome (pSS).
Patients with pSS and chronic respiratory symptoms may present direct and/or indirect radiological signs of small airway disease. Small centrilobular nodules (with or without "tree-in-bud" pattern) and bronchiectases (Panel a) are among the most common direct signs, while expiratory air trapping is among the most typical indirect ones (Panel b). Multiple lung cysts (Panel c) and CT findings compatible with interstitial lung disease such as honeycombing, septal thickening and/or traction bronchiectases (Panel d) are less frequently encountered.

(4, 5, 8, 23, 24)], design and selection criteria [*e.g.* inclusion of symptomatic (4, 24), asymptomatic patients (5) or mixed populations (20, 21)]. Hence, existing literature has not clarified yet whether SAD or ILD is the most prevalent pattern of respiratory disease.

The present study is in agreement with previous observations that clinical lung disease may develop in 10 to 20% of patients with pSS (2, 25). Our inclusion criteria for patients undergoing further work-up with hrCT and PFTs enhances our confidence that abnormal imaging and/or functional findings were related to pSS, and did not represent manifestations of other bronchopulmonary disease. In line with our results, several clinical studies in mixed populations of symptomatic and asymptomatic patients indicate the particularly significant role of SAD in pulmonary involvement associated with pSS (6, 20, 26, 27). On the contrary, other investigators have mostly emphasised that findings consistent with ILD (*e.g.* NSIP, UIP, or LIP) are the predominant hrCT pattern in pSS (5, 8, 21-23). Nevertheless, some of these studies have either included asymptomatic patients with subclinical ILD and mild functional impairment (5) or mixed populations with pSS and SS in the context of other autoimmune disease (21), or may have a selection bias due to retrospective design (8, 21, 23) and/or exclusive enrolment of patients having undergone surgical lung biopsy (8, 23, 28).

Multiple and heterogeneous techniques have been used so far for the assessment of small airway function, but none of them can be considered as the "gold standard" for the diagnosis of SAD. A combined use of different methods may be a rational approach in this setting (29). In our study, SAD was defined as the presence of a compatible abnormal physiologic ($FEF_{25\%-75\%}$ <60% pred.) and/or hrCT pattern. $FEF_{25\%-75\%}$ has been traditionally considered a marker of distal airway involvement in COPD patients (30). Despite its great variability and dependence on FVC alterations, previous studies in COPD and asthma have provided evidence that it is closely correlated to air trapping as detected with CT scans (31, 32). However, it is worth noting that approximately two thirds of our patients with a SAD functional pattern had also an abnormal hrCT scan consistent with SAD and vice versa. CT signs indicative of SAD despite normal FEV1 to FVC ratio, $FEF_{25\%-75\%}$ and flow-volume curves is an observation also made by two previous studies in symptomatic patients with suspected chronic airway disease (31) and smoking individuals with pSS (33) and could reflect a milder extent of pulmonary involvement.

From the analysis of possible associations between clinical and laboratory features of pSS and symptomatic pulmonary disease or ILD, we concluded that Raynaud's phenomenon was more prevalent in patients with chronic respiratory symptoms and that monoclonal gammopathy was more frequent in patients with ILD compared with other non-ILD lung disease. Two recent studies have also observed a higher prevalence of Raynaud's phenomenon in pSS with pulmonary involvement (2) or ILD (34). Although a hypothetical mechanism of microangiopathy and ischaemic process leading to onset of ILD has been implied (34), it is unclear whether a true pathogenetic connection underlies this association. Raynaud's phenomenon was more prevalent in our ACA(+) *versus* ACA(-) pSS patients, in accordance with previous studies (35-37), but prevalence of chronic respiratory symptoms did not differ between these two subgroups. Patients with pSS have a high risk for developing non-Hodgkin's lymphoma, which affects the lung in about 20% of cases (38). Extranodal marginal zone cell lymphoma of the MALT-type is among the most common subtypes and usually presents with alveolar opacifications with peribronchial or peripheral distribution, associated or not associated with "air bronchogram" sign, multiple lung nodules and/or masses, and areas of ground glass attenuation (10). One of our patients with a history of MALT lymphoma had multiple pulmonary cysts of variable size as the only abnormal CT finding, while another

one had ground glass opacities in the contex of ILD. However, the observed associations of ILD with monoclonal gammopathy or lymphoma should be interpreted cautiously, due to the very small sample size (n=2 and n=6, respectively).

We acknowledge some limitations in this study. First, the small group of patients studied with hrCT and PFTs (n=39) is a limiting factor for generalising our conclusions. Significant information may have been missed due to the 20 patients who refused to undergo further investigation. Nonetheless, the present study is one of the larger existing studies (4, 5, 8) that integrate clinical, radiological and functional diagnostic methods in order to assess pulmonary involvement in pSS. Moreover, some patients may have underestimated symptoms' severity and declared to be asymptomatic during the initial screening interview. Of course it remains debatable whether pSS patients should be screened with specific imaging and respiratory function tests or receive systematic treatment for subclinical respiratory disease (39). In addition, prevalence of clinically significant ILD may have been somewhat underestimated, since approximately one fifth of our patients had already been treated with immunosuppressive agents, thus suggesting a possible positive effect of treatment on the progression of mild asymptomatic ILD. Finally, the majority of our patients with ILD were treated with classical immunosuppressants such as azathioprine. Despite the fact that recent publications indicate the efficacy of novel agents such as rituximab in ILD associated with pSS (40) or other connective tissue disease (41), none of our patients with ILD could receive rituximab monotherapy due to significant restrictions on its off-label use.

In conclusion, roughly 20% of a large cohort of patients with pSS had chronic respiratory symptoms such as dyspnea and/or cough, which, in 2/3 of cases, were not linked to any other respiratory conditions or comorbidities. PFTs and/or CT imaging findings were compatible with SAD in the majority (>50%) of symptomatic patients, while symptoms were attributed to xerotrachea or ILD in the remaining cases. Apart from Raynaud's phenomenon, the present study did not substantiate any association of clinical and laboratory characteristics with the presence of respiratory complaints. Patients with ILD seem to have a higher prevalence of monoclonal gammopathy, but it is unclear whether this finding reflects a causal relationship or a random association.

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