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Evaluation of patients diagnosed with primary Sjogren's syndrome with and without pulmonary involvement

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Abstract. *Background and aim:* Interstitial lung disease (ILD) is the most severe pulmonary complicationin Primary Sjögren's Syndrome (pSS). We aimed to evaluate and compare the pulmonary involvement patterns, respiratory parameters, clinical, radiological, pathological, and laboratory features, disease activity scores, treatment choices, and the relationships between these findings at diagnosis in pSS patients with and without pulmonary involvement. *Methods:* Patients at Ankara Ataturk Sanatorium Training and Research Hospital were included in the analysis. Patients with ILD who met the classification criteria were included as the study group. Patients who met the SS classification criteria but had no findings in the lungs were included as the control group. *Results:* The median disease duration of ILD patients included in the study was 9.98 months. In pSS patients, patients with ILD had demographic (older age, male gender, more frequent smoking), symptomatology (frequent dry eyes), auto-antibody positivity (more frequent antinuclear antibodies (ANA), anti-Sjögren's Syndrome-related antigen A (SS-A), anti-Sjögren's Syndrome-related antigen B (SS-B)), higher disease activity and more frequent immunosuppressive use. When patients with pSS and ILD were compared according to high resolution computed tomography (HRCT) uptake pattern as nonspecific interstitial pneumonia (NSIP) (fibrotic or not) and unclassified, there were more male gender, lower forced vital capacity (FVC) values, and more frequent immunosuppressive and anti-fibrotic use in the NSIP group. When patients with ILD were classified according to gender, males had more smoking, SSB positivity, fibrotic NSIP, and lower FVC and diffusing lung capacity for carbon monoxide (DLCO) values. *Conclusion:* A multidisciplinary approach involving pulmonologists, radiologists, and rheumatologists who are experts in ILD is important to increase diagnostic reliability. Pulmonary involvement in pSS is an important cause of morbidity and mortality and should be managed more carefully in male patients.

Key words: Sjögren's Syndrome, pulmonary involvement, interstitial lung disease, antifibrotic therapies

Introduction

Primary Sjögren's Syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands and sicca symptoms (1). The disease is prevalent among middle-aged women, with a prevalence rate ranging from 0.1% to 4.8% and a female-to-male ratio of 9:1 (2). Pulmonary

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involvement primarily includes interstitial lung disease (ILD), small airway disease, and bronchus-associated lymphoid tissue lymphoma (3). The true prevalence of ILD in patients with pSS remains a subject of debate and varies significantly across different studies (4), with the most recent literature indicating a prevalence of approximately 20% (5). High resolution computed tomography (HRCT) is considered the gold standard imaging modality for diagnosing ILD in patients with pSS (6). Radiologically, the most observed patterns include nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia, lymphocytic interstitial pneumonia (LIP), and organizing pneumonia (OP). In addition to these patterns, ground-glass opacities, bronchiectasis are also observed (7). In advanced forms of the disease, fibrosis develops in the lungs. It is known that the presence of ILD increases morbidity and mortality (8). The early detection of ILD is of great importance. Because imaging evaluation in pSS can vary among clinicians and patient-specific heterogeneity can make the diagnosis of lung involvement challenging. While lung involvement may be a subclinical, non-progressive disease that does not require specific treatment in some patients, it is rapidly progressive in others and can lead to death. Therefore, identifying predictors that can identify progressive lung involvement at diagnosis is a critical clinical need, as these patients will require more accurate lung screening and more aggressive treatment. The current literature contains some controversial data regarding the incidence of lung involvement and the factors associated with the development of serious complications. These concerns may partly explain why lung involvement in pSS patients remains a significant challenge, leading to increased morbidity and mortality (9). Therefore, it is important to evaluate pSS with and without lung involvement, which constitute two different subsets. In our study, we aimed to evaluate and compare the pulmonary involvement patterns, respiratory parameters, clinical, radiological, pathological, and laboratory features, disease activity scores, treatment choices, and the relationships between these findings at diagnosis and follow-up in pSS patients with and without pulmonary involvement.

Methods

Patient selection

107 patients with ILD diagnosis who were referred from the Chest Diseases Clinic of Ankara Ataturk Sanatorium Training and Research Hospital to the Rheumatology Clinic between December 1, 2023 and December 1, 2024 and who met the SS classification criteria were included in the study. Our hospital has been a reference center for chest diseases since 1953. Patients with smoking-related ILD or hypersensitivity pneumonia based on clinical findings and lung HRCT results were excluded. 107 patients who met the SS classification criteria but had no findings in the lungs were included as the control group.

Diagnosis and evaluation of Sjögren's syndrome

Patients' demographic characteristics, such as age, gender, smoking history at any time, comorbidities were recorded. The following queries were made for the diagnosis of SS: dryness complaints, Schirmer test (≤ 5 mm was considered significant), autoantibodies, complement levels, salivary gland biopsy (focus score ≥ 1 and/or grade ≥ 3 was considered significant). Constitutional symptoms, musculoskeletal findings, skin findings and organ involvement were also noted. To determine SS activity, the parameters of EULAR Sjögren's syndrome disease activity index (ESSDAI) were recorded (10). Clinical organ involvement of the patients was evaluated according to ESSDAI. For example, Hematological involvement: For anemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered exclusion of vitamin or iron deficiency, drug-induced cytopenia and Muscular domain involvement: Diagnosis of myositis should be made on the association of clinical symptoms (muscular pain or weakness) and/or CK elevation and either muscular involvement confirmed by needle detection on EMG, by diffuse inflammation on MRI and/or active myositis on biopsy. Therefore, having one positive examination among EMG, MRI or biopsy is mandatory, but all are not necessary. It was noted whether the patients met the American College of Rheumatology (ACR)- European League Against Rheumatism (EULAR) 2016 and ACR 2012 SS classification criteria. Only those meeting the ACR-EULAR 2016 criteria were included in the study. (Patients with isolated SSB positivity had negative SSA but positive minor salivary gland biopsy and Schirmer test. According to the ACR-EULAR 2016 classification criteria for Sjogren's disease, they scored 4 points or higher and were diagnosed with pSS. Furthermore, these patients had accompanying clinical findings

such as sicca symptoms, arthralgia, and arthritis, which would suggest a diagnosis of pSS.). Antinuclear antibodies (ANA), Rheumatoid factors (RF), anti-cyclic citrullinated peptide (anti-CCP), anti-Sjögren's Syndrome-related antigen A (Anti-SSA), anti-Sjögren's Syndrome-related antigen B (Anti-SSB), and complement levels were noted. RF was measured by turbidimetry and values greater than limit of normal (ULN) (14 IU/mL) were considered abnormal. Anti-CCP was measured by enzyme-linked immunosorbent assay (ELISA) and values greater than ULN (20 U/mL) were considered positive. ANA was performed by indirect immunofluorescence (IIF) technique using HEp-2 cells at both 1:100 and 1:320 dilutions and fluorescence patterns and intensity were noted. For the ANA value, values of 1:1000 dilutions and above were considered strongly positive. Anti-SSA and anti-SSB were measured by ELISA and values greater than ULN (15 U/mL) were considered positive. Extractable nuclear antigen (ENA) test was performed by immunoblot technique according to the manufacturer's instructions (Euroimmun, Germany).

Evaluation of pulmonary involvement

Definition of SS and pulmonary involvement: regardless of the presence of pulmonary symptoms, it was deemed mandatory that an abnormality be present on lung HRCTs to classify SS patients as having pulmonary findings.

HRCT findings: Patients' initial HRCT findings were evaluated by two different chest disease specialists and a radiology expert, and a decision was reached by consensus. Pulmonary involvement patterns were categorized as NSIP, Fibrotic NSIP, OP, and LIP. Images that did not conform to any pattern were grouped as unclassifiable. On HRCT, the involved region (lower, middle, upper lobes), distribution (diffuse, two lobes, single lobe), and pattern of involvement (accentuation of interstitial markings, ground-glass opacity, reticular pattern, honeycombing, interlobular septal thickening, cyst, traction bronchiectasis, consolidation, nodule) were noted.

Other evaluations of ILD: Patients were asked about pulmonary symptoms. The presence or absence of persistent cough and dyspnea was noted. The patients' respiratory function test (PFT) were noted, with ratios of forced vital capacity (FVC), forved expiratory volume (FEV1), FEV1/FVC and diffusing lung capacity for carbon monoxide (DLCO) were recorded. Classification of subgrouping were made according to the ESSDAI grouping, with FVC cut off being given as above 80, between 60 to 80 and below 60 percent, and DLCO cut off being given as above 70, between 40 to 70, and below 40 percent. Obstructive and restrictive pattern evaluation were made accordingly to the cut off of FEV1/FVC of 70%. For patients' undergone bronchoscopy, videothorascopy or endobronchial ultrasonography; the results of any bronchoalveolar lavage results were noted, with cell distribution reported from either pathology reports or from flow cytometry evaluation.

Treatment for SS and pulmonary involvement: Immunosuppressive (Mycophenolate Mofetil (MMF), Azathioprine, Glucocorticoids, Hydroxychloroquine) and antifibrotic (Nintedanib) therapies that were newly initiated or were in use due to pulmonary involvement were recorded.

Our study was in accordance with the 2013 amendment of the Helsinki declaration and ethical approval was obtained from Health Sciences University Ankara Atatürk Sanatorium Training and Research Hospital Institutional Review Board (2024-BÇEK/157, 23/10/2024).

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows, Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). The distribution of parameters was evaluated by Q-Q plots as graphical confirmation and by the Kolmogorov-Smirnov test. Results with parametric distribution were given as mean and standard deviation (SD), while nonparametric results were given with median and 25^{th} to 75^{th} percentiles. Categorical data comparisons were made with the Chi-Square or Fisher Test when appropriate and given with frequencies and percentages. Comparison of scale parameters was made by independent samples T test or Mann-Whitney U test according to distribution pattern. P values of or below 0.05 were accepted as statistically significant. Parameters that were deemed statistically significant in analyses were then evaluated by binomial regression analysis to investigate independent factors and their role between groups. Regression model validity was confirmed by the Omnibus test, and model reliability and goodness of fit were evaluated by the Hosmer and Lemeshow test.

Results

General characteristics

Of the patients enrolled in the study, 80.4% were female. The median age was 62 years. The median disease duration for pSS was 7.86 months. 30.4% patients had a history of smoking. The median disease duration for ILD was 9.98 months. The characteristics of patients with and without ILD in pSS are shown in Table 1. In patients with and without ILD among those with pSS, the following were determined: fatigue/lethargy (43% vs 27.1%, p=0.015), weight loss (23.4% vs 2.8%, p<0.001), arthralgia (79.4% vs 83.2%, p=0.48), myalgia (38.3% vs 87.9%, p<0.001), morning stiffness (63.5% vs 63.5%, p=1), arthritis (18.7% vs 19.6%, p=0.86), urticaria (1.9% vs 7.5%, p=0.05), photosensitivity (18.7% vs 3.7%, p=0.001). When the positivity of the extraglandular domains included in the ESSDAI was evaluated individually in patients with and without ILD, respectively; renal domain (22 (20.6%) vs 15 (14%), p=0.2), muscular domain (6.5% vs 7.5%, p=0.78), articular domain (88 (82.2%) vs 89 (83.2%), p=0.85), hematological domain (22 (20.6%) vs 15 (14%), p=0.2), cutaneous domain (24%) (22.4%) vs 12 (11.2%), p=0.02), peripheral nervous system domain (3 (2.8%) vs 8 (7.5%), p=0.12), constitutional domain (25 (23.4%) vs 3 (2.8%), p<0.001), biological domain (2 (1.9%) vs 2 (1.9%), p=1). ANA was found to be negative in 7 patients with ILD-pSS. Of the 100 patients with positive ANA values, 9 (9%) had homogeneous pattern positivity, 86 (86%) had nuclear speckled pattern positivity, 4 (4%) had nucleolar pattern positivity, and 1 (1%) had nuclear topo-1-like pattern positivity. ANA was found to be negative in 38 patients without ILD-pSS. Of the 69 patients with positive ANA values, 5 (7.2%) had homogeneous pattern positivity, 54 (78.3%) had nuclear speckled pattern positivity, 10 (14.5%) had nucleolar pattern positivity. When the two groups were compared, there was no statistically significant difference between the ANA patterns (p=0.08).

A binomial regression model was performed to investigate the role of separate parameters in validating any independent risk factors. The model included parameters deemed statistically significant in the former analysis; however, it excluded ESSDAI and treatment modalities due to multilinearity and collinearity in the case of ESSDAI and the nature of the treatment modalities being reliant on the diagnosis of ILD. The model also included parameters separate if a grouping was present, such as having dry eye and dry mouth as separate parameters rather than grouped under one. The model was statistically significant (chi-square 175.154 and p-value of 0.001 in omnibus test), had a high Nagelkerke R square (0.730), had a good fit for the data (Hosmer and Lemeshow test result of 0.730) and predicted 87.9% of the patients regarding ILD diagnosis (Table 2). In the regression model, gender (male), smoking history, dry eye, Anti-SSA and dyspnea or coughing presence were independent risk factors for ILD presence among patients diagnosed with pSS (p values of 0.001, 0.012, 0.001, 0.044 and 0.002, respectively). Dry mouth, however, was observed to be a negative predictive factor, as patients with dry mouth had a predisposition to pSS without ILD (p-value of 0.001) (Table 2).

Results according to HRCT pattern in patients with pSS and pulmonary involvement

In patients with ILD, the distribution of HRCT pulmonary involvement patterns was as follows: cellular NSIP 33 (30.8%), fibrotic NSIP 19 (17.8%), OP 2 (1.9%), LIP 1 (0.9%), unclassifiable 52 (48.6%). According to the region involved on HRCT, the lower lobe was involved in 81 (75.7%), the middle lobe in 21 (19.6%), and the upper lobe in 21 (19.6%); in terms of distribution, diffuse involvement was observed in 9 (8.4%), two lobes in 22 (20.6%), and a single lobe in 76 (71%); regarding the pattern of involvement, accentuation of interstitial markings was noted in 84 (78.5%), ground-glass opacity in 78 (72.9%), reticular pattern in 70 (65.4%), honeycombing in 26 (24.3%), interlobular septal thickening in 69 (64.5%), cyst in 8 (7.5%), traction bronchiectasis in 39 (36.4%), consolidation in 13 (12.1%), and nodules in 28 (26.2%). When comparing pSS with ILD patients according to HRCT involvement pattern, categorized as NSIP (fibrotic or non-fibrotic) and unclassifiable, the NSIP group had a higher proportion of males, lower DLCO and FVC values, and more frequent use of MMF, glucocorticoids, and antifibrotic agents. Dry eyes and positive Schirmer test positivity were more frequent in the unclassifiable group (Table 3). Two patients with an OP pattern and one patient with a LIP pattern (n=1) were not included in the analysis.

Table 1. Comparison of SS with and without ILD

			All Patients 214 (%100)	Patients with ILD 107 (%50)	Patients without ILD 107 (%50)	P- Value
Demographic findings and comorbidities	Age		62 (30-86)	63 (46-81)	60 (30-86)	0.010
	Gender (Female)		172 (80.4)	74 (69.2)	98 (91.6)	<0.001
	SS disease duration (months)		7.86 (0.07-299)	6.30 (0.07-227.2)	9.82 (2.23-299)	0.039
	Smoking history		65 (30.4)	49 (45.8)	16 (15)	<0.001
	Hypertension		57 (26.6)	32 (29.9)	25 (23.4)	0.279
	Diabetes Mellitus		22 (10.3)	9 (8.4)	13 (12.1)	0.368
	Coronary Artery Disease		18 (8.4)	14 (13.1)	4 (3.7)	0.014
	Chronic Renal Failure		8 (3.7)	6 (5.6)	2 (1.9)	0.28
	COPD/Asthma		26 (12.1)	23 (21.5)	3 (2.8)	<0.001
Clinical Findings of SS	Dry Eyes		118 (55.1)	89 (83.2)	29 (27.1)	<0.001
	Dry Mouth		155 (72.4)	67 (62.6)	88 (82.2)	0.001
	Schirmer Positivity		195 (91.1)	99 (92.5)	96 (89.7)	0.471
Salivary Gland Biopsy	Focus Score ≥ 1 or Grade ≥ 3		154 (94.5)	75 (90.4)	79 (98.8)	0.02
Auto-antibodies	ANA		169 (79)	100 (93.5)	69 (64.5)	<0.001
	RF		48 (22.4)	25 (23.4)	23 (21.5)	0.743
	Anti-SSA		112 (52.3)	65 (60.7)	47 (43.9)	0.014
	Anti-SSB		45 (21)	30 (28)	15 (14)	0.012
	Anti-SSA or SSB*		125 (58.4)	73 (68.2)	52 (48.6)	0.004
	Hypocomplementemia		4 (1.9)	2 (1.9)	2 (1.9)	1.0
ESSDAI Median (min-max)	ESSDAI		12 (0-51)	19 (5-51)	6 (0-25)	<0.001
	ESSDAI (excluding lung)		6 (0-36)	8 (0-36)	6 (2-25)	0.003
	ESSDAI (excluding lung)	low-modarete	171 (79.9)	80 (74.8)	91 (85.0)	0.061
		high	43 (20.1)	27 (25.2)	16 (15)	
	ESSDAI (excluding lung)	low	66 (30.8)	23 (21.5)	43 (40.2)	0.008
		modarete	105 (49.1)	57 (53.3)	48 (44.9)	
		high	43 (20.1)	27 (25.2)	16 (15)	
Pulmonary Symptoms	Persistent Cough		38 (17.8)	29 (27.1)	9 (8.4)	0.001
	Shortness of Breath		39 (18.2)	37 (34.6)	2 (1.9)	<0.001
	Cough or Shortness of Breath		54 (25.2)	43 (40.2)	11 (10.3)	<0.001
Treatments	Mycophenolate Mofetil		42 (19.6)	38 (35.5)	4 (3.7)	<0.001
	Azathioprine		31 (14.5)	30 (28)	1 (0.9)	<0.001
	Glucocorticoid		110 (51.4)	79 (73.8)	31 (29)	<0.001
	Hydroxychloroquine		177 (82.7)	82 (76.6)	95 (88.8)	0.19
	Antifibrotic		19 (8.9)	19 (17.8)	0 (0)	<0.001

With the term "Anti-SSA or Anti-SSB," we intended to express isolated Anti-SSA, isolated Anti-SSB, or both positivity. Isolated Anti-SSB positivity was present in 7 patients in the ILD-pSS group and 4 patients in the non-ILD pSS group.

Another regression model was made regarding NSIP (fibrotic or not) grouping and assessing any independent risk factor. In this model, patients diagnosed with NSIP were compared to those without any subgrouping, in which the model was observed to be statistically significant (chi-square 72.273 and p-value of 0.001), had an acceptable Nagelkerke R square (0.668), was a good fit for the data (Hosmer

Table 2. Binomial regression analysis for interstitial lung disease presence

Parameters	B	S.E.	Wald	P-Value	Odds Ratio	95% C.I. for Odds Ratio	
						Lower	Upper
Sjogren Disease Duration	0.009	0.006	2.143	0.143	1.009	0.997	1.020
Gender	-2.918	0.752	15.053	0.001	18.518	0.012	0.236
Smoking History	-1.350	0.537	6.324	0.012	3.861	0.091	0.742
Myalgia	2.490	0.542	21.070	0.001	12.063	4.166	34.934
Dry Eye	-3.908	0.666	34.443	0.001	50	0.005	0.074
Dry Mouth	2.639	0.678	15.167	0.001	13.999	3.709	52.831
Anti-SSA	-1.029	0.510	4.066	0.044	2.80	0.131	0.972
Dyspnea and/or Coughing	-2.041	0.653	9.765	0.002	7.69	0.036	0.467

Abbreviations: C.I: Confidence Interval, S.E: Standard Error.

Table 3. Comparison of pSS with ILD patients according to HRCT involvement pattern

		NSIP (fibrotic or non-fibrotic) 52 (50%)	Unclassifiable 52 (50%)	P-Value
Gender (Male)		21 (40.4)	11 (21.2)	0.03
Dry Eyes		39 (75)	47 (90.4)	0.03
Schirmer Positivity		45 (86.5)	51 (98.1)	0.02
Respiratory Function Test	DLCO	75 (23–122)	88.5 (26–128)	0.01
	FVC	80.5 (42–133)	89 (58–138)	0.06
Treatments	MMF	26 (50)	9 (17.3)	<0.001
	Glucocorticoids	45 (86.5)	31 (59.6)	0.002
	Antifibrotic agents	19 (36.5)	0 (0)	<0.001

and Lemeshow test result of 0.242) and predicted 86.5% of the patients according to possible NSIP classification. The model consisted of parameters evaluated in the former evaluation, radiological findings that could be attributed to ILD, and treatment modalities. The analysis revealed that ground glass opacity was the sole statistically significant parameter (p-value 0.001). Regarding classification according to DLCO subgrouping, there were no statistical differences between groups (Table 4). Bronchoscopy was performed in 26 patients; bronchoalveolar lavage (BAL) cytology was obtained in 22, BAL biochemistry (lymphocyte cell predominance) in 17, and BAL pathology results in 7. Video-assisted thoracic surgery (VATS) was performed in 5 patients, and Endobronchial Ultrasonography (EBUS) in 3 patients.

Distribution of SS and ILD according to gender

Among patients with SS and ILD, 33 (30.8%) were male. Male patients had a higher prevalence of smoking [22 (66.7) vs 27 (36.5), p=0.004]. Fatigue [38 (51.4) vs 8 (24.2), p=0.009] was more frequent in females, and anti-SSB positivity [14 (42.4) vs 16 (21.6), p=0.02] was more common in males. Middle lobe involvement [19 (25.7) vs 2 (6.1), p=0.01] was more frequent in females. Honeycombing [14 (42.4) vs 12 (16.2), p=0.004], traction bronchiectasis [18 (54.5) vs 21 (28.4), p=0.009] and fibrotic NSIP [11 (33.3) vs 8 (10.8), p=0.005] were more frequent in males, whereas the unclassifiable group [42 (56.8) vs 12 (36.4), p=0.05] was more frequent in females. Male patients had lower FVC [85 (57–133) vs 90.5 (42–147), p=0.04] and DLCO [78 (23–105) vs

Table 4. Respiratory function test comparison according to underlying interstitial lung disease

Parameters		NSIP (Fibrotic and non-fibrotic) n (%)	Uncategorized n (%)	Total Count	P- Value
Respiratory Function Test Evaluation	*Obstructive*	4 (57.1)	3 (42.9)	7	0.158
	Restrictive	15 (68.2)	7 (31.8)	22	
	Normal	21 (43.8)	27 (56.3)	48	
Forced Vital Capacity (%)	Below 60	4 (0.67)	2 (0.33)	6 (100)	0.054
	Below 80	14 (0.7)	6 (0.3)	20 (100)	
	Above 80	17 (0.4)	26 (0.6)	43 (100)	
	Below 60	24 (0.73)	9 (0.27)	33 (100)	0.006**
	Above 60	18 (0.4)	27 (0.6)	45 (100)	
Diffusing Capacity of the Lung for Carbon Monoxide (%)	Below 40	4 (0.8)	1 (0.2)	5 (100)	0.003*
	Below 70	12 (0.86)	2 (0.14)	14 (100)	
	Above 70	19 (0.4)	29 (0.6)	48 (100)	
	Below 70	16 (0.84)	3 (0.16)	19 (100)	0.002*
	Above 70	19 (0.4)	29 (0.6)	48 (100)	
	Below 40	4 (0.8)	1 (0.2)	5 (100)	0.196
	Above 40	31 (0.5)	31 (0.5)	62 (100)	

The Chi-square test was used to compare the groups. * The Values compared could not be evaluated due to inadequate patient distribution. ** The Comparison was made using Fisher's Exact T-test.

88 (38–128), p=0.005] values. The use of MMF [16 (48.5) vs 22 (29.7), p=0.06] and antifibrotic agents [11 (33.3) vs 8 (10.8), p=0.005] was more frequent in males.

Distribution of pulmonary findings according to autoantibody status in SS and ILD

Patients were also compared in terms of pulmonary findings according to their autoantibody status. The HRCT findings were similar in those with strongly and weakly positive ANA, RF positive or negative, anti SSA/SSB positive and negative. However, cough, dyspnea, and cough or dyspnea were more frequent in patients with RF-positive patients. With this cough and cough or dyspnea were more frequent in patients with strongly positive ANA patients. No difference was found based on SS-A/SS-B antibody positivity. While patients with strongly positive ANA had higher FVC and DLCO values, there was no difference between groups based on RF or SS-A/SS-B antibody positivity. The use of azathioprine was more frequent in the strongly ANA-positive group and the RF-positive group, while the use of glucocorticoids was more frequent in the strongly ANA-positive group and the SS-A/SS-B antibody positive group (Table 5).

Patients' findings according to ESSDAI score

In our study, the ESSDAI score was found to be higher in the ILD group compared to the non-ILD group. When all patients were divided into two groups as low-moderate and high according to ESSDAI scores (excluding pulmonary involvement), fatigue [21 (48.8%) vs 54 (31.6%), p=0.03], weight loss [14 (32.6%) vs 14 (8.2%), p<0.001], photosensitivity [12 (27.9%) vs 12 (7%), p=0.000] and dermatological involvement [15 (34.9%) vs 21 (12.3%), p=0.000] were seen to be more frequent in the high group. In addition to this when ILD patients were divided into two classes as low-modarete and high according to ESSDAI scores (excluding pulmonary involvement), weight loss [13 (48%) vs 12 (15%), p<0.001], dermatological involvement [13 (48%) vs 11 (13.8%), p<0.001] and photosensitivity

Table 5. Comparison of pSS with ILD patients according to autoantibody status

		ANA			RF			Anti SS-A/SS-B		
		Strongly Positive 43 (43)	**Weakly Positive 57 (57)**	**P-Value**	**Positive 25 (23.4)**	**Negative 82 (76.6)**	**P-Value**	**Positive 73 (68.2)**	**Negative 34 (31.8)**	**P-Value**
Pulmonary Symptoms	Cough	17 (39.5)	11 (19.3)	0.02	10 (40)	19 (23.2)	0.09	20 (27.4)	9 (26.5)	0.92
	Dyspnea	19 (44.2)	18 (31.6)	0.19	13 (52)	24 (29.3)	0.03	29 (39.7)	8 (23.5)	0.1
	Cough or Dyspnea	23 (53.5)	19 (33.3)	0.04	14 (56)	29 (35.4)	0.06	33 (45.2)	10 (29.4)	0.12
Respiratory Function Test	FVC	94 (57–138)	82 (42–147)	0.04	78 (42-118)	88 (54-147)	0.37	87 (57-147)	89 (42-133)	0.58
	DLCO	91 (38–122)	82 (23–128)	0.05	82.5 (26-128)	83 (23-128)	0.3	87 (23-128)	79 (26-128)	0.88
Treatments	Mycophenolate Mofetil	12 (27.9)	22 (38.6)	0.26	9 (36)	29 (35.4)	0.95	25 (34.2)	13 (38.2)	0.68
	Azathioprine	19 (44.2)	11 (19.3)	0.007	11 (44)	19 (23.2)	0.04	24 (32.9)	6 (17.6)	0.1
	Glucocorticoid	38 (88.4)	38 (66.7)	0.01	20 (80)	59 (72)	0.42	59 (80.8)	20 (58.8)	0.01
	Antifibrotic	5 (11.6)	12 (21.1)	0.21	4 (16)	15 (18.3)	0.79	15 (20.5)	4 (11.8)	0.26

[12 (44.4%) vs 8 (10%), p<0.001] were more common in the high group. When the patients in the ILD group were divided into two groups as moderate and high ESSDAI scores without excluding lung involvement, weight loss [24 (27.3%) vs 1 (5.3%), p=0.04], shortness of breath [36 (41%) vs 1 (5.3%), p=0.003], cough [28 (31.8%) vs 1 (5.3%), p= 0.018], dry mouth [60 (68.2%) vs 7 (36.8%), p<0.001], photosensitivity [20 (22.7%) vs 0 (0%), p=0.02], dermatological involvement [24 (27.3%) vs 0 (0%), p=0.01] were more frequent in the high group. However, smoking [46 (52%) vs (3 (15.8%), p<0.001] was more common in the high group, while there was no difference between gender and age.

Discussion

In our study, we found that male gender, smoking history, dry eyes, anti-SSA, and the presence of dyspnea and/or cough were independent risk factors for the presence of ILD in patients diagnosed with pSS. However, patients with dry mouth were predisposed to pSS without ILD. Furthermore, while in the normal population 10% or less of pSS patients are male, in our cohort, the presence of pulmonary involvement increases the male proportion to up to 30%. In our cohort, all 107 pSS patients with ILD were cases referred from the chest diseases outpatient clinic with an ILD diagnosis, and the pSS diagnosis was made after the ILD diagnosis. In earlier studies, the frequency of ILD in pSS was associated with disease duration and was defined as a late finding (11). Newer studies have shown that ILD can develop in 10% to 51% of patients with pSS, in 10% of cases even years before the pSS diagnosis, concurrently with other systemic findings of pSS, and in the remaining portion, in the late stage of the disease (5). Additionally, it has been reported that pSS with a non-sicca initial presentation is associated with older age and male gender (12). In a meta-analysis, pSS patients with ILD were older than those without ILD, with an average age difference of 9.25 years across six studies. Additionally, ILD was associated with male gender with an OR of 1.92 (4). In another meta-analysis, the ages of pSS-ILD patients ranged from 55 to 61 years, and the male-to-female ratio was 2:8 (5). Consistent with the literature, in our study the ILD patient group was older, had a higher prevalence of male gender, and a higher rate of smoking. When patients in our study were classified according to gender, male patients were more frequently smokers and had a higher rate of SSB positivity. In the literature, two studies have shown that the positivity of serum anti-La/SSB antibodies is higher in male patients compared to females (13,14). In line with our cohort, the literature has shown that fatigue is more frequently observed in female SS patients (15,16). Furthermore, in male patients, honeycombing, traction bronchiectasis, and fibrotic NSIP were more frequent, FVC and DLCO values were lower, and the use of MMF and antifibrotic agents was higher. In other words, a more fibrotic course is observed in males, and SFT follows a worse course. This situation is also reflected in treatment decisions, and MMF and antifibrotic agents have been more frequently preferred in male patients. In other words, males generally tend to develop a more severe interstitial lung disease (17). Studies have shown that the majority of pSS-ILD patients are symptomatic (18). Among the most frequently observed symptoms are exertional dyspnea in 30–40% and dry cough in 40–50% (1). However, the most concerning aspect is that ILD can occur in pSS patients in the early stages without causing any respiratory symptoms. In a retrospective study conducted in China, only 41 out of 66 pSS-ILD patients (62.1%) had respiratory symptoms (19). In our study, approximately half of the patients exhibited cough and/or dyspnea. Furthermore, when comparing the pulmonary findings according to autoantibody status in our cohort, we found that patients with strongly positive ANA and RF positivity had cough and dyspnea more frequently. In our study, dry eyes were more frequent in the ILD group, whereas myalgia and dry mouth were more common in the non-ILD group. It has been reported that pSS patients presenting with ILD generally exhibit milder sicca symptoms (possibly overshadowed by respiratory symptoms) yet display a similar rate of positive anti-Ro compared to pSS patients with a classic sicca onset (20). In addition, studies comparing pSS patients with and without ILD have demonstrated that the rate of anti-Ro52 positivity in the pSS-ILD group is significantly higher than in the non-ILD group (21,22). However, in a recently conducted study, the anti-SSB antibody was found more frequently in pSS-ILD patients compared to patients without ILD (23). In our study, a higher rate of anti-SSA and SSB positivity was also detected in the ILD group. Contrary to these findings, this relationship was not observed in another observational study that

only analyzed the prevalence of anti-SSA, and the importance of evaluating anti-Ro60 and anti-Ro52 autoantibodies separately was emphasized (24-26). In conclusion, the data regarding the relationship between the presence of anti-Ro/SSA antibodies and pSS-ILD are controversial, and this relationship should be elucidated. Additionally, in a cohort investigating risk factors associated with the development of pSS-ILD, ANA and RF positivity were found to be risk factors (27). In our study, ANA positivity was also detected at a higher rate in the ILD group. However, one study showed that globulin levels were higher in patients with pSS-LIP compared to patients with pSS-ILD. When globulin, immunoglobulin IgG, RF, and ESR levels increased and the albumin/globulin ratio decreased, alveolar capillary membrane damage was more severe and DLCO decreased more significantly. Furthermore, positivity rates for ANA, anti-SSA52KD antibody, anti-SSA60KD antibody, and anti-SSB antibody were higher in patients with pSS-LIP compared to patients with pSS-ILD (28). These findings suggest that autoantibody levels may differ even among ILD subgroups. This supports the controversial results of studies in the literature. As a result of all these findings, we can say that ILD may be present years before the diagnosis of pSS. These patients are usually seronegative with mild sicca symptoms. In seronegative patients with mild or no sicca symptoms, recognizing underlying pSS can be challenging. All patients at risk should undergo a complete diagnostic evaluation, including a minor salivary gland biopsy and, in some cases, a lung biopsy (29). In our cohort, the most common HRCT pattern was NSIP. A meta-analysis has shown that NSIP is the most frequently observed pattern with a pooled prevalence of 52% (CI: 41–64) (9). In our study, cellular NSIP was observed more frequently than fibrotic NSIP, whereas in the literature there are studies reporting fibrotic NSIP to be much more common than cellular NSIP (ratios ranging from 19:1 to 19:3) (30,31). The NSIP pattern is characterized histologically by uniformly distributed fibrosis and interstitial inflammation of variable intensities. The architecture of the lungs is often retained. In patients with Sjögren's syndrome, the lung structure often remains largely intact. Although honeycombing is uncommon, interstitial fibrotic regions associated with dilated airspaces can lead to the development of traction bronchiectasis. This fibrotic manifestation represents the most frequently encountered pattern of NSIP in these individuals (30). These histopathological changes produce a characteristic appearance on chest CT, typically showing bilateral, symmetric reticular opacities in the lower lung zones, accompanied by traction bronchiectasis and peri-bronchovascular distribution. Ground-glass opacities are commonly seen, while subpleural sparing and pulmonary consolidations are less frequently observed (32). On imaging, UIP is characterized by bilateral intralobular reticulation, often associated with traction bronchiectasis and scattered small cysts. These findings predominantly affect the basal and peripheral lung regions and exhibit a temporally heterogeneous distribution (33). These CT abnormalities help distinguish NSIP from UIP. In our cases, the presence of honeycombing was consistent with fibrotic NSIP in 19 of 26 patients. 7 did not fully conform to any pattern. In accordance with the literature, which shows that an indeterminate radiological pattern can be seen in up to 40% of pSS patients, approximately half of the patients in our study constituted an unclassifiable group that did not fit a definite radiological pattern (30). Although LIP is classically associated with pSS, it is observed in only 4–9% of cases (31). In our study, LIP was identified in only 1 patient and an OP pattern in 2 patients. The most common radiological findings in pSS-ILD are ground-glass opacities, reticular abnormalities, consolidation, honeycombing, cysts, and nodules (34,35). In our cohort, consistent with the literature, the most frequently observed abnormalities were ground-glass opacities and accentuation of interstitial markings. Even in the absence of symptoms on PFTs, restrictive respiratory failure characterized by decreased FVC, decreased FEV1, and decreased DLCO is observed (3). In our cohort, approximately half of the patients did not show a restrictive or obstructive pattern. However, in our cohort, in a regression analysis comparing the NSIP and unclassifiable groups, when evaluated in terms of FVC using a cutoff value of 60%, a greater number of patients in the NSIP group were found to have an FVC below 60%. However, at the onset of ILD, a decreased DLCO may be observed in conjunction with a preserved FVC (36). In our study, among 42 patients with preserved FVC, 6 had a low DLCO value. In our study, the ESSDAI score was found to be higher in the ILD group compared to the non-ILD group. In one study, in multivariate analysis, the baseline ESSDAI ($p = 0.05$) was identified as an in-

dependent predictor of ILD development (20). In addition to this we can conclude that constitutional symptoms such as weight loss and fatigue, photosensitivity and dermatological involvement are generally more common in the high group according to ESSDAI. Due to the high variability in the clinical onset and histopathological subtypes of ILD, an optimal treatment regimen for pSS-ILD has not yet been established. In asymptomatic patients with normal PFTs and with mild or non-progressive involvement on HRCT, a "watch and wait" strategy may be acceptable. In severe or progressive cases, immunosuppressive treatment in combination with steroids is recommended as first-line therapy (37). MMF and azathioprine are currently accepted as first-line agents. In cases of predominant inflammation, second-line immunosuppressive therapy is recommended with rituximab or calcineurin inhibitors or cyclophosphamide, while antifibrotic agents are primarily recommended for patients with progressive fibrosis (38). The INBUILD® study compared the efficacy and safety of nintedanib with placebo in reducing the progression of lung fibrosis in patients diagnosed with ILD, including those with connective tissue diseas (other than idiopathic pulmonary fibrosis) who had widespread progressive fibrosis. Patients treated with nintedanib exhibited a lower rate of decline in FVC (39). We also applied glucocorticoid and MMF treatment most frequently to our patients. Approximately 18% of our patients were treated with nintedanib. A limitation of our study is that, due to its retrospective nature, the PFT values of some patients could not be obtained. The absence of a separate evaluation of anti-SSA (60kD and 52kD) is another limitation of the study. Nevertheless, we plan to examine disease progression, treatment responses, and the factors influencing them in a larger cohort with a longer follow-up period. In conclusion, a multidisciplinary approach involving pulmonologists, radiologists, and rheumatologists who are experts in ILD is important in order to increase diagnostic reliability. While pSS generally carries a low risk of mortality, the presence of ILD is associated with an increased risk of death with a relative risk of 2.54 (40). Therefore, new research is needed regarding the prevalence and improved management of ILD in pSS. In summary, pulmonary involvement in pSS is an important cause of morbidity and mortality and should be managed more carefully in male patients.

Key messages

1. It is recommended that patients with Primary Sjögren's Syndrome (pSS) interstitial lung disease (ILD) be evaluated in multidisciplinary councils with pulmonologists, radiologists, and rheumatologists specialized in ILD, held in specialized centers in order to increase the reliability of diagnosis and treatment.
2. The presence of pSS ILD is associated with increased risk of morbidity and mortality; early detection of ILD is crucial and should be managed carefully.
3. Male gender, smoking history, dry eye, anti-Sjögren's Syndrome-related antigen A (Anti-SSA) and the presence of dyspnea and/or cough are independent risk factors for the presence of ILD in pSS patients. Male patients in particular should be managed more carefully.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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