THE EVALUATION OF LUNG INVOLVEMENT AND FUNCTIONAL CAPACITIES IN PATİENTS DİAGNOSED WITH PRIMARY SJOGREN'S SYNDROME

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Abstract

ABSTRACT Introduction: Sjögren syndrome is a chronic, systemic, inflammatory disease characterized with lymphocytic infiltration of the exocrine glands, frequently manifested by dryness in the region affected. Although the most common extraglandular involvement in SS is pulmonary involvement. Early diagnosis and treatment is considered to be important. It was aimed to evaluate the frequency of early lung involvement, high resolution computed tomography (HRCT) findings and data of pulmonary function test (PFT) in SS in this study. Material-Method: Thirty five patients diagnosed with SS and referred by the Department of Rheumatology to determine potential lung involvement to the 8th chest diseases outpatient clinic of our hospital between September 2015 and December 2018 were included in this study. Respiratory signs, demographic features, length of disease and treatment regimens, PFT, data of 6-minute walk test (MWT) and findings of HRCT of the patients were retrospectively obtained from hospital information system and patient files. Results: The mean age of the patients was 54.4 ± 9.2. The majority of the patients were women (94.3%). When the HRCT findings were evaluated, 28 (80%) patients had CT findings, while 7 (20%) patients had no CT findings. The most common HRCT findings found in patients were peribronchial thickening (48.6 %), ground glass appearance (28.6%) and prominence in interstitial scars. Conclusion: We think that the evaluation of HRCT and PFTs in patients diagnosed with SS for assessing early pulmonary involvement will be guiding in terms of follow-up and treatment.

INTRODUCTION

Sjogren's syndrome (SS) is a chronic, systemic, inflammatory disease characterized with lymphocytic infiltration of the exocrine glands, frequently manifested by dryness in the region affected. Women are mostly affected by it and it is seen between the ages of 40-50 (1,2). Local involvement may be seen in salivary and lacrimal glands but it may also cause systemic, extraglandular involvement (3).

Although the most common extraglandular involvement in SS is pulmonary involvement; it is an underresearched disorder with important clinical consequences. The prevalence of pulmonary involvement in SS patients has been reported to be about 20% (4). Pulmonary involvement in SS is in the form of interstitial lung

disease (ILD) and airway disease. While patients are generally asymptomatic, the most common symptoms described are dyspnea on exertion and cough. Dry cough is more common due to decreased secretions in the airways. Due to drying of the secretions and impaired clearance; bronchiectasis, bronchiolitis, pneumonia and small airway obstruction can be observed. The disease is more mortal with reduced quality of life in interstitial involvement and is one of the independent risk factors for poor prognosis. Therefore, early diagnosis and treatment is considered to be important (1).

Lung involvement is the main cause of mortality in patients with systemic sclerosis and the development of interstitial lung involvement in the first 3 years, i.e in the early period, is one of the poor prognostic factors (5).

The course of lung involvement and the factors causing it, are not clear as in systemic sclerosis. It is stated in the current literature that although interstitial involvement may be seen as a late manifestation of SS in SS patients, it may sometimes appear at the onset of the disease. However, studies investigating early involvement and its effect on the course are not adequate.

Therefore it was aimed to evaluate the frequency of early lung involvement, HRCT findings and data of PFT in SS in this study.

MATERIALS-METHODS

Thirty five patients diagnosed with SS and referred by the Department of Rheumatology to determine potential lung involvement to the 8th chest diseases outpatient clinic of our hospital between September 2015 and december 2018 were included in this study. Respiratory signs, demographic features, length of disease and treatment regimens, pulmonary function test (PFT), data of 6-minute walk test (MWT) and findings of high resolution computed tomography (HRCT) of the patients were retrospectively obtained from hospital information system and patient files.

The diagnosis of SS was made according to the 2002 international classification Criteria for SS and / or 2016 ACR / EULAR Classification criteria when the hospital registration details was examined (6,7).

A clinical spirometer was used to conduct pulmonary function tests (PFTs) (SensorMedics Vmax spectra 229, Bilthoven, The Netherlands). Patients performed the maximal expiratory flow maneuver. Forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC), maximum expiratory flow at 50% of vital capacity (FEF25- 75%) and DLCO values were obtained and FEV1 / FVC was measured. According to the previously defined guidelines, standard PFTs like spirometry and lung volumes were examined (8).

The patients were classified into four groups according to their PFT : obstructive (FEV1 / FVC $<$70%), restrictive (FEV1 / FVC $<$70% and FVC $<$80% and DLCO $<$80%) and small airway obstruction (FEF25-75% $<$65%) and normal (8).

6MWT is a technique that measures exercise capasity within six minutes in individuals with chronic lung disease. The distance walked, initial and final oxygen saturation, the changes in the heart rate and dyspnea indoors within six minutes at a distance of 30 meters were recorded.

According to the HRCT findings, the patients were classified into two groups as with or without CT findings, and the ground glass densities in the lung parenchyma, consolidation, bronchiectasis, interstitial thickening, peribronchial thickening, reticular appearance, and honeycomb appearance were identified as positive findings.

RESULTS

The mean age of the patients was 54.4 $\pm$ 9.2. The majority of the patients were women (94.3%). Dyspnea (28.6 %), effort dyspnea (22.9 %) and dry cough (17.1 %) were the most common clinical complaints of patients at the time of admission.

Median diagnosis time was 74 months. When the medical treatments of the patients were examined, Hydroxychloroquine (88.6%) and Corticosteroid (68.6%) were the most common. Most of the patients (79%)

using steroid were using prednisolone less than 10 mg or its equivalent. When the comorbid lung diseases were investigated, 5 patients had asthma and 4 patients had chronic obstructive pulmonary disease (COPD) (11.4%). The general characteristics of the patients are shown in Table 1.

When the HRCT findings were evaluated, 28 (80%) patients had CT findings, while 7 (20%) patients had no CT findings. Distribution of CT findings; Peribronchial thickening in 17 (48.6%) patients, ground glass in 10 (28.6%) patients, prominence in interstitial scars in 8 (22.9%) patients, bronchiectasis in 7 (20%) patients, reticular appearance in 6 (17.1%) patients, 5 (14.3%) reticulonodular infiltration in the patient, consolidation in 4 (11.4%) patients, solitary nodule in 2 (5.7%), mosaic perfusion in 2 (5.7%), honeycomb appearance in 2 (5.7%) patients, parenchymal band appearance in 1 (2.9%) patient.

No significant difference was found when the data of PFT were evaluated in patients with and without CT findings. Although DLCO values were not statistically significant, lower values were found in patients with CT findings (Table 2).

No statistically significant difference was observed between patients with and without CT findings when we grouped the PFT data as normal, obstructive, restrictive and small airway obstruction ($p = 0.471$, Table 3).

The relationship between the patients' age and duration of illness with PFT parameters is shown in Table 4. According to this no statistically significant difference was found between the duration of illness and PFT results. On the other hand, the disparity between age and FEV1 ($p < 0.001$), FEV1% ($p = 0.011$), FVC ($p < 0.001$), FEV1 / FVC ($p = 0.005$) and FEF25-75 ($p = 0.046$) was statistically significant. In elderly patients at 6MWT, the walking distance was statistically significantly shorter ($p = 0.029$).

When the CT outcomes were analyzed by dividing the duration of the disease into the first 3 years and after; no significant difference was found (Table 5).

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 21.0 was used for the statistical analyses. The categorical variables are presented as frequencies and percentages. The continuous variables were assessed by Kolmogorov-Smirnov test and histograms to find out if their distributions were normal or not. The normally distributed numerical parameters were compared by student's t-test in two groups, while those with non-normal distributions were analyzed by Mann-Whitney U test. The categorical variables were compared by Chi-squares or Fisher's Exact tests where appropriate. The strength of the relationship between the two variables was carried out using Spearman's or Pearson correlation coefficient. A p-value < 0.05 was considered as statistically significant.

DISCUSSION

The most common pathological findings in pulmonary involvement of SS are ILD and small airway defects. HRCT is the most sensitive diagnostic method for the detection of noninvasive and early parenchymal injury (9).

The number of studies evaluating the characteristic results of HRCT in ILD due to primary SS is quite limited. The most common involvement patterns among the HRCT findings in SS lung involvement are peribronchial wall thickening, ground glass appearance, nodules and bronchiectasis (10,11).

It has been reported in a study conducted by Dong et al.with 527 patients diagnosed with primary SS, that SS-related involvement is found to be widespread and affects multiple anatomical structures (airways, alveoli, vascular structures and pleura) and also it has been stated that different histological patterns may be seen simultaneously such as nonspecific interstitial pneumonia (NSIP), organized pneumonia (OP) and the union of NSIP and usual interstitial pneumonia (UIP) (12).

In our study, the most common HRCT findings found in patients were peribronchial thickening (48.6 %), ground glass appearance (28.6%) and prominence in interstitial scars were, in accordance with the literature.

We think that the absence of NSIP and OP patterns are due to the fact that our patients were in the early phase of disease and they had mild disease findings. Patients with ILD show restrictive functional dysfunction. PFT data is also a tool used to diagnose this respiratory disorder (even in asymptomatic patients) in the early period (13).

Decreased FVC, FEV1 and DLCO in PFT are among the predicted findings. However, the most important parameter among these is the decreased DLCO levels that were detected in the early period, and it is associated with the high mortality rate (13,14).

Although it was not possible to compare PFT results since there was no control group in our study; there was a significant decrease in FEV1 and FVC values in older SS patients. However, it was not possible to exclude possible age-related changes in these patients. In studies carried out, İt was detected that decreased DLCO is generally associated with widespread involvement in HRCT (15).

In our study, while the DLCO value in patients with CT findings was found to be lower, it was not statistically significant. Again, no substantial difference was observed in our research when the patients with and without CT findings were compared according to the PFT results.

The relatively younger age of our patients, shorter illness length and limited involvement in HRCT findings may explain this circumstance. The inability of PFT to detect early findings, especially in CT, was shown to be similar to our outcome In the analysis of Palm et al.

While 85% of the patients had HRCT findings in this study, only 15% of the patients were diagnosed with PFT alone (14).

6MWT is an exercise test used to assess exercise capacity and treatment response in patients with chronic lung diseases such as chronic obstructive pulmonary disease (COPD), interstitial fibrosis, pulmonary arterial hypertension, and it has been used as a prognostic tool in patients with heart failure and lung disease in recent years (16).

According to the American Thoracic Society guidelines, 6MWT is stated to be a simple, low-cost, reproducible and easy-to-apply method (17).

Generally, there are studies evaluating pulmonary functional capacity in conditions such as idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease (18-20).

However, there are not enough studies on 6MWT data for lung involvement in SS. In our study, the lack of significant difference between 6MWT and lung involvement supports the absence of diffuse pulmonary involvement.

The prevalence of pulmonary symptoms in primary SS patients is stated to be between 9-25%; in the literature consistent with our research (12,21).

Dry cough and/or effort dyspnea are the most common among the clinical findings. In a report, it was reported that symptoms were linked to the underlying chronic respiratory conditions in 1/3 of the patients who had clinical symptoms (21).

This rate was approximately $\frac{1}{4}$ in our study. It has been reported in the literature that respiratory symptoms are observed in 10% of patients within 1 year after diagnosis, reaching 20% in 5 years (4,12).

In our research, more than half of the patients had CT findings in the first 3 years. However, its correlation with the clinic could not be clearly evaluated because of the small number of patients. However, these results show that, lung involvement in patients typically occurs in the first years of the illness in line with the literature. In a study, it was found that 15-20 % of patients had chronic ILD outcomes even before an overt connective tissue disease develops (22).

In another cohort study, it was demonstrated that 60% of patients were diagnosed with ILD before the diagnosis of SS in 60% of patients (13).

It was stated in some research, that pulmonary findings did not have a negative effect on prognosis. In the study of Davidson et al. involving 30 British patients, it was shown that after 10 years of follow-up, pulmonary functions remained stable in most patients (23).

However, there are several studies contradicting these studies in the literature. ILD is a poor prognostic factor in SS patients and the cumulative mortality rate reaches 16% in 5 years (14, 24,25).

In addition, in a study by Chen et al. high HRCT scores were found to be an independent risk factor for mortality (9).

It is very important to determine the predictive factors of the disease in the prevention and early treatment of pulmonary disease. Studies investigating prognostic variables of lung involvement in SS are not sufficient and the findings are contradictory. Although some studies have shown that advanced age and long duration of the disease may be associated with poor prognosis, publication is also available. There are also researches that indicate that this relationship is not important (26).

When the laboratory parameters are examined; Although it has been reported that hypergammaglobulinemia, lymphopenia, rheumatoid factor (RF) and anti Ro / La positivity may be predictive factors in lung involvement, the results of the study are not statistically significant (15).

In our study, the relationship of these parameters with pulmonary involvement could not be investigated because the patients' laboratory parameters were not analyzed in a single center and the findings of certain patients were not available.

In researches investigating clinical results and lung involvement, it was observed that the Reynoud syndrome was more prominent in patients with lung involvement (14,27).

This situation can be interpreted as the development of ischemic process depends on microangiopathy due to the initiation of ILD development. Similarly, CT involvement was detected in 6 of 8 patients with the Reynoud phenomenon in our study.

The treatment of primary SS pulmonary involvement is generally based on clinical practice and no widely accepted algorithm is currently available. The use of immunosuppressants such as Cyclophosphamide, Azathioprine and high-dose steroids and biological agents such as Rituxumab and Belimumab, along with symptomatic therapy, is used to manage the treatment of these patients. The most common use in our patients was hydroxychloroquine and / or low-dose steroid use.

This outcome indicates that there was no widespread intervention and no associated symptoms in our patients.

Its retrospective nature, the limited number of patients, and the inability to assess the relationship between autoantibodies and lung involvement were the limitations of our research.

CONCLUSION

We think that the evaluation of HRCT and pulmonary function tests in patients diagnosed with SS for assessing early pulmonary involvement will be guiding in terms of follow-up and treatment.

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TABLES

Table 1. Main characteristics of the participants

Parameters	Total (n=35)	Without CT findings (n=7)	With CT findings (n=28)	p

Parameters	Total (n=35)	Without CT findings (n=7)	With CT findings (n=28)	p

Age	54.4 ± 9.2	52.1 ± 8.4	55 ± 9.4	0.469
Gender Female, n (%) Male, n (%)	33 (94.3) 2 (5.7)	7 (100) 0 (0)	26 (92.9) 2 (7.1)	0.466
Asthma, n (%)	5 (14.3)	2 (28.6)	3 (10.7)	0.256
COPD, n (%)	4 (11.4)	0 (0)	4 (14.3)	0.562
DM, n (%)	3 (8.6)	0 (0)	3 (10.7)	0.365
HT, n (%)	5 (14.3)	1 (14.3)	4 (14.3)	1
CRF, n (%)	1 (2.9)	0 (0)	1 (3.6)	0.612
CAD	1 (2.9)	0 (0)	1 (3.6)	0.612
Hypothyroidism, n (%)	2 (5.7)	0 (0)	2 (7.1)	0.466
RA	1 (2.9)	0 (0)	1 (3.6)	0.612
Alergic rhinitis,n (%)	1 (2.9)	0 (0)	1 (3.6)	0.612
ILD, n (%)	1 (2.9)	0 (0)	1 (3.6)	0.612
Multiple Sclerosis, n (%)	1 (2.9)	1 (14.3)	0 (0)	0.200
Hydroxychloroquine, n (%)	31 (88.6)	4 (57.1)	27 (96.4)	**0.019**
Steroid, n (%)	24 (68.6)	5 (71.4)	19 (67.9)	0.856
MTX, n (%)	2 (5.7)	2 (28.6)	0 (0)	**0.035**
Azathioprine, n (%)	8 (22.9)	3 (42.9)	5 (17.9)	0.312
Colchicine, n (%)	2 (5.7)	2 (28.6)	0 (0)	**0.035**
Dry cough, n (%)	6 (17.1)	2 (28.6)	4 (14.3)	0.576
Effort dyspnea, n (%)	8 (22.9)	2 (28.6)	6 (21.4)	0.648
Raynaud phenomenon, n (%)	8 (22,8)	2 (28,5)	6 (21,4)	0.644
Duration of illness, median (min-max)	74 (1-180)	80 (2-120)	32 (1-180)	0.214

COPD: Chronic obstructive lung disease, CAD: Coronary artery disease, DM: diabetes mellitus, HT: hipertansion, CRD: Chronic renal disease, RA: Rheumatoid arthritis, ILD: Interstitial lung disease, CT: computed tomography

Table 2: Comparison of functional parameters of patients with and without CT findings

Parameters	Total (n=35)	Without CT findings (n=7)	With CT findings (n=28)	p
FVC	2.45 ± 0.9	2.44 ± 0.22	2.46 ± 0.59	0.945
FVC %	91.87 ± 2.66	91.5 ± 7.09	91.96 ± 16.72	0.916
FEV1	2.22 ± 0.9	2.09 ± 0.19	2.25 ± 0.54	0.255

Parameters	**Total (n=35)**	**Without CT findings (n=7)**	**With CT findings (n=28)**	**p**
FEV1 %	90.51 ± 2.94	93.66 ± 6.37	89.81 ± 18.47	0.390
FEV1/FVC %	82.12 ± 1.36	84.83 ± 6.04	81.51 ± 8.13	0.356
Fef 25-75 %	67 (45-111)	67 (64-84)	67 (45-111)	0.887
DLCO	94.16 ± 3.58	108.6 ± 12.70	91.28 ± 19.70	0.071
6MWT, metre	450 (60-570)	450 (260-485)	443 (60-570)	0.549
Pre-test Saturation	97 (92-99)	96 (93-99)	97 (92-98)	0.466
Post-test Saturation	96 (74-98)	95 (89-98)	97 (74-98)	0.736
Test time	6 (2-6)	6 (6-6)	6 (2-6)	0.372

FEV1: 1. Forced expiratory volume in 1 second, FVC: Forced vital capasity, FEF: Forced expiratory flow rate, 6DYT: 6 minute walk test, DLCO: diffusing capacity of the lungs for carbon monoxide, CT: computed tomography

Table 3: Evaluation of lung involvement in CT according to PFT findings

	Pulmonary function test	Pulmonary function test	Pulmonary function test	Pulmonary
	Normal	SAO	Obstructive	Restrictive
With CT findings, n (%)	16 (80)	4 (66.7)	3 (100)	4 (100)
Without CT findings, n (%)	4 (20)	2 33.3)	0 (0)	0 (0)

SAO: Small airway obstruction, CT: computed tomography, PFT: pulmonary function test

Tablo 4: Relationship between age, duration of disease and other parameters

		Age	**Duration of illness**	**Duration of illness**	
Age			0.156	r	r
			0.372	p-value	p-value
Duration of illness	0.156	0.156		r	r
	0.372	0.372		p-value	p-value
FEV1	**-0.609**	**-0.609**	-0.159	r	r
	< 0.001	**< 0.001**	0.400	p-value	p-value
FEV1 %	**-0.438**	**-0.438**	-0.034	-0.034	r
	0.011	**0.011**	0.851	0.851	p-value
FVC	**-0.612**	**-0.612**	-0.230	-0.230	r
	< 0.001	**< 0.001**	0.220	0.220	p-value
FVC %	-0.297	-0.297	-0.113	-0.113	r
	0.094	0.094	0.532	0.532	p-value
DLCO	-0.347	-0.347	0.028	0.028	r
	0.060	0.060	0.883	0.883	p-value
Rate	**-0.474**	**-0.474**	-0.087	-0.087	r
	0.005	**0.005**	0.631	0.631	p-value
6MWT Distance	**-0.368**	**-0.368**	-0.076	-0.076	r
	0.029	**0.029**	0.664	0.664	p-value
Fef 25/75	**-0.350**	**-0.350**	**-0.349**	**-0.349**	r
	0.046	**0.046**	**0.046**	**0.046**	p-value
6MWT Time	-0.185	-0.185	0.007	0.007	r
	0.288	0.288	0.970	0.970	p-value

FEV1: 1. Forced expiratory volume in 1 second, FVC: Forced vital capasity, FEF: Forced exspiratory flow rate, 6MWT: 6 minute walk test, DLCO: diffusing capacity of the lungs for carbon monoxide

Table 5: The relationship between duration of disease and HRCT Findings,

	With CT finding (n=28)	Without CT finding (n=7)	p
3 years and above n (%)	12 (42.9) 16 (57.1)	6 (85.7) 1 (14.3)	0.088
3 years and below, n (%)			

CT: computed tomography

REFERENCES

1. Yong W, Ziliang H, Meihua Q, Qiao Y. Risk factors for primary Sjögren syndrome-associated interstitial lung disease. J. Thorac Dis. 2018;10(4):2108-2117.
2. Cain HC, Noble PW, Matthay RA. Pulmonary manifestations of Sjögren's Syndrome. Clin Chest Med 1998; 19:687-99.
3. Ana-Luisa S, Christian T, Uwe P. The Diagnosis and Treatment of Sjögren's Syndrome. Dtsch Arztebl Int. 2017;114(20):354-361.
4. Flament T, Bigot A, Chaigne B, et al. Pulmonary manifestations of Sjögren's syndrome. Eur Respir Rev. 2016 Jun;25(140):110-23.
5. Jaeger VK, Wirz EG, Allanore Y, et al. Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study. PLoS One. 2016;11(10):e0163894.)
6. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* . 2002;61(6):554-558.
7. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* . 2017;69(1):35-45.
8. Pellegrino R, Viegi G, Brusasco V. et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26: 948-68.
9. Chen MH, Chou HP, Lai CC et al. Lung involvement in primary Sjögren's syndrome: Correlation between high-resolution computed tomography score and mortality. J Chin Med Assoc. 2014;77(2):75-82.
10. Hatron PY, Tillie-Leblond I, Launay D, et al. Pulmonary manifestations of Sjögren's syndrome. Presse Med. 2011;40:49–64.
11. Egashira R, Kondo T, Hirai T, et al. CT findings of thoracic manifestations of primary Sjögren syndrome: Radiologic-pathologic correlation. RadioGraphics. 2013;33:1933–1949.
12. Dong X, Zhou J, Guo X, et al. A retrospective analysis of distinguishing features of chest HRCT and clinical manifestation in primary Sjögren's syndrome-related interstitial lung disease in a Chinese population. Clin Rheumatol. 2018;37(11):2981-2988.
13. Reina D, Roig Vilaseca D, Torrente-Segarra Vranera M, et al. Sjögren's syndrome-associated interstitial lung disease: A multicenter study. Reumatol Clin. 2016;12(4):201-5.
14. Palm O, Garen T, Berge Enger T et al. Clinical pulmonary involvement in primary Sjögren's syndrome: prevalence, quality of life and mortality–a retrospective study based on registry data. Rheumatology 2013;52(1):173-9.
15. Yazisiz V, Arslan G, Ozbudak IH, et al. Lung involvement in patients with primary Sjögren's syndrome: what are the predictors? Rheumatol Int 2010;30:1317e24.
16. Kotloff RM, Tino G, Palevsky HI et al. Comparison of short-term functional outcomes following unilateral and bilateral lung volume reduction surgery. 1998; 113(4):890-5.

17. Enright PL. The six-minute walk test. Respir Care. 2003 Aug; 48(8):783-5.
18. Lama V. N, Flaherty K. R, Toews G. B, et al. Prognostic value of desaturation during a 6 minute walk test in idiopathic interstitial pneumonia. *American Journal of Respiratory and Critical Care medicine.* 2003;168(9):1084–1090.
19. Hallstrand T. S, Boitano L. J, Johnson W. C, et al. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. *European Respiratory Journal.* 2005;25(1):96–103.
20. Lederer D. J, Arcasoy S. M, Wilt J. S, et al. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine.* 2006;174(6):659–664.
21. Kampolis CF, Fragkioudaki S, Mavragani CP et al. Prevalence and spectrum of symptomatic pulmonary involvement in primary Sjögren's syndrome. Clin Exp Rheumatol. 2018;36 Suppl 112(3):94-101.
22. Strange C, Highland KB. Interstitial lung disease in the patient who has connective tissue disease. Clin Chest Med. 2004;25(3):549-59.
23. Davidson BK, Kelly CA, Griffiths ID. Ten year follow up of pulmonary function in patients with primary Sjo¨gren's syndrome. Ann Rheum Dis 2000;59:709e12.)
24. Nannini C, Jebakumar AJ, Crowson CS et al (2013) Primary Sjogren's syndrome 1976-2005 and associated interstitial lung disease: a population-based study of incidence and mortality[J]. BMJ Open 3(11):003569–003576.
25. Ito I, Nagai S, Kitaichi M, et al. Pulmonary manifestations of primary Sjogren's syndrome: a clinical, radiologic, and pathologic study. Am J Respir Crit Care Med. 2005 Mar 15;171(6):632-8.
26. Sebastian A, Misterska-Skóra M, Silicki J, Sebastian M, Wiland P. Chest HRCT findings in patients with primary Sjögren's syndrome. Adv Clin Exp Med. 2017;26(7):1101-1106.
27. Roca F, Dommique S, Schmdt J et al. Interstitial lung disease in primary Sjögren's syndrome. Autoimmun Rev 2017; 16: 48-54.

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