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RESEARCH ARTICLE
KLİNİK ÇALIŞMA

Evaluation of pulmonary involvement in systemic rheumatic diseases with high resolution computed tomography and pulmonary function test: A single-center experience

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ABSTRACT

Evaluation of pulmonary involvement in systemic rheumatic diseases with high resolution computed tomography and pulmonary function test: A single-center experience

Introduction: The objective of this study was to investigate the clinical and radiological features and pulmonary function tests (PFTs) in patients with the pulmonary involvement of systemic rheumatic diseases (SRDs).

Materials and Methods: This study was conducted as a retrospective and single-center study. Patients diagnosed with an SRD and admitted/referred to the department of chest diseases of our hospital between January 2015 and June 2019 were enrolled. All patients were evaluated using High Resolution Computed Tomography (HRCT) and PFT.

Results: This study included 68 patients (15 males, 53 females) with a mean age of 62.38 ± 12.4 years. Forty-one (60.2%) patients had diagnosis of rheumatoid arthritis (RA), 10 (14.7%) patients had sjögren's syndrome (SS), 8 (11.7%) patients had systemic lupus erythematosus (SLE), 6 (8.8%) patients had systemic sclerosis (SSc), and 3 (4.4%) patients had mixed connective tissue disease (MCTD). While RA, SLE, MCTD patients were more commonly

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symptomatic, most of the SS patients were asymptomatic. Overall, 30 (44.1%) patients had normal PFT. Although 30 (%44.1) patients were asymptomatic and 30 (%44.1) patients had normal PFTs, at least one imaging finding was found in all patients according to HRCT imaging. "Bronchiectasis" was the most common HRCT finding in RA, followed by "chronic fibrotic changes" and "peribronchial thickening". "Chronic fibrotic changes" and "peribronchial thickening" were the most common changes in SS. Similarly, "peribronchial thickening" was the most common radiologic finding in SLE. As for SSC, "chronic fibrotic changes", "interlobular septal thickening", and "pleural effusion" were the most common radiologic findings.

Conclusion: Pulmonary involvement in systemic rheumatic diseases can occur with various radiological images even in asymptomatic patients. PFTs can be normal as well as an obstructive, restrictive or mixed pattern can be seen. Heterogeneous and combined HRCT findings can be seen in SRD patients.

Key words: Rheumatoid arthritis; systemic lupus erythematosus; sjögren's syndrome; systemic sclerosis; pulmonary involvement; high-resolution computed tomography

ÖZ

Sistemik romatizmal hastalıklarda akciğer tutulumunun, yüksek çözünürlüklü bilgisayarlı tomografi ve solunum fonksiyon testi ile değerlendirilmesi: Tek merkez deneyimi

Giriş: Bu çalışmanın amacı, sistemik romatizmal hastalıklarda (SRH) akciğer tutulumu olan hastalarda klinik, radyolojik özellikler ve solunum fonksiyon testlerini (SFT) araştırmaktır.

Materyal ve Metod: Bu çalışma retrospektif, tanımlayıcı ve tek merkezli olarak gerçekleştirildi. Ocak 2015 - Aralık 2019 yılları arasında SRH tanısı alan ve üçüncü basamak sağlık kurumu olan hastanemiz göğüs hastalıkları bölümüne başvuran/sevk edilen hastalar çalışmaya alındı. Tüm hastalar Yüksek rezolüsyonlu akciğer tomografisi (HRCT) ve SFT kullanılarak değerlendirildi.

Bulgular: Çalışmaya ortalama yaşı $62,38 \pm 12,4$ yıl olan 68 hasta (15 erkek, 53 kadın) dahil edildi. Hastaların 41'inde (%60,2) romatoid artrit (RA), 10'unda (%14,7) sjögren sendromu (SS), 8'inde (%11,7) sistemik lupus eritematozus (SLE), 6'sında (%8,8) sistemik skleroz (SSc) ve 3'ünde (%4,4) mix bağ dokusu hastalığı (MBDH) mevcuttu. RA, SLE, MBDH hastaları genellikle semptomatik iken, SS hastaları genellikle asemptomatiktir. Toplam 30 (%44,1) hastada SFT normal olarak değerlendirildi. 30 (%44,1) hasta asemptomatik olduğu halde ve diğer 30 (%44,1) hastada normal SFT bulguları saptanmasına rağmen, HRCT ile tüm hastalarda birden fazla görüntüleme bulgusu saptandı. RA'da en sık görülen HRCT bulgusu "bronşektazi" idi, bunu "kronik fibrotik değişiklikler" ve "peribronşiyal kalınlaşma" izledi. "Kronik fibrotik değişiklikler" ve "peribronşiyal kalınlaşma", SSc'deki en yaygın değişikliklerdi. Benzer şekilde, "peribronşiyal kalınlaşma" SLE'de en sık görülen HRCT bulgusuydu. SSc'de ise, "kronik fibrotik değişiklikler", interlobüler septal kalınlaşma ve plevral efüzyon en sık görülen HRCT bulgularıydı.

Sonuç: Sistemik romatizmal hastalıklarda pulmoner tutulum, asemptomatik hastalarda dahi çeşitli radyolojik görüntülerle ortaya çıkabilir. SFT normal olabileceği gibi obstruktif, restriktif veya mikst paternde olabilir. Birçok (heterojen) HRCT bulgusu görülebilir.

Anahtar kelimeler: Romatoid artrit; sistemik lupus eritematozus; sjögren sendromu; sistemik skleroz; pulmoner tutulum; yüksek çözünürlüklü bilgisayarlı tomografi

INTRODUCTION

Pulmonary involvement is an important cause of morbidity and even mortality in systemic rheumatic diseases (SRDs) (1). Previous studies have already shown that pulmonary involvement can present with different manifestations comprising the involvement of respiratory muscles, pleura, lung parenchyma, airways, interstitium and blood vessels (2-4). Respiratory complaints may be masked and the diagnosis can be challenging due to the limitation of exercise capacity because of the involvement of the musculoskeletal system (2).

In the literature, lung involvement of SRD patients were reported between %9-48 (5-7). Accordingly, the aim of this study was to investigate the clinical and radiological features and pulmonary function tests (PFTs) in patients with the pulmonary involvement of SRDs.

MATERIALS and METHODS

This study was conducted as a retrospective, descriptive and single-center study. Patients diagnosed with systemic rheumatic disease and admitted or referred to the department of chest diseases of a tertiary hospital between January 2015 and June 2019 were enrolled. The data were obtained from the hospital automation system records and digital archives. Patients who had any inflammatory disease other than SRD, infectious disease, granulomatous diseases, malignancy or history of drug usage that could lead to any pulmonary side effects were excluded. All patients were evaluated using a high-resolution computed tomography (HRCT) and spirometry. The current study protocol was approved by the Tokat Osmaniye University Ethics Committee (Number: TOGU 83116987/621 and date: 10.10.2019).

Data Collection and Evaluation

Demographic characteristics, duration of disease, pulmonary symptoms and PFT results were recorded, and radiological findings of each patient were interpreted by an expert radiologist and classified according to the systemic rheumatic disease type. All patients were evaluated with HRCT. HRCT is the gold standard technique to evaluate and diagnose early pulmonary involvement and subclinical lung involvement of SRD (8). The patients were also evaluated using spirometry. All PFTs were performed according to ATS / ERS guideline. Spirometry is the main pulmonary function test for the accurate and reproducible measurement of lung functions (9). If the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV_1) are within 80% of the reference value, the results are considered normal. The obstructive

pattern was defined by a low FEV_1/FVC ratio, which is defined as less than 70%. A restrictive pattern on spirometry was defined as an FEV_1/FVC ratio > 0.7 and an FVC $< 80\%$ of the predicted value. $FEV_1/FVC < 0.7$ and FVC $< 80\%$ of the predicted value is described as a "mixed" ventilatory defect (10). Example images of our patients are shown in Figure 1 and Figure 2.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS, Inc. Chicago, Illinois).

After checking the normal distribution with Shapiro Wilk Test and histogram graphics, the data were given as mean, standard deviation, count, and percentage. Categorical variables were compared using the Chi-Square test. Numeric variables were com-

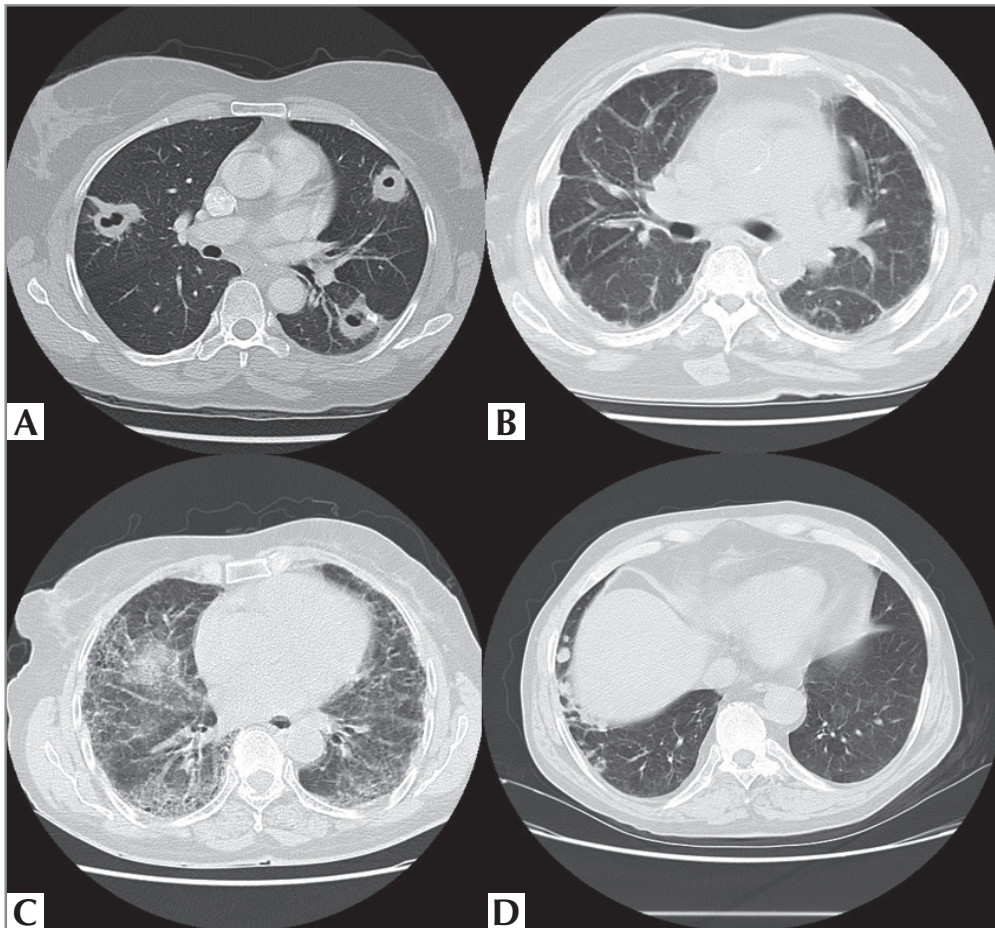


Figure 1. A. Cavitary lesions in a 56-year-old female patient with RA, B. Pleural, interlobular-septal and peribronchovascular thickening in a 61-year-old patient with RA, C. A 56-year-old female SSC patient with ground-glass appearance and intralobular interstitial thickening, D. A 63-year-old male patient with RA had necrobiotic and pulmonary nodules.

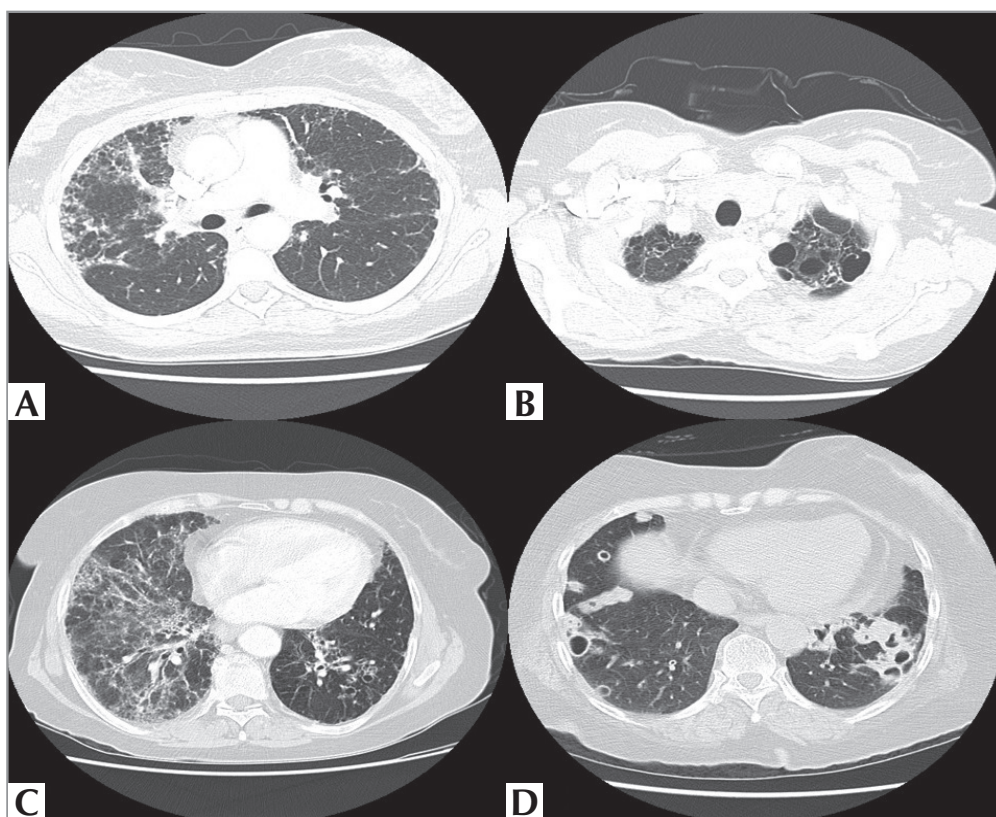


Figure 2. A. A 42-year-old female patient diagnosed as SS with a honeycomb appearance, B. Apicobullous and chronic fibrotic changes, 64-year-old female SSC patient, C. A 48-year-old female MCTD patient with bronchiectasis intralobular interstitial thickening and ground-glass appearance, D. Cavitary lesions and pulmonary nodules in a 68-year-old male RA patient.

pared using the One Way ANOVA Test. Post-hoc analyses were performed to determine the difference between the groups. A P value of <0.05 was considered statistically significant.

RESULTS

Clinical and Demographical Features of Patients

A total of 68 patients (15 males, 53 females) with a mean age of 62.38 ± 12.4 years (ranges: 39 to 82 years) were included in this study. Of the patients, 41 (60.2%) had rheumatoid arthritis (RA), 10 (14.7%) had Sjogren's syndrome (SS), 8 (11.7%) had systemic lupus erythematosus (SLE), 6 (8.8%) had systemic sclerosis (SS) and 3 (4.4%) had mixed connective tissue disease (MCTD). Clinical and demographical features of the subjects are summarized in Table 1. Mean age of RA patients was higher than other systemic rheumatic disease groups ($p < 0.001$). Duration of diseases was similar between all SRDs ($p = 0.13$).

Pulmonary Symptoms and Findings of PFTs

Pulmonary symptoms and PFTs are shown in Table 2. No statistical difference was found between the groups in terms of pulmonary symptoms ($p > 0.05$). While RA, SLE, MCTD patients were more commonly symptomatic, most of the SS patients were asymptomatic. There was no difference in the duration of the disease between symptomatic and asymptomatic patients. (10.7 years, 12.1 years, respectively; $p = 0.51$). According to the results of PFTs, there was no difference between the groups in forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and FEV_1/FVC ratios ($p = 0.72$, $p = 0.67$, $p = 0.97$, respectively). Overall, 30 (44.1%) patients had normal PFTs. The numbers of obstructive and restrictive patterns were similar in all groups except the SLE statistically.

Radiological Findings

Although 30 (%44.1) patients were asymptomatic and 30 (%44.1) patients had normal PFTs, more than

Table 1. Clinical and demographical features of the patients

Variables	RA (n= 41)	SS (n= 10)	SLE (n= 8)	Systemic sclerosis (n= 6)	MCTD (n= 3)	p
Age	67.65 ± 10.13	56.90 ± 14.53	51.87 ± 6.27	57.83 ± 12.04	45.66 ± 6.11	0.001*
Gender						0.29
Male (n,%)	12 (29.3)	0 (0)	2 (25)	1 (16.6)	0 (0)	
Female (n,%)	29 (70.7)	10 (100)	6 (75)	5 (83.4)	3 (100)	
Disease duration (year)	14.43 ± 9.72	6.20 ± 3.16	7.00 ± 2.83	9.00 ± 6.84	6.33 ± 1.53	0.13
Pulmonary symptom						0.16
Yes (n,%)	15 (36.5)	8 (80)	3 (37.5)	3 (50)	1 (33.3)	
No (n,%)	26 (63.5)	2 (20)	5 (62.5)	3 (50)	2 (66.7)	

RA: Rheumatoid arthritis, SS: Sjogren's syndrome, SLE: Systemic lupus erythematosus, SSC: Systemic sclerosis, MCTD: Mixed connective tissue disease.

Table 2. Pulmonary symptoms and function test results (n, %)

Variables	RA (n= 41)	SS (n= 10)	SLE (n= 8)	SSC (n= 6)	MCTD (n= 3)
Symptoms					
Asymptomatic/sympmtomatic	15 (36.5)/26 (63.5)	8(80)/2(20)	3(37.5)/5(62.5)	3(50)/3(50)	1 1(33.3)/2 (66.7)
Cough	9 (22)	6 (60)	1 (13)	2 (33)	1 (33)
Dyspnea	12 (29)	5 (50)	3 (38)	2 (66)	1 (33)
Sputum	3 (7)	1 (10)	0 (0)	1 (33)	0 (0)
Chest pain	4 (10)	2 (20)	1 (13)	2 (66)	0 (0)
Wheezing	4 (10)	0 (0)	0 (0)	0 (0)	0 (0)
Hemoptysis	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
PFTs					
FVC (lt)	2.26 ± 0.97	2.24 ± 0.69	2.39 ± 0.50	2.70 ± 0.93	2.72 ± 0.08 (p= 0.67)
FEV ₁ (lt/sn)	1.80 ± 0.79	1.83 ± 0.61	1.97 ± 0.49	2.24 ± 0.91	2.15 ± 0.15 (p= 0.72)
FEV ₁ /FVC (%)	78.48 ± 12.40	80.30 ± 7.52	80.1 ± 10.9	80.33 ± 11.07	78.00 ± 4.58 (p= 0.97)
PFTs					
Normal	13 (32)	6 (60)	4 (50)	4 (67)	3 (100)
Obstructive patern	11 (27)	2 (20)	1 (13)	1 (17)	0 (0)
Restrictive patern	11 (27)	2 (20)	3 (38)	1 (17)	0 (0)
Mixed patern	6 (15)	0 (0)	0 (0)	0 (0)	0 (0)

RA: Rheumatoid arthritis, SS: Sjogren's syndrome, SLE: Systemic lupus erythematosus, SSC: Systemic sclerosis, MCTD: Mixed connective tissue disease, PFTs:Pulmonary function tests, FVC: Forced vital capacity, FEV₁: Forced expiratory volume in the first second.

one imaging finding was found in all patients with SRD according to the HRCT imaging. All imaging findings are shown in Table 3. Predominantly bronchiectasis, chronic fibrotic changes, peribronchial thickening, pulmonary nodules, pleural thickening, subsegmental linear atelectasis, ground-glass nodules/opacity, and interlobular septal thickening findings were seen in HRCT evaluation. Mosaic perfusion pattern, cavity, necrobiotic nodules and intralobular interstitial thickening were seen only RA patients. Diaphragmatic thickening/involvement was seen in only two SLE patients. Pleural effusion was seen only

two SSC patients. Comparisons of radiological findings of symptomatic and asymptomatic patients are shown in Table 4.

DISCUSSION

This study aimed to explore the clinical and radiological features of pulmonary involvement in SRDs, using the HRCT and PFTs. There are three main findings according to our results. First, pulmonary involvement can present with various symptoms and radiological images, event in asymptomatic patients. PFTs can be normal as well as an obstructive, restric-

Table 3. Radiological findings of high resolution computed tomography (n, %)

Findings	RA (n= 41)	SS (n= 10)	SLE (n= 8)	SSC (n= 6)	MCTD (n= 3)
Bronchiectasis	27 (65.8)	2 (20)	1 (12.5)	1 (16.6)	2 (66.6)
Chronic fibrotic changes	22 (53.6)	4 (40)	2 (25)	2 (33.3)	0 (0)
Peribronchial thickening	20 (48.7)	4 (40)	5 (62.5)	1 (16.6)	2 (66.6)
Pulmonary nodules	18 (43.9)	2 (20)	2 (25)	1 (16.6)	1 (33.3)
Pleural thickening	14 (34.1)	3 (30)	1 (12.5)	1 (16.6)	1 (33.3)
Subsegmentary linear atelectasis	13 (31.7)	2 (20)	4 (50)	1 (16.6)	1 (33.3)
Ground-glass nodules/opacity	12 (29.2)	2 (20)	2 (25)	1 (16.6)	1 (33.3)
Interlobular septal thickening	11(26.8)	3 (30)	0 (0)	2 (33.3)	1 (33.3)
Mosaic perfusion pattern	9 (21.9)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary vascular enlargement	9 (21.9)	1 (10)	1 (12.5)	0 (0)	0 (0)
Ground-glass appearance	9 (21.9)	3 (30)	2 (25)	0 (0)	0 (0)
Paratracheal/subcarinal/prevascular LAP	8 (19.5)	2 (20)	1 (12.5)	0 (0)	0 (0)
Honeycombing	6 (14.6)	1 (10)	0 (0)	1 (16.6)	1 (33.3)
Mediastenal/hilar LAP	5 (12.1)	2 (20)	2 (25)	0 (0)	0 (0)
Cavity	5 (12.1)	0 (0)	0 (0)	0 (0)	0 (0)
Pleural effusion	3 (7.3)	0 (0)	0 (0)	2 (33.3)	0 (0)
Necrobiotic nodules	3 (7.3)	0 (0)	0 (0)	0 (0)	0 (0)
Apicobullous changes	2 (4.8)	0 (0)	0 (0)	1 (16.6)	0 (0)
Intralobular interstitial thickening	2 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)
Patchy infiltrate	2 (4.8)	2 (20)	0 (0)	0 (0)	0 (0)
Reticulonodular appearance	1 (2.4)	2 (20)	0 (0)	2 (33.3)	0 (0)
Diaphragmatic thickening/involvement	0 (0)	0 (0)	2 (25)	0 (0)	0 (0)

RA: Rheumatoid arthritis, SS: Sjogren's syndrome, SLE: Systemic lupus erythematosus, SSC: Systemic sclerosis, MCTD: Mixed connective tissue disease, LAP: Lymphadenopathy.

Table 4. Comparisons of radiological findings of symptomatic and asymptomatic patients (n, %)

Findings	Symptomatic (n= 30)	Asymptomatic (n= 38)
Bronchiectasis	17(57)	18(47)
Chronic fibrotic changes	13 (43)	17(45)
Peribronchial thickening	16(53)	16 (42)
Pulmonary nodules	7(23)	17 (45)
Pleural thickening	10(33)	10 (26)
Subsegmentary linear atelectasis	8(27)	13(34)
Ground-glass nodules/opacity	6(20)	12(32)
Interlobular septal thickening	11(37)	6(16)
Mosaic perfusion pattern	2(7)	1(3)
Pulmonary vascular enlargement	6(20)	5(13)
Paratracheal/subcarinal/prevascular LAP	4(13)	7(18)
Honeycombing	6 (20)	3(8)
Mediastenal/hilar LAP	4(13)	5(13)
Cavity	1(3)	4 (11)
Pleural effusion	3(10)	2(5)
Necrobiotic nodules	0(0)	3(8)
Apicobullous changes	0(0)	3(8)
Intralobular interstitial thickening	1(3)	1(3)
Patchy infiltrate	3 (10)	1 (3)
Reticulonodular appearance	2(7)	3(8)
Diaphragmatic thickening/involvement	0 (0)	2 (5)

RA: Rheumatoid arthritis, SS: Sjogren's syndrome, SLE: Systemic lupus erythematosus, SSC: Systemic sclerosis, MCTD: Mixed connective tissue disease, LAP: Lymphadenopathy.

tive or mixed pattern can be seen. Third, heterogeneous and multiple HRCT findings can be seen in SRD patients. In our study, bronchiectasis was the most common HRCT finding in RA, followed by chronic fibrotic changes and peribronchial thickening. Chronic fibrotic changes and peribronchial thickening are the most common changes in SS. Similarly, peribronchial thickening is the most common HRCT finding in SLE. As for the SSc, chronic fibrotic changes, interlobular septal thickening, and pleural effusion are the most common HRCT findings.

Pulmonary findings and involvements in SRD have been previously studied in different studies. Vitali et al. have highlighted a high prevalence of asymptomatic lung involvement among patients with different SRD (11). Only 17.8% of the patients were symptomatic and mild dyspnea on exercise was the most common symptom in SRDs. Moreover, Renzoni et al. have compared 17 patients who had idiopathic pulmonary fibrosis (LIPF) with pulmonary fibrosis associated with connective tissue disorders (PFCTD) whereby no significant difference was determined between two groups in terms of PFT parameters (12). However, patients in the PFCTD group were more asymptomatic. In our study, more than half of the patients (55.8%) were asymptomatic, and 30 (44.1%) patients had normal PFTs. The most common PFT abnormalities were the obstructive (22%) and restrictive patterns (25%). Dyspnea (33.2%) and cough (27.9%) were common symptoms.

In the literature, there are reports of different rates of lung involvement in patients with SRD. Fujii et al. have reported a 50% rate of lung involvement using HRCT (13). In another study evaluating 20 RA, 20 AS and 20 healthy individuals, the authors have stated that 70% of RA and 50% of AS patients had abnormal HRCT findings and the most common HRCT abnormalities are interstitial lung disease, bronchiectasis and pleural disease (14). It is not clear whether bronchiectasis represents with the inflammatory disease being directly responsible for the bronchial damage, or results from a preexisting pulmonary complication such as alveolitis or bronchiolitis obliterans organizing pneumonia (15). Bronchiectasis was the most common radiological finding in our examinations.

While early-onset RA patients have common ground-glass opacities, many studies have shown that HRCT has a more reticulonodular and honeycomb appearance than ground-glass opacities in RA patients (14,

16-17). HRCT findings in SS are ground-glass opacities, nodules, and thin-walled cysts (18). In the study of Matsuyama et al. (19), centrilobular thickening and lymphoproliferative disorders have been observed to be characteristic of SS patients. Honeycomb appearance and pulmonary fibrosis are reported to be relatively rare features of SS (20). Fenlon et al. have found interstitial lung disease findings in HRCT in one-third of SLE patients. Only two of the 34 patients included in the study had a honeycomb appearance (21). In addition, Bankier et al. have found pulmonary fibrosis in one-third of 45 asymptomatic SLE patients with HRCT (22). More importantly, in both publications, interlobular septal thickening was the most common interstitial change. Further studies have not been conducted on the HRCT features of MCTD. In a study involving 41 patients, the appearance of ground glass in all patients, nodules and reticular opacities are also commonly seen in predominantly peripheral lower zones and honeycomb appearance is less common (23). In our study, we found more than one HRCT findings in each patient in systemic rheumatic disease groups. According to our observations, the most common HRCT findings in RA were bronchiectasis, chronic fibrotic changes and peribronchial thickening. In SS patients, the most common HRCT findings were chronic fibrotic changes and peribronchial thickening, the latter is also the most common in SLE. Chronic fibrotic changes, interlobular septal thickening, and pleural effusion are the most common HRCT findings in SSc patients.

Limitations

The retrospective study design is the main limitation. Since the study had a retrospective design, diffusion capacity of the patients could not be measured. Sample size of the study is acceptable when compared with several previous studies. However, subgroup analysis could not be performed because the number of patients was too small to perform statistical analysis.

CONCLUSION

Pulmonary involvement in SRDs can present with various symptoms and radiological images, and events in asymptomatic patients. PFTs can be normal as well as an obstructive, restrictive or mixed pattern can be seen. In conclusion, proper diagnosis and management of pulmonary involvement are crucial in SRD patients.

Ethical Committee Approval: This study was obtained from Tokat Gaziosmanpaşa University Ethical Committee (Decision No: 83116987-GRI Date: 24.09.2019)

CONFLICT of INTEREST

The authors of this meta-analysis declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ACP, TE

Analysis/Interpretation: ACP, HİK, HİY

Data Acquisition: ACP, HİY, RYÇ

Writing: ACP

Clinical Revision: ACP, TE, HİK

Final Approval: ACP, HİY, HİK, RYÇ, TE

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