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Connective tissue disease related interstitial lung disease: a single center experience

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ABSTRACT

Objectives: We aimed to determine the clinical features of the patients followed by our hospital with the diagnosis of connective tissue disease related interstitial lung disease (CTD-ILD).

Methods: The study included 113 patients who were followed up with the diagnosis of CTD-ILD, admitted to Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Rheumatology Department between January 2019 and December 2020. Demographic characteristics, laboratory data and high-resolution computed tomography (HRCT) patterns of the patients were recorded retrospectively.

Results: Of 113 patients diagnosed with CTD-ILD; 90 were female, 23 were male. When the distribution of connective tissue disease (CTD) evaluated; 50 were rheumatoid arthritis, 41 were systemic sclerosis, 8 were sjogren's syndrome, 4 were systemic lupus erythematosus, 7 were overlap syndrome and 3 were undifferentiated connective tissue disease. There was no statistically significant difference between laboratory parameters. In the HRCT evaluation, 86 patients had nonspecific interstitial pneumonia (NSIP), 25 patients had usual interstitial pneumonia (UIP), and 2 patients had lymphocytic interstitial pneumonia (LIP) pattern. The most common pattern, including rheumatoid arthritis, was NSIP.

Conclusions: In our study, as inconsistent with the literature the most common pattern in RA patients was found to be NSIP.

Keywords: Interstitial lung disease, connective tissue disease, radiological pattern

Connective tissue diseases (CTD) are a group of systemic disorders characterized by autoimmunity and autoimmune-mediated organ damage. Although the incidence of CTD varies in many studies, the general incidence rate in the world is accepted as 1-3% [1].

The lung is a common target and all components of the respiratory system (pleura, interstitium, large and small airways, vascular structures) are at risk [1]. The pathologies that most affect mortality and morbidity are interstitial lung disease and pulmonary hypertension. The main causes of interstitial lung disease (ILD) due to CTDs are: Systemic sclerosis (SSc), Rheumatoid Arthritis (RA), Systemic Lupus Erythe-

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matosus (SLE), Sjögren's Syndrome (SjS), Overlap syndrome (OLS), and Undifferentiated Connective Tissue Disease (UnCTD). High Resolution Computed Tomography (HRCT) is accepted as the gold standard noninvasive imaging method in the diagnosis of CTD-ILD [2, 3].

The radiologic interstitial pneumonia (IP) patterns of CTD-ILD are; nonspecific IP (NSIP), usual IP (UIP), organizing pneumonia (OP), respiratory bronchiolitis-associated ILD (RB-ILD), desquamative IP (DIP), diffuse alveolar damage (DAD), and lymphocytic IP (LIP) [2, 4].

The histopathological and radiological features of ILDs associated with CTDs are the same as their idiopathic counterparts. The histopathologic findings of CTD-ILD are follicular lymphoid hyperplasia and prominent plasma cell infiltration in interstitial inflammation suggestive of interstitial pneumonia [5].
Previous studies have clearly shown that the presence of CTD in ILD has great impact on the prognosis. Progressive fibrosing interstitial lung disease (PF-ILD) is a phenotype defined by rapid clinical progression towards respiratory failure. While idiopathic pulmonary fibrosis is the archetype of PF-ILD, CTD-ILD can also manifest as PF-ILD [6].

The treatment option is given according to the underlying CTD disease. Due to complexities in diagnosis and treatment of CTD itself and lack of evidence, current guidelines do not clearly provide strategies for evaluation and management of CTD-ILD despite its significance [7].

As a general opinion the NSIP pattern is more common in all CTD-ILDs except RA [4]. However, studies in recent years have shown that there may be epidemiological variations [8-10]. But epidemiological studies on CTD-ILD are limited. Based on this idea, in this study, we aimed to retrospectively evaluate the laboratory and radiological features of CTD-ILD patients in Kahramanmaraş city, located in the Eastern Mediterranean region of Turkey.

METHODS

The files of a total of 1589 patients, diagnosed with RA according to 2010 ACR/EULAR (American College of Rheumatology/ European Alliance of Associations for Rheumatology) classification criteria, diagnosed with systemic sclerosis according to 2013 ACR/EULAR classification criteria, Sjögren's disease according to 2016 ACR/EULAR classification criteria, diagnosed with SLE according to the 2012 SLICC (Systemic Lupus International Collaborating Clinics) classification criteria, and diagnosed with overlap syndrome and Undifferentiated Connective Tissue Disease (UnCTD) in line with EULAR and ACR recommendations followed up in the outpatient clinic of Kahramanmaraş Sütçü İmam University Faculty of Medicine, Rheumatology Department between January-2019 and January-2020 were scanned retrospectively . 113 CTD-ILD patients identified.

Radiological pattern, Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), Pulmonary Function Test (PFT) values of 113 CTD-ILD patients were scanned. Laboratory and spirometry data closest to the date of radiological diagnosis of ILD were noted. As a general approach in our hospital, HRCT examination for CTD-ILD is performed when respiratory system related symptoms or signs develop. Those with chronic or acute lung disease other than CTD-ILD were excluded.

The approval for the study was obtained from the Clinical Research Ethics Committee of Kahramanmaras Sutcu Imam University, Faculty of Medicine, with the number of 29.04.2021-191.

Our research is a retrospective descriptive study. Since it is a retrospective descriptive study, tables and graphs were created by giving the ratios. Statistical evaluation and p-value not studied.

RESULTS

If we look at the gender distribution, male/female ratio was 289/1281 of a total of 1589 CTD. HRCT of 113 patients was compatible with CTD-ILD and disease distribution was as follows; 50 RA, 41 SSc, 8 SjS, 4 SLE, 7 OLS and 3 UnCTD. The female/male ratio of 113 patients was 90/23. The male/female ratios of RA, SSc, OLS and UnCTD patients were 13 (26%)/37 (74%), 6 (14%)/35 (85.4%), 2 (28.5%)/5 (71.5%), 2 (66.3%)/1 (33.3%), respectively. SLE and SjS patients were all female.

The mean age of the RA patients was 64.7 ± 9.5 years, the mean age of the SSc patients was 56.6 ± 12

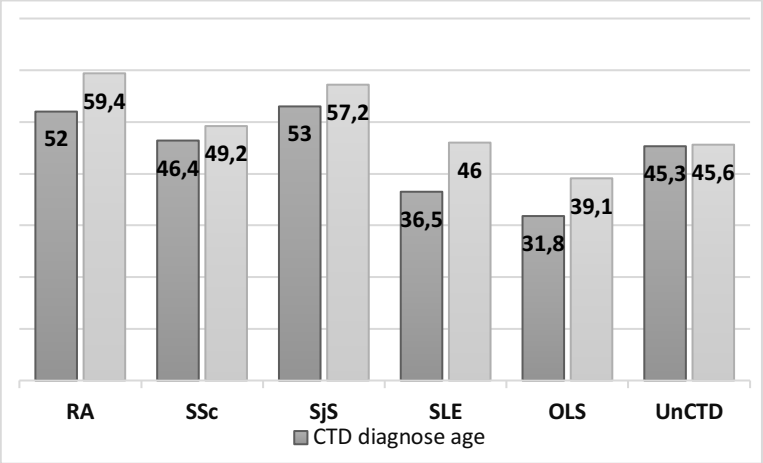

Fig. 1. The mean age of CTD diagnosis and the mean age of CTD-ILD diagnosis. RA = Rheumatoid Arthritis, SSc = Systemic Sclerosis, SjS = Sjogren's Syndrome, SLE = Systemic Lupus Erythematosus, OLS =Overlap syndrome, UnCTD = Undifferentiated Connective Tissue Disease, CTD = Connective Tissue Disease, CTD-ILD = Connective Tissue Disease related Interstitial Lung Disease

years, the mean age of the SjS patients was 61.3 ± 12.1 years, the mean age of the SLE patients was 50.2 ± 10.3 years, the mean age of the OLS patients was 45.1 ± 14.9 years and the mean age of the UnCTD patients was 52.3 ± 11.5 years.

The mean age of CTD diagnosis and the mean age of CTD-ILD diagnosis in different CTD diseases were mentioned in Fig. 1. FEV1, FVC and FEV1/FVC values of the patients were examined (Fig. 2). But we were able to access the spirometry records of only 69 of 113 patients. Laboratory parameters are summarized in Table 1. The radiological patterns of patients are summarized in Table 2.

When we analyzed ESR and CRP values between NSIP and UIP patterns; the mean ESR value for the NSIP pattern was 31.62 ± 20.73 mm/h, while it was found to be 29.04 ± 18.57 mm/h for the UIP pattern ($p > 0.05$). When the LDH values were examined, the mean LDH value was 230.46 ± 66.70 U/L in NSIP pattern and 265.08 ± 146.45 U/L in UIP pattern. No significant difference was observed between NSIP and UIP patterns in terms of LDH level ($p = 0.08$). When the mean CRP values were considered, the mean CRP in patients with NSIP pattern was 20.21 ± 33.45 mg/L, and the mean CRP value in patients with UIP pattern was 9.12 ± 6.80 mg/L. According to this result, the CRP value in patients with NSIP pattern was significantly higher than those with UIP pattern ($p = 0.005$).

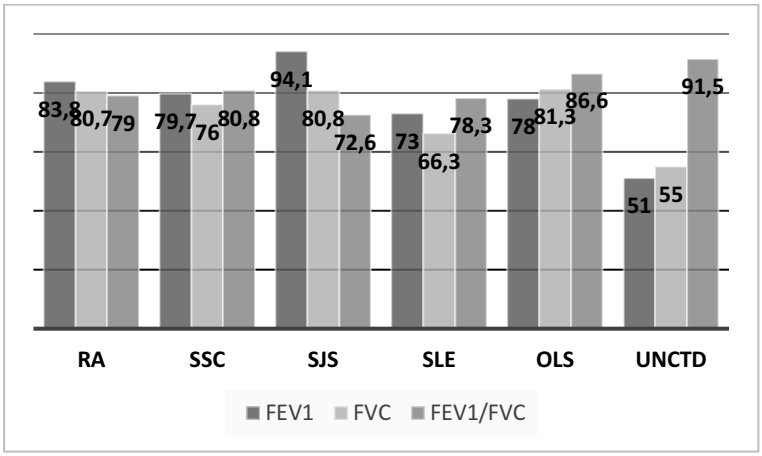

Fig. 2. Spirometry values of patients at the time of radiological diagnosis of CTD-ILD. FEV1 = Forced Expiratuar Volume in 1 second, FVC = Forced Vital Capacity, RA = Rheumatoid Arthritis, SSc = Systemic Sclerosis, SjS = Sjogren's Syndrome, SLE = Systemic Lupus Erythematosus, OLS = Overlap syndrome, UnCTD = Undifferentiated Connective Tissue Disease

Table 1. Laboratory characteristics of CTD-ILD patients

	CRP (mg/L)	ESR (mm/h)	LDH (U/L)	WBC ($\times10^9$/L)	Neutr ($\times10^9$/L)	Lymp ($\times10^9$/L)	Hb g/dL	PLT ($\times10^9$/L)
RA	27.2 ± 5.8*	32 ± 21.3	238.9 ± 91.1	8.4 ± 3.2	6.51 ± 1.05	2.28 ± 0.9	12.1 ± 2	301.6 ± 92.5
SSc	8.3 ± 1.5*	29.7 ± 17.7	260.8 ± 126	7.7 ± 3.3	6.58 ± 0.78	2.14 ± 0.73	12.4 ± 2.1	311.1 ± 109
SjS	11 ± 5.1*	47 ± 38.4	193.7 ± 47.1	8.4 ± 3.9	5.81 ± 1.14	2.33 ± 1.11	11.7 ± 4.3	326 ± 167.6
SLE	19.7 ± 16.8	39 ± 29.2	273 ± 51.3	7.8 ± 3.6	6.7 ± 1.43	2.3 ± 1.23	10.8 ± 1	298.2 ± 181
OLS	10.7 ± 7.9	28.2 ± 11.7	214.1 ± 35.4	14.6 ± 5.7	6.94 ± 0.48	1.9 ± 0.46	12.6 ± 2.1	384.5 ± 174
UnCTD	12 ± 10	26 ± 15.5*	255.6 ± 15	10.1 ± 1.3	6.33 ± 0.57	2.2 ± 0. 1	15.2 ± 1.8	258 ± 31.2

CRP = C-Reactive Protein, ESR = Erythrocyte Sedimentation Rate, LDH = Lactate Dehydrogenase, WBC = White Blood Cell, Neutr = Neutrophil, Lymp = Lymphocyte, Hb = Hemoglobin, PLT = Platelet, RA = Rheumatoid Arthritis, SSc = Systemic Sclerosis, SjS = Sjogren's Syndrome, SLE = Systemic Lupus Erythematosus, OLS=Overlap syndrome, UnCTD = Undifferentiated Connective Tissue Disease

*Standart error

DISCUSSION

Kahramanmaraş province is located in Eastern Mediterranean region, and our study is the first study to investigate the general characteristics of CTD-ILDs in this region.

In our clinic RA was the most common, and other diseases were SjS, SLE, SSc, OLS, and UnCTD in order of frequency. ILD was developed in 7.2% (n = 113) of these 1589 patients. The highest incidence of ILD development was in SSc (54%). ILD was developed in 4.4% of RA patients, and this rate was found to be quite low in other CTDs. The present findings were found to be compatible with the literature [8, 9]. When the gender distribution of all 1589 patients diagnosed with CTD with and without lung involvement was examined, the number of female patients (n = 1281) was approximately four times higher than that of men (n = 289). The gender distribution of 113 patients with lung involvement was similar to the general population, with the number of female (n = 90) nearly four times higher than that of men (n = 23). These findings were consistent with the literature [13, 14].

According to the literature data, while RA is common in female in the community, it is more likely to cause ILD in men. When we evaluated the patients with RA in our study, ILD was developed in 5.5% of male patients with RA, while this rate was 4.1% in female patients. From this point of view, the rate of ILD development was higher in male RA patients, which seemed compatible with the literature [15, 16].

When RA-ILDs were evaluated within them-

Table 2. Radiological patterns of patients

Disease, n (%)	Radiological pattern		
	UIP	**NSIP**	**LIP**
RA (n = 50)	9 (18%)	41 (82%)	-
SSc (n = 41)	14 (34.1%)	27 (65.9%)	-
SjS (n = 8)	-	6 (75%)	2 (25%)
SLE (n = 4)	-	4 (100%)	-
OLS (n = 7)	1 (14.2%)	6 (84.8%)	
UnCTD (n = 3)	1 (33.3%)	2 (66.3%)	

RA = Rheumatoid Arthritis, SSc = Systemic Sclerosis, SjS = Sjogren's Syndrome, SLE = Systemic Lupus Erythematosus, OLS =Overlap syndrome, UnCTD =Undifferentiated Connective Tissue Disease, NSIP = Nonspecific Interstitial Pneumonia, UIP = Usual Interstitial Pneumonia, LIP =Lymphocytic Interstitial Pneumonia

selves, the number of female (n:37) RA-ILD patients was three times higher than that of men (n:13). In studies evaluating the gender distribution among RA-ILD patients, there are articles that support our study, indicating that it is more common in female. For example, in the study performed by Zang *et al*. [17], 64% of RA-ILD patients were found to be female, while Jayasinghe *et al*. [18] found 52.8% to be female in both studies, it was stated that female predominance was more common in RA-ILD, contrary to the general belief. They explained this situation with epidemiological variation. However, in both studies, gender distribution was evaluated within patients with RA-ILD. Namely, these studies did not mention what percentage of male RA patients develop ILD.

In our study, RA and SjS patients had both CTD and CTD-ILD diagnosis at an older age than the other groups. Zamora *et al*. [19], in their study with 181 patients at the Mayo clinic between 1998 and 2015, found the age of diagnosis of RA as 58.5 ± 13.5 years and the age of RA lung involvement as 67.4 ± 9.9 years, similar to our study. The age ranges reported for the diagnosis of SjS-ILD in the literature are quite wide. For example, in a study including 178 patients with SjS diagnosis, Goa *et al*. [20] calculated the median age of the SjS-ILD group as 61.59 ± 11.69 advanced age, similar to our study.

The age at which the patients were diagnosed with CTD and CTD-ILD were similar for the SSc and UnCTD groups. The age at diagnosis for SLE was 36.5 ± 9.8 years, and the age of lung involvement was 46 ± 10.6, which was consistent with the literature [21].

The earliest age at diagnosis of CTD (31.8 ± 17.6) and the earliest age of lung involvement (39.1 ± 13.4) were OLS patients. More than one CTD is present in OLS. Therefore, we think that the symptoms, signs and complications of diseases may contribute to both early diagnosis and acceleration of progression by creating a synergistic effect.

The time between the diagnosis of CTD and lung involvement was the longest in SLE, and the shortest in UnCTD.

Both CRP and ESR values of the patients were above the normal range in all groups, and the CRP value was the highest in the RA-ILD group. The plasma CRP concentration above 10 mg/L CRP in healthy adults is considered high. There are studies indicating that CRP levels are persistently above 20 mg/L in RA patients [22]. However, all of these studies are randomized controlled drug studies, and retrospective and observational real-life studies argue that CRP levels may be normal even when the disease is active in the joint [23, 24].

Yang *et al*. [24] found the basal CRP level to be (29.5 ± 35.3 mg/L) in patients with RA-ILD as similar our study. CRP is a general marker of systemic inflammation and is moderately correlated with hard-to-reach tests such as IL-6 [24]. However, a threshold value that can be used to predict radiological progression has not yet been determined.

Kaduri *et al*. [25] investigated the parameters that may play a role in the early diagnosis of ILD in RA in a study that screened 52 RA-ILD patients. They argued that the high ESR level (median value: 50 mm/h [min:30, max: 77]) could guide the prediction of ILD in RA patients.

In our study, the mean ESR value was found to be higher than normal although it was not as high as in this study. We think that CRP and ESR can be a guide in predicting lung involvement in RA patients.

Spirometry is widely used in the diagnosis of ILD, and the most common restrictive pattern is seen [30]. In the restrictive pattern, FEV1 and FEV1/FVC were normal or above normal, while the FVC value decreased. In our study we were able to access the spirometry records of only 69 of 113 patients. For this reason, we did not consider it appropriate to discuss the spirometry results.

When radiological patterns are compared, between UIP and NSIP patterns; There was no statistically significant difference in gender, time between CTD and CTD-ILD development, age at developing CTD-ILD, ESR and CBC values. However, CRP was significantly higher in patients with NSIP pattern compared to those with UIP pattern ($p = 0.005$). According to literature data, UIP is the most common radiological pattern in patients with RA-ILD [32]. Zamora *et al*. [16] were examined CT scans of 63 RA-ILD patients in North America and UIP pattern was found in 26 (41%) patients, NSIP pattern was found in 19 (30%) patients, bronchiolitis was found in 11 (17.4%) patients, and OP was found in 5 (8%) patients. Kelly *et al*. [13] were examined RA-ILD types in a study in England, they found the most common pattern as UIP with a rate of 44-66%, and the NSIP pattern was observed with a

rate of 24-44%. Again, Kelly *et al*. [13] was found the patterns of RA-ILD patients as; 65% UIP, 24% NSIP, and 5% OP in a large multicenter study in the UK. Nakamura *et al*. [33], in a study with 54 patients in Japan, found the most common pattern as NSIP (30%), followed by the UIP pattern with (28%) patients. In the study with 237 RA-ILD patients in China performed by Zhang *et al*. [14], 137 patients (57.8%) were found to have NSIP, and 44 patients (18.6%) were found to have UIP. Jayasinghe *et al*. [15] found that the NSIP pattern (55.8%) was more common than the UIP pattern (34.9%) on HRCT in 44 RA-ILD patients in Sri-Lanka. In our study, 9 (18%) patients with RA-ILD had UIP, while 41 (82%) patients had NSIP pattern. According to these data, it was thought that the radiological pattern in RA-ILD showed epidemiological variation, while UIP was more common in western societies, NSIP was more common in eastern societies.

HRCT is performing to RA patients in our clinic when there are respiratory system-related symptoms, signs or worsening in pulmonary function tests compared to baseline. Li *et al*. [7] scanned 1121 RA patients with HRCT and they found that 30.12% had ILD. They reported that 39.12% of the patients with RA-ILD had respiratory symptoms. HRCT is considered as the most sensitive method in the diagnosis of ILD. From this point of view, undetected ILD is possible in our RA patients who did not undergo HRCT because they did not have respiratory system-related symptoms.

Diffuse ground glass infiltrates are often seen on HRCT in Ssc-ILD, generally consistent with NSIP. Coarse reticulation and honeycomb appearance are less common. Bourus *et al*. [34] found NSIP (commonly fibrotic NSIP) in 77% of 80 patients diagnosed with SSc-ILD, and UIP in 23%. In our study, there were 14 (34.1%) patients with UIP and 27 (65.9%) patients with NSIP pattern, and the results are consistent with the literature.

The most common radiologic pattern of SLE-ILD was found to be NSIP. Although ILD is seen at a lower rate in SLE than in other CTD, NSIP pattern was seen in all patients in our study [35].

LIP is the most common radiological pattern in SjS, and it is a benign pathology that occurs with bronchial-associated lymphoid tissue (BALT) proliferation. It is seen in 1% of SjS. In our study, NSIP pattern was observed in 6 (75%) patients, and LIP pattern was observed in 2 (25%) patients. The results were consistent with the literature [36].

These different patterns of involvement in CTD-ILD patients are also important for early treatment and the selection of the right treatment in the prevention of respiratory failure [37].

Limitations

The limitations of our study are as follows: Our study includes only the patients in Kahramanmaraş region and CTD patients without respiratory symptoms were not screened with HRCT only patients with clinically suspected ILD were screened with HRCT.

CONCLUSION

According to the literature data, while RA is common in female in the community, it is more likely to cause ILD in men. But it should be noted that when RA-ILDs were evaluated within themselves, the number of female RA-ILD patients was higher than that of men. We think that the symptoms, signs and complications of OLS and UnCTD diseases coexistence of two or more CTD disease features may contribute to both early diagnosis and acceleration of progression by creating a synergistic effect. We think that CRP and ESR height can be a guide in predicting lung involvement in RA patients. ILD patterns of CTD patients may show ethnic differences. More research is needed in this area. There is not yet a multicenter study in our country that collects demographic data on CTD-ILD and compares it with the world literature. We hope that our study, which includes single center data, will shed light on more comprehensive studies.

Authors' Contribution

Study Conception: TG, NA, GYÇ, BA, FB, BK, AÇ, HK; Study Design: TG, NA, GYÇ, BA, FB, BK, AÇ, HK; Supervision: TG, NA, GYÇ, BA, FB, BK, AÇ, HK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: TG, NA, GYÇ, BA, FB, BK, AÇ, HK; Statistical Analysis and/or Data Interpretation: TG, NA, GYÇ, BA, FB, BK, AÇ, HK; Literature Review: TG, NA, GYÇ, BA, FB, BK, AÇ, HK; Manuscript Preparation: TG, NA, GYÇ and Critical Review: NA, GYÇ.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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