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Assessment of the clinical features of rheumatoid arthritis-related interstitial lung diseases: a retrospective evaluation

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Abstract. – OBJECTIVE: Rheumatoid Arthritis (RA) stands as the most prevalent form of inflammatory arthritis, affecting approximately 1% of the population. Among individuals diagnosed with RA, a notable proportion, ranging from 10% to 40%, also experience Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD). This coexistence of RA and ILD has been identified as a detrimental factor contributing to increased mortality rates. Furthermore, RA-ILD often exhibits an insidious nature, posing challenges in its timely detection and management. Hence, our objective was to conduct a retrospective analysis of the clinical characteristics observed in patients who underwent evaluation for RA-ILD.

PATIENTS AND METHODS: A total of 87 patients who were evaluated for RA-ILD within one year were included in the study. This study was conducted retrospectively using a cross-sectional and descriptive approach to analyze the demographic and clinical data of the included patients.

RESULTS: Among the 87 patients, eight were diagnosed with RA-ILD, with four being male and four being female. Of the eight patients, two had non-specific interstitial pneumonia, five had usual interstitial pneumonia, and one had nodules consistent with RA. Subpleural fibrosis increased the likelihood of RA-ILD by 6.9 times. In the group with ILD, the residual volume and total capacity were found to be lower compared to the other group. Among the eight patients diagnosed with RA-ILD, five had used methotrexate before the diagnosis.

CONCLUSIONS: In order to mitigate the risk of delayed diagnosis of RA-ILD, which can lead to increased mortality and has a subtle onset, it is recommended that patients with RA who possess certain risk factors undergo regular monitoring. It is advisable for RA patients to undergo annual assessments involving carbon monoxide diffusion capacity and spirometry function tests. In cases, where deemed necessary, more advanced investigations such as high-resolution computed tomography should be conducted.

Key Words:
Rheumatoid arthritis, Interstitial lung disease, Carbon monoxide diffusion capacity, Spirometric function tests.

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, with a 0.2-1% prevalence. The incidence in men ranges from 12 to 70 per 100,000 individuals, while in women, it ranges from 25 to 130 per 100,000. The male-to-female ratio is approximately 1:3[1]. Although joint involvement is the most well-known manifestation, RA is a systemic disease with many extra-articular manifestations[2]. In addition to joint involvement, RA can also be associated with extra-articular manifestations such as skin, ocular, cardiac, neurological, vascular, renal, musculoskeletal, and pulmonary. One of the most known extra-articular involvement is interstitial lung disease (ILD), observed in 10-40% of patients diagnosed with rheumatoid arthritis[3].

The importance of recognizing RA-ILD is in its relationship with mortality. ILD has prognostic implications, as RA patients with ILD have a three-fold higher risk of mortality than those without ILD[2,4]. Age, male gender, tobacco use, genetic predisposition, and disease severity are considered risk factors for RA-ILD[5]. The most specific non-invasive method for diagnosing RA-ILD is performing a high-resolution computed tomography (HRCT) of the chest[6]. In conjunction with HRCT, measurement of the Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) and pulmonary function testing (PFT) assist in demonstrating small airway involvement and indicating ILD. HRCT can provide patterns such

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as Organizing Pneumonia (OP), Usual Interstitial Pneumonia (UIP), and Non-specific Interstitial Pneumonia (NSIP). The most common type of RA-ILD is the UIP pattern[7]. Due to factors such as aging and comorbidities, pulmonary biopsy is not a commonly favored diagnostic method in cases of suspected ILD due to the potential risk of complications. HRCT and PFT are two non-invasive methods that are easily accessible. When comparing the effectiveness of HRCT and PFT in detecting and monitoring ILD, PFT has been found to be more successful. HRCT and PFT hold distinct significance in the diagnosis and monitoring of ILD. Mainly, HRCT takes precedence for assessing the pattern of pulmonary involvement[8]. There is a lack of evidence-based, widely accepted recommendations and algorithms for the follow-up and treatment of RA-ILD. More research and data are needed in this area. Diagnosing RA-ILD can be challenging, and relies on laboratory parameters, HRCT findings, and histopathological methods[9].

Until now, there has been a lack of consensus on treatment options that would effectively improve pulmonary fibrosis in patients with RA-ILD or lead to improvements significant enough to be reflected in PFT. Iguratimod, a disease-modifying antirheumatic drug currently used to treat RA, has been gaining evidence of its positive contributions in managing RA-ILD[10].

In this study, considering the insufficient evidence-based recommendations and algorithms for evaluating and treating RA-ILD, we aimed to retrospectively evaluate the clinical characteristics of patients who presented to our clinic within one year and were assessed for RA-ILD. Additionally, we aimed to assess the methods we applied to treat these patients.

Patients and Methods

A total of 87 patients diagnosed with RA according to the 2010 American College of Rheumatology RA classification criteria, aged 18 and above, and who underwent evaluation for RA-ILD through HRCT, PFT, and clinical assessment were included in the study. Patients under 18, those with an inconclusive diagnosis of RA, and those not evaluated for RA-ILD were not included in the study. The radiological classification of RA-ILD patients was determined by an expert radiologist based on HRCT findings, categorizing them as NSIP, UIP, NSIP-UIP overlap, LIP, and others that did not fit into these categories. Demographic and laboratory data that could serve as risk factors for RA-ILD were recorded from the hospital information system. This study was designed retrospectively as a 1-year cross-sectional observational study.

Statistical Analysis

Descriptive analyses were conducted to provide information about the general characteristics of the study population. Due to the non-normal distribution of patients in the RA-ILD and non-RA-ILD groups, non-parametric tests were used in this retrospective, cross-sectional, descriptive study. The Mann-Whitney U test was used for comparing numerical variables, while Fisher's exact Chi-square test was used for categorical variables. Numerical variables were expressed as median [interquartile range], and categorical variables were presented as numbers (%). The odds ratio was calculated to determine the risk of RA-ILD in the presence of velcro rales, and it was expressed with a confidence interval. A significance level of $p<0.05$ was considered statistically significant. IBM SPSS 23 (IBM Corp., Armonk, NY, USA) software was used for statistical analysis.

Results

The median ages [interquartile range] of all patients, non-RA-ILD patients, and RA-ILD patients were 59 [18], 59 [18], and 59 [13.5], respectively. The distribution of gender in the groups was as follows: female (percentage within the group) 64 (73.56%), 23 (26.44%), male (percentage within the group) 60 (75.95%), 19 (24.05%), 4 (50%), 4 (50%). The median duration since the diagnosis of RA was 3 [10], 4 [11], and 1 [6.5] years. Among smokers, the median values of pack years were 0 [15], 0 [15], and 5 [22.5]. The number of former smokers (percentage within the group) was 18 (20.69%), 15 (18.99%), 3 (37.5%), while the number of current smokers was 15 (17.24%), 14 (17.72%), 1 (12.5%). The number of individuals who never smoked was 54 (62.07%), 50 (63.29%), and 4 (50%). There was no statistically significant difference between these data ($p>0.05$).

A comparison of comorbidities, including ischemic heart disease, chronic obstructive pulmonary disease (COPD), asthma, and chronic bronchitis, between patients with and without RA-ILD was performed. No statistically significant difference was observed among these variables ($p>0.05$).

A comparison was made regarding the medications used by patients with and without RA-ILD. In the RA-ILD group, 7 patients (87.5%) did not use methotrexate, while 1 (12.5%) used it. In the RA-ILD-free group, 39 patients (49.37%) did not use methotrexate, while 40 (50.63%) used it. However, this difference was not statistically significant (p=0.061). In the RA-ILD group, 5 patients (62.5%) did not use rituximab, while 3 (37.5%) used it. In the group without RA-ILD, 78 patients (98.73%) did not use rituximab, and 1 patient (1.27%) used it. A statistically significant difference was observed between the two groups regarding rituximab use (p=0.002), (Table I).

The Disease Activity Score with 28 joint (DAS28) evaluations based on the medical history and physical examination findings were categorized according to disease activation in patients with and without RA-ILD. In the RA-ILD group, 4 out of 8 patients (50%) had disease activation, while in the group without RA-ILD, 60 out of 79 patients (75.95%) did not have disease activation. The difference in disease activation between the two groups was not statistically significant (p>0.05).

Regarding lung auscultation, 50% of patients in the RA-ILD group had velcro rales, while only 12.66% of patients in the non-RA-ILD group had velcro rales. This difference was statistically significant (p=0.021), indicating a higher prevalence of velcro rales in the RA-ILD group compared to the group without RA-ILD.

Antinuclear antibody (ANA) was categorized as positive or negative. Rheumatoid Factor (RF) and anti-cyclic Citrullinated Peptide (anti-CCP) levels were calculated numerically and categorized as unfavorable up to the upper limit of normal (RF: 0-15.9, anti-CCP: 0-5), low positive from the upper limit to three times the upper limit, and high positive for values greater than three times the upper limit. Anti-double-stranded DNA (anti-ds-DNA) was categorized as positive or negative. When autoimmune diseases and RA-related parameters were compared between RA-ILD patients and those without, no statistically significant difference was found (p>0.05).

The carbon monoxide diffusion test (DLCO) and spirometric pulmonary function tests, including Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), maximal expiratory flow 25-75 (MEF25-75), total capacity, residual volume, DLCO, and Diffusing Capacity of the Lungs for Carbon Monoxide divided

Table I. Comparison of demographic characteristics, chronic diseases, and medications between two groups with and without rheumatoid arthritis-associated lung disease.

		Total (n=87)	Without ILD (n=79)	With ILD (n=8)	p
Gender	Female	64 (73.56%)	60 (75.95%	4 (50%)	0.2
	Male	23 (26.44%)	19 (24.05%)	4 (50%)	
Age, year		59 [18]	59 [18]	59 [13.5]	0.406
RA diagnosis duration, year		3 [10]	4 [11]	1 [6.5]	0.141
Smoking status	Ex smoker	18 (20.69%)	15 (18.99%)	3 (37.5%)	0.5
	Continues to smoke	15 (17.24%)	14 (17.72%)	1 (12.5%)	
	Never smoked	54 (62.07%)	50 (63.29%)	4 (50%)	
Cigarettes (Pack/Year)		0 [15]	0 [15]	5 [22.5]	0.573
Chronic diseases					
Ischemic heart disease	+	6 (6.9%)	5 (6.33%)	1 (12.5%)	0.45
Chronic obstructive pulmonary disease	+	0 (0%)	0 (0%)	0 (0%)	NA
Asthma	+	5 (5.75%)	4 (5.06%)	1 (12.5%)	0.39
Chronic bronchitis	+	0 (0%)	0 (0%)	0 (0%)	NA
Medications used for rheumatoid arthritis					
NSAII	+	1 (1.15%)	1 (1.27%)	0 (0%)	1
Steroid	+	72 (82.76%)	66 (83.54%)	6 (75%)	0.622
Methotrexate	+	41 (47.13%)	40 (50.63%)	1 (12.5%)	0.061
anti-TNF	+	6 (6.9%)	6 (7.59%)	0 (0%)	1
Leflunomide	+	24 (27.59%)	22 (27.85%)	2 (25%)	1
Hydroxychloroquine	+	11 (12.64%)	8 (10.13%)	3 (37.5%)	0.06
Sulfasalazine	+	3 (3.45%)	3 (3.8%)	0 (0%)	1
Rituximab	+	4 (4.6%)	1 (1.27%)	3 (37.5%)	0.002

Interstitial lung disease: ILD. Comparisons were made using Mann-Whitney U test for numerical variables and Fisher's exact test for categorical variables. The median [interquartile range] value for numeric variables is expressed using numeric (%) values for categorical variables.

by Alveolar Volume (DLCO/VA) parameters were compared between patients with RA-ILD and those without. In the non-RA-ILD group, the DLCO % was 85 [21], while in the RA-ILD group, it was 63 [22]. However, the difference between the groups was insignificant (p>0.063). The total capacity % in the non-RA-ILD group was 88 [20], whereas it was 75 [33] in the RA-ILD group, and there was a statistically significant difference (p=0.019) between the groups. The residual volume % was 103 [37] in the non-RA-ILD group and 71 [45] in the RA-ILD group, showing a statistically significant difference (p=0.018) (Table II).

The presence of velcro rales on lung auscultation was investigated as a potential risk factor for RA-ILD using the odds ratio. The likelihood of developing RA-ILD was 6.9 times higher (95% CI: 1.485-32.07) in the presence of velcro rales (p=0.021).

Discussion

In a cross-sectional study, the mean age at RA-ILD diagnosis was 59.9 (±11.89) years, and the median duration from RA diagnosis to RA-ILD diagnosis was 40 months[11]. In our study, the age of RA-ILD diagnosis was 59 years (minimum 49, maximum 87), and the median duration from RA diagnosis to RA-ILD development was two years (minimum 0, maximum 49). These results are consistent with the literature.

A cohort study[3] comprising 31,333 patients detected RA-ILD in 679 (2.2%) patients. In a cohort study[12] that followed patients with RA for approximately 16 years, the estimated prevalence was around 4-8%. The cumulative incidences for 10, 20, and 30 years were found to be 3.5%, 6.3%, and 7.7%, respectively. This indicates that the rate of RA-ILD has increased over the years. In another study[13] involving 2,702 patients diagnosed with RA,

Table II. Comparison of clinical and laboratory findings between two groups with and without rheumatoid arthritis-associated lung disease.

Variables		Total (n=87)	Without ILD (n=79)	With ILD (n=8)	p
DAS28	In remission	64 (73.56%)	60 (75.95%)	4 (50%)	0.2
	Low, medium and high activation	23 (26.44%)	19 (24.05%)	4 (50%)	
Velcro rales	-	73 (83.91%)	69 (87.34%)	4 (50%)	0.021
	+	14 (16.09%)	10 (12.66%)	4 (50%)	
ANA	<1:320	61 (70.93%)	56 (70.89%)	5 (71.43%)	1
	≥1:320	25 (29.07%)	23 (29.11%)	2 (28.57%)	
RF, IU/mL		15 [80]	15 [83]	24 [77]	0.55
RF	Negative, [0-16] IU/mL	44 (51.16%)	41 (51.9%)	3 (42.86%)	0.575
	Low positive, [16-47.7] IU/mL	13 (15.12%)	11 (13.92%)	2 (28.57%)	
	High positive, ≥47.7 IU/mL	29 (33.72%)	27 (34.18%)	2 (28.57%)	
anti-CCP, IU/ml		48 [172.5]	47.5 [147.5]	116 [199.5]	0.948
Anti-CCP	Negative, [0-5] IU/ml	33 (38.82%)	30 (38.46%)	3 (42.86%)	1
	Low positive, [5-15] IU/ml	5 (5.88%)	5 (6.41%)	0 (0%)	
	High positive, ≥15 IU/ml	47 (55.29%)	43 (55.13%)	4 (57.14%)	
C3, mg/dL		1.225 [0.25]	1.22 [0.255]	1.29 [0.23]	0.619
C4, mg/dL		0.235 [0.09]	0.235 [0.09]	0.235 [0.1]	1
Anti-dsDNA, IU/mL	Positive	1 (1.18%)	1 (1.28%)	0 (0)%	1
FEV1, %		89 [25]	89 [25.5]	76 [25]	0.259
FVC, %		86 [24]	86.5 [22,5]	72 [26]	0.172
MEF25-75		92 [40]	93.5 [40]	87 [31]	0.61
Total Capacity, %		87 [20]	88 [20]	75 [33]	0.019
Residual Volume, %		101.5 [40.5]	103 [37]	71 [45]	0.018
DLCO, %		84 [27]	85 [21]	63 [22]	0,063
DLCO/VA, %		94.5 [25]	94 [22]	105 [51]	0.439

DAS28: Disease Activity Score 28, ANA: Antinuclear Antibody, RF: Rheumatoid Factor, Anti-CCP: Anti-Cyclic Citrullinated Peptide, C3-4: Complement, Anti-dsDNA: anti-double-stranded DNA, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, MEF25-75: Maximal Expiratory Flow at 25% to 75% of Forced Vital Capacity, DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide, DLCO/VA: Diffusing Capacity of the Lungs for Carbon Monoxide divided by Alveolar Volume. Comparisons were made using Mann-Whitney U test for numerical variables and Fisher's exact test for categorical variables. The median [interquartile range] value for numeric variables is expressed using numeric (%) values for categorical variables.

the patients underwent HRCT for evaluation, and 261 (9.7%) were diagnosed with RA-ILD. Most patients with RA-ILD are asymptomatic. Clinical manifestations of RA-ILD are observed in approximately 10% of cases[14]. In our study, which followed 87 patients diagnosed with RA, RA-ILD was detected in 8 cases (approximately 10%). This rate was consistent with the literature. If all patients visiting our clinic had undergone HRCT to evaluate for RA-ILD, we would have expected an increase in the proportion of patients diagnosed with RA-ILD.

RA-ILD is associated with almost all histopathological patterns of idiopathic interstitial pneumonia. The most common type is UIP, followed by NSIP. Other patterns that can be observed include OP, NSIP-OP overlap, and LIP[15]. In a study[16] involving 54 patients, the most common histopathological pattern observed on biopsy was NSIP in 16 patients (30%). This was followed by the UIP pattern, identified in 15 patients (28%). A total of 63 patients with RA-ILD were investigated using computed tomography. Among them, 26 patients (41%) were found to have UIP, 19 patients (30%) had NSIP, 11 patients (17.4%) had bronchiolitis, and 5 patients (8%) had OP[17]. In a study[18] examining RA-ILD types, the most common type encountered was UIP, with a frequency range of 44-66%. NSIP was observed in a frequency range of 24-44%. In a large-scale, multicenter study[19] similar to the previous one, the distribution of RA-ILD types was found to be 65% UIP, 24% NSIP, 6% NSIP-OP overlap patterns, and 5% OP pattern. In our study, out of the total cases, 5 (62%) patients showed UIP, 2 (25%) patients showed NSIP, and 1 patient (13%) exhibited a nodular involvement pattern associated with RA. Consistent with the literature, UIP was the most common pattern observed in our RA patients, followed by NSIP. All our patients were diagnosed with RA-ILD based on radiological findings with HRCT, and none of them required a biopsy to diagnose RA-ILD. Indeed, the most common pattern observed the literature is UIP, as also seen in our study. Various factors, such as the inclusion criteria, imaging techniques, histopathological evaluation, and geographical variations, can influence the distribution of interstitial lung patterns in RA-ILD. Therefore, it is essential to consider these factors when interpreting and comparing the findings of different studies. A study[20] shedding light on this issue observed that due to the progressive nature of fibrosis, the boundaries of patterns could not be sharply defined, and significant patterns tend to overlap. It was demonstrated that 27% of the patients in the study exhibited the coexistence of NSIP/UIP patterns.

Some researchers19 compared 230 RA-ILD patients with 230 control RA patients. They found that being male, having a smoking history [35 (15-120) pack-years], positive RF and anti-CCP status, and higher levels of anti-CCP antibodies were statistically associated with an increased risk of RA-ILD. In another study[21], it was reported that RF positivity was significant in the RA-ILD group. However, there was no significant difference in the rates of anti-CCP and ANA positivity when compared. Our study showed no statistically significant difference between the two groups regarding smoking history, anti-CCP, RF, and ANA.

A study[21] involving RA-ILD patients reported that 41% of the patients experienced respiratory symptoms, such as cough and velcro rales were detected upon auscultation. Another study[22] found that 70.2% of the patients had rales detected during lung auscultation. The electronic stethoscope-like VECTOR device can detect velcro rales in RA-ILD patients with an accuracy rate of 85%[23]. In our study, when comparing two groups based on the presence of velcro rales, it was found that 50% of patients in the RA-ILD group had velcro rales, while only 12.66% of patients in the non-RA-ILD group had crepitus rales. When examining the odds ratio to determine whether the presence of velcro rale is a risk factor for RA-ILD, it was found that the likelihood of having RA-ILD was increased by 6.9 times (95% CI: 1.485-32.07) in the presence of crepitus rales (p=0.021).

DLCO-PFT is one of the supportive tests for the diagnosis of RA-ILD. In these patients, it is expected to observe an increase in the FEV1/FVC ratio due to fibrosis, a decrease in lung volumes, and a decrease in carbon monoxide diffusion capacity. Song et al[24] retrospectively examined the course of 84 RA-ILD patients with UIP patterns. They found that the decline in FVC and DLCO over 6 months was associated with mortality[24]. Zamora et al[17] conducted a single-center cohort study involving 181 patients diagnosed with RA-ILD. They found a low baseline DLCO level associated with mortality. The total lung capacity % and residual volume % in the non-RA-ILD and RA-ILD groups were 88 [20], 75 [33], 103 [37], and 71 [45], respectively, indicating that they were lower in the RA-ILD group as expected. The difference in total lung capacity and residual volume between the two groups was statistically significant (p=0.019, p=0.018). The

presence of velcro rales, RF positivity, and male gender, along with other risk factors for RA-ILD, should be considered in the evaluation. Even in the absence of velcro rales, it is argued[25] that performing DLCO-PFT once a year in RA patients and comparing it to previous results would help diagnose asymptomatic RA-ILD.

Drug-induced pneumonitis, mainly induced by methotrexate, has been extensively discussed in the literature. Roubille and Haraoui[26] conducted a systematic review, scanning 910 publications on disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents-induced or exacerbated ILD in RA patients. Their review consisted of 88 references, reporting 32 publications on methotrexate-related pneumonitis, 27 on anti-TNF-related pneumonitis, 12 on leflunomide-related pneumonitis, 5 on tocilizumab-related pneumonitis, 4 on sulfasalazine, and 3 on azathioprine-related pneumonitis. Of the 8 patients diagnosed with RA-ILD, 5 had used methotrexate before receiving the UIP diagnosis. In 3 patients, methotrexate was discontinued, and rituximab was initiated; in 1 patient, leflunomide was discontinued, and rituximab was initiated; and in 1 patient, azathioprine was discontinued, and rituximab was initiated. One patient, initially stable while taking oral methotrexate, was switched to subcutaneous methotrexate. The relationship between methotrexate and RA-ILD is still a matter of debate. The clinician must adjust the treatment based on the patient's clinical presentation and history. Rituximab therapy has been successful for severe refractory RA-ILD in small case series.

Limitations

One of the main limitations of this study is its retrospective design, which introduces inherent constraints. Additionally, the fact that it is a single-center study further limits its generalizability. Another significant limitation is the dissimilarity in patient distribution among the statistically compared groups.

Conclusions

RA-ILD can have an insidious onset at the time of RA diagnosis and is associated with increased mortality. In order to avoid a delayed diagnosis of RA-ILD, it is important to consider risk factors such as anti-CCP and RF positivity, smoking history, male gender, and the presence of velcro rales. Additional advanced investigations such as DLCO-PFT and HRCT can be helpful in clinical evaluation. Further randomized controlled trials are needed to establish widely accepted treatment options for RA-ILD.

Authors' Contributions

Conceptualization: ACG, EG, YA, FTG.
Literature Search: ACG, EG, YA, ZO.
Methodology: ACG, EG, YG, ZO.
Data: ACG, EG, YA, FTG, ABK.
Formal analysis and investigation: ACG, EG, YG, ABK.
Writing - original draft: ACG, EG, FTG, ZO, ABK.
Writing - review and editing: ACG, EG, YG, FTG, ABK.
Supervision: all authors read and approved the final manuscript.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Ethics Approval

The research study strictly followed the ethical guidelines stipulated in the Declaration of Helsinki. Prior to its initiation, the study obtained the necessary ethical approval from the Ethics Committee of Sakarya University Faculty of Medicine (Data: 02.10.2019, Protocol No.: E-71522473-050.01.04-95).

Informed Consent

Informed consent was waived due to the retrospective nature of the study.

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