Original Article

Asymptomatic Interstitial Lung Disease in Patients with Rheumatoid Arthritis

Khalida E. El-Refaei[1], Hend M. Maghraby[1], Bahera M. Fath Allah[2], Hala M. Maghraby[2], Hala K. Keshk[1]

Departments of Internal Medicine[1], Radiology[2], Al-Azhar University, Egypt

ABSTRACT

Background: Rheumatoid arthritis (RA) has long been considered a systemic disease with extra-articular involvement including interstitial lung disease (ILD). ILD is a common extra-articular manifestation of rheumatoid arthritis (RA) and a significant cause of morbidity and mortality. Early detection and treatment for interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) may ameliorate disease progression. **Objectives:** This study was done to evaluate the frequency of asymptomatic interstitial lung disease in patients with rheumatoid arthritis and to compare it with the clinical status. **Methods:** The current study enrolled 60 RA patients were diagnosed according to 2010 ACR-EULAR criteria. All patients were subjected to full history taking and thorough clinical examination. ESR, CRP, Anti CCP and RF were done to the patients. RA disease activity was assessed using DAS 28 score, Radiological joint damage was assessed by larsen score. HRCT and pulmonary function test were also done. **Results:** Out of 60 RA patients 51 had RA-ILD identified by HRCT. There was statistically significant increase in the mean of the age and DAS 28 score among RA patients with ILD when compared to that of the RA patients with out ILD ($P<0.01$ and $P<0.01$). There was a statistically significant positive correlation between HRCT score and disease duration, DAS score and Duration of methotrexate therapy ($P<0.01$ to all). There was a statistically significant negative correlation between HRCT score and (FVC), (FEV1) and (TLC). **Conclusions:** Asymptomatic preclinical ILD has a high prevalence in RA patients, proved by HRCT and pulmonary function test and lung involvement should always be considered in RA patients even in absences of respiratory symptoms. **[Egypt J Rheumatology & Clinical Immunology, 2015; 3(1): 69-75]**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic and inflammatory disease that is primary affecting synovial joints and leading to bone and cartilage destruction, as well as extra-articular manifestations[1].

Interstitial lung disease (ILD) is a common extra-articular manifestation responsible for significant morbidity and mortality among patients with rheumatoid arthritis (RA)[2]. RA-ILD is often asymptomatic, at least initially, clinical detection has been reported to be <5% using plain radiology, but 20-30% with High-Resolution CT (HRCT) [3].

The Early Rheumatoid Arthritis Study (ERAS) group previously showed an association between RA-associated ILD (RA-ILD) and increased age, increased ESR and high HAQ scores in a group of 52 patients with the condition [4]. RA represents additional risk factors for the development of ILD. Reports of the prevalence of RA-ILD are widely variable and likely comprise significant underestimates owing to inconsistency of clinical criteria used to define the condition, methods used for disease detection, and heterogeneity of study populations. Identification of ILD is further confounded by the fact that many of the medications used for the treatment of RA have potential deleterious effects on the lungs[5]. A recent population-based study from the Rochester Epidemiology Project suggested that as many as 1 in 10 patients with RA will be diagnosed with ILD over the course of the disease. An association between positive RF and ILD in RA is well established, and a similar link with antibodies to CCP has been reported[6].

The aim of this study was to evaluate the frequency of asymptomatic interstitial lung disease in patients with rheumatoid arthritis and to compare it with the clinical status.

For Correspondence: khalidabrhm@yahoo.com

PATIENTS AND METHODS

This study was conducted on 60 patients with rheumatoid arthritis fulfilling the 2010 ACR-EULAR classification criteria. They were recruited from Rheumatology and Internal medicine outpatient clinic and the inpatients in internal medicine department, Al Azahraa university hospital.

All patients gave their informed consent prior to their inclusion in the study.

We have excluded: Chronic smokers, other rheumatological diseases as (SLE and systemic sclerosis), Parenchymatous lung diseases and

Inhalation exposure to fibrogenic substances as silicosis.

All patients were subjected to the following:

Full medical history with special emphasis on age, disease duration and drug in use, thorough clinical examination including musculoskeletal system. Functional disability was measured by Health Assessment Questionnaire (HAQ).[7] Assessment of disease activity using disease activity sore 28 (Remission was defined as DAS 28 < 2.6, Low disease activity as DAS 28 ≤ 3.2, Moderate disease activity as DAS 28 > 3.2 to < 5.1 and high disease activity as DAS 28 > 5.1)[8].

Laboratory Assessment:

Routine investigations were collected from patient's records, - Complete blood count (CBC) using coulter counter (T660), Erythrocyte Sedimentation Rate (ESR): first hour by Westegren method. C-reactive protein (CRP) was done by using latex agglutination. Rheumatoid Factor (RF): RF was assayed by using latex agglutination test kits. - Anti-CCP was measured using by latex slide test.

Radiological Assessment:

- Plain X-ray chest, using Northen scoring system[9].
- X ray on both hands, using Larsen scoring method.[10]
- High-Resolution Computed Tomography (HRCT) of the chest and Interpretation of the finding was done by using, Semi quantitative scoring method[11] as follows : (score 0 : normal , score 1: ground glass opacity alone, score 2:mixed ground glass and reticular disease, score 3 :reticular disease alone and score 4: honey combing).

Pulmonary Function Test (PFTs): Pulmonary function was assessed according to American Thoracic Society recommendations[12] using spirometry and expressed as percent predicted: Forced vital capacity (FVC), Forced expiratory volume in the first second (FEV1), FEV1/FVC, Total lung Capacity (TLC).

Statistical Analyses

Statistical analyses were performed using SPSS software. All descriptive data were expressed as mean values ± SD. While Student's t-test was used to compare distributed quantitative data, chi-squared testing with Yates correction was used to compare frequencies. In all analyses, a two-tailed P-value less than 0.05 was considered statistically significant.

RESULTS

The present study was conducted on 60 adult RA patients without respiratory symptoms who were diagnosed according to the 2010 ACR-EULAR criteria. Their age ranged from 21 to 70 years with mean age (47.68±10.73) years. They were 57 (95%) females, 3 (5%) males. The duration of the disease ranged from (2 to 25 years) with mean±SD (9.63±5.71) and the other Characteristics of the patients were shown in Table (1). Out of 60 RA patients 52(86.7) had positive Anti-ccp., Laboratory data of the studied RA patients (Table 2). Categorization of RA patients according to disease activity by DAS 28 score (Figure 1). Out of 60 RA patients 54 was on methotrexate 44 of them had ILD (Table 3).

We have found that 51 (85%) of 60 RA patients had preclinical ILD identified by HRCT and its categorization according HRCT score (Figure 2). Twelve (20%) of 60 RA patients had normal CXR, 6 of them had HRCT finding in the form of ground glass appearance. Comparing between RA patients with and without ILD as regard age and disease activity we found a statistically significant increase in the mean of age, DAS sore and FEV1/FVC in patients with ILD ($p<0.01$, $p<0.01$, $p<0.01$ respectively) but no significant difference as regard other parameters as shown in Table (4).

A significant positive correlation was found between HRCT score and age, disease duration, DAS score, radiological joint damage score and duration of methotrexate therapy as shown in Figures (3,4, 5 and 6).

Table 1. Characteristics of the studied 60 RA patients.

Variable			Range	Mean±SD
Gender	Female: No.	7(95%)		
	Male: No	3(5%)		
Age			21 - 72	47.68±10.37
Disease duration			2 - 25	9.63±5.71
HAQ			1 - 3	1.85±0.82
DAS			2.14-5.30	4.03±0.82

Table 2. Laboratory data of all RA patients.

Variable	Range	Mean±SD	No.60	%
RF (IU/ml)	6-128	60.67±30.15	Positive :58 Negative :2	96.6% 3.34%
Anti ccp (IU/ml)	0.5-150	54.52±35.07	Positive:52 Negative:8	86.7% 13.3%
CRP (mg/dl)	4-48	20.92±11.60	Positive:59 Negative:1	98.3% 1.6%
ESR (mm/h)	13-105	51.30-19.26		

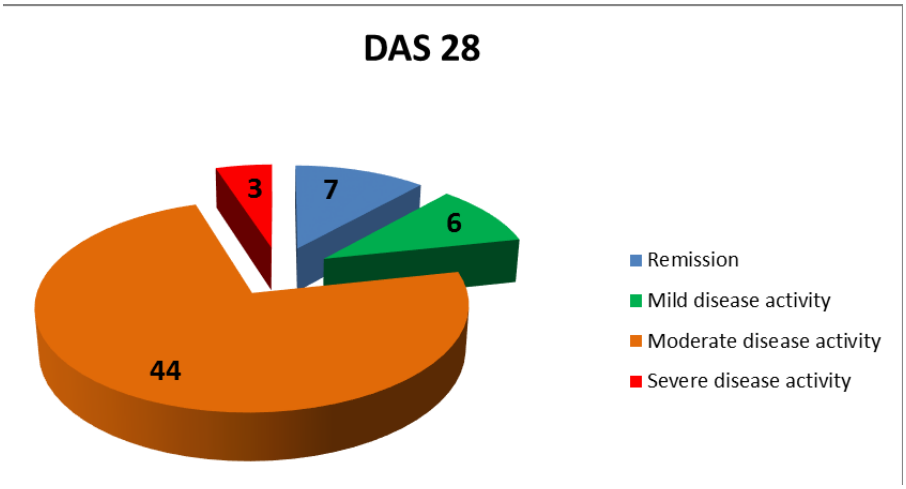

Figure 1. Disease Activity Score 28 (DAS 28) among the studied RA patients.

Table 3. Drug therapy in all RA patients.

Drug therapy	No.60	%
Methotrexate	54	90%
Hydroxychloroquine	47	78.3%
Corticosteroid	34	56.5%

Table 4. Comparison between RA patients with and without ILD.

Variable	RA with ILD (No.:51)	RA with ILD (N0.:9)	P-value
Age	(49.35±9.84)	(38.22±11.36)	<0.01
Disease duration	(10.88±5.27)	(2.55±5.17)	1.91
RF	(60.68±31.38)	(59.11±28.16)	0.865
Anti CCP	(55.68±33.95)	(50.3±33.1)	0.729
DAS	(4.13±0.81)	(3.43±0.970)	<0.01
FVC	(41.58±16.74)	(72.66±20.58)	6.2
FEV1	(45.41±17.32)	(78.55±21.44)	8.7
FEV1/FVC	(0.809±0.029)	(0.823±0.122)	<0.01
TLC	(43.90±18.32)	(77.11±22.08)	2.65

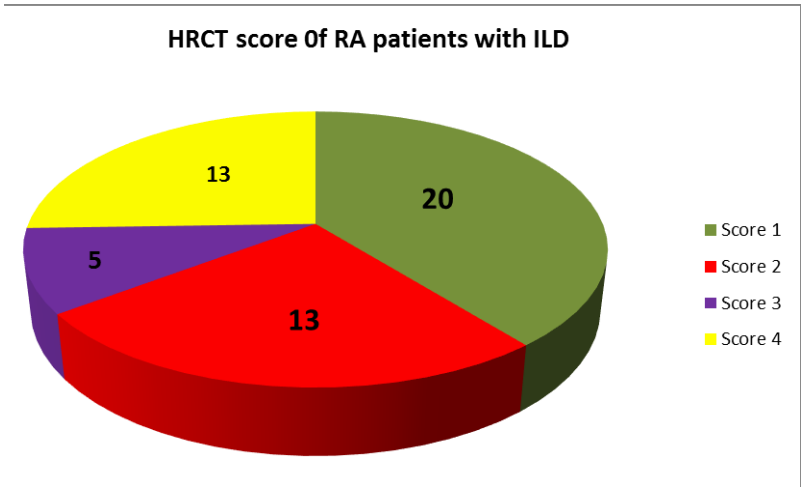

Figure 2. HRCT score among RA patients with ILD.

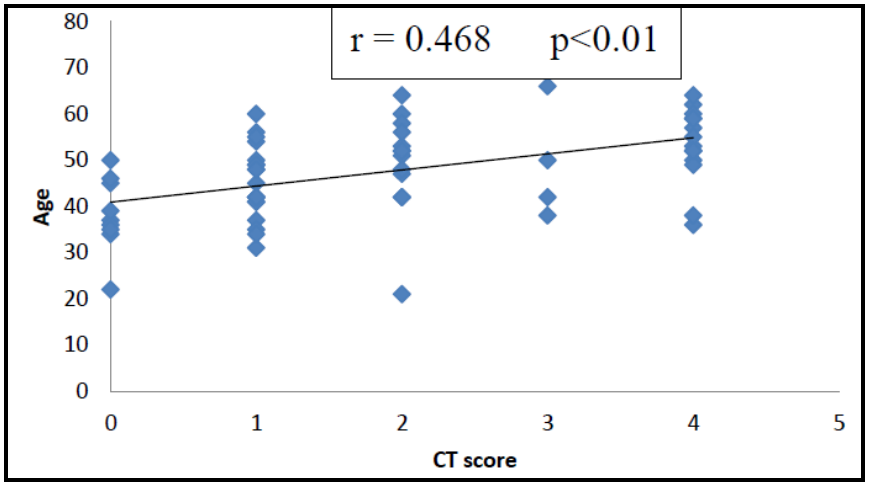

Figure 3. Correlation between HRCT score and age of RA-ILD patients.

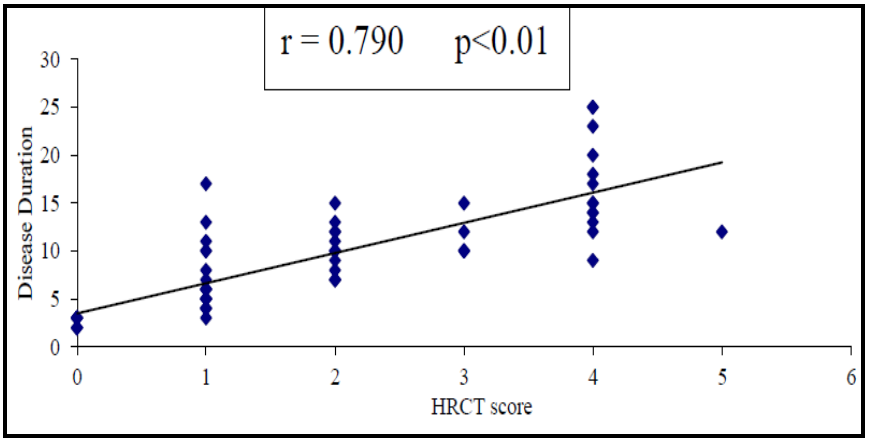

Figure 4. Correlation between HRCT score and disease duration.

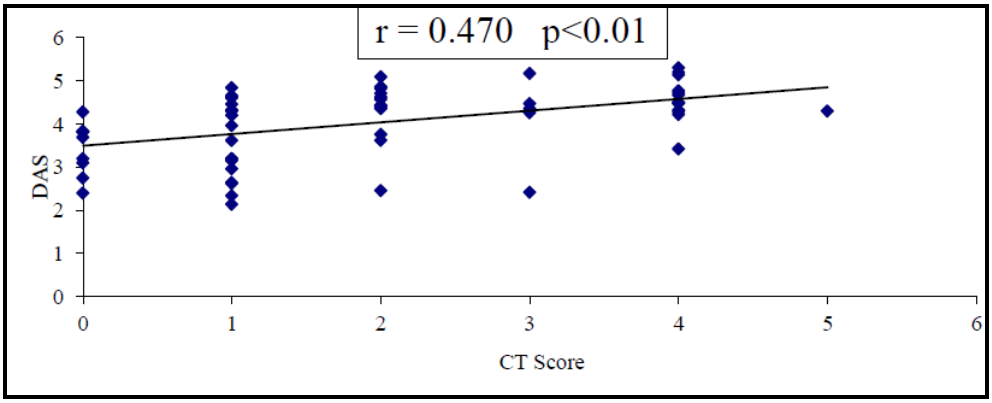

Figure 5. Correlation between HRCT score and DAS score.

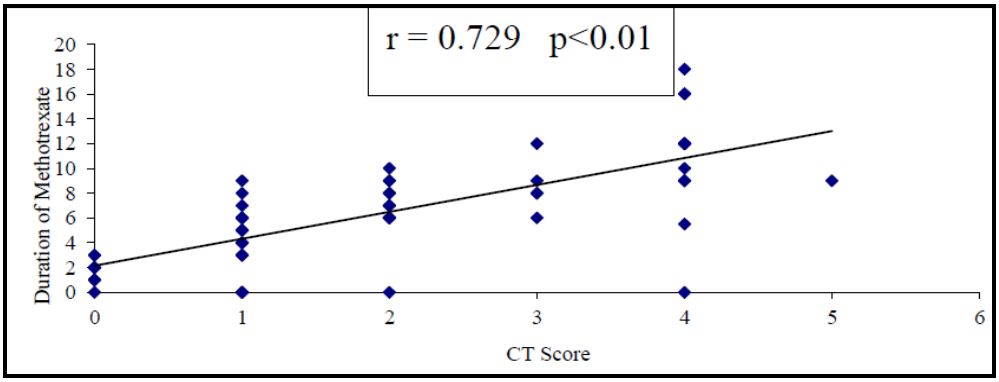

Figure 6. Correlation between HRCT score and methotrexate therapy.

DISCUSSION

Interstitial lung disease (ILD) is the most important pulmonary manifestation of rheumatoid disease, being the commonest pulmonary cause of death in RA and a significant contributor to morbidity. RA-ILD is often asymptomatic, at least initially. Clinical detection has been reported to be <5% using plain radiology, but 20-30% with high-resolution CT (HRCT).[13]

High-resolution computed tomography (HRCT) is the method of choice for assessment of pulmonary abnormalities in RA. It plays an important role in early detection and characterization of interstitial lung disease associated with RA. HRCT can detect early parenchymal lung affection before clinical symptoms are established.[14]

In the present study we found that 51 of 60 (85%) patients with RA without respiratory symptoms had preclinical ILD identified by HRCT and pulmonary function tests, this is in agreement with Juan and his colleague[15], who found that 63 of 103 (61%) of RA patients were diagnosed with RA-ILD by HRCT and PFTs, while 40 of 103 (39%) did not meet criteria for ILD, 57 of 63 RA-ILD patients lacked symptoms of significant dyspnea or cough at the time of HRCT and PFTs assessment, whereas 6 patients of RA-ILD manifested these clinical features. Also Bernadette and his colleague[16] using HRCT to screen patients with RA for ILD, they identified preclinical ILD in 21(33%) of 64 patients having RA without symptoms of lung disease.

Ground- glass opacity which is an indicator for inflammation or early fibrosis were present in RA patients in 33.3% (n=20) in our study, relatively nearer to study by Noor and his colleague[17], who found that ground- glass opacification is present in 38.1% of his RA patients.

The detected HRCT findings of pulmonary fibrosis in RA patients in our study were seen in 29% (n = 18), relatively similar to the results by Zrour et al.[18], where interstitial fibrosis was only seen in 28% of the cases.

Honeycombing representing an end stage of fibrosis was in 21.7% (n = 13) of our RA patients, relatively similar to Chung et al.[19], where honeycombing was seen in 22% of cases.

In the present study, we have found a statistically significant positive correlation between CT score, age and disease duration indicating that risk of developing and severity of ILD was higher in RA patients with older age and longer disease duration. A similar finding was found by Tim and his colleague[20] on follow up study for 16 years found that the lifetime risk of developing ILD was 7.7% for RA patients and risk of developing ILD was higher in RA patients who were older at the time of disease onset, in male patients, and in individuals with more severe RA. The results of the study showed statistically significant correlation between RA disease activity and HRCT score in RA patients. The same was reported by Juan and his colleague[14], who found RA-ILD patients were older and had longer disease duration, greater articular disease activity.

Pulmonary function test abnormalities served as another sensitive indicator for preclinical RA-ILD, in our study we found that pulmonary function test abnormalities in 34 patients (56.7%) had restrictive ventilator defect, 22 patients (36.7%) had mixed restrictive and obstructive ventilator defect and 12 (6.7%) of them have normal finding. Obstructive ventilator defect seen in our patients may be due to obliterative bronchiolitis, which is the hallmark of diffuse lung disease of RA. Also Lower FEV1, FVC and TLC were found in RA-ILD patients which was similar to the one reported by Juan and his colleague[14], who found reductions in percent predicted FEV1, FVC, TLC in RA-ILD. In contrary, Bernadette et al 2008[15], found that there were no statistically significant differences among RA-ILD patients in the percentages of predicted FEV_1, FVC, and TLC when compared to RA patients without ILD.

Methotrexate (MTX) is the most commonly used disease-modifying drug (DMARD) in rheumatoid arthritis (RA). The pathogenesis of MTX pulmonary toxicity remains unclear. Hypersensitivity reaction is suspected when histopathological findings demonstrate interstitial pneumonitis.[21] In the present study we found that 44 of 51 patients had ILD were on methotrexate therapy and there was statistically significant positive correlation between duration of the therapy and HRCT score in those patients .This is opposite to what seen by Dawson and his colleague[22], who found chronic ILD proved by HRCT and pulmonary function in about 20% of 55 RA patients treated with low dose methotrexate but no significant correlation with the duration of the therapy. The possibility that the risk of ILD may have been due to RA itself or due to the use of therapy, we do not know because it is difficult to differentiate drug-induced toxicity from RA-related.

In the current study we found that 44(86%) of 51 RA-ILD patients had Anti-CCP positive but there is no significant correlation of Anti-CCP levels with HRCT score. Also Kelly and his colleague (2014)[23] found that Anti-CCP antibody titres were highly positive in 94% of 225 RA-ILD patients in both sexes. In contrary to us Fleur and his colleague (2011)[23] found that High anti-CCP2 levels are associated with lung disease in the 230 RA patients.

Patients with RA may develop lung disease from the medications used to treat the joint disease and the disease process itself.

In conclusion, lung involvement should always be considered in RA patients even in absences of respiratory symptoms and early detection of asymptomatic subclinical interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) may influence the choice of DMARDs and deterioration can be prevented.

[Disclosure: Authors report no conflict of interest]

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