Interstitial lung disease in patients with rheumatoid arthritis attending a tertiary care hospital in Uttarakhand, India

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KEYWORDS

DAS28; ILD, Nonspecific interstitial pneumonia, Rheumatoid arthritis, Usual interstitial pneumonia.

ABSTRACT

Background: Interstitial lung disease (ILD) is an important cause of mortality in rheumatoid arthritis (RA). This study was done to determine the prevalence of ILD in patients with RA and the association between ILD and duration and severity of disease activity of RA. **Methods**: Ninety-six patients with RA, diagnosed as per American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria, were evaluated for severity of clinical disease activity by the disease activity score with 28- joint counts (DAS28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and visual analogue scale (VAS). They were subjected to spirometry and high-resolution CT (HRCT) chest for the assessment of ILD. **Results**: ILD was present in 16 (16.6%) patients. Majority of patients with ILD had more than 10 years of illness (7 [43.7%] patients) and high severity of disease activity (12 [75%] patients). Usual interstitial pneumonia (UIP) was the predominant pattern (13 patients, 81.2%) while only 3 (18.7%) patients belonged to nonspecific interstitial pneumonia (NSIP) subtype of ILD. Spirometry showed restrictive pattern in 11 (68.7%) patients with ILD. ILD did not show a significant association with duration of disease ($p = 0.19$) and severity of disease activity of RA ($p = 0.14$).Conclusions: ILD was common in patients with RA. ILD was not dependent on duration and severity of disease activity of RA.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that comprises joint swelling, and tenderness and in later stages, destruction of synovial joints.[1] The overall prevalence of RA in the world is approximately 0.5-1% among adults.[2] There are numerous extra-articular complications of RA out of which lung complications are the most commonly seen. Pulmonary features include pulmonary nodules, pleural effusion, bronchiectasis, and interstitial lung disease (ILD).[3] ILD is the commonest pulmonary manifestation of RA lung disease while pleural involvement occurs commonly in RA but only about 3–5% of patients become symptomatic. [4]

ILD is an umbrella term that consists of diseases of inflammatory lung parenchyma that share frequent radiological, pathological, and scientific features.[5] In 2013, the American Thoracic Society (ATS)/European Respiratory Society (ERS) updated the 2002 ATS/ERS classification of idiopathic interstitial pneumonias (IIPs), and they are now categorized as:

major, rare, and unclassifiable interstitial pneumonias. The major IIPs are similarly divided into: Chronic fibrosing interstitial pneumonia (idiopathic pulmonary fibrosis [IPF] and idiopathic nonspecific interstitial pneumonia), smoking related interstitial pneumonia (respiratory bronchiolitis-interstitial lung disease [RB-ILD] and desquamative interstitial pneumonia [DIP]), and acute/subacute interstitial pneumonia (cryptogenic organizing pneumonia [COP] and acute interstitial pneumonia [AIP]). IPF is associated with radiologic and/or pathologic-morphologic pattern of usual interstitial pneumonia (UIP) and idiopathic nonspecific interstitial pneumonia with that of nonspecific interstitial pneumonia (NSIP). [5, 6]

Around 8–15% of patients with RA have clinically significant restrictive lung disease. Around 30% of patients with RA are expected to have subclinical ILD, which is detectable only by means of HRCT.[7] The most frequent subtype of RA-ILD is UIP and it is associated with the worst prognosis.[8] UIP is characterized by bilateral sub-pleural reticulation in presence or absence of honeycombing. NSIP consists of ground-glass opacities and is frequently associated with signs and symptoms of fibrosis along with traction bronchiectasis.[9]

Cough and progressive exertional dyspnoea are the main clinical features of ILD. The nature of cough in ILD is usually dry. Other features like clubbing of digits and “Velcro” like crackles on lung auscultation are seen in advanced disease.[10] It has been shown that high levels of circulating rheumatoid factor (RF) in patients with RA lead to increased chances of developing ILD. An association has been found between the degree of articular damage and the presence of extra articular features in RA with anti-cyclic citrullinated peptide (anti-CCP) antibodies.[11] It has been proven that the risk of pleuro-pulmonary complications is increased in patients with RA who have co-existent rheumatoid nodules.[12]

ILD is an important cause of lung disease associated with RA but the prevalence of ILD varies in patients with RA in different parts of the world which may have an impact on the magnitude of associated mortality and morbidity. So far there is no report regarding its prevalence from Uttarakhand region in north India. Hence this study was undertaken to determine the prevalence of ILD in patients with RA and the association of ILD with duration and severity of disease activity of RA.

Materials and Methods

This analytical cross-sectional study was conducted at the Himalayan Institute of Medical Sciences, Dehradun, a tertiary care centre in Uttarakhand, India from January 2019 to December 2020. The work was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). Ethical clearance for the study was obtained from the Ethics Committee of Swami Rama Himalayan University, Dehradun (No. SRHU/HIMS/ETHICS/2018/503 dated 24.10.2018).

Subjects were recruited from patients presenting in medicine and rheumatology out-patient department (OPD) and medical wards of the hospital, with a primary diagnosis of RA. A written informed consent was taken from all the patients. A sample size of 96 was estimated taking the prevalence of ILD in RA as unknown (50 percent) with a Z score of 1.96 at 0.05 level of significance and taking relative error of 20 percent.

Inclusion criteria

Patients diagnosed as having RA.

Exclusion criteria

People working in silica factories, coal mine workers, smokers, bird handlers, people with history of exposure to drugs like nitrofurantoin, amiodarone, and bleomycin, any known case of chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, bronchial asthma, overlap syndrome or mixed connective tissue disease.

Study protocol

Detailed history of a suspected case was taken and clinical examination was done. Relevant investigations were done such as complete hemogram, erythrocyte sedimentation rate (ESR) by Westergren method, rheumatoid factor (RF), C-Reactive protein (CRP), anti-CCP antibodies (ELISA method, Euroimmuno kit from Germany), x-ray chest – postero anterior view, x-ray of both hands including wrists, serum uric acid, and antinuclear antibody (ANA) level.

The clinical assessment of severity of RA was made as per disease activity score with 28-joint counts (DAS28) based on tender joint count, swollen joint count, general health or patient's global assessment of disease activity on a visual analogue scale (VAS) of 100 mm, and ESR.

The level of disease activity was interpreted as:

Low (DAS28 2.6-3.1), moderate (DAS28 3.2-5.1), high (DAS28 >5.1).

A DAS28 <2.6 corresponded with being in remission.[13]

Patients diagnosed as having RA were subjected to various tests including high-resolution CT (HRCT) thorax, spirometry, and diffusion lung capacity of carbon monoxide.

The diagnosis of ILD was made by HRCT findings. Chest HRCT scans were assessed for the presence and extent of ground glass attenuation, reticulation, honeycombing, decreased attenuation, centrilobular nodules, other nodules, consolidation, and emphysema and were categorized in a particular radiological pattern as per criteria of the ATS/ERS International Multidisciplinary Consensus Classification of the IIPs. Various pulmonary patterns ascertained by chest HRCT scans were UIP, NSIP and other patterns (bronchiolitis obliterans [BO], organized pneumonia [OP] and mixed patterns).[14, 15]

Patients were further evaluated for pulmonary manifestations by pulmonary function tests. A restrictive spirometry pattern was indicated by a reduced forced vital capacity (FVC) (<80% of the predicted normal), and a normal FEV1/FVC ratio (≥ 0.7).[16, 17]

Data management and statistical analysis

Statistical analysis was performed using SPSS software version 22. Descriptive statistics was used for quantitative data. Qualitative data were represented by frequency and percentages. Student's t test (unpaired) was used for the comparison of quantitative data. Difference between proportions or association between two variables was determined by Chi-square test. A p-value of less than 0.05 was taken as statistically significant.

Results

Baseline characteristics of the patients with RA are shown in table 1. The mean age of patients was 51.21 ± 11.39 years. Most (63.5%) of the patients were of 50-74 years. In the majority (93.7%) of patients, duration of illness was more than 1 year. The most commonly involved joints were metacarpophalangeal (MCP) joints (81.2%) and proximal interphalangeal (PIP) joints (62.5%).

Table 1. Showing baseline characteristics and clinical profile of patients with rheumatoid arthritis

Characteristics	Number of patients (%)
Age group (years)	
18-25	1 (1.04)
26-33	8 (8.33)
34-41	14 (14.58)
42-49	12 (12.5)
50-74	61 (63.54)
Gender	
Male	26 (27.08)

Female	70 (72.92)
Socioeconomic status	
High	3 (3.12)
Middle	37 (38.54)
Low	56 (58.33)
Place of residence	
Rural	71 (73.95)
Urban	25 (26.04)
Duration of illness (years)	
<1	6 (6.25)
1-5	37 (38.54)
6-10	29 (30.20)
>10	24 (25.0)
Severity of disease activity as per DAS28	
Remission (<2.6)	1 (1.04)
Low (<3.2)	7 (7.29)
Medium (3.2-5.1)	41 (42.70)
High (>5.1)	47 (48.95)
ILD	
Present	16 (16.66)
Absent	80 (83.33)
Type of ILD	
UIP	13 (81.25)
NSIP	3 (18.75)

DAS28- Disease activity score with 28-joint counts; ILD- Interstitial lung disease; UIP- Usual interstitial pneumonia; NSIP- Nonspecific interstitial pneumonia.

Symmetrical joint involvement was seen in 78.1% and asymmetrical joint involvement in 21.9% patients. High disease activity was seen in 48.9% patients. ILD was present in 16.6% patients with RA. The mean age of patients with ILD was 60.13 $\pm$ 8.41 years and without ILD 49.43 $\pm$ 11.10 years. The majority of patients with ILD belonged to the age group of >50 years (93.7%). 43.7% of patients with ILD had more than 10 years of illness. 75% patients with ILD had high clinical severity as per DAS28 score. Spirometric pattern in patients with RA showed restrictive pattern in 28.1% patients, obstructive pattern in 2.1% patients and mixed pattern in 1% patients while spirometric pattern in patients with ILD was mainly restrictive (68.7%). UIP type of ILD was seen in majority (13 patients, 81.2%) of patients with RA and ILD. Only 3 (18.7%) patients belonged to NSIP subtype. Cough, shortness of breath and substernal discomfort were the main symptoms in patients with ILD. There was no significant difference between the mean DAS28 scores in patients with ILD and patients without ILD (Table 2).

Table 2. Clinical profile and laboratory parameters in patients having rheumatoid arthritis with and without ILD

Parameter	**Mean ± SD/ Number of patients (%)**			**p-value**
	Patients overall N=96	**Patients with ILD N = 16**	**Patients without ILD N = 80**	**Patients with ILD vs. patients without ILD**
Symptoms & Signs				
Morning stiffness	96 (100.0)	16 (100.0)	80 (100.0)	1
Joint pain	96 (100.0)	16 (100.0)	80 (100.0)	1
Joint swelling	92 (95.83)	16 (100.0)	76 (95.0)	0.60
Weakness	50 (52.08)	11 (68.75)	39 (48.75)	0.17
Fatigue	74 (77.08)	13 (81.25)	61 (76.25)	0.75
Shortness of breath	36 (37.5)	12 (75.0)	24 (30.0)	0.001
Cough	27 (28.12)	10 (62.5)	17 (21.25)	0.001
Anorexia	17 (17.7)	3 (18.75)	14 (17.5)	1
Sub-sternal discomfort	16 (16.66)	6 (37.5)	10 (12.5)	0.02
Nausea	4 (4.16)	1 (6.25)	3 (3.75)	1
Vomiting	3 (3.1)	1 (6.25)	2 (2.5)	0
Fever	7 (7.29)	2 (12.5)	5 (6.25)	0.59
Joint tenderness	92 (95.8)	16 (100.0)	76 (95.0)	0.60
Crepitations	35 (36.4)	16 (100.0)	19 (23.75)	<0.0001
Pleural effusion	3 (3.12)	1 (6.25)	2 (2.5)	0.28
Presence of joint deformities	23 (23.95)	6 (37.5)	17 (21.25)	0.14
Laboratory parameters				
Hb (g/dL)	11.59 ±1.84	12.24±2.0	11.46±1.79	0.12
TLC (thousand/cubic mm)	8.57±3.19	9.78±4.84	8.33±2.73	0.10
Platelet count (thousand/cubic mm)	284.39±121.13	271.51±120.32	286.97±121.88	0.64
ESR (mm in 1st hour)	43.03±20.90	47.43±17.24	42.15±21.54	0.35
CRP (mg/L)	8.41±15.59	13.80±18.76	7.34±21.54	0.13
RF (IU/mL)	166.99±204.11	226.55±395.19	155.07±139.95	0.20
RF positivity	84 (87.5)	13 (15.47)	71 (84.52)	0.68
Anti-CCP antibody (EU/mL)	110.84±71.14	105.68±63.52	111.87±72.89	0.75
Anti-CCP antibody Positivity	88(91.66)	16 (18.18)	72 (81.81)	0.34
DAS28	5.00±1.14	5.28±0.83	4.94±1.18	0.27
Tender joint count	8.10±3.43	8.68±4.52	7.98±3.20	0.46
Swollen joint count	5.91±3.56	4.87±2.65	6.12±3.69	0.20

ILD- Interstitial lung disease, Hb- Haemoglobin; TLC- Total leucocyte count; ESR- Erythrocyte sedimentation rate; CRP- C-reactive protein; RF- Rheumatoid factor; Anti-CCP antibody- Anti-cyclic citrullinated peptide antibody, DAS28- Disease activity score with 28-joint counts.

The most common HRCT scan findings seen in patients having ILD were honeycombing, reticulation, nodules and fibrosis. Honeycombing was mostly subpleural (Table 3).

Table 3. Chest x-ray and HRCT scan findings in patients with rheumatoid arthritis

Finding	Number of patients (%)		
	Overall N = 96	Patients with ILD N = 16	Patients without ILD N = 80
Pattern on Chest X-ray			
Normal	64 (66.66)	5 (31.25)	59 (73.75)
Bronchitis	12 (12.5)	2 (12.5)	10 (12.5)
Cardiomegaly	8 (8.33)	2 (12.5)	6 (7.5)
Consolidation	3 (3.12)	2 (12.5)	1 (1.25)
Fibrosis	3 (3.12)	3 (18.75)	0 (0)
Pleural effusion	3 (3.12)	1 (6.25)	2 (2.5)
Bronchiectasis	2 (2.08)	1 (6.25)	1 (1.25)
Emphysema	2 (2.08)	0 (0)	2 (2.5)
Pattern on HRCT chest			
Normal	58 (60.41)	0 (0)	58 (72.5)
Honeycombing	8 (8.33)	8 (50.0)	0 (0)
Reticulation	6 (6.25)	5 (31.25)	1 (1.25)
Pleural thickening	9 (9.37)	2 (12.5)	7 (8.75)
Pleural effusion	3 (3.12)	1 (6.25)	2 (2.5)
Nodules	7 (7.29)	4 (25.0)	3 (3.75)
Fibrosis	6 (6.25)	4 (25.0)	2 (2.5)
Bronchiectasis	6 (6.25)	3 (18.75)	3 (3.75)
Ground glass appearance	3 (3.12)	3 (18.75)	0 (0)
Consolidation	4 (4.16)	3 (18.75)	1 (1.25)
Interstitial thickening	2 (2.08)	1 (6.25)	1 (1.25)
Emphysematous changes	2 (2.08)	0 (0)	2 (2.5)

HRCT- High-resolution CT; ILD- Interstitial lung disease

The majority (75%) of patients with ILD had high severity of disease. ILD did not show a significant association with age, duration of disease, duration of morning stiffness, severity of RA, presence of joint deformities, type of cough, and VAS. ILD had a significant association with gender, cough, shortness of breath, and spirometric pattern ($p < 0.05$ each) (Table 4).

Table 4. Association of ILD with various parameters concerning rheumatoid arthritis

Parameter	Number of patients (%)		p-value
	Patients with ILD N= 16	Patients without ILD N= 80	
Age (years)			
18-25	0 (0)	1 (1.25)	
26-33	0 (0)	8 (10.0)	
34-41	0 (0)	14 (17.5)	
42-49	1 (6.25)	11 (13.75)	
≥50	15 (93.75)	46 (57.5)	0.09
Gender			
Male	8 (50.0)	18 (22.5)	
Female	8 (50.0)	62 (77.5)	0.02
Duration of illness (years)			
<1	1 (6.25)	5 (6.25)	

1-5	3 (18.75)	34 (42.5)	0.19
6-10	5 (31.25)	24 (30.0)	
>10	7 (43.75)	17 (21.25)	
Duration of morning stiffness (minutes)			
<30	1 (6.25)	12 (15.0)	0.26
30-60	7 (43.75)	44 (55.0)	
>60	8 (50.0)	24 (30.0)	
Joint deformities			
Present	6 (37.5)	17 (21.25)	0.14
Absent	10 (62.5)	63 (78.75)	
Severity as per DAS28			
Remission (<2.6)	0 (0)	1 (1.25)	0.14
Low (<3.2)	1 (6.25)	6 (7.5)	
Medium (3.2-5.1)	3 (18.75)	38 (47.5)	
High (>5.1)	12 (75.0)	35 (43.75)	
VAS (mm)			
1-50	10 (62.5)	50 (62.5)	0.41
51-75	3 (18.75)	23 (28.75)	
>75	3 (18.75)	7 (8.75)	
Cough			
Present	9 (56.25)	18 (22.5)	0.009
Absent	7 (43.75)	62 (77.5)	
Type of cough			
Dry	7 (77.77)	17 (94.44)	0.51
Productive	2 (22.22)	1 (5.55)	
Shortness of breath			
Present	11 (68.75)	55 (68.75)	0.006
Absent	5 (31.25)	25 (31.25)	
Spirometric pattern			
Normal	4 (25.0)	61 (76.25)	0.001
Restrictive	11 (68.75)	16 (20.0)	
Obstructive	0 (0)	2 (2.5)	
Mixed	0 (0)	1 (1.25)	
Not done	1 (6.25)	0 (0)	

ILD- Interstitial lung disease; VAS- Visual analogue scale.

Discussion

ILD is the most common pulmonary manifestation of RA.[18, 19] Clinically significant ILD is seen in about 10% of patients with RA. It is responsible for 10–20% of mortality, with an average survival rate of 5–8 years. In our study, ILD was found in 16.6% of patients with RA. Though figures of ILD in RA may vary all over the globe, much higher figures of 34% have been reported for ILD in RA in another study.[20] Similarly, Koduri demonstrated that ILD was present in 25% of patients with RA who were diagnosed at first visit and another 25% developed ILD within a time frame of 3 years.[21]

In our study, most of the patients with RA (63.5%) were above the age of 50 years. The mean age of patients with RA was 51.21 $\pm$ 11.39 years. It is in agreement with the mean age of patients with RA observed as 49.5 $\pm$ 13.5 years by Banotra et al [20] and 57.7 $\pm$ 15.1 years by Bongartz et al. [22] The mean age of our patients with RA and ILD (60.13 $\pm$ 8.41 years) was higher than that of patients having RA without ILD (49.43 $\pm$ 11.10 years). The majority (93.8%) of patients with ILD belonged to the age group of >50 years. The association between ILD and age among patients with RA was found to be statistically not significant.

Our results are in accordance with findings of a mean age of 58 ± 11.6 years of patients with RA and ILD in a study by Assayag et al.[23] However, the mean age of patients with RA and ILD was higher than a mean age of 50.15 ± 9 years reported by Fadda et al [24] and lower than the mean age of 71.3 ± 12.2 years observed by Bongartz et al.[22] In a study by Banotra et al, the mean age of patients with RA was 49.5 ± 13.5 years.[20]

In our study, male: female ratio was 1: 2.69 among patients with RA but ILD occurred with greater frequency in males (females 8/70, 11.4%; males 8/26, 30.7%). The association between gender and ILD was found to be statistically significant. Other studies done earlier, showed male predominance of RA-ILD.[25, 26] Similarly, Bongartz et al observed that 58.7% of male patients and 41.3% of female patients with RA had ILD though total number of female patients with RA (with and without ILD) outnumbered males by a ratio of 2.7:1 as is characteristic of an autoimmune disorder.[22] However, female predominance was observed among patients with RA and ILD in a study by Tanaka et al.[27] Similarly, in a study done by Assayag et al,[23] males were 34.8% and females 65.2% while in a study by Fadda et al,[24]. males were 15% and females 85%.

The duration of RA has been linked to the development of ILD with longer duration of RA leading to increased risk of ILD.[28, 29] The pulmonary symptoms can be the initial presentation in up to 20 percent of patients with RA. In our study, in maximum number of patients with RA, duration of illness was more than 1 year while the mean duration of illness was 8.78 years. A sizeable proportion (43.7%) of patients with RA and ILD had more than 10 years of illness. Only 6.2 % of patients who developed ILD had duration of illness less than 1 year. Similarly, in a study by Fadda et al, mean duration of illness was 10.1 years.[24] However, we did not find a statistically significant association between duration of illness and ILD.

The commonest joints involved were proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints. Similarly, in a study conducted by Chandrasekaran et al, the involvement of PIP joint was 85% and MCP joint 68% which shows the predilection for those joints in RA globally.[30] The majority of patients with RA and ILD had more than 60 minutes of morning stiffness (50%). The association between the duration of morning stiffness and ILD was found to be statistically not significant.

Among RA patients with ILD, joint deformities were present in 37.5% patients. The association between the joint deformities and ILD was found to be statistically not significant. Most (75%) of the patients with RA and ILD had high disease severity. In a study by Banotra et al, high disease severity was present in 64% patients and a significant association was observed between clinical disease severity and pulmonary involvement.[20] However, we did not find a significant association between the severity of disease activity and ILD.

The most frequent chest HRCT finding of a reticular pattern with presence of subpleural honeycombing in our patients with ILD is in accordance with observations of Dawson et al.[29] Similar results were seen in another study[20] with findings of reticulation (35.7%) and honeycombing (53.6%) in patients with RA and ILD but ground glass opacities (42.9%) were seen with a higher frequency than in our study (18.7%).

Pulmonary function testing in patients with ILD generally reveals a restrictive pattern with reduced diffusing capacity (less than 70%).[30] In our patients with RA and ILD, spirometry showed restrictive pattern in 68.7% patients. In another study, pulmonary function tests (PFTs) were normal in 28.6% of patients, restrictive pattern was seen in 50% of patients, and obstructive pattern in 7.1% of patients while 14.3% of patients were not cooperative for PFT.[20] We observed a statistically significant association between spirometric pattern and ILD implying that a restrictive spirometric pattern in patients with RA can offer a valuable clue to the presence of ILD.

Our study has some limitations. ILD could not be assessed in some patients with RA as they did not complete the diagnostic work-up for ILD. The exclusion of patients with RA having co-existing conditions that could lead to ILD could also affect the estimates of ILD in patients with RA. Moreover, being a hospital-based study, it may not reflect the exact prevalence of ILD in patients with RA in the community.

Conclusion

ILD was common in patients with RA and affected patients of older age. Dry cough and a long-standing disease with high disease activity and a restrictive spirometric pattern were generally seen in patients with RA and ILD. However, no significant association was present between ILD and the duration as well as disease activity of RA. PFTs may be useful in assessing the disease as well as follow up of these patients.

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