Patterns of pulmonary manifestations in ILDs in rheumatoid arthritis

Mohammad Ismail Abdelkareem[a], Wael Abdelmohsen Abo zaid[b], Hagagy Mansour[c], Fatma Badry Makhloof Hussein[b*]

[a]Department of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Al-Azhar University (Assiut Branch), Assuit, Egypt
[b]Department of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, South valley University, Qena, Egypt
[c]Department of Chest Diseases, Faculty of Medicine, South valley University, Qena, Egypt

Abstract

Background: Interstitial lung diseases (ILD) may be manifested with extra-articular manifestations in rheumatoid arthritis patients; these manifestations may be occur as a preceding entity or several years after the RA diagnosis and can cause important effect on morbidity and mortality.

Objectives: is to evaluate the Patterns of pulmonary manifestations in ILDs in rheumatoid arthritis

Patients and methods: This is cross-sectional study was conducted at Qena university hospital, South Valley University, Qena through evaluation of 50 rheumatoid arthritis patients were selected from those attending the outpatient clinic and those admitted in the inpatients of Physical Medicine, Rheumatology and Rehabilitation Department at Qena University Hospital.

Results: Mean morning stiffness is 42.2 ± 18.77 minute and the most prevalent symptom presented was subcutaneous nodules (60%) followed by dryness of the mouth (16%).

Conclusion: Interstitial lung diseases caused by rheumatoid arthritis is a serious complication of RA causing increased morbidity and mortality.

Keywords: Pulmonary, Interstitial lung disease (ILD), Rheumatoid arthritis (RA), Rheumatoid.

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***Correspondence**: fatmaabadry92@gmail.com
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Introduction

Interstitial lung disease (ILD) may be manifested with extra-articular manifestations in patients with rheumatoid arthritis, these manifestations may be occur as a preceding entity or several years after the RA diagnosis and can cause important effect on morbidity and mortality **(Castelino et al., 2015)**.
RA patients may have restrictive or obstructive lung disease, which is frequently under diagnosed clinically **(Doyle et al., 2010)**. Although in 8-15% rheumatoid arthritis patients develop clinically significant restrictive lung diseases.

ILD is classified into two clinical and histological patterns: usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NIP) **(Nanniniet al., 2008)**.

Despite of being less frequently seen, organizing pneumonia (OP) associated with RA is frequently included among the forms of ILD that occur in RA. While the lung disease course in patients with OP is frequently characterized by a sub acute sickness lasting less than three months, it can develop to fibrosis or overlap with NSIP, resulting in severe interstitial inflammation. **(Travis et al., 2013)**.

Clinically, ILD symptoms are variable. The most prevalent symptoms are dyspnoea and cough. Histopathological patterns are particularly helpful in classifying and distinguishing the various types of ILD, which sometimes overlap. **(Assayaget al., 2014)**.

Because there is many variable clinical outcomes for RA-ILD, predicting survival rates in these patients is difficult, hence clinicians may benefit from using a staging approach. The gender, age, lung physiology (GAP) model, which was originally established for idiopathic pulmonary fibrosis and a secondary non-idiopathic ILD model (ILD-GAP) may present an opportunity to better predict mortality in the RA-ILD patient population.**(Ryerson et al., 2014)**.The aim of the current study is to evaluate the Patterns of pulmonary manifestations in ILDs in rheumatoid arthritis.

Patients and methods

This is a cohort study carried out at Qena University Hospitals, South Valley University, Qena, Egypt. A total of 50 rheumatoid arthritis patients fulfilling the criteria for classification of rheumatoid arthritis 2010 ACR/EULAR **(Aletahaet al., 2010)**, **(Funovitset al., 2010)** selected from those attending the outpatient clinic and those admitted in the in patients of Physical Medicine, Rheumatology and Rehabilitation Department of Qena University Hospital

Exclusion criteria: Age <18yrs, other systemic autoimmune diseases e.g (SLE, PCS, AS, Scleroderma), other disease causing ILDs e.g : Idiopathic (IPF, DIP, NSIP, COP, LIP, AIP), Secondary (SLE, Sarcoidosis, Pneumoconiosis, Lymphamgitic carcinomatosis), HCV and HBV infection.

Study tools: The following was applied to all of the participants: Full medical history (demographic information and personal history including smoking status as well as a detailed medical and history of general health), therapeutic history of hormonal treatment and family history of RA). General examination including vital signs, systematic examinations and investigations: CBC, ESR, RFTs, urine analysis, RF, blood glucose level (random and 2 hrs postprandial), plain X-ray of both hands and both feet PA view, HRCT chest, pulmonary function tests and ABG.

This study has been given approval by the Ethics Committee of Faculty of Medicine, South Valley University, Qena, Egypt. (**Ethical approval code is** SUV-MED-PRR022-1-21-1-115)

Data management and Statistical analysis

For statistical data analysis, IBM's Statistical Package for Social Sciences (IBM-SPSS), version 24 (May 2016); IBM, Chicago, USA were utilized. The mean, standard deviation (SD), number and percentage were used to represent the data. For quantitative data, the mean and standard deviation will be utilized as descriptive values. When comparing the means of more than two groups, the one-way analysis of variance (ANOVA) test was used. When the data was non-parametric, the Mann Whitney test was employed. When comparing percentages of qualitative variables Pearson Chi square test was used while the Fisher exact test was

employed instead of the usual chi square test to compare percentages of qualitative variables.

Results

Regarding history taking there was 68% of the patients were smoker, there was also 33 diabetic patients and 17 COPD among the studied patients.**(Fig. 1)**. Patients included 23 males and 27 females with mean age is 52.14 years, mean BMI is 26.12 kg/m^2, meanwhile disease duration is 7.23 ± 1.65 years. (**Table 1**). Mean FVC is 56.43%, mean FEV1 is 67.9% and mean FEV1/FVC ratio is 96.4. (**Table 2**). The most prevalent finding on X-ray is small lung volume (20%) followed by nodular (16%). Hilar LN percentage is 8% and the least prevalent is reticular (4%). However 52% of the patients are normal x-ray.(**Table 3**).

The most prevalent finding is GGO (72%) followed by reticulonodular interstitial pattern (64%) and the least prevalent finding is crazy paving (6%).(**Table 4**). The most prevalent pattern is UIP (62%) followed by NSIP (14%) and the least prevalent pattern is OP (2%).(**Table 5**)

Comparison different ILD patterns shows that no statistical significance between different patterns.(**Table 6**). There is no significant difference between the different patterns of ILD. **Table (7)**

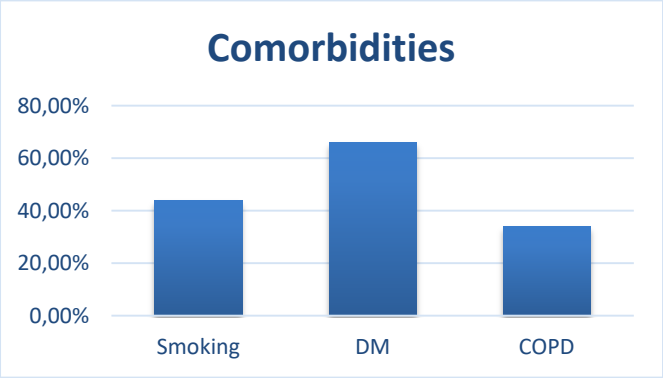

Fig.1. Frequency percentages of co-morbidities among the studied patients

Table1. Demographic data of the studied patients

Variable		**Patients**(n=50)
Age (years) Mean ± SD Range		52.46 ± 16.47 22 – 84
Sex	Male	23 (46%)
	Female	27 (54%)
BMI (kg/m^2) Mean ± SD		26.12 ± 4.54
Disease duration (years) Mean ± SD Range		5.92 ± 4.26 0.5 – 18

Table 2. Pulmonary function tests of the studied patients

Parameters	**Patients**(n=50)
FVC % Mean ± SD	56.43 ± 14.76
FEV1 % Mean ± SD	67.9 ± 7.17
FEV1/FVC ratio Mean ± SD	96.4 ± 10.53

Table 3. X-ray findings among the studied patients

	Patients (n=50)	
	N	%
Normal	26	52
Nodular pattern	8	16
Reticular pattern	2	4
Hilar LN enlargement	4	8
Small lung volume	10	20

Table 4. Chest high-resolution CT findings of the studied patients

	Patients(n=50)	
	N	%
GGO	36	72
Traction bronchiectasis	30	60
Reticulo-nodular interstitial pattern	32	64
Honeycombing	25	50
Crazy paving	3	6
Bronchiectasis	12	24
Pleural effusion	8	16
Pleural plaques	15	30
Consolidation	10	20

Table 5. ILD patterns among the studied patients

	Patients(n=50)	
	N	%
Usual interstitial pneumonia (UIP)	31	62
Non-specific interstitial pneumonia (NSIP)	7	14
Organizing pneumonia (OP)	6	12
Diffuse alveolar damage (DAD)	1	2
Others	5	10

Table 6. Patient characteristics according to different ILD patterns

Variable		UIP (n=31)	NSIP (n=7)	OP (n=6)	DAD/Others (n=6)	P
Age (years) Mean ± SD		50.84 ± 15.1	64 ± 17.01	43.67 ± 13.9	56.17 ± 21.3	121
Sex	Male	18 (58.1%)	4 (57.1%)	3 (50%)	4 (66.7%)	.951
	Female	13 (41.9%)	3 (42.9%)	3 (50%)	2 (33.3%)	
BMI (kg/m^2) Mean ± SD		25.04 ± 4.69	23.82 ± 4.58	28.03 ± 4.86	23.75 ± 2.62	.315
Disease duration Mean ± SD		5.58 ± 4.06	9.57 ± 4.92	4.17 ± 2.79	5.12 ± 4.28	.082
SBP (mmHg) Mean ± SD		120.32 ± 11.1	125 ± 5.77	123.3 ± 11.26	123.3 ± 9.31	.673
DBP (mmHg) Mean ± SD		72.26 ± 6.93	71.43 ± 8.99	76.67 ± 4.08	77.5 ± 4.18	.181
Smoking		20 (64.5%)	4 (57.1%)	5 (83.3%)	5 (83.3%)	.604
DM		11 (35.5%)	1 (14.3%)	2 (33.3%)	3 (50%)	.587
COPD		9 (29%)	3 (42.9%)	2 (33.3%)	3 (50%)	.736

Table 7. Laboratory data according to different ILD patterns

Variable	UIP (n=31)	NSIP (n=7)	OP (n=6)	DAD/Others (n=6)	P
Hb (g/dL) Mean ± SD	11.93 ± 1.48	11.47 ± 1.35	11.45 ± 1.53	12.17 ± 0.683	.707
Albumin (g/dL) Mean ± SD	3.83 ± 0.902	3.34 ± 1.12	3.62 ± 1.16	3.58 ± 0.646	.514
Cr. (mg/dL) Mean ± SD	0.853 ± 0.127	0.967 ± 0.186	0.881 ± 0.181	0.858 ± 0.201	.356
ESR (mm/hr) Mean ± SD	24.77 ± 9.68	20.29 ± 7.52	39.67 ± 33.55	23 ± 15.74	.099
CRP (mg/L) Mean ± SD	18.1 ± 11.9	14.57 ± 9.07	19.01 ± 15.38	10 ± 3.1	.406
RF (IU/ml) Mean ± SD	26.91 ± 46.97	73.93 ± 87.74	33.3 ± 44.57	75.45 ± 140.2	.325
pH Mean ± SD	7.41 ± 0.055	7.41 ± 0.058	7.39 ± 0.043	7.39 ± 0.073	.517
HCO3 Mean ± SD	23.35 ± 5.14	24.43 ± 4.61	21.5 ± 6.98	25.67 ± 2.81	.529
FVC % Mean ± SD	72.8 ± 14.6	69.7 ± 11.48	73.5 ± 12.61	70.1 ± 10.78	.621
FEV1 % Mean ± SD	69.26 ± 7.71	63.57 ± 7.23	66.33 ± 3.14	67.5 ± 5.75	.269
FEV1/FVC ratio Mean ± SD	97.48 ± 11.33	93.43 ± 6.08	96.83 ± 12.24	93.83 ± 9.66	.752

Discussion

Rheumatoid arthritis is a systemic inflammatory disorder that most commonly affects the joints, causing progressive, symmetric, erosive destruction of cartilage and bone, which is usually associated with autoantibody production. Rheumatoid arthritis affects ~1% of the population in developed countries. The incidence and prevalence of rheumatoid arthritis in developing countries is thought to be lower, but is difficult to quantify. Although joint disease is the main presentation, there are a number of extra-articular manifestations including subcutaneous nodule formation, vasculitis, inflammatory eye disease and lung disease. Of these manifestations, lung disease is a major contributor to morbidity and mortality.

The main aim of this study was to evaluate the Patterns of pulmonary manifestations in ILDs in rheumatoid arthritis.

In the study of **Robles-Perez et al., (2016),**A total of 18 individuals (45%) had changes in their PFTs. The DLCO was 80% of in all cases, with no significant drop in FVC values (Figures 1 and 2). Only one patient had a FEV1 that was less than 80% of the anticipated value. In this subgroup of patients, the DLCO had a mean value (SD) of 68 percent (9.74).Although many patients have abnormal PFTs, the majority of these abnormalities are clinically insignificant and silent. There are no lung disease screening recommendations for RA patients and deciding how to manage minor pulmonary function impairment remains a difficulty. **(Robles-Perez et al., 2016)**.There were no changes in the PFT values based on the patient's age.

In the study of **Assayag et al., (2014)** revealed that The patients have mostly been female (65%, 45 of 69) with an average age of 58 years (55 years for women and 63 years for men; P =.003).

Pulmonary function tests (PFTs), such as the lung's carbon monoxide diffusing capacity (DLCO), can detect pulmonary disease. However, the variability within the normal range and the occurrence of concurrent emphysema limit the utility of PFTs as a screening tool for ILD in RA. PFT outcomes in patients with RA-ILD vary depending on the study cohorts and severity of the disease. PFT abnormalities are present in 45–65 percent of patients with RA, whether or not they have respiratory symptoms. Airway obstruction, restrictive patterns and poor DLCO are among the patterns. A restrictive pattern is found in 5%–25% of people with RA and impaired DLCO is detected in approximately 20%–45% of patients with RA.

Furthermore, **Assayag et al., (2014)**, demonstrated that pulmonary function was moderately impaired in patients with a mean forced vital capacity of 69%predicted and a mean diffusing capacity of lung for carbon monoxide of 61 percent expected.

While in the study of **Nieto et al., (2021),** the mean FVC % at baseline was 94.3 19.9, with two patients having FVC % values below 70%. In contrast, baseline DLCO % levels were between normal values (> 80 %) in 28% of the patients, while 35% had mild DLCO % deterioration (60–80 %), another 28% had moderate DLCO % deterioration (40–60 %) and the remaining 9% had severe DLCO % deterioration (less than 40 %).

Moreover, **Doyle et al., (2010),** revealed that the patients in the study had significant pulmonary function impairments. Five of the 17 patients had abnormal lung volumes, three of whom had restriction (prevalence 18%) defined as a total lung capacity (TLC) less than 80% of that expected. When defined as a FEV1 less than 80% of expected without restriction, two showed obstruction (12%).

The use of a chest X-ray to detect ILD in RA patients is insensitive. Up to 64% of patients with ILD on HRCT will not have evident interstitial changes on a chest X-ray. As a result, if ILD is suspected, HRCT must be performed as part of the diagnostic process. Lung abnormalities were found in 47 percent to 67 percent of unselected patients with RA who underwent HRCT examination; ILD, respiratory illness, and bronchiectasis were all prevalent findings. Ground glass opacities, reticulation, consolidation, honeycombing and nodules are common radiological findings in RA-ILD similar to other ILD subtypes. UIP and NSIP are the most common HRCT patterns in RA-ILD, with organising pneumonia (OP) and bronchiolitis being less common. HRCT and histological results have a fairly good correlation in studies, with the least concordance in the diagnosis of UIP and NSIP (non-specific interstitial pneumonia).**(Nieto et al., 2021)**.

The current study showed that regarding radiology; the most prevalent finding on X-ray was small lung volume (20%) followed by nodular (16%). Hilar LN percentage was 8% and the least prevalent was reticular (4%). However, 52% of the patients were normal x-ray. For chest high-resolution CT; the most prevalent finding was

GGO (72%) followed by reticulonodular interstitial pattern (64%), and the least prevalent finding was crazy paving (6%).
The most prevalent pattern was UIP (62%) followed by NSIP (14%), and the least prevalent pattern was OP (2%).

In accordance with our results, the study of **Robles-Perez et al., (2016),**An HRCT was performed on 19 patients, with abnormalities identified in 11 of them. One of these patients had nonspecific nodules and ground glass opacities with traction bronchiectasis indicating nonspecific interstitial pneumonia (NSIP)and another one presented with ground glass opacities and focal alveolar consolidations indicating organising pneumonia (OP). Emphysema, nonspecific pulmonary nodules, nonspecific air trapping or cylindrical bronchiectasis and matching Fleischner criteria were also detected in additional cases.

Furthermore, **Assayag et al., (2014)**, found that in 29% of patients, a radiologic UIP pattern was observed (20 of 69). The others had a probable UIP pattern (n = 18) and a pattern that was not meeting the criteria of UIP (n = 31). Extensive ground-glass opacities (n = 22), peri-bronchovascular predominance (n = 12), discrete cysts (n = 4), presence of consolidation (n = 4), diffuse mosaic and/or air-trapping in more than three lobes (n = 2), upper-mid lung zone predominance (n = 1) and/or presence of profuse micronodules (n = 1) were among the reasons for an inconsistent UIP pattern. Using strict criteria (definite vs possible plus inconsistent), the integrator agreement for radiologic UIP pattern on CT scans was 87 percent, with a κ value of 0.67 (P is less than .0001).The integrator agreement for radiologic UIP pattern on CT scans was 75% using the broad criteria (definite plus possible vs inconsistent) with a κ value of 0.52 (P is less than .0001).

In the study of **Tanaka et al., (2010)** pulmonary abnormalities were found in 146 of the 208 patients (70.2%): ILD (38.9%), nodular lesions (21.6%), and AD (55.3%). Reticular pattern (20.2 % of all patients), honeycombing (6.7 %), GGO (6.3 %), and consolidation were the most prevalent ILD lesions (7.7 %). In regards of nodular lesions, 14.4% of the patients had a nodular pattern, whereas 12.0% had a minor nodular pattern. Bronchitis was seen in 40.4 percent of AD patients, while bronchiectasis was found in 41.3 percent. In 13.0 percent of patients, a low attenuation area was observed. Several pulmonary lesions frequently coexisted in the same individual.

Moreover, **Banik et al., (2018)** demonstrated that total 18 (28.57%) patients had an obstructive picture in spirometry which is clearly more than the restrictive pattern patients. The finding varies from that of **Cavagna et al., (2013)** who reported that restrictive pattern in majority of RA-ILD patients.
In the study of **De Lauretis, et al., (2011)**, UIP pattern is the most common abnormality in HRCT of RA patients which was in line with our study.
Finally, our results showed that in comparison different ILD patterns, patient characteristics of different patterns were comparable without statistical importance. There was no significant difference between the different patterns of ILD as regard laboratory measures.

However, in the study of **Banik et al., (2018)** they reported that there was no significant difference between the different patterns of ILD as regard gender. But there was significant correlation between bronchiectasis and increased duration of disease (p=0.011). Bronchial wall thickening in HRCT thorax is usually found after long standing airway inflammation; so, it was plotted against age (p<0.001) and duration of disease (p=0.024) and in both cases found to be significant. Pleural effusion showed a significant correlation with disease duration (p=0.022).
The study of **Kaushik et al., (2004)** and another by **Demoruelle et al., (2012)** are supporting the fact that bronchiectasis is now rather common in nonsmoker RA patients.

Conclusion

Pulmonary parenchymal diseases (interstitial lung disease (ILD)) and inflammation of the pleura (pleural thickening and effusions), airways and pulmonary vasculature are among the pulmonary manifestations of rheumatoid arthritis (vasculitis and pulmonary hypertension). The type and severity of involvement influence the prognosis. Although the exact incidence varies depending on the population investigated and the diagnostic method employed to identify the disease, ILD is the most prevalent pulmonary symptom of rheumatoid arthritis lung disease. Interstitial lung disease linked with rheumatoid arthritis is a serious complication of the disease that leads to significant increased morbidity and mortality.

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