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Original Article

Internal Medicine Section

A Study on Pulmonary Manifestations of Rheumatoid Arthritis

SANDIPAN BANIK[1], SUMIT ROY TAPADAR[2], ANIRUDDHA RAY[3], ARUNABHA DATTA CHAUDHURI[4]

ABSTRACT

Introduction: In approximately 50%, are Rheumatoid Arthritis (RA), there are extra articular manifestations. Pulmonary involvement ranges between 10%-67%. Interestingly, mortality in patients of RA is further increased with extra-articular affection, among which pulmonary involvement accounts for 10-20% mortality.

Aim: To evaluate the spectrum, relevant factors and frequency of pulmonary affection in diagnosed patients of RA.

Materials and Methods: A cross-sectional, study was done in RG Kar Medical College, a tertiary care teaching hospital of Kolkata, India. A total of 63 consecutive patients of RA were enlisted and evaluated – clinically, High Resolution Coaxial Tomography (HRCT) scan of thorax, spirometry and echocardiography.

Results: About one third (n=19) of the RA patients had respiratory symptoms; half (n=31) showed abnormal spirometry results and less than half (n=28) had some abnormality in HRCT. The most common abnormality was decreased attenuation, found in 36.5% patients. Others were bronchiectasis (n=19, 30.2%), bronchial wall thickening (n=16, 25.4%), pulmonary nodules (n=3, 4.8%), pleural effusion (n=10, 15.9%), pleural thickening (n=5, 7.9%), ground glass opacity (n=6, 9.5%), reticulo-nodular shadow (n=8, 12.7%) and air trapping (n=11, 17.5%). Pulmonary Hypertension (PH) was found in about one quarter (n=17) of the study population and in about half (n=8) of them it was clinically silent.

Conclusion: Pulmonary manifestations are quite common in RA and they often remain clinically silent particularly in early part of the disease. They increase with duration of RA and age of the patient with exception of pleural effusion which is more prevalent early in the disease. Pulmonary evaluation should be considered early in RA patients irrespective of having any respiratory symptoms.

Keywords: Extra-articular manifestations, Pleural effusion, Spirometry

INTRODUCTION

Rheumatoid Arthritis (RA) is a common Connective Tissue Disease (CTD), having a prevalence of 0.5 to 2% in general population [1]. In patients of RA, extra-articular manifestations are common, approximately 50% and lung being the common site of affection [2]. Lung involvement ranges between 67% to as low as 10% in different studies [3,4]. Interestingly, mortality in patients of RA further increases in cases of extra-articular affection, of which pulmonary involvement accounts for 10-20% mortality, mostly attributable to Interstitial Lung Disease (ILD) [5,6]. Common RA associated ILDs are: Non Specific Interstitial Pneumonia (NSIP); Usual Interstitial Pneumonia (UIP); Organizing Pneumonia (OP); Desquamative Interstitial Pneumonia (DIP); Lymphocytic Interstitial Pneumonia (LIP); Diffuse Alveolar Damage (DAD); and Acute Interstitial Pneumonia (AIP) [7,8].

High titer of Rheumatoid Factor (RF) and Anticyclic Citrullinated Peptide antibody (anti-CCP), higher age, male gender, family history of RA, smoking etc. increases the likelihood for developing RA associated ILD [9]. Affection of airway in the forms of – bronchiolitis, bronchiectasis, crico-arytenoid arthritis, airway hyper-reactivity is common, seen in 39-60% patients [10]. Other types of pulmonary affection are-pleuritis or pleural effusions, pulmonary nodules and Pulmonary Arterial Hypertension (PAH). RA associated pleural effusions are often exudative, low pH (71.4%) and low glucose (80%) [11]. Pulmonary vascular affection in RA occurs in the form of rheumatoid vasculitis.

Till date, there is paucity of study on pulmonary manifestations of RA from Eastern India. The present study has intended to bridge this gap by evaluating the spectrum of pulmonary affection in RA patients in a tertiary care hospital of West Bengal, by clinical, spirometric, thoracic C.T scan and echocardiographic assessment. This will enhance the understanding of clinical course of the pulmonary manifestations of RA and will facilitate early detection and appropriate management for better outcome.

MATERIALS AND METHODS

The present cross-sectional study was done at RG Kar Medical College, a tertiary care teaching hospital of Kolkata, in eastern part of India. It was approved by the Institutional Ethical Committee. During the period of February 2014 to July 2015, consecutive patients, who were attending the outpatient or inpatient facilities of General and Respiratory Medicine Departments, aged over 17 years and a ACR/EULAR score ≥6 (American College of Rheumatology and European League Against Rheumatism 2010 criteria); were taken up for initial screening [12]. From a total of 80 such patients, 17 patients were excluded from study, who were having any of the following: cardio vascular disease, asthma, COPD, or other diagnosed pulmonary disease, malignancy, active infections like HIV/AIDS or were unwilling to participate. Informed consent was taken from all the 63 patients and they were evaluated by clinical assessment, spirometry, echocardiography and HRCT of thorax. A preformed questionnaire and a standard pro-forma were used for clinical evaluation including history and physical examination. Necessary blood reports including RF, anti CCP antibodies, C-reactive protein and ESR etc., were utilised for case confirmation and evaluation. Spirometry was done by RMS Helios 702, version 2 machine following the ATS/ERS guideline [13]. HRCT of thorax was done at end inspiration in supine position by 16 slice multidetector Brivo CT385 of Hangwei. Echocardiography was done with Siemens Acuson CV70 machine.

STATISTICAL ANALYSIS

All collected data were first entered into a Microsoft excel spread sheet, 2007 version and then analysed by SPSS, version 20 software. Descriptive statistics including-percentage, ranges, means, standard deviation etc. were calculated where the variables are normally distributed. 95% Confidence Interval of data are calculated. Chi-square test, Kruskal Wallis test, Mann Whitney U tests are used for categorical variables.

RESULTS

This study was carried out on 63 adult (age>17 years) patients. The mean age was 45.22 years (median 46.13 years) with age range between 25-66 years [Table/Fig-1].

Age group distribution			Duration of disease		
Age group	Frequency	Percentage	Duration	Frequency	Percentage
≤35 years	18	28.6%			
36-45 years	10	15.9%	<05 years	32	50.8%
46-55 years	21	33.3%	5-10 years	13	20.6%
56+years	14	22.2%	10+ years	18	28.6%

[Table/Fig-1]: Age group frequency and duration of disease in Rheumatoid Arthritis patients.

Regarding duration of RA, majority (n=32, 50.8%) of the patients had disease for less than five years. The lowest and highest duration being one year and 30 years respectively with a mean±SD=7.48±7.052 years.

Out of 63 patients 48 (76.19%) patients were taking or had a history of Methotrixate administration, while rest 15 did not.

Respiratory symptoms and signs: 29 (46.03%) out of 63 patients had some form of symptom like cough in 13(20.63%), shortness of breath in 10(15.87%), wheezing in 6 (9.52%) while 34 (53.96%) had no respiratory symptoms. On examination crepitations were found in 10 (16%) patients.

Spirometry showed a predominantly obstructive pattern in 18 (28.57%). Amongst them 11 (17.46%) patients show FEV1/FVC < 0.7 predicted (ATS & ERS Guideline) [13]. Rest 7(11.11%) patients showed normal FEV1/FVC ratio but significantly (<50% predicted) reduced mid expiratory flow signifying small airway obstruction. Most of the patients having normal spirogam were non-smokers 28 (60.86%). Smokers show more obstructive 7(41.17%) than restrictive 5 (29.41%) defects. A correlation was found between the duration of disease and development of Spirometry abnormalities. Association of smoking and spirometric abnormality patterns are found to be significant, with p= 0.048. However, no significant correlation is found between gender and Spirometry changes, (Chi-Square Test p= 0.064) [Table/Fig-2].

Decreased attenuation is the most common HRCT abnormality. Plotting the abnormality against age and duration of RA, there was correlation with both (p<0.00). Second most frequent finding was bronchiectasis; when adjusted with smoking and duration of disease, no significant associations was found. 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). Reticulo-nodular shadows and ground-glass opacities when found in HRCT indicates interstitial involvement. It showed positive correlation with the disease duration (p<0.001 for reticulo-nodular shadows and p=0.006 for ground-glass opacities). When these interstitial changes were adjusted with Methotrixate usage, no significant correlation

Parameters	p-value	Variables of Parameter	Ob-struc-tive	Restric-tive	Mixed	Normal
Gender (n=63)	p=0.064	Male	6 (9.52%)	7 (11.11%)	1 (1.58%)	7 (11.11%)
		Female	12 (19,04)	5 (7.93%)	0	25 (39.68%)
Duration of disease (in years)	p<0.001	Less than 5 years (n=32)	3 (9.37%)	4 (12.5%)	0	25 (78.12%)
		5-9 years (n=13)	5 (38.46%)	2 (15.38%)	0	6 (46.15%)
		More than10 years (n=18)	10 (55.55%)	6 (33.33%)	1 (5.55%)	1 (5.55%)
Smoking	p=0.048	Smoker (n=17)	7 (41.17%)	5 (29.41%)	1 (5.88%)	4 (23.52%)
		Non-smoker (n=46)	11 (23.91%)	7 (15.21%)	0	28 (60.86%)
Respiratory Symptoms (n=63)	p=0.046	Symptomatic	10 (15.87%)	8 (12.7%)	1	0
		Asymptomatic	8 (12.70%)	4 (6.34%)	0	32

[Table/Fig-2]: Spirometric findings in patients with rheumatoid arthritis.
Kruskal-Wallis test (duration of disease) and Chi-Square test (others); 95% C.I.

(p= 0.150 for reticulo-nodular shadows and p=0.091 for ground-glass opacities) has been found between them.

Among total 63 patients 17 (26.98%) had significant P.H as evidenced in echocardiography. There was a correlation between age (p=0.001) and duration of RA (p<0.001) with development of P.H. No significant correlation was found for development of P.H, with smoking status (p=0.792) or gender (p=0.771) of RA patients.

DISCUSSION

Lung disease in RA occurs as: an extra-articular manifestation of the disease; related to the drug therapy for RA; or due to co morbid conditions. Pulmonary parenchyma, airways, pleura and vasculature all can be involved in RA; either in the forms of infection or inflammation [14]. However, there are only few studies on this issue in Indian subcontinent especially from the eastern India.

Evidently our study population is relatively young. Mean age of the patients was 45.22 years, (median 46.13 years); with proportionally more number of patients presenting early in the disease with a median 4 years and mean disease duration±SD=7.48±7.052 years with more than half (50.8% or 32 patients) has a disease duration <5 years. Non-smoker patients are much more (n= 46) than smokers (n= 17) among our RA patients. Assayag D et al., has pointed out the importance of age and smoking habit as the risk factors for developing RA-ILD [15]. The compounding effect of smoking for RA-ILD is also suggested by Klareskeg L et al., [16].

In our study 44 (69.84%) of the 63 RA patients had no respiratory symptoms. The prevalence of symptoms was lesser than the findings of another similar study carried out by Wilsher M et al., from New Zealand revealing that 30% patients with RA reported respiratory symptoms: cough (11%), dyspnoea (11%) and wheeze (8%) [17]. However, a Malaysian study by Mohd. Nur et al., revealed 48% patients of RA with pulmonary symptoms, among them 20% having cough, 18% having dyspnoea and about 11% wheezing [18]. These findings are in agreement with ours.

Total 18 (28.57%) patients had an obstructive picture in spirometry which is clearly more than the restrictive pattern patients [Table/Fig-2]. Our finding varies from that of Cavagna L et al., who reported restrictive pattern in majority of RA-ILD patients [19].

In our study, there is an association between disease duration with spirometric changes (p=0.001) and obstructive spirometric changes with smoking (p=0.048). These findings were corroborated in an Asian study from Japan by Mori S et al., where 30% of study population had small-airway obstruction [20].

HRCT abnormality [Table/Fig-3] was found in 28 (44.4%) of our patients, the rest 35 (55.5%) being normal. Among them, 09 (32.14%) were asymptomatic though having HRCT abnormalities.

HRCT findings	Frequency	Percentage	Respiratory symptomatic	Respiratory asymptomatic
Abnormal	28	44.4%	19 (67.85%)	(32.14%)
a) Decreased attenuation	23	82.14%	20	3
b) Bronchiectasis	19	67.85%	18	1
c) Bronchial wall thickening	16	57.14%	15	1
d) Reticulo-nodular pattern	8	28.57%	8	0
e) Air trapping	11	39.28%	10	1
f) Pulmonary nodules	3	10.71%	3	0
g) Ground glass opacities	6	21.42%	6	0
h) Pleural effusion	10	35.71%	10	0
Pleural thickening	5	17.85%	2	3
Normal	35	55.5%	0	35

[Table/Fig-3]: Correlation of HRCT findings and respiratory symptoms in Rheumatoid Arthritis patients.

Prevalence of HRCT changes in different previous studies vary to a considerable extent as found by different authors; ranging from no specific type reported by Doyle TJ, Lee JS, Dellaripa PF, Lederer JA et al. [21]. While de Lauretis A, et al., found UIP pattern as the most common abnormality in HRCT of RA patients [22]. Details of few studies, in comparison to present study are shown below in [Table/Fig-4] [17,23-26].

This wide variation of results in different study reflects differences in study design, study population and the way that HRCT findings in RA are interpreted. Yet findings of our study are close to the study by Kochbati S et al., from Tunisia [23]. Adding up our commonest spirometric and HRCT findings together we presume either mere geographical variation or prevalence of smoking plus indoor air pollution in eastern India may be a possible explanation of its variation from the occidental studies.

HRCT findings	Wilsher M et al., [17] New Zealand	Kochbati S et al., [23] Tunisia	Mansaur et al., [24] Saudi Arabia	Metafratzi ZM et al., [25] Greece	Perez T et al., [26] France	Present study Eastern India
Decreased attenuation	67	-		-	13 (26%)	23 (82.14%)
Bronchiectasis	35	16.6%	30%	58%	15 (30%)	19 (67.85%)
Bronchial wall thickening	50	-		52%	5 (10%)	16 (57.14%)
Reticulo-nodularity	12	6.7%		-	15 (30%)	8 (28.57%)
Air trapping	-	-		69%	16 (32%)	11 (39.28%)
Pulmonary nodules	-	3.3%		-	17 (34%)	3 (10.71%)
Ground glass opacities	18	-		35%	-	6 (21.42%)
Pleural effusion	-	-		-	-	10 (35.71%)
Pleural thickening	-	-		-	-	5 (17.85%)
Normal	-	-		-	-	35 (55.5%)

[Table/Fig-4]: Comparison of H.R.C.T findings of this study with some previous studies from other parts of the globe [17,23-26].

After the advent of HRCT technique, prevalence of bronchiectasis in RA patients is found to be in the range of 20-58% [22,23].

No definite correlation was found between smoking and bronchiectasis in our study (p= 0.251). One study from Saudi Arabia in 2015 by Mansour et al., also did not show any relationship between smoking status and Bronchiectasis, majority of their patients with RA and Bronchiectasis were non-smokers (88.6%) [24].

We found a correlation with bronchiectasis to the age (p=0.001) and duration of disease (p=0.011). These findings corroborate with the study of Bilgici A, et al., [4]. One study by Kaushik W et al., and another by Demoruelle MK et al., are supporting the fact that bronchiectasis is now rather common in non smoker RA patients [27,28].

In our study, diagnosis of ILD was based upon clinical parameters (e.g., bi-basal fine crepitations) and HRCT findings (ground glass opacities, reticulo-nodularity etc.,) supported by a restrictive pattern in spirometry. Diffusion Capacity of Lung for Carbon Monoxide (DLCO) could not be done due to logistical insufficiency.

Out of our 10 (15.87%) patients having bi-basal crepitations on clinical examination, 7 (70%) patients had HRCT findings suggestive of ILD (ground glass opacity and reticulo-nodularity). All of them also had a restrictive pattern of spirometric change.

In our study, the development of pulmonary interstitial change had a correlation with age (p=0.006) and duration of disease (p=0.0001) but not with smoking or methotrexate usage (p=0.091).

A North American study carried out by Fischer A et al., found a significant correlation with advanced age and duration of disease to the development of ILD, thus corroborating our finding [29].

Another study from New Zealand by Wilsher M et al., also showed no significant differences in the HRCT patterns or lung function parameters between smokers and nonsmokers [17].

Though Methotrixate has a well-recognized side-effect of acute hypersensitivity pneumonitis in approximately 5% of patients, some authors have questioned whether this pulmonary toxicity is actually a reflection of progressive lung injury due to RA [30-32], but in our study there is no clinico-radiological evidence of pulmonary affection in patients who received methotrixate. A prospective study in UK, regarding chronic pulmonary effects of low-dose oral methotrexate in patients with RA by Dawson JK et al., found no evidence to suggest from clinical, HRCT assessment or serial pulmonary function tests that low-dose methotrexate is associated with chronic interstitial lung disease, thus supporting the finding in our study [31]. Similarly, Rojas-Serrano J et al., in their study also found that methotrixate is not negatively influencing the outcome of treatment in RA patients [33].

In our study about 24% of all patients showed pleural disease on HRCT. Pleural effusion was found in 35.71% and pleural thickening in 17.85%. Among patients having pleural effusion all (n =10) were symptomatic. In a Greek study by Metafratzi ZM et al., and another study by Helmers R et al., pleural thickening and effusion were observed in a frequency, which is slightly lower than our values [26,35]. However, this relatively higher prevalence of pleural effusion can be explained by the fact that pleural effusion occurs early in the disease and affect more the middle aged patients, as found by KA Stanek and KA Mills [35].

PH was found in 17(26.98%) out of 63 patients of RA, as evidenced by echocardiography. Out of them 47% was asymptomatic and rest had at least one respiratory symptom. In our study, a correlation to PH was found with the age (p= 0.001) and duration of disease (p< 0.001) of the RA patients. However, no significant correlation was found with smoking or gender of the patient [Table/Fig-5]. A study by Dawson JK et al., found about 30% prevalence of PH among the RA patients and the prevalence was increasing with age and duration of disease thus corroborating our findings [31]. Another

Parameters	p-value	Variables of Parameter	Frequency	Percentage
P.H* with age	p=0.001	Less than 35 years (n=18)	1	5.55%
		36-45 years (n=10)	1	10%
		46-55 years (n=21)	6	28.57%
		More than 56 years (n=14)	9	64.28%
P.H with gender	p=0.771	Male (n=21)	5	23.8%
		Female (n=42)	12	28.57%
P.H with smoking	p=0.792	Smoker (n=17)	5	29.41%
		Non-smoker (n=46)	12	26.08%
P.H with symptoms	p=0.714	Asymptomatic	9	14.28%
		Symptomatic	8	12.7%
P.H with disease duration	p<0.001	Less than 5 years (n=32)	1	3.125%
		5-9 years (n=13)	5	38.46%
		10 years (n=18)	11	61.11%

[Table/Fig-5]: Distribution of pulmonary hypertension in rheumatoid arthritis patients. (overall frequency=17).
*P.H: Pulmonary hypertension, Chi-Square test with 95% C.I.

study by Young ID et al., reported PH in about 23% patients [36]. Previous study by Venkatesan UN also suggested that there was a strong correlation between the pulmonary artery pressure and the disease duration (r= 0.68, p<0.0001) corroborating similar finding in our study [37].

So, from this present study some facts about the clinical course, factors and effects of RA regarding its pulmonary affections are quite evident. Like - RA manifestations are found in relatively younger population (mean age 45.22 years). Majority patients are respiratory asymptomatic (69.84%). There is a significant correlation of features of ILD in HRCT with age and duration of disease, but not with smoking and methotrixate usage (p=0.091). Development of PH in RA patients is found to be related to age and disease duration but not with smoking or gender. Till date there is no prospective study on evaluating response of pulmonary manifestations of RA patients on treatment, paving the path for following these patients focusing on this aspect.

LIMITATION

DLCO is a sensitive tool for early diagnosis of ILD which could not be done here due to logistic insufficiencies. Our study was conducted in a tertiary care center so the possibility of referral bias could not be ruled out. Lastly, it was cross sectional study with a relatively small number of study populations from a small geographic area. Prospective multicentric studies involving large number of patients can provide more definitive answer to type and prevalence of different pulmonary manifestations in RA and their strength of association with different factors.

CONCLUSION

It seems from the findings of our study that-most of the pulmonary manifestations of RA are usually related to the duration of RA and age of the patient, with exception of pleural effusion, which is more prevalent early in the disease. Smoking is significantly related to spirometric changes in RA patients, but is not related to the development of Bronchiectasis and ILD. Use of methotrixate is also not related to the development of ILD in RA patients. Awareness about these facts are likely to help physicians to evaluate their RA patients early, with optimum utilization of resource, formulating the management and prognostication of cases.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of General Medicine, R.G. Kar Medical College, Kolkata, West Bengal, India.
2. Associate Professor, Department of Respiratory Medicine, R.G. Kar Medical College, Kolkata, West Bengal, India.
3. Professor, Department of General Medicine, R.G. Kar Medical College, Kolkata, West Bengal, India.
4. Professor, Department of Respiratory Medicine, R.G. Kar Medical College, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sumit Roy Tapadar,
12/10, Bireswar Dhole Lane, Kolkata, West Bengal, India.
E-mail: sumittapadar@gmail.com

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