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A Study of Pulmonary Manifestations in Rheumatoid Arthritis and Its Correlation with Disease Activity

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Abstract

Introduction: Pulmonary involvement is the one of the most common extra-articular manifestations of rheumatoid arthritis which contributes significantly to morbidity and mortality of patients with rheumatoid arthritis. Therefore a study was conducted to study Pulmonary manifestation in patients with rheumatoid arthritis, irrespective of the presence of respiratory symptoms and to correlate pulmonary manifestations with disease activity. *Methods:* The study conducted was a cross-sectional descriptive study on fifty patients of Rheumatoid Arthritis, new or follow up, who presented to Medicine OPD or admitted to the wards of ESIC Medical College Hospital, Bangalore. Data was collected with the aid of a proforma, which included patient bio data, relevant history, a routine clinical examination with special attention to joints and respiratory system. *Results:* Age of the study individuals ranged from 22–64 years. Mean age of the patients in the study was 46.3±9.75.7 years. The female to male ratio was 3.2:1. Mean duration of the disease was 5.18 ±6.52 years (range 1-26 years). Rheumatoid factor was positive in 39 (78 %) patients. In our study, twenty (40%) patients had respiratory symptoms. *Conclusion*: Pulmonary manifestations were found in more than half of patients with RA. Asymptomatic pulmonary involvement was seen in one third of patients with RA. This highlights the importance of actively looking for asymptomatic pulmonary manifestations in RA patients.

Keywords: Arthritis; Rheumatoid; Echocardiography; Hypertension, Pulmonary; Methotrexate; Pleural Effusion; Rheumatoid Factor.

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Introduction

Pulmonary involvement in RA is frequent although not always clinically recognized. Pleural disease is common but usually asymptomatic; autopsy studies reported pleural involvement in 50% of cases, with only 10% clinically detected [1-5]. Pleural effusions are more common in patients with long standing active articular disease and in those with rheumatoid nodules. Pleural effusions are commonly exudates with mixed cell counts, high protein concentration and low glucose.

Parenchymal involvement in RA may be in the form of rheumatoid nodules, Caplan's syndrome and interstitial lung disease. Rheumatoid nodules are the only specific pulmonary lesions observed in patients with RA. They are single or multiple nodules seen more commonly in males, patients with extra-articular manifestations and those with subcutaneous nodules. The syndrome of bilateral lung nodules in silica-exposed patients with RA is known as Caplan's syndrome [6].

The interstitial lung disease associated with rheumatoid arthritis is similar to that of idiopathic pulmonary fibrosis. The prevalence of interstitial lung disease (ILD) in Rheumatoid arthritis ranges from 19% to 44% [7]. Risk factors for development of ILD include male gender, smoking, and longstanding disease. Onset of ILD is generally in the fifth to sixth decade.

Rheumatoid arthritis can cause upper, lower, and small airway disease. Upper airway involvement includes cricoarytenoid arthritis, rheumatoid nodules in the vocal cords and vocal cord paresis. Lower

airway involvement includes bronchiectasis, bronchiolitis with or without organizing pneumonia.

There is a high incidence of radiographic bronchiectasis, up to 30% in some HRCT studies [21-23]. However, clinically significant disease is much less frequent. Pulmonary involvement can be studied using HRCT, DLCO and Echocardiography for anatomical and physiological abnormalities res. However these diagnostic tests may not be widely available and cost effective. Pulmonary assessment using an office spirometer & Chest X-ray is simpler, cheaper and more widely available tools for screening patients with RA for pulmonary involvement.

Rheumatoid Arthritis (RA) affects approximately 1% of the adult population, with a female preponderance. Pulmonary involvement in Rheumatoid arthritis is seen in nearly 30% of the cases. Pulmonary causes, are a significant contributor to excess morbidity and mortality in patients with RA, ranking as the second major cause of death in RA [8].

Rheumatoid arthritis can affect lung parenchyma, airways and pleura. Pulmonary manifestations include pleural effusions, rheumatoid nodules, and parenchymal lung disease [8]. Pleural disease, the most common pulmonary manifestation of RA, may produce pleuritic chest pain and dyspnea.Exudative Pleural effusions are common in RA. Interstitial lung disease (ILD) occurs in patients with RA and is heralded by symptoms of dry cough and progressive shortness of breath. Diagnosis is readily made by High-resolution chest CT scan. Pulmonary function testing shows a restrictive pattern. The presence of ILD confers a poor prognosis. The prognosis is not quite as poor as that of idiopathic pulmonary fibrosis because ILD secondary to RA responds more favorably than idiopathic ILD to immunosuppressive therapy. Pulmonary nodules may be solitary or multiple. Other less common pulmonary findings include respiratory bronchiolitis and bronchiectasis.

In addition to the disease, drugs used in the treatment of RA can cause pulmonary involvement. Often the pulmonary involvement in RA is asymptomatic. Since ILD secondary to RA responds more favorably than idiopathic ILD to immuno suppressive therapy, it is necessary to identify pulmonary involvement at an early stage.

Methodology

Inclusion Criteria

- Patients diagnosed with RA newly or those being followed up for the disease.
- Consenting to participate in the study.

Exclusion Criteria

- Patients with Pre-existing lung disease-COPD,Pulmonary Tuberculosis, Bronchiectasis, Bronchial asthma.
- Smokers.
- Patients with Thoracic abnormality.
- Patients with Vertebral abnormalities.

Method of Collection of Data

All patients newly / previously diagnosed to have RA & were willing to participate in the study were evaluated as per the proforma designed for the purpose of the study. All patients were diagnosed as rheumatoid arthritis on the basis of 2010 ACR / EULARRheumatoid Arthritis Classification Criteria

All patients were subjected to a detailed clinical examination with particular reference to the musculoskeletal & the respiratory systems.

Results

Twenty (40%) patients had respiratory symptoms. The symptoms included, cough in 18 (38%) patients, of whom 4 (8%) of had associated expectoration,

Table 1: Prevalence of Respiratory symptoms

Respiratory symptoms	Number of patients	Percentage of patients
Absent	30	60%
Present	20	40%

Table 2: Types of respiratory symptoms

Respiratory symptoms	Number of patients	Percentage of patients
Cough	18	38%
Expectoration	4	8%
Breathless ness	12	24%
Chest pain	4	8%

breathlessness in 12(24%) patients, and chest pain in 4 (8%) patients. None of the patient had hemoptysis.

Patients who had cough were again sub classified into acute, sub-acute and chronic.Twelve patients among the eighteen had chronic cough,three patients had subacute cough and three patients had acute cough.

Cough was taken as an indicator of respiratory involvement and an attempt was made to identify possible predictors of this symptom.

Mean duration of RA in patients with and without cough were 9.72 ± 8.93 (range 1 -26 years) and 2.625 ± 2.16 (range 1 -10 years) respectively. The duration of RA was found to be significantly longer in patients with cough ($p < 0.001$).

Mean DAS 28 score was in patients with and without cough were 6.21±2.26 and 5.45±1.85 respectively.There was no significant association between presence of cough and DAS 28 score ($p = 0.205$)

Table 3: Classification of cough according to the duration

Cough	Number of Patients	Percentage of Patients
Acute		
(< 3 weeks)	3	6%
SUBACUTE (3 to 8 weeks)	3	6%
Chronic		
(> 8 weeks)	12	24%
Absent	32	64%

Table 4: Cough and duration of RA

Cough symptoms	Number of patients	Mean	Minimum	Maximum	Standard deviation	p-value
Absent	32	2.625	1	10	2.16	<0.001
Present	18	9.72	1	26	8.93	

Table 5: Cough and DAS 28 score

Cough symptoms	Number of Patients	Mean DAS28	Minimum DAS28	Maximum DAS28	Standard deviation	p-value
Absent	32	5.45	2.06	8.9	1.85	0.205
Present	18	6.21	2.06	8.9	2.26	

Table 6: Prevalence of Breathlessness (MRC Grading)

Breathlessness	Number of Patients	% of Patients
Grade-1	4	8%
Grade-2	6	12%
Grade-3	2	4%
Absent	38	76%

Breathlessness (Dysnoea)

Breathlessness was present in twelve patients. The severity was graded according to the MRC classification for dyspnea.

An attempt was made to identify factors that could predict the presence of dyspnea in these patients. The mean age of patients with dyspnea was higher than those without dyspnea.The difference was statistically significant ($p < 0.001$).

Table 7: Dyspnoea and Age

Dyspnoea	Number of Patients	Mean Age in Years	Minimum Age in Years	Maximum Age in Years	Standard Deviation	p-value
Absent	38.00	43.50	22.00	58.00	9.01	<0.001
Present	12.00	55.17	45.00	64.00	6.16	

10 (26%) of the 38 female patients had dyspnea compared with 2 (17%) of the 12 male patients. The difference was not statistically significant ($p = 0.47$)

Table 8: Dysnoea and Gender

Dyspnoea	Female	Male	Total
Absent	28	10	38
Present	10	2	12
Total	38	12	50

Table 9: Dyspnoea and Duration of RA

Dyspnoea	Number of patients	Mean duration in years	Minimum duration in years	Maximum duration in years	Standard deviation	p-value
Absent	38.0	2.5	1.0	10.0	2.1	<0.001
Present	12.0	13.8	1.0	26.0	8.3	

Table 10: Dyspnoea and DAS 28 score

Dyspnoea	Number of patients	Mean DAS 28 score	Minimum DAS 28 score	Maximum DAS 28 score	Standard deviation	p-value
Absent	38.0	5.3	2.1	8.9	1.9	0.009
Present	12.0	7.0	2.1	8.9	1.8	

Table 11: Respiratory Signs Prevalence

Respiratory Signs	Number of Patients	Percentage of Patients
Bronchial breath sounds	1	2%
Crackles	9	18%
Wheeze	1	2%
Wheeze & Crackles	1	2%
Absent	38	76%

Table 12: Respiratory signs and Mean DAS 28 score:

Respiratory Signs	Number of Patients	DAS 28				p-value
		Mean	Minimum	Maximum	Standard Deviation	
Absent	38.0	5.5	2.1	8.9	1.9	0.103
Present	12.0	6.6	2.1	8.9	2.3	

Mean duration of RA was more in patients with dyspnoea than those without dyspnoea.The difference was statistically significant ($p < 0.001$).

Mean DAS 28 score was more in patients with dyspnoea than with patients without dyspnoea.The difference was statistically significant ($p = 0.009$).

Respiratory signs were present in twelve (24%) out of fifty patients. Nine (18%) had crackles, one(2%) had wheeze, one(2%) had wheeze &crackles, one(2%) had Bronchial breath sounds.

Eight(40%) out of twenty patients who had respiratory symptoms dint have any respiratory signs. Mean DAS 28 score was more in patients with respiratory signs compared to patients without any respiratory signs. However, the difference was not statistically significant ($p = 0.103$)

Discussion

In our study, twenty (40%) patients had respiratory symptoms. The symptoms included, cough in 18 (38%) patients, of whom 4 (8%) of had associated expectoration, breathlessness in 12(24%) patients, and chest pain in 4 (8%) patients. None of the patient had hemoptysis. Respiratory signs were present in twelve (24%) out of fifty patients. Nine (18%) had crackles, one(2%) had wheeze, one(2%) had wheeze & crackles, one(2%) had bronchial breath sounds.

In the study conducted by Raniga et al, 6 of the 30 patients had respiratory complaints (20%). The symptoms included cough, breathlessness, wheeze, sputum production and chest pain. Only 3 patients (10%) had clinical signs of respiratory involvement

(presence of rhonchi and crackles). This is much less than the figures documented in our study.

In the study done by Youssef AA et al nearly two-thirds of the patients reported one or more pulmonary symptom like dyspnea, cough, wheezing, or phlegm. Dyspnea was the most frequent symptom. Dyspnea and dry cough were the most common presenting symptoms (76.47 %) in another study conducted by R Prasad et al on pulmonary manifestation in rheumatoid arthritis. These are much higher than the figures documented in our study. Though the figures vary, these studies, including ours indicate that respiratory manifestations are common in patients with RA & need to be specifically looked into.

In our study, Mean duration of RA in patients with and without cough were 9.72 ± 8.93 (range 1 -26 years) and 2.625 ± 2.16 (range 1 -10 years) respectively. The duration of RA was found to be significantly longer in patients with cough ($p < 0.001$). Mean duration of RA was more in patients with dyspnoea than those without dyspnoea. The difference was statistically significant ($p < 0.001$). This is concordance with study done by Mary laly, which showed patients with longer duration of RA had more respiratory symptoms. In our study, Mean DAS 28 score was in patients with and without cough were 6.21±2.26 and 5.45±1.85 respectively. There was no significant association between presence of cough and DAS 28 score ($p = 0.205$). Mean DAS 28 score was more in patients with dyspnoea than with patients without dyspnoea. The difference was statistically significant ($p = 0.009$).This is similar to study conducted by Dimitrios A Pappas et al in which DAS score was higher in patients with respiratory involvement [9,10].

In our study, Thirteen (26%) patients had abnormalities on chest radiograms. The abnormal findings included reticular opacities in 5 (10 %) patients, bilateral lower zone infiltrates in 2 (4%) patients, fibrosis in 1(2%) patients, prominent broncho-vascular markings in 1 (2%) patients, honey combing in 3(6%) patients, obliteration of costophrenic angle in 1 (2%) patient. Thirteen (65%) out of twenty patients with respiratory symptoms had abnormalities in chest X-ray. Whereas remaining Seven (35%) patients with respiratory symptoms had normal chest X-ray.

In the study conducted by Kulkarni AA, 8 (10.7%) patients had an abnormal chest radiogram. The abnormal findings included: reticulonodular opacities in 3 patients (4%), alveolar opacities in 2 patients (2.7%) and hyper inflated chest without other evidence of COPD in 3 patients (4%). In our study 10 (20 %) patients had radiographic features suggestive of ILD (reticular opacities, lower zone infiltrates & honeycombing).

Reticulonodular & alveolar opacities accounted for most of the radiological abnormalities in both studies, indicating interstitial lung involvement is the most common radiological abnormality in these patients.

In the study conducted by Mary laly, Sixteen (26.2%) patients had abnormalities on chest radiograms. The abnormal findings included: reticular opacities in 6 (9.8%) patients, bilateral lower zone infiltrates in 2 (3.3%) patients, fibrosis in 2 (3.3%) patients, prominent bronchovascular markings in 2 (3.3%) patients, honey combing in 2 (3.3%) patients, obliteration of costophrenic angle in 1 (1.6%) patient and diaphragmatic hump in 1 (1.6%) patient.

In our study, Mean duration of RA was more in patients with chest X-ray abnormalitiesthan those with normal chest X-ray.The difference was statistically significant ($p < 0.001$). Mean DAS 28 score was higher in patients with abnoramalities in chest X-ray compared to patients with normal chest X-ray. However, the difference was not statistically significant ($p=0.222$).This is similar to study conducted by Mary laly in which duration of RA and DAS score were higher in patients with abnormal chest radiogram.

In our study, HRCT was proposed for all patients but only 30(60%) patients had HRCT done as remaining 20(40%) patients were not eligible for special radiology investigations under ESIC scheme and due to financial constraints. HRCT was not done in 20(40%) of patients, 11(22%) patients had normal HRCT, 13(26%) had geatures suggestive of ILD, 2(4%) had pleural thickening, 2(4%) had minimal pleural effusion, 1(2%) had obliterative bronchiolitis, 1(2%) had paraseptal emphysema. In the study conducted by Mary laly, HRCT was proposed for many patients but only 7 (11.5%) patients had HRCT done in view of financial constraints and out of the 7, 5 (71.4%) had abnormal HRCT findings. Abnormal HRCT findings included features suggestive of ILD in 3 patients, paraseptal emphysema in 1 patient and atelectasis of anterior basal segment of left lower lobe in 1 patient.

Among the patients who under went HRCT, mean duration of RA was higher in patients with HRCT abnormalities compared to patients who had normal HRCT. The diffenrence was statistically significant ($p = 0.037$). This is similar to study conducted by Kelly. C.A et al in 2013, in which mean duration of RA was higher in patients with HRCT abnormalities. 108Among the patients who under went HRCT,mean DAS 28 score was higher in patients with HRCT

abnormalities compared to patients who had normal HRCT. However, thediffenrence was not statistically significant (p = 0.661). Six (32%) out of nineteen patients who had HRCT abnormalities had normal chest X-ray. Though HRCT was better in detecting respiratory abnormality,statistical analysis to establish its significance could not be done due to small sample size. Seven (36%) out of nineteen patients who had HRCT abnormalities had no respiratory symptoms.Though HRCT was better in detecting asymptomatic respiratory abnormality,statistical analysis to establish its significance could not be done due to small sample size.

Conclusion

Pulmonary manifestations were found in more than half (56%)of patients with RA.

- Pulmonary manifestations were significantly higher in seropositive RA patients.
- Restrictive lung disease was the most common pulmonary function abnormality in RA.
- HRCT thorax was better than chest radiogram in detecting pulmonary involvement in patients with RA.
- Pulmonary manifestations increased significantly with increased duration of Methotrexate use.
- Disease activity (DAS 28 score) was higher in patients with pulmonary manifestations.

However, there was no significant correlation between pulmonary manifestations and higher disease activity.

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