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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Romatoid artritte plöropulmoner bulgular için risk faktörleri: Bir pilot çalışma

Risk factors for pleuropulmonary manifestations in rheumatoid arthritis: A pilot study

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ÖZ

Amaç: Çalışmanın amacı, romatoid artritte (RA) pulmoner bulguların gelişiminde olası plöropulmoner bulguların paternini ve olası risk faktörlerini belirlemektir.

Yöntem: Toplam 70 romatoid artrit hastası alındı. Akciğer değerlendirmesi, medikal öykü, göğüs röntgeni, solunum fonksiyon testi (SFT), göğsün yüksek çözünürlüklü bilgisayarlı tomografisi ve spirometri ile yapıldı.

Bulgular: Yetmiş hastanın 38'inde akciğer komplikasyonları görüldü. Bunların 35'inde SFT anormaldi. SFT'de restriktif patern 22 hastada ve obstrüktif patern 9 hastada görüldü. Yaşlılık, hastalık süresi, nabız sayısı, solunum sayısı ve romatoid faktör, RA'lı hastalarda anormal SFT ile ilişkili bulundu ($p < 0.05$). RA hastalarında anormal SFT gelişimi için bağımsız risk faktörü olarak hastalık süresi ve romatoid faktör belirlendi.

Sonuç: Hastalık süresi ve romatoid faktör, akciğer hastalığının bağımsız risk faktörüdür..

Anahtar Kelimeler: İnterstisyel Akciğer Hastalığı, Romatoid artrit, Romatoid faktör, Spirometri, Plöropulmoner

ABSTRACT

Background and Aim: The aim of study was to find out the pattern of pleuropulmonary manifestations and possible risk factors for the development of pulmonary manifestations in rheumatoid arthritis.

Methods: A total of 70 rheumatoid arthritis patients were recruited. Pulmonary evaluation was done including medical history, Chest x-ray, Pulmonary Function Test, High-Resolution Computerized Tomography of chest and Spirometry.

Results: Out of 70 patient's pulmonary complications was seen in 38 patients out of whom 35 patients had abnormal PFT. Restrictive and obstructive pattern on PFT was seen in 22 and 9 patients respectively. Older age, duration of illness, pulse rate, respiratory rate and rheumatoid factor were found significantly associated with abnormal PFT in RA patients ($p < 0.05$). Duration of illness and rheumatoid factor were observed as independent risk factor for the development of abnormal PFT in RA patients.

Conclusion: Duration of illness and rheumatoid factor were identified as independent risk factor of lung disease.

Keywords: Interstitial Lung Disease, Pleuropulmonary, Rheumatoid arthritis, Rheumatoid factor, Spirometry

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Introduction

Rheumatoid arthritis (RA) is a disabling autoimmune inflammatory disease of unknown cause that may affect numerous tissues and organs, but predominantly attacks synovial joints, chiefly affecting the peripheral joints in a symmetrical pattern. It manifests as inflammatory arthritis of multiple joints and produces a wide variety of extra-articular manifestations that affects 1-2% of the general population and increases with advancing age.1 The disease is commonly seen in women; however, thoracic manifestations (2-54%) occur more commonly in males (5:1). Pulmonary disease occurring in RA a case report was first broadcasted by Ellman and Ball in 1948. Pleuropulmonary involvement often occurs after joint involvement in 85% of cases and in patients with high serum rheumatoid factor titers.2 Variety of pleuropulmonary manifestations are associated with RA and 7% of the RA patients died due to pleuropulmonary manifestations. 3 Pleural diseases is associated with subcutaneous nodules, interstitial lung disease (ILD), and pericarditis, often in seropositive males.2 Voluminous literature is available reporting the incidence of pleuropulmonary complications in rheumatoid arthritis however the data from central India is lacking. With this background, we undertook this study to determine the occurrence and spectrum of pleuropulmonanry manifestation in RA patients from central India and associated risk factor for the same.

MATERIAL AND METHODS

Study design: This prospective cross sectional pilot study was done in the Department of Medicine, Sri Aurobindo Medical College and PG Institute, Indore, India from October 2012 to September 2014. Prior ethical clearance was taken from the Institutional ethical committee before conducting this study.

Subjects: Patients of both sexes and more than 16 years of age satisfying the 1987 or 2010 American College of Rheumatology (ACR) classification criteria for RA4,5 were included in the study. Patients with a history of RA before 2010 were diagnosed by 1987 criterion whereas patients diagnosed after 2010 were selected according to ACR/EULAR 2010 criterion.

Patients with history of smoking, pulmonary malignancy, sputum positive pulmonary tuberculosis were excluded as these are well known risk factors for pleuropulmonary complication. Patients with other possible reasons for obstructive and restrictive disorders (occupational and environmental exposures, asthma, chronic obstructive pulmonary disease, obesity (BMI>35 kg/m2) were also excluded from the study. Written informed consent was taken from all patients.

Clinical assessments: Pre-tested semi-structured questionnaire for all patients, included demographic data, occupational history, presenting symptoms like cough, sputum production, dyspnea, wheeze and meticulous examination was filled to look for signs suggestive of respiratory system involvement. Pulmonary function test was done in all patients using Spirometer test (CareFusion MasterScreen™ PFT system, USA). Baseline spirometry was executed for all patients and in those with evidence of an obstructive defect, two puffs of short acting beta-agonist bronchodilator was administered and the test was repeated after 15-20 minutes in order to look for signs of reversibility in spirometry parameters. We were not able to perform diffusion capacity of lung for carbon monoxide (DLCO) due to certain limitations.

Chest X-ray was done to rule out underlying lung disease. High resolution computed tomography (HRCT) chest was performed in only those individuals who have abnormal PFT. HRCT chest performed to look for lung parenchymal abnormalities like airspace consolidation, ground-glass opacity (GGO), reticulation, honeycombing, nodules etc. were assessed. HRCT findings can differentiate usual interstitial pneumonia (UIP) and bronchiolitis obliterans with organizing pneumonia (BOOP) on the basis of traction bronchiectasis, interlobular septal thickening, and intralobular reticular which are more prevalent in UIP than in BOOP whereas lung parenchymal nodules and peripheral distribution are more prevalent in BOOP than in UIP6.

Laboratory measurements: All the routine blood investigations were done as per standard protocol. Complete blood count was performed on automated Sysmex Kx-21(Transasia-Japan). Erythrocyte sedimentation rate(ESR) was measured using Wintrobe Method. IgM Rheumatoid factor titers was measured by quantitative turbidimetric immunoassay for Rheumatoid factors(Tulip, India) kit on an automated turbidimeteric analyzer. Anti Anti-cyclic citrullinated peptide (Anti-CCP) Antibody was measured using automated chemiluminescence analyzer (Elecsys 2010 Systems, Hitachi, Japan).

Statistical analysis: Fisher exact test was used to see the difference in frequency of discrete variable in two groups. Independent sample t test was applied to see the difference in mean of quantitative data in between two groups. Multinomial logistic regression analysis was performed using backward stepwise method to see the independent risk factor associated with pulmonary manifestation in RA patients taking RA patients without pulmonary manifestation as a control group.

RESULT

A total of 70 patients with a history of rheumatoid arthritis following exclusion and inclusion criterion were recruited for the study. Out of which 15 patients were diagnosed using 2010 ACR/EULAR criterion and rest of 55 cases were already diagnosed as RA before 2010 by 1987 criterion.

Mean age of patients was 48.2±12.6 years and mean duration of disease was 11.1±7.0 years. There was female preponderance of the rheumatoid arthritis as 54(77.1%) were female in present study.

Rheumatoid factor positivity with a mean of 47.62±28.98 IU/ml were seen in 67(95.7%) cases Anti-

CCP antibodies was done in only 15 patients who were diagnosed as per 2010 ACR/EULAR criterion, and found postive in 14 patients. Out of these 14 patients anti- CCP was > 300 U/ml in 8 patients.

Pulmonary menifestations was observed in 38 case, among them dyspnea was the most common presenting symptom which was present in 18(25.7%) cases followed by cough(n=8) and wheezing(n=4) (Table 1). Coarse crepitation was present in 10(14.2%) cases whereas sign of pleural effusion and rhonchi was present in 3(4.2%) patients each.

Chest X ray was done in 70 cases which were found abnormal in only 18(25.7%) cases. Pulmonary function test was done by spirometry in 66 patients as 4 patients refused to do so. PFT test revealed the presence of restrictive pattern in 22 cases, obstructive pattern in 9 cases while mixed pattern was seen in 2 cases. 26 (48%) of the 54 women

and 7 (43%) of the 16 men had an abnormal PFT.

Table 1: Demographic, Clinical and Biochemical profile of patients according to PFT findings

Parameter	Abnormal PFT (33)	Normal PFT(33)	P value
Age(years)	51.58±12.74	44.03±11.9	**0.016**
Sex (Female:Male)	26:7	28:5	0.751
Duration of Illness (years)	14.52±6.71	7.24±5.5	**<0.0001**
Cough	7(21.2%)	0(0.0%)	**0.005**
Dyspnea	19(57.6%)	1(3.0%)	**<0.0001**
Wheezes	4(12.2%)	0(0.0%)	0.113
Chest Pain	4(12.2%)	0(0.0%)	0.113
Pulse rate(per min)	83.0±5.69	77.88±8.58	**0.006**
Respiratory Rate(Per min)	15.67±3.43	14.24±1.71	**0.037**
Hemoglobin(g/dl)	10.41±2.32	10.55±20.6	0.799
ESR(mm per min)	25.59±11.23	21.97±7.1	0.125
Rheumatoid factor(IU/ml)	56.97±33.42	40.56±22.82	**0.027**

Clinical and biochemical profile in patients with normal and abnormal PFT was compared and we observed that there was a significant difference in age, duration of illness, occurrence of cough and dyspnea, pulse rate, respiratory rate and rheumatoid factor in between two groups(Table 21). No significant difference in clinical and biochemical profile profile except respiratory rate was observed between obstructive and restrictive pattern of PFT (Table 2).

Table 2: Demographic and Biochemical profile of patients according to PFT findings

Parameter	Restrictive(22)	Obstructive(9)	P value
Age(years)	49.23±13.65	53.44±6.74	0.387
Sex (Female: Male)	19:3	6:3	0.320
Duration of Illness(years)	12.91±6.85	16.11±4.1	0.204
Pulse rate(per min)	82.32±6.2	84.44±4.33	0.361
Respiratory Rate(Per min)	14.95±2.93	17.78±4.17	**0.040**
Hemoglobin(g/dl)	9.86±2.3	11.44±2.2	0.095
ESR(mm per min)	27.90±12.53	20.22±7.10	0.098
Rheumatoid factor(IU/ml)	54.40±32.80	52.11±17.85	0.847

High resolution computed tomography (HRCT) chest was performed in patients having abnormal PFT. 13(39.4%) out of 33 patients had abnormal high resolution computed tomography (HRCT) chest and usual interstitial pneumonia (UIP) were seen in 10(30.3%) whereas bronchiolitis obliterans with organizing pneumonia (BOOP) associated with UIP seen in 2(6.1%) and pleural effusion in 1(3.03%). In 10 patients of UIP, predominant ground glass opacity was seen in 4, thickened interlobular septum seen in 5, traction bronchiectasis seen in 6, pulmonary nodule and honey combing was seen in 1 patient each.

To see the independent risk factor associated with development of pulmonary complication in RA patients multinominal logistic regression analysis was performed using backword setpwise model and taking RA patients with normal PFT as a control. Duration of illness (OR =1.278, 95% CI=1.121-1.4569), and rheumatoid factor(OR= 1.030, 95% CI=1.003-1.059) were found independent risk factor for pulmonary complication in RA pateints (Table 3).

Table 3: Multinomial regression analysis of the patients

Parameter	ExpB (OR)	P value	95% confidence interval
Duration of Illness	1.278	**<0.0001**	1.121-1.456
Rheumatoid factor	1.030	**0.030**	1.003-1.059

Patient were treated with DMARDS(methotrexate based) where as those patients showing pulmonary fibrosis were switched

over to leflunamide 20 mg od and perfenidone 200 mg bd.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic multi-system disease of unknown cause. ACR had given two classification systems in 1987 and 2010 respectively for characterizing RA. ACR 2010 classification criteria was used to pick up patients with early RA and those with undifferentiated arthritis who are potential candidates to develop RA, so that treatment can be started early to prevent erosions. This criterion can over diagnose case of RA and its sensitivity is more than specificity. Whereas, 1987 criteria include radiographic erosions, rheumatoid nodules which may take years to develop, so it may underdiagnose cases of RA and its specificity is more than sensitivity.

In the present study, rheumatoid factor positivity is found in 96% cases. Similar to our study, RA factor was positive in 83.3% and 87.5% patients in studies done by Raniga et al6 al7 and Prasad et al7 al8 respectively.

A variety of pulmonary manifestations are associated with RA. In our study total 35 38 patients had pleura-pulmonary complications but only 18(25.7%) patients had abnormal chest X-ray. In the study conducted by Raniga et al6al7, chest radiograph abnormalities were detected in 13.33% whereas abnormal chest x-ray was found only in 5.6% of patients by Panda et al.89

Restrictive pattern of PFT was seen in 22(31.4%) patients whereas obstructive pattern was seen in 9(12.8%) patients. In contrast to our study; Prasad et al7 al8 observed restrictive pattern in 52.9% patients and obstructive pattern in 11.8 % patients. As compared to our study, Prasad et al8 found greater percentage of restrictive lung disease, probably because their study included only patients who manifest with pleuropulmonary symptoms. Spirometric abnormalities seen in 26.6% of the patients by Rangia et al.67

Similar to our study, previous studies also reported interstitial lung disease as most common pleuropulmonary disease associated with RA.6,77,8,910 Based on the HRCT findings, pulmonary involvement was detected in 13 out of 33 patients having abnormal PFT. Our findings are apparently less than that of some other studies (49%1011, 48%1112, 67.3%12 13 and 63%1314). This is probably attributed to the fact that we had excluded smokers were from our study. Saag et al14 al15 also reported that smoking was the most consistent independent risk factor predicting the development of ILD in RA.

RA-associated pulmonary diseases appear to be more common in the setting of older age10age11,143,156, 176,178, disease severity16,17,187-19, rheumatoid factor19factor20, and male sex20sex21. In present study, the duration of illness and rheumatoid factor were independent risk factors for the development of pulmonary complications associated with RA.

There were certain limitations of the study. Firstly this pilot study has small sample size and therefore we were not able to designate the prevalence of pleuropulmonary complications of rheumatoid arthritis. Secondly due to being cross sectional observation study we have selected patients who were diagnosed using either 1987 or 2010 criterion which may bias patient's selection. To conclude the result of our study, pleuropulmonary complication affected significant proportion of the patients with RA and one of the common causes of morbidity and mortality. Duration of illness and RF factor were identified as independent risk factor of lung disease as determined by PFTs. Further

larger studies are needed to confirm these findings.

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