Pulmonary involvement in rheumatoid arthritis: A cross-sectional study in Iran

Habib Zayeni, Asghar Haji-Abbasi, Seyed Ali Alavi Foumani, Mehdi Tohidi, Irandokht Shenavar Masooleh, Banafsheh Ghaavdel Parsa, Mehrdad Aghaei, Amir Hassankhani, Pooneh Ghaavdel Parsa, Alireza Amir Maafi

Rheumatology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Respiratory Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Student Research Center, Guilan University of Medical Sciences, Rasht, Iran

ABSTRACT

Background: Interstitial lung disease (ILD) is a type of pulmonary manifestation in patients with rheumatoid arthritis (RA). Mostly RA-ILD has no symptoms and is only diagnosed by clinical examination, pulmonary function test (PFT), and high-resolution computed tomography (HRCT); hence it seems that the diagnosis of pulmonary involvement in early stages of RA is of great importance. Therefore, we decided to answer this question whether the evaluation of RA patients without pulmonary symptoms using methods such as PFT and HRCT are justifiable and reasonable or not. Methods: We conducted a cross-sectional study in a referral rheumatology clinic in Razi hospital of Rasht, Iran. Forty-four consecutive patients, diagnosed with RA, were enrolled. Physical examination of the joints was performed by an rheumatologist. The activity of RA was evaluated in all patients by Disease Activity Score 28. An expert pulmonologist performed the respiratory examination in all participants. Then, all subjects were referred for chest X-ray, PFT, and HRCT of lungs. Results: Patients included in this study, 9 (20.45%) males and 35 (79.55%) females, were 21–73 years old and their mean age was 49 ± 13 years. Significant relation between PFT and respiratory complaints was observed (P = 0.016). PFT had significant relation with respiratory examinations (P = 0.009). Our results indicated a significant relation between disease activity rate and PFT (P = 0.038). While HRCT had any significant relation with above items. Conclusion: We concluded, using PFT in the respiratory assessment of RA patients can be limited to persons with high disease activity, respiratory complaints, and positive findings in the clinical respiratory examination.

KEY WORDS: High-resolution computed tomography, pulmonary function test, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory systemic disease with unknown etiology that is characterized with peripheral symmetric polyarthritis. The prevalence of this disease is about 1% in general population.[1-3]

Extra-articular manifestations of RA can emerge during the course of the disease and even before the onset of arthritis.[4]

One of the most important extra-articular manifestations of RA is pulmonary involvement that usually can be seen in patients with a high titer of rheumatoid factor and in smokers.[4]

Pulmonary involvement in RA patients can be assessed as interstitial pneumonitis and fibrosis, pleural involvement, pulmonary nodule, bronchiolitis obliterans organizing...
pneumonia, arthritis associated with pulmonary hypertension, and involvements of small and large airways.[5,6]

Interstitial lung disease (ILD) is another type of pulmonary manifestation in patients with RA that usually has a poor prognosis. Mostly RA-ILD has no symptoms and is only diagnosed by clinical examination, pulmonary function test (PFT), and high-resolution computed tomography (HRCT); so it seems that diagnosis of pulmonary involvement in early stages of RA is of great importance.[1,4,7-9]

Therefore, we decided to evaluate RA patients in terms of history, clinical examination, chest X-ray (CXR), PFT, and HRCT to ascertain that the evaluation of RA patients without pulmonary symptoms by using the above-mentioned methods is justifiable, reasonable, and cost-effective.

METHODS

We conducted a cross-sectional study in a referral rheumatology clinic in Razi Hospital of Rasht, Iran, during 2011–2012.

In this study, forty-four consecutive patients, diagnosed with RA according to American College of Rheumatology-European League Against Rheumatism classification criteria for RA 2010,[10] were enrolled. Patients with a history of smoking, known pulmonary diseases, collagen vascular diseases associated with known pulmonary effects and the use of gold, penicillamine, sulphasalazine, methotrexate (MTX) (more than a year), and cytotoxic drugs were excluded from the study.

Demographic and clinical data such as sex, age, occupation, comorbidities, drug history and history of systemic and respiratory symptoms were collected.

A complete physical examination of the joints was performed by an expert rheumatologist in all subjects. The activity of RA was evaluated in all patients by Disease Activity Score 28 (DAS28).[11]

An expert pulmonologist performed a complete respiratory examination in all participants. Then all subjects were referred for CXR, PFT, and HRCT of lungs.

The Local Ethical Committee approved this study and informed consent for participation in the study was obtained from all subjects.

Statistical analysis

The analysis was performed by t-test, Chi-square, and Fisher’s exact tests. All statistical analyses were done by SPSS software 17.0 (Kivuto Solutions Inc, Ottawa, ON, CA). A P < 0.05 was considered significant.

RESULTS

Patients included in this study, 9 (20.45%) males and 35 (79.55%) females, were 21–73 years old and their mean age was 49 ± 13.

Symptoms and respiratory findings of patients were listed in Table 1.

Of the forty-four RA patients, 41 subjects were in their 1st year of the disease and among them only two individuals (4.5%) had systemic symptoms (including fever and weight loss).

Dyspnea and chest pain were the most common complaints of patients (10 patients [22.7%] and 12 patients [22.3%], respectively), and crackles were the most common finding in the respiratory examination of patients heard in all subjects in the bibasilar areas. Stridor, decreased respiratory sounds, abnormal bronchial sound, and clubbing were not found in these patients.

Table 2 shows HRCT findings and pulmonary function test findings were summarized in Table 3.

Among the 44 participants, nine individuals had no CXR and one person, due to obesity, could not undergo

| Table 1: Symptoms and respiratory findings of patients |
|-------------|-------------|
| Symptoms    | n=44 (%)    |
| Fever       | 1 (2.3)     |
| Weight loss | 2 (4.6)     |
| Dyspnea     | 10 (22.7)   |
| Dry cough   | 6 (13.6)    |
| Productive cough | 8 (18.2)   |
| Hemoptysis  | 0           |
| Chest pain  | 12 (27.3)   |
| Respiratory findings |
| Wheezing    | 2 (4.5)     |
| Crackles    | 5 (11.4)    |
| Pleural friction rub | 1 (2.2) |

| Table 2: HRCT findings of patients |
|-------------|-------------|
| HRCT findings |
| Nodule      | 7 (16.2)    |
| Fibrosis    | 19 (44)     |
| Cyst        | 2 (4.6)     |
| Bronchiectasis |
| Localized   | 6 (13.9)    |
| Generalized | 8 (18.6)    |
| Bronchiolectasia | 2 (4.6) |
| Air trapping| 12 (28)     |

| Table 3: Pulmonary function test findings of patients |
|-------------|-------------|
| Pulmonary function test findings |
| Normal      | 21 (47.7)   |
| Air trapping| 17 (38.6)   |
| Obstructive |
| Mild        | 1 (2.3)     |
| Moderate    | 1 (2.3)     |
| Total       | 2 (4.5)     |
| Restrictive |
| Mild        | 2 (4.5)     |
| Moderate    | 2 (4.5)     |
| Total       | 4 (9)       |
HRCT procedures. Only one of the subjects (2.9%) had abnormal findings in CXR (reticular opacities). The most common findings in patients' HRCTs were fibrosis and bronchiectasis (19 patients [44%] and 14 patients [32.5%], respectively). In addition, air trapping was the most abnormal finding in patients' PFTs.

Of the 23 subjects with respiratory complaints, 15 patients (65.2%) had abnormal HRCTs and 16 patients (69.2%) had abnormal PFTs. On the other hand, among the participants who did not have respiratory complaints, 15 patients (71.4%) had abnormal HRCTs and 7 patients (33.3%) had abnormal PFTs. These findings showed no significant relation between respiratory complaints and HRCT findings, while the significant relation between PFT and respiratory complaints was observed ($P = 0.659$ and 0.016, respectively).

All patients with abnormal clinical respiratory examination (seven subjects) had abnormal HRCTs and abnormal PFTs, while among subjects with normal respiratory examination, 23 patients (62.2%) had abnormal HRCTs and 16 patients (43.2%) had abnormal PFTs. According to these data, there was no significant relation between clinical respiratory examination and HRCT findings, while PFT had significant relation with respiratory examination ($P = 0.578$ and 0.009, respectively).

We observed that among patients, who had respiratory complaints and abnormal respiratory examination, 19 subjects (70.4%) had abnormal HRCTs and 18 subjects (66.7%) had abnormal PFTs but in subjects who had no respiratory complaints and abnormal respiratory examination, 11 patients (64.7%) had abnormal HRCTs and 5 patients (29.4%) had abnormal PFTs. These findings did not show significant relation between HRCT and total of respiratory complaints and abnormal respiratory examination, while PFT had significant relation with both of these positive findings ($P = 0.694$ and 0.016, respectively).

The average disease activity of patients, based on DAS28, was 3.84 ± 1.21. Of the 15 patients with low disease activity (DAS28 <3.2), 6 patients (40%), among the 23 subjects with moderate disease activity (3.2 ≤ DAS28 ≤ 5.1), and 11 patients (47.8%) and in all patients (6 persons) with high disease activity (DAS28 > 5.1) PFTs were abnormal. These results indicated a significant relation between disease activity rate and PFT ($P = 0.038$).

Moreover, 11 patients (73.3%) in low DAS28, 16 patients (69.6%) in moderate DAS28, and 3 patients (50%) in high DAS28 group had abnormal HRCTs; but these results did not show significant relation between disease activity rate and HRCT ($P = 0.527$).

Gender had no significant relation with respiratory complaints, clinical respiratory examination, HRCT, PFT, and activity of RA disease ($P = 1.0, 0.619, 1.0, 1.0, and 0.689$, respectively).

In addition, this study showed that HRCT findings had significant relation with aging, unlike PFT.

**DISCUSSION**

Rheumatoid arthritis mostly is seen in the 25-55 year age group. Patients usually experience morning stiffness lasting at least 30 min that often improves gradually after physical activity. Pulmonary involvement is one of the most important extra-articular manifestations of RA. Results of a prospective study about RA showed that RA-ILD is the second cause of mortality in these patients, ILD characterized with dry cough and increasing dyspnea with restricting pattern in spirometry. The major risk factor of RA-LID to be prevented is smoking.

Diagnosis of RA-ILD is based on clinical examination, PFT, and HRCT. Bronchoscopy and broncho-alveolar lavage were used in some past studies for the diagnosis of RA-ILD, but these instruments are usually used to rule out other diffuse pulmonary diseases and are not necessary in the diagnosis of RA-ILD.

A total number of registered patients in our study were 50 individuals, but six of them withdrew from participation because of personal reasons.

In the present study, female participants were approximately four times more than men, while in past similar studies, the ratio of women to men was about 2-3 to 1. This difference is likely due to considering smoking as an exclusive criterion for participants in the present study; because in our society, due to cultural issues, smoking is more common in men as compared to women.

Previous studies have shown that pulmonary involvement in RA patients is associated with aging, a higher severity of the disease, higher titers of rheumatoid factor, and male gender. In our study, PFT and HRCT findings had no significant differences in two gender groups that may be due to small sample size and elimination of smokers from this study; because smoking is a preventable risk factor for ILD.

DAS28 is a system to determine the disease activity in RA patients that is based on the evaluation of 28 joints and also erythrocyte sedimentation rate or C-reactive protein lab results of patients. In the recent study, abnormal PFT had significant relation with increasing disease activity (based on DAS28), unlike abnormal HRCT. These results are similar to Al-Tayyar et al. study. Hence, we can conclude that DAS28 can be a predictor factor for abnormal PFT and, with increasing disease activity in RA patients, serial PFTs can be helpful in assessment, and prediction of pulmonary involvement.
In our study, with the increasing frequency and severity of clinical examination findings and respiratory complaints, abnormal PFTs also increased significantly, unlike HRCT findings but in Youssef’s study, patients’ respiratory complaints had significant relation with both PFT and HRCT findings. The results of our study support this issue that HRCT, regardless of respiratory symptoms or clinical examination as independent parameters, can have positive findings and in the evaluation of asymptomatic patients, using of HRCT is more rational than PFT.

The most common finding in abnormal HRCTs, in the present study, was bronchiectasis (with the prevalence of 38.6%) that was approximately similar to reported the prevalence in Perez and Cortet studies (30% and 30.5%, respectively). On the other hand, in recent study, the most common PFT finding was air trapping (with the prevalence of 36.8%) that indicates the involvement of small airways; also the prevalence of air trapping in Perez study was 32%, respectively.

Use of MTX (10–20 mg/week) is associated with the progression of RA-ILD regarding MTX pneumonitis was reported between 1% and 11% in RA patients who were treated with MTX. Hence, in this study, to eliminate the confounding effect of this drug, we excluded the patients who used this drug for more than 1 year, while in past similar studies use of MTX was not limited in the subjects.

This study indicates using PFT in respiratory assessment of RA patients may be limited to persons with high grades of disease activity (based on DAS28), respiratory complaint and positive findings in clinical respiratory examination, while the assessment of respiratory involvement in these patients, using HRCT, may be planned regardless of disease activity, respiratory complaint, and clinical respiratory examination.

We warranted further studies with a larger sample size and a control group for comparison with the results of healthy subjects.

Acknowledgments
The authors thank all the colleagues’ at the Guilan University of Medical Sciences, Rasht, Iran who were coordinate in this research.

Financial support and sponsorship
Funding is Guilan University of Medical Sciences.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Shah A, St Clair EW. Rheumatoid arthritis. In: Dan LL, Anthony FS, Dennis KL, Stephen HL, Larry JJ, Joseph L, editors. Harrison’s Principles of Internal Medicine. 18 ed., Vol. 2. New Delhi: McGraw Hill Medical; 2012. p. 2745.
2. Dale DC. Neutropenia and neutrophilia. In: Kaushansky K, Lichtman M, Beutler E, Kipps T, Prchal J, Seligsohn U, editors. Williams Hematology. 8 ed. New York, NY: McGraw Hill; 2010. p. 939-50.
3. O’Dell JR. Rheumatoid arthritis. In: Arend WP, Armitage JO, Clemmons DR, editors. Goldman’s CECIL Medicine. 24 ed. Philadelphia, PA: Elsevier Saunders; 2012. p. 1681-9.
4. Fishman AP, Elias JA, Fishman JA, Grippi MA, Senior RM, Pack AJ, editors. Pulmonary Manifestation of the Collagen Vascular Diseases. Fishman’s Pulmonary Diseases and Disorders. 4th ed. New York, NY: McGraw Hill Medical; 2008. p. 1193-212.
5. Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: Results from an inception cohort. Rheumatology (Oxford) 2010;49:1483-9.
6. Parambil JG, Myers JL, Ryu JH. Diffuse alveolar damage: Uncommon manifestation of pulmonary involvement in patients with connective tissue diseases. Chest 2006;130:553-8.
7. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 2008;168:159-66.
8. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63 Suppl 5:v1-58.
9. Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritis-associated interstitial lung disease: The relevance of histopathologic and radiographic pattern. Chest 2009;136:1397-405.
10. Aleta da T, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.
11. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology (Oxford) 2010;49:683-90.
12. Brusselle G. Rheumatoid arthritis and interstitial lung disease. Rheumatology (Oxford) 2010;49:1425-6.
13. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology (Oxford) 2007;46:350-7.
14. Saag KG, Kolluri S, Koehnke RK, Georgou TA, Rachow JW, Hunninghake GW, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. Arthritis Rheum 1996;39:1711-9.
15. Shidara K, Hoshi D, Inoue E, Yamada T, Nakajima A, Taniguchi A, et al. Incidence of and risk factors for interstitial pneumonia in patients with rheumatoid arthritis in a large Japanese observational cohort, IORRA. Mod Rheumatol 2010;20:280-6.
16. Pappas DA, Giles JT, Connors G, Lechtzin N, Bathon JM, Danoff SK. Respiratory symptoms and disease characteristics as predictors of pulmonary function abnormalities in patients with rheumatoid arthritis: An observational cohort study. Arthritis Res Ther 2010;12:R104.
17. Al-Tayyar H, Mohammad H, Jasim A. Pulmonary involvement for patients with rheumatoid arthritis: Spirometric study. J Fac Med Baghdad 2012;54:361-4.
18. Youssef AA, Machaly SA, El-Dosoky ME, El-Maghraby NM. Respiratory symptoms in rheumatoid arthritis: Relation to pulmonary abnormalities detected by high-resolution CT and pulmonary functional testing. Rheumatol Int 2012;32:1985-95.
19. Cortet B, Perez T, Roux N, Flipo RM, Duquesnay B, Delcambre B, et al. Pulmonary function tests and high resolution computed tomography of the lungs in patients with rheumatoid arthritis. Ann Rheum Dis 1997;56:596-600.
20. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: Clinical, functional, and HRCT findings. Am J Respir Crit Care Med 1998;157 (5 Pt 1):1658-65.
21. Cosgrove GP, Schwarz M. Pulmonary manifestation of the collagen vascular diseases. In: Fishman AP, Elias JA, Fishman JA, Grippi MA, Senior RM, Jack AJ, editors. Fishman’s Pulmonary Diseases and Disorders. 4th ed., Ch. 71. New York: McGraw Hill Medical; 2008. p. 1193-212.