Original Article

Pleuropulmonary manifestation in patients with rheumatoid arthritis in Saudi Arabia

Omer S. B. Alamoudi, Suzan Mansour Attar

Department of Internal Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Address for correspondence:
Prof. Omer S. B. Alamoudi, Department of Medicine, King Abdulaziz University, P. O. Box 80215, Jeddah 21589, Saudi Arabia.
E-mail: dramoudi@yahoo.com

Submission: 25-11-2016
Accepted: 23-05-2017

Abstract:

BACKGROUND AND OBJECTIVES: Pleuropulmonary (PP) involvement in rheumatoid arthritis (RA) is associated with high morbidity and mortality. Nevertheless, limited data are available regarding lung complications in the Middle East, especially in Saudi Arabia. The objectives of the current study were to determine the prevalence of PP manifestations and to identify the associated risk factors.

METHODS: This was a retrospective study involving 419 patients diagnosed at a tertiary center over a 12.5-year period. The frequency of pulmonary manifestations was recorded based on combined results from chest X-rays, pulmonary function tests, and high-resolution computed tomography scan of the chest.

RESULTS: The overall frequency of lung involvement was 25.8%. Pneumonia, bronchiectasis, and interstitial lung disease were the most common abnormalities (36%, 35%, and 23%, respectively). The presence of comorbid illness (odds ratio [OR]: 3.19; 95% confidence interval [CI]: 2.02–5.1), male gender (OR: 2.4; 95% CI: 1.3–4.24), and the presence of extra-articular manifestations of RA (ExRA) (OR: 2.35; 95% CI: 0.4–4.01) were predictive of lung involvement.

CONCLUSIONS: Pneumonia, bronchiectasis, and interstitial lung disease were the most common abnormalities seen in RA patients. The presence of comorbidity, male gender, and ExRA was significantly associated with lung involvement.

Keywords:

High resolution computed tomography, lung disease, pleuropulmonary manifestations, rheumatoid arthritis, Saudi Arabia

Pleuropulmonary (PP) involvement in rheumatoid arthritis (RA) is associated with high morbidity and mortality. It may precede the development of arthritis symptoms by years and has been reported to be the second cause of death following sepsis.[1-6] The prevalence of PP ranges between 6% and 23%.[7-12]

The risk factors for PP involvement in RA are currently unknown. Several studies have been performed to identify possible risk factors, with older age, male gender, long-standing disease, high levels of serum rheumatoid factor (RF), increased inflammatory markers, high erythrocyte sedimentation rate (ESR), positive genetic markers (e.g., human leukocyte antigen DR4 [HLA-DR4]), therapeutic factors, cigarette smoking, and/or the presence of extra-articular manifestation of RA (ExRA) all showing some associations though results were variable.[8,9,11]

In the Kingdom of Saudi Arabia (KSA), no previous studies have been carried out to identify the prevalence of PP in RA patients nor have the risk factors for its development been evaluated. However, there is one study which showed a relationship between early RA and interstitial lung disease (ILD).[10]

Therefore, the objectives of this study were to assess the prevalence and the pattern of

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.ATM_392_16

How to cite this article: Alamoudi OS, Attar SM. Pleuropulmonary manifestation in patients with rheumatoid arthritis in Saudi Arabia. Ann Thorac Med 2017;12:266-71.

PP involvement in RA and to determine the risk factors related to its development.

Methods

Study design, patient population, and setting

This was a retrospective study that included 419 RA patients diagnosed at a tertiary center (Jeddah, KSA) over a 12.5-year period (January 2001–June 2014). Patients were enrolled if they RA diagnosed according to the International Classification of Diseases (ICD) (ICD-9 and ICD-10 coding system [714.0–714.33], Ninth Edition) and the 2010 American College of Rheumatology/European League Against Rheumatism criteria.[12] Patients were excluded from the study if they had another inflammatory arthropathy, were pregnant, and/or had pulmonary tuberculosis diagnosed before RA onset. The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Biomedical Ethics Research Committee of the Faculty of Medicine at King Abdulaziz University (KAU) (Reference No. 49-14).

Data collection

Data obtained from the medical records included demographic features (age, gender, and duration of disease), smoking habits (active, ex-smoker, and nonsmoker), existence of comorbid illnesses including nonrespiratory diseases such as diabetes mellitus, hypertension, cardiovascular, renal, malignancy, and respiratory diseases such as bronchial asthma and emphysema,[7] and the presence of ExRA.[2] Disease activity was assessed using the 28-joint Disease Activity Score Index (DAS28) and C-reactive protein (CRP) levels.[1] Medication and biological therapy use were also documented. Chest symptoms, such as a cough, shortness of breath, hemoptysis, fever, musculoskeletal pain, and pleuritic chest pain. Laboratory parameters included ESR (normal: 0–20 mm/h), CRP levels (reference range: 0–3 mg/L as measured by immunonephelometry), RF (normal: 0–20 IU/L as measured by nephelometry), and anti-cyclic citrullinated peptide (anti-CCP) antibody (normal: 0-20 EU as measured via enzyme-linked immunosorbent assay) were taken from the patients file.[4]

Pleuropulmonary manifestations

The PP manifestations were reviewed by a pulmonologist, who gathered the information using available clinical data and abnormalities on pulmonary function tests (PFTs). Chest X-rays (CXRs) and high-resolution computed tomography (HRCT) of the lung were reevaluated by a two senior radiologists, who confirmed the abnormalities and the conclusion reached by consensus.

The following PP abnormalities were recorded: Pleural disease (pleurisy, pleural effusion/thickening), airway disease (obliterative bronchiolitis, cryptogenic organizing pneumonia [COP], and bronchiectasis), ILD, methotrexate (MTX)-induced lung injury, Caplan's syndrome, rheumatoid nodules, pneumonia, vascular disease (pulmonary hypertension, vasculitis, pulmonary embolism, and diffuse alveolar hemorrhage [DAH]), and airway obstruction due to cricoarytenoid arthritis.[3,5,6,13]

Statistical analysis

Descriptive statistics (mean ± standard deviation, ranges, and frequencies) were calculated for quantitative data, and proportions were used to describe categorical variables. The Student's *t*-test was employed when comparing means of continuous variables, whereas proportions were compared using the Chi-squared test. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated. Results were considered statistically significant when the $P < 0.05$. All data analyses were performed using the Statistical Package for Social Sciences (SPSS version 18, SPSS Inc., Chicago, Illinois, USA).

Results

A total of 419 RA patients were analyzed [364 women and 55 men; Table 1]. The overall cohort displayed a mean age of 45.7 ± 15.9 years (range: 18–83). The mean disease duration was 3.5 ± 4.6 years, and the mean DAS28 score was 3.9 ± 1.4.

A total of 108 patients (25.8%) were found to have PP involvement. Compared to RA patients with no pulmonary manifestations, those with PP involvement were significantly older ($P = 0.001$), more likely to be male ($P = 0.004$), and had a greater mortality rate ($P = 0.001$). Furthermore, they displayed a significantly longer disease duration ($P = 0.002$); higher rates of ExRA ($P < 0.001$); more comorbid illnesses ($P < 0.001$); and higher ESR ($P = 0.001$), CRP ($P = 0.001$), and RF levels ($P = 0.007$). Sulfasalazine was found to be significantly associated with PP ($P = 0.001$). In addition, patients with PP involvement displayed lower levels of anti-CCP ($P = 0.007$) although the proportion of anti-CCP-positive patients was not significantly different between the two groups. Notably, there was no difference with regard to DAS28 scores.

Data concerning chest symptoms, CXR and HRCT imaging, and PFT findings are presented in Table 2. A total of 52 patients (12.4%) were noted to have chest symptoms. HRCT scans revealed a high incidence of pulmonary abnormalities in our cohort (67.1% of those scanned) while PFT abnormalities were detected in 32.1% of the 106 patients who underwent testing. Mean values for forced expiratory volume after 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC were found to be 95.5 ± 16.2, 89.6 ± 17.1, and 81.7 ± 11.8,

Table 1: Demographic and clinical characteristics of 419 rheumatoid arthritis patients

Variable	RA patients with pulmonary involvement (*n*=108)	RA patients without pulmonary involvement (*n*=311)	*P*
Age, years±SD	53.0±15.0	43.2±15.4	0.001*,†
Male gender, *n* (%)	23 (21.3)	32 (10.3)	0.004*,‡
Disease duration, years±SD	4.7±6.1	3.1±3.8	0.002†
ExRA, *n* (%)	29 (26.9)	42 (13.5)	0.001*,‡
DAS28, mean±SD	3.7±1.3	3.9±1.4	0.323†
Comorbid illness, *n* (%)	53 (49.1)	72 (23.2)	0.001*,‡
Death, *n* (%)	16 (14.8)	8 (2.6)	0.001*,‡
Smoking, *n* (%)			
Active	12 (11.1)	30 (9.6)	0.9‡
Nonsmoker	90 (83.3)	263 (84.6)	
Ex-smoker	11 (10.2)	14 (4.5)	
Medication, *n* (%)			
MTX	75 (69.4)	180 (57.9)	0.86‡
Leflunomide	19 (17.6)	36 (11.6)	0.63‡
Sulfasalazine	27 (25.0)	26 (8.4)	0.001‡
Biologics	33 (30.6)	58 (18.6)	0.27‡
ESR			
Mean±SD	45.4±26.3	33.4±21.8	0.001*,†
High, *n* (%)	86 (80.0)	220 (70.7)	0.049*
CRP			
Mean±SD	33.2±53.0	16.9±31.0	0.001*,†
High, *n* (%)	86 (80.0)	233 (74.9)	0.36‡
RF			
Mean±SD	287±921	107.0±435.0	0.007*,†
Positive, *n* (%)	63 (58.3)	136 (43.7)	0.01*,‡
Anti-CCP			
Mean±SD	205±249	273.0±314.0	0.007*,†
Positive, *n* (%)	85 (78.7)	227 (73.0)	0.25‡

Reference ranges: ESR: 0-20 mm/h, CPR: 0-3 mg/L, RF: 0-20 IU/L, and anti-CCP: 0-20 EU. *Significant positive association - *P*<0.05. Test of significance via †*t*-test or ‡Chi-square test. CCP = Cyclic citrullinated peptide, CRP = C-reactive protein, DAS28 = 28-Joint Disease Activity Score, ESR = Erythrocyte sedimentation rate, ExRA = Extra-articular manifestations of RA, RA = Rheumatoid arthritis, RF = Rheumatoid factor, SD = Standard deviation, MTX = Methotrexate

respectively (*n* = 106). Low carbon monoxide diffusing capacity was reported for ten patients (29%; *n* = 34).

A total of 108 patients (25.8%) displayed pulmonary manifestations, and their diagnoses are presented in Table 3. Pneumonia was the most commonly found abnormality (36.1%), followed by bronchiectasis (35.2%), and then ILD (23.1%).

Table 4 shows the risk factors associated with PP involvement. The presence of comorbidities was found to be the strongest predictor (OR: 3.2; 95% CI: 2.0–5.1; *P* = 0.001), followed by male gender (OR: 2.4; 95% CI: 1.3–4.2; *P* = 0.001) and ExRA (OR: 2.4; 95% CI: 1.4–4.0; *P* = 0.004). Both nonrespiratory and respiratory co-morbidities were considered to be a statistically significant risk factor (OR: 3.1; 95% CI: 1.97–4.87; *P* = 0.001) and (OR: 5.3; 95% CI: 2.48–11.33; *P* = 0.001), respectively.

By multivariate regression analysis, the most significant predictor was the presence of comorbid illness (*P* < 0.001), followed by a positive RF (*P* < 0.027).

In addition, given that HRCT is more sensitive for detecting pulmonary abnormalities, we independently evaluated risk factors that predicted abnormal HRCT findings [Table 5]. This analysis revealed that comorbidities (OR: 3.8; 95% CI: 1.7–8.3; *P* = 0.001), high CRP levels (OR: 3.5; 95% CI: 1.7–7.5; *P* = 0.001), and a positive test for anti-CCP (OR: 2.5; 95% CI: 1.2–5.3; *P* = 0.026) were the most important risk factors.

As shown in Table 6, 66.7% of the RA patients that died during the study had pulmonary manifestations, in comparison to 23.3% of those that lived (OR: 6.6; 95% CI: 2.7–15.9; *P* = 0.001). The likelihood of death was also increased for patients with an abnormal CXR (OR: 1.2; 95% CI: 1.0–1.3; *P* = 0.003). A respiratory cause was attributed to 16 of the 24 deaths that occurred, these included ILD (*n* = 6), pneumonia (*n* = 4), tuberculosis (*n* = 3), COP (*n* = 1), DAH (*n* = 1), and MTX-induced lung disease (*n* = 1).

Discussion

This was a retrospective study of 419 RA patients that was conducted over a 12.5-year period. We observed

Table 2: Chest symptoms, chest X-ray, high-resolution computed tomography, and pulmonary function test findings in the 419 rheumatoid arthritis patients

Investigation	Patients, *n*/*N* (%)
Chest symptoms	
Symptomatic	52/419 (12.4)
CXR	249/419 (59.4)
Abnormal	70/249 (28.1)
HRCT	149/419 (35.6)
Abnormal	100/149 (67.1)
Ground glass opacity	31/100 (31.0)
Honeycomb	31/100 (31.0)
Bronchiectasis	31/100 (31.0)
Air space consolidation	28/100 (28.0)
Lymphadenopathy	25/100 (25.0)
Pleural effusion	19/100 (19.0)
Atelectasis/collapse	16/100 (16.0)
Septal thickening	14/100 (14.0)
Rheumatoid nodule	13/100 (13.0)
Bronchial dilatation	11/100 (11.0)
Emphysema	1/100 (1.0)
PFT	106/419 (25.3)
Abnormal	34/106 (32.1)
Restrictive	21/34 (61.8)
Obstructive	9/34 (26.5)
Obstructive/restrictive	1/34 (2.9)
Low DLCO	10/34 (29)
Variable as UAO	2/34 (5.9)

CXR = Chest X-ray, DLCO = Carbon monoxide diffusing capacity, HRCT = High-resolution computed tomography, PFT = Pulmonary function test, UAO = Upper airway obstruction

Table 3: Final clinical diagnoses in rheumatoid arthritis patients with lung involvement based on clinical symptoms, chest X-ray, high-resolution computed tomography, and pulmonary function test findings* (*n*=108)

Final clinical diagnosis	Patients, *n* (%)
Pneumonia	39 (36.1)
Bronchiectasis	38 (35.2)
Interstitial lung disease	25 (23.1)
Pleural disease	16 (14.8)
Tuberculosis	13 (12.0)
MTX-induced lung disease	9 (8.3)
Rheumatoid nodule	9 (8.3)
Collapse	8 (7.4)
BOOP	5 (4.6)
Pulmonary embolism	4 (3.7)
Small airway disease	3 (2.7)
Vasculitis	2 (1.9)
DAH	1 (0.9)
Caplan's syndrome	0

*Some patients present multiple features. BOOP = Bronchiolitis obliterans organizing pneumonia, DAH = Diffuse alveolar hemorrhage, MTX = Methotrexate

the following important findings: (a) Lung involvement occurred in 25.8% of patients, (b) pneumonia and bronchiectasis were the most common abnormalities,

Table 4: Risk factors associated with pulmonary manifestation in rheumatoid arthritis patients (*n*=108)

Predictor	Patients, *n* (%)	χ^2	*P*	OR	95% CI
Clinical					
Male gender	23 (21.3)	8.5	0.004*	2.4	1.3-4.2
ExRA	29 (16.9)	10.1	0.001*	2.4	1.4-4.0
Comorbidities	53 (49.1)	25.7	0.001*	3.2	2.0-5.1
Biochemical					
ESR-high	86 (79.6)	3.2	0.049*	1.6	0.95-2.7
CRP-high	86 (79.6)	1.0	0.36	1.3	0.8-2.2
RF positive	63 (58.3)	6.8	0.01*	1.8	1.2-2.8
Anti-CCP positive	85 (78.7)	1.4	0.25	1.4	0.8-2.3

*Significant positive association - *P*<0.05. CCP = Cyclic citrullinated peptide, CI = Confidence interval, CRP = C-reactive protein, ESR = Erythrocyte sedimentation rate, ExRA = Extra-articular manifestations of RA, OR = Odds ratio, RA = Rheumatoid arthritis, RF = Rheumatoid factor

Table 5: Risk factors associated with abnormal high-resolution computed tomography findings in 100 rheumatoid arthritis patients with pulmonary findings (*n*=100)

Predictor	Patients, *n* (%)	χ^2	*P*	OR	95% CI
Clinical					
ExRA	24 (24.0)	1.44	0.23	1.7	0.7-4.1
Comorbidities	49 (49.0)	11.2	0.001*	3.8	1.7-8.3
Biochemical					
ESR-high	78 (78.0)	3.64	0.45	2.1	0.9-4.4
CRP-high	80 (80.0)	11.62	0.001*	3.5	1.7-7.5
RF positive	59 (59.0)	0.25	0.72	0.8	0.4-1.7
Anti-CCP positive	81 (81.0)	5.54	0.026*	2.5	1.2-5.3

*Significant positive association - *P*<0.05. CCP=Cyclic citrullinated peptide, CI = Confidence interval, CRP = C-reactive protein, ESR = Erythrocyte sedimentation rate, ExRA = Extra-articular manifestations of RA, OR = Odds ratio, RA = Rheumatoid arthritis, RF = Rheumatoid factor

and (c) preexisting comorbid illnesses, male gender, and ExRA were risk factors associated with lung involvement.

Prevalence of pleuropulmonary manifestations in rheumatoid arthritis

It is difficult to assess the true prevalence of lung involvement in RA patients. Indeed, rates can vary widely based on the study design, criteria used to define the pulmonary manifestations, and/or on methods employed for diagnosis (e.g., CXR vs. CXR combined with HRCT scan of the chest). In this respect, CXR is routinely performed on RA patients before therapeutic interventions. However, while there are some abnormalities that are more easily recognized by CXR (for instance, rheumatoid lung nodules), others require an HRCT scan or PFT for efficient detection (e.g., early ILD or vasculitis).[14] Nevertheless, investigations analyzing lung diseases in RA have reported rates ranging from 16.1% in Korea[15] to 23.4% in the US.[16] In this study, in which CXR, HRCT, and PFT were used collectively to assess pulmonary involvement, an overall rate of 25.8% was found for the KSA.

Table 6: Factors associated with mortality in rheumatoid arthritis patients

Variable	Total number	Dead (*n*=24), *n* (%)	Alive (*n*=395), *n* (%)	χ^2	*P*	OR	95% CI
Pulmonary manifestation	108	16 (66.7)	92 (23.3)	22	0.001*	6.6	2.7-15.9
Abnormal HRCT	100	11 (45.8)	89 (22.5)	0.9	0.5	1.9	0.5-7.1
Abnormal CXR	70	12 (50.0)	58 (14.7)	9.9	0.003*	1.2	1.0-1.3
Sex (male)	55	6 (25.0)	49 (12.4)	3.15	0.11	2.4	1.0-6.2
ESR-high	306	20 (83.3)	286 (72.4)	1.4	0.34	1.9	0.6-5.7
CRP-high	319	19 (79.2)	300 (75.9)	0.13	1	1.2	0.4-3.3
RF positive	199	12 (50.0)	187 (47.3)	0.06	0.8	1.1	0.5-2.5
Anti-CCP positive	312	19 (79.2)	293 (74.2)	0.3	0.8	1.3	0.5-3.6

*Significant positive association - *P*<0.05. CCP = Cyclic citrullinated peptide, CI = Confidence interval, CRP = C-reactive protein, CXR = Chest X-ray, ESR = Erythrocyte sedimentation rate, HRCT = High-resolution computed tomography, OR = Odds ratio, RF = Rheumatoid factor

HRCT-scanning revealed abnormalities in 67% of RA patients, which is similar to values reported in other studies, which varied between 49.3% and 90%.[17] However, only 10%–30% of these patients displayed respiratory symptoms.[4,18] Thus, HRCT scanning is considered more effective in detecting lung involvement in RA patients.

Risk factors

Several potential risk factors for lung involvement in RA have been reported in the literature, including older age, male gender, long-standing disease, high serum RF, high ESR, genetic polymorphisms (e.g., HLA-DR4), therapeutic factors, smoking, and ExRA.[8,9,11,19] However, there are conflicting results related to these. For instance, studies were contradictory with regard to the association between tobacco smoking and pulmonary disease in RA.[8,20] In this respect, this study showed no association between tobacco smoking and pulmonary disease. However, male gender, older age, the presence of comorbid illnesses, and longer disease duration were all associated with PP involvement, in agreement with the previous studies.[8,11,19] Finally, our study did not show an association between lung involvement and disease activity (DAS28), which is in agreement with Dawson *et al*. and Demoruelle *et al*.[21,22]

With regard to laboratory results, Bilgici *et al*. reported that high ESR and RF were associated with PP involvement, similar to our data.[8,23] Indeed, the lung has always been considered an early target of autoantibodies, even before disease onset.[22] In this respect, the correlation between anti-CCP and the lung has become an important area of research. Bronchoalveolar lavage from healthy smokers was found to contain citrulline more often compared to nonsmokers[24] suggesting that the lung might represent a possible antigenic source. In our patient cohort, we observed a novel association between anti-CCP and HRCT abnormalities, possibly supporting a relationship between these autoantibodies and respiratory insult. Furthermore, Aubart *et al*. reported that high anti-CCP level was an independent risk factor,[16] and in a large UK registry, it was strongly associated with ILD.[11] On the other hand, Korkmaz *et al*. and Inui *et al*. reported no association.[18,25,26] Since anti-CCP antibodies negatively affect the lung tissue, HRCT may be more sensitive in detecting this kind of early antibody-mediated insult in RA patients who are anti-CCP positive.

Mortality

PP manifestations in RA are often associated with high morbidity and mortality due to infection and side effects of therapies.[27] When compared to controls, it has been reported that the standard mortality ratio with PP ranged from 2.5 to 5.0.[27] In this analysis, we have confirmed that RA patients with PP were more likely to die during the study compared to those without. Notably, ILD was the most commonly occurring cause of death (25%), which is consistent with published data.[10,14,17] Despite the effort to treat to target, the high death rate could have resulted from late presentation, delayed therapeutic intervention, and none compliance with therapy as it has been shown that only 30%–80% of patients use their medication regularly.[28] Furthermore, despite recommendations, not all patients receive influenza and pneumococcal vaccines, which could represent another important contributing factor.[29]

Conclusions

Although that RA is a multisystem disease, many patients may present with respiratory manifestations in the absence of symptoms. We identified PP involvement in around a quarter of RA patients. Comorbid illness, male gender, and ExRA were significantly associated with developing lung manifestations.

Acknowledgments

Both authors contributed to the conceptualization and design of this study. In addition, they both participated in data analysis/interpretation as well as drafting and revising of the manuscript.

The authors would like to thank Professor Bassem Al-Deek (Department of Community Medicine at KAU) for their help with regards to statistical analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. Arthritis Rheum 2005;52:2625-36.
2. Al-Ghamdi A, Attar SM. Extra-articular manifestations of rheumatoid arthritis: A hospital-based study. Ann Saudi Med 2009;29:189-93.
3. Amital A, Shitrit D, Adir Y. The lung in rheumatoid arthritis. Presse Med 2011;40(1 Pt 2):e31-48.
4. Hafström I, Engvall IL, Rönnelid J, Boonen A, van der Heijde D, Svensson B; BARFOT study group. Rheumatoid factor and anti-CCP do not predict progressive joint damage in patients with early rheumatoid arthritis treated with prednisolone: A randomised study. BMJ Open 2014;4:e005246.
5. Leslie KO, Trahan S, Gruden J. Pulmonary pathology of the rheumatic diseases. Semin Respir Crit Care Med 2007;28:369-78.
6. Lioté H. Pulmonary manifestation of rheumatoid arthritis. Rev Mal Respir 2008;25:973-88.
7. Attar SM. Can we predict depression in patients with rheumatoid arthritis? J Kuwait Med Assoc 2014;46:219-24.
8. Bilgici A, Ulusoy H, Kuru O, Celenk C, Unsal M, Danaci M. Pulmonary involvement in rheumatoid arthritis. Rheumatol Int 2005;25:429-35.
9. Gauhar UA, Gaffo AL, Alarcón GS. Pulmonary manifestations of rheumatoid arthritis. Semin Respir Crit Care Med 2007;28:430-40.
10. Habib HM, Eisa AA, Arafat WR, Marie MA. Pulmonary involvement in early rheumatoid arthritis patients. Clin Rheumatol 2011;30:217-21.
11. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, *et al.* Rheumatoid arthritis-related interstitial lung disease: Associations, prognostic factors and physiological and radiological characteristics – A large multicentre UK study. Rheumatology (Oxford) 2014;53:1676-82.
12. Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, *et al.* The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. Arthritis Rheum 2010;62:2582-91.
13. Massey H, Darby M, Edey A. Thoracic complications of rheumatoid disease. Clin Radiol 2013;68:293-301.
14. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, *et al.* American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
15. Jearn LH, Kim TY. Level of anticitrullinated peptide/protein antibody is not associated with lung diseases in rheumatoid arthritis. J Rheumatol 2012;39:1493-4.
16. Aubart F, Crestani B, Nicaise-Roland P, Tubach F, Bollet C, Dawidowicz K, *et al.* High levels of anti-cyclic citrullinated peptide autoantibodies are associated with co-occurrence of pulmonary diseases with rheumatoid arthritis. J Rheumatol 2011;38:979-82.
17. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, *et al.* Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population-based study. Arthritis Rheum 2010;62:1583-91.
18. Korkmaz C, Us T, Kasifoglu T, Akgün Y. Anti-cyclic citrullinated peptide (CCP) antibodies in patients with long-standing rheumatoid arthritis and their relationship with extra-articular manifestations. Clin Biochem 2006;39:961-5.
19. Chanin K, Manzur FV, Sternbach GL, Fromm R, Varon J. Pulmonary manifestation of rheumatoid arthritis. Hosp Physician 2001;37:23-8.
20. 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.
21. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. Thorax 2001;56:622-7.
22. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? Curr Opin Rheumatol 2014;26:64-71.
23. Skare TL, Nakano I, Escuissiato DL, Batistetti R, Rodrigues Tde O, Silva MB. Pulmonary changes on high-resolution computed tomography of patients with rheumatoid arthritis and their association with clinical, demographic, serological and therapeutic variables. Rev Bras Reumatol 2011;51:325-30, 336-7.
24. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, *et al.* A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38-46.
25. Inui N, Enomoto N, Suda T, Kageyama Y, Watanabe H, Chida K. Anti-cyclic citrullinated peptide antibodies in lung diseases associated with rheumatoid arthritis. Clin Biochem 2008;41:1074-7.
26. Kanat F, Levendoglu F, Teke T. Radiological and functional assessment of pulmonary involvement in the rheumatoid arthritis patients. Rheumatol Int 2007;27:459-66.
27. Brown KK. Rheumatoid lung disease. Proc Am Thorac Soc 2007;4:443-8.
28. van den Bemt BJ, Zwikker HE, van den Ende CH. Medication adherence in patients with rheumatoid arthritis: A critical appraisal of the existing literature. Expert Rev Clin Immunol 2012;8:337-51.
29. Singh JA, Saag KG, Bridges SL Jr., Akl EA, Bannuru RR, Sullivan MC, *et al.* 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1-26.