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Original Article

# Interstitial lung disease in Egyptian patients with rheumatoid arthritis: Frequency, pattern and correlation with clinical manifestations and anti-citrullinated peptide antibodies level

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ABSTRACT

*Introduction:* Interstitial lung disease (ILD) represents 13% of the overall mortality in rheumatoid arthritis (RA) patients.
*Aim of the work:* To determine the frequency and pattern of ILD among RA patients, correlate it with clinical manifestations and with anti-citrullinated peptide antibodies (ACPA) titer.
*Patients and methods:* This study included 88 RA patients. ILD was diagnosed by high-resolution computed tomography (HRCT) and assessed by a severity score. Disease activity was assessed by clinical disease activity index (CDAI) and functional status by the modified health assessment questionnaire (MHAQ). Serum ACPA titer was assayed by ELISA.
*Results:* The mean age of the patients was 50.15 ± 9 years, disease duration was 10.2 ± 6.2 years and they were 75 females and 13 males. ACPA was positive in 84 (95.5%). The frequency of ILD among RA patients was 71.6%. ILD patterns were: usual interstitial pneumonia (UIP) 62%, non-specific interstitial pneumonia (NSIP) 27%, others (Cryptogenic and mixed) in 11%. In RA-ILD, the mean ACPA titer was 225 ± 121.5 U/mL versus 154.3 ± 121.8 U/mL in RA only. In RA-ILD, ACPA titer negatively correlated with morning stiffness, CDAI, MHAQ and six-minute walk test ($r = -0.3$, $p = .008$, $r = -0.6$, $p < .0001$, $r = -0.5$, $p < .0001$ and $r = -0.5$, $p < .0001$ respectively), while it significantly correlated with IPF severity score ($r = 0.09$, $p < .0001$) and erythrocyte sedimentation rate (ESR) ($r = 0.5$, $p < .0001$).
*Conclusion:* ILD frequency has increased among RA patients due to improved detection by HRCT. High titer of ACPA was associated with extent and patterns of severity of ILD in RA patients. When high ACPA titer is associated with low CDAI score, physician could suspect lung involvement.

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disorder. It affects principally the joints and is usually accompanied by one or more of extra-articular manifestations [1]. Interstitial lung disease (ILD) is the most common presentation of rheumatoid lung disease [2]. It represents 13% of the overall mortality of RA. [3] Clinically significant RA associated ILD (RA-ILD) is observed in 8–10% of RA patients over the course of their disease [4], while ~30% of RA patients have subclinical ILD noted on high-resolution computerized tomography (HRCT) scans [3]. However, RA-ILD is not a single type. A spectrum of lung histopathology is seen and is generally categorized according to American Thoracic Society/European Respiratory Society's (ATS/ERS) classification system for idiopathic interstitial pneumonia (IP). The most common types are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) [5]. If treatment is indicated, many forms of ILD can respond significantly to immunosuppressive anti-inflammatory therapies. However, ILD accompanied by extensive fibrosis may be difficult to treat [6].

Anti-citrullinated peptide/protein antibodies (ACPAs) are both highly sensitive and specific for RA [7]. They also have a high prognostic significance as they are associated with higher disease activity, radiographic progression [8] and poorer response to therapy [9].

One of hypothesis concerning RA pathogenesis suggested that the HLA-DRB1 'shared epitope' smoking and ACPA interact to increase the

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risk of RA [10]. Smoking [11] and high titer ACPA also increase the risk of RA-ILD [5]. There is even evidence pointing to the important role of secondhand smoking on disease activity in Egyptian RA patients [12]. It must be considered that smoking is obviously not the only etiologic agent involved in the development of the disease as demonstrated by the fact that RA and RA-ILD often occur in nonsmokers. This suggests that other environmental or infectious [13] factors are probably involved. In RA and idiopathic ILD, it remains unclear whether citrullination of lung proteins represents a mechanistic link between respiratory exposures and autoimmunity in RA, and/or whether citrullinated proteins in the lung become immune targets for a circulating pathogenic autoantibody generated against citrullinated proteins sharing common antigenic epitopes in other tissues, such as the synovium [14].

The aim of the current study was to estimate the frequency and pattern of ILD in RA patients and correlate it with clinical manifestations and ACPA titer in order to predict proper therapeutic intervention.

## 2. Patients and methods

The present cross sectional study including 88 RA patients diagnosed according to the 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria; they all had definite RA and scored ≥6/10 [15]. The study was approved by the ethics committee of the faculty of Medicine, Cairo University, Egypt. They were selected from patients attending the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University. The study was explained to patients and an informed consent was given by each. Patients were not eligible if they had history or current pulmonary tuberculosis, acute respiratory infection, Hepatitis C viral infection (HCV) or any overlapped syndrome. Patients with methotrexate (MTX) pneumonitis were also excluded.

Patients were thoroughly examined. Disease activity was assessed by the clinical disease activity index (CDAI) [16], functional status was assessed according to the modified health assessment questionnaire (MHAQ) [17]. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured. Immunological studies included rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA) in serum CCP3 IgG. RF was assayed with a quantitative immunonephelometry test (Behring, Marburg, Germany), it was considered to be positive when the concentration was higher than the cut-off value of the kit (15 IU/ml). The quantitative detection of *CCP3 IgG* in serum levels was performed using a commercially available enzyme linked immunosorbent assay (ELISA) kit provided by *INOVA Diagnostics, Inc.USA* Following the manufacture recommendations. The cut-off value of anti-CCP3 for positivity was 20 U/mL. *Plain X-ray* for *hands* and feet postero-anterior view was done using Scott's modification to Larsen scoring method [18].

Diagnosis of ILD depended on radiographic evidence of ILD on HRCT; bilateral outlying reticular opacities or honeycombing with or without activity for ground-glass pattern > 5% [19]. Chest assessment was done for RA-ILD through chest examination, pulmonary function test (PFT), arterial blood gases (ABG) and six-minute walk test (6MWT) [20]. Scoring the severity of idiopathic pulmonary fibrosis was according to ATS/ERS classification [21].

Subjects performed a standard forced vital capacity (FVC) maneuver, inspiring fully to total lung capacity (TLC), then exhaling as rapidly and forcibly as possible to residual volume (RV). The spirogram was produced by computer generated graphics using Sensor Medics V max 229 and the following data collected: FVC, forced expiratory volume in the first second (FEV1) and FEV1/FVC. Flow at any lung volume over the vital capacity (VC) can be read from the maximum expiratory volume breathing. Forced expiratory flow at 75%, 50% and 25% of the VC were reported as FEF25%, FEF50% and FEF75%, respectively.

Arterial blood gases on ambient air were done to detect hypoxaemia; hypercapnia or any acid-base balance. Six minute walk test (6-MWT) was performed according to the ATS recommendations, along a flat, straight indoor corridor of hard surface, with monitoring of oxygen arterial saturation with pulse oximetry, heart rate and breathing frequency. During the test, patients were asked to walk as fast as possible and were allowed to slow down or to stop as necessary. At the end of the test, the covered distance in meters was calculated [20].

All patients proved to have different patterns of pulmonary fibrosis as diagnosed by HRCT (Simens 16-channelMDCT). The technique used included slice thickness 1 mm, scan spacing 10 mm, scans taken during full inspiration, patient lying in supine position, no intravenous contrast material was given and the whole lung from the lung apices down to the diaphragm was covered. Reconstruction with ultra-high resolution algorithm for the lungs was done for all patients.

### 2.1. Statistical analysis

The statistical program SPSS version 15 was used for statistical analysis. Results were expressed as mean ( ± standard deviation) for quantitative variables which were normally distributed, while median and range was used for variables which were not normally distributed, or number (percentage) for qualitative variables. Comparison between groups was done by using chi-square test for qualitative variables. Independent sample T-test and analysis of variance (ANOVA) for quantitative variables which were not normally distributed, while non parametrical Mann-Whitney and Kruskal-Wallis test were used for quantitative variables which were not normally distributed. Correlations were done to test for linear relations between variables. Logistic regression analysis model was performed to test for significant predictors for ILD. The level of statistical significance was set at $p < .05$ (2-tailed).

## 3. Results

Eighty-eight RA patients were included in the present study. They were 75 (85.2%) females and 13 (14.8%) males, their mean age was 50.15 ± 9 years (27–68 years) and disease duration was 10.2 ± 6.2 years. All were non-smoker except one patient. RF was positive in 70 (79.5%), while ACPA was positive in 84 (95.5%). The frequency of ILD detected by HRCT Chest among RA patients was (n = 63) 71.6%, among which (n = 33) 52.4% were symptomatized. *By history*, all RA-ILD patients demonstrated articular manifestations before ILD diagnosis except two (2.2%) who presented by ILD first; a smoker male by 10 years and a non smoker female by 20 years before joint involvement, both demonstrated high ACPA titer > 200 at presentation and severe restrictive pattern in PFT. Table 1 illustrates comparison in clinical, laboratory, scores, radiologic variables and MTX treatment duration between RA-ILD and RA only. Fig. 1 illustrates ACPA titers in RA patients with and without ILD.

Logistic regression analysis was done to test for significant predictors of ILD among RA patients. Age, disease duration, CDAI and ACPA titer were entered in the regression model, but only ACPA titer and MTX treatment duration were found to be significant predictors of ILD. Table 2 illustrates logistic regression analysis for predictors of ILD in RA patients.

Patterns of ILD were in the form of UIP in 62%, NSIP in 27% and others (Cryptogenic and mixed 11%) in RA-ILD. Fig. 2 illustrates significant changes in HRCT chest in UIP and NSIP. Table 3 illustrates comparison between different patterns regarding clinical and lab parameters in RA-ILD. There was significant difference in sex predilection towards females (p = .04), ACPA titer (p = .003), FVC (p = .01), 6 MWT (p = .02), diffusion (p = .03), ABG (p = .002), severity score of ILD (p = .002) among different patterns.

Table 4 illustrates ACPA titer correlation with some disease variable in RA-ILD patients. Severity score of ILD negatively correlated with