Anti-citrullinated peptide antibodies with interstitial lung disease in patients with rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) disease is a chronic inflammatory disease that involves synovial joints and shows extra-articular manifestations, causing physical function impairment and marked morbidity and mortality [1,2].

Extra-articular manifestations are presented in \textasciitilde 40\% of the patients with the disease [3]. Among the extra-articular events of RA were pulmonary complications such as interstitial lung disease (ILD0), pleural disease, pulmonary nodules, and airway disease [4]. The prevalence of ILD is up to 61\% in patients with RA. Patients with RA with ILD had a threefold increased risk for mortality compared with RA without ILD [5,6].

Autoantibody biomarkers are valuable for assessing RA and its extra-articular manifestations. Biomarkers, such as anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF), have been evaluated in patients with RA [7]. ACPA is defined in the development of RA and used for evaluation of articular injury worsening [8]. Besides, ACPA has a high specificity for the appearance of extra-articular manifestations such as ischemic heart disease [9], insulin-dependent diabetes mellitus [10], serositis [11], and atherosclerosis [12]. However, little and controversial information about the association of RF and ACPA with the evolution of ILD in patients with RA is known [13,14].

Background

Rheumatoid arthritis (RA)-associated diffuse interstitial lung disease (ILD) is a common extra-articular manifestation that causes significant morbidity and mortality. Anti-citrullinated peptide antibodies (ACPA) are a valuable marker in assessing worsening of articular injury in patients with RA. We studied the correlation of ACPA in patients with RA with ILD.

Patients and methods

A randomized controlled trial involving 45 patients with RA fulfilling the American College of Rheumatology/European League Against Rheumatism criteria was conducted. Patients were grouped into two groups: group I: RA with ILD (15 cases) and group II: RA without ILD (30 cases). Data, such as disease activity score (DAS), disease duration, ACPA by enzyme-linked immunosorbent assay technique, pulmonary functions, and radiographic evidence of ILD by chest high-resolution computed tomography, with estimation of ground-glass and reticular pattern scores, were collected.

Results

A total of 34 (75.6\%) cases were ACPA positive, whereas 11 (24.4\%) cases were anti-cyclic citrullinated peptide negative. Diffusion capacity for carbon monoxide reduced significantly in RA with ILD group (P=0.002). Reticular and DAS were significantly high in the ACPA-positive group (P=0.005). Moreover, there were statistically significant increases in erythrocyte sedimentation rate, C-reactive protein, and platelets but statistically significant decrease in white blood cells in the ACPA-positive group. ACPA positively correlated with DAS (r=0.610) and erythrocyte sedimentation rate (r=0.472). RA disease duration positively correlated with the presence of ILD (P=0.000) and showed a strong negative correlation with diffusion capacity for carbon monoxide (P=0.04). The positive predictive value of positive ACPA was 78.8 for ILD, of which, 70\% for ground glass, 100\% for the reticular pattern.

Conclusion

ACPA is positively correlated with the presence of ILD in patients with RA.

Keywords:
anti-citrullinated peptide antibodies, interstitial lung diseases, rheumatoid arthritis

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Inducible bronchus-associated lymphoid tissue was identified in patients with RA-related lung disease, and it was associated with the production of inflammatory cytokines and ACPA [15]. Smoking may induce RA-ILD by stimulating citrullination of lung proteins, and development of ACPA [16]. Therefore, the study aims to test the association of ACPA levels and ILD in patients with RA and its predictive value for ILD development.

Patients and methods
A total of 45 patients with RA were included according to American College of Rheumatology/European League Against Rheumatism, 2010 criteria [17], attending the rheumatology and pulmonology clinics in an outpatient center in Jeddah Saudi Arabia. Patients diagnosed as having asthma or pulmonary tuberculosis, patients with active respiratory infection, or patients with spirometry showing obstructive pattern or methotrexate pneumonitis were excluded from this study. Institutional ethical research approval and written consent from patients were obtained.

The activity of the disease in patients was individually evaluated by the disease activity score (DAS) [18]. The duration of the disease was considered from the initial joint swelling or tenderness. Other tests such as complete blood count, liver and kidney functions, and urine analysis were done as routine laboratory investigations. The Westergren method was used to measure the erythrocyte sedimentation rate (ESR), and nephelometry for serum C-reactive protein (CRP). Serum ACPA and RF were measured by enzyme-linked immunosorbent assay using Euroimmun, Lubeck Kits (Behring, Germany) are used to measure RF and ACPA. A positive ACPA result is defined by an ACPA2 titer of more than 20 IU.

Diagnostic criteria for RA-ILD included the following: dry cough, bilateral crackles, and breathlessness; also the restrictive pattern on spirometry, that is, a decrease in forced vital capacity (FVC) less than 80% compared with the predicted rate; and radiographic evidence of ILD on high-resolution computed tomography (HRCT).

High-resolution computed tomography
HRCT was performed using Siemens SOMATOM AR.T. equipment (Siemens, Raigarh, Chhattisgarh, India). ILD features in HRCT included reticular pattern, ground-glass pattern, interstitial thickening, and traction or bronchiectasis, mostly traction.

Table 1 Gay and colleagues scoring system; ground-glass score and reticular scores

| Alveolar score | Description                                      |
|---------------|--------------------------------------------------|
| 0             | No alveolar disease                              |
| 1             | Ground glass opacity involving <5% of the lobe   (minimal disease) |
| 2             | Ground glass opacity involving <25% of the lobe  |
| 3             | Ground glass opacity involving 25–49% of the lobe |
| 4             | Ground glass opacity involving 50–75% of the lobe |
| 5             | Ground glass opacity involving >75% of the lobe  |

| Reticular score | Description                                      |
|-----------------|--------------------------------------------------|
| 0               | No interstitial disease                          |
| 1               | Interlobular septal thickening, no discrete honeycombing |
| 2               | Honeycombing ± septal thickening involving up to 25% of the lobe |
| 3               | Honeycombing ± septal thickening involving 25–49% of the lobe |
| 4               | Honeycombing ± septal thickening involving 50–75% of the lobe |
| 5               | Honeycombing ± septal thickening involving >75% of the lobe |

Evaluation of chest was done in a blinded manner by an expert radiologist, as stated by the American/European Respiratory Society consensus for idiopathic interstitial pneumonia [19]. Ground-glass score and reticular scores were assessed using Gay et al. [20] (Table 1). Patients then were grouped into two groups:

(1) Group I: RA with ILD, with 15 cases.
(2) Group II: RA without ILD, with 30 cases.

Pulmonary function tests
Spirometry was performed with spiroAir pulmonary functions device (Morgan Scientific Inc., Haverhill, Massachusetts, USA) according to American/European Respiratory Society, 2005, recommendations [21]. Spirometric parameters such as forced expiratory volume in 1 s, FVC, and the forced expiratory volume in 1 s /FVC ratio were evaluated. Moreover, residual volume, total lung capacity, (residual volume/total lung capacity) ratio, and diffusion capacity of the lung for carbon monoxide were assessed.

Statistical analysis
The data were coded and registered by the mathematical package SPSS, version 17 (SPSS Inc.). The information was analyzed by descriptive statistics such as mean, SD, and values for quantitative variables, and number and percentage for qualitative values. \( \chi^2 \) test was used for qualitative variable difference between groups, and Student’s \( t \) test between two groups for quantitative normally distributed variables. Mann–Whitney test and Kruskal–Wallis test were used for nonparametric
quantitative variables. Linear relations between variables were tested as correlations. A *P* value of less than 0.05 was considered statistically significant.

**Results**

The mean patient age was 56.64±11.8. Thirteen (28.9%) cases were males, whereas 32 (71.1%) were females. The duration of the disease was 14.4±2.05 years. Thirty-four (75.6%) cases were ACPA positive, whereas 11 (24.4%) cases were anti-cyclic citrullinated peptide (CCP) negative. Descriptive criteria of patients are presented in Table 2.

HRCT scan of the chest results are as follows: ILD in 15 (33.3%) cases and ground glass opacity was present in 10 (22.2%) cases, of which eight (17.8%) cases showed minimal ground glass, whereas two (4.4%) cases showed diffuse ground glass (Fig. 1). Ground glass opacity was pure in four cases and overlapped with reticular opacities in six cases. The ground glass score was 2.47±4.88, with minimum score 0 and maximum 18. Reticular opacities were present in 10 (22.2%) cases, with subpleural reticular opacities in four (8.89%) cases, subpleural and interlobular opacities in three (6.7%) cases, and three (6.7%) cases showed extensive reticular opacities, including honeycombing in two (4.4%) of cases. The reticular pattern score was 3.53±5.54, with minimum score of 0 and maximum 20 (Table 3, Fig. 2).

Comparing group I (patients with RA with ILD) with group II (patients with RA without ILD) showed no significance in the age and sex distribution; however, in

| Variables                  | RA-ILD (N=15) | RA only (N=30) | *P* value |
|----------------------------|---------------|----------------|-----------|
| Age (years)                | 58.07±15.06   | 55.93±10       | 0.625     |
| Female [n (%)]             | 11 (24.44)    | 21 (46.67)     |           |
| Male [n (%)]               | 4 (8.89)      | 9 (20)         |           |
| Disease duration (years)   | 7.0 (1.0–35.0) | 8.4±5.3 (2–26) |           |
| Cigarette smoking [n (%)]  | 35 (77.8)     | 10 (22.2)      |           |
| DAS28 [mean (SD)]          | 5.2 (1.8)     | 5.5 (1.7)      |           |
| Laboratory test [n (%)]    |               |                |           |
| Positive rheumatoid factor | 15 (100)      | 30 (100)       |           |
| ACPA +ve                   | 13 (28.9)     | 21 (46.67)     |           |
| ESR mm/1st hour            | 56.2 (34.5)   | 56.1 (35.0)    |           |
| CRP [mean (SD)] (mg/dl)    | 39.4 (48.5)   | 40.2 (56.3)    |           |
| DMARDs [n (%)]             |               |                |           |
| Methotrexate               | 1 (6.6)       | 30 (100)       |           |
| Azathioprine               | 9 (60)        | 2 (6.6)        |           |
| Prednisone                 | 11 (73)       | 8 (26)         |           |
| Biological DMARD           | 3 (20)        | 6 (20)         |           |

ACPA, anti-citrullinated peptide antibodies; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; RA, rheumatoid arthritis.

Figure 1

A 30-year-old female patient with RA. HRCT shows diffuse ground-glass opacities. HRCT, high-resolution computed tomography; RA, rheumatoid arthritis.
Comparing the age of RA with positive ACPA patients (58.53±11.58 years) with RA with negative ACPA patients (50.82±11 years) showed no significant difference (P=0.062); similarly, there was no significance in sex distribution between the groups.

There was no significant difference in pulmonary function results except for DLCO (P=0.049). ILD was found in ACPA-positive group in 13 cases out of 34, whereas in the ACPA-negative group, ILD was found in only two cases of 11 cases. Ground-glass score

### Table 3 Variations between cyclic citrullinated peptide-positive and cyclic citrullinated peptide-negative cases as well as interstitial lung disease and no interstitial lung disease cases

|                | CCP positive | CCP negative | P value | ILD | No ILD | P value |
|----------------|--------------|--------------|---------|-----|--------|---------|
| Age            | 58.53±11.58  | 50.82±11     | 0.062   | 58.07±15.06 | 55.93±10 | 0.625   |
| Sex [n (%)]    |              |              |         |     |        |         |
| Male           | 11 (24.44)   | 2 (4.44)     | 0.467   | 4 (8.89) | 9 (20)  | 0.816   |
| Female         | 22 (48.89)   | 9 (20)       |         | 11 (24.44) | 21 (46.67) |         |
| FEV1           | 2.18±0.71    | 2.46±0.55    | 0.177   | 2.11±0.46 | 2.32±0.77 | 0.275   |
| FEV1%          | 94.85±20.85  | 100.45±8.21  | 0.209   | 98.53±11.34 | 95.07±21.48 | 0.488   |
| FVC            | 2.640±2.09   | 3.087±0.87   | 0.161   | 2.53±0.65  | 2.87±1    | 0.179   |
| FVC%           | 95.52±20.28  | 102.82±15.98 | 0.235   | 98.67±16.89 | 96.66±20.8 | 0.732   |
| FEV1/FVC       | 98.67±21.5   | 98.18±12.64  | 0.928   | 104.13±15.1 | 95.66±21.12 | 0.133   |
| FEV25–75       | 2.79±0.97    | 2.8±0.96     | 0.962   | 2.76±1.06  | 2.84±0.92 | 0.833   |
| FEV25–75%      | 92.15±25.48  | 87.55±29.95  | 0.654   | 94.67±31.97 | 89.10±23.39 | 0.557   |
| RV              | 1.98±0.97    | 1.69±0.33    | 0.151   | 1.89±1.23  | 1.92±0.82 | 0.940   |
| RV%            | 106.2±4.11   | 105.55±32.36 | 0.957   | 106.87±51.43 | 105.62±31.77 | 0.933   |
| TLC             | 4.53±1.25    | 4.93±1.17    | 0.340   | 4.17±0.98  | 4.86±1.1  | 0.057   |
| TLC%           | 96±24.8      | 100.36±24.03 | 0.611   | 92.1±22.94 | 99.66±25.15 | 0.326   |
| RV/TLC         | 104.3±27.9   | 97.7±8.9     | 0.240   | 103.79±19.63 | 102.14±27.13 | 0.825   |
| DLCO           | 5.83±2.25    | 7.2±1.82     | 0.049   | 4.88±1.73  | 6.96±2.16 | 0.002   |
| DLCO%          | 80.82±28.09  | 106.38±47.36 | 0.114   | 68.93±21.65 | 96.66±35.57 | 0.003   |

### ILD by HRCT [n (%)]

|                | ILD | No ILD | P value |
|----------------|-----|--------|---------|
| CCP Positive   | 13 (28.9) | 2 (4.44) |         |
| Negative       | 2 (4.44) | 9 (20)  | 0.288   |
| Ground-glass score | 1.73±2.76 | 4.5±3.3 | 0.385   |
| Reticular score | 4.64±6.1 | 0.5±0.93 | 0.005   |
| Biological [n (%)] |     |        |         |
| Biological     | 19  | 3      | 0.165   |
| No biological  | 15  | 8      | 10 (22.22) | 13 (28.89) | 0.14   |

### CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS, disease activity score; DLCO, diffusion capacity for carbon monoxide; ESR, erythrocyte sedimentation rate; FEF, forced expiratory flow; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HBG, hemoglobin; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; RV, residual volume; TLC, total lung capacity; WBC, white blood cell. The bold values are significant value less than 0.05.

Both groups, females were more than males. Pulmonary functions showed a significant reduction in diffusion capacity for carbon monoxide (DLCO) in group I (RA with ILD group) (P=0.002). In both groups, the numbers of ACPA-positive cases were higher than ACPA negative (13 vs. 2 in the ILD group with 22 vs. 9 in no ILD group; P=0.22). The results of laboratory tests were similar between both groups and also the distribution of patients regarding biological versus nonbiological treatment (Table 3).
was similar between ACPA-positive and ACPA-negative groups. The reticular score was significantly higher in the CCP-positive group ($P=0.005$). DAS was considerably more in the positive group ($P=0.000$). Moreover, ESR, C-reactive protein, and platelets were increased but white blood cells were decreased in the positive group. However, there were no significant variations in the rest of the laboratory tests and even in the distribution of treatment, either biological or nonbiological (Table 3).

On studying the correlations of ACPA with other variables, there was a strong positive correlation with DAS and ESR, whereas other relationships were weak. There was a strong positive association between ILD and disease duration, with $P$ value 0.000, and a strong negative correlation with DLCO ($P=0.04$); other relationships were weak (Table 4). The positive predictive value of positive ACPA was 78.8% for ILD, 70% for ground glass, and 100% for reticular pattern (Table 5).

**Discussion**

Half a century ago was the first time to report pulmonary manifestations in patients with RA [22]. Approximately 10–20% of patients with RA had pulmonary manifestations, with the association of increased mortality [23]. HRCT-chest is the standard noninvasive mean for diagnosis and follow-up of ILD in patients with RA [24]. HRCT results are now correlated closely with those of open lung biopsy [2]. In the present study, HRCT showed ILD in 15 (33.3%) of 45 patients with RA, and their patterns were ground-glass opacity in 10 cases, reticular opacities in 10 cases, and honeycombing in two cases. RA with ILD group showed higher DAS and increased disease duration than the group of RA with no ILD. DLCO was significantly reduced in the RA with ILD group, whereas other pulmonary function test (PFT) results were similar and showed no significant differences. RA with ILD group was highly correlated with disease duration, and negatively with DLCO. In contrast, Karazincir et al. [25] studied the HRCT findings, disease activity, RF positivity, PFT results, and disease duration correlations and declared no significant association between them. However, a subsequent study done in Kuwait on 60 patients with RA found substantial variations between a group of patients with ILD than those with no ILD regarding disease duration and PFT with restrictive pattern and lower DLCO in the RA-ILD group [26].

In this study, 34 cases were ACPA positive, whereas 11 cases were ACPA negative. In the ACPA-positive group, ILD was found in 13 cases, whereas in the ACPA-negative group, ILD was

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**Table 4 Correlations of anti-citrullinated peptide antibodies and interstitial lung disease with other variables**

|                  | ACPA | P    | ILD | P    |
|------------------|------|------|-----|------|
| Age              | 0.284| 0.059| 0.086| 0.547|
| FEV1             | −0.184| 0.23 | −0.145| 0.348|
| FVaC             | −0.217| 0.157| −0.182| 0.236|
| FEV1/FVC         | 0.011| 0.944| 0.208| 0.157|
| FEF25–75         | 0.007| 0.962| −0.034| 0.825|
| RV               | 0.146| 0.346| −0.014| 0.926|
| TLC              | −0.145| 0.349| −0.268| 0.079|
| RV/TLC           | 0.118| 0.447| 0.031| 0.841|
| DLCO             | −0.279| 0.067| −0.430| 0.004|
| Ground glass     | 0.055| 0.718|      |      |
| Ground glass score| −0.255| 0.173|      |      |
| Reticular score  | 0.336| 0.07 |      |      |
| ILD              | 0.183| 0.229|      |      |
| Disease activity score| 0.610| 0.000| 0.313| 0.036|
| CCP              | 0.183| 0.229|      |      |
| ESR              | 0.472| 0.011| 0.245| 0.105|
| CRP              | 0.365| 0.014| 0.006| 0.968|
| SGPT             | 0.209| 0.168| −0.159| 0.297|
| SGOT             | −0.045| 0.770| −0.198| 0.192|
| Creatinine       | 0.064| 0.675| 0.172| 0.258|
| Hemoglobin       | 0.145| 0.343| 0.169| 0.268|
| WBCs             | −0.445| 0.002| −0.201| 0.158|
| Platelets        | 0.361| 0.011| −0.115| 0.920|
| Biological       | −0.066| 0.665| 0.220| 0.146|
| Disease duration | 0.246| 0.103| 0.558| 0.000|

ACPA, anti-citrullinated peptide antibodies; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DLCO, diffusion capacity for carbon monoxide; ESR, erythrocyte sedimentation rate; FEF, forced expiratory flow; FEV1, forced inspiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; RV, residual volume; TLC, total lung capacity; WBC, white blood cell.
found in only two. Ground-glass score was similar between both groups, but the reticular score was considerably higher in the ACPA-positive group. Fadda and colleagues found that ACPA titer was higher in the bad prognostic UIP pattern than the good prognostic (NSIP, COP) pattern. Moreover, they found a strong correlation between ACPA titer and fibrosis score [27]. In the present study, regarding DAS, the score was considerably higher among the anti-CCP positive group and was firmly in a positive correlation with ACPA titer. Similarly, Pérez-Dórame et al. [28] declared a significant correlation between DAS and ground-glass score and not the fibrosis score. Kelly et al. [29] stated that ACPA titer was the most relevant factor correlated with ILD in RA. The meta-analysis study by Fan et al. [30], which involved 14 reviews, involving 702 patients, suggested that both ACPA antibodies and RF were highly correlated with ILD in RA in both Asian and white populations. This comes in accordance with our study, as the positive predictive value of anti-CCP was 78.8% for ILD (70% for ground glass and 100% for reticular pattern). In contrast, Korkmaz et al. [31] could not demonstrate this positive correlation between ACPA and extra-articular manifestations; they explained the negative results by sample size, disease duration, and treatment.

**Table 5 Predictive value of anti-cyclic citrullinated peptide**

|               | Positive ACPA (%) | Negative ACPA (%) | P value |
|---------------|-------------------|-------------------|--------|
| ILD           |                   |                   | 0.442  |
| Yes           | 78.6              | 21.4              |        |
| No            | 71                | 29                |        |
| Ground glass pattern |       |                   | 0.539  |
| Yes           | 70                | 30                |        |
| No            | 74.3              | 25.7              |        |
| Reticular pattern |             |                   | 0.029  |
| Yes           | 100               | 0                 |        |
| No            | 65.7              | 34.3              |        |

ACPA, anti-citrullinated peptide antibodies; ILD, interstitial lung disease.

**Conflicts of interest**

There are no conflicts of interest.

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**Financial support and sponsorship**

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