Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis

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KEYWORDS
Rheumatoid arthritis; Pulmonary function tests; CT scan; Interstitial lung disease; Bronchiectasis

Summary

Background: Pulmonary disease is a well recognised and important extra-articular manifestation of rheumatoid arthritis (RA). The objective of this study was to determine the prevalence of airway and parenchymal abnormalities in newly diagnosed patients with RA and to correlate these with clinical measures of RA severity and laboratory tests.

Methods: 60 patients with a new (symptom duration < 12 months) diagnosis of RA (43 females, 42 European, mean age 54, 33 ever smoker, 17 current) underwent lung function testing and high resolution computed tomography (HRCT) scored by two independent radiologists.

Results: Eighteen (30%) patients reported respiratory symptoms: dyspnoea (11), cough (11), and wheeze (8). Twelve (20%) patients had physiologic evidence of airflow obstruction and 24 (40%) had reduced gas transfer. The prevalence of HRCT abnormalities (in any lobe) was as follows: decreased attenuation 67%, bronchiectasis 35%, bronchial wall thickening 50%, ground glass opacification 18%, reticular changes 12%. All abnormalities were more common in the lower lobes. With the exception of reduced DLCO, there were no significant differences in the prevalence of HRCT patterns or lung function parameters between smokers and non-smokers. Anti-CCP antibodies and rheumatoid factor (RF) correlated strongly with DLCO and variably with other physiologic measures but poorly with radiologic abnormalities.

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Introduction

Pulmonary disease is a well recognised and important extra-articular manifestation of rheumatoid arthritis (RA) with autopsy studies suggesting that it is the second most common cause of death after infections.1 Although the focus has been on interstitial disease there is increasing recognition of airway involvement. Such manifestations are usually recognised late in the course of the disease, possibly because respiratory involvement has a sub-clinical phase as the patient may well be limited by articular disease.2

It is not clear whether all of the pulmonary manifestations of RA are present at the outset or indeed precede the articular manifestations of the disease. Gabbay et al. reported radiologic or bronchoalveolar lavage abnormalities consistent with interstitial lung disease in 21 of 36 patients with newly diagnosed RA but made no comment on airways disease.3 More recently Mori et al. performed lung function and high resolution computed tomography (HRCT) in 65 Japanese patients with recent onset RA and found a high proportion of patients with bronchial dilatation (33.8%) and bronchial wall thickening (6.2%) together with features of interstitial disease.4 Associations between pulmonary disease and serological measures or rheumatoid clinical parameters have not been clearly established.

The aims of this study were to determine the prevalence of airway and parenchymal abnormalities in newly diagnosed RA patients and whether these correlate with clinical measures of RA severity and laboratory parameters.

Methods

Patients and clinical assessments

Sixty patients, age ≥18 years, with newly diagnosed RA (symptoms less than one year) were consecutively recruited from the rheumatology clinic of a major teaching hospital. All patients met the 1987 ARA classification criteria for RA,5 and all had the following assessments recorded:

1) Rheumatology and respiratory symptoms, medications and smoking history.
2) Examination of the respiratory and musculoskeletal systems
3) Laboratory testing including C-reactive protein (CRP), rheumatoid factor by ELISA, and anti-cyclical citrullinated peptides (CCP) (INOVA, 2nd generation).
4) The DAS28-ESR (4 variables with erythrocyte sedimentation rate (ESR)), a composite measure of RA inflammatory disease activity.6

Lung function testing

Spirometric and plethysmographic lung volumes together with DLCO were measured by the single breath technique as previously described and according to the American Thoracic Society Guidelines using European Community Coal and Steel (ECCS) reference values.7–9 Results are expressed as percent predicted.

High resolution computed tomography

Studies were performed using a Prospeed Advantage CT scanner, GE Medical Systems, Milwaukie, Wis. One millimetre collimation scans were performed at 10 mm intervals at full inspiration. Limited further inter-spaced sections were performed at end expiration. The CT scans were assessed in random order, by two experienced observers (DM, MT), without knowledge of clinical findings or lung function tests. The HRCT images were scored using a modified Bhalla scoring system.10,11 This is a lobar analysis of severity and extent of bronchiectasis with additional scoring of large airways wall thickness, the presence of small and large airways mucus plugging, emphysema and decreased attenuation. The extent and severity of bronchiectasis and the degree of bronchial wall thickening are each scored on a 4 point scale, the extent of small airways mucus plugging, emphysema and decreased attenuation (pulmonary lobules or conglomerates of pulmonary lobules which are reduced in density) was scored to the nearest 5% of the lobe involved. Large airways mucus plugging was described as either present or absent for each lobe. The lingula was described as a separate lobe giving a set of 6 lobar scores for each patient. The scoring system for interstitial abnormalities was a numerical semiquantitative lobar extent score based on quartile of whole lobe involvement for each of ground glass opacity, reticulation and consolidation.12

Statistical evaluation

Continuous data were summarised as mean values (SD) if normally distributed or as median (range) if skewed. Categorical data were summarised as frequency and percentage. For continuous data, comparisons between groups were performed by the Student’s t test or Mann–Whitney U test where appropriate. Categorical data were compared using the two proportions Z test. Inter-relationships between variables were evaluated using Spearman’s nonparametric rank correlation analysis. To adjust for confounding (smoking status) in the correlation analysis, Spearman’s partial nonparametric correlation
coefficient was calculated. Weighted Kappa coefficients were calculated to quantify the agreement between two independent researchers’ for each of the four HRCT patterns. A P value <0.05 was considered to be statistically significant. The SAS statistical package version 9.2 was used for analysis (SAS Institute Inc., Cary, NC, USA).

Approvals

This study had the approval of the New Zealand Ministry of Health Northern Regional Ethics Committee (Approval number AKX/02/01/005) and the Auckland District Health Board Research Office. All patients provided written informed consent.

Results

Clinical characteristics

The patient characteristics are summarised in Table 1. Patients were predominantly middle aged females of European ancestry with median symptom duration of 7 months. Disease activity was moderately high, and the majority of patients were seropositive for rheumatoid factor and anti-CCP antibodies. All but two patients had a history of asthma (either past or current) but only two had abnormal lung function; one had an FEV1 83% predicted and the other, a non-smoker, had chronic airflow limitation with FEV1 44%. Four of those patients reported current respiratory symptoms including the two with abnormal FEV1 measurements. Three patients self reported a diagnosis of COPD, one being the same non-smoking patient with asthma and FEV1 of 44%, and the other two asymptomatic smokers with mild physiologic impairment (FEV1 of 74% and 85% predicted respectively). No patients reported a history of bronchiectasis, interstitial lung disease or emphysema.

Respiratory symptoms and lung function

Less than one third of patients had any respiratory symptoms despite a moderate prevalence of physiologic abnormalities (Table 2). One fifth had evidence of airflow limitation (FEV1/VC ratio <70%) and 40% had depression of gas transfer. There were no significant differences between smokers and non-smokers with respect to respiratory symptoms or lung function parameters, except for lower DLCO in smokers. The median lung function results did not change after excluding the 10 patients with either a history of asthma or COPD although the inter-quartile ranges narrowed.

HRCT patterns

A number of HRCT patterns were observed (Table 2). There was very good agreement between the radiologists with kappa statistics ranging from 0.64 to 0.78 for the individual radiologic patterns. The most common abnormality was decreased attenuation which was present in two-thirds of patients. Eleven (18%) patients had decreased attenuation of greater than 20% in one or more lobes, which would be considered clinically abnormal. Less frequent HRCT abnormalities were bronchiectasis and bronchial wall thickening. One patient had bronchial dilatation and two had bronchial wall thickening scores of 2 or greater and 12 (20%) patients had bronchiectasis extent scores of 2 or 3 – parameters that would be considered clinically significant. Parenchymal abnormalities were less common. All abnormalities were more common in the lower lobes. There were no significant differences between smokers and non-smokers in relation to these patterns.

Relationships between respiratory symptoms. Lung function tests and HRCT patterns

Lung function parameters correlated modestly with CT features of Airways disease including bronchial wall thickening, and extent and severity of bronchiectasis (Table 3). However, there was no association between CT patterns of interstitial disease (ground glass opacification and reticular changes) and lung function. Furthermore, there was no relationship between lung function parameters and respiratory symptoms (data not shown). Similarly, there was no relationship between HRCT patterns and respiratory symptoms, with the exception of an association between dyspnoea and bronchiectasis; patients reporting dyspnoea had higher median HRCT scores for bronchiectasis extent (4 vs. 0, p = 0.01) and severity (2 vs. 0, p = 0.02), compared with those without dyspnoea.
There was no significant correlation between lung function parameters or HRCT abnormalities and RA inflammatory disease activity, as measured by the DAS28-ESR. However, there were associations between serological and pulmonary measures (Table 4). In particular, the concentration of anti-CCP antibodies correlated with reduced lung volumes and impaired gas transfer (DLCO), and with the pattern of bronchial wall thickening on HRCT. Rheumatoid factor concentration only correlated with the physiologic measure DLCO, and on HRCT with the parenchymal pattern of ground glass opacification suggesting this serological measure may associate with interstitial injury in RA. There was a modest correlation between CRP and bronchial wall thickening on CT ($r = 0.34$, $p < 0.03$), and with DLCO ($r = -0.32$, $p < 0.05$).

### Discussion

This study demonstrates a moderate prevalence of airway and parenchymal abnormalities in patients with newly diagnosed RA, despite a relative paucity of symptoms and irrespective of smoking history. These pulmonary abnormalities do not associate with global measures of RA inflammatory disease activity but both lung function and HRCT parameters exhibit moderate albeit variable associations with serological markers.

Although parenchymal lung abnormalities have been reported, the presence of airways disease in patients with newly diagnosed RA is a novel finding of this study.3 Previous studies have demonstrated that airways disease is evident on HRCT in up to a third of patients with established RA and the prevalence appears to be higher in patients with longstanding disease. 4,13,14 This study has

### Table 2 Respiratory symptoms, lung function tests and HRCT patterns.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 60)</th>
<th>Previous/current smoker (n = 33)</th>
<th>Non-smoker (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number with respiratory symptoms, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptoms</td>
<td>18 (30%)</td>
<td>12 (36%)</td>
<td>6 (22%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>11 (18%)</td>
<td>5 (15%)</td>
<td>6 (22%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (18%)</td>
<td>8 (24%)</td>
<td>3 (11%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cough with sputum</td>
<td>11 (18%)</td>
<td>9 (27%)</td>
<td>2 (7%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Wheeze</td>
<td>8 (13%)</td>
<td>6 (18%)</td>
<td>2 (7%)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Lung function, median (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>96 (48–131)</td>
<td>98.5 (48–131)</td>
<td>95 (49–123)</td>
<td>0.51</td>
</tr>
<tr>
<td>VC%</td>
<td>93 (57–130)</td>
<td>93 (57–130)</td>
<td>92.5 (60–127)</td>
<td>0.74</td>
</tr>
<tr>
<td>FEV1/VC ratio</td>
<td>0.76 (0.37–0.89)</td>
<td>0.77 (0.54–0.86)</td>
<td>0.76 (0.37–0.87)</td>
<td>0.60</td>
</tr>
<tr>
<td>DLCO%</td>
<td>85 (53–143)</td>
<td>78 (53–143)</td>
<td>86 (61–109)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Number with abnormal lung function parameters, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 &lt; 80% predicted</td>
<td>15 (25%)</td>
<td>7 (21%)</td>
<td>8 (30%)</td>
<td>0.45</td>
</tr>
<tr>
<td>VC &lt; 80% predicted</td>
<td>15 (25%)</td>
<td>6 (18%)</td>
<td>9 (33%)</td>
<td>0.18</td>
</tr>
<tr>
<td>FEV1/VC ratio &lt; 70%</td>
<td>12 (20%)</td>
<td>7 (21%)</td>
<td>5 (19%)</td>
<td>0.80</td>
</tr>
<tr>
<td>DLCO &lt; 80% predicted</td>
<td>24 (40%)</td>
<td>18 (55%)</td>
<td>6 (22%)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>HRCT patterns, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased attenuation</td>
<td>49 (82%)</td>
<td>27 (82%)</td>
<td>22 (81%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>29 (48%)</td>
<td>18 (55%)</td>
<td>11 (41%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>35 (58%)</td>
<td>19 (58%)</td>
<td>16 (59%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Ground glass opacification</td>
<td>14 (23%)</td>
<td>12 (36%)</td>
<td>2 (7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Reticular changes</td>
<td>11 (18%)</td>
<td>8 (24%)</td>
<td>3 (11%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Dense consolidation</td>
<td>4 (7%)</td>
<td>1 (3%)</td>
<td>3 (11%)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

### Table 3 Correlation between lung function parameters and HRCT patterns.

<table>
<thead>
<tr>
<th>Lung function</th>
<th>HRCT Pattern</th>
<th>Spearman partial correlation coefficients (p-value)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decreased Attenuation</td>
<td>Extent of Bronchiectasis</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>-0.15 (0.27)</td>
<td>-0.21 (0.13)</td>
</tr>
<tr>
<td>FVC% predicted</td>
<td>-0.18 (0.20)</td>
<td>-0.29 (0.03)</td>
</tr>
<tr>
<td>FEV1/VC ratio</td>
<td>-0.12 (0.37)</td>
<td>-0.06 (0.65)</td>
</tr>
<tr>
<td>DLCO% predicted</td>
<td>-0.15 (0.26)</td>
<td>-0.13 (0.36)</td>
</tr>
</tbody>
</table>

\(^a\) adjusted for cigarette smoking.
demonstrated that structural airway abnormalities may be present early in the course of the disease despite the patients being asymptomatic or having few respiratory symptoms. Although the severity of the airway abnormalities was relatively mild, a significant proportion of patients had bronchiectasis affecting at least two lobes and/or radiologic evidence of air trapping (decreased attenuation on HRCT).

Whilst many studies report the prevalence of radiologic abnormalities in asymptomatic or symptomatic patients with RA, few have examined associations with physiologic parameters. Although it appears that there are relationships between physiologic measures of airflow limitation and morphologic features of airways involvement, it is not always clear whether this is independent of the impact of cigarette smoking which is variably taken into account. Data from this study reveal positive associations between morphologic and physiologic parameters of pulmonary disease in patients with newly diagnosed RA, and these exist independently of smoking history. However, the finding of a low DLCO and the HRCT pattern of ground glass opacification (albeit a non significant association) in more smokers than non smokers does raise the possibility that some of the smokers have respiratory bronchiolitis-interstitial lung disease (RBILD), an smoking related interstitial process independent of RA.

Of particular interest are the differential associations observed between anti-CCP antibodies and rheumatoid factor in relation to lung function and HRCT abnormalities. Anti-CCP antibodies are highly specific for RA and are associated with poor articular prognosis. Consistent with most other studies in RA, we have not identified a relationship between anti-CCP antibodies and HRCT features of RA-ILD. However, our study has demonstrated a novel association between anti-CCP antibodies and both physiologic abnormalities and bronchial wall thickening on HRCT suggesting that this antibody is associated with an RA related respiratory insult. The important interaction between cigarette smoking and anti-CCP antibodies may be of relevance, noting that tobacco exposure (which induces citrullination of proteins) increases the risk of anti-CCP antibodies in shared epitope positive patients with RA. However, even after adjusting statistically for cigarette smoking, we observed a persistent association between anti-CCP antibodies and physiologic or HRCT abnormalities, suggesting that this association cannot be explained by cigarette smoking alone. In contrast to anti-CCP antibodies, our results suggest a weak association between rheumatoid factor and parenchymal lung disease in RA, as indicated by depression of gas transfer and extent of ground glass opacity on HRCT.

Neither lung function abnormalities nor HRCT patterns of disease associate with global measures of RA inflammatory disease activity. This apparent dislocation between measures of articular involvement and other organ system involvement has been reported previously, albeit not in early RA. A further key finding of our study is that respiratory symptoms are an unreliable guide to the presence or absence of RA associated pulmonary disease. Our results are not sufficiently compelling to support routine screening for respiratory disease in newly diagnosed RA because despite the high prevalence of CT abnormalities the severity and extent of such was relatively minor in the majority of patients and there was a poor correlation with pulmonary function measures or respiratory symptoms. What is unknown is the significance of these changes. Currently there are no published longitudinal studies of patients with early RA demonstrating the natural history of baseline pulmonary abnormalities, or the role of autoantibodies in progression of RA associated pulmonary disease. Furthermore, it is unknown whether intensive treatment of RA using nonbiological or biological disease modifying anti-rheumatic drugs (DMARDs) or other interventions alter progression of lung disease in RA. Such studies are required to guide the type and frequency of surveillance for the pulmonary manifestations of RA.

This study has a number of limitations: the number of patients studied is relatively small and eight had prior respiratory disease, albeit mild in all but one. Although we have adjusted our analyses for smoking history an ideal cohort would consist of nonsmokers. Additionally, almost the entire cohort had taken or was currently taking DMARDs at the time of study and that may have influenced the prevalence of respiratory abnormalities and the CRP. None the less, and notwithstanding the high prevalence of smoking, the lung would appear to be susceptible to rheumatoid associated injury early in the course of the disease. However, the clinical significance of the findings remain unclear and can really only be answered with a longitudinal cohort.

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**Conflict of interest statement**

The authors have no conflict of interest in respect of the material in this manuscript, in particular none have any financial, personal, academic or intellectual conflict.
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