Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests

J K Dawson, H E Fewins, J Desmond, M P Lynch, D R Graham

Abstract

Background—Fibrosing alveolitis (FA) is a common and serious complication of rheumatoid arthritis (RA). Before the availability of high resolution computed tomographic (HRCT) scanning, it was difficult to diagnose accurately without recourse to biopsy. Prospective studies have reported a prevalence of interstitial lung disease (ILD) of 19–44%. The term ILD used by these authors encompasses a variety of appearances on HRCT scans. This prospective study used HRCT scanning to determine the true prevalence of FA in hospital outpatients with RA, and to study associated clinical characteristics. Methods—One hundred and fifty consecutive patients with RA were selected from a hospital outpatient department, irrespective of the presence or absence of chest disease. All underwent a detailed clinical assessment, chest HRCT scanning, and conventional chest radiography within 4 weeks of full pulmonary function tests. Results—Seventy percent of patients were current or reformed cigarette smokers. Twenty eight (19%) had FA, most frequently of reticular pattern, and 12 of this group (43%) also had emphysematous bullae. None of the previously suggested risk factors for developing FA were confirmed. Fifty percent of patients with HRCT evidence of FA had bilateral basal chest crackles, 82% had a reduced carbon monoxide transfer factor (TLCO), and 14% had restrictive pulmonary function tests, and 14% had bilateral chest radiographic signs of FA. Conclusions—HRCT evidence of FA was present in 19% of hospital outpatients with RA. Abnormalities on chest examination or on full pulmonary function tests, even without restrictive changes or chest radiographic abnormalities, should prompt physicians to request a chest HRCT scan when investigating dyspnoea in patients with RA.

Keywords: fibrosing alveolitis; rheumatoid arthritis; high resolution computed tomography

Rheumatoid arthritis (RA) is a common disease that affects approximately 1% of the population, and perhaps up to 5% of women over the age of 65 years. Ellman and Ball first noted the association between fibrosing alveolitis (FA) and RA in 1948. It is now known that this is both the most common and most serious pleuropulmonary complication of RA. Although the course of FA is highly variable, the median survival of patients with diffuse interstitial fibrosis treated in hospital is less than 4 years.

The introduction of HRCT scanning since the late 1980s has revolutionised the approach to FA. The pattern of abnormality may be characteristic in certain diseases and virtually pathognomonic in most cases of cryptogenic fibrosing alveolitis (CFA). Studies have shown that chest HRCT scanning is more sensitive than plain chest radiography and more accurate in diagnosing FA.

The literature on FA in patients with RA is confusing and varies from series to series, depending on diagnostic criteria. Chest radiographic changes occur in 1–5% of patients with RA, depression of carbon monoxide transfer factor (TLCO) in up to 41%, and pulmonary fibrosis in 60% of volunteers undergoing open lung biopsy. HRCT based studies have reported changes consistent with FA in up to 62.6% of patients with RA. However, these studies have been retrospective in symptomatic patients or the appearances consistent with interstitial lung disease (ILD) have not been specifically identified as being in keeping with FA.

The aim of this study was to determine the prevalence of FA, as assessed by HRCT scanning, in a hospital outpatient population of patients with RA. By investigating a large cohort of patients with RA with a systematic prospective protocol, including clinical features and lung function together with HRCT scanning, we aimed to identify the clinical characteristics of patients with FA.

Methods

SUBJECTS
The study population consisted of 150 consecutive patients attending St Helens and Knowsley Trust Hospitals rheumatology outpatient departments. This hospital is based in North West England and its catchment population is from an industrialised area. Patients were diagnosed with definite RA, as defined by the American Rheumatism Association 1987 revised criteria, and enrolled irrespective of
Fibrosing alveolitis in patients with rheumatoid arthritis

Fibrosing alveolitis in patients with rheumatoid arthritis

naire (functional score, range 0–3).
SD = standard deviation; HAQ = Health Assessment Questionnaire

PULMONARY FUNCTION TESTING

Lung function was measured using a standard protocol and included spirometric tests (Sensor Medics water spirometer, California, USA), lung volumes (Sensor Medics helium dilution analyser), and carbon monoxide transfer factor (TLco) (Sensor Medics autolink breath system). The highest of three reproducible measurements was used and expressed as % predicted for age, height, and sex according to standardised tables.14 They were performed in the cardiorespiratory department at Whiston Hospital by one senior technician within 4 weeks of the HRCT scan.

HRCT SCANNING

All the study population underwent chest HRCT scanning using a Siemens Somatom hiQ scanner. Scanning time was 1.3 s. Supine and prone views were taken. Serial slices 2 mm in width and 10 mm apart were taken. All images were obtained at window levels appropriate for lung parenchyma settings (window width 1300 HU; window level –600 HU) and mediastinum (window width 350 HU; window level 40 HU). A chest radiograph was taken at the same time as the HRCT scan. The HRCT scans were interpreted and graded for FA by two consultant radiologists who were blind to the clinical details. Each radiologist reviewed the scans independently of the other and a consensus opinion between them was taken in the event of disagreement.

STATISTICAL ANALYSIS

The Mann-Whitney U test was used to compare quantitative data and χ² with Yates’ correction was used to compare frequencies. The Student’s t test was used to compare normally distributed quantitative data. Interobserver variability before consensus agreement was evaluated for the presence of FA on HRCT pattern. Agreement between observers was expressed as a kappa value, with values of 0.40–0.75 taken to indicate fair to good agreement between observers. Potentially significant parameters were tested for possible interrelationship by multiple logistic regression analysis. All statistical analyses were performed with version 9 SPSS software package (SPSS, Chicago, IL, USA).

INTERPRETATION OF HRCT SCAN

A ground glass pattern was defined as a patchy or diffuse increase in lung density that did not obscure pulmonary vasculature. A reticular pattern was defined as the presence of intersecting lines that formed anything from a fine network to frank honeycombing,15 and was defined as FA if the appearances were thought to be typical of usual interstitial pneumonia.16 Other lung disease present on the HRCT scan was systematically noted. The kappa score for level of agreement between the radiologists on the presence of FA was 0.741.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>150</td>
</tr>
<tr>
<td>F:M</td>
<td>100:50</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>58.9 (10.3)</td>
</tr>
<tr>
<td>Mean (SD) duration of RA (years)</td>
<td>12.7 (8)</td>
</tr>
<tr>
<td>Mean (SD) HAQ score</td>
<td>1.7 (0.7)</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>116 (77%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>58 (39%)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>47 (31%)</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>45 (30%)</td>
</tr>
<tr>
<td>On methotrexate</td>
<td>66 (44%)</td>
</tr>
</tbody>
</table>

SD = standard deviation; HAQ = Health Assessment Questionnaire (functional score, range 0–3).

Table 2 Abnormalities detected on thoracic HRCT scan

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosing alveolitis</td>
<td>28</td>
</tr>
<tr>
<td>predominantly reticular pattern</td>
<td>22</td>
</tr>
<tr>
<td>predominantly ground glass</td>
<td>3</td>
</tr>
<tr>
<td>ground glass = reticular pattern</td>
<td>3</td>
</tr>
<tr>
<td>Thickened interlobular lines</td>
<td>28</td>
</tr>
<tr>
<td>Bronchiectasis typical of obstructive lung disease</td>
<td>12</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>2</td>
</tr>
<tr>
<td>Emphysematous bullae</td>
<td>23</td>
</tr>
<tr>
<td>Decreased attenuation of pulmonary parenchyma</td>
<td>5</td>
</tr>
<tr>
<td>suggestive of air trapping</td>
<td></td>
</tr>
<tr>
<td>Pleural abnormalities</td>
<td>5</td>
</tr>
<tr>
<td>Pleural abnormalities</td>
<td>5</td>
</tr>
</tbody>
</table>

HRCT pattern. Agreement between observers was expressed as a kappa value, with values of 0.40–0.75 taken to indicate fair to good agreement between observers. Potentially significant parameters were tested for possible interrelationship by multiple logistic regression analysis. All statistical analyses were performed with version 9 SPSS software package (SPSS, Chicago, IL, USA).

INTERPRETATION OF HRCT SCAN

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Table 3  Clinical features of patients with rheumatoid arthritis with and without fibrosing alveolitis (FA)

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>FA (n=28)</th>
<th>No FA (n=122)</th>
<th>p Value (z test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>18</td>
<td>65</td>
<td>0.4</td>
</tr>
<tr>
<td>Dyspnoea: NYHA grade II</td>
<td>15</td>
<td>69</td>
<td>0.84</td>
</tr>
<tr>
<td>Dyspnoea: NYHA grade III</td>
<td>5</td>
<td>8</td>
<td>0.07</td>
</tr>
<tr>
<td>Productive cough</td>
<td>13</td>
<td>44</td>
<td>0.39</td>
</tr>
<tr>
<td>Never smoked</td>
<td>5</td>
<td>40</td>
<td>0.17</td>
</tr>
<tr>
<td>Finger clubbing</td>
<td>5</td>
<td>11</td>
<td>0.182</td>
</tr>
<tr>
<td>Bilateral crackles</td>
<td>15</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CXR diagnostic of FA</td>
<td>4</td>
<td>6</td>
<td>0.09</td>
</tr>
<tr>
<td>Restrictive PFTs</td>
<td>4</td>
<td>5</td>
<td>0.06</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>23</td>
<td>91</td>
<td>0.13</td>
</tr>
</tbody>
</table>

NYHA = New York Health Association grading of dyspnoea; CXR = chest radiograph; PFT = pulmonary function test.

PULMONARY FUNCTION TESTS
The results of pulmonary function tests are shown in table 5. A statistically significantly difference was seen between the groups in the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) and in TLCO and TLCO corrected for haemoglobin. Clinically, when pulmonary function tests with a restrictive pattern and lung volume readings below the normal range (<80% predicted) were considered, there was no significant difference between the two groups with only a TLCO below the normal range (<75% predicted) remaining significantly different.

Pulmonary function tests in patients with RA revealed that 52% of patients had a reduced TLCO without having FA. Even after correction for anaemia, this is still reduced in 55 of the patients without FA (45%). In 29 patients the pulmonary function tests and HRCT scan suggested that the reduction in TLCO was a result of obstructive lung disease. In four others physical incapacity resulted in their inability to achieve a vital capacity above 80% predicted and, in such situations, TLCO is less reliable. Fourteen patients had thickened interlobular lines or pleural abnormalities that may have been the cause of the reduced TLCO, leaving eight patients with an unexplained isolated reduction in TLCO.

CHEST RADIOGRAPHY
As reported by other groups, chest radiography was insensitive in diagnosing FA and was not independently predictive of FA. Only four patients had chest radiographic changes consistent with FA, a further five with FA had unilateral fibrotic radiographic shadowing (four basal), one patient had bilateral consolidation, leaving 18 (64% of those with FA) with a normal chest radiograph or changes consistent with obstructive airways disease.

PREDICTION OF FA
Multiple logistic regression analysis was performed to determine the characteristics that predicted FA. The presence of FA on the HRCT scan as judged by two consultant radiologists with a special interest in thoracic HRCT scanning was taken as the dependent variable. No risk factors were found in patients with RA that predicted the occurrence of FA. As found in univariate analysis, the presence of bilateral crackles (p<0.0001), %FEV1/FVC (p=0.03), and TLCO (p=0.009) (estimated odds ratio 0.0875, 95% confidence interval 0.0332 to 0.2301) were significantly associated with FA on the HRCT scan. This logistic equation identified 25 out of 28 cases of FA.
Table 6 Predictors of fibrosing alveolitis (FA) on HRCT scan

<table>
<thead>
<tr>
<th>Feature</th>
<th>No FA (n=122)</th>
<th>FA (n=12)</th>
<th>Sensitivity</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA grade III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bibasal cracks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLCO &lt;75% predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV &lt;80% predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrictive PFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR-FA</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

NYHA = New York Health Association grading for dyspnoea; TLCO = carbon monoxide transfer factor; RV = residual volume; PFT = pulmonary function test; CXR = chest radiograph.

Table 6 shows abnormal findings in terms of sensitivity and positive predictive values. A reduced transfer factor is the single most sensitive test for FA and the presence of bibasal cracks is the clinical feature that gives the best positive predictive value.

Discussion

This study was designed to assess the prevalence of FA as this has a significant morbidity and mortality in patients with RA. Chest HRCT scanning has been shown to correlate with lung biopsy findings in FA in up to 93% of cases. Patients have been taken from a typical district general hospital outpatients department, irrespective of the presence or absence of lung disease. We have prospectively assessed the lungs of 150 patients with RA clinically, physiologically, by chest radiography, and thoracic HRCT scanning.

In this large cohort of patients with RA we have diagnosed FA in 19% by HRCT scanning. In 82% of these patients the RA associated FA was predominantly of a reticular pattern. In our patients 43% of those with FA also had apical emphysematous bullae visible on the HRCT scan. This association occurred in patients who were current smokers or in those who had previously smoked. We did not find emphysematous changes in addition to FA of a pure ground glass pattern. The association between emphysema and CFA has previously been described. It is thought to be coincidental and related to the patients’ smoking habits as an association with alpha-1-antitrypsin has not been consistently found.

Our observation that purely restrictive pulmonary function test results were not statistically significant is interesting. This may be partly explained by the fact that HRCT scanning detects FA at a much earlier stage, before significant loss of lung volume. A further explanation is the relationship of obstructive lung disease with the patients’ smoking habits. We found emphysema with preservation of lung volumes in nine of the 12 patients with dual lung disease.

In our population a reduced TLCO was the most sensitive test for predicting the presence of FA on the HRCT scan, with eight patients having an unexplained isolated reduction in TLCO. There are two possible explanations for this finding. Firstly, and as suggested by other researchers, other systemic aspects of RA such as vascular disease or inflammatory activity may influence TLCO. Tumour necrosis factor alpha (TNFα) is an important mediator of inflammation in RA and has been shown to alter alveolar permeability in other situations where TNFα is released. Secondly, TLCO may be more sensitive than HRCT scanning in identifying FA in some patients. The 96% limits of normality for percentage predicted TLCO are 75% to 125%, which means that a patient with a TLCO of 70% at presentation could have lost between 5% and 55% of their gas transfer. In the situation where the developing lung disease has caused a fall in gas transfer of 5% from the previous normal level for that patient, it may be that FA is not yet visible on the HRCT scan although the TLCO is below the normal range. This would be in keeping with reports of milder forms of idiopathic pulmonary fibrosis that are not evident on HRCT scans but have been found in lung biopsy specimens. We intend to follow this cohort of patients for 3 years to determine if further signs of FA develop.

Previous HRCT based studies are of limited value because they used retrospective review of case notes to determine the clinical state and no formal comparison with pulmonary function tests was made. Four prospective studies have reported a prevalence of ILD of 19–44%. One reason for the variability in the prevalence of ILD is the terminology used by different authors. The HRCT appearance of keeping with “ILD” encompasses a variety of abnormalities including bronchiectasis,12 interstitial fibrosis,12 thickening of non-septal and septal lines,11 ground glass attenuation,11–25–27 honeycombing,11–25–27 and traction bronchiolectasis.11 The HRCT study by Fewins et al11 of patients with RA revealed a high prevalence of ILD (44%). The descriptions of the ILD patterns were not sufficiently detailed to determine the exact frequency of FA type ILD. If all forms of our HRCT diagnosed ILD—that is, FA and interlobular thickening—are combined, there is a closer level of prevalence (37%) of ILD to that study.

McDonagh and colleagues studied a population with RA from the North East of England, 80% of whom were smokers, and found a 20% prevalence of FA when the 20 patients in their RA case-control group, thought to be without lung disease, were investigated by HRCT scanning. When the clinical features of all the patients with RA and FA were analysed, they also found a low incidence of finger clubbing. The frequent association of emphysema and FA was also noted. When the pulmonary function of all the patients with FA was compared with that of patients with a normal HRCT scan or nodules or pleural disease alone, reductions in FEV1 and TLCO became significant in this group. Our patients did not have a significant reduction in FEV1, which may be because there were more smokers in the study by McDonagh et al. Cortet et al10 prospectively assessed HRCT scans and pulmonary function tests in patients with RA of whom only 23.5% were smokers; 30% were found to have bronchiectasis and this was the focus of their paper. Ground glass changes were observed on the HRCT scan in 11 patients (17%) and honeycombing was seen in two (2.9%). This is a similar prevalence to that found in our study, although the proportion
with ground glass changes is quite different. In contrast to our findings and those of McDонаgh et al, they found that ground glass attenuation was associated with a significant decrease in FVC but not with a low TLCO. These differences may be partly explained by the different smoking habits of the study groups resulting in less frequent dual lung disease in the patients studied by Cortet et al.

We did not find any relation between the presence of FA and previously described predisposing factors such as male sex, nodular disease, extra-articular disease, longer disease duration, or disease severity. This lack of association has also been confirmed in one other HRCT centred study where these clinical features have been recorded. Gabbay et al studied 36 patients with RA of less than 2 years’ duration prospectively for ILD. The analysis for risk factors for developing clinically significant ILD was ultimately derived from only five patients with this complication. They noted an association between male sex and clinically significant lung disease in their study of patients with early onset RA, a different population from ours.

Saag et al recently reported that smoking was the most consistent independent risk factor predicting the development of ILD in RA. Notably, the diagnosis of ILD was based on reduced FVC, TLCO (<80%) and/or chest radiographs and HRCT scanning. The association of emphysema with ground glass changes is quite different. In contrast to our findings and those of McDонаgh et al, they found that ground glass attenuation was associated with a significant decrease in FVC but not with a low TLCO. These differences may be partly explained by the different smoking habits of the study groups resulting in less frequent dual lung disease in the patients studied by Cortet et al.

Suggestion of obstructive pulmonary function tests or chest radiographic changes suggestive of chronic obstructive pulmonary disease (COPD) were found also in one study on the HRCT scans of a normal chest radiograph or basic investigations suggesting a diagnosis of obstructive lung disease should not therefore deter a physician from investigating for additional FA by HRCT scanning.

Further work should now be directed towards defining the natural progression of HRCT diagnosed FA in patients with RA, and comparing the different HRCT patterns seen in RA with the extended classification of lung histology found in CFA. As yet, neither of these studies has been specifically performed on a population with RA, and this is essential before the development of well designed treatment trials.

At the time the study was devised, John Kenny was integral to the undertaking of the study as well as initial interpretation of chest radiographs and HRCT scans. It is with much regret that we note his passing in 2016. His contribution was significant and will be much missed by all concerned with these studies. It was a privilege to work with John, and we would like to thank him for his support and advice.

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