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High resolution computed tomography of the lungs in patients with rheumatoid arthritis

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Abstract Pulmonary involvement is one of the most common extra-articular manifestations of rheumatoid arthritis (RA). The aim of this prospective study was to assess pulmonary involvement with high resolution computerized tomography (HRCT) in lifelong non-smoking patients with RA. Twenty-six female and eight male patients with a mean age of 45.26 ± 11.6 years and without any evidence or symptoms of a respiratory disease were included in the study. Data were obtained regarding duration of disease, clinical symptoms and disease activity parameters. Standard chest roentgenographs, pulmonary function tests (PFT) and HRCT were performed. PFT was abnormal in eight (23.5%) and HRCT was abnormal in 23 patients (68%). The most frequent abnormalities obtained on HRCT were interstitial involvement including septal and peribronchial thickening and fibronodular infiltration, which were found in 23 patients, and bronchiectasis was found in nine patients. Using a highly sensitive technique such as HRCT the incidence of pulmonary abnormalities in asymptomatic rheumatoid patients may be much higher than previously reported.

Key words Rheumatoid arthritis · Pulmonary involvement · High resolution computerized tomography (HRCT)

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Introduction

Pulmonary involvement is one of the most common extra-articular manifestations of rheumatoid arthritis (RA) and the second cause of death after infection [1]. Pulmonary involvement includes pleurisy, paranchymal nodules, interstitial involvement, and airway disease. Rheumatoid pulmonary vasculitis is rare [1–3]. The most frequently recognized include pleural effusions, pulmonary nodules and interstitial lung disease. Although previous studies commonly describe interstitial involvement of the lungs such as fibrosing alveolitis, in practice a wide range of pathological changes have been noted in the interstitium of the lungs in patients with RA [4, 5].

Invasive investigations have been previously required to establish a firm histological diagnosis in such patients and to provide guidance as to therapy and prognosis. However, the advance of high resolution computed tomography (HRCT) offers the possibility of a non invasive assessment of interstitial lung disease [6]. Using HRCT, bronchiectasis seems to be one of the most frequent manifestations, particularly in patients complaining of respiratory symptoms; according to the authors [7, 8] its frequency ranges from 20% to 30%. The aim of this prospective study was to assess pulmonary involvement with HRCT in clinically asymptomatic and lifelong non-smoking patients with RA.

Materials and methods

In total, 34 patients with RA, as defined by the American Rheumatism Association (ARA) [9] classification, were included in the study. Informed consent had been obtained from the patients. All patients were lifelong non-smokers. Any patient with evidence of a respiratory disease or having symptoms and signs (cough, dyspnea, chest pain, sputum production) or radiological evidence of respiratory disease were excluded from the study. None of the patients had previously been exposed to silica and none had a chest infection in the previous 3 months.

Data were obtained regarding ages, duration of disease, smoking history, clinical symptoms and medication of the patients. Standard chest roentgenographs were evaluated by an experienced radiologist. All patients had normal chest radiographs. The pulmonary function tests (PFT) including forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), and FEV1/FVC were performed by Sensorimedics Vitalograph Spirometry. Results for pulmonary function tests are expressed as a percentage of those predicted for each individual adjusted for age, gender and height.

Rheumatological evaluation included the assessment of morning stiffness, number of swollen joints, erythrocyte sedimentation rate (ESR), Ritchie articular index (RAI), C-reactive protein (CRP) concentration and rheumatoid factor. According to these data, the Stoke index [10] was used to assess disease activity. Pulmonary evaluation comprised questions about the presence of any respiratory symptoms, such as dyspnea, cough and sputum production, and a thorough physical examination.

HRCT of the thorax was performed using a Sytec FRI, General Electrics. Serial slices were taken through the chest, each 1 mm in width and 10 mm apart. Technical factors were 135 kV and 200 mA. Images were reconstructed using a high spatial frequency algorithm for paranchymal analysis. The HRCT was reported by an experienced radiologist in the absence of clinical information. Multiple radiological criteria for the diagnosis of lung involvement were assessed. The screened abnormalities included: nodules, ground glass attenuation, honeycombing defined as areas of cystic spaces with thickened walls, bronchiectasis defined as bronchial dilatation according to the criteria of Naidich et al. [11], air trapping defined by a decreased attenuation of pulmonary parancyhma and pleural effusion.

Differences between patients with and without pulmonary involvement were assessed using the Mann-Whitney *U*-test. Contingency tables were analysed for statistical significance by using chi square and Fisher's exact tests. A value of $P < 0.05$ was considered statistically significant. All analysis were performed using Statistical Packages for the Social Sciences (SPSS) software.

Results

The study included 26 female and eight male RA patients. The mean age was 45.26 ± 11.6 years and disease duration was 5.38 years. The activity parameters of the disease are shown in Table 1. Rheumatoid factor was positive in 26 patients. According to the Stoke index, there were seven patients with minimal or mild disease and 27 with moderate and severe disease; 27 patients were classified as stage 2, and 7 patients were classified as stage 3 according to the Steinbrocker index. PFT was abnormal in eight (23.5%) patients compared with values predicted for age, sex and height. Combined obstructive-restrictive type ventilation disorder was diagnosed in one subject, while small airways obstruction ventilation disorder was reported in seven patients. Table 2 summarizes the results of PFTs of these patients. Table 3 shows the results of HRCT of the patients. HRCT was abnormal in 23 patients (68%). The most frequent abnormalities obtained on HRCT were interstitial involvement including septal and peribronchial thickening and fibronodular infiltration, which were found in 23 patients and bronchiectasis found in 9 patients.

Discussion

Since the first description of the association between RA and pulmonary fibrosis, the prevalence of pulmonary fibrosis has varied in different reports according to the diagnostic criteria and methods used [1]. Through chest radiography the diagnosis of rheumatoid lung disease was made in 1–5% of RA patients in previous studies [1,12,13]. In contrast, 40% may have restrictive abnormalities when pulmonary function tests were performed [14]. Cervantes Peres et al. [15] found histological signs of interstitial pulmonary disease in 80% of 25 RA patients in whom a pulmonary biopsy was performed. Popp et al. [16] reported an incidence of pulmonary abnormalities to be as high as 72.4% in 58 RA patients detected with bronchoalveolar lavage. Our study was an uncontrolled study using a sensitive technique – HRCT – to detect pulmonary abnormalities in asymptomatic RA patients. We were surprised, however, to find that 68% of our patients had interstitial involvement, including septal and peribronchial thickening and fibronodular infiltration, while 26% of the patients had bronchiectasis. In contrast, none of the patients had a variety of pulmonary abnormalities, such as ground glass attenuation and honeycombing appearance. We were unable to find a correlation between pulmonary abnormalities and sex, Steinbrocker index and inflammatory activity assessed according to the Stoke index. Our results are in accordance with the results of Donagh et al. [17] in that no association was found between HRCT findings and disease activity parameters. Also, there was no correlation between seropositivity and HRCT findings of our patients, but this could be explained by the selection of our patients from an asymptomatic population.

Table 1 Clinical characteristics of rheumatoid arthritis (RA) patients

Duration of disease (years)	5.38 ± 2.8
Rheumatoid factor (IU/mL)	89.9 ± 9.2
CRP (mg/L)	12.9 ± 4.3
Ritchie articular index	27.8 ± 10.1

Table 2 Abnormal pulmonary function test (PFT) results of patients. (*FEV1* forced expiratory volume in 1 sec, *FVC* forced vital capacity, *VC* vital capacity) FEF 25-75-forced expiratory flow between 25% and 75% of vital capacity

PFT measurement	Percentage of predicted values (%) $n = 7$[a]	Percentage of predicted values (%) $n = 1$[b]
FEV1	65	73
FVC	63	73
FEV1/FVC	64	72
FEF 25–75	69	75
VC	89	70

[a] Small airways obstruction ventilation disorder
[b] Combined obstructive restrictive type disorder

Table 3 High resolution computerized tomography (HRCT) findings of RA patients

HRCT findings	Number of cases	%
Abnormal pattern	23	68
Interstitial disease[a]	23	68
Bronchiectasis	9	26
Nodules	–	0
Ground glass attenuation	–	0
Honeycombing	–	0
Pleural effusion	–	0

[a] Septal and peribronchial thickening and fibronodular infiltration

The prognosis of interstitial fibrosis varies in rheumatoid arthritis; if progressive, the effects of this fibrosis on functional capacity may become even more important than the physical deformities of RA. On HRCT the most frequent abnormality was bronchiectasis, which was found in 30.5% of RA patients [17]. Hassan et al. [18] studied 20 lifelong non-smoking patients with RA and found bronchiectasis without interstitial involvement in 25% subjects. Cortet et al. [19] reported a 30.5% incidence of bronchiectasis and 80.9% of abnormal patterns in their RA patients on HRCT; in contrast to our study, however, most of their patients were smokers and had respiratory symptoms. The fact that we studied only patients with normal chest radiographs and normal physical examinations could explain the decreased frequency of pulmonary abnormalities such as the honeycombing appearance and ground glass attenuation observed in our patients.

Some authors believed that bronchiectasis might precede RA by many years and that chronic suppuration in the lung may lead to antigenic stimulation in susceptible individuals, thus causing RA [18]. However, it is difficult to explain whether bronchiectasis preceded RA in our patient group since all the subjects in our study were free of symptoms, HRCT findings were mild and our sample was small. Bronchiectasis is a common sequela of fibrotic interstitial lung disease. As the fibrosis progresses cicatrization occurs, applying traction on the adjacent bronchus with consequent ectasia of the airway [7]. As the HRCT findings were mild in our patients and the patients were asymptomatic, we explained HRCT findings as bronchiectasis, caused by interstitial pulmonary abnormalities.

Pulmonary disease may also be observed as a toxic event consequent to treatment for RA [1]. There was no significant difference between the treatment with disease modifying antirheumatic drugs (DMARD) in our patients with and without pulmonary involvement demonstrated by HRCT. In our study group, only one of 23 patients with interstitial fibrosis had been taking methotrexate (MTX) for 6 months. The prevalence of pulmonary disease in RA patients receiving MTX has been estimated by Carson et al. at 5.5%, with an incidence of 3.9 cases per 100 patient-years of treatment [20]. Although pneumonitis is the most common manifestation of MTX-induced disease, fibrosis, bronchospasm, noncardiogenic pulmonary oedema and pleural effusion are also reported [20]. The other 12 of 23 patients with interstitial fibrosis were taking salazopyrine, five were taking chloroquine and five were taking nonsteroidal antiinflammatory drugs (NSAID). The pulmonary disease as an adverse effect of sulphasalazine is reported to be rare. A review of 774 RA patients treated with sulphasalazine over 11 years did not identify any cases of pulmonary disease [21]. NSAID have also been associated with the development of acute pneumonitis, bronchospasm and noncardiogenic pulmonary oedema, but these symptoms develop early and can return with rechallenge [20]. There is no report on the association of chloroquine and pulmonary reaction in the literature. The mean duration of DMARD usage was 2.5 years (minimum, 2 months; maximum, 4 years), and only one patient was receiving MTX. The treatment with DMARD was similar between patients with and without pulmonary changes demonstrated on HRCT; hence the pathological findings do not seem to be secondary to the drug usage in our study group. We cannot, however, exclude the effect of MTX in one patient who had interstitial lung disease and had been receiving MTX for 6 months.

The frequency of small airway involvement in RA is not clear. The prevalence of small airways involvement defined on the basis of these different results can be explained by the assessment of specific pulmonary disease by the nonspecific pulmonary function tests. Hassan et al. [22] studied RA patients and reported a high prevalence of airway obstruction and bronchial reactivity. The exact mechanism for the development of airway obstruction in RA is not known. One possibility is that the mucosal oedema secondary to preexisting airway inflammation may lead to bronchial narrowing and hence cause airway obstruction [22]. McDonagh et al. [17] reported that the HRCT findings of patients with abnormal PFT showed advanced interstitial disease. In patients of McDonagh et al. pulmonary function was often impaired in a pattern similar to that of advanced interstitial lung disease. There were eight patients with PFT abnormalities in our study. The interstitial lung disease of our 15 asymptomatic patients assessed by HRCT was mild, initial findings, whereas the patients with abnormal PFT also had mild HRCT abnormalities.

In conclusion, using a highly sensitive technique such as HRCT, the incidence of pulmonary abnormalities in asymptomatic RA patients may be much higher than previously reported. It appears that HRCT offers an accurate, noninvasive and safe method of diagnosing interstitial pulmonary abnormalities in asymptomatic RA patients.

References

1. Anaya JM, Diethelm L, Ortiz LA et al (1995) Pulmonary involvement in rheumatoid arthritis. Semin Arthritis Rheum 4:242–254

2. Kelly CA (1993a) Rheumatoid arthritis: classical rheumatoid lung disease. Baillieres Clin Rheumatol 7:1–16
3. Kelly CA (1993b) Rheumatoid arthritis: other rheumatoid lung problems. Baillieres Clin Rheumatol 7:17–29
4. Bacon PA (1993) Extraarticular rheumatoid arthritis. In McCarthy DJ, Koopman WJ (eds) Arthritis and allied conditions, 20th edn, Lea & Febiger, Philadelphia, pp 811–840
5. Shannon TM, Gale E (1992) Noncardiac manifestations of rheumatoid arthritis in the thorax. J Thorac Imaging 7:19
6. Hansell DM, Kern IH (1991) The role of high resolution computed tomography in the diagnosis of interstitial lung disease. Thorax 46:77–85
7. McMahon MJ, Swinson DI, Shattar IS et al (1993) Bronchiectasis and rheumatoid arthritis: a clinical study. Ann Rheum Dis 52:776–779
8. Radoux V, Menard HA, Begin R, Decrary F, Koopman WJ (1987) Airway disease in rheumatoid arthritis patients. Arthritis Rheum 82:765–771
9. Arnett FC, Edworthy SM, Bloch DA, et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1:315–324
10. Davis MJ, Dawes PT, Fowler PD, et al (1990) Comparison and evaluation of a disease activity index for use in patients with rheumatoid arthritis. Br J Rheumatol 129:111–115
11. Naidich DP, Me Cauley DI, Nagi F, Khour NF, Stitik FP et al (1982) Computed tomography of bronchiectasis. J Comput Assist Tomogr 6:437–444
12. Wiedeman HP, Matthay RA (1989) Pulmonary manifestations of the collagen vascular disease. Clin Chest Med 10:677–722
13. Hyland RH, Gordon DA, Broder I et al (1983) A systematic controlled study of pulmonary abnormalities in rheumatoid arthritis. J Rheumatol 10:395–405
14. Roschmann RA, Rothenberg RJ (1987) Pulmonary fibrosis in rheumatoid arthritis: a review of clinical features and therapy. Semin Arthritis Rheum 613:174–185
15. Cervantes-Peres P, Toro-Perez AH, Rodriguez-Jurado P (1980) Pulmonary involvement in rheumatoid arthritis. J Am Med Assoc 243:1715–1759
16. Popp W, Rauscher H, Ritschka L et al (1992) Prediction of interstitial lung involvement in rheumatoid arthritis. Lung 102:391–394
17. McDonagh J, Greaves M, Wright AR et al (1994) High resolution computerized tomography of the lungs in patients with rheumatoid arthritis and interstitial lung disease. Br J Rheumatol 3:118–122
18. Hassan WU, Keaney NP, Kelly CA (1995) High resolution computed tomography of the lung in lifelong nonsmoking patients with rheumatoid arthritis. Ann Rheum Dis 54:308–310
19. Cortet B, Flipo RM, Remy-Jardin M et al (1995) Use of high resolution computed tomography of the lungs in patients with rheumatoid arthritis. Ann Rheum Dis 54:815–819
20. Cannon GW (1993) Antirheumatic drug reaction in the lung. Baillieres Clin Rheumatol 7:147–171
21. Fewins HE, Mc Gowan 1, Whitehouse GH, Williams J, Malliya R (1991) High definition computed tomography in rheumatoid arthritis associated pulmonary disease. Br J Rheumatol 10:214–216
22. Hassan WU, Keaney NP, Holland CD, Kelley CA (1994) Bronchial reactivity and airflow obstruction in rheumatoid arthritis. Ann Rheum Dis 53:511–514