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Several high-resolution computed tomography findings associate with survival and clinical features in rheumatoid arthritis-associated interstitial lung disease

Hanna M. Nurmi[a,b,*], Hannu-Pekka Kettunen[c], Sanna-Katja Suoranta[c], Minna K. Purokivi[b], Miia S. Kärkkäinen[a,d], Tuomas A. Selander[e], Riitta L. Kaarteenaho[f]

[a] Division of Respiratory Medicine, Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, POB 1627, 70211 Kuopio, Finland
[b] Center of Medicine and Clinical Research, Division of Respiratory Medicine, Kuopio University Hospital, POB 100, 70029 Kuopio, Finland
[c] Diagnostic Imaging Center, Division of Radiology, Kuopio University Hospital, POB 100, 70029 Kuopio, Finland
[d] Home Care, Rehabilitation and Medical Services for Elderly Care, Tulliportinkatu 37E, 70100 Kuopio, Finland
[e] Science Services Center, Kuopio University Hospital, POB 100, 70029 Kuopio, Finland
[f] Respiratory Medicine, Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, POB 20, 90029 Oulu, Finland

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ABSTRACT

Objective: To compare the presence and extent of several high-resolution computed tomography (HRCT) observations in different subtypes of rheumatoid arthritis-related interstitial lung disease (RA-ILD) and to examine associations between radiological findings, hospitalization, age, RA duration, pulmonary function tests (PFT) and survival.

Materials and methods: HRCTs from 60 RA-ILD patients were independently evaluated and re-categorized into usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), diffuse alveolar damage (DAD) and unclassified subtypes by two radiologists. The presence and extent, which was reported using a semi-quantitative scoring system, of e.g. reticulation, ground-glass opacity, honeycombing, emphysema, traction bronchiectasis and architectural distortion were further evaluated and compared between the subtypes. Associations between radiological findings and survival were identified with the Kaplan-Meier method and Cox's univariate model. The correlations between radiological findings, hospitalization, age, pack years, RA duration and PFT were calculated using Spearman's correlation coefficient.

Results: The extents of reticulation (HR 1.144, $p = 0.041$), traction bronchiectasis (HR 1.184, $p = 0.030$), architectural distortion (HR 1.094, $p = 0.044$) and the presence of pleural fluid (HR 14.969, $p < 0.001$) were associated with decreased survival. A negative correlation was observed between ground-glass opacity (GGO) and the duration of RA ($r = -0.308$, $p = 0.023$). The extents of honeycombing ($r = 0.266$, $p = 0.046$), traction bronchiectasis ($r = 0.333$, $p = 0.012$) and architectural distortion ($r = 0.353$, $p = 0.007$) correlated with hospitalizations due to respiratory reasons.

Conclusions: Many radiological findings associate with the course of the disease of RA-ILD and could potentially be useful when planning the RA treatment or evaluating the risk of death in these patients.

Key points

- High Resolution Computed Tomography helps clinicians to assess patients with rheumatoid lung disease.
- The extents of reticulation, traction bronchiectasis, architectural distortion and the presence of pleural fluid associate with decreased survival in patients with RA-ILD.
- HRCT evaluation can be useful when evaluating the course of the disease in RA-ILD, especially with regard to the risk of hospitalization.

Abbreviations: ANA, antinuclear antibodies; CTD, connective tissue diseases; DAD, diffuse alveolar damage; DLCO, diffusion capacity to carbon monoxide; FEV1, forced expiratory volume; FVC, forced vital capacity; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonias; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KUH, Kuopio University Hospital; MTX, methotrexate; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function tests; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; RF, rheumatoid factor; UIP, usual interstitial pneumonia

* Corresponding author. Center of Medicine and Clinical Research, Division of Respiratory Medicine, Kuopio University Hospital, PO Box 100, 70029 KYS Kuopio, Finland.
E-mail address: hanna.nurmi@kuh.fi (H.M. Nurmi).

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1. Introduction

Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) causes significant morbidity and mortality in patients with RA. It manifests as many different subtypes, of which usual interstitial pneumonia (UIP) is the most common [1,2]. Even though it is recommended in non-definite UIP cases, most patients do not undergo surgical lung biopsy due to the risks associated with it [3]. Therefore, the diagnostics of RA-ILD is nowadays mainly based on high-resolution computed tomography (HRCT) i.e. similar to the situation in other types of ILDs.

The role of HRCT in predicting the prognosis of patients with ILD has been examined mostly in idiopathic pulmonary fibrosis (IPF) [4–6] but in the recent years some studies have also investigated this in connective tissue disease-related ILDs (CTD-ILDs) [7,8] with some proposing that the UIP pattern in RA-ILD associates with a shorter survival [8,9]. The extent of abnormalities in HRCT, often categorized as limited (< 20%) vs. extensive disease (> 20%), has associated with shorter survival [10–12]. Reticulation and honeycombing are often combined as one measure of the extent of ILD changes; this so-called fibrosis score has been shown to correlate with prognosis in several IPF studies [13].

Nowadays computer assisted tools have been developed for providing rapid estimations of disease extent but these are not available in all clinics. Therefore, straightforward methods for providing estimations of the disease extent are still needed, and for example in systemic sclerosis- related ILDs, a good correlation has been observed between visual reader-based scoring and computer-aided quantification [14,15]. Since the reports of the survival associations of observations made with HRCT have mainly focused in IPF, there is a need to evaluate this aspect in patients with RA-ILD to fill the gaps in our current knowledge i.e. what are the precise HRCT findings that predict survival, going beyond the major radiological subtypes. In addition, the correlation between HRCT findings and PFT, as well as hospitalization or other clinical issues, is unclear and mostly has been evaluated in IPF patients.

The purpose of this study was to evaluate the HRCT findings in patients with RA-ILD and to compare the presence and extent of different radiological findings in different RA-ILD subtypes. We also aimed to identify associations between radiological findings and clinical factors, survival and pulmonary function tests.

2. Material and methods

2.1. Patient selection and collection of the data

Sixty RA-ILD patients were identified from the Kuopio University Hospital (KUH) pulmonology clinic in-patients and out-patients database between 1.1.2000 and 31.12.2014. The search was three-pronged and performed using International Classification of Diseases (ICD-10) codes. The first search entailed codes J84.X, the second M05.X/M06.X with a visit to the pulmonary clinic and the third was performed using the code J99.0*M05.1. Patients were included only if they had a high-resolution computed tomography (HRCT) or other comparable radiological examination available and if the RA diagnosis had been made according to the 1987 classification criteria [16] as described previously [17,18]. Patients with other connective tissue diseases, idiopathic ILDs and those with asbestosis or allergic alveolitis were excluded. The HRCT scans of all patients deemed appropriate for this study based on their medical records were evaluated by an experienced radiologist (H-P.K); if the CT findings were not reliably identified as consistent with ILD changes, the patient was excluded. Atypical cases were discussed by a multidisciplinary group consisting of a radiologist, pulmonologists and a pathologist.

Clinical information and the results of baseline pulmonary function tests (PFT), including forced vital capacity (FVC), forced expiratory volume (FEV1) and diffusion capacity to carbon monoxide (DLCO) were retrospectively gathered using a specially designed form, as presented previously [17]. Data was compiled from the patient records of KUH, primary health care centers and other hospitals.

The study protocol was approved by the Ethical Committee of Kuopio University Hospital (statement 17/2013) and by the National Institute for Health and Welfare (Dnro THL/1052/5.05.01/2013).

2.2. The CT protocol

Due to the retrospective nature of this study, the HRCT protocol was diverse. In 47 of 57 cases (82.5%) the CT had been obtained with the patient inhaling in the prone position, in 10 cases also when the patient was exhaling and in three cases the data about position was not available. In 42 out of 60 patients, the baseline scans were digital HRCT scans and 16 cases were older analogue film images. In three cases the baseline radiological evaluation was based on venous phase contrast enhanced CT, pulmonary CT angiogram with HRCT reconstruction and volumetric HRCT, each in one case. The used collimation was variable and the interval also varied between 10 and 28 mm, with the most common interval being 18 mm in 17 cases. The quality of scans was rated as good in 60.7% and suboptimal in the remainder, mainly due to analogue film images and sometimes due to breathing artefacts. All digital images were reconstructed using a high-resolution algorithm and obtained at the window level appropriate for lung parenchyma and mediastinum.

2.3. Radiological re-categorization

Two radiologists (H-P.K, S-K.S), blinded to the demographic data and without consideration of the report accompanying the original CT results, independently re-classified the cases according to the 2013 idiopathic interstitial pneumonias (IIP) classification [19] as UIP, NSIP, organizing pneumonia (OP), diffuse alveolar damage (DAD) and "unclassified" subgroups. The last of the subgroups consisted of the patients that did not fit the definition of any specific subtypes. The radiological RA-UIP criteria that were applied were those for the diagnosis of IPF [20]. RA-NSIP was defined as the predominance of ground-glass opacity (GGO), possible visible subpleural sparing and possible fine reticulation with minor or no honeycombing. RA-OP was defined as single or multiple patchy consolidations. In addition to the baseline CT, the most recent HRCT was also evaluated in a similar manner from 33 patients who had a follow-up CT available. In those patients, the final subgroup was determined based on the analysis of both CTs.

2.4. Further interpretation of the CTs and the scoring system

As well as the radiological subgrouping performed by the two radiologist, the radiological findings were further assessed in detail by the first radiologist (H-P.K) using a form designed for the study (Suppl.file 1). The presence and the extent of the following findings were evaluated separately: GGO, reticulation, honeycombing, emphysema, consolidation, crazy-paving appearance, bronchiectasis, traction bronchiectasis, nodules, thickening of the bronchovascular bundle, cysts, mosaic attenuation, air trapping (when applicable), rounded atelectasis, architectural distortion, pleural plaques, pleural effusion and tumours. The definitions of these findings used in this study are those issued by the Fleischner Society [21]. The most prominent observation was appointed in each HRCT.

Both lungs were divided into three zones. The upper zones were at or superior to the aortic arch, the middle zones were between the aortic arch and pulmonary veins and the lower zones were at or below the pulmonary veins. The extents of GGO, reticulation and honeycombing were semi-quantitatively graded on a scale from 0 to 4 as follows: 0 = finding absent, 1 = minor peripheral scattered changes, 2 = uniform peripheral or minor central changes, 3 = substantial peripheral changes that penetrated deeply to the lung parenchyma, 4 = very abundant peripheral and central changes. The total score of these three findings was obtained by summing the grades for all six zones i.e. the maximum score 24 (Fig. 1).