Ultrasound screening for interstitial lung disease in rheumatoid arthritis

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Abstract

Objective

As interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients is associated with increased mortality due to loss of diffusion capacity and pulmonary hypertension, regular screening for structural abnormalities of the lung is advised. In addition to standard radiological examination with computed x-ray tomography, ultrasound of the lung could allow non-invasive and radiation-free structural monitoring of the lung. The objective of this study was to test the frequency of abnormalities in lung sonography in patients with RA who did not have clinical signs or symptoms of lung disease.

Methods

In a prospective study of 64 consecutive patients with rheumatoid arthritis and 40 healthy volunteers, we screened the pleura and the pulmonary parenchyma for sonographic abnormalities. All RA patients underwent high resolution computer tomography of the lung.

Results

28% of RA patients showed pleural nodules or B-line phenomena. In these patients, CT scans showed signs of incipient interstitial lung disease. Lung sonography showed sporadic abnormalities in 7% of the healthy controls.

Conclusion

Transthoracic ultrasound of the lung is an inexpensive and safe tool to screen patients with RA for incipient pulmonary structural changes.

Key words

interstitial lung disease, rheumatoid arthritis, ultrasound

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Received on May 8, 2013; accepted in revised form on November 12, 2013.

Funding: this study was funded by the "Forschungspreis des Landes Steiermark", Austria.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease affecting up to 1% of the population worldwide (1, 2). Interstitial lung disease (ILD) occurs as an extraarticular manifestation of this systemic autoimmune illness. As mortality is increased in RA patients with ILD, there should be more awareness of this complication (2-4).

Post-mortem studies show that up to 70% of all RA patients have at least minor pleural changes as a sign of lung involvement. RA patients without dyspnoea showed signs of ILD in 17% of cases; among patients with circulating anticitrullinated antibodies (ACPA) the rate was 23% (2, 3, 5-7).

High resolution computed tomography (HRCT) is the standard radiographic technique to diagnose lung involvement in patients suffering from respiratory symptoms or presenting with a pathological pulmonary function test (8, 9). HRCT is able to detect changes in the lung before they are apparent on conventional x-ray. Recently, sonography of the lung was introduced as a safe and easily available method for detecting lung fibrosis, bronchiolitis or pneumothorax (9-14). Sonographic signs like tissue B-lines, irregularities of the pleura or the absence of lung sliding might be a suitable screening tool for lung involvement (15).

We set out to estimate the value of transthoracic lung ultrasound as a diagnostic screening tool in patients suffering from rheumatoid arthritis without respiratory symptoms.

Patients and methods

We performed a prospective study on sixty-four consecutive outpatients fulfilling the diagnostic criteria for RA (9, 16). Patients with known lung diseases, signs of infection, present or previous dyspnea, coughing or thoracic pain, or abnormal results from previous chest radiographs were excluded. Clinical examination of the chest was found to be normal in all cases. All patients underwent chest ultrasound, pulmonary function testing including diffusion capacity of carbon monoxide (DLCO) as well as high resolution computer tomography (HR-CT). A control group consisting of forty age- and sex-matched healthy volunteers (HC) was included to compare the prevalence of sonography findings. HC were not subjected to HR-CT because of ethical reasons. Demographic data, results of clinical composite scores and current therapy was recorded.

This study protocol was approved by the Ethics Committee of the Medical University of Graz (EK-Number: 20-452 ex 08/09) and performed according to the Declaration of Helsinki. All patients gave written informed consent.

Ultrasound methodology

All transthoracic sonograms of the lungs were independently repeated by another rheumatologist before referral to HRCT. There was disagreement on the interpretation of the ultrasound study in two cases; they were excluded from further evaluation.

We used a convex 3.5 MHz transducer for the parenchyma and a linear probe for the pleural changes (LOGIQ 7, General Electric). Using a published anatomical scheme (17) the thoracic wall was divided in 18 regions that were scanned systematically in each individual. This anatomical scheme correlates well with other reports (17, 18). The anterior pleural surface was investigated with the patient in a supine position while the lateral and posterior surfaces were scanned with the patient seated. Scans were performed in a longitudinal or intercostal plane and the following ultrasound signs were recorded.

B-lines (Fig. 1a): These are vertical artifacts reminiscent of comet tails arising from the pleural line and projecting the coexistence of elements with a major acoustic impedance gradient. While this sonographic phenomenon is reported in pulmonary oedema, pulmonary fibrosis, pneumonia or acute respiratory distress syndrome, singular B-lines can also be observed in healthy individuals (11, 15, 19-21) Volpicelli *et al.* described multiple B lines as the sonographic sign of lung interstitial disease (15).

Pleural line (Fig. 1b): The pleural line is a hyperechoic structure created by the reflexion on the parietal and visceral pleura. The normal pleural line

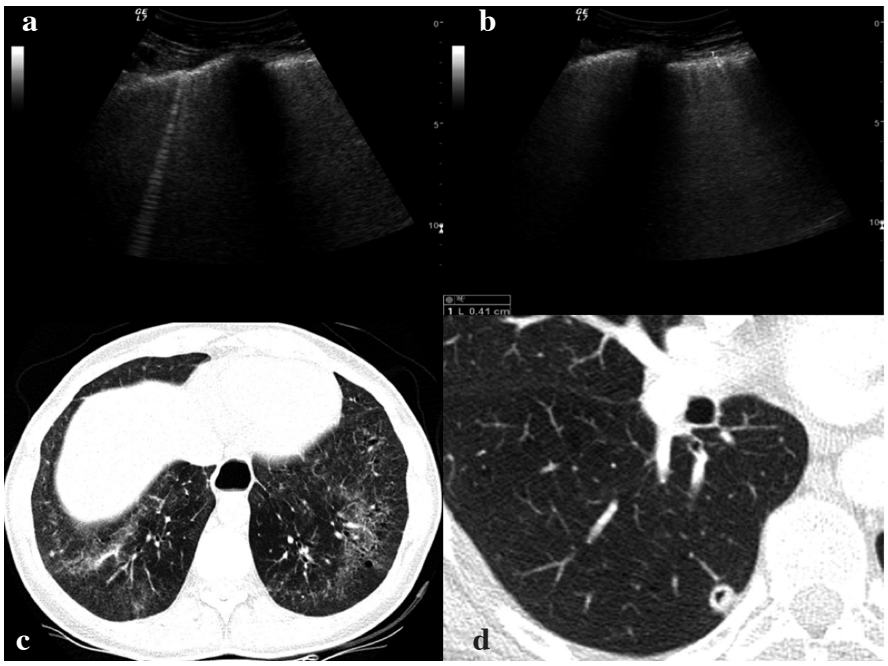

Fig. 1. a) B line; **b**) irregular (unsteady) pleural line of 4.1 mm and subpleural node; **c**) HRCT scan showing typical changes for ILD including alveolitis, ground glass phenomena and bronchiectasis and **d**) subpleural node as seen in ILD of rheumatoid arthritis.

Table I. Demographic data.

	RA patients	controls
Sex (female/male)	54/10	25/15
Age (years)	59 ± 12	52 ± 22
Current smokers no. of patients (%)	4 (6%)	12 (30%)
Treatment with biological response modifiers no. of patients (%)	37 (57%)	0
Treatment with methotrexate no. of patients (%)	40 (62%)	0
RF / ACPA Pos (%)	61/ 57 (93/89)	0
ESR (erythrocyte sedimentation rate) mm/h	27 ± 20	11 ± 4
C-reactive protein (mg/l)	16 ± 14	5 ± 2
Years of disease duration (mean, max/min) (yrs)	9.4 (2-21)	

appears thin and regular without any nodular thickenings. Irregularities of the pleural line more than 2.8 mm were deemed to be pathologic.

Pleural noduli (Fig. 1d): The normal pleural surface appears thin and regular. Subpleural nodes of several millimeters in size were first described in miliary tuberculosis; they also occur in several variants of pleural disease (18, 22).

Statistical analyses

Statistical analyses were performed using SPSS 18.0 software (SPSS Inc, Chicago).

Results of HRCT were assumed to represent the "true" morphological changes and used as the reference standard (8, 9, 23, 24). Data are expressed as mean ± standard deviation. For the measurement of observer agreement we calculated kappa statistics.

Results

The clinical characteristics of the patients are described in Table I. Lung function tests showed normal results in all cases. Eighteen of the sixty-four patients (28%) fulfilled the predefined sonographic criteria for lung involvement. Sixteen of eighteen subjects (89%) showed signs of pulmonary fibrosis including ground-glass opacities, bronchiectasis and subpleural micronodules accented in the lower lobes on HRCT scan. Two of these eighteen patients did not show pulmonary abnormalities on HRCT scan. We carefully searched the clinical records and history of our well-known patients for episodes of pneumonia or another parenchymatous or vascular lung disease; however these seem to be true technical false negatives when CT is the gold standard. One out of 64 RA patients had radiographic changes for pulmonary involvement without sonographic abnormalities. Judging the qualities of a screening test, the absolute agreement between sonography and radiography yields a sensitivity of 97.1% and a specificity of 97.3%. The predefined criteria yield a positive predictive value of 94.3% and a negative predictive value of 98.6% with a significant p-value <0.001.

In two patients, the sonographic judgment of the two investigators differed, this yielded a Kappa value for absence/presence of interstitial lung disease of 0.92.

Interestingly, 28% of the patients with RA but only 7% of the healthy cohort had B-lines on at least two locations (p<0,029). 3 subjects of the healthy cohort (7%) had B lines in more than 2 locations, whereas only 1 patient (3%) had subpleural noduli. A singular B line was seen in 2 RA patients. Pleural nodules were seen sonographically in 12 (18%) patients with RA, all of whom showed ILD pathologies on HRCT scan. One healthy subject displaying nodules on lung ultrasound did not fulfill the criteria. On HRCT scan, there were bilateral subpleural nodules and ground glass opacities.

Three of the sixty-four RA patients (4%) displayed the artifact of a fragmented pleura (discontinuous pleura line); negative lung sliding was detected in 1/64 (1.5%) patients. Sixteen out of eighteen (89%) patients with pathological ultrasound patterns showed equivalent changes including subpleural micronodules on HRCT (Table II). The frequency of ACPA positive patients was similar in the groups of RA patients with or without ILD (91 *vs*. 88%). In the RA + ILD group, 13/17 (76%) patients received a biological therapy. Infliximab was given to 9 subjects (53%), adalimumab to one patient (6%), etanercept to one patient (6%) and tozilizumab to 2 patients (12%). Interestingly, methotrexate (MTX) was applied in 14/17 (82%) patients and lefunomide in 2/17 (12%)

Table II. Occurrence of sonographic and radiographic abnormalities. Lung involvement as judged by HRCT was defined by the presence of at least two of the following CT signs in >2 locations: B lines, pleural nodules, fragmented pleura or negative lung sliding. Sonographic and radiographic abnormalities occurred in the very same patients. Using these abnormalities 4 healthy 4 subjects from the healthy cohort would have been judged to have ILD; this could not be evidenced by HRCT.

	Rheumatoid arthritis patients n=64	Healthy controls n=40
Lung involvement as judged by HRCT	17 (26,5%)	NA
Lung involvement as judged by sonography	18 (28%)	4 (10%)
Sonographic B Lines (>2 locations)	18 (28%)	3 (7%)
Radiographic pleural thickening	18 (28%)	NA
Sonographic nodules	12 (18%)	1 (2%)
Radiographic nodules	12 (18%)	NA
Sonographic pleural fragmentation	3 (4%)	0
Radiographic pleural fragmentation	3 (4%)	NA
Sonographic negative lung sliding	1 (1%)	0

Table III. Number of patients in the RA+ ILD (n=17) and RA-ILD (n=46) groups compared with current treatment. Biologicals were given to 37/64 patients. TNF inhibitors (TNFI) and methotrexate (MTX) were applied in 13/17 (82%) patients in the RA+ ILD group in comparison to 24/46 (53%) TNFI and 26/46 (56%) MTX treated subjects in the RA-ILD group. Interestingly, disease duration >5 years was observed more frequently in the RA-ILD group than in the RA+ILD subjects (83% *vs*. 74%). The occurrence of ACPA in both groups was similar. Interestingly, the erythrocyte sedimentation rate (ESR) (17±12 mm/h *vs*. 34±23 mm/h) and the C-reactive protein (CRP) (9.4±8.8 mg/L *vs*. 18.1 +/I 16.3 mg/L) were significantly elevated in the RA+ ILD group (p<0.001).

	Rheumatoid arthritis patients with ILD (n=18)	Rheumatoid arthritis patients without ILD (n=46)	p-value
Treated with methotrexate (%)	77	57	0.117
Treated with TNF-inhibitors (%)	77	53	0.063
Disease duration >5 years (%)	5.5	10.9	0.515
ACPA positives (%)	89	87	0.835
Mean C-reactive protein (CRP) (mg/L)	18.1 ± 16.3	9.4 ± 8.8	<0.001
Mean erythrocyte sedimentation rate (ESR) (mm/h)	34 ± 23	17 ± 12	<0.001

patients. In the RA-ILD group (n=46) 24 patients (52%) received biologicals. Infliximab was given to 9 patients (19%), tozilizumab to 8 patients (17%), adalimumab to 3 patients (6%), abatacept to 3 patients (6%) and rituximab to one patient (2%). The mean dosage of MTX per week was 9.1 mg/week in the RA+ILD group *vs*. 7.6 mg/week in the RA-ILD group (Table III). Disease duration in the RA+ILD group was shorter than in the RA-ILD group. (7.6 years *vs*. 11.2 years).

Discussion

In the present study we showed a high sensitivity and specificity of lung sonography to detect underlying interstitial lung disease as determined by HR-CT. The use of lung sonography as a screening tool has been suggested also for systemic sclerosis (24).

In our cohort of RA patients without clinical pulmonary symptoms, the tissue changes seen upon lung sonography were confirmed in 88% of the patients by the results of HRCT. Among our pulmonologically inconspicous RA patients we found a rate of 26.5% showing radiographic signs of ILD. Our patients showed glass ground phenomena, ascending alveolitis from the basal lung segments, and subpleural nodules according to radiological criteria for ILD (24-26). Our findings are in in line with the concept of lung fibrosis as a comorbidity of several inflammatory processes (27, 28).

A limitation of the method is that 7% of healthy volunteers showed B-lines or nodules. Among the limitations of our study it has to be mentioned that we could not perform HR-CT in healthy controls for ethical reasons; however, the aim of our study was to determine sensitivity and specificity of sonography to detect ILD in RA patients and not to assess the value of this method in other cohorts. Since HRCT or lung biopsy was not feasible in these individuals for ethical reasons, the final clinical specificity of such changes cannot be judged. Furthermore, false negative ultrasound may be an anatomical (depth of organ) or technical limitation.

Ultrasound investigation of the lung takes approximately 12 minutes of the physician's time; it reportedly can be used to 8 minutes when using simplified B line scoring (18). On the average, the price of the ultrasound investigation can be estimated as a quarter of the price for the HRCT scan.

In conclusion, this pilot study supports ultrasound investigation if a longitudinal screening tool for interstitial lung disease in rheumatoid arthritis is needed. This may be a very important issue during the treatment with biologicals.

Acknowledgements

We thanks Eugenia Lamont for the language editing.

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