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Original article

Pulmonary magnetic resonance imaging is similar to chest tomography in detecting inflammation in patients with systemic sclerosis

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ABSTRACT

Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are prevalent complications of systemic sclerosis (SSc) and are currently the leading causes of death related to the disease. The accurate recognition of these conditions is therefore of utmost importance for patient management.

A study was carried out with 24 SSc patients being followed at the Rheumatology Department of the Hospital de Clínicas of Universidade Federal do Paraná (UFPR) and 14 healthy volunteers, with the objective of evaluating the usefulness of lung magnetic resonance imaging (MRI) when assessing ILD in SS patients. The results obtained with lung MRI were compared to those obtained by computed tomography (CT) of the chest, currently considered the examination of choice when investigating ILD in SS patients.

The assessed population was predominantly composed of women with a mean age of 50 years, limited cutaneous SS, and a disease duration of approximately 7 years. In most cases, there was agreement between the findings on chest CT and lung MRI. Considering it is a radiation-free examination and capable of accurately identifying areas of lung tissue inflammatory involvement, lung MRI showed to be a useful examination, and further studies are needed to assess whether there is an advantage in using lung MRI instead of chest CT when assessing ILD activity in SS patients.

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Ressonância magnética pulmonar é semelhante à tomografia de tórax para detectar inflamação em pacientes com esclerose sistêmica

Palavras-chave:
Esclerose sistêmica
Ressonância magnética
Tomografia computadorizada

RESUMO

A doença intersticial pulmonar (DIP) e a hipertensão arterial pulmonar (HAP) são complicações prevalentes na esclerose sistêmica (ES) e constituem atualmente as principais causas de morte relacionadas à doença. O reconhecimento preciso dessas condições é, portanto, de fundamental importância no manejo dos pacientes.

Fez-se um estudo com 24 pacientes com ES em acompanhamento no serviço de reumatologia do Hospital de Clínicas da Universidade Federal do Paraná (UFPR) e 14 voluntários sadios com objetivo de avaliar a utilidade do exame de ressonância magnética (RM) do pulmão na avaliação da DIP em pacientes com ES. Os resultados obtidos com a RM pulmonar foram comparados com os obtidos na tomografia computadorizada (TC) de tórax, exame atualmente considerado de eleição na investigação da DIP em pacientes com ES.

A população avaliada era predominantemente composta por mulheres com idade média de 50 anos, ES cutânea limitada e tempo de doença de aproximadamente sete anos. Na maioria dos casos, houve concordância entre os achados na TC de tórax e RM do pulmão. Em se tratando de um exame isento de radiação e capaz de identificar com adequada precisão áreas de acometimento inflamatório do tecido pulmonar, a RM do pulmão de revelou um exame útil. São necessários mais estudos para avaliar se há vantagem da RM do pulmão sobre a TC de tórax na avaliação da atividade da DIP em pacientes com ES.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease of unknown origin and worldwide distribution that predominantly affects women in the third or fourth decades of life, which is characterized by fibrosis of the skin and internal organs, vasculopathy and immune dysregulation.[1,2]

SSc has high morbidity and mortality, with pulmonary involvement in the form of interstitial lung disease (ILD) and/or pulmonary arterial hypertension (PAH) being the main cause of death in this disease.[3,4]

ILD is a fairly common complication of SSc, present in approximately 50% of patients with diffuse cutaneous SSc and in up to a quarter of patients with limited cutaneous SSc.[5,6] In SSc, the most frequent pattern of interstitial lung involvement is nonspecific interstitial pneumonia (NSIP), characterized by the presence of ground-glass opacity, representing inflammatory involvement of lung tissue (alveolitis), and traction bronchiectasis and bronchiolectasis, which correspond to pulmonary parenchymal fibrosis. In NSIP, pulmonary involvement predominantly affects the lower lobes, is bilateral and symmetrical, and commonly shows an adequate response to immunosuppressants.[3,7]

Therefore, as the treatment of ILD in SSc involves the use of immunosuppressants, these should be initiated early during disease evolution, i.e., in pre-fibrotic stages, in cases with inflammatory involvement (alveolitis) of the lung parenchyma. Likewise, it is plausible to consider that the immunosuppressive treatment, which is not free of complications and side effects, should only be maintained as long as there is an inflammatory substrate which it can act upon.

Several methods are available for the evaluation of ILD in SSc, with chest CT being the one most commonly used test (the "gold standard"). It is a fast, widely available examination and its high resolution allows an excellent analysis of the lung parenchyma when compared, for instance, to a plain chest X-ray. However, in comparison to the latter, it involves a much higher dose of radiation.[8]

Complementing the chest CT findings, pulmonary function tests, including spirometry, lung volume determination, carbon monoxide diffusion capacity measurement and the 6-minute walking test are also performed in the ILD investigation.

To identify areas of pulmonary inflammation, magnetic resonance imaging (MRI) presents as a promising examination.[9–11] Regarding the examination technique, one can identify, according to the tissue characteristics (hydrogen proton organization, response to the magnetic field and the radiofrequency stimulus), relaxation times T1, T2 and density of hydrogen protons (DP), with these being the parameters that yield image brightness or signal. By choosing the parameters of each sequence, it is possible to weight the image in T1, T2 and other types of sequence, allowing the differentiation between normal and pathological tissues. Commonly, there is an increase in T2 signal in pathological processes.[12] In pulmonary MRI, the low density of protons, which generates a low-density signal, and multiple air–tissue interfaces (susceptibility artifact), as well as movement artifacts (respiratory, cardiac, and vascular), are great challenges.[13] However, MRI is a non-invasive, relatively high-resolution, ionizing radiation-free examination.

However, in the field of SSc, few studies have reported on MRI use for the evaluation of ILD, which is more commonly used to analyze cardiac involvement in the disease.[14] The theoretical basis for performing MRI in the assessment of ILD in patients with SSc would be the increase in the number of

inflammatory cells in the lungs, resulting in an increase in the number of protons, with a consequent signal increase in the T2 images at the MRI examination. In summary, we consider there is a role for pulmonary MRI when differentiating pulmonary parenchyma active disease with ground-glass opacity (increase in T2-weighted images) from non-active disease, with fibrosis only (absence of signal increase in T2 images).

Therefore, the aim of this study is to evaluate the usefulness of pulmonary MRI in the identification of inflammation areas in the pulmonary parenchyma in patients with ILD and SSc.

Material and methods

A cross-sectional study was carried out at the Rheumatology Department of Hospital de Clínicas of UFPR, which assessed 24 patients with a diagnosis of SSc and 14 healthy volunteers (convenience sampling) that comprised the control group. The inclusion criteria were: patients should be 18 years of age or older and have a diagnosis of SSc according to the 1980 ACR criteria.[15] The following were excluded from the study: patients who were unable to undergo pulmonary MRI, such as patients with a cardiac pacemaker or hearing aid; smokers; patients with irregular appointment and/or scheduled examination attendance; patients who refused to sign the study consent form.

The patients were submitted to routine laboratory tests and evaluated for SSc activity at each visit to the outpatient clinic (intervals of 3–5 months), according to the EUSTAR (Eular Scleroderma Trials and Research) criteria. Using the latter, scores are assigned according to parameters of cutaneous, vascular, articular, and cardiopulmonary involvement, as well as complementary tests, and the disease is considered active if the sum of the scores is ≥ 3.[16] All patients were submitted to high-resolution chest CT, pulmonary function tests and echocardiography every year. In addition to the usual outpatient follow-up, the patients in the study were referred for lung magnetic resonance imaging (Siemens Magnetom Avanto 1,5T – Erlangen, Germany), in a specialized medical center. T2-weighted images with respiratory synchronization were used. The date of the lung MRI was coincident with that of the lung CT. Both tests were analyzed by the same investigator (DW), who was not blinded to the results of the comparison method. The research project was approved by the Research Ethics Committee and CONEP (CAAE number: 03691412.4.0000.0096).

Statistical analysis

Data are expressed as mean ± standard deviation or percentage (%). To evaluate the agreement between the tests, Cohen's Kappa, general agreement, positive and negative agreement indices were used. Statistical analysis was performed using the statistical software JMP 7.0®, SAS Institute, Inc., Cary, NC.

Results

Lung MRI was performed in 24 SSc patients and 14 healthy volunteers, who constituted the control group (Table 1). Patients were predominantly female (95.8%), with a mean age of 49.6 ± 12 years and disease duration (estimated from the first symptom other than Raynaud's phenomenon) of 6.9 ± 7.1 years. The majority had limited cutaneous SSc (62.5%) and less than one fifth of the patients had active disease according to the EUSTAR activity score. Two patients had overlapped disease with rheumatoid arthritis and one patient with juvenile idiopathic arthritis.

Table 1 – Clinical data of patients and control group.

Data	Patients ($n = 24$)	Controls ($n = 14$)
Female gender, *n* (%)	23 (95.8)	8 (57.1)
Age in years, mean (±SD)	49.6 (12)	28.8 (6.8)
Disease duration in years, mean (±SD)	6.9 (7.1)	–
Limited cutaneous SSc (%)	62.5	–
Diffuse cutaneous SSc (%)	25.0	–
Overlapping disease (%)	12.5	–
Active disease (%)	16.7	–

When assessing patients and controls submitted to chest CT and chest MRI, it was possible to verify that the findings by both techniques were very similar. Among the SSc patients ($n = 24$), 79.2% ($n = 19$) had ground-glass opacity areas on chest CT, of which 100% had lung MRI with increased T2-weighted signals in the areas corresponding to the ground-glass opacity findings. Of the remaining 5 patients with chest CT with no evidence of ground-glass opacity, 3 had normal lung MRI results and 2 patients had MRI with areas of increased T2-weighted signals (Figs. 1 and 2).

As the primary endpoint of the study, we evaluated the performance of chest MRI *versus* chest CT (the "gold standard") in the assessment of ILD. In this analysis, restricted to patients, we obtained for MRI: sensitivity of 100% (82.35–100); Specificity of 60% (14.66–94.73); Positive likelihood ratio of 2.50 (0.85–7.31); Negative likelihood ratio of 0; Positive predictive value of 90.5% (69.62–98.83); Negative predictive value of 100% (29.24–100). The results are shown in Table 2.

In a secondary analysis, regarding how lung MRI would behave in the control group, the presence of ground-glass opacity was used as the "gold standard" in the chest CT, attaining 100% of sensitivity for the MRI (82.35–100); Specificity of 71.43% (41.90–91.00); Positive likelihood ratio of 3.50 (1.53–8.00); Negative likelihood ratio of 0; Positive predictive value of 82.61% (61.22–95.05); Negative predictive value of 100% (69.15–100).

In the analysis of agreement between the tests, Cohen's Kappa was 0.704 (CI: 0.328–1.0) and the overall agreement was 91%. The positive agreement was 100% and the negative agreement was 60%.

Discussion

Pulmonary interstitial involvement and PAH in SSc are currently the main causes of disease-related mortality, so early recognition is critical to provide appropriate therapy and achieve increased survival. Pingitore et al. described the identification of myocardial and pulmonary involvement through MRI assessment in an asymptomatic patient with

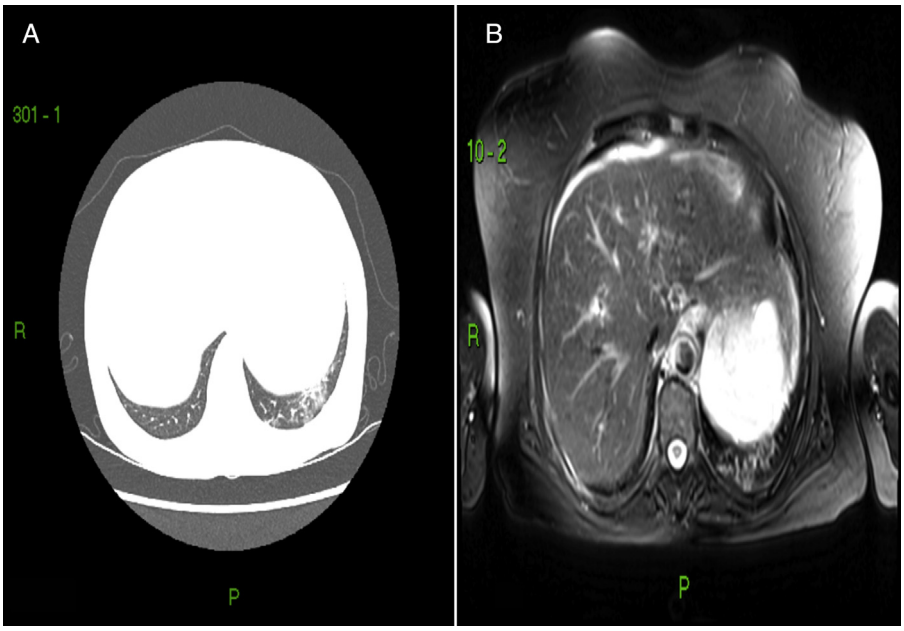

Fig. 1 – Respectively, chest CT and chest MRI of patient with SSc. A, shows ground-glass attenuation area in the lower lobe of the left lung; B, shows an area of T2 increase in the corresponding area.

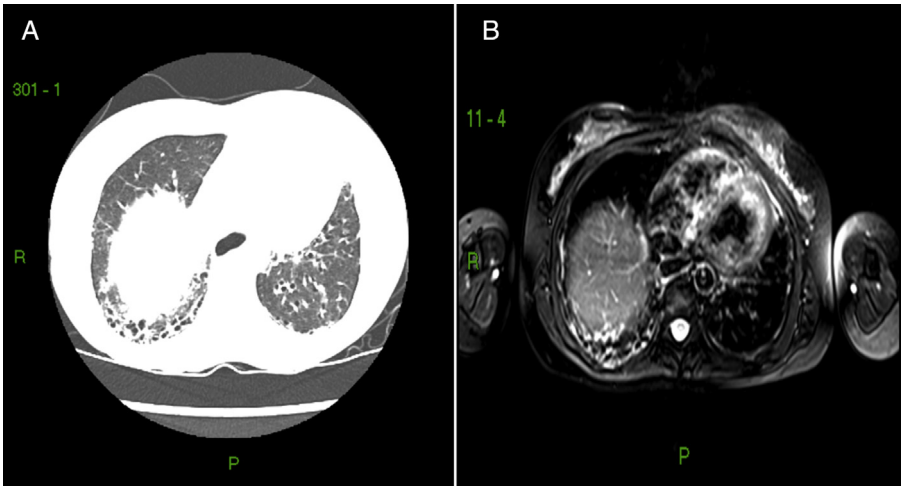

Fig. 2 – Respectively, chest CT and chest MRI of patient with SSc. A shows an area of reticular infiltrate in the lower lobe of the right lung, with traction bronchiectasis and minimal ground-glass attenuation areas; B, shows an increase in T2 signal in the corresponding area.

scleroderma, which allowed specific treatment and patient recovery.[17]

In the case of Collagen vascular diseases, SSc is the prototype of the most characteristic pulmonary involvement. Establishing the usefulness of chest MRI assessment in the detection of ILD in these patients is of utmost importance, as the examination does not require radiation use and can be repeated with minimal risk.

Table 2 – Chest MRI performance compared to chest CT in the assessment of ILD.

Data	Sensitivity	Specificity	LR+	LR−	PPV	NPV
	100%	60%	2.50	0	90.5%	100%

MRI, magnetic resonance imaging; CT, chest tomography; ILD, interstitial lung disease; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

MR imaging is an extremely useful screening tool for diseases involving a variety of structures, such as the chest wall, pleura, heart, and mediastinum. In several situations, it is shown as an equivalent or superior examination when compared to chest CT, as for instance, in the evaluation of primary chest wall tumors, paraspinal masses and in the evaluation of local tumor extension. Its positive points are the absence of ionizing radiation, an excellent contrast resolution between the normal and pathological tissues, obtaining multiplanar images and sensitivity to blood flow.

When the use of contrast medium for MRI is required, gadolinium-based agents are commonly used, which allows an examination with greater sensitivity when compared to contrast-enhanced CT and has a lower incidence of adverse reactions and complications. When assessing the pulmonary parenchyma, however, the MRI use is still restricted, due to several factors, such as the lower spatial resolution and a longer time for image acquisition when compared to chest CT, movement artifacts caused by breathing and cardiac movements, low amount of signal-generating hydrogen protons due to the presence of air in the airways and loss of signal induced by magnetic susceptibility at the border between the wall and the alveolar gas. In recent years, however, MRI assessment of the lungs has significantly advanced, with new equipment, techniques that allow faster image detection and new contrast agents, such as inhaled hyperpolarized gases that allow increased signal and excellent spatial resolution of the pulmonary parenchyma images.[9,13,18]

In the present study, we evaluated the usefulness of chest MRI in identifying inflammation areas of the pulmonary parenchyma in the presence of ILD in SSc patients, compared with chest CT findings. The agreement between the tests was high, which was corroborated by the *kappa* values and agreement indices. We found that the lung MRI showed a sensitivity of 100% in the assessment of ILD and 100% in relation to chest CT. These are significant data, because this is a severe disease, where false-negative results will cause serious harm to the patient. The specificity of 60% of the lung MRI compared to chest CT and of 71.43% in the assessment of ILD is reasonable. In the "false-positive" cases, in which chest CT did not disclose a ground-glass opacity pattern, but the lung MRI showed an increased T2-weighted signal ($n = 2$), it would be possible to question whether the MRI was superior to the CT in detecting alveolitis inflammation in the initial form. However, the analysis of the control group demonstrated a higher number of "false positives", which does not corroborate the hypothesis.

As study limitations, we can mention the fact that the examinations were performed by a single examiner and the examiner was not blinded to the results of the examination comparison (CT and MRI). The small sample size and the single research center are also emphasized. New studies with a larger sample size and specialized centers will be important to broaden the data analysis.

In patients with SSc, chest MRI has good sensitivity when compared to chest CT and may add useful information to the assessment of ILD activity.

Conflicts of interest

The authors declare no conflicts of interest.

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