THE ROLE OF DCE-MRI IN THE EVALUATION OF PROGRESSIVE MASSIVE FIBROSIS AND CENTRILOBULAR NODULES IN CASES OF SILICOSIS DUE TO DENIM SANDBLASTING

Adem Karaman[1]*, Omer Araz[2], Fatih Alper[1], Irmak Durur Subasi[1], Erol Bozdogan[3], Dilek Karatas[1], Elif Yilmazel Ucar[2], Metin Akgun[2]

[1]Department of Radiology, Ataturk University, Medical Faculty, Erzurum - [2]Department of Pulmonary Disease, Ataturk University, Medical Faculty, Erzurum - [3]Department of Radiology, Sevgi Can Hospital, Adana, Turkey

ABSTRACT

Aims: *To investigate the role of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in the evaluation of progressive massive fibrosis and centrilobular nodules in patients who had silicosis due to denim sandblasting.*

Materials and methods: *Thirty-seven progressive massive fibrosis lesions and three centrilobular nodules were evaluated in 33 patients. The kinetic curves of each of the lesions on DCE-MRI was obtained; signal intensities on T2 weighted images were evaluated, along with the contrast characteristics of progressive massive fibrosis lesions and the correlation between the progressive massive fibrosis load and the diameter of the pulmonary arteries.*

Results: *Progressive massive fibrosis tended to develop earlier in this subtype of silicosis. The visibility of progressive massive fibrosis on MRI compared to computed tomography was higher than that of centrilobular nodules. While DCE-MRI showed gradual contrast enhancement and no washout pattern for progressive massive fibrosis, centrilobular nodules had an earlier and higher maximum peak with a washout pattern. The degree of fibrosis was not correlated with the contrast values and a more progressive massive fibrosis load was associated with a greater degree of pulmonary vascular dilatation.*

Conclusions: *MRI should be used in the evaluation of silicosis, especially in patients who have progressive massive fibrosis, because it is better at characterizing tissues and can be repeated without the danger of exposing the patient to radiation.*

Key words: *MRI, silicosis, progressive massive fibrosis, centrilobular nodule, denim sandblasting.*

Received *May 18, 2014;* ***Accepted*** *September 02, 2014*

Introduction

Silicosis is an occupational pulmonary disease known to occur due to the inhalation of silica particles. Silicosis has three clinical forms: acute, accelerated and chronic. It also has two radiologic forms: simple silicosis, in which nodules are prominent, and complicated silicosis, which is also called progressive massive fibrosis (PMF)[1, 2]. Centrilobular nodules (CLN) are the most characteristic finding of simple silicosis; however, “tree-in-bud”, peri-lymphatic and randomized nodules may also be seen[3]. Progressive massive fibrosis is defined as a fibrotic lesion that has a diameter of more than 1 cm[4] and it is classically described as a fibrotic mass surrounded by emphysematous lung fields[5].

In the cases with silicosis due to denim sandblasting, acute and accelerated forms of silicosis have been reported to be more common clinical presentations and PMF is not an uncommon complication[6, 7].

In the diagnosis of silicosis, a clinical history that includes silica exposure and corresponding radiological findings (i.e. chest x-ray) are sufficient to confirm the diagnosis. Computed tomography (CT) is sometimes used in the diagnosis and follow-up of silicosis, especially when the chest x-ray is normal despite the patient being symptomatic and having a history of exposure to silica; it is also used in the evaluation of PMF. Although CT can give morphological information about the size and shape of a lesion, it is insufficient for tissue characterization and has some limitations, for example it is not always able to differentiate between silicosis and pulmonary cancer. CT also exposes patients with silicosis, who may be very young, to large amounts of radiation, especially if follow-up is required[6-9]. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) has begun to be used in thoracic radiology, especially in the differentiation of nodular pathologies, where dynamic-DCE-MRI may be used routinely to differentiate cancer from inflammatory pathologies[10].

Although there are a few MRI studies on silicosis, to the best of our knowledge, there are no studies on silicosis due to denim sandblasting in the literature. In this study, we aimed to determine the MRI findings for silicosis due to denim sandblasting, showing how DCE-MRI may be used in the evaluation of kinetic patterns of CLN and PMF lesions, the T2 signal intensity (SI) of PMF lesions, and the correlation between PMF load and the diameter of the pulmonary arteries. We also assessed whether MRI should be used routinely in the differential diagnosis and follow-up of PMF in patients with silicosis.

Materials and methods

Study population

Between December 2010 and March 2011, among 110 patients with silicosis, 33 male patients who were diagnosed as having acute or accelerated silicosis due to denim sandblasting based on chest x-ray findings, and who had undergone CT to evaluate PMF, were enrolled in the study. All patients were informed about the study protocol and gave their consent to participate. The study was planned according to the ethics guidelines of the Helsinki Declaration and the study protocol was approved by the Ataturk University local ethical committee.

Magnetic Resonance Imaging (MRI)

The patients underwent DCE-MRI. PMF was defined as a large opacity exceeding 1 cm, while CLN was defined as a nodule located centrally in a secondary lobule and ranging from a few mm to over 1 cm in diameter. A total of 37 PMF lesions were determined and all the patients in the study had numerous CLN of various sizes. Among the visible CLN, the most prominent three nodules were selected for analytical measurement. The morphological characteristics of the lesions were described and kinetic characteristics were evaluated. After DCE-MRI examination, all patients had a follow-up scan after two years, at which point no malignancies were detected.

The DCE-MRI examinations were obtained on a 1.5-Tesla Magnetom Avanto (Siemens Medical Systems, Erlangen, Germany) using a body coil with an electrocardiographic trigger. At first, a TRUFI (true fast imaging with steady state free precession) sequence was obtained, which included thorax and upper abdomen images to localize the lesions. Following this, axial T1 weighted TSE (turbo gradient spin echo) and T2 weighted TSE sequences were obtained. Breath-hold fat-suppressed T1-weighted FLASH (fast low-angle shot) 3D images were sequenced (TR/TE: 6/2.51; FA: 10, voxel size: 2.3 x 1.4 x 5 mm). After the first images had been obtained without contrast administration, the contrast medium (0.1 mmol/kg gadolinium-DPTA) was administered intravenously through an automatic injector with an 18- to 20-gauge cannula positioned in an antecubital vein at a flow rate of 3 ml/s. Approximately 15 ml of saline was injected following the gadolinium. Dynamic images were obtained at 30, 60, 90, 120, 150, 180, 210, 240 and 600 s with an 8- to 12-second breath-holding episode per series. For dynamic evaluation the axial plain was used.

Morphological Evaluation

The lesion location, size, contour and signal characteristics were assessed using a T1- and T2-weighted turbo spin echo. The signal characteristics (iso-, hypo-, hyper-intense and heterogeneous) were established and the SIs were calculated.

Using the T1 and T2-weighted images (WI), SIs of the PMFs were evaluated in terms of fibrosis and/or inflammation. Fibrosis was described as lesions that were hypointense on T1 and isointense or hypointense on T2-weighted images, presence of hyperintense lesion on T2-weighted images was considered in favour of inflammation but not fibrosis[11].

PMF lesions were first evaluated according to signal intensities on T1- and T2-WI relative to muscle intensities. All lesions were hypointense on T1-WI. To evaluate the presence of inflammation and fibrosis of PMFs, signal intensities of the lesions on T2-WI relative to muscle were taken into consideration. Three groups were defined as follows: group 1 had lesions that were hyperintense on T2-WI (inflammation predominant), group 2 had lesions that were isointense on T2-WI, and group 3 had lesions that were hypointense on T2-WI (fibrosis predominant).

Peak contrast-enhancement values for each group were calculated. Additionally, diameter measurements were taken in the pulmonary artery phase on the appropriate T1-weighted axial images within 30 seconds. The patients were classified into 4 groups according to their PMF load: mild, moderate, intense and very intense.

Kinetic Evaluation

Signal intensity measurements were calculated by positioning the circular region of interest (ROI) at the most contrast-enhancing central-solid part of each PMF and CLN lesion. Any pulmonary parenchyma and pulmonary vessels adjacent to the lesion area were excluded (in order to avoid the partial volume effect). The ROIs were selected and measurements were taken in a duodecimal window in all series obtained by the DCE-MRI. The area of the ROI varied between 0.23 and 1.60 cm2 and after SI measurement; the following equation was used to establish the ratio increase (SI %) for each point in time (t): $SI\%t = [(SIt - SIt0)/SIt0] / 100$. The term t0 refers to the value before injection of the contrast medium. Time-SI curves were converted to time-contrast curves (SI %) for each lesion using this equation and these curves were then evaluated using the classification system of Schaefer et al.[12]. The other parameters evaluated were the early peak (EP) value (the maximum relative contrast level within the 1st minute following t0) and the maximum peak (MP) value (the maximum relative contrast level during the procedure).

Graphical representations of the SI/time curves and SI/increases by percentage were drawn using the values obtained from the lesions, this allowed average PMF and CLN graphics to be obtained.

Statistical Analysis

Analyses were performed using SPSS 17.0 software. Mann-Whitney U and Spearman correlation tests were used to evaluate the difference in contrast values between the groups according to the degree of fibrosis and the correlation between PMF load and pulmonary artery diameter. Statistical significance for all analyses was accepted at a level of $p < 0.05$.

Results

Thirty-three patients (all male) were included in this study. Their average age was 33.5±9.7 years (range 23-54 years). The average length of exposure of these patients to silica particles was 41.2±26 months.

Twenty-one patients had a history of smoking an average of 8.2±2.4 packs per year. Respiratory function values were as follows: FVC (%): 54.2±27.1; FEV1 (%): 47.8±27.6; and FEV1/FVC: 76.6±17.9. For the blood gas analysis the average readings were: PaO_2: 70.4±7.1; $PaCO_2$: 32±5.1; and SaO_2: 90.5±6.8.

A total of 37 PMF lesions were evaluated. PMF lesions were most commonly seen in left upper lobe (n=13, 35.1%); however, they were also frequently found in the right upper lobe (n = 10, 27 %) and the right middle lobe (n = 8, 21.6%), though less frequently in the right lower lobe (n = 3, 8.1%) and the left lower lobe (n = 3, 8.1%) (Figure 1a-d).

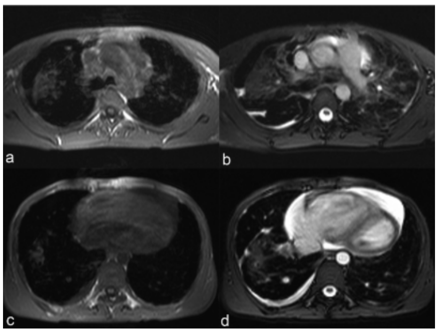

Figure 1: (a, b) Axial T1 and T2 weighted images of the upper zone of the lungs showing bilateral PMF lesions, parenchymal distortion, right pleural effusion and pericardial effusion. (c, d) Axial T1 and T2 weighted images of the lower level of the lungs showing PMF lesions in the right lower lobe, parenchymal distortion, right pleural effusion, pleural irregularity and pericardial effusion.

PMF lesions showed an early gradual increase followed by a plateau pattern in the DCE-MRI images. Enhancement of the PMF lesions began with the first contrast enhanced series and reached the maximum peak (MP) in the 8^{th} series. The percentage contrast enhancement of PMFs showed an increase of between 10% and 227%, with an average SI increase rate of 90% at the MP. Although no washout pattern was seen in the PMFs, in some cases the EP was up to 60%.

Measurements were taken from the three most prominent CLNs found on MRI for each patient. Their SIs on the T1-weighted images were lower than those of the PMFs and the CLN were less visible on MRI than on other imaging modalities (Figure 2a, b). Contrast enhancement began with the first series and reached the MP in the 4^{th} and 5^{th} series (120-150 sec).

Contrast enhancement at the MP increased between 71% and 207%, and the average MP contrast enhancement ratio was 115% (Figure 3). In the late series, washout was generally seen. The EP was 90% in some of the CLN, with averages of between 60% and 140%.

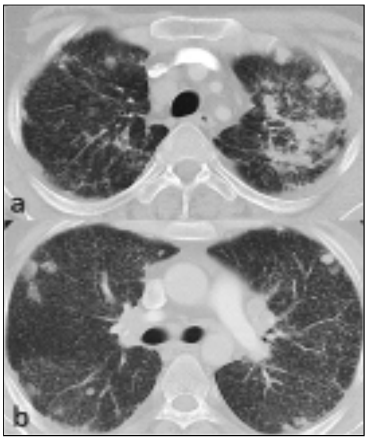

Figure 2: (a) Axial contrast enhanced T1 weighted image showing many CLN lesions in both lungs. (b) Axial contrast enhanced T1 weighted MIP image showing may more CLN lesions than in conventional axial images.

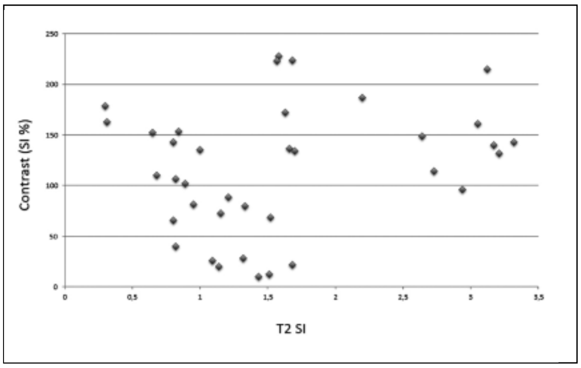

Figure 3: T2 SI-contrast enhancement (%) graphics show discordance of high and low ratios.

PMFs were classified according to SIs on T2. In T2 hypointense images, fibrosis and inflammation were suspected; fibrosis was also suspected in T2 hyperintense images. In the evaluation of T2 SIs, there were 11, 17 and 9 PMF lesions in groups 1, 2 and 3, respectively. There was no statistically significant difference among percentage increase peak values for PMF lesions (Figure 4).

After evaluation of the PMF load, 13 patients were classified as having a mild form of the disease, 9 moderate, 7 intense and 4 very intense. The average pulmonary artery diameter of patients was 30.0±5.2 mm (21-37 mm), and in patients with a low PMF load, the pulmonary artery diameter was close to normal. As the diameter increased, the load increased, and a significant correlation was found between pulmonary artery diameter and PMF load ($p = 0.01$, $r = 0.883$) (Figure 5a, b).

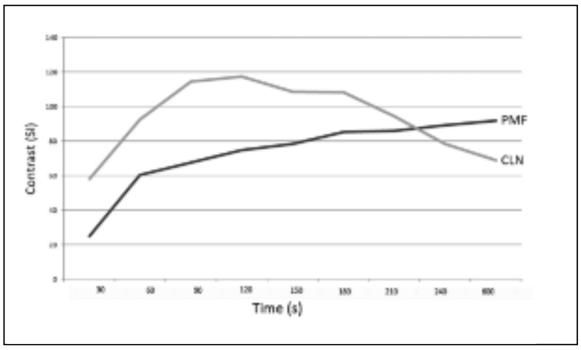

Figure 4: Mean PMF and CLN time-contrast enhancement curve graphics showing the different characteristics of PMF and CLN lesions.

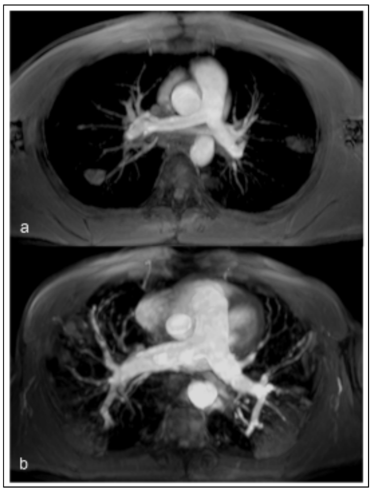

Figure 5: (a) Axial contrast enhanced T1 weighted MIP image showing normal pulmonary artery and branches, and low burden of PMF lesions. Only two small PMF lesions were seen. (b) Axial contrast enhanced T1 weighted MIP image showing an enlarged pulmonary artery and branches with a high burden of PMF lesions. There were several PMF lesions in both lungs.

Discussion

Our study showed that acute and accelerated silicosis, commonly manifesting as PMF, developed in a very young worker population. When imaging PMF, results using MRI were almost identical to those found using CT. PMF was mostly located in the upper lobes of the lungs and DCE-MRI showed gradual contrast enhancement and no washout pattern. Although CLNs were more visible on CT, only intense CLN were visible on MRI. Compared to PMF, CLNs had higher EP and MP values with washout pattern. A higher degree of fibrosis was determined in some PMFs, but there were no difference in their contrast values. Additionally, a higher PMF load was associated with more pulmonary vascular dilatation.

Although the kinetic behaviour of PMF has been examined in a few studies, no specific study has focused on the characteristics of PMFs and CLNs in cases of silicosis due to denim sandblasting. Silicosis is an occupational pulmonary disease that occurs due to the inhalation of silicon dioxide, also known as silica. Silica dust accumulates in the lungs where it reacts with tissues, resulting in fibrosis. Silicosis has three clinical appearances according to the formation process: acute, accelerated and chronic. In cases of high exposure, the disease may have a much earlier onset. For example, due to the level of exposure during denim sandblasting, the disease can develop in a matter of months (acute or accelerated silicosis). In occupations where the exposure rate is lower, or where preventive precautions are taken, it can take much longer to develop (chronic silicosis)[3, 6, 7]. In silicosis, CLN, PMF, fibrosis, inflammation, parenchymal distortion and pulmonary arterial dilatation can all exist together. Since accelerated and acute cases are more frequently seen in denim sandblasting, PMF may occur at earlier stages[2, 7]. This group also shows abundant CLN.

PMF (progressive massive fibrosis), also known as complicated silicosis, results from the expansion and coming together of silicosis nodules[13]. PMF is composed of fibrosis and pigment deposition[14]. It usually involves the apical and posterior segments of the upper lobes and PMF lesions may traverse the interlobar fissures and extend to adjacent lobes[15]. In our cases, the lesions were usually located in the upper and middle lobes, and were less likely to appear in the lower lobes; this is similar to previous findings in the literature. The most noticeable CT feature is mass-like consolidation associated with parenchymal scarring and adjacent bullae[16]. It is rarely possible to distinguish PMF from lung cancer by computed tomography. Although CT has some inherent advantages for the diagnosis of pneumoconiosis, it requires ionizing radiation and the use of iodinated contrast material. From this point of view, pulmonary MRI presents a good alternative modality[17]. MRI can be helpful for distinguishing PMF from lung cancer by both morphological and kinetic patterns[14, 16].

Matsumoto et al. reported that PMF is characteristically of low signal intensity on T1-and T2-weighted images[18]. However, Jung et al. reported that lesions mostly had high signal intensity on T1-weighted images and low or dark signal intensity on T2-weighted images in coal workers. They concluded that the difference in T1-weighted signal intensities of the lesions may result from differences in the amount of mineral dust in the lesions. In all of our cases T1 had a lower signal intensity than that of muscle. Eleven of the lesions in the study were hypointense, 9 isointense and 17 hyperintense on T2 weighted imaging. Jung et al. also reported that the dynamic pattern of PMF showed a gradual increase in signal intensity over three minutes, reaching a plateau at 15 minutes. They claimed that since PMF results in pulmonary veins that have intimal fibrosis and thrombosis, although it is an inflammatory fibrous mass, rapid washout changes do not occur[14]. Our PMF lesions showed an early gradual increase followed by a plateau pattern in the DCE images. Enhancement began with the first contrast enhanced series and reached the MP value in the 8th series. No washout pattern was seen. This was consistent with the findings of Jung et al.[14].

Kauczor et al. stated that areas of PMF in silicosis show marked contrast enhancement (18, 19). Our PMF lesions demonstrated contrast enhancement of between 10% and 227%. As in other fibrotic tissues in the body, these had low EP values and usually reached the MP values in late series, eventually creating plateaus. Some PMFs demonstrated a slight increase in contrast enhancement, as expected, but the average EP was lower than 60%, with MP lower than 100%. These values are contrary to the high EP ratios and washout values reported, especially in malignant pathologies[20]. This feature, along with the lack of radiation exposure, means that MRI may be used in the differential diagnosis of PMF in silicosis with malignant lesions. Hekimoglu et al. reported there were no difficulties in detecting PMFs by the MRI due to their high volume, and the contrast enhanced volume interpolated breath-hold examination sequence was shown to be especially useful in follow-up examinations[17].

In a CT study by Alper et al., CLN were found to be a frequent radiological finding in silicotics, with an appearance rate of 94%. CLN appeared on their own in 30 patients (60%), with tree-in-bud in 2 patients (4%), with perilymphatic nodules in 15 of patients (30%), and randomized in 3 cases (6%)[3]. The visibility of the CLNs on MRI is lower than that of PMFs because of their smaller size; however, contrast enhanced series and reconstruction software (e.g. maximum intensity projection) may increase their visibility. The MRI characteristics of nodules have been investigated in many studies in the literature, but nothing has been mentioned about the DCE characteristics of CLNs seen in silicosis. In our study, these showed a wash-in pattern in earlier phases, EP in some phases, and a washout pattern in later stages, that was not evident in PMFs. Additionally, some CLNs showed prominent EPs, followed by a washout patterns as defined in malignant nodules[20]. The washout patterns seen in CLN graphics are indicative of the absence of fibrosis. Different contrast dynamics are seen in fibrosis that occurs when CLNs increase in number and unite. These findings indicated that, in light of the MRI characteristics, visibility and contrast enhancement found using MRI, this modality may be of limited use in the evaluation of cases that only show CLN.

MRI signal intensities are reported to be useful in the differentiation of fibrosis and inflammation[10]. Values of T1 SI are generally similar in PMF lesions, but there is considerable variability in the T2 SI values. While hypointense T2 SI values may be seen in some cases, making it difficult to differentiate from adjacent lung parenchyma, some cases may be very hyperintense. In this study, quantitative methods were used to differentiate between fibrosis and inflammation. Less contrast enhancement and lower MP values were expected in fibrosis, but surprisingly PMFs were also found that had a low MP for inflammation and high MP for dense fibrosis. Moreover, T2 SI was not shown to affect the contrast dynamics.

Our study also indicated that, in the cases with acute and accelerated silicosis, pulmonary artery diameters were correlated with the aggressiveness of the disease. Thus, this should be taken into account in the radiological evaluation as it may relate to pulmonary hypertension.

A limitation of our study was the small number of patients; however, the PMF and CLN numbers were adequate for statistical analysis. It is not possible to detect calcified lymphadenopathy or parenchymal calcified changes using MRI, but in this study we did not look for calcification. The most common problem when using thoracic MRI is motion artefacts and distortion of the images. This disadvantage was addressed by ECG triggering and using breath-hold sequences in the young patients. Following this, adequate ROI values were obtained by selecting lesions in the multi-window. Micronodules are detected less often on the MRI when compared with CT, but the ones we detected were adequate in number to reflect the contrast dynamics. Another limitation was a lack of comparison with pathology. Interventional procedures may worsen the prognosis, shorten the survival or lead to progression of the disease by means of additional inflammation. That is why we did not perform biopsies on any of the patients.

In patients diagnosed with silicosis, multiple pathologies are seen as CLNs, PMFs and pulmonary artery changes. MRI can give comprehensive morphological information about PMFs and CLNs, allowing for the functional evaluation needed for characterization; it is also possible to measure the diameters of pulmonary arteries. Understanding the contrast dynamics of PMFs and CLNs may be useful in the differentiation of other lung pathologies as well. It is hoped that MRI will become more important in patient management, especially in patients for whom diagnostic procedures and follow-up evaluations are performed frequently.

References

1) Wagner GR. *Asbestosis and silicosis*. Lancet 1997; 349: *1311-15*.

2) Akgun M, Araz O, Akkurt I, et al. *An epidemic of silicosis among former denim sandblasters*. Eur Respir J 2008; 32: *1295-303*.

3v Alper F, Akgun M, Onbas O, Araz O. *CT findings in silicosis due to denim sandblasting*. Eur Radiol 2008; 18: *2739-44*.

4) Gibbs AR. *Occupational lung disease. In: Halsleton PS, editor. Spencer's pathology of the lung*. New York: McGraw Hill; 1996: *461-504*.

5) Bergin CJ, Müller NL, Vedal S, Chan-Yeung M. *CT in silicosis: correlation with plain films and pulmonary function tests*. AJR Am J Roentgenol 1986; 146: *477-83*.

6) Akgun M, Gorguner M, Meral M, et al. *Silicosis caused by sandblasting of jeans in Turkey: a report of two concomitant cases*. J Occup Health 2005; 47: *346-9*.

7) Akgun M, Mirici A, Ucar EY, Kantarci M, Araz O, Gorguner M. *Silicosis in Turkish denim sandblasters*. Occup Med (Lond) 2006; 56: *554-8*.

8) Marchiori E, Ferreira A, Saez F, et al. *Conglomerated masses of silicosis in sandblasters: high-resolution CT findings*. Eur J Radiol 2006; 59: *56-9*.

9) Bakan ND, Özkan G, Çamsari G, et al. *Silicosis in denim sandblasters*. Chest 2011; 140: *1300-4*.

10) Wielpütz M, Kauczor HU. *MRI of the lung: state of the art*. Diagn Interv Radiol 2012; 18: *344-53*.

11) Yi CA, Lee KS, Han J, Chung MP, Chung MJ, Shin KM. *3-T MRI for differentiating inflammation- and fibrosis-predominant lesions of usual and nonspecific interstitial pneumonia: comparison study with pathologic correlation*. AJR Am J Roentgenol 2008; 190: *878-85*.

12) Schaefer JF, Vollmar J, Schick F, et al. S*olitary pulmonary nodules: dynamic contrast-enhanced MR imaging perfusion differences in malignant and benign*

lesions. Radiology 2004; 232: *544-53*.
13) Chong S, Lee KS, Chung MJ, Han J, Kwon OJ, Kim TS. *Pneumoconiosis: comparison of imaging and pathologic findings*. Radiographics 2006; 26: *59-77*.
14) Jung JI, Park SH, Lee JM, Hahn ST, Kim KA. *MR characteristics of progressive massive fibrosis*. J Thorac Imaging 2000; 15: *144-50*.
15) Williams JL, Moller GA. *Solitary mass in the lungs of coal miners*. Am J Roentgenol Radium Ther Nucl Med. 1973; 117: *765-70*.
16) Barreto MM, Rafful PP, Rodrigues RS, et al. *Correlation between computed tomographic and magnetic resonance imaging findings of parenchymal lung diseases*. Eur J Radiol 2013; 82: *492-501*.
17) Hekimoğlu K, Sancak T, Tor M, Beşir H, Kalaycioğlu B, Gündoğdu S. *Fast MRI evaluation of pulmonary progressive massive fibrosis with VIBE and HASTE sequences: comparison with CT*. Diagn Interv Radiol 2010; 16: *30-7*.
18) Matsumoto S, Mori H, Miyake H, Yamada Y, Ueda S, Oga M, et al. *MRI signal characteristics of progressive massive fibrosis in silicosis*. Clin Radiol 1998; 53: *510-14*.
19) Kauczor HU, Kreitner KF. *Contrast-enhanced MRI of the 20- Alper F, Kurt AT, Aydin Y, Ozgokce M, Akgun M. The role of dynamic magnetic resonance imaging in the evaluation of pulmonary nodules and masses*. Med Princ Pract 2013 ;22: *80-6*.

Correspoding author
ADEM KARAMAN MD
Department of Radiology
Ataturk University, Medical Faculty
Erzurum
(Turkey)