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Clinical Research

The Role of Diffusion-Weighted MR Imaging Differentiating Transudative and Exudative Pleural Effusions in Asbestos-Related Pleural Diseases

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ABSTRACT

Objective: The aim of this study was to evaluate the ability of diffusion weighted magnetic resonance imaging (dMRI) in differentiating transudate pleural effusions from exudate pleural effusions with asbestos-related pleural diseases.

Material and Method: This study included 55 patients. Thirty-three had a benign form of the disease and 22 had malignant pleural mesothelioma (MPM). The patient files and records belonging to ones who underwent dMRI on a 1.5 T MR system between January 2015 and February 2016 in our clinic were examined retrospectively. The dMRI was done with b values of 0,500 and 1000 s/mm^2. The apparent diffusion coefficient (ADC) maps were generated and mean ADC values were measured from pleural effusions.

Results: Appropriate ADC maps were obtained in 55 patients. The mean pleural effusion ADC values were $3.61 \pm 0.55 \times 10^{-3}$ mm^2/s in benign pleural disease and $3.12 \pm 0.62 \times 10^{-3}$ mm^2/s in MPM, respectively. The optimum cutoff point for ADC values was 3.43×10^{-3} mm^2/s with a sensitivity of 88.6% and specificity of 84%. The mean ADC value of the effusions in malignant mesothelioma was significantly lower than that of benign pleural disease ($p < 0.05$).

Conclusion: dMRI may help in the differential diagnosis of transudate and exudate pleural effusions that indicate to early detection of MPM with asbestos-related pleural diseases.

Keywords: *Asbestosis, Malignant Mesothelioma, Pleural Effusion, Diffusion-Weighted MR Imaging.*

ÖZET

Asbestos ile İlişkili Plevral Hastalıklarda, Plevral Efüzyonların Transuda ve Eksüda Ayırımını Yapmada, Difüzyon Ağırlıklı MR Görüntülemenin Rolü

Amaç: Bu çalışmanın amacı asbestos ile ilişkili plevral hastalıklarda, plevral efüzyonların transuda ve eksuda ayrımını yapmada, difüzyon ağırlıklı MR görüntülemenin (dMRG) rolünü değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 33' ü benign form ve 22' si malign plevral mezotelyomalı olmak üzere 55 hasta dahil edildi. Kliniğimizde Ocak 2015 ve Şubat 2016 yılları arasında, 1.5 T MR ile dMRG incelemesi yapılan hasta dosyaları, retrospektif olarak incelendi. Difüzyon MR b değerleri 0,500, ve 1000 s/mm^2 idi. Görünür Difüzyon Kat Sayısı (ADC) haritaları oluşturuldu. Plevral efüzyonlardan ortalama ADC değerleri ölçüldü.

Bulgular: Ellibeş hastanın uygun ADC haritaları elde edildi. Benign plevral hastalıklı olgularda ortalama plevral efüzyon ADC değerleri; $3.61 \pm 0.55 \times 10^{-3}$ mm^2/s, malign plevral mezotelyomalı (MPM) olgularda, ortalama plevral efüzyon ADC değerleri; $3.12 \pm 0.62 \times 10^{-3}$ mm^2/s ölçüldü. ADC değerlerinin optimum cut-off değeri; 3.43×10^{-3} mm^2/s, sensitivite %88.6 ve spesifite %84 bulundu. MPM li olgularda plevral efüzyon ortalama ADC değeri, benign plevral hastalıklı olgulardaki plevral efüzyon ortalama ADC değerinden anlamlı olarak düşük bulundu ($p < 0.05$).

Sonuç: dMRG, asbestos ile ilişkili hastalıklarda plevral efüzyonların transuda ve eksuda ayırımını yapmada yardımcı olarak, MPM nin erken teşhis edilmesini sağlayabilir.

Anahtar Sözcükler: *Asbestoz, Malign Mezotelyoma, Plevral Efüzyon, Difüzyon Ağırlıklı MR Görüntüleme.*

Asbestos affects many people in the world. Pleural effusions, pleural plaques, diffuse pleural thickening, asbestosis, malignant mesothelioma (MPM) are some thoracic diseases caused by asbestos. Asbestos is the most common cause of MPM. In asbestos-related pleural diseases, pleural effusions are often encountered as a clinical finding, and they form the most widespread example for cytological assessment. Pleural effusions are separated into two, which are transudates and exudates. The true diagnosis of effusions is critical for patient management. Making a distinction between transudates and exudates is important because in case that fluid is transudate, then the treatment process is carried out in underlying pathology without any further diagnostic procedures; however, if the effusion is an exudate, then this time a wide diagnostic investigation is needed. The effusions due to MPM are always exudates. It is advised that MPM is taken into consideration with either pleural fluid or pleural thickening, particularly when the patient has a chest pain. For MPM, pleural fluid cytology and histology of blind biopsy examples provide a low yield, but they are critical first steps for differential diagnosis. For a true diagnosis, histopathological examination is needed, and it is advised that a diagnosis of MPM should always be based on an immuno-histochemical examination (1).

To characterize lung cancer, lymph nodes and pulmonary metastases in chest imaging, dMRI is suggested (2). The extent of tissue cellularity and the presence of unharmed cell membranes provide help in determining

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the rate of water molecule diffusion. Tumor, cytotoxic edema, and abscess tissue types are said to be related to impeded diffusion. Tissues with low cellularity or the ones consisting of cells with disrupted membranes allow greater movement of water molecules (3).
The number of studies on pleural fluids with dMRI is a few. dMRI is identified as an effective non-invasive imaging technique in making a distinction between serous fluids and purulent fluids. As an alternative to the thoracentesis, the use of diffusion gradients to examine pleural fluid can be a way (4, 5).
In this study, we evaluated the contribution of dMRI in the differentiation of transudate/exudate pleural effusions with asbestos-related pleural diseases. dMRI yields both qualitative and quantitative information about the content of effusions, that can be helpful for early detection of MPM.

MATERIAL AND METHOD

Patients

This study included 55 patients. Thirty-three had a benign form of the disease and 22 had MPM. The mean age of the patients was 51 years±11.8 (standard deviation; range, 21-68 years). The mean age of the patients with benign group was 33±11.7 (standard deviation; range, 21-45 years), and that of patients with MPM was 44.1±9.6 (standard deviation; range, 37-66 years).
After clinical research ethics board approval received, the patient files and records belonging to ones who underwent dMRI on a 1.5 T MR system between January 2015 and February 2016 in our clinic were examined retrospectively. The dMRI was done with b values of 0,500, and 1000 s/mm^2. The apparent diffusion coefficient (ADC) maps were generated and mean ADC values were measured from pleural effusions. Patients with at least 2 cm pleural fluid thickness were included to study. Patients with little pleural effusions were excluded so that avoiding from partial volume effects. Fine needle aspiration and cytological analysis of pleural fluid had been examined.

Diffusion-Weighted Imaging

All dMRI examinations were performed using a 1.5 T superconducting unit (Magnetom Symphony; Siemens Medical Solutions, Erlangen, Germany) with a body phased-array coil. All patients were examined in the supine position throughout the examination. Cardiac gating and respiratory compensation techniques were routinely used. Transverse diffusion-weighted images were obtained using a single-shot echo-planar imaging sequence (5000/139 ms TR/ TE, 6 mm slice thickness, 2 mm slice interval, 350 x 350 mm FOV, and 256 x 512 matrix) with 0,500, and 1000 s/mm^2 b values. The diffusion gradient was applied sequentially in the three orthogonal directions. MRI, including DWI, consisted of a multi section acquisition with a slice thickness of 6 mm, an intersection gap of 1 mm, and an acquisition matrix of 128 x 256. The field of view varied between 455 and 500 mm. All sequences were acquired using a partially parallel imaging acquisition and SENSE reconstruction. The scan time of the acquisition of each DWI series during a single breath-hold was 25 seconds. ADC maps were reconstructed. Scan time was <2 min.

Image Analysis, Quantitative Assessment of ADC

Measurement of ADC was made using regions of interest (ROI) on the ADC map. ADC measurements were performed on a personal computer with OsiriX MD software (v.6.5). Three circular regions of interests with diameter of 1.0 cm each were located to pleural fluid. The ADC values were expressed as 10^{-3} mm^2/s. Then the mean ADC values of the effusion were noted. ROIs were placed into pleural fluid avoiding from pleural thickening. Neither radiologist was given any information about the histological results.
Pleural effusions were classified into transudates or exudates according to the clinical criteria and histological results (6).

Statistical Analysis

The statistical analysis of the data was done using SPSS for Windows software, version 10.0 (SPSS, Chicago, IL). The parameters were described using their mean and standard deviation. The mean ADC values of pleural effusions with benign pleural thickening and MPM were compared using unpaired two- tailed Student's *t*-tests. $p < 0.05$ was considered statistically significant. To define the performance of ADC values in the diagnostic separation of transudates and exudates, receiver operating curve (ROC) was used. The area under the curve with 95% confidence intervals was calculated. The Pearson's correlation test was used to define the correlation between the ADC values.

RESULTS

Appropriate ADC maps were obtained in all 55 patients. 5 patients' fluids (15,2%) were exudative and the remaining 28 patients' fluids (84,8%) were transudate in benign pleural disease group. Congestive heart failure was the common cause for a transudate pleural effusion and the causes of exudative effusions were inflammation-pneumonia. At the same time 22 patients' fluids (100 %) were exudative in MPM group. The mean ADC values in benign pleural effusions were $3.61 \pm 0.55 \times 10^{-3}$ mm^2/s and the corresponding values in MPM were $3.12 \pm 0.62 \times 10^{-3}$ mm^2/s (Figure 1-2).
The mean ADC values of the effusion in MPM group were lower than that of benign pleural disease ($P < 0.05$). The mean ADC values are shown in the Table 1. The optimum cutoff point for ADC values was 3.43×10^{-3} mm^2/s with a sensitivity of 88.6 % and specificity of 84 %.

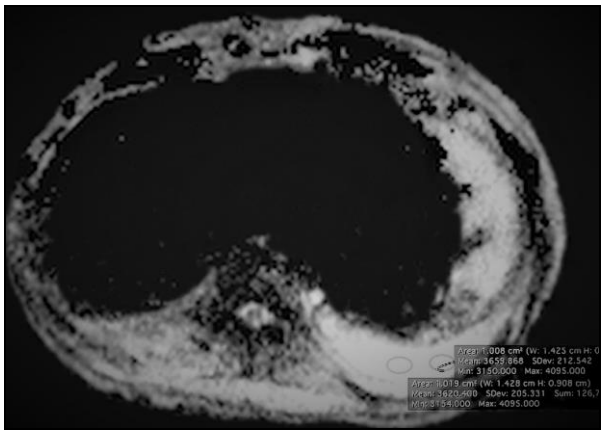

Figure 1. *Measurement of ADC was made using ROI on the ADC map from left transudative pleural effusion. ADC was measured 3.62 ± 0.55 x 10^{-3} mm^2/s.*

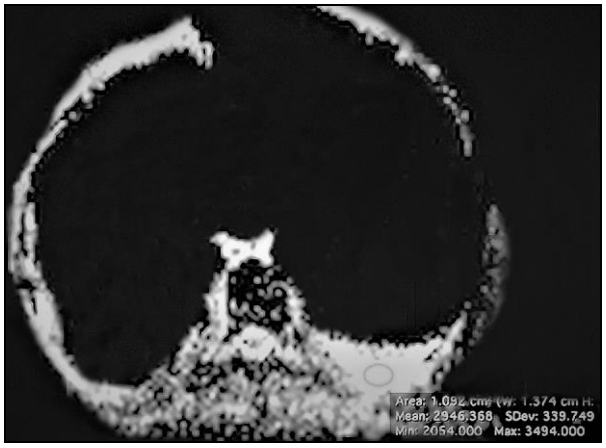

Figure 2. *Measurement of ADC was made using ROI on the ADC map from left exudative pleural effusion. ADC was measured 2.94 ± 0.62 x 10^{-3} mm^2/s.*

The positive and negative predictive value, diagnostic accuracy were determined to be 64, 67, 66 %, respectively.

Table 1. *Mean ADC value of pleural effusions.*

Cytology	No of patients	Mean ADC value
Transudate effusions	33	3.61±0.50 (p =0.01)
Exudate effusions	22	3.12±0.62 (p =0.01)

Data are mean ± S.D, ADC value (10^{-3} mm^2/s)
The optimum cutoff point for ADC values was 3.43 x 10^{-3} mm^2/s
The PPV, NPV, DA were 64, 67, 66%, respectively.

DISCUSSION

Pleural effusion is a widespread clinical problem and it can arise from various diseases. In United States in a year, 1.5 million people are affected by pleural effusions (7). The first step in assessing it is to decide if the pleural fluid is a transudate or exudate. In patients who have a systemic disease, serous (transudate) effusion is a common finding. This case can also indicate a local disorder. The majority of the clinically recognized effusions in adults and children are related to reactive conditions (8). In systemic disorders, Involvement of more than one cavity is common. Exudative effusions usually happen because of inflammation, either regional or systemic and malignant neoplasms. Nearly all of the effusions because of cancer are exudates. Hemorrhagic effusions are generally related to malignancy, but just around 11% of malignant effusions are bloody (9). Trauma, infections and infarcts are benign causes of hemorrhagic effusions (10). While unilateral pleural effusions reflect regional pathologies like pneumonias, bilateral pleural effusions usually occur in systemic diseases.

Via imaging techniques, we can assess the amount, distribution, accessibility of a pleural effusion, as well as possible thoracic pathologies. In order to assess the pleura and the pleural space, several imaging techniques can be employed. Ultrasonography (US) let us specify pleural fluid easily, and make a distinction between pleural masses (11). In making distinction between pleural effusions, multidetector computed tomography (MDCT) has been used in specifying pleural fluid depending on attenuation values (12, 13). The clinical using of the MDCT attenuation in specifying pleural fluid is not suggested due to the overlapping the Hounsfield Unit (HU) values, even though the mean attenuation of exudates was critically higher than transudates. While assessing pleural diseases and effusions, US, MDCT, and magnetic resonance imaging (MRI) use as a supporting radiological modalities. In MRI, T1W and T2W signal intensity (SI) of effusions depended on the concentration of protein, while this signal depended chiefly on the concentration of blood on gradient echo images. MRI examination could be useful in making distinction between an exudative or hemorrhagic effusion and a serous one. Yet, the values belonging to these two groups overlapped, differentiation depending on only SI was not usually sufficient (14).

The use of dMRI to assess extra cranial diseases is increasingly used. So as to evaluate cancer patients, utilizing dMRI is getting popular. It is not require using contrast agents. The aforementioned techniques can also be utilized as well as the other ones, and this does not make an important change in examination duration. Moreover, not only qualitative, but also quantitative information can be obtained via dMRI, and this can be useful for tumor assessment (15).

The use of fast imaging techniques along with parallel imaging techniques have provided the chance to incorporate dMRI into chest MRI, and this process makes no image degradation caused by motion artefacts. Through dMRI, it is possible to see microscopic movements of water molecules in tissues. This movement is called Brownian motion and it is because of thermal agitation. By the way, cellular environment of water, intracellular organelles and macromolecules affect this movement. Water molecules face different restrictions and impediments, while they move inside of tissues. So, concerning gross anatomy, dMRI provides a functional assessment of microstructure. The flow of water movements causes phase dispersion, and this process result

to signal intensity loss. This signal intensity loss can be quantified by calculating the ADC. By changing the b-value which depends in a particular mathematical way on the diffusion encoding gradient waveforms, it is possible to vary the sensitivity of the imaging sequence to water diffusion (16). This b-value grows with the square of the gradient amplitude, the square of the gradient diffusion length, and approximately with the time between the two pulses. In order to observe cellular structures, we can utilize dMRI. Because of high cell density, proliferation and cell swelling in the tissue, low ADC in organic systems is regarded to mirror reduced mean-squared displacement of water molecules. When compared to normal tissue, malignant tumors are labelled with increased cellularity, larger nuclei and more abundant macromolecular proteins, a larger nuclear/cytoplasm ratio with less extracellular space. Due to these reasons, the diffusion of water molecules in malignant tumors is restricted, and this case ends in decreased ADC (2, 17).

Some limitations like physiologic motion artefact caused by respiration and cardiac motion make it hard to use dMRI in the thorax. Employing breath-hold and pulse-triggered sequences can cut down the effects of respiration and cardiac motion. The best image was captured with breath-hold SS-SE-EPI sequences, due to the rapid acquisition capabilities and high signal-to-noise ratio (18, 19). We assessed trace images (b factors of 0,500 and 1000) and ADC maps quantitatively and qualitatively in our study. Critical differences between the SI of pleural effusions were discovered on images with b factors of 0,500 and 1000 s/mm^2. SI of exudative effusion was higher than transudate effusion with b factors of 0,500 and 1000. The mean ADC values of the effusion in MPM were significantly lower than that of benign pleural disease.

It is generally very important to determine if a patient has a transudate or exudative pleural effusion especially with asbestos-related pleural diseases. Because of the effusions due to malignant pleural mesothelioma are always exudates. The identification of a pleural effusion with low diffusion should suggest the radiologist to search for additional signs of exudates. Meanwhile, an effusion with increased diffusion is an indicator of a transudate. It is may be possible to diagnose pleural effusions via specific morphologic features (thickening-nodularity of pleura, internal structure or calcification), laboratory evaluation, and clinical information. It is advised that thoracentesis be applied.

A variety of imaging techniques can be used to evaluate the pleura and the pleural space. But still it is difficult to differentiate between malign and benign nature. Since Para pneumonic effusions, malignant effusions, and tuberculous pleuritis have proteinaceous fluid and rich cell counts (inflammatory cells, tumor cells, and lymphocytes), with these fluid collections have a decreased ADC. In this case, it may be impossible to diagnose with dMRI also. At the same time, dMRI has some advantages, for example; it is a totally non-invasive method, and in this method it is not require exposed to ionizing radiation. Moreover, administration of contrast media in not needed, and the patients feel no discomfort.

This study has a number of limitations. It is quite difficult to avoid the susceptibility artefacts on dMRI of pulmonary lesions. We faced image distortion arising from artefacts associated with echo-planar imaging sequences and macroscopic movement, even though we employed a phased-array coil with cardiac gating and respiratory compensation techniques to improve image quality and speed. The causes of exudative effusions can be related with inflammation and pneumonia. In this case, having asbestos-related pleural diseases, the patient must be evaluated other clinical findings.

Conclusion

Our preliminary data suggest that dMRI may be helpful in differential diagnosis of benign or malignant pleural effusions with asbestos-related pleural diseases. In daily practice, this sequence can easily be added to routine thorax dMRI give clues to the radiologist for interpretation of pleural effusions about benign or malignant that indicates to early detection of MPM.

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