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CAN DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING DIFFERENTIATE BETWEEN INFLAMMATORY-INFECTIOUS AND MALIGNANT PLEURAL EFFUSIONS?

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Aim: **To assess exudative pleural effusions with diffusion-weighted magnetic resonance imaging (DW-MRI) in order to determine non-invasive differentiation criteria for inflammatory-infectious and malignant effusions.**
Materials and methods: **Thirty-two patients with pleural effusions underwent DW-MRI with 4 different *b* values (10, 500, 750 and 1000 s/mm^2). ADC maps were generated automatically. Signal intensity and ADC values were measured. Following MRI, pleural fluid of 10-15 ml was obtained and analyzed. AUC values were compared for different diffusion levels of ADC and SI measurements. The relationship between ADC values and pleural effusion LDH and total protein levels was examined.**
Results: **The cut-off values obtained from signal intensity and ADC measurements to differentiate exudates with malignant pathology were not found to be statistically significant. In the inflammatory-infectious group, a significant negative correlation was observed between ADC values and pleural fluid LDH measurements in all *b* values. In the malignant group, a significant positive correlation was observed between ADC values and pleural fluid total protein measurements in *b* values of 500 and 1000.**
Conclusion: **Infectious/inflammatory and malignant effusions overlap strongly and cannot therefore be differentiated using DW MRI.**

Key-words: Lung, effusion – Lung, MR – Magnetic resonance (MR), diffusion study.

Pleural effusions are usually diagnosed on the basis of clinical, radiological and pathological findings. The main types of pleural effusions are defined as transudate and exudate according to their biochemical features, mostly separated by Light's criteria (measurement of lactate dehydrogenase (LDH) and protein concentrations in both pleural fluid and serum) (1). However, transudate and exudate classification of pleural effusions with Light's criteria can occasionally fail, especially in cases that have undergone diuresis (2, 3). If the pleural effusion is definitely identified as a transudate, no further diagnostic procedures are needed (1, 4). If it is found to be an exudate, additional diagnostic procedures such as pleural fluid cytopathology, Gram staining, culture, etc. are necessary (2, 5). Differentiation of transudate and exudate before thoracentesis therefore becomes mandatory in order to avoid unnecessary interventional procedures and their potential complications.

Exudative effusions can have benign (bacterial pneumonia, viral infection, pulmonary embolism, etc.) and malignant (lung cancer, breast cancer, lymphoma, etc.) causes. We believe that there is a need for an alternative non-invasive diagnostic method for inflammatory-infectious and malignant differentiation of exudative pleural effusions.

In this study, we aimed to assess exudative pleural effusions with diffusion-weighted magnetic resonance imaging (DW-MRI) in order to determine differentiation criteria for inflammatory-infectious and malignant processes.

Materials and methods

This prospective study was approved by the institutional review board and written informed consent was provided by all subjects.

A total of 43 patients who presented to Canakkale Onsekiz Mart University Research and Application Hospital between January 2011 and December 2012 with various symptoms and in whom the chest x-ray, ultrasound (US) and computed tomography (CT) examinations revealed pleural effusion were included in the study. The study inclusion and exclusion criteria were as follows:

1. The amount of pleural effusions had to be adequate for accurate measurement of apparent diffusion coefficient (ADC) without being affected by the partial volume effect and motion artifact. The thickness of the pleural effusions detected on chest x-ray was evaluated by US. The thickness of the pleural effusions detected on CT examination was measured. Pleural effusions less than 1 cm in thickness were excluded from the study.
2. Cases where pleural effusion aspiration and analysis were planned were included in the study.
3. Cases who were severely dyspneic, and would not be able to lie in the supine position during the entire diffusion-weighted imaging (DWI) examination or had claustrophobia were excluded from the study.

All patients were examined with a 1.5 T MRI scanner (GE Signa, HDxt). The maximum gradient power of this system was 30 mT/m and the slew rate was 150 mT/m/msec. T1- and T2-weighted conventional images on the axial plane were obtained to evaluate the anatomical detail better and to determine the pleural effusion localization and signal characteristics. Subsequently, 4 series of single-shot spin-echo echo-planar (SS-SE-EPI) diffusion-weighted (DW) images (TR 4050 ms, TE 78.2 ms, field of view 38 × 30.4 cm^2, matrix size 128 × 160, slice thickness 8 mm, interslice gap 2 mm) were obtained using 4 different *b* values (10, 500, 750 and 1000 s/mm^2) on the axial plane.

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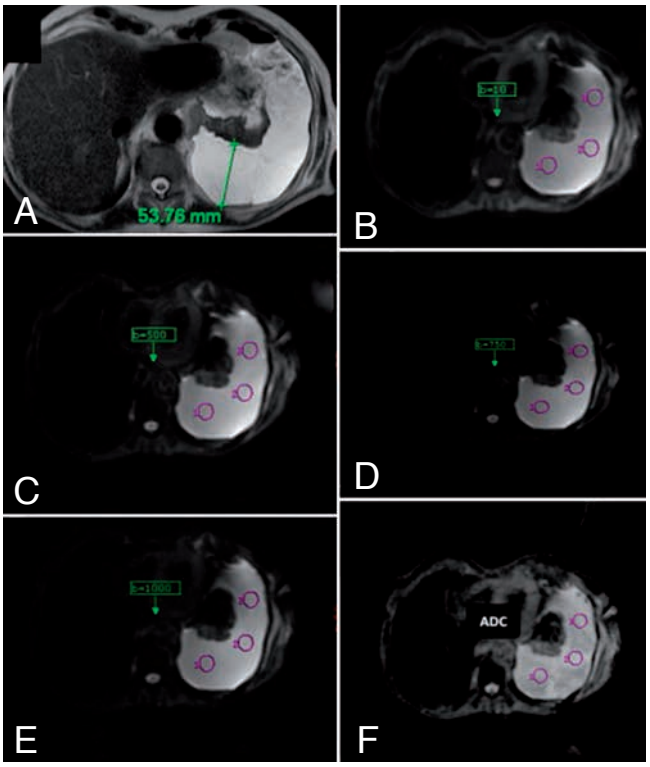

Fig. 1. — A fifty-six year old male diagnosed with parapneumonic effusion. Axial T2W image shows a 53 mm wide left pleural effusion with high signal intensity (A). Three different ROI placement for SI measurement on DW images obtained with a *b*-value of 10 (B), 500 (C), 750 (D) and 1000 (E) and ADC measurement on corresponding ADC map (F) are shown.

Unidirectional diffusion gradients (readout direction; right-left, R-L) were applied. ADC maps were generated automatically from the DW images obtained.

Quantitative analyses were performed on a dedicated workstation (General Electric, Advantage workstation, 4.4 edition). An average of 203 mm^2 elliptical or spherical regions of interest (ROI) were placed in 3 different locations of the pleural effusion in order to measure signal intensity values (SI) on DW images and the ADC values on ADC maps (Fig. 1). Both values were averaged separately and the resulting values were considered the final quantitative values. ROI of the same dimensions was used for each *b* factor. In order not to be affected from possible magnetic susceptibility and motion artifacts, we stayed away from the lung-pleural fluid sections, diaphragmatic areas and the regions where the heart and major vascular structures were present during ROI placement and measurement, placing the ROI's at the most homogeneous segments possible of the pleural effusions.

Thoracentesis was performed by a thoracic surgeon after MRI. Pleural fluid of 10-15 ml was obtained and analyzed. The pleural fluid was primarily classified as transudate or exudate according to Light's criteria (6). The pleural fluid sample was then microbiologically and pathologically analyzed. Whether the fluid was of benign or malignant origin was determined.

Statistics

Data was presented as median (minimum-maximum) values. ROC (receiver operating characteristic) analysis was used for obtaining cut-off values for inflammatory-infectious/malignant differentiation and comparing the AUC (Area under the curve) values for different diffusion levels of ADC and SI measurements. The relationship between ADC values and pleural effusion LDH and total protein levels was examined by performing correlation analysis and Spearman correlation coefficient was computed. The minimum sample size required for each group was determined at least n = 30 (desired statistical power: 0.80). Statistical significance was set at $p < 0.05$. MedCalc v.12.7.5.0 were used for statistical analyses.

Results

Seven patients could not keep still during MR imaging and the obtained images were of poor quality, so they were excluded from the study. Of the remaining 36 patients, 4 patients who were found to have transudative pleural effusions were also excluded. Finally we included 6 females and 26 males for a total of 32 patients. The median age was 63 (min: 26, max: 88) years. The causes for exudative pleural effusion are given in table I.

We evaluated DWI in terms of inflammatory-infectious/malignant differentiation of exudative pleural effusions and found that the SI and ADC values measured with different *b* values were not appropriate for inflammatory-infectious/malignant differentiation of the exudates. After ROC Analysis, the cut-off values obtained from SI and ADC measurements to differentiate exudates with malignant pathology were not found to be statistically significant. No difference was found between ROC curves obtained with different *b* values for SI and ADC. There was no significant difference between the AUC in the analyses performed for each *b* value. The p value was > 0.05 for all analyses in both tables (Table II).

When inflammatory-infectious and malignant groups are analysed separately, in the former group, a significant negative correlation was observed between ADC values and pleural fluid LDH measurements in all *b* values of 10 ($r = -0.46$, $p = 0.021$), 500 ($r = -0.76$, $p < 0.001$), 750 ($r = -0.70$, $p < 0.001$), and 1000 ($r = -0.59$, $p = 0.002$) (Fig. 2) and no statistically significant correlation was found between ADC values and pleural fluid total protein measurements.

In the malignant group, a significant positive correlation was observed between ADC values and pleural fluid total protein measurements in *b* values of 500 ($r = 0.67$, $p = 0.012$) and 750 ($r = 0.73$, $p = 0.005$) (Fig. 3) and no statistically significant correlation was found between ADC values and pleural fluid LDH measurements. The correlation analysis results of ADC values with LDH and total protein levels of pleural effusion in both groups are given in table III.

Table I. — Causes of pleural effusions.

Etiology	
Benign (n = 19)	
Parapneumonic effusion	12
Empyema	4
Tuberculosis	1
Sarcoidosis	1
Ruptured hydatid cyst	1
Malignant (n = 13)	
Non-small cell lung carcinoma	3
Small cell lung carcinoma	2
Adenocarcinoma	2
Malignant mesothelioma	2
Deciduoid mesothelioma	1
Breast carcinoma metastasis	1
Non-specific primary	2
Total	n = 32

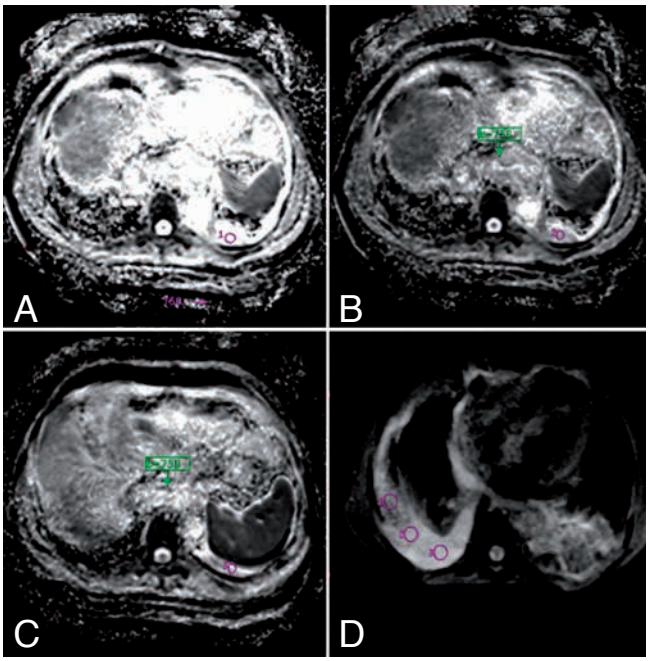

Fig. 2. — Fifty-five (A, B and C) and seventy-four (D) year old male patients diagnosed with empyema. The former patient who has higher pleural effusion LDH level (2388 U/L), demonstrates lower ADC measurement (0.002757) compared with the latter patient who has a LDH level of 151 U/L and mean ADC measurement of 0.004057.

Table II. — ROC analysis results of SI and ADC values calculated for each b factor for differentiation of inflammatory-infectious / malignant exudative pleural effusions.

SI	AUC	SE	p-value
b = 10	0.60	0.11	0.319
b = 500	0.55	0.10	0.625
b = 750	0.54	0.10	0.710
b = 1000	0.54	0.10	0.712
Comparison of ROC curves between b factor levels			
	DBA	SE	p-value
b = 10-*b* = 500	0.06	0.10	0.580
b = 10-*b* = 750	0.07	0.11	0.530
b = 10-*b* = 1000	0.07	0.11	0.534
b = 500-*b* = 750	0.01	0.05	0.812
b = 500-*b* = 1000	0.01	0.04	0.800
b = 750-*b* = 1000	0	0.02	1.00
ADC	AUC	SE	p-value
b = 10	0.65	0.10	0.131
b = 500	0.55	0.11	0.667
b = 750	0.55	0.11	0.675
Comparison of ROC curves between b factor levels			
	DBA	SE	p-value
b = 10-*b* = 500	0.10	0.13	0.425
b = 10-*b* = 750	0.10	0.13	0.411
b = 10-*b* = 1000	0.05	0.15	0.729
b = 500-*b* = 750	0.01	0.07	0.977
b = 500-*b* = 1000	0.05	0.11	0.662
b = 750-*b* = 1000	0.05	0.09	0.577

AUC: Area under ROC curve, DBA: Difference between ROC areas.

Table III. — The correlation analysis between ADC values and pleural fluid LDH and total protein levels in all *b* values.

ADC value		Benign					Malignant			
		b = 10	*b* = 500	*b* = 750	*b* = 1000		*b* = 10	*b* = 500	*b* = 750	*b* = 1000
LDH U/L	r	-0,46	-0,76	-0,70	-0,59	r	-0,02	-0,21	-0,25	-0,34
	p	0,021*	<0,001*	<0,001*	0,002*	p	0,943	0,494	0,409	0,263
TOTAL PROTEIN	r	-0,05	-0,09	-0,13	0,13	r	0,13	0,67	0,73	0,28
	p	0,817	0,678	0,532	0,551	p	0,674	0,012*	0,005*	0,353

*Significant correlation.

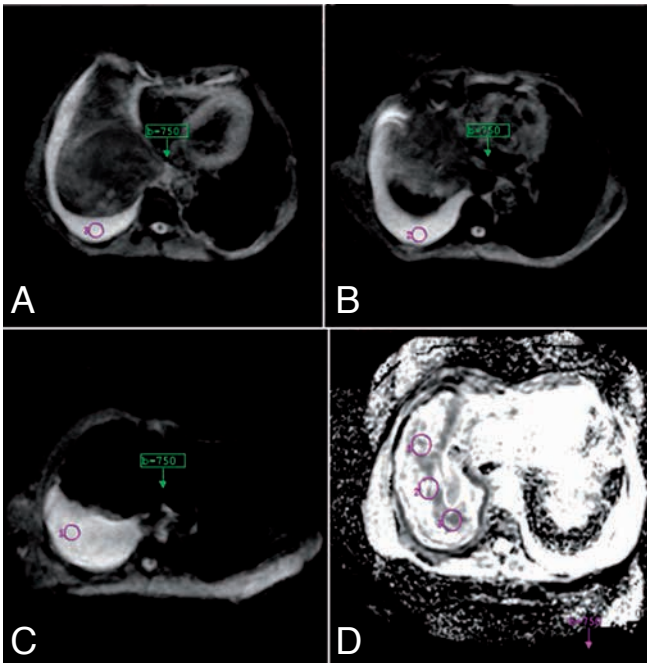

Fig. 3. — Fifty-nine (A, B and C) and seventy-nine (D) year-old male patients diagnosed with non-small cell lung carcinoma. The former patient who has higher pleural effusion total protein level (7 gr/dl), demonstrates higher ADC measurement (0.004913) compared with the latter patient who has a total protein level of 2.5 gr/dl and mean ADC measurement of 0.00197.

Discussion

DWI is an MR imaging method providing tissue analysis based on the diffusion of water molecules inside the tissue (7). Carr and Purcell were the first to report that the MRI signal is affected by the diffusion of water molecules in 1954 (8). DWI was first used to determine acute cerebral ischemia and then in other body regions in recent years thanks to developing technologies (7, 9, 10). A high image quality could not be obtained in areas outside the brain in the first studies conducted with DWI and the ADC quantification was not very successful. These problems have later been overcome by the introduction of stronger gradient fields, parallel imaging techniques and phased-array coils (9, 10). However, application to thoracic imaging is still difficult since DWI is very sensitive to artifacts (7).

Stimulated-echo and SE pulse sequences that require a very long acquisition time and are therefore very sensitive to motion artifacts were used in the first DWI applications (11). Today, SS-SE-EPI sequence that is not markedly affected by motion artifacts is used (7).

The differentiation of whether the effusion is a transudate or exudate has been mainly attempted in studies on the detection of the nature of the pleural effusion by DWI (1, 2). When DWI was applied with the appropriate *b* values, the ADC values were found to be significantly lower in exudative pleural effusions than the transudative ones. The reason was thought to be the high proteinaceous and cellular content of pleural fluid in exudative effusions leading to a decrease in ADC values. DWI was performed with $b = 0$ s/mm^2 and $b = 1000$ s/mm^2 values and the mean ADC values were calculated as $3.42 \pm 0.76 \times 10^{-3}$ mm^2/s and $3.18 \pm 1.82 \times 10^{-3}$ mm^2/s in transudative and exudative effusions by Baysal et al. (1). DWI was performed with $b = 0$ s/mm^2, $b = 500$ s/mm^2 and $b = 1000$ s/mm^2 values and the ADC cut-off value was found to be 3.6×10^{-3} mm^2/s for the transudative/exudative pleural effusion differentiation with DWI by Inan et al. (2).

We aimed to perform the inflammatory-infectious/malignant differentiation of exudative pleural effusion with DWI in our study. Our main objective was therefore different from the two previous studies. The SI and ADC measurements we conducted by using 4 different *b* values ($b = 10$, 500, 750 and 1000) did not lead to statistically significant results for inflammatory-infectious/malignant differentiation in exudates.

In the inflammatory-infectious group, a significant negative correlation was observed between ADC values and pleural fluid LDH measurements in all *b* values. This result was in accordance with Baysal et al's study supporting the higher the viscosity of the pleural fluid, the smaller is the diffusion (1). On the other hand, in the malignant group, a significant positive correlation was observed between ADC values and pleural fluid total protein measurements in *b* values of 500 and 1000. This result can be explained by decrease in serum protein levels relative to pleural fluid (hypoalbuminemia). Due to this relative decrease of proteins, an increase in diffusion of water molecules may develop leading to increase in ADC values (1).

In another study, Coolen et al. investigated combination of DWI and dynamic contrast enhanced MRI

(DCE-MRI) for differentiation of benign and malignant lesions of pleura. They made the ADC measurements of the pleural lesions taking care to exclude necrotic areas and considering the most solid parts for ROI placement. Similar to Baysal et al's and Inan et al's study, they calculated ADC values of malignant pleural diseases significantly lower than benign lesions (1.40×10^{-3} mm^2/s ± 0.33 and 2.49×10^{-3} mm^2/s ± 0.81, respectively). They stated that this result was most likely because of hypercellularity and hypervascularity of malignant lesions causing diffusion restriction. They concluded that DWI can differentiate malignant pleural diseases from benign lesions with high accuracy especially with the combination of DCE-MRI. They also concluded that by using a purely ADC-based diagnosis, false-negative diagnoses may occur mostly due to necrotic and inflammatory area within the tumor (12).

In our study, we aimed to assess only the pleural effusions with DWI and we disregarded the solid parts of the malignant pleural lesions in order to make a truer comparison between the ADC values of inflammatory-infectious and malignant effusions. Because we were not be able to assess the cellularity of the effusions due to technical limitations, we could not give support to Coolen et al. (12) regarding their assumption about the higher the cellularity of the lesion, the smaller is the diffusion.

The main limitation in our study was the inadequate number of cases. We believe that much larger number of patients should be included in the study to perform inflammatory-infectious/malignant differentiation of the exudative qualified effusions with DWI first and then to perform subgrouping within the malignant processes afterwards, and that perhaps more statistically significant results can be obtained with a large case series. Another limitation was our application of unidirectional diffusion gradient in DWI. The patients in our study had marked pleural effusions and therefore many suffered respiratory distress, especially in the supine position. We tried to keep the examination short by applying a unidirectional diffusion gradient in order to avoid respiratory distress and to ensure that patients could stay motionless during the examination so that we could obtain better image quality. However, at least three orthogonal directions should be used in DWI imaging. Molecular diffusion is a tridirectional process and diffusion can be anisotropic as in the cerebral white matter (13). We believe that data obtained by applying tridirectional diffusion gradient will provide statistically healthier results. Another limitation was that the DW images we obtained with the EPI sequence had low signal-to-noise ratio especially when a high *b* value was used and this caused image distortion. In addition, the EPI sequence can also cause anatomic distortion with its susceptibility effect (14). We did not perform pulse-triggered DWI in our study. Mürtz et al used the SS-SE-EPI sequence with ECG triggering in their study to avoid the negative effect of cardiac pulsation and emphasized that the accuracy of ADC measurements was reduced in DWI without pulse-triggering (15). We believe that the ADC values obtained by DWI using the pulse-triggering technique will provide more accurate results.

Conclusion

DWI did not provide sufficiently accurate results in inflammatory-infectious/malignant differentiation of the exudative effusions in our study. Prospective studies with larger series are required to support the efficacy of DWI which can be performed within a short time and also can easily be added to routine thoracic MRI examination for transudate/exudate differentiation of pleural fluids and inflammatory-infectious/malignant differentiation of exudates.

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