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Diffusion weighted Image MRI in Assessment of Patients with Multiple Myeloma

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ABSTRACT

Background: Recent developments in diagnostic imaging techniques have magnified the role and potential of MRI in patients with multiple myeloma. Quantitative diffusion-weighted imaging of the bone marrow is adjunct tool for the diagnosis of a diffuse MR imaging pattern in patients with multiple myeloma.

Aim of the Work: This study aimed to evaluate the apparent diffusion coefficients (ADCs) of magnetic resonance (MR) imaging patterns in the bone marrow of patients with multiple myeloma (MM) and to determine a threshold ADC that may help distinguish a diffuse from a normal pattern with high accuracy

Patients and Methods: This study was carried out in Radiology Department of Ain Shams University Hospitals. This study included 30 patients newly diagnosed, untreated MM and 16 healthy control subjects underwent spinal MR imaging including diffusion-weighted imaging, and bone marrow ADCs were calculated. Pattern assignment was based on visual assessment of conventional MR images.

Results: Mean ADCs 6 standard deviation in patients with MM for the normal, focal, and diffuse MR imaging patterns were 0.360 x 10-3 mm2/sec +/- 0.110, 1.046 x 10-3 mm2/sec +/- 0.232, and 0.770 x 10-3 mm2/sec +/- 0.135, respectively. There were significant differences in ADCs between diffuse and normal (P .001), diffuse and focal (P.001), and focal and normal (P.001) patterns. Patients with a diffuse pattern had more features of advanced disease, higher international staging system score, increased incidence of high-risk cytogenetics, and higher revised international staging system score. ADCs greater than 0.548 x 10-3 mm2/sec showed 100% sensitivity (9 of 9) and 98% specificity (10 of 11) for the diagnosis of a diffuse (vs normal) MR imaging pattern, whereas an ADC greater than 0.597 x 10-3 mm2/sec showed 100% sensitivity (9 of 9) and 100% specificity.

Conclusion: ADCs of MR imaging patterns in patients with MM differ significantly. A diffuse MR imaging pattern can be distinguished more objectively from a normal MR imaging pattern by adding quantitative diffusion-weighted imaging to standard MR imaging protocols.

Keywords: Multiple Myeloma, DW MRI.

INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal plasma cells in the bone marrow and/or in extramedullary sites, urinary and/or serum monoclonal immunoglobulin, and osteolytic lesions in most patients [(1)]. The Durie and Salmon staging system for MM, which was introduced in 1975, is still used to assess tumor burden and prognosis. The plain radiographic skeletal survey is an important part of this system, since multiple osteolytic lesions define stage III disease [(1,2)]. The prognostic implications of magnetic resonance (MR) imaging of the bone marrow for MM have already been established for abnormal versus normal MR imaging results and for individual MR imaging patterns of involvement[(3,4)]. For example, abnormal spinal MR imaging results have been shown to help identify patients with asymptomatic (smoldering) myeloma who are likely to benefit from early treatment[(3)]. More recently, it was shown that patients with smoldering myeloma and more than one unequivocal focal lesion on whole-body MR images have an increased risk of developing myeloma-related symptoms and should receive treatment[(5,6)]. Accordingly, the most recent International Myeloma Working Group criteria for MM incorporate MR imaging findings in the definition of symptomatic disease[(1,7)]. Diffusion-weighted imaging (DWI) with calculation of apparent diffusion coefficients (ADCs) may be used as an adjunct method to increase diagnostic confidence and to better distinguish a diffuse MR imaging pattern from a normal MR imaging pattern. So far, this technique has been applied to a relatively small number of patients with myeloma, with promising results for initial assessment and prognosis [(8; 9)].

AIM OF THE WORK

To evaluate the apparent diffusion coefficients (ADCs) of magnetic resonance (MR) imaging patterns in the bone marrow of patients with multiple myeloma (MM) and to determine a threshold ADC that may help distinguish a diffuse from a normal pattern with high accuracy.

PATIENTS AND METHODS

Patients: The study was conducted in the period between October 2016 and May 2018 in Radiology Department at Ain Shams University Hospitals. The patients underwent MR examination using a 1.5 T machine (Philips Healthcare, Best, Netherlands) using phased array coil. ***Inclusion Criteria:*** Any age group and sex. Patients with newly diagnosed, untreated MM and healthy control subjects underwent spinal MR imaging including diffusion-

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weighted imaging, and bone marrow. ***Exclusion Criteria:*** Patient with pacemaker, Metallic foreign body in the eye, cerebral aneurysm, clips or cochlea implantation. ***Ethical Considerations:*** The study was approved from The Ethical Committee of the Department of Radiology, Faculty of Medicine, Ain Shams University. Written consents were taken from all participates before recruitment in the study after explanation of the purpose and procedures of the study. ***MR Imaging protocol:*** Our standard MR imaging protocol for bone marrow assessment of thoracolumbar /lumbosacral consisted of the following pulse sequences: **Sagittal T1WI**, **Sagittal T2WI, STIR** of the thoracic and lumbosacral spine were evaluated. spine signal intensity was compared with the signal intensity of non degenerated intervertebral discs and muscles and Axial imaging was added if it was deemed appropriate. **Short TI inversion-recovery and paired in-phase and opposed-phase T1 gradient-echo** in selected cases were used to better characterize lesions and increase diagnostic confidence. ***Diffusion study:*** DWI Sequence was performed with a sagittal single-shot echo-planar imaging sequence of the lumbosacral spine by using the following parameters: repetition time msec/echo time msec, 2000/75; field of view, 300 mm; section thickness, 5.0 mm; gap, 1.0 mm; number of signals acquired, eight; orthogonal directions, three; and b values, 0, 150, 250, 500, and 750 sec/mm2 with spectrally selected fat suppression. Mono exponential ADC maps were generated with the system software by using all five b values and taking an average value for the three directions of diffusion sensitization. ADC measurements in all patients and control subjects were collected. ADC value was usually expressed in ($\times 10^{-3}$) square millimeters per second. ***MRI data Analysis:*** Choice of lesions measured depended on size (larger lesions is preferred) and absence of artifacts. In these patients, an additional region of interest was placed on an uninvolved vertebra (or, when all visible vertebrae had one or more focal lesions, in an apparently uninvolved part of a vertebra) to record the ADC of apparently normal bone marrow. A focal pattern of MM was diagnosed when sagittal T1-weighted images of the spine showed one or more lesions with a diameter of at least 5 mm and lower signal intensity than intervening, normal-appearing marrow. A variegated pattern was assigned when innumerable tiny hypointense foci against a background of normal-appearing marrow were observed. A diffuse pattern of myelomatous involvement was diagnosed when low-signal-intensity marrow (either iso- or hypointense to intervertebral discs and muscle) was observed on T1-weighted images of the spine without any intervening normal-appearing marrow. Finally, we assigned a normal MR imaging pattern when no abnormal marrow was detected on the basis of the qualitative imaging criteria described previously. Myeloma lesions either focal or diffuse are defined as: those with signal intensity equal to or lower than that of muscle or non-degenerated intervertebral discs on T1-weighted images, increased signal intensity on short TI inversion-recovery images, absence of signal intensity and decrease on opposed-phase images; 1) normal appearing marrow in a known multiple myeloma patient, 2) A focal pattern of MM was diagnosed when sagittal T1 weighted images of the spine showed one or more lesions with a diameter of at least 5 mm and lower signal intensity than intervening normal-appearing marrow. 3) A diffuse pattern of myelomatous involvement is diagnosed when low-signal-intensity marrow (either iso- or hypointense to intervertebral discs and muscle) is observed on T1-weighted images of the spine without any intervening normal-appearing marrow (no healthy marrow). 4) A combined pattern of focal and diffuse was assigned when innumerable tiny hypointense foci against a background of normal-appearing marrow were observed resulting in a variegated pattern/ moasic marrow appearance. 5) Salt and pepper infiltrated pattern. Finally, we assigned a normal MR imaging pattern when no abnormal marrow is detected on the basis of the qualitative imaging criteria described previously. **ADC calculation:** -The mean ADC was measured by drawing a region of interest (ROI) over the lesion. The ADC was measured twice and the two measurements were averaged. To ensure that the same areas were measured. ROI was copied and pasted from DW images to ADC map. ***Statistical Analysis:*** Data were analyzed using MedCalc© version 18.2 (MedCalc© Software bvba, Ostend, Belgium). Normality of numerical data distribution was examined using the D'Agostino-Pearson test. Normally distributed numerical data were presented as mean ± standard deviation and intergroup differences were compared using one-way analysis of variance (ANOVA) with application of the Tukey test for post hoc comparisons. The diagnostic value of ADC was examined using receiver-operating characteristic (ROC) curve analysis, P-values <0.05 were considered statistically significant

RESULTS

When the groups of patients with diffuse and normal MR imaging patterns were compared for

various characteristics, several significant differences were observed: Patients with a diffuse pattern had higher levels of clonal bone marrow plasma cells at trephine biopsy and higher levels of serum monoclonal (M) peak and b2 -microglobulin and lower values of hemoglobin and albumin). A diffuse MR imaging pattern also was associated with a significantly higher ISS score than was a normal MR imaging pattern. There was also a significant difference in the presence of chromosomal abnormalities between the two groups. High-risk cytogenetics, defined as the presence of at least one of del (17p), translocation t (4;14), and translocation t (14;16). ***Statistical methods:*** Data were analyzed using MedCalc© version 18.2 (MedCalc© Software bvba, Ostend, Belgium). Normality of numerical data distribution was examined using the D'Agostino-Pearson test. Normally distributed numerical data were presented as mean ± standard deviation and intergroup differences were compared using one-way analysis of variance (ANOVA) with application of the Tukey test for post hoc comparisons. The diagnostic value of ADC was examined using receiver-operating characteristic (ROC) curve analysis was. The area under the ROC curve (AUC) is interpreted as follows: P-values <0.05 were considered statistically significant. **Results:** 30 patients newly diagnosed multiple myeloma were examined and 16 control subjects: On the basis of visual assessment of conventional MR images, 7 patients with MM had focal, 9 patients had diffuse, 3 patients had variegated (focal in normal), and 11 patients had normal MR imaging patterns.

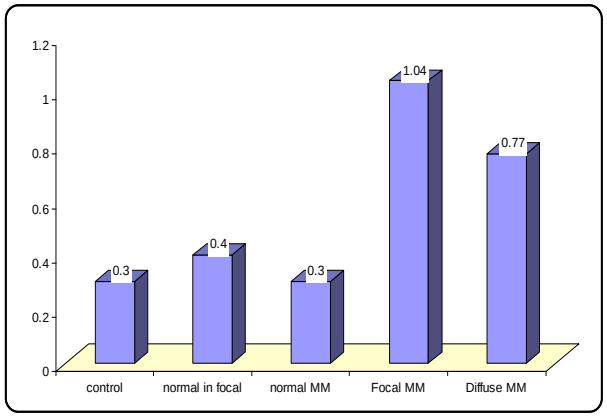

Fig. (1): The ADC value among different multiple myeloma subtypes showed range of bone marrow ADCs (x 10^{-3} mm^2 /sec) in different MR imaging patterns. Control = healthy control group, Diffuse MM = diffuse MR imaging pattern of MM, Focal MM = focal MR imaging pattern of MM, Normal in Focal MM = apparently uninvolved marrow in focal MR imaging pattern of MM, Normal MM = normal MR imaging pattern of MM.

Table (1): Comparison of the ADC value among different multiple myeloma subtypes

MM subtype	Control subjects		Normal (n=11)	Diffuse (n=9)	Focal (n=7)	Focal in normal (n=3)
Mean ADC value (x10^{-3} mm^2/s)	0.325 (± 0.130)		0.360 (± 0.110	0.770 (± 0.135)	1.046 (± 0.232)	0.415 (± 0.108)
P-value	0.25 (Compared to Normal)	0.078 (Compared to Focal in Normal)	<0.001	<0.001	<0.001	0.055
Significance	NS	NS	HS	HS	HS	NS

HS: Highly significant
NS: Non significant

Mean ADCs of the bone marrow in the patient group were 0.360 x 10^{-3} mm^2/sec -/+ 0.110 (range: 0.153–0.593 x 10^{-3} mm^2/sec) for those with a **normal MR** imaging pattern, 1.046 x 10^{-3} mm2/sec +/- 0.232 (range, 0.715–1.536 x 10^{-3} mm^2/sec) for those with a **focal pattern**, and 0.770 x 10^{-3} mm^2/sec +/- 0.135 (range, 0.552–1.017 x 10^{-3} mm^2/sec) for those with a **diffuse pattern.** One way analysis of variance (ANOVA) showed a significant difference in ADC values within the groups of the study (p value 0.0001). Further analysis using t-test showed that there was a statistically significant difference in mean ADCs (± SD, x10-3 mm2 /sec) between the different MR imaging patterns of MM with a mean rank ADC of 65.73 x 10^{-3} mm2/sec for the **diffuse MR imaging pattern**, 81.95 x 10^{-3} mm^2/sec for the **focal MR imaging pattern** and 25.02 x 10^{-3} mm^2/ sec for **the normal MR imaging pattern**.

The mean ADC of **apparently normal marrow in the focal MR imaging** pattern group was 0.415 x 10^{-3} mm^2/sec +/- 0.108 (range: 0.113–0.589 x 10^{-3} mm^2/sec), while that in the **healthy control** subject group was 0.325 x 10^{-3} mm^2/sec +/- 0.135 (range, 0.152–0.542 x 10^{-3} mm^2/sec.

There were significant differences in ADCs between patients with **diffuse and focal** MR imaging patterns (P.001), **diffuse and normal** MR imaging patterns (P.001**), focal and normal** MR imaging patterns (P.001**), diffuse MR imaging patterns and control subjects** (P , .001**), focal MR imaging patterns and control subjects** (P , .001), **diffuse and apparently normal marrow in focal** MR imaging patterns (P , .001), and finally, between **focal and apparently normal marrow in focal MR** imaging patterns (P , .001).

No significant differences were found between **normal MR imaging patterns and control subjects** (P = .250), **normal and apparently normal marrow in focal** MR imaging patterns (P = .055), and between **apparently normal marrow in focal MR imaging patterns and control** subjects (P = .078)

Table (2): Receiver-operating characteristic (ROC) curve analysis for discrimination between focal and non-focal (diffuse or normal) multiple myeloma using the ADC

ROC parameter	Value
Area under the ROC curve (AUC)	1.000
Standard Error	0.000
95% Confidence interval	0.884 to 1.000
Cut-off criterion ($x10^{-3}$ mm^2/s)	>0.548 / >0.593
Sensitivity	100%
Specificity	98 % / 100 %

The 95% confidence intervals of the ADC values for each group were calculated and a receiver operating characteristic (ROC) analysis was performed to determine the cut-off value with the highest accuracy to distinguish a diffuse myeloma pattern from normal patterns (normal MM pattern, apparently normal marrow in focal MM pattern, normal marrow in healthy controls).

Table (3): Estimated specificities at fixed sensitivities and vice versa for discrimination between focal and non-focal (diffuse or normal) multiple myeloma using the ADC

Estimated sensitivity at fixed specificity		
Specificity	**Sensitivity**	**Criterion**
98 % (10/11) normal CI 85.6 %,99.1 %	100% (9/9) diffuse CI: 84.6 %,100.0 %	>0.548
100% (11/11)normal CI: 87.6%,100.0%	100% (9/9) diffuse CI: 77.7 %, 100.0 %	>0.597

95% CI = 95% Confidence interval.

An ADC greater than 0.548 x 10-3 mm2/sec showed 100% sensitivity (9 of 9; 95% confidence interval: 83.7%, 100.0%) and 98% specificity (10 of 11; 95% confidence interval: 85.6%, 99.1%) for the diagnosis of a diffuse (vs a normal) MR imaging pattern, whereas a value greater than 0.597 x 10-3 mm2/sec showed 100% sensitivity (9 of 9; 95% confidence interval: 77.7%, 100.0%) and 100% specificity (11 of 11; 95% confidence interval: 87.6%, 100.0%).

Finally, An ADC value above 0.593x10-3 mm2 /sec was found to be diagnostic of diffuse myelomatous infiltration of the bone marrow with a sensitivity and specificity of 100%.

DISCUSSION

MR imaging pattern assignment in patients with MM is important because it has been shown to have prognostic value in patients with newly diagnosed disease who have not undergone treatment. The following bone marrow MR imaging patterns have been described in patients with MM: normal, focal, variegated, and diffuse [10-13]. A pattern of combined focal and diffuse infiltration has also been described by some authors [14,15]. In the era of conventional chemotherapy, the median overall survival of patients with newly diagnosed MM was reported to be significantly shorter if they had a diffuse MR imaging pattern (24 months vs 51, 52, and 56 months for those with focal, variegated, and normal patterns, respectively; P = .001) [16]. A possible explanation is that a diffuse MR imaging pattern correlates with increased angiogenesis and advanced disease features [4,16]. In a group of 228 patients with symptomatic MM who received upfront therapy with novel agents, those with a diffuse MR imaging pattern had inferior survival compared with patients with other patterns. Furthermore, the combination of diffuse MR imaging pattern, ISS stage III, and high-risk cytogenetics allowed identification of a subgroup of patients with very poor survival [16]. In another study [4] involving 126 patients with newly diagnosed symptomatic MM who underwent autologous stem cell transplantation, researchers showed that the diffuse and variegated MR imaging patterns had independent predictive value for disease progression. In a whole body MR imaging study of patients with asymptomatic MM, the presence of a focal MR imaging pattern and a number of greater than one focal lesion were the strongest adverse prognostic factors for progression to symptomatic MM. A diffuse MR imaging pattern was also an adverse prognostic factor for progression-free survival in the same patient group[17]. In a recent study by Mai et al.[18] in which the authors proposed an MR imaging–based

scoring system to predict outcome in transplantation-eligible patients with MM. They found that moderate to severe diffuse infiltration on MR images had a negative prognostic effect on progression-free and overall survival when compared to other patterns. More than 25 focal lesions on whole body MR images or more than seven on axial MR images were also associated with an adverse prognosis. Although, the definition of a focal MR imaging pattern in patients with MM is straightforward, there were different definitions of a diffuse MR imaging pattern in the literature. Our group, as well as other authors [4,12,14,19,20] defined a diffuse MR imaging pattern in MM as present when, on T1-weighted images, the signal intensity of the spine is equal to or lower than the signal intensity of non-degenerated intervertebral discs or muscle with no visible normal-appearing marrow. On T2-weighted images with fat suppression (eg, short TI inversion recovery), signal intensity was increased (more often diffusely, but occasionally, with multiple superimposed foci of even higher signal intensity) and on postcontrast T1-weighted images, pronounced enhancement is noted. Lack of signal intensity decrease on opposed-phase T1-weighted gradient echo images was helpful to exclude red marrow hyperplasia, which could cause diffuse hypointensity on T1-weighted images. Other authors subdivide the diffuse MR imaging pattern into more than one grade (eg, low, intermediate, and high grade or minimal, moderate, and severe). Lower grades generally, defined according to the same criteria that we used for the definition of a normal MR imaging pattern and intermediate to moderate grades defined according to the presence of moderately lower signal intensity on T1-weighted images but still higher than that of intervertebral discs [15,18,21]. We believe that MR imaging grading of diffuse infiltration according to qualitative criteria such as moderately decreased signal intensity may be confusing and difficult to reproduce. It also can be argued that the term "normal MR imaging pattern" is more appropriate, because it describes an MR imaging pattern in which bone marrow appears normal and cannot possibly be distinguished according to imaging criteria from non diseased marrow. In our study, we found no significant differences between marrow ADCs in patients with the normal MR imaging pattern and in healthy control subjects. Furthermore, no significant differences were found between marrow ADCs of these two groups and ADCs of normal appearing marrow in the focal MR imaging pattern group. The presence of more than one unequivocal focal marrow lesion larger than 5 mm on MR images recently had been incorporated in the updated criteria of the International Myeloma Working Group for the definition of symptomatic MM that requires therapy[1]. Regarding the diffuse MR imaging pattern, the International Myeloma Working Group advocates in a consensus statement[11] reported that additional studies are needed before its incorporation in the definition of symptomatic MM. Lack of agreement among investigators about what constitutes a diffuse pattern may be one of the reasons for the shortage of such studies. Therefore, adding a quantitative measurement, such as the ADC, to more objectively define a diffuse MR imaging pattern in patients with MM might prove useful for future investigations. DWI, which derives its contrast mainly from differences in the diffusivity of water molecules in tissue, had been applied to bone marrow with varying results. Quantitative analysis of DWI can be achieved by calculating the ADCs from images with two or more different diffusion weightings. ADCs of normal bone marrow are very low (range, 0.2–0.5 x 10^{-3} mm^2/sec), mainly due to low proton density and to the abundance of marrow fat, which acts as a physical barrier to the free diffusivity of water molecules [22]. Bone trabeculae and decreased vascularity also may contribute to the restricted diffusion of normal marrow[23]. Any pathologic process, including focal or diffuse myelomatous infiltration, which replaces normal marrow will therefore, appear as an area of increased diffusivity (ie, with higher ADCs) compared to the restricted diffusion of normal marrow. To our knowledge, there are very limited data in the literature regarding bone marrow ADCs in patients with MM. Messiou et al.[8] reported that the ADCs of metastatic bone disease (prostate and breast) and MM had a mean ADC of 1.235 x 10^{-3} mm^2/sec +/- 0.595. Although, they included a separate analysis of focal and diffuse disease, these categories included both patients with metastatic disease and those with MM. Padhani et al.[9] studied the ADCs of abnormal marrow in 21 patients with bone metastatic disease from breast cancer and 12 patients with MM, either newly diagnosed (n = 7)

or relapsed (n = 5). The mean ADC of 34 myeloma lesions was 0.875 x 10^{-3} mm^2/sec +/- 0.187. Eight patients had a focal or multifocal disease pattern, and four had diffuse disease, but no separate ADCs were provided for the two groups. To our knowledge, ours is the first study in which ADCs of the different MR imaging patterns of MM were calculated and compared. Our aim was twofold: to provide a range of ADCs for the various MR imaging patterns determined on the basis of a large group of patients with newly diagnosed untreated MM and to determine a threshold ADC that may help to distinguish a diffuse from a normal pattern with high accuracy. When we compared ADCs of all study groups, we found that the values of the diffuse MR imaging pattern ranged from 0.552 x 10-^{3} mm^2/sec to 1.017 x 10^{-3} mm^2/sec and differed significantly from those of the other myeloma MR imaging patterns and those of healthy control subjects. An ADC greater than 0.548 x 10-^{3} mm^2/ sec showed 100% sensitivity and 98% specificity for the diagnosis of a diffuse (as opposed to a normal) MR imaging pattern, whereas a value greater than 0.597 x 10^{-3} mm^2/sec showed 100% sensitivity and 100% specificity. The higher ADCs of the diffuse MR imaging pattern group compared to those of the normal MR imaging pattern group might be explained by the higher ratio of tumor cells to adipose cells in the former. In accordance with previous studies, our patients with a diffuse pattern had more extensive marrow infiltration, more severe anemia, and higher incidence of ISS stage compared to patients with a normal pattern. Moreover, Patients with a diffuse pattern had a significantly higher incidence of a high-risk cytogenetics compared to patients with a normal pattern. We therefore, believe that adding quantitative DWI to the MR imaging protocol of MM enables more confident identification of this high-risk group of patients who might need innovative treatment strategies. Regarding the focal MR imaging pattern, our results showed that focal lesions demonstrated significantly higher ADCs compared with the diffuse and normal patterns of MM (1.046 x 10^{-3} mm^2/sec +/- 0.232 vs 0.770 x 10^{-3} mm^2/sec +/- 0.135 and 0.360 x 10^{-3} mm^2/sec +/- 0.110, respectively). According to the authors of many studies [6,13,17] when a focal MR imaging pattern is encountered, the number of detected focal myelomatous lesions has prognostic value. Knowing the range of ADCs of focal lesions might aid characterization in cases of equivocal findings in other pulse sequences. The higher ADCs of the focal pattern compared to the diffuse pattern might in part be explained by the fact that in focal lesions the diffusion-impeding elements (mainly marrow fat, and secondarily, bone trabeculae) were completely replaced, whereas in the diffuse pattern, they may coexist with tumor cells to varying degrees. Although differences in tumor cellularity between the two patterns also may be involved, this is difficult to assess in view of the absence of direct histologic evaluation of focal lesions. Regarding the independent prognostic value of marrow ADC in patients with MM, it remains to be evaluated prospectively. Long-term follow-up and correlation with progression-free and overall survival will show whether pretreatment ADCs are relevant for prognosis in patients with MM. Our study had several limitations. We sought to compare marrow ADCs by using established patterns on the basis of conventional MR images as reference. Direct histologic confirmation of our findings was not performed, because it would have been unethical to obtain bone marrow biopsies from every observed site of abnormality. Moreover, patterns were assigned on the basis of consensus, not independent reading. Our MR imaging examinations were limited to the lumbosacral and thoracic spine; however, the aim of our study was to define an MR imaging pattern and obtain marrow ADC measurements and not to assess extent of disease. Another limitation was that the sensitivity and specificity of the ADC cut-off points between diffuse and normal patterns were not validated in an independent validation cohort. Finally, ADCs are influenced by MR imaging protocol and, particularly, by the choice of diffusion weighting (ie, b values) and method of fat suppression. In our study, we included the b value of 0 (which potentially raises marrow ADCs) and used spectral saturation fat suppression (which tends to lower marrow ADCs compared to the inversion-recovery method) [9]. This means that ranges and thresholds might vary slightly depending on choice of protocol. MR imaging patterns of bone marrow involvement carry important prognostic implications for patients with MM. DWI as a quantitative means of assessing bone marrow involvement noninvasively assists in the interpretation of other MR imaging sequences and helps improve accuracy of pattern assignment. We

showed that marrow ADCs of MR imaging patterns in patients with MM differed significantly and that a diffuse MR imaging pattern, a known adverse prognostic factor, might be defined more objectively by adding quantitative DWI to standard MR imaging protocols.

CONCLUSION

The bone marrow MR imaging pattern had been reported to have prognostic significance in patients with newly diagnosed MM, and a diffuse pattern had been shown to correlate with poor prognosis and advanced disease features. Adding quantitative diffusion weighted imaging to standard MR imaging protocols for MM could help identify more precisely this subgroup of patients who may require innovative treatment strategies and more aggressive regimens. Normal, focal, and diffuse MR imaging patterns of the bone marrow in patients with multiple myeloma (MM) had distinct ranges of apparent diffusion coefficients (ADCs) on diffusion weighted images (mean ± standard deviation, 0.360×10^{-3} $mm^2/sec \pm 0.110$, 1.046×10^{-3} $mm^2/sec \pm 0.232$, and 0.770×10^{-3} $mm^2/sec \pm 0.135$, respectively). ADCs could be used to increase diagnostic confidence in MR imaging pattern assignment. A bone marrow ADC greater than 0.548×10^{-3} mm^2/sec had 100% sensitivity and 98% specificity. An ADC value above 0.593×10^{-3} mm^2/sec is diagnostic of diffuse myelomatous infiltration of the bone marrow with extremely high accuracy and could be used in cases where a diffuse pattern could not be differentiated from a normal pattern on conventional MRI.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1- Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O (2014): International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet Oncology, 15(12):e538-e548.

2- Palumbo A and Anderson K (2011): Multiple Myeloma."*New England Journal of Medicine*, 364(11): 1046–1060.

3- Moulopoulos LA, Dimopoulos MA, Smith TL, Weber DM, Delasalle KB, Libshitz HI, Alexanian R (1995): Prognostic significance of magnetic resonance imaging in patients with asymptomatic multiple myeloma. Journal of Clinical Oncology, 13(1):251-256.

4- Song MK, Chung JS, Lee JJ, Min CK, Ahn JS, Lee SM, Shin DY, Bae SH, Hong J, Lee GW, Lee IS (2014): Magnetic resonance imaging pattern of bone marrow involvement as a new predictive parameter of disease progression in newly diagnosed patients with multiple myeloma eligible for autologous stem cell transplantation. British Journal of Haematology, 165(6):777-85.

5- Fechtner K, Hillengass J, Delorme S, Heiss C, Neben K, Goldschmidt H, Kauczor HU, Weber MA (2010): Staging monoclonal plasma cell disease: comparison of the Durie-Salmon and the Durie-Salmon PLUS staging systems. Radiology, 257(1):195-204.

6- Kastritis E, Moulopoulos LA, Terpos E, Koutoulidis V, Dimopoulos MA (2014): The prognostic importance of the presence of more than one focal lesion in spine MRI of patients with asymptomatic (smoldering) multiple myeloma. Leukemia, 28(12):2402-2403.

7- Dimopoulos M, Terpos E, Comenzo RL, Tosi P, Beksac M, Sezer O, Siegel D, Lokhorst H, Kumar S, Rajkumar SV, Niesvizky R (2009): International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. Leukemia, 23(9):1545.

8- Messiou C, Collins DJ, Morgan VA, deSouza NM (2011): Optimising Diffusion Weighted MRI for Imaging Metastatic and Myeloma Bone Disease and Assessing Reproducibility.*European Radiology*, 21(8): 1713–18.

9- Padhani AR, van Ree K, Collins DJ, D'Sa S, Makris A (2013): Assessing the relation between bone marrow signal intensity and apparent diffusion coefficient in diffusion-weighted MRI. American Journal of Roentgenology, 200(1):163-170.

10- Criteria for the Classification of Monoclonal Gammopathies, Multiple Myeloma and Related Disorders: A Report of the International Myeloma Working Group (2003): *British Journal of Haematology*, 121(5): 749–57.

11- Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, Raje N, Sezer O, Zweegman S, Shah J, Badros A (2015): Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J Clin Oncol., 33(6):657-64.

12- Moulopoulos LA, Varma DG, Dimopoulos MA, Leeds NE, Kim EE, Johnston DA, Alexanian R, Libshitz HI (1992): Multiple myeloma: spinal MR imaging in patients with untreated newly diagnosed disease. Radiology, 185(3):833-40.

13- Walker R, Barlogie B, Haessler J, Tricot G, Anaissie E, Shaughnessy Jr JD, Epstein J, Van Hemert R, Erdem E, Hoering A, Crowley J (2007): Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. Journal of Clinical Oncology, 25(9):1121-8.

14- Libshitz HI, Malthouse SR, Cunningham D, MacVicar AD, Husband JE (1992): Multiple myeloma: appearance at MR imaging. Radiology, 182(3):833-7.

15- Stäbler A, Baur A, Bartl R, Munker R, Lamerz R, Reiser MF (1996): Contrast enhancement and quantitative signal analysis in MR imaging of multiple myeloma: assessment of focal and diffuse growth patterns in marrow correlated with biopsies and survival rates. AJR. American Journal of Roentgenology, 167(4):1029-36.

16- Moulopoulos LA, Dimopoulos MA, Kastritis E, Christoulas D, Gkotzamanidou M, Roussou M, Koureas A, Migkou M, Gavriatopoulou M, Eleutherakis‐Papaiakovou E, Gika D (2012): Diffuse pattern of bone marrow involvement on magnetic resonance imaging is associated with high risk cytogenetics and poor outcome in newly diagnosed, symptomatic patients with multiple myeloma: a single center experience on 228 patients. American Journal of Hematology, 87(9):861-864.

17- Hillengass J, Fechtner K, Weber MA, Bauerle T, Ayyaz S, Heiss C, Hielscher T, Moehler TM, Egerer G, Neben K, Ho AD (2010): Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol., 28(9):1606-10.

18- Mai EK, Hielscher T, Kloth JK, Merz M, Shah S, Raab MS, Hillengass M, Wagner B, Jauch A, Hose D, Weber MA (2015): A magnetic resonance imaging-based prognostic scoring system to predict outcome in transplant-eligible patients with multiple myeloma. Haematologica, 100(6):818-25.

19- Carroll KW, Feller JF, Tirman PF (1997): Useful internal standards for distinguishing infiltrative marrow pathology from hematopoietic marrow at MRI. Journal of Magnetic Resonance Imaging, 7(2):394-8.

20- Lecouvet FE, Vande Berg BC, Michaux L, Malghem J, Maldague BE, Jamart J, Ferrant A, Michaux JL (1998): Stage III multiple myeloma: clinical and prognostic value of spinal bone marrow MR imaging. Radiology, 209(3):653-60.

21- Baur A, Stäbler A, Nagel D, Lamerz R, Bartl R, Hiller E, Wendtner C, Bachner F, Reiser M (2002): Magnetic resonance imaging as a supplement for the clinical staging system of Durie and Salmon?. Cancer, 95(6):1334-45.

22- Biffar A, Dietrich O, Sourbron S, Duerr HR, Reiser MF, Baur-Melnyk A (2010): Diffusion and perfusion imaging of bone marrow. European Journal of Radiology, 76(3):323-8.

23- Messiou C and Kaiser M (2015): Whole Body Diffusion Weighted MRI--a New View of Myeloma. *British Journal of Haematology*, 171(1): 29–37.