Diagnostic value of apparent diffusion coefficients to differentiate benign from malignant vertebral bone marrow lesions

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Abstract

Aim: The aim of this study is to evaluate the value of the apparent diffusion coefficient (ADC) obtained in diffusion-weighted (DW) MR sequences for the differentiation between malignant and benign bone marrow lesions.

Method: Forty-five patients with altered signal intensity vertebral bodies on conventional MR sequences were included. The cause of altered signal intensity was benign osteoporotic collapse in 16, acute neoplastic infiltration in 15, and infectious processes in 14; based on plain-film, CT, bone scintigraphy, conventional MR studies, biopsy or follow-up. All patients underwent isotropic DW MR images (multi-shot EPI, \(b\) values of 0 and 500 s/mm\(^2\)). Signal intensity at DW MR images was evaluated and ADC values were calculated and compared between malignancy, benign edema and infectious spondylitis.

Results: Acute malignant fractures were hyperintense compared to normal vertebral bodies on the diffusion-weighted sequence, except in one patient with sclerotic metastases. Mean ADC value from benign edema (1.9 ± 0.39 × 10\(^{-3}\) mm\(^2\)/s) was significantly \((p<0.0001)\) higher than untreated metastasic lesions (0.9 ± 1.3 × 10\(^{-3}\) mm\(^2\)/s). Mean ADC value of infectious spondylitis (0.96 ± 0.49 × 10\(^{-3}\) mm\(^2\)/s) was not statistically \((p>0.05)\) different from untreated metastasic lesions. ADC value was low (0.75 × 10\(^{-3}\) mm\(^2\)/s) in one case of subacute benign fracture.

Conclusions: ADC values are a useful complementary tool to characterize bone marrow lesions, in order to distinguish acute benign fractures from malignant or infectious bone lesions. However, ADC values are not valuable in order to differentiate malignancy from infection.

1. Introduction

Although the spine is the most common site of bone metastases [1], benign vertebral fractures due to osteopenia occur in one third of cancer patients, making it essential to determine whether the cause of vertebral collapse is benign or malignant [2].

Conventional magnetic resonance (MR) techniques are the imaging test of choice in the diagnosis of pathologic fractures; however, they are unable to differentiate acute benign collapse from malignant collapse in most cases. Because osseous edema secondary to acute osteopenic fracture produces signal changes similar to those observed in bone metastases on T1- and T2-weighted and STIR images, conventional MR is very sensitive but not always specific [3,4], motivating the search for new sequences to provide different information to enable benign

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lesions to be confidently distinguished from malignant ones. The majority of the authors have used balanced steady-state free precession (SSFP) sequences because they provide very good image quality and the acquisition time is short [5–9]. These studies have generated much controversy because this sequence does not allow an objective evaluation of the lesion. Some investigators have used other diffusion weighted imaging (DWI) techniques that allow for the calculation of apparent diffusion coefficient (ADC) values [10–13], showing significant separation between pathologic and benign compression fractures ADC values. Nevertheless, the value of the differentiated malignant from benign vertebral body fractures is not yet clear.

The purpose of this study is to assess the usefulness of diffusion-weighted imaging and of the apparent diffusion coefficient (ADC) obtained in a multishot echo-planar sequence in the differentiation between acute benign bone marrow lesions and malignant lesions in order to increase the specificity of MR.

2. Patients and methods

From October 2005 to June 2006, 45 consecutive patients (23 men and 22 women; mean age, 61 yrs; range 25–94) presenting vertebral collapse and/or altered signal intensity in one or more vertebral body on conventional MR sequences were studied. Ethics committee approval was considered unnecessary as no ionizing radiation, contrast agents, or invasive techniques were employed. All patients gave informed consent to participate in the study. Nineteen patients had a history of a known primary tumor (breast neoplasm in eight, multiple myeloma in two, paraganglioma in one, synovial sarcoma in one, lung neoplasm seven). Twenty-six patients had no known history of neoplasm. In all cases, the final diagnosis was based on the findings at plain-film radiography, computed tomography, bone scintigraphy, conventional MR sequences and clinical follow-up. In fifteen patients, it was based on histological confirmation. Ethical considerations precluded histological confirmation in the rest of the patients because the biopsy was not clinically indicated. Thirty patients presented benign collapses and 15 patients presented metastatic lesions.

All MR studies were performed on a 1.5 T unit (Intera; Philips Medical Systems, Eindhoven, RELEASE 11, The Netherlands) with gradient echo-planar capabilities (23 mT/m maximum gradient strength, 184-μs rise time) and a standard phased-array surface receiver coil for imaging the spine. The imaging protocol included axial and sagittal T1-weighted spin-echo sequences (600/17/90/2 [TR/TE/angle/NSA]), axial and sagittal T2-weighted turbo spin-echo (3446/130/90/3) sequences, sagittal STIR (1757/14/160/3 [TR/TE/TI/NSA]) sequences, and sagittal diffusion-weighted sequences.

Diffusion images were acquired using a multisection, fat suppression spin-echo-type multishot echo-planar imaging (EPI) sequence in the sagittal plane. Sensitizing diffusion gradients were applied sequentially in the phase-encoding direction with b value of 0 and 500 s/mm². Sequential sampling of the k-space was used with TR/TE, 1600/95 ms; acquisition matrix, 176 × 256; thickness, 6 mm; interslice gap, 1 mm; field of view 40 × 20 cm; acquisitions, 4. Peripheral pulse unit (PPU) triggering, navigator-echo motion correction (18–22), and segmented signal averaging (serial motion artifact reduction technique [SMART]) were used to minimize the effects of motion. In order to measure the ADC of the lesions, a region of interest (ROI) was placed within the lesion, and the ADC values were then obtained. The total duration of the diffusion-weighted imaging acquisition was 3 min and 18 s per spine. The numeric value was calculated for the most representative lesion in each patient. The combined ADC values of the acute benign fractured vertebral bodies, the spondylitis and the malignant vertebral bodies were compared using the ANOVA test (analysis of variance).

3. Results

The ADC values are summarized in Fig. 1.

Benign collapse occurred in 30 patients. The majority were acute fractures (n = 15), two of whom had a previous history of neoplasm (one lung neoplasm and one breast cancer). One patient presented a subacute benign fracture. Fourteen of the 30 benign lesions were due to infectious spondylitis.

All benign vertebral body lesions were diffusely hypointense at T1-weighted images, hyperintense on T2-weighted images and STIR sequences. Qualitative evaluation of the diffusion-weighted images yielded variable results, with the signal intensity of the different lesions being always higher than normal vertebral bodies or isointense.

The quantitative study found high mean ADC values (1.9 ± 0.39 × 10⁻³ mm²/s) for the acute benign collapsed vertebral bodies (Fig. 2), and lower mean ADC values for the infectious lesions (0.963 ± 0.491 × 10⁻³ mm²/s), (Fig. 3). The patient with two-month-old subacute benign osteopenic fracture had and ADC value of 0.75 × 10⁻³ mm²/s (Fig. 4).

Fifteen patients presented metastatic lesions. Fourteen were hypointense in T1-weighted sequences and hyperintense in T2-weighted images, STIR and diffusion-weighted sequences. There was one patient with a blastic metastasis, being hypointense on these sequences. The mean ADC values obtained (0.917 ± 0.13 × 10⁻³ mm²/s) were lower than traumatic or osteopenic benign lesions statistically significant (p < 0.001), although greater than those of normal bone marrow (Fig. 5).

The mean ADC values from the malignant lesions (0.917 ± 0.13 × 10⁻³ mm²/s) were not statistically differ-

![Fig. 1. ADC values. Malignant lesions (M), spondylitis (I), acute benign traumatic/osteopenic fractures (AB).](image-url)
Fig. 2. A 69-year-old woman with benign acute compression fracture of the vertebral body. (a) Sagittal T1-weighted spin-echo MR image showing hypointense signal with respect to normal bone marrow in part of the L1 vertebral body. (b) Sagittal STIR image shows diffuse hyperintensity in the fractured vertebral body due to bone marrow edema. (c) High ADC values for the fractured vertebral body ($1.809 \times 10^{-3}$ mm$^2$/s).

ent from the infectious spondylitis group ($0.963 \pm 0.491 \times 10^{-3}$ mm$^2$/s) ($p > 0.05$).

4. Discussion

Diffusion-weighted sequences provide dynamic and microscopic information to supplement the static and macroscopic information provided by conventional sequences. Diffusion-weighted sequences reflect the random movement of water molecules (which includes both intracellular and extracellular movement, as well as transcellular and intracapillary movement). A fundamental use for this technique has already been established in the study of hyperacute cerebral infarction, but its uses in other areas, such as the musculoskeletal system, are still being explored [5].

Although several articles have been published about the use of diffusion-weighted imaging as a noninvasive method to differentiate between benign and malignant vertebral collapse, most authors have used balanced steady-state free precession (SSFP) sequences because they provide very good image quality and the acquisition time is short. Besides, SSFP sequence resulted in a very high specificity in a large series of patients, so it seems not to be necessary to calculate the ADC [6–9]. Nevertheless, these studies have generated controversy because this sequence does not allow an objective evaluation of the lesion and is only available on Siemens scanners and the signal behavior is very complex and partially not yet understood. The signal of diffusion-weighted SSFP sequences depends on the relaxation times T1 and T2; thus, their signal is related to the one seen in T1 and T2-weighted sequences, rather than exclusively to a restriction of diffusion caused by the high cellularity of the neoplastic process [14–16]. In our series, the MR signal seen in the diffusion-weighted sequence (qualitative evaluation) was not useful, as benign lesions exhibited heterogeneous behavior and were in most of cases hyperintense like malignant lesions. This phenomenon can be attributed to the T2 effect.

The above-mentioned problems have led several authors to try other diffusion techniques that enable quantitative analysis of the information diffusion-weighted images through the numeric calculation of the ADC [14,17–20]. The ADC is essential because it eliminates the T2 effect from the diffusion images and provides a quantifiable signal that is directly proportional to the degree of diffusion of water. The problem is that almost every quantitative study published yet uses different $b$ values and sequences so that the ADC values found cannot be compared with each other.

Spin-echo (SE) sequences were the first to be used [19,21], but they suffered from long acquisition times and susceptibil-
Fig. 3. An 11-year-old boy with tuberculous spondylitis. (a) Sagittal T1-weighed spin echo MR image showing L2 and L3 vertebral body signal hypointensity with respect to normal bone marrow. (b) Sagittal STIR image showing diffuse signal hyperintensity in the affected vertebral bodies. (c) Sagittal MR T1-weighted image after contrast agent injection showing signal hyperintensity in the affected vertebral bodies and the disk. (d) The ADC value was low ($0.899 \times 10^{-3} \text{mm}^2/\text{s}$).

...ity to motion artifacts. We employed echo-planar sequences (EPI) in this study. Unlike SE sequences, EPI sequences are acquired in a few seconds and are therefore not susceptible to motion artifacts. Their main drawback is their low signal-to-noise ratio, which means they have a strong tendency to suffer susceptibility artifacts involving signal loss and distortion, limiting their use in the musculoskeletal system. At cervical and thoracic spine sometimes do not result in sufficient signal [5].

Even so, EPI sequences are currently the most widely accepted diffusion sequences and have been proposed as the technique of choice for the quantitative analysis of diffusion images, as the diffusion and relaxation effects contribute independently to the MR signal and can be easily separated [10,19,20].

Our results using EPI sequences mostly corroborate the results reported in the literature regarding quantitative ADC values. Lesions with high cellularity, i.e., malignant lesions, present...
Fig. 4. A 60-year-old woman with subacute (8 weeks) benign compression fracture of the vertebral body. (a) Sagittal T1-weighed spin-echo MR image showing hypointense T9 vertebral body with respect to normal bone marrow. (b) Sagittal T2-weighed fast spin echo MR image showing T9 vertebral body fracture. The linear area of hyperintensity anterior and adjacent to the fractured superior end plate represents the fluid sign. (c) Sagittal STIR image shows diffuse hyperintensity in the fractured vertebral body caused by bone marrow edema. (d) Calculated ADC of the fractured vertebral body was low ($0.941 \times 10^{-3}$ mm$^2$/s) similar to malignancy.
reduced diffusion of free water and therefore low ADC values (although not as low as normal vertebral bodies). Contrarily, posttraumatic osseous edema (benign) shows increased diffusion with consequent high ADC values (higher than malignant pathology with high cellularity and than normal bone marrow) [10–12,22]. In the benign group, lesions corresponding to infectious spondylitis presented values similar to malignancy, as it has been reported [23]. In fact, that is the only study in the literature that compares directly ADC values in infection with those of malignant lesions, carried out in 51 patients, concluding that the diffusion technique is not useful due to the overlap in ADC values.

Our series included a case of an eight-week-old benign fracture that had low ADC values. When interpreting the ADC, it seems to be essential to determine the exact age of a benign fracture, as these values will theoretically decrease progressively.
until they reach the practically null values of a normal bone marrow in a chronic collapse (minimal diffusion of water does occur in normal bone marrow). Therefore, evaluating the ADC in the subacute period can result in a false positive for malignancy with ADC values within the malignant range [10].

5. Conclusions

Despite the lack of histological proof in some patients, we conclude from our results that ADC values represent a useful complementary tool in the differentiation between acute benign fractures from malignant and infectious lesions, but they do not help differentiate malignancy from infection. It is of vital importance to know the age of subacute benign lesions, as the ADC values for these lesions overlap with those of malignant and infectious lesions. Further studies with larger series are necessary to confirm these results.

References
