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ARTICLE

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MRI gadolinium enhancement of bone marrow: age-related changes in normals and in diffuse neoplastic infiltration

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Abstract *Objective:* To quantify gadolinium-related enhancement in the bone marrow of the spine in normals and in patients with homogeneous diffuse malignant bone marrow infiltration.
Design and patients: The patients consisted of two groups: group 1 comprised 94 healthy adults (18–86 years) without bone marrow disease and group 2 comprised 30 patients with homogeneous diffuse malignant bone marrow infiltration due to myeloma (n=20) or breast carcinoma (n=10). All patients received intravenous gadopentetate dimeglumine (Gd-DTPA), 0.1 mmol/kg body weight. Pre- and postcontrast signal intensity (SI) on T1-weighted spin-echo (SE) images (TR/TE: 572 ms/15 ms) was measured over a region of interest (ROI) and the percentage SI increase was calculated. The results were confirmed by bone marrow biopsy (n=20) and clinical parameters (n=10). Dynamic contrast-enhanced studies using a spoiled gradient-recalled-echo (GRE) sequence (TR/TE/α: 68 ms/6 ms 75°) were performed in 10 controls with normal bone marrow.
Results and conclusion: Contrast material enhancement in healthy persons can vary greatly (range 3–59%, mean 21%, SD 11%). With increasing age there is a significant decrease in contrast enhancement (Pearson's correlation, P<0.01). The percentage SI increase in patients with intermediate-grade (biopsy 20–50 vol%) and high-grade (biopsy >50 vol%) diffuse malignant bone marrow infiltration was significantly higher than in normals (mean 67%, SD 34%, P<0.001). Low-grade (biopsy <20 vol%) diffuse malignant bone marrow infiltration can not be assessed by non-enhanced T1-weighted SE images or Gd-DTPA application. In conclusion, contrast material enhancement in healthy persons can vary greatly and is dependent on age, while intermediate-grade and high-grade diffuse malignant bone marrow infiltration can be objectively assessed with SI measurements.

Key words Bone marrow · MRI · Spine · Gadopentetate-dimeglumine · Diffuse infiltration · Contrast enhancement

Introduction

Nodular bone marrow involvement of the spine in malignant diseases and the use of contrast media has been the subject of previous MRI studies [1–3]. Diffuse malignant bone marrow infiltration was rarely reported and no attempts were made towards quantitative assessment of signal intensity (SI) changes [4–7]. Homogeneous diffuse decrease in SI in bone marrow on T1-weighted images and contrast enhancement is clearly subjective and is not as obvious as nodular bone marrow involvement, which is readily appreciated due to the high contrast between tumorous tissue and normal bone marrow. Moreover, SI of bone marrow can vary greatly among individ-

uals. In younger age groups, SI of bone marrow can be low on T1-weighted images [8]. The aim of this study was to quantify the SI increase in bone marrow on T1-weighted spin-echo (SE) images following contrast material application in healthy individuals and in patients with diffuse malignant bone marrow infiltration.

Patients and methods

The examination protocol included sagittal T1-weighted SE sequences (TR/TE: 572/15 ms) before and after intravenous gadopentetate dimeglumine (Gd-DTPA) application (0.1 mmol/kg body weight). Additionally, T2-weighted SE sequences (TR/TE: 3900/90 ms) and/or STIR sequences (TI/TR/TE: 150/3660/60 ms) and/or opposed phase gradient-recalled-echo (GRE) sequences (TR/TE/α: 572 ms/17 ms/90°) were employed. The post-contrast scan was started 1 min after contrast material injection. All patients were scanned at 1.0 T (Impact, Siemens Erlangen, Germany), using a spinal surface coil (field of view 280 mm). Scan parameters on pre- and post-contrast acquisitions were identical. In order to assess changes in SI within the same patient as a variable of time, dynamic contrast sutdies with a spoiled GRE sequence (Flash, TR/TE/α=68 ms/6 ms/75°) were performed in ten individuals without bone marrow disease. For a total time of 7 min the GRE sequences were repeated every 20–21 s. Injection followed the first non-enhanced scan in this series.

SI measurements were made within circular region of interests (ROIs; mean 1.2 cm^2, range 0.2–2.1 cm^2). ROIs were placed in three vertebral bodies of each patient and the mean SI value was calculated to compensate for SI differences within the bone marrow of the same patient, dependent on changes in the ROI's position. Only vertebral bodies near to the centre of the spinal coil were measured to avoid areas of coil-related signal loss. Midsagittal slices, including areas of the basivertebral vein, were excluded from the measurements. The ROIs were placed in identical positions of the vertebral body in T1-weighted images before and after injection of contrast material. The percentage SI increase was calculated as:

$$x_2 = \frac{[(\text{SI after contrast applic.}) - (\text{SI before contrast applic.})]}{\text{SI before contrast applic.}} \times 100\%$$

The patients consisted of two groups: 94 patients (42 male, 52 female) without bone marrow abnormalities (group 1) and 30 patients with homogeneous diffuse malignant bone marrow infiltration caused by myeloma (n=20) or breast cancer (n=10) (group 2).

In order to evaluate the normal increase in SI following injection of contrast material, a control group of 94 persons without bone marrow disease was examined. These examinations were performed to rule out or to confirm spinal pathologies such as disc herniation or spinal stenosis. Patients with bone marrow abnormalities in erosive osteochondrosis, with acute or chronic infection or neoplastic disease were not included. To evaluate age-dependent differences in contrast enhancement we examined patients over a wide age range (18–86 years, mean 50 years).

Twenty patients in group 2 suffered from multiple myeloma. All these patients underwent bone marrow biopsy from the posterior iliac crest and magnetic resonance imaging of the lumbar and/or thoracic spine prior to chemotherapy or radiation therapy. Volume percentage of plasma cell infiltration was evaluated by an experienced histologist (low, 5–20 vol%; intermediate, 20–50 vol%; high, >50 vol%). Ten patients in group 2 suffered from metastatic breast carcinoma, with homogeneous diffuse signal decrease in all vertebral bodies on T1-weighted SE images. Diagnosis in these patients was confirmed by laboratory parameters and clinical follow-up examinations. The mean length of clinical follow-up was 5 years. The laboratory parameters alkaline phosphatase, indicating high bone matrix turnover, and the breast-cancer-specific tumor marker CA 15/3 were chosen. In one patient diagnosis was confirmed at autopsy.

Statistical significance was calculated by Student's t-test and Pearson's correlation.

Results

Dynamic contrast-enhanced studies showed a steep increase in bone marrow SI following intravenous Gd-DTPA within the first 40–60 s. SI after contrast material

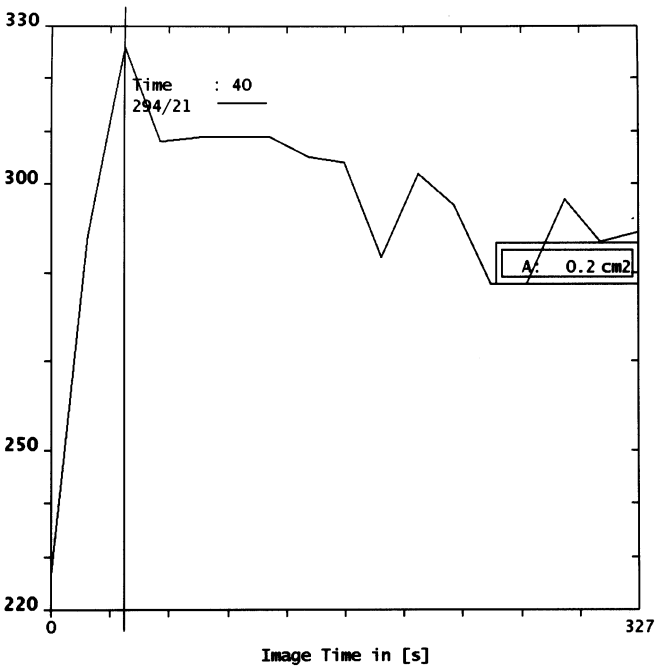


Fig. 1 Dynamic contrast study in bone marrow of a healthy person shows a steep increase within the first 40 s and a slow decrease in the following 7 min

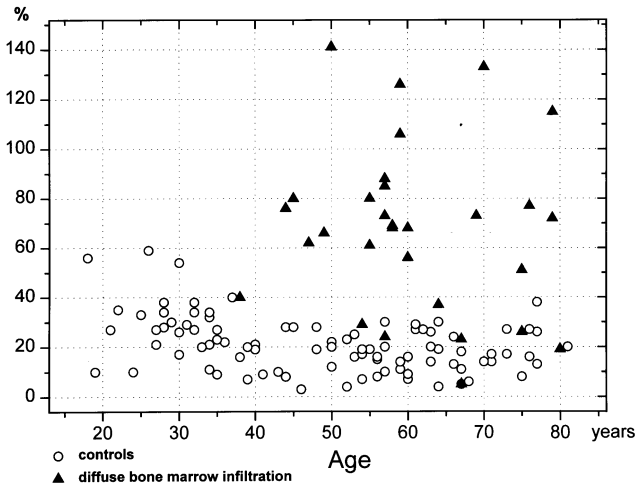
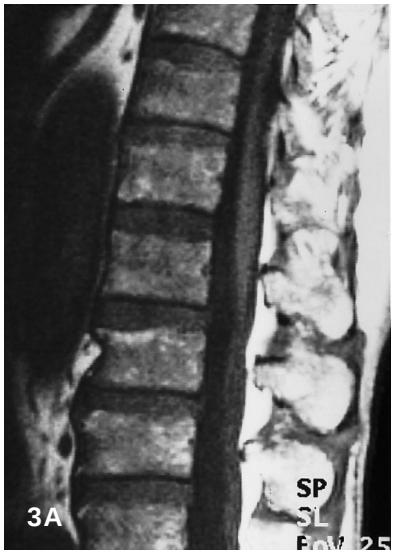


Fig. 2 The plot diagram shows the values of the signal intensity (SI) increase after gadopentetate dimeglumine (Gd-DTPA) in normals and in patients with diffuse bone marrow infiltration



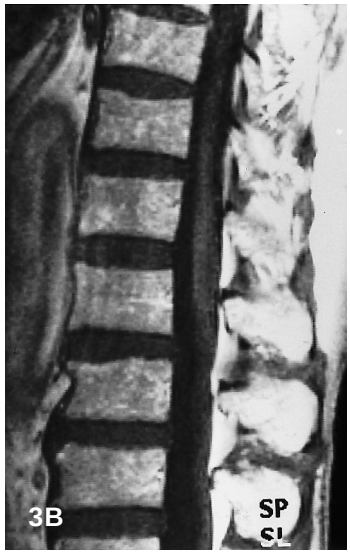
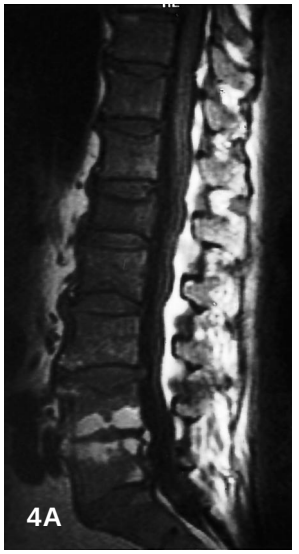


Fig. 3A, B A 57-year-old patient with newly diagnosed multiple myeloma. A decrease in SI on T1-weighted SE images is not obvious. The SI increase after Gd-DTPA application was 51%, corresponding to intermediate-grade plasma cell infiltration



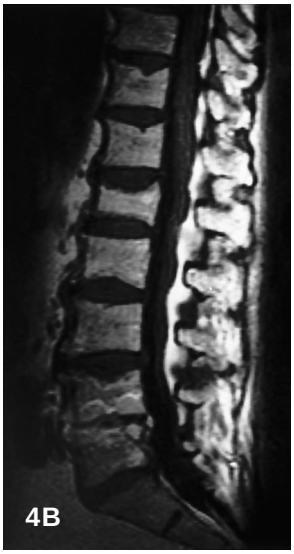
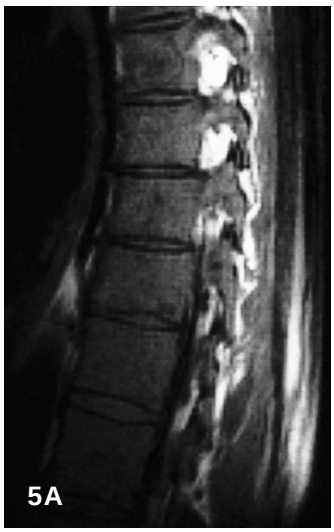
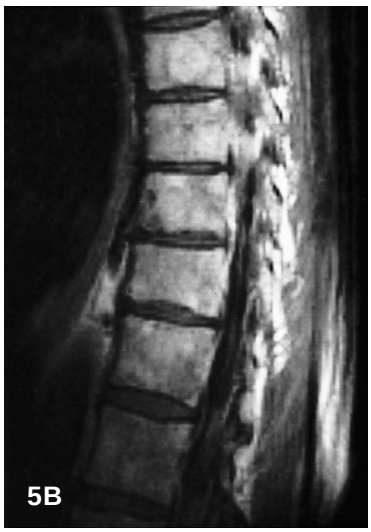


Fig. 4A, B A 61-year-old patient with newly diagnosed multiple myeloma. T1-weighted SE sequence shows a homogeneous decrease in SI in all lumbar vertebral bodies, due to high-grade infiltration with myeloma cells and fat cell displacement. The percentage increase in SI after Gd-DTPA injection was 115%. Degenerative disc disease Modic type II [22].





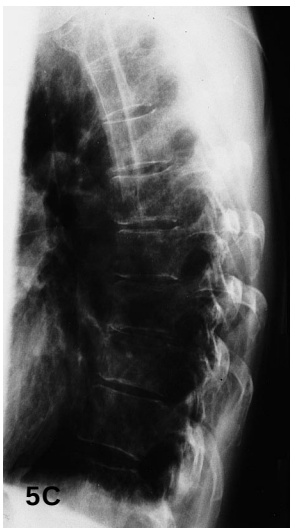


Fig. 5A–C A 47-year-old patient with metastatic breast carcinoma. T1-weighted SE images show the same infiltration patterns as in myeloma patients, with diffuse decreased SI and marked Gd-DTPA enhancement of 89%. **C** Plain radiograph of the same patient showed no alterations of bony structures of the spine

injection did not stay on a stable plateau, but showed a slow decrease within the following 7 min (Fig. 1). The mean percentage decrease in SI per minute after Gd-DTPA injction was 6%. The percentage increase in SI on T1-weighted SE images varied greatly among the healthy individuals (mean 21%, SD 11%, range 3–59%). Except for three young female patients <30 years the SI increase did not exceed 40%. There was a significant decrease in contrast material enhancement with increasing age (P<0.01) (Fig. 2).

Eight patients with multiple myeloma had low-grade interstitial infiltration by plasma cells at biopsy. These patients showed no visible alteration of SI on non-enhanced T1-weighted SE images and no significant difference in SI increase compared with normals (mean 25%, SD 11%, range 5–40%).

Eight patients had intermediate infiltration of bone marrow by plasma cells at biopsy. On non-enhanced T1-weighted SE images they showed either no SI alterations or a mild to moderate decrease in SI. The increase in SI after Gd-DTPA was significantly (P<0.001) higher in these patients than in the normals (mean 75%, SD 19%, range 51–115%) (Fig. 3).

Four patients with multiple myeloma had high-grade diffuse infiltration at bone marrow biopsy. They showed a marked decrease in SI on T1-weighted SE images (Fig. 4). The intervertebral discs were isointense or relatively brighter than the bone marrow. The SI increase after Gd-DTPA application was significantly (P<0.001) higher in these patients than in the normals (mean 88%, SD 27%, range 62–126%), but not significantly (P>0.05) higher than in the patient group with intermediate-grade myeloma infiltration.

Ten patients with metastatic breast cancer also showed diffuse bone marrow involvement with a decrease in SI in all vertebral bodies on T1-weighted SE images. Following contrast enhancement the SI increase was significantly ($P<0.001$) higher than in normals (mean 89%, SD 37%, range 66–141%) (Fig. 5). The SI increase did not differ significantly ($P<0.05$) when compared with that in myeloma patients. Alkaline phosphatase was high in all these patients (mean 514 U/ml, SD 262 U/ml). CA 15/3 was also high in all patients (mean 335 U/ml, SD 212 U/ml) and showed a steep increase over the 2–3 months prior to MRI.

Discussion

The SI increase within the bone marrow of healthy individuals without bone marrow disease has been measured in one previous study [9]. The aim of that study was to assess bone marrow blood supply by gadolinium-enhanced MRI. The results gave no indication of the quantity of blood supply. Some authors conclude that there is no gadolinium enhancement in normal bone marrow [10]. Our study clearly demonstrates major interindividual variations of contrast enhancement in normal individuals (3–59%) (Fig. 2). Our results show a significantly higher contrast enhancement in younger individuals; three young females had a SI increase of 54–59% and are therefore within the range typical of diffuse malignant bone marrow infiltration. Laboratory parameters, including differential blood, creactive protein and ESR were normal. SI on T1-weighted SE images was low over all vertebral bodies, similar to the findings in diffuse malignant infiltration. This variability in signal pattern of young adults should not be misdiagnosed as malignant infiltration. Despite age, interindividual differences in the fat cell content in normal bone marrow may be responsible for the different SI increases after Gd-DTPA application [11]. Dynamic contrast-enhanced studies in normal bone marrow of vertebral bodies have not been carried out previously, although some studies have investigated nodular malignant involvement [2, 12]. Our results show that the time interval between contrast material injection and the MRI scan can contribute to differences in the SI increase. However, this is not a major factor, since the increase in SI persists for longer periods and the peak level of SI increase was reached after 40–60 s.

Screening of bone marrow for metastatic foci in malignancies is a routine procedure in MRI. Due to the good contrast compared with normal bone marrow, the malignant focal deposits are easily recognized. Other pulse sequences, such as STIR, opposed phase GRE sequences or fat saturation pulse sequences, can improve the contrast relative to normal bone marrow [13–15]. Homogeneous diffuse decrease in the SI of bone marrow on T1-weighted SE images can be found in four different conditions: osteomyelofibrosis, uncontrolled stem cell proliferation (e.g. in myelodysplastic syndrome), stem cell stimulation in haemolytic anaemia or leukaemic inflammatory reaction, and malignant replacement of normal bone marrow [16]. In the last three conditions the homogeneous diffuse decrease in SI in all vertebral bodies on T1-weighted SE images results from a homogeneous replacement of fat cells within the bone marrow, with an increase in water-bound protons. In addition to multiple myeloma, diffuse malignant bone marrow infiltration is found in leukaemia and Hodgkin's lymphoma [17].

Focal multiple myloma infiltration was the subject of several previous studies [5–7, 12, 17, 19, 20] whereas diffuse infiltration in multiple myeloma has been mentioned by only a few authors [5–7]. However, homogeneous diffuse bone marrow involvement in myeloma is not a rare condition. In a previous study by our group, diffuse and combined diffuse/nodular involvement in multiple myeloma was found in 48% of patients; Libshitz et al. [6] and Moulopolous et al. [7] detected diffuse marrow involvement in multiple myeloma in 48% and 24%, respectively. Since no contrast relative to normal bone marrow exists, this type of diffuse marrow infiltration may easily be overlooked. If quantitative measurements are not performed, a homogeneous decrease in SI can only be assessed visually and is dependent on the experience of the reader. Moreover, windowing of the images may play an important role in these cases. In previous studies on patients with multiple myeloma, contrast enhancement was not found to be useful for the detection of foci of myeloma since the contrast of myeloma nodules relative to adjacent normal bone marrow is decreased or lost after contrast enhancement [12, 18]. However, diffuse myeloma infiltration was not taken into consideration in these studies. Especially in cases of intermediate-grade diffuse bone marrow infiltration, a decrease in SI on non-enhanced T1-weighted SE images can be absent or only minor.

Low-grade interstitial malignant bone marrow infiltration can not be assessed by non-enhanced or enhancd T1-weighted SE sequences. This may be explained by the fact that variations in the fat/water ratio in low-grade myeloma infiltration do not exceed the interindividual variations in haematopoietic and fat cell composition of normal bone marrow. However, biopsy-proven low-grade myeloma infiltration is an important diagnosis, although without therapeutic consequence. Intermediate- or high-grade diffuse malignant bone marrow infiltration, requiring therapy, can be verified by contrast-enhanced MRI and subsequent SI measurements. In the age group >30 years an increase in SI of more than 40% reflects diffuse bone marrow infiltration. Although contrast enhancement in intermediate-grade diffuse bone marrow infiltration tends to be less severe than in high-grade infiltra-

tion, in our study these two degrees of tumorous infiltration did not differ significantly in terms of contrast enhancement. This may be due to the fact that fat cells are not displaced totally in cases of high-grade myeloma infiltration, while in cases of intermediate plasma cell infiltration, fat cells can totally be displaced [21].

Breast cancer is a systemic disease and even in the early stages low-grade interstitial diffuse infiltration of cancer cells in the bone marrow can appear. We demonstrated that diffuse bone marrow involvement in multiple myeloma and in breast cancer may be missed using T1-weighted SE sequences alone. Contrast enhancement with SI measurements can identify diffuse infiltration and can be helpful in selected cases where initial imaging findings are equivocal.

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