Magnetic Resonance Imaging of Femoral Marrow in Patients With Myelodysplastic Syndromes or Leukemia

By Shojiro Takagi, Osamu Tanaka, and Yasusada Miura

We evaluated magnetic resonance imaging (MRI) of femoral marrow in 85 untreated adult patients with myelodysplastic syndromes (MDS) (N = 27), aplastic anemia (N = 9), and leukemia (N = 49). Images of femoral marrow were obtained using a T1-weighted spin-echo (SE) method and a short T1 inversion recovery (STIR) technique. In patients with MDS, the change in MRI pattern from a fatty or nodular pattern to a uniform pattern correlated with disease progression. Evolution to acute leukemia in MDS patients was associated with a higher signal intensity on STIR images (lower signal intensity on T1-weighted SE images) and an extended area of involvement. The femoral marrow in patients with de novo acute myeloid leukemia (AML) showed increased signal and varied patterns (scattered to uniform) on STIR images. However, the faint pattern (grade 4a) was characteristic of M2 AML. In patients with chronic myelogenous leukemia (CML) in the chronic phase, increased leukemic mass was represented by replacement of the femoral marrow with a region of abnormal signal intensity. The extent of involved areas in these CML patients correlated with the spleen size. This study indicates that MRI of femoral marrow is an important tool for the accurate diagnosis and management of patients with MDS and leukemia that may function as an adjunct to bone marrow aspiration and biopsy.

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Patients. Twenty-seven adult patients with MDS [RA, 8; RARS, 4; RAEB, 5; RAEB-T, 7; chronic myelomonocytic leukemia (CMMoL), 3] were studied. We also evaluated 29 adult patients with de novo acute leukemia, 11 adult patients with acute myeloid leukemia (AML) preceded by MDS, and 9 adult patients with chronic myelogenous leukemia (CML). To assess the role of femoral marrow...
MRI in diagnosing MDS, we also studied nine adult patients with aplastic anemia. The patients' ages ranged from 16 to 85 years (median, 56 years). There were 50 male patients and 35 female patients. The diagnoses of MDS and acute leukemia were made according to the FAB criteria. In all patients, MRI studies were performed at the time of diagnosis and during therapy. Patients with other diseases, such as malignant tumors and hematologic disorders, which might influence the MRI evaluation, were excluded from this study.

**MRI.** MRI was performed using SE sequences with the whole-body coil in a 1.5-Tesla superconducting system (MRT 200FX/II; Toshiba, Tokyo, Japan). Coronal T1-weighted SE images of the femurs were obtained in contiguous 10-mm slices in a 256 × 256 matrix with TR, 400 ms; TE, 20 ms; and number of signal acquisitions, 2. In these T1-weighted SE images, tissues with a short proton TI, such as fatty tissue, have a high signal intensity and appear bright, whereas those with a long TI, such as cellular marrow, have a low signal intensity and appear dark. STIR coronal images of the femurs were obtained in 10-mm slices in a 256 × 256 matrix with TR, 1,500 ms; TE, 20 ms; and TI, 150 ms. In STIR images, signal from fatty tissue is eliminated, whereas signal from tissues with a longer TI is progressively brighter. Figure 1 shows T1-weighted SE and STIR images of normal adult femoral marrow. The results of the MRI were evaluated by two observers, and the general patterns in femurs were categorized as follows: grade 1, fatty or normal; grade 2, fatty with small nodules (nodular); grade 3, focal marrow fat replacement with scattered (3A) or uniform pattern (3B); and grade 4, displacement of marrow fat throughout the femur in a scattered (4A [faint], the signal intensity of femoral marrow on STIR is equal to or lower than that of muscle; 4A, the signal intensity of femoral marrow on STIR is higher than that of muscle) or uniform pattern (4B) (Fig 2).

**Fig 1.** MRI appearance of normal adult femoral marrow. STIR image (A) and T1-weighted SE image (B).

**Statistical analysis.** Correlation between the MRI patterns and clinical diagnosis of MDS was determined by Cochran-Mantel-Haenszel test. The differences between the MRI patterns in M2 AML patients were analyzed with Fisher’s exact method. The significance of differences between rates of complete remission or relapse in patients with de novo acute leukemia was analyzed with the chi-square test. The differences were considered significant if the $P$ value was < .05.

**RESULTS**

**MRI patterns of femoral marrow in patients with MDS.** Fatty (grade 1), nodular (grade 2), and faint (grade 4a) patterns of femoral marrow MRI were observed in 10 of the 12 MDS patients with good prognoses (RA or RARS) (Table 1). Only two of these patients (17%) showed grade 4A or 4B patterns. Eleven of 12 (92%) MDS patients with poor prognoses (RAEB or RAEB-T) had femoral marrow MRI that showed grade 4A or 4B patterns. The marrow MRI of one patient with RAEB showed the grade-3 pattern. The differences in MRI patterns between these two MDS groups were statistically significant ($P = .007$). These data suggest that the grade 4A or 4B pattern of femoral marrow MRI in MDS patients implies advanced disease. The involvement of the greater trochanters and capitofemoral epiphyses was observed in two patients with RAEB-T and one patient with CMMoL. In patients with CMMoL, the pattern of MRI was similar to that of patients with RAEB and RAEB-T. The STIR images of patients with MDS are shown in Fig 3.

**MRI patterns of femoral marrow in patients with aplastic anemia.**

![Fig 2. Patterns of femoral marrow MRI based on STIR images.](image-url)
Table 1. MRI Patterns of Femoral Marrow in Patients With Aplastic Anemia or MDS

<table>
<thead>
<tr>
<th>Pattern of MRI</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4a</th>
<th>Grade 4A &amp; 4B</th>
<th>Total</th>
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<td>0</td>
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<td>2</td>
<td>3</td>
<td>0</td>
<td>8</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
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<tr>
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<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>4 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>RAEB-T</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>7 (6)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>CMMoL</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>10</td>
<td>3 (1)</td>
<td>5</td>
<td>14 (8)</td>
<td>36 (9)</td>
</tr>
</tbody>
</table>

Parentheses indicate number of patients whose disease evolved into acute myeloid leukemia.

Abbreviation: AA, aplastic anemia.

The MRI patterns of femoral marrow are very important for distinguishing between the diagnoses of MDS and aplastic anemia. As shown in Table 1, all nine patients with aplastic anemia showed a fatty (grade 1) or nodular (grade 2) pattern on their femoral marrow MRI (Fig 4). No patients with aplastic anemia showed a grade 3 or grade 4 pattern. Whereas the fatty (grade 1) or nodular (grade 2) pattern of femoral marrow MRI was not a specific finding for patients with aplastic anemia, grade 3 and grade 4 patterns were seen only in patients with MDS. These data indicate that grade 3 and grade 4 patterns of femoral marrow MRI support the diagnosis of MDS rather than aplastic anemia.

Femoral marrow MRI patterns in MDS patients who developed AML. In this study, nine patients with MDS developed AML during their follow-up course (median, 5 months; range, 2 to 41 months). Marrow MRI patterns of these patients at the time of their diagnosis with MDS showed grades 3A (one patient), 4A (five patients), or 4B (three patients) patterns. These patients also underwent marrow MRI when they were diagnosed with leukemia. All 11 AML patients, including two patients who had not had marrow MRI at the time of their diagnosis with MDS, showed grade 4A or 4B patterns. STIR images in these patients at the time of their diagnosis with leukemia showed abnormally involved areas that appeared brighter and more extensive than those obtained at the time of their diagnosis with MDS (Fig 5). These data suggest that the increase in abnormal signal intensity and extension of involved areas may be indicators of leukemic evolution in patients with MDS.

MRI patterns of femoral marrow in patients with de novo acute leukemia. Twenty-nine untreated patients with de novo acute leukemia underwent marrow MRI. Three MRI patterns of femoral marrow were observed in these patients: (1) grade 4a (faint) (N = 9), (2) grade 4A (N = 8), and (3) grade 4B (N = 12). Interestingly, the grade 4a pattern was seen only in patients with the FAB subtype, M2 (Fig 6). Of 14 patients with M2-AML, 9 patients (64%) showed the grade 4a pattern. This femoral marrow MRI was specific for M2-AML patients (P < .001). The rates of complete remission and relapse did not statistically differ among patients illustrating these three types of MRI patterns (P = .898, and .950, respectively). In patients with acute leukemia who achieved a complete remission, the abnormal MRI patterns of femoral marrow usually evolved into a normal fatty pattern. Regions of high signal intensity on STIR images re-

Fig 3. STIR images of femoral marrow in patients with MDS. MDS patients of different FAB categories [(A), RA; (B), RAEB; (C), RAEB-T; (D), CMMoL] showed various patterns of femoral marrow MRI [grade 3A (RA), grade 4A (RAEB), grade 4B (RAEB-T) and grade 4a (CMMoL)].
solved earlier than did areas of low signal intensity on T1-weighted SE images after chemotherapy. However, the MRI patterns of some patients who achieved a complete remission remained abnormal, despite localization of the involved areas. In these patients, marrow relapse occurred within a short period of time after their MRI evaluation. Abnormal MRI findings became more obvious at the time of marrow relapse. These data suggest that the faint pattern of femoral marrow MRI (grade 4a) is characteristic of M2-type de novo acute leukemia, and that femoral marrow MRI may be able to detect foci of residual leukemia.

The MRI pattern of femoral marrow in patients with CML. Nine patients with chronic phase CML underwent MRI evaluation of their femoral marrow. All of these patients had the grade 4B pattern (Fig 7). However, the extent of the areas involved with abnormal signal intensities clearly differed among these patients. This difference was associated with the presence of palpable splenomegaly. In all six patients with palpable splenomegaly, an intense signal focus was usually seen throughout the femoral marrow. Involved areas occupied the proximal half of the femoral marrow in all three patients without palpable splenomegaly. The involvement of the normal yellow marrow areas of the greater trochanters and capitofemoral epiphyses was observed in six patients (67%). In patients who responded to interferon or hydroxyurea, the involved area of femoral marrow was localized, and the degree of abnormal signal intensity was reduced, and the pattern of femoral marrow MRI changed from grade 4B to grade 4A. A blastic crisis occurred in three patients with palpable splenomegaly. The MRI pattern of a blastic crisis in these patients was the same as that associated with the chronic phase of CML (grade 4B pattern involving the greater trochanters and capitofemoral epiphyses).

DISCUSSION

This study indicates that MRI of femoral marrow is a useful tool for the accurate evaluation and follow-up of MDS and leukemia. In patients with MDS, the MRI pattern of femoral marrow changes from a fatty or nodular pattern to a uniform pattern in association with disease progression. Evolution to AML in patients with MDS is associated with abnormally high signal intensities on STIR images (lower signal intensities on T1-weighted SE images) and extension of the involved areas on femoral marrow MRI. In patients with de novo acute leukemia, the faint pattern (grade 4a) was characteristic for M2 AML. Response to chemotherapy was evaluated easily by changes in the femoral marrow MRI pattern. MRI of femoral marrow could detect residual leukemia even in patients with pathologic marrow remission. The increased leukemic mass in patients with CML was shown by abnormal signal intensity replacement of femoral marrow. The extent of the involved area shown by femoral marrow MRI correlated with palpable spleen size.

Different stages of disease also can be reflected by femoral marrow MRI. In this study, 92% of the patients with RAEB or RAEB-T showed grade 4A or 4B patterns on femoral marrow MRI. The fatty (grade 1), nodular (grade 2), and faint (grade 4a) patterns seen with femoral MRI in patients with RA or RARS were not observed in patients with advanced disease states. Most of the MDS patients (89%) who evolved to AML showed the grade 4A or 4B patterns on femoral marrow MRI at the time of their diagnosis with MDS. Various prognostic factors have been proposed for patients with MDS: advanced age, anemia, neutropenia, thrombocytopenia, a high percentage of marrow blasts, extensive dyspoiesis, and cytogenetic abnormalities (particularly involving chromosomes 5 and 7). These data suggest that the grade 4A and 4B patterns of femoral marrow MRI may be an indicator of a poor prognosis and that patterns seen with femoral marrow MRI are helpful in diagnosing FAB subtypes.

Aplastic anemia is one disease that should be distin-
guished from MDS, especially hypoplastic MDS.\textsuperscript{12} In patients with aplastic anemia, it has been reported that marrow MRI shows a fatty pattern.\textsuperscript{13,14} In this study, we observed a fatty (grade 1) or nodular (grade 2) pattern on the femoral marrow MRI of such a patient. A nodular pattern on marrow MRI has been reported in treated patients with aplastic anemia.\textsuperscript{22} None of our patients with aplastic anemia showed the grade 3 or 4 patterns of femoral marrow MRI.

Recently, we evaluated a patient with pancytopenia and a hypoplastic marrow. Repeated BM aspirations from the sternum and the iliac bone and biopsy samples from different sites showed a severely hypoplastic marrow without dysplastic features. There were a few erythroblasts in the peripheral blood, suggesting ineffective erythropoiesis. The MRI pattern of this patient’s femoral marrow showed the grade 4A pattern, although the pelvic marrow was not evaluated by MRI. Several months later the patient developed AML. We now believe that this patient had MDS, rather than aplastic anemia, based on our present knowledge of femoral marrow MRI. Our results confirm the observations of a previous investigator that marrow MRI of the spine yields a heterogeneous diffuse cellular pattern in patients with hypoplastic MDS.\textsuperscript{11} These results suggest that femoral marrow MRI is useful in diagnosing MDS.

Evolution to leukemia occurs in as high as 66\% of MDS patients.\textsuperscript{9} It has been reported that the T1 relaxation times of the vertebral marrow in two MDS patients who evolved to AML were significantly prolonged when compared with normal values.\textsuperscript{12} In our study, evolution to leukemia also influenced the MRI pattern of the femoral marrow. Abnormally involved areas appeared to be brighter on STIR images (and darker on T1-weighted images) and more extensive.

Fig. 5. STIR image of femoral marrow in a patient who evolved to acute leukemia (M6). Grade 4A pattern (A) of femoral marrow MRI observed at the time of diagnosis of RAEB converted to the grade 4B pattern (B) in association with leukemic evolution.

Fig. 6. STIR images (A) and T1-weighted SE images (B) of femoral marrow in patients with de novo acute leukemia. MRI of femoral marrow in a patient with M1 AML (left) showed the grade 4B pattern, whereas the faint pattern (grade 4a) was observed in a patient with M2 AML (right).
than at the time of diagnosis of MDS. The replacement of marrow fat by increased numbers of leukemia cells may be responsible for the abnormal signal intensity of femoral marrow MRI in these patients.

In patients with de novo acute leukemia, MRI of femoral marrow was classified into three patterns: grade 4a, 4A, and 4B patterns. If abnormal signal intensity of femoral marrow reflects the leukemic volume, responses to chemotherapy might be different among these patterns. Poor prognoses might be suspected in patients with the grade 4B pattern. However, the response rates to induction therapy and relapse rate did not differ among these patterns, although disease-free survival has not been fully evaluated because of the short follow-up duration. Other factors such as age, cytogenetic abnormalities, FAB categories, and performance status before chemotherapy may be more important prognostically.

The faint pattern (grade 4a) of femoral marrow MRI was not observed in patients with FAB subtypes other than M2 AML. The reason why patients with M2 AML show this MRI pattern remains unclear. This subtype represents leukemia associated with some degree of maturation. The heterogeneity of the population of leukemic cells that constitute M2 AML may influence the MRI pattern.

It is known that the T1-relaxation time is increased twofold to threefold at the time of diagnosis of acute leukemia. This increased T1-relaxation time decreases toward the normal range in patients with a complete remission, whereas it remains prolonged in patients who do not respond successfully to treatment. After chemotherapy, patients who showed a conversion to the fatty pattern with femoral marrow MRI achieved a durable complete remission. Alternatively, patients in marrow remission who illustrated a persistently abnormal pattern with their femoral marrow MRI relapsed within a short period of time after their MRI evaluation.

In CML it is known that splenomegaly is an important sign of advanced disease. Our study clearly indicates that spleen size correlates with an increased volume of leukemic cells in the BM. White blood cell counts and serum lactic dehydrogenase (LDH) levels did not correlate with the pattern of femoral marrow MRI in these patients.

In this study, the MRI evaluation of femoral marrow was restricted to adult patients because of age-related changes in the marrow distribution. In children and early teenagers, normal hematopoietic marrow is present in the diaphysis and metaphysis of the femoral marrow. Marrow reconversion from red to yellow marrow occurs first in the diaphysis, then in the distal metaphysis of the femur. This must be taken into consideration when using femoral marrow MRI in patients of this age group.

Benign marrow processes may either mask or stimulate MDS or early acute leukemia. Athletes (particularly marathon runners) have peripheral red marrow expansion that causes abnormal signal intensity on marrow MRI of the distal femur. Other benign processes, such as sickle cell anemia, thalassemia, or Gaucher’s disease, may also obscure or simulate marrow malignancies. Therefore, MRI images must always be interpreted in view of their clinical context.

MRI of femoral marrow presents a global view of the BM compartment. This study indicates that femoral marrow MRI plays a very important role in the diagnosis and management of patients with MDS and leukemia.

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