Evidence for Clonal Disease by Magnetic Resonance Imaging in Patients With Hypoplastic Marrow Disorders

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Some patients with hypoplastic marrow disorders, including aplastic anemia (AA), are at risk for clonal evolution to myelodysplastic syndromes (MDS) and leukemia. Magnetic resonance imaging (MRI) of marrow of the spine, pelvis, and femurs was performed in 24 patients with hypoplastic marrow disorders. In 12 patients (three AA, nine MDS) MRI was compatible with the clinical and biopsy diagnoses and served to define the spectrum of marrow patterns in these disorders. In eight patients with hypocellular marrow biopsies and a clinical diagnosis of AA, MRI showed an unexpected inhomogeneous or diffuse cellular pattern. Concurrent or subsequent marrow or cytogenetic studies have led to diagnoses of hypoplastic MDS in seven of these patients. In four patients with prolonged hypoplasia after bone marrow transplantation for lymphoma, a speckled pattern superimposed on a fatty background appeared in serial MRI studies. One case evolved to AML, two developed megaloblastic foci, and one remains hypoplastic at 19 months. This study suggests that MRI is able to detect early clonal disease in patients with AA, and can distinguish AA from hypoplastic MDS.

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Hypoplastic bone marrow disorders result in cytopenias affecting red blood cells (RBCs), granulocytes, and platelets. Primary disorders include aplastic anemia (AA), myelodysplastic syndromes (MDS), and myelofibrosis (MF). Secondary disorders result from extensive marrow infiltration by cancer or lymphoma or from toxic effects of chemotherapy or radiotherapy. Severe AA, as defined by the International Aplastic Anemia Study Group (IAASG),1 has a hypocellular, fatty marrow. MDS, as defined by the French-American-British (FAB) classification,2 has a cellular or hypercellular marrow, frequent cytogenetic abnormalities,3,4 and known risk of evolution to acute myelogenous leukemia (AML).5

Recent studies have suggested clonal evolution from AA to MDS and subsequently AML.6,10-16 The distinction between severe AA and MDS is not always clear, and some cases with features of MDS have hypocellular marrows.12 Hypocellular marrows with scattered foci of myelodysplastic hematopoiesis may easily be misinterpreted as AA if the bone marrow biopsy is small or not representative of the rest of the marrow. In patients with previously treated cancers or lymphomas who are also at risk for MDS and AML,17 more than one factor may contribute to unexplained cytopenias, including recurrent tumor within the marrow and secondary aplasia.

Magnetic resonance imaging (MRI) provides a noninvasive means to examine grossly a large fraction of bone marrow in a relatively short study. Its usefulness derives from the different proton NMR relaxation properties of fatty and cellular tissues. The literature on MRI of the marrow has been reviewed.18-20 The normal age-related distribution of hematopoietic and fatty marrow21-23 and hematopoietic hyperplasia19,20 are readily observed. MRI has been used to study AA,24,25 MDS,26 acute and chronic leukemias,27-31 and myeloproliferative disorders.18,26-34

Severe AA is expected to have a typical appearance in MRI, due to fatty replacement of the marrow. This has been observed in some studies27-31 but not others,24,25 and in one series five of eight patients with AA had inhomogeneous foci.30 In this report, we establish the spectrum of findings in MRI studies of the bone marrow in 12 patients with AA and MDS. We then describe 12 patients with primary or secondary hypoplasia and evidence for cellular foci in the MRI who concurrently or subsequently were found to have clonal marrow disease.

Materials and Methods

Patients were recruited from a tertiary care hematology practice. Signed informed consent was obtained under Institutional Review Board guidelines. Severe AA was defined according to criteria of the IAASG—less than 25% normal cellularity in marrow biopsy and two or three of the following: anemia with reticulocytes less than 1%, corrected for hematocrit (less than approximately 50 x 10⁹/L), granulocytes less than 0.5 x 10⁹/L, and platelets less than 20 x 10⁹/L. MDS with normocellular or hypercellular marrow was defined according to the FAB classification: RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; CMMI, chronic myelomonocytic leukemia; RAEBT, MDS in transformation to leukemia. The term hypoplastic MDS was applied to patients with morphologic or cytogenetic evidence for MDS but less than 20% cellularity in the marrow.

Patients had bone marrow aspirates and biopsies from the posterior superior iliac crest within 6 weeks of the MRI study, and complete blood counts within 3 weeks of the MRI study. Marrow cellularity was determined from the biopsy and estimated to the nearest 10%. Cytogenetic analysis of cells in the bone marrow was performed using both Q-banding and G-banding techniques.

Peripheral blood counts in these patients were stable or worsening, so that hematopoietic response to therapy was not a factor in this study.

Two heavily transfused patients with hemosiderosis, which has a magnetic susceptibility effect causing a marked signal loss within the bone marrow, liver, and spleen in MRI,31 were excluded from this report.

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### Table 1. Clinical Features and MRI Patterns in Patients With AA and MDS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age &amp; Sex</th>
<th>Hgb (g/dL)</th>
<th>Granulocytes (10^9/L)</th>
<th>Platelets (10^9/L)</th>
<th>Dx</th>
<th>Cytogenetics</th>
<th>Marrow Cellularity (%)</th>
<th>MRI Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22 M</td>
<td>8.8</td>
<td>17</td>
<td></td>
<td>AA</td>
<td>Normal</td>
<td>&lt;10</td>
<td>Fatty</td>
</tr>
<tr>
<td>2</td>
<td>32 F</td>
<td>3.6</td>
<td>0</td>
<td></td>
<td>AA</td>
<td>NO</td>
<td>&lt;20</td>
<td>Fatty</td>
</tr>
<tr>
<td>3</td>
<td>64 F</td>
<td>10.1</td>
<td>1.88</td>
<td>32</td>
<td>AA</td>
<td>NO</td>
<td>&lt;20</td>
<td>Fatty</td>
</tr>
<tr>
<td>4</td>
<td>42 F</td>
<td>7.9</td>
<td>0.50</td>
<td>30</td>
<td>MDS</td>
<td>Monosomy 7</td>
<td>&lt;10</td>
<td>Fatty with nodules</td>
</tr>
<tr>
<td>5</td>
<td>17 M</td>
<td>6.5</td>
<td>0.12</td>
<td>16</td>
<td>MDS(RARS)</td>
<td>18q single, dup(1p)</td>
<td>&lt;10</td>
<td>Fatty with nodules</td>
</tr>
<tr>
<td>6</td>
<td>39 F</td>
<td>5.5</td>
<td>2.37</td>
<td>39</td>
<td>MDS(RA)</td>
<td>NO</td>
<td>30</td>
<td>Inhomogeneously cellular</td>
</tr>
<tr>
<td>7</td>
<td>42 M</td>
<td>7.3</td>
<td>2.21</td>
<td>586</td>
<td>MDS(RARS)</td>
<td>5q single, 11p single</td>
<td>40</td>
<td>Inhomogeneously cellular</td>
</tr>
<tr>
<td>8</td>
<td>81 F</td>
<td>8.2</td>
<td>0.10</td>
<td>20</td>
<td>MDS(RAEB)</td>
<td>Normal</td>
<td>30</td>
<td>Inhomogeneously cellular</td>
</tr>
<tr>
<td>9</td>
<td>32 F</td>
<td>8.1</td>
<td>0.07</td>
<td>25</td>
<td>MDS(RAEB)</td>
<td>Monosomy 7</td>
<td>30</td>
<td>Diffusely cellular</td>
</tr>
<tr>
<td>10</td>
<td>33 F</td>
<td>7.0</td>
<td>0.35</td>
<td>13</td>
<td>MDS(RA)</td>
<td>Normal</td>
<td>55-90</td>
<td>Inhomogeneously cellular</td>
</tr>
<tr>
<td>11</td>
<td>45 M</td>
<td>10.7</td>
<td>1.33</td>
<td>37</td>
<td>MDS(RARS)</td>
<td>Trisomy 5, 18, 22</td>
<td>90</td>
<td>Diffusely cellular</td>
</tr>
<tr>
<td>12</td>
<td>43 M</td>
<td>7.6</td>
<td>0.99</td>
<td>13</td>
<td>MDS(RA)</td>
<td>Monosomy 7</td>
<td>70</td>
<td>Diffusely cellular</td>
</tr>
</tbody>
</table>

Abbreviations: Dx, diagnosis; EB, excess blasts; NO, not obtainable; or insufficient quantity of marrow cells; RS, ringed sideroblasts; Hgb, hemoglobin.

MRI was performed using spin-echo radiofrequency pulse sequences with the whole-body transmitter/receiver coil in a 1.5 Tesla Siemens (Iselin, NJ) instrument. Sagittal and coronal T1-weighted images of the spine, sacrum, pelvis, hips, and femurs were obtained in contiguous 7- to 8-mm slices in a 256 x 256 matrix with TR = 550 millisecond, TE = 22 ms, and acquisitions = 2. Presaturation pulses were used to reduce motion artifact from movement in the anterior chest and abdomen. In these T1-weighted images tissues with a short proton T1, such as fatty tissue, have high signal and appear bright, while those with a long T1, such as cellular marrow, have low signal and appear dark. Short time-interval inversion recovery (STIR) sagittal images of the spine and coronal images of the femurs were obtained in 7-mm slices with a 3.5-mm gap in a 256 x 256 matrix with TR = 1,500 ms, TE = 22 ms, and TI = 130 ms. The TI of 130 ms was selected because it resulted in the most complete elimination of the signal from fatty tissues. In

Fig 1. MR images of patient no. 3 (Table 1) with AA. Sagittal T1-weighted image of spine (A) shows some inhomogeneity but predominantly high signal and STIR image (B) shows absence of signal, compatible with a diffusely fatty marrow.
Fig 2. Patterns observed in sagittal T₁-weighted MRI of the spine in patients with MDS. (A) Patient no. 5 (Table 1) illustrates the pattern of small nodules superimposed on a fatty background. (B) Patient no. 10 (Table 1) illustrates the inhomogeneously cellular pattern of MDS. (C) Patient no. 11 (Table 1) illustrates the diffusely cellular pattern of MDS. (D) STIR image of the patient in (B) confirms a mixture of fatty and cellular regions.
MRI OF MARROW IN HYPOPLASTIC DISORDERS

Table 2. Clinical Features of Patients With a Diagnosis of AA and MRI Evidence for Focal or Diffuse Cellularity

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age &amp; Sex</th>
<th>Hgb (g/dL)</th>
<th>Granulocytes (10^9/L)</th>
<th>Platelets (10^9/L)</th>
<th>Marrow Cellularity (%)</th>
<th>MRI Pattern</th>
<th>Adjunctive Evidence for Clonal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>26 M</td>
<td>5.7</td>
<td>1.62</td>
<td>11</td>
<td>10</td>
<td>Fatty with nodules</td>
<td>Megaloblastic foci</td>
</tr>
<tr>
<td>14</td>
<td>57 M</td>
<td>6.4</td>
<td>0.63</td>
<td>15</td>
<td>15</td>
<td>Inhomogeneously cellular</td>
<td>Trisomy 8</td>
</tr>
<tr>
<td>15</td>
<td>59 M</td>
<td>7.9</td>
<td>0.87</td>
<td>37</td>
<td>&lt;5</td>
<td>Inhomogeneously cellular</td>
<td>Rare blast in buffy coat; macrocytes</td>
</tr>
<tr>
<td>16</td>
<td>66 M</td>
<td>9.6</td>
<td>0.30</td>
<td>48</td>
<td>10</td>
<td>Inhomogeneously cellular</td>
<td>Blasts in buffy coat</td>
</tr>
<tr>
<td>17</td>
<td>27 M</td>
<td>12.4</td>
<td>1.08</td>
<td>184</td>
<td>&lt;20</td>
<td>Inhomogeneously cellular</td>
<td>None, at 10 mo follow-up</td>
</tr>
<tr>
<td>18</td>
<td>12 M</td>
<td>6.1</td>
<td>0.10</td>
<td>13</td>
<td>&lt;10</td>
<td>Diffusely cellular</td>
<td>Monosomy 7</td>
</tr>
<tr>
<td>19</td>
<td>45 F</td>
<td>10.7</td>
<td>1.40</td>
<td>45</td>
<td>20</td>
<td>Diffusely cellular</td>
<td>Acrocentric fragments. Evolved to AML (M7)</td>
</tr>
<tr>
<td>20</td>
<td>25 M</td>
<td>13.0</td>
<td>1.46</td>
<td>13</td>
<td>&lt;15</td>
<td>Diffusely cellular</td>
<td>Dysplastic and sideroblastic foci in sternal aspirate</td>
</tr>
</tbody>
</table>

Abbreviations are the same as in Table 1.

the STIR images, signal from fatty tissue, which has a very short T1, is eliminated while signal from tissues with progressively longer T1 are progressively brighter. Proton density and T2-weighted images of selected sites were obtained in contiguous 7-mm slices in a 128 x 128 matrix with TR = 2,500 ms, TE = 35 and 90 ms, and acquisitions = 2.

MRIs were reviewed by two observers, and the general pattern in the spine, pelvis, and femurs was categorized as: (1) fatty, (2) fatty with small cellular nodules, (3) inhomogeneously cellular, and (4) diffusely cellular.

RESULTS

Spectrum of marrow MRI patterns in patients with AA or MDS. The clinical and MRI features of 12 patients in this category are summarized in Table 1. Three had AA, two hypocellular MDS, and seven cellular or hypercellular MDS. These patients serve as a reference set.

Figure 1A shows the appearance of a fatty marrow in a patient with aplastic anemia: abnormally bright signal in the T1-weighted image. This image, while clearly fatty, is somewhat inhomogeneous. The fact that inhomogeneity is not caused by cellular foci is shown by the total absence of signal in the marrow in the STIR image (Fig 1B).

Three abnormal marrow patterns in MRI were observed in patients with MDS: (1) multiple small nodules, often superimposed on a fatty background (Fig 2A); (2) inhomogeneously cellular lesions (Fig 2B); and (3) relatively diffuse cellularity (Fig 2C). That the inhomogeneous pattern of Fig 2B consists of fatty and cellular regions is shown in the STIR image in Figure 2D.

In the patients in Table 1, the marrow biopsy results were representative of the remainder of the marrow assessed with MRI. Hypocellular marrows were fatty or fatty with small nodules in MRI; normocellular or hypercellular marrows were inhomogeneously or diffusely cellular in MRI.

Detection of cellular foci in AA by MRI. Eight patients with hypocellular marrow biopsies were referred to us with clinical diagnoses of AA, but had abnormalities in MRI of the marrow not compatible with AA alone but suggestive of MDS. The clinical and MRI features of these patients (nos. 13 through 20) are summarized in Table 2.

MR images from patient no. 14 show a multifocal inhomogeneous pattern with an admixture of fatty regions (Fig 3). Additional support for a diagnosis of MDS in this patient is provided by the finding of a trisomy 8 cytogenetic abnormality. None of these patients had more than 5% blasts in their bone marrow at the time of, or just preceding, the MRI study, but adjunctive evidence for MDS was found concurrently or during subsequent follow-up in seven of these eight patients. Two had cytogenetic abnormalities, one had megaloblastic foci, two had blasts detected in the buffy coat, and one evolved to AML (M7). One (patient no. 20) had hypoplastic iliac crest biopsies but dysplastic and sideroblastic foci in a sternal aspirate. In the eighth (patient no. 17), who has only mild anemia and moderate leukocytopenia, the clinical diagnosis remains AA at 10 months follow-up, but the MR study clearly shows a predominantly cellular marrow.

In these patients with a diagnosis of AA and MRI evidence of inhomogeneous or diffuse cellularity (Table 2), the marrow biopsies were not representative of the remainder of the marrow assessed with MRI.

Suspected clonal disease in previously treated lymphoma patients with pancytopenia. This group consists of four patients (nos. 21 through 24 in Table 3) who had previously received intensive treatment for lymphoma, and now had

Table 3. Clinical Features of Patients With Prolonged Or Recurrent Pancytopenia After Prior Chemotherapy And Bone Marrow Transplantation for Lymphoma, With MRI Evidence for Clonal Disease

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age &amp; Sex</th>
<th>Hgb (g/dL)</th>
<th>Granulocytes (10^9/L)</th>
<th>Platelets (10^9/L)</th>
<th>Marrow Cellularity (%)</th>
<th>MRI Pattern</th>
<th>Adjunctive Evidence for Clonal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>29 M</td>
<td>7.5</td>
<td>0.16</td>
<td>26</td>
<td>10-20</td>
<td>Evolution to AML (M4)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>33 F</td>
<td>6.7</td>
<td>0.81</td>
<td>31</td>
<td>10</td>
<td>Megaloblastic foci</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>26 F</td>
<td>9.4</td>
<td>2.00</td>
<td>73</td>
<td>10</td>
<td>Megaloblastic foci</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>60 M</td>
<td>11.8</td>
<td>0.10</td>
<td>94</td>
<td>&lt;10</td>
<td>Nucleated RBCs in peripheral blood</td>
<td></td>
</tr>
</tbody>
</table>
Fig 3. MR images of patient no. 14 (Table 2) with an initial diagnosis of AA, but a final diagnosis of hypoplastic MDS. (A) Coronal T₁-weighted image of spine shows multifocal defects (inhomogeneously cellular pattern). (B) Sagittal STIR image confirms extensive cellular areas.
unexplained pancytopenias and hypocellular marrow biopsies. The T₁-weighted MR images generally showed a somewhat fatty background marrow pattern, but superimposed on this was a speckled pattern of small nodular lesions. The sequence of events in case no. 21 is shown in Fig 4. The speckled pattern preceded by 2 months a diagnosis of secondary AML. In the course of serial studies in over 100 patients following bone marrow transplantation, this pattern has appeared in three patients (nos. 22 through 24). Although this pattern can be a manifestation of normal hematopoietic recovery, this was not the case in these patients because of the persistent hypocellularity of their marrow biopsies, occurring at 15, 10, and 19 months after transplantation, respectively. Therefore, we suspect that the speckled pattern, which is very similar to that observed in patients with established hypoplastic MDS (Fig 2A), indicates early clonal disease. In fact, two of these patients have developed otherwise unexplained megaloblastic foci in their marrow biopsies, and the third (no. 24) has progressively severe neutropenia with peripheral nucleated RBCs at 19 months after transplantation.

DISCUSSION

These results suggest a role for MRI as a problem-solving tool in selected patients with hypoplastic marrow disorders. In particular, MRI appears to be able to distinguish aplastic anemia from hypoplastic MDS, and to provide evidence for clonal disease (MDS or AML) at an early stage.

MRI is complementary to the bone marrow biopsy in that, although it shows only the gross anatomy of the marrow, it can sample a large fraction of the active marrow in a single, noninvasive, clinical study. Abnormal marrow patterns in MRI are not specific. For example, the diffusely cellular pattern also occurs in acute and chronic leukemias, and the inhomogeneously cellular pattern also occurs in lymphoma and multiple myeloma. Howevcr, once an abnormal pattern is detected in MRI, then MRI can be used in place of biopsies when serial studies are desired.

The ability of MRI to distinguish patients with hypoplastic MDS from those with AA relies primarily on the finding of multinodular or inhomogeneous foci superimposed on either a normal or a fatty background. It should be emphasized that the typical appearance of fatty marrow in MRI—bright signal in T₁-weighted images and no signal in STIR images—can be altered by the presence of hemosiderosis. The typical fatty appearance of AA can also be altered by effective treatment, in which foci of normal hematopoiesis appear. Therefore, interpretation of MRI must take into account the patient’s transfusion history and any recent treatments, neither of which were factors in the patients presented here.

The MRI methods we used in this study permit imaging of a fairly large area of marrow in a period of time (45 minutes) tolerated by virtually all patients. In our experience the combination of T₁-weighted and STIR images are most useful. The sensitivity of MRI to marrow disease might be improved by a quantitative separation of fat and water signals, made possible by the chemical shift differ-
ence of water and methylene protons. One way to accomplish this is to perform chemical shift imaging, and another is to perform $^1$H NMR spectroscopy. However, the latter can only be obtained from a limited portion of the marrow in a reasonable amount of time. Quantitative information derived from the images might improve the diagnostic value of MRI, either as derived T1 relaxation times or as signal intensities in regions of interest expressed relative to internal or external standards.

The results of this study may have therapeutic implications. First, MRI may be useful to detect early clonal disease in patients with AA who are at high risk for MDS and leukemia. Secondly, MRI evidence for clonal disease might prompt earlier consideration of bone marrow transplantation. Thirdly, MRI patterns may be useful in stratification of patients when evaluating the outcome of therapeutic trials in AA and MDS.

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