Detection of Lymphomatous Bone Marrow Involvement With Magnetic Resonance Imaging

By B. Richard Hoane, Anthony F. Shields, Bruce A. Porter, and Howard M. Shulman

We reviewed magnetic resonance (MR) staging examinations of 98 patients with malignant lymphoma who failed other therapy and were under evaluation for bone marrow transplantation. MR scan results were compared with blind posterior iliac crest aspirations and biopsies. Images of vertebral, pelvic, and femoral marrow were obtained using a standard T1-weighted, short repetition time (TR), short time to echo (TE) [TR/TE], spin-echo (T1-SE) method in 92 patients and short T1 inversion recovery (STIR) technique [TR/TE/ TI] in all. On standard T1-SE sequence, normal marrow is bright due to the predominance of marrow fat, and tumor is dark. With STIR images, water containing tumor has a very high signal intensity in a dark (fat suppressed) background. Thirteen patients had positive MR scans and marrow biopsies, whereas 49 had negative MR scans and biopsies. Of 36 discordant MR/histology results, 10 had positive biopsies and negative MR exams; eight of these had microscopic infiltration (≤5%) with tumor. MR detected marrow tumor either in the crests or elsewhere in 25 of 75 (33%) patients with negative study biopsies. We could confirm marrow involvement in 15 of these 25 (60%) by clinical methods. Therefore, up to one third of the patients evaluated with routine biopsies may have occult marrow tumor detectable by MR exam. In patients with negative marrow biopsies, especially those with Hodgkin’s disease or intermediate to high-grade non-Hodgkin’s lymphomas, MR scans found focal lesions distant from the crests. Biopsy better detected lower grade microscopic involvement. We conclude that optimal marrow staging of lymphoma patients incorporates both biopsy and MR imaging.

posterior iliac crests within 30 days of the MR examination and before bone marrow transplantation. Specimens obtained in Seattle included 72 bilateral biopsies and aspirates, 21 unilateral biopsies and aspirates, and 1 unilateral aspirate. Four of the biopsies and aspirates (two negative bilateral and two positive unilateral) were obtained from outside and confirmed on review. Biopsy specimens were fixed in formalin, sectioned, and stained with hematoxylin and eosin. Lymphomas were classified pathologi-
cally as either Hodgkin's disease or NHL and then subclassified using the Working Formulation. The amount of disease present in the specimen was either taken from the original report, or, if not clearly stated, was determined by one of us (H.M.S.).

Imaging was performed with a 0.15 T MR system (Picker International, Cleveland, OH) using two-dimensional Fourier transform methods for 97 patients. One patient was imaged on a 0.5 T Picker 2055HP MR system. Coronal and occasional sagittal images were obtained at 10-mm intervals through the vertebral, pelvic, and femoral marrow. T1-SE images (TR$_{1000}$/TE$_{30}$) were obtained on 92 patients, and STIR images (TR$_{1500}$/TE$_{30}$/TI$_{100}$) were obtained on all patients.

Fig 2. Case 8, a 30-year-old woman with the second relapse of Hodgkin's disease last treated 5 years before scan. Grade +3 sacral lesion seen on both (A) T1-SE and (B) STIR (arrows). On STIR, the bright areas seen beneath the lesion are iliac blood vessels. Based on this MR scan, therapy was changed from autologous to allogeneic bone marrow transplantation.
Marrow MR scans were evaluated blindly by one of us (B.A.P.) without knowledge of the patient’s marrow histology, treatment history, tumor type, or stage. The area of sampled crest marrow was assessed by both T1-SE and STIR images, with each type of scan scored separately on a visual scale of −2 to +4 (Table 1).

Relative marrow signal intensity was compared with adjacent muscle, intervertebral disks, and with extensive prior marrow imaging experience using these sequences. Noncrest marrow was similarly evaluated and assigned a scale value. The highest of these two scale values determined whether the MR scan was considered...
were interpreted as not indicating tumor involvement but as

chemotherapy in males, nonmenstruating females, or elderly pa-

Time from scan to biopsy ranged from 0 to 28 (mean 3.7) days.

from their somewhat more extensive red marrow. Recent biopsy

sites, clearly identified by a bone marrow defect with adjacent

tissue edema, were not considered to indicate tumor involvement.

lesions graded as +2 (Fig 3) to diffusely

abnormalities on MR ranged from discrete, small (3 to 5

mm) lesions (T1-SE .1, STIR 

... -1, decreased signal intensity.

+2 Scattered miliary (3 to 5 mm) lesions (T1-SE ↓, STIR ↑)

+3 Focal larger (>5 mm) lesions (T1-SE ↓, STIR ↑)

+4 Marked signal abnormality (T1-SE ↓, STIR ↑)

Abbreviations: ↑, increased signal intensity; ↓, decreased signal intensity.

RESULTS

Compared with normal marrow (Fig 1), the patterns of

abnormalities on MR ranged from discrete, small (3 to 5

mm) marrow lesions graded as +2 (Fig 3) to diffusely

abnormal marrow representing near-complete marrow re-

placement (graded as +4, Fig 4). Table 2 presents study

biopsy and MR exam results classified by histology. MR

scan and biopsy results are compared in Table 3.

Of the 23 positive biopsy patients, 13 showed evidence of

bone marrow tumor by MR scan. Ten patients had positive

marrow samples but negative MR scans. Five of these had

low-grade and three intermediate-grade NHL with 5% or

less tumor involvement at biopsy. The remaining two were

intermediate-grade NHL and had biopsies of 17% and

23%.

Of the 75 classified as negative by crest marrow biopsy, 49

had normal MR marrow exams. One patient found negative

by both scan and biopsy (case D.H.) had a positive marrow

sampling 28 days before MR exam. He had no intervening

treatment and was considered to be a false-negative study

biopsy and MR exam.

The remaining 26 patients had abnormal MR marrow

images and were bone marrow biopsy negative. Fifteen had
disease in noncrest marrow areas (Table 4). Eleven had
disease in both crest and noncrest marrow (Table 5).

Of the 15 patients with noncrest marrow lesions, two had

marrow involvement confirmed by CT scan (cases 1 and 2),
two by other positive biopsies (cases 3 and 4), and four by
resolution on follow-up MR scan (cases 5 through 8). Two

patients (cases 9 and 10) had hypoplastic marrow speci-

mens removed from MR class -2 to -1 marrow. Case 9

received 3,000 cGy of pelvic irradiation 14 years before

scan, with biopsies having scattered foci of hematopoietic
cells amid 80% aplasia. Case 10 had 2,500 cGy whole

abdominal followed by 2,000 cGy pelvic irradiation 6 and 3

years before scan. His biopsies showed less than 5% hematopoietic cellularity. Seven of the 15 had treatment in

the past 3 months, with one growing during treatment and

one partially treated. Six received chemotherapy and one

(case 5) radiation therapy (time from previous therapy, 38
days). Marrow involvement in six patients (cases 9 through
14) could be neither confirmed nor denied. Due to blinded

evaluation, a sternal lesion in case 15 was falsely classified

as MR positive. The postoperative marrow changes from

 sternotomy were blindly interpreted as tumor.

In the group of 11 with negative biopsy but positive MR
images for crest and noncrest marrow, three patients (cases
16 through 18), despite bilateral negative study biopsies,
had prior positive biopsies. These ranged from 16 to 57
(mean 43) days before MR evaluation. None had any

treatment during the interval. We consider these to be

false-negative marrow biopsies and true-positive MR ex-

ams.

In the remaining eight patients, four (cases 19 through
22) showed resolution of their marrow and lymph node

abnormalities on follow-up MR scan. Seven patients had

recent treatment (prior 3 months). Six patients had

received chemotherapy and one (case 19) radiation therapy
(time from previous therapy, 39 days). Five patients (cases
19 through 21, 23 through 24) had known prior positive

histology samples obtained 62 to 522 (median 132) days

before scan. In four patients (cases 23 through 26), there

were no data to confirm or deny marrow involvement.

In summary, we could confirm the positive MR scan
results in 15 of the 25 patients (60%) who had negative

study biopsies. Some or all of the other 10 positive MR

results may be correct but were not confirmed by other

methods.

T1-SE and STIR were compared for their abilities to
detect marrow lymphoma in the 92 patients studied by both

methods. The T1-SE method identified 16 patients with
crest marrow lymphoma. STIR images detected tumor in
these 16 plus an additional seven (Fig 5). STIR also

improved discrimination of marrow sclerosis (dark on

tumor by clinical agreement.” This term was defined as

the presence of bone marrow disease based on all accessible

clinical tests and was performed by one of us (B.R.H., Table

6). In addition to all patients with positive study biopsies,

this group includes five patients with earlier positive biopsi-
ses (cases D.H., 3, 16 through 18), eight with resolution of

MR scan marrow lesions by follow-up scan (cases 5 through


<table>
<thead>
<tr>
<th>Scale</th>
<th>Signal Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>Diffuse change (T1-SE ↑, STIR ↓) (fatty, aplastic, irradiated marrow)</td>
</tr>
<tr>
<td>-1</td>
<td>Patchy change (T1-SE ↑, STIR ↓) (fatty, hypoplastic, irradiated marrow)</td>
</tr>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>+1</td>
<td>Mild heterogeneous change (T1-SE ↓, STIR ↑)</td>
</tr>
<tr>
<td>+2</td>
<td>Males, nonmenstruating females, and elderly: recovering marrow</td>
</tr>
<tr>
<td></td>
<td>Menstruating females (15-45 y): considered normal</td>
</tr>
</tbody>
</table>

|Mild heterogeneous change (T1-SE ↓, STIR ↑) | Males, nonmenstruating females, and elderly: recovering marrow |
| Menstruating females (15-45 y): considered normal | +2 |
| +2 | Scattered miliary (3 to 5 mm) lesions (T1-SE ↓, STIR ↑) |
| +3 | Focal larger (>5 mm) lesions (T1-SE ↓, STIR ↑) |
| +4 | Marked signal abnormality (T1-SE ↓, STIR ↑) |

Abbreviations: ↑, increased signal intensity; ↓, decreased signal intensity.
Fig 3. A 41-year-old man with low-grade NHL whose marrow MR scans demonstrate grade +2 tumor nodules scattered throughout. (A) Small, greater than 3-mm areas of decreased signal noted on T1-SE. Possible etiologies include fibrosis, sclerosis, or tumor. Also noted is a focal biopsy defect (arrow). (B) The irregular hyperintensity seen on STIR scan indicates probable viable tumor. The brightest focus represents the biopsy site. This was the lowest tumor involvement detected with our current methods. Marrow tumor of 1% to 3% was observed on the biopsy specimens.

8, 19 through 22), two confirmed by CT scan (cases 1 and 2), and one confirmed by a positive bone marrow harvest 1 day after his MR scan (case 4).

With regard to study biopsy, 15 of 75 patients with negative histologic samplings had positive marrow by MR exam and confirmed by the above methods. Thirteen of these 15 patients had undergone bilateral and two unilateral study examinations. Further, three patients (cases 6, 8, and 22), all without any past-positive marrow evaluations, had positive MR scan results that were confirmed by lesion resolution with therapy as seen on follow-up MR exams. In case 8 (Fig 2), the planned bone marrow transplantation was changed from autologous to allogeneic based on the MR detection of unsuspected marrow tumor.
Groups of patients were analyzed by their pathologic diagnoses. The positive biopsy/negative MR group consisted of five low- and five intermediate-grade NHL patients. Hence, lower grade NHL was more frequently missed by MR exam. The negative biopsy/positive MR group contained 9 Hodgkin’s disease, 2 low-, 10 intermediate-, and 5 high-grade NHL cases. Therefore, in those patients with Hodgkin’s disease and higher grade NHL, marrow tumor was more frequently noted by MR but not evident on biopsy.
MR DETECTION OF MARROW LYMPHOMA

**Table 2. Histology Versus Biopsy and MR Scan Results**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Biopsy Positive (%)</th>
<th>MR Scan Positive (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade NHL</td>
<td>44</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Intermediate-grade NHL</td>
<td>25</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>High-grade NHL</td>
<td>12</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>5</td>
<td>46</td>
<td>22</td>
</tr>
</tbody>
</table>

Percentage of studies with abnormal results for each given histology.

**DISCUSSION**

In this study, MR scans detected occult marrow lesions in 25 of 75 patients (33%) with negative study marrow biopsies. Using all accessible clinical data, we confirmed marrow lymphoma in 15 of these cases. As shown by chromosomal analysis and culture techniques, histologically normal marrow often harbors malignant lymphoma cells. Hence, we did not use marrow biopsy data to calculate sensitivity and specificity as biopsy data do not appear to be an adequate “gold standard” against which to compare MR. Instead, because of the often focal nature of marrow lymphoma involvement, MR imaging and crest marrow sampling are complementary procedures for improved marrow staging. Marrow biopsy detects microscopic, presumably disseminated marrow tumor more readily than MR imaging, whereas MR detects focal marrow lesions distant from the iliac crests.

The accuracy of a biopsy is confined to the sampled site. Biopsies may falsely underestimate or overestimate marrow tumor burden depending on whether focal tumor, normal,

**Table 3. MR Scan Versus Crest Biopsy**

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>MR Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>13</td>
</tr>
<tr>
<td>-</td>
<td>26*</td>
</tr>
</tbody>
</table>

*Includes 15 showing normal iliac crest MR scan but positive MR scan for marrow disease elsewhere.

**Table 4. Negative Biopsy With MR Scan Positive in Noncrest Marrow**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Disease</th>
<th>Prior Marrow Tumor by MR Scan</th>
<th>Days Since Prior Therapy</th>
<th>Validation of Marrow Tumor</th>
<th>MR Scan Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HD</td>
<td>Rt ilial ramus</td>
<td>41*</td>
<td>Resolution</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>HD</td>
<td>T3, T6, Lt inferior ilium</td>
<td>215</td>
<td>Resolution</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>L-G</td>
<td>Lt acetabulum, ribs, humerus</td>
<td>219</td>
<td>Positive aspirates day after MR</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>H-G</td>
<td>T-spine, L-spine, sacrum</td>
<td>38</td>
<td>Resolution on f/u MR exam</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>I-G</td>
<td>Rt distal femur, ribs</td>
<td>71†</td>
<td>Resolution on f/u MR exam</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>I-G</td>
<td>L2, L4</td>
<td>65</td>
<td>Resolution on f/u MR exam</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>H-G</td>
<td>Lt ilium, L-spine, ribs</td>
<td>27</td>
<td>Resolution on f/u MR exam</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>HD</td>
<td>Rt sacral wing</td>
<td>1,851</td>
<td>Resolution on f/u MR exam</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>L-G</td>
<td>Rt scapula, Lt humerus, rib</td>
<td>954</td>
<td>Irradiation to sampled marrow</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>I-G</td>
<td>Spine, ribs, ilium</td>
<td>240</td>
<td>Irradiation to sampled marrow</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>HD</td>
<td>Lt acetabulum, L4, L5</td>
<td>35</td>
<td>Past positive biopsy and therapy</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>HD</td>
<td>Sacrum, L1, L4</td>
<td>293</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>HD</td>
<td>Lt anterior ilium</td>
<td>781</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>I-G</td>
<td>Spine, acetabulum</td>
<td>53</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>I-G</td>
<td>Sternum</td>
<td>—</td>
<td>Prior sternotomy</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: HD, Hodgkin’s disease; L-G, low-grade NHL; I-G, intermediate-grade NHL; H-G, high-grade NHL; Rt, right; Lt, left; f/u, follow-up.

*Patient’s disease grew during therapy.
†Patient’s femur treated.

**Table 5. Negative Biopsy With MR Scan Positive in Crest and Noncrest Marrow**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Disease</th>
<th>Prior Marrow Tumor Histology</th>
<th>Days Since Positive Biopsy</th>
<th>Days After Prior Therapy</th>
<th>Marrow by f/u MR Exam</th>
<th>MR Scan Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>16*</td>
<td>I-G</td>
<td>+</td>
<td>16</td>
<td>No therapy</td>
<td>No f/u MR exam</td>
<td>+</td>
</tr>
<tr>
<td>17*</td>
<td>I-G</td>
<td>+</td>
<td>56</td>
<td>No therapy</td>
<td>No f/u MR exam</td>
<td>+</td>
</tr>
<tr>
<td>18*</td>
<td>HD</td>
<td>+</td>
<td>57</td>
<td>No therapy</td>
<td>Resolution</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>HD</td>
<td>+</td>
<td>62</td>
<td>No therapy</td>
<td>33</td>
<td>Resolution</td>
</tr>
<tr>
<td>20</td>
<td>I-G</td>
<td>+</td>
<td>522</td>
<td>No therapy</td>
<td>32</td>
<td>Resolution</td>
</tr>
<tr>
<td>21</td>
<td>I-G</td>
<td>+</td>
<td>161</td>
<td>No therapy</td>
<td>78</td>
<td>Resolution</td>
</tr>
<tr>
<td>22</td>
<td>I-G</td>
<td>+</td>
<td>161</td>
<td>No therapy</td>
<td>78</td>
<td>Resolution</td>
</tr>
<tr>
<td>23</td>
<td>H-G</td>
<td>+</td>
<td>101</td>
<td>No therapy</td>
<td>11</td>
<td>Resolution</td>
</tr>
<tr>
<td>24</td>
<td>H-G</td>
<td>+</td>
<td>132</td>
<td>No therapy</td>
<td>35</td>
<td>Resolution</td>
</tr>
<tr>
<td>25</td>
<td>H-G</td>
<td>+</td>
<td>26</td>
<td>No therapy</td>
<td>26</td>
<td>Resolution</td>
</tr>
<tr>
<td>26</td>
<td>I-G</td>
<td>+</td>
<td>176</td>
<td>No therapy</td>
<td>176</td>
<td>Resolution</td>
</tr>
</tbody>
</table>

See Table 4 for abbreviations.

*Negative biopsy, positive scan, and prior positive biopsies without intervening treatment.
or fatty marrow happens to be punctured. They cannot be relied on to detect focal tumor infiltration distant from the biopsy site, which occurs in many lymphomas. By displaying a large volume of marrow, MR scanning offers a sensitive method to detect occult involvement.

Table 2 displays the percentage of each histologic classification found positive by study biopsy and by MR exam. Analysis shows biopsy somewhat better at finding low-grade disease; however, MR better detected intermediate- and high-grade NHL and Hodgkin’s disease. Examination of
patterns of bone marrow involvement 3:105, 1977

lymphoma: A report NHL involve the marrow more frequently and in a more the histologic diagnoses in each of the various biopsy/scan subsets substantiates these points.

These data concur with previous reports. Lower grades of NHL involve the marrow more frequently and in a more disseminated manner than those of higher grades.19 Hodgkin's disease and intermediate- to high-grade NHL are more likely to form focal lesions distant from the crests.2232 If one excludes the single false-positive MR patient from the group listed in Table 4, 12 of the remaining 14 had Hodgkin's disease or intermediate- to high-grade NHL. Although technically difficult in many cases, one would expect that selective biopsies of such lesions would likely show evidence of lymphomatous involvement.

We have been impressed with the additional information supplied by the STIR images. This technique generates images in which even small lesions (3 to 5 mm) are highly conspicuous. In 7 of 23 (30%) patients studied using both techniques, STIR detected marrow tumor missed by the conventional T1-SE sequence.

These MR studies were read blindly. However, detailed knowledge of the patient's clinical and treatment history is clearly very important when interpreting marrow MR scans and can significantly increase diagnostic accuracy. We recognize that the patient population for this study was a most difficult test of MR marrow imaging capability. Not only had these patients undergone multiple therapies before presenting for bone marrow transplantation, but many also had recent treatment at the time of scan and biopsy. Results may be expected to be significantly better in previously untreated patients undergoing initial staging evaluations.

There are several limitations to this method and areas for future improvement. The extent and complex geometry of the marrow space makes imaging of the entire marrow rather difficult and time consuming. Hence, we concentrated on the extensive red marrow areas of the pelvis, vertebrae, and upper femurs. The need for extensive coverage also required a longer repetition time than desired for optimal T1-weighting. Our current techniques use TR/TE at 0.5 T.

Many current standard MR techniques may not reliably detect scattered microscopic disease of less than 3 to 5 mm in size. A recent report describes the use of measured thoracolumbar vertebral T1 relaxation times to detect disseminated microscopic marrow lymphoma in patients before initial therapy.31 The combination of this technique with that described in this report may increase the ability of MR to detect both microscopic and focal macroscopic marrow disease. Further, marrow lesions detected by MR scan may be due to a variety of nonneoplastic causes including marrow infarction, avascular necrosis, and benign marrow or bone neoplasms. While STIR images aid in explaining many of these areas, interpretation should be in the proper clinical context. Problematic lesions should be considered for biopsy, if clinically warranted.

In this study, aspirations and biopsies did not identify up to one third of the patients with tumor involvement as assessed by MR imaging. We routinely use MR to determine if crest biopsy results accurately assess marrow tumor infiltration. We believe that the combined use of MR imaging and marrow biopsy is the current best method for determination of marrow involvement in patients with malignant lymphoma.

**REFERENCES**


11. Richards MA, Webb JAW, Jewell SE, Amess JAL, Wrigley

| Table 6. Marrow Involvement by Clinical Agreement Versus Study Biopsy and MR Scan Results |
| Marrow Involvement by Clinical Agreement* | Study Biopsy | MR Scan (all areas) |
| + | 23 | 19 | + | 28 | 11‡ |
| - | 0 | 60† | - | 1115 | 48 |

*Marrow involvement confirmed by other biopsies, CT scan, or resolution on follow-up MR.
†Includes 10 without data either confirming or refuting marrow involvement.
‡Includes eight with microscopic disease (≥5% tumor); one false-negative scan.
§Includes one false-positive scan.

The histologic diagnoses in each of the various biopsy/scan subsets substantiates these points.
PFM, Lister TA: Low field strength magnetic resonance imaging of bone marrow in patients with malignant lymphoma. Br J Cancer 57:412, 1988


Detection of lymphomatous bone marrow involvement with magnetic resonance imaging [see comments]

BR Hoane, AF Shields, BA Porter and HM Shulman