Magnetic resonance imaging of pelvic and femoral bones for detection of bone marrow infiltration in patients with non-Hodgkin's lymphoma

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ABSTRACT

Objective: Detection of the residual bone marrow (BM) involvement is essential in treatment of patients with non-Hodgkin's lymphoma (NHL). Bilateral iliac crest BM biopsies appear to have low sensitivity for BM infiltration, while magnetic resonance imaging (MRI) presents more global view of BM. This study was conducted to determine the advantage of femoral marrow MRI as a non-invasive technique over bilateral iliac crest BM biopsies in detecting BM infiltration before treatment and residual disease after completion of treatment.

Methods: Over a period of 27 months from January 2002 to March 2004, a total of 30 patients with newly diagnosed NHL were included in the study. Magnetic resonance imaging of 26 patients were conducted in King Fahd Hospital of the University, Al-Khobar, Kingdom of Saudi Arabia. Magnetic resonance imaging of 4 patients were referred from different hospitals in the Eastern Province. Twenty-five patients were of B-cell type and 5 patients were of T-cell type. Coronal MRI of the pelvis and femoral marrow were obtained by the T1, T2-weighted spin echo sequences and short TI inversion recovery technique.

Results: Magnetic resonance images showed BM infiltration in 17 cases (56.7%) before treatment and positive biopsy results were found in 9 cases (30%); all had abnormal MR images. There was a significant difference between both methods in the detection of infiltration (p=0.037). Magnetic resonance imaging showed that 58.8% of cases have scattered pattern, 23.5% were uniform and 17.6% of cases have nodular patterns. Magnetic resonance images after completion of treatment showed residual BM infiltration in 6 out of 17 cases who previously had positive MR images and only one case of them had a positive BM biopsy with a significant difference between both methods and all of them relapsed within 6 months (p=0.034).

Conclusion: Magnetic resonance images of the pelvis and femoral marrow were superior than BM biopsy on detection of BM infiltration before treatment and residual infiltration after treatment.

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Bone marrow (BM) biopsy is an integral component in staging patients with malignant lymphoma, but blind biopsies appear to have low sensitivity for detection of BM involvement due to the frequent involvement in non-crest marrow.[1] Magnetic resonance imaging (MRI) technique is useful in characterizing normal and abnormal BM due to its ability to distinguish fat from denser, more cellular tissues, such as tumors and lymphomatous BM infiltration.[2] Magnetic resonance imaging also

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allows one to assess the entire marrow compartment, providing information on regions that cannot be sampled by biopsy or aspiration, thus providing better understanding of the disease progression and remission.[3-5]

Marrow is infiltrated by lymphoma cells in 50% of non-Hodgkin's lymphomas (NHL). The incidence is highest in the low grade small lymphocytic lymphomas (80%) and follicular small cleaved cell lymphomas (50%), lower in follicular mixed lymphomas (30%) and less than 25% in intermediate and high grade diffuse large cell NHLs (5-25%).[6-9] At birth, almost all marrow is cellular, but by the age of 25 years, cellular marrow is restricted to the axial skeleton and the proximal femoral and humeral metaphyses. The remainder consists of 80% fat, 15% water, and 5% protein.[2] However, the pelvis and femur seem to be the most suitable bone for the detection of lymphomatous foci for several reasons; first the pelvis and femoral marrow are largely fatty in adult, and the detection of abnormal MRI signal intensity is therefore easier. Secondly, the femur is the longest bone and this allows evaluation of BM within a single bone as a means of assessing the disease extent over time.[10]

Normal adult femoral marrow appears bright on T1-weighted spine echo (SE) sequence and appear dark on short TI inversion recovery images (STIR), indicating a large fatty marrow. Conversion from a fatty to a cellular marrow occurs in many diffuse disease states, including malignant lymphoma.[11] This study was conducted to determine the advantage of MRI of pelvic and femoral marrow as a non-invasive technique over bilateral iliac crest BM biopsies in detection of BM infiltration before treatment and residual disease after completion of treatment.

Methods. Over a period of 27 months from January 2002 to March 2004, a total of 30 patients with newly diagnosed NHL were included in the study. Magnetic resonance imaging of 26 patients were conducted in King Fahd Hospital of the University, Al-Khobar, Kingdom of Saudi Arabia. Magnetic resonance imaging of 4 patients were referred from different hospital in the Eastern Province. They were classified according to Working Formulation.[12] Magnetic resonance imaging of the pelvis and both femoral marrow was performed at the time of diagnosis and after 8 cycles of treatment. Bilateral BM biopsies were obtained from the posterior iliac crest as part of the staging procedures at diagnosis and were repeated after completing the treatment.

Magnetic resonance imaging was performed using 1.5 Tesla superconducting magnet system. Coronal T1-weight SE images of the pelvis and femur were obtained in continuous 5-mm slices in a 256 x 256 matrix with TR=400 msec; TE=20 msec and number of excitations 2 (NEX=2). Tissues with short T1, such as fatty tissues, have high signal intensity and appear bright on T1-weighted SE images, whereas those with a long T1, such as cellular marrow, have a low signal intensity and appears dark. Short TI inversion recovery coronal images of the pelvis and both femura were obtained in 5-mm slices in a 256 x 256 matrix with TR=1500 msec; TE=20 msec; TI=150 msec and NEX=2. In STIR images, the signal from fatty tissues is eliminated, whereas the signal from tissues with longer T1 is progressively brighter. Coronal T2-weighted images were obtained with TR=2200 mses, TE=70 msec, 5-mm slices and NEX=2. The positive findings on femoral marrow were categorized as follows: nodular, scattered and uniform patterns.

Results. Thirty patients with newly diagnosed NHL were included in this study with an age ranging from 18-45 years (18 males, 12 females). Patients were classified according to the Working Formulation,[12] which showed that 7 cases (23.3%) were of the low grade type, 18 cases (60%) were intermediate grade and 5 cases were high grade NHLs (16.7%). Twenty-five patients had the immunophenotypic features of B-cell NHL (83.3%), while only 5 (16.7%) belonged to the T-cell variety. Seventeen patients (56.7%) had abnormal MRI findings of pelvis and femoral marrow. Nine patients (30%) had positive findings on both MRI and BM biopsy. All patients with a positive BM biopsy showed abnormal images of their pelvic and femoral marrow. Therefore, 8 patients (26.7%) showed abnormal MRI findings of the pelvic and

Table 1 - Comparative results of pelvic and femoral marrow magnetic resonance imaging (MRI) and bone marrow (BM) biopsy in the studied patients.

MRI	Negative		Positive		Total	
	n	(%)	n	(%)	n	(%)
Biopsy results before treatment *(p=0.37*)*						
Normal	13	(43.3)	0		**13**	**(43.3)**
Positive	8	(26.7)	9	(30)	**17**	**(56.7)**
Total	**21**	**(70)**	**9**	**(30)**	**30**	**(100)**
Biopsy results after treatment *(p=0.34*)*						
Normal	11	(64.7)	0		**11**	**(64.7)**
Positive	5	(29.4)	1	(5.9)	**6**	**(35.3)**
Total	16	**(94.1)**	1	**(5.9)**	**17**	**(100)**

*Significant *p* value

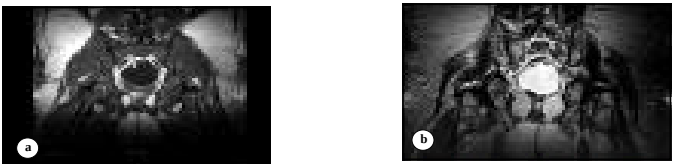

Figure 1 - Coronal T1WI **(a)** and **(b)** corresponding T2WI of a patient with B-cell non-Hodgkin's lymphoma showing scattered type of bone marrow lymphomatous infiltration at the pelvic bones and proximal parts of both femora. The lesions appear poorly defined hypointense on T1WI and of scattered areas of mixed hypointense and hyperintense areas on T2WI.

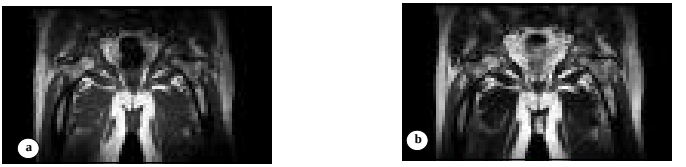

Figure 2 - Coronal T1 **(a)** and **(b)** T2 images of a patient with T-cell non-Hodgkin's lymphoma showing scattered bone marrow infiltration involving pelvic bones as well as upper thirds of both femora. These lesions appear as low signal scattered areas on T1 and of mixed high and and low signal areas on T2.

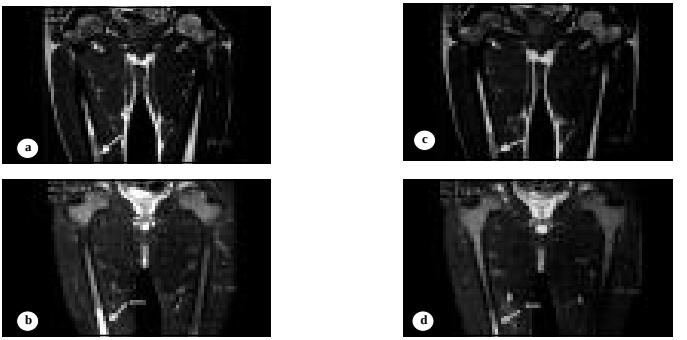

Figure 3 - Coronal T1WI **(a)** and **(b)** corresponding short TI inversion recovery technique (STIR) image of a patient with B-cell non-Hodgkin's lymphoma showing the nodular type of lymphomatous infiltration. The lesion appears at the distal 1/3 of the right femur (arrow) as a low signal patch on T1 and of high signal patch on STIR. **(c)** and **(d)** Follow up coronal T1 and STIR images of the same patient after treatment showing significant diminished size of the lesion suggesting residual infiltration (arrow).

Figure 4 - Coronal T1WI **(a)** and **(b)** coronal short TI inversion recovery technique (STIR) image of a patient with B-cell non-Hodgkin's lymphoma showing low signal intensity of the upper 2/3 of both femora as well as pubic bones on T1 and of high signal intensity on STIR sequence due to uniform pattern of femoral marrow lymphomatous infiltration. Associated hydrocele is noted (arrow).

femoral marrow despite a normal BM histology, with a significant difference between both techniques (p=0.037) (**Table 1**). Magnetic resonance imaging findings of the pelvis and femoral marrow were classified into 3 patterns (**Figures 1-4**). Of the 17 patients with a positive MRI, 10 patients (58.8%) exhibited a scattered pattern, 4 patients (23.5%) demonstrated a uniform pattern, and 3 patients (17.6%) exhibited a nodular pattern. Of the 9 patients with positive BM biopsy, 4 demonstrated a scattered pattern on MRI, 4 patients showed a uniform pattern and only one patient had a nodular form. Four cases of the MRI positive images were of the T-cell type (23.5%) and 13 cases were of B-cell type (76.5%). A uniform MRI pattern was observed only in patients with B-cell lymphomas. As regards to the relation of MRI with pathologic findings; 2 patients with low grade lymphomas, 4 patients with intermediate grade lymphomas and 2 patients with high grade lymphomas had positive MRI findings and negative BM biopsy. Two patients with low grade lymphomas, 6 patients with intermediate grade lymphomas and one patient with high grade lymphoma had both positive MRI and BM biopsy findings (**Table 2**). Follow up of our patients after completion of chemotherapy disclosed the presence of abnormal MR images in 6 patients with previously positive MR images, of which only one had showed evidence of BM infiltration on biopsy. All of those patients relapsed within 6 months of follow up with a significant difference between both techniques in detection of BM infiltration (p=0.034) (**Table 1**).

Table 2 - Distribution of magnetic resonance (MRI) and biopsy findings according to histology.

Histology	MRI/biopsy			
	-/-	-/+	+/-	+/+
LG (n=7)	3	0	2	2
IG (n=18)	8	0	4	6
HG (n=5)	2	0	2	1

LG - low grade, IG - intermediate grade, HG - high grade, BM - bone marrow
-/- Normal MRI / negative BM biopsy
-/+ Normal MRI / positive BM biopsy
+/- positive MRI / negative BM biopsy
+/+ positive MRI / positive BM biopsy

Discussion. Detection of BM involvement is important for staging and treatment decision in patients with lymphoma. Although routine BM evaluation is based on aspiration and BM biopsies, new diagnostic tools are required to improve diagnostic accuracy. Assessment of the BM by MRI is useful for detection of occult lymphomatous marrow involvement. Bone marrow infiltration was detected by MRI of pelvic and femoral bone in 17 of 30 patients (56.7%). However, only 9 of them had evidence of BM infiltration by biopsy. Results of MRI of the marrow in patients with lymphoma have been reported in several series and suggest that involvement of the BM may be detected by MRI and that results of MRI may complement those obtained by biopsy.[13-17] In these reports, abnormal marrow MRI was detected in 18-52% with 86% sensitivity and 90% specificity. In the present study, none of the patients with marrow involvement detected by BM biopsy showed a normal MRI of the pelvis and femoral marrow. Although the present study is limited to pelvic and femoral marrow, MRI images in additional areas of the marrow may increase the probability of a correct diagnosis.

Magnetic resonance imaging is more sensitive than blind biopsy in detecting BM invasion. Although a positive biopsy result is usually accepted as proof of BM infiltration, results indicate that negative biopsy findings do not exclude tumor

involvement due to frequent involvement in non crest marrow.[18] Bone marrow imaging is particularly indicated in patients with high grade NHL with a negative BM biopsy and abnormal clinical (stage B, bone pains) or biochemical data (elevated alkaline phosphatase) and those who have relapsed.[19] False negative results have been reported in low grade NHL.[1,18,20,21] In spite of that, Tsunoda et al [13] have suggested that femoral marrow MRI may be advantageous for detection of marrow infiltration in patients with low grade NHL. Nodular, scattered, or uniform MRI patterns were found in our patients before initiation of treatment. A nodular pattern implies a limited involvement of the BM by lymphoma cells and conversely, a uniform pattern indicates a diffuse involvement of the marrow. The frequency of lymphomatous involvement of the marrow detected by BM biopsy from the posterior iliac crest should be correlated with these patterns.[20-23]

In the present study, the frequency of marrow involvement was detected by BM biopsy in 20% of patients with nodular pattern, 66.7% with scattered, and 100% with uniform patterns. Interestingly, all patients in our study who showed a uniform pattern on MRI had B-cell lymphomas, the same observation was found in the study by Tsunoda et al.[13] Further studies are needed to determine whether B-cell lymphomas involve BM more uniformly than T-cell lymphomas.

Follow up MRI showed the presence of abnormal MR images in 6 of our patients with previously positive images, of which only one of them had a positive BM biopsy. Although, these patients have been considered to be in complete remission, the knowledge of post-therapeutic patterns is essential to avoid misinterpretations. The main drawback with this technique is its inability to differentiate between residual lesions from fibrosis[11,24,25] and it may be influenced by other factors as age related changes in marrow distribution, anemia or other space-occupying marrow disease.[3,26,27] Our patients had no other disease of the marrow that could have influenced the MRI. In addition, all patients with abnormal MR images relapsed during follow up within 6 months, indicating that the lesions were lymphomatous in nature.

In conclusion, the present results indicate that coronal MRI of the pelvic and femoral bones is a sensitive method for detection of bone marrow lymphomatous infiltration before treatment that are not revealed by BM biopsy, and follow up MRI is essential for high risk patients for detection of early relapse.

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