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Bone Marrow Infiltration in Hairy Cell Leukemia after Interferon Therapy Detected by Magnetic Resonance Imaging

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Abstract—*Magnetic resonance imaging (MRI) can detect bone marrow infiltration by neoplastic cells in many hematological malignancies. We studied 10 patients affected by hairy cell leukemia (HCL) and treated with interferon (IFN) with both MRI and bone marrow biopsy. T1-weighted MR scans of femurs and pelvis proved to be effective to score hairy cell infiltration, while less information was obtained from the study of the lumbar vertebral column. A good correlation (<10% difference) was noted between biopsy and MRI in over 90% of cases. MR scans showed, in general, a higher grade of infiltration. MR scan, however, can be useful for monitoring the course of HCL and the response to the treatment. Moreover, MRI evaluating a large amount of tissue, can detect a nodular type of infiltration which can be missed in biopsy specimens.*

INTRODUCTION

HAIRY CELL LEUKEMIA (HCL) is a lymphoproliferative disease characterized by splenomegaly, pancytopenia and typical mononuclear cells (hairy cells, HCs) present in the peripheral blood and bone marrow [1]. Since the first report of Quesada *et al.* [2], interferon (IFN) has been widely employed as first line or salvage therapy in the treatment of HCL [3–7]. The degree of marrow infiltration is the best parameter to evaluate the response to therapy. Residual HCs after IFN discontinuation cause the recurrence of the disease; thus, HC infiltration and fibrosis are usually scored on bone marrow specimens before and after therapy. However, biopsy can offer only a partial picture of the whole tissue. This can be misleading especially when patch infiltration is present.

Magnetic resonance imaging (MRI) can detect marrow infiltration by neoplastic cells in acute leukemia (AL), chronic myeloid leukemia (CML) and non-Hodgkin's lymphomas (NHL). Recently Thomspon *et al.* [8] have performed an MRI study in HCL, demonstrating a correlation with the response to therapy.

We examined the bone marrow of 10 patients affected by HCL after IFN treatment with both MRI and biopsy to verify how useful the MR scan is to evaluate the stage of disease and the response to therapy.

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MATERIALS AND METHODS

Ten patients affected by HCL were treated with Ly-IFN (Wellferon) at 3 MU/day s.c. for progressive disease. In three patients IFN therapy was administered after splenectomy failure. The response to treatment was stated according to the Consensus Resolution (Leeds, 1986) [9].

MRI was performed within a week before the trephine biopsy. A total of 12 determinations were obtained: at diagnosis in two cases, after at least 3 months of therapy in six cases and after discontinuation of IFN treatment in four cases. In two patients both analyses were performed before therapy and after 3 months of treatment.

Coronal examinations of proximal femurs and pelvis were obtained with a field of view of 40 cm, using a Sigma 1.5 Tesla MR imaging system (General Electrics, Milwaukee, U.S.A.). T1 weighted spin-echo sequences with 800 ms TR and 20 ms TE were performed. T2 weighted sequences were not performed [10]. Contiguous 1 cm thick coronal slices were selected, employing two excitations with 128 × 256 or 256 × 256 matrices. The high resolution matrix was not carried out successively because it does not improve the sensitivity of the analysis. Proton chemical shift techniques were not performed [11]. We selected a

coronal section for pelvis and femurs, while a sagittal scan was obtained for the study of the lumbar vertebral column. This shows in adults a low signal due to the high presence of red marrow, while the prevalence of yellow marrow produces a higher signal in femurs and pelvis. Thus, as neoplastic infiltration always shows a low aspecific signal, we examined only femurs and pelvis for the evaluation of the response to IFN treatment.

RM scans were submitted independently to different reviewers. Infiltration was expressed as percentage of leukemic cells in the bone marrow [10]: 0% when a high signal, like fat, was recorded in the pelvis and femur scan (Fig. 1), 100% when a diffuse low signal in the pelvis, greater trochanter and femural capital epiphysis were noted (Fig. 2).

In order to obtain the best reproducibility of the results, similar thicknesses and skip of slices were examined for each patient. With differences in the grading lower than 10%, an average value was considered; with discrepancies exceeding 10%, the evaluators should come to a consensus value: however, no case displayed such a discrepancy. The MR scan was graded independently to the biopsy results.

Biopsy specimens were analyzed by an experienced pathologist as to morphology and to tartrate-resistant acid phosphatase activity. Marrow infiltration was graded as percentage of hemopoietic tissue replaced by hairy cells.

The biopsy results were then compared with the data yielded from MRI.

RESULTS

After IFN therapy, two patients obtained a complete remission, six a partial remission and two a minimal response. The results of the 12 MR scans are summarized in Table 1, and they are compared with data obtained from bone marrow biopsy. We found a good correlation (difference $<10\%$) in over 90% of cases. We noted a significant discordance in two cases only. In a patient (I.P.) in complete clinical remission and off therapy for many months, the MR scan suggested a bone marrow infiltration of 30% (Fig. 3). In another patient (N.M.), in which examinations had been performed before and after IFN therapy, a marked reduction of HC infiltration was evident in marrow specimens (from 90 to 5%), in spite of a little improvement in the MR scan. A review of the bone marrow biopsy confirmed the scant HC infiltration, but stressed a marked hyperplasia of normal hemopoiesis associated with a reduction of fat. In the other patient in which MRI was performed before and after treatment, we noted a similar reduction of bone marrow involvement with both examinations: from 20 to 10% in marrow specimens and from 25 to 15% in MR scans.

DISCUSSION

Neoplastic cells replacing the normal marrow fat, which represents the majority of marrow volume in adults, improve the water content. As fat has a higher signal than water in T1 weighted MR scan [1, 12], this difference led many authors [10, 12–14] to employ MRI to detect marrow involvement in many hematological malignancies. Proximal femurs and pelvis above all are evaluated to grade marrow infiltration, and a low signal in these areas is normally an expression of advanced disease. Many authors [12, 14], however, reported that it is difficult to discriminate between low signal intensity areas due to infiltration and a relatively low signal caused by normal marrow hyperplasia. In some circumstances abnormal MRI can persist for many months after therapy, even if there is no evidence of disease in bone marrow biopsy specimens [14]. Neoplastic infiltration in AL [13] becomes apparent at MR scan as a diffuse low signal, while CML [10] gives a patch type of MR imaging. Lymphomas tend to form focal nodules of tumors in bone marrow, and these lesions appear at MR scan either as focal areas of low signal intensity within normal marrow or as nodules of very low signal within a background of moderately diminished marrow signal [10].

Recently, Thompson *et al.* [8] studied five patients affected by HCL, demonstrating a good correlation between the MR imaging and the grade of marrow involvement during IFN treatment. Our results confirm these observations; only two cases failed to demonstrate a correlation between MRI and bone marrow biopsy. In one case (N.M.), we noted a marked discrepancy between biopsy and MR scan. The patient was in fact at that time in complete clinical remission, as shown by normal peripheral blood values, absence of circulating HCs and less than 5% of leukemic involvement in biopsy specimens [9]. On the other hand, an impressive hemopoietic hyperplasia was observed on the bone marrow analysis. Low MR signals are usually detected in the presence of decreased fat content and increased marrow cellularity [10], such as in acute or chronic leukemias. In the reported case the marked hemopoietic hyperplasia might have determined a diffuse MR signal reduction, thus suggesting a false positive scan.

Although the results obtained with bone marrow biopsy and MR imaging were consistent, it should be emphasized that, in general, the latter showed a higher grade of infiltration. A 5–10% higher score was obtained with MRI in nine out of 12 examinations performed. In their series Thompson *et al.* [8] reported two cases in which a $>50\%$ difference was present between histology and MR scan.

These data suggest that MRI must still be per-

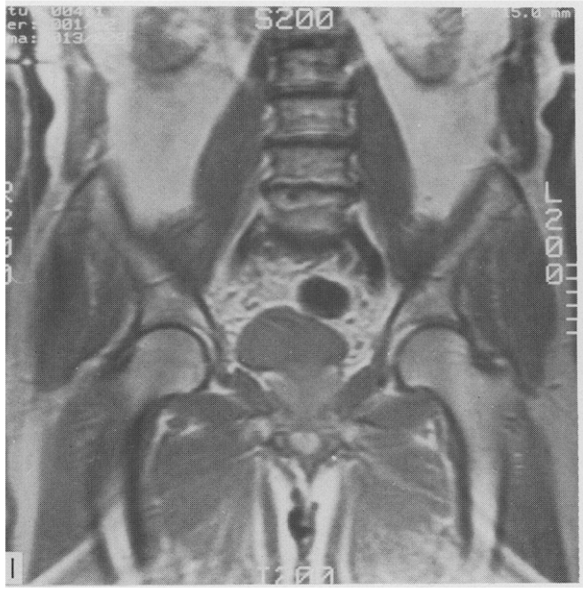

Fig. 1. MRI appearance of normal bone marrow has high signal intensity.

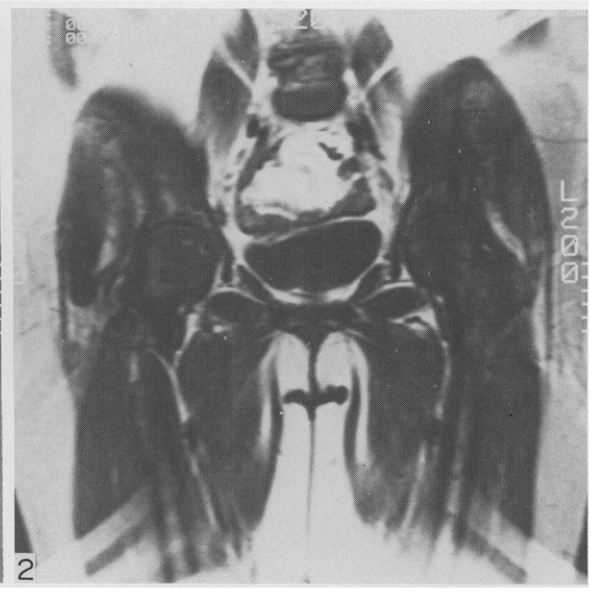

Fig. 2. Hairy cell leukemia before IFN treatment. MR scan of hips showed a very low signal. Bone marrow infiltration was 100%.

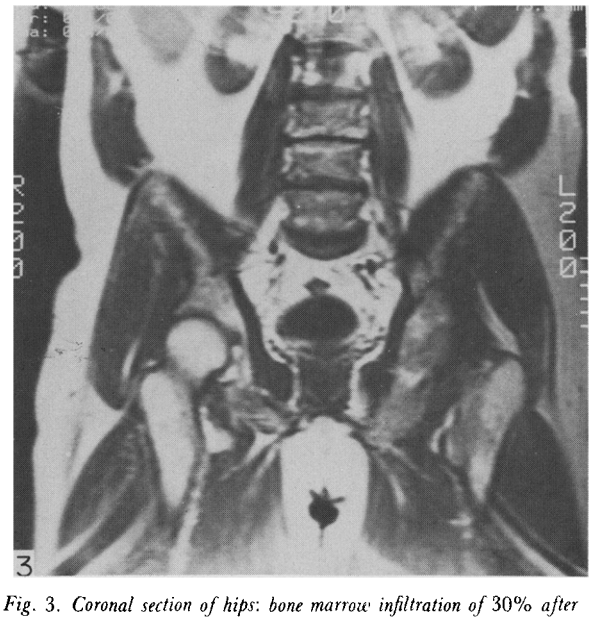

Fig. 3. Coronal section of hips: bone marrow infiltration of 30% *after IFN therapy.*

Table 1. *Bone marrow and MRI results*

Patient	Age	Prior splenectomy	IFN therapy	Bone marrow involvement(%)	MRI involvement(%)
D.I.	65	—	During	20	15
G.L.	38	Y	After	70	70
L.V.	55	Y	After	80	75
I.A.	55	—	During	0	15
I.P.	54	—	After	0	30
T.L.	59	—	During	15	30
M.E.	61	—	During	10	25
M.L.	45	—	After	60	50
C.G.	64	—	Before	20	25
C.G.*	64	—	During	10	15
N.M.	63	Y	Before	90	100
N.M.†	63	Y	During	5	80

*†The same patient after 3 months of IFN therapy.

formed together with bone marrow biopsy to evaluate the response to IFN treatment, because a hyperplastic normal hemopoiesis can produce pictures mimicking leukemic infiltration.

In conclusion, we believe that MRI is an extremely sensitive, non-invasive and easily performed analysis that can be useful in monitoring the response to IFN therapy and the course of the disease in HCL. Moreover, an MR scan can evaluate a larger amount of tissue than marrow biopsy, thus rendering the search for a nodular type of infiltration more reliable.

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