

# Value of bilateral bone marrow biopsy specimens in non-Hodgkin's lymphoma

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## Abstract

A study of 260 patients with non-Hodgkin's lymphoma (NHL) who underwent bilateral bone marrow biopsy at initial diagnosis showed marrow disease in 99 (38%) cases. The highest incidence of disease (83%) was seen in small lymphocytic lymphoma (SLL) and the lowest (19%) in diffuse large cell lymphoma (DLCL). Among cases with positive marrows, disease was bilateral in all 15 cases of SLL but in only 10 of 20 (50%) of the DLCL cases. In 30 of 99 (30%) positive marrows disease was unilateral. Follicular lymphomas were strongly associated with a paratrabeular pattern, with 40 of 45 positive cases showing this. Discordant histology was seen in six of 20 positive cases of DLCL and two of 37 positive cases of follicular small cleaved cell lymphomas (FSCCL). A bone marrow aspirate was positive in only 56 of the 99 (57%) cases. Peripheral blood disease was present in 15% of the bone marrow positive cases and in 6% of the cases overall.

The incidence of marrow disease varies with the histological subtype of lymphoma. The paratrabeular pattern is associated with follicular lymphoma, and bilateral biopsy specimens increase the positivity rate in most subtypes of NHL.

Examination of bone marrow is generally routinely carried out during the evaluation and staging of patients with non-Hodgkin's lymphoma (NHL). Marrow involvement in the presence of nodal disease indicates stage IV disease. Bone marrow disease in diffuse large cell lymphoma has been associated with a higher incidence of central nervous system disease and a poor prognosis.<sup>1,2</sup> Characteristic patterns of disease in the marrow have been described in some histological subtypes of NHL.<sup>3,4</sup>

This study was undertaken with the following aims: (1) to establish the incidence of bone marrow disease in NHL at initial diagnosis in a large series of patients who had undergone bilateral biopsy; (2) to compare the patterns of disease in various histological subtypes; and (3) to establish the incidence of peripheral blood disease at presentation.

## Methods

Between 1983 and 1988 260 patients with

NHL underwent bilateral iliac crest biopsy. The bone marrow biopsy was carried out under local anaesthesia with a Jamshidi gauge 11 needle. Part of the aspirate was spread on glass slides and the remainder made into a clot section whenever possible. The bone marrow aspirates were stained with May-Grünwald Giemsa stain. The biopsy specimens were fixed in formalin, embedded in paraffin wax, and sections cut at 3  $\mu$ m were stained with haematoxylin and eosin. The median length of the biopsy specimen from the right and the left posterior superior iliac crests was 19 mm and 18 mm, respectively. The median combined length of the two biopsy specimens was 37 mm. The NHL in the primary site, mostly lymph node, was classified according to the Working Formulation.<sup>5</sup>

The bone marrow biopsy specimens were reviewed for the study by one of us (SJ). The pattern of marrow disease was classified as diffuse, focal (non-paratrabeular), paratrabeular and interstitial, essentially as defined by Bartl *et al*<sup>4</sup> and described below. Diffuse = replacement of a portion or all the marrow in the biopsy specimen, with obliteration of fat spaces; focal = aggregates inbetween the bone trabeculae; paratrabeular = lymphoid aggregates abutting the bony trabeculae; interstitial = infiltration inbetween the fat spaces.

## Results

Ninety nine (38%) of the 260 patients had marrow disease. The incidence varied according to histological subtype (table 1); the highest (83%) was seen in small lymphocytic lymphoma (SLL), followed by follicular small cleaved cell lymphoma (FSCCL), 58% of which were affected. Cases of diffuse large cell lymphoma (DLCL) had the lowest incidence (19%). All cases of SLL had bilateral disease. Among the positive cases, unilateral disease was seen in 10 of 37 (27%) of cases of FSCCL, 10 of 20 (50%) cases of DLCL, and in others with a variable incidence (table 1).

## PATTERN OF INFILTRATION (table 2)

Several cases had more than one pattern of disease. A paratrabeular pattern was seen in 34 of 37 (92%) cases of FSCCL with a positive marrow biopsy specimen. Fifteen cases had a paratrabeular pattern of disease only; in the remaining 19 cases it was associated with focal or diffuse patterns. Among the follicular mixed cell lymphoma (FMCL), seven of eight (87%) had a paratrabeular pattern of disease, and five had this as the only type. In none of the three

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Table 1 Incidence of bone marrow disease in different subtypes of non-Hodgkin's lymphoma

Histological subtype	No of cases	No of cases with marrow disease		
		Total (%)	Bilateral	Unilateral
<i>Low grade:</i>				
SL	18	15 (83)	15	0
FSCC	64	37 (58)	27	10
FMC	23	8 (35)	4	4
<i>Intermediate grade:</i>				
FLC	3	0 (0)	—	—
DSCC	13	6 (38)	4	2
DMC	23	10 (43)	7	3
DLC	107	20 (19)	10	10
<i>High grade:</i>				
SNC	7	2 (29)	1	1
LL	2	1 (50)	1	0
Total	260	99 (38%)	69	30

SL, small lymphocytic; FSCC, follicular small cleaved cell; FMC, follicular mixed cell; FLC, follicular large cell; DSCC, diffuse small cleaved cell; DMC, diffuse mixed cell; DLC, diffuse large cell; SNC, small non-cleaved cell; LL, lymphoblastic lymphoma.

cases of follicular large cell lymphoma (FLCL) was the marrow affected. Therefore, in follicular lymphomas with positive biopsy specimens 41 of 45 (91%) had paratrabeular disease compared with 17 of 39 (44%) cases of diffuse lymphoma ( $p < 0.0001$ , two tailed Fisher exact test). Seven out of 20 cases of DLCL had a diffuse pattern and eight had a focal pattern with large lymphoid cells. In eight cases of DLCL there was paratrabeular disease and six of these consisted only of small cleaved cells. One of 15 (73%) cases of SLL had interstitial and seven of 15 had focal disease; four cases had paratrabeular infiltration. Cases of diffuse mixed cell lymphoma (DMCL) had diffuse disease in five out of 10 cases and a focal or paratrabeular pattern in others. Cases of diffuse small cleaved cell lymphoma (DSCCL) were associated with a paratrabeular pattern in five of the six cases showing disease.

As stated above, six cases of DLCL had paratrabeular lymphoid aggregates of small cleaved cells; the latter were considered to represent infiltration by a low grade lymphoma. Similarly, two cases of FSCL had only large cells and a mixture of small and large cells, respectively, on the bone marrow aspirate.

In 56 of the 99 cases positive at biopsy the bone marrow aspirate was considered to be abnormal. Lymphocytosis with or without abnormal morphology was seen in 38 cases, and in the remaining 18 cases there was no lymphocytosis but the lymphoid cells were morphologically abnormal. Positivity on the aspirate also varied with histological subtype of NHL. Of the 37 cases of FSCCL that were positive at biopsy, a satisfactory aspirate was

obtained in 35 cases and 20 of these were positive. Similarly, eight of 20 cases of DLCL and 12 of 15 cases of SLL were positive on the aspirate, the latter on the basis of lymphocytosis.

Peripheral blood was affected at diagnosis in 15 (6%) cases. In nine of these the absolute lymphocyte count was less than  $4.0 \times 10^9/l$  and therefore the diagnosis of disease was based on abnormal morphology and on immunological markers showing a monoclonal B cell proliferation. One of these cases had only  $0.03 \times 10^9/l$  abnormal lymphoid cells in the peripheral blood. In the remaining six cases there was absolute lymphocytosis of more than  $4.0 \times 10^9/l$ . Ten of these 15 cases had low grade lymphoma (SLL  $n = 6$ , FSCCL  $n = 3$ , FMCL  $n = 1$ ); the others consisted of DLCL ( $n = 2$ ), DSCCL ( $n = 2$ ), and DMCL ( $n = 1$ ).

### Discussion

In our series of 260 patients of NHL who underwent bilateral bone marrow biopsy at presentation, the incidence of disease was 38% (99/260). This varied with the histological subtype, the highest incidence being seen in SLL (83%) and the lowest in DLCL (19%). As the incidence of disease varies with the histological subtype of NHL, it follows that the overall incidence would vary according to the number of cases of a particular histological subtype included in the study. This could be part of the reason for a variable reported incidence of 16–75%.<sup>6-8</sup> In our study the largest histological subtype was DLCL, which had the lowest incidence of disease, both in our study as well as in other published series.<sup>2,3</sup> The variation in the reported incidence of marrow disease could also depend on whether the biopsy specimens are unilateral or bilateral. In our study 30% of the cases had unilateral disease. This varied from 0% in SLL to 50% in DLCL. There were too few cases of high grade histology to draw meaningful conclusions. If we had carried out unilateral biopsy only, we might have missed marrow disease in 15% of cases overall and in 25% of cases of DLCL. Brunning *et al*<sup>9</sup> and Coller *et al*<sup>3</sup> reported an increased yield of 10–22% in bilateral biopsy specimens. A question that remains unresolved is whether taking two biopsy specimens from the one side would achieve the same results with less discomfort for the patient.

The pattern of disease also seemed to correlate with histology in the lymph node. Cases of follicular lymphoma were associated

Table 2 Patterns of bone marrow disease in non-Hodgkin's lymphoma

Histological subtype (No of positive cases)	Pattern of disease			
	Paratrabeular	Diffuse	Interstitial	Focal (non-paratrabeular)
SL (15)	4	5	11	7
FSCL (37)	34	6	0	14
FML (8)	7	0	0	2
DSCC (6)	5	2	1	2
DMC (10)	3	5	1	5
DLC (20)	8	7	4	8
SNC (3)	1	1	2	0
LL (1)	0	1	0	0

with a paratrabeular pattern and cases of DLCL with a diffuse or focal pattern. Cases of SLL usually had an interstitial or focal pattern. The predominance of a paratrabeular pattern in follicular lymphomas has also been reported in previous studies.<sup>4,6</sup> No cases of follicular lymphoma showed an interstitial pattern of infiltration in our study.

In eight cases discordant histological findings between the lymph node and the bone marrow were observed. In six of 20 cases of DLCL paratrabeular foci of small cleaved cells were present. One of the possible explanations for this discrepancy is that the large cell histology in these cases had evolved from the FSCCL. It has been documented from cytogenetic studies<sup>10</sup> that t(14; 18) (q32; q21), which is characteristic of follicular lymphomas, is seen in a small proportion of patients with DLCL. The biological and clinical importance of these findings needs to be clarified further. The superiority of the biopsy specimen to the aspirate in the detection of the marrow disease has also been described previously. Coller *et al* found the aspirate to be positive in only one third of all patients positive on biopsy specimen.<sup>3</sup> In our study the aspirate yielded positive results in 57% of cases shown to be positive on the biopsy specimens.

The 6% incidence of peripheral blood disease is comparable with that previously reported<sup>11,12</sup>; most cases were low grade lymphomas. Only two of 107 cases of DLCL had peripheral blood disease, confirming the rarity of such an occurrence at diagnosis. More sophisticated techniques such as immunoglobulin and T cell receptor gene rearrangements, however, have been shown to increase the detection of lymphoma cells in the peripheral blood.<sup>12</sup>

In summary, in cases with NHL at initial presentation: (1) bone marrow disease varies with the histological subtype; (2) bilateral biopsy specimens increase the positivity rate in most types; and (3) follicular lymphomas are strongly associated with a paratrabeular pattern of marrow disease.

- 1 Bunn PA Jr, Schein PS, Banks PM, deVita VT Jr. Central nervous system complications in patients with diffuse histiocytic and undifferentiated lymphoma: Leukemia revisited. *Blood* 1976;47:3-10.
- 2 Morra E, Lazzarino M, Castello A, *et al*. Bone marrow and blood involvement by non-Hodgkin's lymphoma: A study of clinicopathologic correlations and prognostic significance in relationship to the Working Formulation. *Eur J Haematol* 1989;42:443-53.
- 3 Coller BS, Chabner BA, Gralnick HR. Frequencies and patterns of bone marrow involvement in non-Hodgkin's lymphoma: Observations on the value of bilateral biopsies. *Am J Hematol* 1977;3:105-19.
- 4 Bartl R, Frisch B, Burkhardt R, *et al*. Assessment of bone marrow histology in the malignant lymphoma (non-Hodgkin's): correlation with clinical factors for diagnosis, prognosis, classification and staging. *Br J Haematol* 1982;51:511-30.
- 5 Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphoma: Summary and description of working formulation for clinical usage. *Cancer* 1982;49:2112-35.
- 6 Dick F, Bloomfield CD, Brunning RD. Incidence, cytology and histopathology of non-Hodgkin's lymphoma in the bone marrow. *Cancer* 1974;33:1382-98.
- 7 McKenna RW, Bloomfield CD, Brunning RD. Nodular lymphoma and blood manifestations. *Cancer* 1975;36:428-40.
- 8 Stein RS, Ulmann JE, Byrne GE, Moran M, Golomb HM, Oetzel N. Bone marrow involvement in the non-Hodgkin's lymphoma. *Cancer* 1976;37:629-36.
- 9 Brunning RD, Bloomfield CD, McKenna RW, Peterson L. Bilateral trephine bone marrow biopsies in lymphoma and other neoplastic diseases. *Ann Intern Med* 1975;82:365-6.
- 10 Koduru PRK, Filipa DA, Richardson ME, *et al*. Cytogenetic and histologic correlations in malignant lymphoma. *Blood* 1987;69:97-102.
- 11 Come SE, Jaffe ES, Anderson JC, *et al*. Non-Hodgkin's lymphomas in leukemic phase: clinicopathologic correlations. *Am J Med* 1980;69:667-74.
- 12 Brada M, Mizutani S, Molgaard H, *et al*. Circulating lymphoma cells in patients with B and T non-Hodgkin's lymphoma detected by immunoglobulin and T-cell receptor gene rearrangement. *Br J Cancer* 1987;56:147-52.