Bone Marrow Involvement in Malignant Lymphomas (Non-Hodgkin's)

Eman Sadiq Jalal

MSc

Abstract:

Background: Bone marrow biopsies are taken routinely in the initial investigation of patients with non-Hodgkin's lymphomas to estimate the progression of disease at time of presentation (staging) and to type mode of proliferation (growth pattern) in the bone marrow.

Method: Initial pretreatment bone marrow biopsies were taken from twenty-four patients diagnosed by the established criteria on lymph node biopsies as suffering from one of the non-Hodgkin's lymphomas. All biopsies were examined histologically.

Result: Frequency of bone marrow involvement in different types of non-Hodgkin's lymphomas (at time of initial diagnosis) was found in 75%. In the low grade lymphoma the age incidence was 28-75 years (mean50 years); while for the high grade type it was 6-25 years (mean15years).

Conclusion: The results clearly demonstrate that at first presentation over half of the patients with malignant lymphoma have positive bone marrow biopsies indicating disseminated disease, i.e. stage IV. Malignant lymphoma of low grade malignancy more frequently involves the bone marrow than malignant lymphoma of high grade malignancy. Thus, in the bone marrow biopsy the clinician has a tool at his disposal which supplies decision information on the diagnosis and therapy of any given patient with non-Hodgkin's lymphomas.

Keywords: Non-Hodgkin's lymphomas, bone marrow biopsy.

Materials & Methods

This study was carried out 2006, from patients admitted to the medical city teaching hospital, bone marrow biopsies of twenty four patients diagnosed by the established criteria on lymph node biopsies, or other masses biopsies as suffering of non-Hodgkin's lymphomas was examined . Eleven of these patients' bone marrow biopsies were done as one of the diagnostic procedures to exclude hematological disease, patients with chronic lymphocytic leukemia were included in this study, but individuals with acute lymphoblastic leukemia were excluded. All biopsies were fixed and decalcified in Bouin's solution, then processed and embedded in paraffin, cut each 5 μ in thickness and stained with haematoxylin and eosin, silver impregnation for reticulin and Van Gieson's stain for collagen. Biopsy cores less than 0.5x 0.5 mm were not included. Clinical data of all patients, including full history and physical examination were done, plus hematological studies (complete blood picture, bone marrow aspirate and imprints of the biopsy).

Results

Clinical: The age range of participants was 6-75years (mean38.7 years), in the low grade lymphoma the age incidence was 28-75 years (mean50 years), with a lower age range in the high grade type of 6-25 years (mean15years). Concerning the sex distribution, 13/24 (54%)

Introduction

It is over a decade since the value of bone marrow biopsies in the staging of non-Hodgkin's lymphomas has been recognized. Biopsy of the bone marrow is now widely employed in the initial investigation and staging of patients with malignant lymphomas[1]. A positive biopsy is taken as evidence of systemic spread. In addition, a bone marrow biopsy may assist in the initial diagnostic evaluation of patients with signs of haematopoietic failure, with unexplained hepatic or spleenic enlargement, or with fever of unknown origin. A bone marrow biopsy may be diagnostic in patients without peripheral lymphadenopathy, and may aid classification when inconclusive or divergent histologies are found at other sites[2].A bone marrow biopsy also provides information on the extent of tumor cell burden (volume percentage) and on the function and response to therapy of the residual marrow and of the neoplasia. A bone marrow biopsy thus offers insight into the biological behavior of the disease process in the individual patient.[3, 4]

Bone marrow involvement in non-Hodgkin's lymphomas shows certain mode of spread called growth patterns, but with progressive expansion and replacement of the hematological tissue all patterns merged into the packed marrow type i.e. complete occupation of the marrow cavities by the neoplastic cells. These modes of spread are of prognostic significance.[3]

61% of patients with positive bone marrow biopsy had anemia which was normochromic normocytic, while thrombocytopenia encountered in 56% of these patients, (table 1).

Histological: The overall division of the biopsies into the different entities is shown in (table 2).The mean section area available for examination was 50 mm^2.

were male, while the remaining 11/24 (46%) were females, with a male: female ratio of 1.2:1. Lymph node enlargement and / or splenomegaly was found in 88% of cases with low grade malignant lymphoma, while extranodal involvement (e.g. small intestine, ovary, liver) was noticed mainly in the high grade type of malignant lymphoma.

Table 1:clinical and blood picture in patients with*NHL with Bone Marrow involvement versus those with negative Bone Marrow

Clinical features, CBP	+BMB (No.18)		- BMB (No.6)	
	no.	%	no.	%
Fever	9	50	1	17
Itching	1	6	0	0
Weight loss	4	22	0	0
Lymphadenopathy	9	50	1	17
Splenomegaly	9	50	0	0
Hepatomegaly	10	56	0	0
Iliocecal mass	0	0	4	67
Ovarian mass	0	0	1	17
Anemia Hb < 10g/dl	11	61	1	17
Leucopenia <4x 10^9/l	4	22	0	0
Leukocytosis >11x 10^9/l	8	44	4	67
Leukemic blood picture	7	39	0	0
Thrombocytopenia <100x10^9/l	10	56	0	0
Male/female	1.6:1		0.5:1	
Age , mean, years	47		14	

*NHL. Non Hodgkin's lymphoma

Table 2: Non-Hodgkin's lymphoma histological groups

Malignancy	**No. of patients**
NHL. of low grade malignancy	16
lymphocytic	7
Hairy cell leukemia HCL	3
Lymphoplasmacytic LPL	2
Follicular lymphoma FL Grade 2 (Mixed, CB/CC) Grade 3 (Centroblastic CB)	 3 1
NHL. of high grade malignancy	8
Immunoblastic IB	1
Burkett's	4
Lymphoblast LB	3

Frequency of bone marrow involvement in different types of non-Hodgkin's lymphoma (at time of initial diagnosis) was75%. The bone marrow biopsy was the only material available for initial histological diagnosis of malignant lymphoma in 61% of the positive bone marrow biopsies of NHL patients, patients with malignant lymphoma of low grade malignancy exhibited a significantly ($P < 0.05$) higher frequency of bone marrow involvement than patients with malignant lymphoma of high grade malignancy, (figure 1).

There were also significant variations in the frequency of bone marrow involvement by the different types of malignant lymphoma of the low grade malignancy, the highest frequency was in the leukemic variants of the malignant lymphoma i.e. malignant lymphoma lymphocytic 38%,(figure 2).

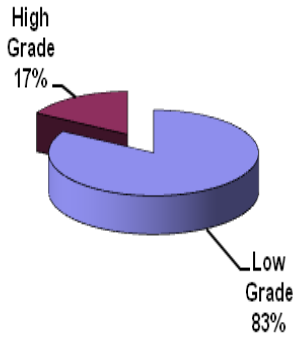

Figure 1: NHL +ve BM frequency of low and high grade

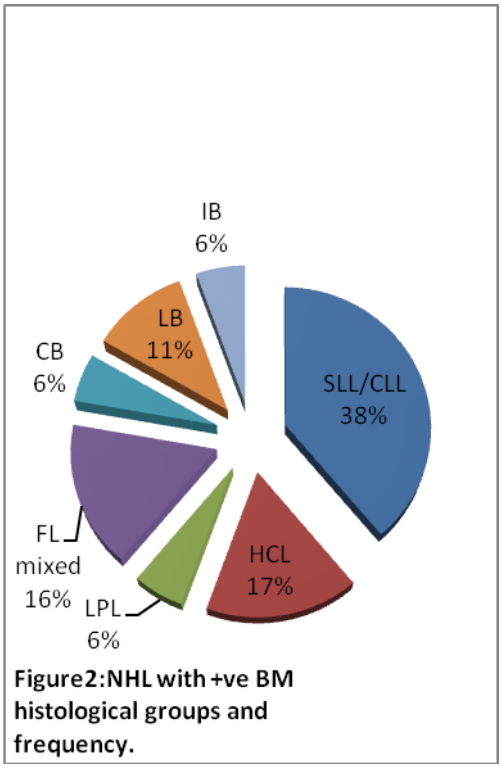

Figure2:NHL with +ve BM histological groups and frequency.

The interstitial pattern of bone marrow involvement was the most frequent pattern encountered in the lymphocytic type of malignant lymphoma; reticulin fibers were thin and sparse, most of the patients in this group, were leukemic and had clinical features of chronic lymphocytic leukemia. The growth pattern in hairy cell leukemia was patchy marrow involvement with fairly dense fibrosis which was the cause behind diluted or dry marrow aspirate, bone marrow biopsy established the initial diagnosis, and so constitutes the primary diagnostic procedure in this type of lymphoma, all patients in this category presented with pancytopenia and splenomegaly. The nodular pattern, (figure 3), encountered mainly in follicular lymphoma mixed cell type with reticulin fibrosis of the involved area. Packed marrow pattern was mainly seen in patients with intermediate and high grade lymphoma with marked fibrosis of the marrow, (figure 4).

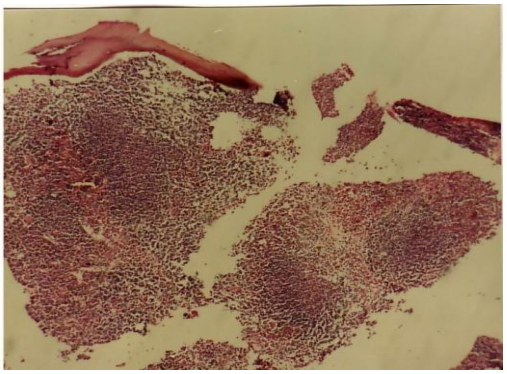

Figure 3: nodular growth pattern of BM infiltration H&E x63.

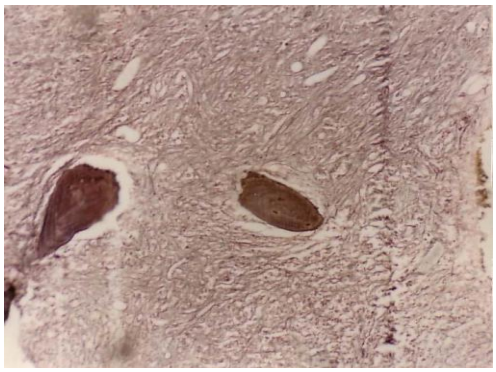

Figure 4: NHL with diffuse course Fibrosis Gomori x100

Discussion

Various factors may be implicated to account for the wide range in the frequency of detection reported over the past decade. These include the use of aspirate which has a high rate of false negatives, the non-uniformity of definitions for the malignant lymphoma leading to varying distribution of patients in each category, and the fact that biopsy size, site and technical preparation differ between reporting centers. However, it is now clear that detection of focal bone marrow involvement is related to biopsy size rather than site. It is not known what factors influence lymphoid cells to assume certain architectural arrangement in the bone marrow though these might include an inherent behavioral tendency to aggregate; a propensity to form local topographic influence or a chemotactic attraction to specific areas in the bone marrow. It might be significant that whereas red and white cell and platelet precursors have preferred topographic localizations in the bone marrow none is known for lymphopoiesis.

The histopathological grading of malignancy in the bone marrow (low or high according to the Kiel classification), show that classification is feasible, reproducible and has prognostic significance.

Recent work has re-emphasized the migratory nature of lymphoid cells, and that they normally circulate through lymph nodes, lymph, and blood and bone marrow. Investigations with sophisticated marker techniques have demonstrated that neoplastic lymphocytes also circulate in the peripheral blood in high percentage of cases of malignant lymphoma. Therefore it is clear that all patients with malignant lymphoma have cells, either constantly or intermittently, though these may not be identifiable by morphology alone. Further more the bone marrow is natural "habitat" for lymphoid cells whether as a permanent home, a transient abode or a site of origin and production[4, 11]. Viewed in this light, most malignant lymphoma could well be considered systemic diseases from the outset so that the emphasis shifts from whether the bone marrow is involved to the extent of its involvement, from nondetectable with routine methods to massive replacement of haematopoietic tissues. Nevertheless, even within the concept of the malignant lymphoma as systemic diseases from the start, it is clear that some tissues and organs are more affected than others in the different malignant lymphoma; and with respect to the bone marrow three categories were distinguished: (1) the cumulative lymphomas such as chronic lymphocytic leukemia, hairy cell leukemia with a systemic presentation in which stage is indicated by the amount of infiltration in the bone biopsy[12] (i.e. vol. % in the biopsy), (2) the primarily regional lymphomas with centrifugal spread in which bone marrow involvement indicates stage IV, and (3) lymphomas with a metastatic behavior, these were the 'plastic' types, there was unpredictable pattern of spread analogous to a metastatic sarcoma. These observations indicate conclusively that bone marrow biopsy is a useful diagnostic tool for histological classification and clinical staging of any given patient with non-Hodgkin's lymphoma.

References:

1-A.V.Hoffbrand, D.Catovsky.Post graduate hematology, ed.5.Blackwell, 2005.

2-B.J.Bain. Blood Cells a Practical Guide, ed.4. Blackwell, 2006

3- Bartle R., Frisch B., and Jager K. Lymphoproliferation in the bone marrow: identification and evolution. J. clin. Pathol. 1984; 37, 233-254.

4- Benjamin, D.; Magrath, I.T.; Derivation of lymphoma cell lines from microscopically normal bone marrow in patients with undifferentiated lymphomas. Blood 1983; 5: 1017-1019.

5- D.Provan, C.Singer. Oxford Handbook of Clinical Haematology, ed.2. Oxford University Press 2004.

6-Harris NL, Jaffe ES, Stein H *et al.* 1994A revised European-American Classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. *Blood* 84: 1361–92.

7-Juan Rosai. Ackerman's Surgical Pathology, ed.9. Vol, 7.8- 2004.

8-Lymphoma Classification Project 1997 A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 89: 3909–18.

9-Marti GE, Rawstron AC, Ghia P, Hillmen P,Houlston RS, Kay N *et al.* on behalf of The International Familial CLL Consortium 2005 Diagnostic criteria for monoclonal B-cell lymphocytosis.Br J Haematol, 130, 325–332.

10- McKenna RW, Frizzera G, Brunning RD. Incidence and patterns of bone marrow and blood involvement by lymphoma in relationship to the Lukes-Collins classification. Blood 1979; 14: 1417-22.

11-R. Hoffman, E. Benz, S. Shattil, B. Furie, H. Cohen, Hematology basic principle and practice.ed.4. Churchill Livingstone, 2004.

12- Sommerfeld, W. Bone marrow histology in hairy cell leukemia. Am. J. Clin. Path. 1983; 79: 531-545.

13-Thieblemont C, Berger F, Dumontet C *et al*. 2000 Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 95: 802–6 (Review).

Hematology unit, AlKarama Teaching Hospital Baghdad, Iraq