

BONE MARROW INVOLVEMENT IN NON-HODGKIN'S LYMPHOMA

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
BM	Bone Marrow
CBC	Complete Blood Count
ESR	Erythrocyte Sedimentation Rate
Hb	Haemoglobin
HGL	High Grade Lymphoma
IGL	Intermediate Grade Lymphoma
LGL	Low Grade Lymphoma
LN	Lymph Node
NHL	Non-Hodgkin's Lymphoma
WBC	White Blood Cells

Abstract



A prospective study done over a period of 12 months on 30 patients aged 15 to 70 years with initial tissue biopsies of NHL who were seen at the Baghdad Teaching Hospital. Trepine and aspiration BM biopsy were performed with routine evaluation including CBC. All biopsies were classified according to the commonly used classification system, international Working Formulation. Patients are staged according to the Ann-Arbor staging system. Intermediate grade NHL (IGL) comprised the most common type of NHL (43.3%); high grade NHL (HGL) comprised (36.7%); low grade NHL (LGL) comprised the least common type (20.0%).

BM was involved in 10 patients out of 30 patients with NHL (33.3%) LGL exhibited a higher incidence of involvement (50.0%) than did patients with IGL (30.8%) and HGL (27.2%),.

Hematological abnormalities were observed frequently with and without BM involvement.

Key words: Incidence: Non-Hodgkin's Lymphoma; Bone Marrow

اصابة نخاع العظم بالورم اللمفاوي اللاهوجني

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دراسة مستقبلية اجريت للفترة من بداية شهر اذار سنة 2010 م ولغاية نهاية شهر اذار 2011 م. تم اخذ عينة مؤلفة من ثلاثون مريضاً تتراوح اعمارهم ما بين 15-70 سنة مصابين بورم لمفاوي لاهوجني، ادخلوا الى مستشفى بغداد التعليمي- مدينة الطب- قسم الأمراض الباطنية. أخذت معلومات سريرية دقيقة وتم اجراء فحوصات سريرية ومختبرية دقيقة، كما اجري لهم فحص نسيجي لخزعة نخاع العظم وصنف المرضى الى مراحل مختلفة من المرض وفقاً لنظام أن- آر بور العالمي. أظهرت الدراسة النتائج التالية:

- وفقاً لدرجة شدة المرض :- (34,3%) كانوا ذو درجة متوسطة، (36,7%) ذو درجة عالية، (20%) ذو درجة واطنة.



- عشرة مرضى من أصل ثلاثين (33,3 %) أصيب نخاع العظم بالخلايا الخبيثة للمرض ومعظمهم كانوا ذو درجة واطئة من الشدة (50 %).

Introduction

Lymphomas are a group of malignant lymphoid neoplasm's arising in lymph nodes or in any extranodal lymphoid tissue. The lymphomas are a heterogeneous groups of malignancies from the pathologic, clinical, and treatment viewpoints. The two major groups of lymphomas include Hodgkin's disease and the non – Hodgkin's lymphomas (NHL). In both groups, the most common clinical presentation is an asymptomatic enlargement of lymph nodes in the cervical, axillary, or inguinal regions, usually first noticed by the patient. Usually the duration of lymph node enlargement is uncertain.⁽¹⁾

Non-Hodgkin's lymphomas are a heterogeneous groups of malignant neoplasms characterized by monoclonal proliferation of a malignant cell of lymphoid origin, usually either a T cell or a B cell. The cause of most NHL is not known. Viruses have been implicated in African Burkitt's lymphoma (AIDS) - related lymphomas, and in lymphomas arising from immunosuppressive therapy after organ transplantation (Epstein – Barr virus).⁽¹⁾

The incidence and pattern of bone marrow (BM) and blood involvement by non – Hodgkin's lymphoma (NHL) have been a subject of several reports^(2, 4, 13, 14, 15, 19, 21). While bone marrow trephine biopsy is now recognized as important in staging patients with malignant lymphoma, few pathologic studies comparing between the bone marrow histopathology and cytology with lymph node pathology as described in the Rappaport classification of NHL or it's modifications by Lukes have been done⁽³⁾. Determination of the incidence of marrow involvement in each histologic type has important implications regarding the manner of spread of lymphoma and the role of curative radiotherapy in its treatment.

In addition, knowledge of the incidence of BM involvement may help to determine the manner in which efforts should made to assess the presence or absence of such involvement in patients with NHL⁽⁴⁾.

Immunogenetic analysis may detect BM involvement in NHL, which may not be detected by morphologic examination because of patchy distribution⁽⁵⁾.

Because magnetic resonance imaging presents a more global view of the BM than does biopsy material, such imaging may provide a better understanding of disease progressing and remission^(6, 11).

The classification systems for NHL are being revised. The one commonly used has been the so – called International Working Formulation (IWF) (Table 1), which is juxtaposed with the now outdated Rappaport system⁽¹⁾.



The Ann Arbor staging system developed for Hodgkin's disease has also been used in staging NHL. This staging system focuses on the number of tumor sites (nodal and extranodal), location and the presence or absence of systemic symptoms. In stage I and stage II, sites of disease are on the same side of the diaphragm. In stage III, the disease involves both sides of the diaphragm, whereas stage IV is defined as extranodal lymphomatous involvement, most frequently of the BM and liver(12).

Table 2 summarizes Ann Arbor staging system. Hepatomegaly by sonar or physical examination considered as a sign of hepatic involvement by NHL(4).

Table 1 Classification of NHL ⁽¹⁾

International Working Formulation	Rappaport Classification
I- Low grade lymphoma	
a- Small lymphocytic cell.	<ul style="list-style-type: none"> • Diffuse lymphocytic, well differentiated.
b- Follicular mixed cleaved cell.	<ul style="list-style-type: none"> • Nodular lymphocytic. Poor differentiated.
c- Follicular mixed small cleaved and large cell.	<ul style="list-style-type: none"> • Nodular mixed lymphocytic – histiocytic.
II- Intermediate grade lymphoma	
d- Follicular large cell.	<ul style="list-style-type: none"> • Nodular histiocytic.
e- Diffuse, small cleaved cell.	<ul style="list-style-type: none"> • Diffuse lymphocytic, poorly differentiated.
f- Diffuse, mixed small cleaved cell.	<ul style="list-style-type: none"> • Nodular mixed lymphocytic – histiocytic
g- Diffuse large cell.	<ul style="list-style-type: none"> • Diffuse histiocytic.
III- High grade lymphoma	
h- Large cell immunoblastic.	<ul style="list-style-type: none"> • Diffuse histiocytic.
i- Lymphoblastic cell.	<ul style="list-style-type: none"> • Diffuse undifferentiated.
j- Small noncleaved cell "Burkitt's and non – Burkitt's".	

Table 2 Ann Arbor Staging System ⁽¹²⁾

Stage I	Involvement in single lymph node (LN) region or single extralymphatic site.
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Stage II	Involvement of 2 or more LN region on the same side of the diaphragm. Localized contagious involvement of only one extralymphatic site and LN region (Stage IIE).
Stage III	Involvement of LN regions on both sides of the diaphragm; may include spleen.
Stage IV	Disseminated involvement of one or more extralymphatic organs with or without LN involvement.

Patients and Methods

Thirty patients are selected randomly between the ages of 15 and 70 years; there were twenty males and ten females with initial tissue biopsies of NHL diagnosed between March 2010 and March 2011 seen at the Baghdad Teaching Hospital – Medical City. Patients agreement has been taken according the standards of the hospital and health directorate.

The trephine and aspiration BM biopsy were performed on the posterior superior iliac spine on all patients. The biopsies were performed using 2% xylocaine local anaesthesia.

All initial lymph nodes and other tissue biopsies were examined and classified according to the commonly used classification system, The International Working Formulation.

Patients are staged clinically according to the criteria adapted at the ANN Arbor staging system for Hodgkin's disease which is also used in staging NHL table 2.

Routine evaluation included complete blood count, comb's test, erythrocyte sedimentation rate, serum alkaline phosphatase, serum uric acid, renal and liver function tests, chest X – ray and abdominal ultrasonography. Liver biopsy was performed in selected cases. We considered liver enlargement by physical examination or ultrasonography as a sign of hepatic involvement.

Patients in whom the distinction between leukemia and lymphoma was clinically and pathologically unclear were excluded from the study. A comparison of cytology was made between bone marrow biopsy and initial biopsy (lymph node or tissue biopsy).

Fisher exact probability test was used for the statistical analysis. For comparison between age groups, types and stages of the disease, statistical tests are not valid due to small sample size.

Results

The mean age group of studied patients was (43 ± 17.05); male patients comprise the larger group which is 20 patients (66.7%) of the total 30 patients, as



compared with the female patients who were comprising 10 patients (33.3%). This is showed in Table 3.

The incidences of NHL in the initial LN and tissue biopsies according to the pathologic classes are shown in the Table 4. The intermediate grade NHL comprised the highest incidence of NHL (43.3%) followed by the high grade NHL (36.7%), and lastly the low grade NHL which comprised the lowest incidence of NHL (20.0%).

Bone marrow was involved in 10 patients from 30 patients which comprised (33.3%) and not involved in the remainder 20 patients (66.7%) at the time of initial diagnosis as shown in the Table 5.

Patients with low grade NHL exhibited a higher incidence of BM involvement (50.0%) than did patients with intermediate grade NHL (30.8%) and patients with high grade NHL exhibited the least incidence of bone marrow involvement (27.2%) as shown in Table 6.

Hematological abnormalities associated with NHL in the presence of BM involvement are shown in Table 8. Although anemia ($Hb < 12 \text{ gm/dl}$), thrombocytopenia (platelets $< 100.00 \text{ cells/mm}^3$) and lymphocytosis (lymphocytes $> 5000 \text{ cells/mm}^3$) were more likely associated with BM involvement in NHL, however the association is not statistically significant ($p > 0.05$).

Leucopenia ($WBC < 4000 \text{ cells/mm}^3$), elevated ESR $> 15 \text{ mm/hr}$ and elevated serum alkaline phosphatase $> 125 \text{ IU/L}$ are present frequently with BM involvement and without BM involvement in NHL and again the association not statistically significant ($p > 0.05$).

Table 3 Distribution of patients according to the age and gender

Age groups (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
15 – 34	6	75	2	25	8	26.6
35 – 54	8	57.2	6	42.8	14	46.8*
55 – 70	6	75	2	25	8	26.6
All age groups	20	66.7	1	3.3	3	100

* Mean age group = (43 ± 17.05)

Table 4 Pathological classification of 30 patients with NHL



Lymphoma	No. of patients	Percentage (%)
HGL	11	36.7
IGL	13	43.3
LGL	6	20.0
Total	30	100

Table 5 The overall incidence of BM involvement in 30 patients with NHL

	No. of patients	Percentage (%)
BM involvement	10	33.3
No. BM involvement	20	66.7
Total	30	100

Table 6 Incidence of BM involvement in each grade of NHL for 30 patients with NHL

Type of NHL	Patients with BM involvement		Patients with no BM involvement		Total	
	No.	%	No.	%	No.	%
HGL	3	27.2	8	72.8	11	100
IGL	4	30.8	9	69.2	13	100
LGL	3	50	3	50	6	100
Total	10	33.3	20	66.7	30	100

Table 7 : Relationship between the presence and absence of BM involvement and the stage of disease

Type of NHL	Marrow involvement	No. of patients	No. of patients in stage		
			I or II	III	IV

HGL	+ve	3	0	0	3
	-ve	8	5	1	2
IGL	+ve	4	0	0	4
	-ve	9	2	1	6
LGL	+ve	3	0	0	3
	-ve	3	1	0	2
All types	+ve	10	0	0	10
	-ve	20	8	2	10

Table 8 Hematological finding in the total patients group

	Total no. of patients	No. of patients with:											
		Hb <12gm/dl		WBC <4000cell/mm ³		Lymphocyte >5000 cell/mm ³		Platelets <100.00 cell/mm ³		ESR >15 mm/hr		Serum Alkaline Phosphatase >125 IU/L	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
BM involvement	10	6	60	2	20	4	40	3	30	10	100	3	30
No. BM involvement	20	10	50	1	5	2	10	4	20	19	95	3	15

* P value > 0.05 for all, not significant.

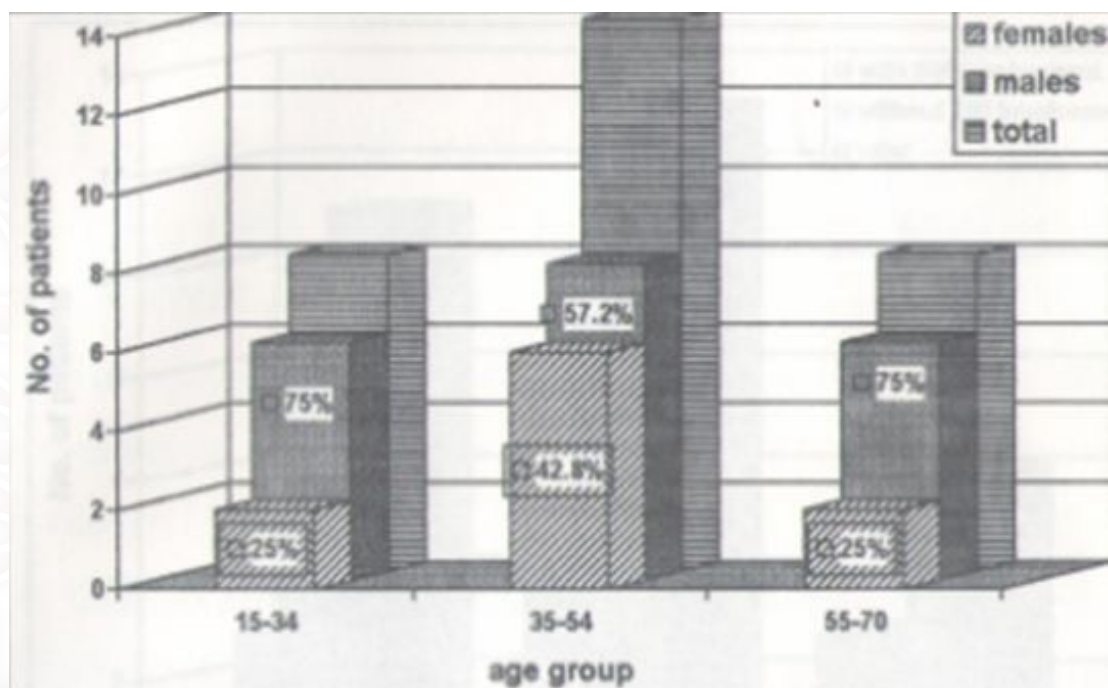


Figure 1: A histogram showing the age and gender distribution in 30 patients with NHL

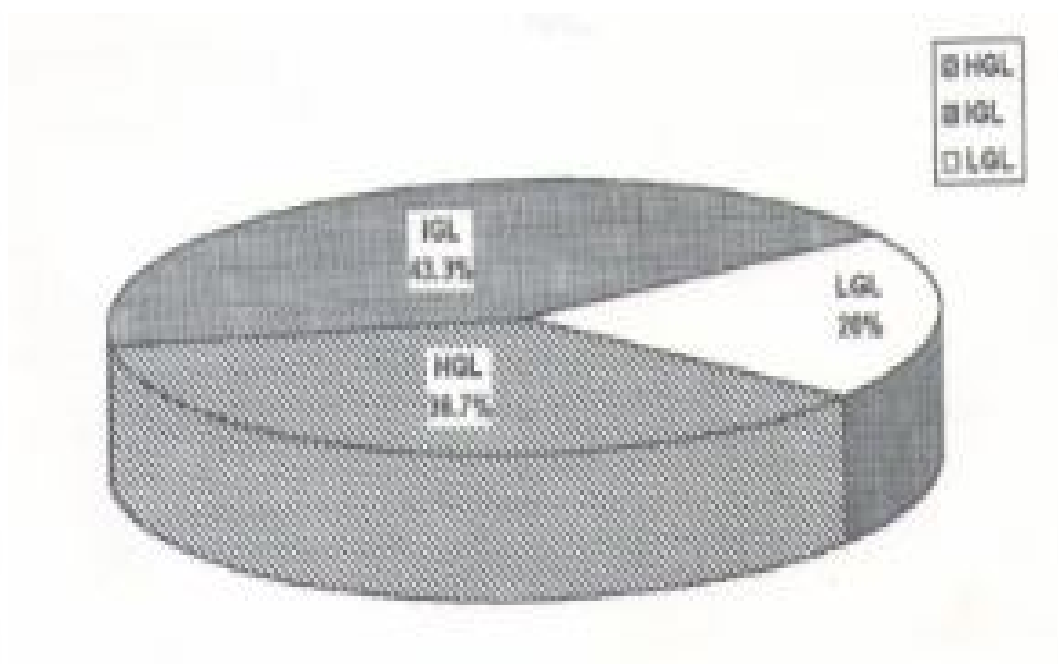


Figure 2: A Pie chart showing the number and percent of each grade of NHL in 30 patients with NHL at initial biopsy

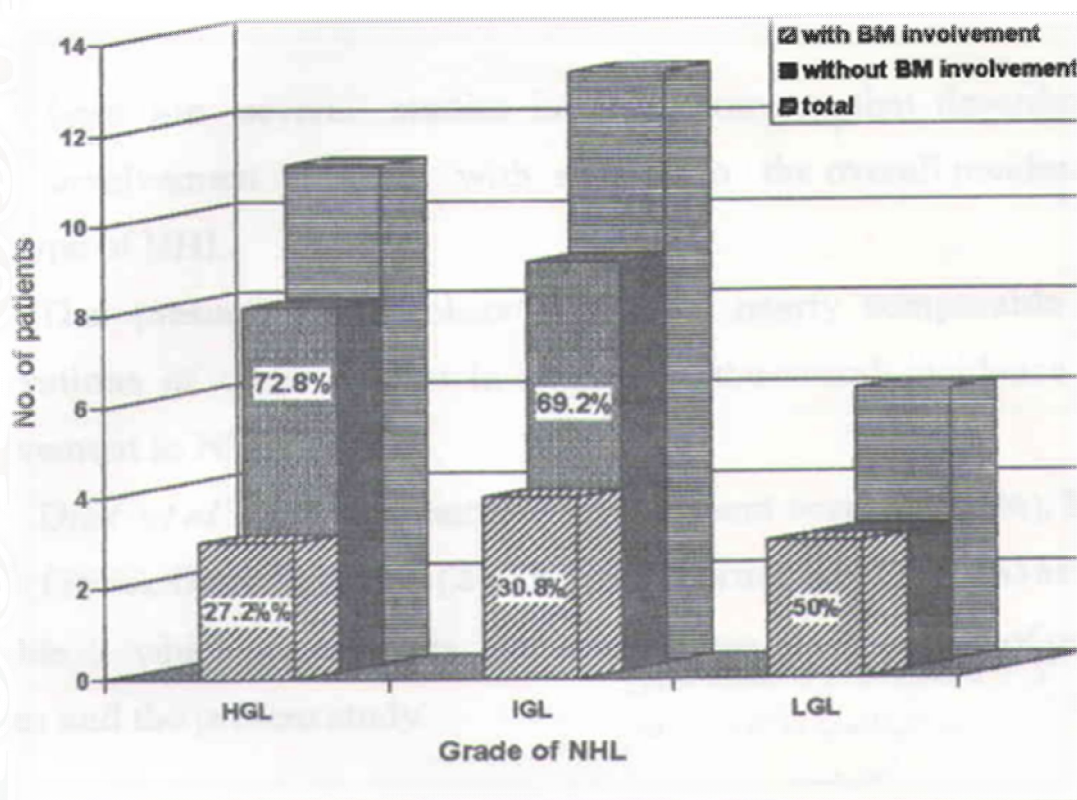


Figure 3: A histogram showing the BM involvement in relation to the grade of NHL in 30 patients with NHL

Discussion

There are several studies in the literatures that described BM involvement in NHL, with respect to the overall incidence and each type of NHL.

The present study observations are nearly comparable to the observations of other studies in respect of the overall incidence of BM involvement in NHL.

Dick et al⁽²⁾ showed that BM involvement occur in (37%), stein et al⁽⁴⁾ (36%), Baroni et al (14) (21.8%) and Morra et al (15) (39%) as shown in table (9) which

summarizes the comparison of the results of previous studies and the present study.

Table 9 A comparison between the previous studies and the present study regarding the incidence of BM involvement in NHL

The study	No. of patients	No. of patients with BM involvement	Percent (%)
Dick et al ⁽²⁾	108	40	37
Stein et al ⁽⁴⁾	121	44	36
Baroni et al ⁽¹⁴⁾	151	33	21.8
Morra et al ⁽¹⁵⁾	172	67	39
Present study	30	10	33.3

The LGL is the most common type of NHL involve the BM followed by IGL and HGL which comprises the least incidence as described in Morra et al ⁽¹⁵⁾ study, Conlan et al (16), and Hassan et al(18) study. These findings are comparable with our study as shown in table 10.

Khalil's study⁽²⁰⁾, which is done in Al – Rasheed Military Hospital (1993) showed that the incidence of BM involvement in NHL is (40%) at diagnosis, LGL comprises the most common type of involvement (60%) followed by HGL (53%). IGL comprises the least common type of NHL involvement of BM in this study. These observations were inconsistent with those observed in present study, probably due to the larger number of patients involved in the study and the gender of the patients (all patients were male) (Table 10).

Table 10 BM involvement in NHL in the present study and other studies



The study	Country of study	Year of study	Percent of patients with BM involvement		
			LGL	IGL	HGL
Morra et al⁽¹⁵⁾	Italy	1989	59	25	20
Conlan et al⁽¹⁶⁾	USA	1990	39	36	18
Khalil study⁽²⁰⁾	Iraq	1993	60	33	53
Hassan et al⁽¹⁸⁾	Pakistan	1995	50	32.5	17.5
Present study	Iraq	2011	50	30.8	27.2

Stein et al(4) showed that abnormalities of blood count were observed infrequently. Anemia and neutropenia, as well as elevated ESR and serum alkaline phosphatase occurred with similar frequency in patients with and without BM involvement. Lymphocytosis and thrombocytopenia were observed only in patients with marrow involvement, these phenomena identified in fewer than 20%⁽⁴⁾.

Conlan et al(21), showed that the presence of BM involvement in lymphoma was more likely to be associated with leucopenia (6%) and thrombocytopenia (16%) than the absence of BM lymphoma (42%) than in those without BM lymphoma. The differences was not statistically significant.

The present study showed that the hematological abnormalities are comparable with these studies in which anemia, thrombocytopenia and lymphocytosis are slightly more common in patients with BM involvement in NHL, than in those



without BM involvement in NHL, but the association was not statistically significant. This is also applied for the associations of leucopenia, elevated ESR and elevated serum alkaline phosphatase with and without BM involvement in NHL ($p>0.05$).

Conclusion

Trephine BM biopsy is important in staging patients with NHL.

Low –grade lymphoma exhibited a higher incidence of BM involvement.

We recommended for future that BM examination should be done for all patients with NHL, especially when the technology for autologous BM transplantation becomes available, because it has been shown to improve long – term remission.

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