



STUDY OF PREVALENCE AND PATTERN OF BONE MARROW INVOLVEMENT IN LYMPHOMAS - A TERTIARY CARE HOSPITAL STUDY IN KASHMIR.

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ABSTRACT

BACKGROUND: BM infiltration by lymphoma places the patient in Stage IV disease and these patients manifest poor prognosis and response to treatment. In patients with bone marrow involvement by lymphomas, the marrow smears and trephine sections are collectively interpreted for cytology, pattern of bone marrow infiltration, and sometimes Immunophenotyping.

Materials and methods: A 5 year (Jan 2013 to Dec'17) study was conducted in the Deptt. of Pathology and Clinical Hematology, SKIMS. All the cases reported as NHL & HL were reviewed and analyzed. The data included bone marrow aspiration and bone marrow biopsy samples and relevant blocks and slides. In this study we tried to study prevalence and pattern of bone marrow involvement in NHL & HL.

Results: NHL to HL ratio was (7:1). DLBCL was the most common (54.3%) subtype followed by FL (7.8%), SLL (6.8%). NHL pts. were in the age group of 41-60 yrs whereas HL were of 21-40 yrs. Male to female ratio is equal to 2:1. Infiltration was seen in 22.6% cases in BMB and in 18.3% cases in BMA. Infiltration was commonest in LPL (75% cases), f/b SLL 63%, FL (50%), ALCL (42.9%), MZL (37%), DLBCL (20.8%), BL (25%), MCL (16%) & HL (7%). Diffuse pattern of infiltration was most common followed by interstitial, mixed, paratrabeular and nodular. The reliability of BMB was significantly higher than that of BMA.

Conclusion: We conclude that Bone marrow examination is an important investigation in cases of Lymphoma which has a prognostic and at times diagnostic relevance. The highest frequency of marrow disease was encountered in elderly patients with indolent lymphomas. The BMB had a higher diagnostic validity whereas; BMA served a good test in screening lymphomas positive for marrow disease. However, a negative BMA does not exclude marrow involvement. Pattern of infiltration showed significant variation in bone marrow involvement. Immunohistochemistry increased the diagnostic accuracy. HL had a low rate of BM involvement.

KEYWORDS

Bone Marrow, Lymphomas

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INTRODUCTION

The Lymphoma is a complex and heterogeneous group of malignant diseases, which are increasing in incidence in the developed world.¹ The incidence has increased from 6.9 / 100,000 to 17.4 / 100,000 in UK and the USA. NHL is slightly more common in males than in females and incidence rises with age. Patients usually present with painless lymphadenopathy but in some cases primary site may be skin, GIT, salivary glands, lungs, CNS and renal tract.² Lymphomas represent clonal malignancies of lymphoreticular system in which the majority of the cells are arrested at a single stage of normal differentiation.¹ The white blood cells start to divide abnormally and continuously and they are not naturally dying off as they usually do. So lymphoma cell population is composed of identical lymphocytes, arising from a single lymphocyte of either T or B-cell origin. These cells may divide slowly and not die, or divide rapidly. Either way the end result is an accumulation of a large number of identical lymphocytes which can cause lymph nodes to enlarge.²

Two broad types of lymphoma are named as Hodgkin's lymphoma and Non-Hodgkin's lymphoma.^{3,4} About 85% of lymphomas are of B-cell origin and 15% of T-cell origin. B-cells originate and mature (differentiate) in the bone marrow while T-cells also start out in the bone marrow but they differentiate and mature in the thymus gland.⁵

Diagnosis in lymphomas especially with regard to their histological sub-classification is best made with tissue sections. Cytological

evaluation of marrow smears and imprints, however, many provide a chance for reasonably accurate diagnosis of these disorders.^{6,7} They are of help in the recognition of the cell type of lymphoproliferative disorders.⁸ Cytological NHL infiltration in the marrow shows morphologic features similar to those observed in lymph nodes from the same patients,⁹ but does not preserve the normal architecture so that the estimation of cell distribution varies widely. Bone marrow biopsy, on the other hand, yields a core cut of the bone marrow with its architecture preserved and is excellent for providing a section of infiltrated, packed, or empty marrow for the assessment of infiltrative processes; most of these disorders prevent aspiration and result in a dry tap.¹ Therefore, aspiration and biopsy of bone marrow are two techniques through which bone marrow is examined and the thorough evaluation include both since the two complement each other. Worldwide comparative studies for both sampling techniques favor the BMB over BMA smears.^{10,11,12} In patients with bone marrow involvement by lymphomas, the marrow smears and trephine sections are collectively interpreted for cytology, pattern of bone marrow infiltration, and sometimes immunophenotyping.¹³

This study was conducted to see how many patients presenting to us have bone marrow infiltration at the time of diagnosis. This places them in Stage IV disease, which is associated with poor prognosis.

AIMS AND OBJECTIVES

To study the prevalence and pattern of Bone Marrow involvement in Lymphomas.

MATERIAL AND METHODS

The present study entitled “Prevalence and pattern of Bone Marrow Involvement in Non-Hodgkin's and Hodgkin's Lymphoma at Sher-i-Kashmir Institute of Medical Sciences - A Tertiary Care Hospital”, was conducted in the Department of Pathology and the Department of Clinical Hematology, SKIMS, Soura and it includes a three and a half year retrospective study and one and a half year prospective study extending from January 2013 to December 2017.

Inclusion criteria:

1. Cases diagnosed as Hodgkin's and Non-Hodgkin's Lymphoma on lymph node/tissue biopsy were included in the study.
2. Patients of all ages were included.

Exclusion Criteria:

1. Patients already on treatment and relapsed cases were excluded.
2. Patients with other non-hematological disorders affecting the bone marrow were excluded.

In the retrospective study, all the cases reported as Non-Hodgkin's or Hodgkin's Lymphoma were reviewed and analyzed. The data, including bone marrow aspiration and bone marrow biopsy reports, were retrieved as per proforma (Annexure I & II) from the record sections of Pathology and Clinical Hematology departments. The relevant paraffin embedded blocks were retrieved and sections taken and slides were made to review the cases. In the prospective study, the patients of Non-Hodgkin's and Hodgkin's Lymphoma as diagnosed on tissue biopsy (nodal and extra nodal) were included in the study. A detailed clinical history of patients, as per the proforma (Annexure I & II), was gathered, which included information on age, sex, complete blood count and biochemistry profile, other relevant investigations and most common presenting clinical features. Bone marrow aspiration and trephine biopsy were performed from posterior iliac crest, under adequate local anesthesia (Annexure III). Bone marrow aspiration specimens received were also processed with according to the standard procedure for cytological examination. Marrow aspirates were stained with Leishman's stain. The positive ones were subjected to special stains (Annexure IV) wherever necessary. Bilateral BM biopsies, performed under local anesthesia, were obtained using the conventional technique with a Jamshidi needle from the posterior superior iliac spines, fixed in 10% formalin solution and decalcified using 10% formal – formic acid for 4-6h followed by routine processing and paraffin embedding; 5-6 μ thick sections were cut and stained with routine hematoxylin and eosin stains (Annexure IV & V). Assessment was made on cytological features of cells in aspirate smears. Trephine biopsies were evaluated for architecture, vessels, stroma, haemopoietic tissue and pattern of lymphoid infiltrates (diffuse, interstitial, focal, nodular, focal patchy and paratrabeular). The results obtained on aspiration and biopsy specimens were correlated. Immunohistochemistry was done wherever necessary.

OBSERVATION AND RESULTS

This study was conducted in the department of Pathology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar. It was a retrospective study of 5 years. A total of 400 cases of bone marrow biopsies and bone marrow aspirations were received to study the infiltration by Non-Hodgkin's and Hodgkin's Lymphoma, already diagnosed on lymph node biopsy. The cases of Non-Hodgkin's Lymphoma were reclassified into various types to study the variation in the prevalence and pattern of infiltration among them.

	Frequency	Percent
Non-Hodgkin's lymphoma	347	87.2
Hodgkin's lymphoma	51	12.8
Total	398	100.0
2 cases were missing		

In our study, Non-Hodgkin's Lymphoma constituted 87.2% of cases while Hodgkin's Lymphoma constituted only 12.8% of the cases.

	Frequency	Valid Percent
DLBCL	216	54.3
HL	51	12.8
Follicular Lymphoma	31	7.8
SLL	27	6.8

Mantle cell NHL	18	4.5
T cell lymphoblastic Lymphoma	16	4.0
Burkitt Lymphoma	12	3.0
Marginal zone NHL	8	2.0
Anaplastic large cell lymphoma	7	1.8
Lymphoplasmacytic Lymphoma	4	1
Extranodal NK/T cell NHL	2	.5
Immunoblastic large cell lymph.	1	.3
MALT lymphoma	1	.3
NLPHL	1	.3
PTCL	1	.3
S/C panniculitis like T cell NHL	1	.3
Splenic marginal zone NHL	1	.3
Total	398	100.0
400		

As indicated in the table above DLBCL was the most common (54.3%) type of Non-Hodgkin's lymphoma followed by Follicular Lymphoma (7.8%), SLL (6.8%) and Mantle cell lymphoma (4.5%) while as Hodgkin's Lymphoma constituted 12.8% of the total cases of Lymphomas.

Table17: BM Biopsy Infiltration by various types of Non-Hodgkin's Lymphomas and by Hodgkins Lymphoma.

Subtype	BM-infiltration			Total
	No.	Yes		
Anaplastic large cell lymphoma	No.	4	3	7
	%	57.1%	42.9%	100.0%
Burkitt Lymphoma	No.	9	3	12
	%	75.0%	25.0%	100.0%
DLBCL	No.	171	45	216
	%	79.2%	20.8%	100.0%
Follicular Lymphoma	No.	26	5	31
	%	50%	50%	100.0%
Lymphoplasmacytic Lymphoma	No.	2	2	4
	%	25%	75%	100.0%
Mantle cell NHL	No.	15	3	18
	%	83.3%	16.7%	100.0%
Marginal zone NHL	No.	5	3	8
	%	62.5%	37.5%	100.0%
PTCL	No.	1	0	1
	%	100.0%	0.0%	100.0%
SLL	No.	10	17	27
	%	37.0%	63.0%	100.0%
T cell lymphoblastic Lymphoma	No.	14	2	16
	%	87.5%	12.5%	100.0%
HL	No.	47	4	51
	%	92.2%	7.8%	100.0%
Others	No.	5	2	7
	%	71.4%	28.5%	100.0%
Total	No.	308	90	398
	%	77.4%	22.6%	100.0%

In biopsy, Bone Marrow infiltration was seen frequently in LPL (75%), SLL (63%), FL (50%), ALCL (42.9%), DLBCL (20.8%), Burkitts lymphoma (25%), Mantle cell (16%) and Marginal zone lymphoma (37%) but only few cases of Hodgkin's lymphoma (7%).

Table 18: Pattern of infiltration of Bone Marrow Biopsies shown by various types of Lymphomas

Type of Lymphoma	Diffuse	Interstitial	Paratrabeular	Nodular	Mixed
DLBCL	28	7	2	0	8
Follicular Lymphoma	1	0	2	2	0
SLL	13	4	0	1	0
Anaplastic large cell lymphoma	3	0	0	0	0
Mantle cell lymphoma	1	1	1	0	0
Burkitt lymphoma	3	0	0	0	0

Lymphoplasmacytic Lymphoma	2	0	0	0	0
T cell Lymphoblastic Lymphoma	2	0	0	0	0
Marginal zone lymphoma	0	0	1	0	0
Immunoblastic Large cell Lymphoma	1	0	0	0	0

SLL = Small lymphocytic leukemia; DLBCL = Diffuse large B-cell lymphoma

Diffuse pattern of infiltration was most common followed by interstitial, mixed, paratrabeular and nodular. 72% of SLL and 62% of DLBCL showed diffuse infiltration while follicular lymphoma showed paratrabeular and nodular infiltration.

Table 21: Overall BM biopsy-infiltration

HL/NHL		BM-infiltration		Total
		No	Yes	
HL	No.	47	4	51
	%	92.2%	7.8%	100.0%
NHL	No.	261	86	347
	%	75.2%	24.8%	100.0%
Total	No.	308	90	398
	%	77.4%	22.6%	100.0%

Infiltration of bone marrow was much less frequent in HL than in NHL and in total 22.6% of cases of Lymphoma showed infiltration in bone marrow biopsy.

Table 22: Bone Marrow Aspiration - infiltration by various types of Non-Hodgkin's Lymphomas and by Hodgkin's Lymphoma.

Subtype	BMA-infiltration		Total	
	Infiltration seen	No infiltration		
Anaplastic large cell lymphoma	No.	2	5	7
	%	28.6%	71.4%	100.0%
Burkitt Lymphoma	No.	4	8	12
	%	33.3%	66.7%	100.0%
DLBCL	No.	38	178	216
	%	17.6%	82.4%	100.0%
Follicular Lymphoma	No.	2	29	31
	%	6.5%	93.5%	100.0%
Lymphoplasmacytic Lymphoma	No.	3	1	4
	%	66.7%	33.3%	100.0%
Mantle cell NHL	No.	2	16	18
	%	11.2%	88.8%	100.0%
Marginal zone NHL	No.	2	6	8
	%	25%	75%	100.0%
PTCL	No.	0	1	1
	%	0.0%	100.0%	100.0%
SLL	No.	13	14	27
	%	48.2%	51.8%	100.0%
T cell lymphoblastic Lymphoma	No.	2	14	16
	%	12.5%	87.5%	100.0%
HL	No.	3	48	51
	%	5.9%	94.1%	100%
Others	No.	2	5	7
	%	28.5%	71.4%	100%
Total	No.	73	325	398
	%	18.3%	81.7%	100.0%

On bone marrow aspiration, infiltration was seen less frequently but was in the same order as on bone marrow biopsy

Table 23: Overall BMA-infiltration

HL/NHL		BMA-infiltration		Total
		Infiltration seen	No infiltration	
HL	No.	3	48	51
	%	5.9%	94.1%	100.0%
NHL	No.	70	277	347
	%	20.2%	79.8%	100.0%

Total	No.	73	325	398
	%	18.3%	81.7%	100.0%

Infiltration of bone marrow was much less frequent in HL than in NHL and in total 18.3% of cases of Lymphoma showed infiltration in bone marrow aspiration.

DISCUSSION

Lymphoma is the fifth common cancer in our state. The evaluation of bone marrow status is a key process in the initial workup of patients diagnosed with lymphoma as Bone marrow is the most common site of extranodal involvement in lymphoid malignancies and determining Bone Marrow status is important for the prognosis of patients. A limited number of studies have been conducted to evaluate the diagnostic utility of bone marrow examination in lymphoid malignancies. Present study has been conducted to assess the role of bone marrow aspiration and trephine biopsy in Hodgkin's and non-Hodgkin's lymphoma.

In our study, Bone marrow biopsies showed infiltration in around 7.8% of Hodgkin's Lymphoma and 24.8% of non-Hodgkin's Lymphoma cases (Table 21, Fig. 21). Overall infiltration was seen in 22.6% cases of lymphoma in bone marrow biopsies. **Lai and his colleagues** also recorded a relatively low incidence of BM involvement of 30% in a 94 lymphoma patients.¹⁴ **Lee and his colleagues** also had a similar incidence of marrow disease (35%) in 156 patients with lymphomas.¹⁵ **Yong Park et al** carried out a similar study in Korea University in which 20% of NHL and 5% of HL showed Bone marrow infiltration. HL showed a low incidence (5-10%) of the BM affection in the studies done by **Wang J et al and Moid F et al**.^{6,16} In contrast, in a study conducted by **Tarek M.N. El Bolkainy, et al**. 44.8% of lymphoma patients had BM involvement at initial diagnosis, which is in agreement with **Arber and George** who conducted their study on a large series of 450 patients and detected a 44% BM involvement at initial diagnosis.¹⁷ Moreover, **Bratl and his colleagues** studied a series of 678 patients with established lymphomas and BM was involved in 468 cases with an overall frequency of 69%¹⁸ and another study done by **Bratl et al** in a larger series of 3229 patients with lymphoproliferative disorders, the incidence of marrow disease was higher accounting for 64% of NHLs.¹⁸ It is noteworthy that incidence of BM involvement varies among different series of studies due to the differences in histopathologic types and methods of obtaining the specimens as well as the time elapsed between initial diagnosis and bone marrow sampling.¹⁹ This explains the lower prevalence of Bone marrow involvement in our study as DLBCL was the most prevalent histological subtype which shows relatively less involvement of bone marrow. This is in consistency with other series showing a near figure of 30%.^{19,17,15} Also, **Tarek et al** showed a relatively high frequency of marrow disease (28.6% of all HLs) in HL. Such disagreement could be best explained by the prevalence of high-risk group, having an advanced systemic disease and unfavorable histology (lymphocyte depletion) in his study. Such histopathologic subtype is frequently associated with a BM disease (40-79%).^{20-22,23}

Bone marrow aspirations studied showed infiltration by 5.9% of Hodgkin's lymphoma cases and 20.2% of non-Hodgkin's Lymphoma cases (Table 23, Fig. 23). Overall infiltration was seen in 18.3% cases of lymphoma in bone marrow aspirations. There were 18 cases that showed infiltration in bone marrow biopsy but were negative upon aspiration and 2 cases showed infiltration in aspiration but were negative in bone marrow biopsy. Correlation between Bone marrow biopsy and aspiration showed p<0.999 by McNemar test which is significant. Results obtained upon correlation between bone marrow biopsy and bone marrow aspiration were comparable to a study done by **Yun Fei Shi** at Northern China.²⁴ The reliability of BMB was much higher than that of BMA in the diagnosis of marrow disease. This is in accordance with many different worldwide studies having sensitivity rates ranging from 82% up to 100% for the bilateral BMB.^{15,16,25} In BMA, 18 false negative results or deferred inconclusive diagnosis are best explained by one or more of five reasons, namely inadequacy or dry tap of packed marrow or, in cases with myelofibrosis, non-representative sample of a focal disease, bland tumor cell cyto-morphology, mostly in the indolent small cell NHLs with relatively hypocellular smears.^{6,32}

Although for some types of lymphoma it was difficult to evaluate the accuracy of the involvement rate from a relatively limited number of cases, we extracted our results from those types with higher number

of cases. In biopsy, Bone Marrow infiltration was seen frequently in LPL (75%), SLL (63%), FL (50%), ALCL (42.9%), DLBCL (20.8%), Burkitts lymphoma (25%), Mantle cell (16%) and Marginal zone lymphoma (37%) but only few cases of Hodgkin's lymphoma (7%). On bone marrow aspiration, infiltration was seen less frequently but was in the same order as on bone marrow biopsy (Table17, Fig.17; Table 22, Fig.22). In a study conducted by **Park Y et al**²⁶, Bone marrow biopsy infiltration was frequently seen in Lymphoplasmacytic Lymphoma (>80%), SLL (>70%), and Follicular Lymphoma (50-60%), DLBCL (20-30%), Burkitt lymphoma (>40%). A higher frequency of marrow disease for small cell NHLs was also recorded by western authors like **Bartl R** and could be explained by the higher life expectancy and the subsequent prevalence of elderly patients.¹⁸ DLCL had a relatively lower frequency of marrow disease. This is in consistency with other studies by **Arber DA**¹⁷, **Hodges G**²⁰, etc., reporting a near figure of 30%. Moreover, in a study conducted by **Lee et al**⁶ on 59 DLCL cases, 20 patients (33.9%) showed evidence of bone marrow involvement.

Diffuse pattern of infiltration was most common followed by interstitial, mixed, paratrabeular and nodular. 72% of SLL and 62% of DLBCL showed diffuse infiltration while follicular lymphoma showed paratrabeular and nodular infiltration (Table 18, Fig.18). Our results were comparable to a study done by **Lee W et al**⁶ who reported the predominance of the interstitial and the diffuse patterns (56% and 31%, respectively). Moreover, the paratrabeular infiltrate was rarely seen (4%). **Durosinni MA et al**²⁷ in his study found out that the most common pattern of marrow involvement in NHL was diffuse type.²⁷ Peritrabeular infiltrates are typical for follicular lymphoma as was found by **Kremer M et al**²⁸ and by **Sovani V et al**³³ in a study at Nottingham, UK. In contrast, **Arber DA et al**¹⁷ and **Tarek MN et al**²⁹ reported the relatively high incidence of both paratrabeular and nodular infiltrates over the diffuse and interstitial patterns. This could be explained by the difference in incidence of various histological subtypes.

Distribution of types of Lymphoma

Among 400 cases studied over the period of 5 years, there were 51 cases of Hodgkin's and 347 cases of Non-Hodgkin's Lymphoma comparable to the study done by **Deliliers L et al**³⁰ who found the same ratio of Hodgkin's and non-Hodgkin's Lymphoma cases (Table 1, Fig.1). As the number of Hodgkin's lymphoma cases was quite insignificant as compared to Non-Hodgkin's lymphoma, we did not study the subtypes of Hodgkin's lymphoma individually. DLBCL was the most common (54.3%) subtype of Non-Hodgkin's lymphoma followed by Follicular Lymphoma (7.8%), SLL (6.8%), PTCL (0.3%), Mantle cell lymphoma (4.5%) and T cell lymphoblastic Lymphoma (4%) (Table 2, Fig.2). Our results were comparable to the study done by **Lone A**³¹ who reported DLBCL subtype (56%) followed by SLL (24%), Marginal zone lymphoma (12%), T Lymphoblastic Lymphoma (6%) and PTCL (1%). Prevalence of various subtypes resulted in variation in prevalence of Bone marrow disease in different studies.

CONCLUSION

From our study, we concluded that Diffuse pattern of infiltration was most common followed by interstitial, mixed, paratrabeular and nodular. 72% of SLL and 62% of DLBCL showed diffuse infiltration. Follicular lymphoma showed only paratrabeular and nodular pattern of infiltration. Infiltration was seen in 22.6% cases in bone marrow biopsies and in 18.3% cases in bone marrow aspirations. In Bone marrow biopsy, infiltration was commonest in LPL (75% cases), followed by SLL (63%), FL (50%), ALCL (42.9%), Marginal zone lymphoma (37%), DLBCL (20.8%), Burkitt's lymphoma (25%) and Mantle cell lymphoma (16%). Only few cases of Hodgkin's lymphoma (7%) showed bone marrow involvement.

1. Sweetenham J, Hieke K, Kerrigan M, Howard P, Pamela F, Smartt M et al. Cost - minimization analysis of CHOP, Fludarabine and Rituximab for the treatment of relapsed indolent B-cell NHL in UK. *Br J Haematol* 1999; 106: 47-54.
2. Hoffbrand VA, Catovsky D, Tuddenham EGD. Aetiology and management of non-Hodgkin's lymphoma. Postgraduate haematology. 5th ed. Blackwell 2005: 735.
3. Sukpanichnant S. Analysis of 1983 cases of malignant lymphoma in Thailand according to the World Health Organization classification. *Hum Pathol* 2004; 35(2): 224-30.
4. Weber AL, Rahemtullah JA. Hodgkin and non-Hodgkin lymphoma

of the head and neck: clinical, pathologic and imaging evaluation. *Neuroimaging Clin N Am* 2003; 13(3): 371-92

5. Sahni CS, Desai SB. Distribution and clinicopathologic characteristics of non-Hodgkin's lymphoma in India: a study of 935 cases using WHO classification of lymphoid neoplasms (2000). *Leuk Lymphoma* 2007; 48(1): 122-33.
6. Moid F, DePalma L. Comparison of relative value of bone marrow aspirates and bone marrow trephine biopsies in the diagnosis of solid tumor metastasis and Hodgkin lymphoma: institutional experience and literature review. *Arch Pathol Lab Med* 2005; 129(4): 497-501.
7. Lancu D, Hao S, Lin P, Anderson SK, Jorgenson JL, McLaughlin P, Medeiros LJ. Follicular lymphoma in staging bone marrow specimens: correlation of histologic findings with the results of flow cytometry immunophenotypic analysis. *Arch Pathol Lab Med* 2007; 131(2): 282-7.
8. Luoni M, Declich P, De Paoli Aft p4, Fava S, Marinoni P, Montalbetti L, Sangalli G, Sciuccati P, Tocci A, Tosi A, et al. Bone marrow biopsy for the staging of non-Hodgkin's lymphoma: bilateral or unilateral trephine biopsy? *Tumori* 1995; 81(6): 410-3.
9. Buhr T, Langer F, Schlue J, V Wasielewski R, Kreipe H. Histopathology of leukemic non-Hodgkin's lymphoma in bone marrow. *Pathologie* 2002; 23(6): 438-47.
10. Sabharwal B, Malhotra V, Aruna S, Grewal R. Comparative evaluation of bone marrow aspirate particle smears, imprints and biopsy sections. *Postgrad Med.* 1990; 36(4): 194-8.
11. Brynes RK, McKenna RW, Sundberg RD. Bone marrow aspiration and trephine biopsy. An approach to a thorough study. *Am J Clin Pathol.* 1978, 70 (5): 753-9.
12. Grann V, Pool JL, Mayer K. Comparative study of bone marrow aspiration and biopsy 'in patients with neoplastic disease. *Cancer.* 1966; 19: 1898-900.
13. Bain, BJ Bone marrow aspiration. *J Clin Pathol* 2001; 54: 657-63
14. Lai H, Tien H, Hsieh H, Chen Y, Su I, Wang C, et al. Bone marrow involvement in non-Hodgkin's lymphoma. *Taiwan Yi Xue Hui Za Zhi.* 1989; 88(2): 114-21.
15. Lee WI, Lee JH, Kim IS, Lee KN, Kim SH. Bone marrow involvement by non-Hodgkin's lymphoma. *J Korean Med Sci.* 1994; 9(5): 402-8.
16. Wang J, Weiss LM, Chang KL, Slovak ML, Goal K, Forman SJ, et al. Diagnostic utility of bilateral bone marrow examination: Significance of morphologic and ancillary techniques. *Cancer.* 2002; 94: 1522-31.
17. Arber DA, George TI. Bone marrow biopsy involvement by non-Hodgkin's lymphoma: Frequency of lymphoma types, patterns, blood involvement and discordance with other sites in 450 specimens. *Am J Surg Pathol.* 2005; 29(12): 1549-57.
18. Bartl R, Frisch B, Burkhardt T, Kettner G, Mahl G, Fateh A et al. Assessment of bone marrow histology in malignant lymphoma (non-Hodgkin's): Correlation with clinical factor for diagnosis, prognosis, classification and staging. *Br. J. Haematol.* 1982; 51: 511-30.
19. Bartl R, Frisch B, Burkhardt R. Lymphoproliferations in the bone marrow: Identification and evolution, classification and staging. *J Clin Pathol.* 1984; 37: 233-54.
20. Hodges G, Lenhardt T, Cotelingam J. Bone marrow involvement in large-cell lymphoma. Prognostic implications of discordant disease. *Am J Clin Pathol.* 1994; 101(3): 305-11.
21. Günther C, Püschel W, Helbig W, Schwenke H, Kubel M, Hoffmann FA, et al. Prognostic significance of histobiopsy findings in bone marrow of malignant lymphomas in adults. *Z Gesamte Inn Med.* 1982; 37(15): 491-7.
22. Kinney NC, Greer JP, Stein RS, Collins RD, Cousar JB. Lymphocyte depletion Hodgkin's disease. Histopathologic diagnosis of marrow involvement. *Am J Surg Pathol.* 1986, 10: 219-26.
23. Munker R, Hasenclever D, Brosteanu O, Hiller E, Diehl V. Bone marrow involvement in Hodgkin's disease: an analysis of 135 consecutive cases. German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 1995; 13: 403-409.
24. Shi Y-F, Li X-H, Song Y-Q, Song W-W, Lai Y-M. Involvement of bone marrow in lymphoma: Pathological investigation in a single center from Northern China. *Int J Clin Exp Pathol.* 2015; 8: 7102002D11.
25. Neiman RS, Rosen PJ, Lukes RJ. Lymphocyte depletion Hodgkin's disease: A clinicopathologic entity. *N Engl J Med.* 1973; 288: 751-4.
26. Park Y, Park BB, Jeong JY, Kim WY. Assessment of bone marrow involvement in patients with lymphoma: report on a consensus meeting of the Korean Society of Hematology Lymphoma Working

- Party. *Korean J Intern Med* 2016; 31: 1030-1041.
27. Durosinmi MA, Mabayoje VO, Akinola NO. A review of histology of bone marrow trephine in malignant lymphomas. *Niger J Med* 2003; 12(4):198-201.
 28. Kremer M, Spitzer M, Mandl-Weber S, Stecker K, Schmidt B, Höfler H, Quintanilla-Martínez L, and Fend F. Discordant bone marrow involvement in diffuse large B-cell lymphoma: comparative molecular analysis reveals a heterogeneous group of disorders. *Lab Invest.* 2003 Jan; 83(1): 107-14.
 29. Tarek M.N., El Bolkainy, Wael S. Abo Deif. Evaluation of Bone Marrow in 143 Lymphomas: The Relative Frequency and Pattern of Involvement, Secondary Myelopathies, Pitfalls and Diagnostic Validity. *Journal of the Egyptian Nat. Cancer Inst., 2008; Vol. 20, No. 1: 17-30.*
 30. Deliliers L, Annaloro G, Soligo D. *Ann Hematol* 1992; 65: 61.
 31. Lone A, Naeem S. Frequency and pattern of bone marrow infiltration in non-Hodgkin's lymphoma. *Annals* 2011; 17: 4.
 32. Brunning RD, Bloomfield CD, McKenna RW, Peterson LA. Bilateral trephine bone marrow biopsies in lymphoma and other neoplastic diseases. *Ann Intern Med.* 1975; 82(3): 365-6.
 33. Sovani V, Harvey C, Haynes AP. Bone marrow trephine biopsy involvement by lymphoma: review of histopathological features in 511 specimens and correlation with diagnostic biopsy, aspirate and peripheral blood findings. *J Clin Pathol* 2014; 67: 389–395.