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Original Article

Significance of Clinical and Laboratory Variables in Early Detection and Prognosis of Malignant Lymphoma

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Abstract

Background: To study clinical, laboratory and radiological variables including bone marrow assessment in patients with malignant lymphomas.

Methods: In this cross sectional study cases of malignant lymphoma were included. Clinical variables included age, gender, lymphadenopathy and hepatosplenomegaly. Laboratory variables included blood complete counts and bone marrow aspiration and bone trephine biopsy.Immunohistochemistry was performed to identify the specific lineage and developmental stages of lymphoma.Serum LDH, BUN, Creatinine, and SGPT were also performed . Statistical analysis were performed by Student t-test and Pearson Chi Square test

Results: Hepatosplenomegaly, Haemoglobin, CT scan chest abdomen and immunohistochemistry were found significant factors in patients diagnosed to have lymphoma with bone marrow involvement. Variables such as WBC, BUN, Creatinine, LDH and SGPT had no significant correlation.

Conclusion: The Variables in the study are in favour of the previous studies. Whereas regarding serum LDH levels the results were found insignificant which are not in favor of previous studies .

Key Words: Malignant Lymphoma, Immunohistochemistry, LHH,

Introduction

The variables like age, gender, bone marrow involvement, visceromegaly, lymphadenopathy and certain biochemical and radiological variables provides important information regarding, prognosis and planning of optimal therapeutic strategies in patients suffering from malignant lymphoma. Over the last two decades there has been a continuous enhancement in the measures which are helpful in the laboratory to evaluate malignant lymphoma. This has proved critical in providing the consistent and accurate information that is needed for clinical decision making in these patients. The laboratory evaluation of patients with malignant lymphoma remains centred on 4 primary aspects:(1) recognition and diagnosis of disease; (2) appropriate classification (3) providing information regarding disease stage; and (4) providing prognostic indications that predict the risk of death from disease.[1-3]

The early detection of lymphoma allows for more treatment options. The best way to diagnose lymphoma is to pay attention to possible symptoms. The most common symptom is the painless enlargement of one or more lymph nodes. The most frequent site is the side of the neck, in the groin or in the armpit. The accompanying features include fever unexplained weight loss and night sweats [4].Bone marrow examination is routinely carried out during the evaluation of patients in malignant lymphoma. Bone marrow involvement indicates stage IV disease and is indicative of poor prognosis.

Accurate staging is essential for the physician to plan an effective treatment strategy. Bone marrow infiltrations of prime importance not only in staging the disease but also in deciding the treatment protocols [5]. Bone marrow involvement is one of the most important prognostic factors in patients with lymphoma, thus in patients with high grade lymphoma or intermediate grade lymphoma is associated with significantly shorter survival. Therefore, bone marrow biopsy is now included as a part of the essential evaluation for the initial staging in patients with malignant lymphoma [6]

Anaemia is prevalent among patients with cancer at initial presentation. Patients with non–Hodgkin's lymphoma have usually anaemia at diagnosis.[7]Bone marrow biopsies are commonly performed for the initial diagnosis or staging of malignant lymphoma, and the frequency of bone marrow involvement in staging marrows for lymphoma is quite variable in the literature.[8,9]The lymphomas has a unique feature that

is these are considered as clonal proliferation of lymphocytes arrested at different stages of cell differentiation, thereby recapitulating stages of normal lymphocyte differentiation. Immunohistochemistry (IHC) with various antibodies identifies the specific lineage and developmental stage of the lymphoma. A panel of markers is decided based on morphologic differential diagnosis (no single marker is specific) which includes leukocyte common antigen (LCA), B-cell markers (CD20 and CD79a), T-cell markers (CD3 and CD5) [10] Immunophenotyping and molecular genetic studies are useful, yet the importance of morphology can not be undermined.[11,12]

Patients and Methods

In this cross sectional study, conducted in the clinical laboratory of Aga Khan University Hospital Karachi. Following were the variables related to the clinical presentation such as the age, gender, lymphadenopathy and hepato splenomegaly. As far as the Laboratory data is concerned the results of the following at the time of presentation were considered.CBC performed on STKs Coulter and peripheral films were stained by Leishman stain. Bone marrow & Bone Trephine were performed with Salah and Jamshadi needles and Leishman stain was applied on bone marrow aspirate and haematoxylin stain on Bone Trephine and slides were reviewed by Consultant Haematologist & Histopathologist. In immunohistochemistry, IHD markers,CD3 stains T cells from the stage of late thymocytes,positive in T cell neoplasms and some natural killer cell neoplasms.CD15 which stains cell membranes and Golgi bodies of Reed Sternberg cells in Hodgkin's Lymphoma, large cells in some T cells and B cell Lymphoma.CD30 which is characteristically positive in Hodgkin's Lymphoma.LDH, BUN, Creatinine and SGPT were performed on synchron cx-7 & cx-9 pro. Observations were recorded and subjected to the student's t test and Pearson chi-square test for statistical analysis. The results were taken as significant considering the p-value found equal to or less than 0.05.

Results

Age was found insignificant with the involvement of bone marrow in our sample (p value>0.05). In 33 cases out of 58 the mean Haemoglobin level was found 9.6 mg/dl with involvement of bone marrow and more than 11.7 mg/dl in 22(40%) cases (P value>0.001*, Significant)(Table 1).The ratio of involvement of bone marrow in females was found less, i.e. 25% as compared to non-involvement of bone marrow in 75% cases. (p value=0.05*,Significant) (Table 2; Figure 1 &2).In males it was 54% in which bone marrow was involved and in 46% cases bone marrow was not involved. (p value>0.50),11 (91.7%) cases presented with hepatosplenomegaly with involvement of bone marrow by lymphoma, only 01(8.3%) case had enlargement of liver and spleen without bone marrow involvement,(P value<0.004*),Ref Table 2..Enlarged Lymph nodes present in 13(72.2%) cases with bone marrow involvement and 5(27.8%) cases presented with enlarged lymph nodes without BM involvement,(P value=0.05*).Regarding CT Scan chest 08 (100%)cases shows signs of moderate to large lymph nodes enlargement similarly 07 (87.5%) cases in abdomen the lymph nodes involved in cases in which bone marrow were involved (P value=0.00* and P value< 0.05* respectively) (Table 2). The results of serum LDH, Serum creatinine, BUN and SGPT were found insignificant.

Table 1 Clinical & laboratory investigation with and without involvement of bone marrow in lymphoma

Variables	Bone marrow involved by lymphomas Mean(n)	Bone marrow not involved Mean(n)	P-Value	p-vlaue Sig* / Non Sig
Age	42.8 years(24)	43.4 years (24)	0.879	>0.05
Haemoglobin (mg/dl)	<9.6 (33)	>11.7 (22)	<o.oo 1	<o.oo1*
White cells count (Per cubic mm of blood)	8.7 (33)	8.5 (23)	0.773	>0.05
Platelets (Per cubic mm of blood)	227 (33)	226 (23)	0.828	>0.05
Serum LDH	723 (28)	501 (6)	0.073	>0.05
BUN	24 (16)	15.7 (4)	0.572	>0.05
Serum Creatinine	1.1 (17)	0.8 (4)	0.108	>0.05
SGPT	100 (14)	28.3 (3)	0.59	>0.05

P Value Significant, <0.05*

As per data available regarding Immunohistochemistry which was done for the subtyping, prognostication and potential for targeted therapy were found positive in 26(100%) cases (P value=0.00*) whereas Immunohistochemistry was found negative in 2 cases(13.3%) in patients having

involvement of bone marrow with lymphomas(P value=0.005*) (Table 3).

Table 2 Clinical and radiological parameters with and without involvement of bone marrow in lymphoma.

Variables	Bone marrow involved by Lymphoma No (%)	Bone marrow not involved No (%)	P-Value	P-Value Sig* / Non Sig
Sex	M=54% F= 25%	M=46% F=75%	0.75 0.053	>0.50 0.05*
Lymph node				
Yes	13 (72.2)	5 (27.8)	0.059	0.05*
No	12 (46.2)	14 (53.8)	0.695	>0.50
Hepatosplenomegaly				
Yes	11 (91.7)	1 (8.3)	<0.004	<0.004*
No	17 (53.1)	15 (46.9)	0.724	>0.50
CT scan chest				
Yes	8 (100)	O		
No	6 (33.3)	12 (66.7)	0.157	0.20
CT abdomen				
yes	7 (87.5)	1 (12.5)	0.034	<0.05*
no	6 (38.9)	11 (61.1)	0.346	>0.10

p- Value Significant, <0.05*

Table 3.Immunohistochemistry in Lymphoma
(n=41 cases)

Variable	Bone marrow involved by lymphoma No(%)	Bone marrow not involved by lymphoma No(%)	p-value	p-value sig* / non sig
Positive	26 (100)	0	0.000	0.000*
Negative	2 (13.3)	13 (86.7)	0.005	0.005*

p Value Significant, <0.05*

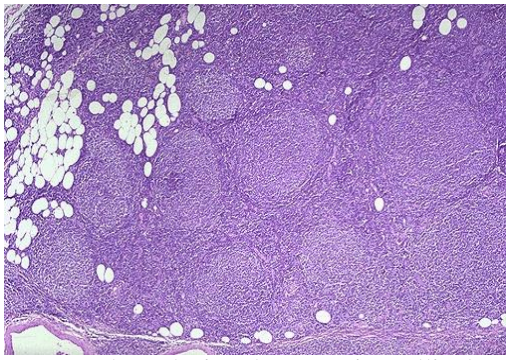
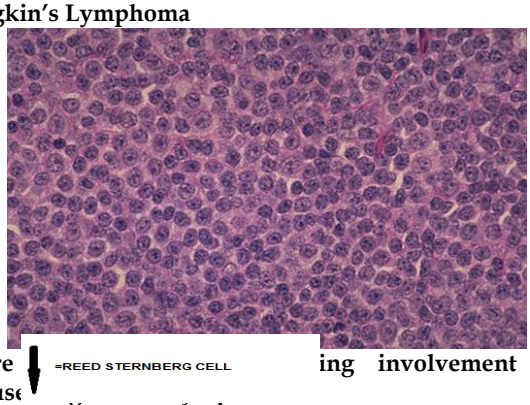


Figure 1. Lymph node involvement in Follicular Non – Hodgkin's Lymphoma



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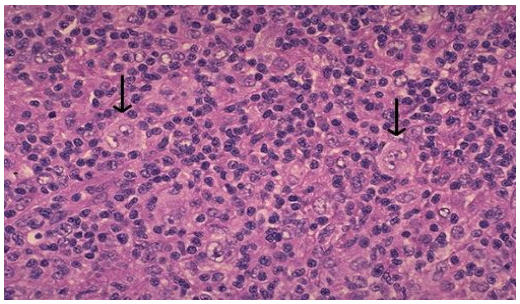

Figure 3:Bone Trephine showing involvement with Hodgkin's Lymphoma

Discussion

In the present study haemoglobin, hepatosplenomegaly, CT scan chest & abdomen and immunohistochemistry were found significant factors in patients having lymphoma with bone marrow involvement. Cancer patients treated with chemotherapy often suffer from
anaemia, which is a major contributing factor to fatigue leading to compromised quality of life.[13,14] In addition, the presence of anaemia is associated with shorter survival of patients with malignancies.[15]

In our study the results obtained regarding the level of haemoglobin in patients of malignant lymphoma with bone marrow involvement is in favour of the study conducted by Jacobi N in which the author signifies the role of haemoglobin as a prognostic factor at initial diagnosis. [16] It was found statistically significant in univariate log-rank comparisons of Kaplan-Meier survival curves used to build a multi-variate proportional hazard regression model of overall survival. Median overall survival for these patients were 10.3 years. Overall survival differed only with high (>12 g/dl) versus low (<12 g/dl) hemoglobin (p=0.001).Our study signifies the role of immunohistochemistry in patients having lymphoma .This was again in favour of the study conducted by Paydas S. [17]

Regarding the role of biopsy, in the literature we found a study conducted by Quereux **G** et al studied retrospectively 62 cases of cutaneous B-cell lymphomas in which bone marrow biopsy was performed and it was demonstrated that it is not indispensable to perform a routine bone marrow biopsy for a Primary cutaneous B-cell lymphoma with cutaneous lesions and with negative CT Scan and blood laboratory evaluations. [18]Another study conducted by Simon E, Richardson et.al stated that Conventional bone marrow biopsy staging in Hodgkin's lymphoma is extremely insensitive. F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) can rule out bone marrow involvement in Hodgkin's lymphoma. The bone marrow biopsy should be targeted to a minority of patients with FDG-PET/CT + bone/marrow uptake and only when management would be altered by the result.[19]Although the 1989 Cotswold modification limited the routine use of invasive procedures in favour of improved imaging diagnostics. Routine bone marrow biopsy was restricted to patients with CT-assessed advanced stage disease or disease at initial stage with adverse factors and in case a finding would alter the management. [20]

Regarding the results related to the white blood cell count, our study is not in favour of the study conducted by the Porrata LF et al in which the author assessed the prognostic significance of absolute lymphocyte count at the time of first relapse in diffuse large B-cell lymphoma. [21] ALC-R was found an independent prognostic factor for overall survival [RR = 0.4, P < 0.01] and progression-free survival [RR = 0.5, P < 0.005]. ALC-R predicts survival suggesting that host immunity is an important variable predicting survival in first relapsed DLBCL. Again a large population based study is required for absolute Lymphocyte count to reach the conclusion.

The results obtained in our study regarding serum LDH level are not in favour of the 25-year study in Japan conducted by Katsumata N et al in which the author stated the importance of age and serum LDH as significant predictors of survival in Japanese patients with follicular lymphoma. [22] In addition the levels of serum LDH are again not in favor of the study conducted by Hung Chang et.al in which they reported eleven out of twelve had elevated levels of Lactate dehydrogenase however a study on large population is required to address the occurrence of serum LDH in such cases. [23]

Conclusion

1.Hepatosplenomegaly, haemoglobin, CT scan chest & abdomen and immuno histochemistry were significant factors in patients diagnosed to have lymphoma with bone marrow involvement.

2.Variables such as WBC, BUN, Creatinine, LDH and SGPT had no significant correlation.

References

1. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK. A revised European-American classification of lymphoid neoplasms: A proposal from the International Study Group. Blood 84:1994:1361-65
2. Shipp MA: Prognostic factors in aggressive non-Hodgkin's lymphoma: Who has "high-risk" disease? Blood 83: 1994:1165 -70
3. Shipp MA: Can we improve upon the International Index? Ann Oncol: 1997:8:43-46
4. Juneja SK, Wolf MM, Cooper IA: Value of bilateral bone marrow biopsy in non-Hodgkin's lymphoma. J Clin Pathol : 1990 :43:630-35
5. S Muzahir[1], M Mian, I Munir M. Clinical utility of [18]F FDG-PET/CT in the detection of bone marrow disease in Hodgkin's lymphoma, British Journal of Radiology, 2014;85 (1016): 1121-24
6. Hori HNM,Obara K. Primary isolated bone marrow diffuse large B-cell lymphoma with the initial presentation as severe thrombocytopenia, successfully treated with chemotherapy: a case report and review of the literature. Journal of Cancer Therapeutics & Research.2012; 1:28-31
7. Moullet I, Salles G, Ketterer N. Frequency and significance of anemia in non-Hodgkin's lymphoma patients. Ann Oncol 1998; 9:1109–15.
8. Lambertenghi-Deliliers G, Annaloro C, Soligo D. Incidence and histologic features of bone marrow involvement in malignant lymphomas. Ann Hematol. 1992; 65:61-65.
9. McKenna RW, Hernandez JA. Bone marrow in malignant lymphoma. Hematol Oncol Clin North Am. 1988; 2:617-35

10. Rao IS.Role of immunohistochemistry in lymphoma.Indian J Med Paediatr Oncol. 2010 ; 31(4): 145–47.
11. Crotty PL, Smith BR, Tallini G. Morphologic, immunophenotypic, and molecular evaluation of bone marrow involvement in non-Hodgkin's lymphoma. Diagn Mol Pathol. 1998; 7:90-95.
12. Kang YH, Park CJ, Seo EJ. Polymerase chain reaction-based diagnosis of bone marrow involvement in 170 cases of non-Hodgkin lymphoma. Cancer. 2002; 94:3073-82
13. Groopman JE, Itri LM. Chemotherapy-induced anaemia in adults: incidence and treatment. J Nat'l Cancer Ins 1999; 91:1616–34.
14. Causes of Fatigue in Cancer Patients—General information about fatigue.Cancer.gov for NCI-USA – Updated May 7, 2015
15. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic Factor for survival in patients with cancer. Cancer 2001; 91:2214–21.
16. Jacobi N, Rogers TB, Peterson BA,Prognostic factors in follicular lymphoma: a single institution study.. Oncology reports 2008 ; 20(1):185-93.
17. Paydas S, Seydaoglu G, Ergin M, Erdogan S, Yavuz S. The prognostic significance of VEGF-C and VEGF-A in non-Hodgkin lymphomas. Leuk Lymphoma. 2009; 50(3):311-14.
18. Quereux G, Frot AS, Brocard A, Leux C, Renaut JJ, Dreno B Routine bone marrow biopsy in the initial evaluation of primary cutaneous B-cell lymphoma does not appear justified. Eur J Dermatol 2009;19(3):216-20.
19. Simon E. Richardson, Jagoda Sudak. Routine bone marrow biopsy is not necessary in the staging of patients with classical Hodgkin lymphoma in the ^{18}F-fluoro-2-deoxyglucose positron emission tomography era, Journal Leukemia & Lymphoma 2012;53(3):381-85.
20. El-Galaly TC, Amore F, Mylam KJ . Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography–staged treatment-naive patients with Hodgkin Lymphoma, Journal Of Clinical Oncology,2012; 30:4508-14.
21. Porrata LF, Ristow K, Habermann TM, Witzig TE, Inwards DJ. Absolute lymphocyte count at the time of first relapse predicts survival in patients with diffuse large B-cell lymphoma. Am J Hematol 2009 ; 84(2):93-97.
22. Katsumata N, Matsuno Y, Nakayama H, Takenaka T, Kobayashi Y. Prognostic factors and a predictive model of follicular lymphoma: a 25-year study at a single institution in Japan. JPN J Cl Oncol 1996 ; 26(6):445-54
23. Chang H, Hung YS, Lin TL. Primary bone marrow diffuse large B cell lymphoma: a case series and review. Annals of Hematology, 2011;90(7):791–96