Frequency of Bone Marrow Involvement in Different Stages of Diffuse Large B cell Lymphoma (Dlbcl)

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ABSTRACT

OBJECTIVE: To assess the frequency of bone marrow involvement in different stages of diffuse large B cell lymphoma patients.
STUDY DESIGN: A cross sectional interventional study.
PLACE AND DURATION: At Oncology Department of Combined Military Hospital Rawalpindi, from 15th Jan 2015 to 30th Oct 2015.
METHODOLOGY: One hundred and twenty one patients were selected by purposive sampling technique. Diagnostic and staging work-up excluding bone marrow biopsy was done. Then all patients were subjected to the unilateral iliac bone marrow trephine biopsy. Samples were examined to see its invasion by lymphoma. Stage wise involvement of bone marrow was recorded and frequency of bone marrow involvement in different stages was calculated.
RESULTS: Out of 121 patients, 33.8% were stage I, 30.6% stage II, 27.3% stage III and 8.3% were stage IV (excluding bone marrow examination). Stage wise involvement of bone marrow on trephine biopsy was 12%, 42%, 54% and 80% for stage I, II, III and IV respectively. Combined early stage (Stage I and II) patients had bone marrow involvement in 20% of cases.
CONCLUSION: Stage wise bone marrow involvement in cases of diffuse large B cell lymphoma, is higher in patients presenting to our hospital, than reported in International literature. Exact cause of this increase in frequency should be determined by further studies.
KEYWORDS: Bone Marrow, Trephine Biopsy, Diffuse Large Cell Lymphoma, Non-Hodgkin's Lymphoma, Lymphoproliferative Disease, Lymphoma Staging

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INTRODUCTION

Non-Hodgkin's lymphomas (NHLs) are a group of lymphoproliferative disorders which are heterogeneous and originate from T, B, or natural killer (NK) lymphocytes.1 Diffuse large B cell lymphoma (DLBCL) is included in group of mature B cell neoplasms.[2] Diffuse large B cell lymphoma (DLBCL) is the most common type of NHLs worldwide[3,4] and in Pakistan.[5,6] An excisional or incisional lymph node biopsy is performed to establish the diagnosis of NHL.[7] Prognostic stage grouping of NHL is done using the Lugano classification system.[8]

Bone marrow involvement occurs in 11.2% of patients having diffuse large B cell lymphoma.[9] Replacement of both myeloid elements and fat by a monotonous atypical cellular population not respecting the normal bone marrow topographic distribution is called bone marrow involvement.[10] Bone marrow aspirates alone have usually low yield of being positive in the absence of a positive bone marrow biopsy, and are very often negative even when the bone marrow is involved. So bone marrow trephine biopsy is always done.

These days, examination of the bone marrow is considered one of the most valuable diagnostic tools to diagnose, evaluate and stage the hematologic disorders.[11] The effects of bone marrow biopsy on the management or on the prognosis of lymphoma patients has not been proven in prospective clinical trials.[7] If

the bone marrow is involved, the stage is upgraded to stage IV.[8] PET/CT also provides uptake in bone marrow and predicts bone marrow involvement. Recent studies have shown that bone marrow biopsy should not be excluded even if PET/CT is done.[12, 13]

The purpose of this study was to determine the frequency of positive bone marrow in Diffuse Large B cell Lymphoma patients presenting to our hospital. And find the percentage of patients of each stage having bone marrow involvement. This study will guide us whether this invasive procedure can be excluded in staging work-up of early stage Diffuse Large B cell Lymphoma patients or not. The study was conducted with objective is to assess the frequency of bone marrow involvement in different stages of diffuse large B cell lymphoma in patients.

METHODOLOGY

This cross sectional, interventional study was carried out in Oncology Department of Combined Military Hospital Rawalpindi from 15th Jan 2015 to 30th Oct 2015. One hundred and twenty one patients, from out-patient department were taken by non-probability purposive sampling fulfilling inclusion criteria. Only patients with histopathologically confirmed diffuse large B cell lymphoma were included in study. Study was done after permission from concerned authorities and Hospital Ethical Committee, and informed written consent from patients. OPD registration numbers, name, age, gender, address with contact phone number and presence of B-symptoms, were noted. Staging workup was done excluding bone marrow examination and documented on the Performa. Staging workup included, clinical examination, CT scan of neck, chest, abdomen and pelvis with contrast enhancement and biopsy for histopathology. After the diagnostic and staging work-up, all patients were subjected to the unilateral iliac bone marrow trephine biopsy, done by consultant Hematologist at Armed Forces Institute of Pathology Rawalpindi, to see invasion of bone marrow by lymphoma. Number of patients having bone marrow invasion in different stages was recorded. All data was checked by authors before being recorded in the performa, to reduce observer bias.

Data Analysis: Data analysis was done with the use of SPSS version 16. Frequency and percentages were computed for categorical variables like bone marrow involvement on trephine biopsy in various stages of NHL. Chi square test was applied to find p-value. Results were significant with a p value of <0.01.

RESULT

A total of 121 patients were included in study. The mean age of the patients was 48 years (range 18–70). There were 84 (69.4%) males and 37 (30.6%) females, with a male to female ratio of 2.27: 1. All of these patients had histology of diffuse large B cell lymphoma according to the Working Formulation. Out of 121 patients, 41 (33.8%) were stage I, 37 (30.6%) stage II, 33 (27.3%) stage III and 10 (8.3%) were stage IV (excluding bone marrow examination).

Bone marrow trephine biopsy was positive in 42 (34.7%) patients of all stages. Stage wise involvement of bone marrow on trephine biopsy is given in table I. Stage 1 patients had relatively lower risk of bone marrow involvement, 12% on trephine but still it is significant. Similarly, stage II, III and IV patients had bone marrow involvement in 42%, 54% and 80% of cases respectively. Early stage patients (stage I and II) had bone marrow positive in 20% cases (16 positive cases out of 78), which is quiet significant.

DISCUSSION

Non-Hodgkin's lymphoma represents a spectrum of disease entities each having distinct presentation, staging workup and treatment options. The outcome of non-Hodgkin's lymphoma patients depends upon histology and stage.[14] Bone marrow (BM) involvement in non-Hodgkin's lymphoma (NHL) has a clear impact on patients' stage and survival.[15] Recently PET/CT is used for initial evaluation and staging of FDG avid lymphomas. But in regions where PET/CT is not available, a CT scan based classification and evaluation is done.[16, 17] Recent evidence has shown that bone marrow biopsy should not be excluded even if PET/CT is available.[12, 13]

To find the involvement, a bone marrow (BM) aspiration and trephine biopsy should be done. Bone marrow involvement in 72.7% DLBCL is focal.[18] Thus, BM aspirates alone have usually low yield of being positive in the absence of a positive BM biopsy, and are very often negative even when the bone marrow is involved. The yield of bone marrow biopsy may be increased by performing multiple biopsies at different sites, for example bilateral posterior iliac crests. A 20 mm thick unilateral core biopsy can be helpful in eliminating the need of a bilateral biopsy.[19]

TABLE-I: Frequency of stage wise involvement of bone marrow on trephine biopsy (N=121)

		Positive	Negative	Total	Ratio of positive cases
		n (%age)	n (%age)	n (%age)	
Stage excluding bone marrow exam	Sage I	5 (4.1%)	36 (29.8%)	41 (33.9%)	5/41 =12%
	Stage II	11 (9.0%)	26 (21.5%)	37 (30.5%)	11/37 =42%
	Stage III	18 (14.9%)	15 (12.4%)	33 (27.3%)	18/33 =54%
	Stage IV	8 (6.6%)	2 (1.7%)	10 (8.3%)	8/10 =80%
Total all stages		42 (34.6%)	79 (65.4%)	121 (100%)	42/121 =34.6%

Bone marrow biopsy and aspirate specimens are typically evaluated for their immune-phenotype and morphology. Aspirated cells can be subjected to analysis of cell surface markers by cytogenetic analysis as well as flow cytometry, both of which may provide key diagnostic information.[20] If the material is crushed or scanty, immunohistochemistry can be used to increase the diagnostic accuracy.[21]

In international literature, Bone marrow involvement is seen in 18 to 36 percent of patients with aggressive and highly aggressive NHL.[11] Bone marrow involvement is present in ~10% to 15% of diffuse large B cell lymphoma (DLBCL) cases, in most international studies.[9, 22, 23] For example, the incidence of bone marrow invasion was 14.4% in B-cell lymphomas cases in a Northern Chinese study.[18] Bone marrow was involved in 12.5% of cases of diffuse large B cell (DLBCL), in Nottingham University Hospital, United Kingdom study.[24]

In regional studies, incidence of bone marrow involvement is higher. For example, in an Indian study bone marrow was involved in 52.26% cases (21/38) of the B-cell lymphomas, and 54.54% cases (6/11) of the T-cell lymphomas.[25] In our study bone marrow was involved in 34.7% cases of diffuse large B cell lymphoma, which was higher than international studies (10-15%) but lower than Indian study.

The aim of present study was to find out the frequency of bone marrow involvement in different stages of the Diffuse Large B Cell lymphoma in patients presenting to our hospital. In present study a total number of 121 patients of DLBCL were studied to find out the frequency of bone marrow involvement in different stages of DLBCL. One of the limitations in this study was un-availability of PET/CT scan at our center. The results may have been different if PET/CT scan had been used for staging.

CONCLUSIONS

Stage wise bone marrow involvement in cases of diffuse large B cell lymphoma, is higher in patients presenting to our hospital, than reported in International literature. Exact cause of this increase in frequency should be determined by further studies.

RECOMMENDATIONS

The cause of increase in frequency of bone marrow invasion in our population is not known. Hence, it should be determined by further studies, with larger number of patients.

CONTRIBUTION OF AUTHORS

Nadeem MS: Conceived idea, Designed methodology, Data collection and Analysis, Manuscript writing
Haider N: Patient sampling, Proof reading of manuscript
Rasul S: Patient sampling
Ali U: Data analysis, Manuscript writing
Khan MY: Data collection, Statistical analysis

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