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# The Study On Changes In Bone Marrow And Peripheral Blood In Non-Hodgkin Lymphoma Patients.

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**ABSTRACT**

Lymphomas is a primary malignant neoplasm of the lymphoid tissue among which Non Hodgkin lymphomas (NHL) is common than Hodgkin lymphoma. Peripheral smear and bone marrow aspiration are routinely performed to diagnose lymphoproliferative disorders. Peripheral smear in lymphoma usually reveals lymphocytosis which is an indication for performing further tests. Bone narrow study is done for staging and pattern of involvement by lymphoma. The present study was conducted with the aim of investigating the bone marrow involvement and changes in bone marrow and peripheral blood smear in lymphoma cases. This prospective observational study was conducted in the department of pathology, Kidwai memorial institute of oncology, Bengaluru between November 2019 to May 2021. The epidemiology, changes in bone marrow and peripheral blood in various immunomorphological subtypes of Non-Hodgkin Lymphoma were studied. All de novo cases clinically suspected of NHL sample received in the department of pathology were included in the study. Clinical details and patients' history was recorded, lab tests including a complete hemogram, Peripheral smear examination and immunohistochemistry staining was done. We had a total of 136 cases of lymphoma out of which 56 cases were of Hodgkin lymphoma and 80 cases were of non-Hodgkin lymphoma. Mean age was 51.96 ± 17.17 years, with male majority including 46 males (57.5%). The most common site of the biopsy in our study was from cervical lymph node with 25 patients (31.3%). Most common clinical finding was lymphadenopathy seen in 58 cases (72.5%). Peripheral smear showed bicytopenia in 11 cases (13.8%), followed by atypical cells which was seen in 8 cases (10%). Most commonly we had B-cell type of NHL in 65 cases (81.2%) followed by T-cell in 13 cases (16.2%) and NK/T – cell in 1 case (1.25 %). Bone marrow was hypercellular in 13 cases (16.2%). Bone marrow erythropoiesis wise distribution showed normoblastic maturation in 64 cases (80%) and decreased erythropoiesis in 15 cases (18.8%) and 1 case of erythroid Hyperplasia (1.2%) was noted. Bone marrow biopsy findings showed no marrow involvement in 63 cases (78.8%), diffuse pattern marrow involvement in 14 cases (17.5%) and Follicular pattern in 3 cases (3.8%). We found that NHL cases were common in 5th decade with male predominance, with most common involvement in cervical lymph nodes. We conclude that a detailed clinical and histopathological evaluation f NHL cases is important for better patient management and prognosis.

**Keywords:** Non-Hodgkin Lymphoma, Peripheral smear and marrow involvement.

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## INTRODUCTION

Lymphomas is a primary malignant neoplasm of the lymphoid tissue which constitutes 55.6% of all haematological malignancies. Non-Hodgkin lymphomas (NHL) is common (87.4% of all lymphoma) than Hodgkin lymphoma (12.6%). Peripheral smear and bone marrow aspiration are routinely performed to diagnose lymphoproliferative disorders. Peripheral smear in lymphoma usually reveals lymphocytosis which is an indication for performing further tests. Bone narrow study is done for staging and pattern of involvement by lymphoma. The role of bone marrow along with peripheral film is to assess the stage and therapeutic monitoring for Hodgkin and non-Hodgkin lymphoma. The incidence rates of NHL is increasing in India like other parts of the world [1-3]. The part of the increase has been attributed to recent diagnostic improvement as well as AIDS related neoplasms following the HIV epidemics [4, 5]. NHL have propensity to infiltrate extra lymphoid tissue especially bone marrow as part of their natural history and frequency of involvement depends on the lymphoma type [6]. Compared to the aggressive lymphoma, indolent lymphomas have got relatively high frequencies of bone marrow involvement [6, 7]. As the bone marrow involvement in lymphoma is definite evidence of disseminated disease, assessment of bone marrow status in patients with lymphoma provides important for decision regarding treatment [8]. Currently CT, MRI or PET scan cannot fully assess bone marrow involvement, which is possible only by pathological staging. Bone marrow status can influence both stage and extra nodal involvement [9].

## METHODS

This prospective observational study was conducted in the department of pathology, Kidwai memorial institute of oncology, Bengaluru between November 2019 to May 2021. The epidemiology and various immunomorphological subtypes of Non-Hodgkin Lymphoma were studied. All de novo cases clinically suspected of NHL sample received in the department of pathology were included in the study. Clinical details and patients' history was recorded and immunohistochemistry staining was done.

## RESULTS

We have reported a total of 136 cases of lymphoma during the study period out of which 56 cases were of Hodgkin lymphoma and 80 cases were of non-Hodgkin lymphoma. The present study included a total of 80 cases of non-Hodgkin lymphoma. Out of which 65 were B cell non-Hodgkin lymphoma, 13 cases were of T cell non-Hodgkin lymphoma and 1 cases of NK/T cell lymphoma. One of the cases which was diagnosed as non- Hodgkin lymphoma could not be subcategorized on IHC due to depletion of sample.

We observed that the most common age group was 40 to 59 years with 34 participants (42.5%) followed by 60 and above with 28 (35%) and 20 to39 with 15 cases (18.8%). Mean age was 51.96 ± 17.17 years. There were 46 males (57.5%) and 34 females (42.5%) in our study. Male: Female ratio was 1.35:1. Anemia was seen in 38 cases (47.5%). Low RBCs were seen in 34 cases (42.5%).

Leukocytosis was seen in 20 cases (25%) and Leukocytopenia in 8 cases (10%). Thrombocytosis was observed in 2 cases (2.5%) and thrombocytopenia in 21 cases (26.2%). Neutropenia was seen in 16 cases (20%) and Neutrophilia in 13 cases (16.2%). Lymphopenia was seen in 24 cases (30%) and Lymphocytosis in 14 cases (17.5%). Monocytosis was seen in 10 cases (12.5%). Eosinophilia in 9 cases (11.2%). Basophilia was observed in 6 cases (7.5%).

Peripheral smear findings showed that 56 cases had normal smear (70%), while most common finding was bicytopenia in 11 cases (13.8%), followed by atypical cells which was seen in 8 cases (10%) and pancytopenia was seen in 4 cases (5%). Out of the 16-bone marrow involved cases atypical cell in the peripheral blood was seen in 8 cases that is 50%.

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**Table 1: Different Lab parameters in the study**

| Lab parameter | Normal | % | Low | % | High | % |
|---|---|---|---|---|---|---|
| Hemoglobin | 42 | 52.50% | 38 | 47.50% | - | - |
| RBC | 46 | 57.50% | 34 | 42.50% | - | - |
| TLC | 52 | 65.00% | 8 | 10.00% | 20 | 25.00% |
| Platelets | 57 | 71.20% | 21 | 26.20% | 2 | 2.50% |
| Neutrophils | 51 | 63.70% | 16 | 20.00% | 13 | 16.20% |
| Lymphocytes | 42 | 52.50% | 24 | 30.00% | 14 | 17.50% |
| Monocytes | 70 | 87.50% | - | - | 10 | 12.50% |
| Eosinophils | 50 | 62.50% | 21 | 26.20% | 9 | 11.20% |
| Basophils | 74 | 92.50% | - | - | 6 | 7.50% |

**Table 2: Descriptive statistics of Quantitative variables**

| | **Minimum** | **Maximum** | **Mean** | **Std. Deviation** |
|---|---|---|---|---|
| Age (years) | 6.00 | 80.00 | 51.96 | 17.17 |
| RBC (x $10^6$/ ul) | 1.50 | 7.12 | 3.95 | 0.90 |
| TLC (x $10^3$/ ul) | 1.59 | 64.20 | 10.81 | 10.56 |
| Platelet count (x $10^3$/ ul) | 6.69 | 629.00 | 246.42 | 133.31 |
| Neutrophil | 5.60 | 95.50 | 56.50 | 21.74 |
| Lymphocytes | 1.76 | 80.90 | 29.49 | 19.99 |
| Monocytes | 1.20 | 24.20 | 8.57 | 4.21 |
| Eosinophils | 0.00 | 60.00 | 4.35 | 7.51 |
| Basophils | 0.00 | 5.00 | 0.45 | 0.77 |
| LDH (U/L) | 139.00 | 1660.00 | 372.08 | 269.87 |

The descriptive statistics of quantitative variables are as show in in the table, mean age was 51.96 years. Mean TLC was 10.81x$10^3$/ ul thousand and mean LDH was 372.08 U/L.

Bone marrow was hypercellular in 13 cases (16.2%). Bone marrow erythropoiesis wise distribution showed normoblastic maturation in 64 cases (80%) and decreased erythropoiesis in 15 cases (18.8%) and 1 case of erythroid Hyperplasia (1.2%) was noted. Bone marrow myelopoiesis was normal in 65 cases (81.2%) and decreased in 15 cases (18.8%). Bone marrow lymphocytes evaluation showed normal picture in 42 cases (52.5%),

Lymphocytosis in 14 cases (17.5%). Bone marrow megakaryocytes were decreased in 15 cases (18.8%). Decreased erythropoiesis, myelopoiesis and megakaryocytes were seen in bone marrow involved cases.

**Table 3: Bone marrow parameters wise distribution of study participants**

| Bone Marrow Parameters | Normal | % | Low | % | High | % |
|---|---|---|---|---|---|---|
| Bone marrow Cellularity | 67 | 83.80% | - | - | 13 | 16.20% |
| Bone marrow Erythropoiesis | 64 | 80.00% | 15 | 18.80% | 1 | 1.20% |
| Bone marrow myelopoiesis | 65 | 81.20% | 15 | 18.80% | - | - |
| Bone marrow Lymphocytes | 42 | 52.50% | 24 | 30.00% | 14 | 17.50% |
| Bone marrow Megakaryocytes | 65 | 81.20% | 15 | 18.80% | - | - |
| Bone marrow Plasma cells | 66 | 82.50% | 14 | 17.50% | - | - |

Bone marrow biopsy was obtained in around 72 cases. In rest 8 cases was not sent. Out of the 72-bone marrow biopsy studied marrow was not involved by lymphoma in 56 cases (77.7%) and diffuse

pattern of involvement by lymphoma was seen in 12 cases (16.6%) and follicular pattern of involvement was seen in 2 cases (2.7%).

**Table 4: Comparison between number of cases obtained for bone marrow examination and involvement by Lymphoma**

| Subcategory of NHL | No of cases obtained for bone marrow examination | No of cases involved by lymphoma | % |
|---|---|---|---|
| DLBCL | 26 | 3 | 11.5 |
| High grade B cell lymphoma | 5 | 0 | 0.0 |
| Burkitt's lymphoma | 2 | 0 | 0.0 |
| Mantle cell lymphoma | 8 | 3 | 37.5 |
| Marginal zone lymphoma | 8 | 1 | 12.5 |
| CLL/SLL | 4 | 4 | 100.0 |
| Follicular Lymphoma | 9 | 3 | 33.3 |
| Low grade B cell lymphoma | 1 | 0 | 0.0 |
| MALT lymphoma | 1 | 0 | 0.0 |
| T lymphoblastic lymphoma | 6 | 0 | 0.0 |
| Precursor T cell lymphoma (PTCL) | 5 | 2 | 40.0 |
| Angioimmunoblastic T cell lymphoma | 2 | 0 | 0.0 |
| Plasmablastic lymphoma | 1 | 0 | 0.0 |
| NK/ T cell lymphoma | 1 | 0 | 0.0 |
| Tissue inadequate for IHC | 1 | 0 | 0.0 |
| Total Number | 80 | 16 | 20.0 |

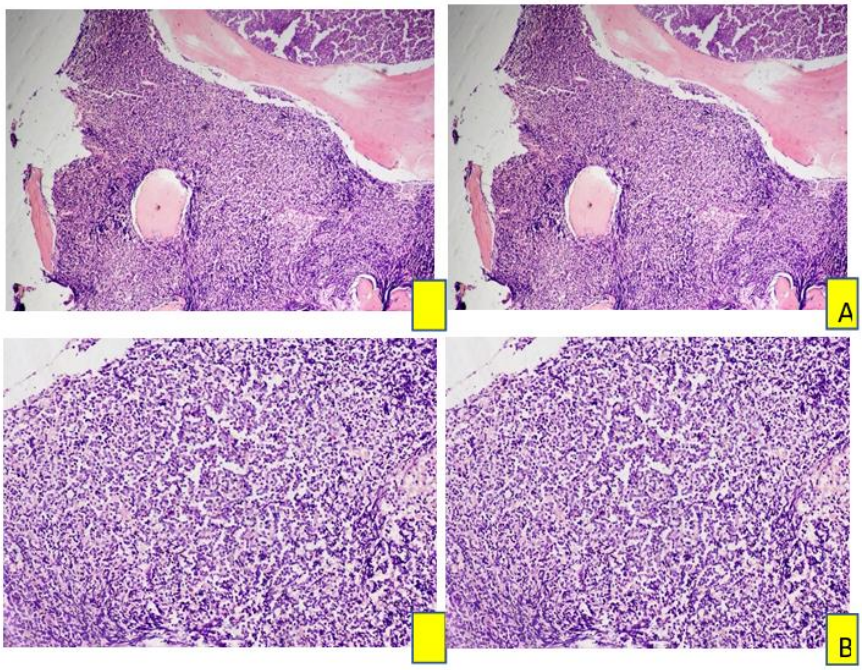


**Figure 1: A shows diffuse pattern of involvement of the bone marrow by atypical lymphoid cells. B shows small to medium sized cell infiltrating the bone marrow. This was the case of mantle cell lymphoma involving bone marrow**

There was total 16 out of 80 cases obtained for bone marrow examination involved by lymphoma (20%). For 26 cases with DLBCL, involvement by lymphoma was seen in 3 cases (11.5%), for 8 cases with Mantle cell lymphoma, involvement by lymphoma was seen in 3 cases (37.5%), all 4 cases of CLL/ SLL were involved by lymphoma (100%), for 9 cases of Follicular Lymphoma, involvement by lymphoma was seen in 3 cases (33.3%) and in 5 cases of Precursor T cell lymphoma (PTCL), involvement

by lymphoma was seen in 2 cases (40%). 2 cases were bone marrow appeared involved in the aspiration slide could not be confirmed on biopsy as it was not available.

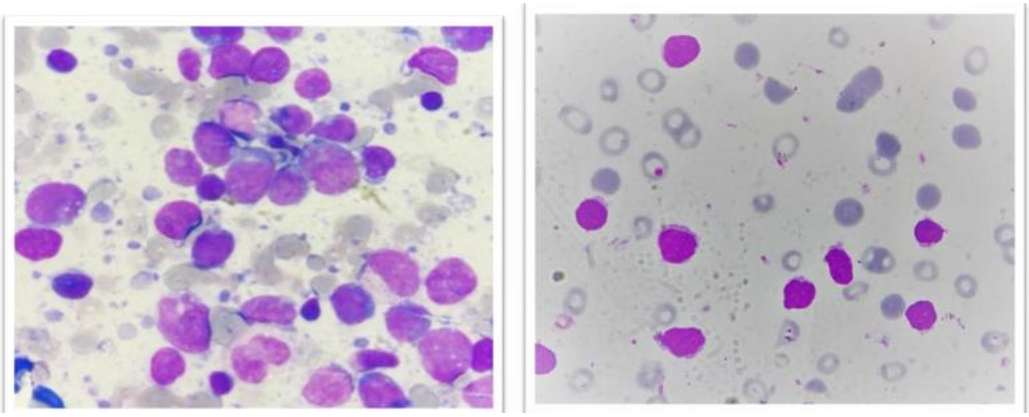

**Figure 2: Bone marrow aspirate and peripheral smear of mantle cell lymphoma**

## DISCUSSION

` The Non-Hodgkin Lymphoma (NHL) are a heterogeneous group of lymphoproliferative malignancies, with distinct causes and shows distinctive patterns of behaviour and response to treatment consists of many subtypes, each with distinct epidemiology, aetiology, morphology, immunophenotypic, and clinical features. It is not a single cancer, but rather a wide group of cancer, each with a distinct geographical distribution, age profile and prognosis [10].

The results are discussed below: Anaemia was seen in 38 cases (47.5%). Low RBCs were seen in 34 cases (42.5%). Leucocytosis was seen in 20 cases (25%) and leukocytopenias in 8 cases (10%).

Thrombocytosis was observed in 2 cases (2.5%) and thrombocytopenia in 21 cases (26.2%). Neutropenia was seen in 16 cases (20%) and neutrophilia in 13 cases (16.2%). Lymphopenia was seen in 24 cases (30%) and lymphocytosis in 14 cases (17.5%). Monocytosis was seen in 10 cases (12.5%). Eosinophilia in 9 cases (11.2%). Basophilia was observed in 6 cases (7.5%).

Peripheral smear findings showed that 56 cases had normal smear (70%), while most common finding was Bicytopenia in 11 cases (13.8%), followed by atypical cells in 8 cases (10%) and Pancytopenia in 4 cases (5%). LDH level was normal in 29 cases (36.2%) and increased in 34 cases (42.5%). We observed that one case was HIV positive in our study (1.2%).

EJ Lim et al [11] reported that at least one abnormal parameter in the full blood count irrespective of the lymphoma subtype. The frequency of anemia ranged from 60% to 80%. Lymphocytopenia was generally seen more commonly than lymphocytosis with the exception of LB patients.

Similar findings of anemia, lymphocytopenia, thrombocytopenia and multiple cytopenia were largely similar to those noted by Hanson et al [12]. Wiesenberger et al [13] reported a similar incidence (64%, 25 of 39 patients) of lymphocytopenia in their series. Serum LDH levels was studied by many authors for its prognostic evaluation [14]. Dumontet C et al [15] found that LDH levels were increased in patients with an advanced stage of the disease.

H Mantina et al [16] reported association between the HIV cases and certain types of NHL in their study, thus giving the importance of serological testing in NHL cases. Many other studies have discussed the association between the HIV positivity and NHL in the patients [17-19].

Bone marrow aspirate studied was Hypercellular in 13 cases (16.2%). Bone marrow Erythropoiesis wise distribution showed Normoblastic maturation in 64 cases (80%) and Decreased Erythropoiesis in 15 cases (18.8%) and 1 case of Erythroid Hyperplasia (1.2%). Bone marrow myelopoiesis was normal in 65 cases (81.2%) and decreased in 15 cases (18.8%). Bone marrow

Lymphocytes evaluation showed Normal picture in 42 cases (52.5%), Lymphocytopenia in 24 cases (30%) and Lymphocytosis in 14 cases (17.5%). Bone marrow megakaryocytes were decreased in 15 cases (18.8%). Bone marrow Plasma cells showed decreased distribution in 14 cases (17.5%).

Bone marrow biopsy was obtained in around 72 cases. In rest 8 cases was not sent. Out of the 72-bone marrow biopsy studied marrow was not involved by lymphoma in 56 cases (77.7%) and diffuse pattern of involvement by lymphoma was seen in 12 cases (16.6%) and follicular pattern of involvement was seen in 2 cases (2.7%).

EJ Lim et al [11] found that regarding the bone marrow changes, about 50% had marrow involvement. Infiltration was questionable in one case of PTCL-u, where pleomorphic medium to large-sized lymphoid cells with prominent nucleoli and high mitotic rate were seen, occurring interstitially and in groups of two or three in one area in the trephine biopsy. These cells did not appear to express either T or B-cell antigens. No lymphoma cells were detected in the marrow smear of this patient but an increase in ruptured cells was seen in some areas.

Diffuse marrow infiltration was more commonly seen compared to the other patterns of infiltration. However, this finding was not statistically significant (p=0.078, binomial test). 21 of 47 patients had marrow eosinophilia, and of these, only 2 had a spill-over of eosinophils into the blood.

The other manifestations were uncommon: increased marrow vascularity in 1 case of PTCLu with MI, necrosis in another case of PTCL-u with MI, increased histiocytes in one case of BLCNHL without MI and one TCRBCL patient with infiltration, increased plasma cells in one BLCNHL patient without MI. MI was noted in 80% (24 out of 30) by Hanson et al [12], 73% (27 out of 37) by Gaulard et al [20], and 60% by McKenna et al [21]. Foucar et al [22] reported a 65% incidence (11 of 17 cases) of infiltration in T-cell lymphoma patients. It appears that the reported incidences of marrow disease in Asian patients are lower than the Western figures.

## CONCLUSION

This study highlights the incidences and pattern of involvement in the bone marrow by NHL**. T**he bone marrow biopsy had a higher diagnostic validity compared to bone marrow aspirate. However, BMA served as a good positive screening test ion lymphoma. However, a negative BMA does not exclude the involvement, hence taken as complimentary procedure rather than a substitute for biopsy. Peripheral blood parameters, as well as the thorough examination of the smear hence, are important for early diagnosis. As the anatomical staging is an important aspect in NHL because of its prognostic and therapeutic implications, accurate determination of bone marrow infiltration is important for the lymphoproliferative disorders.

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