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EPIDEMIOLOGY AND IMMUNOHISTOCHEMICAL PROFILE OF NON HODGKIN LYMPHOMA- EXPERIENCE OF A TERTIARY CANCER CENTER

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Abstract

Background: 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. The present study was conducted with the aim of investigating the epidemiology of various subtype of NHL by using immunohistochemistry.

Materials and methods: This prospective observational study was conducted in the department of pathology, Kidwai memorial institute of oncology, Bengaluru between the periods of 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.

Result: 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%). 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 %).

Conclusion: 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 of NHL cases is important for better patient management and prognosis.

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Key Words: Non-Hodgkin Lymphoma, Epidemiology, Immunohistochemistry

Introduction:

The Non-Hodgkin Lymphoma (NHL) are a heterogenous 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 [(1)]. NHLs consist of a diverse group of hematologic malignancies deriving from mature or immature lymphocytes (B, T or NK). B-cell lymphomas (BCLs) account for 80 to 85% of the cases especially in the Western world and United States (US) and T-cell lymphomas (TCLs) accounts for the rest 15 to 20% [(2)].

NHL is the most prevalent hematopoietic neoplasm ranking seventh in frequency among all cancers [(3)]. There appears to have various subtype of NHL. The NHL subtypes variation in each country appears to be related to population characteristics and environmental factors. For example, the incidence in the US is greater than other countries with a predominant nodal disease. Although NHL incidence is relatively low in Asian countries, Asians generally present with a higher proportion of T Cell Lymphomas [(4)].

Around 23,718 new cases of NHL are reported every year in India. Although the incidence of NHL in India is lower compared to the developed country, but mortality remains the same. The distribution of major subtypes NHL differs across geographical regions. Further the different subtypes of NHL are known to have different age and sex distribution. While adequate information is available on epidemiology from developed country such information in scarce in developing country like India [(5)].

Patients can acquire aggressive NHL (fast-growing) or indolent (slow growing) lymphoma that can be formed from B cells or T cells [(6)]. According to research conducted in the UK in 2008, of the 27 countries in the European Union, Finland had the highest NHL mortality rates for both men and women, at approximately five and seven cases per 100,000 persons, respectively[(7)] . The understanding of pathogenesis of non-Hodgkin lymphoma has improved in the recent days. The recent advances in the molecular biology and genetics have led to identification of several oncogenic pathways which has led to the development of this lymphoma. Further this knowledge will help in improving diagnostic and therapeutic strategies for patient with non-Hodgkin lymphoma [(8, 9)] .

Age and sex are important factors in the epidemiology of lymphoma. NHL is more common in men than in women. Notable exceptions to male predominance are MALT lymphoma and mediastinal large B-cell lymphoma, which are more common in women. In NHL, incidence increases with advancing age, with a median age of diagnosis in the seventh decade. NHL incidence continues to increase with age in men. In women, NHL also increases with age, but at a lower rate, and then decreases at ages 80 years or older. NHL is basically a disease of older adults, with a median age of most NHL subtypes in the sixth to seventh decade, except BL, precursor NHL (acute lymphoblastic lymphoma/leukemia, ALL/LBL), and mediastinal large B-cell lymphoma [(10)] .

The death rate from NHL is rising, with an estimated 143,000 deaths in 1990 to 210,000 deaths in 2010 [(11)]. The incidence and mortality rates in men are more observable than women and there is an upward trend among elderly people. Significant elevation in the

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incidence of this disease among patients over 50 years old indicates the importance of environmental factors [5]. The careful utilization of IHC (Immunohistochemistry), flow cytometry and molecular diagnosis aids for identification of the various subtypes of the NHL and helps to classify them based on World health organization (WHO) classification of lymphoid neoplasm. The present study was conducted with the aim of investigating the epidemiology of various subtype of NHL.

Methods:

This prospective observational study was conducted in the department of pathology, Kidwai memorial institute of oncology, Bengaluru in time period of 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. Majority of the patients were from Karnataka, 76 cases (95%). 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 to 39 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.

The most common site of the biopsy in our study was from cervical lymph node with 26 patients (32.5%) of the population followed and axillary lymph node and other sites. The most common presenting complain in our study population was swelling in the neck 18 cases (22.5%) followed by others complaint involving like nasal cavity, GIT and oral cavity, mediastinum etc . Presence of Group B symptoms (unexplained fever > 38 0 c, unexplained weight loss > 10% body weight within the preceding 6 months and drenching night sweats) were present in 18 cases (22.5%).

Presence of Group B symptoms (unexplained fever > 38 0 c, unexplained weight loss > 10% body weight within the preceding 6 months and drenching night sweats) were present in 18 cases (22.5%).Most common clinical finding was lymphadenopathy seen in 58 cases (72.5%) followed by pallor in 33 (41.2%) and splenomegaly in 11 cases (13.8%). CNS involvement was seen in 3 cases (3.8%) one case was of high-grade B cell lymphoma and other two cases were of Diffuse large B cell lymphoma.

Histopathological diagnosis was made on H and E sections. The cases were diagnosed as Non – Hodgkin lymphoma in 69 cases (86.2%). Around 9 (11.2%) cases were diagnosed as poorly differentiated neoplasm and 2 (2.5%) cases were diagnosed as malignant round cell tumour which is the close differential diagnosis for NHL which were further confirmed by immunohistochemistry and were subcategorized into different subtype of non-Hodgkin lymphoma.

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We studied immunohistochemistry / flow cytometric subcategory wise distribution of study participants and we found that the most common type was diffuse large B cell lymphoma in 26 cases (32.5%) followed by follicular lymphoma in 9 cases (11.2%), mantle cell lymphoma in 8 cases (10%), marginal zone lymphoma in 8 cases (10.0%) and T lymphoblastic lymphoma in 6 cases (7.5%). Other lymphomas obtained in the studied are high grade B cell lymphoma in 5 cases (6.25%) peripheral T cell lymphoma in 5 cases (6.25%), small lymphocytic lymphoma in 4 cases (5%), angioimmunoblastic lymphoma in 2 cases (2.5%), low grade B cell lymphoma in (1.25%), mucosal associated lymphoid neoplasm in 1 case (1.25%), Plasmablastic lymphoma 1 case (1.25%) and NK T cell lymphoma in 1 case (1.25%). In one of the cases IHC could not subcategorize the type of lymphoma as tissue was in adequate for any opinion.

Significant association was seen between the age and distributions of different IHC/FC type of NHL ($p = 0.04$) In age group less than 20 years most common was Peripheral T cell lymphoma (66.7%). In age group 20 to 39 years, most common was Peripheral T cell lymphoma (40%) and DLBCL (26.7%). In age group 40 to 59 years, most common type was DLBCL (38.2%). In age group 60 and above, most common was DLBCL (32.1%) followed by others (28.6%).Significant association was seen between the sex and distributions of different IHC/FC type of NHL.($p = 0.004$) In females, most common was DLBCL in 23 out of 34 cases (67.65%) followed by Mantle cell lymphoma (17.65%) and in males most common was Follicular lymphoma (13.04%) followed by T Lymphoblastic Lymphoma (10.87%).

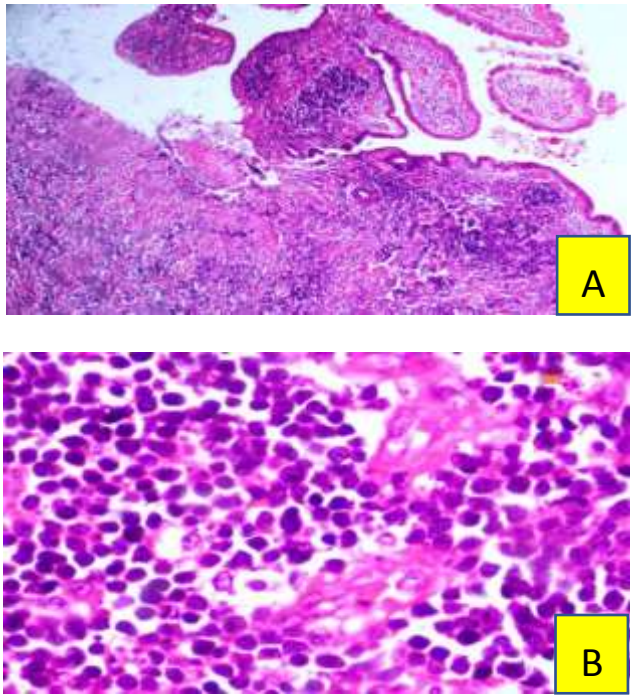

Figure 1 & 2: H and E sections of the case of Burkitt lymphoma in 6-year-old male child presenting as ileocecal mass. A. H and E section focused at 200x B. H and E sections focused at 400x shows monotonous population of intermediate sized cells with squared off bord

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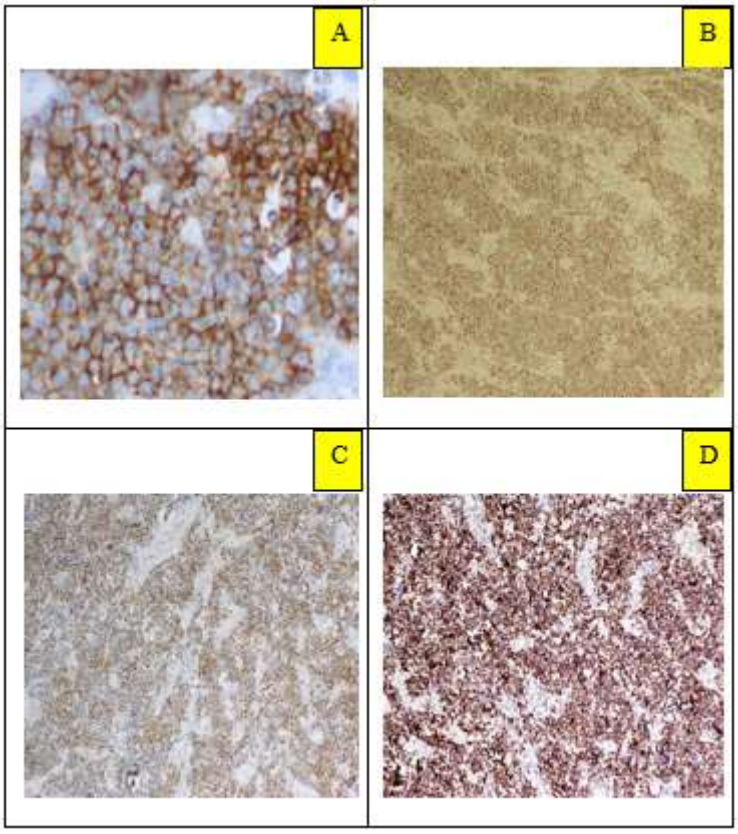

Figure 3-6: Immunohistochemistry in a case of Burkitt lymphoma. A shows CD20 staining which is strongly positive in Burkitt lymphoma. B shows BCL6 staining which is strongly and diffuse positive. Suggestive of follicular origin. C shows CMYC positivity in most of the cells. D shows K167 index of 100%

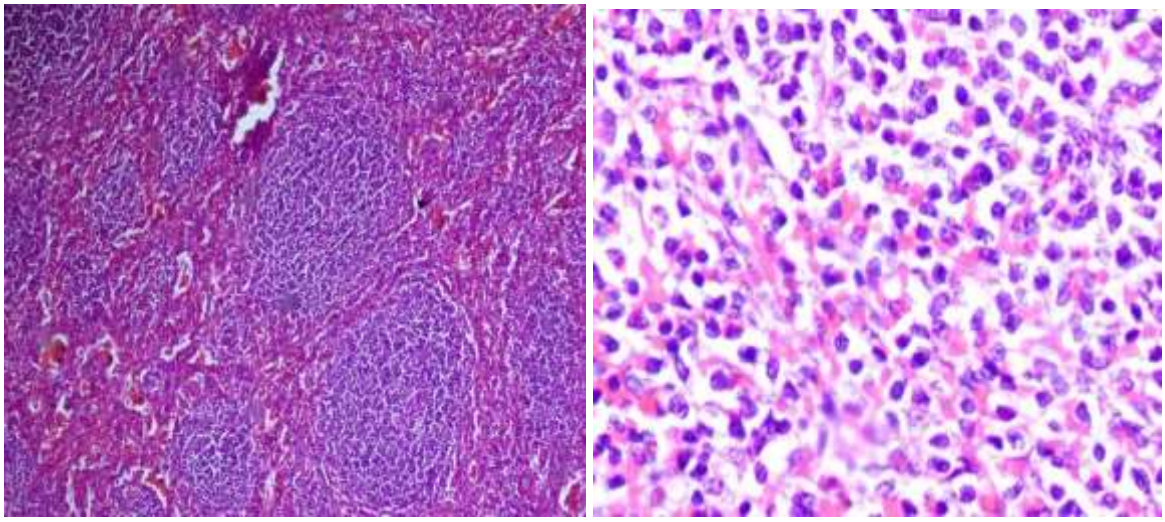

Figure7&8: H and E section in a case of splenic extranodal marginal zone lymphoma focused in 200x H and E sections of case of splenic marginal zone lymphoma focused at 400x shows infiltration by small, atypical lymphocytes

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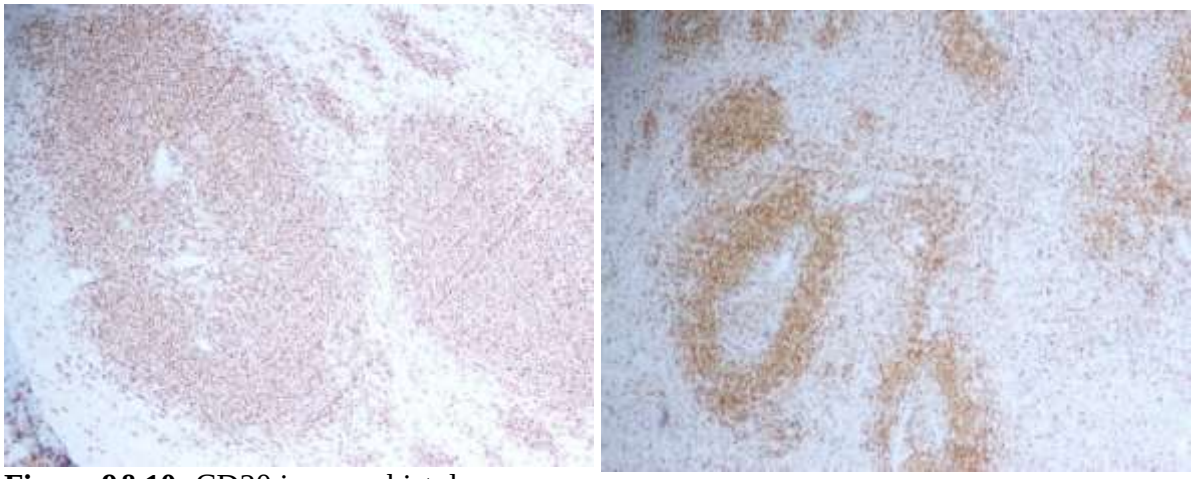

Figure 9&10: CD20 immunohistology staining comprising the majority of lymphocytes within the lymphoid aggregates with intrasinusoidal infiltration in splenic marginal zone lymphoma**:** BCL2 staining in splenic marginal zone lymphoma

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, etiology, 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 [12-14].

The results are discussed below: 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 to 39 with 15 cases (18.8%). Mean age was 51.96 ± 17.17 years. There were 3 cases with age less than 14 years. Significant association was seen between the age and distributions of different IHC/FC type of NHL. (p = 0.002) In age group less than 20 years there was one case each of DLBCL (33.3%) and Mantle cell Lymphoma. In age group 20 to 39 years, out of 15 cases, most common was DLBCL in 5 cases (33.3%) and Follicular Lymphoma (26.7%). In age group 40 to 59 years, most common type was DLBCL (32.4%). In age group 60 and above, most common was DLBCL (32.1%).

There were 46 males (57.5%) and 34 females (42.5%) in our study. Male: Female ratio was 1.35:1. Significant association was seen between the sex and distributions of different subtype of NHL. (p = 0.004) In females, most common was DLBCL in 23 out of 26 cases (88.5%) followed by Mantle cell lymphoma (66.6%) and 86 in males most common was Follicular lymphoma seen in 6 out of 9 cases (66.7%) followed by T Lymphoblastic Lymphoma (83.3%). This male preponderance has been reported in other studies too [15-20]. EJ Lim et al 72 studied 47 patients, out of which their patients' ages ranged from 3 to 78 years; the mean age was 34.2 years. 11 patients were 12 years old or younger, while the remaining 36 were more than 12 years old. A significant difference was noted between the mean ages of patients in the different subtypes of NHL (p=0.001). They observed that there were 32 male

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patients (68.1%) and 15 female patients (31.9%). This difference was statistically significant (p=0.020). The male patients predominated in every subtype seen in this series.

Maximum incidence of NHL including both sexes was seen in age group 31-40: (21.3%) followed by age group 61-70 (19%). NHL is more common in older adults than younger adults; hence age presents to be strong risk factor for this disease. Incidence data obtained from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program accounted that the incidence of total lymphoid neoplasms increased monotonically with age in all race and sex subgroups. Steep increases in incidence with age were observed for most subtypes. It reported that 63.6% NHL occurred after the age of 40 years with a peak between 51 and 60. Similarly, in a study conducted by Vallabhajosyula et al. [(18)], the median age of study population was 55.5 years (interquartile range 41-67 years). Padhi S et al., too reported that peak incidence was during the 4th to 5th decade of life. [(19)]

Most common site was cervical Lymphnode in 26 cases (32.5%), followed by axillary lymph node in 6 cases (7.6%), inguinal lymph node in 5 cases (6.3%) and bone marrow in 3 cases (3.8%). Sharma M et al noted that out of 77 cases, Cervical Lymph Nodes were most common site of biopsy (31 cases – 40.26%). Vallabhajosyula et al [(18)] noted that Cervical lymph nodes (36%) was the most common involved site followed by axillary lymph nodes (6%).

Group B symptoms were present in 18 cases (22.5%). Padhi S et al [(21)] reported that the Group B symptoms were present in 24% cases, similar to our study.

Most common clinical finding was lymphadenopathy seen in 58 cases (72.5%) followed by pallor in 33(41.2%) and Splenomegaly in 11 cases (13.8%). Vallabhajosyula et al [(18)] noted that most common clinical finding was lymphadenopathy seen in 70% of the cases followed by pallor in 39% and splenomegaly in 24% of the cases. History of weight loss was also seen in 42% of their cases.

Conclusion:

Incidence of Non-Hodgkin's lymphoma is increasing worldwide, and this has been observed in developing countries including India also. The distribution of NHL subtypes in the India shows important differences with those from the rest of the world. FL and MCL are less common in India compared to Europe and the USA. While T-cell lymphoblastic lymphoma and anaplastic large T/null cell lymphoma are more prevalent in India. Immunohistochemistry is a useful and necessary diagnostic aid and helps in sub-typing different types of NHL.

We conclude that a detailed clinical and histopathological evaluation of NHL cases is important for better patient management and prognosis. Limitation of study is that we had a small number of cases as they were taken over a limited time period. We recommend a multi centric prospective study to gather data on patient management, prognosis and survival.

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