Malignant lymphoma in Eastern India: A retrospective analysis of 455 cases according to World Health Organization classification

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ABSTRACT

Background: Malignant lymphoma (ML) is one of the most common cancers and is most prevalent in developed countries. The distribution of different subtypes of ML varies in the different geographical locations according to World Health Organization (WHO) Classification. **Aims and Objectives**: The study was aimed to analyze the different patterns of ML in Eastern India and to compare it with other geographical locations. **Materials and Methods:** Four hundred and fifty five patients of two large hospitals in Eastern India were included over a period of four years and were categorized according to WHO classification, using the morphology and immunohistochemistry. **Results:** There were 347 (76.3%) non Hodgkin lymphomas (NHL), and 108 (23.7%) Hodgkin lymphomas (HL). Diffuse large B-cell lymphoma was the most common of the NHL type (35.2%) followed by the follicular lymphoma (19.3%). B-cell lymphoblastic lymphoma was the least common type of NHL (1.4%). Mixed cellularity (33.3%) and nodular sclerosis (26.9%) were the two most common type of HL. Childhood lymphoma comprised of 12.5%of all ML. T-cell NHL and HL were the common lymphomas in this age group. **Conclusion:** Incidence of follicular lymphoma is lower compared to western studies and mixed cellularity is the most common subtype of HL unlike nodular sclerosis subtype in Western world. Burkitt's type NHL though is the most common subtype of childhood ML in many studies. However, in our study, T-cell NHL is the most common type of childhood ML.

Key words: *Eastern India, immunophenotyping, lymphoma, World Health Organization*

INTRODUCTION

The World Health Organization (WHO) classification of malignant lymphoma (ML) has become popular since its introduction in 2001 and has been applied to the classification of ML in different countries around the world.[1] Different studies from America, Europe, Jordan, Iran, Japan, China, India, Iraq have revealed that the relative proportion of various ML according to WHO classification differ with geographical regions.[2-5]

Only a few studies of ML are undertaken in India so far.[6,7] To the best of our knowledge, this is the first study from Eastern India. The present study was undertaken to subtype the ML in this part of the world according to WHO classification and to compare it with other studies to find out geographical variation of ML.[8,9]

MATERIALS AND METHODS

In the present study, 455 cases of malignant lymphomas, which included various subtypes of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL); collected from two large hospitals over a period of four years (2008 to 2011). Of these two hospitals, one is a Tertiary Care Cancer Hospital of Eastern India and another is the medical college and hospital. Additional clinical data including, age, gender, and site of sampling were recorded.

All cases were reviewed by three pathologists, which included the first author. Tissue sections of 3-4 μ thickness from paraffin embedded tissue and decalcified bone marrow specimens (trephine biopsy) were examined by hematoxylin and eosin and a panel of immunocytological

marker using the streptavidin-biotin peroxidises method. The panel of immunohistochemistry (IHC) markers included CD45 (LCA), CD45RO, CD79, CD20, CD23, CD10, CD5, CD3, CD56, CD4, CD8, CD15, CD30, CD34, EMA, MUM1, BCL6, TdT, BCL2, MIB1/KI67, ALK1, Kappa and lambda light chains.[10,11] Other IHC markers were also utilized if needed for evaluation of some unknown neoplasm/ML.

All patients were subjected to routine hematological (estimation of hemoglobin, total, and different leucocyte count, platelet count, peripheral smear for abnormal/blast cells etc.) and biochemical (liver function tests, urea, creatinine, uric acid) investigations. The radiological examination included chest radiograph, computed tomography, and ultrasonography of abdomen. Reticulin stain was carried out in trephine biopsies to assess the marrow involvement by neoplastic cells and reactive fibrosis.

RESULTS

There are 455 cases of ML in the present study. NHL was diagnosed in 347 cases (76.3%) and HL in 108 cases (23.7%). Out of these 455 cases of ML adult cases were 398 (NHL 216 and HL 92) and pediatric cases (<15 years) were 57 (NHL 41 and HL 16). Male-female ratio was 345:110 = 3.1:1 and the NHL: HL ratio was 3.2:1.

NHL

Among 347 cases of NHL 218 patients were males (62.8%) and 69 were females (19.9%) and male to female ratio was 3.2:1. The age range was 2-79 years with a mean

age of 39.4 years. Among NHL cases B-cell lymphomas were the predominant type (257 cases) accounting for 74.1% of all cases [Table 1]. T-cell lymphomas constitute 90 cases (25.9%). Of the B-cell neoplasms, diffuse large B-cell lymphoma (DLBCL) was the most common subtype (122, 35.2%) cases, followed by follicular lymphoma (67 cases, 19.3%). Among the follicular lymphomas, Grade 3 was most common type (28 cases), followed by Grade 2 (25 cases) and Grade 1 (14 cases). Third common B-cell NHL was Burkitt's lymphoma (20 cases, 5.8%) followed by small lymphocytic lymphoma (19 cases, 5.5%).

T-cell NHL comprised of 90 cases (25.9%) and anaplastic large cell lymphoma (ALCL) was the most common subtype (42 cases, 12.1%), followed by precursor T lymphoblastic lymphoma (30 cases, 8.6%). Other T-cell NHL were Mycosis Fungoides (7 cases, 2%), peripheral T-cell lymphomas (6 cases, 1.7%) and angioimmunoblastic (5 cases, 1.4%).

A total of 251 cases (72.3%) were nodal and 96 cases (27.7%) were extranodal. Cervical lymph node was the most common site (52 cases, 20.7%) followed by axillary nodes (36 cases, 14.35), the inguinal nodes (20 cases, 7.9%), the mediastinal nodes (14 cases, 5.6%), abdominal nodes (13 cases, 5.2%) and others. The most frequent extra nodal site was intestine (23 cases, 23.9%), followed by tonsil (21 cases, 21.9%), stomach (9 cases, 9.4%). parotid (6 cases, 6.2%) and others.

HL

Out of 108 cases of HL, 88 patients were males and 20 patients were females with a male-female ratio of 4.4:1.

Table 1: Distribution of types of 347 patients with NHL according to the WHO classification

NHL type	No. of cases (%)	Mean age in years	Gender (M/F)	No. of cases with bone marrow involvement	Percentage with bone marrow involvement %
B-cell lymphomas					
Diffuse large cell B-cell	122 (35.2)	48.6	108/14	17/88	19.3
Follicular lymphoma	67 (19.3)	51.8	06/03	23/48	47.9
Mantle cell lymphoma	09 (2.6)	56.9	03/02	03/06	50
Precursor/lymphoblastic	05 (1.4)	15.4	05/03	01/03	33.3
T-cell rich B-cell lymphoma	08 (2.3)	42.6	13/07	01/03	33.3
Burkitt lymphoma	20 (5.8)	7.9	04/03	02/12	16.6
Extranodal marginal (MALT) lymphoma	07 (2)	43.2	13/06	00/04	0
Small lymphocytic	19 (5.5)	61.3	57/33	09/15	60
T-cell lymphomas					
Precursor	30 (8.6)	18.2	18/12	04/15	26.7
ALCL	42 (12.1)	34.8	28/14	07/27	25.9
Angioimmunoblastic	05 (1.4)	57.7	03/02	01/03	33.3
Peripheral T-cell	06 (1.7)	31.4	04/02	02/04	50
Mycosis fungoides	07 (2)	42.7	04/03	00/03	0

NHL – Non hodgkin lymphoma; WHO – World health organization; ALCL – Anaplastic large cell lymphoma

The age range for HL was 3-67 years with a mean age range of 31.3 years. All cases of HL were of nodal origin and no extra nodal case was detected in the present study. The most frequent site was cervical group of lymph nodes (71 cases, 65.7%) followed by axillary nodes (23 cases, 21.3%), mediastinal nodes (9 cases, 8.3%) and others.

Mixed cellularity variant was the commonest type (36 cases, 33.3%). followed by nodular sclerosis (29 cases, 26.8%), lymphocytic rich (16 cases, 14.8%), classic not otherwise specified (NOS) (11 cases, 10.2%) and lymphocyte depleted (8 cases, 7.4%) [Table 2].

Among the 29 cases of nodular sclerosis 27 cases were Grade 1 and two cases were Grade 2. There were 11 cases of classic HL, which could not be subtyped due to small tissue specimen, and they were classified into classic NOS type.

Bone marrow involvement
Out of the 347 cases of NHL, trephine biopsy material was available in 231 cases and marrow involvement was noted in 70 cases (30.3%). Highest marrow involvement was seen in small lymphocytic lymphoma type NHL (60%) followed by mantle cell lymphoma (50%), follicular lymphoma (47.9%) [Table 1].

Among the HL trepine biopsies were available in 43 cases out of total 108 cases and marrow involvement was detected in 4 cases (9.3%) [Table 2].

Extranodal NHL
Out of 347 cases of NHL; extra nodal cases were found in 96 cases (27.7%). The most frequent affected site was the small and large intestine (23 cases, 23.9%) followed by the tonsil (21 cases,21.8%) other sites were stomach (9 cases, 9.4%), parotid (6 cases, 6.4%), testis (5 cases, 5.2%), nasopharynx (4 cases, 4.2%), orbit (3 cases, 3.1%), brain (3 cases, 3.1%), etc. [Table 3].

Childhood lymphoma
In the present study, childhood lymphoma (<15 years of age) comprised of 57 cases (1.25%) cases out of total 455 cases. In this age group commonest type of ML was HL (16 cases, 28%) followed by the peripheral T-cell lymphoma (13 cases, 22.8%), precursor lymphoblastic T-cell lymphoma (8 cases, 14%), Burkitt's lymphoma (6 cases, 10.5%), precursor lymphoblastic B-cell lymphoma (6 cases, 10.5%) and others [Table 4]. There were 42 male patients and 15 female patients with a male female ratio of 2.8:1. The age range was 7 months - 14 years and median age was 9.3 years. Trephine biopsy examination was carried out in 32 cases, out of which 6 cases showed bone marrow involvement (18.7%). Highest marrow involvement was seen in ALCL (33.3%) followed by precursor lymphoblastic B-cell lymphoma (25%) and peripheral T-cell lymphoma (25%) [Table 4].

DISCUSSION

The classification of malignant lymphomas has changed over the years and WHO classification or WHO classification with minor modifications has been adopted

Table 2: Extranodal NHL distribution according to the primary site

Extranodal site of NHL	Number (*n* = 96)
Intestine (small and large)	23
Tonsil	21
Stomach	09
Parotid	06
Testis	05
Nasopharynx	04
Orbital mass	03
Brain tumor	03
Retroperitoneum	03
Bone	03
Others	16
Total	96

NHL – Non hodgkin lymphoma

Table 3: Distribution of types of 347 patients with NHL according to the WHO classification

HL type	No. of cases (%)	Mean age±SD	Gender (M/F)	No. of with marrow involvement	No. of with marrow involvement %
Classic type	89 (82.4)				
Lymphocyte rich	16 (14.8)	33.6	13/03	01/07	14.3
Mixed cellularity	36 (33.3)	29.7	32/04	07/12	8.3
Lymphocyte depleted	08 (7.4)	34.6	07/01	01/05	20
Nodular sclerosis					
Grade 1	27 (25)	26.8	20/07	07/11	5.1
Grade 2	02 (1.8)	31.5	02/01	00/11	0
Nodular lymphocytic	8 (7.4)	25.7	07/01	00/03	0
Classic type (NOS)	11 (10.2)	37.1	7/4	00/04	0

NHL – Non hodgkin lymphoma; HL – Hodgkin lymphoma; WHO – World health organization; NOS – Not otherwise specified

Table 4: Distribution of 57 cases of various childhood lymphomas

Types of lymphoma	No. of cases	Mean age±SD	Gender (M/F)	No. of with marrow involvement	No. of with marrow involvement %
Hodgkin lymphoma	16	8.8	14/12		14.3
B-cell NHL			11/04		
Burkitt's lymphoma	06	6.6	04/02	00/03	0
Precursor lymphoblastic	06	9.2	05/01	01/04	25
Diffuse large B-cell	03	8.7	02/01	00/02	0
T-cell NHL			17/9		
Peripheral T-cell lymphoma (NOS)	13	12.3	09/04	02/08	25
Precursor lymphoblastic	08	10.2	05/03	01/05	20
ALCL	05	9.1	03/02	01/03	33.3

NHL – Non hodgkin lymphoma; NOS – Not otherwise specified; ALCL – Anaplastic large cell lymphoma

in most centers.[1] By using the WHO classification with IHC evaluation, both NHL and HL are easily classified.[12] Classifying ML according to B and T-cell type has prognostic significance to the oncologists.[13] Due to the limited availability of the panel of IHC markers, WHO classification of ML is being studied in very few centers of Eastern India. The importance of the current study is that it documents the various types of ML based on the WHO classification in a geographical area (Eastern India) that has not been previously investigated.

In India, the first population based cancer registry was established in Mumbai (Bombay) by the Indian Cancer Society in 1964. Other urban registries available are Delhi, Chennai, Bhopal and Bangalore under the network of National Cancer Registry Program (NCRP) of Indian Council of Medical Research.[14] However, no such urban cancer registry is available from Eastern India.

In our study, HL comprised 23.7% of ML cases, and ratio of NHL to HL is 3.2:1. In another Indian study, this ratio was 1.58:1 and reported a higher percentage of HL (38.7%) compared to our study (23.7%).[6] The rate of HL is lower than west (30%)[1] and almost similar in Jordan (21.6%) and Northern Iran (24%).[2,15] A higher percentage (41%) of HL was found in UAE.[15] Much lower frequency of HL was seen in some Asian countries like Japan (7%), Thailand (8.5%), and China (6.6%).[16,17] In our study, mixed cellularity is the most common subtype (33.3%) followed by the modular sclerosis subtype (26.8%). Similar trend was found in Pakistan and also in one Indian study.[6,18] However, in Jordan, Europe, USA and other western world, modular sclerosis is the most common subtype.[1,15] Getachew A reported lymphocyte predominant subtype as the common type of HL in Western Ethiopia of Africa.[19] Increased incidence of mixed cellularity subtype in India, Pakistan and other Asian countries may be due higher risk of childhood exposure to Epstein Barr virus that is more likely to be associated with a mixed cellularity than nodular sclerosis.[20] With regards to specific subtypes of NHL,

the present study showed DLBCL is the most common subtype (35.2%) which is comparable to USA and Europe (25-30%).[1,21] The trend is similar in Jordan (28.2%), China (3.5:1) in India.[11,22] However, a higher proportion of DLBCL was noted in northern Iraq (52.2%), UAE (59%) and in Pakistan (66.1%).[2,11,18]

FL was the second most common subtype of NHL (19.3%) in our study, which is comparable in other Indian study.[22] A higher proportion is noted in Western studies (28-32%). Lower incidence of FL (4-8%) was reported from Saudi Arabia, Egypt, UAE, North Jordan and Pakistan.[2,18] Naresh *et al.* opined that the low rates of FL in developing countries might be due to many DLBCL progressed from previously undiagnosed FL and that unique environmental or genetic factors may have contributed to such progression.[22]

Bone Marrow involvement was noted in 30.3% of NHL cases and 9.3% of HL cases. Bone marrow involvement in NHL varies from 20% to 40% in different Western studies, which is similar to our studies.[1,6,23] In, different Indian studies bone marrow involvement in HL is 8.33-9.68% which is almost similar to our study.[6,7] Extranodal lymphomas (ENL) are common and accounted for 27.7% of ML cases. This figure is close to the incidence in USA (26%) and slightly lower than Jordan (30.5%), UAE (29%) and Bahrain (41%).[11] DLBCL was the most common subtype of ENL and gastrointestinal tract is the most common site in a study in Kuwait, similar to our findings.[24] However, higher incidence of ENL (44.9%) was seen in Taiwan.[25] While NHL and HL have long been regarded as distinct entities, recent study showed a closer association of these two entities. The analysis of cases in which both diseases are present in the same anatomic site (composite lymphomas), or in separate sites (sequential or simultaneous NHL and HL), indicates that this phenomenon occurs more frequently than would be expected by chance alone.[26,27]

CONCLUSION

The present study from Eastern Indian shows higher number of NHL cases (76.3%) then HL cases (23.7%) and male–female ratio is 3.1:1. A lower percentage of follicular lymphoma is seen compared to Western studies and Grade 3 is the most common subtype of follicular lymphoma. Among the extranodal NHL, tonsil is most frequently involved site and is second most common site of extranodal NHL in our study. Mixed cellularity type of HL is the most common subtype like in other Asian, and Indian studies; however, unlike western studies where nodular sclerosis is the commonest type. T-cell NHL is the most common type of childhood NHL unlike Burkitt's lymphoma in other studies. Highest bone marrow involvement is seen in mantle cell lymphoma among NHLs and lymphocyte depleted variant among HLs and ALCL among childhood lymphomas.

REFERENCES

1. Jaffe ES, Harris NL, Stein H, Vardman JS. World Health Organization. Classification of Tumours. Pathology and Genetics. Tumours of Hematologic and Lymphoid Tissues. 4th ed. 2007, Lyon: IARC Press 2008.
2. Yaqo RT, Hughson MD, Sulayvani FK, Al-Allawi NA. Malignant lymphoma in northern Iraq: A retrospective analysis of 270 cases according to the World Health Organization classification. Indian J Cancer 2011;48:446-51.
3. Aoki R, Karube K, Sugita Y, Nomura Y, Shimizu K, Kimura Y, *et al*. Distribution of malignant lymphoma in Japan: Analysis of 2260 cases, 2001-2006. Pathol Int 2008;58:174-82.
4. Almasri NM. Hodgkins lymphoma in North Jordan. Does it have a different pattern? Saudi Med J 2004;25:1917-21.
5. Naresh KN, Advani S, Adde M, Aziz Z, Banavali S, Bhatia K, *et al*. Report of an International Network of Cancer Treatment and Research workshop on non-Hodgkin's lymphoma in developing countries. Blood Cells Mol Dis 2004;33:330-7.
6. Chakrabarti S, Sarkar S, Goswami BK, Mondal S, Roy A, Das S. Hodgkin's and Non-Hodgkin's lymphomas in an Indian rural medical institution: Comparative clinicopathologic analysis. Asian Pac J Cancer Prev 2010;11:1605-8.
7. Ramani A, Kumar KA, Rao KK, Vidyasagar MS, Kundaje GN. Clinico-pathological profile of lymphomas in south India: A prospective rural referral hospital study of 103 cases. J Assoc Physicians India 1991;39:322-5.
8. Higgins RA, Blankenship JE, Kinney MC. Application of immunohistochemistry in the diagnosis of non-Hodgkin and Hodgkin lymphoma. Arch Pathol Lab Med 2008;132:441-61.
9. Steven HS, Elias C, Nancy LH, Elaine SJ, Stefano AP, Herald S, *et al*. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue. Lyon: IRC Press; 2008.
10. Rao IS. Role of immunohistochemistry in lymphoma. Indian J Med Paediatr Oncol 2010;31:145-7.
11. Haddadin WJ. Malignant lymphoma in Jordan: A retrospective analysis of 347 cases according to the World Health Organization classification. Ann Saudi Med 2005;25:398-403.
12. Turner JJ, Hughes AM, Kricker A, Milliken S, Grulich A, Kaldor J, *et al*. Use of the WHO lymphoma classification in a population-based epidemiological study. Ann Oncol 2004;15:631-7.
13. Akpek G, Seifter EJ, Barowitz MJ. A clinicians guide to the update REA WHO classification of non-Hodgkin's lymphoma: Part II (aggressive lymphoma). Turk J Cancer 2000;30:53-67.
14. Yeole BB. Trends in the incidence of Non-Hodgkin's lymphoma in India. Asian Pac J Cancer Prev 2008;9:433-6.
15. Haddadin WJ. Malignant lymphoma in Jordan: A retrospective analysis of 347 cases according to the World Health Organization classification. Ann Saudi Med 2005;25:398-403.
16. Sukpanichnant S, Sonakul D, Piankijagum A, Wanachiwanawin W, Veerakul G, Mahasandana C, *et al*. Malignant lymphoma in Thailand: Changes in the frequency of malignant lymphoma determined from a histopathologic and immunophenotypic analysis of 425 cases at Siriraj Hospital. Cancer 1998;83:1197-204.
17. Yin HF, Li T, Li JX. Retrospective analysis of 304 cases of malignant lymphomas in pathology: Study and practice of the WHO classification of lymphoid neoplasms. Zhonghua Yi Xue Za Zhi 2003;83:1556-60.
18. Mushtaq S, Akhtar N, Jamal S, Mamoon N, Khadim T, Sarfaraz T, *et al*. Malignant lymphomas in Pakistan according to the WHO classification of lymphoid neoplasms. Asian Pac J Cancer Prev 2008;9:229-32.
19. Getachew A. Malignant lymphoma in western Ethiopia. East Afr Med J 2001;78:402-4.
20. Al-Diab AI, Siddiqui N, Sogiawalla FF, Fawzy EM. The changing trends of adult Hodgkin's disease in Saudi Arabia. Saudi Med J 2003;24:617-22.
21. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: Distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 1998;9:717-20.
22. Naresh KN, Srinivas V, Soman CS. Distribution of various subtypes of non-Hodgkin's lymphoma in India: A study of 2733 lymphomas using REAL and WHO classifications. Hematology 2008;13:163-9.
23. Lee WI, Lee JH, Kim IS, Lee KN, Kim SH. Bone marrow involvement by non-Hodgkin's lymphom. J Korean Med Sci 1994;9:402-8.
24. AlShemmari SH, Ameen RM, Sajnani KP. Extranodal lymphoma: A comparative study. Hematology 2008;13:163-9.
25. Chen WL, Tsai WC, Chao TY, Sheu LF, Chou JM, Kao WY, *et al*. The clinicopathological analysis of 303 cases with malignant lymphoma classified according to the World Health Organization classification system in a single institute of Taiwan. Ann Hematol 2010;89:553-62.
26. Jaffe ES, Zarate-Osorno A, Kingma DW, Raffeld M, Medeiros LJ. The interrelationship between Hodgkin's disease and non-Hodgkin's lymphomas. Ann Oncol 1994;5:7-11.
27. Amini RM, Enblad G. Relationship between Hodgkin's and non-Hodgkin's lymphomas. Med Oncol 2003;20:211-20.