Diagnosis Of Lymphoma With Limited Resources: A Two Year Study

[1]Dr. Vinamrata Soni, [2]Dr. Ashok Yadav, [3]Dr. Shikha Ghanghoria*, [4]Dr. Ashok Panchonia
[1]Resident Medical Officer, [2] Professor, [3] Professor,[4] Professor and Head,
Department of Pathology, Mahatma Gandhi Medical College, Indore, Madhya Pradesh, India

*Corresponding Author:
Dr. Shikha Ghanghoria
Professor, Department of Pathology, Mahatma Gandhi Medical College, Indore, Madhya Pradesh, India

Abstract

Introduction- Lymphoid malignancies are a heterogeneous group of disorders that are generally divided into Hodgkin's lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL). We plan to establish minimal panels of immunohistochemistry for suspected B cell and T cell lymphomas.

Methods and materials- This study was conducted at a tertiary centre in Madhya Pradesh.44 lymphomas were diagnosed during 2 years duration. Cases were initially diagnosed on morphological basis. Consequently, a preliminary panel of monoclonal antibodies using CD3, CD5, CD10, CD15, CD20, CD23, CD30, PAX-5, Tdt , CD45, Cyclin D1 and Bcl2 were employed. Also Ki-67 applied and indexing of prognosis was done.

Results- There were 37 (84.1%) NHL, and 7 (15.9%) HL. Out of 37 NHL cases, 28 cases (75.6%) were of B-Cell Lymphomas and 9 cases (24.4%) of T- Cell Lymphomas. Diffuse large cell B-cell (DLBCL) (20.5%) was highest followed by T cell lymphomas (18.3%) & Follicular lymphoma (11.3%), Extranodal marginal lymphoma (11.3%), Mixed Cellularity Hodgkin Lymphoma comprised (11.3%). Among 7 HL cases, Mixed Cellularity type was highest. 9 (20.4%) cases were Extranodal and Mucosa-associated lymphoid tissue (MALT) lymphoma was the most common subtype. Ki67 expression was related to high-grade lymphoma, expressed in (9/9) of DLBCL than in (7/10) cases of low-grade lymphomas ((3/3) SLL, (1/2) MCL and (3/5) FL with a statistically significant relationship ($p < 0.005$).

Conclusion: For diagnosis and management of lymphoma extended panel application of monoclonal antibodies is required. But as per our study planning of minimum essential markers panel to reach the diagnosis can be done and basic therapy of lymphoma can be started.

Keywords: B Cell Lymphomas, hodgkin's lymphomas, immunohistochemistry

Introduction

In India, approximately 23,718 new NHL cases reported each year. [1] Malignant lymphoma comprises 3.37% of all malignancy worldwide. [2] Incidence of lymphomas increases with age, but Hodgkin's lymphoma has a bimodal incidence curve; that is, it occurs in two separate age groups, the first being in young age (age 15–35) and the second being in those over 55 years old.[3] World Health Organization (WHO) divides lymphomas into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma is further subdivided based on the maturation stage (immature vs. mature) and cell of origin (T cell, B cell, or natural killer cell (NK) cell).[4]With the help of IHC better interpretation of the pathogenesis of lymphomas has become possible and its cautious application helps in identification and the characterization of immune-phenotype in most of the lymphomas.[5] This helps to addresses the three-important role of IHC in the lymphoma – sub-typing, prognostication and potential for targeted therapy in commonly encountered nodal lymphomas (Rituximab for CD 20 positive lymphomas).

1040

Complete knowledge of the type of positivity (membrane, cytoplasmic nuclear) with an awareness of associated caveats is important for the correct sub-typing and differentiating from reactive processes. [6]

The aim of our study is to reduce the panel of markers which is required for diagnosis of lymphoma and to make it cost-effective. Thus all the cases diagnosed as Hodgkin's Lymphoma morphologically were further subjected for immunophenotyping using CD15 and CD30 to study immunoreactivity of Reed-Sternberg cells. Likewise all cases of NHL that were initially diagnosed on morphology were divided into B or T cell type employing pan B cell marker CD20and pan T cell marker CD3 respectively. Thus, we have applied only essential markers to reach the diagnosis so that basic therapy for lymphoma can be started in our hospital.

Methods And Materials

Forty Four cases of Lymphoma were diagnosed in the Department of Pathology, Mahatma Gandhi Memorial Medical College and M.Y Hospital, Indore (Madhya Pradesh) over a period of two years Patients were informed about the importance of the study and consent was taken in all the cases. After obtaining clinical information like age, sex, site of biopsy, specimens which were subjected to tissue processing according to the standard tissue processing protocol. The slides were stained with Haematoxylin and eosin stains and first observed under the light microscope and later immunohistochemistry was done using a panel of markers based on the suspected diagnosis at light microscopy.

IHC Panel Employed in the Study

The panel for antibodies used for immunohistochemistry included monoclonal antibodies to CD45, CD3, CD5, CD10, CD15 , CD20, CD23, CD30, PAX-5, Tdt , Bcl-2 and Ki -67. Panel of antibodies used in a given case was dependent on the morphological evaluation. Immunohistochemistry was performed according to enzyme –antibody conjugate method, after pretreatment of antigen retrieval, by heating in Antigen Retrieval chamber in Tris-EDTA buffer (10 mM Tris base, 1 mM EDTA solution, 0.05% Tween 20, pH 9.0).

Inclusion criteria: All cases suspected on clinical grounds (patients with generalized lymphadenopathy,

long history of lymphadenopathy, and recurrent disease) and through cytological screening were taken into the study.

Exclusion criteria: All known cases which were undergoing treatment, badly preserved specimens and cases of Metastatic deposits in lymph node and reactive hyperplasia were excluded.

Results

There are 44 cases of Lymphoma in the present study. NHL was diagnosed in 37 cases (84.1%) and HL in 7 cases (15.9%).Out of these 44 cases of Lymphoma adult cases were 30 (NHL 27 and HL 3) and pediatric cases (<18yr) were 14 (NHL 10 and HL 4). Male-female ratio was 31:13 = 2.3: 1and the NHL: HL ratio was 5.2.

In our study, among 44 cases of lymphoma, maximum number of male lies between age 50-59 yrs (16%), followed by 30-39 yrs (19%). Among female maximum number of cases lies between age <10 yrs and 50-59 yrs (23%), followed by 10-19 yrs and 60-69 yrs (15%).

NHL

Among 37 cases of NHL 26 patients were males (70.2%) and 11 were females (29.8%) and male to female ratio was 2.3:1. The age of patient ranged from 3 to 78 years. Most common involved age group in NHL was 6th decade (21.6 %). Adult cases were 27 and Paediatric cases were 10.

B-Cell NHL were the predominant type (28 cases) accounting for 76.5% of all cases. T cell NHL constituted 9 cases (24.4%).Among, B-Cell Lymphomas most common cases were of Diffuse large cell B-cell i.e. 9 cases (24.3%) followed by 5 cases (13.5% each) of Follicular lymphoma and Extranodal marginal (MALT) lymphoma. [Table 1] B-cell NHL expressed CD45 and CD20 positivity on immunostaining, while T cell NHL expressed CD45, CD3 and CD5 positivity.

The most common presentation amongst patients was enlargement of cervical and axillary lymph nodes. 25 cases presented with generalized lymphadenopathy. Among 37 cases of NHL 28 cases were nodal. Among nodal cases maximum patients presented with cervical lymph node enlargement accounting for 25 cases (89.2%) followed by axillary nodes 20 cases (71.4%), inguinal nodes 19 cases (67.8%), abdominal

Page1041

nodes (39.2%), polyadenopathy 21 cases (75%), supraclavicular node 1 case (3.5%) .

Among 37 cases of NHL, 34 cases (91.8 %) showed positive Ki-67 expression. Maximum number of cases showed Ki – 67 Score 3 (41%), followed by Ki – 67 score 2 (35%). Ki67 expression was related to high grade lymphoma as it was expressed in (9/9) of DLBCL higher grade lymphoma than in (7/10) cases of low grade lymphomas ((3/3) SLL, (1/2) MCL and (3/5) FL together) with a statistically significant relationship (p<0.005).

Table 1: Distribution of the Types of NHL According to the WHO Classification

NHL Type	Total Number	Percentage
B-Cell Lymphomas		
Diffuse large cell B-cell	9	24.3%
Small Lymphocytic Lymphoma	3	8.1%
Mantle cell Lymphoma	2	5.4%
Follicular lymphoma	5	13.5%
T cell rich B cell Lymphoma	1	2.7%
Extranodal marginal (MALT) lymphoma	5	13.5%
Extranodal diffuse large B cell lymphoma	3	8.2%
T-Cell Lymphomas		
T cell NHL	8	21.6%
Extranodal T cell lymphoma	1	2.7%
Total	**37**	**100.0%**

HL

Out of 7 cases of HL, 5 patients were Males (70.2 %) and 11 were female (29.7 %) with the male: female was 2.5:1. The age of patient ranged from 5 to 55 years with a mean age range of 30 years. Most common involved age group was 1st decade (42.8 %) followed by 6nd decade (28.5%). Adult cases were 3 and Paediatric cases were 4, i.e. paediatric cases were more than adult cases.

All cases of HL were of nodal origin and no extra nodal case was detected in the present study. The most common presentation amongst patients of HL was enlargement of cervical which was present in all patients followed by axillary nodes (3 cases, 42.8%), inguinal node (2 cases, 28.5%) and only 2 cases (28.5%) of HL presented with generalized lymphadenopathy.

Mixed cellularity variant was the commonest type (5 cases, 71.4%). followed by nodular sclerosis (1 case, 14.2%), lymphocytic rich (1 cases, 14.2%) [Table 2]. Reed-Sternberg cells (RS cells) are the diagnostic hallmark cells of HL lymphoma. Classical RS cells are positive for CD15 and CD30. In our study R-S cells in all cases except 3 showed strong immunoreactivity to CD15 and CD30 irrespective of the Histopathological subtype. Out of three cases, two cases diagnosed as Mixed Cellularity and one case diagnosed as Nodular Sclerosis Hodgkins

Lymphoma exhibited CD 30 positive and CD 15 negative immunoreactivity**.**

All 7 cases of HL showed positive Ki-67 expression. All the Mixed cellularity (5 cases) expressed Ki67 with 2 cases showing Score I and 3 cases showing score II. One case of Nodular sclerosis expressed Ki-67 with Score I and one case of Lymphocyte rich expressed Ki-67 with Score II.

Table 2: Histopathologic distribution of 7 cases of HL

Type	Total Number of cases (%)	CD 15 +	CD 30 +
Mixed Cellularity	5(71.4%)	3	5
Nodular Sclerosis Hodgkins Lymphoma	1(14.2%)	-	1
Lymphocyte rich	1(14.2%)	1	1

Extranodal NHL

Lymphoma cases were also classified according to site, Nodal and Extranodal. Out of 44 cases 35(79.5%) cases were Nodal and 9 (20.4%) cases were Extranodal cases .Amongst the extra nodal cases, most cases were presented as intra-abdominal lump 4(44.4%) (three were small intestine mass and one was colonic mass presented as per rectal bleeding) followed by 2 (22.2%) cases which were seen as retroperitoneal mass and remaining 3 cases (11.1% each) presented as stomachache, swelling at submandibular region and mediastinal mass.[Table 3]

Table 3: Extranodal NHL Distribution According to The Primary Site and histological typing

Extranodal site of NHL	Total Number	Percentage	Morphology
Intestine (small and large)	4	44.4 %	All MALT lymphomas
Stomach	1	11.1%	MALT lymphomas
Retroperitoneal region	2	22.2 %	Two Diffuse large B cell lymphoma
Submandibular swelling	1	11.1 %	Diffuse large B cell lymphoma
Mediatinal mass	1	11.1 %	T cell Lymphoma

Most common histopathological subtype of NHL in extranodal sites, in the present study, is mucosa-associated lymphoid tissue (MALT) lymphoma. Out of nine cases of extranodal lymphoma six are males and three are females. The ratio between males and females was 2:1. The maximum cases were in the age group 10-19 and 50-59 years (2 each). The males were commonly affected than females. Four cases were in the Paediatric age (<18 yrs).

Identified five lymphomas that had very characteristic morphology and thus required a short panel of immunostains to confirm the diagnosis. These included the following:

1. Suspected small lymphocytic lymphoma (SLL): the characteristic presence of proliferation centers and cytological features. Confirmation of SLL with CD20 (positive), CD5 (positive), CD23 (positive), CD10 (negative), and cyclin D1 (negative).

2. Suspected mantle cell lymphoma (MCL): the characteristic monomorphic centrocyte

cytology and mantle zone pattern. Confirmation of MCL with CD20 (positive), CD5 (positive), and cyclin D1 (positive).

3. Suspected follicular lymphoma (FL): characteristic prominent follicular pattern and with presence of centrocytes along with variable numbers of centroblasts. Confirmation of FL with CD20 (positive), CD5 (negative), CD10 (positive), BCL2 (positive), and cyclin D1 (negative).

4. Suspected DLBCL: characteristic presence of sheets of large cells with morphology of centroblasts or immunoblasts. Confirmation of DLBCL with CD20 (positive), CD5 (negative), CD10 (+/-), TdT(negative) and Ki67 (high proliferation rate, >50%).

5. Suspected Burkitt lymphoma (BL): characteristic diffuse infiltration of monomorphic, medium size cells with abundant basophilic cytoplasm, non-cleaved round nuclei with coarse chromatin and 2 - 5 distinct nucleoli, starry sky pattern, and high mitotic rate. Confirmation of BL with CD20 (positive), CD10 (positive), BCL2 (negative), terminal deoxynucleotidyl transferase (negative), cyclin D1 (negative), and Ki67 (high proliferation rate, 100%).

Discussion

Lymphoid malignancies are a heterogeneous group of disorders that are generally divided into HL and NHL. Diagnosing lymphoid malignancies based on morphology in combination with immunohistochemistry (IHC) forms the basis of WHO classification and this has prognostic implications. Thus, the application of a preliminary panel of antibodies in conjunction with morphological diagnosis enabled us to primarily classify NHL into B or T cell types and further subtype each type. With this background, this study was designed thus including all the lymphoid malignancies both NHL and HL. Thus this study was planned. Also, Immunophenotyping provided to be useful in cases where a final diagnosis could not be made on morphology alone.

In the present study, 44 cases of lymphomas were studied for their morphology and immunophenotype. Diagnosis of HL is made by the identification of RS cells in an appropriate reactive milieu comprising small lymphocytes, histiocytes, epithelioid histiocytes, neutrophils, eosinophils, plasma cells and fibroblasts in different proportions. In most of the cases, HL can be diagnosed morphologically. However, application of immunophenotyping has enabled the recognition of subgroup.

The ratio of incidence of NHL- HL is inconsistent among European and Asian countries. The ratio of NHL-HL is 3.69 in the USA and 4.47 in European Union. [7, 8] In the present study, the ratio is 5.2 i.e. 84.1% of NHL and 15.9 % of HL which was similar to the findings of Mondita et al i.e., 4.2. [9]

B-cell lymphoma cases outnumbered T-cell lymphoma cases. Similar results have also been reported by Naresh et al. [10] Aparna et al.[11] Among, B-Cell Lymphomas the most common cases were of DLBCL i.e. 9 cases (24.3%) followed by 5 cases (13.5% each) of Follicular lymphoma ,Small Lymphocytic Lymphoma (8.1%), Mantle cell Lymphoma (5.4%), and T cell rich B cell Lymphoma (2.7%). Extranodal marginal zone B-Cell Lymphomas (MALT) which accounted for 5 cases (13.5%) and Extranodal diffuse large B cell Lymphoma which accounted for 3 cases (8.2%). B-cell NHL expressed CD45 and CD20 positivity on immunostaining, while T cell NHL expressed CD45, CD3, and CD5 positivity. The present study showed DLBCL is the most common subtype (24.3%) which is comparable to the USA and Europe (25-30%).[12,13] The trend is similar in Jordan (28.2%).[14] Roy et al., [15] and Kalyan et al., [16] too revealed DLBCL to be the most common subtype of NHL comprising 29.3% [13] and 26% [11] of cases respectively.

FL was the second most common subtype of NHL (13.5%) in our study, which is comparable to other Indian studies done by Mondal, et al., [17] which showed 67 cases, (19.3%) of FL. FL represents about 20% to 25% of cases of NHL in the U.S. and Europe [18].In Western studies, a higher proportion is noted (28-32%). Incidence of FL (4-8%) was reported to be lower from Saudi Arabia, Egypt, UAE, North Jordan, and Pakistan. [19, 20]

Among 7 HL lymphoma cases, the maximum cases were of Mixed Cellularity 5(71.4%) followed by Nodular Sclerosis Hodgkins Lymphoma 1(14.2%) and Lymphocyte rich 1(14.2%). Classical RS cells

are positive for CD15 and CD30. In our study, irrespective of the Histopathological subtype, R-S cells in all cases except 3 showed strong immunoreactivity to CD 15 and CD30. Out of three cases, two cases were diagnosed as Mixed Cellularity and one case diagnosed as Nodular Sclerosis Hodgkins Lymphoma exhibited CD 30 positive and CD 15 negative immunoreactivity. Our findings were similar to a study done by Mondal, et al. [17] and Chakrabarti S et al. [21] they revealed that the commonest histological subtype in HL was mixed cellularity.

Among NHL cases, cervical lymph node was the most common site (25 cases, 89.2%) followed by axillary nodes ,inguinal nodes, abdominal nodes and supraclavicular node .Camille Laurent [22] in their study revealed that the most frequently involved sites were cervical lymph nodes (36.8% of all cases), followed by inguinal lymph nodes and others.

Among HL, all patients presented with cervical node enlargement followed by 3 cases (42.8%) of axillary node, 2 cases (28.5%) of inguinal node, and 2 cases (28.5%) of polyadenopathy. Aparna Bhardwaj, et al. [11] and Camille Laurent, [22] in his study showed the commonest site of involvement was cervical region followed by axillary region.

ENL are common and accounted for 24.3% of lymphoid malignancy cases. This figure is close to the incidence in the USA (26%), and slightly lower than Jordan (30.5%).Our study showed that the GIT is the predominant site of extranodal NHL accounting for almost 44.4% of all primary extranodal NHL ,which is fairly correlated with the findings of Kroll A.D. G. et al.[23] and Chen WL et.al.[24] However, head and neck region including waldeyer's ring have been reported to be the most common sites of origin of ENL in done by Yang QP et al.[25]

The most common histopathological subtype of NHL in extranodal sites, in the present study, was mucosa-associated lymphoid tissue (MALT) lymphoma followed by DLBCL. Abbondanzo S.L. &Sobin L.H.[26] and Yoon S.et al.[27] studies showed that MALT lymphoma was the majority group of cases among primary gastrointestinal tract lymphoma ,our finding was comparable with their study.Our findings were different from study of Arora et al., [28]and Mondal et al. [17] in their study diffuse large B-cell lymphoma (DLBCL) was the commonest subtype .

Ki67 expression was related to high-grade lymphoma as it was expressed in (9/9) of DLBCL higher-grade lymphoma than in (7/10) cases of low-grade lymphomas ((3/3) SLL, (1/2) MCL and (3/5) FL together) with a statistically significant relationship (p<0.005)

Afaf T Elnashar et al. [29] in their study showed thatKi67 was expressed in 82.8 %, (74/90) of the studied cases of NHL. All the DLBCL lymphoma (48 cases) expressed Ki67 with a strong relationship between over-expression of the proliferation marker (Ki67) and both the higher histological grading (p<0.001) and advanced clinical stage (p< 0.005) of the disease.

Conclusion

Though lymphomas can be confidently diagnosed on morphology, the application of monoclonal antibodies and identification of immunophenotypic profile has enhanced the diagnostic accuracy. So we have applied minimum essential markers to reach the diagnosis, by doing this we can start the basic therapy of lymphoma. As India is a developing country with major population of low socio-economic status, the purpose of our study, was to reduce the panel and to make it cost-effective, so that poor patients can be benefited. Further, the immunophenotyping of lymphoid tumors is now considered to be vital for better management, prognosis, and for routine pathological evaluation of lymphoproliferative disorders.

References

1. Yeole BB. Trends in the incidence of Non-Hodgkin's lymphoma in India. Asian Pac J Cancer Prev. 2008;9(3):433

2. Huh J. Epidemiologic overview of malignant lymphoma. Korean J Hematol. 2012 Jun;47(2):92-104. doi: 10.5045/kjh.2012.47.2.92. Epub 2012 Jun 26. PMID: 22783355; PMCID: PMC3389073.

3. *Mauch P, Armitage J, Diehl V, et al. Hodgkin's Disease.* Lippincott Williams & Wilkins. *pp. 62–64.* ISBN 0-7817-1502-4.Jaffe ES, Harris NL, Stein H, et al. Introduction and overview of the classification of the lymphoid neoplasms. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours

of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008:158-166.

4. Jaffe ES, Harris NL, Stein H, et al. Introduction and overview of the classification of the lymphoid neoplasms. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008:158-166.

5. Higgins RA, Blankenship JE, Kinney MC. Application of immunohistochemistry in the diagnosis of non-Hodgkin and Hodgkin lymphoma. Arch Pathol Lab Med. 2008;132(3):441–61.

6. Rao SI. Role of immunohistochemistry in lymphoma. Indian J Med PaediatrOncol. 2010;31(4):145–47.

7. Greiner TC, Mederios LJ. Jaffe E.S. Non Hodgkin's Lymphoma. Cancer. 1995;75:370-380.

8. Medeiros LJ, Greiner TC. Hodgkin's disease. Cancer. 1995 Jan 1;75(1 Suppl):357-69.

9. MonditaBorgohain et al, Spectrum of Malignant Lymphoma in a Tertiary Care Hospital of North Eastern India. Annals of Pathology and Laboratory Medicine. 2018 March;5(3):188-193.

10. Naresh KN, Srinivas V, Soman CS. Distribution of various subtypes of non-Hodgkin's lymphoma in India: a study of 2773 lymphomas using R.E.A.L. and WHO Classifications. Ann Oncol. 2000;11 Suppl 1:63-7. PMID: 10707782.

11. Bhardwaj Aparna, Kishore Sanjeev, KusumAnuradha. Morphological Typing of Lymphomas with Immunohistochemistry. Indian Medical Gazette. 2015 Apr; 149 (4): 127-133.

12. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011 May 12;117(19):5019-32. doi: 10.1182/blood-2011-01-293050. Epub 2011 Feb 7. PMID: 21300984; PMCID: PMC3109529.

13. 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

14. 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.

15. Roy A, Kar R, Basu D, Badhe BA. Spectrum of histopathologic diagnosis of lymph node biopsies: A descriptive study from a tertiary care center in South India over 5½ years. Indian J PatholMicrobiol. 2013;56:103-8.

16. Kalyan K, Basu D, Soundararaghavan J. Immunohistochemical typing of non-Hodgkin's lymphoma-comparing working formulation and WHO classification. Indian J PatholMicrobiol. 2006 Apr;49(2):203-7. PMID: 16933715.

17. Mondal SK, Mandal PK, Samanta TK, Chakaborty S, Roy SD, Roy S. Malignant lymphoma in Eastern India: A retrospective analysis of 455 cases according to World Health Organization classification. Indian J Med PaediatrOncol 2013;34:242-6.

18. Salles G. Clinical features, prognosis and treatment of follicular lymphoma. *Hematology. American Society of Hematology. Education Program. 2007: 216-25.*

19. 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.

20. 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

21. 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.

Page 1046

22. Laurent C, Do C, Gourraud PA, de Paiva GR, Valmary S, Brousset P. Prevalence of Common Non-Hodgkin Lymphomas and Subtypes of Hodgkin Lymphoma by Nodal Site of Involvement: A Systematic Retrospective Review of 938 Cases. Medicine (Baltimore). 2015 Jun;94(25):e987. doi: 10.1097/MD.0000000000000987. PMID: 26107683; PMCID: PMC4504656.

23. Kroll AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol. 2003 Jan;14(1):131-9. doi: 10.1093/annonc/mdg004. PMID: 12488305.

24. 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.

25. Yang QP, Zhang WY, Yu JB, Zhao S, Xu H, Wang WY, et al. Subtype distribution of lymphomas in Southwest China: Analysis of 6,382 cases using WHO classification in a single institution. DiagnPathol 2011;6:77.

26. Abbondanzo S.L. Sobin L.H. Gastric ''Pseudolymphoma'' A Retrospective Morphologic and Immunophenotypic Study of 97 Cases. CANCER. 1997; 79: 9, 1656 – 63

27. Yoon SO,SuhC,LeeDH,Chi H-S,ParkCJ,Jang S-S.et al. Distribution of lymphoid neoplasms in the Republic of Korea: Analysis of 5318 cases according to the World Health Organization classification. Am. J. Hematol. 2010; 85:760–4.

28. Arora N, Manipadam MT, Pulimood A, Ramakrishna BS, Chacko A, Kurian SS, Nair S. Gastrointestinal lymphomas: pattern of distribution and histological subtypes: 10 years experience in a tertiary centre in South India. Indian J PatholMicrobiol. 2011 Oct-Dec;54(4):712-9. doi: 10.4103/0377-4929.91502. PMID: 22234096.

29. Afaf T Elnashar, Omar A El-Tabry. The Prognostic Value Of Cd44v6 And Ki67 In B-Cell Non Hodgkin Lymphoma. Al-Azhar Med. J. 2012 April; 41(2).

Page 1047