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Original Article

Lymphoma Distribution Trends from Single Institute of Pakistan: Spectrum of 212 Cases

Durr-e-Sameen Kamran*, Hira Salam, Uzma Bukhari* and Shaheen Sharafat*****

*Department of Pathology, **Department of Oral Pathology, ***Basic Medical Sciences, DIMT, Dow Diagnostic, Research & Reference Laboratory. Dow University of Health Sciences, Ojha Campus, Karachi, Pakistan

Abstract:

Objective: Lymphoid neoplasms encompass an enormous group with diverse subtypes. The incidence is contrastingly diminished in developing countries. Pakistan lacks a national cancer registry for exact characterization of statistics. The objective of this study was to draw histopathological spectrum of lymphoma subtypes diagnosed and characterized at Histopathology section of Dow University of Health Sciences, Karachi.

Methods: Every lymphoma case diagnosed at Dow Diagnostic Reference and Research Lab and Dow University of Health Sciences Karachi during study period (January 2014 – December 2015) was included without exception. Pertinent clinicopathological information was entered in a proforma. Paraffin-embedded tissue blocked were retrieved from histopathology archives and cross-examined. Data was analyzed using SPSS 16.0.

Results: Out of 212 lymphoma cases, 79% were of Non-Hodgkin Lymphoma (NHL) and 21% were of Hodgkin Lymphoma (HL). Diffuse Large B-cell Lymphoma (DLBCL) was the prevalent subtype. Nodular Sclerosis (NS) dominated the HL class. Mean age at onset was significantly higher for NHL ($p<0.01$). Male to female ratio was 1.7:1. Cervical lymph nodes are most frequently involved site for primary nodal lymphomas, whereas GIT is predominantly involved by extra-nodal group.

Conclusion: Lymphomas render a considerable measure of morbidity and mortality globally. Due to pronounced heterogeneity in divergent subtypes, their prevalence also varies and hinders understanding of etiologic factors. Epidemiologic studies are paramount for improving our understanding and subsequent delivery of healthcare. We have described the spectrum of lymphoma as registered in one hospital in Pakistan. More studies from developing countries on broader scale are imperative for streamlining future research goals.

Keywords: Lymphoma, HL, NHL, WHO, spectrum.

Introduction

Lymphoma is an all-encompassing term for a diversified group of lymphoid malignancies displaying heterogenous biological and morphological characteristics, and multifarious clinical outcomes [1]. They originate from neoplastic transformation of lymphoid cells at various stages of differentiation [2]. Several classification schemes have persisted and undergone rapid evolution to establish a standard for categorization of this vast group of malignancies [3-6]. Lack of a universal classification system posed greatest challenge to epidemiological studies [2].

AUTHOR'S CORRESPONDENCE:
Dr. Hira Salam
BDS, MDS Trainee (Oral Pathology)
E-mail: hirasalam@gmail.com

In 1994, the International Lymphoma Study Group (I.L.S.G) published the 'Revised European-American Classification of Lymphoid Neoplasms' (REAL)[6]. Following popular adaptation of REAL classification, the WHO classification of hematologic and lymphoid neoplasms was first published in 2001[4]. With expansion of scientific knowledge, updates to the WHO classification with refinement of existing definitions and addition of new entities and variants have been published in 2008, and latest in 2016[3, 7].

Lymphomas are primarily categorized into two broad groups: Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL)[3]. NHL surpasses HL both, in number of subtypes encompassed, as well as in contribution to the overall disease burden[8].

Geographical variations exist in lymphoma incidence with NHL reportedly more common in developed countries[9, 10]. Incidence of malignant lymphomas has inflated by 3-4% globally, of interest however, is

not yet apprehended lower incidence in East Asia[10]. The precise rationalism for observed trends remains to be explicitly exemplified. A few factors that have been contemplated as prospective culprits include improved diagnostic accuracy, AIDS epidemic, increased prevalence of high age group in population, and various cancer-promoting behavioral factors[10].

Deficiency of a national cancer database massively encumbers exact characterization of cancer statistics from Pakistan. Isolated public and private sector hospital-based and provincial level studies have been published, however, and report an increase in NHL incidence over past two decades[9, 11-14]. This study has been undertaken with the aim to ascertain lymphoma distribution in Pakistani population and compare it with trends reported in previous studies from Pakistan as well as those from other parts of the world. With this cross-sectional study, we aspire to delineate histopathological spectrum of lymphoma subtypes diagnosed and characterized (per revised 2008 WHO classification of hematologic and lymphoid malignancies) at Histopathology section of Dow University of Health Sciences, Karachi, Pakistan over a period of two years.

Material & Methods

This cross-sectional study was conducted at Histopathology section of Dow Diagnostic Reference and Research Lab (DDRRL), Dow University of Health Sciences (DUHS), Karachi. After obtaining exemption from the Institutional Review Board (IRB), patients' records were retrieved from archival data spanning over a period of two years from January 2014 to December 2015. Every patient diagnosed with lymphoma during study period was included in the study. Patients' demographic data, including age and gender, as well as pertinent clinical information, such as tumor site, was retrieved from archives and recorded in specifically designed Proforma. Participants were stratified into four groups per their age at diagnosis (Figure 1).

Formalin-fixed and paraffin-embedded (FFPE) tissue blocks were retrieved from histopathology archives for each case selected. Slides were prepared using standard Hematoxylin and Eosin (H&E) protocol and analyzed for morphology and provisional diagnosis. Immuno-histochemical (IHC) staining was used for characterization of subtype as previously described[16]. IHC staining against CD45 (leukocyte common antigen or LCA) was used to ascertain lymphoid lineage. CD 20, CD79a and PAX-5 were used for highlighting B-cells. CD3 was used to delineate T-cells. Proliferation index was estimated in percentage using Ki-67/Mib-1. A large panel of antibodies was used, as needed to distinguish specific subtype. These included CD15, CD30, BCL2, BCL6, CyclinD1, CD5, CD10, CD23, TdT, and Mum-1 etc.

Data was gathered and listed in SPSS version 16.0 for statistical analysis. In following section, 1.3 we have presented our results as mean +/- standard deviation. Student's t-test was used for comparison of means keeping P-value <0.05 as significant

Results

A total of 212 lymphoma cases were diagnosed and categorized in accordance with 2008 WHO classification of lymphoid malignancies during the study period (Jan 2014 – Dec 2015). More than half of these cases were recorded in men (n=135). Peak incidence was observed in > 40 years' age group in both genders (Mean age in men = 39.42 +/- 20.73, women = 38.62 +/- 16.61) (Figure 1).

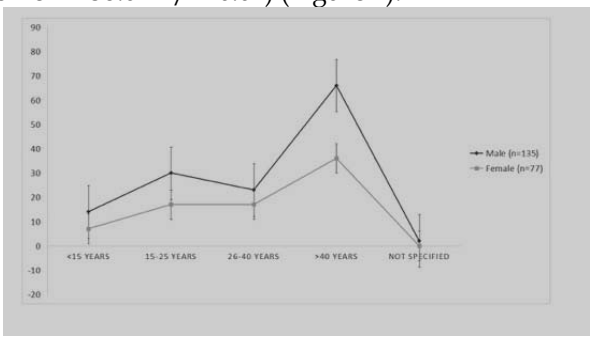

Figure 1: Age and gender distribution of all lymphoma cases. Each group exhibits a comprehensive male predominance. People above 40 retain strongest predisposition.

Out of 212, majority of the cases were of NHL (n=168) type. In the NHL group, diffuse large B-cell lymphoma (DLBCL) was most frequently diagnosed (n= 100). Trend was similar in both genders. Most of the subtypes exhibited a slight male preponderance, except marginal zone lymphoma of MALT (n=3) and follicular lymphoma (n=8) (Table 1).

In HL group (n=44), nodular sclerosis (NS) variant of classic HL was the predominant subtype (n=38). Statistically significant difference was observed using *t-test* between mean age at diagnosis of NHL (Mean age = 42.9 +/- 18.4 years) and HL (Mean age = 24.47 +/- 15) ($p<0.001$) (Table 1).

Table 1. Distribution of various WHO lymphoma subtypes according to mean age and gender.

Lymphoma	Number of Cases	Proportion	Mean Age (Minimum-Maximum Range)	Sex Ratio M/F	Number of Male Cases	Number of Female Cases
Hodgkin Lymphoma (HL)	44	20.75%	24.47 (3-58)	3:1	33	11
Mixed cellularity classical HL	6	13.6%	19.67 (10-27)	5:1	5	1
Nodular Sclerosis classical HL	38	86.4%	25.24(3-58)	2.8:1	28	10
Non-Hodgkin Lymphoma (NHL)	168	79.25%	42.9 (1-85)	1.54:1	102	66
B-cell lymphoma	149	88.7%	44.5 (1-85)	1.5:1	90	59
T-cell lymphoma	19	11.3%	27.5 (13-60)	1.7:1	12	7
Diffuse large B-cell lymphoma	100	59.5%	43.72(1-85)	1.32:1	57	43
Lymphoblastic lymphoma – T-cell	17	10.1%	22.92 (13-38)	1.43:1	10	7
Lymphoblastic lymphoma – B-cell	3	1.8%	45.33 (17-64)	3:0	3	0
Chronic lymphocytic leukemia	14	8.3%	54.77 (40-70)	2.5:1	10	4
Mantle cell lymphoma	5	3%	68 (60-80)	5:0	5	0
Follicular lymphoma	8	4.7%	48.5 (7-60)	0.6:1	3	5
MALT lymphoma	3	1.8%	58 (50-65)	0:3	0	3
Burkitt's lymphoma	8	4.7%	25.44 (8-42)	3:1	6	2
Anaplastic large cell lymphoma	8	4.7%	37.45 (5-82)	3:1	6	2
Peripheral T-cell lymphoma	2	1.2%	42.33 (12-60)	2:0	2	0

Majority (65%) of the cases were primary nodal lymphomas. Cervical lymph node was the most frequently recorded site for former (n=64), followed by inguinal (n=17), and axillary lymph nodes (n=15). Amongst the extra-nodal (27%) group, stomach (n=11) was the most frequently noted site whereby DLBCL was the predominantly recorded type (n=10), remainder case being of MALT lymphoma (Figure 2) (Table 2).

Table 2: Distribution of primary extra-nodal lymphoma sites according to mean age, gender ratio, and lymphoma subtypes. DLBCL – Diffuse large B-cell lymphoma, ALCL- Anaplastic large cell lymphoma, T-LL- Lymphoblastic lymphoma T-cell, FL- Follicular lymphoma, BL- Burkitt's lymphoma, MCL- Mantle cell lymphoma, B-LL- Lymphoblastic lymphoma – B-cell

Site	Total	Mean Age	Sex Ratio M/F	DLBCL	ALCL	T-LL	FL	BL	MALT	MCL	B-LL
GIT	17	42.4	2.4:1	15	0	0	0	1	1	0	0
Oral Cavity (including salivary gland)	11	47.4	2.6:1	8	1	0	1	0	0	0	1
Mediastinum (including chest wall)	8	40.5	7:1	3	1	3	0	0	0	1	0
Others	22	53.2	1:1	17	1	1	0	3	0	0	0

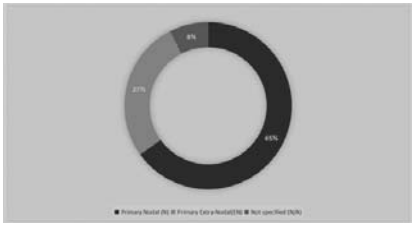

Figure-2: Site distribution of all cases. Primary nodal lymphoma predominates, but 27% occur in extra-nodal tissues.

Discussion

Cancer is the second leading cause of death after heart disease[8]. According to recently published statistics from US, NHL is 6th most commonly diagnosed malignancy in both men and women, encompassing ~ 4-5% of all tumors[8]. It is also held accountable for 4% of all cancer related deaths recorded in 2016 in men and 3% in women[8]. In up to 39 years' age group, NHL is amongst top five leading causes of cancer mortality. Survival rate for NHL has increased over

past 4 decades from 47% (1975-1977) to 72% (2005-2011)[8]. In a recently published study from Pakistan, however, NHL was 9th most frequently recorded malignancy in both genders and HL ranked at 12th hinting support for claim that lymphoid malignancies are relatively more prevalent in the West. Despite their predisposition for older age group, lymphoid neoplasms constitute two-thirds of cancers in children[17].

Owing to marked heterogeneity that exists in this group of neoplasms, the risk factors are also varied and not very well established for every subtype[18]. T/natural killer (NK) cell neoplasms, for instance have an established association with Epstein Barr virus (EBV) and are relatively more prevalent in Asia[19]. Both, immune suppression (HIV/AIDS, or post-transplant), and immune activation (chronic infections and inflammatory conditions) contribute to malignant transformation of B-cells[18]. Certain life-style factors (e.g., smoking and obesity) have been reported to augment risk of follicular lymphoma (FL) and DLBCL, respectively[18]. Interestingly, a recent study reported widowed individuals to be at greater risk of cancer specific mortality due to HL[20].

In our study, 79% of lymphoma cases were NHL and 21% HL. This trend is consistent with various other studies, including study by Ye Xibiao et al.[21], (90% NHL 6% HL), Waravita TS et al., (84.6%NHL, 15.4%HL)[1], Jian Sun et al., (91%NHL, 8.6%HL)[15], and Shahid R et al., (75% NHL, 25% HL)[12].

We noted a significant male predominance (male to female ratio: 1.7:1) which is also consistent with previous reports[1, 12, 15]. NHL occurred with peak incidence in >40 years age group (mean age at diagnosis= 42.9) irrespective of gender. The incidence of HL was, however recorded in relatively younger age group (mean age at diagnosis= 24.7) in both genders. Results are comparable with previous studies[1, 12, 15, 17].

In present study, DLBCL comprised 59.5% of all NHL cases diagnosed. This figure is slightly inconsistent with previously published results by Waravita T S et al., (38.3%), Jian Sun et al., (36.2%), and Madhu P et al., (30-40%). Notwithstanding this slight discrepancy in relative percentage, DLBCL was still the predominant subtype in aforementioned studies[1, 15, 22]. Our results are, however consistent with previous studies from Pakistan by Shahid R et al., (69.95%), and Bukhari U et al., (58.8%)[9, 12].

In the HL group, we have recorded NS variant as predominant (86.3% of all HL). This is inconsistent with previous studies that have reported mixed cellularity HL as predominant subtype[1, 12, 15].

In the extra-nodal group, DLBCL the predominant subtype, consistent with previous studies[1, 9, 15]. Gastrointestinal tract (GIT) has been reported in previous studies to be most common site for primary extra-nodal lymphoma, a finding consistent with present study whereby stomach was the most frequent site[9, 15]. In contradiction to this finding, however, Waravita et al., have reported skin as most frequent site for extra-nodal lymphoma, followed by GIT[1]..

Conclusion

Lymphomas render a considerable measure of morbidity and mortality globally. Due to pronounced heterogeneity in various subtypes, their prevalence also varies and hinders understanding of etiologic factors. Epidemiologic studies are paramount for improving our understanding and subsequent delivery of healthcare. We have described the spectrum of lymphoma as registered in one hospital in Pakistan. More studies from developing countries on broader scale are imperative for ascertaining future research goals.

Conflicts of Interest: None to declare.

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CONTRIBUTION OF AUTHORS	
Author	**CONTRIBUTION**
Yasir Adnan	
Lubna Noor	
Muhammad Habeel Dar	
Haris Adnan	
Muhammad Hafizullah	

KEY FOR CONTRIBUTION OF AUTHORS:

A. Conception/Study Designing/Planning
B. Experimentation/Study Conduction
C. Analysis/Interpretation/Discussion
D. Manuscript Writing
E. Critical Review
F. Facilitated for Reagents/Material/Analysis

ABBREVIATIONS:

NHL – Non-Hodgkin Lymphoma
HL- Hodgkin Lymphoma
DLBCL- Diffuse Large B-cell Lymphoma
NS – Nodular Sclerosis, Hodgkin Lymphoma
GIT- Gastrointestinal Tract
EN- Extra-nodal
DDRRL – Dow Diagnostic Reference & Research Lab