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Small B Cell Non-Hodgkins Lymphoma in Pakistan

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Original Article

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Abstract

Objective: To study the pattern of small B cell lymphomas in Pakistan.

Methods: This descriptive study was carried out at the Aga Khan University Hospital pathology department including 1721 cases of Non-Hodgkins Lymphoma (NHL) diagnosed during a period of five years (1998-2002) and classified according to REAL/WHO classification. The antibodies used included Leukocyte Common Antigen (LCA), Pan B (CD20, CD79a), Pan T (UCHL-1), Bcl 2, Mib 1(Ki 67) and Cyclin D1 (Dako, Denmark).

Results: Out of the 1721 NHL cases, only 140 (8.1%) could be categorized as small B-cell NHL. The study group comprised small lymphocytic lymphoma/chronic lymphocytic leukemia (58 cases; 41.4%) followed by follicular lymphoma (46 cases; 32.9%), mantle cell lymphoma (15 cases; 10.7%), extra nodal marginal zone B cell lymphoma of MALT type (15 cases; 10.7%), lymphoplasmacytic lymphoma (5 cases; 3.6%) and splenic marginal zone B-cell lymphoma (1 case; 0.7%). No case of nodal marginal zone lymphoma was diagnosed.

The age ranged from 18 to 98 years with a mean and median of 54.64 and 58.50 years respectively. Small B-cell NHL was more common in males; with male to female ratio of 2.1. Majority of the small B-cell NHL were nodal at presentation with a nodal to extranodal ratio of 3.4.

Conclusion: It is concluded that the frequency of these small B-cell NHL is very low in our population in contrast to the western literature. Further studies based on epidemiologic and etiological factors are required to look into this marked difference of occurrence of these indolent lymphomas (JPMA 56:22;2006).

Introduction

In 1994, the International Lymphoma Study Group proposed a Revised European American Lymphoma (REAL) classification for lymphoid neoplasm. This classification system was developed because new lymphoid disease entities were recognized that were not part of the National Cancer Institute (NCI) Working Formulation (WF) and there was a growing need to develop a common classification system that could be used internationally.[1]

The REAL classification and the derived World Health Organization (WHO) classification are structured to

mirror normal B/T cell differentiation.[2] In these modern classifications distinct disease entities are defined based on the combination of morphology, immunological and molecular techniques and clinical features.[2,3] As defined in the proposed WHO classification of neoplastic diseases of the hematopoietic and lymphoid tissues, the small B cell lymphomas include B cell small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), mantle cell lymphoma (MCL), follicular lymphoma (FL), lymphoplasmacytic lymphoma (LPL), extra nodal marginal zone B cell lymphoma of MALT type (MALT-L), nodal marginal zone B-cell lymphoma (NMZL), and splenic marginal zone B-cell lymphoma (SMZL).

The ability to diagnose and distinguish the types of small B-cell lymphoid neoplasms is extremely important because of differences in presentation, treatment options, clinical course and prognosis. The small B cell lymphomas are among the best examples of how malignant lymphomas can be related to the normal immune system.[4] Immunophenotypic analysis is critical in categorizing small B-cell neoplasms and numerous paraffin-reactive antibodies are available for differentiating these neoplasms.[5-7]

The WHO has made a conceptual grouping of non Hodgkin's lymphoma (NHL) into four categories (indolent, aggressive, highly aggressive and localized indolent). Except extra marginal zone B-cell lymphoma of MALT type all other small B-cell lymphomas are grouped as indolent lymphomas. Mostly these are diseases of older adults, almost always above the age of 40 years. Extra nodal marginal zone MALT type is grouped in the localized indolent lymphomas and occur at any age.[8] One study showed that these indolent lymphomas represent 40-50% of all NHL.[9] As a group small cell NHLs are relatively uncommon in Pakistan and are therefore not widely studied particularly according to the guidelines of REAL/WHO classification.[10-13]

The objective of this study is to determine the pattern of small B cell lymphomas in Pakistan.

Patients and Methods

This descriptive study was carried out at the Aga Khan University Hospital (AKUH) pathology department. The study included 1721 cases of Non-Hodgkin lymphoma (NHL) which were diagnosed in the section of histopathology during a five years period (1998-2002).

The pathology department receives surgical specimens from the AKUH in Karachi and through 65 pathology laboratory collection points in Pakistan. It covers a large geographical area, with collection points located in all major cities like Karachi, Hyderabad, Multan, Lahore, Quetta, Peshawar, Islamabad, Rawalpindi, Larkana and also many rural locations. Quality control for diagnostic pathology at AKUH is maintained through internal and external quality checks. External quality assurances for diagnostic pathology are maintained by the College of American Pathologists (CAP) surveys. Internal quality assurances are maintained by the use of histochemical stains and immunohistochemical techniques. Biological markers are used for malignancies, which necessitated cellular typing and subtyping. The departmental consensus committee confirms the diagnosis.

All specimens for the present study were grossed, processed and initially evaluated on Hematoxylin and Eosin (H&E) stained sections. Subsequently immunohistochemical analysis was performed by employing envision technique. The antibodies used in immunohistochemical staining included Leukocyte Common Antigen (LCA), Pan B (CD20, CD79a), Pan T (UCHL-1), Bcl 2, Mib 1(Ki 67) and Cyclin D1 (Dako, Denmark). Parallel positive and negative controls were always run with each new batch of staining.

All the cases were characterized on the basis of morphology and immunohistochemical features and classified according to REAL/WHO classification of lymphoid neoplasms. The following entities were recognized, small lymphocytic lymphoma/leukemia (SLL/CLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), extra nodal marginal zone B-cell lymphoma of MALT type (MALT-L), lymphoplasmacytic lymphoma (LPL), nodal marginal zone B-cell lymphoma (NMZL) and splenic marginal zone B-cell lymphoma (SMZL).

Demographic variables recorded were the hospital patient-number, date, name, age, sex, address, topography, morphology, and grading. The cases were categorized by tumor site, age and sex of the patient. The data obtained was analyzed using SPSS version 12.5.

Results

A total of 1721 NHLs were diagnosed during the study period of five years (1998-2002) according to REAL/WHO classification and out of these only 140 (8.1%) were in the category of small B-cell NHL. The study group comprised SLL/CLL (58 cases; 41.4%) followed by FL (46 cases; 32.9%), MCL (15 cases; 10.7%), MALT-L (15 cases; 10.7%), LPL (5 cases; 3.6%) and SMZL (1 case; 0.7%). No case of nodal marginal zone lymphoma was diagnosed (Table 1).

The age ranged from 18 to 98 years with mean and median of 54.64 and 58.50 years respectively. As a group small B-cell NHL were more common in males as compared to females; with male to female ratio of 2.1. Majority of small B-cell NHL were nodal at presentation with a nodal to extranodal ratio of 3.4. In 8 cases site of biopsy was not

Table 1. Frequencies of Small B- cell lymphomas.

Diagnosis	Number of Cases	Percent of small B-NHL (n=140)	Percent of all NHL (n=1721)	Nodal NHL n(%)	Extranodal NHLn(%)	Site not mentioned n(%)
SLL/CLL	58	41.1	3.37	45(77.5)	7(12.0)	6 (10.3)
FL	46	33.0	02.6	40(86.9)	5(10.8)	1 (2.1)
MALT-L	15	10.8	0.87	-	15(100)	-
MCL	15	10.8	0.87	13(86.6)	1(06.6)	1 (6.6)
LPL	05	03.6	0.29	04(80.0)	1(20.0)	-
SMZL	01	00.7	0.06	-	1(100)	-
Total	140	100.0	8.06	102(72.8)	30(21.4)	8 (5.7)

mentioned in the clinical data (Table 1).

SLL/CLL, FC, LPL, and MCL more commonly involved the lymph nodes at the time of presentation. Most common extranodal NHL category was MALT-L. Salivary gland (7 cases) was the commonest site of involvement followed by gastrointestinal tract (5 cases), thyroid (1 case), lid (1 case), and nasopharnyx (1 case).

SLL/CLL accounted for 41.4% of small B-cell NHL and 3.4% of all NHL in our study. The mean and median ages were 57.3 and 60 years respectively. It showed male dominance with a M/F ratio of 3.8:1. FL was the second commonest small B-cell NHL and accounted for 32.9% of small B-cell NHL and 2.6% of all NHL. The mean and median ages were 54.2 and 56.0 years respectively with M/F ratio of 1.1:1. (Table 2) Majority of FL were grade II (45.6%) followed by grade I (34.7%) and grade III (19.5%).

MCL and MALT lymphomas each accounted for a similar number of cases in our study, 10.7% of small B-cell NHL and 0.87% of all NHL. The mean and median ages of MCL were 51.8 and 55 years respectively and of MALT lymphoma, 46.3 and 45 years respectively. Both showed a male dominance with the M/F ratio of 4:1 and 2.7:1 for the MCL and MALT lymphoma respectively. In our study there were only 5 cases of LPL which accounted for 3.6% of small B-cell NHL and 0.29% of all NHL, mean and median ages were 59.4 and 65 years with M/F ratio of 1:1.5 (Tables 1 and 2).

Discussion

Small B-cell NHL are derived from the B-lymphocyte and represent a heterogeneous group of diseases in terms of clinical, pathological and molecular aspects.[14] These lymphomas have been included in the low-grade category by pathologists, and indeed, these patients do present a disease that is initially indolent.[15]

The incidence of lymphoma is increasing worldwide largely contributed by NHL.[15] According to Karachi (South) Cancer Registry (1995-1999) NHL is the 9th most common malignancy among males in Karachi and ranked 10th among the females.[16,17] In Pakistan no comprehensive data is available about the frequency of small B-cells NHL. In the present study, 140 cases of small B-cell NHL were diagnosed over a period of five years according to WHO/REAL classification by using histological as well as immunohistochemical studies. As a group small B cell lymphomas accounted for 8.1% of NHLs. In contrast to this, however the western studies show much higher incidence of small B-cell lymphomas.

In this study, among the small B-cell NHL, SLL/CLL accounted for the largest group and it was 3.3% of all NHL. This does not correlate with western data which shows it to be 6.7% amongst all NHL according to the NHL classification Project data.[18] The second commonest small B-cell non-Hodgkin's lymphoma in our study was Follicular lymphoma and it was 2.6% of all NHL. This is again in contrast to western data accounting for 25-30% of all NHLs in the USA[14], FL are also uncommon in other developing countries and reported incidence in various series from other parts of Asia ranged from 3.4% to 13%.[10,19]

Table 2. Age and sex distribution of Small B-cell lymphomas.

Diagnosis	Number of cases	Mean (years)	Standard deviation	MIE Ratio
SLL/CLL	58	57.31	12.299	3.8:1
FL	46	54.26	15.538	1.1:1
MCL	15	51.87	15.896	4:1
MALT	15	46.33	14.994	2.7:1
LPL	05	59.40	20.959	1:1.5
SMZL	01	57.31	-	-

The median ages of SLL/CLL, FL, MCL, MALT-L, LPL and SMZL in our study correlate with the median ages given in literature.[18, 20]

NHL is more common in males however there is significant difference in the male to female ratio in various series. Data from developed countries report a male to female ratio of 1.4:1 while from developing countries the ratio ranges from 4.5 to 3.1.[10,21] In small B-cell NHL SLL/CLL, MCL and LPL are also more common subcategories in males. However FL and MALT-L have slightly female preponderance.[18] Analysis of our data revealed that small B-cell NHL are more common in males.

In the present study, majority of small B-cell NHL were nodal at presentation with the nodal to extranodal ratio of 3.4 and this is similar to another study that showed 20% as primary extranodal NHL.[22] In extranodal lymphomas, in the present study 50.0% were MALT-L. This also does not correlate with the western data which shows 8% of all NHL.[23] We found that salivary gland was the commonest site of presentation in MALT-L where as in literature, gastrointestinal tract represents the most common site.[14,15]

Low and intermediate-grade lymphomas including small B-cell NHL are not AIDS-associated and we had expected a higher component of this neoplasm in our series, considering the low prevalence of HIV/AIDS.[24,25] Biological studies are required to determine the cause of a higher component of aggressive NHL in our population in comparison to the low grade NHL.

We conclude that the frequency of these small B-cell NHL is very low in our population, in sharp contrast to the western literature. Further studies are required to look into this marked difference of occurrence of these indolent lymphomas.

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