

Spectrum of lymphoma in Bahrain. A retrospective analysis according to the World Health Organization classification

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ABSTRACT

Objectives: To determine the spectrum of various types of lymphoma in Bahrain according to the latest World Health Organization classification criteria.

Methods: A retrospective review was conducted for all new lymphoma cases diagnosed at Salmaniya Medical Complex, Manama, Bahrain during the period from January 2010 to December 2015.

Results: Two hundred and twenty-one new cases of lymphoma in Bahraini patients were diagnosed in the study period. Eighty patients had Hodgkin lymphoma, 140 had non-Hodgkin lymphoma, and one patient had composite lymphoma. In the Hodgkin lymphoma group, nodular sclerosis type was the most frequent type (48.75%), followed by mixed-cellularity type (27.5%), and nodular-lymphocyte predominant type (16.25%). In the non-Hodgkin lymphoma group, 124 (88.6%) cases were B-cell lymphomas, while the remaining were T-cell lymphomas. Diffuse large B-cell lymphoma was the most frequent type of non-Hodgkin B-cell type lymphoma (55.7%), followed by follicular lymphoma (10%).

Conclusion: The distribution of lymphoma in Bahrain is similar to neighboring Middle East countries with a predominance of Hodgkin lymphoma and diffuse large B-cell lymphoma.

Saudi Med J 2018; Vol. 39 (7): 736-739
doi: 10.15537/smj.2018.7.23065

Lymphoma is the third most common type of cancer in the Bahraini population, representing 7% of all new cancer cases in 2011.¹ Shome et al,² published a retrospective analysis of malignant lymphoma in Bahrain in 2004, which analyzed patients diagnosed between January 1996 and December 2001. During the study period, the use of immunohistochemistry was not established in Bahrain, and therefore an accurate sub-classification of these cases was not feasible. In

addition, multiple new entities of lymphoma were also introduced by the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues after the previously mentioned study.

In our study, we aimed to analyze all newly diagnosed cases of lymphoma at our institution, with a detailed lymphoma classification according to the updated 4th edition of the WHO classification,³ and compare it with other studies from the Middle East region and developed world.

Methods. The records of the Pathology Department at Salmaniya Medical Complex (SMC) were searched for all newly diagnosed cases of lymphoma in the period from January 2010 to December 2015. Salmaniya Medical Complex houses the principal hemat oncology center under the Ministry of Health in the Kingdom of Bahrain during the study period. The cases were reviewed by at least one of 3 pathologists involved in this study (EAA, SMG, and SAA). The records of all patients were reviewed, and information on age, gender, nationality, primary site of involvement, and bone marrow status was recorded. Cases of post-transplant lympho-proliferative disorders and plasma cell neoplasms were excluded. Cases were categorized as primary extra-nodal if samples originated from tissues other than the lymph nodes, spleen or thymus at the time of the initial diagnosis.

Sections from paraffin-embedded tissue blocks were prepared and used for standard hematoxylin and eosin (HE) staining, in addition to immunohistochemical staining using the BenchMarkXT automated staining system (Ventana Medical Systems, Oro Valley, AZ, USA). The panel of antibodies used varied according to the morphology and included CD3, CD4, CD5, CD8, CD10, CD15, CD20, CD21, CD23, CD30, CD43, CD45 (leukocyte common antigen), CD79a, anaplastic lymphoma kinase-1 (ALK-1), BCL2, BCL6, Bob-1, cyclin D1, EMA, MUM-1, OCT-2, PAX-5, PD-1, terminal deoxynucleotidyl transferase (TdT), and Ki67. Some cases were sent overseas for fluorescent in situ hybridization (FISH) studies to look for c-myc, bcl-2 and bcl-6 rearrangements.

Based on the morphological findings and appropriate immunohistochemistry results, cases were diagnosed according to the updated 4th edition of the WHO classification of tumors of hematopoietic and lymphoid tissues.³ For statistical analysis applied in this study, 2016 Microsoft Excel was used. This study was approved by the Ministry of Health's research committee in Bahrain.

Results. We retrieved 266 newly diagnosed cases of lymphoma in the period from January 2010 to December 2015. Two hundred and twenty-one cases were identified among Bahraini patients, while another 45 cases were among non-Bahraini patients.

In the Bahraini patients, the age at presentation ranged from 3 to 90 years, with a median age of 48 years. Sixteen cases were of children less than 14 years of age. There were 126 male patients and 95 female patients (male to female ratio = 1.36:1). Patients comprised 80 cases (36.2%) of Hodgkin lymphoma (HL), 140 cases (63.3%) of non-Hodgkin lymphoma (NHL), and one case of composite lymphoma (HL and diffuse large B-cell lymphoma). The single case of composite lymphoma was diagnosed in a 23-year-old woman with gastric mass biopsy, which showed diffuse large B-cell lymphoma and a mediastinal mass biopsy that revealed HL, as well as diffuse large B-cell lymphoma.

The age range for HL was 6 to 79 years at presentation, with a median age of 31 years. There were 49 male and 31 female patients. Of the 80 cases of HL, 67 (83.75%)

were classic HL (cHL), while 13 cases (16.25%) were nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). The majority of cases presented in patients under the age of 55 years, with a distribution peak corresponding with young adults and middle-aged patients (Table 1). Bone marrow biopsy was obtained in 64 cases with 7 patients (10.9%) showing marrow involvement.

The age range for NHL was 3 to 90 years at presentation, with a median age of 56 years. There were 63 female and 77 male patients. Among the 140 cases of NHL, 124 patients (88.6%) had B-cell lymphoma, while the remaining cases were T-cell lymphoma. The distribution of NHL cases according to histologic type are summarized in Tables 2 & 3. Bone marrow biopsy was obtained from 108 patients, with 26 cases (24.1%) showing marrow involvement.

Diffuse large B-cell lymphoma (DLBCL) cases included 3 cases of T-cell/histiocyte-rich large B-cell lymphoma (LBCL), 2 cases of primary mediastinal (thymic) LBCL, 2 cases of primary DLBCL of the CNS,

Table 1 - Distribution of Hodgkin lymphoma cases by age group in Bahraini patients.

Age group (years)	No of cases (%)	Male to female ratio	Nodular sclerosis	Mixed cellularity	Lymphocyte rich	Nodular lymphocyte predominant
0-14	12 (15)	9:3	4	5	1	2
15-34	32 (40)	20:12	17	5	3	7
35-54	25 (31)	14:11	13	8	2	2
>54	11 (14)	6:5	5	4	0	2
Total	80 (100)	49:31	39	22	6	13

Table 2 - Distribution of B-cell non-Hodgkin lymphoma in Bahraini patients.

B-NHL type	No. of cases	Age range (years)	Median age (years)	Gender
Diffuse large B-cell lymphoma	78	5-90	60	37 F, 41 M
Follicular lymphoma	14	40-81	56	8 F, 6 M
Small lymphocytic lymphoma	7	33-80	64	4 F, 3 M
Burkitt lymphoma	6	3-80	18.5	3 F, 3 M
Mantle cell lymphoma	5	47-66	49	3 F, 2 M
High grade B-cell lymphoma	4	35-58	39	2 F, 2 M
MALT lymphoma	3	35-63	38	3 M
Primary cutaneous follicle center lymphoma	2	48-50	49	2 M
Splenic marginal zone lymphoma	2	52-66	59	1 F, 1 M
Lymphoplasmacytic lymphoma	1	52	52	M
Nodal marginal zone lymphoma	1	44	44	M
B-lymphoblastic lymphoma, NOS	1	45	45	M
Total	124	3-81	57	58 F, 66 M

NOS - not otherwise specified, MALT lymphoma - extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue

Table 3 - Distribution of T-cell Hodgkin lymphoma (T-NHL) in Bahraini patients.

T-NHL subtype	No. of cases	Age range (years)	Median (years)	Gender
T-lymphoblastic lymphoma	8	5 - 37	19.5	2 F, 6 M
Mycosis fungoides	4	27 - 63	51.0	2 F, 2 M
Peripheral T-cell lymphoma, NOS	2	49 - 52	50.5	2 M
Enteropathy associated T-cell lymphoma	1	47	47.0	1 F
Angioimmunoblastic lymphoma	1	71	71.0	1 M
Total	16	5 - 71	32.0	5 F, 11 M

NOS - not otherwise specified

and 2 cases of primary cutaneous DLBCL, leg type. The remaining cases were diagnosed as DLBCL, NOS. Lack of EBV in situ hybridization prevented subclassification of cases into EBV-positive DLBCL, NOS.

There were 4 cases of high-grade B-cell lymphoma. Three of them showed *c-myc* and *bcl-2* rearrangements. Therefore, they were diagnosed as high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements. FISH studies failed in the fourth case.

Forty-six patients (32.9%) with NHL presented at extranodal sites. Of these patients, 14 cases occurred in the gastrointestinal tract and 10 cases occurred in the skin. Other extranodal sites included: maxilla, nasopharynx, liver, tonsil, tongue, nose, thyroid gland, bone, brain, breast, kidney, and abdominal wall.

Discussion. Geographical differences in the incidence and distribution of different lymphoma types are well documented.⁴⁻⁶ The introduction of the WHO classification for lymphoma has led to a unification in the terminology used for diagnosing lymphoma and made studies addressing the types and incidences of lymphoma from different parts of the world easier to compare.

In Bahrain, most, if not all, lymphoma patients are treated at Salmaniya Medical Complex. Therefore, our study reflects the frequency of different lymphoma types in the Bahraini population as a whole.

Hodgkin lymphoma represented 36% of our total cases, which is comparable to the findings from other studies from neighboring countries,^{7,8} but much higher than the 8% incidence reported from the USA.⁹ This can be due partly to a bigger pediatric and young adult population and smaller elderly population in our region. In Western countries, HL shows a bimodal age distribution with a peak incidence in the third and sixth decades of life, while developing countries show high incidence in childhood.³ In our series, a bimodal

distribution was not apparent. However, there was a high incidence of HL among the young adult group rather than children. Nodular sclerosis type was the most common subtype, which differs from a previous study where mixed-cellularity was the most common subtype.² This change has been observed in other recent studies from the Middle East.¹⁰ The shift in age and cHL-subtype distribution reflect the change in epidemiology to a pattern more closer to that described in developed countries. This might be due to the improvement in economic status and health services, as well as a change in lifestyle among Bahrainis, in recent years.

Nodular-lymphocyte predominant type represented 16% of the HL cases in this study. This is notably higher than the 2-8% figure reported in most neighboring countries.^{7,10,11} This difference might be due to ethnic heterogeneity, environmental factors, and increased awareness of this entity and the availability of immunohistochemistry studies to distinguish the nodular-lymphocyte predominant type from cHL, as well as T-cell/histiocyte-rich large B-cell lymphoma. Detailed epidemiological studies are needed to uncover the factors behind these differences, as is the case with many other types of lymphoma.

Among NHL, B-cell lymphomas were predominant in our analysis, which is similar to other studies from the Middle East region, Europe, and North America.^{4,7,12} Diffuse large B-cell lymphoma was the most common subtype similar to other Middle East countries.^{7,13} However, follicular lymphoma was more common in Bahrain than Burkitt lymphoma, which is in contrast to studies from other countries in the region,⁷ but follicular lymphoma was still less common than Western countries.¹⁴ This difference in follicular lymphoma incidence has been noted previously and was attributed to different molecular pathways that cause development of lymphoma in patients from differing

regions, difference in life style, and the possibility that some cases presented only after transformation to diffuse large B-cell lymphoma due to a lack of significant symptoms in low-grade lymphomas.^{7,14}

A large proportion of the NHL lymphomas examined in this study were extra-nodal (35%), which is similar to other neighboring countries and higher than developed countries.^{7,13} Most of the studied patients had gastrointestinal or cutaneous lymphomas. Therefore, geographical differences in *Helicobacter pylori* incidence may play a key role in this difference, as well as other lifestyle factors.

Although the updated WHO classification³ advise to specify cell of origin in DLBCL cases, this was not possible in this retrospective study due to lack of needed immunohistochemical staining results. Therefore, further future studies to detail the cell of origin and its relation to the clinical and pathological features in DLBCL cases is needed.

In conclusion, our study highlights some of the differences in the distribution of lymphoma in the Middle East region compared to other developing countries. Our pattern of cHL is changing and evolving to resemble the patterns observed in developed countries. However, NLPHL is more frequent in Bahrain as compared to other countries. For NHL, DLBCL is still the most common type, but our incidence of follicular lymphoma is increasing, with this ratio possibly changing in the coming years to resemble developing countries. This shift in epidemiology strengthens the evidence regarding life style and socio-economic factors in the development of different types of lymphoma.

Acknowledgment. *We would like to thank Editage (www.editage.com) for English language editing.*

Received 9th April 2018. Accepted 6th June 2018.

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