

Spectrum of malignant lymphomas in Bahrain

Leitmotif of a regional pattern

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ABSTRACT

Objective: To determine the clinicopathologic features of malignant lymphomas in Bahraini patients.

Methods: A retrospective hospital-based study was conducted. All new cases of malignant lymphoma diagnosed during the period January 1996 to December 2001 at the Salmaniya Medical Complex in Bahrain were included in the study.

Results: Seventy-two cases met the inclusion criteria. This included 24 (33.3%) cases of Hodgkin's disease (HD) and 48 (66.7%) cases of Non-Hodgkin lymphomas (NHL). A young age at presentation (median 20 years) mixed cellularity histology, lack of extra nodal involvement and rare marrow involvement characterized HD. The majority of NHL showed diffuse high or

intermediate grade lesions. A high number of primary extra nodal neoplasms (41.7% of NHL) and frequent involvement of the gastrointestinal tract with *Helicobacter pylori*-associated gastric lymphomas were notable features among NHL cases. Immunohistochemical staining in 30 cases showed 26 cases (86.7%) of B cell and 4 cases of T cell origin.

Conclusion: The study highlights common features that distinguish malignant lymphoma reported from countries of the Arabian Gulf region. This pattern distinguishes them from the disease encountered in the Western world.

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The distribution pattern of malignant lymphoma (ML) has been well documented in the Western world, Indian subcontinent, the Far east and Africa.¹⁻¹⁰ There have been similar reports from different countries in the middle east region namely Kingdom of Saudi Arabia (KSA), Iran, United Arab Emirates (UAE) and Sultanate of Oman.¹¹⁻¹⁶ These reports indicate some common demographic and clinicopathologic characteristics of ML occurring in this geographic region. A published abstract of a study conducted at Salmaniya Medical Complex (SMC) in Bahrain reported that ML were among the most common malignant neoplasms in the Bahraini population.¹⁷ The present study was undertaken in

view of the absence of a published account of the pattern of ML seen in this country and to find out whether ML in Bahrain mirrors the regional pattern.

Methods. All cases of ML that were diagnosed at SMC which is the principal referral hospital under the Ministry of Health, Kingdom of Bahrain, during the 6-year period between January 1996 to December 2001 were analyzed. Tissue and bone marrow biopsies were fixed in neutral buffered formalin and paraffin embedded sections were stained with Hematoxylin eosin, periodic acid-Schiff (PAS) and reticulin stains for light

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microscopy. For non-Hodgkin lymphoma (NHL), additional sections were immunostained using the peroxidase-antiperoxidase (PAP) method with antibodies to leucocyte common antigen (LCA), CD45RB, B cells (CD20) and T cells (CD45RO). For cases of Hodgkin disease (HD), antibodies to CD15 and CD30 were used as markers for Reed-Sternberg (RS) cells. Antibodies were commercially purchased from Dako A/S. The stain protocol used was according to the manufacturer's instructions, with appropriate positive and negative controls.

The data related to age, gender, nationality, and primary site of involvement were available from the records. Slides prepared from routinely fixed; decalcified and processed marrow trephine biopsies were also available from the archives. Sections showing the primary tumors were classified according to the World Health Organization histological classification of Hodgkin lymphoma and the terminology of the International Working Formulation study group for NHL. All the primary gastric lymphomas were examined for *Helicobacter pylori* (*H. pylori*).

Results. Patient characteristics. A total of 86 cases of malignant lymphomas were diagnosed during the period of study. Fourteen of these cases were expatriates and were excluded from the study. The rest, 72 cases, were all Bahrainis. The ages ranged from 4-76 years (median age 38 years). Nine cases were pediatric. The overall male to female ratio was 1.48:1. Twenty-four cases (33.3%) were classified as HD and the rest were NHL. **Table 1** shows the distribution of cases according to age and gender. Half of HD cases were less than 20 years of age and only 2 cases were seen above the age of 40 years.

Histopathological features. 1. Hodgkin disease. No extranodal involvement was seen in the cases of HD. The most common histological subtype seen in half of all HD cases was mixed cellularity (MC). **Table 2** shows the frequency distribution of histological subtypes of HD. Bone

marrow involvement was seen only in one case out of a total of 19 cases in which bone marrow biopsies were available. This was diagnosed as the lymphocyte rich subtype of HD. The 2 cases of NLP showed definite staining of the RS variant cells with the CD20 antibody. Staining for CD45 was also positive but CD30 was negative. Both were young males aged 31 and 33 years.

2. Non-Hodgkin lymphoma. **Table 1** shows the age and gender distribution of cases. **Table 3** shows distribution of cases according to site, histological pattern, immunophenotype and histological grade according to the International Working Formulation. The peak incidence was seen in the fifth decade with 13 cases (27.1%) in this age group. All the follicular lymphomas were seen in adults.

Table 4 shows the distribution of extranodal sites primarily involved by NHL. Histologically, these were all of the diffuse type. The gastrointestinal tract was the most frequently involved extra-nodal site and this was seen in 10 cases. Primary gastric involvement was present in 6 cases. Four of these cases were diagnosed as high grade NHL while *H. pylori* were present in 5/6 cases of gastric lymphomas. The specific types of B-cell lymphoma included 2 cases of Burkitt lymphoma, involving the mandible in a 7-year-old male and the ovary in a 33-year-old female. There were 4 cases of T cell rich B cell lymphoma (TCRBCL) all of which were primarily nodal, involving the cervical, axillary or inguinal lymph nodes. T cell lymphomas included 2 cases of Lennert lymphoma and 2 peripheral T cell lymphomas. All these involved lymph nodes primarily. The bone marrow was examined in 37 cases of NHL. Ten cases (27%) showed infiltration (4 intermediate grade, 3 high grade and 3 low grade). When childhood lymphomas (<15 years) were considered separately, HD was the most common (7/9 cases) and mixed cellularity HD was the most frequent subtype (5 cases). Only 2 cases of NHL were noted of which one was a Burkitt lymphoma and the other a diffuse high grade B cell lymphoma of tonsil that was bcl2 negative.

Table 1 - Age and gender distribution of Hodgkin Disease and non-Hodgkin lymphoma.

	Total n	Age (years)		Children* n (%)	Adults n (%)	Gender		Ratio
		Range	Mean (median)			Male	Female	
Hodgkin disease	24	4-61	22.9 (20)	7 (29.2)	17 (70.8)	13 (54.2)	11 (45.8)	1.18: 1
Non-Hodgkin lymphoma	48	7-79	43.7 (43)	2 (4.2)	46 (95.8)	30 (62.5)	18 (37.5)	1.66: 1
*children age <15 years								

Table 2 - Frequencies of histologic types of Hodgkin disease.

Histological type	n (%)
Mixed cellularity	12 (50)
Nodular sclerosis	6 (25)
Lymphocyte rich	4 (16.7)
Nodular lymphocyte predominant	2 (8.3)
Lymphocyte depleted	0 (0)
Total	24 (100)

Table 3 - Classification of non-Hodgkin lymphoma.

Classification	n (%)
Site	
Nodal	28 (58.3)
Extranodal	20 (41.7)
Pattern	
Diffuse	41 (85.4)
Follicular	7 (14.6)
Immunophenotype*	
T cell	4 (13.3)
B cell	26 (86.7)
Histological grade	
High	18 (37.5)
Intermediate	20 (41.7)
Low	10 (20.8)
*Immunophenotype of 30 cases	

Table 4 - Extranodal sites of non-Hodgkin lymphoma.

Extranodal site	n
Stomach	6
Duodenum	3
Tonsils	2
Other sites* (one each)	9
Total	20
* other sites: ileum, mouth, thyroid, mandible, ovary, soft tissue (hip), skin, kidney, nasal	

DISCUSSION. Practically all malignant disorders diagnosed in Bahrain are referred to SMC. Therefore, although there are drawbacks of this hospital-based study, the data has some epidemiological significance. It has been observed that the incidence of ML in Bahrainis appears to be nearly twice that in England and Wales.¹⁷ Published estimates of incidence of malignant neoplasms reported from Iraq, Iran, KSA, Kuwait, Yemen, Lebanon, Libya, Egypt and Gaza indicate that malignant lymphomas (ML) are among the top 4 most-common tumors in the middle-east region.¹⁸⁻²⁶ The relative frequency of ML in some of these countries (KSA, Yemen, and Libya) may be as high as 14-16% of all cancers.^{20,23,25} In males, the relative frequency is even higher partly as the male/female ratio of ML patients is high. In children too, comparison of regional incidences shows that ML are relatively common neoplasms in countries of the Middle East along with Brazil and New Guinea.²⁷

The proportion of HD among cases, which was 33% in this study, is similar to observations from KSA (27%), Oman (35%) and UAE (41%).^{15,16,20} In contrast, HD has a much lower incidence in the Far East. Examples are Japan (5%), China and Korea (18% in each).^{6,10,28}

Hodgkin disease. In economically developed countries of the west, HD has a characteristic bimodal distribution with peaks in the third decade and after the age of 50-years.²⁹ In this study, HD was predominantly seen in children and young adults. Studies from Oman, KSA, Iran and Kuwait also suggest a regional peak occurrence in childhood with highest frequencies occurring within the first 2 decades of life.^{16,20,30,31}

A recurrent feature of the histopathology of HD in developing countries is that mixed cellularity (MC) is the most common subtype. In this region, MC accounts for approximately half or more of all cases of HD as was also seen in our study.^{16,31,32} Nodular sclerosis (NS) is noticeably less common than in North America and Europe where it accounts for 63-74% of cases.³³ The lymphocyte depletion subtype is rare.^{16,31,32} Nodular lymphocyte predominance (NLP) Hodgkin disease is a later addition to HD histological subtypes and does not find mention in other similar studies from this region.

Non-Hodgkin lymphoma. In the Middle East, NHL constitutes 60-75% of all cases of lymphomas as suggested by several series and the present one.^{15,16,19} The proportions of B and T cell neoplasms in this study and in Oman and the UAE are also quite similar (B cell: 80-87%; T cell: 7-13%). Comparison of frequencies of histological subtypes of NHL reported in different studies from this region shows discordance. For example, frequencies of low grade NHL vary from as little as 2.4-7%

(KSA and UAE) to 21-30% (present study and Oman).^{13,15,16} While larger numbers of cases need to be studied, lack of uniform application of classification criteria may be responsible for such differences. The frequency of Burkitt/Burkitt-like cases in this series is lower than in tropical Africa.

A notable feature in this study, similar to observations from Jordan and Lebanon was the increased frequency of extranodal involvement in NHL with the gastrointestinal tract being the most frequently observed site.^{34,35} In addition, frequent association of *H. pylori* with gastric NHL seen in this series is of interest although the question of causality needs further study.

This study is based on the review of pathology records of cases diagnosed as lymphoma using routine histology stains supplemented by immunohistochemistry. The incidence of lymphoma in the Arabian Gulf region is higher than in other countries and there are distinctive patterns of its subtypes. This may indicate common clues towards its causation. To follow up these clues it is necessary to undertake careful epidemiological work in a larger perspective.

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