ORIGINAL ARTICLE

Spectrum of Malignant Lymphoma in Queen Elizabeth Hospital, Sabah

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Summary

Lymphomas, ranked twelve among all cancers world-wide in the 1990s, in which it is more prevalent in males compared to females. A previous study on lymphomas in East Malaysia for a period of 3 years from 1981-1983 showed that the pattern of lymphomas conformed to the general pattern observed in Asia. Current study reviews lymphoma cases from the Department of Pathology, Queen Elizabeth Hospital, Sabah between 1997 and 1999, with the aim of investigating if the spectrum and pattern in Sabah has since changed, a decade later. A total of 91 confirmed lymphoma cases were phenotyped with a panel of antibodies and classified using the new WHO proposed list of lymphoid neoplasms. The 1981-1983 series was reviewed and cases reclassified accordingly for comparison. There are 83 (91.2%) NHL and 8 (8.8%) HL cases in this series, a ratio of NHL to HL of 9:1. Of the 83 cases of NHL, 66 (79.5%) were confirmed B-cell type, 13 (15.7%) T-phenotype, 1(1.2%) null cell type and one case unclassified. Diffuse large B-cell lymphoma is the most prevalent, (65.1%), followed by Burkitt's lymphoma and follicular lymphoma, (10.6%) each. Lymphoma pattern concurs with the previous series from Sabah, with higher prevalence of diffuse large cell lymphoma and lower incidence of follicular lymphoma and HL, as seen elsewhere in Asia. There is an overall increase in the number of cases of NHL in the 1990s. However, the proportion of T-NHL is reduced when compared to the series in the 1980s.

Key Words: EBV, Lymphoma, Malaysia, Sabah

Introduction

Malignant lymphoma involves neoplastic transformations of cells that reside predominantly within lymphoid tissues. Both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphomas (NHL) differ in clinical behaviour and response to treatment. NHLs are derived from subpopulations of B and T cells[1], and recent reports also indicate lymphoid derivation of HL[2,3]. Cell-surface molecules involved in cellular growth and microenvironmental localization provides the basis needed to immunophenotype malignant lymphomas. Advances in immunophenotyping and improvement in the classification of haematological malignancies rendered better epidemiological comparison in the incidence and pattern of lymphoma[4].

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in males when compared to females[5]. Hence, this disease brings about profound personal and economic impact[5]. Mortality and incidence rates from NHLs have also been reported to increase in both sexes in most countries over recent decades[1,6]. These increases have been more significant for extranodal disease, particularly those arising in the brain and in high grade tumors[6]. The emergence of acquired immunodeficiency syndrome-related non-Hodgkin's lymphomas has been implicated to cause a rise in NHL in recent years[1]. In contrast, there has been significant decline in HL mortality rates in both sexes since the early 1970s[1].

Viruses, immunosuppression, and certain occupations have been identified as risk factors for the development of NHL[1,7]. The human T lymphotrophic virus type 1(HTLV-1), induces a specific form of lymphoma called the adult T cell leukaemia/lymphoma (ATL)[8,9,10,11], whereas Epstein-Barr virus is implicated in the etiology of Burkitt's lymphoma, HL, some varieties of T-cell lymphoma, HIV-associated and post-transplant lymphoproliferative lesions [12,13,14,15,16].

Hospital-based studies can yield useful information on the epidemiological pattern of lymphomas. Previous study on lymphomas in East Malaysia for a period of 3 years from 1981-1983 revealed that the pattern of lymphomas in East Malaysia concurred with the general pattern in Asia[17]. This current study on the surgical specimens retrieved from the Department of Pathology, Queen Elizabeth Hospital, Sabah between the year 1997 and 1999 aims to elucidate if the spectrum and pattern of lymphoma in Sabah has since changed 15 years later in the 1990s.

Materials and Methods

Patients' Material

Over a period of three years from January 1997 to December 1999, 125 surgical biopsies were diagnosed as malignant lymphomas in the Department of Pathology, Queen Elizabeth Hospital, Sabah where a total of 25,871 surgical biopsies were received during this period. The haematoxylin and eosin (H&E) stained slides of these cases were reviewed and lymphoma cases were classified according to the WHO proposed list of lymphoid neoplasms[18] with the aid of immunohistochemical stain performed on serial sections of the archival tissue using a panel of antibodies. Confirmed lymphoma cases were also probed for the presence of the Epstein-Barr virus by *in situ* hybridization detection technique. Patients' demographic data were extracted from the Queen Elizabeth Hospital clinical records. Queen Elizabeth Hospital, Sabah is the major government hospital in Sabah serving a population of 1,863,659[19]. It is the only hospital with histopathological laboratory service in the state. Pathological biopsies from other hospitals in Sabah are sent to this hospital for histopathological diagnosis. In the early 1980s pathological biopsies from East Malaysia (Sabah and Sarawak) were sent to the Department of Pathology, University Hospital for histological diagnosis, as there were no pathologists in service in these 2 states. The archival collection constituted the material for the earlier study by Chai et al, 1999[17]. Lymphoma cases from the state of Sabah in the series reported by Chai et al[17] were retrieved and reclassified according to the new WHO proposed list of lymphoid neoplasia for the purpose of comparison in this study.

Immunohistochemical staining

Immunohistochemical staining of 4µm tissue section was performed with a panel of antibodies mostly from Dako (Denmark) unless otherwise specified. The panel of lymphoid antibodies included: CD3, CD5 (Novocastra, United Kingdom), CD10 (Novocastra, United Kingdom), CD15 (Leu-M1, Becton-Dickson, USA), CD20 (L26), CD21, CD23 (Novocastra, United Kingdom), CD30 (BerH2), CD43 (MT1, a gift from S.Poppema), CD45 (LCA), CD56 (Novocastra, United Kingdom), CD57 (Leu-7, Becton-Dickson, USA), CD79, Ki-67, Bcl-2 and Anaplastic lymphoma kinase (ALK). Cases diagnosed as non-lymphoma after careful study with additional

antibodies such as epithelial membrane antigen (EMA, Dako, Denmark)), S-100 (Dako, Denmark), cytokeratin (MNF116, Dako, Denmark), Mic 2 (Dako, Denmark), melanoma antigen (HMD45, Dako, Denmark) and vimentin (Dako, Denmark), pending the need of individual cases were subsequently excluded from analysis.

In situ hybridization

A non-isotopic in-situ hybridization technique was employed to detect the presence of EBV. The tissue sections were hybridized with fluorescein-conjugated oligonucleotide probe for EBV early RNAs, EBER (NCL-EBV, Novocastra, United Kingdom). Hybridization products were visualized by alkaline phosphatase-conjugated rabbit anti-FITC developed in the substrate, 4-nitro-blue-tetrazolium chloride/ 5-bromo-4-chloro-3-indolyl-phosphate (NBT/BCIP). These tissue sections were then lightly counterstained with Mayer's haematoxylin. A known EBV-positive nasopharyngeal carcinoma case was used as an external control for the staining procedure.

Results

Of the 125 cases retrieved for this study, 34 were excluded for further analysis due to either absence of tumour in the remaining archival tissue, insufficient tissue for further investigation, or the cases were not reconfirmed as lymphoma. The remaining 91 cases, representing 0.35% of total biopsies of the hospital are composed of 83 (91.2%) NHL and 8 (8.8%) of HL. The ratio for NHL to HL is 9:1. There are 56 male and 32 female patients, male: female ratio is 2:1. The gender information of three patients are not available in the clinical record. The ages of these patients range from 7 to 84 years, with a mean age of 42.1 years. The age distribution pattern is presented in Figure 1. The highest preponderance is in the age group of 51 to 60 years old, (20 cases, 22.0%). Distribution in the major ethnic groups showed 27 Kadazan, 7 Malay, 8 Chinese, 8 Bajau and 6 Dusun. The remaining 30 are from other minor indigenous groups (Indian, Murut, Indonesian, Pribumi, Bugis, Brunei, Jawa, Filipino, Timor, Sungai, Rungus, Nocano). The ethnic identification is missing in 5 cases. The distribution of different lymphoma subtypes according to the ethnic group is listed in Table I. Diffuse large B-cell lymphoma (DLBCL) is uniformly the commonest subtype, constituting approximately 50% of lymphoma in all these ethnic groups.

Table II summarizes the distribution of NHL and HL subtypes according to age group and EBV association. Of the 83 cases of NHL, 66 (79.5%) are confirmed B-cell type, 13 (15.7%) T-phenotype, 1 (1.2%) null cell type and one case is unclassified. DLBCL is the most prevalent group among the B-NHL, a total of 43 cases (65.1%), followed by Burkitt's (BL) and follicular lymphomas (FL) of 7 cases (10.6%) each. There are 6 cases (9.1%) of mucosa-associated lymphoid tissue (MALT) type, in which 5 (7.6%) originate in the stomach. All the FL cases show CD10 expression in the neoplastic follicles where as none of the MALT cases expressed CD10. Common B-NHL in children (<15 years) are BL (3 cases) and lymphoblastic lymphoma (1 case). None of the peripheral T-cell lymphoma (PTCL) unspecified and natural killer (NK)/Tcell type are diagnosed in children. There are 4 cases of nodular sclerosis HL (NSHL) , 2 cases of mixed cellularity (MCHL) and 1 case each of lymphocyte rich (LRHL) and lymphocyte depleted HL (LDHL). All HL, except one case of MCHL are from patients in older age group (≥15 years).

The main sites of disease presentation are in the lymph nodes in 43 cases (47.2%) and extranodal sites in 42 (46.1%). The sites of presentation for six cases cannot be determined. All the HL cases presented in lymph node. The majority of lymph node biopsies were from the head and neck region (20, 22.0%), followed by superficial nodes of the axillary and inguinal regions (11, 12.1%), and mesentery (2, 2.3%). The sites of the remaining 10 (11.0%) cases are not indicated. The common extranodal sites were gastrointestinal tract (14), tonsil (4), oral cavity (4), testis (2), spine (2), nose (2), and others (14). All the 14 cases of lymphoma

from the gastrointestinal tract are B-cell NHL: DLBCL (4), gastric MALT-type (5), FL (4), and B-NHL NOS (1).

EBV are detected in 6/8 (72.5%) of HL and 8/83 (9.6%) of NHL cases (Table II). Three of 43 (7.0%) DLBCL, 2 of 7 BL (28.6%) are EBV associated. Three of 13 T-cell NHL are EBV associated (23.1%), in which 2 are NK/T cell type and 1 PTCL unspecified subtype. Ethnic Kadazan (6/14) has the highest rate of EBV association in their lymphomas (DLBCL 2; NSHL 1; MCHL 1; BL 1; NK/Tcell 1), followed by Malay (PTCL unspecified 1; LRHL 1), one case each from the ethnic Indian (NSHL), Murut (DLBCL), Bajau (BL), Jawa (NK/Tcell), Chinese (NSHL) and 1 case of MCHL without information of ethinicity.

Table I: Ethnic distribution of lymphoma subtype in Queen Elizabeth Hospital, Sabah (1997-99)

Diagnosis	Ethnic Group							Total
	Malay	Kadazan	Chinese	Bajau	Dusun	Others	NA	
Hodgkin's Lymphoma	**1**	**2**	**1**	**-**	**-**	**3**	**1**	**8**
Lymphocyte rich	1		-	-	-	-	-	1
Nodular scleroris	-	1	1	-	-	2	-	4
Mixed cellularity	-	1	-	-	-	-	1	2
Lymphocyte depleted	-	-	-	-	-	1	-	1
Non-Hodgkin's Lymphoma	**6**	**25**	**7**	**7**	**7**	**27**	**4**	**83**
Diffuse large B-cell	3	13	5	4	2	15	1	43
Burkitt's	-	2	1	1	1	2	-	7
Follicular	-	1	1	-	1	1	3	7
Gastric MALT type	-	1	-	1	1	2	-	5
MALT type	-	1	-	-	-	-	-	1
B-lymphoblastic	-	1	-	-	-	-	-	1
Plasmacytoma	-	-	-	-	1	-	-	1
B-NHL NOS	-	2	-	-	-	1	-	3
PTCL unspecified	1	-	-	1	1	2	-	5
NK/T cell	-	2	-	-	-	1	-	3
ALCL T cell	1	-	-	-	-	-	-	1
null-cell	-	-	-	-	-	1	-	1
T-immunoblastic	-	1	-	-	-	1	-	2
T-lymphoblastic	1	1	-	-		-	-	2
NHL NOS	-	-	-	-	-	1	-	1
TOTAL	**7**	**27**	**8**	**7**	**7**	**30**	**5**	**91**

NA : data not available ; NHL : Non-Hodgkin's lymphoma ; MALT: mucosa-associated lymphoid tissue; PTCL: peripheral T cell lymphoma; NK: natural killer; ALCL: anaplastic large cell lymphoma; ML: malignant lymphoma; NOS: not otherwise specified

Table II: Distribution of Queen Elizabeth lymphoma cases by age and subtypes (1997-99)

Diagnosis	Subtype	Age			EBV Association* (%)
		<15 yrs No. (%)	> 15 yrs No. (%)	NA No. (%)	
Hodgkin's Lymphoma (N=8,8.8%)	Lymphocyte rich		1(1.3)		1/1(100.0)
	Nodular sclerosis		3(3.8)	1(33.3)	3/4(75.0)
	Mixed cellularity	1(11.1)	1(1.3)		2/2(100.0)
	Lymphocyte depleted		1(1.3)		0/1(0.0)
Non-Hodgkin's Lymphoma (N=83, 91.2%)	**(a) B cell**				
	Diffuse large B-cell		41(52.0)	2(66.7)	3/43(7.0)
	Burkitt's	3(33.3)	4(5.1)		2/7(28.6)
	Follicular		7(8.9)		0/7(0.0)
	Gastric MALT type		5(6.3)		0/5(0.0)
	MALT type		1(1.3)		0/1(0.0)
	B-lymphoblastic	1(11.1)			0/1(0.0)
	Plasmacytoma		1(1.3)		0/1(0.0)
	B-NHL NOS		3(3.8)		0/4(0.0)
	(b) T cell				
	PTCL unspecified		5(6.3)		1/5(20.0)
	NK/T cell		3(3.8)		2/3(66.7)
	ALCL T-cell	1(11.1)			0/1(0.0)
	null-cell		1(1.3)		0/1(0.0)
	T-immunoblastic	1(11.1)	1(1.3)		0/2(0.0)
	T-lymphoblastic	1(11.1)	1(1.3)		0/2(0.0)
	NHL(NOS)	1(11.1)			0/1(0.0)
	TOTAL	**9(100)**	**79(100)**	**3(100)**	**14/91(15.4)**

NA : data not available ; NHL : Non-Hodgkin's lymphoma ; MALT: mucosa-associated lymphoid tissue; PTCL: peripheral T cell lymphoma; NK: natural killer; ALCL: anaplastic large cell lymphoma; ML: malignant lymphoma; NOS: not otherwise specified

(EBV association: EBER positive cases out of the total number of cases from each subtype.

Table III: Comparison of Sabah series from 1981-83 and 1997-99

Diagnosis	Series from Sabah	
	1981-83*	1997-99
Hodgkin's lymphoma	**4(9.1)**	**8(8.8)**
Lymphocyte predominant	1(2.3)	-
Lymphocyte rich	-	1(1.1)
Nodular sclerosis	1(2.3)	4(4.4)
Mixed cellularity	2(4.5)	2(2.2)
Lymphocyte depleted	-	1(1.1)
Non-Hodgkin's lymphoma	**40(90.9)**	**83(91.2)**
Diffuse large B-cell	19(43.2)	43(47.2)
Burkitt's	6(13.6)	7(7.7)
Follicular	2(4.5)	7(7.7)
Gastric MALT type	1(2.3)	5(5.5)
MALT type	-	1(1.1)
B-lymphoblastic	-	1(1.1)
Plasmacytoma	-	1(1.1)
B-NHL NOS	1(2.3)	3(3.3)
PTCL unspecified	10(22.7)	5(5.5)
NK/T cell	-	3(3.3)
ALCL T-cell	-	1(1.1)
null cell type	-	1(1.1)
T-immunoblastic	1(2.3)	2(2.2)
T-lymphoblastic	-	2(2.2)
NHL NOS	-	1(1.1)
TOTAL	**44(100)**	**91(100)**

*Adapted from Chai et al. Pattern of malignant lymphoma in East Malaysia patients as experienced in University Hospital, Kuala Lumpur. Malaysian J Pathol 1999; 21(1): 45-50

Table IV: Frequency of Diffuse and Follicular NHL from different study groups within Asia

Research Groups	No. of cases	Percentage of all NHL	
		Diffuse No. (%)	Follicular No. (%)
Taiwan (9)	90	31 (34.4%)	11 (12.2%)
Hong Kong (10)	69	60 (87.0%)	9 (13.0%)
Sarawak, Malaysia (23)	58	38 (54.3%)	5 (7.2%)
Guangzhou, China (29)	192	158 (82.3%)	24 (12.5%)
Klang, Malaysia (30)	66	31 (47.0%)	11 (16.7%)
New Delhi, India (31)	238	206 (87.0%)	21 (9.0%)
Thailand (32)	1391	1271 (91.4%)	53 (3.8%)
UH, Kuala Lumpur (33)	121	70 (57.9%)	15 (12.4%)

NHL; Non-Hodgkin's Lymphoma, UH ; University Hospital.

Table V: Percentage of Patients' Ethnic Distribution Admitted in Queen Elizabeth Hospital, Sabah in the year 1997, 1998 and 1999

Year	Ethnic Group						
	Kadazan	Chinese	Malay	Bajau	Murut	Other Pribumis	Others
1997	33.3%	13.2%	4.3%	12.9%	1.3%	15.7%	19.2%
1998	33.0%	13.6%	4.3%	10.2%	1.5%	14.5%	21.9%
1999	33.2%	13.4%	5.1%	11.3%	1.7%	14.4%	19.6%

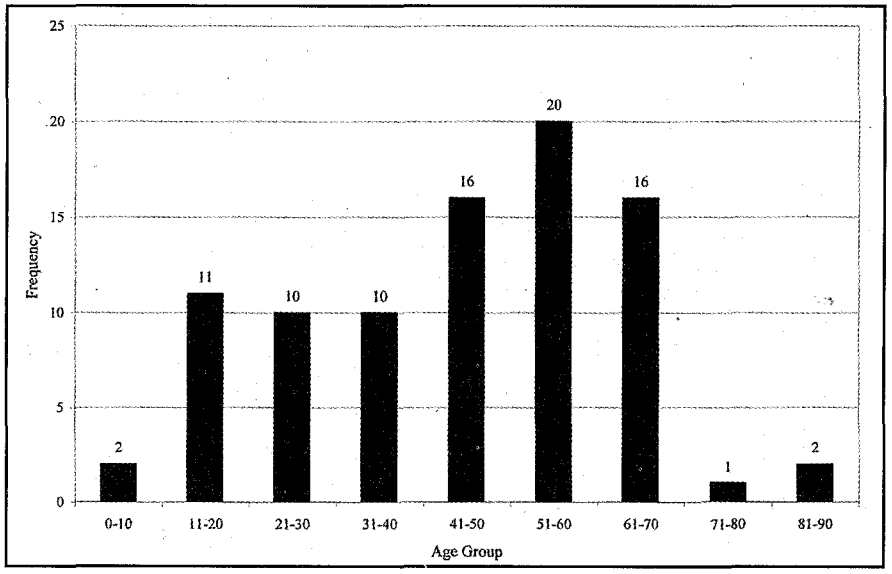

Fig. 1: Distribution of Sabah Lymphoma Cases According to the Age Groups (1997-99)

Discussion

The HL: NHL ratio in this series concurs with earlier study of 1:9 by Chai et al[17] indicating there is no significant change in the pattern of lymphoma in Sabah (Table III). In both these series from Sabah, the frequency of HL is low, similar to other reports from Asia that HL is uncommon[9,20,21,22]. There is an increase in the number of NHL cases in Sabah compared to the previous series and this appears to echo reports from Western countries of a rise in NHL[1,6], in which the incidence rates rose by about 50% or more in less than two decades[1,6]. The incidence of NHL in Asia was also reported to increase but in a more modest rate[19]. This increase in the incidence of NHL was believed to be partly due to AIDS[1,9,23].

Other factors implicated include occupational exposures to chemical agents and viruses [1,24,25,26,27]. Occupational statistics of Sabah inhabitants (1991) showed a high proportion of them being involved in agricultural and animal husbandry, which accounted for 41.8% of the employed population, and in the remaining employed population, 23.5% is working as industrial labourers who are also exposed to chemical agents[19]. However, a larger cohort and a longer period of study are required to confirm if the increase is significant.

Asia reported high frequency of high-grade DLBCL and low frequency of FL when compared to the West[1,20,28]. The ratio of high grade DLBCL to low grade FL in Sabah is 3.2:1 in the 1980's and 6.1:1 in the 1990's. The low incidence of FL were also reported in other Asian countries (Table IV). Harrington et al[29] proposed that the prevalence of high grade diffuse lymphomas are related to environmental factors associated with agricultural activity. Others suggested that delay in patients seeking medical care may explain the high ratio of DLBCL to FL[29], since FL can progress into a more aggressive DLBCL by acquiring secondary genetic alterations[34,35,36]. BL does not constitute a big proportion of NHL in both the earlier and present Sabah series. The association of EBV with this disease is less than 30%. Although the rarity of occurrence of BL had been reported in Hong Kong[22], it is unexpected since malaria is endemic in Sabah[37,38].

T-cell lymphoma constituted only 17.1% of the total NHL cases in this series, which is comparable with reports from Klang[30], Singapore[34], East Malaysia[17], University Kebangsaan Malaysia[21] and Thailand[32], but differ from reports of high incidence of T-NHL in Taiwan[9], Hong Kong[10] and Japan[39]. It appears that there is a decline in the occurrence of T-NHL when compared to the earlier series of 27.5%. The reason for this phenomenon is not immediately apparent, and it also contradict reports that T-NHL is on a rise[10,40].

Ethnic Kadazan constitute highest numbers of lymphoma cases (30%) when compared to other ethnic groups. However, Queen Elizabeth Hospital patient admission data for the year 1997, 1998 and 1999[41] also reveal higher admission of ethnic Kadazan patients when compared to others (Table V), eventhough the Sabah State Population Census Report showed that ethnic Kadazan constitutes only 6.1% of the people in the state[19]. It appears that there is higher utilization of the hospital service by Kadazans, and therefore the ethnic distribution of lymphomas may actually reflect patients composition in the hospital rather than disease predilection[41].

In conclusion, lymphoma pattern in Sabah in the 1990s appears to concur with the earlier pattern in 1980s, higher prevalence of DLBCL, and lower incidence of FL and HL, showing a pattern similar to elsewhere in Asia. The current series shows an overall increase in the numbers of NHL in the 1990s but a drop in the proportion of T-NHL, and a low EBV association rate in BL. The reasons for the 2 latter observations are not immediately apparent. A study involving a larger series would be necessary to establish the findings from this study as statistically significant and reliable.

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