

The pattern of lymphoma in East Malaysian patients as experienced in the University Hospital, Kuala Lumpur

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Abstract

Lymphoma is a highly heterogeneous group of malignant disease. This study aimed to elucidate the pattern of lymphoma in the East Malaysian patient population. 107 cases of confirmed lymphomas from East Malaysian biopsy material were retrieved from the files of the Department of Pathology, University of Malaya, in the 3-year period between 1981 to 1983. With the use of a panel of lymphoid antibodies, the disease was sub-classified using the Rye classification for Hodgkin's lymphoma (HL) and the REAL classification for non-Hodgkin's lymphoma (NHL). All of the cases were tested for the presence of the Epstein-Barr virus by EBER-ISH.

There were 11 (10.3%) HL, 80 (74.7%) B-NHL and 16 (15%) T-NHL. The HL: NHL ratio was 1:9. The most common tumour in children was Burkitt's lymphoma 7/13 (53.8%). In the adult group, there were 72/94 (76.6%) B-NHL {diffuse large cell type 51 (of which 2 were CD30+), Burkitt's lymphoma 8, follicular lymphoma 5, low grade MALT 2, mantle cell type 1 and not otherwise specified due to poor morphology 5}, 13/94 (13.8%) T-NHL and 9/94 (9.6%) HL. Of the 9 adult HL, the most common subtype was nodular sclerosis (6, 66.7%). The EBER positive rate in classical HL, T-NHL, BL and B-NHL were 33.3%, 56.3%, 60.0% and 3.1% respectively. In conclusion, the spectrum of lymphoma seen in East Malaysia was rather similar to West Malaysia except for the very low prevalence of peripheral T-cell lymphoma (PTCL) in Sarawak (3.3%).

Key words: EBER, Hodgkin's lymphoma, immunophenotype, *in-situ* hybridization, and non-Hodgkin's lymphoma.

INTRODUCTION

Lymphoma is a highly heterogeneous group of malignant disease. With the expansion of knowledge on the immune system and improved techniques for investigation, various biological subtypes of lymphoma can be identified, each with distinct biological behaviour.] Hence, recently evolved classification of lymphoma emphasises the utilisation of immunophenotyping to enable the distinction of these various entities.

The disparity in incidence rate and various sub-types of lymphoma among different populations is notable, which leads to the speculation that environmental factors such as infectious agents and/or host factors, genetic or immunological, may play important pathogenetic roles, and influence the development of these malignancies.²⁻⁵ There are strong associations between the pattern of lymphoma and socio-economic status.² Many infectious agents such as Epstein-Barr virus (EBV), human herpesvirus-8, human T-cell leukaemia virus, hepatitis C

virus and *Helicobacter pylori* have been aetiologically associated with lymphatic malignancies.²⁻⁴ The chances of acquiring infections especially at a young age are higher in developing countries.² In tropical African countries where a higher incidence of Burkitt's lymphoma is present in children, it is believed to be the result of concomitant infection by EBV and malaria, associated with low socio-economic status. A hypothesis has been put forward recently incriminating immunosuppression for the increased incidence of non-Hodgkin lymphoma (NHL) world wide, through increased exposure to sunlight which possesses immunosuppressive effects, and/or exposure to herbicides, insecticides and organic solvents which can alter cell-mediated immunity.'

The ethnic distribution of East Malaysian populations differs between the two states of Sabah and Sarawak, and also from that of West Malaysia. The socio-economic status probably also differs amongst these populations. Hence, the pattern and frequency of different types of lymphoma are likely to vary. This study aims to

analyse cases of lymphoma in East Malaysia using a recently proposed scheme of classification.

MATERIALS AND METHODS

Between June 1981 and December 1983, a total of 16,533 surgical biopsies from East Malaysia (9,719 from Sarawak; 6,742 from Sabah) were sent to the Department of Pathology, University of Malaya for histological diagnosis, of which a total of 142 cases of lymphoma were diagnosed histologically. They were retrieved from the files for the study. The pathologist (SCP) reviewed all these cases with additional immunohistochemical staining on serial sections using a panel of antibodies.⁶ 35 cases were excluded from further analysis. 17 of these cases were found to be non-lymphoma while 18 others were excluded because of insufficient material for further study. The remaining 107 lymphoma cases were studied and classified using the Rye classification for Hodgkin's lymphoma (HL)⁷ and the Revised European-American Classification of Lymphoid Neoplasm (REAL) classification for non-Hodgkin's lymphoma (NHL).⁸ All of the cases were tested for the presence of Epstein-Barr virus by *in-situ* hybridisation for Epstein-Barr virus encoded RNAs (EBER).

Immunohistochemistry

A standard three-stage immunoperoxidase method was performed using LSAB®+ kit (Dako, Denmark) and a panel of lymphoid antibodies mostly from Dako (Denmark) unless otherwise specified: CD3, CD15 (Leu-M1, Becton-Dickinson, USA), CD20 (L26), CD21, CD30 (BerH2), CD43 (MT1, compliment from Professor S Poppema), CD45RO (UCHL1), CD57 (Leu-7, Becton-Dickinson, USA), CD68 (PGM1), a-kappa, α-lambda, CD79α (compliment from Professor D. Mason), CD5 and CD23 (compliment from Dr. Imam). Additional antibodies such as Neuron-Specific Enolase (NSE), cytokeratin (MNF116), and vimentin (V9) were applied for reconfirmation or exclusion of lymphoma. Antigen retrieval methods with microwave treatment or pre-digestion in trypsin were used in most instances and without retrieval steps for CD15, UCHL1 and CD68 (PGM1).

In-situ hybridisation

All sub-groups of lymphoma were tested for the

presence of EBV by using EBV encoded RNAs (EBER) *in-situ* hybridisation (ISH) technique with the fluoroisothiocyanate labelled peptide nucleic acid (PNA) probes (Y5200, Dako, Denmark). The hybridisation steps were performed in RNase free environment. Subsequently, visualisation was achieved with PNA-ISH detection kit (K5201, Dakopatts, Denmark). A known EBV-positive nasopharyngeal carcinoma was used as an external positive control.

RESULTS

Of the 107 cases of lymphoma, 61 (57.0%) and 46 (43.0%) were from Sarawak and Sabah respectively (Table 1). There were 66 (62.0%) males, 41 (38.0%) females, and a male:female ratio of 1.6:1. Their ages ranged from 2 to 78 years with a mean age of 41 years old. There were 13 (12.1%) children (14 years old and below) and 94 (87.9%) adults (above 14 years old). The ethnic distribution was 17 (15.8%) Malay, 13 (12.1%) Chinese, 1 (1.1%) Indian, 35 (32.7%) Sarawak and 41 (38.3%) Sabah indigenous groups respectively. The majority of the cases were from the indigenous populations (76/107, 71%). The Ibans and Kadazans were the most common indigenous groups in Sarawak and Sabah respectively. The indigenous ethnic population in Sabah constituted 91.2% (41/46) of all the cases from that state.

There were a total of 11 cases (10.3%) of Hodgkin's lymphoma and 96 (89.7%) non-Hodgkin's lymphoma (Table 2). The HL: NHL ratio was 1:9. The most common Hodgkin's lymphoma type was nodular sclerosis (6/11). The non-Hodgkin's lymphoma were composed of 80 (83.3%) B-cell and 16 (16.7%) T-cell phenotypes. The most common lymphoma in East Malaysia was B-cell large cell type (46.7%), followed by Burkitt's lymphoma (14%) and peripheral T-cell lymphoma (PTCL) unspecified (11.2%).

In children, both the cases of HL were of the lymphocyte predominance subtype. Burkitt's lymphoma ranked the highest (7/13, 53.8%) among the children. There was one case each of B-cell large cell type, peripheral T-cell lymphoma unspecified, T-anaplastic large cell lymphoma and T-cell acute lymphoblastic lymphoma.

In the adult group, there were 9 cases of Hodgkin's lymphoma (9.6%), 72 (76.6%) B-cell lymphoma and 13 (13.8%) T-cell lymphoma, giving a B:T ratio of 6:1. The most common

TABLE 1: Distribution of East Malaysian cases of lymphoma by sex, ethnicity and location

State	Race	Children (n=13, 12.1%)		Adult (n=94, 87.9%)		Total
		Female	Male	Female	Male	
Sarawak (n=61, 57%)	Malay	0	0	4	11	15
	Chinese	1	2	2	6	11
	Indian	0	0	0	0	0
	Sarawak indigenous tribes	1	4	18	12	35
Sabah (n=46, 43%)	Malay	0	0	0	2	2
	Chinese	0	0	1	1	2
	Indian	0	0	1	0	1
	Sabah indigenous tribes	1	4	12	24	41
Total		3	10	38	56	107

subtype of Hodgkin's lymphoma in the adults was nodular sclerosis. Diffuse large cell B-cell lymphoma constituted the largest group of tumours (54.3%), followed by peripheral T-cell

lymphoma unspecified (11.6%) and Burkitt's lymphoma (8.5%). Others were follicular lymphoma (5.3%), MALT (2.1%), mantle-cell lymphoma (1.1%), T-cell anaplastic large cell

TABLE 2: Pattern of malignant lymphoma in East Malaysia

Diagnosis		Children (< 15 years)		Adult (≥ 15 years)		Total	
		No	%	No	%	No	%
Hodgkin's lymphoma (n=11, 10.3%)	Lymphocyte predominance	2	15.4	0	0	2	1.9
	Mixed cellularity	0	0	3	3.2	3	2.8
	Nodular sclerosis	0	0	6	6.4	6	5.6
Non-Hodgkin's lymphoma (n=96, 89.7%)	B-NHL large cell	1	7.7	49	52.2	50	46.7
	B-NHL large cell CD30+	0	0	2	2.1	2	1.9
	Burkitt's lymphoma	7	53.8	8	8.5	15	14
	Follicular lymphoma	0	0	5	5.3	5	4.7
	MALT	0	0	2	2.1	2	1.9
	Mantle cell lymphoma	0	0	1	1.1	1	0.9
	B-NHL (NOS)	0	0	5	5.3	5	4.7
	PTCL unspecified	1	7.7	11	11.6	12	11.2
	T-ALCL	1	7.7	1	1.1	2	1.9
	T-ALL	1	7.7	1	1.1	2	1.9
TOTAL		13	100	94	100	107	100

NHL = non-Hodgkin's lymphoma, NOS = not otherwise specified, MALT = mucosa associated lymphoid tissue, PTCL = peripheral T-cell lymphoma, T-ALCL = T-anaplastic large cell lymphoma, T-ALL = T-cell acute lymphoblastic lymphoma

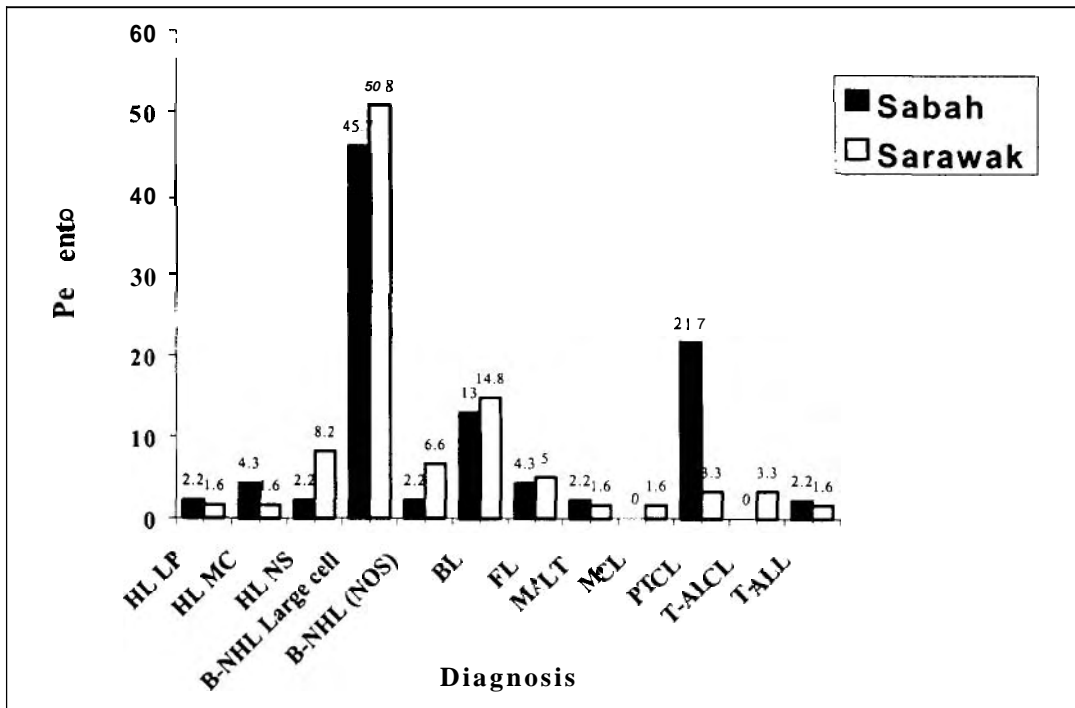


FIG. 1: Prevalence distribution of lymphoma in Sabah and Sarawak.

lymphoma (1.1%) and T-cell acute lymphoblastic lymphoma (1.1%). Five cases of B-cell lymphoma could not be subtyped (not otherwise specified, NOS) due to sub-optimal morphology in the study material.

The distribution pattern of lymphomas in Sabah and Sarawak is as shown in Figure 1. In both the states, the most common lesion was diffuse large cell B-cell lymphoma. The most common subtype of Hodgkin's lymphoma in Sabah was mixed-cellularity and nodular sclerosis in Sarawak. The prevalence of

peripheral T-cell lymphoma unspecified was very low in Sarawak (3.3%) when compared to Sabah (21.7%).

It was clearly shown that Hodgkin's lymphoma, Burkitt's lymphoma and T-NHL are more commonly associated with EBV compared to B-NHL. EBV were detected in the tumour cells of 33.3% (3/9) of classical Hodgkin's lymphoma, 56.3% (9/16) of T-cell lymphoma, 60.0% (9/15) of Burkitt's lymphoma and 3.1% (2/65) of B-NHL (Table 3).

TABLE 3: EBV association in Hodgkin's lymphoma, Non-Hodgkin's lymphoma and Burkitt's lymphoma in East Malaysian patients

Diagnosis	Total Number of cases	EBV Positive No (%)
Hodgkin's lymphoma		
Lymphocyte predominance	2	0 (0.0%)
Mixed cellularity	3	2 (66.7%)
Nodular sclerosis	6	1 (14.7%)
T-NHL	16	9 (56.3%)
B-NHL	65	2 (3.1%)
Burkitt's lymphoma	15	9 (60.0%)
Total	107	23 (21.5%)

T-NHL = T-cell non-Hodgkin's lymphoma, B-NHL = B-cell non-Hodgkin's lymphoma

DISCUSSION

Lymphoma constituted 4.5% and 3.5% of cancers in Sarawak and Sabah respectively in the period between 1981 to 1983, and ranked among the top ten cancers in East Malaysia." The indigenous population in Sabah and Sarawak were well represented in this cohort of cases, as they constituted the majority of patients in this study. The results showed that the overall pattern of lymphoma in East Malaysia was rather similar to West Malaysia,¹⁰ Hong Kong" and Japan," where the HL: NHL ratio was 1:9. The incidence of Hodgkin's lymphoma in this region was low when compared to the figures of approximately 40% from various studies involving Western populations.¹⁷ The most common subtype of Hodgkin's lymphoma in the adults of East and West Malaysia was nodular sclerosis,¹³ whereas in West Malaysian children, it was the mixed-cellularity subtype. The number of childhood HL in East Malaysia was very small and both cases were of the lymphocyte predominance subtype. The prevalence of Burkitt's lymphoma in East Malaysian children (58.3%) was similar to Papua New Guinea.¹⁴

The pattern of NHL in adults showed some differences from West Malaysia.¹⁰ There were fewer follicular lymphoma in East Malaysia (5.4%) when compared to West Malaysia (13.0%).¹⁶ The latter appeared to concur with data published from studies on other Asian populations, such as Japan (10.0%)¹² and Hong Kong (13.2%).¹¹ Reports from the United States of America and Europe indicated that follicular lymphoma were far more common in these countries, constituting 44.0% and 21.0% of lymphoma in United States of America and Europe respectively,¹² implying geographical differences in disease incidence. The low prevalence of T-NHL in East Malaysian patients (14.9%) was more similar to the pattern seen in the Western countries (10-20%)¹² and Thailand (16.1%)¹⁷ but differ from many other Asian countries.¹⁸⁻²²

The pattern of lymphoma in Sabah and Sarawak were relatively similar, except for a very low prevalence of T-NHL in Sarawak (3.3%). The observed difference may be due to the genetic factors, since both groups were living in comparable environment.

There was a relatively lower association of EBV with Hodgkin's lymphoma in East Malaysia (33.3%) when compared with studies from West Malaysia (60%)¹³ and Kenya (92%).¹⁵ The reason is not clear. It may be due to the small number

of childhood classical Hodgkin's lymphoma cases encountered in the East Malaysian patient group since the West Malaysia data showed a very close association of EBV and childhood Hodgkin's lymphoma.¹³ However, the EBV association rate in Burkitt's lymphoma (60%) and T-cell lymphoma (56.3%) were higher when compared to West Malaysian studies, being 38.0% and 33.0% respectively.¹⁰ This might be due to the differences in the socio-economic status.

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