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Spectrum of malignant lymphomas in Klang Hospital, a public hospital in Malaysia

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Abstract

Background: Lymphoma is a relatively common group of neoplasms diagnosed in hospital practice. This study aims to elucidate the pattern of this disease encountered in a public service hospital of the Ministry of Health, Malaysia. Materials and methods: A total of 98 biopsies from 92 patients were 'retrieved from the archives of Klang General Hospital, from January 1993 to June 1999. The histopathology of these biopsies were reviewed by two pathologists, and confirmed cases were sub-classified according to the WHO proposed scheme. Immunohistochemical staining with a panel of lymphoid antibodies was performed in aid of sub-typing. All cases were screened for Epstein-Barr virus association by ***in-situ*** hybridisation technique. Results: 15 biopsies were excluded from further analysis due to inadequate material for further study or diagnosed as non-lymphoma. The remaining 83 biopsies were from 80 patients. 52 were males and 28 females. The male: female ratio was 1.9: 1. There were 64 Malays, 4 Chinese and 12 Indians. The ages of patients ranged from 3 to 86 years with a mean age of 50.5 years. 73.8% of the diagnostic materials were nodal tissue. Fourteen patients had Hodgkin's lymphomas (HL), 6 being mixed-cellularity, 4 nodular-sclerosis, 1 lymphocyte-rich, 2 lymphocyte-depleted, 1 lymphocyte-predominant, and 66 had non-Hodgkin's lymphomas (NHL). The HL: NHL ratio was 1:4.7. Of the 66 cases of NHL, 9 (13.6%) were T- and 57 (86.4%) B-cell types. The most common NHL encountered was diffuse large B-cell type. Follicular-lymphoma constituted 16.7% of these NHL. 77.8% of T-NHL and 10.5% of B-NHL was EBV associated. Double staining of EBER with CD20 and EBER with CD3 in the T-NHL cases showed that in a majority of the cases, EBER-positive large cells did not express the T- or B- cell antigen. Conclusion: There is a relatively small proportion of T-cell lymphoma in this series of Asian patients. The reason is thought to be the lower utilisation rate of this hospital service by ethnic Chinese, as reflected by the hospital admission data.

Key words: Epstein-Barr virus, Hodgkin's lymphoma, non-Hodgkin's lymphoma.

INTRODUCTION

Lymphoma is a heterogeneous group of neoplasm. Geographical variations in incidence rate and relative frequency of subtypes of lymphomas around the world have been well documented,[1-5] for example, a greater percentage of follicular lymphoma is seen in the Western countries,[1-2] T-cell lymphomas are more common in Asia[1-2] and Burkitt's lymphoma occurs more frequently in tropical African countries.[4-6] One possible explanation for these disparities might be a complex interplay between various environmental and inherited genetic factors.[2-7] Many infectious agents such as Epstein-Barr virus, human herpes virus-8, human T-cell lymphotrophic virus-1, human imrnunodeficiency virus and ***Helicobacter pylori*** have been implicated as possible aetiological agents in lymphoid malignancies.[3,5-7] Some studies have also shown strong association between the pattern of lymphomas and socio-economic status.[3,6] Many recent reports indicated that exposure to insecticides, herbicides, organic solvents and sunlight can alter the immune system and play a role in the pathogenesis of lymphomas,[3] and was proposed as a possible explanation for the worldwide trend of increased incidence of non-Hodgkin's lymphomas.[3]

With advancement of knowledge on the immune cells achievable with improved histologic and molecular techniques for investigations, applicable even on archival

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materials, recent classifications of lymphomas exploit this new knowledge on their biological properties to subtype lymphomas. However, these methods of investigation and sub-typing of these tumours are usually readily available only in research-based, tertiary-education-affiliated hospitals in Malaysia.[8-11] Therefore, there is generally a lack of information on the spectrum of lymphomas encountered in other hospitals in Malaysia. In collaboration with the academic Department of Pathology, University Hospital Kuala Lumpur, this study aimed to elucidate the pattern of lymphomas encountered in Klang Hospital, a public service hospital that serves a large coastal town and the nearby rural populations from the villages. The utilisation of the services by the various ethnic groups. is known to differ from the collaborating teaching hospital.

MATERIALS AND METHOD

A total of 98 biopsies from 92 patients were retrieved from the files of the Department of Pathology, Klang General Hospital over a period of six and a half years (January 1993 to June 1999). All these archival materials were formalin-fixed and paraffii-embedded. The Haematoxylin and Eosin (H&E) stained slides were reviewed by two pathologists (SCP & NT). Immunohistochemical staining methods were performed on serial sections of the archival tissue using a panel of antibodies in aid of the diagnosis. Sub-typing of these lymphomas was based on the recently proposed WHO scheme. Cases with poorly preserved morphology for proper sub-typing were classified as not-otherwise specified (NOS). All confirmed cases of lymphoma were tested for the presence of Epstein-Barr virus (EBV) by *in situ* hybridisation detection technique for EBV early RNAs (EBER). All cases of T-cell lymphomas were double-stained with EBER and CD3 or CD20 (L26). The demographic data of patients and the site of biopsies were extracted from the case information recorded in the Department of Pathology, Klang General Hospital.

Immunohistochemistry

Imrnunohistochemical staining was performed routinely using a panel of antibodies to lymphoid markers and oncogene products: CD3 (polyclonal), CD20 (L26), CD21 (1F8), CD30 (BerH2), CD45RO (UCHL1), CD68 (PGM1), a-kappa, a-lambda, Bcl-2 (124) and Ki-67 (polyclonal) all from Dako, Denmark; CD5, CD23 (1B12), CD56 (1B6) from Novocastra, United Kingdom; CD15 (Leu-M1), CD57 (Leu-7) from Becton Dickinson, USA; CD79a (HM57, gift from Professor D. Mason); CD43 (MT1, gift from Professor S. Poppema). Additional antibodies such as cytokeratin (Mnf116), Vimentin (V9), epithelial membrane antigen, EMA (E29), Desmin (D33), Actin (1A4), melanoma antigen (HMB45), all from Dako, Denmark were also applied when deemed necessary for reconfirmation or exclusion of lymphomas. Antigen retrieval with microwave pre-treatment or pre-digestion in trypsin was routinely carried out depending on the antibodies used. A standard peroxidase-labelled Avidin-Biotin Complex (ABC) system (Dako, Denmark) was employed in the staining technique. DAB was used as the substrate for colour development.

In Situ Hybridisation

All confirmed cases of lymphoma were tested for the presence of EBV by in *situ* hybridisation detection technique for EBV early RNAs (EBER). EBV peptide nucleic acid (PNA) probes labelled with fluoroisothiocynate, FITC (Y5200, Dako, Denmark) was employed and detected by alkaline phosphatase-conjugated rabbit anti-FITC antibodies. Colour development was achieved by using the substrate, 4-nitro-blue-tretrazolium chloride/5-bromo-4-chloro-3-indolyl-phosphate (NBT/BCIP). A known case of EBV-infected nasopharyngeal carcinoma was used as external positive control for the staining technique.

Double-stained EBER in situ hybridisation and CD3 or CD20 immunohistochemistry

Double labelling of EBER and CD3 or CD20 was performed in all cases of confirmed T-cell non-Hodgkin's lymphoma. The EBER-ISH step was first performed then followed by immunohistochemical stain for T-cell (CD3) or B-cell (CD20) antigens. In brief, the tissue sections were pretreated with proteinase digestion, followed by hybridization and detection procedures. After colour development, the sections were then subjected to microwave pretreatment and then primary antibody incubation. To achieve better contrast of visualisation, AEC (Amino -Ethyl-Carbazole) which gives a red colour reaction was used as the substrate for the peroxidase-conjugated detection system employed in the immunohistochemical staining steps. The ISH-

immunohistochemical double-stained sections were finally lightly counter-stained in Meyer's haematoxylin.

RESULTS

Of the 98 biopsies from 92 patients, materials from twelve patients (15 biopsies) were excluded from analysis due to insufficient or inadequate remaining tissue for further study, or re-classification as non-lymphoma. There were 80 patients with re-confirmed lymphomas, 52 (65%) males and 28 (35%) females, giving a male: female ratio of 1.9: 1. The ages of these patients ranged from 3 to 86 years, with a mean age of 50.5 years (Fig.1). Five patients (6.3%) were children, aged <15 years old. There were 64 (80%) Malays, 4 (5%) Chinese and 12 (15%) Indians, giving a Malay: Chinese: Indian ratio of 1: 0.06: 0.19.

There were 14 (17.5%) patients with Hodgkin's lymphoma (HL) and 66 (82.5%) with non-Hodglun's lymphoma (NHL). The HL: NHL ratio was 1: 4.7 (Table 1). Classical Hodgkin's lymphomas constituted 92.8% (13/14), the most frequent morphological subtype encountered was mixed-cellularity (6/13). Seven of these 13 classical Hodgkin's lymphomas (53.8%) showed presence of EBER in the Reed-Sternberg cells, of which 3 were mixed cellularity (50%). Among the two cases of childhood Hodgkin's lymphoma (one each of mixed-cellularity and nodular sclerosis), the mixed-cellularity subtype was EBV associated. There was only one case of lymphocyte predominant Hodgkin's lymphoma, which did not show the presence of EBER in the L&H cells.

Amongst the NHL, there were 57 (86.4%) B-cell and 9 (13.6%) T-cell types (Table 1). The most common subtype of B-NHL encountered was diffuse large B-cell type (47.0%, 31/66), followed by follicular lymphoma (16.7%, 11/66). The small-cell lymphomas, lymphocytic and lymphoplasmacytic types occurred infrequently, there being 1 and 2 cases diagnosed respectively. There were 6 cases of marginal-zone lymphoma, 1 occurred in the lymph node and 5 were in extra-nodal tissue. All the three cases of Burkitt's lymphoma were from children <15 years old. Six (10.5%) of the B-NHL were EBV associated, 2 of them were Burkitt's lymphomas, and both showed extra-nodal presentation. All the T-cell lymphomas were peripheral types: 6 unspecified, 1 angio-immunoblastic, 2 T/NK-cell type. Both the T/NK-cell lymphomas expressed CD56 and EBER (Fig. 2a). Double-stainingshowed co-expression

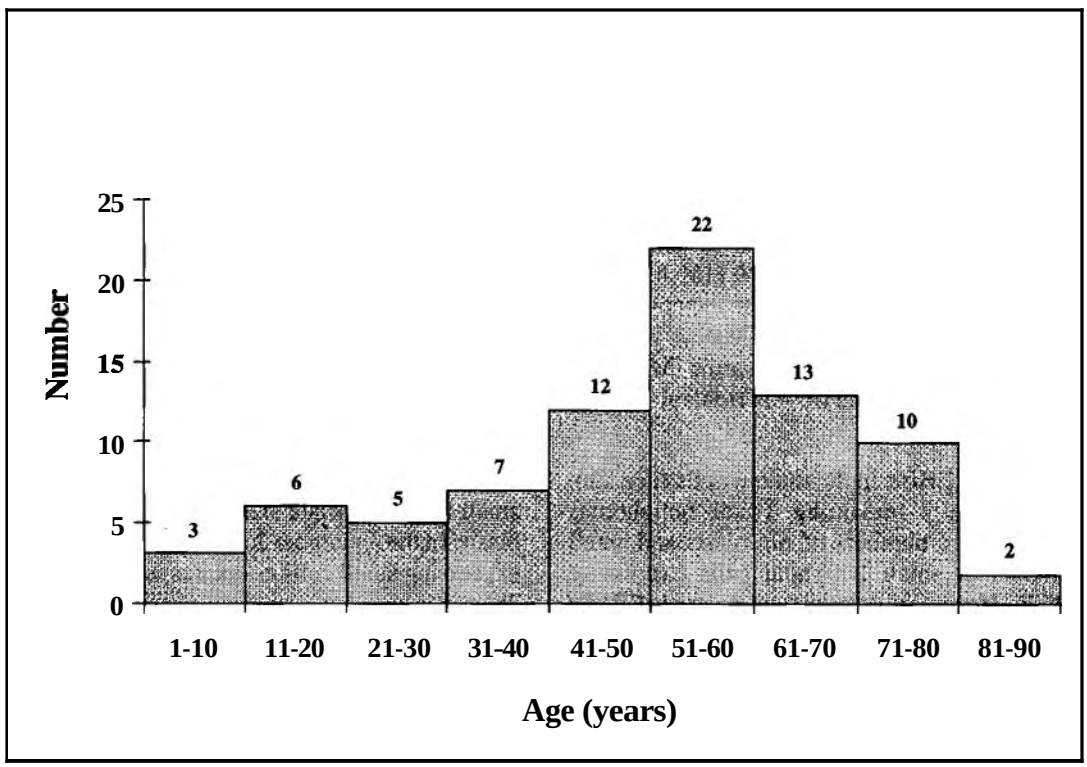

FIG. 1: Age distribution of lymphoma patients in Klang Hospital, January 1993 to June 1999.

Table 1: Spectrum of lymphomas in Klang General Hospital by ethnic and age group distribution and EBV association

Diagnosis	No. (%)	Ethnic group			Age group		EBER +ve
		M	C	I	<15 yr.	215 yr.	No. (%)
B-NHL	57 (71.3)	47	4	6	3	54	**6(10.5)**
Lymphocytic	1 (1.3)	1	–	–	–	1	–
Lymphoplasmacytic/ Immunocytoma	2 (2.5)	2	–	–	–	2	–
Marginal Zone / MALT	6 (7.4)	5	1	–	–	6	–
a. Nodal	*1 (1.3)*	*1*	–	–		*1*	–
b. *extranodal*	*5 (6.1)*	*4*	*1*	–	–	*5*	–
Follicular	11 (13.7)	11	–	–	–	11	–
Diffuse large B-cell	31 (38.8)	29	3	5	–	31	4 (12.9)
a. Unspecified variant	*30 (37.5)*	22	*3*	*5*	–	*30*	*3*
b. T-cell rich	*1 (1.3)*	*1*	–	–	–	*1*	*1*
Burkitt's lymphoma	3 (3.8)	3	–	–	3	–	2 (66.7)
NOS	3 (3.8)	3	–	–	–	3	–
T NHL	**9 (11.2)**	7	–	2	–	**9**	7 (77.8)
PTCL-unspecified	6 (7.4)	5	–		1 –	6	4 (66.7)
PTCL-AILD	1 (1.3)	–	–	1	–	**1**	1 (100.0)
T-NK cell lymphoma	2 (2.5)	2	–	–	–	2	2 (100.0)
Hodgkin's Lymphomas	**14(17.5)**	10	–	4	2	12	**7** (50.0)
Mixed cellularity	6 (7.4)	4	–		2 1	5	3 (50.0)
Nodular sclerosis	4 (5.0)	3	–		1 1	3	1 (25.0)
Lymphocyte depleted	2 (2.5)	1	–		1 –	2	2 (100.0)
Lymphocyte rich	1 (1.3)	1	–	–	–	1	1 (100.0)
Lymphocyte predominant	1 (1.3)	1	–	–	–	1	**0** (0)
Total Cases	SO (100.0)	64	4	12	5	75	20 (25.0)

C = Chinese; I = Indian; M = Malay; yr = years; AILD = angioimmunoblastic lymphadenopathy dysproteinaemia; MALT = mucosa associated lymphoid tissue; NOS = not otherwise specified; PTCL = peripheral T-cell lymphoma; T/NK - T/natural killer cell; +ve =positive

of CD3 and EBER in the tumour cells (Fig. 2b). Five of the 7 remaining T-cell lymphomas showed large numbers of big blasts and small numbers of small lymphoid cells expressing EBER. However, double-staining with EBER/ CD3 and EBER/CD20 (L26) revealed that a majority of the EBER-positive cells, especially the big blasts did not co-express CD3 or CD20. Two cases showed co-expression of EBER and CD3 in a small proportion of cells (–10%) ranging from small cells to big blasts (Fig. 3a), one case showed co-expression of the above in small to intermediate size cells, but not the big blasts. In the remainder 2, minority of the EBER-expressing small cells co-expressed CD20 (Fig. 3b).

Lymph nodes were the most common tissue excised for confirmation of diagnosis (68.7%, 57/84), the majority was from the head and neck region (66.7%, 38/57) (Table 2). All cases of Hodgkin's lymphomas were diagnosed in the lymph nodes. The 5 extra-nodal marginal-zone

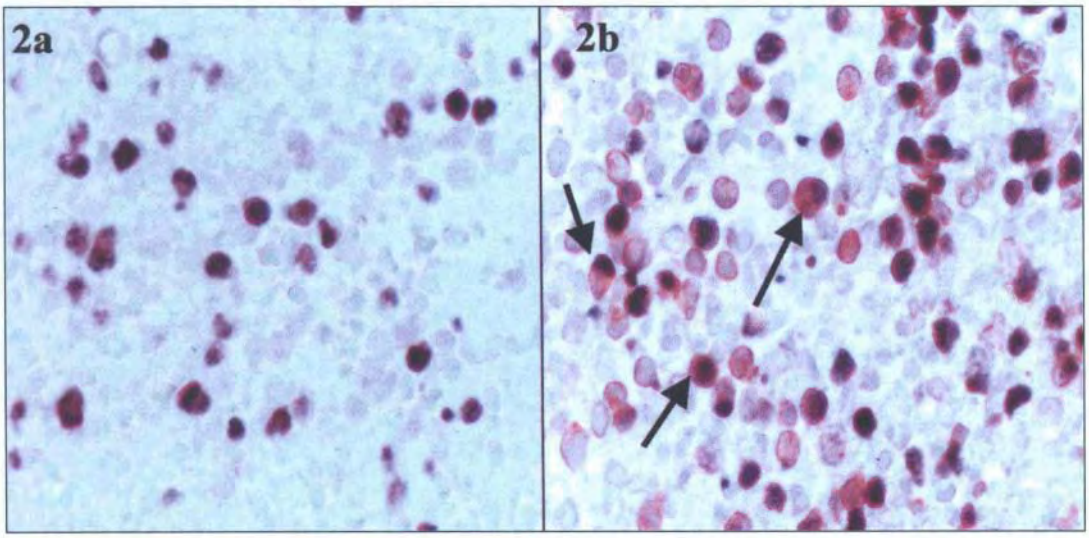

FIG. 2: T/NK-cell lymphoma (a) EBER positive cells, EBER-ISH. (b) Co-expression of CD3 and EBER in the tumour cells. Double-staining of EBER-ISH and CD3 immunohistochemistry (X600).

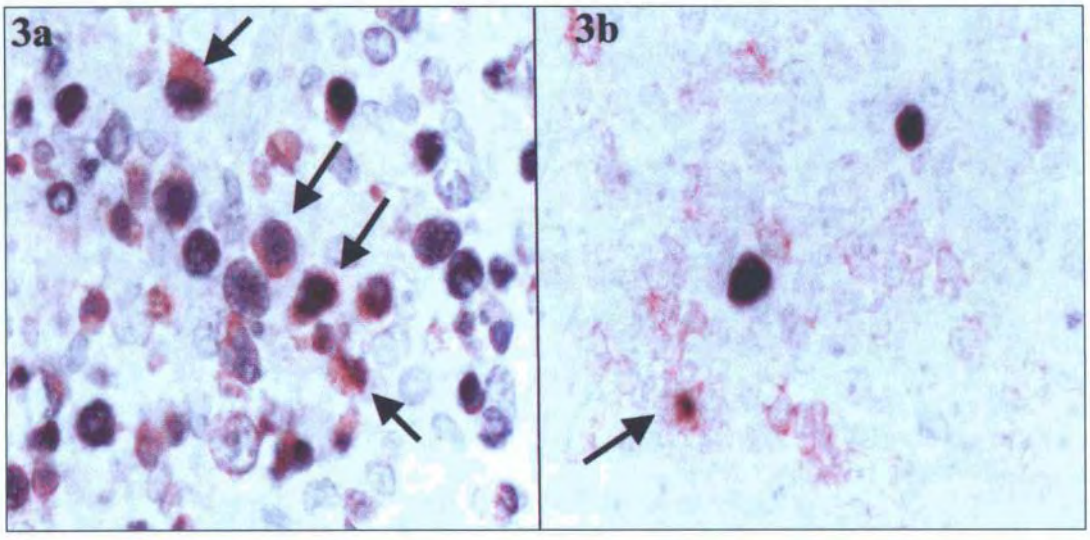

FIG. 3: Peripheral T-cell lymphomas: (a) Small proportion of small cells to big blasts showed co-expression of EBER and CD3. Double-stained EBER-ISH and CD3 immunohistochemistry. (b) Co-expression of EBER/CD20 in small cells but not in big blasts. Double-stained EBER-ISH and CD20 immunohistochemistry. (X 600)

B-cell/MALT lymphomas were seen in the orbit (3), thyroid (1) and gastrointestinal tract (1). Of the 3 cases of Burkitt's lymphomas, 2 were extra-nodal (gut and gum). The 2 T/NK lymphomas occurred in extra-nodal tissue, one each in upper-aerodigestive tract (maxillary sinus) and skin (inguinal region). One other case of peripheral T-cell lymphoma occurred in the jejunum.

DISCUSSION

Klang, a district in the state of Selangor, and Klang Hospital serves a population of four hundred thousand in the district.[12] In this series, we noticed a much higher percentage of Malay patients (80%) when compared to Chinese (5%) and Indians (15%), whereas the population census of 1991 showed that the ethnic distribution in this district was 38.1% Malays, 37.0% Chinese, 20.2% Indians and 4.8% others.[12]

Table 2: Site of Biopsy of Lymphoma cases in Klang General Hospital

Site of Biopsy	B-NHL No.	T-NHL No.	HL No.	Total No. (%)
Nodal	38	5	**14**	57 (68.7%)
Head & Neck	24	4	10	38
Deep nodes#	2	–	2	4
Axillary & inguinal	7	1	1	9
Unspecified	5	–	1	6
Extranodal	**19**	**4**	**0**	23 (27.7%)
Gastrointestinal	5	1	–	6
Nasal	–	1	–	1
Tonsil	3	–	–	3
Thyroid	1	–	–	1
Testis	2	–	–	2
Orbital	3	–	–	3
Gum	1	–	–	1
Adrenal gland	1	–		1
Thigh mass	1	–	–	1
Bone	2	–	–	2
Skin	–	1	–	1
Maxillary	–	1	–	1
Unavailable	3	–	–	3 (3.6%)
Total Biopsies	**60**	**9**	**14**	**83* (100.0%)**

Deep nodes = hilar, mesentric and para-aortic lymph nodes
* Three patients had two biopsies each.

However, unpublished hospital admission data from 1993 to 1998 showed an ethnic distribution of 53.1% Malays, 13.9% Chinese, 26.8% Indians and others 6.1%. Hence, our observation could be partly explained by the higher utilisation of the hospital facilities by ethnic Malays.

The HL: NHL ratio in this hospital was 1: 4.7, showing a higher incidence of HL when compared to other studies from the University Hospital Kuala Lumpur (UHKL),[10] East Malaysia,[13] Hong Kong[14] and Japan.[15] The reason is not immediately apparent. However, the EBV association in adult classical HL (54.5%, 6/11) was rather similar to that from the report of Peh et *al*[11] in the other Malaysian series. EBV association in the childhood HL were rather low compared to reports from Peh et *al*[11] and the Kenya series[5] which showed an almost 100% EBV association, but was similar to the Italian series[5] (33%). This discrepancy could be due to the small number of childhood HL (2 cases only) seen in this study.

The pattern of B-NHL observed in this study was rather similar to the study of Peh[10] and other Asian countries, such as Hong Kong,[14] Japan,[15] and Thailand,[16] where the most common subtype encountered was diffuse large B-cell type. Similar to other Asian experience, there is a lower incidence of follicular lymphomas (–15%) when compared to Western countries (> 30%).[1,2,16] All the three cases of Burkitt's lymphoma were diagnosed in children, in keeping with reports that claimed more common occurrence of Burkitt's lymphoma in children.[4,10,17] T-NHL comprised only 13.6% in this series. This finding was similar to the reports from East Malaysia,[13] Thailand,[16] United States of America[16] and Nigeria[18] (<20%), but differs from other 'Chinese' populated Asian countries such as Taiwan,[16] Hong Kong,[19-20] China[21] and Korea.[22] The small numbers of Chinese patients admitted to this hospital is thought to be responsible for this observed characteristic.

77.8% of our PTCL were EBV associated. It was higher when compared to other reports from Hong Kong,[23] Korea[24] and the Europeans[25] which showed 40-58% EBV positive rates in their cases. The double stained EBER/CD3 and EBER/CD20 pattern differs from reports of Ho et *al*[23] and d'Amore et *al*.[26] Ho et *al*[23] showed

that a majority of their T-NHL co-expressed EBER/CD20 in the small to large atypical blast-like cells whereas d'Amore *et al*[26] showed EBER/CD3 co-expression in a majority of neoplastic cells. Our findings however concurs with De Bruin *et al*,[27] who showed 80% of the EBV positive cells did not co-express either T- or B-cell markers. The reasons for these heterogeneous discrepancies between series were not immediately known. Worthy of note was De Bruin *et al*'s[27] proposal that the EBV infected cells might have caused the down-regulation of these specific cellular markers.

CONCLUSION

The pattern of lymphomas encountered in Klang Hospital did not differ significantly from that shown by other studies in Malaysia and other Asian countries except for a lower incidence of T-NHL. The predominance of Malay patients in this series, possibly due to higher utilisation of the hospital facilities by ethnic Malay may explain the observed difference.

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