Malaysian J Pathol 1990; 12(2): 77 – 88

THE SPECTRUM OF LYMPHOMA IN MALAYSIA: A HISTOPATHOLOGICAL STUDY UTILIZING IMMUNOPHENOTYPING.

K MANCER M D BSc (Med) FRCPC.

Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur.

Summary

A retrospective study was made to determine relative incidence of lymphoma subtypes in Malaysia. High grade non-Hodgkin's lymphoma was found to be common. Low grade non-Hodgkin's lymphoma and Hodgkin's disease were relatively rare in this Malaysian series. Non-Hodgkin's lymphoma of B-cell immunophenotype was four times as common as that of T-cell lineage. There was a high incidence of primary extranodal non-Hodgkin's lymphoma.

Keywords: Lymphoma, Hodgkin's, non-Hodgkin's, immunophenotype.

INTRODUCTION

During a sabbatical spent in Malaysia it became apparent that there was considerable difference in incidence of the various lymphoma types as compared to North America and Europe, the sources of most of the published experience. Accordingly, a retrospective histopathological study was initiated to determine incidence of the types of lymphoma in Malaysia.

MATERIALS AND METHODS

Paraffin blocks from cases diagnosed as lymphoma over the years 1983 to 1987 were retrieved from storage at the Medical Faculty of Universiti Kebangsaan Malaysia. Haematoxylin and eosin stained sections were classified without knowledge of the original diagnosis. Depending on the working diagnosis, various immunohistochemistry techniques were employed, these procedures being done in the Immunopathology Laboratory of the Hospital for Sick Children, Toronto. The monoclonal antibodies ML, MT1, MB2, MT2 and LN1 (Biotest) were used, with controls, to indicate non-Hodgkin's lymphoma as B or T immunophenotype. Leu M1 was used as an indicator of Reed-Sternberg cells when Hodgkin's disease was being considered. When the diagnosis of lymphoma was in doubt, the monoclonal antibodies to cytokeratin (Becton-Dickinson) vimentin (BIOGENEX), NSE (Dako), S-100 (Dako) were used, when indicated.

Hodgkin's disease was classified according to the Rye classification.[1] The presence of lacunar cells and birifringent collagen was taken as indicating nodular sclerosis subtype.[2]

Non-Hodgkin's lymphoma was classified according to the Working Formulation.[3] An attempt was made to be as objective as possible in assignment of cases to the various subtype of non-Hodgkin's lymphoma. Nodular lymphoma was defined by presence of follicular or nodular histologic pattern. Large cells were those over three erythrocyte diameters (21 microns). More than fifteen of these per high power field qualified a tumour as large cell lymphoma. Small cells were defined as those less than two erythrocyte diameters. Less than five of larger than that size per high power field qualified as small cell lymphoma. The remainder of the tumours were considered as mixed small and large cell lymphoma. Non-cleaved cells have rounded nuclei and prominent nucleoli whereas the opposite features characterize cleaved cells. The presence of multinucleate cells indicated that a large cell lymphoma be classified as high grade.

RESULTS

Table 1 summarizes the 57 cases of lymphoma and indicates the relative incidence of Hodgkin's disease and non-Hodgkin's lymphoma.

Table 2 summarizes Hodgkin's disease cases by histological subtype. The biopsy that could not be further classified was a needle biopsy of liver that was too small to indicate a pattern for subclassification, but did show the diagnostic Reed-Sternberg cell, which was confirmed by the presence of the Leu M1 marker.

Table 3 summarizes 49 cases of non-Hodgkin's lymphoma, including the results of immunophenotyping.

Address for reprint requests: Dr. Kent Mancer, Department of Pathology, The Toronto Hospital, 200 Elizabeth Street, Toronto M5 G2 C4, Canada.

The patterns of staining of normal tonsillar controls with the antibodies used for B- and T-cell irnmunophenotyping are indicated in Table 4. In our laboratory, the antibodies ML and MT1 were reactive to the lymphocytes of the zones occupied predominantly by T-cells in normal lymphoid tissue (Fig. 1). Reactivity of the malignant cells of a lymphoma with these antibodies was considered as evidence of T-cell origin of the malignancy. ML is actually a mixture of MT1 and MB1 antibodies. The sample used in this study did not have activity against B-cell areas of control tonsil, and behaved similarly to MT1. The degree of staining of T-cell areas by ML was slightly increased over the sample of MT1.

The antibodies LN1, MT2 and MB2 concentrated in the B-cell zones of normal tonsil. When they stained the malignant cells of a lymphoma, B-cell origin was indicated. LN1 concentrated in the lymphocytes of the germinal centres (Figs 2 and 3). MT2 concentrated at the mantle zone (Fig. 4).

The reaction of the monoclonal antibody MB2 with normal tonsil simulated the combined effects of LNI and MT2, but with slightly lesser activity in the germinal centre than the mantle zone (Fig 5). It was considered a marker for all B-lymphocytes whereas mantle and germinal centre lymphocytes marked with MT2 and LN1 antibodies respectively. Activity of MT2 and LNI was most prominent at the periphery of the cell indicating that the marker antigen is located at the cell surface. An exception occurred in the case of LN1, which was found in some cases of lymphoma to also mark the cytoplasm in the form of a large dot at the hof of the cell (Fig. 6) This occurred in addition to the peripheral staining that was common to all the antibodies. MB2, reactive to a cytoplasmic antigen, concentrated in the entire cytoplasm.

TABLE 1
MALIGNANT LYMPHOMAS – 57 CASES

		Number of cases	Age range	Median age
I.	Hodgkin's disease	1	34	34
	Lymphocyte predominance			
	Mixed cellularity	3	51 – 58	52
	Lymphocyte depleted	1	27	27
	Nodular sclerosis	2	15 – 48	31
	Unclassified	1	52	52
	Total	8	15 – 58	50
II.	Non-Hodgkin's lymphoma			
	Low grade: 1			
	Follicular, mixed	1	38	38
	Intermediate grade: 29			
	Follicular, large cell	3	30 – 64	33
	Diffuse, small cleaved	6	27 – 72	48
	Diffuse, mixed	19	27 – 71	55
	Diffuse, large cell	1	63	63
	High grade: 19			
	Immunoblastic	13	4 – 70	56
	Lymphoblastic	5	8 – 26	16
	Small. non-cleaved	1	15	15
	Total	49	4 – 72	50

TABLE 2
8 HODGKIN'S DISEASE CASES : CLINICAL DATA

Histological subtype	Age	Sex	Race	Site of biopsy	Presenting symptoms and signs
Lymphocyte predoniinancc	37	M	Chinese	nasal	
Mixed cellularity	51	F	Chinese	supraclavicular node	right hypochondrial pain (hepatosplenomegaly)
	52	M	Malay	axillary node	axillary mass
	58	M	Malay	cervical node	cervical mass
Lymphocyte depleted	27	F	Chinese	supraclavicular node	fever
Nodular sclerosis	15	M	Malay	axillary node	anorexia, loss of weight fever, generalized lyriiphadenopathy
	48	M	Indian	inguinal node	sweats, inguinal mass
Unclassified	55	F	Chinese	liver (needle biopsy)	hepatosplenomegaly

When the antibodies were applied to lymphomas. the depth of staining was generally less than observed with controls, probably relating to decreased amount of antigen with dedifferentiation. Poorly differentiated lymphomas generally had lesser depth of staining than did well differentiated ones.

Nodular lymphomas retained the ability to react with the B-cell antibodies in a zonal fashion, with LNI concentrating centrally in the nodules and MT2 and MB2 concentrating at the periphery. As is observed with standard histological stains, the periphery of the nodule of a lymphoma is less sharply defined than the periphery of a germinal centre of normal lymphoid tissue (Fig. *6)*.

Diffuse lymphomas characteristically had immunoreactivity of a proportion of the component cells with each of the markers. It was important to observe immuno-localization in the malignant cells, generally the larger of the lymphoid cells comprising the malignant population. All lymphomas whether of B or T lineage tended to have a component of small normal T-lymphocytes.

Some larger apparently reactive T-cells were seen in some B-cell tumours. This feature was less prominent in the high grade tumours, particularly lymphoblastic and Burkitt-type lymphomas and some of the more histologically homogeneous immunoblastic lymphomas.

Diffuse B-cell lymphomas varied in the marker present in the malignant cells, some marking predominantly as follicular centre cells, some as mantle cells, and some with components of both of these cell types.

Hodgkin's disease lesions were made up of mixed groups of cells of B and T lineage with T-cells predominating. In all but one of the examples of Hodgkin's disease, the Reed-Sternberg cells were reactive to Leu M1. The case that had non-reactive Reed-Sternberg cells was of lymphocyte predominence type. In two Hodgkin's disease lesions (both mixed cellularity), the Reed-Sternberg cells reacted to MB2.

Cases originally considered as lymphoma that were deleted from the series included examples of reactive lymphoid tissue, and metastatic non-lymphomatous neoplasms. The reactive lesions were sometimes very difficult to differentiate from lymphoma on routine histology. Immunohistochemistry was helpful

TABLE 3
49 NON-HODGKIN'S LYMPHOMA CASES: CLINICAL DATA: HISTOLOGY AND IMMUNOPHENOTYPE

W.F. classification	Age	Sex	Race	Site of biopsy	Presenting	Histology	Immuno-phenotype
LOW GRADE							
Follicular, Mixed	38	F	Malay	cervical node	cervical mass		B
INTERMEDIATE GRADE							
Follicular, Large cell	30	M	Chinese	node	generalized nodes, hepato-splenomegaly		B
	33	M	Chinese	cervical node	cervical mass; fever, lethargy, loss of weight		B
	64	M	Indian	cervical node	cervical masses		B
Diffuse, Small cleaved	27	F	Malay	submandibular node	submandibular mass node	signet ring lymphoma	B
	35	F	Chinese	orbit	subconjunctival mass		B
	46	M	Malay	inguinal	inguinal mass		B
	50	F	Chinese	node			B
	64	F	Chinese	cervical node	cervical mass		B
	72	M	Malay	orbit	proptosis, anemia		B
Diffuse, Mixed	27	F	Chinese	nasal	nasal obstruction		T
	37	F	Chinese	node			N
	45	F	Malay	trephine			B
	48	F	Malay	inguinal node	fever, loss of weight, anorexia, inguinal mass		B
	48	F	Indian	skin	skin lesions for 4 yrs.	cutaneous T-cell lymphoma	T
	48	M	Chinese	cervical node, nasal	nasal and cervical masses		B
	48	M	Malay	epitroch-lear	generalized nodes, hepato-splenomegaly		B
	50	M	Malay	trephine	cervical, mass, hepatomegaly, pleural effusion		B
	52	F	Malay	naso-pharynx	cervical and right tonsillar masses		B
	53	M	Chinese	tonsil	tonsil mass		B
	55	M	Malay	rectal	fungating anal mass		B
	56	M	Malay	renal	acute renal failure abdominal mass		B
	57	M	Malay	cervical node	cervical mass		B
	59	F	Chinese	inguinal node	inguinal mass		B

	60	M	Malay	cervical node	cervical mass, abdominal pain		B
	62	F	Malay	inguinal node	inguinal mass		B
	64	F	Chinese	rectal	diarrhoea, cervical masses		B
	67	F	Malay	nasal	epistaxis, nasal mass		B
	71	F	Chinese	naso-pharynx	dysphagia		B
Diffuse, Large	54	M	Malay	inuinal node	inguinal mass		B
HIGH GRADE							
Large Cell, Immunoblastic	4	F	Malay	retroperitoneal node	vomiting, loss of weight, abdominal mass	clear cell	B
	9	M	Chinese	cervical node	cervical mass	poly-morphous	T
	27	M	Malay	submandibular node	orbital, submandibular masses	poly-morphous	T
	29	M	Malay	skin biopsy	skin lesions	poly-morphous (cutaneous T-cell lymphoma)	T
	47	M	Malay	nasal biopsy	nasal obstruction; antrum mass	plasrnacytoid	B
	55	M	Malay	tonsil	left tonsil mass	polymorphous	T
	56	M	Malay	cervical node	anorexia, loss of weight, cervical mass	plasmacytoid	B
	60	M	Chinese	cervical node	cervical mass	clear cell	B
	61	M	Malay	supra-clavicular node	anorexia, loss of weight, melena; gastric mass	clear cell	B
	63	M	Malay	nasal	nasal mass	polymorphous	B
	63	M	Malay	stomach		polymorphous	B
	64	F	Chinese	stomach	anorexia, loss of weight, epigast. mass	clear cell	B
	70	M	Malay	cervical node	dysphagia, cervical mass	plasmacytoid	B
Lymphoblastic	8	M	Indian	axillary node			T
	10	M	Malay	supra-clavicular node	right hypochondrial pain, hepatosplenomegaly		T
	16	M	Malay	cervical node	cervical mass		T
	21	F	Indian	cervical	generalized lymphadenopathy		T
	26	F	Indian	breast	masses, thyroid, breast, abdomen		B
Small, non-cleaved	15	M	indian	Omentum; retroperitoneal node	epigastric mass	non-Burkitt's	B

TABLE 4
CHARACTERISTIC STAINING PATTERNS OF ANTIBODIES IN NORMAL TONSIL

Antibody	Germinal centre	Mantle	Interfollicular zone
ML	–	–	t
MT1	–	–	t
LN1	t	–	–
MT2		t	–
MB2	t	t	–

in such cases in indicating the basically normal architecture of the lymphoid tissue, and the normal distribution of B- and T-cells.

Metastatic lesions that had originally been diagnosed as lymphoma included small cell carcinomas and neuroblastoma. These lesions failed to mark as T- or B-cells or with common lymphocyte antigen. In some cases other markers such as cytokeratin or S-100 protein were present.

TABLE 5
COMPARISON OF INCIDENCE OF NON-HODGKIN'S LYMPHOMA SUBTYPES: WESTERN AND UKM DATA

Working formulation subtypes	Percentages				
	MSKCC USA n=456	SEER USA n=6807	NCI USA n=1014	FINSEN INST. DENMARK n=632	UKM MALAYSIA n=49
LOW GRADE	**31.2**	**31.8**	**38.3**	**28.2**	**2.0**
Small lymphocytic	9.2	11.4	4.0	8.1	0
Follicular, small	17.1	15.4	25.5	14.7	0
Follicular. mixed	4.8	5.1	8.8	5.4	2.0
INTERMEDIATE GRADE	**56.4**	**63.8**	**42.1**	**28.6**	**59.2**
Follicular, large cell	3.3	2.4	4.3	3.6	6.1
Diffus small cleaved	14.6	22.6	7.8	5.1	12.2
Diffuse, small	2.2	7.6	7.6	7.9	38.8
Diffuse, large cell	36.2	31.3	22.4	12.0	2.0
HIGH GRADE	**12.5**	**4.4**	**19.5**	**38.4**	**38.8**
Large cell, immunoblastic	6.1	1.9	9.0	23.1	26.5
Lymphoblastic	3.9	0.2	4.8	10.4	10.2
Small non-cleaved cell	2.4	2.3	5.7	4.9	2.0

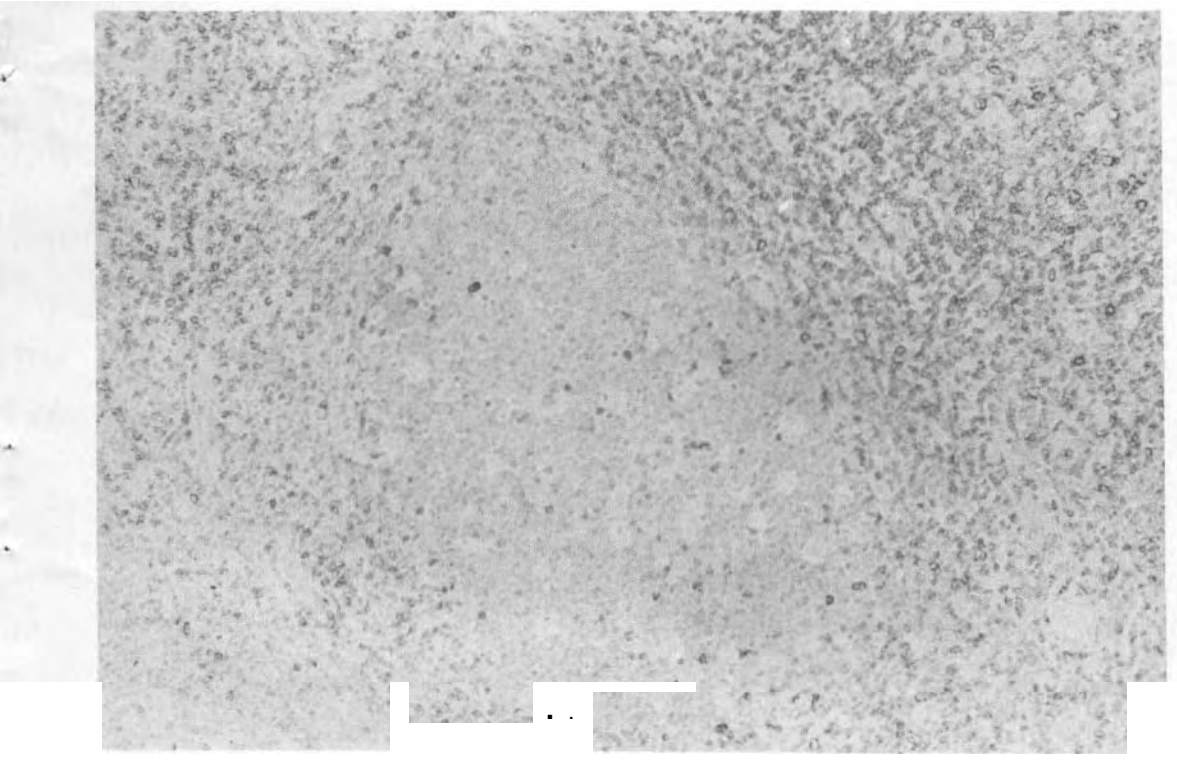

FIG. 1: Immunolocalization of ML antibodies in normal control tonsil: The T-lyrnphocytes are reactive to this combination of antibodies, and are situated in the interfollicular zone. Small numbers of T-lymphocytes are also found in the follicle (ML antibodies, immunoperoxidase, 115x).

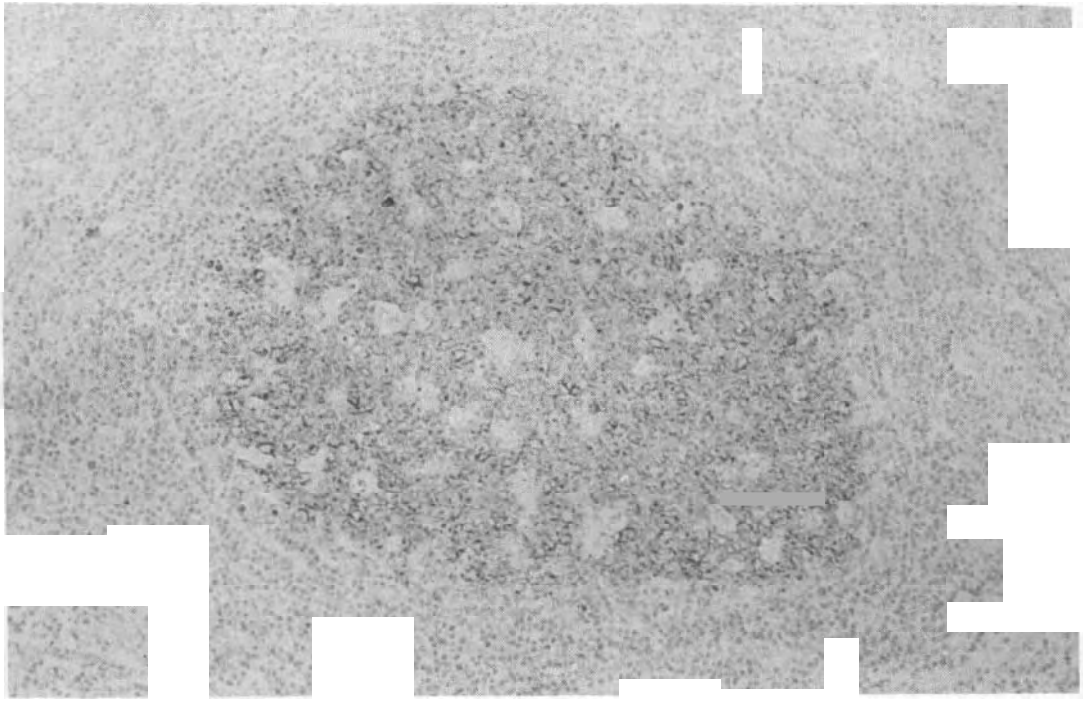

FIG. 2. Immunolocalization of LN1 antibody in normal control tonsil. The B-lymphocytes of the germinal centre show strong imrnunoreactivity (LNI antibody, immunoperoxidase, 115x).

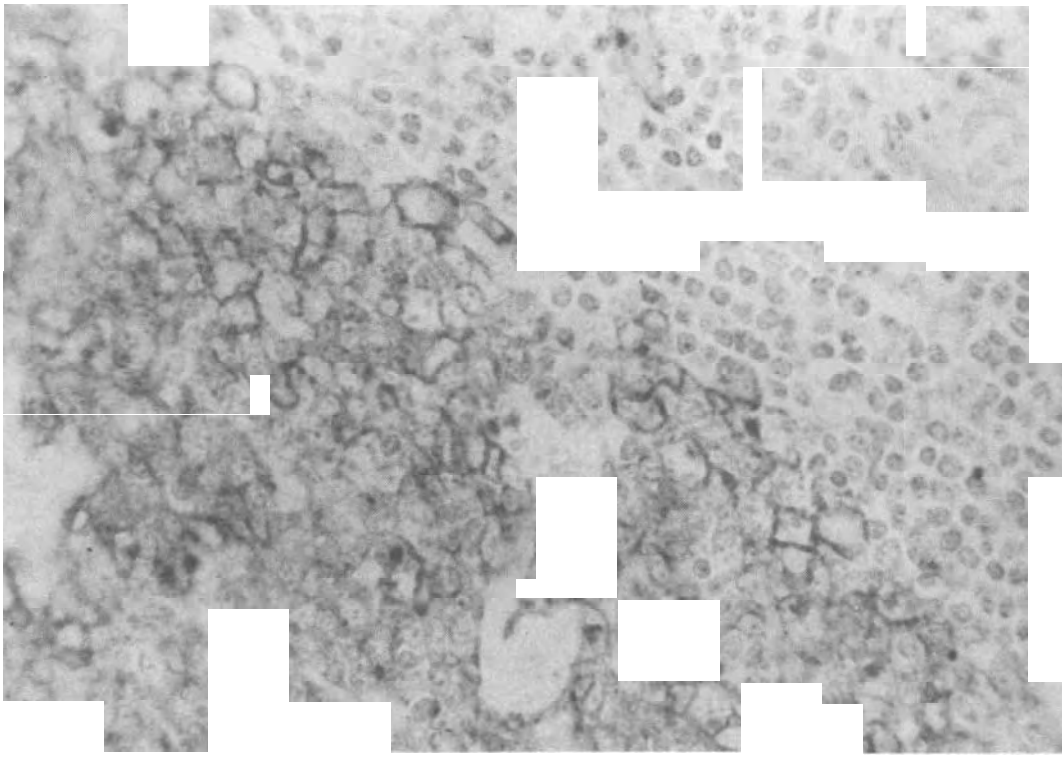

FIG. 3. Higher magnification of the edge of the germinal centre in Fig. 1. The antibody concentrates at the surface membrane of the B-cells. (460x).

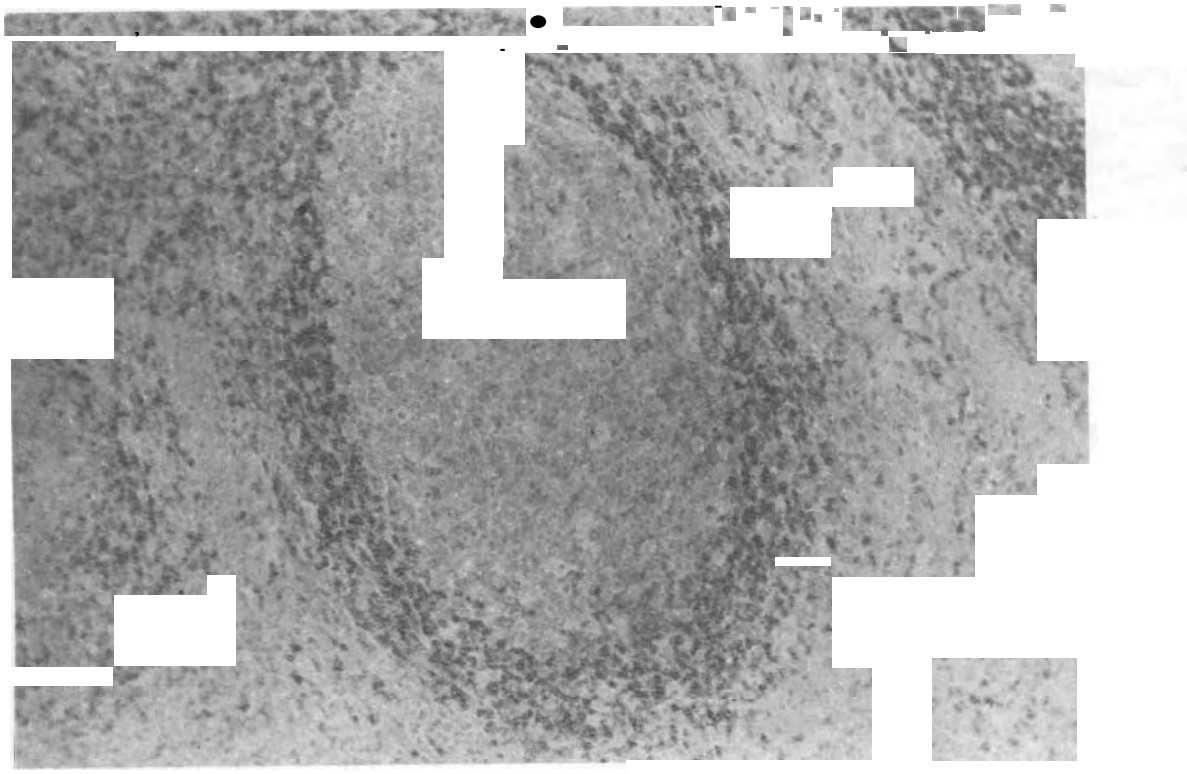

FIG. 4. Immunolocalization of MT2 in normal control tonsil. B-lymphocytes of the mantle zone show strong immunoreactivify; those of the germinal centre are only weakly reactive. (MT2 antibody, immunoperoxidase, 115x).

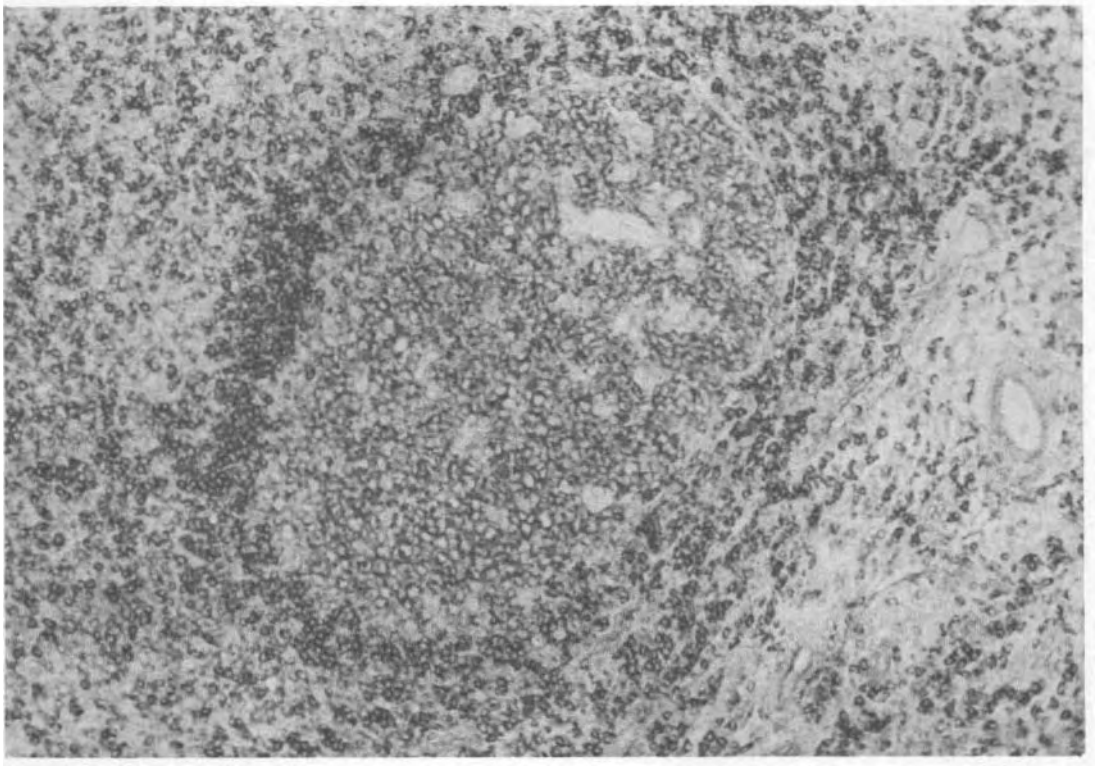

FIG. 5: Immunolocalization of MB2 antibodies in normal control tonsil. This combination of antibodies is immunoreactive to both germinal centre and mantle lymphocytes, to the latter most strongly. Lesser numbers of B-cells are also found in the interfollicular region, the T-cell zone (MB2 antibodies, immunoperoxidase, 115x).

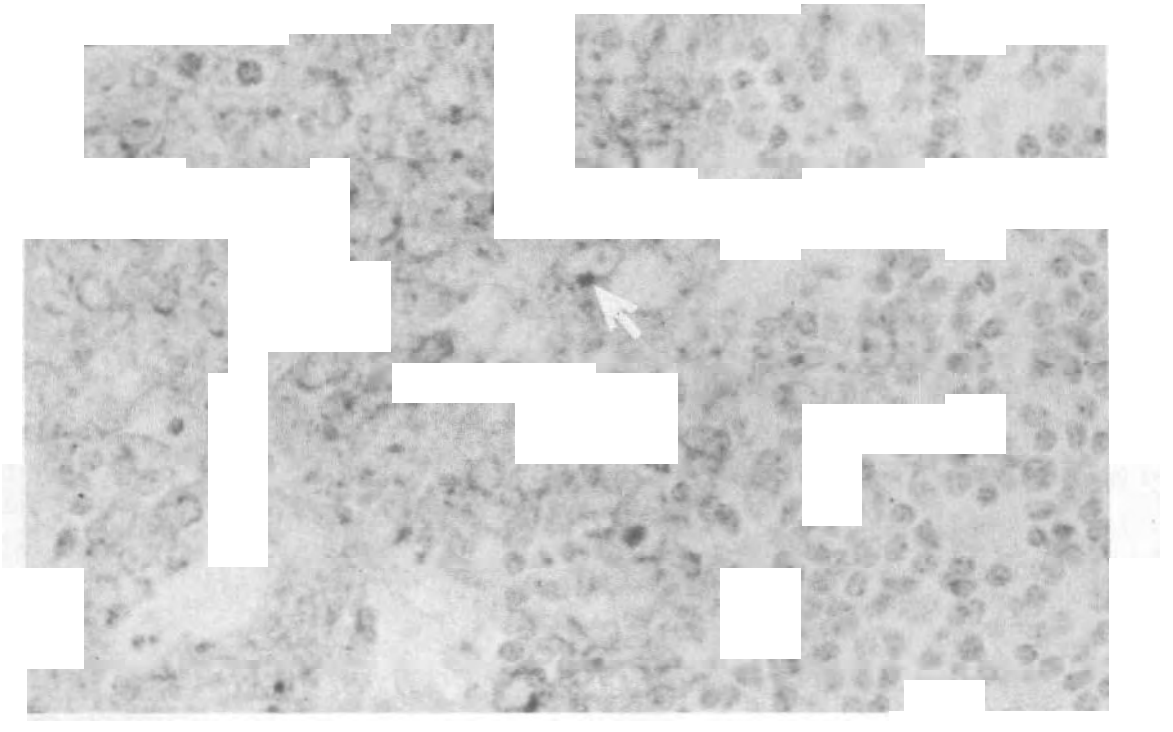

FIG. 6. Immunolocalization of LN1 in a nodule from a case of nodular lymphoma. It is usual for the reactivity to be less strong in lymphomas than normal controls. The antibody marks the surface membranes of these cells. In B-cell lymphomas, LN1 sometimes concentrates near the hof of the cell (eiiow) (LN1 antibody, immunoperoxidase, 115x).

DISCUSSION

Hodgkin's disease

Proportionate to the total number of lymphomas in this series, Hodgkin's disease makes a much lesser number than would be expected on the basis of data from America. The Malaysian proportion of Hodgkin's disease is 14% of the total, as compared to 38% of 545 cases[4] and 59% of 376 cases.[5] It is uncertain whether this is due to a lower incidence of Hodgkin's disease in the Malaysian population, a higher incidence of non-Hodgkin's lymphoma, or to a combination of both factors. All of the major subtypes of Hodgkin's disease occur in this Malaysian population. The figures in this series are insufficient to indicate relative incidence.

Non-Hodgkin's lymphoma

There is a major difference in relative incidence of the subtypes of non-Hodgkin's lymphoma in this series as compared to data from America and Euro'pe. Though the numbers are not large there is a striking difference in proportion of low grade lymphomas to those of high and intermediate grades (Table 5).[3,6,7,8] These differences are probably real, as clinical experience independently supports the histopathological observations. Pathologists may debate the specific classification of a given tumour as to whether it is a small, mixed or large cell lesion. There may be differences of opinion about a diagnosis of diffuse large cell lymphoma of intermediate grade versus immunoblastic sarcoma, a high grade lesion. Such differences of opinion are less likely between the low grade lymphomas and those of high and intermediate grade.

The low grade lymphomas are either nodular lesions or, when diffuse, are made up of well differentiated small lymphocytes or plasmacytoid small lymphocytes. The only nodular lymphoma that is not of low grade is the type composed of large follicular centre cells.

Clinically, the absence of small cell lymphocytic lymphoma correlates with the known rarity of chronic lymphocytic leukaemia in the Malaysian population.

There are important differences in behaviour and response to therapy of low grade as opposed to high grade lymphomas. The low grade lesions are clinically indolent but respond poorly to radiotherapy and chemotherapy. Consequently they are currently considered to be incurable.[9] By contrast, the high and intermediate prade lesions are aggressive, progress rapidly, have a short survival when untreated, but respond well to chemotherapy and radiotherapy. They should be treated vigourously with intent to cure."

Clinical experience in Malaysia suggests an increased frequency of extranodal presentation of non-Hodgkin's lymphoma. A recent series of 30 Malaysian cases indicated that 37% were extranodal.[11] The present series supports that finding, with 37% of high grade lymphomas being extranodal and 28% of the intermediate grade lesions. Estimates of the frequency of extranodal lymphoma in USA range from 10%to 25%.[12,13,14]

Immunophenotypes of Non-Hodgkin's lymphoma

The proportion of non-Hodgkin's lymphomas that was of B-cell immuno-phenotype (78%) closely correlated with the series from Memorial-Sloan Kettering Cancer Centre in which 80% of over 1000 cases typed as B.[6]

As would be expected, all of the nodular lymphomas and all of the small cleaved cell lyniphomas were of B-cell lineage.

Of the five lymphoblastic lymphomas, four were T and one typed as B-cell. This is in keeping with the experience of other investigators.[15] These lymphonias tend to occur in young individuals.

Two of the nineteen diffuse mixed lymphomas and four of thirteen immunoblastic lymphomas were T-cell tumours. Lymphomas in these categories may be either of B- or T-cell type. The more pleomorphic immunoblastic sarcomas tend to be T-cell lesions.'[6] Four of our six polymorphous immunoblastic sarcomas were T-cell tumours.

In our experience, all of the more histologically uniform plasmacytoid and clear cell types of imniunoblastic lymphoma were of B-cell lineage.

The single case of small-cleaved high grade lymphoma was of B-cell immunophenotype, as expected. This tumour was classified as non-Burkitt's because the variability of nuclear size and shape was greater than should be expected in Burkitt's lymphonia. All Burkitt's lymphomas are said to be of B-cell lineage as well as over 80% of the non-Burkitt's type of small non-cleaved cell high grade lymphoma.[16]

Racial incidence

The three major racial groups of Malaysia were represented in the present series, Malays accounting for 54% of the cases, Chinese for 33% and Indians for 12%. These figures are close to the racial composition of the Malaysian population.

Immunohistochemistry of formalin-fixed paraffin-embedded tissue

Although the irnmunohistochemical study of lymphomas is ideally done on cryostat sections and suspensions of viable cells, fresh specimens are often not available, necessitating use of formalin-fixed material. Such is the case at Hospital Besar, Kuala Lumpur, a very large and complex tertiary care hospital. Specimens originating internally as well as external to the institution cannot be expected to be sent fresh to the pathology department. Consequently it is necessary to use methods applicable to fixed tissue if lymphomas are to be classified by immunophenotype. The antibodies used in this study are meant to be active on formalin-fixed paraffin-embedded tissue.

In this study it was possible to classify nearly all non-Hodgkin's lymphomas using the ML, MTI, MB2, MT2 and LNI panel of markers. It was helpful to have more than one B- and one T-cell marker as, in some cases, one of the pair failed to react. The strongest immunostaining was in the controls. In lymphomas the strongest staining was in the reactive cells and residual lymphoid tissue. The obvious tumour cells stained less strongly and poorly differentiated cells usually stained very weakly. Among the weakest staining examples were cases of lymphoblastic lymphoma and Burkitt-type lymphoma.

Conclusions

1. Hodgkin's disease accounted for an unexpectedly low proportion of total lymphomas in this series.
2. Low grade lymphoma was unexpectedly low in incidence relative to intermediate and high grade lymphomas.
3. Follicular lymphomas were relatively infrequent as compared to diffuse lymphomas.
4. The proportion of lymphoblastic and small non-cleaved high grade lymphomas to total numbers of non-Hodgkin's lymphomas was similar to data from America and Europe.
5. The relative scarcity of Hodgkin's disease, follicular lymphoma, and low grade lymphoma may possibly be partially explained by an increased absolute incidence of high grade lymphomas in the Malaysian population.
6. There was a high incidence of primary extranodal non-Hodgkin's lymphoma.
7. Among non-Hodgkin's lymphomas, the proportion of B to T-cell immunophenotype was 4 to 1.
8. A larger study comprising all lymphoma cases presenting to the major tertiary care institutions in Malaysia should be done to determine incidence and whether there are differences in racial incidence. Such data may eventually provide clues to aetiology.

REFERENCES

1. Lukes RJ, Craver LF, Hall TC, Rappaport H, Ruben P. Report of the nomenclature committee. Cancer Res 1966; 26: 1311.
2. Rappaport H, Berard CW, Butler JJ, Dorfman RF, Lukes RJ, Thomas LB. Report of the committee on histopathological criteria contributing to staging of Hodgkin's disease. Cancer Res 1971; 31: 1864–5.
3. The non-hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphorna. Summary and description of a working formulation for clinical usage. Cancer 1982; 49: 2112–35.
4. Gall EA, Mallory TB. Malignant lymphoma. A clinicopathological survey of 618 cases. Am J Path 1942; 18: 381–429.
5. Lumb G, Newton KA Prognosis in tumors of lymphoid tissue: an analysis of 602 cases. Cancer 1957; 10: 976–93.
6. Lieberman PH, Filippa DA, Straus DJ, Thaler HT, Cirrincione C, Clarkson BD. Evaluation of malignant lymphomas using three classifications and the Working Formulation. Am J Med 1986; 81: 365–80.
7. Percy C, O'Conor G, Reis LG, Jaffe ES. Non-Hodgkin's lymphomas. Application of the International Classification of diseases for Oncology (ICD-O) to the Working Formulation. Cancer 1984; 54: 1435–8.
8. Ersboll J, Schultz HB, Hongaard P, Nissen NI, Hou-Jensen K. Comparison of the Working Formulation of non-Hodgkin's

lymphoma with the Rappaport, Kiel and Lukes & Collins classifications. Translational value and prognostic significance based on review of 658 patients treated at a single institution. Cancer 1985; 55. 2442–58.

9. Rosenberg SA. Current concepts in cancer: Non-Hodgkin's lymphoma: Selection of treatment on the basis of histologic type. N Engl J Med 1979; 301: 924–8.
10. De Vita VT Jr, Canellos GP, Chabner GP, Schein P, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma: a potentially curable disease. Lancet 1975; 1: 248–50.
11. Aziz AB, Hla Myint H, Zainol H. Non-Hodgkin's lymphoma in Hospital USM, Kelantan: A retrospective clinico – pathological study. Presented at 14th Annual General and Scientific meeting of Malaysian Society of Pathologists, 10 – 12 Nov 1989 (abstract). Malays J Pathol 1990; 12: 61–2.
12. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972; 29: 252–60.
13. Rudders RA, Ross ME, De Lellis RA. Primary extranodal lymphoma: Response to treatment and factors indicating prognosis. Cancer 1978; 42: 406–16.
14. Paryani S, Hoppe RT, Burke JS *et al.* Extralymphatic involvement in diffuse non-Hodgkin's lymphoma. J Clin Oncol 1983; 1: 682–8.
15. Cossman J, Chused TM, Fisher RI, Magrath I, Bollum F, Jaffe ES. Diversity of immunologic phenotypes of lymphoblastic lymphoma. Cancer Res 1983; 43: 4485–90.
16. Cossman J, Jaffe ES, Fisher RI. Immunologic phenotypoes of diffuse, aggressive non-Hodgkin's lymphomas: Correlation with clinical features. Cancer 1984; 54: 1310–7.