Non-Hodgkin lymphoma research (excluding all B cell lymphoma) in Malaysia: A review

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Introduction: Lymphoma is a diverse group of malignant proliferations that arise as discrete tissue masses. The 5th edition of the World Health Organization classification of Tumours of Haematopoietic and Lymphoid Tissues was released on 22nd June 2022. The WHO-HAEM5 classification of Mature T and NK neoplasms is further subclassified into various categories which are detailed in this review.

Methods: A search was conducted using bibliographic databases, various repositories, and the Clinical Research Centre website retrieving journal articles, conference proceedings, book Chapters, guidelines, and thesis. The search terms used were Malaysia AND lymphoma.

Results: The search earmarked a total of 561 papers. There were nine case series retrieved from 1967 to 2022. The site, age distribution, prognostic markers, and the various subclassification of NK/T cell lymphomas were studied. The gastrointestinal tract was the commonest site for extranodal lymphomas. Prognostic markers associated were EBV, C-MYC protein and staining for CD2, CD3, CD20, CD56, and CD57 antigens.

For anaplastic large cell lymphoma (ALCL), CD30 (Ki-1) and ALK antigens were noted as important. The use of 18F-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has emerged as an important investigation. Various chemotherapeutic regimens, surgical interventions where necessary and autologous peripheral blood stem cell transplantation when indicated are the mainstay of treatment.

Conclusion: Research on NK/T cell lymphoma, including ALCL, has been ongoing in recent years. This review adds on to the existing literature on lymphoma in Malaysia that can lead to further research, into the diagnosis and treatment of lymphoma in Malaysia and around the world.

Keywords: *Lymphoma, NK/T cell, anaplastic large cell lymphoma (ALCL), Malaysia*

INTRODUCTION

The haematopoietic system develops from stem cells that divide into myeloid and lymphoid progenitor cells. The myeloid cells form erythrocytes, platelets and myelocytes which in malignant states are leukaemias. Lymphoid progenitor cells give rise to B-cells, T-cells and natural killer cells and their subsequent derivatives. In malignancy, lymphoid cells give rise to lymphomas. Lymphoma is a diverse group of malignant proliferations that arise as discrete tissue masses. There are geographic variations in the incidence of subtypes of lymphoma that have been studied.[1,2] For example, follicular lymphoma is prevalent in Western countries, while T-cell lymphomas are more common in Asia.[1,3] Virchow is credited with naming the disease in 1858 and the history of classification of the disease and notable geographical variations has been discussed by Peh and Poppema.[4]

The malignant lymphomas were historically broadly categorised as Hodgkin lymphoma/disease (HL) and non-Hodgkin lymphoma (NHL), with a worldwide prevalence of 5% to 6% of all malignancies.[5] Malignant lymphomas are the fourth most common

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cancer encountered in Malaysia, according to the Malaysian National Cancer Registry Report 2012-2016. The lifetime risk for males is 1 in 176; 1 in 167 for Malays, 1 in 189 for Chinese and 1 in 283 for Indians. The lifetime risk for females is 1 in 252; 1 in 245 for Malays, 1 in 280 for Chinese and 1 in 324 for Indians. These rates have all increased from the previous report covering the period 2007-2011. Staging was reported for 1,394 (40.9%) and 1,027 (42.5%) cases respectively for males and females. Of these 62% in males and 59% in females were detected at late stage (III & IV).[6]

The 5th edition of World Health Organization classification of Tumours of Haematopoietic and Lymphoid Tissues was released on 22nd June 2022.[7] A relatively conservative approach was taken in making changes to the nomenclature to allow for continuity in daily practice and ongoing clinical trials. The WHO-HAEM5, like all 5th Edition WHO tumour volumes, applies a hierarchical system for classification. That is, it organises diseases in order of increasing levels of specification: category (e.g, mature B-cell), family/class (e.g, large B-cell lymphomas), entity/type (e.g, diffuse large B-cell lymphoma, not otherwise specified) and subtype (e.g, diffuse large B cell lymphoma, not otherwise specified, germinal center B-cell-like). Entities and subtypes have been formulated such that the implementation of the WHO-HAEM5 classification system is possible globally, in all settings.[7]

The aim of this study is to provide clinicians who manage lymphoma in Malaysia and investigators a resource of background information about lymphoma in Malaysia. It is also to facilitate future research by collecting what is known so that the gaps can be identified.

METHODOLOGY

The objectives of this study are to look at the prevalence and reports of non-Hodgkins lymphoma in Malaysian literature and also review some aspects of the disease including treatment and outcomes where available.

A search was conducted on the following: (1) bibliographic databases (PubMed and Scopus); (2) Individual journal search of Malaysian health-related journals; (3) A targeted search of Google and Google Scholar; (4) Searching of Malaysian institutional repositories; (5) Searching of Ministry of Health and Clinical Research Centre websites including the National Cancer Registry. The citations were manually entered or imported into the bibliographic software Zotero.

The search terms used were Malaysia AND lymphoma, and information in this report was extracted from a more comprehensive library of published data that covered all lymphomas till July 2022. The search was performed on 18th May 2021 and repeated on 3rd July 2022 and shown in the PRISMA flowchart in the results section (Figure I). The review of Diffuse Large B Cell Lymphoma (DLBCL) has been published separately.[8]

Inclusion criteria included the following: All published reports (case reports and case series) in Malaysia of lymphoma in general, NK/T cell and ALCL, articles published in English and published between 1967 until 2022. Exclusion criteria for our review included

articles which were reported from countries other than Malaysia, articles published in languages other than English, articles which included only other lymphomas other than NK/T cell lymphoma and ALCL and those published prior to 1967.

RESULTS

The search earmarked a total of 451 publications. An additional 65 publications were noted on 3rd July 2022. Six authors (LKG, SPV, AFS, PTK, IAS and NIJ) carefully examined all 516 publications and deleted unrelated publications. The final number of publications used in this study was 83. Our review on DLBCL has recently been published.[8]

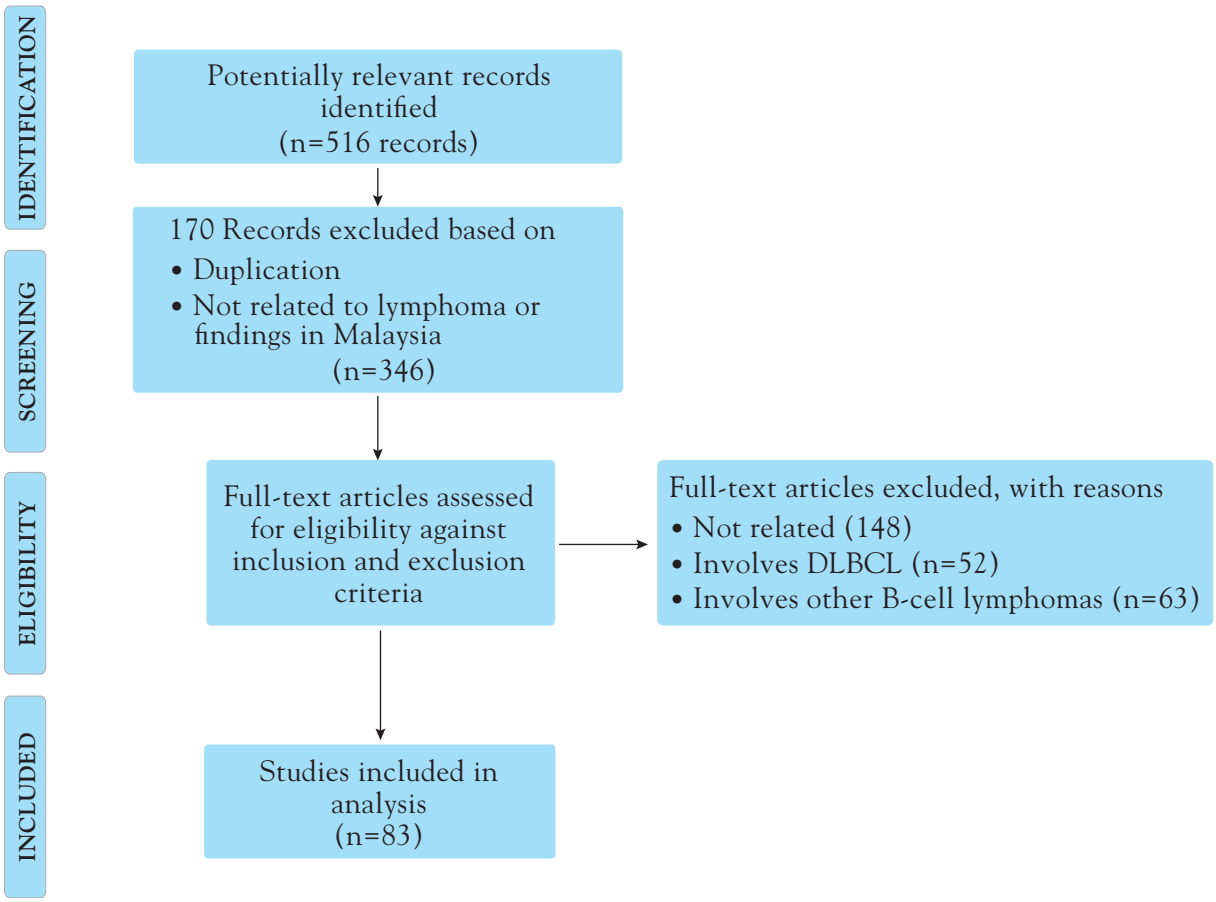

Figure 1: PRISMA diagram of workflow

OVERVIEW

Table I is a summary of hospital-based collections of case series from various institutions, many from the Klang valley but some focusing on East Malaysia. The classification of lymphoma in the early years was of Hodgkins and non-Hodgkins lymphoma but it has changed over the years. Later series use the WHO classification and its subsequent revisions.

Table I: Summary of case series showing the demographic distribution and types of lymphoma

AUTHOR	YEAR	NUMBER OF CASES	LOCATION	M:F RATIO	AGE	ETHNICITY CHINESE MALAY INDIANS	B-CELL	T-CELL	HL	NOT SPECIFIED
Sinniah, Tan, Lin [9]	1967-1980	24	University Hospital (UH)	19:5	1-12	Chinese 16 Malay 3 Indian 5	10		14	
Bosco and Cherian [10]	1980- 1984	149	University Hospital (UH)			Chinese 92 Malay 36 Indian 17	100		49	
Chai, *et al* [11]	1981- 1983	61 Sarawak 46 Sabah		66:41	2-78 yrs Mean 41 yrs	Chinese 11 Malay 15 Ind Sarawak 35 Chinese 2 Malay 2 Indian 1 Ind Sabah 41	80	16	11	
Mancer [12]	1983-1987	57	Universiti Kebangsaan Malaysia (UKM)	34:23	4-72 yrs Mean 50 yrs	Chinese 19 Malay 31 Indian 7			8	Low grade 1 Intermediate 29 High 19
Peh, *et al* [13]	1993- 1999	80	Klang	52:28	3-86 yrs 51-60 (27.5%)	Chinese 4 (5%) Malay 64 (80%) Indian 12 (15%)	57	9	14	
Peh, *et al* [14]	1996-1998	70	Sarawak	46:23	4-85 yrs Mean 49.9 yrs	Iban 27 Malay 22 Chinese 9 Bidayuh 8 Unknown 4	58	1	9	Null cell 1 Unclassified 1
Peh, *et al* [15]	1997-1999	91	Sabah	56:32	51-60 (22%)	Chinese 8 Malay 7 Kadazan 27 Bajau 8 Dusun 6 Other Ind Sabah 30	68	14	8	1
Menon, *et al* [16]	2005-2006	77	Paediatrics Hospital Kuala Lumpur (HKL)				27	37	13	
Salam [17]	2010-2015	210	Pantai Premier Pathology	116:94		Chinese 111 Malay 58 Indian 16 Others 21	175	10	25	

Lymphoma was diagnosed in 7% of 350 childhood malignancies seen in the University Hospital from 1967-1980 (Table I). Sinniah *et al*, noted that of 24 cases of paediatric lymphoma, 13 refused treatment and they presented late. Eight of the 14 cases with HL were in Stage IV. Nevertheless, four of their HL patients and one with NHL were alive at the time of reporting.[9] Reporting about 40 years later, Menon *et al*. found that lymphomas formed 11% of 730 childhood malignancies over an 18-month period seen at the clinic of the Paediatric Institute of Hospital Kuala Lumpur.[16]

Distribution of sites

In cases from Sabah, Peh SC *et al*.[15] found that 43 (47.2%) presented with the disease in the lymph nodes and 42 (46.1%) were extranodal. The sites for six (6.7%) cases could not be determined. The common extranodal sites were the gastrointestinal tract (4), tonsil (4), oral cavity (4), testis (2), spine (2), nose (2), and the remainder 4 were in other sites.

In a series of gastrointestinal lymphomas seen from 1967 to 1973 in the University Hospital, Ti *et al*. reported that of 17 cases (5% of gastrointestinal malignancies), the small intestine was the commonest site involved although many had multiple sites of disease. All were adults with ages ranging from 21 to 76, averaging 49 years.[18]

Among 210 cases in Kuala Lumpur, Salam *et al*.[17] noted 96 (46%) with lymph node disease versus 114 (54%) with extranodal disease (Figure II). The common extranodal sites were the gastrointestinal tract (31, 27%), Waldeyer ring (15, 13%) thyroid and mediastinal (10 each, 9%) and other sites (48, 41%).

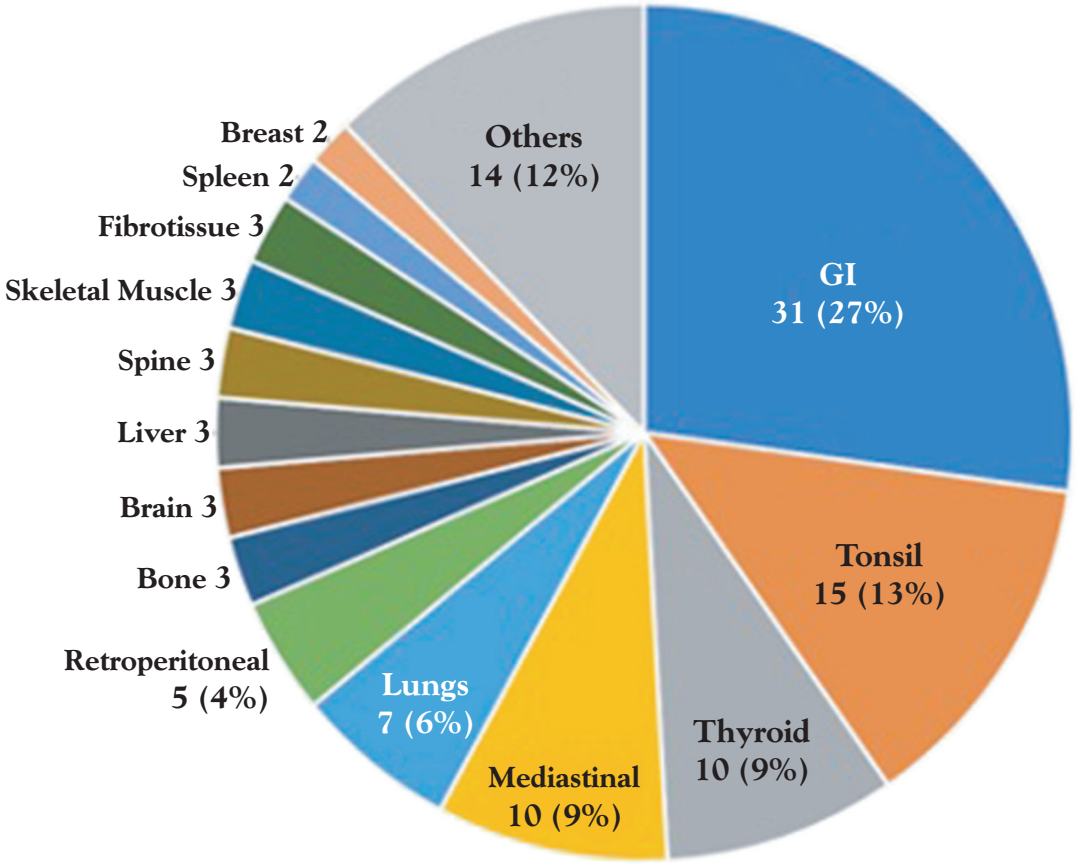

Figure II: Distribution of extranodal lymphomas among 114 patients in Malaysia. (Salam)[17]

Age groups

Salam *et al.*[17] noted that among the series of 210 cases, the elderly (>70 years) Chinese formed the majority (18/29, 62%). However, in the 20–30-year age group, Malays were 59% (13/22). The types of lymphoma could account for this difference, as well as a change of incidence in age cohorts.

Prognostic Markers

Peh noted that all EBV associated lymphomas were of the type A virus and none were of type B nor were there mixed infections.[19] EBV was detected in 6/8 (72.5%) of HL and 8/83 (9.6%) of NHL cases. Peh *et al.*[13] who reviewed cases in Klang, 7/9 of T-NHL and 6/57 of B-NHL were associated with EBV. Most Epstein-Barr virus encoding region (EBER)-positive cases did not express the T- or B- cell antigen, shown by double staining T-NHL with CD20 and CD3 antigens. Yunos noted that 11% (2/18) NHL of the lower GI tract demonstrated positive signals for EBV/EBER.[20]

Dendritic cells are antigen presenting cells within the immune system responsible for initiating T-cell based responses. Hussin *et al.* examined lymph node tissue from 32 cases of various types of lymphoma compared with lymph nodes with inflammatory disease and found a reduction in dendritic cell counts in lymphoma tissue, and found immature dendritic cells located within tumour tissue while mature dendritic cells were more in the peri-tumoural areas.[21]

The International Working Formulation divided non-Hodgkin's lymphoma (NHL) into three grades: low, intermediate, and high. Wang and Peh reported that Ki-67 immunostaining is a useful adjunct to the histological grading of NHL.[22] Peh studied the frequency of NHL in different ethnicities in Malaysia and reported the highest frequency in Chinese (107/232), Malays (41/232) and Indians (21/232).[22]

Norizan *et al.* looked at the DNA ploidy status of 37 case of all lymphomas in HKL between 1990-1995 and noted that 12% were near diploid, 67% were hyperdiploid and 21% were hypodiploid. The majority of hyperdiploid lymphomas were B cell NHL.[23]

C-MYC

A review of 634 lymphomas in the department of Pathology, Hospital USM from 2001 to 2018 found that 55 (8.8%) were NK and T cell lymphomas. Thirty-two with adequate tissue samples were selected for C-MYC immunochemistry staining. Among them 21 (65.6%) were males and 11 (34.4%) females. The median age was 38 years (8 to 81). Malays accounted for 90.6% (29), with 2 Chinese and 1 Indian. Ten (31.3%) were lymph nodes and 22 (68.8%) extranodal biopsies. C-MYC protein expressions were detected in 25/32 (78.1%) cases, 5/6 were T lymphoblastic lymphoma, 7/8 T-cell lymphoma, not subtyped, 4/6 ALK-positive ALCL, 4/6 peripheral T-cell lymphoma, not otherwise specified, 3/3 extranodal NK/T-cell lymphoma, nasal type and 2/3 of others. There is no significant association between C-MYC protein expression and the patient's age, gender, Ann Arbor staging, LDH levels, B symptoms, extra-nodal involvement, and ECOG status. Only 17 (53.2%) patients received chemotherapy. Ten (31.3%) were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) as the first line treatment. Eleven (34.4%) patients died in the follow-up period, eight of whom had C-MYC expression.[24]

Types of lymphoma

NATURAL KILLER (NK) T-CELL LYMPHOMA

NK cells account for 5–10% of peripheral lymphocytes and have some T-cell markers but they do not have to pass through the thymus to mature. In the Asian populations in Hong Kong, Japan, Taiwan, China and Malaysia, approximately 90% of nasal lymphomas show natural killer (NK)/T-cell phenotype whereas the majority of lymphomas of the nasal region in Western populations are B-cell phenotypes. Nasal lymphoma accounts for 4-7% of all lymphomas. Over a period of 20 years, a total of 41 formalin-fixed and paraffin-embedded biopsy tissues from 31 patients (22 males, 9 females) with these nasal lymphomas were examined in the Department of Pathology, University of Malaya. Their ages ranged from 8 to 77 years. Eight were nasal T-NHL, 19 were nasal NK/T cell lymphomas and 4 nasal-type lymphomas of NK/T-cell phenotype. Among the 19 nasal NK/T cell lymphomas, there were 7 Malays, 11 Chinese, 1 Kadazan and in the nasal-type NK/T cell lymphomas, there were 1 Malay, 2 Chinese and 1 Indian. All nasal and nasal-type NK/T-cell lymphoma cases expressed CD3 and CD56. CD57 expression was observed only in one case. Of the nasal NK/T-cell lymphoma cases, 12/19 (63%) expressed CD2, but none in the three cases of nasal-type NK/T-cell lymphoma. TIA-1 is equally and strongly expressed by all the nasal, nasal-type and T-cell NHL cases. EBER was detected in 18/19 (95%) of the nasal NK/T cell lymphoma.[25]

A 31-year-old Malay man with nasal NK/T cell lymphoma presented with prolonged fever of unknown origin and had enlarged mesenteric nodes at laparotomy, died nine days after diagnosis.[26] These nasal lesions may be misdiagnosed as infection, and missed on biopsy and then treated as such before it is diagnosed correctly at an advanced stage.[27-30] Noradina *et al.* reported a 37-year-old man who presented with one week of diplopia with a large enhancing nasopharyngeal mass with intracranial extension to the cavernous sinuses and local infiltration together with intracranial abscesses. He died before treatment could be started.[31] Another 56-year-old Indonesian man presented with myiasis alongside his NK/T cell lymphoma in Sabah. Whether maggots were of any use or detrimental was not known as he went back to Indonesia and his outcome was not known.[32]

A 56-year-old man presented with right eye redness, reduced vision, and periorbital swelling for five weeks duration and had a two-month history of nasal obstruction. He was treated with antibiotics. When improvement was not seen after a week, biopsy of the nasal tissue was done and immunohistochemical staining of tissue was positive for CD3, TIA, EBER-ISH and negative for CD20, CD10, TdT, cyclin-D1, CD4, CD8, CD5, CD30 and ALK. The Ki-67 proliferative index was high (~60–70%). Sadly, he succumbed after one month of chemotherapy.[33] Another 39-year-old man presented with bilateral nasal obstruction for four months. A nasal endoscopy showed irregular mucosa of the nasal cavity and biopsy reported as extranodal NK/T cell lymphoma, nasal type. EBER-ISH was positive. He was treated with six cycles of gemcitabine, oxaliplatin and L-asparaginase and peripheral blood stem cell transplant. He was asymptomatic until nine months and developed a splenic abscess which required splenectomy. He was asymptomatic for a further two years.[34]

NK/T-cell lymphoma mimicked Crohn's disease in a 46-year-old Chinese man who presented with six months history of abdominal pain, weight loss and rectal bleeding. Colonoscopy revealed multiple aphthous ulcers within the ileo-caecal region and distal transverse colon, separated by normal mucosa, as in skip lesions of Crohn's colitis. Immunohistochemical studies on the resected bowel confirmed a T-cell monoclonality, presence of cytotoxic granules and Epstein-Barr virus (EBV) infection.[35] Tai *et al.* reported a high frequency of EBV association with NK/T-cell lymphomas.[36] Yap reported a case of a 73-year-old man with NL/T-cell lymphoma involving the left pectoral muscle with a rare, but possibly significant, peripheral eosinophilia. The patient did not have lymphadenopathy but had a 1cm liver lesion and a pathological fracture of the femur.[37]

SUBCUTANEOUS PANNICULITIC T-CELL LYMPHOMA (SPTL)

SPTL is a rare variant of peripheral T-cell lymphoma characterized by infiltration of lymphoma cells within the subcutaneous tissue. Ng et al. reported five cases (1M, 4F), aged from 13 to 35 years, between 2001 to 2004 seen in Hospital Kuala Lumpur. CD3 was positive in four cases. CD 8, CD30, and TIA were noted in one case each. Two patients achieved remission, two died and one was lost to follow-up.[38] SPTL was also diagnosed in a 25-year-old man in Johor Bharu who presented initially with lymph node like swellings. Biopsy from the forearm and thigh later achieved the diagnosis. The SPTL cells expressed CD2, CD3, CD8, CD7, TIA, Perforin and TCR Alpha/Beta.[39]

Five cases of SPTL were seen during the period from 2001-2004 at the Department of Dermatology, Hospital Kuala Lumpur. All five presented with multiple subcutaneous nodules on the face, trunk and limbs of one week to six months duration with associated fever and weight loss. Skin biopsy of all patients showed infiltration with atypical lymphoid cells in the upper dermis and subcutaneous fat. These neoplastic cells showed CD3 and CD30 positivity in three patients with CD8, TIA-1 and LCA (Leucocyte common antigen) being positive in one patient. One patient was treated with prednisolone and subcutaneous Roferon and were in remission. Two patients who were planned for chemotherapy had deteriorated rapidly and succumbed to septicaemia from pancytopaenia.[40]

A 10-year-old Malay boy with stage IV T-cell NHL (pulmonary involvement), diagnosed through a biopsy of a forearm soft tissue swelling, developed pure red cell aplasia (PRCA) and autoimmune haemolytic anaemia (AIHA) after beginning therapy on the EORTC-VHR protocol.[41]

PRIMARY CUTANEOUS LYMPHOMA

Guan and Gan in 2016 reported a rare case of primary cutaneous T-cell lymphoma gamma-delta subtype of cutaneous T-cell lymphomas in a 66-year-old Malay man who presented with a three-week history of rapidly growing skin nodules and skin rashes all over his body.[42]

Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is a rare subtype of primary cutaneous lymphoma. They usually present as nodules which

can ulcerate over the head and neck region. Heng *et al.* reported a 73-year-old man who presented with two painless, ulcerating nodules over the right pre-auricular and angle of the mandible. A hypodense lesion in the liver indicated metastasis. Biopsy revealed PC-ALCL. Tumour cells were positive for CD30, CD4, CD5, EMA, and CD25. They were CD3, CD8, CD20 and ALK- negative. He responded well to chemotherapy.[43] Lee has reviewed cutaneous T-cell lymphoma among Asians, including Malaysians.[44]

ADULT T-CELL LEUKAEMIA/LYMPHOMA (ATLL)

ATLL is a rare T lymphoproliferative neoplasm commonly associated with Human T-cell lymphotropic virus type-1 (HTLV-1).[45] ATLL is most prevalent in Japan; however, some sporadic cases are reported worldwide. Cases of ATLL are rarely seen in Malaysia, and HTLV-1 is not endemic in Malaysia. One case of ATLL with positive HTLV-1 infection was found in a 51-year-old Indian woman with incidental lymphocytosis while being investigated for pallor and giddiness. On examination, there were bilateral enlarged cervical lymph nodes with no hepato-splenomegaly or skin lesions.[45]

INTESTINAL T-CELL LYMPHOMA (ITL)

Intestinal T-cell lymphoma (ITL) is an aggressive neoplasm of intraepithelial T cells that affects the small bowel. One form, enteropathic-asssociated T-cell lymphoma (EATL) occurs as a complication of coeliac disease common in Western countries. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) was previously known as EATL type 2 and is more common in Asia.

Liong *et al.* reported EATL type 2 in a 50-year-old Chinese man with chronic diarrhoea for six months and weight loss of 17 kg. Initial CT scan and endoscopy did not confirm the diagnosis. Repeat CT scan showed a well-defined large enhancing mass in the mesentery adjacent to an area of thickened jejunum and surgical resection proved the diagnosis. The tumour cells were strongly positive for CD3, CD8 and CD56, and negative for CD4, CD5, CD30 and EBER. The patient recovered from surgery and was given chemotherapy but died four months after diagnosis.[46]

Another 36-year-old man who presented with a five-week history of intractable diarrhoea was found on CT scan to have mural thickening at the duodenojejunal junction. Subsequent jejunofiberoscopy showed a circumferential ulceration at the jejunum. Histoimmunopathology confirmed the diagnosis of EATL type 2. His disease was refractory to standard front-line chemotherapy and was given second-line salvage therapy in view of CNS and intracranial involvement. He died nine months after the initial diagnosis.[47]

Kasinathan[48] reported a previously healthy 70-year-old woman of Chinese ethnicity who presented with a four-week history of abdominal pain, persistent vomiting, and jaundice. There were no palpable lymphadenopathies or organomegaly. A whole-body CT imaging was consistent with stage 1E disease (Ann Arbor staging) showing a mass at the 2nd part of the duodenum only. The histology was consistent with monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). The tumour cells were positive for CD3, CD5, CD7, CD8, CD56, TCR gamma/delta,

TIA-1 and granzyme B. Ki67 proliferation index was 70%.[48] She was treated with two cycles of CHOP and then two cycles of gemcitabine and platinum-based chemotherapy before she succumbed to the disease.

PERIPHERAL T-CELL LYMPHOMA (PTCL)

Peripheral T cell lymphoma comprises 10-15% of NHL and usually carries a poor prognosis. The expressions of NOTCH1, GATA3, and c-MYC have been linked to a poorer prognosis in PTCL.[49] Chang CY reported a rare case of PTCL presenting as a pleural effusion with no prior illness. He reported that lung involvement occurs in 8% of lymphoma cases. The patient declined treatment and succumbed in three months.[50]

T-CELL LYMPHOMAS (not specified)

T-cells constitute 65-80% of the circulating pool of small lymphocytes. In lymph nodes, they are located in the inner subcortical region, and not the germinal centres.

An 11-month-old girl was admitted to the Paediatric Allergy Unit with severe allergic angioedema and no response to treatment with antihistamines and corticosteroid therapy at another hospital.[51] Investigations revealed a lymphoproliferative malignant pathology found in the supradiaphragmatic and infradiaphragmatic areas. A final diagnosis of T-cell NHL was made on lymph node biopsy.[51]

A high-grade T-cell NHL was diagnosed concurrently with AIDS in an 18-month-old boy with gross hepatosplenomegaly and generalized lymphadenopathy. His disease responded to chemotherapy, but he defaulted for three months returning with fever, bruises and cervical lymphadenopathy. Despite having opportunistic infections on return to chemotherapy, he responded to treatment again and survived disease free for 2 ½ years. He succumbed to febrile illness at four years and ten months with no evidence of recurrence of the lymphoma.[52]

ANAPLASTIC LARGE CELL LYMPHOMA (ALCL)

ALCL which are considered a subset of T-cell lymphomas, are rare tumours, accounting for 2-3% of adult non-Hodgkin lymphomas and often involves both lymph nodes and extranodal sites. The most common mutation in ALCL is a translocation involving the anaplastic lymphoma kinase (ALK) gene that results in ectopic expression of ALK protein in lymphoid tissue. Using immunostaining targeting at the 2p23 region of the ALK protein and fluorescence in situ hybridisation (FISH), Tai *et al.* detected this in 24/34 (71%) of the cases in Kuala Lumpur, and it was significantly higher in childhood cases (100%) when compared to adult cases (47%).[53] The analyses by FISH were consistent with the results from immunostaining of ALK protein, but the analyses were only successful in 15/34 (44%) cases.

Jayaram and Abdul Rahman[54] reported three cases of lymphatic ALCL from University Malaya in 1997 that were positive for CD30 (or Ki-1 antigen), which was first described in 1985. They were in a 9-year-old girl, a 15-year-old boy and a 66-year-old man.[54]

In 2008, Siti-Aishah *et al.* reported a case of a 44-year-old woman who presented with a firm, mobile mass in the left iliac fossa region, bilateral axillary

lymph nodes and a mass encasing the right upper lobe bronchus.[55] Histopathological examination revealed that the mass was infiltrated by large lymphoid cells with marked nuclear atypia, including kidney-shaped nuclei which expressed ALK, CD30 and EMA but not for T-cell (CD45RO and CD3), and B-cell (CD20 & CD79α) markers. FISH analysis showed a t (2;5) (p23; q35) chromosomal translocation. She was staged at Stage IIA, received six cycles of CHOP chemotherapy, and remained disease-free two years after diagnosis, despite also having pulmonary tuberculosis after one year and completing treatment for that as well.

Yaakup *et al.* described a 34-year-old immunocompetent woman with a primary oesophageal ALCL, CD30 and ALK^+ of T-cell phenotype presenting with a two-year history of dysphagia.[56] She was treated with chemotherapy and endoscopic oesophageal dilations and stenting, resulting in complete remission of the lymphoma and resolution of the dysphagia. She underwent autologous peripheral blood haematopoietic stem cell transplantation and remained disease-free two years after the diagnosis.

The diagnosis of a small cell variant of ALCL in a 13-year-old boy with a huge mass on his right arm of six months duration was also reported in 2008.[57] Histopathology revealed sheets of malignant small round blue cells immunopositive for LCA, CD43, CD45Ro, CD30, EMA, ALK-1 and CD99, but negative for CD20, TdT, myogenin, myoD1, NSE, bcl-6, bcl-2 and CD10. FISH testing excluded the diagnosis of Ewing's sarcoma/PNET. The mass resolved with chemotherapy, but he died of septic shock.

A 29-year-old man presenting with backache and left thigh pain was found to have an inflammatory mass on CT scan and initially treated with antibiotics. At surgery, the left psoas muscle was found filled with unhealthy reddish looking inflammatory tissues. Histopathological examination revealed an anaplastic large T-cell lymphoma immunohistochemically positive for CD 30, EMA and ALK1.[58]

A 10-year-old Malaysian girl was seen for a seven-month history of multiple swellings over the left thigh, upper arm, and anterior chest which continued to increase in size and to ulcerate. There were shotty cervical and inguinal lymph nodes palpable. The chest and thigh masses were debulked at surgery and the specimens confirmed a diagnosis of ALK-1-positive ALCL involving the muscle.[59]

A 30-year-old Malay gymnasium instructor with a history of chronic intramuscular testosterone enanthate presented with six weeks of night fevers, weight loss, and bony pain. 18-FDG PET/CT imaging showed a hypermetabolic large anterior mediastinal mass with diffuse hypermetabolism in the liver, spleen and axial skeleton.[60] Bone marrow trephine and mediastinal tissue histology were consistent with leukaemic ALK-negative ALCL. He was treated with CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone) induction chemotherapy in which he required intensive antibiotic and blood support but succumbed to the disease.[60]

ALCL with a monomorphic small-cell pattern was found in a 34-year-old woman with intractable epigastric pain with multiple gastric erosions and

nodules that were first diagnosed as inflammatory lesions both endoscopically and histologically.[61] She developed severe back pain due to a pathologic T3 thoracic vertebral body fracture, and imaging studies confirmed disseminated systemic disease involving abdominopelvic lymph nodes and cervical and thoracic vertebral bodies. In addition, the needle biopsy of the pelvic lymph node disclosed diffuse proliferation of monomorphic small round cells that were diffusely positive for CD30 and ALK. ALCL was also diagnosed in a 26-year-old man who presented with a mass in the jaw. His lymphoma was also present in the T4 vertebra and skull.[62]

LYMPHOMA IN EXTRA-NODAL SITES AND/ OR NON-SPECIFIED TYPES

Although classification and understanding of lymphoma has advanced, there still remains a collection of cases that are hard to label correctly. In addition, historical reports from the period before the tools and systems of the latest WHO classification were applied, bear the mark of the times but are worth noting in this review, if not for anything but to appreciate the past, and remember the future too will be different. These are indicated site wise below.

Waldeyer's Ring

Waldeyer's ring refers to a ring of lymphoid tissue found in the throat, the tonsils, adenoids and back of the tongue. In a series over 10 years of 30 patients (14 males, 16 females), aged 14 to 76 years, there were 20 patients (67%) with tonsillar involvement, 8 (27%) with nasopharyngeal involvement, 1 (3%) with tongue base lymphoma, and 1 with anterior tongue involvement. Most patients (77%) presented at an early stage. Histologically, 25 patients (83%) had high-grade diffuse large B-cell lymphoma, 4 (13%) had T-cell lymphoblastic lymphoma, and 1 (3%) had follicular lymphoma. Twenty-one patients (70%) were treated with chemotherapy, 4 (13%) received adjuvant chemotherapy with either radiotherapy or surgery, 3 (10%) resorted to other forms of treatment (primarily traditional remedies), and 2 (7%) declined treatment altogether.[63]

Nose and paranasal sinuses including parapharyngeal spaces

Tan *et al.* detected seven cases of malignant non-Hodgkin's lymphoma of the nose and paranasal sinuses at HUKM over a three-year period from 1983 to 1986. Three patients had "histiocytic" (large cell) lymphomas and two had mixed lymphocytic "histiocytic" (small and large cell) lesions. One patient had a poorly differentiated lymphocytic lymphoma. All the patients received 4000-4500 rads of radiotherapy. In six patients, the response was dramatic with relief of local symptoms within two to three weeks of commencement of treatment.[64]

Sharudin *et al.* reported a rare case of Parapharyngeal space (PPS) B-cell non-Hodgkin lymphoma with superimposed tuberculosis (TB) and fungal infection that presented with several episodes of syncope and hemodynamic depression.[65] T-Cell type lymphoma has also been found as a mass eroding the nasal septum in a 48-year-old man.[66]

Eyelid and Lacrimal sac

In a study of 136 patients with eyelid tumours in Alor Star, Kedah, Tan *et al.* found that 22 (16.2%) were malignant. Six of them were lymphoma, five MALT

and one FL.[67] Lymphoma has also been reported in the lacrimal sac.[68,69]

Oral

Reviewing 42 extranodal cases of oro-maxillofacial NHL at the University Hospital from 1980 to 2012, Ramanathan *et al.* recorded 9 mandible, 8 cheek, 7 maxilla, 7 palate, 4 salivary gland, 2 soft palate, 2 gingival cases and 1 each from the tongue, lip and floor of the mouth. Their mean age was 41.6 years. There were 24 males and 18 females. Nineteen were Malays, 18 Chinese, 3 Indian and 2 Indonesian. Twenty-six were B-cell type, of these six cases were Burkitt's lymphomas. Only ten cases were T-cell lymphoma, with three cases of NK/T-cell lymphoma.[70]

Abdelrahim *et al.* supported the view that at least a relatively smaller proportion of B-cell NHLs that occur in the oral cavity and maxillofacial region do not have a pathogenic association with EBV from their study.[71]

Respiratory Tract

Peh *et al.* studied archival material of 29 NHL cases from University Malaya and found a preponderance of T-cell lymphoma of the upper aerodigestive tract in the ethnic Chinese group of Malaysian patients, and EBV was strongly associated with T-NHL but not with B-NHL. Their results also suggested that type-A EBV is the prevalent sub-type in Asian NHL of the upper aerodigestive tract.[72]

Deng *et al.* noted a case of pulmonary lymphoma which initially presented like tuberculosis in a 11-year-old boy who presented with productive cough, left-sided chest pain, fever and night sweats and chest radiograph showed consolidation and cavitation in the lung.[73] He was treated with anti-tuberculosis drugs for 12 months without improvement. A left pneumonectomy was performed, and non-Hodgkin's lymphoma was diagnosed on histopathology. He was treated with chemotherapy but defaulted follow-up a few weeks after starting therapy.[73]

Abdomen

A 14-year-old girl with Stage III B-NHL presented with a hard suprapubic mass fixed to the anterior rectum with a four-week history of pain. At laparotomy, a large inoperable pelvic tumour was found. Examination of the bone marrow and CSF showed no abnormality. At seven years of age, she had been diagnosed and treated for acute lymphoblastic leukaemia and relapsed four years but was well for three years after re-treatment.[74]

Malignancies of the small bowel are rare, but lymphomas can occur there. A histiocytic NHL, not further defined, arising from the terminal ileum in a 50-year-old Malay man causing an entero-vesical fistula has been noted.[75]

Bone

Non-Hodgkin's lymphoma of the bone has been reported in the pelvis of a ten-year old child.[76] The patient absconded after one course of chemotherapy.

Other organs

Non-Hodgkin's lymphoma not further specified has also been reported in the male breast.[77] Ng *et al.* described a case of primary spinal lymphoma in a 15-year-old girl who first presented with chronic

low backache and acute urinary retention.[78] Spinal surgery was performed on her. Two years later she was readmitted with similar symptoms and the MRI showed a soft tissue mass at the previous surgical site with bony erosion of S1 to S3. Surgery was again performed, and a biopsy was taken. The histology and immunophenotype were suggestive of primary spinal cord lymphoma. Due to the localised nature of the tumour and the intractable pain, the patient was treated with radiotherapy to which she responded.[78]

DISCUSSION

NK/T-cell lymphomas are rare EBV-related malignancies. They have a predilection for Asian and South American populations. Majority of these lymphomas are of NK-cell lineage, and a minority of T-cell lineage. They are predominantly of extranodal origin.[79]

Clinically, three subtypes can be distinguished: nasal, non-nasal, and disseminated. Nasal NK/T-cell lymphomas usually present as stage I/II disease and involve the nose, nasopharynx and the upper aerodigestive tract. Non-nasal NK/T-cell lymphomas often present as stage III/IV disease and involve the skin, gastrointestinal tract, testis and other soft tissues. Disseminated NK/T-cell lymphoma may present with a leukaemic phase, is rapidly fatal and involves multiple organs.[79]

General management

Although lymphomas are a wide spectrum of diseases, several features in the investigations and supportive care can apply across the spectrum.

Staging

In the 21st century, 18F-FDG-PET-CT has emerged as an important imaging modality in lymphoma management, improving the accuracy of staging, assessing treatment response and surveillance. A Malaysian consensus statement has been published based on the Deauville scoring system (2009) and the Lymphoma Response Assessment Criteria (2014), so that clinicians can share a common language in the reporting of FDG PET-CT imaging.[80] Initial evaluation of NK/T-cell lymphoma requires PET/CT and quantification of circulating EBV DNA.[79]

Treatment

NK/T-cell lymphomas are radiosensitive tumours, but radiotherapy alone is inadequate with relapse rates that are unacceptable. Conventional regimens containing anthracycline are ineffective. Regimens that incorporate asparaginase are currently considered the standard of care. Combined chemotherapy and radiotherapy results in very high response rates and cure in a significant proportion of patients with stage I/II disease. Asparaginase-containing regimens are needed for stage III/IV disease. Interim and end-of-treatment PET/CT scan and circulating EBV DNA are prognostic and useful in the evaluation for additional therapy.[79]

Autologous peripheral blood stem cell transplantation

Autologous peripheral blood stem cell transplantation is an easily available source of hematopoietic stem cells, but with limited potential for the treatment of lymphoproliferative disease. Hassan *et al.* reported their series of 70 patients, half of whom

had lymphoma (19 NHL, 16 HL). The other half were patients with multiple myeloma.[75] Sixty five (92.9%) and 63 (90.0%) showing neutrophil and platelet engraftment, respectively. Patient's weight (< 60/≥ 60 kg), stage of disease at diagnosis and pre-transplant radiotherapy were significantly different for engraftment of both neutrophil and platelets. In addition, the number of previous chemotherapy cycles (< 8 v ≥ 8) was significant for neutrophil engraftment, while gender and CD34+ dosage (< 5.0 v ≥ 5.0 × 10^6/kg and < 7.0 v ≥ 7.0 × 10^6/kg) were significant for platelet engraftment.

Nur Adila Anuar *et al.* reported a promising outcome of non-Hodgkin's Lymphoma patients post high dose therapy with autologous haematopoietic stem cell transplant (AHSCT). They reported that the overall survival and event-free survival at three years were 68.9% and 60.8%, respectively of the post AHSCT.[77]

The median neutrophil engraftment time was faster than in patients with multiple myeloma than lymphoma, at 15 and 20 days, respectively. On the other hand, there was not much difference in platelet engraftment time (17 and 16 days) respectively. Among those who failed engraftment, five (out of six females with NHL) died within 30 days of transplant and had neutropenic sepsis within the first week of transplantation.[81]

AHSCT is of limited efficacy, whereas allogeneic HSCT may be useful in patients with stage III/IV and relapsed diseases if a remission can be achieved. Immunotherapy, including the use of antibodies against CD30, programmed cell death protein 1 and CD38, holds promises and should be considered for relapsed/refractory disease.[82]

Outcomes in Lymphoma survivors

Gan *et al.* evaluated the prevalence of erectile dysfunction (ED) in all types of male lymphoma survivors and reported that 81.7% of sexually active patients reported the presence of ED, with only 4.2% having severe ED. Prevalence of ED among younger patients (age ≤ 50 years old) was 64.5%. Their study prompted that the prevalence of ED and absence of sexual activity in lymphoma survivors was high and reminded that this should be considered by the treating clinician to offer early treatment and counselling.[83]

Quality of Life

Priscilla *et al.* used the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) questionnaire to study 105 patients at the Ampang Hospital, Kuala Lumpur who had haematological malignancies.[84] The haematological cancers included NHL (23.8%), acute myelogenous leukaemia (AML) (22.9%), acute lymphoblastic leukaemia (ALL) (14.3%), HL (10.5%), multiple myeloma (MM), (5.7%), other lymphomas (12.4%), other leukaemia (9.5%), and histiocytosis (1.0%). HL patients had more dyspnoea symptoms; and the NHL patients had reduced role functioning and more constipation, but they tended to be older than patients with the other cancers. The global quality of life of the female patients was much better than that of the male patients. Patients who were 40 years old or younger had a better global quality of life and physical functioning, as well as fewer symptoms of constipation, nausea, and vomiting. Employed patients were in less pain but showed greater impairments of cognitive function

than did unemployed patients. Patients who earned a monthly wage of RM1000 or less had reduced physical function, more symptoms of pain, and more financial difficulties compared with patients who earned more.[84]

Limitations of the study: This study does not represent the prevalence of lymphoma in Malaysia as it captures only what is published and many are case reports and series. We acknowledge that our literature search may miss out information despite our search efforts. It is hoped that this study is an indication of the gaps in literature that can guide investigators in moving forward.

Conclusion

While progress has been made in the diagnosis and treatment of lymphoma, issues persist with classification changes, patient care, and treatment adherence. Immunotherapy shows promise for improving patient outcomes. In Malaysia, recent research on rare subtypes of lymphoma has provided important insights. Continued research in this field will lead to further improvements in lymphoma diagnosis and treatment worldwide.

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