

Original Article

Distribution of Lymphoma Immunophenotypes in Nakhon Si Thammaraj

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Abstract : **Objective :** To study distribution of lymphoma immunophenotypes in Maharaj Nakhon Si Thammaraj Hospital which have not been reported before.

Methodes : We analyzed pathological data of lymphoma at the Pathology Department, Maharaj Nakhon Si Thammaraj Hospital for a period of three years (1995-1997). Each cases had been immunophenotypic characterized by using immunoperoxidase technique with basically selected four monoclonal antibodies, including L-26 for B-cell, UCHL1 for T-cell, Ki-1 for anaplastic large cell lymphoma, and bcl-2 for follicular carcinoma. The diagnoses based on Revised European-American Classification of Lymphoid Neoplasm.

Results : There were 37 cases of lymphoma, 18 of nodal and 19 of extranodal sites. Three cases of Hodgkin's disease were found, all of nodal in origin. Most cases of non-Hodgkin's disease were B-cell phenotype (88.89% nodal and 94.74% extranodal). The age of nodal group ranged from 2 to 83 years old (mean = 51 years) and male:female ratio=1:2, The extranodal group ranged from 21 to 82 years old (mean = 53 years) and male:female ratio=1.7:1. Two Ki-1 anaplastic large cell lymphomas were included.

Discussion & Conclusion : Our finding of B cell lymphomas predominance in all of the non-Hodgkin's lymphomas was comparable to other studies. The immunophenotyping of lymphoma provides important informations to categorize the useful diagnoses. Thus, the pathologist can classify them in more specific categories and entities which aid the clinician to treat the patients more effectively. At the present time, immunophenotyping of lymphoma is an essential method that should be used routinely, For economic proposes a minimum set of monoclonal antibodies may be desired with the additional monoclonal antibodies for resolving some troublesome cases.

Key Words: ● Lymphoma ● Immunophenotyping ● Phenotype

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ต้องการสำเนาต้นฉบับติดต่อ นพ.สุธี รุจิวนิชย์กุล กลุ่มงานพยาธิวิทยา
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The histologic classifications of lymphoma are not entirely satisfactory. Since the histologic diagnosis by routine paraffin sections may provide conflict or inconclusive results depending on different categorizations. Kiel Classification and Working Formulation has been used worldwide for a decade with the heterogeneous categories and arbitrary distinction. In 1994, the "Revised European-American Classification" (REAL Classification), proposed by the international lymphoma study group, added more informations of the available immunologic, cytogenetic, and molecular biologic techniques together with morphology to approach the practical categorization providing a list of well-defined disease entities.

To meet the criteria of the REAL Classification we have done immunophenotyping of all lymphoma cases seen in the Pathology Department, Maharaj Nakhon Si Thammaraj Hospital since 1995. Thus, we report the accumulated cases analysis in the past three years.

Materials and Methods

The pathological data of lymphoma of any types and sites, nodal and extra-nodal, were collected from 1995 to 1997, documented to morphology (routine H/E sections), immunology (immunoperoxidase sections from paraffin embedded specimens) and pathologic diagnoses.

The routine sections were performed by standard tissue preparation method. The neutral buffered formalin fixed specimens were sub-

mitted within 48 hours to process in standard sequences - running with automatic tissue processor, embedding in paraffin blocks, four microns thick sectioning, and hematoxylin/eosin (H/E) staining.

Immunophenotyping was performed at the Institute of Pathology, Ministry of Public Health with the avidin-biotin immunoperoxidase technique by using four microns paraffin embedded sections. Monoclonal rabbit or mouse anti-human antibodies were used as primary antibodies. The secondary or link antibodies were biotinylated (biotin) anti-rabbit or anti-mouse immunoglobulins. Avidin-labeled with horseradish-peroxidase was used to form complex with biotin and visualized by using diaminobenzidine (DAB) as a chromogen.

A panel of four monoclonal antibodies (DAKO[®]) was used.

1. L-26 is a marker for detecting B cell. The antibody reacts with the intracytoplasmic epitope localized on the CD20 antigen.¹

2. *bcl-2* (anti-apoptosis) is used to differentiate follicular lymphoma from follicular hyperplasia. *bcl-2* reacts with the *bcl-2* oncoprotein encoded by a gene involved in the t(14;18) chromosomal translocation. It is also found to associated with some hematologic malignant cells, e.g. B cell lineage diffuse large cell lymphoma², splenic lymphoma with villous lymphocytes³, acute myeloid leukemia⁴, non small cell lung carcinoma⁵, carcinoma of prostate⁶, and thyroid oxyphilic tumors.⁷

3. Ki-1 (CD30) is used to detect a group of

large cell lymphomas designated Ki-1 lymphomas.⁸ It also immunoreacts to Reed-Sternberg and mononuclear Hodgkin's cells, and large cell population of lymphomatoid papulosis.^{9,10}

4. UCHL1 (CD40RO) is used to detect T cell.

The minimal set of monoclonal antibodies was desired to mark the major groups of T and B cell, and large pleomorphic Ki-1 cell lymphomas, which it was considered to be useful when evaluated together with morphologic features. However, some additional monoclonal antibodies were also applied to controversial cases such as undifferentiated malignant, neuroendocrine tumors. These included leukocyte common antigen(LCA), carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), chromogranin, neurospecific enolase(NSE), S-100 protein, vimentin, cytokeratin, and desmin.

Pathological diagnoses were categorized by the REAL Classification¹¹ and Working Formulation.^{12 (page 51-69)}

Results

There were 37 cases of lymphoma diagnosed at the department of pathology during 1995 to 1997, shown in detail in Table 1.

Lymph nodes of the cervical, submandibular, supraclavicular, axillary and inguinal were the most common submitted specimens. The less frequent sites of biopsy, presented as mass lesions, including gastrointestinal tract, intra-abdominal cavity, retroperitoneum, cutis and subcutis. The others uncommon sites were spine, ethmoidal sinus, nasal cavity, nasophar-

ynx, salivary gland, and testis.

Related to organs, sites, age and sex - twenty cases were lymphoid organs (nodal), accounting for 48.65% of all cases, with the age ranged from 2 to 83 years old (mean = 51 years) and 1:2 (10/20) of male:female ratio. Nineteen cases were extranodal lymphomas, 51.35% of all cases, with the age ranged from 21 to 82 years old (mean = 53 years) and 1.7:1 (11/6) of male:female ratio. (Table 2) The youngest patient was 2-year-old female with diffuse large B-cell lymphoma in the cervical lymph node.

The nodal non-Hodgkin's lymphomas comprised of fifteen B cell, one T cell, and one Ki-1(+) null cell phenotypes. The extranodal lymphomas showed sixteen B cell phenotype and one case of T cell with Ki-1 expression. (Table 3)

Three HD were encountered (8% of entire cases) which all occurred in lymph nodes. The subtypes included one lymphocyte predominance, one mixed cellularity, and one lymphocyte depletion. No nodular sclerosis subtype was seen.

Discussion

Thirty seven cases of lymphoma were found in our department of pathology, which representing at least the yearly incidence of 12 cases in 1.5 millions (0.8 / 100,000 / year) of population in Nakhon Si Thammaraj province. The figure was considered to be lower than true incidence because of some cases of lymphoma were not encountered in our hospital. The inci-

Table 1 Detail of the 37 lymphoma cases found during the year 1995 to 1997

No.	Sex	Age	Type	Site	Diagnosis	IPX (+)	IPX (-)
1.	m	20	LN	Axilla , left	Hodgkin's disease, lymphocyte predominance	L-26 (RS-cell)	Ki-1, UCHL1 (RS-cell)
2.	f	40	LN	Axilla , right	Hodgkin's disease, mixed cellularity	Ki-1, L-26 (RS-cell)	UCHL1 (RS-cell)
3.	f	36	LN	Cervical	Hodgkin's disease, lymphocyte depletion	Ki-1 (RS-cell)	UCHL1, L-26 (RS-cell)
4.	f	68	LN	Axilla , left	Diffuse large B-cell lymphoma	L-26	UCHL1, Ki-1
5.	m	18	LN	Axilla, left	Anaplastic large cell lymphoma, null-cell type (Ki-1 cell)	Ki-1(CD30)	L-26, UCHL1
6.	m	67	LN	Cervical	Follicular follicular center lymphoma, B-cell (grade 3)	L-26	UCHL1, Ki-1
7.	m	66	LN	Cervical	Diffuse large B-cell lymphoma	L-26	UCHL1, Ki-1
8.	f	39	LN	Cervical	Follicular follicular center lymphoma, B-cell (grade 2), with diffuse area	L-26, bcl-2	UCHL1
9.	f	52	LN	Cervical , left	Follicular follicular center lymphoma, B-cell (grade 1)	L-26	UCHL1
10.	f	62	LN	Cervical, left	?mantle or follicular center lymphoma (Diffuse small cleaved, B-cell)	L-26	UCHL1
11.	m	70	LN	Inguinal, left	Diffuse large B-cell lymphoma	L-26	UCHL1
12.	f	60	LN	Inguinal, right	Diffuse large B-cell lymphoma	L-26	UCHL1
13.	m	2	LN	Cervical	Diffuse large B-cell lymphoma (immunoblastic)	L-26	UCHL1, Ki-1
14.	m	65	LN	Para-aortic	Diffuse large B-cell lymphoma (immunoblastic)	L-26	UCHL1, Ki-1
15.	m	54	LN	Submandible, right	Angioimmunoblastic T-cell lymphoma	UCHL1	L-26, Ki-1
16.	m	57	LN	Submandible, right	Follicular follicular center lymphoma, B-cell (grade 1)	L-26, bcl-2	UCHL1
17.	f	76	LN	Submandible, left	Diffuse large B-cell lymphoma	L-26	UCHL1
18.	f	83	LN	Supraclavicle, left	?mantle or follicular center lymphoma (Diffuse small cleaved, B-cell)	L-26	UCHL1
19.	m	54	Tonsil	Palatine, bilateral	Follicular follicular center lymphoma, B-cell (grade 3)	L-26, bcl-2	UCHL1
20.	f	47	Tonsil	Palatine, left	Diffuser B-cell small lymphocytic lymphoma	L-26	UCHL1
21.	m	82	Mass	Abdominal wall	Follicular follicular center lymphoma, B-cell	L-26	UCHL1

					(grade 3)		
22.	m	58	Mass	Caecum	Diffuse large B-cell lymphoma	L-26	UCHL1
23.	f	54	Mass	Caecum	Diffuser small lymphocytic B-cell lymphoma	L-26	UCHL1
24.	m	23	Mass	Ethmoid sinus, left	Diffuse large B-cell lymphoma	L-26	UCHL1
25.	f	52	Mass	Eyelid, lower	Diffuser small lymphocytic B-cell lymphoma	L-26	UCHL1
28.	m	68	Mass	Jejunum	Diffuse large B-cell lymphoma	L-26	UCHL1, Ki-1
27.	m	63	Mass	Nasal cavity, right	Diffuse large B-cell lymphoma	L-26	UCHL1
28.	m	62	Mass	Nasopharynx	Diffuse large B-cell lymphoma	L-26	UCHL1
29.	f	35	Mass	Parotid gland	Follicular follicular center lymphoma, B-cell (grade 1)	L-26	UCHL1
30.	m	21	Mass	Pelvic (retrovesicular)	Diffuse large B-cell lymphoma	L-26	UCHL1, Ki-1
31.	m	65	Mass	Retroperitoneal	Diffuser small lymphocytic B-cell lymphoma	L-26	UCHL1
32.	m	26	Mass	Skin, Axillary	Diffuse large B-cell lymphoma	L-26	UCHL1
33.	f	56	Mass	Skin, submental	Follicular follicular center lymphoma, B-cell (grade 1)	L-26	UCHL1
34.	m	60	Mass	Skin, chest wall	Anaplastic large cell lymphoma, T-cell type (Ki-1 cell)	UCHL1, Ki-1	L-26
35.	f	65	Mass	Spine	Follicular follicular center lymphoma, B-cell (grade 1)	L-26	UCHL1
36.	f	55	Mass	Stomach	Diffuse large B-cell lymphoma	L-26	UCHL1
37.	m	60	Mass	Testis, right	?mantle or follicular center lymphoma (Diffuse small cleaved, B-cell)	L-26	UCHL1

(IPX = immunoperoxidase, m = male, f = female, LN = lymph node, RS-cell = Reed-Sternberg's cell)

NOTE:- In cases number 10, 18 and 37 were morphologically diffuse small-cleaved lymphomas expressing B-cell phenotype.

They were questionable for mantle or follicular center cells because of non-availability of CD5 and CD43 antibodies to be supplementary.

Table 2 Distribution of the lymphoma cases related to sites, age, and sex

Sites	Number of cases	Age range (mean), years.	Male: female ratio
Nodal	18 (48.65%)	2 - 83 (51)	1 : 2
Extranodal	19 (51.35%)	21 - 82 (53)	1.7 : 1

Table 3 Distribution of the immunophenotypes of non-Hodgkin's lymphomas

Sites	Number of cases		
	B cell	T cell	non-B, non-T
Nodal	16 (88.89%)	1(5.55%)	1(5.55%)*
Extranodal	18 (94.74%)	1(5.26%)*	0

(* Ki-1 positive)

dence of lymphomas in Songkla province which located nearby our province was 5.6 / 1000,000 / year (1992-1994) [personal contact data from Dr. Hutchia Sriplung, Department of pathology, Faculty of Medicine, Songkla Nakarin University]. When compared to 8,743 cases of surgical specimens during 1995 to 1997, the lymphomas were accounted to be 0.42% of our total surgical pathologic cases.

The distribution of the phenotypes were mainly B cell lymphomas both nodal and extranodal which were comparable to other studies.^{13,14} In one study of a series of 520 cases of non-Hodgkin's lymphoma revealed 72% B, 25% T, 1% non-B/non-T, and 2% undetermined phenotypes.¹⁵ In addition, the series of 520 cases reported the association of Epstein-Barr virus (EBV) infection in 7% B and 31% T lymphomas, among T cell cases EBV-genomic positivity was confined to angioimmunoblastic (85%), Lennert's lymphoma (71%), and pleomorphic T cell (36%) types. Mycosis fungoides, lymphoblastic, and Ki-1 (CD30)-positive anaplastic large T cell cases were consistently EBV-negative. The patients with EBV-positive T lymphoma have a very poor clinical outcome.¹⁵

Among the 24 cases of nodal and extranodal B cell lymphoma, we had 8 follicular types. Three of these cases revealed *bcl-2* positivity which distinguished them from follicular hyperplasia. The others were not stained with *bcl-2* antibody because of their characteristic morphology of follicular lymphoma.

The extranodal cases mainly arised in gas-

trointestinal tract with the majority of B cell phenotype, which were comparable to other studies.^{14,16} One of these was diffuse small lymphocytic cell type which might be extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. The others were diffuse large B cell lymphomas. No *bcl-2* marker was applied. For review, a series of study in Japan showed that primary gastric lymphomas had *bcl-2* protein over expression in both gastric MALT-low grade and node based high-grade B cell lymphomas, while the later were *bcl-2* negative in some reports from Western countries.¹⁷

Some extranodal lymphomas e.g. brain, hepatosplenic, mediastinum and mycosis fungoides of the skin were not found in our study. Other studies of malignant lymphomas initially diagnosed in soft tissues and brain revealed most commonly large cell with a B cell phenotype.^{14,18} Primary mediastinal large cell lymphoma are the thymic medullary B cell subpopulation (CD19+/CD21- and absence of HLA-class 1 antigen expression) affected predominantly in young women.²⁰ Hepatosplenic $\gamma\delta$ T cell lymphoma is an uncommon with poor prognosis entity that has so far not been widely recognized.²¹

We found two case of Ki-1 anaplastic large cell lymphoma. One was L-26 and UCHL1 negative which presumably non-T/non-B/ Ki-1 cell (null-cell Ki-1 positive) located in the axillary lymph node of a young male, 18-year-old. The other was a lump in the skin on anterior chest

wall of 60-year-old male with T cell expression. Review of a Series of 71 cases of Ki+ large cell lymphoma revealed the expression of 60% T cell, 22% null cell, and 18% B cell phenotypes.²¹ In fact, large Ki+ B cell lymphoma is not included in the group designated as anaplastic large cell lymphoma in REAL Classification. T and null cell phenotypes were found in younger individuals with median age of 22 years.²¹ Most of the primary cutaneous Ki-1 positive anaplastic large T cell lymphomas have a unique CD4+, CD8-, cytotoxic T cell phenotype and have a favorable prognosis.²² The overall prognosis for cutaneous T cell lymphoma was good, even for disseminated cutaneous forms, survival at 48 months was 78% for T and 89% for B phenotype, however, the course frequent cutaneous relapses, particularly with the disseminated forms (extracutaneous involvement was rare, but always indicative of poor prognosis), raising the problem of adjuvant treatment after complete remission.²³ Ki-1 anaplastic large cell lymphoma has been reported in about 10% of NHD of childhood.²⁴ Ki-1 was also positive in lymphomatoid papulosis (a cutaneous clonal or polyclonal Ki-1+ T cell lymphoproliferative disorder), usually has a characteristic benign clinical course with remissions and relapses of the cutaneous eruptions, which should be differentiated from Ki-1 anaplastic large cell lymphomas and HD.⁹

We seen one nasal and one ethmoid sinus lymphomas of B cell lineage, in contrast with a study in Japan by NakamuraK, et al.²⁵ Reported that T cell lymphomas were mostly found in

the nasal cavity and ethmoidal sinus, while B cell lymphomas were found mainly in the maxillary sinus. The 5-year survival rates in relation to the primary site of the tumor were 64% for the nasal cavity, 50% for the ethmoidal sinus, and 100% for the maxillary sinus²⁵. The EBV-positive nasal T cell lymphoma may be derived from the lineage of NK-like T cell or gamma delta T cell.²⁶

Three cases of Hodgkin's disease (HD) were included with characteristic morphologic features. The morphologic subtypes were one lymphocyte predominance, one mixed cellularity, and one lymphocyte depletion. The typical Hodgkin's (Reed-Sternberg) and their atypical neoplastic cells showed immunoreactivity to Ki-1 in two cases, one of these also expressed L-26 antigen. The other one only reacted to L-26. This findings were similar to other studies.^{27,31}

Lymphocyte depletion HD may be sometimes difficult to differentiate from Ki-1 anaplastic large cell lymphoma of null cell phenotype since both may express Ki-1 antigen and show no T or B cell markers. Detection of the t(2;5) translocation by molecular genetics is a highly specific marker for Ki-1 anaplastic large cell lymphoma which may useful to distinguish these two entities.²¹

Conclusion

As the diagnosis and categorization of lymphoma had been a frustrated subject for the past decades, immunophenotyping is one of the most useful tool to overcome the even. Oth-

ers are cytogenetic and molecular techniques which are applied for lymphoma characterization of the genetic derangement and etiologic or associated viral infections.

Immunophenotyping of lymphoma provides the very helpful informations for treatment and prognosis. For examples, T cell lymphomas are usually high grade with worse prognosis may response well to some proper chemotherapeutic regimens²⁸, and Ki-1 anaplastic large cell lymphoma is a high grade lymphoma with a relatively good prognosis when treated with multiagent intensive chemotherapy.^{29,30}

We conclude that characterization of the lymphoma phenotypes should be applied to routine pathological diagnosis for the lymphoid neoplasm. A minimum set of monoclonal antibodies can be desired for economic proposes to classify the major groups of lymphomas. To complete the categorization with REAL Classification the additional monoclonal antibodies should be properly applied.

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Distribution of Lymphoma Immunophenotypes in Nakhon Si Thammaraj

สุธี รุจิวนิชย์กุล

กลุ่มงานพยาธิวิทยา โรงพยาบาลมหาราชนครศรีธรรมราช อ.เมือง จ.นครศรีธรรมราช 80000

บทคัดย่อ : วัตถุประสงค์ : เพื่อศึกษาการกระจายของ immunophenotypes ของมะเร็งต่อมน้ำเหลือง ในผู้ป่วยที่มา
รับการตรวจที่ รพ.มหาราชนครศรีธรรมราช

วิธีการ : รวบรวมข้อมูลผลการตรวจทางพยาธิวิทยาที่ให้การ วินิจฉัยเป็นโรคมะเร็งต่อมน้ำเหลืองทั้งชนิดที่พบในต่อมน้ำ
เหลืองและนอกต่อมน้ำเหลือง ใน รพ.มหาราชนครศรีธรรมราช รวม 3 ปี (พ.ศ.2538-2540) ทุกรายได้ทำการตรวจ
หา immunophenotypes โดยใช้ monoclonal antibodies เป็นพื้นฐาน 4 ชนิดคือ (1) L-26 สำหรับ B-cell, (2)
UCHL1 สำหรับ T cell, (3) bcl-2 ใช้แยก follicular lymphoma จาก follicular hyperplasia และ (4) Ki-1 ใช้
วินิจฉัย anaplastic large cell lymphoma และใช้ monoclonal antibodies อื่นๆ เพิ่มเติมในรายที่มีปัญหา และ
แบ่งชนิดตาม Revised European-American Classification of Lymphoid Neoplasm

ผลการศึกษา : รวบรวมได้ 37 ราย มี Hodgkin's disease (HD) 3 ราย (ทั้ง 3 ราย เป็นที่ต่อมน้ำเหลือง) และ non-
Hodgkin's disease (NHD) 34 ราย แบ่งเป็นสองกลุ่มใหญ่ๆ คือ กลุ่มที่ 1 พบในต่อมน้ำเหลือง (18 ราย) กลุ่มที่ 2 พบ
นอกต่อมน้ำเหลือง (19 ราย) มีอายุเฉลี่ย 51 ปี (พิสัย 2-89 ปี) และ 53 ปี (พิสัย 21-82 ปี) ตามลำดับ โดยที่ NHD
ทั้งสองกลุ่มส่วนมากเป็น B cell phenotype (กลุ่มที่ 1 88.89%, กลุ่มที่ 2 94.74%) ส่วนน้อยเป็น T cell และ null cell
phenotypes และพบ Ki-1 anaplastic large cell type 2 ราย ชนิดที่พบนอกต่อมน้ำเหลืองเป็น non-Hodgkin's
ทั้งหมด โดยพบในลำไส้และกระเพาะอาหารมากที่สุด สัดส่วนตามเพศ ชาย:หญิง กลุ่มที่ 1=1:2 และ กลุ่มที่ 2 =1.7:1

วิจารณ์และสรุป : การกระจายชนิดตาม immunophenotypes พบ B cell phenotype มากเช่นเดียวกับรายงานอื่นๆ
เมื่อวินิจฉัยร่วมกับลักษณะทาง morphology จะช่วยจำแนกชนิดของมะเร็งต่อมน้ำเหลืองที่คุณสมบัติจำเพาะ ได้ถูกต้อง
มากกว่าการแบ่งชนิดตาม morphology อย่างเดียว ซึ่งช่วยให้การรักษาเป็นไป ในแนวทางที่เหมาะสมตามชนิดของมะเร็ง
ต่อมน้ำเหลือง และให้ผลการรักษาที่ดี ดังนั้นการวินิจฉัยทางพยาธิวิทยาสำหรับมะเร็งต่อมน้ำเหลือง โดยจำแนกชนิด
immunophenotypes จึงมีความจำเป็นในปัจจุบัน ซึ่งอาจทำได้โดยประหยัด ด้วยการเลือกใช้ monoclonal anti-
bodies น้อยชนิดที่สุดเท่าที่จำเป็น และใช้ monoclonal antibodies อื่นๆ เพิ่มเติมตามความเหมาะสมในแต่ละราย

Key Words: ● Lymphoma ● Immunophenotyping ● Phenotype

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