Extranodal Malignant Lymphoma of the Upper Aerodigestive Tract in King Chulalongkorn Memorial Hospital According to WHO Classification

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Background : *The Working Formulation commonly used to classify NHL in Thailand has been recognized as imperfect for primary extranodal lymphoma, especially in head and neck regions.*
Objective : *To study the clinicopathological and immunohistochemical features of extranodal malignant lymphoma of the upper aerodigestive tract according to WHO classification.*
Setting : *King Chulalongkorn Memorial Hospital.*
Design : *Descriptive study.*
Patients : *77 Thai patients who presented between 1998 and 2003.*
Methods : *Routine histology was performed and stained with H&E and immunohistochemistry, and clinical characteristics were recorded.*
Results : *The patients included 42 males and 35females, with an average age of 53.87years. Tumor sites were as follows: Waldeyer's ring (n =42, 54.55%), sinonasal areas (n =19, 24.67%), oral cavity (n =9, 11.69%), hypopharynx (n =4, 5.19%), and larynx (n = 3, 3.90%). Immunohistochemically, 57 tumors (74.02%) were of B-cell phenotype and 19 tumors (24.68%) were of T-cell phenotype. According to the WHO classification, 45cases (58.43%) were large B-cell, 3 (3.90%) were Burkitt, 3 (3.90%) were marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT), 4 (5.19%) were follicular lymphoma, 1 (1.30%) was precursor B-lymphoblastic lymphoma, and 1 (1.30%) were mantle cell lymphoma. Among the T-cell lymphomas, 9 (11.69%) were of peripheral T-cell lymphoma, unspecified, 9 (11.69%) were extranodal NK/T cell lymphoma, nasal type, and 1 (1.30%) were anaplastic large-cell lymphomas. In nasal cavity, 8 tumors (42.11%) were extranodal NK/T-cell lymphoma, nasal type, 5 (26.32%) were diffuse large B-cell lymphoma, 4 (21.05%) were peripheral T-cell lymphoma, unclassified, and 1 (5.26%) was Burkitt lymphoma.*
Conclusion : *Our data correspond with series from Japan, Hong Kong, and Korea, but there is a significant difference from Western population in T-cell lymphomas of sinonasal area especially extranodal NK/T cell lymphoma of nasal type and peripheral T-cell lymphoma, unspecified which had a higher frequency in Thailand, Japan, Hong Kong, and Korea.*

Keywords : *Lymphoma, Upper aerodigestive tract, WHO classification, Extranodal, Thai*

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The pattern of malignant lymphoma is known to vary in different populations. However, it is still not clear if the difference is due to genetic or environmental factors, or both. Especially in the nasal cavity, non-Hodgkin lymphoma of this area is a relatively uncommon neoplasm representing 0.17% of all lymphoma in the Kiel Lymphoma Node Registry in a Western population [1] while the Asian and South American population have been reported to have a higher incidence[2-9].

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The upper aerodigestive tract is the most common extranodal site of all cases of NHL (20-29.1%) followed by the gastrointestinal tract (16.4%)[10-,11]. Patients with non-Hodgkin's lymphoma in the head and neck with tumors > or = 5 cm in diameter appear to have a worse prognosis than those with smaller tumors[12].

Although the Working Formulation is commonly used to classify non-Hodgkin lymphoma (NHL) in Thailand, it has been recognized as imperfect for primary extranodal lymphoma, especially in head and neck regions such as extranodal NK/T-cell lymphoma that is difficult to classify this type of lymphoma according to Working Formulation because this

classification was not based on the origin of tumor cells but on the morphology of tumor tissues. In the last 2 decades, increased understanding of the immune system and the genetic abnormalities associated with NHL has led to the identification of several previously unrecognized types of lymphoma. Recently, the World Health Organization (WHO) classification of tumors of haematopoietic and Lymphoid tissues proposed by the European Association for Haematopathology and Society for Haematopathology has included several new entities that were not included in Working Formulation[13].

The present study reclassified types of malignant lymphoma and investigated the clinical characteristics of extranodal non-Hodgkin lymphoma of upper aerodigestive tract according to WHO classification.

Material and Method

All malignant lymphoma biopsy specimens diagnosed in the Department of Pathology, King Chulalongkorn Memorial Hospital, Thailand from 1998 to 2003 were analyzed. Those without enough material for study were excluded. Individual clinical records were reviewed.

Routine histology was performed by fixation in 10% buffered formalin, followed by embedment in paraffin. Sections were stained with Hematoxylin and Eosin (H&E). Immunophenotypes were performed by react the tissue with the following antibodies: ALK, CD3, CD5, CD10, CD15, CD20, CD30, CD43, CD45RO, CD56, CD79a, Bcl-2, CyclinD1, EMA, Kappa, Lambda, and Ki-67. Pathological specimens of all patients were evaluated by two of the authors (Assanasen T and Wannakrairot P) according to WHO classification[13-18].

Results

Seventy-seven cases of extranodal non-Hodgkin lymphoma of the upper aerodigestive tract were included in the present study. The age of the patients at clinical presentation spanned a wide range of 3 to 85 years, with a mean of 53.87 years. There was a slight male predominance (approximately 1.2:1 according to male: female ratio). The location of the lesions and clinical presentation are presented in Table 1 and appeared to be primarily in the Waldeyer's ring (54.55%). Tumor sites were additionally separated as follows: nasal cavity (n =14, 18.18%), paranasal sinuses (n =5, 6.49%), nasopharynx (n =11, 14.29%), oral cavity, unspecified (n =7, 9.09%), hard and soft palate (n = 2, 2.60%), base of the tongue (n = 6, 7.79%), tonsil (n = 25, 32.47%), larynx (n =3, 3.90%), and hypopharynx (n = 4, 5.19%).

Histologic types of extranodal non-Hodgkin lymphoma of upper aerodigestive tract according to WHO classification are shown in Table 2. The histopathology of the 77 cases of extranodal upper aerodigestive tract showed that only non-Hodgkin's lymphomas were observed; Hodgkin's lymphoma was not observed.

Among these, the B-cell lymphoma is significant much more than T-cell lymphoma (3:1 according to B cells: T cells), and the most common histologic type was diffuse large B-cell lymphoma (58.43%), followed by peripheral T-cell lymphoma, unclassified (11.69%), and extranodal NK/T-cell lymphoma, nasal type (11.69%).

Interestingly among 19 cases of extranodal non-Hodgkin lymphoma of nasal cavity, the most common histologic type was extranodal NK/T-cell lymphoma, nasal type (42.11%), followed by diffuse large B-cell lymphoma (26.32%), and peripheral T-cell

Table 1. Clinical presentation of extranodal malignant lymphoma of the upper aerodigestive tract according to the site of involvement

	Waldeyer's ring	Sinonasal areas	Oral cavity	Hypopharynx	Larynx	Total
Mass	15	8	5	1	-	29
Cervical lymph node enlargement	12	-	1	2	-	15
Air way obstruction	5	3	-	-	2	10
Sore throat	9	-	-	1	-	10
Ulcer	1	2	2	-	-	5
Bleeding	-	2	1	-	-	3
Nasal discharge	-	2	-	-	-	2
Regurgitation	-	1	-	-	-	1
Cough	-	-	-	-	1	1
Ptosis	-	1	-	-	-	1
Total (%)	42 (54.55)	19 (24.67)	9 (11.69)	4 (5.19)	3 (3.90)	77(100)

Table 2. Histologic types of extranodal malignant lymphoma of the upper aerodigestive tract according to WHO classification.

Histologic Type	Waldeyer's ring	Sinonasal areas	Oral cavity	hypopharynx	larynx	Total (%)
B cells						
DLBCL*	32	5	6	1	1	45(58.43)
Burkitt lymphoma	1	1	1	-	-	3(3.90)
Precursor B-lympho-blastic lymphoma	-	-	1	-	-	1(1.30)
Mantle cell lymphoma	1	-	-	-	-	1(1.30)
MALT- lymphoma**	1	-	-	1	1	3(3.90)
Follicular lymphoma	3	-	-	1	-	4(5.19)
T cells						
Extranodal NK/T-cell lymphoma, nasal type	1	8	-	-	-	9(11.69)
Peripheral T-cell lymphoma, unspecified	3	4	-	1	1	9(11.69)
ALCL (null cell)***	-	-	1	-	-	1(1.30)
Unclassified	-	1	-	-	-	1(1.30)
Total (%)	42(54.55)	19(24.67)	9(11.69)	4(5.19)	3(3.90)	77(100)

Note: * Diffuse large B-cell lymphoma
** Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue
*** Anaplastic large cell lymphoma

lymphoma,unclassified (21.05%). The tumor cells with positive T-cell markers were predominant in lymphoma of sinonasal areas (2:1 according to T cells: B cells).

Discussion

NHL is the most common type of malignant lymphoma followed by Hodgkin lymphoma. For the non-Hodgkin lymphoma, B-cell lymphomas are much more common than T-cell lymphomas. The extranodal site is slightly more common than nodal site[19-22].

NHL in extranodal sites in the head and neck such as nasopharynx, Waldeyer's ring, oral cavity, and larynx manifests frequently as a submucosal mass accompanied by polypoid, bulky masses with a smooth mucosal surface. Clinically aggressive lymphomas, such as Burkitt lymphoma, diffuse large B-cell lymphoma, and NK/T-cell lymphomas are characterized by destruction of the maxilla, mandible, and bones around the paranasal sinuses[23]. Though anatomically in close proximity, lymphomas arising in these sites have distinct clinical characteristics. Factors that appear to influence the pattern of disease include concurrent conditions, such as Sjogren's syndrome, and geographic factors, particularly with regard to nasal lymphomas. It is still not clear if the difference is due to genetic or environmental factors, or both. The treatment and prognosis of patients with head and neck lymphoma depends on the histologic types of disease and extent of involvement at time of presentation[24]. Currently, there is a paucity of information regarding the pattern of upper aerodigestive NHL occurring in Thailand and Southeast Asia. This study was undertaken to obtain a clearer definition of the disease among Thais and to compare this information with data from other Asian and Western countries.

According to the sites of involvement, the most common site is tonsil and if the nasopharynx (14.29%), tonsil (32.47%) and base of the tongue (7.79%) are grouped together, this combined site (Waldeyer's ring) become the most common site of disease (54.55%). This fact is also true when compared to other series (Fig. 1).

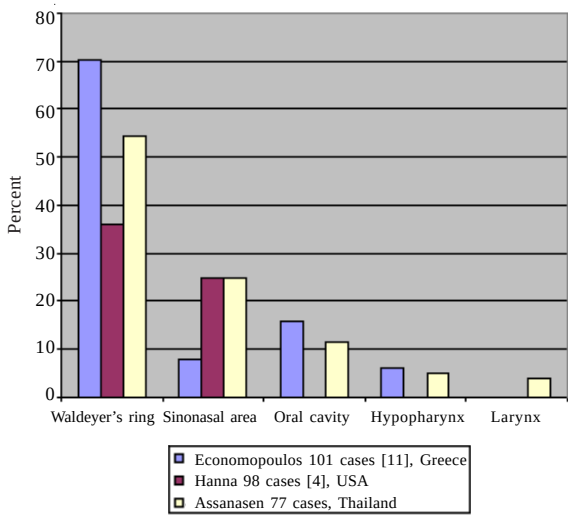


Fig. 1 Sites of involvement of extranodal malignant lymphoma of the upper aerodigestive tract

Focusing on the histologic types, the most common histologic type was diffuse large B-cell lymphoma (58.43%), followed by peripheral T-cell lymphoma, unclassified (11.69%), and extranodal NK/T-cell lymphoma, nasal type (11.69%), but if only sinonasal areas are concerned, the most common histologic type is extranodal NK/T-cell lymphoma, nasal type (42.11%), followed by diffuse large B-cell lymphoma (26.32%), and peripheral T-cell lymphoma, unclassified (21.05%). These findings correspond to the data from Asian countries, but distinct difference from the Western countries in which there is a low incidence of sinonasal T-cell lymphoma, especially extranodal NK/T cell lymphoma of nasal type (Fig. 2).

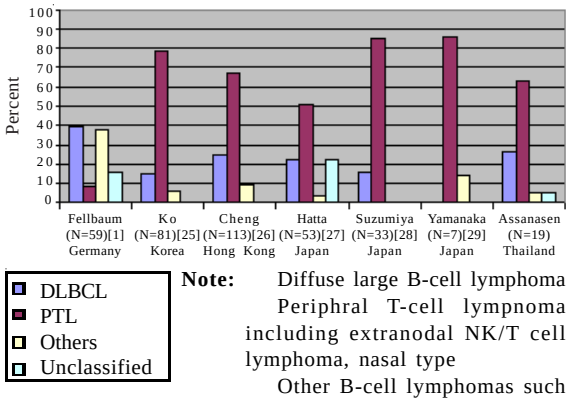
In Asian countries, extranodal NK/T cell lymphoma of the nasal type and other peripheral T-cell lymphoma had a higher frequency, but B-small lymphocytic lymphoma and follicular lymphoma were less common in this group than in Western countries[30]. Natural Killer (NK) cell lymphomas, which include the nasal and the "nasal type" varieties, are defined as angiocentric lymphomas in the Revised European American Lymphoma (REAL) classification. This group of diseases is rare in the United States and Europe but is more common in Asia and Central America. It is associated with the Epstein-Barr virus (EBV) and its response to treatment and prognosis are usually very poor compared with DLBL[21,31].

Regarding the oral cavity and Waldeyer's ring, The ratio of B- and T-cell lymphoma seem to be similar with other series, and most are B-cell lymphoma [32]. (Table 3) B-cell lymphomas predominate in the oral cavity and Waldeyer's ring, and T-cell lymphomas predominate in nasal cavity.

Yamanaka et al[29] have shown that patients with sinonasal lymphoma had a poorer prognosis than those with Waldeyer's and nodal lymphoma; this difference relates to the phenotype of the tumors because Waldeyer's and nodal lymphoma are mainly B-cell type, whereas nasal neoplasms are T-cell type.

Table 3. The frequency of phenotype of malignant lymphoma of the oral cavity and Waldeyer' ring

	B-cell	T-cell	Unclassified
Oral cavity			
Ho[33]16 cases Hong Kong	75%	25%	-
Takahashi[34] 70 cases Japan	34%	28%	38%
Solomides[35]71 cases USA	92%	8%	-
Assanasen 9 casesThailand	89%	11%	-
Waldeyer's ring			
Yamanaka[29]22 casesJapan	86%	14%	-
Assanasen42 casesThailand	90%	10%	-



Note: Diffuse large B-cell lymphoma
Periphral T-cell lympnoma including extranodal NK/T cell lymphoma, nasal type
Other B-cell lymphomas such as Burkitt lymphoma, lymphoplasmacytic lymphoma, and unspecified B-cell lymphoma

Fig. 2 Frequency of mlignant lymphoma of the sinonasal tract

The present study examined age, presenting symptoms, primary sites, and WHO classification in order to demonstrate epidemiologic database of extranodal malignant lymphoma of the upper aerodigestive tract in Thai patients and compared with other reports from other countries identified through a computerized search on Pubmed. The authors found that the present data corresponded with other countries in Asia such as Japan, Hong Kong, and Korea, but there is a significant difference from Western populations in T-cell lymphomas of the sinonasal area especially extranodal NK/T cell lymphoma of nasal type and peripheral T-cell lymphoma, unspecified which had a higher frequency in Thailand, Japan, Hong Kong, and Korea. Geographic variations in the histopathologic pattern of non-Hodgkin's lymphoma (NHL) are well documented. Insight into this epidemiologic data might shed light on the underlying etiology.

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การแบ่งแยกชนิดของมะเร็งต่อมน้ำเหลืองที่เกิดขึ้นในระบบทางเดินหายใจส่วนบนที่อยู่นอกต่อมน้ำเหลือง ของผู้ป่วยโรงพยาบาลจุฬาลงกรณ์ตามระบบขององค์การอนามัยโลก

ธรรมธร อาศนะเสน, พงษ์ศักดิ์ วรรณไกรโรจน์, สมบูรณ์ คีลาวัฒน์, นุชนาฏ เปรมประยูร, มุกดา ชัยพิพัฒน์

ที่มา *: การแบ่งแยกชนิดของมะเร็งต่อมน้ำเหลืองที่เกิดขึ้นในระบบทางเดินหายใจส่วนบนที่อยู่นอกต่อมน้ำเหลืองโดยระบบเดิมที่ใช้อยู่ (Working Formulation) นั้นเป็นที่ยอมรับกันว่าไม่สามารถแยกชนิดได้เหมาะสมต่อการรักษาในปัจจุบัน*

วัตถุประสงค์ *: เพื่อศึกษาชนิดของมะเร็งต่อมน้ำเหลืองที่เกิดขึ้นในระบบทางเดินหายใจส่วนบนที่อยู่นอกต่อมน้ำเหลืองตามระบบขององค์การอนามัยโลกรวมถึงข้อมูลพื้นฐานทางคลินิก*

สถานที่ศึกษา *: โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย *: การศึกษาเชิงพรรณนา*

ผู้ป่วยที่ได้ทำการศึกษา *: ผู้ป่วยชาวไทย 77 รายตั้งแต่ปี 2541 ถึง 2546*

วิธีการศึกษา *: ตรวจชิ้นเนื้อทางพยาธิโดยย้อมชิ้นเนื้อด้วย H&E และ Immunohistochemistry เพื่อแยกชนิดตามระบบขององค์การอนามัยโลก พร้อมกับบันทึกข้อมูลพื้นฐานทางคลินิก*

ผลการศึกษา*: ผู้ป่วยชาย 42 คน หญิง 35 คน มีอายุโดยเฉลี่ย 53.87 ปี พบมะเร็งต่อมน้ำเหลืองตามตำแหน่งต่าง ๆ ดังนี้ : Waldeyer's ring (n =42, 54.55%), ช่องจมูก และโพรงข้างจมูก (n =19, 24.67%), ช่องปาก (n =9, 11.69%), คอหอยส่วนล่าง (n =4, 5.19%), และ กล่องเสียง (n =3, 3.90%) มะเร็งต่อมน้ำเหลืองเป็นชนิด บีเซลล์ 74.02%โดยมีชนิดย่อยดังนี้ : diffuse large cell (58.43%), Burkitt (3.90%), marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) (3.90%), follicular lymphoma (5.19%), precursor B-lymphoblastic lymphoma (1.30%), และ mantle cell lymphoma (1.30%) ส่วนทีเซลล์พบ 24.68%โดยมีชนิดย่อยดังนี้ : peripheral T-cell lymphoma, unspecified (11.69%), extranodal NK/T cell lymphoma, nasal type (11.69%), และ anaplastic large-cell lymphomas (1.30%) สำหรับช่องจมูก และ โพรงข้างจมูกนั้นพบ extranodal NK/T-cell lymphoma, nasal type 8 ราย (42.11%), diffuse large B-cell lymphoma 5 ราย (26.32%), peripheral T-cell lymphoma, unclassified 4 ราย (21.05%) และ Burkitt lymphoma 1 ราย (5.26%)*

สรุป *: ข้อมูลต่าง ๆ ที่ได้มาสอดคล้องกับประเทศ ญี่ปุ่น ฮ่องกง และ เกาหลี แต่แตกต่างจาก ประเทศทางตะวันตกตรงมะเร็งต่อมน้ำเหลืองของช่องจมูก และ โพรงข้างจมูกที่พบว่ามะเร็งชนิด extranodal NK/T cell lymphoma of nasal type และ peripheral T-cell lymphoma, unspecified พบได้บ่อยกว่าในประเทศแถบบ้านเราอย่างชัดเจน*