Mature T-Cell and NK-Cell Lymphomas in Thailand: An Analysis of 71 Cases

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Objective: *To identify the distribution of mature T-cell and NK-cell lymphomas in Siriraj Hospital and compare to the other world regions, using the latest WHO classification (2008).*

Material and Method: *Newly diagnosed cases of such lymphomas between January 1, 2004 and December 31, 2006 at Siriraj Hospital were recruited and reviewed. Additional immunohistochemical studies and/or EBV-encoded RNA (EBER) in situ hybridization were performed from the formalin-fixed paraffin-embedded tissue. Then, lymphomas were reclassified according to the WHO classification (2008).*

Results: *Seventy-one cases including extranodal NK/T-cell lymphoma, nasal type (ENKTL, 31.0%), anaplastic large cell lymphoma (18.3%), angioimmunoblastic T-cell lymphoma (14.1%), peripheral T-cell lymphoma, not otherwise specified (12.7%), mycosis fungoides (MF, 8.5%), subcutaneous panniculitis-like T-cell lymphoma (SPTCL, 7.0%), primary cutaneous anaplastic large cell lymphoma (PCAL, 5.6%), primary cutaneous gamma-delta T-cell lymphoma (PCGDTL, 1.4%), and enteropathy-associated T-cell lymphoma (1.4%) were included in this study. In terms of changing version of the WHO classification from 2001 to 2008, only one case had the diagnosis changed from MF to PCGDTL, a newly proposed entity in the 2008 version.*

Conclusion: *ENKTL was the most common in the present series and it had a significantly higher frequency than those reported in other previous studies. The frequency was relatively higher in SPTCL, PCAL, and MF when compared to the other series. Furthermore, changing the WHO classification from the 2001 version to the recently published 2008 version may not affect the proportion of NK/T-cell lymphoma.*

Keywords: *Lymphoma, T-cell, NK cell, Epidemiology, WHO classification, Thailand*

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Lymphoma is a common malignancy. In Thailand, at Siriraj Hospital, it is the fifth most common cancer with approximately 5 to 6% of the cancer patients newly diagnosed each year. At present, the most worldwide accepted classification of lymphoid neoplasms is the WHO classification (2008)[1]. This classification requires a combination of clinical, morphologic, immunophenotypic, and genetic features for making diagnosis-the same principle as that used in the previous one[2].

The frequencies of some lymphomas between the Western and Asian countries are different, especially mature T-cell and NK-cell lymphomas[2-5]. Moreover, only a few studies on frequency of various types of lymphoma were previously conducted in Thailand and they were using the older lymphoma classifications[6-8]. Thus, in the present study, with more markers available, the authors analyzed the frequencies of various types of mature T-cell and NK-cell lymphomas according to the WHO classification (2008) and compared them with those reported from the other regions of the world.

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Material and Method

The present study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si064/2008).

The study samples were consecutive cases of newly diagnosed mature T-cell and NK-cell lymphomas during 3 years between January 1, 2004 and December 31, 2006 at Department of Pathology, Siriraj Hospital. Exclusion criteria were known cases of

lymphoma, consultation slides and paraffin blocks from other hospitals, and cases with inadequate material for complete study.

Cases of mature T-cell and NK-cell lymphomas were recruited from the computer filing system. Clinical information was gathered from those given in the requisitions. If more information was requested, it was also gathered from the medical records. All cases were initially classified according to the WHO classification (2001), by using the preexisting materials with or without additional paraffin-section immunoperoxidase and/or in situ hybridization techniques. Then the diagnoses were reviewed according to the latest version of WHO classification (2008) by consensus made between TP and SS. The available antibodies for lymphoid neoplasm used in the present study including CD3, CD4, CD5, CD7, CD8, CD10, CD15, CD20, CD23, CD30, CD34, CD43, CD45, CD56, CD79a, CD99, CD138, beta T-cell receptor (TCR), ALK, CD1a, TdT, TIA-1, granzyme B, perforin, PAX5, Oct2, BOB.1, IRF4/MUM1, EBV-LMP1, EMA, kappa light chain, lambda light chain, BCL2, BCL6 and cyclin D1. The panel of immunostaining varied from case to case, depending on the immunophenotypic requirement for subclassifying. EBV-encoded RNA (EBER) in situ hybridization and T-cell receptor (TCR) rearrangement were additionally performed only in possible cases for ENKTL. The TCR gene rearrangement was evaluated by gel and fluorescence capillary electrophoresis, using beta, gamma and delta TCR gene primers for DNA amplification[9]. Descriptive statistics were used to summarize the data as frequency and percentage, mean, median and range.

Results

Seventy-one cases of mature T-cell and NK-cell lymphomas were diagnosed during the 3-year period at Siriraj Hospital. A case of blastic NK-cell lymphoma was not included in this analysis because this type of lymphoma proposed in the 2001 version of the WHO classification had been considered to be a new entity of "blastic plasmacytoid dendritic cell neoplasm" under the category of acute myeloid leukemia and related precursor neoplasms in the 2008 version[1,2]. The demographic data of mature T-cell and NK-cell lymphomas are shown in Table 1.

Twenty-two cases of ENKTL were diagnosed from the biopsies obtained from the nasal cavity and/or nasopharynx (17 cases, 77%), oral cavity (3 cases, 14%), and orbit (2 cases, 9%). Most cases of ENKTL had a typical true NK-cell phenotype, positive for CD3, CD56, and TIA-1, but negative for CD5, CD4, CD8, beta TCR immunoperoxidase and TCR gene rearrangements (both gel and fluoresence capillary electrophoresis). Thirteen cases of anaplastic large cell lymphoma (ALCL) were divided into ALK positive group (6 cases, 8.5%) and ALK negative group (4 cases, 5.6%). However, three cases of ALCL did not have enough tissue for evaluation of ALK expression. Among the ALK positive group, the diagnostic materials were obtained from lymph nodes (5 cases,

Table 1. Demographic data of mature T-cell and NK-cell lymphoma types at Siriraj Hospital

Type	No. of cases (%)	Sex		Age (range)	Median (age)
		M	F		
Extranodal NK/T-cell, nasal type	22 (31.0)	15	7	26-76	46
Aanaplastic large cell lymphoma (ALCL)	13 (18.3)	6	7	7-71	25
ALCL, ALK positive	6 (8.5)	3	3	7-33	21.5
ALCL, ALK negative	4 (5.6)	1	3	25-71	53.5
ALCL, unknown ALK expression	3 (4.2)	2	1	15-37	18
Angioimmunoblastic T-cell lymphoma	10 (14.1)	5	5	30-73	56.5
Periperal T-cell lymphoma, not otherwise specified	9 (12.7)	5	4	17-75	52
Mycosis fungoides	6 (8.5)	2	4	13-66	41.5
Subcutaneous panniculitis-like T-cell lymphoma	5 (7.0)	1	4	13-42	24
Primary cutaneous anaplastic large cell lymphoma	4 (5.6)	2	2	34-56	39.5
Primary cutaneous gamma-delta T-cell lymphoma	1 (1.4)	1	0	69	69
Enteropathy-associated T-cell lymphoma	1 (1.4)	0	1	13	13
Total	71 (100)	37	34	7-76	43

83%) and bone (1 case, 17%), while the ALK negative group were from lymph node (3 cases, 75%) and bone (1 case, 25%) and the other three cases of ALCL with unknown ALK status were obtained from lymph nodes (2 cases) and epidural soft tissue (1 case). For angioimmunoblastic T-cell lymphoma, all 10 cases were diagnosed from lymph node biopsy. Among the nine cases of peripheral T-cell lymphoma not otherwise specified, the diagnoses were made from lymph node (4 cases, 44%), nasopharynx, orbit, skin, tonsil and stomach (1 case each, 11% each).

A case of primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL), previously diagnosed as nodular MF based on the WHO classification (2001), was also identified. This case showed dense medium-sized lymphoid cell infiltration, predominantly in dermis, and focally in epidermis and subcutaneous fat. Immmunostaining demonstrated the absence of beta TCR despite the presence of external and internal positive control. Apart from this particular case, when using the WHO classification (2008), there was no other case with changing of diagnosis from that given initially according to the 2001 version.

Discussion

Geographic distribution of lymphomas is clearly distinct between the Western and Asian countries, especially in mature T-cell and NK-cell lymphomas, the Western countries have a lower rate of mature T-cell and NK-cell lymphomas than the Asian countries[2-5,10]. Even among the Asian countries, there is also a variation of distribution in types of these lymphomas. The frequencies of T/NK-cell lymphomas (including precursor lymphoblastic lymphoma) in Thailand, Japan, Taiwan, and India were 24.9%, 27.7%, 14.5% and 15.2%, respectively[8,11-13]. Table 2 compares the distribution of various types of mature T-cell and NK-cell lymphomas between the Western and Asian countries reported in the literature using the WHO classification. The difference between the present study and the previous study at Siriraj Hospital was due to the design of the study and the limited resource in

Table 2. Comparison of mature T-cell and NK-cell lymphoma types among different countries and regions in percentage according to the WHO classification (the number of cases in parenthesis)

Type	The present study (71)	Thailand[8] (456)	Japan[11] (554)	Taiwan[12] (65)	India[13] (251)	North America[4]	Europe[4]
ENKTL	31.0	15.1[a]	6.3	26.2	7.6	5.1	4.3
ALCL	18.3	14.7	8.1	12.3	47.4	23.8	15.8
AITL	14.1	7.2	20.9	4.6	11.2	16.0	28.7
PTCL-NOS	12.7	37.5	18.4	35.4	21.1	34.4	34.3
MF	8.5	5.0	2.0	3.1	9.6	-[b]	-[b]
SPTCL	7.0	2.0	0	4.6	1.2	1.3	0.5
PCAL	5.6	1.1	0	3.1	1.6	5.4	0.8
ETL	1.4	0.2	0.2	9.2	0	5.8	9.1
PCGD-TCL	1.4	-[c]	-[c]	-[c]	-[c]	-[c]	-[c]
HSTCL	0.0	0.7	0.2	1.5	0.4	3.0	2.3
ATLL	0.0	0.0	40.8	0	0	2.0	1.0
Unclassifiable	0.0	0.0	3.1	0	0	2.3	3.3
Total	100	100	100	100	100	100	100

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ATLL = adult T-cell leukemia/lymphoma; ENKTL = extranodal NK/T-cell lymphoma = nasal type; ETL = enteropathy-associated T-cell lymphoma; HSTCL = hepatosplenic T-cell lymphoma; MF = mycosis fungoides; PCAL = primary cutaneous anaplastic large cell lymphoma; PCGD-TCL = primary cutaneous gammadelta T-cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma = not otherwise specified; SPTCL = subcutaneous panniculitis-like T-cell lymphoma

[a] ENKTL in the series from Thailand[8] was not separated out in the original report. It was included in the PTCL-NOS but mentioned as having angiocentric growth pattern described in ENKTL.

[b] Not included in the study

[c] New entity in WHO classification (2008), not defined in other comparative studies

(Note: There is modification of the original data in the above studies published in the literature due to inclusion of non-Hodgkin lymphoma only for comparison)

immunostaining in the latter, since all cases of lymphoma diagnosed in the previous study included cases in the hospital and pathological consultation cases from another hospital[8].

In the present study, ENKTL was the most common type of mature T-cell and NK-cell lymphomas diagnosed at Siriraj Hospital during the 3-year period (2004-2006). The frequency of ENKTL is significantly higher than that reported in other parts of the world except for Taiwan. However, the cause of this high frequency is not known. The pathologists in Siriraj Hospital do not seem to be overdiagnosing because all of the ENKT cases had typical morphology, immunophenotype, and diffuse EBV positivity. Therefore, this is not a contributing factor to this high frequency. In the present study, ENKTL occurred more commonly in adult males, similar to other parts of the world[14]. It was the only type that showed sex predilection in the present study.

The thirteen cases of anaplastic large cell lymphoma could be divided into ALK positive and ALK negative. By morphology, there was no distinct feature to distinguish between the two types. However, based on the WHO classification (2008), immunostaining for ALK protein is now a must in order to make a definite diagnosis and subclassification, since the difference in clinical outcomes between these two lymphoma types is the most significant reason for such a distinction[1].

The frequency of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) in the present study was also high. It was comparable to that reported in Taiwan[12]. According to the WHO classification (2008), the diagnosis of SPTCL is restricted only for those cases with beta TCR subtype[1] and of the cases in this particular study were positive for beta TCR, if not, the PCGD-TCL should be considered. Furthermore, ENKTL should be excluded before making diagnosis of SPTCL, since a few cases with morphology resembling SPTCL, in the authors' experience, could be proven to be ENKTL by immunohistochemistry and EBER in situ hybridization, but these cases were not included in the present study period.

The frequency of mycosis fungoides (MF) was shown to be higher in Thailand when compared to Japan and Taiwan, but it was similar to India[11-13]. According to the WHO classification (2008), it is mandatory to characterize the subtype of cutaneous T-cell lymphomas, other than MF, because there is a provisional diagnosis of primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma. Furthermore, ENKTL can produce epidermotropism and should be excluded from MF[15]. Thus, making a diagnosis of MF based on morphology and CD3 (a pan T-cell marker) only is therefore considered insufficient. Clinical information is also important for making a definite diagnosis.

It is not possible to make a diagnosis of adult T-cell leukemia/lymphoma (ATLL) in the present study because the information of HTLV-1 infection was not available. ATLL can produce any morphologic features of lymphomas, however, it is not considered in practice here in Thailand where the prevalence of HTLV-1 infection is very low (0.017% in 12,006 subjects)[16-18]. In the authors' experience, some peculiar clinical manifestations described in ATLL and detection of flower cells in peripheral blood smears should prompt investigations for the possibility of ATLL, but the authors have not been able to identify any definite case of ATLL since 1993. In addition, the serologic study in a few cases suspected of ATLL all turned out to be non-reactive for HTLV-1.

Hepatosplenic T-cell lymphoma (HSTCL) was rarely found in the authors' experience, and it was not included in the present study period.

In the present study, other types of mature T-cell and NK-cell lymphomas did not show any significant difference from those reported previously either from Thailand or other countries. The present study did not show any change in the diagnosis according to the 2001 and 2008 versions of the WHO classification except for the only case of primary cutaneous gamma-delta T-cell lymphoma, a new entity proposed in the 2008 version. It was originally diagnosed as MF according to the 2001 version of the WHO classification, but additional immunophenotypic findings obtained from the present study changed the diagnosis of MF to this new entity. Interestingly, blastic NK-cell lymphoma, that the authors diagnosed during the study period, was not included from the present study because it has been classified as blastic plasmacytoid dendritic cell neoplasm, a new entity proposed in the 2008 version of WHO classification under the category of acute myeloid leukemia and related precursor neoplasms[1].

In summary, the distribution of various types of mature T-cell and NK-cell lymphomas in Siriraj Hospital has been demonstrated in the present study according to the 2008 version of WHO classification. The variation in geographic distribution has been again demonstrated, but awaiting for more epidemiologic studies.

While few entities of lymphoma in the 2001 version of WHO classification were moved to other categories in the 2008 version as shown in the present study, a number of new entities proposed in this new version require more immunophenotypic and genetic findings. Thus, the authors should be aware of the importance of a complete immunohistochemistry panel and genetic studies since it is not possible to make a distinction by morphology alone. Nevertheless, clinical information and morphologic features are very important for the first step of approach to reach a definite diagnosis of lymphoma.

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Potential conflicts of interest

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Mature T-cell และ NK-cell lymphomas ในประเทศไทย: การศึกษาในผู้ป่วย 71 ราย

ธวัชชัย พงศ์พฤฒิพันธ์, ปราโมช พงษ์ทองเจริญ, สัญญา สุขพณิชนันท์

จุดประสงค์: *เพื่อศึกษาความถี่และการกระจายของ lymphoma ในกลุ่ม mature T-cell และ NK-cell lymphoma ในโรงพยาบาลศิริราช และเปรียบเทียบกับภูมิภาคอื่นของโลก โดยใช้เกณฑ์การวินิจฉัยตาม WHO classification ล่าสุด (ปี 2008)*

วัสดุและวิธีการ: *ประชากรที่นำมาศึกษาคือ ผู้ป่วยรายใหม่ที่ได้รับการวินิจฉัยเป็นโรคในกลุ่มนี้ ที่โรงพยาบาลศิริราช ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2547 จนถึงวันที่ 31 ธันวาคม พ.ศ. 2549 โดยสไลด์ทางพยาธิวิทยาจะถูกนำมาทบทวนการวินิจฉัยอีกครั้ง และอาจจะมีการย้อมทางอิมมูโนฮีสโตเคมีและการตรวจหา EBV เพิ่มเติมจากนั้นจึงให้ การวินิจฉัยใหม่ตาม WHO classification ปี 2008*

ผลการศึกษา: *มีผู้ป่วยทั้งหมด 71 ราย โดยแบ่งเป็น extranodal NK/T-cell lymphoma, nasal type (ENKTL, 31.0%), anaplastic large cell lymphoma (18.3%), angioimmunoblastic T-cell lymphoma (14.1%), peripheral T-cell lymphoma, not otherwise specified (12.7%), mycosis fungoides (MF, 8.5%), subcutaneous panniculitis-like T-cell lymphoma (SPTCL, 7.0%), primary cutaneous anaplastic large cell lymphoma (PCAL, 5.6%), primary cutaneous gamma-delta T-cell lymphoma (PCGDTL, 1.4%) และ enteropathy-associated T-cell lymphoma (1.4%) การศึกษายังพบว่า เมื่อเปลี่ยนเกณฑ์การวินิจฉัยจาก WHO classification ปี 2001 เป็นปี 2008 มีผู้ป่วยเพียงหนึ่งรายที่ถูกเปลี่ยนการวินิจฉัยจาก MF เป็น PCGDTL โดย PCGDTL เป็น lymphoma ชนิดใหม่ที่เพิ่งได้รับการบรรจุไว้ใน WHO classification ปี 2008*

สรุป: *ENKTL เป็น lymphoma ที่พบได้บ่อยที่สุดในการศึกษาครั้งนี้ และพบได้บ่อยกว่าการศึกษาอื่นที่เคยมีการรายงานมาก่อนในประเทศไทย การศึกษาครั้งนี้ยังพบว่า SPTCL, PCAL และ MF มีความถี่สูงกว่าการรายงานก่อนหน้านี้ นอกจากนี้การเปลี่ยนเกณฑ์การวินิจฉัยจาก WHO classification ปี 2001 เป็นปี 2008 นั้น พบว่าไม่มีผลกระทบในสัดส่วนของ lymphoma กลุ่มนี้มากนัก*