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WHO Classification of Malignant Lymphomas in Korea: Report of the Third Nationwide Study

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Background: The aim of study was to determine the relative frequency of malignant lymphoma according to World Health Organization (WHO) classification in Korea. **Methods:** A total of 3,998 cases diagnosed at 31 institutes between 2005 and 2006 were enrolled. Information including age, gender, pathologic diagnosis, site of involvement and immunophenotypes were obtained. **Results:** The relative frequency of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) was 95.4% and 4.6%, respectively. B-cell lymphomas accounted for 77.6% of all NHL, while T/natural killer (T/NK)-cell lymphomas accounted for 22.4%. The most frequent subtypes of NHL were diffuse large B-cell lymphoma (42.7%), extranodal marginal zone B-cell lymphoma (MZBCL) of mucosa-associated lymphoid tissue (19.0%), NK/T-cell lymphoma (6.3%) and peripheral T-cell lymphoma (PTCL), unspecified (6.3%), in decreasing order. The relative frequency of HL was nodular sclerosis (47.4%), mixed cellularity (30.6%), and nodular lymphocyte predominant (12.1%) subtypes. Compared with a previous study in 1998, increase in gastric MZBCL and nodular sclerosis HL, and slight decrease of follicular lymphoma, PTCL, and NK/T-cell lymphoma were observed. **Conclusions:** Korea had lower rates of HL and follicular lymphoma, and higher rates of extranodal NHL, extranodal MZBCL, and NK/T-cell lymphoma of nasal type compared with Western countries. Changes in the relative frequency of lymphoma subtypes are likely ascribed to refined diagnostic criteria and a change in national health care policy.

Key Words: Lymphoma; Malignant; WHO; Korea

Malignant lymphoma comprised of a diverse group of malignant lymphoid neoplasms comprising of B, T, and natural killer (NK) cell lineage, which accounts for 2.3% of malignant neoplasm in Korea and the crude incidence is 9.0 per 100,000 in general population.[1] Classification of malignant lymphoma has been evolving over the last 30 years and the most recent World Health Organization (WHO) classification divided lymphoid neoplasm into more than 30 lymphoma entities based on the characteristics of neoplastic cells including morphology, immunophenotype, and clinical findings such as the location of the lesion, and genetic changes.[2] As it is well known, the frequency of subtypes of malignant lymphoma is different according to geographic regions. Compared with Western countries, regions of Asia have reported higher rates of T-cell lymphoma and lower rates of follicular lymphoma and Hodgkin's disease.[3-7] Because the frequency of subtypes provides fundamental information for the study of malignant lymphoma, the Hemato-lymphoreticular Study Group of the Korean Society of Pathologists had carried out a nationwide study in 1992 based on the Working Formulation and in 1998 based on the revised European-American lymphoma (REAL) classification and determined the relative frequency of malignant lymphoma.[6,8]

Since the second nationwide study, more than 10 years has passed. During that period, the report of the 2nd nationwide study has provided valuable information to many lymphoma researchers; however, most people now feel the need to update the data. To meet increasing demands on the updated information for the relative frequency of lymphoma entities, we carried out the third nationwide study on a total of 3,998 cases of malignant lymphoma, including Hodgkin lymphoma (HL), based on the WHO classification.

MATERIALS AND METHODS

A total of 3,998 cases of malignant lymphoma, including HL, diagnosed at 31 institutes between January 2005 and December 2006 were enrolled in the study. All the participants in the study were regular members of a Korean Study Group of Hematopathology. The cases were classified according to the 2001 WHO classification.[9] Histologic features and immunohistochemical results were carefully reviewed and additional immunohistochemistry was performed in several selected cases. Antibody panels included CD20, CD3, CD56, CD4, CD8, CD21, CD10, cyclinD1, CD23, CD30, CD15, kappa, lambda light chain, and anaplastic lymphoma kinase-1. Epstein-Barr virus (EBV)-encoded RNA *in situ* hybridization was performed in the cases indicated. Information including age, gender, pathologic diagnosis, site of involvement, and immunophenotypes were obtained. The cases were classified into B-non-Hodgkin lymphoma (NHL), T/natural killer (NK)-NHL, and HL based on lymphoma type. The histologic and clinical results were compared with those of the previous study reported in 1998, which included studied cases diagnosed between January 1994 and October 1996.

RESULTS

The median age of the patients with malignant lymphoma was 52 years and the male to female ratio was 1 : 3. Biopsy sites included the lymph node (30.4% of cases) and extranodal sites (69.6% of cases). Malignant lymphomas arising in the lymph node account for 26.3% of B-cell NHL and 35.2% in T/NK-cell NHL.

The relative frequency of Hodgkin lymphomas and comparison with the previous nationwide study in 1998 (Tables 1 and 2)

HL accounts for 4.6% of malignant lymphomas and the proportion between NHL was similar to that of data in 1998 (Fig. 1). Nodular sclerosis subtype was markedly increased, accounting for 47.4% of HL while the relative frequency of mixed cellularity decreased (Fig. 2).

Relative frequency of NHL and comparison with the previous study in 1998 (Tables 1 and 2)

The ratio between T/NK-cell lymphoma and B-cell lymphoma did not change and was similar to that of study in 1998. Diffuse large B-cell lymphoma (DLBCL) was the most frequent subtype (42.7%) of NHL, followed by extranodal marginal zone B-cell lymphoma (MZBCL) (19.0%), extranodal NK/T-cell lymphoma (6.3%), peripheral T-cell lymphoma (PTCL), unspecified (6.3%) (Fig. 3). The rank in frequencies was similar to those of the previous study performed in 1998. Follicular lymphoma accounted for only 2.9% of NHL and seems to have decreased compared with the 1998 study (6.2%). PTCL, unspecified and extranodal NK/T-cell lymphoma were slightly decreased.

Table 1. Relative frequency of histologic subtypes of malignant lymphoma

Diagnosis	Cases	%	Age (M/F)
Hodgkin lymphoma		4.6	41 (2.0)
Nodular lymphocyte predominant	23	12.1	43 (1.3)
Lymphocyte-rich	18	9.2	54 (4.3)
Mixed cellularity	58	30.6	50 (3.4)
Nodular sclerosis	91	47.4	33 (1.4)
Lymphocyte-depleted	1	0.6	14 (M)
Total	191	100	
Non-Hodgkin lymphoma	3,807	95.4	
B-cell lymphoma (78%)	2,971		55 (1.2)
Precursor B-lymphoblastic leukemia	61	1.6	23 (1.3)
Chronic lymphocytic leukemia/small lymphocytic lymphoma	49	1.3	63 (1.3)
B-cell prolymphocytic leukemia	1	0.03	69 (M)
Lymphoplasmacytic lymphoma	11	0.3	62 (1)
Splenic marginal zone lymphoma	8	0.2	59 (0.4)
Hairy cell leukemia	4	0.1	41 (2)
Solitary plasmacytoma of bone	8	0.2	67 (5)
Plasma cell myeloma	15	0.4	62 (1.6)
Extranodal marginal zone B-cell lymphoma	723	19.0	52 (0.7)
Nodal marginal zone B-cell lymphoma	46	1.2	46 (1.8)
Follicular lymphoma	110	2.9	52 (1.3)
Mantle cell lymphoma	91	2.4	62 (3.5)
Diffuse large B-cell lymphoma	1,626	42.7	58 (1.3)
Mediastinal large B-cell lymphoma	19	0.5	34 (0.8)
Primary effusion lymphoma	4	0.1	71 (1)
Burkitt lymphoma/leukemia	76	2.0	36 (2.3)
T/NK-cell lymphoma (22%)	836		48 (1.8)
Precursor T-lymphoblastic leukemia	91	2.4	28 (2.5)
Blastic NK-cell lymphoma	4	0.1	53 (0.5)
T-cell prolymphocytic leukemia	1	0.03	68 (F)
Aggressive NK-cell leukemia	4	0.1	47 (M)
Adult T-cell leukemia/lymphoma	1	0.03	58 (F)
NK/T-cell lymphoma, nasal type	240	6.3	50 (2.1)
Enteropathy type T-cell lymphoma	15	0.4	57 (0.6)
Hepatosplenic T-cell lymphoma	8	0.2	43 (1)
Subcutaneous panniculitis-like T-cell lymphoma	27	0.7	32 (0.6)
Mycosis fungoides	24	0.6	54 (1.4)
Sezary syndrome	4	0.1	43 (0.5)
Primary cutaneous anaplastic large cell lymphoma	8	0.2	42 (2)
Peripheral T-cell lymphoma, unspecified	240	6.3	53 (2.1)
Angioimmunoblastic T-cell lymphoma	65	1.7	63 (1.4)
Anaplastic large cell lymphoma	118	3.1	41 (1.4)
Total	3,998	100	

NK, natural killer.

Table 2. Comparison with the data collected in 1998

Diagnosis	1998[8] (%)	Present (%)	Diagnosis	1998 (%)	Present (%)
Hodgkin lymphoma	5.3	4.6	Subtypes of NHL		
Nodular lymphocyte predominant	9.8	12.1	MZBCL of MALT	16.7	19.0
Lymphocyte-rich	NA	9.2	Mantle cell lymphoma	1.5	2.4
Mixed cellularity	46.3	30.6	Follicular lymphoma	6.2	2.9
Nodular sclerosis	31.7	47.4	Diffuse large B-cell	43.2	42.7
Lymphocyte-depleted	7.3	0.6	Burkitt lymphoma	1.1	2.0
Non-Hodgkin lymphoma	94.7	95.4	NK/T-cell lymphoma	8.7	6.3
B-cell NHL	74.8	78.0	PTCL, unspecified	9.4	6.3
T-cell NHL	25	22.0	Anaplastic large cell	1.5	3.1

NHL, non-Hodgkin lymphoma; MZBCL, marginal zone B-cell lymphoma; NK, natural killer; MALT, mucosa-associated lymphoid tissue; NA, not applicable; PTCL, peripheral T-cell lymphoma.

Comparison of the relative frequency of lymphoma subtypes among Asian countries (Table 3)

To compare the relative frequency of lymphoma subtypes based on WHO classification among Asian countries, we have reviewed the reports published since 2000. Among Asian countries, the pattern of distribution was not uniform and showed slight differences. Japan[4] was similar to Korea in its lower rate of Hodgkin lymphoma, but was different in its higher rate of adult T-cell leukemia/lymphoma (ATLL), and lower rate of EBV-associated extranodal T/NK-cell lymphoma and extranodal MZ-BCL. The lymphomas from Shanghai[3] were characterized by relatively frequent Hodgkin lymphoma, lower rate of NK/T-cell lymphoma, and rare ATLL. In Taiwan, a relatively high rate

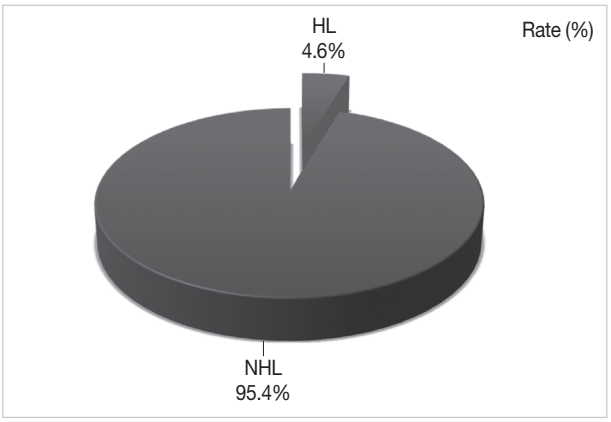

Fig. 1. Relative frequencies of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL).

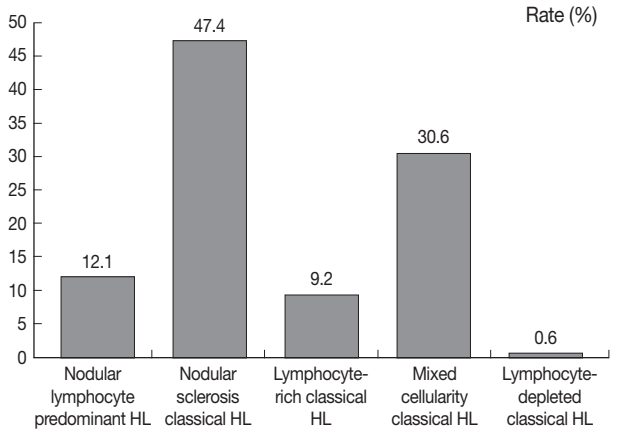

Fig. 2. Relative frequencies of the histologic subtypes of Hodgkin lymphoma.
HL, Hodgkin lymphoma.

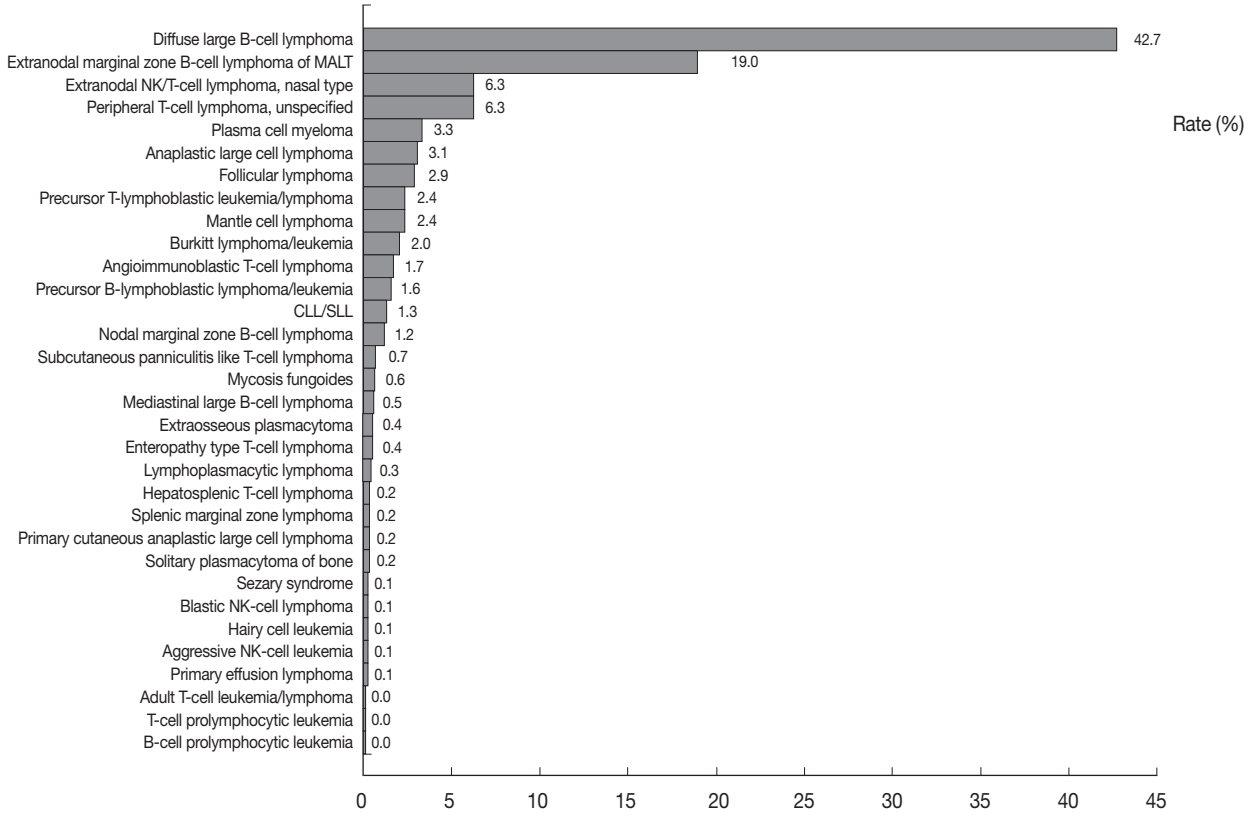

Fig. 3. Relative frequencies of the histologic subtypes of non-Hodgkin lymphoma.
MALT, mucosa-associated lymphoid tissue; NK, natural killer; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

of follicular lymphoma was noted.[10,11] In Thailand, HL and follicular lymphoma showed higher rates compared with Korea.[5]

Relative frequency of primary site of involvement in NHL and comparison with the 1998 study (Table 4)

The relative frequency of nodal and extranodal lymphomas was 30.4% and 69.6%, respectively. For extranodal lymphomas, the most frequent sites of involvement included the stomach, Waldeyer's ring, eye, sinonasal cavity, and small intestine, in decreasing order. Compared with the 1998 study, the relative frequency of extranodal, gastric, and ocular lymphomas increased.

Table 3. Comparison of the relative frequency of malignant lymphoma in Asian countries

Diagnosis	Korea (2010)	Japan[4] (2000)	Shanghai[3] (2008)	Taiwan[10] (2006)	Tailand[5] (2004)
No. of cases	3,998	3,194	831	598	1,983
Hodgkin lymphoma	4.6	4.41	12.4	7.0	7.9
B-cell NHL	74.4	68.53	68.4	80.6	69
T/NK-cell NHL	21.0	24.92	18.2	12.4	23
Diffuse large B-cell lymphoma	42.7	33.34	29.1	39	50.5
MZBCL of MALT	19.0	8.45	2.5	5.7	4.1
Follicular lymphoma	2.9	6.70	7.0	16.4	8.4
NK/T-cell lymphoma	6.3	2.60	0.6	2.8	NA
ATLL	<1	7.45	NA	0	NA
PTCL, unspecified	6.3	6.67	5.5	3.8	13

NHL, non-Hodgkin lymphoma; NK, natural killer; NA, not applicable; MZBCL, marginal zone B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; ATLL, adult T-cell leukemia/lymphoma; PTCL, peripheral T-cell lymphoma.

Table 4. Relative frequency of site of involvement in NHL and comparison with the data in 1998

Site	1998[8]		2010		
	No. of cases	%	No. of cases	%	Age (yr)/Sex ratio (M/F)
Lymph node	538	36.7	1,157	30.4	54/1.4
Extranodal	926	63.3	2,650	69.6	53/1.2
Waldeyer's ring	210	10.2	340	9.0	56/1.7
Nasal and PNS	81	5.5	221	5.8	52/1.7
Oral cavity	43	2.9	72	1.9	59/1.5
Gastrointestinal	303	20.7	1,112	29.2	55/1.2
Stomach	196	13.4	761	20.0	56/1.0
Small intestine	60	4.1	209	5.5	54/1.6
Large intestine	47	3.2	145	3.8	56/1.4
Eye	57	3.9	247	6.5	46/0.6
Skin	58	4.0	160	4.2	49/1.1
Soft tissue	55	3.8	76	2.0	58/1.2
CNS	39	2.7	133	3.5	55/1.6
Bone	26	1.8	61	1.6	48/1.3
Breast	14	1.0	23	0.6	50/0.2
Mediastinum	14	1.0	42	1.1	28/1.4
Lung	12	0.8	42	1.1	53/1.5
Salivary	12	0.8	8	0.2	53/0.3
Ovary	NA	NA	15	0.4	51/0
Uterus	NA	NA	15	0.4	60/0
Liver	NA	NA	53	1.4	54/1.5
Spleen	NA	NA	27	0.7	53/1.6

NHL, non-Hodgkin lymphoma; PNS, paranasal sinus; CNS, central nervous system; NA, not applicable.

Table 5. Relative frequency of the histologic subtypes in NHL according to the site of involvement

	LN	Waldeyer ring	Nasal and PNS	Stomach	Small intestine	Colorectum	CNS	Skin	Eye	Bone
No. of cases (%)	1,157 (100)	340 (100)	221 (100)	761 (100)	209 (100)	145 (100)	133 (100)	160 (100)	247 (100)	61 (100)
CLL/SLL	35 (4.2)	3 (0.9)	0 (0)	1 (0.1)	1 (0.5)	0 (0)	0 (0)	1 (0.6)	2 (0.8)	6 (9.8)
MCL	45 (3.9)	10 (2.9)	0 (0)	7 (0.9)	11 (5.3)	8 (5.5)	1 (0.8)	0 (0)	1 (0)	2 (3.3)
FL	93 (8.0)	10 (2.9)	0 (0)	0 (0)	0 (0)	3 (2.1)	0 (0)	0 (0)	2 (0.8)	0 (0)
DLBCL	579 (50)	208 (61.2)	32 (14.5)	267 (35.1)	118 (56.5)	88 (60.7)	115 (86.5)	25 (15.6)	9 (3.6)	24 (39.3)
MZBCL	4 (0.3)	7 (2.1)	1 (0.5)	427 (56.1)	29 (13.9)	25 (17.2)	3 (2.3)	7 (4.4)	215 (87.0)	0 (0)
PTCL	131 (11.3)	27 (7.9)	13 (5.9)	16 (2.1)	8 (3.8)	7 (4.8)	9 (6.8)	19 (11.9)	0 (0)	5 (8.2)
NK/T	5 (0.4)	29 (8.5)	153 (69.2)	2 (0.3)	4 (1.9)	4 (2.8)	0 (0)	15 (9.4)	3 (1.2)	2 (0)
AITCL	62 (5.4)	1 (0.3)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)	0 (0)
ALCL	78 (6.7)	3 (0.9)	1 (0.5)	4 (0.5)	4 (1.9)	1 (0.7)	1 (0.8)	18 (11.3)	0 (0)	2 (3.3)
MF	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	23 (14.4)	0 (0)	0 (0)
SQPTCL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	27 (16.9)	0 (0)	0 (0)
ETCL	0 (0)	0 (0)	0 (0)	1 (0.1)	9 (4.3)	3 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)
LBL-B	14 (1.2)	6 (1.8)	2 (0.9)	1 (0.1)	0 (0)	0 (0)	1 (0.8)	6 (3.8)	0 (0)	7 (11.5)
LBL-T	40 (3.5)	6 (1.8)	0 (0)	1 (0.1)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	8 (0)
Others	70 (6.1)	30 (8.8)	18 (8.1)	34 (4.5)	25 (12.0)	5 (3.4)	3 (2.3)	18 (11.3)	15 (6.1)	5 (8.2)

Values are presented as number (%).

NHL, non-Hodgkin lymphoma; LN, lymph node; PNS, paranasal sinus; CNS, central nervous system; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; MZBCL, marginal zone B-cell lymphoma; PTCL, peripheral T-cell lymphoma; NK, natural killer; AITCL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; MF, mycosis fungoides; SQPTCL, subcutaneous panniculitis-like T-cell lymphoma; ETCL, enteropathy type T-cell lymphoma; LBL, lymphoblastic lymphoma/leukemia.

Relative frequency of subtypes in NHL according to site of involvement (Table 5)

In nodal lymphoma, half of the cases were DLBCL, followed by PTCL, unspecified, follicular lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, and mantle cell lymphoma, in decreasing order. For gastric lymphoma, the most common type was extranodal MZBCL of mucosa-associated lymphoid tissue, followed by DLBCL, Burkitt lymphoma, PTCL, unspecified, and mantle cell lymphoma, in decreasing order. In small and large intestinal lymphomas, the most common type was DLBCL, followed by extranodal MZBCL. The most common central nervous system (CNS) lymphoma was DLBCL. Other types were very rare in CNS.

DISCUSSION

This study confirms characteristics of malignant lymphoma in Korea, which shows a higher rate of extranodal lymphoma, lower rate of HL and follicular lymphoma, and a relatively higher rate of T/NK-cell lymphoma and extranodal MZBCL compared with Western countries. The overall distribution pattern of malignant lymphoma types was similar to those of the previous nationwide study performed in 1998;[8] however, several changes were notable. Although the frequency of HL remained unchanged, the relative frequency of the nodular sclerosis subtype showed a marked increase from 31.7% in 1998 to 47.4% in 2010, whereas the frequency of mixed cellularity markedly decreased. Such a change in frequency for the HL subtype is attributed to the accumulation of knowledge on the morphologic spectrum of nodular sclerosis. Many cases, which were previously diagnosed as mixed cellularity, were reclassified as nodular sclerosis subtype this time. In addition, there was a slight decrease in frequency for PTCL, unspecified. The changes are more likely because of better defined diagnostic criteria for T-lineage lymphomas in the 2001 WHO classification compared with the REAL classification. Further, the application of an antibody panel for immunohistochemistry makes it possible to better classify a T-lineage lymphoma of unspecified subtype to other subtypes. Interestingly, the frequency of follicular lymphoma decreased. Follicular lymphoma only accounts for 2.9% of non-Hodgkin lymphoma, which is the lowest among Asian countries. An increase in gastric lymphoma and extranodal MZBCL compared with the data in 1998 may reflect a screening effect caused by the wide use of endoscopic examinations by the National Cancer Screening program which is covered by the National Insurance System since 2005.

In comparison with other East Asian countries, the Korean data showed both similarities and differences. The differences may be partly derived from case selection bias. Alternatively, the differences in subtype distribution in Asian countries may reflect differences in environmental factors, as well as racial factors related to disease. For example, the prevalence of the EBV, which is the major contributing factor related to NK/T-cell lymphoma, is different between regions, even within the Asian countries. And, it should reflect the significant differences in the incidence of NK/T-cell lymphoma. Interestingly, the frequency of NK/T-cell lymphoma is relatively high in Korea. Moreover, the overall frequency of NK/T-cell lymphoma relative to Korea, was lower in Shanghai, Japan, and Taiwan.[3,4,10,11] ATLL associated with HTLV-1 is very rare in Asian countries except Japan.[4] One of the unique findings in the distribution of non-HL in Korea is the high frequency of extranodal MZBCL associated with *Helicobacter pylori* infections. Korea has the highest prevalence of *H. pylori* infections. A nationwide survey conducted in Korea in 1998 on the serologic prevalence of *H. pylori* concluded that the overall seroprevalence of *H. pylori* infection was 46.6%, and dichotomized this to 17.2% among children (< 16 years), and 66.9% among adults (> 16 years).[12]

The present study has limitations because the lymphoid neoplasm presented in the bone marrow was missing. Such cases are usually not submitted to the surgical pathology department in most hospitals in Korea and the real incidence of bone marrow origin tumors such as lymphoblastic leukaemia/lymphoma and multiple myeloma should be underestimated. Aside from these limitations, our data are collected from all hospitals where the hematopathologists diagnose cases and the results represent the current status of lymphoma subtypes in Korea.

In conclusion, the relative frequency of malignant lymphoma in Korea was not significantly changed and shows similarities with a previous nationwide study performed in 1998. Nevertheless, there were slight differences in the relative frequency of some subtypes, which may be caused by refined diagnostic criteria or a change of national healthcare policy. A population-based epidemiologic study would be helpful to determine the true incidence of malignant lymphoma subtypes.

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