REAL Classification of Malignant Lymphomas in the Republic of Korea

Incidence of Recently Recognized Entities and Changes in Clinicopathologic Features

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BACKGROUND. The clinicopathologic characteristics of malignant lymphomas vary according to geography. The aim of this study was to determine the clinical characteristics of malignant lymphomas and the relative frequency in the Republic of Korea of lymphomas belonging to the newly described REAL (revised European-American lymphoma) classification categories.

METHODS. The Hematolymphoreticular Study Group of the Korean Society of Pathologists conducted a consensus-based morphologic review of a nationwide collection of 1548 malignant lymphomas, including Hodgkin's disease (HD), diagnosed at 23 institutes over a recent 2-year period. Slides stained with hematoxylin and eosin or other immunohistochemical stains were reviewed. All cases were classified according to the histologic criteria proposed by the International Lymphoma Study Group. Clinical data, including age, gender, and site of disease involvement, were reviewed.

RESULTS. The Republic of Korea had lower rates of HD and follicle center lymphoma and higher rates of extranodal lymphoma, diffuse large B-cell lymphoma, and angiocentric lymphoma compared with Western countries. The most frequent subtypes of non-Hodgkin's lymphoma (NHL) were diffuse large B-cell lymphoma, extranodal marginal zone B-cell lymphoma, peripheral T-cell lymphoma, unspecified type, and angiocentric lymphoma, in decreasing order. Compared with a previous nationwide study, the rates for follicular lymphoma and NHL involving the stomach, orbit, and central nervous system were increased. The rate of T-cell NHL in the current study was much lower than that reported in a previous study for the Republic of Korea and was also lower than that reported for other Far East countries. For HD, the relative frequency of nodular sclerosis subtype was higher compared with that in the previous study, and lymphocyte predominance and lymphocyte depletion were lower.

CONCLUSIONS. The occurrence rates for various subtypes of malignant lymphoma

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in the Republic of Korea are distinct from those in Western countries and similar in many ways to those in other countries in the Far East. Compared with other Far East countries, the Republic of Korea has a higher rate of extranodal lymphoma, rare adult T-cell lymphoma, and a relatively low rate of T-cell lymphomas. It appears that over time there have been changes in the relative rates for follicular lymphoma, subtypes of Hodgkin's disease, and gastric and orbital lymphoma. The authors attribute these changes primarily to refined criteria for diagnosing new clinicopathologic entities. ***Cancer* 1998;83:806–12.**

KEYWORDS: lymphoma, REAL classification, Korea, Hodgkin's disease, non-Hodgkin's lymphoma.

Malignant lymphoma is a diverse group of malignancies containing many different histologic categories. As is already known, the relative frequency of the occurrence of different histologic and immunophenotypic subtypes varies according to geography, and this may be ascribed to genetic and environmental etiologic factors. Compared with Western countries, regions of Asia (including Hong Kong, Japan, and China) have reported higher rates of T-cell lymphoma and lower rates of follicular lymphoma and Hodgkin's disease (HD).[1] In the Republic of Korea, a previous nationwide study[2] that used the Working Formulation demonstrated a similar pattern in the distribution of malignant lymphomas, with a higher rate of T-cell lymphoma.[3]

Recent developments in immunologic and molecular genetic techniques provided additional information about malignant lymphoma and assisted in the recognition of new entities and the refinement of previously recognized disease categories. The REAL (revised European-American lymphoma) classification proposed by the International Lymphoma Study Group[4] has provoked criticism of its usefulness in the routine practice of diagnostic pathology and clinical validity. However, it includes several new entities that were not included in previous classifications and has provided common terminology to these entities. In this study, the hematolymphoreticular study group of the Korean Society of Pathologists sought to determine the relative frequency of REAL entities in the Republic of Korea by conducting a nationwide retrospective review of 1548 cases of malignant lymphoma, including HD, according to the REAL classification.

MATERIALS AND METHODS

A total of 1548 cases of malignant lymphoma, including HD, diagnosed at 23 institutes between November 1994 and October 1996 were enrolled in the study. The participating institutes included 21 university hospitals and 1 cancer center, which were large hospitals representative of each local area and evenly distributed across the central, southeastern, and southwestern parts of the Korean peninsula. For convenience of study, these institutes were divided into 5 groups according to geographic area (Fig. 1). In each group, H & E–stained slides and immunohistochemical stains for basic B- and T-cell markers (CD20 and/or MB2, CD3 and/or CD45RO) were histologically evaluated and classified by schema proposed by the International Lymphoma Study Group.[4] The cases showing discordance between more than 30% of participants in each group were reevaluated by a panel of reviewers (J. D. Lee, I. S. Kim, H. J. Cho, J. H. Lee, C. S. Kang, C. W. Kim, Y. H. Ko, and W. I. Yang), and the diagnosis was finalized by reviewer's consensus. For the cases requiring further immunophenotypic characterization, additional immunostaining, including cyclin D1 and CD30, was performed. Clinical data relating to age, gender, and sites of biopsy were obtained from the medical records.

The histologic and clinical results were compared with those of a previous nationwide study reported in 1991,[2] which analyzed the diagnoses of 1165 cases at 21 institutes between 1985 and 1987. Immunophenotypic results were compared with those of a previous study in 1992,[3] which reported the immunophenotypic analysis of 253 cases of non-Hodgkin's lymphoma (NHL).

RESULTS

Incidence of Disease According to Age and Gender

The median age at the onset of disease was 52 years for NHL patients and 41.5 years for HD patients. The peak age of disease was in the 20s for HD and in the 50s for NHL. Bimodal distribution of the age specific incidence rate was not obvious in HD. Compared with that reported in 1991, the age incidence pattern has not changed. The male-to-female ratio was 1.6:1.

Relative Frequency of Hodgkin's Disease and Non-Hodgkin's Lymphoma

Of 1548 cases, there were 1466 cases of NHL (94.7%) and 82 cases of HD (5.3%) (Table 1). This rate was very

FIGURE 1. The geographic distribution of 23 participating institutes is shown for 1548 cases of malignant lymphoma, including Hodgkin's disease, between November 1994 and October 1996.

TABLE 1
Relative Frequency of HD and NHL

	Year of study			
	1991		1997	
	No. of cases	%	No. of cases	%
HD	62	5.3	82	5.3
NHL	1103	94.7	1466	94.7
Total	1165	100	1548	100

HD: Hodgkin's disease; NHL: non-Hodgkin's lymphoma.

similar if not identical to that reported in 1991 (94.7% vs. 5.3%).

Immunophenotype of Non-Hodgkin's Lymphoma

Of 1466 cases of non-Hodgkin's lymphoma, 1097 cases (74.8%) were B-lineage and 366 cases (25%) were T- (or putative natural killer [NK])-lineage, including 42 cases (2.9%) of T-lymphoblastic lymphoma (Table 2). In comparison with data reported in 1992, from a study of the immunophenotype of 253 cases of NHL, the proportion of T-lineage lymphoma was markedly decreased. At that time, the T-lineage of lymphoma accounted for 35.2% of malignant lymphomas.

TABLE 2
Relative Frequency of Immunophenotypes of NHL

	Year of study			
	1992		1997	
Type of NHL	No. of cases	%	No. of cases	%
B-cell	148	58.5	1097	74.8
T- or NK-cell	89	35.2	366	25
Histiocyte	1	0.3	0	0
Unclassified	15	6.0	3	0.2
Total	253	100	1466	100

NHL: non-Hodgkin's lymphoma; NK-cell: natural killer–cell.

TABLE 3
Relative Frequency of Histologic Subtypes of NHL Classified by REAL Schema (1997 Data)

Subtype	No. of cases	%
B-lymphoblastic	8	0.5
B-CLL	33	2.3
Lymphoplasmacytoid	11	0.8
Mantle cell	22	1.5
Follicle center	91	6.2
MZBL, extranodal	243	16.7
MZBL, nodal	9	0.6
Plasma cell tumor	17	1.1
Diffuse large B-cell	634	43.2
Mediastinal large B-cell	7	0.5
Burkitt's	16	1.1
High grade B-cell	6	0.4
T-lymphoblastic	42	2.9
T-CLL	1	0.1
Large granular cell	3	0.2
Mycosis fungoides	5	0.3
Peripheral T-cell, unspecified	138	9.4
Subcutaneous T-cell	11	0.7
Angioimmunoblastic T-cell	15	1.0
Angiocentric T-cell	129	8.7
Intestinal T-cell	1	0.1
Adult T cell leukemia	1	0.1
Anaplastic large cell	22	1.5
Anaplastic large cell, HD-like	1	0.1
Total	1466	100.0

NHL: non-Hodgkin's lymphoma; REAL: revised European-American lymphoma; MZBL: marginal zone B-cell lymphoma; HD: Hodgkin's disease.

Histologic Types by REAL Classification

Non-Hodgkin's lymphoma

Among 1466 cases of NHL, the most common histologic type was diffuse large B-cell lymphoma, followed

TABLE 4
Relative Frequency of Histologic Subtypes of NHL Defined by the Working Formulation (1991 Data)

Subtype	No. of cases	%
Small lymphocytic	52	4.7
Follicular	18	1.6
Diffuse small cleaved cell	198	18
Diffuse small and large cell	143	13
Diffuse large cell	419	38
Immunoblastic	83	7.5
Lymphoblastic	46	4.2
Small noncleaved cell	34	3.1
Mycosis fungoides	9	0.8
Polymorphic reticulosis	77	7
Malignant histiocytosis	24	2.1
Total	1103	100

NHL: non-Hodgkin's lymphoma.

TABLE 5
Relative Frequency of Subtypes of HD

	1991		1997	
Subtype	No. of cases	%	No. of cases	%
Lymphocyte predominance	7	12.5	8	9.8
Nodular sclerosis	13	23.2	26	31.7
Mixed cellularity	26	46.4	38	46.3
Lymphocyte depletion	8	14.3	6	7.3
Unclassifiable	2	3.6	4	2.6
Total	56[a]	100	82	100

HD: Hodgkin's disease.
[a] Of 62 cases included in the 1991 study, information on subtype was available for only 56.

by extranodal marginal zone B-cell lymphoma, peripheral T-cell lymphoma, unspecified type angiocentric lymphoma, and follicle center lymphoma, in decreasing order of frequency (Table 3). In comparison with the study in 1991 using the Working Formulation of the National Cancer Institute (Table 4), there was an increase in follicle center lymphomas from 18 cases (1.6%) to 91 cases (6.2%).

Hodgkin's disease

Of 82 cases of Hodgkin's disease, the most common subtype was mixed cellularity, followed by nodular sclerosis, lymphocyte predominance, and lymphocyte depletion, in decreasing order of frequency (Table 5). In comparison with the data in 1991, there was an increase in nodular sclerosis from 13 cases (23.2%) to 26 cases (31.7%) and a decrease in lymphocyte predominence and lymphocyte depletion.

TABLE 6
Relative Frequency of Site of Involvement in NHL

	Year of study			
	1991		1997	
Site	No. of cases	%	No. of cases	%
Lymph node	364	40	538	36.7
Extranodal	547	60	926	63.3
Waldeyer's tonsillar ring	177	19.4	116	7.9
Nasal and PNS	61	6.7	81	5.5
Nasopharynx	36	4.0	33	2.3
Oral cavity	0	0	43	2.9
Gastrointestinal	147	16.1	303	20.7
Stomach	70	7.7	196	13.4
Small intestine	53	5.8	60	4.1
Large intestine	24	2.6	47	3.2
Orbit	5	0.5	57	3.9
Skin	39	4.3	58	4.0
Soft tissue	19	2.1	55	3.8
CNS	9	0.9	39	2.7
Bone	11	1.2	26	1.8
Breast	8	0.9	14	1.0
Mediastinum	5	0.5	14	1.0
Lung	5	0.5	12	0.8
Salivary	2	0.2	12	0.8
Others	23	2.7	63	4.2
Total	911	100	1464	100

NHL: non-Hodgkin's lymphoma; PNS: paranasal sinus; CNS: central nervous system.

Sites of Involvement

Non-Hodgkin's lymphoma

Information for sites of biopsy was available in 1464 of 1466 cases in the current study and in 911 of 1103 cases in the study conducted in 1991 (Table 6). In the current study, 926 cases (63.3%) were classified as extranodal lymphoma and the remainder (538 cases) involved the lymph nodes. The most common extranodal site was the gastrointestinal tract, with the stomach involved in 13.4%, the small intestine in 4.1%, and the large intestine in 3.2% of cases. In comparison with data in 1991, the proportion of extranodal lymphomas was not changed. There was an increase in lymphomas involving the stomach from 70 cases (7.7%) to 196 cases (13.4%) and the orbit from 5 cases (0.5%) to 57 cases (3.9%). Most of these cases were categorized as marginal zone B-cell lymphoma. The frequency of primary central nervous system lymphoma was increased as well. Lymphoma involving Waldeyer's tonsillar ring was decreased from 177 cases (19.4%) to 116 cases (7.9%).

Hodgkin's disease

Of 82 cases, 77 (94%) involved the lymph nodes. Other sites of involvement included the lungs in two cases,

TABLE 7
Relative Frequency of Histologic Subtypes of NHL, According to Site of Involvement

Subtype	Age, yrs (median)	Gender ratio (M:F)	LN (n = 538) %	GI (n = 303) %	WR (n = 116) %	Nasal and PNS (n = 81) %	Skin (n = 58) %
Small lymphocytic	61	1.8:1	3.3	0	0.9	0	0
Mantle cell	58.5	1:1.2	2.6	1.3	0.9	0	0
Follicle center cell	52	2.1:1	11.9	0	3.4	0	0
Diffuse large B-cell	57	1.5:1	49.7	30.4	69	14.8	15.5
Marginal zone	57.5	1:1.2	1.7	59.4	2.6	0	0
T-lymphoblastic	16	2:1	5	0	1.7	0	0
Peripheral T-cell	48	3.2:1	13.4	2	8.7	4.9	39.6
Subcutaneous T-cell	41	1.2:1	0	0	0	0	15.5
Angiocentric	44	2.6:1	0	2	11.2	74.1	13.8
Immunoblastic T-cell	67	7.5:1	2.8	0	0	0	0
Anaplastic large cell	27	3.2:1	3.2	0	0	0	1.7
Mycosis fungoides	42	1.5:1	0	0	0	0	8.6
Other	49	1.6:1	6.4	4.9	1.6	6.2	5.3
Total	52	1.6:1	100	100	100	100	100

NHL: non-Hodgkin's lymphoma; LN: lymph nodes; GI: gastrointestinal tract; WR: Waldeyer's tonsillar ring; PNS: paranasal sinus.

the mediastinum in one case, and the spleen in one case.

Histologic Subtypes of NHL According to Site

The distribution of histologic subtypes was different according to the site of involvement (Table 7). In the lymph nodes, diffuse large B-cell lymphoma was most common, followed by peripheral T-cell lymphoma and follicle center lymphoma. In the gastrointestinal tract, large B-cell lymphoma was classified into marginal zone B-cell lymphoma or diffuse large B-cell lymphoma, depending on the presence or absence of residual low grade marginal zone B-cell lymphoma. With this criteria, marginal zone B-cell lymphoma was more common than diffuse large cell lymphoma in the stomach. Over 70% of nasal and paranasal sinusoidal lymphomas were angiocentric lymphomas. T- (or putative NK)-lineage lymphoma accounted for 81.1% of lymphomas involving the skin. Mycosis fungoides was diagnosed as such when there were characteristic clinical features and epidermotropism. With these criteria, mycosis fungoides was not common. The most frequent type was peripheral T-cell lymphoma, followed by subcutaneous panniculitic T-cell lymphoma and angiocentric lymphoma.

DISCUSSION

The cases included in this study were collected from 23 large institutes covering all geographic regions of the Republic of Korea except the eastern region. Considering the numbers of participating institutes and collected cases, and complete histologic reexamination by participants, the results of this study would be representative of malignant lymphoma in the Republic of Korea, although we admit that there are some weaknesses in the study related to the exclusion of the eastern part of Korea.

The data demonstrated that the relative frequency of the different subtypes of malignant lymphomas in the Republic of Korea is distinct from that in Western countries and shares many similarities with other Far East countries. The low relative frequency of HD, which accounts for less than 10% of malignant lymphomas, is a common finding in regions of the Far East, including China, Japan, Taiwan, and Hong Kong.[5–9] This is in contrast to the high frequency (40–45% of cases) reported in the U.S. and Europe. Epstein–Barr virus has been detected in 69% of HD cases in the Republic of Korea.[10] Compared with the data reported in 1991, the increase in the relative frequency of nodular sclerosis over time suggests that the patterns of malignant lymphoma occurrence in the Republic of Korea might be gradually changing, probably due to westernization. Alternatively, diagnostic criteria applied in this study might be more refined than that of the study in 1991. The lower rate of follicular lymphoma in the Far East when compared with that in Western countries is well recognized. The relative rate of follicular lymphoma in this study is comparable to that for other countries in the Far East.[1] Compared with the previous study, the increase in the relative frequency of follicle center lymphoma may represent an increase in the true incidence of follicular lymphoma in the Republic of Korea. On the other hand, the follicular lymphoma category in this study contains many cases of partially follicular lymphoma that

might have been overlooked as diffuse lymphoma in the previous study. Another explanation for the increased frequency of follicular lymphoma could be that the recent increase in the availability and utilization of early medical care has made it possible to detect follicular lymphoma sooner, while it is in a completely follicular stage. A similar trend in completely follicular lymphoma has been reported for Japan.[11]

It is noteworthy that the frequency of NHLs arising in the stomach was increased compared with the previous study in 1991, whereas the relative frequency of lymphomas in the small intestine and colon did not change. Considering that marginal zone B-cell lymphoma accounted for more than 70% of gastric lymphomas but only 30% of intestinal lymphomas, the increased rate of gastric lymphoma may be attributable to the enhanced ability of pathologists to differentiate marginal zone B-cell lymphoma from chronic active gastritis and gastric pseudolymphoma. As in the stomach, a similar increase was found in lymphoma of the orbit. More than 50% of NHLs in this site were marginal zone B-cell lymphomas, most of which were previously diagnosed as pseudolymphomas.

Mantle cell lymphoma is a recently redefined entity. The relative frequency in the Republic of Korea was lower than that of a population-based study in Europe[12] (1.2% vs. 3.7%).

In regard to the frequency of the immunologic subtypes, this study demonstrated that the rate of T- (or putative NK)-cell lymphomas in the Republic of Korea was much less than that of other Far East regions,[7,8,11,13] excluding Hong Kong.[15] This low rate of T- (or putative NK)-cell lymphoma was unexpected. Previous studies from the Republic of Korea in 1992 had reported a high incidence of T-cell lymphoma, accounting for about 35.2% of NHL.[3] However, a similar trend in the decreased rate of T-cell lymphoma has been seen in Japan. Previously, the rate of T-cell lymphoma in human T-cell lymphoma virus (HTLV)-I nonendemic areas of Japan was reported to be 40.1%[7], but a recent study revealed that 23% of NHLs were T/NK lineage.[16] This rate of T- (or putative NK)-cell lymphoma was comparable to rates in the Western population or slightly higher. The change in the rate of T- (or putative NK)-cell lymphoma over time might represent a true decrease in T- (or putative NK)-lineage lymphoma in the Far East; however, we speculate that previous studies overestimated the rate of T-cell lymphoma due to case selection bias and the small number of cases enrolled in the study.

Of postthymic T-cell lymphomas, HTLV-I–associated adult T-cell lymphoma/leukemia is the rarest in Korea. Until now, only three cases have been reported.[17] In healthy individuals, a seroepidemologic study of anti-HTLV-I antibody revealed a low prevalence of 0.25%.[18]

As in other Far East countries, Korea has a relatively high rate of angiocentric lymphomas, with more than 70% of them arising in the nose and paranasal sinus. Previous immunohistochemical and molecular genetic analysis in Korea revealed that angiocentric lymphomas arising in these sites were often negative for T-cell receptor gene rearrangement and positive for CD56 and cytoplasmic CD3, suggesting that most Korean angiocentric lymphomas in the nose and paranasal sinus belong to NK lineage. EBV was positive in 63.6% of entire angiocentric lymphomas and in 80% of nasal and paranasal angiocentric lymphomas.[19,20]

A clinical analysis revealed that the rate of extranodal lymphoma exceeded that of lymph node lymphoma (63.3% vs. 36.7%). This rate is much higher than that for the U.S. (26%), Hong Kong (28.5%), Japan (45%), and Taiwan (37.9%),[9,21] but similar to that of recent Japanese series (60%).[16] Although this study was based on the biopsy materials and lacked complete information on staging, a consistent excess of extranodal lymphoma in the current study and the previous study suggested that extranodal predominance might be one of characteristics of malignant lymphoma in the Republic of Korea. Also notable was that the median age of patients at the time of presentation was younger than in the U.S. (52 years vs. 65 years),[22] which might be attributable to the lower frequency of lymph node type lymphoma, including follicle center lymphoma, that tends to occur in older patients.

In conclusion, the occurrence rates of malignant lymphomas in Korea are distinct from those in Western countries and share many similarities with those in other Far East countries. Compared with other Far East countries, Korea has a higher rate of extranodal lymphoma, rare adult T-cell lymphoma, and a relatively low rate of T-cell lymphomas. There have been changes in the relative rate of follicular lymphoma, subtypes of HD, and gastric and ocular lymphomas over time. These changes are primarily attributable to refined diagnostic criteria of new clinicopathologic entities.

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