

## Clinicopathologic and Immunophenotypic Study of Non-Hodgkin's Lymphoma in Korea

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*This study sponsored by the Lymphoreticular Study Group of the Korean Society of Pathologists was carried out to provide nationwide data about the histopathologic-immunophenotypic features of malignant lymphomas in Korea. Two hundred and ninety Non-Hodgkin's lymphoma (NHL) among 312 malignant lymphomas collected from three representative areas in Korea were histologically reclassified. Two hundred and fifty three cases were immunohistochemically studied. T-cell lymphoma comprised 35.2% of NHL in this study and showed a quite comparable incidence to that of Japan and China, but it was much higher than in Western countries. A very low prevalence rate of the follicular variety (4.0%) and a higher propensity of primary extranodal involvement (60%) are additional characteristics of NHL in Korea. The most common histologic subtype of B cell lymphoma was diffuse large cell type, whereas the most common subtype of T cell lymphoma was diffuse mixed small and large cell type.*

**Key Words:** Malignant lymphoma, Korean, Classification, Immunophenotype, Non-Hodgkin's lymphoma

### INTRODUCTION

Since surface marker analysis has been applied to the study of lymphoreticular disorders, our understanding of the biologic behavior of these lesions has been markedly enhanced (Greaves MF, 1974; Lukes RJ and Collins RD, 1974; Jaffe ES et al. 1982). There have been several reports which indicate considerable differences in lymphomas around the world, particularly in the relative incidence of immunophenotype subclasses (Suchi T and Tajima K, 1979; Su IJ et al. 1985). Although it has been shown that the relative frequency of T cell lymphoma in Korea seems to be higher than that of

Western countries (Yang WI et al, 1989), nationwide data has not been available up to now. This study is sponsored by the Lymphoreticular Study Group of the Korean Society of Pathologists in order to provide a basic idea about clinico-pathologic findings and the immunophenotypic characteristics of NHL in Korea.

### MATERIALS AND METHODS

Three hundred and twelve recent cases of malignant lymphoma (most of them diagnosed during 1990) were collected from the three representative areas-210 cases from Seoul (Seoul National University Hospital, Yonsei University Hospital, Haewha Hospital of Korea University, Hanyang University Hospital, Sanggye Paik Hospital of Inje University), 46 cases from Southeastern (Keimyung University Hospital), and 56 cases from Southwestern (Chonbuk University Hospital, Wonkwang University Hospital, Chonnam University Hospital, Chosun University Hospital) areas of Korea. All the microscopic slides of the cases in this study were critically reviewed by the authors (at least six pathologists attended in analysing the cases from each institute). We finalized diagnosis as the reviewer's consensus in-

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**Table 1.** Monoclonal Antibodies Used in this Study

|                    |                         |  |
|--------------------|-------------------------|--|
| B cell markers     |                         |  |
| L26 (CD20)         | Dako corporation        | All B cells                                |
| MB2                | Biotest                 | All B cells except plasma cells            |
| LN1 (CDw75)        | ICN Immuno-Biochemicals | B cells of germinal center                 |
| LN2 (CD74)         | ICN Immuno-Biochemicals | B cells of germinal center and mantle zone |
| T cell markers     |                         |  |
| UCHL1 (CD45RO)     | Dako corporation        | Activated, memory T cells                  |
| CD3                | Dako corporation        | All T cells                                |
| MT1                | Biotest                 | All T cells                                |
| Histiocyte markers |                         |  |
| CD68               | Dako corporation        | All macrophages                            |
| Lysozyme           | Dako corporation        | All macrophages                            |

**Table 2.** Age and Sex Distribution of Subtypes in Non-Hodgkin's Lymphoma

| Subtypes                  | Age/Sex |   | -10 |   | 11-20 |   | 21-30 |   | 31-40 |   | 41-50 |   | 51-60 |   | 61-70 |   | 71-80 |   | 81- |   | Total |   |   |   |
|---------------------------|---------|---|-----|---|-------|---|-------|---|-------|---|-------|---|-------|---|-------|---|-------|---|-----|---|-------|---|---|---|
|                           | M       | F | M   | F | M     | F | M     | F | M     | F | M     | F | M     | F | M     | F | M     | F | M   | F | M     | F | F |   |
| Low grade                 |         |   |     |   |       |   |       |   |       |   |       |   |       |   |       |   |       |   |     |   |       |   |   |   |
| Small lymphocytic         |         |   |     |   |       |   | 1     | 2 |       |   |       | 3 |       | 3 | 1     |   |       |   |     |   |       |   | 7 | 3 |
| Follicular, small cleaved |         |   |     |   |       |   |       |   |       |   |       |   |       |   |       |   |       |   | 1   |   |       |   | 0 | 1 |
| Follicular, mixed         |         |   |     |   |       |   |       |   | 1     |   | 1     |   |       |   |       | 1 | 1     |   |     |   |       |   | 3 | 1 |
| Intermediate grade        |         |   |     |   |       |   |       |   |       |   |       |   |       |   |       |   |       |   |     |   |       |   |   |   |
| Follicular, large         |         |   |     |   |       |   | 1     |   | 1     | 1 | 2     |   | 1     |   |       |   |       |   |     |   |       |   | 3 | 3 |
| Diffuse, small cleaved    |         |   | 1   |   |       |   | 1     | 1 |       |   |       |   | 1     | 1 |       |   |       | 1 |     |   |       |   | 2 | 4 |
| Diffuse, mixed            |         |   | 2   |   | 4     |   | 2     | 6 | 4     | 7 | 6     | 5 | 9     | 3 | 6     | 5 | 4     | 1 |     |   |       |   | 4 | 2 |
| Diffuse, large            |         |   | 1   |   | 6     | 2 | 1     | 3 | 1     | 2 | 6     | 1 | 6     | 1 | 2     | 1 | 9     | 9 | 8   | 2 | 1     | 2 | 8 | 6 |
| High grade                |         |   |     |   |       |   |       |   |       |   |       |   |       |   |       |   |       |   |     |   |       |   |   |   |
| Large, immunoblastic      |         |   |     |   |       |   | 1     |   | 7     | 3 | 3     |   | 6     | 4 | 4     | 6 | 1     | 1 |     |   |       |   | 2 | 1 |
| Lymphoblastic             |         |   | 4   | 2 | 1     |   | 5     |   | 3     |   |       |   |       |   |       |   |       |   |     |   |       |   | 1 | 4 |
| Small noncleaved          |         |   | 2   | 2 | 3     |   | 1     |   |       |   | 1     |   | 1     |   |       |   |       |   |     |   |       |   | 6 | 4 |
| Miscellaneous             |         |   |     |   |       |   |       |   |       |   |       |   |       |   |       |   |       |   |     |   |       |   |   |   |
| Mycosis fungoides         |         |   |     |   |       |   |       |   | 1     |   | 1     |   | 1     |   |       |   |       |   |     |   |       |   | 3 | 0 |
| Subtotal                  |         |   | 8   | 6 | 1     | 5 | 2     | 3 | 1     | 3 | 2     | 1 | 6     | 3 | 5     | 2 | 2     | 3 | 0   | 1 | 2     | 1 | 1 | 1 |
| Total                     |         |   | 1   | 4 | 2     | 0 | 3     | 6 | 4     | 2 | 4     | 8 | 5     | 7 | 5     | 1 | 1     | 9 | 3   | 2 | 9     | 0 | 2 | 9 |

stead of the original one, when discrepancies occurred between them.

Among 312 cases, 290 Non-Hodgkin's lymphomas were reclassified according to the Rappaport classification (Rappaport H, 1986) and the International Working Formulation (Rosenberg SA et al, 1982). An immunohistochemical analysis in routinely processed paraffin sections was done in 253 cases. Monoclonal antibodies used in immunophenotyping are listed in Table 1.

After steps for blocking of endogenous peroxidase

activity and nonspecific antibody binding the primary antibodies were applied for an hour in room temperature. Biotinylated second antibody (goat-antimouse) and streptavidin labelled peroxidase applied sequentially for 30 minutes in each steps. Aminoethyl carbazole (AEC) was used as chromogen-substrate. Labelled streptavidin-Biotin kit was purchased from Dako corporation (Denmark).

## RESULTS

## Histologic Classification of Non-Hodgkin's Lymphoma

Of 312 cases of malignant lymphomas, there were 290 cases (92.9%) of non-Hodgkin's lymphoma and 22 cases (7.1%) of Hodgkin's disease.

Age and sex distribution in NHL was shown in table 2. Male to female ratio was 1.9:1. The highest occurrence rate (19.7%) was found in the age group between 51 and 60 years of age.

Among the cases of low grade lymphoma by Working Formulation, 10 (3.4%) were of the small lymphocytic type and 5 (1.7%) were included in the follicular type of small cleaved cell or mixed cell type. The follicular large cell type was encountered in 6 (2.1%) of which two cases of mixed pattern (follicular with diffuse areas) were included. The diffuse large cell type was the most common histologic subtype and was seen in 133 cases (45.9%). Sixty four cases (22.1%) of diffuse

mixed, small and large cell type were followed. There were only six cases (2.1%) of diffuse small cleaved cell type. In high grade lymphomas, immunoblastic type (36 cases, 12.4%), lymphoblastic type (17 cases, 5.9%) and small noncleaved cell type (10 cases, 3.4%) were listed in order of decreasing frequency (Table 3).

The anatomical sites of primary involvement in NHL are summarized in Table 4. One hundred and seventy four cases (60%) were disclosed as extranodal lymphomas and the remainder (116 cases) were primarily involved in lymph nodes. The common sites were the gastro-intestinal tract, tonsil, and oro-nasal cavity.

## Immunophenotype Analysis of Non-Hodgkin's Lymphoma

One hundred and forty eight cases (58.5%) were confirmed as B-cell lineage and 89 cases (35.2%) were T-cell phenotype among 253 cases of NHL, which were available in an immunohistochemical study. Only one

Table 3. Relative Frequency of Subtypes in Non-Hodgkin's Lymphoma by Working Formulation and Rappaport Classification

| W-F                       | Rappaport | NPDL   | NM     | NH     | WDL    | DPDL    | DM       | DH        | LB      | BK     | NBK    | MF     | Total (%) |
|---------------------------|-----------|--------|--------|--------|--------|---------|----------|-----------|---------|--------|--------|--------|-----------|
| Low grade                 |           |        |        |        |        |         |          |           |         |        |        |        |           |
| Small lymphocytic         |           |        |        |        | 5      | 5       |          |           |         |        |        |        | 10(3.4)   |
| Follicular, small cleaved | 1         |        |        |        |        |         |          |           |         |        |        |        | 1(0.3)    |
| Follicular, mixed         |           | 4      |        |        |        |         |          |           |         |        |        |        | 4(1.4)    |
| Intermediate grade        |           |        |        |        |        |         |          |           |         |        |        |        |           |
| Follicular, large         |           |        | 6      |        |        |         |          |           |         |        |        |        | 6(2.1)    |
| Diffuse, small cleaved    |           |        |        |        | 6      |         |          |           |         |        |        |        | 6(2.1)    |
| Diffuse, mixed            |           |        |        |        |        |         | 64       |           |         |        |        |        | 64(22.1)  |
| Diffuse, large            |           |        |        |        |        |         |          | 133       |         |        |        |        | 133(45.9) |
| High grade                |           |        |        |        |        |         |          |           |         |        |        |        |           |
| Large, immunoblastic      |           |        |        |        |        |         |          | 36        |         |        |        |        | 36(12.4)  |
| Lymphoblastic             |           |        |        |        |        |         |          |           | 17      |        |        |        | 17(5.9)   |
| Small noncleaved          |           |        |        |        |        |         |          |           |         | 7      | 3      |        | 10(3.4)   |
| Miscellaneous             |           |        |        |        |        |         |          |           |         |        |        |        |           |
| Mycosis fungoides         |           |        |        |        |        |         |          |           |         |        |        | 3      | 3(1.0)    |
| Total (%)                 |           | 1(0.3) | 4(1.4) | 6(2.1) | 5(1.7) | 11(3.7) | 64(22.1) | 169(58.3) | 17(5.9) | 7(2.5) | 3(1.0) | 3(1.0) | 290(100)  |

W-F: Working Formulation

NPDL: Nodular, poorly differentiated lymphocytic

NM: Nodular, mixed

NH: Nodular, histiocytic

WDL: Well differentiated lymphocytic

DPDL: Diffuse, poorly differentiated lymphocytic

DH: Diffuse, histiocytic

LB: Lymphoblastic

BK: Burkitt's

NBK: Non-Burkitt's

MF: Mycosis fungoides

**Table 4.** Distribution of Extranodal Sites of Involvement in Non-Hodgkin's Lymphoma

| Sites                     | No. of cases(%) |
|---------------------------|-----------------|
| Tonsil                    | 36(20.7)        |
| Stomach                   | 35(20.1)        |
| Colon and small intestine | 28(16.1)        |
| Skin and soft tissue      | 22(12.6)        |
| Nasal cavity              | 18(10.3)        |
| Oropharynx                | 8(4.6)          |
| Central nervous system    | 7(4.0)          |
| Orbit                     | 7(4.0)          |
| Bone                      | 3(1.7)          |
| Testis                    | 2(1.1)          |
| Ut. cervix and vagina     | 2(1.1)          |
| Breast                    | 1               |
| Mediastinum               | 1               |
| Muscle                    | 1               |
| Kidney                    | 1               |
| Liver                     | 1               |
| Retroperitoneum           | 1               |
| Total                     | 174(100)        |

case was classified as true histiocytic type and 15 cases (6%) cannot be classified properly with only the limited stainability of monoclonal antibodies used in this study (Table 5).

The proportion of T cell lymphomas was slightly higher in extranodal sites (37.6%) than in lymph nodes (31.7%) (Table 6). Whereas the cases of small lymphocytic, follicular and small noncleaved type were exclusively B-cell phenotype, all the cases of lymphoblastic and mycosis fungoides type showed T cell lineage of neoplastic cells. The most common histologic subtype of B cell lymphomas was the diffuse large cell type and the most common subtype of T cell lymphomas was the diffuse mixed, small and large cell type. The B and T cell phenotype ratio in immunoblastic subtype was about 3 to 1 and was similar to that in diffuse large cell cases.

## DISCUSSION

We admit that some weakness exists in this study to provide statistical significance in data analysis. Firstly, the number of cases was not large enough to represent nationwide data on malignant lymphoma in Korea. Se-

**Table 5.** Distribution of Non-Hodgkin's Lymphoma by Histology and Immunophenotype

| Histology              | Phenotype |        |            |              | Total |
|------------------------|-----------|--------|------------|--------------|-------|
|                        | B-cell    | T-cell | Histiocyte | Unclassified |       |
| Small lymphocytic      | 10        |        |            |              | 10    |
| Follicular             | 10        |        |            |              | 10    |
| Diffuse, small cleaved | 4         | 1      |            | 1            | 6     |
| Diffuse, mixed         | 11        | 40     | 1          | 5            | 57    |
| Diffuse, large         | 81        | 20     |            | 8            | 109   |
| Immunoblastic          | 23        | 8      |            | 1            | 32    |
| Lymphoblastic          |           | 17     |            |              | 17    |
| Small noncleaved       | 9         | 1      |            |              | 10    |
| Mycosis fungoides      |           | 2      |            |              | 2     |
| Total                  | 148       | 89     | 1          | 15           | 253   |

**Table 6.** Distribution of Non-Hodgkin's Lymphoma by Immunophenotype and Site

| Phenotype    | Site      |            | Total     |
|--------------|-----------|------------|-----------|
|              | Nodal     | Extranodal |           |
| B-cell       | 65        | 83         | 148(58.5) |
| T-cell       | 33        | 56         | 89(35.2)  |
| Histiocyte   | 0         | 1          | 1(0.3)    |
| Unclassified | 6         | 9          | 15(6.0)   |
| Total        | 104(41.1) | 149(58.9)  | 253(100)  |

condly, the sample collection method was not well-designed from the epidemiologic aspect. For example, several important factors-population numbers in each participating area and consecutive case selection-are not critically considered in this study.

In spite of the above limitations, this study can provide some valuable basic ideas on the histologic-immunophenotypic characteristics of NHL in Korea. It is also worthy of comment that this is the first time a nationwide study has been conducted on this issue with a collective review and discussion by all participants of histologic diagnosis and immunophenotype classification.

For information on the histologic subtypes of malignant lymphoma in Korea, the data in this study was quite comparable to the results of previous studies (Shin SS et al, 1983; Chi JG et al, 1987).

The incidence of low grade lymphoma, especially the follicular variety, was definitely less common among Koreans. Follicular lymphoma comprised 4.1% in this study, and was much less than that of Japan (10%) and the U.S.A. (30%) (Kadin ME, et al, 1983). Another feature was that the rate of extranodal lymphoma (60%) exceeded that of primary nodal involvements. The ratio of nodal to extranodal lymphoma was highest in the U.S.A. and the ratio in Japan was in between that of the U.S.A. and Korea (Kadin ME et al 1983). However, the frequency of primary extranodal NHL in Taiwan (Shih LY and Liang D-C, 1991) was 37.9% and was quite lower than that of this study, the distribution patterns of involving sites were very similar to each other. This fact, that extranodal lymphoma is more common in Korea, may contribute to a higher rate of large cell and immunoblastic lymphoma compared to the follicular type, because early diagnosis is rather difficult in NHL of the internal organs and the incidence of follicular lymphoma has been known to be quite rare in extranodal sites (Jaffe ES, 1985).

The proportion of T-cell lymphoma confirmed by immunohistochemical methods in this study was 35.2% among NHL. We had an impression of a rather higher incidence of T-cell lymphoma in Korea. Until now there has not been any responsible data to clarify the actual incidence of T-cell lymphoma in Korea except for a preliminary report suggesting that T-cell lymphoma occupied about 63% of NHL in Korea by analysing the cases from one University Hospital in Seoul (Yang WI et al, 1989). Asian countries including Japan (Suchi T and Tajima K, 1979) and China (Su JI et al, 1985) exhibit a much higher rate of T-cell lymphoma than in Western countries. In Japan, T-cell lymphoma occupied about 40% of NHL and a large proportion of these belonged to the cases of HTLV-1 associated adult T-

cell lymphoma/leukemia (ATLL, 8% of NHL) (Kadin ME et al, 1983). ATLL cases has been also encountered sporadically in Taiwan (Shin LY and Liang D-C, 1991). There was no case showing a characteristic clinical feature of ATLL in this study.

In regard to the higher rate of T-cell lymphoma in Korea, we don't have any good reason to explain it. We can only guess at certain environmental or racial factors, which Asian countries might commonly share, as contributing roles in T-cell oncogenesis.

According to the histologic-immunophenotypic correlation in NHL, B and T cell type ratio in immunoblastic and diffuse large cell cases reached about 3-4 to 1, but in diffuse mixed, small and large cell type, it was reversed to 1 to 4. There was a tendency to classify peripheral T-cell lymphoma (PTCL) as diffuse, mixed cell type by W-F, histologically, because it was not unusual to find abundant non-neoplastic cells admixing with neoplastic T cells especially in some subtypes of PTCL (Kikuchi M et al, 1979).

Immunophenotype restriction according to the involvement sites in extranodal lymphoma was also commentable. However, a large number of lymphoma arising in skin and soft tissue were clarified as T-cell subtype (72.2%), whereas in the gastrointestinal tract B-cell phenotype was much higher than T-cell lineage (79.6%).

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