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Peripheral T-cell Lymphomas

— Clinicopathologic and Immunophenotypic Analysis of 25 Cases —

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The clinicopathologic and immunophenotypic findings of 25 cases of peripheral T-cell lymphoma in Korea were analysed. Seventeen cases (68%) of the 25 T-cell lymphomas presented in the extranodal sites including the nasal mucosa, tonsil, oral cavity, skin and rarely bone, mediastinum and breast. Immounologic studies showed that 12 cases (48%) of the lymphomas were of T-helper phenotype, 5 cases (20%) were of cytotoxic/suppressor phenotype, 1 case (4%) expressed both helper and cytotoxic/suppressor markers, and 7 cases (28%) lacked detectable markers for subsets. Histologically, fourteen cases (56%) showed histologic features suggestive of peripheral T-cell lymphoma. The more frequently seen histologic types by Working Formulation (WF) included large cell type and immunoblastic type. Classification by WF was straightforward in most cases of large cell, immunoblastic type. However, with some cases of small cell, large cell and mixed types, there were problems fitting the morphology seen into the WF category. We hope that the establishment of a world wide immunologic and clinicopathologic classification for peripheral T-cell lymphoma will be made in the near future.

Key Words: *Peripheral T-cell lymphoma, Malignant lymphoma, Immunophenotype, Histologic characteristics, Korea*

INTRODUCTION

With the advent of monoclonal antibodies against the surface antigens of lymphocytes, it has been possible to identify lymphoma cell as either B-cell or T-cell origin.

Non-Hodgkin's T-cell lymphoma (NHL) consists of a heterogeneous group of tumors, of which lymphoblastic lymphoma and mycosis fungoides (MF) are well known clinicopathologic entities (Lutzner et al., 1975, Nathwani et al., 1978, Edelson, 1980), whereas peripheral T-cell lymphoma (PTCL) has no generally accepted classification system and poorly defined clinicopathologic characteristics (Pinkus et al., 1979, Suchi et al., 1979, Watanabe et al., 1979, Suchi & Tajima, 1979, Kikuchi et al., 1979, Brisbane et al., 1983, Brouet et al., 1984, Grogan et al., 1985, Weiss et al., 1985, Borowitz et al., 1986, Horning et al., 1986, Coiffier et al., 1988, Krajewski et al., 1988, Armitage et al., 1989). In the USA and Europe, the incidence of T-cell lymphoma was reported to be less than 20% of NHL (Lukes et al., 1978, Suchi & Tajima, 1979), but in Asian countries, including Japan and Taiwan, T-cell lymphoma occupied more than 40% of NHL (Shimoyama, 1979, Suchi & Tajima, 1979, Su et al., 1985), many of which are associated with the HTLV-I virus (Hanaoka, 1982, Su et al., 1988).

In Korea, a recent study reported that T-cell malignancy occupied about 35.2% of NHL (Kim et al., 1991).

The aim of this study is to present the clinicopathologic and immunophenotypic findings of 25 immunophenotypically proven cases of PTCL in Korea.

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MATERIALS AND METHODS

Twenty five cases of T-cell lymphoma, excluding MF and lymphoblastic lymphoma were identified in our laboratory from January 1987 through June 1989. The seventeen cases were biopsied in our hospital and the remainders were referred from other institutions for marker studies. In all cases, fresh materials were

available. The tissue was fixed in 10% formalin and/or B5 solution and was processed for routine H-E section. Fresh tissue was processed for marker studies. The 6um thick sections were cut from the frozen tissue and immunostained with monoclonal antibodies for B-and T-cell (Table 1), using the avidine-biotin-peroxidase complex (ABC) technique.

The cases were classified using the Working Formulation (WF) from the National Cancer Institute and new classification proposed by the Japanese-European group (Suchi et al, 1987). Clinical information including age and sex of patients, presenting organ, clinical stage, presence of polyclonal gammopathy, HTLV or hypercalcemia, follow up, treatment, and survival, was obtained from clinical records.

The diagnosis of peripheral T-cell lymphoma was based upon a combination of morphologic assessement together with the results of immunophenotyping. Immunophenotypically, the cases stained with one or more T-cell marker without expression of pan-B cell antigens were recognized as a T-cell lymphoma. The tumors exhibiting a spectrum of cell size with nuclear irregularity, clear cells, many venules with prominent endothelial cells, frequent admixture of eosinophils, plasma cells, and histiocytes, were considered as being suggestive of T-cell lymphoma.

Table 1. Monoclonal Antibodies Used for Immunohistochemical Study

Antibody	Specificity	Source
T 11 (CD2)	Sheep E-rosette receptor (pan-T cell)	Coulter
T 4 (CD4)	Inducer/helper T cell	Coulter
T 8 (CD8)	Cytotoxic/suppressor T cell	Coulter
B 1 (CD20)	B-cell lineage	Coulter
Ki-1 (CD30)	Reed-Sternberg cell	Dako

RESULTS

Clinical Findings (Figure 1, Table 2 & 3)

The demographic features are shown in Figure 1. The patients consisted of 19 males and 6 females, giving a ratio of 3.2 with male predominance. Ages ranged from 7 to 68 years with a median of 37 years and a peak in the fifties.

The site of initial presentation is shown in table 2. Seventeen cases (68%) presented in the extranodal

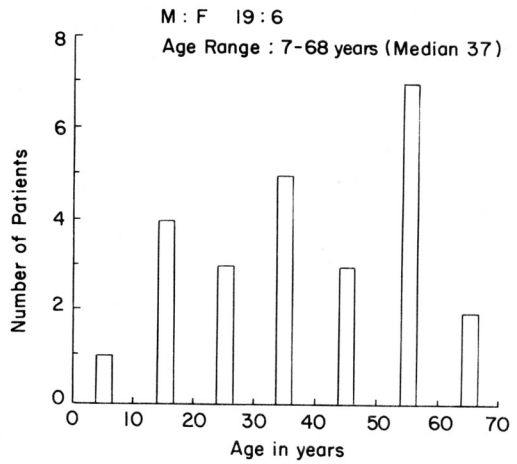

Fig. 1. Age distribution and sex ratio in 25 cases with peripheral T-cell lymphomas.

Table 2. Site of Initial Presentation in 25 Peripheral T-cell Lymphomas

Site	No. of Patient	%
Lymph node	8	32
Oropharynx including tonsil	5	20
Nasal cavity	4	16
Skin	4	16
Oral cavity	1	4
Mediastinum	1	4
Breast	1	4
Bone	1	4
Total	25	100

Table 3. Site of Involvement at the Time of Staging in 25 Peripheral T-Cell Lymphomas

Site	No. of Patients	%
Lymph node	13	52
Oropharynx including tonsil	8	32
Nasal cavity	6	24
Skin	5	20
Spleen	4	16
Liver	3	12
Peripheral blood	2/17*	12
Pleura	1	4
Oral cavity	1	4

* No. of patients with information available

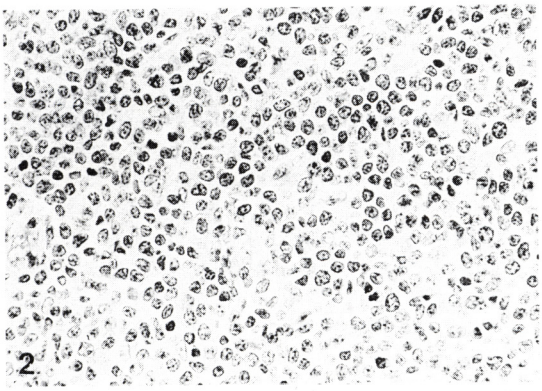

Fig. 2. Small cell, unclassified lymphoma. The tumor is composed of relatively uniform, small to medium sized lymphocytes lacking nuclear irregularity. Abundant venules with prominent endothelial cells are remarkable (H & E, ×400).

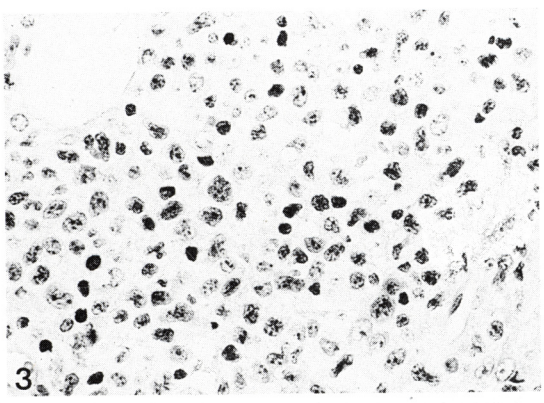

Fig. 3. Mixed small cleaved and large cell lymphoma. Small cleaved lymphocytes are admixed with an equal proportion of medium to large pleomorphic lymphocytes (H & E, ×400).

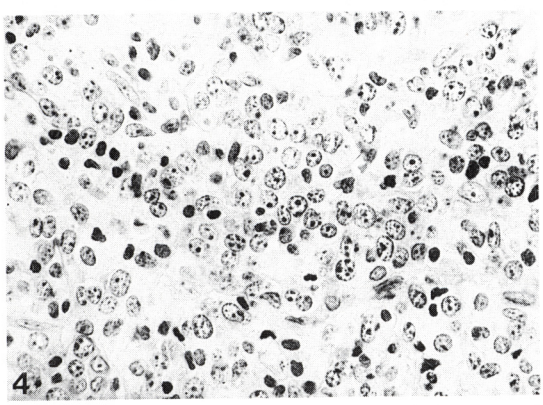

Fig. 4. Large cell lymphoma. The tumor is mainly composed of large cells with vesicular nuclei and consipicuous nucleoli. Some small cleaved lymphocytes are present (H & E, ×400).

locations. The nasal cavity including Waldeyer's ring, involved in 9 cases (36%), was the most common site of presentation and they showed concomitant involvement of other sites such as the regional lymph node, or spleen. There was rare involvement of the mediastinum, breast, and bone-each occurring in one case.

Table 3 presents the incidence of organ involvement noted at the time of staging. The lymph nodes were involved in 13 cases (52%), the oropharynx including the tonsil in 8 cases (32%), the nasal cavity in 6 cases (24%), the skin in 5 cases (20%), the spleen in 4 cases (16%), the liver in 3 cases (12%), and the pleura and oral cavity in 1 case (4%) respectively. Peripheral blood was involved in 2 cases (12%) among the 17 cases for which this information was available. Bone marrow was free from tumor invasion in the 14 cases in which aspiration was done.

There was no hypercalcemia in any of the cases or polyclonal gammopathy in the 3 cases examined for this. Serologic study for HTLV-I was not performed in any of the cases.

Histologic Findings (Table 4)

Based on the characteristic histologic features of T-cell lymphoma with diverse morphology described above, 14 cases (56%) were recognized as T-cell lymphoma. The remaining 7 cases (28%) showed histologic findings suggestive of B-cell lymphoma and 4 cases (16%) were indeterminate for B-or T-cell.

There was prominant irregularity of nuclear contours in 16 cases (64%) and variation of cell size in 14 cases (56%). Abundant venules with prominant endothelium were recognized in 10 cases (40%) and a variable degree of clear cell change in 6 cases (24%). Clusters of epithelioid cells were present in 4 cases (16%) and predominant in one case leading to the masking of the underlying tumor. Although eosinophils and plasma cells admixed with tumor cells in variable proportions were noted in 13 cases (52%), they were not a predominant finding in any case.

In the tumors which presented in the upper respiratory tract, including Waldeyer's ring, widespread necrosis of the tumor was frequently observed. Tumors occurring in other sites showed no necrosis in any case. There was no epidermotropism in all the 4 cases presenting in the skin. In one case, presenting in the lymph node, tumor cells disseminated in the intrasinusoidal pathway imparting an impression of metastatic carcinoma on low power scanning of the slide. In another case arising in the mediastinum, the tumor showed prominant fibrosis dividing the tumor into variable sized nodules giving a false impression of

thymoma.

Histologic Classification (Table 5).

The majority of cases had a morphologic diagnosis of immunoblastic or diffuse, large cell lymphoma by WF. Polymorphous immunoblastic type occurred in 7 cases, plasmacytoid in 3 cases and clear cell type in 1 case. Eight cases (32%) were classified into diffuse, large cell type and 5 cases (20%) into mixed small cleaved and large cell type. Small cell type was encountered in one case.

The classification by WF was compared with the new classification proposed by the Japanese-European group. Eighteen cases (72%) belonged to the pleomorphic type. Seven cases of immunoblastic, polymorphous type were subdivided into 6 cases of pleomorphic, large cell type and one case of Ki-1 positive, anaplastic, large cell type. Three cases of immunoblastic, plasmacytoid type and one case of clear cell type corresponded to immunoblastic type, basophilic variant and non-basophilic variant, respectively, according to the new classification. Eight cases of diffuse,

Table 4. Histologic Findings in 25 Perpheral T-Cell Lymphoma

Subtype by WF	No. (%)	Suggestive of T-cell	Suggestive of B-cell	Indeterminate for B-or T-cell	Marked nuclear irregularity	Variable cell size	Prominent venules	Clear cells	Epithelioid cell	Eosinophils & plasma cells
Immunoblastic	11 (44)	7	3	1	8	6	3	3	1	5
polymorphous	7 (28)	6	0	1	7	5	3	2	0	3
plasmacytoid	3 (12)	0	3	0	0	0	0	0	1	1
clear cell	1 (4)	1	0	0	1	1	0	1	0	1
Diffuse, large	8 (32)	4	2	2	4	4	3	2	0	4
Diffuse, mixed, small cleaved & large	5 (20)	3	1	1	4	4	3	1	3	4
Small cell	1 (4)	0	1	0	0	0	1	0	0	0
Total (%)	25 (100)	14 (56)	7 (28)	4 (16)	16 (64)	14 (56)	10 (40)	6 (24)	4 (16)	13 (52)

Table 5. Histologic Subclassification of Peripheral T-Cell Lymphomas by WF and Japanese-European Classification

Working Formulation	Japanese-European Proposal	No.	Total (%)
Immunoblastic, polymorphous	Plemorphic, large cell	6	7 (28)
	Large cell, anaplastic (Ki-1)	1	
Immunoblastic, plasmacytoid	Immunoblastic	3	3 (12)
Immunoblastic, clear cell	Immunoblastic	1	1 (4)
Diffuse, large cell	Pleomorphic, large cell	7	8 (32)
	Immunoblastic	1	
Diffuse, mixed small cleaved and large	Pleomorphic, medium	5	5 (20)
Small cell, unclassified	Unclassified, low grade	1	1 (4)
Total		25	25 (100)

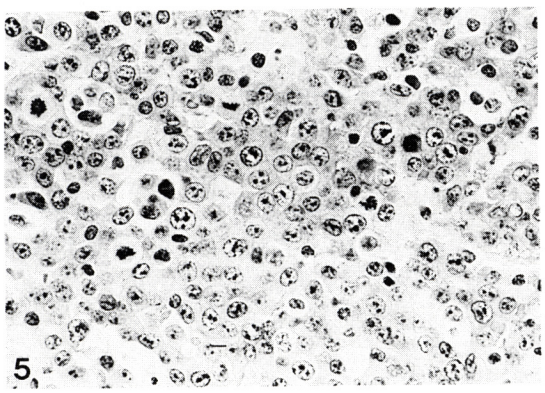

Fig. 5. Immunoblastic lymphoma, plasmacytoid type. The tumor consists of monotonous population of large cells with basophilic cytoplasm resembling plasma cell (H & E, ×400).

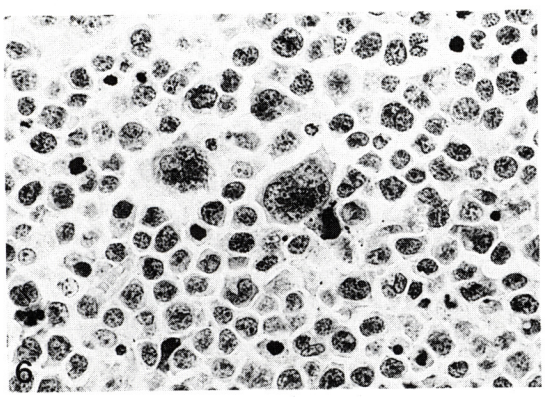

Fig. 6. Immunoblastic lymphoma, polymorphous type. The tumor is composed of immunoblasts with many bizarre giant cells (H & E, ×400).

large cell type were classified as 7 cases of pleomorphic, large cell type showing nuclear irregularity and one immunoblastic type without nuclear irregularity. Diffuse, mixed small cleaved and large cell type corresponded to pleomorphic, medium cell type. One case diagnosed as small cell type, unclassified by WF, consisted of monotonous cells which were actually medium in size and lacking nuclear irregularity, therefore it did not fit into any type in the WF classification. This case belonged to unclassified, low grade T-cell lymphoma according to the new classification.

Immunophenotype (Table 6)

Twelve cases (48%) exhibited helper T-cell type and 5 cases (20%) showed suppressor T-cell type. The remaining 8 cases (32%) showed aberrant immunophenotypes. Among them, one case (4%) exhibited both subset markers and 7 cases (28%) lacked detectable markers for subset.

Clinical stage (Table 7)

The cases presented with stage I in 6 cases (24%), stage II in 7 cases (28%), stage III in 7 cases (28%), and stage IV in 5 cases (20%). Eight cases which presented in the lymph node, showed stage I in one case, stage II in two cases, stage III in three cases, and stage IV in two cases. Among 10 cases presented in the Waldeyer's ring, nasal cavity and oral cavity, there were 4 cases in stage I, 3 in stage II, 2 in stage III, and 1 in stage IV. The cases presented in the skin showed one case in stage II, 2 in stage III, and 1 in stage IV. On the relation of stage with immunophenotype, cases presenting with aberrant immunopheno-

Table 6. Immunophenotypic Expression in 25 Cases of Peripheral T-Cell Lymphomas

Histologic type by WF	Immunophenotype				Total (%)
	T11+T4+T8−	T11+T4−T8+	T11+T4+T8+	T11+T4−T8−	
Immunoblastic					
polymorphous	4	1	0	2	7 (28)
plasmacytoid	1	1	0	1	3 (12)
clear cell	1	0	0	0	1 (4)
Large cell	2	2	1	3	8 (32)
Mixed, small cleaved and large	3	1	0	1	5 (20)
Small cell, unclassified	1	0	0	0	1 (4)
Total (%)	12 (48)	5 (20)	1 (4)	7 (28)	25 (100)

Table 7. Stages of Peripheral T-Cell Lymphomas Related to Immunophenotype Expression

Immunophenotype	Stage				
	I	II	III	IV	Total (%)
T11+T4+T8−	4	3a	4	1a	12 (48)
T11+T4−T8+	1	3	0	1	5 (20)
T11+T4+T8+	0	0	0	1	1 (4)
T11+T4−T8−	1	1	3	2	7 (28)
Total (%)	6 (24)	7 (28)	7 (28)	5 (20)	25 (100)

a: Died of disease in 3 months

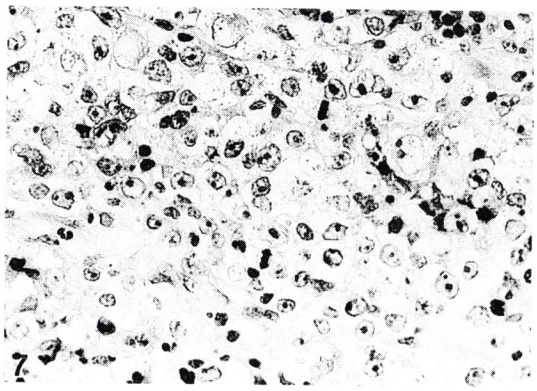

Fig. 7. Immunoblastic lymphoma, clear-cell type. The lymphoma exhibits the cells with large nuclei with abundant clear cytoplasm (H & E, 400).

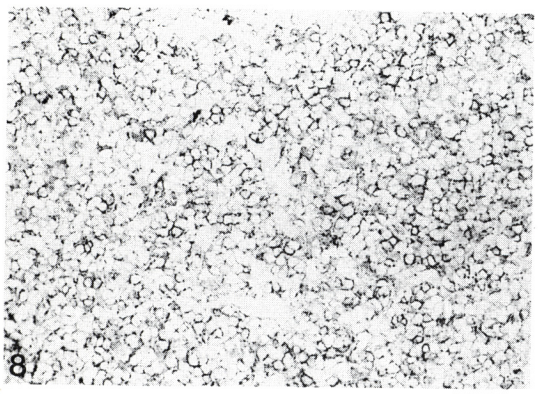

Fig. 8. Cryostat section of a mixed small cleaved & large cell lymphoma stained for T4 by ABC method (×200).

types tended to be in an advanced stage at the time of diagnosis.

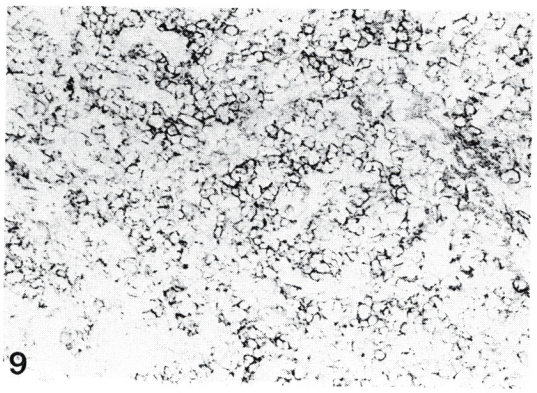

Fig. 9. Cryostat section of a large cell lymphoma stained for T8 by ABC method (×200).

Follow up

Follow up ranged from one month to 7 years with a median of 3 months. The follow up data was too preliminary to properly evaluate the survival rate. All patients were alive at the time of the last follow up, except two patients who died of disease within 3 months of diagnosis, both of them presented with a helper-T cell immunophenotype. Histologically, they were mixed, small cleaved and large cell type and immunoblastic, polymorphous type, respectively.

DISCUSSION

Peripheral T-cell lymphoma (PTCL) indicates a clinicopathologically heterogenous group of post-thymic T-cell proliferations, usually excluding epidermotrophic cutaneous T-cell lymphoma (MF) (Grogan et al., 1985, Borowitz et al., 1986, Horning et al., 1986, Coiffier et al., 1988, Krajewski et al., 1988). Adult T-cell leuke-

mia/lymphoma (ATLL) also belongs to PTCL in a broad sense. However, it is a very peculiar clinicopathologic and virologic entity, and should be separated from PTCL not associated with HTLV-I (Hanaoka, 1982, Jaffe, 1985).

ATLL accounted for 40% of the post-thymic T-cell lymphoma in southwest Japan (Kikuchi, 1979) and 19.3% in Taiwan (Su et al., 1988).

In Korea, the incidence of ATLL had been suspected to be as high as in Japan because the two countries are located very close to each other geographically. However, an epidemiologic study using the indirect immunofluorescent assay and ELISA from the healthy individuals demonstrated only a 0.25% incidence of HTLV-I positivity (Lee et al., 1986). On the basis of this epidemiologic study, Korea would be expected to have a very small number of ATLL cases.

Morphologically, ATLL is remarkable chiefly for the extreme pleomorphism of the neoplastic cells. Many of these tumors are classified as pleomorphic type in the new classification (Hanaoka, 1982). Confirmative diagnosis requires HTLV-I positivity, because morphologic pleomorphism is also noticeable in HTLV-I negative T-cell lymphoma/leukemia (Suchi & Tajima, 1979).

Most cases included in this study lacked the typical clinical features of ATLL, except one case consisting of pleomorphic neoplastic cells involving the skin and peripheral blood with rapid progression leading to death in 3 months. These clinicopathologic features were highly suggestive of ATLL, but DNA study (Data not shown) using polymerase chain reaction and Southern blot technology failed to demonstrate viral DNA in the lymph node. Serologic or virologic study for HTLV-I was not performed.

Seventeen cases (68%) in this study presented in extranodal locations. The upper aerodigestive tract was the most frequent site of extranodal presentation and included the nasal cavity 4 cases, tonsil 4 cases, and oral cavity 1 case. Histologically, the cases arising in the nasal cavity were characterized by widespread necrosis which was possibly caused by angiocentricity of tumor cells. Infiltration of eosinophils and plasma cells tended to be more prominent than in T-cell lymphoma arising in other organs. Two cases among them consisted of polymorphic and pleomorphic atypical lymphoid cells admixed with polymorphic inflammatory cells, therefore these two cases fit into the histology of polymorphic reticulosis or midline malignant reticulosis.

The term polymorphic reticulosis is a descriptive morphologic term coined by Eichel et al (1966) who suggested that this lesion is closely related with the locally aggressive and potentially lethal lymphoreticular neoplastic process. After being described by Eichel, polymorphic reticulosis has been considered a separate entity from malignant lymphoma because of its histologic polymorphism and favorable response to radiotherapy. Since the morphologic features of PTCL have recently become familiar to pathologists, polymorphic reticulosis has been considered to be a variant of peripheral T-cell lymphoma having abundant inflammatory elements such as macrophages, plasma cells and occasional eosinophils (Harrison, 1987). Immunophenotypic studies confirm the T-cell nature of the infiltrated cells (Ishii et al., 1982, Chan et al., 1987, Lipford et al., 1988). This lesion and monomorphic nasal T-cell lymphoma have been closely linked to each other and are considered as a spectrum of a single disease entity (Chan et al., 1987, Harrison, 1987).

Information on the immunophenotype of Waldeyer's ring lymphoma is rather sparse in the literature. A few investigators have reported that the majority of Waldeyer's ring lymphomas were B-cell type, whereas nasal lymphomas were mostly T-cell type (Ishii et al., 1982, Yamanaka et al., 1985). This predominance of B-cell lymphoma in Waldeyer's ring was ascribed to the fact that the tonsils of Waldeyer's ring were a B-cell dominant organ (Yamanaka et al., 1983, Yanamaka et al., 1983). In our series, the 5 cases of tonsillar and oropharyngeal lymphoma were all T-cell type and they represented all the cases occurring in this site during the last 2 years in our hospital.

The four cases presenting in the skin concomitantly involved other organs including the nasal cavity, oropharynx, liver, and spleen. None of the cases involving the skin showed epidermotrophism of tumor cells. When adult T-cell leukemia/lymphoma and PTCL involving the skin show epidermotrophism, it may be difficult to differentiate from MF. Clinical as well as pathologic features may be necessary to distinguish these entities (Matthews, 1985).

Histologically, the tumors presented here displayed a wide variety of histologic patterns. Common histologic features included a spectrum of cell size, irregular nuclear contours, frequent admixture of eosinophils or plasma cells, and abundant venules with prominent endothelial cells. On the basis of the histologic features generally known as those of PTCL, 14 cases could be recognized as a T-cell lymphoma. This immunophenotypic predictability of a histologic features was consistent with that of other series (Weiss et al., 1985). Although the majority of T-cell lymphomas can be recognized by histologic features, the diagnosis of PTCL without surface marker study should be avoided because of phenotypic unpredictability as demon-

strated in 28% of the present cases.

By WF, 11 cases (44%) were diagnosed as large cell, immunoblastic type, 8 cases (32%) as diffuse, large cell type, and 5 cases (20%) as diffuse, mixed, small and large cell type. We had only one case of small cell type, therefore our incidence of this type was lower than that in other series (Weiss et al., 1985, Coiffier et al., 1988, Armitage et al., 1989).

Classification by WF was straightforward in most cases of large cell, immunoblastic type. However, with some cases of small cell, large cell and mixed type, there were problems fitting the morphology seen into a WF category. The reason for this difficulty appears to be due to the presence of intermediate sized cells which do not fit into the WF size criteria and disparity between nuclear size and chromatin pattern. For example, one case classified as large cell type, actually consisted of relatively uniform medium tumor cells with vesicular chromatin pattern which did not fit into any other cell type, therefore it was classified as large cell type.

The new classification proposed by the Japanese-European group (Suchi et al., 1987) appeared to resolve the problems of WF classification and included recently recognized subgroups such as the large cell, anaplastic, Ki-1 lymphoma and angioimmunoblastic T-cell lymphoma. Although the Japanese-European group tried to make the clinicopathologic correlations for each subtype, there were not a sufficient number of cases for proper evaluation (Suchi et al, 1987). We hope that the establishment of world wide immunologic and clinicopathologic classification for PTCL will be made in the near future.

Immunophenotypically, most PTCL had been reported as a T-helper phenotype. In many instances, the surface phenotype was aberrant when assayed with a combination of antibodies (Cossman, 1987). In our series, aberrant phenotypes were noted in 8 cases (32%). On the relation of immunophenotype with clinical behavior, cases with the normal phenotype of peripheral T-cell showed an even distribution from stage I to Stage IV. But most cases showing aberrant immunophenotypes were in an advanced stage at the time of diagnosis. The meaning of this finding cannot be explained at this time. Dedifferentiated tumor cells lacking normal phenotype might be more aggressive biologically.

In summary, we have presented the clinicopathologic features of 25 PTCL cases in Korea. They displayed diverse morphologic features and heterogenous clinical presentations. Because of the inadequacies of the WF system of classification of PTCL, a new world wide classification should be established.

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