J Korean Med Sci 1998; 13: 31-8
ISSN 1011-8934

Pathologic Characteristics of Primary Cutaneous T-cell Lymphoma in Korea

Cutaneous T-cell lymphomas (CTCL) represent a heterogeneous group of peripheral T-cell lymphomas arising in the skin and show considerable variations in clinicopathological features. This study was designed to examine viral genomes and cellular proliferation markers in CTCLs arising in Korea. On the basis of their morphologic characteristics and immunophenotypes, 43 cases of primary CTCL were classified, and evaluated for association with either HTLV-I or EBV, p53 protein immunoreactivity and Ki-67 labeling index (LI). EBV was demonstrated in 15 cases (35%) either by EBER *in-situ* hybridization or PCR; particularly high rates were exhibited by angiocentric T-cell lymphomas. PCR was used to detect HTLV-I proviral DNA, but none was found. The p53 expression rate was higher in large cell lesions, but the Ki-67 LI failed to show any significant differences among the different types. We therefore concluded that in Korea, HTLV-I is less frequently associated with CTCL than in other endemic countries. EBV was found particularly in angiocentric lesions, regardless of cell size or degree of pleomorphism. Because of its high positive rates in high grade lesions, the p53 expression showed positive correlation with histologic grade; however, the Ki-67 labeling index did not correlate with the histologic grade in CTCL.

Key Words : *Cutaneous T-cell lymphoma, HTLV-1, EBV, p53, Ki-67*

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Received : June 7, 1997
Accepted : September 8, 1997

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* This study was partly supported by grants from Seoul National University Hospital (4-93-31).

INTRODUCTION

Cutaneous T cell lymphoma (CTCL) is a monoclonal proliferation of peripheral T lymphocytes with homing receptors for the skin. In classical CTCL, the characteristic course of the disease is that it is at first localized, and this stage is of long duration; late systemic progression follows (1). Other peripheral T cell lymphomas (PTCLs) show early systemic involvement and rapid progression (2). Several types of CTCLs with remarkable variability in clinical and histopathological features have recently been characterized; these are distinguished from classical CTCLs by the presence of mycosis fungoides/Sezary syndrome (3), and the CTCLs are now regarded as a group of distinct disease entities, differentiated according to tissue or site specificity. It has been suggested that in some CTCL cases, human T-cell lymphotropic virus type I (HTLV-I) and Epstein-Barr virus (EBV) are related to tumor progression and are etiologic agents (4-7). In Korea, the incidence of HTLV-I related disease, including adult T cell leukemia/lymphoma (ATL), is extremely low in the general population (8). However, in view of the fact that in neighboring countries such as Japan and Taiwan, HTLV-I associated ATL is endemic (9), we would have expected that more cases of HTLV-1-related disease would be detected by sensitive molecular pathological study, i.e. by polymerase chain reaction at tissue level. In view of the higher prevalence of PTCL in Asia than in Western countries, EBV which has also been associated with various lymphomas (10-12) including PTCL, attracted our attention. Among the numerous factors associated with the prognosis and biologic behavior of malignant lymphoma, p53 overexpression and cell proliferation are known to be reliable markers (13). In this study we classified the primary CTCL into six subtypes, according to its morphologic characteristics, and using polymerase chain reaction analysed the association of HTLV-I and EBV; using the Ki-67 labeling index, we assessed p53 immunoreactivity and cell proliferation rate in each subtype.

MATERIALS AND METHODS

Clinicopathologic analysis

Tissue samples from 43 cases that had been diagnosed as primary cutaneous T-cell lymphomas on the basis of both histologic and immunologic features were selected from the Department of Pathology, Seoul National University Hospital. Thirty were males and 13 were females, and their ages ranged from six to 80 (mean 42) years. Histologic classification was based on the proposals contained in the Revised American-European Classification of Lymphoma (REAL) (14). Formalin fixed and paraffin embedded tissue sections were stained by hematoxylin-eosin. Immunophenotype was determined by immunohistochemical staining using the standard peroxidase labeled avidin-biotin method. Antibodies included were mouse monoclonal anti-human anti-CD20 (L26, Dako), CD45RO (UCHL-1, Dako) and CD30 (BerH2, Dako).

Detection of HTLV-I and EBV

Polymerase chain reaction (PCR)

For DNA extraction, five sections of 10-20 μm-thick paraffin embedded tissue were deparaffinized by repeated treatment with xylene and alcohol. Using a genomic isolation kit (Bio 101, BMS Inc.), the following processes were performed: one to three micrograms of DNA were subjected to 35 cycles of PCR amplification; four pairs of primers complementary to the plus and minus strands of target DNA were used for the detection of HTLV-I proviral DNA in the *gag*, *pol*, and *env* genes which encode structural proteins of HTLV-I, and in *tax*, a unique gene which participates in cellular transformation and cytokine activation. Fifty μl of PCR mixture consisted of 20-30 ng of template DNA, 50 pmol of each primer, 200 μM each of dNTPs, standard reaction buffer containing 1.5 mM $MgCl_2$, and 2.0 units of Taq polymerase. HTLV-1 specific primer sequences were listed as follows. *gag*: 5'>CTGCAGTACCTTTGCTCCTCCCTC<3' (forward primer) / 5'>TTCTACGAAGGCGTGGTAAG<3' (reverse-primer); *pol*: 5'>GTACTTTACTGACAAACCCGACCTAC<3' (forward primer) / 5'>TCATGAACCCCAGTGGTAA<3' (reverse-primer); *env*: 5'>CCCCAGCTGCTGTACTCTCACAA<3' (forward primer) / 5'>TGGGCACTTTAAGGAACAAG<3' (reverse-primer); *tax*: 5'>CGGATACCCAGTCTACGTGT<3' (forward primer) / 5'>GAGCCGATAACGCGTCCATCG<3' (reverse primer). Repeated denaturation, renaturation, and elongation of the primers provided an exponential increase of copies of the region flanked by these primers. The amplified products were electrophoresed on 2% agarose gel. The DNA used for positive control was obtained from a cell line immortalized by HTLV-I and lymph node tissue of ATL patients.

The same procedure and techniques were applied for EBV. Corresponding EBNA-1 primer sequences were 5'>TGATAACCATGGACGAGGAC<3' (forward primer) / 5'>GCAGCCAATGCAACTTGGAC<3' (reverse primer). B 95-8, the cell line immortalized by EBV, was used as a positive control.

In-situ hybridization of Epstein-Barr virus encoded RNA (EBER-ISH)

In-situ hybridization was carried out on 5-μm paraffin sections using fluorescein-conjugated oligonucleotide probes for EBER 1 and 2 (Dako). After deparaffinization and rehydration, the tissues were treated with proteinase K for 30 minutes, and hybridized with the EBER probes for 2 hours. Detection was carried out using alkaline phosphatase-conjugated rabbit anti-FITC and chromogenic substrate (BCIP/NBT). Positive control tissue was obtained from the lymph nodes of EBV-proven Hodgkin's disease patients. Reactive lymph nodes were selected for negative control.

Immunohistochemical staining (IHC)

Immunohistochemical staining for p53 and Ki-67 was performed on 5-μm-thick formalin-fixed, paraffin-embedded sections. The primary antibodies used were anti-human mouse monoclonal antibodies, DO7 (Novocastra) and MIB-1 (Immunotech), both at a dilution of 1:100. Incubation was performed overnight at 4℃, and the following procedure was performed using LSAB-DAB kit (Dako). Meyer's hematoxylin was used as a count staining.

The above data were analyzed using Fischer's extraction test and the Wilcoxon two-sample test.

RESULTS

Clinicopathologic analysis

Patient profiles were summarized in Table 1. The total number of cases was 43, and the mean age was 45 years.

Ki-1 positive anaplastic large cell lymphoma (AL)

Large cells with highly pleomorphic nuclei and prominent nucleoli infiltrated the dermis and subcutis. Giant cells were occasionally found (Fig. 1). Immunostaining for CD30 revealed diffuse positivity in the membrane of most tumor cells. In one case (No. 3, Table 1), cellular pleomorphism was not conspicuous but anti-CD30 im-

Table 1. Summary of profiles of 43 cutaneous T cell lymphoma patients

Case	Sex	Age (yr)	Histologic type	HTLV-I	EBV	p53 expression (%)	Ki-67 positivity (%)
1	F	25	AL	−	−	73	60
2	F	32	AL	−	−	63	50
3	M	16	AL	−	−	15	15
4	M	34	AL	−	−	37	11
5	M	70	AL	−	+	16	11
6	M	49	AL	−	+	41	39
7	M	25	AC-M	−	−	18	8
8	F	35	AC-M	−	+	37	28
9	M	41	AC-M	−	−	45	15
10	F	29	AC-M	−	+	68	15
11	F	42	AC-M	−	+	72	15
12	M	62	AC-M	−	−	40	20
13	F	38	AC-M	−	−	NC	NC
14	M	47	AC-M	−	+	NC	NC
15	M	17	AC-M	−	−	NC	NC
16	M	24	AC-M	−	+*	NC	NC
17	M	40	AC-L	−	−	45	47
18	M	69	AC-L	−	−	15	20
19	M	29	AC-L	−	−	NC	NC
20	M	38	AC-L	−	−	NC	NC
21	F	6	AC-L	−	+	NC	NC
22	M	43	AC-L	−	+	NC	NC
23	M	42	AC-L	−	+	NC	NC
24	M	64	AC-L	−	+	NC	NC
25	F	19	AC-L	−	+	NC	NC
26	M	57	AC-L	−	−	NC	NC
27	F	21	AC-L	−	−	NC	NC
28	F	22	MF	−	−	3	3
29	M	52	MF	−	−	10	5
30	M	64	MF	−	−	10	0.9
31	M	30	PTCL-LC	−	−	75	8.2
32	M	36	PTCL-LC	−	−	68	37
33	M	62	PTCL-LC	−	−	65	8.5
34	M	54	PTCL-LC	−	−	45	20
35	M	80	PTCL-LC	−	+*	47	4.8
36	F	71	PTCL-LC	−	+	80	14
37	F	71	PTCL-LC	−	−	18	35
38	M	34	PTCL-MSC	−	−	1	49
39	M	22	PTCL-MSC	−	−	10	9.3
40	M	48	PTCL-MSC	−	−	10	30
41	M	31	PTCL-MSC	−	−	45	59
42	F	43	PTCL-MSC	−	−	10	9.2
43	F	64	PTCL-MSC	−	+	47	40

AL, anaplastic Ki-1 positive large cell lymphoma; AC-M, angiocentric T-cell lymphoma with more atypism; AC-L, angiocentric T-cell lymphoma with less atypism; MF, mycosis fungoides; PTCL-LC, peripheral T-cell lymphoma, large cells; PTCL-MSC, peripheral T-cell lymphoma, medium to small cells; NC, not checked; *, confirmed by PCR

munoreactivity was diffuse and strong.

Six cases were included and mean age was 38 years.

Angiocentric T cell lymphoma (extranasal T/NK cell lymphoma): more atypia (AC-M)

Highly pleomorphic lymphocytes infiltrated and destroyed the vessel wall, and ischemic necrosis of surrounding tissue occurred. Karyorrhectic debris was frequently found adjacent to tumor cells (Fig. 2).

Ten cases were included and mean age was 39 years.

Angiocentric T-cell lymphoma (extranasal T/NK cell lymphoma): less atypia (AC-L)

Angiocentricity was present, but neoplastic cells were not conspicuously atypical and most tumor cells were small.

Eleven cases were included and mean age was 35 years.

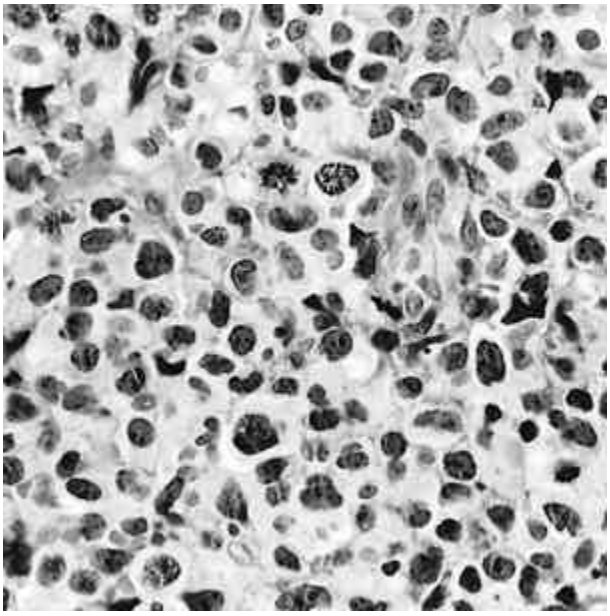

Fig. 1. Ki-1 positive anaplastic large cell lymphoma. Diffuse infiltration of large cells with abundant cytoplasm and oval or horse-shaped nuclei. Occasional multinucleated cells are present.

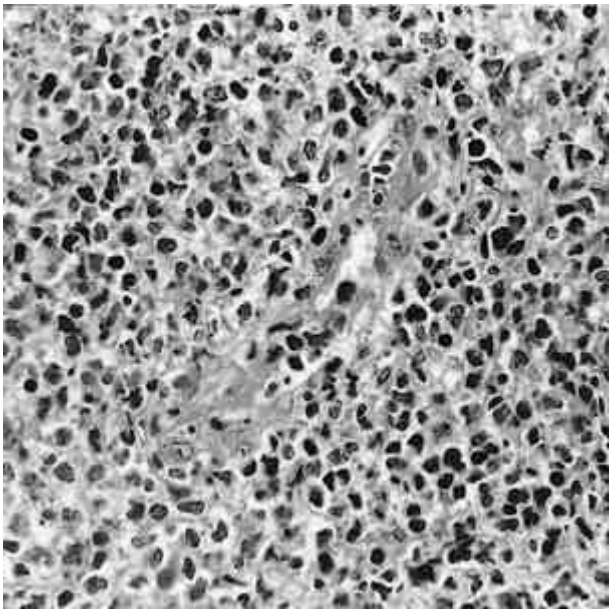

Fig. 2. Angiocentric T-cell lymphoma. Large atypical cells infiltrates the vessel wall.

Mycosis fungoides (MF)

Small atypical cells with cerebriform nuclei linearly infiltrated the epidermis, particularly in the basal cell layer. Pautrier's microabscesses were also identified (Fig. 3).

Three cases were included and mean age was 46 years.

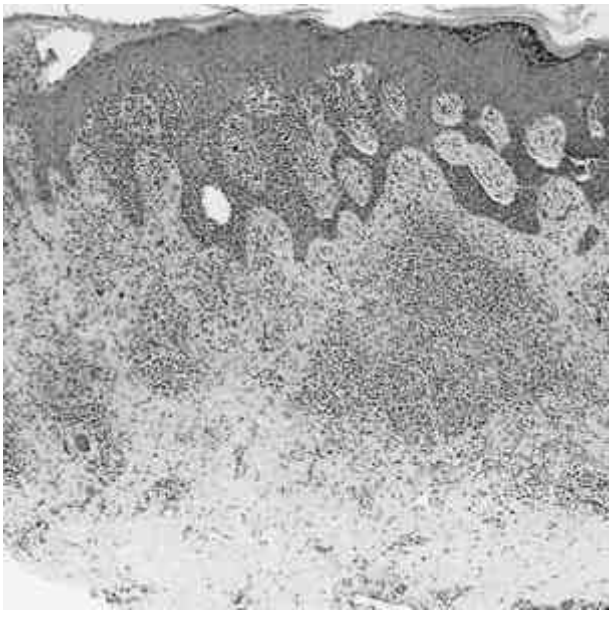

Fig. 3. Mycosis fungoides. Epidermotropism and Pautrier's microabscess are characteristic.

Peripheral T-cell lymphoma, unspecified large cells (PTCL-LC)

Large cells with occasional prominent nucleoli infiltrated diffusely. Immunostaining for CD30 was negative or only focally positive.

Seven cases were included and mean was 58 years.

Peripheral T-cell lymphoma, unspecified medium to small cells (PTCL-MSC)

Aggregations of CD30 negative, small-to-medium-sized pleomorphic atypical lymphoid cells, without any specific histologic features were found.

Six cases were included and mean age was 40 years.

Detection of HTLV-I

There were no clinically suspected cases of adult T-cell lymphoma / leukemia. In seven cases, highly bizzare pleomorphic nuclei were found but the characteristic "clover leaf" feature or embryo shape was not seen. Among the 43 cases of CTCL, HTLV-I genome was not detected, despite repeated tests.

Detection of EBV

EBER-ISH was performed to detect EBV; dark granular perinucleolar staining was interpreted as a positive signal (Fig. 4). In EBER ISH-negative or equivocal cases, EBV-PCR for EBNA-1 was performed; in five cases in

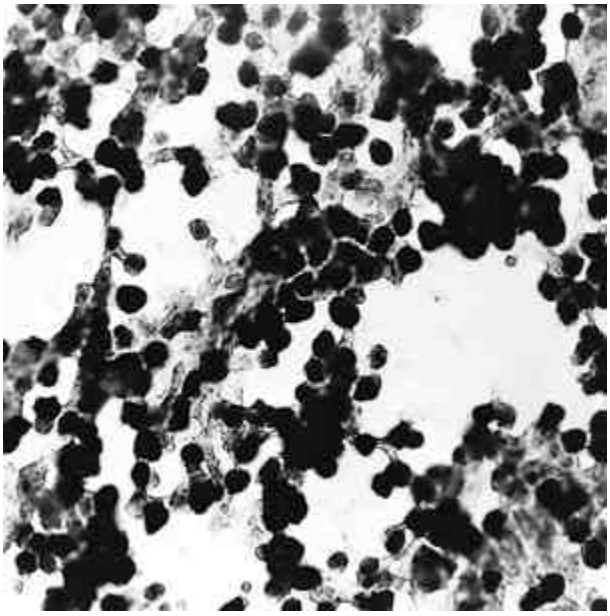

Fig. 4. Epstein-Barr virus encoded RNA (EBER) *in-situ* hybridization. Numerous EBER positive cells showing dense or granular nuclear staining are present.

which EBER-ISH showed diffuse cytoplasmic or interstitial staining, PCR was used to test for the presence of EBV; two were positive (No 16, 31. Table 1) and three were negative. Findings for EBV positivity were as follows: AL, two (33%); AC-M, five (42%); AC-L, five (56%); PTCL-LC, two (29%); and PTCL-MSC, one (17 %) (Table 2). EBV integration in MF was not found. The highest positivity was noted in the angiocentric type (AC-M and AC-L) ($p=0.055$) (Table 3).

Table 2. EBV positivity, p53 expression and Ki-67 LI according to histologic type

Type	No. of cases	EBV / (%)	p53 (mean, %)	Ki-67 (mean, %)
AL	6	2 / (33)	40.8	32.3
AC-M	10	5 / (50)	30.0	16.8
AC-L	11	5 / (45)	30.0	33.5
MF	3	0 / (0)	7.6	3.0
PTCL-LC	7	2 / (29)	56.9	18.2
PTCL-MSC	6	1 / (17)	20.5	32.8
Total	43	15 / (35)	37.6	23.2

LI, labeling index; AL, anaplastic large cell lymphoma; AC-M, angiocentric T-cell lymphoma with more atypia; AC-L, angiocentric T-cell lymphoma with less atypia; MF, mycosis fungoides; PTCL-LC, peripheral T-cell lymphoma, large cells; PTCL-MSC, peripheral T-cell lymphoma, medium to small cells

Immunohistochemical results

IHC staining for p53 and Ki-67 was carried out in 30 CTCL cases. p53 positivity was considered when obvious nuclear staining was present, and calculated as a percentage. When tumors were divided into two groups, large cell (AL and PTCL-LC) and non-large cell (the four other subtypes), p53 positivity was significantly higher in the former ($p<0.05$) (Table 2) (Fig. 5). The mean percentage of p53 positivity was 40.8 in AL, and

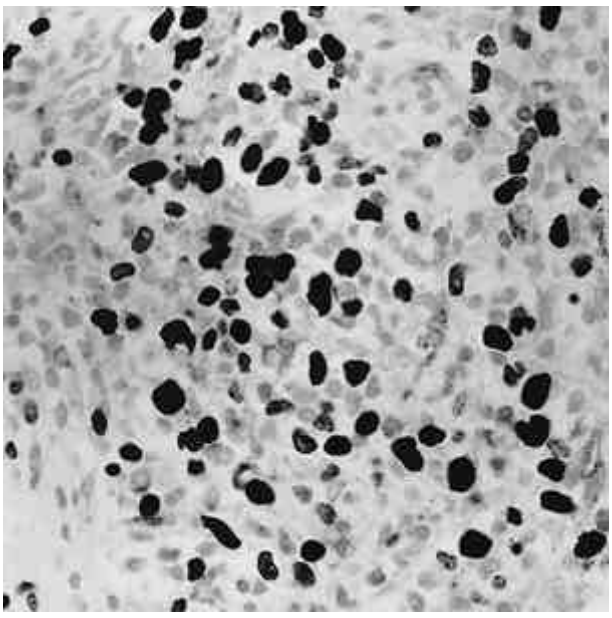

Fig. 5. P53 immunostaining reveals nuclear positivity in large tumor cells.

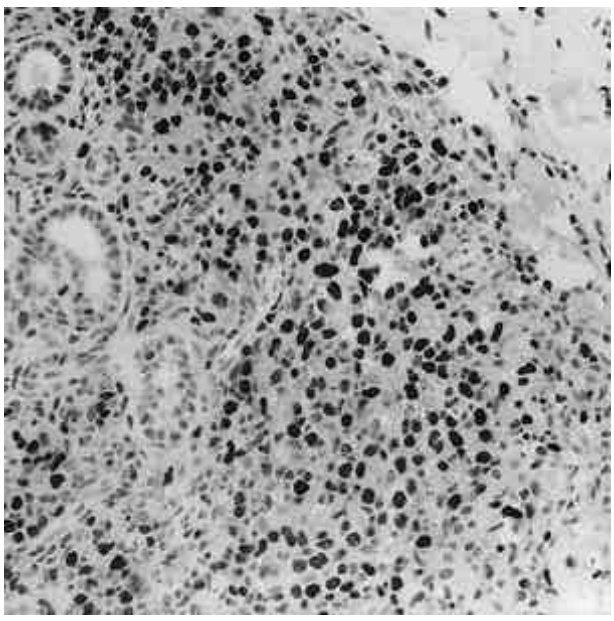

Fig. 6. Ki-67 immunoreactivity is seen in both the large and small cells.

56.9 in PTCL-LC. In the non-large cell group, angiocentric lesions (AC-M) showed the highest p53 positivity (mean 30.0), and this was statistically significant differences ($p<0.05$) (Table 2).

On Ki-67 immunostaining, a higher nuclear intensity than of basal cells of normal epidermis or adjacent reactive lymphocytes was interpreted as positive (Fig. 6). The mean Ki-67 labeling index (LI) of each subtype was as follows: AL, 32.3; AC-M, 16.8; AC-L, 33.5; MF, 3.0; PTCL-LC, 18.2; and PTCL-MSC, 32.8. On the basis of either cell size or angiocentricity, there were no significant differences between the groups (Table 2). The lowest Ki-67 LI was seen in MF; because of small sample size (three cases), this was not statistically significant.

DISCUSSION

Primary CTCL is a distinct disease entity, quite different in its clinicopathologic properties from other PTCLs (15). It has been postulated that in lymphomagenesis, there is organ or site specificity (16). In anaplastic large cell lymphoma, for example, primary cutaneous cases tend to progress slowly, with long survival, whereas nodal cases are usually fatal and progress rapidly. Moreover in cases of other PTCLs, in which skin involvement is secondary, the morphologic features of skin lesions may be rather different from those seen in primary lesions (17).

The classification of primary CTCL has not been firmly established, and various systems exist. Categorization is usually based on histopathologic, immunophenotypic and etiologic characteristics including adult T-cell lymphoma / leukemia, mycosis fungoides / Sezary syndrome, and angiocentric lymphoproliferative disorders, including angiocentric T-cell lymphoma and large cell lymphoma. Our classification emphasizes cell size, CD30 expression, and angiocentricity. Large cell lesions were subdivided into two types, Ki-1-positive and Ki-1-negative. When angiocentricity was seen, cases with distinct cellular pleomorphism were diagnosed as angiocentric lymphoma with more atypia, and the remaining cases as angiocentric lymphoma with less atypia. In general, large cell lesions and angiocentric T-cell lymphoma are considered as high grade lesions (2) but some cases of CD30-positive cutaneous T-cell lymphomas often spontaneously regress (18).

Several oncogenic viruses, including HTLV-I, are believed to be etiologically related to CTCL. In 1981, Poiesz isolated this retrovirus from a patient with rapidly progressive CTCL, and this case was later shown to be an adult T-cell lymphoma (ATL; this entity was described by Takatsuki in 1982). The lymphocytes in an ATL patient's peripheral blood and T-cells immortalized by HTLV-I in vitro show distinct cytological characteristics such as increased cell size, multilobated nuclei, and nuclear pleomorphism (19), and such cells are often known as 'clover leaf cells'. Thus it is essential to investigate HTLV-I in CTCLs displaying such morphologic features. In areas where HTLV-I and ATL are non-endemic, several HTLV-I related CTCLs have been sporadically reported (4, 20), but in most, proviral genomes were defective; in areas where ATL is endemic, proviral genomic integration was found, and this was usually intact. The mechanism of viral lymphomagenesis in ATL and in other non-endemic CTCLs may thus be different (21). Most HTLV-I associated CTCLs are large-cell lesions, with a high incidence of CD 30-positive anaplastic large cell lymphomas, this corresponds to the finding that HTLV-I strongly induces CD 30 antigen in vitro (22). Although HTLV-I antibody positivity in Korea is 0.25% (8), an extremely low rate when compared with Taiwan and Japan, where HTLV-I is endemic, a relatively high proportion of T-cell lymphoma and large cell lesion cases in Korea show a pattern which is analogous to that seen in Japan. However, no primary CTCLs, including six ALs and seven PTCL-LCs, revealed HTLV-I integration; 17 nodal T-cell large-cell lymphomas also showed the same negative result. In this study, four kinds of different primers were used for the detection of defective proviral genomes, so it can be concluded that in Korea, there is little or no association between HTLV-I and CTCL. There have so far been five HTLV-I associated diseases in Korea, comprising four ATLs and one case of HTLV-I-associated myelopathy (23, 24, 33); this latter was a man whose wife was a Korean resident in Japan. It is interesting that ATL-and HTLV-I-related diseases are so rare in Korea despite geographic and cultural proximity to Japan and Taiwan. The supposed pathway of HTLV-I spread is as follows: the virus was transmitted from Africa to Europe via the slave trade, and then to Japan (25); HTLV-I endemicity in Taiwan is presumed to have arisen through frequent cultural exchange with the island of Okinawa, Japan (9). Although the definitive cause of these different endemic patterns has not been verified, genetic differences in susceptibility might contribute; as in the above case of HTLV-I associated myelopathy, who was infected from his healthy carrier wife, Koreans are also susceptible.

In CTCL cases, average EBV-positivity was 35%. In Huh's 1994 study (unpublished data), EBV positivity in nodal T-cell lymphoma was 52%, and in extranodal T-cell lymphoma in Korea it was 63%. Other studies carried out in Western countries have also shown relatively lower EBV positivity in the skin than in the nose and other organs (5, 11). It has been postulated that a more favorable prognosis in CTCL than in nasal cavity

lesions is due to different rates of EBV association (10, 11). Angiocentric lesions are known to be closely related to EBV (12), and this was borne out in our study (Table 2). In general, AC-M exhibits higher EBV positivity than AC-L, and EBER-positive neoplastic cells were also more numerous in AC-M than in AC-L. There is controversy as to whether these two subtypes are separate entities showing only histological resemblance, or are closely related lesions included in the same spectrum; they were previously known as high-grade angiocentric immunoproliferative lesion (AIL) and low-grade AIL, respectively (26). Low grade AIL eventually progresses to systemic lymphoma and in the course of time, tumor cell atypia increases, and the AIL becomes high grade; EBV may be a contributory factor (26). Another lesion likely to be a clue to the interpretation of the relationship between EBV and CTCL has been, in addition, recently described (27). These cases are characterized by necrotizing papulovesicles on the face, marked by long periods of repeated regression and relapse, which eventually progress to CTCL and systemic T-cell lymphoma. In earlier lesions, the most striking pathologic feature is necrosis and inflammation, and EBVs are demonstrated in a small number of tumor cells, but in time, the number of EBV positive cells increases, and tumor cells show marked pleomorphism. This result suggests that EBV participates in the development or progression of CTCLs.

No morphologic features distinguished EBV infected cases from those that were EBV-negative. Our results also showed that EBV infection is not related to cell size or morphology. EBV may not alter cell morphology in the way that HTLV-I does (11); in the AL type, however, EBV was demonstrated in only two of six cases (33%), in which the patients' ages were 49 and 70 years, respectively; the mean age of the remaining patients, with whom the virus was not associated, was 26.8 years. In AL-type CTCL, EBV association may increase with age, though further investigation is needed.

The wild type p53 gene acts as a tumor suppressor gene by fixing transformed cells at the G1 phase and inducing apoptosis (28). Many different types of tumor showing mutation of this gene, including malignant lymphoma, have been identified. Mutant p53 combines with a portion of wild p53 to form an inactive complex, or interferes with the normal function of protein by acquiring a novel function (29). It is impossible to distinguish normal and mutant p53 by immunohistochemistry, yet this method is commonly used as an indication of p53 mutation; differentiation is based on the fact that the half-life of mutant p53 is much extended when it combines with cytoplasmic heat shock protein while that of normal p53 is about 15 minutes (30). In addition, many reports have verified that the IHC correlates with the molecular biologic result of p53 mutation.

It has been demonstrated that in high grade lymphomas, p53 expression is higher than in low grade lesions (29); in our study p53 expression was higher in large cell lesions, i.e., in AL and PTCL-LC. Although there are some exceptional cases, large-cell lesions are usually regarded as high grade, and our results correspond to those of previous studies. In the non-large cell group, AC-M showed higher positivity than AC-L; this finding supports the above suggestion but was not statistically significant. Among large-cell lesions, AL showed slightly lower p53 positivity than PTCL-LC, which is in accordance with the fact that CD 30 antigen expression suggests a favorable prognosis (18). Overall, p53 expression was related to histologic grade and can be used as a prognostic factor.

Cell proliferation activity represents malignant potential in many kinds of neoplasm. In high grade non-Hodgkin's lymphoma it can be used as a prognostic factor as well as a diagnostic tool (21). Anti-Ki-67 is the prototypic antibody which can detect nuclear protein expressed in the G1, S, G2 and M phases of the cell cycle. MIB-1 is an anti-Ki-67 antibody that can be used in paraffin embedded tissue. It is quite sensitive and shows rather selective staining in proliferating cells with no significant background staining (31). In general the Ki-67 labeling index (Ki-67 LI) is higher in diffuse type, T-cell lineage and high grade lymphomas than in follicular lymphoma, B-cell type and low or intermediate grade lymphomas, which suggests that high Ki-67 LI indicates high grade lymphoma (32). Moreover one study showed that in case of non-Hodgkin's lymphoma showing Ki-67 LI more than 80% the prognosis was extremely poor (13). In our study, however, the Ki-67 LI did not vary significantly according to histologic type, grade, or p53 immunoreactivity. It is likely that primary CTCLs are generally lower grade lesions than those of nodal lymphomas; the Ki-67 LI, which is useful in discriminating high grade lesions showed no significant differences between CTCLs. MF, however, showed the lowest Ki-67 LI. Although it was not stastitically significant, the low Ki-67 LI reflected the indolent clinical behavior of MF.

REFERENCES

1. Su IJ, Wu YC, Chen YC, Hsieh HC, Cheng AL, Wang CH, Kadin ME. *Cutaneous manifestation of post-thymic T cell malignancies: Description of five clinicopathologic subtypes. J Am Acad Dermatol 1990; 23: 653-62.*
2. Kurtin PJ, DiCaudo DJ, Habermann TM, Chen MG, Su WP. *Primary cutaneous large cell lymphomas: Morphologic, immu-*

nophenotypic, and clinical features of 20 cases. Am J Surg Pathol 1994; 18: 1183-91.

3. Willemze R, Beljaards RC, Meijer CJLM. *Classification of primary cutaneous T-cell lymphomas. Histopathology 1994; 24: 405-15.*
4. Kaplan M. *Human retrovirus and neoplastic disease. Clinical Infectious Disease 1993; 17(Supple 2): S400-6.*
5. Peris K, Niedermeyer H, Cerron L, Radaskiewiez T, Chimenti S, Hofler H. *Detection of Epstein-Barr virus genome in primary cutaneous T and B cell lymphomas and pseudolymphomas. Arch Dermatol Res 1994; 286: 364-8.*
6. Lessin RS, Vowels BR, Rook AH. *Retrovirus and cutaneous T-cell lymphoma. Dermatologic Clinics 1994; 12: 243-53.*
7. Hall PA, Richards MA, Gregory J, Stein H, Masom DY. *The prognostic value of Ki 67 immunostaining in non-Hodgkin's lymphoma. J Pathol 1988; 154: 223-35.*
8. Lee YY, Lee HB, Seo CW, Kye KC, Kim ES, Park SY, Kim BK, Choe KW, Kim NK, Lee MH. *Seroepidemiology of human T-cell leukemia virus type-I in the Republic of Korea. Korean J Int Med 1986; 31: 141-7.*
9. Pan IH, Chung CS, Komoda H, Imai J, Hinnma Y. *Seroepidemiology of adult T-cell leukemia virus in Taiwan, Jpn J Cancer Res(Gann) 1985; 76: 9-14.*
10. Tsai TF, Su IJ, Lu YC, Cheng AL, Yeh HP, Hsieh HC, Tien HF, Chen JS, Uen WC. *Cutaneous angiocentric T-cell lymphoma associated with Epstein-Barr virus. J Am Acad Dermatol 1992; 26: 31-8.*
11. de Bruin PC, Jiwa M, Oudejans JJ, van der Valk P, van Heerde P, Sabourin JC, Csanaky G, Noorduyn AL, Willemze R, Meijer CJ. *Presence of Epstein-Barr virus in extranodal T-cell lymphomas: Differences in relation to site. Blood 1994; 83: 1612-8.*
12. Ohshima K, Takeo H, Kikuchi M, Kozuru M, Uike N. *Heterogeneity of Epstein-Barr virus infection in angioimmunoblastic lymphadenopathy type T cell lymphoma. Histopathology 1994; 25: 569-79.*
13. Miller TP, Grogan TM, Dahlberg S, Spier CM, Braziel RM, Banks PM, Foucar K. *Prognostic significance of the Ki-67 associated proliferative antigen in aggressive non-Hodgkin's lymphomas: a prospective Southwest Oncology Group trial. Blood 1994; 83: 1460-6.*
14. Chan JK, Banks PM, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC. *A proposal for the classification of lymphoid neoplasms (by the International lymphoma study group). Histopathology 1994; 25: 517-36.*
15. Edelson RI. *Cutaneous T-cell lymphoma: Mycosis fungoides, Sezary syndrome and other variants. J Am Acad Dermatol 1980; 2: 89-106.*
16. Mielke V, Staib G, Boenhnke HW, Duller B, Sterry W. *Clonal disease in early cutaneous T cell lymphoma. Dermatologic Clinics 1994; 12: 351-60*
17. Cerroni L, Rieger E, Hodl S, Kerl H. *Clinicopathologic and immunologic features associated with transformation of mycosis fungoides to large cell lymphoma. Am J Surg Pathol 1992; 16: 543-52.*
18. Beljaards RC, Meijer CJ, Scheffer E, Toonstra J, van Vloten WA, van der Putte SC, Geerts ML, Willemze R. *Prognostic significance of CD30 (Ki-1/Ber-H2) expression in primary cutaneous large cell lymphoma of T-cell origin: a clinicopathologic and immunohistochemical study in 20 patients. Am J Pathol 1989; 135: 1169-78.*
19. Yoshida M, Seiki K, Yamaguchi K. *Monoclonal integration of human T-cell leukemia provirus in all tumors of adult T-cell leukemia suggests a causative role of human T-cell leukemia virus in the disease. Proc Notl Acad Sci USA 1984; 81: 2534-7.*
20. Whittaker SJ, Rustin YL, Mcgibbon DH, Smith NP. *HTLV-1-associated cutaneous disease: a clincopathological and molecular study of patients from the U.K. Br J Dermatol 1993; 128: 483-92.*
21. Hall WW, Liu CR, Schneewind O, Takahashi H, Kaplan MH, Roupe G, Vahlne A. *Deleted HTLV-I provirus in blood and cutaneous lesions of patients with mycosis fungoides. Science 1991; 253: 317-20.*
22. Anagnostopoulos I, Hummel M, Kaudewitz P, Herbst H, Braun-Falco O, Stein H. *Detection of HTLV-I proviral sequences in CD30 positive large cell cutaneous T-cell lymphomas. Am J Pathol 1990; 137: 1317-22.*
23. Lee SS, Hong SI, Lee DS, Kang YK, Kim CW, Jang JJ. *Adult T-cell leukemia/lymphoma in a Korean: a case report. J Korean Med Sci 1994; 9: 458-65.*
24. Park JH, Lee BI, Chun S, Osame M. *A case of HTLV-I associated myelopathy (HAM) in Korea. Yonsei Med J 1991; 32: 190-4.*
25. Gallo RC. *The human T-cell leukemia/lymphotropic retrovirus (HTLV) family: past, present and future. Cancer Res (suppl) 1985; 45: 4524-8.*
26. Jaffe ES, Lipford EH, Margolick JB, Longo DL, Fanci AS. *Lymphomatoid granulomatosis and angiocentric lymphoma. A spectrum of post-thymic T-cell proliferations. Semin Respir Med 1989; 10: 167-72.*
27. Cho KH, Kim CW, Lee DY, Sohn SJ, Kim DW, Chung JH. *An Epstein-Barr virus associated lymphoproliferative lesion of the skin presenting as recurrent necrotic papulovesicles of the face. Br J Dermatol 1996; 134: 791-6.*
28. Suler MA, Martin DW, Deb S. *Inhibition of viral and cellular promoters by human wild-type p53. J Virol 1992; 62: 4757-62.*
29. Korkolopoulou P, Oates J, Kittas C, Crocker J. *p53, c-myc and proliferating cell nuclear antigen (PCNA) expression in non-Hodgkin's lymphomas. J Clin Pathol 1994; 47: 9-14.*
30. Finaly CA, Hinds PW, Levine AJ. *The p53 protooncogene can act as a supressor of transformation. Cell 1989; 57: 1083-93.*
31. Rose DSC, Maadox PH, Brown DC. *Which proliferation markers for routine immunohistology? A comparison of five antibodies J Clin Pathol 1994; 47: 1010-4.*
32. Tominaga K, Yamaguchi Y, Nozawa Y, Abe M, Wakasa H. *Proliferation in non-Hodgkin's lymphomas as determined by immunohistochemical double staining for Ki-67. Hematol Oncol 1992; 10: 163-9.*
33. Kang MS, Lee JH, Kim YH, Yang MH. *Human T-cell lymphoma / leukemia. A case report. Korean J Pathol 1993; 27(2, supple): A68.*