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Altered p53 Expression in Epstein Barr virus positive T cell Lymphomas

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Recent studies have suggested a probable association between Epstein-Barr virus (EBV) and nasal / nasopharyngeal T cell lymphomas but the role of oncogenes or tumor suppressor genes is poorly understood. We have studied the frequency of p53 expression and its relation to the EBV infection in 33 Korean patients with head and neck (H&N) lymphomas. All cases (23 B cell & 10 T cell) were immunostained for p53 protein using the mAb DO7 (Novocastra) and the avidin biotin peroxidase method. EBER in situ hybridization was performed using a fluorescein conjugated EBV oligonucleotide probe (Dako). Among 33 lymphomas, 16 cases stained positively for p53 protein. P53 expression was frequent both in higher grade lymphomas and in advanced stage. Nine cases were EBER positive. EBER was more commonly found in T cell lymphomas than in B cell lymphomas (70 % vs 8.7 %). EBER positive lymphomas showed a higher frequency of p53 positivity than EBER negative lymphomas (78 % vs 38 %), although the difference was not statistically significant (p=0.095). These findings indicate altered expression of p53 protein occurs in H&N lymphomas, especially in late event lymphoma progression and appears to play a role in the development of EBER positive T cell lymphomas.

Key Words: *p53 immunohistochemisty, EBV in situ, Head & neck lymphoma*

INTRODUCTION

P53 is a tumor suppressor gene, located in the short arm of chromosome 17, which encodes for a nuclear phosphoprotein involved in the negative regulation of cellular growth through control of entry of the cell into the S-phase (Finlay et al., 1989). Mutations of the p53 tumor suppressor gene are the most frequent genetic abnormalities detectable in human tumors. Inactivation of p53 may also occur on the protein level. P53 may be stabilized by an alternative mechanism such as binding to an additional protein, for examples, mdm-2, heat shock protein or viral product (Imamura et al., 1994 ; Prokocimer and Rotter 1994). Wild type p53 was found to form a complex with viral proteins such as SV 40 large T Ag, E1b of

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the adenovirus and EBNA of EBV (Szekely et al., 1993). In the case of the papilloma virus, p53 was thought to be inactivated by the degradation by E6 viral encoded protein (Crook et al., 1992). Several viruses have acquired mechanism for the elimination of wild type p53. This is important in the pathogenesis of virus associated tumor.

Epstein-Barr virus(EBV) is well known to be implicated in the pathogenesis of Burkitt's lymphoma and nasopharyngeal carcinoma. Recently EBV genomes and gene products have been detected in Hodgkin's disease and T cell lymphoma arising in the nose (Arber et al., 1993). However the role of oncogene or tumor suppressor gene in these tumor is poorly understood. Recently, p53 gene mutations have been found both in EBV negative and positive Burkitt's lymphoma cases and cell lines (Farrell et al., 1991). By contrast the p53 gene in EBV positive undifferentiated nasopharygeal carcinoma was the wild type (Spruck et al., 1992). The overexpression of p53 in Hodgkin's disease was heterogenous with no correlation between EBV and p53 (Niedobitek et al., 1993). These results have prompted us to analyse 33 cases of head and neck lymphomas to find a possible correlation between EBV infection and p53 protein expression.

MATERIALS AND METHODS

Formalin fixed, paraffin embedded biopsies from 33 head and neck lymphomas were included in this study. Cases were collected from the surgical pathology files of Kyung Hee, Keimyung and Kyung-Pook National Universities, Schools of Medicine, Korea. Diagnoses were based on analysis of histopathology and immunophenotypic findings of cell surface markers. As a control, 2 cases of Hodgkin's disease, 3 cases of carcinoma and 10 cases of normal or benign inflammatory lesion in the head and neck were also analyzed.

Immunohistochemistry

Sections from formalin fixed paraffin embedded blocks were cut on poly L lysine coated slides. The slides were dewaxed, rehydrated and stained using a standard avidin biotin complex method (Vectastain Elite kit). Sections were briefly incubated for 1 hour at 37℃ with a monoclonal mouse anti p53 antibody (DO7, 1 : 100, Novocastra). The DO7 antibody recognizes both human wild and mutant forms of p53 protein. 5' diaminobenzidine tetrahydrochloride was used as a chromogen. Antibodies used in this study and their commercial sources were as follows : leukocyte common antigen (CD45RB, Dako, diluted 1 : 50), L26 (CD20, Dako, diluted 1 : 50), UCHL-1 (CD45RO, Dako, diluted 1 : 50) and CD68 (Dako, diluted 1 : 50). Selected cases were also stained with cytokeratin and S-100 protein.

In situ hybridization

The EBV encoded RNAs (EBER) in situ hybridization was performed using a fluorescein conjugated EBV oligonucleotides probe (Dako) complementary to the two encoded small non polyadenylated RNAs (EBER-1 and EBER-2). The EBERs are the most heavily transcribed up to 10^7 copies per cell in latently infected cells. Briefly, formalin fixed paraffin embedded tissue sections were placed on poly L lysine coated slides, baked at 37℃, deparaffinized, incubated ethanol and air dried. Sections were digested for 30 minutes with protease K, acetylated with acetic anhydride and triethanolamine, dehydrated and air dried. The sections were hybridized overnight at 42℃ with the fluorescein conjugated probes. After washing in 0.1 % triton X-100, detection was performed with alkaline phophatase conjugated rabbit anti-FITC, followed by development with 5-bromo-4-chloro-3-indolylphosphate (BCIP) and nitroblue tetrazolium (NBT). A black or dark blue color within the nucleus was considered to be a positive reaction. A known EBV positive Hodgkin's disease served as a positive control in each run. Any slides negative for EBER and non neoplastic lesion were used as a negative internal control.

Statistical Analysis

Survival analysis was done by Log-Rank and generalized Wilcoxon tests using the NCSS (Number Cruncher Statistical System) program. In order to compare the frequency of p53 in EBER positive and negative lymphomas we calculated the X^2 test.

RESULTS

A total of 33 non Hodgkin's lymphomas and 2 Hodgkin's disease were examined. P53 protein expression and EBV infection in 33 head and neck lymphomas according to histopathologic classification

Table 1. P53 Expression & EBV Infection in Histologic Subtypes of Lymphoma.

Histology	No. of Case	p53	EBER	Phenotype (B/T)
Low grade				
Lymphoplasmacytic	1	0	1	1/0
AIL, low grade	2	0	0	0/2
AILD Like	1	1	1	0/1
Intermediate grade				
Follicular large	3	3	0	3/0
Diffuse mixed	4	2	1	3/1
Diffuse large	18	7	4	13/5
High grade				
Immunoblastic	2	2	1	1/1
Burkitt's	1	1	1	1/0
Undetermined	1	0	0	1/0
Total	33	16	9	23/10

EBER : EBV encoded RNAs
AIL : Angiocentric immunoproliferative lesion
AILD like : Angioimmunoblastic lymphadenopathy like T cell lymphoma

are shown in Table 1. In 10 cases of respiratory mucosa, skin, and lymph nodes showing histologic features of reactive and inflammatory lesion, neither p53 nor EBER positive cells were present. However, many p53 positive cells were scattered in three cases of carcinomas, apart from EBER. Two cases of Hodgkin's disease were positive for both p53 protein and EBER in Hodgkin's cells and Reed-Sternberg cells.

p53 protein expression

Expression of p53 protein was detected in 16 of 33 cases (48 %) of lymphomas. The p53 positive cells were present in 25 % (1/4), 48 % (12/25) and 100 % (3/3) of low-, intermediate-and high grade lymphomas respectively (Table 2). As the grade increased from low through high, so did the percentage of p53. Histologically, p53 was positive in all 3 follicular large cell lymphomas, 7 of 18 diffuse large cell lymphomas (Fig. 1), 2 of 4 diffuse mixed small and large cell lymphomas and AILD like lymphoma. Immunoblastic

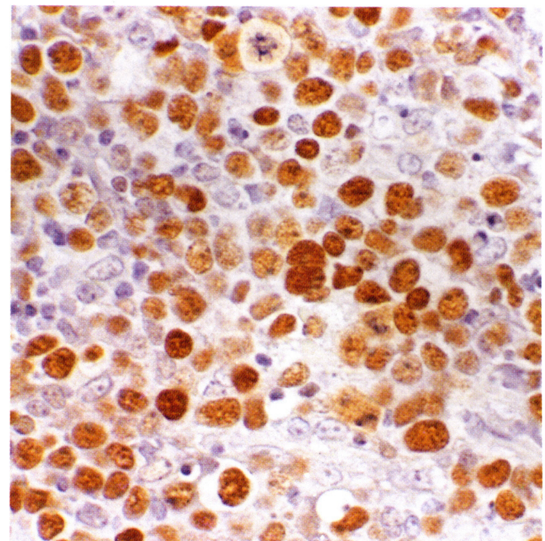

Fig. 1. Immunostaining of p53 in diffuse large B cell lymphoma. Most nuclei of tumor cells are positive.

Table 2. P53 Expression & EBV Infection in Histologic Grade of Lymphoma.

Grade	Number of case	p53(%)	EBER(%)
Low	4	1(25)	2(50)
Intermediate	25	12(48)	5(20)
High	3	3(100)	2(67)
Undetermined	1	0	0

EBER : EBV encoded RNAs

Table 3. Comparison of p53 and EBER.

	p53 positive	p53 negative
B Cell Lymphomas (p=0.846)		
EBER positive	1	1
EBER negative	9	12
T cell Lymphomas (p=0.564)		
EBER positive	6	1
EBER negative	0	3
All Lymphomas (p=0.095)		
EBER positive	7	2
EBER negative	9	15

EBER : EBV encoded RNAs

lymphomas and Burkitt's lymphoma were all p53 positive. Lymphoplasmacytic lymphoma and angiocentric immunoproliferative lesion, low grade were p53 negative. Immunophenotypically, p53 expression was seen in 43 % (10/23) and 60 % (6/10) of B-and T-cell lymphomas (Table 3). One case of B cell lymphoma, undetermined was p53 negative.

Epstein Barr virus infection

EBV infection was detected in 9 cases(27 %). EBER did not show an increase between grades of lymphomas (Table 2). EBER was positive in 50 % (2/4), 20 % (5/25) and 67 % (2/3) of low-, intermediate-and high grade lymphomas, respectively. Histologically, EBER was present in lymphoplasmacytic lymphoma (n=1), 4 of 21 large cell lymphomas (Fig. 2), 1 of 4 diffuse mixed small and large cell lymphomas, 1 of 2 immunoblastic lymphomas and Burkitt's lymphoma (n=1). EBV infections were present in AILD like lymphoma and lymphomas with features of angiocentric immunoproliferative lesion. Immunophenotypically, EBER was found in 2/23 (8.7 %) and 7/10 (70 %) of B-and T-cell lymphomas (Table 3).

Correlation of p53 protein expression with EBV infection

P53 protein was expressed in 7 out of 9 (78 %) EBER positive lymphomas and 9 out of 24 (38 %) EBER negative lymphomas (Table 3). The incidence of p53 expression in EBER positive cases was 2 times higher than in negative ones with a X^2 value of 2.792 (p=0.095). In 15 of 33 cases (45 %), neither p53 nor EBER were expressed, whereas 7 cases (21 %) expressed both p53 protein and EBER. The cases that expressed both p53 and EBER, were phenotypically T cell lineage (6/7). Burkitt's lymphoma was positive both for p53 and EBER.

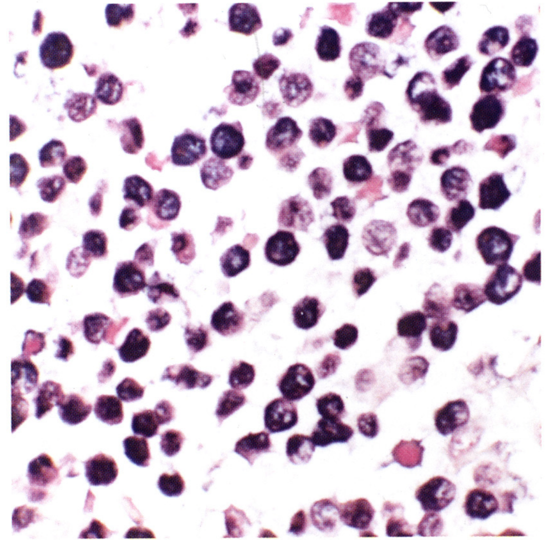

Fig. 2. In situ hybridization of Epstein Barr virus encoded RNAs in T cell lymphoma showed many positive cells.

Clinical features and follow-up

The median age of patients was 45 years (range 6 − 68). Males outnumbered females by 2.4 : 1. The primary biopsy sites were tonsil in 14 cases, lymph node in 9 cases, nose in 5 cases, tongue in 3 cases and oral cavity in 2 cases. Clinical stages of the lymphoma were distributed as follows : stage I in 20 cases, stage II in 10 cases and stage III in 3 cases. P53 protein was found in 45 % (9/20), 50 % (5/10) and 67 % (2/3) of lymphomas in stage I, II & III respectively. EBER showed 30 % (6/20), 20 % (2/10) and 33 % (1/3) of lymphomas in different stages (Table 4). The initial treatment included a combined chemo-and radio-therapy in 16 patients, chemotherapy alone in 8 and a radiotherapy alone in 6 patients.

Table 4. P53 Expression and EBV Infection in Clinical Stage of Lymphoma.

Stage	Number of case	p53(%)	EBER(%)
I	20	9(45)	6(30)
II	10	5(50)	2(20)
III	3	2(67)	1(33)

EBER : EBV encoded RNAs

One patient refused the treatment. There was no information about treatment for two patients. The follow up was available for 31 patients ranging from 1 year to 8 years with 5 years median follow up period. Most patients (18/31, 58 %) had a complete remission after diagnosis. Two patients relapsed after 1 and 4 years after diagnosis, respectively. One patient had a gastric lymphoma 7 years after tonsillar lymphoma. Nine patients died of their disease after a median follow up of 1 year (range 2m—5yrs). One patient died of a cerebrovascular accident 4 years after diagnosis.

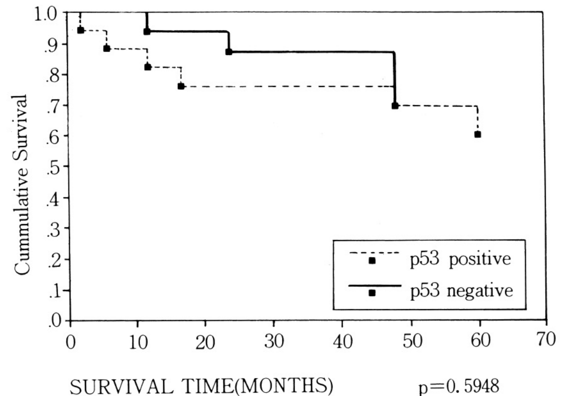

Fig. 3. The survival rate of p53 positive and negative group.

Factors influencing survival

Fig. 3 showed the survival curves of p53 positive or negative groups. Group variables such as p53, immunophenotype, presence of EBER, tumor sites and sex did not significantly affect the survival time. Nonetheless there was a significant difference in survival time among groups defined by clinical stage and treatment ($p<0.05$).

DISCUSSION

Frequent chromosome 17 alterations and p53 mutation strongly suggest their important role in lymphomagenesis and/or disease progression (Yunis et al., 1982 ; Ichikawa et al., 1992). Our study demonstrated p53 protein expression by immunohistochemistry in 48 % (16/33) of lymphomas. This is lower than those reported by Villuendas et al (1992 ; 58 %) and Korkolopoulou et al (1994 ; 61 %) and is higher than those found by Pezzela et al (1993 ; 31 %), Soini et al (1992 ; 31 %) and Said et al.(1992). The p53 positive cells varied according to the grade of malignancy, histologic subtype and whether the lymphomas were B or T cell lineage. The p53 expression was increased from low grade through intermediate- to high- grade lymphomas. Cellular details of p53 positive lymphomas were morphologically, large cell, immunoblasts and small noncleaved cells. The lymphomas in advanced stage showed a relatively higher percentage of p53 than in early stage. Our results are similar to the previous reports suggesting that there is a certain relationship between p53 protein and the aggressiveness of non Hodgkin's lymphomas (Villuendas et al., 1992 ; Korkolopoulous et al., 1994). A difference of p53 expression was also found between B cell and T cell lymphomas (43 % vs 60 %) in our study. T cell lymphomas showed frequent expression of p53. Abnormal expression of p53 has been reported in cases of CD30 positive anaplastic lymphomas (Cesarman et al., 1993) and post-thymic T cell lymphomas (Matsushima et al., 1994).

Immunohistochemistry for p53 is the simplest analysis for p53 integrity but this approach can not directly detect p53 mutations. P53 protein levels under normal conditions are very low due to a short half life of wild p53. However, most point mutations of p53 prolong the half life of the protein, permitting it to be immunohistochemically detectable in tumors. If the p53 mutation results in either a premature stop codon, frame shift or alteration of a splice site or enhancer/promoter region, false negative can occur. These types of p53 mutations represent about 10 % of the total p53 alteration (Imamura et al., 1994). False positives can also occur. Nakamura et al.(1993) found 5 of 26 lymphomas with positive staining for p53 had detectable p53 mutation. The p53 mutation is not a general lesion in lymphoid neoplasia, but rather is specifically associated with Burkitt's lymphoma and chronic lymphocytic leukemia (Gaidano et al., 1991). High levels of p53 protein expression do not correlate with p53 gene mutations in anaplastic large cell lymphoma (Cesarman et al., 1993). Immunohistochemical staining revealed moderate to high levels of p53 protein expression in 12 of 15 (80 %) anaplastic large cell lymphomas studied, but mutations were found in only one of 17 cases. This discrepancy could be explained in part by their failure to analyze for alteration in every region of the gene. Also some rapidly proliferating cells express p53, such as activated T

lymphocyte (Imamura et al., 1994). In addition, p53 might be detected if wild type p53 bound to other cellular or viral protein that inactivated but prolonged its half life. DNA tumor virus oncoproteins including SV40 large T Ag, adenovirus E1b 55-kd protein & E6 protein of HPV type 16 & 18 inactivate the tumor suppressor activity of p53 by complexing to it. Furthermore, p53 mutations have been found with significant frequency in Burkitt's lymphoma, which is often associated with EBV infection (Farrell et al., 1991 ; Gaidano et al., 1991) and in adult T cell leukemia/lymphoma, which is caused by the HTLV-1 human retrovirus (Sakashita et al., 1992). The binding between p53 and viral proteins (EBNA-5) has also been reported for EBV(Szekely et al., 1993). Recently EBV associated malignancies have been analysed for alterations of the p53 gene. EBV positive undifferentiated nasopharyngeal carcinomas consistently harboured a wild type p53 gene (Spruck et al., 1992). Chang et al.(1992) reported mutations of the p53 gene in 20 % of nasopharyngeal carcinomas and the mutations were found irrespective of the EBV status. Niedobitek et al.(1993) reported p53 overexpression was detected in 32 %(27/116) of Hodgkin's disease with no simple correlation between EBV infection and p53 overexpression. However our data revealed that p53 was positive more frequently in EBER positive lymphomas, 7 out of 9 cases (78 %), whereas 9 out of 24 EBER negative lymphomas were p53 positive. The incidence of p53 expression in EBER positive cases was 2 times higher than in negative ones, however, it was not statistically significant. Although this contrasts with the other reports on EBV associated nasopharyngeal carcinoma (Spruck et al., 1992 ; Chang et al., 1992) and Hodgkin's disease (Niedobitek et al., 1993), EBV infection and aberrant p53 expression may be factors contributing to a complex multi-step carcinogenic process synergistically. Recently, apoptosis is induced by wild p53 expression in a myeloid leukemic cell line (Yonish et al.,1991). The inactivation of p53, a mediator of apoptosis, could result in an oncogenic effect. EBV gene BHRF1 encodes a protein with significant homology to Bcl-2 (Henderson et al., 1993) and may therefore protect cells from apoptosis. In addition, the latently expressed EBV protein LMP-1 induces Bcl-2 expression and inhibits apoptosis. The synergism between altered p53 and EBV infection can lead to tumorigenesis by preventing cell from apoptosis. The implication of p53 protein expression in our cases is not clear and further molecular studies are required.

Concerning the clinical significance, abnormalities of chromosome 17 were correlated with a grave prognosis and a short survival (Cabanillas et al., 1989). P53 mutations are associated with evolution from follicular to high grade lymphoma (Sander et al., 1993 ; Ichikawa et al., 1992). However, our study showed no significant differences in survival time among groups defined by variables such as p53, EBER, phenotype and histologic grade of the lymphomas, except at clinical stage. Our cases were too small to give any significant assessment on the possibility of survival. Larger, well conducted cohort studies need to be performed.

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