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Epstein-Barr Virus and Gastrointestinal Lymphomas in Korea

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To analyze the association of Epstein-Barr virus (EBV) with gastrointestinal non-Hodgkin's lymphomas arising in immunocompetent patients, 56 consecutive cases of gastrointestinal lymphomas (B-cell: 52 cases, T-cell: 3 cases, T/NK-cell: 1 case) occurring in the stomach (33 cases), intestine (22 cases) and esophagus (1 case) were investigated for the presence of EBV using polymerase chain reaction analysis as a screening method followed by EBER-1 RNA and DNA in situ hybridization (ISH) and immunohistochemistry for the expression of latent membrane protein 1 (LMP-1). Forty-seven cases demonstrated extractable DNA and EBV DNA was detected only in 4 cases. Among them, RNA (EBER-1) and DNA ISH analysis confirmed the presence of the EBV genome in tumor cells in 3 cases (T/NK-cell lymphoma of ileum, gastric high-grade B-cell lymphoma of mucosa-associated lymphoid tissue, gastric diffuse large B-cell lymphoma). Only the T/NK cell lymphoma showed diffuse positivity of tumor cells while 2 gastric B-cell lymphomas demonstrated a scattered positive reaction and no cases expressed LMP-1. Nine cases without extractable DNA by the PCR method showed no nuclear signal by EBER-1 ISH. These findings suggest that most sporadic primary gastrointestinal lymphomas in Korea are not associated with EBV.

Key Words: Epstein-Barr virus, polymerase chain reaction, in situ hybridization, gastrointestinal lymphomas

Primary gastrointestinal (GI) lymphomas are the most common type of extranodal lymphomas and they have different biologic behaviors compared to nodal lymphomas (Isaacson and Spencer, 1987; van Krieken *et al.* 1990). They arise from mucosa-associated lymphoid tissue (MALT), and the gastric low-grade B-cell lymphomas of MALT as well as enteropathy-associated intestinal T-cell lymphomas are known to have precursor lesions (Isaacson and Wright, 1978; Isaacson *et al.* 1985; Parsonnet *et al.* 1994).

Epstein-Barr virus (EBV) has been implicated in the pathogenesis of various types of reactive and neoplastic lymphoproliferative diseases. It is the etiologic agent of infectious mononucleosis (Henle *et al.* 1968). Endemic Burkitt's lymphoma (Epstein *et al.* 1964) as well as B-cell lymphomas arising in immunocompromised individuals (MacMahon *et al.* 1991; Knowles *et al.* 1995) are strongly associated with EBV. Recently, it has been reported to be also associated with Hodgkin's lymphoma (Weiss *et al.* 1987; Weiss *et al.* 1989) and nasal or paranasal T/NK cell lymphoma (Harabuchi *et al.* 1990; Weiss *et al.* 1992: Tomita *et al.* 1995; Tomita *et al.* 1997). Several large-scale studies have demonstrated that nearly any type of sporadic non-Hodgkin's lymphomas of both B- and T-cell origins could have EBV-infected tumor cells, although its role in lymphomagenesis is

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uncertain (Hamilton-Dutoit and Pallesen, 1992; Hummel *et al.* 1995).

The different rate of EBV infection in relation to the histologic and immunophenotype of lymphomas, sites of involvement and ethnicity has been well documented (Hamilton-Dutoit and Pallesen, 1992; Ott *et al.* 1992; Weiss *et al.* 1992; de Bruin *et al.* 1994; Hummel *et al.* 1995; Tomita *et al.* 1995). Four recent studies from Asia and Europe, which addressed the association of EBV and primary gastrointestinal lymphomas, showed quite different results (Ott *et al.* 1993; Hui *et al.* 1994; Liu *et al.* 1995; Lee *et al.* 1997).

In this study, we examined 56 consecutive cases of primary gastrointestinal lymphomas from immunocompetent Korean patients for the presence of EBV to determine whether our cases also showed the high association with EBV observed in the study from Hong Kong (Hui *et al.* 1994).

MATERIALS AND METHODS

Patients

We selected 56 consecutive cases (resection: 37 cases, biopsy: 19 cases) of primary gastrointestinal lymphomas from the files of the Department of Pathology of Yonsei University College of Medicine diagnosed between January 1989 and December 1994. All 56 patients were immunocompetent and all the cases were classified according to the 'Revised European-American Classification of Lymphoid Neoplasm' (Harris *et al.* 1994). We classified a case showing a sheet-like proliferation of large tumor cells as diffuse large B-cell lymphoma if we could not find an area of low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) component. When both a sheet of large transformed cells and an area of low-grade B-cell lymphoma of MALT were present, we classified the case as high-grade B-cell lymphoma of MALT.

Immunohistochemistry

Immmunohistochemical procedures were performed on newly-cut-paraffin embedded tissue sections using a labeled streptavidin-biotin method. Antigen unmasking using a citrate buffer (0.01 M, pH 6.0) and a microwave oven (750 W, 12 minutes) was done prior to incubation with primary antibodies (CD56, CD79a, CD3, and EBV-encoded latent membrane protein-1). The monoclonal and polyclonal antibodies used in this study, their reactivity and supplies are listed in Table 1. The tissue sections were incubated at 4°C overnight with primary antibodies with the detection being performed by Universal LSAB kit (Dako, Carpinteria, CA, U.S.A.). A diaminodenzidine chromogen kit (Zymed, San Francisco, CA, U.S.A.) was used as a chromogen and hematoxylin was used as a counterstain.

Extraction of DNA

The DNA extraction was performed from the formalin-fixed and paraffin-embedded tissue using chelating resin (Stein and Raoult, 1992). Paraffin blocks without any samples were used for negative controls and DNA extracted from formalin-fixed, paraffin-embedded EBV-positive Burkitt lymphoma cell line of Raji (gift from Dr. H. Mizusawa, National Institute of Hygiene, Tokyo, Japan) was used for positive control of EBV DNA.

Table 1. Antibody panel

Antibody	Immunoreactivity	Vendor
L26	B-cells	Dako Corporation (Carpinteria, CA, USA)
CD79a	B-cells	Dako Corporation
CD3	T-cells	Dako Corporation
UCHL-1	T-cells	Dako Corporation
CD56	NK cells	Zymed Laboratories Inc. (San Francisco, CA, USA)
CS1-4	Latent membrane product	Dako Corporation

PCR amplification of β-globin and ebv genome

Amplification of β-globin and the EBV genome was carried out using PCR as previously described (Tomita *et al.* 1997). Briefly, 10 μl of DNA sample was diluted into 25 μl of PCR solution (Nippon Gene, Toyama, Japan). For the amplification of the β-globin gene, 35 PCR cycles of 94°C - 60°C - 72°C were performed with primers designed to amplify the 123-bp segment in the exon 7-8 region (exon 7, 5'-CTTCTGACACAACTGTGTTCACTAGC-3', and exon 8,5'-TCACCACCAACTTCATCCACGTTCA C-3') (Heller *et al.* 1992). For the amplification of the EVB genome, 35 PCR cycles of 94°C - 58°C - 72°C were performed with primers designed to amplify the 129-bp segment in the BamHI-W region of the EBV genome (5'-CCAGACAGCAGCCAATTG TC-3', and 5'-GGTAGAAGACCCCCTCTTAC-3') (Uhara *et al.* 1990).

Southern blot analysis of amplified samples

The EBV PCR products underwent electrophoresis and were transferred to Hybond N+ membranes (Amersham, Aylesbury, England). Oligonucleotide probes which hybridize to each intervening sequence between two primers of the EBV genome (5'-CCCTGGTATAAAGTGGTCCTGCAGCTATTTCT GGTCGCAT-3'), were labeled with fluorescein-deoxyuracil triphosphate (Fl-dUTP) using 3'-oligolabeling and detection systems (Amersham). Subsequent hybridization and development were performed with the detection system following the manufacturer's protocol.

RNA-ISH

EBV RNA in situ hybridization (RISH) was performed as previously described (Weiss *et al.* 1991) with some modifications (Tomita *et al.* 1997). Briefly, 30-base oligonucleotide probes, which were sense and antisense for a portion of the Epstein-Barr virus early RNA1 (EBER-1) gene, were synthesized using DNA synthesizer. As a positive control, the Raji cell line was used and the hybridizing mixture employed with the sense and antisense probes after RNAse treatment was used as a negative control.

DNA-ISH

A highly-sensitive ISH using digoxigenin-11-dUTP-labeled probes, which were made by PCR (Saeki *et al.* 1993), was used. With the use of 12 sets of primers, a Bam HI-W fragment of EBV was amplified with labeled substrate in individual PCR. Then the 12 probes, with an average size of 120 base pairs, were mixed together and hybridized with the sections. The specificity of the probes and the staining were evaluated by the control studies as published (Tomita *et al.* 1995; Tomita *et al.* 1997).

RESULTS

Location and histologic types

The histologic types and locations of the 56 lymphomas are shown in Table 2. Thirty-three tumors were located in the stomach, 12 in the small intestine, 10 in the large intestine, and 1 in the esophagus. The diffuse large B-cell lymphoma (32 cases) was the most common, followed by 13 cases of low-grade B-cell lymphoma of MALT. Three cases of peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS), were noted and we classified the ileal tumor expressing CD56 in addition to the T-cell marker as T/NK cell lymphoma. Among the 33 cases of gastric lymphomas, 13 cases were classified as diffuse large B-cell lymphoma, 12 cases as low-grade B-cell MALT lymphoma, 7 cases as high-grade B-cell lymphoma of MALT, and 1 case as PTCL, NOS. Most of the intestinal lymphomas were diffuse large B-cell lymphoma but 2 cases of PTCL, NOS, 1 case of low-grade B-cell lymphoma of MALT, and 1 case of T/NK cell lymphoma were also seen.

PCR for EBV

Forty-seven cases showed amplified DNA of the expected size in the ethidium bromide-stained gel by β-globin PCR. The remaining 9 cases not showing the β-globin PCR band were regarded as having poor DNA preservation and were analyzed using EBER-1 ISH. Four cases showed positive EBV products by PCR and their locations and histologic types were as follows: 1 case of gastric diffuse large B-cell lym-

Table 2. Summary of location and diagnoses of 56 primary gastrointestinal lymphomas

Location	Histologic type	Case No.
Stomach	Diffuse large B-cell lymphoma	13
	Low-grade B-cell MALT lymphoma	12
	High-grade B-cell MALT lymphoma	7
	Peripheral T-cell lymphoma, NOS	1
Ileum	Diffuse large B-cell lymphoma	8
	Peripheral T-cell lymphoma, NOS	1
	T/NK cell lymphoma	
Duodenum	Low-grade B-cell MALT lymphoma	
Jejunum	Diffuse large B-cell lymphoma	
Colon	Diffuse large B-cell lymphoma	
Rectum	Peripheral T-cell lymphoma, NOS	
Esophagus	Diffuse large B-cell lymphoma	
Total		56

MALT: mucosa-associated lymphoid tissue, NOS: not otherwise specified

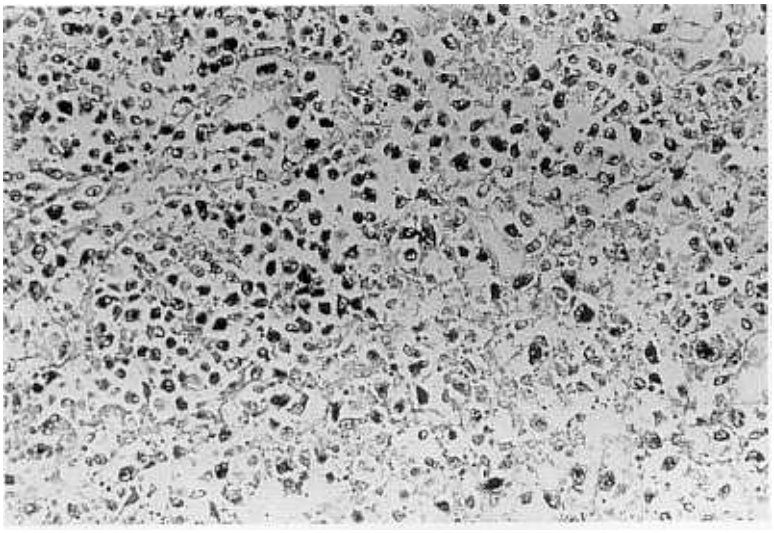

Fig. 1. T/NK cell lymphoma of the ileum showing diffuse strong nuclear signals in the tumor cells by EBER-1 RNA in situ hybridization.

phoma, 2 cases of gastric high-grade B-cell lymphoma of MALT, and 1 case of T/NK cell lymphoma of ileum.

ISH for EBV genomes

RNA-ISH for EBV was performed in the 4 cases listed above which demonstrated the EBV genome by PCR and also in 9 cases which demonstrated no extractable DNA by PCR. Only the T/NK cell lymphoma of ileum showed diffuse strong nuclear signals (Fig. 1). One of the gastric high-grade B-cell lymphomas of MALT demonstrated a scattered nuclear positive reaction in the scattered tumor cells in only a high-grade area and the other gastric high-grade B-cell lymphoma of MALT showed a positive nuclear signal only in the scattered reactive small lymphocytes (Fig. 2). The gastric diffuse large B-

Fig. 2. High-grade B-cell lymphoma of mucosa associated lymphoid tissue of the stomach showing only scattered nuclear signals in reactive small lymphocytes by EBER-1 RNA in situ hybridization.

cell lymphoma revealed scattered positive nuclear signals only to DNA-ISH. Finally, 3 (5.3%) of 56 lymphomas were regarded as EBV positive. None of these cases expressed LMP-1, indicating latency of EBV infection.

DISCUSSION

The results of our study demonstrate a rare association of EBV with gastrointestinal lymphomas occurring in immunocompetent Korean patients. In only 3 cases could we confirm the presence of EBV genomes in the tumor cells by DNA and RNA ISH methods. Even in positive cases, only the T/NK cell lymphoma of the ileum demonstrated diffuse nuclear staining. There have been four reports on the presence of EBV genomes in gastric lymphomas in the English literature and their results were quite different (Ott *et al.* 1993; Hui *et al.* 1994; Liu *et al.* 1995; Lee *et al.* 1997) (Table 3). The data from Germany (Ott *et al.* 1993) and Japan (Liu *et al.* 1995) showed low associations, 5.5% and 8.2%, respectively, while the data from Hong Kong (Hui *et al.* 1994) demonstrated a quite high association (18.0%). A recent study from Korea (Lee *et al.* 1997) reported an intermediate rate of EBV expression (10.9%) in gastric lymphomas. These 4 studies all used EBER1 ISH as a method for detecting the presence of EBV genomes, but we used the PCR method as a way of screening for the detection of EBV. The PCR method used in this study proved to be highly sensitive (Weiss *et al.* 1991; Saeki *et al.* 1993; Uhara *et al.* 1994), and we also used EBER-1 and DNA ISH methods to confirm the results of the PCR study. So these discrepancies of EBV expression in gastric lymphomas do not seem to be caused by the sensitivity of the detection methods. The positive rate of the EBV genome in the gastric lymphoma might be different by area. The reason for the much higher rate of EBER-1 positivity in the study from Hong Kong (Hui *et al.* 1994) remains unclear due to the similar ethnic background of Chinese, Japanese and Koreans, although they differ in socioeconomic conditions, which affect EBV infection rates.

Before the concept of 'malignant lymphoma of mucosa associated lymphoid tissue (MALT)' was introduced by Isaacson and Wright (1983), gastrointestinal (GI) lymphomas had not been classified separately and this caused some trouble in understanding the different biologic behavior of GI lymphomas compared to nodal lymphomas (Isaacson and Spencer, 1987; van Krieken *et al.* 1990). So in this

Table 3. Summary of 5 studies on gastrointestinal lymphomas

	Present study	Lee *et al.* 1997	Liu *et al.* 1995	Hui *et al.* 1994	Ott *et al.* 1993
Race	Korean	Korean	Japanese	Hong Kong Chinese	German
Case Number	Stomach 33 Intestine 22 Esophagus 1	Stomach 64 Intestine 17	Stomach 49	Stomach 61	Stomach 55
Type of the specimens	Stomach 33 Biopsy 14 Resection 19	Stomach 64 Biopsy 36 Resection 28	Resection 49	Data not available	Resection 55
EBER positivity according to the histologic types (Stomach)	Low MALT 0/12 High MALT 1/7 Diffuse large B 1/13 PTCL, NOS 0/1 Plasmacytoma 0/1 Diffuse large, B 5/43 Diffuse large, N 0/2 PTCL, NOS 1/1 Angiocentric 1/1 Unclassified 0/3	Lymphoplas 0/2 MCL 0/2 FCC 0/1 Low MALT 0/8	Low MALT 2/16 Diffuse large, B 2/33	Data not available Diffuse large, B-cell 2/24	Low MALT 0/27 ALCL 1/3 PTCL 0/1
Overall EBER positivity	6.1%	10.9%	8.2%	18.0%	5.5%
LMP expression	No	5 cases	Not done	Not done	1/55 (ALCL case)

MALT: mucosa associated lymphoid tissue, PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified, Lymphoplas: lymphoplasmacytic lymphoma, MCL: mantle cell lymphoma, FCC: follicular center cell lymphoma, ALCL: anaplastic large cell lymphoma, EBER: Epstein-Barr Virus early RNA1, LMP: latent membrane product

study, we adopted the 'Revised European-American classification of lymphoid neoplasm' (Harris *et al.* 1994) for the classification of our cases which clearly defined several histologic types showing a predilection for the GI tract, such as extranodal marginal zone lymphoma (B-cell lymphoma of MALT), enteropathy-associated T-cell lymphoma, and mantle cell lymphoma. Although there has been no consensus on the definition of high-grade B-cell lymphoma of MALT, we classified a case as high-grade B-cell lymphoma of MALT only when we could observe a low-grade component in addition to a high-grade component. Our study included 12 cases of low-grade B-cell lymphoma of MALT, which comprised 36.4% of gastric lymphoma, and this figure was similar to 32.7% in Japan (Liu *et al.* 1994). However, the study from Germany (Ott *et al.* 1993) included a much higher proportion of low-grade lymphoma of MALT cases (49.1%) and that from Korea (Lee *et al.* 1997) included a much lower proportion of low-grade lymphoma of MALT cases (12.5%).

In our study no cases of low-grade B-cell MALT lymphomas expressed EBV genomes. Ott *et al.* Hui *et al.* and Lee *et al.* reported the same results as ours, however Liu *et al.* convincingly demonstrated 2 cases of low-grade B-cell MALT lymphomas expressing EBER-1 (Ott *et al.* 1993; Hui *et al.* 1994; Liu *et al.* 1995; Lee *et al.* 1997). We can't explain the cause of this discrepancy and we think large-scale studies are necessary to assess the EBV expression pattern in low-grade B-cell lymphomas of MALT. In general, low-grade B-cell lymphomas were reported to have a much lower expression of EBV compared to high grade B-cell lymphomas in non-immunocompromised patients, but the presence of EBER-1 in rare cases of immunocytoma suggests the possibility that low-grade B-cell lymphomas could also express EBV genomes (Hummel *et al.* 1995). The EBV expression rates in gastric diffuse large B-cell lymphomas range from 6.1% (Liu *et al.* 1995) to 11.6% (Lee *et al.* 1997) and these figures are similar to those reported by Hummel *et al.* (1995) using the EBER-1 ISH method in sporadic B-cell non-Hodgkin's lymphomas. Ott *et al.* described a case of gastric high-grade MALT lymphoma expressing EBV genomes only in a high- grade area, as in 1 of our cases, and suggested the possibility that EBV may be involved in the high-grade transformation of low-grade B-cell MALT lymphomas (Ott *et al.* 1993). However, the expression of EBER-1 in only 1 of 7 cases of high-grade MALT lymphoma and scattered positive reactions even in positive cases indicate that EBV gene expression is not a critical event in high-grade transformation.

EBV, first identified in African Burkitt's lymphoma (Epstein *et al.* 1964), is a B-lymphotropic, polyclonal activator. EBV can infect T-lymphocytes (Kikuta *et al.* 1988) and several studies confirm the higher rate of EBV expression in sporadic T-cell lymphomas than B-cell lymphomas (Hamilton-Dutoit and Pallesen, 1992; Zhou *et al.* 1994). Moreover, several subtypes of T-cell lymphomas have been known to consistently express EBV (Harabuchi *et al.* 1990; de Bruin *et al.* 1994; Tsang *et al.* 1994; Tomita *et al.* 1995; Kanavaros *et al.* 1996; Tomita *et al.* 1997). The strong relationship between EBV and CD56 expression was reported even in lymphomas occurring outside an upper aerodigestive tract (Tsang *et al.* 1994), as in our case of the T/NK cell lymphoma of the ileum. The 3 cases of PTCL, NOS in our study, did not express EBER-1. Although PTCL in general has been known to show a high rate of EBV expression (Hamilton-Dutoit and Pallesen, 1992; Zhou *et al.* 1994), de Bruins *et al.* (1994) reported no expression of EBER-1 in 7 cases of gastrointestinal T-cell lymphoma. We think the incidence of EBV expression in PTCLs should be re-evaluated after classifying them into CD56 positive and CD56 negative groups because differentiation of T/NK cell lymphoma from PTCL is difficult on purely morphologic grounds. So the different rates of EBV expression in gastric lymphomas reported in previous studies could be affected by the proportion of low- and high-grade lymphomas, as well as the number of peripheral T-cell lymphomas and T/NK cell lymphomas included.

In our study, there was no case of gastrointestinal lymphoma expressing LMP-1 protein as reported by Liu *et al.* (1995). However, LMP-1 expression was reported in 1 case of gastric anaplastic large cell lymphoma by Ott *et al.* (1993) and in 5 of the 8 EBER-1 positive cases by Lee *et al.* (1997), and most of them were T-cell lymphomas. So the discrepancy of LMP-1 expression in various series seems to be caused by the proportion of T-cell lymphoma cases.

Although Helicobacter pylori becomes the established etiologic agent of gastric low-grade B-cell lymphomas of MALT (Wotherspoon *et al.* 1991; Parsonnet *et al.* 1994), EBV may be involved in the lymphomagenesis of the gastrointestinal tract due to the fact that lymphomagenesis is a multistep process and EBV genomes have been detected in various histologic types of nodal and extra-nodal B- and T-cell non-Hodgkin's lymphomas (Hamilton-Dutoit and Pallesen, 1992; Hummel *et al.* 1995). Moreover, several recent reports have demonstrated the presence of EBV genomes in some gastric carcinomas (Shibata and Weiss, 1992) suggesting that the stomach might be an anatomic site showing strong association with EBV irrespective of tumor types as the upper aerodigestive tract (Weiss *et al.* 1992). However, the results of this study indicate that most sporadic gastrointestinal lymphomas in Korea are not associated with EBV.

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