Extranodal Malignant Lymphoma of the Upper Aerodigestive Tract: Prevalence of Epstien-Barr Virus (EBV) Infection in King Chulalongkorn Memorial Hospital

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Background: *High frequency of Epstein-Barr virus (EBV) in the normal mucosa of the upper aerodigestive tract suggests that it may serve as a reservoir for the virus. Malignant lymphomas arising in this site may be associated with EBV.*
Objectives: *To determine the prevalence of EBV infection in extranodal malignant lymphomas of the upper aerodigestive tract.*
Setting: *King Chulalongkorn Memorial Hospital, Thailand.*
Design: *Descriptive study.*
Patients: *42 Thai patients who presented between 1998 and 2003.*
Material and Method: *The expression of EBV mRNAs (EBERs) of malignant lymphoma was studied by means of in situ hybridization in formalin-fixed, paraffin-embedded specimens.*
Results: *The recruited subjects were 26 males and 16 females, and their age ranged from 3 to 85 years with the mean of 51.43 years, in 4 of them human immune deficiency virus (HIV) infection was documented. Ten of 42 cases (23.81%) expressed EBER transcripts and were extranodal NK/T-cell lymphomas, nasal type (7 cases), plasmablastic lymphomas (2 cases) and diffuse large B-cell lymphoma (1 case). Three of 4 cases (75%) of known HIV-seropositive cases were EBV-positive (2 plasmablastic lymphomas and 1 diffuse large B-cell lymphoma).*
Conclusion: *In the upper aerodigestive tract, EBV was present in some but not all malignant lymphoma. It was associated with extranodal NK/T-cell lymphoma, nasal type and B-cell lymphoma arising in HIV-infected patients, but it was not found in B-cell lymphoma arising in immunocompetent patients.*

Keywords: *Epstein-Barr virus, EBV, EBER, Lymphoma, HIV, Upper aerodigestive tract, Extranodal, In situ hybridization, Bangkok, Thai, Thailand*

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Differences in geographic distribution are striking for certain types of malignant lymphoma. Follicular lymphoma is more common in Western countries than elsewhere[1]. Asia and some areas of South and Central America have higher rates of extranodal natural killer (NK)/T-cell lymphoma (nasal type) rarely seen in the United States and Europe[2-4]. In the Middle East, high rates of intestinal extranodal lymphoma are observed, whereas in Africa, endemic Burkitt lymphoma accounts for a substantial proportion[1,5]. The difference is probably related to the underlying etiological factors of these lymphomas such as immunosuppression[6] and a causal link between infectious agents Human T-cell leukemia/lymphoma virus type 1 (HTLV-1), Epstein-Barr virus (EBV) and Helicobacter pylori infections[1]. EBV is a strong candidate among T-cell lymphoma that was unrelated to HTLV-1[7].

EBV is a ubiquitous member of the Gammaherpesvirus Family and the causative agent of infectious mononucleosis[8]. It was found widespread in nearly all human populations and life-long persistent in the vast majority of individuals, asymptomatic infection (chronic virus carriers) of the small numbers of EBV-carrying B-cell pool in the peripheral blood and in

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tissues[9]. EBV is also found in a wide variety of benign and malignant lesions including oral hairy leukoplakia, inflammatory pseudotumor, chronic active EBV infection, B-cell lymphoproliferative syndromes, lymphomas or/and lymphoproliferative diseases in solid organ transplant recipients, lymphomas or/and lymphoproliferative diseases in patients with the acquired immunodeficiency syndrome (AIDS), Hodgkin lymphoma, Burkitt lymphoma, T-cell lymphoma, NK/T-cell lymphoma, nasopharyngeal carcinoma, breast carcinoma and gastric carcinoma, as well as smooth muscle neoplasm associated with immunosuppression[8,10,11].

The normal healthy mucosa of the upper aerodigestive tract could serve as a reservoir for EBV[12] and the sinonasal region was found to be a significant site for EBV-related tumor, especially sinonasal undifferentiated carcinoma[13]; hence, this anatomic site may be important in the development of EBV-related malignant lymphoma. A few studies address the relative frequency of EBV within the group of extranodal malignant lymphoma of the upper aerodigestive tract[14-17]. Nevertheless, some lymphomas of the oral cavity were not included, and the association with immunocom promised status was not emphasized. Furthermore, WHO classification of malignant lymphoma 2001[18] commonly used at present was not applied to specify subtypes.

The aims of our study were: a) to determine the prevalence of EBV infection in extranodal malignant lymphoma of the upper aerodigestive tract in Thai patients at King Chulalongkorn Memorial Hospital; and b) to correlate with histologic and immunophenotypic subtypes of malignant lymphoma according to WHO classification of tumors of haematopoietic and lymphoid tissue 2001[18].

Material and Method

The target population was patients in King Chulalongkorn Memorial Hospital in 1998 to 2003 who were pathologically diagnosed as extranodal malignant lymphoma in the upper aerodigestive tract excluding a plasmacytoma, which could either be primary or secondary. These data including sex, age, human immune deficiency virus (HIV) infection and location of malignant lymphoma derived from pathological requests at the Department of Pathology, King Chulalongkorn Memorial Hospital. They were 77 patients; only 42 had specimens available in paraffin blocks for *in situ* hybridization (ISH). Those without enough material for study were excluded. These specimens was previously sub-classified according to WHO classification of haematopoietic and lymphoid tumors using histomorphologic criteria and immunophenotype with immunohistochemistry in prior study[19].

The detection of latent EBV infection by ISH on formalin-fixed paraffin-embedded tissue sections was done using EBV encoded RNA (EBER) peptide nucleic acid (PNA) Probe/Fluorescein (Dako Cytomation). There was a mixture of four 15-mers complimentary to the EBER1 and the EBER2, encoded from two separate but homologous viral genes[8]. The PNA probes were labeled with the hapten 5-carboxyl Fluorescein for subsequent visualization with DakoCytomation PNA ISH Detection Kit. The positive tissue control was run simultaneously with specimens. Positive staining was recognized under the microscope as a dark blue/black color at the site of hybridization.

Results

Forty-two cases of extranodal malignant lymphoma of the upper aerodigestive tract were included in the present study. The age of the patients at clinical presentation spanned a wide range of 3 to 85 years, with a mean of 51.43 years with a slight male predominance (approximately, male: female ratio = 1.6:1). The HIV-seropositive cases were documented in 4 cases.

Histological and immunophenotypic subtypes of extranodal malignant lymphoma of the upper aerodigestive tract according to WHO classification[19] are shown with correlation to the site of involvement in Table 1. Two cases of diffuse large B-cell lymphoma (DLBCL) in the oral cavity are reclassified as plasmablastic lymphoma due to CD20-, CD138+ and plasmacytoid appearance. Four HIV-seropositive cases are analyzed in Table 2 and presented predominantly in the oral cavity (3 of 4 cases). All are B cells, and two are plasmablastic lymphomas exclusively found in the oral cavity. The other two are DLBCLs found in the oral cavity and nasopharynx.

The results of ISH for detection of EBERs are shown in Table 3. EBV was detected in 10 cases (23.81%). The EBV had strong association with extranodal NK/T-cell lymphoma, nasal type (100%) and plasmablastic lymphoma (100%), whereas the others seemed to be unrelated. In positive cases, EBERs were evenly distributed among the neoplastic cells, whereas no evidence of EBV in associated non-neoplastic lymphocytes or epithelium was seen. Three of four patients infected with HIV were positive for EBV (Table 4).

The relationship between location of lymphoma and EBV is shown in Table5. The malignant

Table 1. Histological and immunophenotypic subtypes (WHO classification 2001[18]) of extranodal malignant lymphoma of the upper aerodigestive tract corresponding to the sites of involvement[19]

Histological and immunophenotypic subtypes	Tonsil	Nasopharynx	Base of tongue	Nasal and paranasal areas	Oral cavity	Total (%)
B cells						
DLBCL	13	6	1	4	4	28 (66.67)
BL	-	-	-	-	1	1 (2.38)
MCL	-	1	-	-	-	1 (2.38)
MALT lymphoma	-	-	1	-	1	2 (4.76)
Plasmablastic lymphoma	-	-	-	-	2	2 (4.76)
T cells						
NK/T-cell lymphoma	-	1	-	6	-	7 (16.67)
PTL, unspec	-	-	-	-	1	1 (2.38)
Total (%)	13 (30.95)	8 (19.05)	2 (4.76)	10 (23.81)	9 (21.43)	42 (100)

Note: MALT lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; NK/T cell lymphoma, extranodal NK/T cell lymphoma, nasal type; and PTL, unspec, peripheral T-cell lymphoma, unspecified

Table 2. Histological and immunophenotypic subtypes (WHO classification 2001[18]) of extranodal malignant lymphoma of the upper aerodigestive tract associated with HIV infection corresponding to the sites of involvement

Histologic and immunophenotypic subtypes	Nasopharynx	Oral cavity	Total (%)
DLBCL	1	1	2 (50)
Plasmablastic lymphoma	-	2	2 (50)
Total (%)	1 (25)	3 (75)	4 (100)

Note: DLBCL, diffuse large B-cell lymphoma

Table 3. The detection of EBERs in extranodal malignant lymphoma of the upper aerodigestive tract according to WHO classification 2001[18]

Histological and immunophenotypic subtypes	EBERs+	EBERs-	% of positivity	Total (%)
B cells				
DLBCL	1	27	3.57	28 (66.67)
BL	-	1	0.00	1 (2.38)
MCL	-	1	0.00	1 (2.38)
MALT lymphoma	-	2	0.00	2 (4.76)
Plasmablastic lymphoma	2	-	100.00	2 (4.76)
T cells				
NK/T-cell lymphoma	7	-	100.00	7 (16.67)
PTL, unspec	-	1	0.00	1 (2.38)
Total	10	32	23.81	42 (100)

Note: MALT lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; NK/T cell lymphoma, extranodal NK/T cell lymphoma, nasal type; and PTL, unspec, peripheral T-cell lymphoma, unspecified

lymphoma arising in nasal and paranasal areas showed the highest percentage of EBV association (60%), but this is not only a site-dependent phenomenon in view of no association with nasal B-cell lymphoma.

Discussion

EBV has been reported to have an important role in tumorigenesis in Hodgkin lymphoma[20], Burkitt lymphoma[21], plamablastic lymphoma[18], mature T-cell lymphoma[22,23] and malignant lymphoma arising in immunosuppressed patients[24]. EBV infects more than 90% of the world's population. A small proportion will develop tumor, while most humans coexist with the virus without serious sequelae[25]. The virus is probably a cofactor in the pathogenesis of some but not all people. The overall prevalence of EBV in all malignant lymphomas in human varies among nations and age groups[20,24,26-29]. The difference is possibly attributed by the difference of the composition of the subtype of lymphoma associated with EBV. In Thailand, the EBV was found in 64% of nodal classical Hodgkin lymphoma, 13% of nodal non-Hodgkin lymphoma (NHL)-B and 51% of nodal NHL-T[28]. In Korea and Japan, the extranodal NHL of B and T-cell types seemed to have more association with EBV than the nodal part[30,31].

The positive rate for EBV in extranodal malignant lymphoma of the upper aerodigestive tract comparing with other series is shown in Fig. 1. Our positive rate is in between that of Germany and other Asian nations. The difference is largely contributed by the percentage of specific subtypes of malignant lymphoma associated with EBV and immunodeficiency status of the recruited patients which have strong association with EBV.

T/NK-cell lymphoma shows higher positive rate than B-cell lymphoma (Fig. 2). Within T/NK-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type is strongly associated with EBV (100%), and this type of the malignant lymphoma is the most important determinant in the overall positive rate for EBV in extranodal T-cell lymphoma of the upper aerodigestive tract. Hence, EBER can be used as the most reliable marker for the diagnosis of NK/T-cell lymphoma, although CD56 is specific it is not very sensitive[32].

For B-cell lymphoma, the immunodeficiency status of the patient played high association with EBV. Our study shows that HIV-related lymphoma was mainly B-cell type (100%), high-graded (DLBCL and plasmablastic lymphoma) and associated with EBV (75%) (Fig. 3). Excluding HIV infection, no association of B-cell lymphoma with EBV was observed. The evidence of high association of EBV with malignant lymphoma occurring in immunosuppressive patients is supported by other studies[6,10,24,32]. EBV may have a

Table 4. The detection of EBERs in extranodal malignant lymphoma of the upper aerodigestive tract associated with HIV infection

Histologic and immunophenotypic subtypes	EBERs+	EBERs-	% of positivity	Total (%)
DLBCL	1	1	50	2 (50)
Plasmablastic lymphoma	2	-	100	2 (50)
Total	3	1	75	4 (100)

Note: DLBCL, diffuse large B-cell lymphoma

Table 5. The detection of EBERs in extranodal malignant lymphoma of the upper aerodigestive tract correlated with the sites of involvement

	Tonsil	Nasopharynx	Base of tongue	Nasal and paranasal areas	Oral cavity	Total (%)
EBER+	0	1*	0	6*	3§	10 (23.81)
EBER-	13	7	2	4$	6	32 (76.19)
% of positivity	0	12.5	0	60	33.33	
Total (%)	13 (30.95)	8 (19.05)	2 (4.76)	10 (23.81)	9 (21.43)	42 (100)

Note: * All were extranodal NK/T-cell lymphomas, nasal type
§ All were HIV-infected patients (2 plasmablastic lymphomas and 1DLBCL)
$ All were DLBCLs (negative antiHIV)

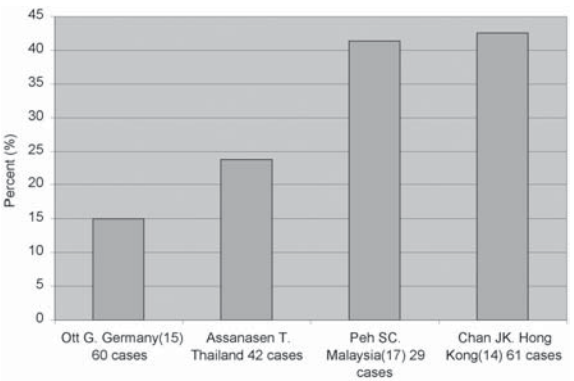

Fig. 1 Positive rate (%) for EBV in extranodal malignant lymphoma of the upper aerodigestive tract comparing with other series

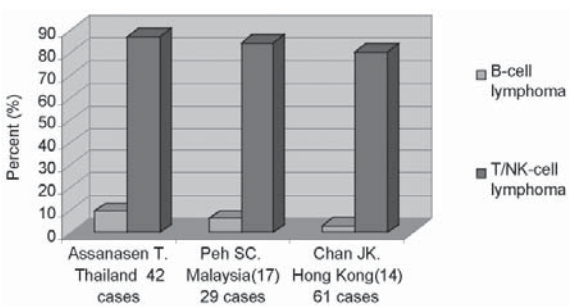

Fig. 2 Positive rate (%) for EBV of each immunophenotype in extranodal malignant lymphoma of the upper aerodigestive tract comparing with other series

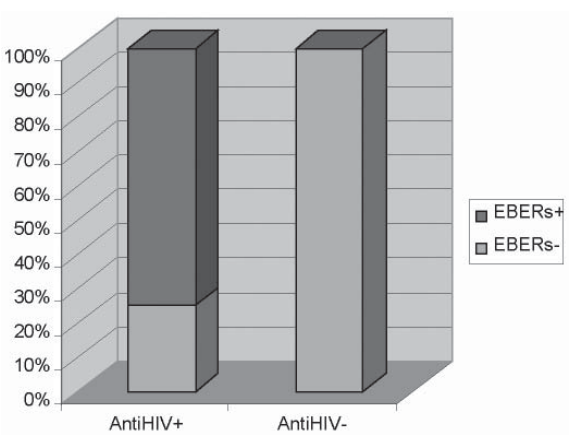

Fig. 3 Extranodal B-cell lymphoma of the upper aerodigestive tract: positive rate (%) for EBV (EBERs) correlated with antiHIV status

limited role in the initiation of B-cell lymphoma in immunocompetent patients.

The character of the viral association varies among these entities; some are consistently associated with EBV, and others with the virus only in some particular circumstances. An example of the former is nasal NK/T-cell lymphoma, whereas the latter, B-cell lymphoma. In contrast to the subtype of malignant lymphoma, the location displayed no association with EBV.

Factors influencing variation in the result, other than subtypes of malignant lymphoma and immune status of the patients, are methods to detect EBV and interpretation of each technique. EBER-ISH detected EBV shows a more frequent positive rate than the immunohistochemical reaction for LMP-1[8]. In some EBV+ mature T-cell lymphoma, EBV is preferentially localized in B cells rather than neoplastic T cells[33]; hence, PCR detected EBV DNA may not be appropriate for such condition. In biopsy formalin-fixed paraffin-embedded tissues, molecular detection of EBER transcripts by ISH is the gold standard of prove that a histopathological lesion is EBV-related[8]. Interpretation is also important. EBER signal must be unequivocally present in neoplastic cells. The cytologic features and distribution of stained cells should match with those on the corresponding Hematoxylin and Eosin (H&E) stained slide to help interpret whether the signal is malignant or reactive. The EBER signal is localized to the nucleus. In some cases, only fractions of malignant cells express EBER due to technical or biological reasons[20]. This approach is effective in the detection of latent EBV infection and has been widely used to analyze the association of EBV with a variety of malignant and non-malignant diseases[8].

So far, no differences in the clinical outcome, histological changes, and the lineage of lymphomas are discernible between EBV-positive and EBV-negative NHL patients[24,34], except one study which demonstrates that extranodal CD56+ EBV- lymphoma at extranasal sites was clinically less aggressive a malignancy and displayed less necrosis than CD56+ EBV+ lymphoma[35]. No significant correlation was found between EBV positivity and tobacco exposure, alcohol exposure, tumor grade[11]. Knowledge of the EBV association is not only important for the understanding of the pathogenesis of these tumors, but it is also increasingly important for their diagnosis, monitoring and treatment.

Conclusion

This study shows that EBV is only associated with certain subtypes of malignant lymphoma of the

upper aerodigestive tract, especially extranodal NK/T-cell lymphomas, nasal type. This is not merely a site-dependent phenomenon, as there is no association with nasal B-cell lymphoma. EBV may not involve lymphomagenesis of B-cell NHL arising in immunocompetent patients, but is associated with B-cell NHL arising in the HIV infected patients. Although anatomically in close proximity, lymphomas arising in these sites have different rate of EBER detection. The virus is probably a cofactor in the lymphomagenesis of some, but not all, NHL of the upper aerodigestive tract.

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ความชุกของ Epstein-Barr virus (EBV) ในมะเร็งต่อมน้ำเหลืองที่อยู่นอกต่อมน้ำเหลือง ของระบบทางเดินอากาศและทางเดินอาหารส่วนบนในผู้ป่วยโรงพยาบาลจุฬาลงกรณ์

ธรรมธร อาศนะเสน, พงษ์ศักดิ์ วรรณไกรโรจน์, สมบูรณ์ คีลาวัฒน์, ปรีชา เรืองเวชวรชัย, นุชนาฏ เปรมประยูร

ที่มา: *ในเยื่อบุทางเดินอากาศและทางเดินอาหารส่วนบนของคนปกติพบมีการติดเชื้อ EBV อยู่มากจึงน่าจะเป็นแหล่งกักเก็บสารพันธุกรรมของเชื้อมะเร็งต่อมน้ำเหลืองที่เกิดในบริเวณนี้จึงน่าจะมีความสัมพันธ์กับตัวเชื้อ*

วัตถุประสงค์: *เพื่อศึกษาความชุกของ EBV ในมะเร็งต่อมน้ำเหลืองที่อยู่นอกต่อมน้ำเหลืองของระบบทางเดินอากาศและทางเดินอาหารส่วนบน*

สถานที่ศึกษา: *โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย: *การศึกษาเชิงพรรณนา*

ผู้ป่วย: *ผู้ป่วยชาวไทย 42 รายตั้งแต่ปี พ.ศ. 2541 ถึง พ.ศ. 2546*

วิธีการศึกษา: *ตรวจหา EBV mRNA (EBER) ในเซลล์มะเร็งต่อมน้ำเหลืองโดยวิธีการ in situ hybridization*

ผลการศึกษา: *ผู้ป่วยชาย 26 คน หญิง 16 คน มีอายุตั้งแต่ 3 ปี ถึง 85 ปี (เฉลี่ย 51.43ปี) มีผู้ป่วยอยู่4 รายที่ถูกวินิจฉัยว่าติดเชื้อ Human immune deficiency virus (HIV) 10 ใน 42 รายตรวจพบ EBER transcripts โดยเป็น extranodal NK/T cell lymphomas, nasal type 7 ราย, plasmablastic lymphomas 2 ราย และ diffuse large B-cell lymphoma 1 ราย 3 ใน 4 รายของผู้ป่วยที่ติดเชื้อ HIV ร่วมด้วยตรวจพบ EBVมี plasmablastic lymphomas 2 ราย และ diffuse large B-cell lymphoma 1 ราย*

สรุป: *ตรวจพบ EBV ในมะเร็งต่อมน้ำเหลืองที่อยู่นอกต่อมน้ำเหลืองของระบบทางเดินอากาศและทางเดินอาหารส่วนบนเพียงบางชนิดเท่านั้น โดยเฉพาะ B-cell lymphomas ในผู้ป่วยที่ติดเชื้อ HIV ร่วมด้วย และ extranodal NK/T-cell lymphomas, nasal type*