ORIGINAL ARTICLE

The prevalence of Epstein-Barr virus infection in head and neck non-Hodgkin's lymphomas in Khorasan, northeast of Iran

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Abstract

Objectives: To investigate the frequency and possible role of Epstein-Barr virus infection in non-Hodgkin's lymphomas of the oral cavity and maxillofacial region in Khorasan (Northeast of Iran).

Methods: The cross-sectional retrospective study assessed the frequency of Epstein-Barr virus infection in non-immunosuppressed non-Hodgkin's lymphoma cases of the oral cavity and maxillofacial region. Formalin-fixed, paraffin-embedded tissue sections from 34 cases of head and neck non-Hodgkin's lymphoma (17 low-grade B-cell lymphoma, 14 diffuse large B-cell lymphoma, and 3 peripheral T cell lymphoma) were selected as a case group, and 10 normal lymph node sections were considered as a control group. Polymerase chain reaction was used to detect the EBV-DNA in tissue specimens. SPSS 16 was used for statistical analysis of the data.

Results: EBV-DNA was detected in 26.5% of NHL samples. Among NHLs, Epstein-Barr virus was found to be positive in 50% cases with diffuse large B-cell lymphoma and 11.8% of low grade B-cell lymphomas. Epstein-Barr virus was not detected in any cases of peripheral T-cell lymphoma.

Conclusion: Although it seems that Epstein-Barr virus appears to be an etiological factor in some subtypes of non-Hodgkin's lymphomas, especially in diffuse large B-cell lymphoma, more researches should be done to investigate the relationship between Epstein-Barr virus infection and head and neck non-Hodgkin's lymphomas.

Keywords: Non Hodgkin Lymphoma, Epstein-Barr virus, head and neck lymphomas, Khorasan, Iran. (JPMA 63: 882; 2013)

Introduction

Lymphomas are malignant neoplasms of component cells of lymphoid tissues. Lymphomas have been traditionally divided into Hodgkin's lymphoma (disease) and non-Hodgkin's lymphoma (NHL). Hodgkin's lymphoma is primarily a disease of lymph nodes.[1] In contrast to Hodgkin's disease, up to 40% of all NHLs arise at extra nodal sites, with the most common site being the gastrointestinal tract.[2] The head and neck is the second most common site for extra nodal NHL, with the majority of cases arising in Waldeyer's ring. NHL presents the second most common malignancy of the head and neck after Squamous Cell Carcinoma.[3] Lymphomas arising within the oral cavity, account for only 3.5% of all oral malignancies. They mostly present as a mass or an ulcerated mass and resemble squamous cell carcinoma or salivary neoplasm.[4]

The non-Hodgkin's lymphomas most commonly originate from cells of the B-lymphocyte series. Tumours with a T-lymphocyte derivation are less common, whereas true histiocyte-derived lymphomas are even rarer.[5]

Little is known of the etiology of NHL. Variations in the incidence in different ethnic groups suggest that there is a strong genetic predisposition. NHL is more common in patients with immunological deficiencies like congenital immunodeficiency, Sjögren's syndrome and AIDS.[6]

The role of viral infections in pathogenesis of some of these diseases has been proven. The most important related viral infections are Human Herpes virus 8 (HHV8), Human T-lymphotropic virus 1 (HTLV-1), and Epstein-Barr virus (EBV).[7] EBV has been implicated in the pathogenesis of numerous human lymphoproliferative disorders, as Hodgkin's lymphoma, nasopharyngeal carcinoma, post transplantation lymphoproliferative Disease, and T-cell and Natural killer cell lymphoma. More over, EBV is strongly associated with specific subtypes of NHLs, including endemic Burkitt's lymphoma and immunosuppression-associated lymphomas.[8]

EBV is a human herpes virus and a sub category of Gamma Herpes virus that naturally has a receptor on B lymphocyte called CR2 (CD21). After primary infection, it remains in a latent state, and most of the virus carriers are asymptomatic during this phase. EBV-infected B-cells

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expressing variable proteins during their latent phase, some of which have been shown to have oncogenic potential.[9] Cells with expression of these latent gene products are rapidly removed by an intact immune system. Latent viral gene products with oncogenic potential include Epstein-Barr nuclear antigen-2 (EBNA2), a specific transcriptional transactivator of viral and cellular genes, and the latency membrane protein-1 (LMP-1), a transmembrane phosphoprotein.[10] In circumstances in which the host's cellular immune system fails to control EBV-induced B-cell proliferation, previously latent virus can then induce malignant transformation. Finding of Clonal EBV infection in tumour cells suggests that EBV infection occurred before neoplastic transformation and implies a pathogenetic role for EBV in tumour cell proliferation.[11]

RNA in Situ Hybridization (EBER-ISH), Immunohistochemistry (IHC) and Polymerase chain reaction (PCR) are widely used methods for identifying EBV in tumour cells.[12]

Iran is the second largest country in the Middle East and the province of Khorasan, which is located in north-eastern Iran, is one of the largest provinces of the country covering 7.8% of the total area of Iran.[13] The present study was conducted to determine the frequency of EBV infection in the NHL samples of the oral cavity and maxillofacial region by PCR method in Khorasan (Northeast of Iran).

Material and Methods

In this retrospective cross-sectional descriptive study, 34 formalin-fixed, paraffin-embedded blocks with diagnosis of Head and Neck NHL (from 1979 to 2011) were selected from the Department of Oral and Maxillofacial Pathology, Mashhad Faculty of Dentistry, Iran. This Department receives nearly most of the oral pathology specimens from private and public hospitals and clinics throughout the entire province. Ten paraffin-embedded blocks which belonged to lymph nodes without reactive changes or metastasis, were considered as Control group.

For PCR technique, 3-4μm sections were cut from paraffin blocks. In this study, paraffin blocks were assessed for EBV-DNA. Statistical analysis was performed by SPSS statistical software package version 16 (Chicago, IL, USA) using Chi-square test. The results were considered statistically significant when p-values were less than 0.05. This research was approved by the ethics committee of Mashhad University of Medical Sciences and the patients were insured that all information obtained during the survey would be confidential.

PCR Procedures

DNA was extracted from Formalin-Fixed Paraffin-Embedded (FFPE) clinical samples by using the QIAamp DNA Mini Kit (Qiagen, Inc) according to the manufacturer's instructions. Paraffin was removed from paraffin-embedded biopsy samples with xylene, and the samples were rehydrated with ethanol. DNA integrity and absence of PCR inhibitors were tested by amplification of β-Globin gene. Only samples with a visible β-Globin gene band in the gel were included in this study.

Extracted DNA (5μL) was added to 25μL of the reaction mixture, which contained 5μL 10× PCR buffer, 10μL 5× Q-solution (QIAGEN), 2.5mmol/L MgCl2, 200μmol/L each dNTP, 2.5 units Taq DNA polymerase (Roche Holding Ltd), and 15pmol of each primer. PCR conditions were as follows: 95°C for 5 min followed by 35 cycles of denaturation at 95°C for 30s; annealing at (58°C/EBV gene or 55°C/β-Globim gene) for 30s; extension at 72°C for 1 min; and a final extension step at 72°C for 5 min. Thermal cycles were performed in an ABI (Applied Biosystems, Inc., Foster City, California, United States) thermal cycler. The PCR Primers, their respective base sequences, size of amplified bands and optimum annealing temperature are shown in Table-1, in all samples; sterile water was used as a substitute for DNA and served as a negative control.

Amplification products were subjected to electrophoresis in a 2% agarose, 1×TAE (Tris-acetate-EDTA) buffer gel stained with green viewer (0.5μg/mL) and examined under UV light.

Results

The age range in the patients group (case group) was 2-78 years with a mean age of 48.06±18.55 years. In the control group, it was from 15 to 90 years with a

Table-1: PCR primers, product length and annealing temperature.

Virus/ Genome	Amplification Region	Sequence (5'-3')	Annealing Temperature	Product size
β-Globin		CAACTTCATCCACGTTCACC GAAGAGCCAAGGACAGGTAC	55°C	268bp
EBV	BamHI-W fragment	TCGCGTTGCTAGGCCACCTT CTTGGATGGCGGAGTCAGCG	58°C	296bp

EBV: Epstein-Barr Virus.

Table-2: Clinical data of selected non-Hodgkin's lymphoma patients.

Patient	Gender	Age (Years)	Type of NHL	Tumor Location	EBV Positivity
1	F	43	Low grade B-cell	2	+
2	F	62	Low grade B-cell	3	-
3	M	78	Peripheral T-cell	4	-
4	F	45	Low grade B-cell	5	-
5	F	37	DLBCL	1	-
6	F	19	DLBCL	5	+
7	F	66	DLBCL	5	+
8	M	42	DLBCL	1	-
9	M	51	Low grade B-cell	2	-
10	F	58	DLBCL	5	-
11	F	31	Low grade B-cell	2	-
12	F	66	DLBCL	5	+
13	F	70	Low grade B-cell	7	-
14	F	42	DLBCL	3	-
15	F	71	Low grade B-cell	6	-
16	F	33	DLBCL	5	+
17	M	6	Low grade B-cell	3	-
18	M	38	Low grade B-cell	5	+
19	F	38	Peripheral T-cell	7	-
20	F	2	Low grade B-cell	3	-
21	F	50	DLBCL	5	+
22	F	64	DLBCL	5	-
23	M	50	Low grade B-cell	7	-
24	F	70	Peripheral T-cell	3	-
25	F	33	Low grade B-cell	5	-
26	F	59	Low grade B-cell	7	-
27	F	58	DLBCL	4	-
28	M	60	DLBCL	1	+
29	F	71	Low grade B-cell	6	-
30	F	60	Low grade B-cell	1	-
31	F	51	Low grade B-cell	5	-
32	F	43	Low grade B-cell	7	-
33	F	20	DLBCL	5	+
34	M	47	DLBCL	1	-

Locations: (1) Tonsil, (2) Maxillary Sinus, (3) Maxilla, (4) Parotid, (5) Lymph node, (6) Tongue, (7) Mandible soft tissue.
NHL: Non-Hodgkin's Lymphomas; EBV: Epstein-Barr Virus.

mean of 45.5±22.57 years, and the t test showed no significant differences between the case and control group (p<0.717). In case group, 8 (23.5%) patients and 26 (76.5%) patients were male and female respectively. Although there was a female predominance in the case group, it was not statistically significant (p< 0.790). In the control group, 2 (20%) were males and 8 (80%) were females. No significant difference was found between case and control groups for gender by the Pearson chi-square test.

The DNA was extracted from all the samples. EBV-DNA was detected in 9 of 34(26.5%) samples of NHL lymphomas, and none of the normal lymph node tissues by PCR. The Pearson chi-square test revealed no significant difference (p<0.068) for detection of EBV-DNA between samples of NHL and control groups. The mean age in NHL patients with positive genome of EBV was 43.88±18.09 years, ranging from 19 to 66. In the patients group, EBV was detected in 25% males and 26.9% females, and no significant difference was observed between the two groups of EBV positive and negative for sex distribution (p<0.914). There was also no relationship between age and EBV positive NHL (p<0.44).

The histologic subtypes were Low grade B-cell lymphoma in 17 cases, Diffuse large B-cell lymphoma (DLBCL) in 14, and Peripheral T-cell lymphoma in 3 cases. Out of nine EBV-positive cases, 7 cases were of the DLBCL and 2 cases were Low grade B - cell lymphoma. None of the Peripheral T-cell lymphomas showed EBV expression. Although DLBCL was the prominent histologic subtype in EBV-positive NHL, but regarding the low number of cases in each group, statistical analysis could not be performed.

The greatest number of tumours occurred in the lymph nodes (12/34), tonsil (5/34), maxilla (5/34) and Mandibular soft tissue (5/34). Three lymphomas were located in the maxillary sinus; 2 tumours presented in the tongue and there were 2 tumours in parotid. Most of EBV positive NHLs (7 cases) were located in lymph nodes. The next other sites include maxillary sinus (1 case) and tonsils (1 case). Because of the low number of lymphomas included in the different locations, the results cannot be statistically well supported.

Detailed information on age, sex, disease subtype, tumour location and EBV positivity are summarized in Table-2.

Discussion

Lymphomas can be simply defined as malignant neoplasms of lymphocytes and their precursor cells. It has been known traditionally to divide lymphomas into Hodgkin's disease (HD) and non-Hodgkin's lymphomas (NHLs) because of their difference in histology and patterns of behaviour.[1] In most instances NHLs initially arise within lymph nodes and tend to grow as solid masses. How ever, they present up to 40% of the time at an extra nodal site. Moreover, 2-3% of these extra nodal cases may arise primarily in the oral cavity and jaws.[14] NHLs are the most frequent non-epithelial neoplasms in the oral cavity and maxillofacial region, and represent the second most common group of malignant lesions in this site following squamous cell carcinoma.[3]

The incidence of NHL has increased over the last four decades. In general, this increase has been noted for all age groups, especially between the fifth and seventh decades of life.[15] Children may be affected too, particularly by the more aggressive intermediate and high-grade Lymphomas.[16] Although a NHL increase has been noted for both genders, it is more common in males than females.[15] In this current study, the mean age of patients was 48.06 years, with 26 females and 8 males. The greater number of female patients in this study is in contrast with the general data that find males to be in more danger of NHL disease. Additionally, these lesions are difficult to recognize because there are no pathognomonic oral clinical symptoms, though chronic tumefaction is the most frequent clinical feature.[17]

The etiology of NHL is uncertain. NHL is more common in patients with immunological deficiencies, like congenital immunodeficiency, Sjögren's syndrome and AIDS.[6] Oral NHLs are strongly associated with HIV infection and NHL is the second most common malignancy associated with HIV infection after Kaposi's sarcoma.[18] De Cesare et al. described that patients infected with Sjögren's syndrome are 40 times more likely than healthy individuals to develop secondary malignant lymphomas.[19] In our study, none of the patients had immunodeficiency states (HIV infection and Sjögren's syndrome included) or history of organ transplantation.

Viral infections, especially by Epstein-Barr virus (EBV), have been implicated in lymphomagenesis. More than 90% of adults worldwide are infected with EBV.[20] EBV preferentially infects B-lymphocytes through the binding of the receptor on the surface of B-cells. After primary infection, the virus remains in an asymptomatic latent state.[21] Under circumstances in which the host's cellular immune system fails to control EBV-induced B-cell proliferation, infected carrier B-cells can transform from their latent state into malignant cells. The finding of clonal EBV-infected cells supports the concept that EBV was present in the cells before neoplastic transformation, and therefore EBV may play a role in the pathogenesis of some kinds of lymphoma.[11] In oral cavity, EBV is transmitted in saliva and initially infects oral and pharyngeal epithelial cells. As the virus replicates and is released from the epithelial cells, B-lymphocytes in the nearby lymphoid tissues become infected. Thus, oral NHL in close proximity to oral mucosal epithelium may show a high rate of EBV infection.[22,23]

Frequency of EBV in patients with head and neck NHL is different, ranges from 0% to 83% in different subtypes of NHL from various anatomical sites.[18] In one study, Bahnassy et al. detected the EBV genome in 70% and 90% of Head and neck extranodal NHL samples by EBER in situ hybridization and PCR in Egypt.[24] The frequency of EBV infection of NHLs is influenced by various factors such as the patient's immune status, the disease histologic subtype, the anatomical site of the tumour, and the sensitivity of the detection method.[18,24] EBV infection is highly associated with lymphoma in immuno-compromised patients. HIV-related NHL is strongly associated with EBV infection. Leong et al. showed that all of the immuno-suppression-related oral NHLs were EBV-infected, whereas the EBV infection rate in the NHLs of the presumably immuno-competent patients was only 9%.[18] Similarly, Iamaroon et al. demonstrated that EBV infection is highly associated with oral NHLs in HIV-infected patients and claimed that the situation in non-infected patients is less clear.[25] Our study showed no significant association between EBV and NHL patients without any history of primary or secondary immuno-deficiencies. In contrast to our results, Solomides et al. detected high frequency of EBV infection (14% of B-cell and 36% of pleomorphic T-cell lymphoma) in oral lymphoma in immuno-competent patients.[26]

It is important to consider the geographic distribution when discussing the association between EBV and NHL. We could not find any similar study that evaluates the impact of EBV in the head and neck NHL in the Iranian population. We also did not find any literature on the prevalence of EBV antibodies in the general population in northeastern Iran, but the frequency of this infection has been reported around 81.3% among children in southeastern Iran.[27] Moreover, in another survey, the incidence of 70% was reported for EBV infection within the asymptomatic population of Iran.[28] Despite the relatively high frequency of EBV infection in the normal Iranian population, our study showed that none of the normal samples were positive for EBV genome by PCR. However, the number of normal samples is relatively small and further studies are required to corroborate these findings.

Histopathologically, B-cell lymphomas are the most common phenotype in head and neck.[29] Although most are DLBCL, other types such as Burkitt's lymphoma, T-cell and natural killer cell lymphomas are seen in different sites of oral cavity and maxillofacial region.[14]

EBV-associated B-cell lymphomas include Burkitt lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma and post- transplant lymphomas.

Furthermore EBV is strongly associated with certain types of NHLs, such as endemic Burkitt's lymphoma and immuno-suppression-associated lymphomas.[9] Most of our lymphoma cases (91%) were of B-cell lineage. The most frequent histologic subtype was Low grade B-cell lymphoma found in 17(50%) cases. Second most common subtype was DLBCL and 14 (41.2%) cases had this type, 3 (8.8 %) cases had peripheral T cell lymphoma. We found a frequency of 26.5% for EBV infection associated with NHLs in our cases. EBV was found to be positive in 50% of DLBCL cases and this ratio was 11.8% in low grade B-cells. None of the peripheral T cell lymphomas showed EBV expression. In contrast to our results, Leong et al. showed a higher association of EBV with T-cell lymphomas than with B-cell lymphomas, especially in immunocompromised patients.[18]

It is generally accepted that the most common site of NHL in head and neck is Waldeyr's ring (tonsil, nasopharynx, base of the tongue, palatine tonsil). Tonsils are the most frequent site among all Waldeyr's ring-NHLs.[30] Oral cavity and the salivary glands are the most common sites of NHL involvement after Waldeyr's ring. In the oral cavity, the most frequent described locations are the hard palate, the gingiva, and the buccal mucosa. In the salivary glands, the vast majority of lymphomas are located in the parotid followed by the submandibular salivary gland. Sublingual or minor salivary glands are rarely involved.[31] Lymphoma arising central in a single bone, known as primary intra-osseous lymphoma, is a rare condition and constitutes 5% of extra nodal lymphomas. The most common primary intra-osseous lymphoma is non-Hodgkin's large cell type. Jaw involvement by NHL is rare, but among jaw lesions, maxilla is more frequently involved than mandible.[32]

In our study nodal NHL was the most frequent site, occurring in 35.2% patients, followed by NHL of Tonsil (14.8% cases), the Maxilla (14.8% cases), the mandible soft tissue (14.8% cases), the maxillary sinus (8.8% cases), of parotid (5.8% cases), and of the tongue (5.8% cases).

Site-based differences can affect EBV prevalence. For example, T-cell/natural killer cell lymphomas in the nasal regions have been shown to be preferentially associated with EBV.[25] In our series, the most frequent site for EBV infection was lymph nodes (58.3% positive and 41.6% negative), the other sites included maxillary sinus (33.30% positive and 66.7% negative) and tonsils (20% positive and 80% negative). EBV was not detected in any other anatomic sites.

Conclusion

In conclusion, the prevalence of EBV in our HNLs is variable depending on the histological type and anatomical location. Furthermore, considering the high frequency of EBV infection among the general Iranian population, we suspect that the presence of the EBV-DNA in only 26.5% of our immuno-competent patients may be due to the endemic nature of EBV infection. However, the sample number of lymphomas is relatively small, a prospective longitudinal study of EBV infection and head and neck NHLs should be further investigated in order to obtain a more reliable picture of this association in the Iranian population. We used PCR for detection of EBV-DNA which is a highly sensitive method; but, using in situ hybridization and immuno-histochemistry for localization of EBV in the cellular component of the tumour is recommended.

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