

## RESEARCH ARTICLE

# Determination of Frequency of Epstein-Barr Virus in Non-Hodgkin Lymphomas Using EBV Latent Membrane Protein 1 (EBV-LMP1) Immunohistochemical Staining

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### Abstract

**Background:** The presence of Epstein-Barr virus (EBV) in Non-Hodgkin's lymphoma can be identified by immunohistochemistry for detection of EBV latent membrane protein (LMP). The role of EBV as an etiologic agent in the development of non-Hodgkin lymphoma has been supported by detection of high levels of latent membrane protein 1 (LMP-1) expression in tumors. However, no study has been conducted in a Pakistani population up till now to determine the frequency of Epstein-Barr virus positivity. The objective of our study was to determine a value for non-Hodgkin lymphoma patients using EBV LMP-1 immunostaining in our institution. **Materials and Methods:** This study was carried out at the Department of Histopathology, Armed Forces Institute of Pathology (AFIP), Pakistan from December 2011 to December 2012. It was a cross sectional study. A total of 71 patients who were diagnosed with various subtypes of NHL after histological and EBV LMP-1 immunohistochemical evaluation were studied. Sampling technique was non-probability purposive. Statistical analysis was achieved using SPSS version 17.0. Mean and SD were calculated for quantitative variables like patient age. Frequencies and percentages were calculated for qualitative variables like subgroup of NHL, results outcome of IHC for EBV and gender distribution. **Results:** Mean age of the patients was  $53.6 \pm 16$  years (Mean  $\pm$  SD). A total of 50 (70.4%) were male and 21 (29.6%) were female. Some 9 (12.7%) out of 71 cases were positive for EBV-LMP-1 immunostaining, 2 (22.2%) follicular lymphoma cases, 1 (11.1%) case of T-cell lymphoblastic lymphoma, 4 (44.4%) cases of diffuse large B cell lymphomas, 1 (11.1%) mantle cell lymphoma and 1 (11.1%) angioimmunoblastic T cell lymphoma case. **Conclusion:** In our study, frequency of EBV in NHL is 12.7% and is mostly seen in diffuse large B cell lymphoma. This requires further evaluation to find out whether this positivity is due to co-infection or has a role in pathogenesis.

**Keywords:** Epstein-Barr virus - NHL - immunohistochemistry - latent membrane protein-1

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### Introduction

Non Hodgkin lymphoma (NHL) is a diverse group of neoplasms both in their natural history and in their response to treatment. Available epidemiological data from various parts of Asia indicate marked geographical variation in the incidence, histopathologic and clinical behavior of NHL. Non Hodgkin lymphoma appears to be more common in developing countries, where a combination of environmental, infectious and genetic factors affect the development of these disorders. In the developed countries, the disease occurs more often in whites than in blacks, and it is about 50% more common among men than women (Mushtaq et al., 2008). In one Pakistani study, 73% of lymphomas were Non-Hodgkin lymphomas (NHL) and 27% were Hodgkin lymphomas (Mushtaq et al., 2008). Amongst the Non-Hodgkin lymphomas, B cell lymphomas were 86% and T cell

lymphomas were 14%. The most common B cell NHL was Diffuse large B cell lymphoma (DLBCL), followed by follicular lymphoma (6%), Burkitt's lymphoma and Lymphoblastic lymphoma (4% each) and others (10%) (Matsushita et al., 2012).

Epstein-Barr virus (EBV) is a widespread tumorigenic human herpes virus that establishes lifelong asymptomatic infection of B cells in the majority of humans, generally without causing disease (Williams et al., 2006; Mao et al., 2013). Epstein-Barr virus is associated with number of lymphoproliferative disorders including Burkitt's lymphoma (98%) (Nourse et al., 2012), post transplantation lymphoproliferative disease (PTLD), Angioimmunoblastic T-cell Lymphomas (AITL) (84.6%), natural killer (NK) cell lymphomas, lymphomatoid granulomatosis and Hodgkin's lymphoma (40%) (Nourse et al., 2012). While the exact role of EBV in the pathogenesis of each type of lymphoma still needs to

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be elucidated, epidemiologic studies have shown strong association between Epstein-Barr virus and Non-Hodgkin lymphomas.

Epstein Barr virus (EBV) is an important example of a transforming virus implicated in several NHL subtypes (Beltran et al., 2011). EBV is usually acquired in early childhood in developing countries. In developed countries, primary infection in adolescence is associated with the clinical syndrome of infectious mononucleosis. Following primary infection, EBV persists lifelong in the host in a latent state in memory B lymphocytes. EBV readily transforms B lymphocytes in vitro. Multiple EBV proteins can be expressed in infected lymphocytes, among which latent membrane protein-1 is thought to be most important for transformation. In healthy infected individuals, outgrowth of EBV-transformed B lymphocytes is prevented by the presence of intact T lymphocyte-mediated immunity (Nourse et al., 2012).

The expression of Epstein-Barr virus in Non-Hodgkin's lymphoma can be identified by immunohistochemistry for detection of Epstein-Barr virus latent membrane protein (LMP). The role of Epstein-Barr virus as etiologic agent in the development of Non-Hodgkin lymphoma has been supported by detection of high levels of latent membrane protein 1 (LMP-1) expression in these tumors. The prevalence of EBV in NHL is 10% (Matsushita et al., 2012).

Study has not been conducted up till now to establish the frequency of Epstein-Barr virus in patients of non-Hodgkin lymphoma in Pakistani population. The objective of our study was to determine the frequency of Epstein-Barr virus in patients of Non-Hodgkin lymphoma by using EBV LMP-1 immunostain in our institution. As EBV is one of the etiological factors for initiation and progression of NHL, so the detection of EBV expression in NHL by immunohistochemistry may offer the prospect for therapeutic interventions targeting EBV encoded proteins

## Materials and Methods

This study was carried out at Department of Histopathology, Armed Forces Institute of Pathology (AFIP), Pakistan from December 2011 to December 2012. It was a cross sectional study. Approval of study was taken from Institutional Review Board (IRB) of AFIP. A total of 71 patients who were diagnosed as various subtypes of NHL after histological and immunohistochemical evaluation were studied. Sampling technique was non-probability purposive. All cases of nodal Non-Hodgkin lymphomas diagnosed on light microscopy and immunohistochemistry according to WHO Classification were included. Scanty tissues, autolyzed tissues, and extranodal NHL were excluded.

The specimens were collected from pathology department. Each was given a case number and medical record number and demographic details of patients were recorded. The specimen were fixed in 10% buffered neutral formalin. After appropriate gross examination, sections were processed and stained with haematoxylin and eosin (H&E). Cases diagnosed as NHL were included. Further subtyping of NHL was done according

to WHO classification of lymphomas by using a panel of immunohistochemical markers, such as, CD45 CD20, CD3, CD79a, PAX5, CD4, CD8, CD23, CD5, CyclinD1, CD10, BCL2, CD56, CD21, CD35 etc. After that LMP1 immunostain was applied on all the selected cases of NHL to determine the expression of EBV. EBV was labeled as positive on finding cytoplasmic staining of tumour cells by EBV-LMP-1 antibody.

Statistical analysis was done using SPSS version 17.0. Mean and SD was calculated for quantitative variables like patients age. Frequencies and percentages were calculated for qualitative variables like subgroup of NHL, result outcome of IHC for EBV antibody and gender distribution. As we found 2 positive cases of EBV among only 8 cases of T-cell lymphomas and 7 positive cases of EBV among 63 cases of B-cell NHL, chi square test was not applicable considering low number of EBV positive cases.

## Results

A total of 71 cases of non Hodgkin lymphomas were included in the study. The mean age of the patients was 53.63±16 years (Mean±SD). The age ranged from 7-82 years. Distribution of patients in various decades was: 1 (1.4%) patient in first decade, 4 (5.6%) in second decade, 2 (2.8%) in third decade, 7 (9.9%) in fourth decade, 14 (19.7%) in fifth decade, 19 (26.8%) in sixth decade, 15 (21.1%) in seventh decade, 8 (11.3%) in eighth decade and 1 (1.4%) in ninth decade.

A total of 50 (70.4%) patients were males and 21 (29.6%) were females. Most of the patients in both the genders were above the age of 40 years.

Our study included 16 (22.7%) cases of small lymphocytic lymphoma, 13 (18.3%) cases of follicular lymphoma, 4 (5.6%) cases of T-lymphoblastic lymphoma, 4 (5.6%) cases of marginal zone lymphoma, 21 (29.6%) cases of diffuse large B cell lymphoma, 2 (2.8%) cases of anaplastic large cell lymphoma, 2 (2.8%) cases of B-lymphoblastic lymphoma, 5 (7.0%) cases of mantle cell lymphoma, 1 (1.4%) case of T-cell rich large B-cell lymphoma, 1 (1.4%) case of ALK negative anaplastic large cell lymphoma, 1 (1.4%) case of angioimmunoblastic T cell lymphoma and 1 (1.4%) case of Burkitt's lymphoma.

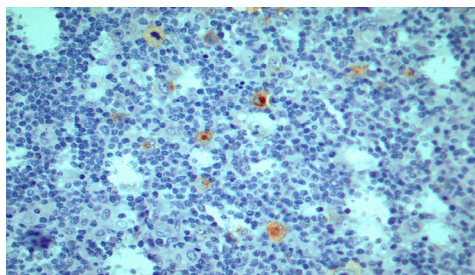
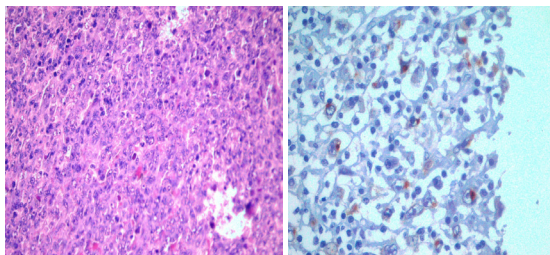
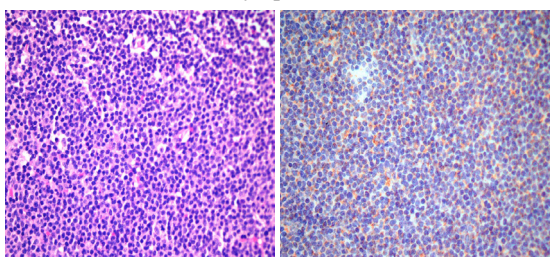
A total of 63 (88.7%) cases were B-cell Non Hodgkin lymphomas and 8 (11.3%) cases were T-cell Non Hodgkin lymphomas.

LMP-1 immunohistochemical marker was positive in 9 (12.7%) cases and negative in 62 (87.3%) cases. EBV-LMP-1 protein expression was observed in 7 (11.1%) cases of B-cell non Hodgkin lymphoma, whereas no expression was seen in 56 (88.9%) cases of B-cell non Hodgkin lymphomas. On the other hand only 2 (25%) cases of T-cell non Hodgkin lymphoma were positive for EBV-LMP-1 and rest (6 cases; 75%) of the cases of T-cell non Hodgkin lymphomas were negative.

Table 1 shows expression of EBV LMP1 antibody in different types of B and T cell Non Hodgkin lymphomas. Out of 9 positive cases, 2 (22.2%) follicular lymphoma cases, 1 (11.1%) case of T-cell lymphoblastic lymphoma, 4 (44.4%) cases of diffuse large B cell lymphoma (Figure 2), 1 (11.1%) case of mantle cell lymphoma (Figure 3) and

**Table 1. Results of EBV-LMP-1 Antibody Expression in Different Non Hodgkin Lymphomas**

Type of lymphoma	EBV Positive	EBV Negative
Small lymphocytic lymphoma/ chronic lymphocytic lymphoma	0	16
Follicular lymphoma	2 (22.2%)	11
T-Lymphoblastic lymphoma	1 (11.1%)	3
Marginal zone lymphoma	0	4
Diffuse large B-cell lymphoma	4 (44.4%)	17
Burkitt's lymphoma	0	1
Anaplastic large cell lymphoma	0	2
B-Lymphoblastic lymphoma	0	2
Mantle cell lymphoma	1 (11.1%)	4
T-cell rich Large B cell lymphoma	0	1
ALK negative anaplastic large cell lymphoma	0	1
Angioimmunoblastic T-cell lymphoma	1 (11.1%)	0
Total	9	62

**Figure 1. Expression of Latent Membrane Protein-1 of EBV in Hodgkin's Lymphoma.** Reed-Sternberg cells (used as control) [40x]**Figure 2. Diffuse Large B-cell Lymphoma Showing Positive Staining of EBV-LMP-1 Antibody (by IHC) in Tumor Cells of DLBCL.** (Positive staining localized in cell membrane and within cytoplasm) [20x]**Figure 3. A and B: EBV-LMP1 Antibody Positivity (by IHC) in Mantle Cell Lymphoma [20x]**

1 (11.1%) case of angioimmunoblastic T cell lymphoma were positive for EBV-LMP-1 antibody.

EBV positivity was mostly seen in sixth decade which had 3 (33.3%) positive cases followed by eighth decade having 2 (22.2%) cases and second, fourth, fifth and seventh decade, each having one (11.1%) positive case.

About 5 (10%) out of 50 males were positive for EBV-LMP-1 immunohistochemical stain, while rest 45 (90%)

did not show any staining pattern. Similarly, 4 (19%) out of 21 females showed positivity for EBV-LMP-1 antibody and 17 (81%) females did not show any staining pattern.

As we found 2 positive cases of EBV among only 8 cases of T-cell lymphomas and 7 positive cases of EBV among 63 cases of B-cell NHL, chi square test was not applicable considering low number of positive cases.

## Discussion

Epstein-Barr virus, first described by Denis Burkitt in 1958, is a member of the herpes virus family. As with other herpes viruses, EBV is an enveloped virus that contains a DNA core surrounded by an icosahedral nucleocapsid and a tegument. Family members include herpes simplex I and II and varicella-zoster virus (alpha virus subfamily), cytomegalovirus and human herpesvirus 6 and 7 (beta herpesvirus subfamily), and human herpes virus 8 and EBV (gamma herpesvirus subfamily) (Mushtaq et al., 2008; Nourse et al., 2012). Human tumors have been attributed to both human herpesvirus 8 (Kaposi's sarcoma, primary effusion lymphoma, and Castleman's disease) and to EBV (Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's and non-Hodgkin's lymphomas).

Immunohistochemistry has developed as an efficient tool to demonstrate presence of EBV. Positive results are considered if there is cytoplasmic staining.

Despite our growing understanding of the role of EBV in the pathogenesis of disease, the optimal management of EBV associated tumors remains unsatisfactory. Exploration of antiviral agents, immune-based therapies, and specific monoclonal antibodies is, however, proceeding with encouraging results (Chabay et al., 2009; Nourse et al., 2012).

Although NHL can be diagnosed in any age group, it is more common in 5<sup>th</sup> and 6<sup>th</sup> decade. The mean age in our study was 53.63±16 years (Mean±SD). The results were comparable to the studies by Mushtaq et al. (2008), Jamal et al. (2006), Veelken et al. (2007) and Young et al. (2009) in which mean ages were 58 years, 55 years, 59 years and 57 years (23-83 years) respectively. In studies by de Jong et al. (2009), Kai et al. (2008) and Lene et al. (2007) mean ages were 68 (22-93 years), 63 (14-90 years) and 65 (29-95 years) respectively. Most of the patients in our study were in 6<sup>th</sup> (26.8%) and 7<sup>th</sup> decades. The results were comparable with most of the above mentioned studies, in which most frequent decades were 6<sup>th</sup> and 7<sup>th</sup> decades. Our study revealed comparatively low mean ages compared with the results of the study in Egypt (Karen et al., 2004) showing 49.5% of NHL cases below 50 years. Age is one of the prognostic factors in a sense that the patients above the age of 60 years generally show poor overall survival.

Globally, NHL is more common in males as compared to females. Similar trend was seen in our study in which 70.4% of patients were males and 29.6% were females. The results were comparable to the studies of Mushtaq et al. (2008), Jamal et al. (2006), de Jong et al. (2009), Young et al. (2009) and Lene et al. (2007) in which males comprised 68%, 70%, 60%, 59% and 65% of the patients respectively.

In our study diffuse Large B-cell lymphoma was the

most common type of NHL (29.6%), followed by small lymphocytic lymphoma/chronic lymphocytic leukemia (18.3%), follicular lymphoma (18.3%), mantle cell lymphoma (7%), T-lymphoblastic lymphoma (5.6%), marginal zone lymphoma (5.6%), B-lymphoblastic lymphoma (2.8%), anaplastic large cell lymphoma (1.4%), ALK-negative Anaplastic large cell lymphoma (1.4%) and angioimmunoblastic T-cell lymphoma (1.4%). Our results were similar with the international data of Armitage et al (Armitage et al., 1997), whose study also showed DLBCL (31%) to be most common type of NHL. Rest of our data was different from his data which showed different frequencies of follicular lymphoma (2.2%), peripheral T-cell lymphoma (7%), small lymphocytic lymphoma (7%), mantle cell lymphoma (6%), anaplastic large T-cell lymphoma (2%), marginal zone lymphoma (2%), T-cell lymphoblastic lymphoma (2%) and Burkitt's lymphoma (<1%). Taken together, the variations in the prevalence of NHL in various studies could be due to different study methodologies of classifications, difference in sample sizes and /or misclassification due to unspecialized personnel used to classify lymphoma. It could also be due to some environmental factors or other unknown causes (Ashraf et al., 2012).

It has been proposed that LMP-1 is expressed in many EBV-associated cancers and is responsible for most of the altered cellular growth properties that are induced by EBV infection (Williams et al., 2006; Tumwine et al., 2010; Montes-Moreno S et al., 2012). In these studies, staining results of the LMP-1 were used to sub classify the NHL into positive EBV or negative EBV.

We used Hodgkin lymphoma case as control since the expression of LMP-1 EBV is higher in Hodgkin lymphoma patients (70%) than in NHL patients (30%) (Gonin J et al., 2011). Few studies showed EBV positivity in 30% of NHL cases (Gonin et al., 2011). In our study, EBV positivity was seen in 12.7% of cases. Diffuse large B-cell lymphomas revealed the highest expression, followed by 2 cases of follicular lymphoma and one case each of T-cell lymphoblastic lymphoma, mantle cell lymphoma and angioimmunoblastic T-cell lymphoma. Rest of the cases did not show any cytoplasmic positivity for LMP-1 EBV stain. It is also worth mentioning that Burkitt's lymphoma is a high grade malignant NHL that is most commonly associated with EBV infection (Malagon et al., 2011). Furthermore, in Africa, Burkitt's lymphoma is associated with Plasmodium Falciparum malaria, and tumours usually present in the jaw. Our study did not report any positive case of Burkitt's lymphoma for EBV-LMP1 antibody. This is most likely due to the fact that our study had just one case of Burkitt's lymphoma. In addition, the above studies confirm that the association of EBV with lymphoma is strongly but variably linked to various environmental factors prevailing in different geographic regions. These include ethnic variations, economic status and health conditions of studied areas as well as the great diversity of lymphoma subtypes (Malagon et al., 2011; Gonin et al., 2011).

Overall EBV expression in our study among all NHL was 12.7% (9 out of 71 cases). Amongst B-cell NHL, EBV positivity was seen in 11.1% (7 out of 63 cases) and

amongst T-cell NHL, EBV positivity was seen in 25% (2 out of 8 cases) of the cases. The high expression of EBV in T-cell NHL is most likely due to lesser number of T-cell NHL cases in our study. Our results were different from an Argentinean study which revealed overall EBV expression of 25% in NHL. When NHL was segregated in B cell and T cell NHL, EBV positivity was seen in 30.43% of B-cell and 11.1% of T-cell NHL (Chabay et al., 2002; George et al., 2012). In another Argentinean study carried out by Paola Chabay which was done on T-cell NHL, revealed 8% positivity for EBV-LMP1 antibody (Paola et al., 2009). In a study by Paydas et al. (2008) overall EBV-LMP1 antibody expression was seen in 14.1% cases (25/177 NHL cases). This result is comparable with our study. However this study had surprising results in a sense that all positive cases were B-cell NHL. Not a single case of T-cell NHL was positive for EBV-LMP1 antibody (Paydas et al., 2008; George et al., 2012). An African study which was done exclusively on B-cell NHL, showed EBV-LMP1 antibody expression in 34.7% of the cases (Tumwine et al., 2010). This high percentage was due to the fact that this study comprised mostly of Burkitt lymphoma which usually shows a very high expression of EBV. On the other hand our study had only one case of Burkitt's lymphoma. It is very well known that Burkitt's lymphoma is very common in Africa as compared to south East Asia. In several other studies carried out by Oyama et al. (2007), Morales et al. (2010) and Park et al. (2007) which were done on B-cell NHL revealed EBV-LMP1 antibody expression ranging from 9 to 15%. These percentages correlated with our results. The variable percentages in different studies may be due to the fact that EBV prevalence may be different in different parts of the world. The results in our study and in other studies regarding association of EBV with NHL suggest that EBV might play a role in pathogenesis of NHL.

In conclusion, frequency of EBV in NHL in our study is 12.7% and is mostly seen in diffuse large B cell lymphomas. This requires further evaluation to find out whether this positivity is due to co-infection or has a role in pathogenesis.

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