

Evaluation of biopsy performed childhood lymphadenopathies: Single center experience

Evaluation of childhood lymphadenopathies

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Abstract

Aim: The aim of the study was to evaluate patients who were followed up with lymphadenopathy and underwent biopsy in Afyon Health Sciences University Pediatric Hematology/Oncology Department and to assess the potential correlations between the presence of antibodies against EBV antigens in serum samples and the presence of EBER in lymph node tissues.

Material and Methods: All cases diagnosed with lymphadenopathy and excisional biopsy performed in the Pediatric Hematology and Oncology Department, between January 2018 to January 2020 were retrospectively evaluated. Medical records (gender, age, medical history, sore throat, fever, cough, history of upper respiratory tract infection, animal contact and travel, duration of symptoms) of patients, as well as their treatment history were examined. Tissue EBER status, serological tests for EBV (EBV VCA IgG, VCA IgM, EBNA IgG, EBNA IgM, and EA IgG) data were recorded from files.

Results: Our study included 22 patients comprising 10 females (%45.4) and 12 males (%54.5). At the time of the diagnosis, the median age was 8 (range, 2 to 17) years. Five (22.6%) of 22 biopsies were reported to be malignant. Reactive lymphoid hyperplasia was seen in 15 (68.1%) patients. Statistical analysis revealed a significant correlation between anti-VCA IgG serology and the EBER status ($p=0.03$).

Discussion: In conclusion, lymphadenopathy is a common clinical condition in childhood and often develops due to reactive hyperplasia. It was determined that patients with serum EBV VCA IgG positive were also EBER positive in the tissue.

Keywords

Lymphadenopathy, Epstein Barr Virus, Reactive Hyperplasia

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Introduction

Epstein-Barr Virus (EBV) has a worldwide distribution, over 90% of people develop antibodies against the Epstein-Barr virus (EBV) before they reach adulthood [1].

It is also the first human cancer virus recognized as the cause of endemic Burkitt lymphoma. Along with Burkitt lymphoma, EBV is linked to the pathogenesis of Hodgkin lymphoma, gastric cancer, nasopharyngeal carcinoma, and a wide range of other cancers in people with inherent or acquired immunodeficiency. Depending on the child’s age, location, and race/ethnicity, the prevalence of EBV infection ranges from 10 to 90% [2].

Infection of the virus includes atypical lymphocytes and heterophile antibodies. Determining the presence of antibodies against EBV major antigens during infection is very useful and is especially important in identifying patients who do not have atypical lymphocytosis and heterophile antibodies, but suspected to have EBV infection. Epstein-Barr Virus serology is also required to differentiate acute infection from reactivation [3].

Major antigens of the virus are EBV nuclear antigen (EBV-nuclear antigen=EBNA), early antigen (early antigen=EA), viral capsid antigen (viral capsid antigen=VCA), membrane antigen (membrane antigen=MA), latent membrane protein (latent membrane protein=LMP). IgM antibodies against the viral capsid antigen are indicative of acute infection and are seen in the first week of infection and are detected for three months. IgG antibodies against the viral capsid antigen appear 4-7 days after the onset of symptoms and remain for life. Epstein-Barr nuclear antigen IgG antibodies are indicative of the transition from acute infection to the convalescent period and may persist for life.

Epstein-Barr virus (EBV)-encoded small RNAs (EBERs) are noncoding RNAs that are expressed abundantly in latently EBV-infected cells. EBERs have been discovered to interact with cellular proteins that play a key role in antiviral innate immunity [4].

The aim of the study was to evaluate the patients who were followed up with lymphadenopathy and underwent biopsy in Afyon Health Sciences University Pediatric Hematology/Oncology Department and to assess the potential correlations between the presence of antibodies against EBV antigens in serum samples and the presence of EBER in lymph node tissues.

Material and Methods

All cases diagnosed with lymphadenopathy and performed excisional biopsy in the Pediatric Hematology and Oncology Department, between January 2018 to January 2020 were retrospectively evaluated. Inclusion criteria were children and adolescents aged between 0 and 18 years who underwent excisional biopsy for lymphadenopathy.

We removed all identifiers from our data after the analyses were completed to protect patient privacy. Medical records (gender, age, medical history, sore throat, fever, cough, history of upper respiratory tract infection, animal contact and travel, duration of symptoms) of patients, as well as their treatment history were examined. Physical examination noted the location, size, laterality, mobility, and tenderness of the lymph node, associated systemic symptoms, including weight loss, night

sweats, fever, and hepatosplenomegaly for each patient.

Tissue EBER status, serological tests for EBV (EBV VCA IgG, VCA IgM, EBNA IgG, EBNA IgM, and EA IgG) data were recorded from the files.

Ethical Approval

Informed consent was obtained from all patients.

The study was performed according to the principles of the Declaration of Helsinki.

The study was approved by the institutional review board of the Afyon Health Science University Faculty of Medicine (2020-05-05). Decision Number: 2020/197.

Statistics

Calculations were made using the Statistical Package for Social Studies (SPSS, version 18). The Kaplan–Meier method was used for survival analysis, and the log-rank test was used to compare different groups (significance level $p < 0.05$).

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Our study included 22 patients comprising 10 females (%45.4) and 12 males (%54.5). At the time of the diagnosis, the median age was 8 (range, 2 to 17) years.

Lymph node biopsy was performed because of one of the following factors: fixed and hard lymph nodes, supraclavicular localization, progressive increase in size, unresponsiveness to empirical antibiotics, the presence of constitutional symptoms like fever of unknown origin, night sweats or weight loss. Five (22.6%) of 22 biopsies were reported to be malignant.

Table 1. Histopathological diagnosis according to the age groups.

Diagnosis	Number (%)
Reactive lymphoid hyperplasia	15(68.1)
Hodgkin lymphoma	4(18.1)
Non-Hodgkin lymphoma	1(4.5)
Tuberculosis lymphadenitis	1(4.5)
Cat scratch disease	1(4.5)

Table 2. EBV VCA IgG, VCA IgM, EBNA IgG, EBNA IgM and EA IgG serology.

EBV Serology	Positive Patient Number (%)
VCA IgG	18(81.8)
VCA IgM	3(13.6)
EBNA IgG	17(77.2)
EBNA IgM	4(18.1)
EA IgG	6(27.2)

Table 3. EBER status comparison with the EBV-VCA IgG serology.

		EBER Status	
		Positive	Negative
EBV VCA	Positive	5	13
IgG	Negative	1	3

Reactive lymphoid hyperplasia was seen in 15 (68.1%) patients. Histopathological diagnosis according to the age groups is shown in Table 1.

EBVCAIgG was positive in 18 (81.8%) patient. EBV VCA IgG, VCA IgM, EBNA IgG, EBNA IgM, EA IgG serology is shown in Table 2.

EBV: Epstein-Barr Virus, VCA: Viral Capsid Antigen, EBNA: Epstein-Barr nuclear antigen, EA: Early antigen

A comparison of EBER status with VCA IgG serology is presented in Table 3.

The statistical analysis revealed a significant correlation between the anti-VCA IgG serology and the EBER status ($p=0.03$).

Discussion

One of the most common causes of pediatric department visits in children is lymphadenopathy (LAP) [5]. Neck masses such as vascular malformations, benign tumors, and congenital cystic lesions can mimic LAP and need to be referred to a pediatrician or a pediatric hematologist/oncologist [6].

LAP can result from many kinds of illnesses, but reactive lymphoid hyperplasia following an acute viral or bacterial infection is the most frequent cause in children [7]. A study by Rajasekaran et al. showed that biopsied lymph nodes were malignant. In a study by Rajasekaran et al., it was shown that 15% of the biopsied lymph nodes in children represented a malignancy [8]. In a study from our country, reactive lymphadenopathy was observed in 80% of patients with cervical lymphadenopathy [9]. In our study, about 70% of the patients had reactive lymphadenopathy. Although tuberculous cervical lymphadenopathy is not so common in children [10], the frequency of tuberculosis is increasing in our country, so it should be kept in mind in patients with lymphadenopathy. In our study, tuberculous lymphadenitis was seen in one patient.

Clinical history, physical examination, and laboratory tests in LAP give helpful indicators for the diagnosis of the majority of patients [11]. Excisional biopsy may be necessary in some circumstances for an exact diagnosis. The reported incidence of malignancy in pediatric cervical LAPs ranges from 1% to 72%. The reported incidence of malignancy in pediatric cervical LAPs ranges from 8% to 76% [12]. In a research, a biopsy was performed in 38.7% of the cases, and in 60% of the biopsy specimens, malignant neoplasms were found [13]. In our study, malignancy rate was 22.6% and it was similar to other centers in our country [14]. Recent studies have shown that one of the most common malignant causes of lymphadenopathy is lymphoma [15]. Hodgkin lymphoma was the main cause of the malignant LAP group in our study, therefore our findings complied with recent studies [16].

Determination of EBV seroprevalence in the population is also necessary in terms of identifying individuals at risk, especially since it is an oncogenic virus and is involved in the etiology of many idiopathic diseases. In patients with nasopharyngeal carcinoma and Burkitt's lymphoma, EBV VCA IgG titers are 8-10 times higher than in healthy individuals [17]. In a study by Sharifipour et al., the seroprevalence of Epstein-Barr virus among children was reported to be 87.5% [18]. EBV VCA Ig G positivity in our study was compatible with the literature.

Previous studies demonstrated that EBER play significant roles in various EBV-infected cancer cells [19]. Recently, it has been reported that EBER is released from EBV-infected cells, resulting in induction of inflammatory cytokines and subsequent immune activation. Furthermore, EBER could be detected in the sera of patients with active EBV infectious diseases, suggesting that it is a causative agent of the diseases. There are some studies that establish a connection between EBV positivity and high antibody levels [20]. In our study, there was a statistically significant correlation between the EBV infection intensity and the EBER status.

Limitation

The limitations of the study were that it was a single-center, retrospective study and had a small number of patients.

Conclusion

In conclusion, lymphadenopathy is a common clinical condition in childhood and often develops due to reactive hyperplasia. There is a correlation between tissue EBER status and EBVCA IgG positivity.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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