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Effect of age and gender on EBV associated-Hodgkin lymphoma among sample of Iraqi patients

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Abstract---Background: Data on the age-specific prevalence of Epstein–Barr virus (EBV) infection. According to most studies, by the age of 35, more than 90% of adults are EBV antibody positive. Comparison of demographic groups could identify factors associated with its acquisition. Methods: The Present study conducted in AL-Najaf Holy City; it is a cross sectional study. All patients were recruited from Middle Euphrates Cancer Research Unit Laboratory, from pre-existing samples. Tissues collected from the previously mentioned laboratory were fixed in 10% formalin and placed in a cassette before being embedded in paraffine. The tissues were examined and diagnosed as with Hodgkin disease. forty samples were subjected in the present study. All study group was diagnosed formerly as paraffin imbedding blocks. Histopathological examination using hematoxylin and eosine stain (H&E) then examining under light microscope to check for twenty block samples of tissues with lymphoma. Results: From a total of 40 FFPET blocks were tested. The mean age was 34.92 years. The age group prevalence was as follows: ≤10 years, 2.5%; 10–20 years, 25%; 21–30 years, 22.5%; 31–40 years, 10%; and 41–50 years, 20%; ≥ 50, 20%.

Keywords---EBV, FFPET, IHC, HL, Hodgkin disease.

Introduction

The Epstein-Barr virus is widespread, infecting more than 90% of the world's population (Sausen et al. 2021). EBV was identified as a tumor virus by the World Health Organization (WHO) in 1997(Mazouni et al., 2015). In the case where the

EBV infects the B cells in-vitro, 6 of the EBV nuclear antigen (EBNA) proteins (EBNA 1, 2, 3-a, 3-b, 3-c, and EBNA-LP) are expressed, in combination with 3 membrane protein types, which are, LMP2A, LMP1 and 2B. The EBERs, 2 small non-polyadenylated RNA transcripts, are likewise highly expressed (Jarrett RF, 2003)(Kang and Kieff 2015). Hodgkin lymphoma (HL) is a B-cell malignancy that has five histological subgroups: lymphocyte-rich, lymphocyte-depleted, nodular sclerosis, and mixed cellularity subtypes, all of which are referred to as classical HL; and the nodular lymphocyte-predominant HL (NLPHL) subtype (Wong et al. 2022).

The epidemiology of HL is complicated, which points to a multiple cause. It's likely that environmental and genetic factors will interact. Depending on the age group and geographic origin, different factors affect EBV's contribution to the HL pathogenesis. EBV has a role in its pathogenesis of Hodgkin lymphoma., the virus is responsible for almost half of all instances of Hodgkin lymphoma (Grewal et al. 2018). EBV infection causes immunosuppression and chronic antigenic activation, both of which are essential components of the neoplastic process (Castillo et al. 2018; Medhat and Aljanaby, 2022). The age of the individual at the time of primary EBV infection, as well as his genetic background, appear to be important factors in the clinical manifestations of the infection. When primary infection with the virus occurs in early childhood, as is common in developing countries, there are few, if any, symptoms. In contrast, if primary infection is delayed until adolescence, as is common in developed countries, it is associated with the clinical syndrome infectious mononucleosis (Hadi and Aljanaby, 2022).

A wide variety of cohort and case-control studies have revealed that mononucleosis is associated with an increased risk of HL. In the largest investigation, a Scandinavian cohort study involving 38,000 mononucleosis patients, mononucleosis was linked to a more than 2.5-fold increased HL risk, which though it declined over time remained significantly elevated for as long as two decades. Furthermore, because mononucleosis commonly affects adolescents, young adults had a 3.5-fold higher risk of developing HL. In contrast to the age group for whom the IM relationship is highest, young adults, EBV is relatively uncommon in HL. It seems that earlier exposure to EBV reduces the risk of developing adolescent mononucleosis, which in turn reduces the risk of developing young-adult-onset EBV+ HL.

Method

Detection of membranous latent protein LMP-1 of EBV from paraffin-embedded tissue blocks of patients with Hodgkin disease was done using immunohistochemistry technique. EBV - LMP1 primary antibody, Monoclonal Mouse Anti –Epstein-Barr Virus, LMP-1, Clones CS1-4, Ready-to-Use. The cytoplasmic and membranous staining pattern was done based on DAKO kit. Blueish staining of the cytoplasm and membrane was regarded as negative for EBV LMP-1, whereas brown granular cytoplasmic and membrane staining was viewed as positive for EBV LMP-1. A tissue that was known to have EBV LMP-1 used as positive control.

Results

These blocks were taken from patients of age groups ranging from (5 to 71)years. The mean age was 40.50 (±17.5) years. Male constituted (23)57.5 % and female account (17) 42.5% of the study group. The maximum age among participants was 71 years, while the minimum age was 5 years. Regarding the distribution of patients with Hodgkin lymphoma according to age group, the current study also revealed that the age group of 10-20 years and 21-30 with higher frequency within Hodgkin lymphomas' patient's blocks, 25%/and 22% Respectively. In other hand the age groups of 31-40 shows a frequency of 10%) and the age group of 41-50 and more than 50 years showed a frequency of 20% for each age group as shown in figure 1. The immunohistochemistry technique which employed for EBV-LMP-1 protein detection for forty from paraffin embedded tissue, the protein was identified in 6/40(15%) of Hodgkin lymphoma blocks samples. The results of the present study showed that the EBV- LMP-1 protein was positive in 6/40 (15%) of patients with Hodgkin lymphoma was positive for of EBV- LMP-1 protein, there was no statistical difference between male and female for EBV-LMP-1, where 4 males are positive of EBV-LMP-1, as well as 2 females were positive of EBV-LMP-1 samples as in (Table 2).

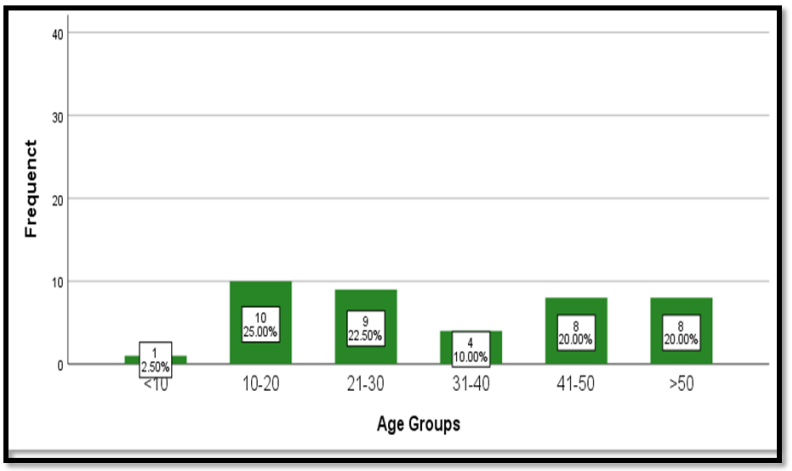

Figure 1. Age groups in Hodgkin Lymphoma

Table 1
Distribution sample for EBV-LMP1-protine according to the age groups

Age Group \ IHC		LMP-1 protein		Total	P-value
		Positive	Negative		
Age Group	<10	0	1	1	0.91
		0.0%	100.0%	100.0%	
	10-20	2	8	10	
		20.0%	80.0%	100.0%	
	21-30	2	7	9	
		22.2%	77.8%	100.0%	
	31-40	0	4	4	

		0.0%	100.0%	100.0%	
	41-50	1	7	8	
		12.5%	87.5%	100.0%	
	>50	1	7	8	
		12.5%	87.5%	100.0%	
Total		6	34	40	
		15.0%	85.0%	100.0%	

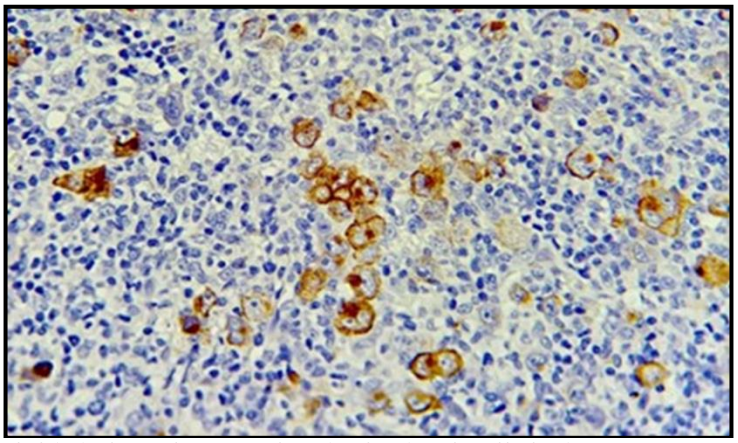

Figure 2. Hodgkin's lymphoma, classical mixed cellularity type, RS cells positive for (brown staining) (Reed-Sternberg cells are the hallmark cells of Hodgkin's lymphoma

Table 2
Distribution sample for EBV-LMP1-gene according to gender LMP1

Gender \ IHC		LMP-1 protein		Total
		Positive	Negative	
Gender	Male	4	19	23
		17.4%	82.6%	100.0%
	Female	2	15	17
		11.8%	88.2%	100.0%
Total		6	34	40
		15.0%	85.0%	100.0%
P-value		0.48		

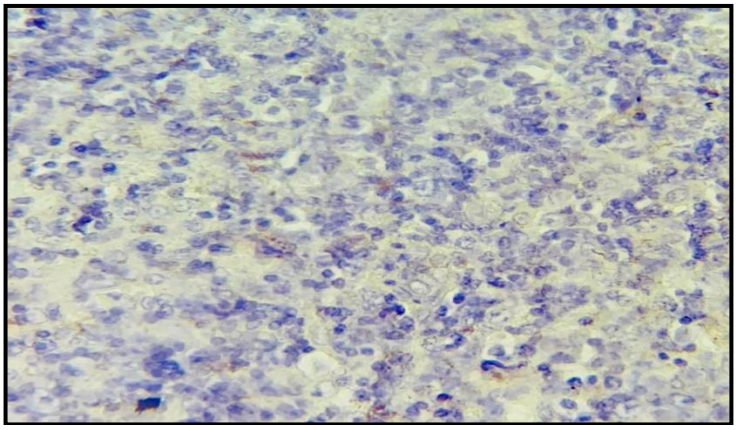

Figure 3. A and B: Hodgkin's lymphoma - classical mixed cellularity type, negative for LMP1. IHC 10x40

Discussion

The incidence of Hodgkin's disease varies greatly depending on age, gender, race, geographical location, social class, and histological subtype (Alhasnawi and Aljanaby, 2022). The EBV is linked to approximately 40% of cases in developed countries, and there is evidence that mixed cellularity Hodgkin's disease is more likely to be EBV-related than nodular sclerosis Hodgkin's disease(A. F. Jarrett, Armstrong, and Alexander 1996). In this study, the results showed a relationship between Hodgkin lymphoma and age; were consistent with most studies. It is well known that the age-incidence curve for Hodgkin diseases in developed countries is bimodal, with the first peak occurring between the ages of 15 and 34 and the second peak occurring in over 60 years (Wang et al. 2019). The results of the current study the age group (20-35) aligned with this line. EBV positivity is common in children (10 years) and older adults (>60 years). Patients with HL. The current results found that HL was more likely to be EBV-associated.

The current study's results aligned with (Houldcroft and Kellam 2015) and (Kimura and Fujiwara 2019; Swerdlow et al. 2016) findings that found young children and older people, EBV-positive HL is more prevalent than EBV-negative HL. Within HL cases, age effects were observed, with young adults being more likely to have EBV-associated disease than older. And these results correspond with many other studies (Nagpal, Descalzi-Montoya, and Lodhi 2021)(Jimenez et al. 2021). Regarding patient gender in present study, there were no appreciable differences in the distribution of lymphoma associated with EBV infection. And this do not correspond with studies conducted by (Singh, D., Vaccarella et al., 2022; Aljanaby et al., 2022) and (Horesh and Horowitz 2014) where across world regions and countries, males consistently had greater incidence and mortality rates than females in HL, and this may be attributed to geographical patterns, sample size and ethnicity.

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