HODGKIN LYMPHOMA AND ITS ASSOCIATION WITH EPSTEIN-BARR VIRUS IN KURDISTAN, NORTHERN IRAQ

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ABSTRACT

Background: Epstein Barr virus (EBV) has been linked to the etiology of several malignancies, including Hodgkin's Lymphoma (HL). However, the degree of this association varies between different geographical regions and age of EBV exposure. No study has addressed such an association in Kurdistan, northern Iraq, and thus this study was initiated.

Patients and methods: A total of 91 patients diagnosed as HL over a 10 year period were studied. These patients had their records and slides reviewed and the additional immunohistochemistry, including that for LMP1 as well as in situ hybridization for EBER performed.

Results: The patients had a mean age (SD) of 28.8 (16.2) years and had a male to female ratio of 1.7:1. They included 3.3% with Nodular Lymphocyte Predominant HL (NLPHL) and 96.7% Classical HL (cHL). The most common 2 subtypes of the latter were nodular sclerosis (NS) and mixed cellularity (MC) at 52.7% and 36.6% respectively. It was found that 40 cases (44.0%) were latent membrane protein 1 (LMP1) and/or EBER positive. The positivity was significantly higher in males (P=0.009), mixed cellularity subtype (P<0.001) and in the ages ≥45 and ≤15 years when compared to those 16- 44 years (P=0.004).

Conclusion: HL in Iraqi Kurdistan demonstrates a frequency of EBV virus infection that approaches the levels seen in Western countries and is coupled with a changing histological pattern of classical HL from MC to NS. This is likely to be a reflection of the improving socioeconomic status of the population of the region.

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Keywords: EBV, Hodgkin Lymphoma, Iraq, EBER, LMP1

Hodgkin lymphomas (HL) is a unique type of lymphoid malignancy, in which the malignant cells (Reed-Sternberg (RS), Hodgkin (H) or Lymphocyte Predominant (LP) cells) constitute only a minority of the total tumor mass, with the bulk of the latter consisting of reactive non-neoplastic cells[1]. HL is classified according to the World Health organization into two distinct clinico-pathological entities: classical Hodgkin lymphoma (cHL) and Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL). The former entity is further sub-classified into four subtypes: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte rich (LR) and lymphocyte depletion (LD) [2].

Several lines of evidence have linked Epstein-Barr virus (EBV) to the etiology of cHL, such as the biological tenability of EBV mediated B- cell transformation, the

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detection of clonal EBV genomes in the RS cells, and epidemiological links with infectious mononucleosis that represents a primary EBV infection[3]. Following primary infection with the EBV, which is a DNA herpes virus, the latently infected B lymphocytes are characterized by expression of six EBV nuclear antigens, three latent membrane proteins (LMP1, LMP2A and LMP2B) and two EBV encoded RNAs (EBER1 and EBER2) [4]. EBV has been detected in the malignant cells in variable proportion of HL, and this varies depending on the geographical origin, age, sex, and histological subtype [3-5]. While a variety of methods exist to detect EBV in the malignant cells, LMP1 and EBER assays in combination have been recommended as the most practical and effective methods[6].

Malignant lymphoma according to the 2010 Iraqi Cancer Registry is the third most frequent malignancy in this country, with Hodgkin lymphoma accounting for 35% of the cases. In the Registry, the crude incidence of HL in 2010 was 1.58/100,000 population[7]. Several studies have addressed the epidemiology and histological patterns of HL in Iraq over the past decades[7-12]. However, studies on its association with EBV infection are very limited in this population[13]. Accordingly, and in an attempt to determine the frequency and the associations of EBV infection among HL diagnosed and referred to a major pathology center in the Kurdistan region of Northern Iraq, the current study was initiated.

MATERIALS AND METHODS

This is a retrospective study on 91 cases diagnosed as HL in the period between January 2008 and July 2018 at the department of pathology, central laboratory diagnostic center at Duhok, Iraqi Kurdistan. Records of included patients were retrieved from the pathology database including: age at the time of diagnosis, gender and clinical presenting features. All cases were reviewed and sub-classified according to the World Health Organization (WHO) classification of hematologic malignancies, based on morphology and immunohistochemistry staining. The latter included at least the following: CD30, CD15, CD20, CD3, PAX5 and MUM1[2]. For each case, additional three representatives sections were prepared. One was stained with Hematoxylin and Eosin (H&E) to revise the histopathological diagnosis, another one was stained immunohistochemically for LMP-1, with the remaining section used for detection of EBER expression by in situ hybridization (ISH).

Statistical analysis, utilized Chi square test, and a *P* value <0.05 was considered significant. Ethical approval for this study was obtained from Kurdistan board for medical specialties and Directorate of Health in Duhok, Kurdistan-Iraq.

Immunohistochemical staining (include-ing that for LMP-1):

Immunohistochemistry (IHC) was performed by polymer based detection method using the tissue microarray (TMA) constructed from representative cores taken from the appropriate formalin-fixed, paraffin-embedded tissue blocks after the original H&E slides were reviewed. The microarray was assembled using a manual TMA kit (3D Histech, Bulgaria). The sections were de-waxed, rehydrated and

the antigen retrieval was performed for 30 minute in citrate based buffer (pH6). A panel of primary monoclonal antibodies was applied CD20, CD30, CD15, CD3, PAX5, MUM1 and LMP1 [clone CS1-4] (Dako, Agilant, USA). Antigen localization was carried out using envision immunohistochemistry detection system (K8000, Dako, Agilant, USA). Antigen retrieval and immunostaining were done using an automated system developed by Dako-cytomatation (PT-link and Link 48, Dako, Agilant, USA). For the visualization of the antigen-antibody reaction: 3, 3 diaminobenzidine was used. Appropriate positive and negative controls were used.

In situ hybridization staining for EBER:

To detect EBER by in situ hybridization the EBV probe ISH kit (Zytovision, Germany) was used according to the manufacturer's instructions. The 4 µ sections of tissue micro-array slides were deparaffinized, dehydrated, and predigested with the enzyme proteinase K. Thereafter, the slides covered with the hybridization solution (containing fluorescein conjugated EBER nucleic acid probe), were incubated in a hybridizer (Agilent, USA). This was followed by the application of alkaline phosphatase conjugated antibody to fluorescein isothiocyanate, and finally the chromogen composed of BCIP/NBT (bromochloroindolylphosphate/ nitroblue tetrazolium chloride). Hematoxylin solution was applied as a counter-stain. The positive cases were defined as a nuclear dark blue staining. A negative control was run for each specimen.

RESULTS

The 91 enrolled patients had ages ranging from 5-75 years (mean 28.8 ± 16.2), and included 57 males and 34 females (M:F 1.7:1). The cohort included 17 children (≤ 15 years) and 13 older adults (≥45 years) constituting 18.7% and 14.3% respectively.

All of the patients had lymph node enlargement at presentation, with cervical lymphadenopathy being most frequent accounting for 59.3%. cHL comprised 96.7% of cases and NLPHL 3.3% (Table 1). The most frequent subtype of cHL was NS at 52.7%, followed by the MC at 36.3%. No cases of lymphocytes depleted cHL were identified in the studied sample. Six cases were classed as cHL, based on the immunophenotype, but could not be sub-classified further because the material was either a tissue block or a bone marrow biopsy.

Table 1: Basic Characteristics and EBV Status in the 91 Iraqi Patients Enrolled.

Parameter	Number (%)
Age (years)	
≤ 15	17 (18.7)
16-44	61 (67.0)
≥ 45	14 (14.3)
Lymph node enlargement	91 (100)
Gender	
Male	58 (62.6)
Female	34 (37.4)
Histology	
Nodular Sclerosis	48 (52.7)
Mixed Cellularity	33 (36.3)
Lymphocyte rich	1 (1.1)
Lymphocyte depletion	0 (0)
Nodular Lymphocyte predominate	3 (3.3)
Classical/Not sub-classifiable	6 (6.6)
EBV status (EBER/LMP1)	
Positive	40 (44.0)

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The current study showed that the neoplastic cells were positive for latent membrane protein 1 (LMP1) in 35 cases (38.5%) and for EBER in 36 (39.6%) cases, while EBV positivity by LMP1 and/or EBER was seen in 40 (44.0%) cases. Table 2 shows the distribution of LMP1/EBER positivity according to age and sex. It was noted that males with HL were much more likely to be EBV positive than females (P=0.009). Furthermore, patients who were ≥45 years had the highest rates of EBV positivity, followed by those ≤ 15 years, while the least rates were noted in those in between, an observation which was significant (P=0.004).

Table 2: The Frequency of EBV Positive Cases of (HL) by Sex and Age;

Parameter	No. LMP1 positive (%)	No. EBER positive (%)	No. LMP1 and/or EBER positive (%)
Gender			
Male (n 57)	26 (45.6)	27 (47.4)	31(54.4)
Female (n 34)	9 (26.5)	9 (26.5)	9(26.5)
P value	**0.07**	**0.049**	**0.009**
Age (years)			
≤15 (n 17)	8 (47.1)	8 (47.1)	8(47.1%)
16-44 (n 61)	18 (29.5)	20 (32.8)	21(34.4%)
≥45 (n 13)	9 (69.2)	8 (61.5)	11(84.6%)
P value	**0.02**	**0.123**	**0.004**

Regarding EBV positivity in relevance to histological subtypes, it was noted that the highest frequencies were noted in the mixed cellularity subtype (84.8%) which was significantly higher than in nodular sclerosis (10.4%) [P<0.001] (Table 3)

Table 3: The Frequencies of EBV Positive Cases of HL by Histological Subtypes

Histological subtype	No. LMP1 positive (%)	No. EBER positive (%)	No. LMP1/EBER positive (%)
Nodular Sclerosis (n 48)	5(10.4)	5(10.4)	5(10.4)
Mixed cellularity (n 33)	27 (81.8)	25(75.8)	28(84.8)
Lymphocyte rich (1)	0(0)	1(100)	1(100)
Nodular Lymphocyte predominant(3)	0 (0)	0 (0)	0 (0)
Classical/Not sub-classifiable (6)	3(50)	4(66.7)	5(83.3)

DISCUSSION

The general characteristics of HL as observed in the current study as expected were similar to those reported in a smaller earlier series from Northern Iraq[11]. The age and sex distribution were also consistent with most earlier Iraqi studies[7,8,10,11,14]. However, it appears that there is a change in the histological patterns, since earlier Iraqi studies, more

than three decades ago, consistently reported MC as the most frequently encountered subtype[8, 9], while the current study and the more recent reports from Northern Iraq found that NS subtype to be the most common[11,12,14]. A similar trend was also noted in some neighboring Eastern Mediterranean countries, like Saudi Arabia and Jordan[15, 16], and the resultant distribution of HL subtypes resembles that reported in developed Western countries[2, 17, 18].

EBV infection rates in HL vary worldwide, with high rates (61-85%) reported from developing countries like India, South Africa, Kenya, Malaysia and Brazil[19-23], while rates from developed countries were lower ranging from 30-48% in UK, France and the USA.[24-26] So our results of 44.0% are nearer to those reported in the developed countries, and to nearby countries like Jordan, UAE and Saudi Arabia[16, 27,28]. This may be related to improvement of the living standards over the past two decades in our region and the latter neighboring countries, and it is well known that one of the important determinants of the EBV viral infection is socioeconomic status[29].

The current study showed that EBV expression was related to the histologic subtype of HL, with the mixed cellularity (MC) subtype being the most likely to be associated with EBV infection, a finding which was highly significant when compared to the more common NS subtype. Such an observation has been well documented by many studies worldwide[2, 3,13,16,23,27,30,31]. The absence of EBV infection among the three patients with NLPHL in the current study is expected, as this subcategory is not usually associated with this virus, as demonstrated by previous studies[16, 31].

The highest frequency of EBV virus detection was encountered in older adults (≥45 years) at 84.6%, followed by children (≤ 15 years) at 47.1%, with the least rates seen among those in between at 34.4%. Furthermore, this variation in EBV positivity in the three above age groups was significant. Such a pattern is similar to that encountered in developed countries[32], while higher rates among children as expected in developing countries were reported from countries like Jordan, UAE, Egypt and Brazil[16, 27, 31,33].

Another association is that with the male sex, this again has been consistently reported in several earlier studies[5,16,32,33], and although the actual reason for such predilection has not been fully elucidated, it has been suggested that females tend to have a better immune response and thus are less likely to have their latent EBV infection transform[34].

In conclusion it appears that the frequency of EBV virus infection in HL in Northern Iraq is approaching the levels seen in Western countries, and this is coupled with a changing histological pattern of classical HL to a pattern similar to the latter countries, which is likely to be a reflection of improving socioeconomic status of the population of the region and possibly reduced early childhood EBV exposure.

Conflict of Interest: None to declare.

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ثوختة

هودجكين ليمفوما وطريَدانا وي ل طةل فيروسي أبستين-بار ل هةريَما كوردستانا العراق

باطراوند: ظايروسىَ ابشتاين بار EBV هاتة طريَدان ب هوكارىَ هةبونا طةلةك وةرماندنيَن ثيس, وةك ليمفوما هودجكين HL , بةلىَ ثلا ظىَ ثةيوةنديىَ يا جياوازة ذ جهةكي بو جهةكي و هةروةسا هةبونا جياوازيا تةمةني بو توشبونا ظايروسىَ EBV، هيض ديراسةك لسةر ظىَ ثةيوةنديىَ نةهاتيةكرن ل هةريَما كوردستانىَ و ئةف ديراسةتة دةستثيَكرية.

مةواد و ريَك: ديراسةت هاتةكرن لسةر 92 نةخوشا كو هاتينة دةستنيشانكرن ب HL ئةظيَن تةمةنيَ وان ثتر ذ 10 ساليىَ و ئةف نةخوشة هاتنة تومماركرن و سلايد بو هاتنةدروستكرن و كيميا مةناعي , دطةل LMP1 و هةروةسا ئةداكرنا EBER

ئةنجام: ناظةنةدا تةمةنىَ نةخوشا SD 29.4 ببو 17.3 سال , ريَذا رةطةزىَ نيَر بو مىَ 1:1.7 و هةروةسا 3.2% بخوظةطرت دطةل يىَن عقدة ليمفاوي يا سائد, NLPHL . و هةروةسا 96.8% HL يا كلاسيك, c HL و هةردوو جوريَن دووىَ زورتربون ذ جوريَ دوىَ كة رةقبونا عقدي بو NS و خانا تيَكةل MC ل 35.8% و 52.1% لديفيَكدا, وديارىو كو 40 حالةت (43.4%) ثروتينا غيشائيبو LMP1 ياو EBER يا ثوزةتيظ , و ثتر لسةر رةطةزىَ نيَر دياربو P=0.01 و جوريَ فرعي يىَ تيَكةل P<0.001 و هةروةسا ل تةمةنىَ مةزنتر ذ 45 سالي و بضيكتر ذ 15 سالي بةراورد دطةل وان يىَن تةمةنىَ وان بضيكتر ذ 45 سالي و مةزنتر ذ 15 سالي. P=0.01.

دوماهيك: HL ل كوردستانىَ نةخوشيا ظايروسىَ EBV ديارديكةت ئةوا نزيكدبيت ل ئاستيَن وةلاتيَن روذئاظا و هةروةسا بةراوردبيت دطةل شيَوازيَن نةسيجي يىَن HL يا كلاسيك ذ MC بو NS , هةروةسا دبيت بواريَ ئابوري و جظاكي بةرةف باشتر ببةت.

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الخلاصة

هودجكين ليمفوما وأرتباطها مع فيروس أبستين–بار في اقليم كردستان، العراق

الخلفية: تم ربط فيروس إبشتاين بار (EBV) بمسببات العديد من الأورام الخبيثة، بما في ذلك ليمفوما هودجكين (HL).ومع ذلك، فإن درجة هذه العلاقة تختلف بين المناطق الجغرافية المختلفة والعمر من التعرض لـ EBV، وبما أن أي دراسة لم تتناول مثل هذه العلاقة في كردستان، بالتالي بدأت هذه الدراسة.

المواد والطرق: تم دراسة مجموع 92 مريض تم تشخيصهم لـ HL على مدى 10 سنوات. كان هؤلاء المرضى قد تم استعراض سجلاتهم والشرائح والكيمياء المناعية الإضافية، بما في ذلك لـ LMP 1 وكذلك التهجين في تأدية EBER.

النتائج: كان متوسط عمر المري (17.3 ±29.4) سنة وكانت نسبة الذكور إلى الإناث 1.7: 1. وشملت 3.2٪ من النوع النسيجي الموسوم العقدة الليمفاوية السائدة ليمفوما هودجكين (NLPHL) و96.8٪ من نوع لومفوما هودجكين الكلاسيكية c HL. وكان الأكثر شيوعاً من النوع الكلاسيكي هما التصلب العقدي (NS) والخلية المختلطة (MC) وبنسبة 35.8٪ و52.1٪ على التوالي. وتبين أن 40 حالة (43.4٪) كانت موجبة (LMP1 و/ أوEBER) وكانت هذه الايجابية أعلى بشكل ملحوظ في الذكور (P = 0.01)، وفي النوع الخلوي المختلط (P <0.001) وفي عمر اكبر من 45 سنة وأصغر <15 سنة بالمقارنة مع تلك > 15– <45 سنة (P = 0.01).

الخلاصة: تبين أن ليمفوما هودجكين في كردستان تتصاحب مع تواتر عدوى فيروس EBV ويقترب الاخير من المستويات في الدول الغربية ويقترن بنمط نسيجي متغير من HL الكلاسيكي. من MC إلى NS، ومن المرجح أن يعكس هذا تحسن الوضع الاجتماعي الاقتصادي لسكان المنطقة.