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Burkitt's lymphoma: incidence among IICC-3 risk-assessed countries emphasizing the Middle East with new data from Iraqi Kurdistan

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Abstract

Background

Burkitt's lymphoma (BL) is rare, with variations in regional incidence related with the age of Epstein-Barr virus (EBV) infection. This study examined the age-specific incidence rate (ASIR) of BL and the age of community EBV infection in Northern Iraq and other countries tabulated in the WHO IICC-3.

Materials and Methods

The ASIR and 95% confidence interval (95%CI) of BL in Sulaimani Governorate were calculated for the years 2010—2020. Tumor EBV latency was determined by in situ hybridization for EBV-encoded mRNA (EBER). Specimens from 515 outpatients were tested for IgG antibodies to EBV viral capsid antigen (VCA).

Results

In the Middle East, BL is predominantly a pediatric tumor, with an ASIR in Sulaimani of 6.2 (4.7–7.7) per million children. This ASIR is not significantly different than that of Egypt, Morocco, Israel, Spain, and France. It is slightly higher than the ASIR of the United States, the United Kingdom, and Germany and markedly higher than for Asia and South Africa. In Africa and much of Asia, EBV is acquired in early childhood. In Sulaimani, EBV seropositivity develops in late childhood and early adolescence. In Europe and North America, seropositivity is acquired in adolescents and young adults (AYD). In countries with AYD infections, adult predominates over childhood BL.

Conclusions

Early childhood EBV infections associate with low rates of childhood BL and few adult BL. In the Middle East, childhood BL is relatively common while adult BL is rare. In our region, half of EBV infections is found in late childhood. This may reflect the Mid East more widely. The high childhood/low adult BL rates may be a regional influence of EBV exposure intermediate between early childhood and AYD infections.

Introduction

Burkitt lymphoma (BL) has three recognized subtypes [1, 2]. Most BL is a sporadic disease [3]. The sporadic disease occurs worldwide, with notable geographic differences in overall and age-specific incidence rates (ASIR) [2]. In many parts of the world, sporadic BL is predominantly a childhood disease, but in Europe, North America, and parts of Asia, adults outnumber children by more than 2:1 [4, 5]. An endemic type of the disease appears restricted to Central Africa and New Guinea [3, 6]. The endemic disease has a uniformly high age-specific incidence rate among children, frequent facial bone

involvement, and is rare among adults. The third subtype affects immunocompromised individuals, most frequently as a complication of HIV infection [3]. Immunocompromise-related BL affects children and adults in Sub-Saharan Africa and overlaps with the endemic disease [6, 7].

BL is related to latent Epstein-Barr virus (EBV) infection, with the extent of the relationship varying geographically and with different disease subtypes. EBV-encoded small nuclear non-polyadenylated mRNA (EBER) is found in nearly all endemic BL of Central Africa but in only 10–40% of sporadic BL in the United States (US) and Europe [2, 3]. In Egypt and Iraq, EBER is demonstrated in more than 70% of tumors [8, 9, 10, 11].

EBV exists as a latent infection in more than 90% of the world's population, but outside of Central Africa, BL is uncommon [2]. On this basis, the endemic BL is considered more closely related to coexisting falciparum malaria than EBV [2, 3].

EBV is a human DNA virus that infects different populations at different ages [12]. In underdeveloped countries, including Africa, EBV infections are asymptomatic or only mildly symptomatic, and 95% or more children acquire the virus before five years of age [12, 13]. In North America, Western Europe, Japan, and South Korea, EBV infection is often delayed until adolescence, when it can cause infectious mononucleosis [12, 13, 14]. Despite the delayed presentation, the EBV serological prevalence in these countries is greater than 70–80% by mid-adulthood.

Smatti et al. [15] examined blood donor samples from Qataris, Jordanians, Palestinians, Saudi Arabians, and Indians and found that more than 95% of persons from all countries were serologically positive by 19 years of age. The age of infection in the Middle and Near East is thought to be early childhood. Yet, studies from Bahrain and Tehran show primary infections in adolescents and young adults that indicate a regional change in EBV exposure may be taking place [16, 17].

In a previous publication, we analyzed rates of lymphoma in Iraqi Kurdistan over the years 2010–2014 and suggested that BL might be four times as frequent as it is in children of similar age in the United States (US) [9]. BL in the Middle East may have elements of an endemic disease; nevertheless, no coexisting infection or promoting factor other than EBV has ever been identified [8, 9, 10].

To further evaluate BL in the Middle East, we determined the ASIR of BL in Sulaimani Governorate of Iraqi Kurdistan over 11 years. EBV serological tests were performed on 515 outpatients. The findings were compared with international data from the Middle Eastern, African, Asian, North American, and European countries tabulated in the World Health Organization's (WHO) International Incidence of Childhood Cancer-3, IICC-3 (18). The study was undertaken to investigate how BL incidence rates and ages of EBV exposure in the Middle Eastern correspond to other regions of the world.

Materials And Methods

Database and calculation of incidence rates

Hiwa Hospital was established in 2005 for public cancer care in the Sulaimani Governorate and to develop a population-based cancer registry. The Pathology Department of Shorsh Teaching Hospital provides surgical pathology services and central pathology reviews for Hiwa patients. Clinical and pathology reports on BL from Hiwa Hospital and the Shorsh Pathology Department were collated for the period January 1, 2010 to December 31, 2020. Pediatric data for Egypt, Algeria, Morocco, Jordan, Israel, Saudi Arabia, Turkey, South Arica, Uganda, Cameroon, the US, Canada, the United Kingdom (UK), Germany, France, Italy, Spain, Japan, Korea, China, Thailand, Korea, and India were obtained for BL from WHO IICC-3 tables [17]. Adult data and EBV relationships were obtained from individual articles from these countries [4, 7, 8, 15, 19–42].

Pediatric patients were defined as 0–19 years of age. For Sulaimani, BL ASIR was calculated as the annual average number of cases. The population of Sulaimani at 2,095,851 was obtained from the 2015 Iraqi Cancer registry. The 0-19-year-old population was 910,510. Age-adjusted incidence rates (AAIR) were estimated using the 2001 WHO World Standard Population [43].

Diagnostic criteria

BL was diagnosed by flow cytometry on fine needle aspirations (FNA) or by immunohistochemistry on formalin-fixed, paraffin-embedded tissue sections. Histology on tissue sections or FNA cell blocks showed rapidly proliferating, undifferentiated lymphoid cells having abundant blue cytoplasm with cytoplasmic vacuoles [Figure 1]. All tumors contained tingible body macrophages. BL was diagnosed when cells were CD20, CD10, and BCL6 positive with bright light chain restricted surface immunoglobulin and when the Ki67 proliferation index approached 100% [2]. TdT was required to be negative. Weak or focal BCL2 was acceptable when other markers were characteristically positive.

EBV latency and MYC translocations in BL

BL EBV latency was assessed by chromogenic in situ hybridization (ISH) using the Novocastra (Leica Biosystems, Wetzler, Germany) probe for EBER. C-MYC/IGH translocations were analyzed by fluorescence in situ hybridization using a break-apart probe (Vysis MYC, Abbott Laboratories, Abbott Park, IL). EBER and MYC translocation studies used formalin-fixed, paraffin-embedded tissue of 24 BL.

EBV serological testing

Samples in serum separator tubes were obtained from 515 patients attending general pediatric and medical clinics. Specimens were used for serum chemistries and held at 4^0C for 48 hours. The specimens were de-identified for all information except age. The samples would otherwise have been discarded, and the Directorate of Health allowed their use.

Samples were analyzed by patient age for IgG and IgM antibodies against EBV viral capsid antigen (VCA) using the Abbot Architect model i1000 immunoassay system (Abbot Diagnostics, Wiesbaden, German). The results were instrument recorded as negative or positive, with the later provided in relative light units.

Data analysis

Data were entered into Excel worksheets and analyzed with Excel mathematical functions and STATA IC10 (STATA, College Station, TX) statistical software. Uncertainty for ASIR was evaluated by comparing 95% confidence intervals in the different geographical regions. The calculation of ASIR 95% CI used the following formula:95% CI (ASIR) = ± 1.96 X $\sqrt{(Ri^2/Ni)}$ where Ri^2 = age-specific incidence in the specified age group, and Ni = the number of patients in the age-specific group [44]. Differences were considered significant if 95% CI did not overlap.

Results

BL in Sulaimani

In the 2010–2020 period, 74 cases of BL were diagnosed in the Sulaimani Governorate. The characteristics of the patients are shown in Table 1.

Table 1. Characteristics of patients diagnosed with Burkitt

lymphoma in the years 2010 through 2020 in Iraqi Kurdistan.

Characteristics	Burkitt lymphomas
No. of patients	74
Male, no. (%)	65 (88%)
Age, yrs: range, median	1.5-56, 5.5 (IQR 4-12)
0-4, no. (%)	28 (38%)
5-9, no. (%)	22 (30%)
10-14, no. (%)	10 (14%)
15-19, no. (%)	2 (3%)
≥ 20, no. (%)	12 (16%)
Immunosuppressed	1 (HIV, hemophilia)
BL presenting site, no. (%)	
Abdomen/intestine	52 (70%)
Cervical LN	10 (14%)
Tonsil	4 (5%)
Mediastinum	1 (1%)
Kidney	2 (3%)
Breast	1 (1%)
No information	2 (3%)

Abbreviations: IQR, interquartile range; LN, lymph node.

The BL patients were 88% male, 84% were 0–19 years old, and 38% were 0–4 years old. Only one patient was immunosuppressed, a 25-year-old HIV-positive hemophiliac male. In 70% of patients, an abdominal tumor was the most common presentation. Cervical lymph node enlargement was next at 14%. Two patients had soft tissue facial masses, but neither had any facial bone involvement. A 32-year-old woman presented with bilateral breast tumors. Two males, four and five years old, had primary kidney tumors. Twenty-four tumors were tested for EBER, all from patients under 20 years old, and 20 cases were positive (83%). All 24 tumors were positive for the MYC translocation.

Incidence of pediatric BL worldwide

Table 2 lists by country the ASIR (95% CI) of pediatric BL, the frequency of males, and the proportion of patients in the 0-5-, 5-14-, and 15–19-year-old age ranges. The table provides the survey period and the number of patients in the IICC-3 registries [18].

Table 2

Burkitt's lymphoma. The table lists the age-specific incidence rate per million children and the distribution of patients in the 0-4-, 5-14-, and 15–19-year-old age ranges. Data from Sulaimani is local. Data from the other countries are compiled from the tables of diagnostic subgroups in the WHO IICC-3 website [https://iirc.iarc.fr/ results/comparative.php].

Country	Years data collected	Cases No.	ASIR (95% CI) per million children, 0–19 yrs old	Male	Age distribution, years		
					0–4	5–14	15–19
Sulaimani	2010-20	62	6.2 (4.7–7.7)	0.89	0.45	0.52	0.03
Egypt	1996–2010	97	5.2 (4.2–6.2)	0.73	0.47	0.46	0.07
Algeria	1996–2014	23	1.0 (0.6–1.4)	0.81	0.43	0.41	0.15
Morocco	2005–2012	60	5.0 (3.7–6.3)	0.82	0.24	0.62	0.14
Jordan	2000–2012	129	3.7 (3.1–4.3)	0.78	0.27	0.64	0.09
Israel-Jew	1990–2012	195	5.0 (4.3–5.7)	0.74	0.32	0.52	0.15
Israel-non Jew	1990–2012	69	4.8 (3.7–5.9)	0.77	0.23	0.63	0.14
Saudi Arabia	1994–2012	121	2.8 (2.3–3.3)	0.68	0.35	0.53	0.13
Turkey	1992–2012	180	3.5 (3.0–4.0)	0.70	0.28	0.64	0.08
S. Africa-black	1998–2012	252	1.4 (1.2–1.6)	0.75	0.50	0.50	na
S Africa-white	1998–2012	34	2.8 (1.9–3.7)	0.75	0.19	0.81	na
Uganda	1996–2013	376	21.6 (19.4–23.8)	0.56	0.20	0.76	0.04
Cameroon	2004–2006	122	40.0 (32.9–47.1)	0.58	0.23	0.64	0.07
Canada	1992–2013	408	2.5 (2.3–2.7)	0.80	0.18	0.59	0.22
US-black	1998–2012	276	1.4 (1.2–1.6)	0.74	0.17	0.63	0.20

Abbreviations: ASIR, age-specific incidence rate. 95% CI, 95% confidence interval.

Country	Years data collected	Cases No.	ASIR (95% CI) per million children, 0–19 yrs old	Male	Age distribution, years		
					0–4	5–14	15–19
US-white	1998–2012	2072	2.8 (2.7–2.9)	0.80	0.16	0.64	0.23
UK	2000–2011	419	2.3 (2.1–2.5)	0.79	0.21	0.62	0.17
Germany-West	1994–2012	198	2.8 (2.4–3.2)	0.82	0.14	0.67	0.18
France	1993–2012	182	4.3 (3.7–4.9)	0.81	0.19	0.68	0.19
Italy	1992–2013	224	4.0 (3.5–4.5)	0.76	0.14	0.68	0.24
Spain	1990–2013	210	4.8 (4.2–5.5)	0.81	0.25	0.59	0.19
Japan	1990–2013	110	1.4 (1.1–1.7)	0.85	0.26	0.66	0.08
Korea	1999–2012	351	2.1 (1.9–2.3)	0.80	0.28	0.59	0.13
China	1990–2013	33	0.4 (0.3–0.5)	0.78	0.33	0.61	0.06
Thailand	1993–2013	41	0.8 (0.6-1.0)	0.81	0.42	0.45	0.13
India	1990–2013	109	0.5 (0.4–0.6)	0.70	0.32	0.63	0.05

Abbreviations: ASIR, age-specific incidence rate. 95% CI, 95% confidence interval.

The ASIR in countries within nearby regions are similar. The central African nations of Uganda and Cameroon harbor endemic forms of BL and have 0–19-year-old ASIRs of 21.6 in Uganda and 40.0 in Cameroon. In South Africa, rates of BL are much lower than in Uganda and Cameroon, and South African blacks have significantly lower rates than South African whites. This racial difference is also seen in the US, where rates of BL among blacks are half that of whites. Also, note that the recorded US and South African pediatric rates are the same for blacks and whites.

Apart from Algeria, the countries of North Africa and the Middle East have ASIRs ranging from 3.5 to 6.2 that resemble the rates in France (4.3), Italy (4.0), and Spain (4.8). The regional effect is seen in Israel, where the ASIR is essentially the same between Jews (5.0) and non-jews (4.8) and overlaps other Middle Eastern regions, including Sulaimani. The ASIR for Saudi Arabia at 2.8 is low compared to other countries

of the Middle East and resembles the ASIR in the UK, the US, and Canada. Algeria has an ASIR of 1 per million children that contrasts with the much higher rates in nearby Morocco (5.0) to the west, Egypt (5.2) to the east, and the historically affiliated France (4.3) to the north. The Far East and India have very low rates of BL (< one child per million). The populous six regions registered in China recorded only 33 pediatric BL in the 23-year period, 1990–2013.

In all parts of the world, BL is a predominantly male disease, with the endemic BL of Central Africa having somewhat less gender disparity than other regions. In all regions, 78% to more than 95% of pediatric patients have symptomatic tumors by 14 years of age.

Pediatric versus adult BL and the relationship to the age of EBV infection (Table 3)

Table 3

Comparison of regional Burkitt's lymphoma. Age-specific incidence rates per million 0–19 year old residents are compared together with the ratio of children to adults, Epstein-Barr virus serology, and frequency of tissue EBV latency.

Country	ASIR 0–19 year-old	Ratio Child:adult	HDI	sEBV	tEBV
Sulaimani	6.2 (4.7–7.7)	1 : 0.19	.674	0.92 LC	0.83
Egypt	5.2 (4.2–6.2)	1 : 0.05	.707	na	0.73
Algeria	1.0 (0.6–1.4)	na	.748	0.83 C	0.88
Morocco	5.0 (3.7–6.3)	na	.686	na	na
Jordan	3.7 (3.1–4.3)	1 : 0.13	.729	0.98 C	na
Israel all races	5.0 (4.3–5.7)	na	.919	0.87 AYD	0.34
Saudi Arabia	2.8 (2.3–3.3)	na	.854	0.98 C	na
Turkey	3.5 (3.0–4.0)	na	.820	0.82 C	0.93
S. Africa all races	1.7 (1.5–1.9)	1 : 2.78	.709	0.95 EBV 0.78 HIV+	na
Uganda	21.6 (19.4–23.8)	1 : 0.21	.544	0.96 EC	> 0.95
Cameroon	40.0 (32.9–47.1)	1 : 0.41	.563	0.97 EC	> 0.95
Canada	2.5 (2.3–2.7)	1 : 2.78	.929	0.95 AYD	na
US all races	2.4 (2.3–2.5)	1 : 3.85	.926	0.83 AYD	0.30
UK	2.3 (2.1–2.5)	1 : 4.78	.932	0.85 AYD	0.10
Germany-West	2.8 (2.4–3.2)	na	.947	0.95 AYD	na
France	4.3 (3.7–4.9)	na	.901	0.82 AYD	na
Italy	4.0 (3.5–4.5)	1 : 0.20	.892	0.65 AYD	0.62
Spain	4.8 (4.2–5.5)	na	.904	0.99 AYD	na
Japan	1.4 (1.1–1.7)	1 : 2.94	.919	0.59 AYD	0.29
Korea	2.1 (1.9–2.3)	Ped < Adult	.916	0.87 AYD	0.00
China	0.4 (0.3–0.5)	1 : 0.55	.761	0.80 EC	0.32

Abbreviations: na, not available; ASIR, age-specific incidence rate with 95% confidence interval (95% CI); HDI, human development index [from the WHO website]; HIV, human immunodeficiency virus; Ped, pediatric; EBV, Epstein-Barr virus; sEBV, population serological EBV frequency; C, childhood infection, not further specified;EC, early childhood infection; LC, late childhood infection; AYD, adolescent and young adult infection; tEBV lymphoma tissue EBER frequency.

Country	ASIR 0–19 year-old	Ratio Child:adult	HDI	sEBV	tEBV
Thailand	0.8 (0.6-1.0)	Ped > Adult	.777	0.95 EC	na
India	0.5 (0.4–0.6)	Ped > Adult	.645	0.90 EC	na

Abbreviations: na, not available; ASIR, age-specific incidence rate with 95% confidence interval (95% CI); HDI, human development index [from the WHO website]; HIV, human immunodeficiency virus; Ped, pediatric; EBV, Epstein-Barr virus; sEBV, population serological EBV frequency; C, childhood infection, not further specified;EC, early childhood infection; LC, late childhood infection; AYD, adolescent and young adult infection; tEBV lymphoma tissue EBER frequency.

In the Middle East, BL is primarily a childhood cancer, but in much of the world, it is more often an adult tumor with a growing frequency in the elderly. Middle East EBV exposure begins in early childhood. There is an adult seropositivity rate of more than 90%, but half of the infections occur in later childhood and early adolescence. The proportion of EBER-positive tumors is also high. The exception seems to be Israel, where data regarding the frequency of adult BL is not reported. One study of male university students indicates EBV seropositivity is frequently negative until adolescence and then increases to 87% by the mid to late twenties [22]. Only 34% of Israeli childhood BL is EBER positive [21].

The countries of Europe, the US, and Canada have rates of pediatric BL that approach or, in the case of Italy, Spain, and France, are equivalent to the Middle East [18]. In these European and North American countries, EBV is frequently contracted in adolescence, and the frequency of adult BL commonly exceeds the childhood disease [4, 5, 14, 27, 28, 32].

In the Far East, Japan and Korea have high development indices, EBV seroconversion often occurs in adolescents and young adults, and adult rates compared to childhood BL are high [35, 36, 37, 38]. The BL in these countries is rarely EBER positive [36, 38]. In contrast, China, Thailand, and India have low rates of childhood BL, and adult BL is rare. Development indices are low, and EBV infects over 90% of children by five years of age [39, 40, 41, 42]. Curiously, however, BL in China seems to rarely be EBER positive [40].

Cameroon and Uganda have the endemic form of BL and very low development indices. The endemic disease does occur in adults but is rare. Cameroon and Uganda contrast with South Africa, where adult BL is nearly 3x more common than pediatric BL [7]. In South Africa, 78% of patients have the combination of HIV and EBV infections, but overall BL rates, both pediatric and adult, are still low compared to countries with high developmental indices [6, 7]. The lower South African overall rates compared to the US reflect the predominantly black population of South Africa and the mostly white population of the US.

EBV serology in Sulaimani outpatients

Serum specimens of 515 patients were tested (Table 4). The instrument recorded 423 IgG anti-VCA (82.1%) and 14 IgM anti-VCA (2.7%) results as positive. All positive IgM results except one were positive for IgG. The IgM positive and IgG negative patient was 13-years-old and likely a primary infection but was otherwise not identifiable. The pattern of EBV infection was unimodal (Table 2). At one year of age, 45%

of infants were IgG positive, and at four years, 54% of children were positive. Seropositivity was 88% at 14, and after 14 years of age, it reached a plateau with an adult seropositivity rate of 92%.

Table 4. Serological testing among 516 non-oncology outpatients for Ig Epstein-Barr virus viral capsid antigen. Results are tabulated by age and as a total.

Age (years)	No. tested	No. positive	Fraction positive
0.25-0.99*	20	9	0.45
1	34	16	0.47
2	33	17	0.52
3	19	13	0.68
4	27	17	0.63
5	25	21	0.84
6	35	24	0.69
7	30	23	0.77
8	26	20	0.77
9	13	9	0.69
10-14	74	65	0.88
15-19	33	32	0.97
20-24	22	16	0.73
25-29	22	22	1.00
30-34	15	14	0.93
35-39	19	17	0.89
40-49	29	29	1.00
50-59	25	23	0.92
60-69	14	14	1.00
Total	516	401	0.78

*Under one year of age, subjects less than three months old were not reported, because maternal antibodies produced passive IgG positive and IgM negative reactions. Three such subjects were found at three and 12 days and two months.

Discussion

The incidence of pediatric BL is very high in the central African countries of Uganda and Cameroon [24, 25]. The rates are low in the Far East and India, where nearly all children are infected by EBV before five years of age. In Europe, North America, and most of the Middle East, rates of BL are intermediate between those of central Africa and Asia [35, 36, 37, 38, 39, 40, 41]. BL of the Middle East is a pediatric neoplasm with few cases reported in adults [8, 9, 10, 19, 21]. Data from Sulaimani, Qatar, and Bahrain indicate that nearly half of EBV seroconversion in the Middle East may occur between four and 15 years old [15, 16, 17]. Three Middle East studies, including ours, show that tumors have a high frequency of EBER positivity [8, 9, 10]. In North America, Japan, Korea, and parts of Europe, BL is more common in adults than children [4, 5, 27, 32, 36, 37]. In these countries, much of the EBV seroconversion is in adolescents and young adults, and the frequency of EBER-positive tumors is low.

The variations in regional EBV exposure and evidence for tumor EBV latency confuse our understanding of the relationship between EBV and BL. EBV is an upper respiratory virus that enters the nasopharynx and infects epithelium and lymphocytes, with B cells being the primary target [45].

The early EBV infection stimulates lymphoblastic proliferation. The lymphoblasts enter the germinal centers and undergo somatic hypermutations in heavy and light chain genes [2, 45]. Random translocations between the chromosome 8 MYC oncogene and the chromosome 14 heavy chain or an alternative light chain locus complicate these hypermutations. The MYC translocation is considered an essential carcinogenic event [2, 45]. The EBV-stimulated lymphoblastic proliferation usually becomes quiescent, and approximately 2% of cells enter a type 3 latency as memory B cells. In a type 3 latency, cells produce nuclear EBER but have little expression of other viral components, and viral replication is limited [2, 45, 46]. If infected memory B cells encounter their cognate antigen, they can transform into proliferating mature B cells, and if they bear the MYC translocation, they can become BL [2, 45].

The age of exposure to EBV affects latency and the risk of tumor development, with early childhood exposure in much of the world being associated with a low risk of BL [2]. The endemic BL is an exception, and the very high risk of lymphoma is attributed to coexisting malaria that stimulates B cells. This stimulation augments the frequency of somatic hypermutations and MYC translocations, with higher translocation rates increasing the risk of BL [2, 45].

The relationship of BL to germinal center MYC translocations means that virtually any antigenic stimulus could promote tumor development [2, 45]. Even in countries with a late age of EBV infection, overall seropositivity is at least 70–80%. The nearly universal nature of the infection and the low rates of BL outside of endemic regions questions the role of EBV in the development of the tumor. The Middle East populations have a bottom-heavy structure, with 30–45% of individuals being under 20 years of age [47]. Large numbers of children in families tend to encourage the childhood spread of EBV. Yet, many infections appear delayed until late childhood, and Middle Eastern rates of pediatric BL are not different from much of Europe. The difference is the adult BL that is not diagnosed with any frequency in the Middle East [5].

While pediatric BL has a generally uniform histologic and clinical appearance, BL in adults can present challenges that may not be adequately addressed in current Middle East pathology practices. The WHO classification of lymphoid neoplasms was introduced into the region around 2010, and the complexity of the classification can be difficult for a general pathologist anywhere [9]. BL is defined as a high proliferation rate mature B-cell lymphoma with an isolated MYC translocation [2, 5]. The distinction between BL and diffuse large B-cell lymphoma can be a problem in children and adults, and high-grade B-cell lymphomas of adults histologically and clinically overlap with BL [2, 5, 48]. To make matters even more complex, data on molecular profiling indicate that BL may not always have a MYC abnormality and that the germinal center CD10 and BCL6 positive phenotype, by itself, might be sufficient for the diagnosis [48].

Analyzing international data provokes as many questions as it provides answers. Detailed information is available through IICC-3 on virtually all pediatric cancers [18]. For adults, the WHO Globocan website records international data for non-Hodgkin lymphoma, but there is no separation into subtypes [49]. This is a problem for BL. Most adult BL occurs in immunocompetent patients, and increased adult BL rates may be related to the aging of populations having late exposure to EBV [4]. But in Europe, North America, Japan, and Korea, it is notable that the higher frequency in adults is associated with a parallel increase in pediatric EBER-negative BL.

BL is an important adult tumor, having a frequency approaching mantle cell lymphoma [5]. The absence of details in Globocan requires investigators to depend upon regional publications. US studies using the SEER database are representative of the general population [4]. In many other countries, the studies are hospital-based and may not embody the entire nation.

Recent investigations of BL emphasize molecular mechanisms related to MYC activity and rarely include an analysis of EBV latency [48]. There also seems to be a declining interest in the relationship between the spread of EBV and lymphoma, although, outside of endemic regions, high rates of early childhood EBV infection are associated with low rates of EBV-positive BL [2, 3, 4]. When infections are more frequent in adolescents and young adults, rates of BL are moderately high, and the frequency of tumor EBV latency is low. These are clear relationships that deserve an explanation.

In Sulaimani, several childhood and adult EBV-related tumors are recognized. These include nasopharyngeal carcinoma, NK/T-cell lymphoma of nasal type, and EBV-related large B cell lymphoma. As a group, they comprise less than 0.1% of our cancers. EBV-positive post-transplant lymphoproliferative disease occurs in approximately 1% of our kidney transplants, a frequency similar to the US [50, 51]. All of these tumors are occurring in a population that has a high EBV seroconversion rate that reaches its peak in mid to late adolescence.

BL in the Middle East has an incidence that resembles countries with high indices of development. We believe this BL is a sporadic disease. There is no identifiable promoting influence coexisting with EBV. The indigenous populations of most of the Middle East, including Iraq, have been malaria-free since the late 1990s, and non-Hodgkin lymphomas associated with other infections such as human herpes virus-8,

Helicobacter pylori, and hepatitis B and C are uncommon or no more common than in Europe or North America [9, 52].

If there is a link with Europe, we should probably be identifying more BL in adults. The reason that adult BL is rare in the Middle East is uncertain. It may be related to a high rate of EBV exposure but with a delayed plateau until late adolescence. This seems to be the third pattern of EBV infection between the early childhood exposure of countries with low developmental indices and the adolescent and young adult exposure of countries with high socioeconomic development. It is notable that until adulthood, rates of Middle Eastern BL resemble those of Southern Europe more than any other region of the world.

The determination of the Sulaimania EBV seropositivity used de-identified clinical specimens initially obtained for other diagnostic purposes. This is a limitation to any generalization about seropositivity in the region. Nevertheless, the limitation is shared with other major studies of population EBV exposure that also analyzed stored clinical specimens or blood donations [12, 15, 16, 22, 26, 29, 30, 31, 32, 46]. The social strata of patients seeking medical attention may be different than the general population, and socio-economic factors can influence infection [12, 14]. A study of EBV infection rates in a general population would raise issues of harm and confidentiality and be difficult to design short of a large project using stored specimens as a general health survey [14]. This leaves the analysis of previously clinical specimens the most available, although less than ideal, method for inferring viral exposure.

Abbreviations

BL, Burkitt's lymphoma; WHO, World Health Organization; IICC-3, International Incidence of Childhood Cancer-3; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; EBER, EBV-encoded small non-polyadenylated mRNA, FNA, fine needle aspiration; VCA, viral capsid antigen; ASIR, age-standardized incidence rate; 95% CI, 95% confidence intervals.

Declarations

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Competing interests

None to declare.

Availability of data and materials

Compiled data and calculations are stored in Excel files in the Shorsh Hospital Pathology Department and will be made available upon request to the corresponding author, MDH.

Authors contributions

Study design and concepts: DNM, RTY, and MDH. Data collection and analysis: DNM, AOA, RTY, HAH, AAA, RMA, and MDH. The first draft of the manuscript: DNM, RTY, and MDH. RMA and MDH coordinated manuscript revisions that were read and approved by all authors.

Ethics approval and consent to participate

The Ethics Committees of the Sulaimami Department of Health and Hiwa Cancer Hospital gave permission for the research. The Ethics Committees' approval included the use of serum samples. The serum samples were to be discarded and were de-identified by name. The study otherwise reviewed existing reports with no additional patient intervention and was considered exempt from informed consent.

Conflict of Interest Statement

The authors declare no conflict of interest. The manuscript has not been previously published in whole or in part.

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Figures

Figure 1

Hematoxylin and Eosin 400X. Burkitts lymphoma in a cervical lymph node of a two-year-old girl. The girl was serologically negative for Epstein-Barr virus infection. The tumor was positive for the MYC translocation but negative for Epstein-Barr virus encoded small nuclear mRNA.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BLincidenceTable1.docx
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