J Hematopathol (2010) 3:11–18
DOI 10.1007/s12308-010-0059-3

ORIGINAL ARTICLE

Epstein–Barr virus and Hodgkin's lymphoma in Cairo, Egypt

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Received: 4 December 2009 / Accepted: 16 April 2010 / Published online: 28 May 2010
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Abstract Fifty-five consecutive cases of Hodgkin's lymphoma (HL), collected between 1996 and 1998 from Cairo, Egypt, were histologically subtyped, phenotyped, and then studied for the presence of Epstein–Barr virus (EBV). We used immunohistochemical stains for EBV latent membrane protein 1 (LMP-1) and in situ hybridization stains for EBV-encoded small RNA (EBER-1) transcripts. Forty-five cases (82%) had classic HL (cHL), and ten cases (18%) had nodular lymphocyte predominant HL (NLPHL), with each group expressing its typical phenotype. LMP-1 stains were positive in 63% and 0% of cHL and NLPHL cases, respectively. EBER-positive Reed–Sternberg cells and variants were also present in 62% and 0% of each group, respectively. The cHL cases showed variable EBER positivity: nodular sclerosis, 58%; mixed cellularity, 100%; lymphocyte depletion, 100%; and unclassifiable, 67%. Our findings are similar to those from other developing countries and point towards a pathogenic role of EBV in cHL.

Keywords Classic Hodgkin's lymphoma · Nodular lymphocyte predominant Hodgkin's lymphoma · Epstein–Barr virus · EBER-1 · LMP-1

Introduction

The Non-Hodgkin's Lymphoma (NHL) Classification Project involves an ongoing epidemiologic study, based on a retrospective review of slides in developed and developing

This manuscript has not been published before and is not under consideration for publication anywhere else. Its publication has been approved by all co-authors.

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countries all around the world, to determine the distribution of the various types of NHL. We reviewed 210 consecutive cases of malignant lymphoma in 1999 in Cairo, Egypt; of these, 55 cases were classified as Hodgkin's lymphomas (HL), which form the basis for this study. The main goals of our study were to determine the frequency of EBV positivity for the various subtypes of HL and to compare our results with those reported in the literature in other regions of the world.

Materials and methods

The material for this study was obtained from a large, privately owned pathology laboratory in Cairo (Professor Dr. Elia Anis Ishak, Professor of Surgical Pathology, Cairo University Centre). All sequential cases of malignant lymphoma, including HL, with available paraffin blocks, received in his laboratory between 1996 and 1998 were retrieved and included in the study, as previously described [1]. The cases of HL were subtyped according to the WHO classification [2, 3].

Immunohistochemistry was performed on 5-μm sections of archival, paraffin-embedded tissue using a three-step immunoperoxidase method with microwave pretreatment in citrate buffer (10 nM, pH 6) and antibodies against CD20 (L26), CD3, CD30 (Ber-H2), epithelial membrane antigen (EMA; E29), LMP-1 (EBV/CS 1/4; Dakopatts, Copenhagen, Denmark), and CD15 (80H5; Immunotech, Marseille, France).

In situ hybridization was also performed on paraffin sections using EBER-1 oligonucleotide FITC-conjugated probes (Biogenex, San Ramon, CA, USA). The results were classified as negative, positive only in small cells, positive in some large tumor cells, or positive in several large tumor cells with or without positive small cells.

Each case was separately studied by five experts (JD, K McL, HK M-H, BN, DW), and a consensus diagnosis was reached for each case when at least four of five experts agreed. This review was completed in 1999. Approval for the study was obtained from the Institutional Review Board at the University of Nebraska Medical Center.

Results

Of the 210 consecutive cases of malignant lymphoma from Egypt, 55 cases (26%) were classified as HL and the remaining 155 (84%) as NHL. The age and sex of the HL patients were correlated with the various histological subtypes, as summarized in Table 1. There were 35 males (64%) and 20 females (36%). Eighty-two percent of the cases were classified as classic HL (cHL), and the remaining 18% were nodular lymphocyte predominant HL (NLPHL).

Classic Hodgkin's lymphoma

Our study included 27 males (60%) and 18 females (40%), with a median age of 35 years and an age range of 2–69 years. Nodular sclerosis (NS) was, by far, the most common subtype (84%) of cHL (Table 1). Hodgkin's cells expressed CD30 in all cases, and CD15 was expressed in 34 cases (75%; Table 2). Only seven cases (15%) of cHL had CD20-positive tumor cells, and the percentage of positive cells varied from 20% to 40%. Tumor cells were positive for LMP-1 in 63% of evaluable cases (Table 2). LMP-1 was detected in 60% of NS subtype cases and 100% of mixed cellularity (MC) and lymphocyte depletion (LD) subtype cases. Overall, EBER-1 was detected in 68% of the cHL cases and in 58% of NS cases (Table 2). Moreover, both tumor and small cells were also positive in 21 of 22 EBER-1-positive NS cases. Although EBER-1 was not detected in tumor cells in 16 NS cases, the small cells were positive for EBER-1 in nine of these cases and negative for EBER-1 in seven of these cases. In the four cases with MC and LD subtypes, both the tumor cells and small lymphoid cells were positive for EBER-1.

Nodular lymphocyte predominant Hodgkin's lymphoma

Of the 55 cases of HL, 10 cases (18%) were classified as NLPHL. These NLPHL cases had a median age of 40.5 years, an age range of 12–53 years and were predominantly male (Table 1). The immunophenotype was typical, as the tumor cells expressed CD20 in all cases and were negative for CD30 and CD15 when performed. Immunostains for EMA were done in all cases, and the tumor cells were positive in eight cases (80%). EBER-1 was not detected in tumor cells in all cases but was detected in scattered small lymphocytes in four cases (40%). Staining for LMP-1 was performed in only two cases, and it was negative in both.

Discussion

As a part of an ongoing epidemiologic study of NHL, five pathologists (J D, K McL, HK M-H, B N, D W) reviewed about 200 consecutive cases of NHL from 12 international cities (Cairo, Johannesburg, Harare, Kuwait City, Bangkok, Mumbai, Riyadh, Jakarta, Guatemala City, Sao Paulo, Buenos Aires and Shanghai) and reached a consensus diagnosis for each case. The results of the above review of NHL cases will be published separately (Weisenburger et al., in preparation). The 210 consecutive cases of malignant lymphoma we reviewed in 1999 were collected from 1996 to 1998 in Cairo as a

Table 1 Correlation of age and sex with histological subtype of HL in 55 patients from Cairo, Egypt (current study)

Classification of Hodgkin lymphoma	Age groups (years)			Sex	
	≤15	16–50	≥51	Male	Female
Classic Hodgkin Lymphoma (cHL): 45 cases (82%)				27 (60%)	18 (40%)
Nodular Sclerosis 38 cases (84%)	7	23	8	25	13
Mixed cellularity 3 cases (9%)	0	3	0	0	3
Lymphoid Depletion (1 case)	0	0	1	1	0
Unclassifiable 3 cases (7%)	0	2	1	1	2
Predominant Nodular Lymphocyte HL: 10 cases (18%)	1	6	3	8	2
Total: 55 cases	8 (14.6%)	34 (61.8%)	13 (23.6%)	35 (64%)	20 (36%)

part of the abovementioned study. However, as Cairo also submitted cases of HL and NHL, this study deals with only the 55 cases in which a consensus diagnosis of HL was reached.

The relative frequency of HL was 26% (55 of 210 cases) of all malignant lymphoma, which is in agreement with the incidence of 30% reported in the 2008 WHO publication [3]. The relative frequency of cHL was 82% (45 of 55 cases) and that of NLPHL was 18% (10 of 55 cases), which is significantly higher than the 5% reported for this lymphoma in the WHO book [3] (Table 1). The reason for this higher NLPHL incidence is unknown. Also, the incidence of the NS type in our series was 84%, which is again higher than the 70% reported in the WHO book [3]. However, immunophenotypically, all of the cHL cases were CD30-positive, whereas 74% of cases were positive for CD15 and 85% were negative for CD20, which is in agreement with the WHO book [3]. In addition, LMP-1 was detected in 63% and EBER-1 was detected in 68% of cases (Table 2). LMP-1 was detected in 60% and EBER-1 was detected in 58% of NS subtype cases, which is higher than that reported in the WHO book [3].

EBV infection has been implicated in the pathogenesis of cHL [32, 40, 45, 46] but not in that of NLPHL, thus leading several investigators from all over the world to report on how often LMP-1 and EBER-1 are detected in lymphoma samples in their own institutions/countries. We, therefore, compared our EBV results with those reported in the literature by grouping together countries according to geographical location for both adults (Table 3) and children (Table 4). This comparison showed major differences in the percentages of EBV-positive HL cases in the various countries and regions. The highest percentages of positive cases were from developing countries and children. The variability in the range of EBV-positive adult cases with HL in various regions of the developing world is summarized (Table 3):

- Middle East (including Tunisia) [4–12]: between 28% of cases in a series from Jordan [12] and 70% of cases from Tunisia [4] were EBV-positive with HL; for Egypt [8], 50% were positive and 67% were of the NS type, which is similar to our findings
- East Africa [13–16]: between 44% and 92% of cases were positive in Kenya
- Central and South America [17–23]: between 31% of cases in Argentina [23] and 84% of cases in Peru [17] were positive
- Asia [14, 24–30]: between 39% of cases in China [30] and 82% of cases in India [24] were positive, and the percentage of positive cases in most other countries was high (50% to 69%).

Table 2 Immunophenotype of tumor cells in different subtypes of cHL

	NS		MC and LD		Unclassifiable		Total cHL	
CD30+	38	100%	4	100%	3	100%	45	100%
CD15+	28	74%	4	100%	2	67%	34	75%
CD20+	6	16%	1	33%	0		7	15%
LMP-1+	21	60%	4	100%	1	50%	26[a]/41	63%
LMP-1-	14	40%	0		1	50%	15[a]/41	37%
EBER-1+	22	58%	4	100%	2	67%	28/45	68%
EBER-1-	16	42%	0		1	34%	17/45	38%

[a] For LMP-1, four cases are not shown in this Table 3 of NS type due to uninterpretable results and one unclassifiable case due to the lack of material

Table 3 Frequency of EBV-positive Hodgkin Lymphoma in adults in different regions/continents of the world

	cHL (%)	NS (%)	MC (%)	LD (%)	NLPHL (%)	TOTAL (%)
Mediterranean Countries, Middle East						
Tunisia 2002 [4]	72	69	87	100	0	70
Turkey 2008 [5]	–	–	91	–	–	61
Saudi Arabia 2001 [6]	56	–	56	–	–	56
Kuwait 2003[7]	60	34	79	100	25	56
Egypt 1996 [8]	60	67	57	0	50	50
Saudi Arabia 1998 [9]	54	47	88	–	0	47
Jordan 2004 [10]	47	29	60	–	0	47
Israel 1997 [11]	30	22	45	–	–	30
Jordan 2004 [12]	28	19	57	–	–	28
East Africa						
Kenya 1996 [13]	94	87	100	100	0	92
Kenya 1998 [14]	80	57	85	80	67	79
Kenya 1996 [15]	67	69	100	50	33	68
Kenya 1997 [16]	–	–	–	–	–	44
Central and South America						
Peru 1993 [17]	84	100	100	50	–	84
Mexico 1995 [18]	70	50	81	86	–	70
Mexico 1995 [19]	69	46	100	83	0	67
Argentina 1994-2004 [20]	52	50	62	0	–	52
Puerto Rico 2003 [21]	50	–	–	–	–	50
Costa Rica 1998 [22]	43	15	86	100	0	40
Argentina 2003 [23]	32	24	39	100	0	31
Asia						
India 2003 [24]	82	86	–	–	–	82
Korea 1996 [25]	70	59	74	64	57	69
Taiwan 1998 [26]	67	64	69	100	0	66
Japan 1996 [27]	64	44	84	–	–	64
Japan 1998 [14]	56	36	67	71	67	58
Malaysia 1997 [28]	61	33	92	50	0	51
Taiwan 2008 [29]	50	–	–	–	–	50
China 2001 [30]	39	25	64	0	0	39
Europe						
Greece 1996 [8]	89	92	86	–	100	91
Switzerland 1992 [31]	79	–	–	–	–	79
Italy 1996 [13]	58	45	92	100	0	56
Germany 1992 [32]	48	41	55	50	100	49
Bosnia 2007 [33]	48	–	–	–	–	48
Hungary 2006 [34]	43	35	50	–	–	43
Spain 2000 [35]	41	–	–	–	–	41
France 1992 [36]	39	10	60	–	0	35
U.K. 1994 [37]	33	44	35	–	–	33
Belgium 2007 [38]	–	–	–	–	–	33
UK 2003 [39]	33	24	60	–	–	33
UK 1993 [40]	37	24	68	14	0	32
Sweden 1999 [41]	27	23	38	100	20	27
USA and Australia						
USA 1989 [42]	68	57	92	100	0	65
USA 1994 [43]	47	27	77	–	–	47
USA 2004 [12]	30	14	75	–	–	30
USA 1994 [44]	28	14	69	66	0	25
Australia 1996 [8]	73	73	100	–	0	69

For each country, the first column shows the number (n°) of cases studied whereas the other columns show the percentages of positive cases. For each region of the world, the countries have been organized according to the percentage of positive cases studied, from the highest to the lowest. For each series, the reference for the publication is given after the year of publication

– absence of case, *0* no EBV-positive case

Table 4 Frequency of EBV positive Hodgkin Lymphoma in children in different regions/continents of the world

	CHL (%)	NS (%)	MC (%)	LD (%)	NLPHL (%)	TOTAL (%)
Peru 1993 [17]	100	100	100	–	–	100
Honduras 1993 [47]	100	100	100	–	100	100
Kenya 1996 [15]	100	100	100	100	100	100
China 2001 [30]	–	–	–	–	–	–
≤ 5 years	–	–	–	–	–	97
6–10 years	–	–	–	–	–	93
11–14 years	–	–	–	–	–	54
India 2007 [48]	97	–	–	–	–	97
Vietnam 2005 [49]	93	–	–	–	100	93
Thailand 2005 [50]	93	75	100	100	0	87
Brazil 2006 [51]	94	83	100	100	0	87
Czechoslovakia 2000 [52]	83	60	100	–	–	83
South Africa 2009 [53]	68	67	80	–	–	68
Argentina 2003 [23]	57	28	77	75	0	55
Argentina 1995 [54]	57	0	76	100	33	53
2–6 years	–	–	–	–	–	80
7–15 years	–	–	–	–	–	33
U.K. 1992 [55]	54	40	84	40	36	51
United Arab Emirates 2008 [56]	–	–	–	–	–	38
USA 1993 [47]	39	19	86	–	0	36
UK 1993 [57]	–	54	33	–	–	35

For each country, the first column shows the number (n°) of cases studied whereas the other columns show the percentages of positive cases. For each region of the world, the countries have been organized according to the percentage of positive cases studied, from the highest to the lowest. For each series, the reference for the publication is given after the year of publication

– absence of case, *0* no EBV-positive case

The frequency of EBV-positive HL in most countries in the developed world was lower for adults than that in the developing world (Table 3):

- Europe [8, 13, 31–41]; between 27% of cases in Sweden [41] and 56% of cases in Italy [13] were positive, with a higher rate in two reports: 79% in Switzerland [31] and 91% in Greece [8]
- USA [12, 42–44]: between 25% and 65% of cases were positive
- Australia [8]: a high frequency of positive cases (69%).

For children (Table 4), the frequency of EBV-positive cases was very high—ranging from 83% to 100%—in the nine developing countries [15, 30, 47–52]. This is in contrast to the low frequencies (35% to 38%) found in the USA [47], the United Arab Emirates [56], and the UK [57]. The age of the children studied was also important, as shown by Zhou et al. [30] in China and by Preciado et al. [54] in Argentina. In pediatric cases of HL, Chabay et al. [58] reported a predominance of the MC subtype (52%) in children in 54 cases of HL from Argentina, in contrast to the NS subtype being the major subtype (83%) in 48 cases of HL from Brazil, and indicated that most of the cases were EBV-positive in both countries.

Differences are also observed between developed and undeveloped areas within the same country, as shown by

Table 5 Developed and undeveloped areas of Brazil: Frequency of EBV-positive Hodgkin lymphoma [59]

	cHL (%)	NS (%)	MC (%)	LD (%)	NLPHL (%)	TOTAL (%)
Developed areas						
<20 years	65	25	76	–	0	54
>20 years	58	0	100	0	–	56
Undeveloped areas						
<20 years	82	40	100	100	–	85
>20 years	31	38	35	0	–	31

reports from Brazil [51, 59] (Table 5). Differences in the percentage of positive cases of cHL may be explained by various ethnic communities with different socioeconomic environments [12, 42–44, 47, 59–62]. Improvement in the socioeconomic environment may also explain differences observed in the same country over time. For example, Chang et al. [29] recently compared the frequency of histological subtypes and the percentage of cases testing positive for EBV in two groups of patients in Taiwan, one comprising HL cases collected between 1982 and 1995 (74 cases) and the other comprising HL cases collected between 1996 and 2007 (99 cases). Overall, a large proportion of patients were male (2.3:1) and the mean age at presentation was 41.5 years. The overall frequency of EBV positivity was 50% (86/173 cases). This comparison demonstrated a change in the distribution of HL subtypes observed in the two time periods with an increased frequency of the NS subtype between 1996 and 2007 (53% vs. 68%) and a decreased frequency of the MC subtype (35% vs. 13%). They also observed a reduced male-to-female ratio (2.9:1 vs. 1.4:1) and a reduced mean age (42.4 vs. 36.6 years) in NS subtype cases, including a significant decrease in EBV positivity (61% vs. 39%), between 1996 and 2007. These results show that the most recent findings from Taiwan closely follow those reported in Japan and other Western countries, and may be interpreted as a change in the epidemiology of cHL associated with improved socioeconomic conditions.

As there is a high incidence of EBV-positive HL in the pediatric age group, the number of pediatric cases included in the various studies may influence the overall EBV positivity rate. The percentage of EBV-associated pediatric cHL (Table 4) ranged from 51% of EBV-associated cHL in one series from the UK [55] to 100% in Peru [17], Honduras [47], and Kenya [15], with the percentages in six other countries ranging from 83–97% [30, 48–51].

In our study, all ten cases of NLPHL were negative for EBER-1. However, some cases showed scattered EBER-positive small lymphocytes, which are probably representative of the number of EBV-positive circulating (background) lymphocytes. In most of the studies reviewed, there was a low frequency of EBV in NLPHL [36, 43, 45–47]; however, others reported a higher frequency, but only a few cases were studied [25, 27, 55]. NLPHL is now well defined by histological and immunohistochemical criteria under the WHO classification [2, 3]. Therefore, before we can accept that cases of NLPHL are associated with EBV infection, strict diagnostic criteria need to be applied.

In our study, 38/45 cases of cHL (84%) and 4/10 cases of NLPHL (40%) showed EBV-positive small lymphocytes [62]. Other studies only report EBV-positive small lymphocytes in cases with EBV-positive tumor cells or adult cases [17, 63]. By contrast, we observed EBV-positive small lymphocytes with or without positive tumor cells, in both the pediatric and adult groups. The extent of small lymphocyte positivity also varied among the cases. Twenty-two percent of our cases had an abundance of EBER-1-positive small lymphocytes, consistent with the report by Herbst et al. [44]. Masih et al. [63] used this finding to argue against the theory of "exclusive" localization of EBV in tumor cells and raised the issue as to whether EBV within tumor cells was a primary or secondary phenomenon. Also, since EBV is a ubiquitous lymphotropic virus, it is to be expected that small lymphocytes can frequently be positive.

Acknowledgements We sincerely thank Martin Bast from the Department of Internal Medicine, University of Nebraska, Omaha, USA, for his support and Serge Bain, Véronique Ducruit, and Catherine Belorgey from the Department of Pathology, Hôtel Dieu Hospital, Paris, France, for their technical help.

Conflict of interest The authors declare that they have no conflict of interest.

This work has not been published before and is not under consideration for publication anywhere else. Its publication has been approved by all co-authors.

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