

Lymphotropic viruses in Latin America

Subjects: Oncology

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The RIAL-CYTED harbors a multidisciplinary Ibero-American network of clinical and basic researchers created to form a platform of multi-center cooperation focusing on increasing our knowledge of lymphoma, particularly for more underdeveloped or developing regions. This network aims to improve the diagnosis and prognosis of these neoplasms throughout LA by way of homogenizing its identification and classification. With that purpose, in this review, we sought to systematically organize and analyze the literature related to the lymphotropic and lymphomagenic viruses EBV, KSHV and HTLV-1, in order to better understand their loco-regional distribution and the risk our population carries in terms of developing lymphoma.

Keywords: Epstein–Barr virus ; Kaposi sarcoma herpesvirus ; human T-lymphotropic virus ; lymphoma ; Latin America

The Epstein–Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV) and human T-lymphotropic virus (HTLV-1) are lymphomagenic viruses with region-specific induced morbidity. The RIAL-CYTED aims to increase the knowledge of lymphoma in Latin America (LA), and, as such, we systematically analyzed the literature to better understand our risk for virus-induced lymphoma. We observed that high endemicity regions for certain lymphomas, e.g., Mexico and Peru, have a high incidence of EBV-positive lymphomas of T/NK cell origin. Peru also carries the highest frequency of EBV-positive classical Hodgkin lymphoma (HL) and EBV-positive diffuse large B cell lymphoma, not otherwise specified (NOS), than any other LA country. Adult T cell lymphoma is endemic to the North of Brazil and Chile. While only few cases of KSHV-positive lymphomas were found, in spite of the close correlation of Kaposi sarcoma and the prevalence of pathogenic types of KSHV. Both EBV-associated HL and Burkitt lymphoma mainly affect young children, unlike in developed countries, in which adolescents and young adults are the most affected, correlating with an early EBV seroconversion for LA population despite of lack of infectious mononucleosis symptoms. High endemicity of KSHV and HTLV infection was observed among Amerindian populations, with differences between Amazonian and Andean populations.

1. Introduction

Neoplasms of an infectious etiology account for about 16% of all cancers, which amounts to about two million cases per year, considering virus-, bacteria- and parasite-derived cancers. Interestingly, this number is significantly higher for developing countries, in which it can be as high as 30%, while in highly industrialized countries, such as the US, it can be as low as 5% ^[1]. The bases for this difference are not clear, but it may be due to the prevalence of the oncogenic infectious agents, or to additional co-factors causally linked to the infectious neoplasms.

Virus-derived cancers almost always originate from established chronic viral infections, because the mechanisms of viral persistence in the infected host are compatible with oncogenesis. Indeed, all human oncogenic viruses express proteins, and/or non-coding RNAs with the capacity to transform cells in culture and induce cancer in transgenic animals ^[2]. Viral oncogenes tend to enhance cell proliferation and survival, aiming to maintain the pool of infected cells during persistent infections. The International Agency for Research on Cancer (IARC) acknowledges seven viruses as direct human oncogenic agents: the Epstein–Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV), human T cell lymphotropic virus type 1 (HTLV-1), high risk human papillomaviruses (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Merkel cell polyomavirus (MCPyV) ^[3]. Although the human immunodeficiency virus (HIV) is also causally associated with several neoplasms, it is as an indirect oncogenic agent, due to the immunosuppression it imposes upon the infected host.

The Epstein–Barr virus (EBV) was the first oncogenic virus discovered 56 years ago by Dr. Anthony Epstein and Dr. Iyonne Barr. EBV was initially observed in samples of Burkitt lymphoma (BL) coming from the equatorial Africa, which represents the perfect example of the unequal geographical distribution of neoplasms of infectious origin. While EBV is responsible for close to 100% of the BL originating in this region, EBV only accounts for about 20% of all BLs in developed countries (see below). We later understood that whilst EBV is evenly distributed around the world, the African BL is also associated with repetitive infections with *Plasmodium falciparum*, an important co-factor of this neoplasm and a parasite endemic to this area. Today, BL is classified within three distinct clinical types, endemic (malaria- and EBV-associated), sporadic (derived from areas in which malaria is not holoendemic) and immunodeficiency-associated ^[4].

The world distribution of the oncogenic viruses varies significantly, while most adults are already infected with EBV, HPV and MCPyV indistinct of the geographic region, the others tend to be more prevalent in specific populations [2]. Even today, despite the global means of transportation and increased immigration that have allowed a more heterogeneous mix of populations, the prevalence of KSHV and HTLV-1 infection is still restricted to particular geographical areas, implying mechanisms of viral persistence in the population that are not explained by mere socioeconomic factors, but in which genetic susceptibilities, ethnic origin, culture and the prevalence of co-factors may be critical (see below). Like EBV, KSHV and HTLV-1 are associated with lymphoid neoplasms [2]. While EBV mainly infects and persists in B cells, KSHV and HTLV-1 persist in B cells and T cells, respectively, and, as such, they have been associated with B and T cell lymphomas [2].

Latin America (LA) comprises the land from Mexico to Argentina and the Spanish speaking Caribbean, countries with a complex mix of geographies, climates, politics, cultures, ethnicities and different levels of socioeconomic development, and, in which, a high prevalence of oncogenic viruses, acute tropical diseases and malnourishment collide. Early epidemiological studies documented a high seroprevalence of KSHV and HTLV-1 in some regions of LA, and to this day, it is common to find in the scientific literature that these viruses are endemic to LA (see below). However, the loco-regional estimation of their prevalence and induced morbidity remains poorly known. The RIAL-CYTED harbors a multidisciplinary Ibero-American network of clinical and basic researchers created to form a platform of multi-center cooperation focusing on increasing our knowledge of lymphoma, particularly for more underdeveloped or developing regions. This network aims to improve the diagnosis and prognosis of these neoplasms throughout LA by way of homogenizing its identification and classification.

2. Epstein–Barr Virus

EBV is a human gamma-1 herpesvirus usually persisting as a harmless passenger; its growth-transforming ability is linked to a range of lymphoproliferative lesions and malignant lymphomas [5]. EBV-associated lymphomas vary according to the geographic location, age, sex, genetic background and socioeconomic condition [6]. Additionally, the age of primary infection varies substantially worldwide, correlating with socioeconomic factors [7]. In underdeveloped and developing populations, EBV infection is acquired at a young age and is usually asymptomatic. A delay in acquiring primary infection until adolescence or young adulthood, which usually occurs in more developed countries, can manifest as infectious mononucleosis (IM) in 25–75% of the late infected persons [8].

EBV infection has been associated with the following lymphomas in addition to BL: Hodgkin lymphoma (HL), lymphomas in immunosuppressed individuals (post-transplant lymphoproliferative disorders (PTLD) and HIV-associated lymphoproliferative disorders and T-cell and NK-cell lymphomas). Furthermore, the last WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues included two new entities specifically associated with EBV: EBV-positive diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) and systemic EBV-positive T-cell lymphoma of childhood [9]. Since the incidence of HIV- and transplant-related lymphoma is more informative of the HIV prevalence or the number of transplanted patients than of the EBV distribution, we will not cover them in this review. See Table 1 for the studies considered and the frequency of EBV association.

Table 1. Summary of studies about Epstein–Barr virus (EBV) associated lymphomas.

Country (Ref)	Lymphoma Type	Type of Study	Methods	EBV Association	Description of the Study
Argentina [10][11][12]	DLBCL (ad/ped)	Cohort	ISH, IHC	12.6% (12/95)	26 DLBCL ped; 69 DLBCL ad from Buenos Aires, Argentina. EBV prevalence 72% ped.
Argentina [13]	PBL	Case report	ISH	100%	1 PBL in HIV+ patient from Buenos Aires, Argentina.

Argentina ^[14]	BL (ped)	Cohort	ISH, IHC	29% IHC (7/24); 100% ISH (3/3)	27 pediatric BL, 3 HIV+ from Buenos Aires, Argentina.
Argentina ^[15]	PBL	4 cases	ISH, IHC	100% (4/4)	4 PBL in HIV+ patients from Buenos Aires, Argentina.
Argentina ^[16]	B-NHL (ped)	Cohort	ISH	40% (16/40) (35% BL; 47% DLBCL)	23 BL ped, 17 DLBCL ped from Buenos Aires, Argentina.
Argentina ^[17]	PBL	Case report	ISH	100%	1 PBL in HIV+ from Buenos Aires, Argentina.
Argentina ^[18]	PBL	Case report	ISH	100%	1 PBL in HIV+ from Buenos Aires, Argentina.
Argentina ^[19]	T-NHL (ped)	Cohort	ISH, IHC	8% (2/25)	16 lymphoblastic, 8 anaplastic, 1 hepatoesplenic T-cell lymphoma ped from Buenos Aires, Argentina.
Argentina/Brazil ^[20]	HL (ped)	Cohort	ISH, IHC	54% (Arg; 60/111); 48% (Bra; 31/65)	111 HL ped from Buenos Aires, Argentina. 65 HL ped from Rio de Janeiro, Brazil.
Argentina ^[21]	PCNSL	7 cases	ISH, PCR	100% (6/6)	7 PCNSL cases HIV+ from Buenos Aires, Argentina.
Argentina ^[22]	HL (ad, ped)	Cohort	ISH	55% ped (51/92); 31% ad (25/81)	92 HL ped, 81 HL ad from Buenos Aires, Argentina.
Argentina ^[23]	HIV+ HL, BL, DLBCL	4 cases	ISH, IHC	100% (4/4)	1 HL, 2 BL, 1 DLBCL ped HIV+ from Buenos Aires, Argentina.
Argentina ^[24]	BL (ped)	Cohort	ISH, PCR	47% (8/17)	17 BL ped from Buenos Aires, Argentina.
Argentina ^{[25][26][27]}	HL (ped)	Cohort	ISH	51% (22/41)	41 HL ped from Buenos Aires, Argentina.

Argentina ^[28]	BL (ped)	Cohort	ISH	25% (4/16)	16 BL ped from La Plata, Argentina.
Brazil ^[29]	DLBCL	Cohort	ISH	30% (28/93)	93 DLBCL ad from Sao Paulo, Brazil.
Brazil ^[30]	NT/NKL	Case report	IHC	100%	1 NK/NKL from Rio Janeiro, Brazil.
Brazil ^[31]	HVL-LD	Case report	ISH	100%	1 HVL- LD from Dom Eliseu City, Pará, Brazil.
Brazil ^[32]	HL (ad/ped, temporal series)	Cohort	ISH	87–46% (817)	155 HL ped, 662 HL ad from Sao Paulo, Brazil.
Brazil ^[33]	Intermediate BL with DLBCL	Case report	ISH	100%	1 int BL DLBCL from Recife, Brazil.
Brazil ^[34]	DLBCL (> 50 yo)	Cohort	ISH	8.45% (6/71)	71 DLBCL ad from Sao Paulo, Brazil.
Brazil ^[35]	T/NKL	Case report	ISH	100%	T/NKL HIV+ from Sao Paulo, Brazil.
Brazil ^[36]	BL (ped)	Cohort	ISH	100% (7/7)	4 BL ped, 3 BL ad from Amazonas, Brazil.
Brazil ^[37]	BL (ped)	Cohort	ISH	54.1% (33/61)	61 BL ped from Rio de Janeiro, Brazil.
Brazil ^[38]	HL (ad, ped)	Cohort	ISH	43% (56/130)	130 HL from Sao Paulo, Brazil.
Brazil ^[39]	HVL-LD	Case report	ISH	100%	1 HVL-LD from Manaus Amazonas, Brazil.
Brazil ^[40]	DLBCL, Palatine tonsil	Cohort	ISH	0% (0/26)	26 DLBCL from Bahia, Brazil.
Brazil ^{[41][42][43]}	HL (ped)	Cohort	ISH	44.8% (43/96)	96 HL ped from Rio de Janeiro, Brazil.
Brazil ^{[44][45]}	HL (ad)	Cohort	ISH	52.6% (51/97)	97 HL ad from Sao Paulo, Brazil.
Brazil ^[46]	ENKTCL (ad, ped)	Cohort	ISH, PCR	100% (74/74)	74 ENKTCL from Sao Paulo, Brazil.

Brazil ^[47]	HL (ad)	Cohort	ISH	22% (5/23)	23 HL ad from Sao Paulo, Brazil.
Brazil ^[48]	CNS DLBCL (ad)	Cohort	ISH	5.5% total (2/36) (40% IS)	36 CNS DLBCL from Sao Paulo, Brazil.
Brazil ^[49]	HL (stomach)	5 cases	ISH	80% (4/5)	5 HL from Sao Paulo, Brazil.
Brazil ^[50]	B-NHL (ped)	Cohort	ISH, qPCR	23% (7/30)	30 NHL ped from Rio de Janeiro and Sao Paulo, Brazil.
Brazil ^[51]	HL + PTL	Case report	ISH	100%	HL PTL from Sao Paulo, Brazil.
Brazil ^[52]	HL (ad, ped)	Cohort	ISH, IHC	50.3% (85/169)	169 HL from Sao Paulo, Brazil.
Brazil ^{[53][54]}	BL (ad, ped)	Cohort	ISH	52.6 % (123/234)	North Region(n = 17 cases), Central West Region(n = 17 cases), Northeast Region(n = 86 cases), Southeast Region(n = 72 cases), South Region(n = 42 cases)
Brazil ^[55]	BL (ped)	Cohort	ISH	66% (33/50)	143 pediaticos y 88 adultos, 3 sin edad).
Brazil ^[56]	BL (ped)	Cohort	ISH	61% (33/54)	San pablo
Brazil ^[57]	PBL	11 cases	ISH, PCR	100% (11/11)	Rio de janeiro
Brazil ^[58]	HL (ad, ped)	Cohort	ISH, IHC	48% (22/46)	San pablo
Brazil ^[59]	PCNSL	10 cases	IHC	10% (1/10)	Florianopolis, South of Brazil
Brazil ^[60]	HL (ad)	Cohort	IHC, PCR	37% (11/30); 43% Circulating EBV	14 patients < 15 years y 32 > 15 years
Brazil ^[61]	HL (ped)	Cohort	ISH	86.7% (78/90)	Niterói RJ
Brazil ^{[62][63][64]}	B-NHL (ped)	Cohort	ISH, PCR	72% (21/29)	29 NHL from Rio de Janeiro, Brazil.
Brazil ^[65]	HL (ad)	Cohort	ISH, IHC	75.6% (28/37)	37 HL ad from Ceara, Brazil.

Brazil ^[66]	HL (ad)	Cohort	IHC	45.8% (38/83)	83 HL ad from Rio de Janeiro, Brazil.
Brazil ^[67]	HL (ad, ped)	Cohort	IHC	55% (35/64)	64 HL ad from Rio de Janeiro, Brazil.
Brazil ^{[68][69]}	HL (ad)	Cohort	ISH, IHC	64.1% (50/78)	78 HL ad from Rio de Janeiro, Brazil.
Brazil ^[70]	HL (ad, ped)	Cohort	ISH	63.5% (61/96)	96 HL from Sao Paulo and Ceara, Brazil.
Brazil ^[71]	ENKTCL	Cohort	ISH	100% (16/16)	16 ENKTCL from Sao Paulo, Brazil.
Brazil ^[72]	BL (ped)	Cohort	ISH	73% (8/11)	11 BL ped from Recife, Brazil.
Brazil ^[73]	HL (ped)	Cohort	ISH	57.7% (15/26)	26 HL ped from Curitiba, Brazil.
Brazil ^[74]	BL (ped)	Cohort	ISH	87% (47/54)	54 BL ped from Bahia, Brazil.
Brazil ^[75]	BL	Cohort	ISH	71% (17/24)	24 BL from Sao Paulo, Brazil.
Brazil ^[76]	HL (ped)	Cohort	ISH	72% (18/25)	25 HL ped from Sao Paulo, Brazil.
Mexico ^[77]	HVL-LD	Cohort	ISH	100% (20/20)	20 HVL-LD ped from Mexico City, Mexico.
Mexico ^[78]	HL (ad, ped)	Cohort	ISH	76.1% ped (22/42); 66.6% ad (16/24)	42 HL ped, 24 HL ad from Mexico City, Mexico.
Mexico ^[79]	PCL	Case report	ISH	100%	1 PCL from Mexico City, Mexico.
Mexico ^[80]	PBL	5 cases	PCR	80% (4/5)	5 PBL ad HIV+ from Mexico City, Mexico.
Mexico ^[81]	DLBCL (> 50 yrs)	Cohort	ISH	7% (9/136)	136 DLBCL ad from Mexico City, Mexico.
Mexico ^[82]	HL (mostly ad)	Cohort	ISH, IHC	61.4% (35/57)	54 HL ad, 3 HL ped from Mexico City, Mexico.

Mexico ^[83]	ENKTCL	Cohort	ISH	96% (22/23)	23 ENKTCL from Mexico City, Mexico.
Mexico/Bolivia ^[84]	HVL-LD /ACTCLC	4 cases	ISH	75% (3/4)	4 ACTCLC ped from Mexico City and La Paz
Mexico ^[85]	PTLD	8 cases	ISH	100% (8/8)	8 PTLD ad from Mexico City, Mexico.
Mexico ^[86]	NHL, Intestinal	Cohort	ISH	63% (12/19)	7 T, 6 high grade B, 6 low grade B-NHLs from Mexico City, Mexico.
Mexico ^{[87][88]}	HL (ad)	Cohort	IHC	70% (35/50)	50 HL ad from Mexico City, Mexico.
Mexico ^[89]	HL (ad, ped)	Cohort	ISH, IHC	67% (18/27)	3 HL ped, 24 HL ad from Mexico City, Mexico.
PR ^[90]	HL & NHL (ad, ped)	Cohort	IHC	50% HL (11/22); 35% NHL (22/63)	22 HL, 63 NHL from San Juan de Puerto Rico, Puerto Rico.
DR ^[91]	HL (ped)	Cohort	IHC	64.3% (18/28)	28 HL ped from Santiago, Dominican Republic
Cuba ^[92]	BL (ped)	7 cases	EBV Serology	85.7% (6/7)	EBV prevalence in 7 BL ped from La Habana, Cuba.
Colombia ^{[93][94]}	HL (ad, ped)	Cohort	ISH, IHC	67% (45/67) 60.4% ad; 84.2% ped	48 HL ad, 19 HL ped from Bogotá, Colombia
Peru ^[95]	DLBCL (ad)	Cohort	ISH	28% (33/117)	117 DLBCL ad from Lima and Arequipa, Peru.
Peru ^[96]	LBCL in cardiac myxoma (ad)	Case report	ISH	100%	LBCL ad from Lima, Peru.
Peru ^[97]	HVL-LD	4 cases	ISH	100% (3/3)	4 HVL-LD ped from Lima, Peru.
Peru ^[98]	EBV+ DLBCL GI (ad)	5 cases	ISH	100% (5/5)	5 DLBCL GI ad from Lima, Peru.

Peru ^[99]	Systemic T/NKL	6 cases	ISH, IHC	100% (6/6)	6 T/NKL ped from Lima, Peru.
Peru ^{[100][101]}	EBV+ DLBCL (> 50 yo)	Cohort	ISH	14% (28/199)	199 DLBCL ad from Lima, Peru.
Peru ^[102]	DLCBL in a HTLV-1+	Case report	ISH	100%	DLBCL ad from Lima, Peru.
Peru ^[103]	Cutaneous T/NKL (11/15 HVL-LD)	Cohort	ISH	100% (15/15)	12 T/NKL ped, 2 T/NKL ad from Lima, Peru.
Peru ^[104]	ENKTCL	Cohort	PCR	99% (76/77)	77 ENKTCL from Lima, Peru.
Peru ^[105]	HVL-LD	6 cases	ISH	100% (6/6)	6 HVL-LD ped from Lima, Peru.
Peru ^[106]	ENKTCL	Cohort	ISH, IHC	96% (27/28)	28 ENKTCL ad from Lima, Peru.
Peru ^[107]	Nasal lymphoma	Cohort	ISH	93% (14/13; 11/11 T-cell)	13 Nasal lymphoma from Lima, Peru.
Peru ^[108]	HL (mostly ped)	Cohort	ISH, IHC	94% (30/32)	32 HL from Lima, Peru.
Ecuador ^[109]	HVL-LD	2 cases	ISH	100%	1 HVL-LD ped, 1 HVL-LD ad from Quito, Ecuador.
Ecuador ^[110]	HL and NHL (ad)	Cohort	ISH, qPCR	55.5% HL (5/9); 59.5% NHL (25/42)	9 HL ad, 42 NHL ad from Guayaquil, Ecuador.
Chile ^[111]	EBV+ DLBCL	Case report	ISH	100% (Leukocytoclastic vasculitis)	DLBCL from Santiago, Chile.
Chile ^[112]	Nasal lymphoma	Cohort	ISH	DLCBL 0% (0/3); T-cell 0% (0/1); NKT 100% (6/6)	3 DLBCL, 1 T-cell lymphoma, 6 NKT from Valdivia, Chile.
Chile ^[113]	ENKTCL	Cohort	ISH	78% (7/9)	9 ENKTCL ad from Santiago, Chile.
Chile /Argentina /Brazil ^[114]	BL (mostly ped)	Cohort	ISH	41% (7/17 Arg); 50% (5/10 Chile); 58% (7/12 Br)	37 BL ped, 2 BL ad from Buenos Aires, Argentina; Santiago, Chile; Campinas, Brazil.

Honduras ^[115]	HL (ped)	Cohort	ISH	100% (11/11)	11 HL ped from Tegucigalpa, Honduras.
CR ^[116]	HL (ad, ped)	Cohort	IHC	40% (16/40)	6 HL ped, 34 HL ad from San Jose, Costa Rica.
CR ^[117]	HL (ped)	Cohort	ISH, IHC	81% (34/42)	42 HL from San José, Costa Rica.
CR/Mexico ^[118]	HL (ad, > 15 yo)	Cohort	ISH, SB	36% (5/14) CR; 77% (24/31) Mexico	45 HL ad from Mexico City, Mexico; San Jose, Costa Rica.
Bolivia ^[119]	NHL	8 cases	ISH	75% (6/8)	8 NHL from Santa Cruz, Bolivia.
Guatemala ^[120]	ENKTCL	Cohort	ISH	87% (73/84)	59 ENKTCL from Guatemala City, Guatemala.

ACTCLC: angiocentric cutaneous T-cell lymphomas of childhood; B-NHL: B-cell non-Hodgkin lymphoma; CNS: central nervous system; CSF: cerebrospinal fluid; DLBCL: diffuse large B cell lymphoma; GI, gastrointestinal; HL, Hodgkin lymphoma; HVL-LD: hydroa vacciniform-like lymphoproliferative disease; IC: immunocompetent; IHC: immunohistochemistry; IS: immunosuppressed; ISH: Epstein–Barr virus-encoded small RNAs (EBERs) in situ hybridization; ENKTCL: extranodal nasal-type T-cell/NK lymphoma, PBL: plasmablastic lymphoma; PCL: plasma cell myeloma; PCNSL: primary central nervous system lymphoma; PTL: peripheral T cell lymphoma; qPCR: quantitative real-time PCR; SB: Southern blot; T-NHL: T-cell Non-Hodgkin Lymphoma; Pt: patient; ad: adult; ped: pediatric. Countries PR, DR and CR: Puerto Rico, Dominican Republic and Costa Rica. virus+ refers to virus positive samples.

2.1. EBV-Associated Lymphoid Neoplasms in Latin America

2.1.1. Hodgkin Lymphoma

There are several series of lymphomas reported in this region, particularly at the end of last century, which, however, were only classified as Hodgkin and non-Hodgkin (NHL), and which obviously did not follow the latest WHO classification. HL has a bimodal age distribution, there is an early peak occurring in adolescents and young adults, and a late peak after 50 years of age in industrialized countries. Developing countries also exhibit a bimodal distribution of the disease, but the early peak starts before adolescence ^[121]. In the US, pediatric HL shows the highest incidence in adolescents between 15–19 years of age, while developing countries present similar incidences than the US for adolescents, but also exhibit a marked augmented incidence in young children ^{[122][123]}. In developing countries, classical HL (cHL) with an early onset (14 yrs or younger) shows high EBV association, more often of the mixed cellularity (HL-MC) subtype. A strong male to female predominance is also observed, particularly in the group younger than 5 yrs, in which the ratio is 5:1. HL in adolescents and young adults displays lower EBV association, nodular sclerosis subtype (HL-NS) predominance and affects male and females almost equally ^[122].

We found 36 studies of HL in LA, including pediatric and adult series from 12 countries. Pediatric series from Argentina exhibited a profile compatible with early cHL (i.e., younger ages, EBV positivity of ~50% and HL-MC as the predominant subtype), while adult HL displayed a 31% of EBV-association, with similar frequencies of both NS and MC subtypes. On the other hand, in the Southeast of Brazil, EBV positivity was 40–50%, HL-NS was the predominant subtype, and there was a smooth peak between adolescents and young adults, which may suggest a transition state in the epidemiology of the disease presentation between the ones observed in developing and developed areas. Indeed, one study in the most affluent Brazilian State (Sao Paulo) reviewed 817 cases of cHL over 54 years (1954–2008), describing that EBV-positive

cases showed a decrease from 87% to 46% during the time of the study, with a remarkable decrease in young adults (85% to 32%). Nevertheless, HL-NS was still the predominant subtype in all periods. On the contrary, HL in the North of Brazil exhibits high EBV association (87%), HL-MC and young age predominance. These results support the hypothesis that the socioeconomic level may determine the presentation features of this neoplasm, also highlighting the role of EBV as an HL driver that is also influenced by socioeconomic factors. Figure 1A–D shows examples of EBV positive HL-NS and HL-MC.



Figure 1. Hodgkin lymphoma. (A–C). Nodular sclerosis Hodgkin lymphoma. (A). Hematoxylin-Eosin staining. (B). CD30 staining with arrows pointing at positive Reed-Sternberg cells. (C). Epstein-Barr virus-encoded small RNAs (EBER) in situ hybridization. (D). EBER in situ hybridization of a mixed cellularity Hodgkin lymphoma, magnification 40×. (E,F). Diffuse large B cell lymphoma, magnification 40×. (E). CD30 staining. (F). LMP1 (latent membrane protein 1) staining.

There is only one large pediatric cohort of 42 cases published from Mexico, with a median age of 5 yrs at diagnosis, and in which a male predominance (2.5:1) was observed. EBV positivity was found in 76.1% of the cases and the HL-MC subtype was the most predominant (71.4%). Other studies from Mexico mostly include young and older adults, with scarce inclusion of children and adolescents, and in which EBV association frequencies vary between 61% and 77%. In those studies, a predominance of HL-MC and HL-NS subtypes was observed. In these Mexican studies, a high EBV association was also observed for the lymphocyte depleted (HL-LD) subtype, with 91.2% positive cases.

In line with the above-described data, a 94% of EBV association was observed in pediatric HL in Peru, while in Colombia, EBV association varied from 60% in adults to 84% in children]. Another study from Honduras that included 11 children younger than 15 yo also found 100% EBV positivity. Series of studies from the Caribbean and continental Central American countries: Puerto Rico, Ecuador, Costa Rica and the Dominican Republic found intermediate EBV association frequencies (50%, 55%, 36–40% and 64%, respectively), which are closer to the frequencies observed in the more developed Argentina. These frequencies should be confirmed with more samples and up-to-date techniques.

2.1.2. Burkitt Lymphoma

BL is a highly aggressive B cell lymphoma, characterized by the translocation of the MYC oncogene to the immunoglobulin loci. It affects mostly children and is also more predominant in males ^[124]. EBV-associated BL conforms almost 100% of endemic BL and around 20% of sporadic cases of North America and Europe. Other regions of the world, especially developing populations, exhibit intermediate frequencies, such as 50–70% in North Africa and Russia ^[125]. Pediatric BL in Argentina has an EBV association frequency closer to the sporadic subtype (25–47%), and the highest incidence of EBV-positive cases is in children younger than 5 yo. As with HL, the frequency of EBV positive cases increase with latitude in Brazil, being ~60% in the South East, and 73–87% in North East. A study including an extensive number of BL cases from five Brazilian geographic regions confirmed this trend, disclosing EBV association frequencies from 29% in the South to 76% in the North. This pattern appears to represent a socio-geographic gradient, which might reflect social development, as well as other unknown environmental, ethnic or genetic factors. A Brazilian study of 14 population-based cancer registries showed that the global age-adjusted incidence rate for pediatric BL does not differ significantly from the expected for a sporadic BL region. However, the incidence was elevated for BL children aged 1–4 years ^[126]. Given the association of EBV positive BL with young age, it is tempting to ascribe this elevated risk to the early EBV seroconversion, which is characteristic of the natural history of EBV infection in our geographic region ^[127]. Indeed, an EBV-associated BL inverse correlation with age has been shown in other studies from Brazil and Argentina.

Unfortunately, we could not find reports on BL series from the Andean and Caribbean regions of LA, which, most probably, does not represent a low frequency of this lymphoma there. Although there are studies including BL from Mexico, they do not address EBV infection, and there is only one case report from a 63 yo male with an EBV positive intraoral BL [128].

2.1.3. Diffuse Large B Cell Lymphoma

DLBCL is a highly aggressive neoplasm that can arise in almost any location of the body. It is very rare in pediatric patients and young adults, but is one of the most common NHLs in older individuals. Due to the median age of presentation of 70 yrs, it is usually associated with underlying immunosuppression. In the former 2008 WHO classification [129], EBV-positive DLBCL of the elderly (> 50 years) was recognized as a provisional entity among the DLBCL subtypes. This provisional entity represented 5–11% of the DLBCL among immunocompetent East Asian patients [130], while in Western populations, the frequency was lower than 5% [131]. The reported series from LA have shown slightly higher EBV association frequencies (7% México, 9% Brazil, 13% Argentina and 14–28% Peru) than the observed in Western countries. LA patients are also younger than the ones described in other series. Peru is particularly interesting, since it has the highest incidence of positive EBV DLBCLs, in addition to the incidence of DLBCL being the highest reported, accounting for up to 45% of all lymphomas [132]. In a Peruvian study of five cases, DLBCL of the gastrointestinal tract was consistently associated with EBV infection in elderly patients. Remarkably, a series of cases of DLBCL of the palatine tonsils from Salvador de Bahia Brazil did not find an association with EBV. Figure 1E,F shows an example of an EBV positive DLBCL.

In the 2016 WHO classification of lymphoid neoplasms, the age factor was eliminated from the association of EBV with DLBCL, leading to the substitution of the modifier “elderly” with “not otherwise specified” (EBV-positive DLBCL, NOS). Therefore, new studies free from the restraint of the age limit are needed, to better characterize the magnitude of this association, as well as the prognostic impact of EBV positivity in LA patients. DLBCL are also distinguished by their phenotype as germinal center or activated, with the former exhibiting an overall better survival rate. No differences were found in a series of Argentinian cases with respect to EBV positivity in these two subtypes of DLBCL.

2.1.4. T and NK Lymphoproliferative Disorders

Although EBV tropism is mainly of B cells and in healthy individuals exclusively localizes in B cells [133], the revised 2016 WHO classification recognizes the chronic active EBV infection (CAEBV) of T/NK cell type, the aggressive NK-cell leukemia, the systemic T-cell lymphoma of childhood and the extranodal NK/T-cell lymphoma, nasal type (ENKTCL), as well as a new provisional entity, the primary EBV-positive nodal T/NK-cell lymphoma [134]. These neoplasms represent a broad spectrum of diseases that occur with higher incidence in Asian populations, and, in which, CAEBV, the aggressive NK leukemia and the systemic T-cell lymphoma are more prevalent in children and adolescents, while ENKTCL mainly affects adults [134]. How the virus infects T or NK cells is still a matter of debate, but exists some evidence of a preferential tropism for T cells for the EBV-2 subtype [135][136].

CAEBV corresponds to a group of reactive LPDs associated with a heightened EBV infection lasting longer than IM, and with the potential to progress to a systemic lymphoma. The clinical picture is diverse and includes the indolent, localized cutaneous form hydroa vacciniform-like LPD (HVL-LPD), renamed by the revised 2016 WHO classification. Several series of patients with HVL-LPD have been described in LA indicating a high incidence of this disease, mainly in countries with a large Amerindian population component, such as Mexico, Bolivia, Peru and Ecuador. In Brazil, two HVL-LPD cases were reported in children from Amazon indigenous tribes, supporting the ethnic bias of this disease. In these series of patients, the association with EBV was virtually 100%. These studies have also greatly contributed to illustrate the clinical and pathological features of this disease in LA as an LPD with 70% of cases being of T-cell origin and 30% of NK origin. This scenario is more similar to Asian CAEBV, since, in the US, CAEBV is very rare, and also presents as a B cell LPD [137]. Although cellular and viral monoclonality has been proven in the majority of T-cell cases, the disease is today considered an LPD, with a high risk to progress into a systemic lymphoma, to reflect the diverse clinical spectrum of the disease presentation, from self-limited HV to HV-like lymphoma, and also to allow for more adequate therapeutic approaches, since patients respond well to immunomodulatory agents as first line of treatment.

Extranodal NK/T cell lymphoma (ENKTCL) is an EBV-positive lymphoma more commonly derived from NK cells. Similar to CAEBV lymphoproliferations, this type of lymphoma has been described mainly in East Asia and LA, in which the ethnic composition includes a high proportion of Amerindians. EBV infection is also confirmed in virtually all cases. Series of cases have been reported from México, Peru, Chile and Guatemala. In Brazil, ENKTCL usually occurs as isolated cases [71]. Recently, a large series was reported that included 122 cases with mostly adults (only three children) from all five Brazilian regions. In this Brazilian cohort, the clinico-pathological characteristics of the neoplasm were similar to the ones described in patients from East Asia and other American countries, in which the disease is considered endemic. No ethnic

data was recorded for the patients included in the study. In a Brazilian unicentric study that included lymphomas involving the midline facial region, 16 were of T/NK cell origin and nine were of B cell origin ($n = 25$). Remarkably, no ethnic differences were found between the patients with T/NK or B cell presentation. Figure 2 shows an example of an ENKTCL.

Figure 2. Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKL). (A). Hematoxylin-Eosin staining. (B). CD56 staining. (C). CD3 staining. (D). EBER in situ hybridization.

References

1. Schottenfeld, D. and J. Beebe-Dimmer, The cancer burden attributable to biologic agents. *Ann Epidemiol.* 2015, 25, 183–187.
2. Morales-Sanchez, A.; Fuentes-Panana, E.M. Human viruses and cancer. *Viruses* 2014, 6, 4047–4079.
3. Biological Agents. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; 100B (Epstein Barr Virus); International Agency for Research on Cancer: Lyon, France, 2012; pp. 49–92.
4. Casulo, C.; Friedberg, J.W. Burkitt lymphoma- a rare but challenging lymphoma. *Best Pract. Res. Clin. Haematol.* 2018, 31, 279–284.
5. Shannon-Lowe, C.; Rickinson, A.B.; Bell, A.I. Epstein-Barr virus-associated lymphomas. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 2017, 372, e20160271.
6. Higgins, C.D., A.J. Swerdlow, K.F. Macsween, N. Harrison, H. Williams, K. McAulay, R. Thomas, S. Reid, M. Conacher, K. Britton, et al. A study of risk factors for acquisition of Epstein-Barr virus and its subtypes. *J. Infect. Dis.* 2007, 195, 474–482.
7. Odumade, O.A.; Hogquist, K.A.; Balfour, H.H., Jr. Progress and problems in understanding and managing primary Epstein-Barr virus infections. *Clin. Microbiol. Rev.* 2011, 24, 193–209.
8. Hsu, J.L.; Glaser, S.L. Epstein-barr virus-associated malignancies: Epidemiologic patterns and etiologic implications. *Crit. Rev. Oncol. Hematol.* 2000, 34, 27–53.
9. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues, 4th ed.; International Agency for Research on Cancer: Lyon, France, 2017; Volume 2.
10. Cohen, M., E. De Matteo, M. Narbaitz, F.A. Carreno, M.V. Preciado, and P.A. Chabay. Epstein-Barr virus presence in pediatric diffuse large B-cell lymphoma reveals a particular association and latency patterns: Analysis of viral role in tumor microenvironment. *Int. J. Cancer* 2013, 132, 1572–1580.
11. Cohen, M., M. Narbaitz, F. Metrebian, E. De Matteo, M.V. Epstein-Barr virus-positive diffuse large B-cell lymphoma association is not only restricted to elderly patients. *Int. J. Cancer* 2014, 135, 2816–2824.
12. Cohen, M., A.G. Vistarop, F. Huaman, M. Narbaitz, F. Metrebian, E. De Matteo, M.V. Preciado, and P.A. Chabay. Cytotoxic response against Epstein Barr virus coexists with diffuse large B-cell lymphoma tolerogenic microenvironment: Clinical features and survival impact. *Sci. Rep.* 2017, 7, 1–10.
13. Corti, M., G. Minue, A. Campitelli, M. Narbaitz, and L. Gilardi, An Aggressive Plasmablastic Lymphoma of the Oral Cavity as Primary Manifestation of Acquired Immunodeficiency Syndrome: Case Report and Literature Review. *Int. Arch. Otorhinolaryngol.* 2015, 19, 354–358.
14. Lara, J., M. Cohen, E. De Matteo, L. Aversa, M.V. Preciado, and P. Chabay, Epstein-Barr virus (EBV) association and latency profile in pediatric Burkitt's lymphoma: Experience of a single institution in Argentina. *J. Med. Virol.* 2014, 86, 845–850.
15. Corti, M., M.F. Villafane, A. Bismans, A. Campitelli, M. Narbaitz, and P. Bare. Oral cavity and extra-oral plasmablastic lymphomas in AIDS patients: Report of five cases and review of the literature. *Int. J. STD AIDS* 2011, 22, 759–763.
16. Chabay, P., J. Lara, M. Lorenzetti, P. Cambra, G. Acosta Haab, L. Aversa, E. De Matteo, and M.V. Preciado, Epstein Barr virus in relation to apoptosis markers and patients' outcome in pediatric B-cell non-Hodgkin lymphoma. *Cancer Lett.* 2011, 307, 221–226.
17. Metta, H., M. Corti, A. Maranzana, R. Schtirbu, M. Narbaitz, and M. De Dios Soler, Unusual case of plasmablastic non-Hodgkin's lymphoma located in the liver. First case reported in an AIDS patient. *Ann. Hepatol.* 2009, 8, 242–245.
18. Chabay, P., E. De Matteo, M. Lorenzetti, M. Gutierrez, M. Narbaitz, L. Aversa, and M.V. Preciado, Vulvar plasmablastic lymphoma in a HIV-positive child: A novel extraoral localisation. *J. Clin. Pathol.* 2009, 62, 644–646.

19. Chabay, P., E. De Matteo, M. Lorenzetti, A.V. Barón, P. Valva, and M.V. Preciado, Low frequency of Epstein Barr virus association and high frequency of p53 overexpression in an Argentinean pediatric T-cell lymphoma series. *Pediatr. Dev. Pathol.* 2009, 12, 28–34.
20. Chabay, P.A., M.H. Barros, R. Hassan, E. De Matteo, G. Rey, M.K. Carrico, I.Z. Renault, and M.V. Preciado, Pediatric Hodgkin lymphoma in 2 South American series: A distinctive epidemiologic pattern and lack of association of Epstein-Barr virus with clinical outcome. *J. Pediatr. Hematol. Oncol.* 2008, 30, 285–291.
21. Fellner, M.D., K. Durand, R.M. Correa, L. Redini, C. Yampolsky, A. Colobraró, G. Sevelever, A.R. Teyssié, J. Benetucci, and M.A. Picconi, Circulating Epstein-Barr virus (EBV) in HIV-infected patients and its relation with primary brain lymphoma. *Int. J. Infect. Dis.* 2007, 11, 172–178.
22. De Matteo, E., A.V. Barón, P. Chabay, J. Porta, M. Dragosky, and M.V. Preciado, Comparison of Epstein-Barr virus presence in Hodgkin lymphoma in pediatric versus adult Argentine patients. *Arch. Pathol. Lab. Med.* 2003, 127, 1325–1329.
23. Preciado, M.V., A. Fallo, P. Chabay, L. Calcagno, and E. De Matteo, Epstein Barr virus-associated lymphoma in HIV-infected children. *Pathol Res. Pract.* 2002, 198, 327–332.
24. Rao, C.R., M.I. Gutierrez, K. Bhatia, F. Fend, J. Franklin, L. Appaji, G. Gallo, G. O'Connor, N. Lalitha, and I. Magrath, Association of Burkitt's lymphoma with the Epstein-Barr virus in two developing countries. *Leuk. Lymphoma* 2000, 39, 329–337.
25. Preciado, M.V., E. Cristobal, J. Menarguez, J.C. Martinez Montero, B. Diez, E. De Matteo, and S. Grinstein, Oncogene expression in tumour cells of pediatric Hodgkin's disease in Argentina—correlation with Epstein Barr virus presence. *Pathol. Res. Pract.* 1998, 194, 25–31.
26. Preciado, M.V., E. De Matteo, B. Diez, and S. Grinstein, Epstein-Barr virus (EBV) latent membrane protein (LMP) in tumor cells of Hodgkin's disease in pediatric patients. *Med. Pediatr. Oncol.* 1995, 24, 1–5.
27. Preciado, M.V., E. De Matteo, B. Diez, J. Menarguez, and S. Grinstein, Presence of Epstein-Barr virus and strain type assignment in Argentine childhood Hodgkin's disease. *Blood* 1995, 86, 3922–3929.
28. Drut, R.M., S. Day, R. Drut, and L. Meisner, Demonstration of Epstein-Barr viral DNA in paraffin-embedded tissues of Burkitt's lymphoma from Argentina using the polymerase chain reaction and in situ hybridization. *Pediatr. Pathol.* 1994, 14, 101–109.
29. Poles, W.A., E.E. Nishi, M.B. de Oliveira, A.I.P. Eugenio, T.A. de Andrade, A. Campos, R.R. de Campos, Jr., J. Vassallo, A.C. Alves, C. Scapulatempo Neto, et al., Targeting the polarization of tumor-associated macrophages and modulating mir-155 expression might be a new approach to treat diffuse large B-cell lymphoma of the elderly. *Cancer Immunol. Immunother.* 2019, 68, 269–282.
30. Guedes, J.C.R., K. Cunha, J. Machado, and L.W. Pinto, Nasal-type extranodal T-cell/NK lymphoma in association with hemophagocytic syndrome. *An. Bras. Dermatol.* 2018, 93, 422–425.
31. Miranda, M.F.R., J. Santos, S.F.R. Muller, M.J.S. Bittencourt, A.C. Brito, J. Barros Junior, and E.M.S. Xerfan, Hydroa Vacciniforme-Like T-Cell Lymphoma: A Further Brazilian Case. *Am. J. Dermatopathol.* 2018, 40, 201–204.
32. Campos, A., A. Moreira, K.B. Ribeiro, R.P. Paes, M.C. Zerbini, V. Aldred, C.A. de Souza, C.S. Neto, F.A. Soares, and J. Vassallo, Frequency of EBV associated classical Hodgkin lymphoma decreases over a 54-year period in a Brazilian population. *Sci. Rep.* 2018, 8, 1–8.
33. Barros, M.H., E. Leite, P. Chabay, V. Morais, G. Stefanoff, and R. Hassan, Diagnosing lymphoma in a setting with a high burden of infection: A pediatric case of Epstein-Barr virus-associated aggressive B-cell lymphoma with t(8;14) (q23;q32) and extensive necrosis mimicking tuberculosis. *Rev. Soc. Bras. Med. Trop.* 2015, 48, 108–111.
34. Andrade, T.A., A.F. Evangelista, A.H. Campos, W.A. Poles, N.M. Borges, C.M. Camillo, F.A. Soares, J. Vassallo, R.P. Paes, M.C. Zerbini, et al., A microRNA signature profile in EBV+ diffuse large B-cell lymphoma of the elderly. *Oncotarget* 2014, 5, 11813–11826.
35. Ferreira, C.R., A. Felipe-Silva, F.P.F. de Campos, and M.C.N. Zerbini, Nodal Epstein-Barr virus-positive T-cell/NK-cell lymphoma associated with immunodeficiency: A rare condition looking for recognition. *Autops. Case Rep.* 2014, 4, 25–34.
36. Rebelo-Pontes, H.A., M.C. Abreu, D.M. Guimarães, F.P. Fonseca, B.A. Andrade, O.P. Almeida, D.D. Pinto Júnior, and F.S. Corrêa-Pontes, Burkitt's lymphoma of the jaws in the Amazon region of Brazil. *Medicina Oral Patologia Oral Y Cirugia Bucal* 2014, 19, e32–e37.
37. Minnicelli, C., M.H. Barros, C.E. Klumb, S.O. Romano, I.R. Zalberg, and R. Hassan, Relationship of Epstein-Barr virus and interleukin 10 promoter polymorphisms with the risk and clinical outcome of childhood Burkitt lymphoma. *PLoS ONE* 2012, 7, e46005.

38. Assis, M.C., A.H. Campos, J.S. Oliveira, F.A. Soares, J.M. Silva, P.B. Silva, A.D. Penna, E.M. Souza, and O.C. Baiocchi, Increased expression of CD4+CD25+FOXP3+ regulatory T cells correlates with Epstein-Barr virus and has no impact on survival in patients with classical Hodgkin lymphoma in Brazil. *Med. Oncol.* 2012, 29, 3614–3619.
39. Santos, M., L. Nogueira, C. Talahri, C. Massone, L. Cerroni, M.T. Mira, and S. Talhari, Hydroa vacciniforme-like lymphoma in a patient from the Brazilian Amazon. *Int. J. Dermatol.* 2013, 52, 641–643.
40. Marques, M., E. Luz, M. Hummel, M. Vieira, R.C. Bahia, M.C. Oliveira, E.M. Netto, I. Luz, and I. Araujo, Prognostic Biomarkers and EBV Infection Research in Diffuse Large B-Cell Lymphoma of the Palatine Tonsils. *ISRN Oncol.* 2012, 2012, 7.
41. Barros, M.H., R. Hassan, and G. Niedobitek, Disease patterns in pediatric classical Hodgkin lymphoma: A report from a developing area in Brazil. *Hematol. Oncol.* 2011, 29, 190–195.
42. Barros, M.H., A. Scheliga, E. De Matteo, C. Minnicelli, F.A. Soares, I.R. Zalcberg, and R. Hassan, Cell cycle characteristics and Epstein-Barr virus are differentially associated with aggressive and non-aggressive subsets of Hodgkin lymphoma in pediatric patients. *Leuk. Lymphoma* 2010, 51, 1513–1522.
43. Barros, M.H., G. Vera-Lozada, F.A. Soares, G. Niedobitek, and R. Hassan, Tumor microenvironment composition in pediatric classical Hodgkin lymphoma is modulated by age and Epstein-Barr virus infection. *Int. J. Cancer* 2012, 131, 1142–1152.
44. Souza, E.M., O.C. Baiocchi, M.A. Zanichelli, A.C. Alves, M.G. Assis, D.P. Eiras, C. Dobo, and J.S. Oliveira, Impact of Epstein-Barr virus in the clinical evolution of patients with classical Hodgkin's lymphoma in Brazil. *Hematol. Oncol.* 2010, 28, 137–141.
45. Souza, E.M., O.C. Baiocchi, M.A. Zanichelli, A.C. Alves, M.G. Assis, J.M. Silva, C. Dobo, and J.S. Oliveira, Matrix metalloproteinase-9 is consistently expressed in Hodgkin/Reed-Sternberg cells and has no impact on survival in patients with Epstein-Barr virus (EBV)-related and non-related Hodgkin lymphoma in Brazil. *Med. Oncol.* 2012, 29, 2148–2152.
46. Gualco, G., P. Domeny-Duarte, L. Chioato, G. Barber, Y. Natkunam, and C.E. Bacchi, Clinicopathologic and molecular features of 122 Brazilian cases of nodal and extranodal NK/T-cell lymphoma, nasal type, with EBV subtyping analysis. *Am. J. Surg. Pathol.* 2011, 35, 1195–1203.
47. Gaiolla, R.D., M.A. Domingues, L. Niero-Melo, and D.E. de Oliveira, Serum levels of interleukins 6, 10, and 13 before and after treatment of classic Hodgkin lymphoma. *Arch. Pathol. Lab. Med.* 2011, 135, 483–489.
48. Gualco, G., L.M. Weiss, G.N. Barber, and C.E. Bacchi, Diffuse large B-cell lymphoma involving the central nervous system. *Int. J. Surg. Pathol.* 2011, 19, 44–50.
49. Gualco, G., V. Ortega, L. Chioato, M.L. Musto, L.M. Bacchi, L.M. Weiss, and C.E. Bacchi, Hodgkin's Lymphoma Presenting as Dominant Gastric Lesion in Immunocompetent Patients: Report of 5 Cases With EBV Analysis. *Int. J. Surg. Pathol.* 2011, 19, 235–240.
50. Machado, A.S., M.C. Da Silva Robaina, L.M. Magalhães De Rezende, A.G. Apa, N.D. Amôdo, C.E. Bacchi, and C.E. Klumb, Circulating cell-free and Epstein-Barr virus DNA in pediatric B-non-Hodgkin lymphomas. *Leuk. Lymphoma* 2010, 51, 1020–1027.
51. Gualco, G., L. Chioato, A. Van Den Berg, L.M. Weiss, and C.E. Bacchi, Composite lymphoma: EBV-positive classic Hodgkin lymphoma and peripheral T-cell lymphoma: A case report. *Appl. Immunohistochem. Mol. Morphol.* 2009, 17, 72–76.
52. Campos, A.H., V.L. Aldred, K.C. Ribeiro, J. Vassallo, and F.A. Soares, Role of immunoexpression of nitric oxide synthases by Hodgkin and Reed-Sternberg cells on apoptosis deregulation and on clinical outcome of classical Hodgkin lymphoma. *Mol. Cell. Biochem.* 2009, 321, 95–102.
53. Queiroga, E.M., G. Gualco, L. Chioato, W.J. Harrington, I. Araujo, L.M. Weiss, and C.E. Bacchi, Viral studies in burkitt lymphoma: Association with Epstein-Barr virus but not HHV-8. *Am. J. Clin. Pathol.* 2008, 130, 186–192.
54. Queiroga, E.M., G. Gualco, L.M. Weiss, D.P. Dittmer, I. Araujo, C.E. Klumb, W.J. Harrington, Jr., and C.E. Bacchi, Burkitt lymphoma in Brazil is characterized by geographically distinct clinicopathologic features. *Am. J. Clin. Pathol.* 2008, 130, 946–956.
55. Pizza, M., P. Bruniera, S.M. Luporini, H.R. Marcelino da Silva, M.L. Borsato, H.C. de Castro, F.A. Soares, and R.A. Paes, Detection of Epstein-Barr virus in children and adolescents with Burkitt's lymphoma by in situ hybridization using tissue microarrays. *Hematology* 2008, 13, 114–118.
56. Hassan, R., C.E. Klumb, F.E. Felisbino, D.M. Guiretti, L.R. White, C.G. Stefanoff, M.H. Barros, H.N. Seuanez, and I.R. Zalcberg, Clinical and demographic characteristics of Epstein-Barr virus-associated childhood Burkitt's lymphoma in Southeastern Brazil: Epidemiological insights from an intermediate risk region. *Haematologica* 2008, 93, 780–783.

57. Ferrazzo, K.L., R.A. Mesquita, A.T. Aburad, F.D. Nunes, and S.O. de Sousa, EBV detection in HIV-related oral plasmablastic lymphoma. *Oral Dis.* 2007, 13, 564–569.
58. Figueiredo, C.P., H.C. Franz-Vasconcelos, G. Giunta, T.L. Mazzuco, T. Caon, A.L. Fernandes, C.M. Simoes, V.L. Antunes, C. Niel, and C.R. Barardi, Detection of Torque teno virus in Epstein-Barr virus positive and negative lymph nodes of patients with Hodgkin lymphoma. *Leuk. Lymphoma* 2007, 48, 731–735.
59. Costa, H., M. Franco, and M.D. Hahn, Primary lymphoma of the central nervous system: A clinical-pathological and immunohistochemical study of ten autopsy cases. *Arq. Neuropsiquiatr.* 2006, 64, 976–982.
60. Musacchio, J.G., G. Carvalho Mda, J.C. Morais, N.H. Silva, A. Scheliga, S. Romano, and N. Spector, Detection of free circulating Epstein-Barr virus DNA in plasma of patients with Hodgkin's disease. *Sao Paulo Med. J.* 2006, 124, 154–157.
61. Araujo, I., A.L. Bittencourt, H.S. Barbosa, E.M. Netto, N. Mendonca, H.D. Foss, M. Hummel, and H. Stein, The high frequency of EBV infection in pediatric Hodgkin lymphoma is related to the classical type in Bahia, Brazil. *Virchows Arch.* 2006, 449, 315.
62. Hassan, R., L.R. White, C.G. Stefanoff, D.E. de Oliveira, F.E. Felisbino, C.E. Klumb, C.E. Bacchi, H.N. Seuanez, and I.R. Zalcberg, Epstein-Barr virus (EBV) detection and typing by PCR: A contribution to diagnostic screening of EBV-positive Burkitt's lymphoma. *Diagn. Pathol.* 2006, 1, 17.
63. Klumb, C.E., R. Hassan, D.E. De Oliveira, L.M. De Resende, M.K. Carrico, J. De Almeida Dobbin, M.S. Pombo-De-Oliveira, C.E. Bacchi, and R.C. Maia, Geographic variation in Epstein-Barr virus-associated Burkitt's lymphoma in children from Brazil. *Int. J. Cancer* 2004, 108, 66–70.
64. Klumb, C.E., R. Hassan, I.R. Zalcberg, L.M. Resende, M.K. Carrico, and R.C. Maia, p53 protein expression does not correlate with EBV status in childhood B non-Hodgkin lymphomas. *Pediatr. Blood Cancer* 2004, 43, 115–119.
65. Pinto, M.T., F.V.d.A. Ferreira, M.d.S. Pitombeira, S.M.M. Magalhães, C.M.B.E.d. Costa, P.W.L. Lima Filho, R.P.C. Férrer, A.L.P.d. Aguiar, and F.D. Rocha Filho, Analysis of the association between Epstein-Barr virus and classic Hodgkin s lymphoma in adult patients from Ceará (Brazil) by immunohistochemistry and in situ hybridization. *Jornal Brasileiro de Patologia e Medicina Laboratorial* 2006, 42, 201–205.
66. Spector, N., C.B. Milito, I. Biasoli, R.R. Luiz, W. Pulcheri, and J.C. Morais, The prognostic value of the expression of Bcl-2, p53 and LMP-1 in patients with Hodgkin's lymphoma. *Leuk. Lymphoma* 2005, 46, 1301–1306.
67. Loureiro, M.M., J.C. Morais, C.B. Milito, R.D. Portugal, W. Pulcheri, and N. Spector, Expression of Epstein-Barr virus in patients with Hodgkin's disease: Report of 64 cases from Rio de Janeiro, Brazil. *Jornal Brasileiro de Patologia e Medicina Laboratorial* 2004, 40, 37–40.
68. Vassallo, J., K. Metze, F. Traina, C.A. de Souza, and I. Lorand-Metze, Expression of Epstein-Barr virus in classical Hodgkin's lymphomas in Brazilian adult patients. *Haematologica* 2001, 86, 1227–1228.
69. Vassallo, J., K. Metze, F. Traina, C.A. de Souza, and I. Lorand-Metze, The prognostic relevance of apoptosis-related proteins in classical Hodgkin's lymphomas. *Leuk. Lymphoma* 2003, 44, 483–488.
70. Elgui de Oliveira, D., M.M. Bacchi, E.S. Abreu, L. Niero-Melo, and C.E. Bacchi, Hodgkin disease in adult and juvenile groups from two different geographic regions in Brazil: Characterization of clinicopathologic aspects and relationship with Epstein-Barr virus infection. *Am. J. Clin. Pathol.* 2002, 118, 25–30.
71. Altemani, A., A.C. Barbosa, M. Kulka, T. Takahashi, L. Endo, J. Vassallo, and I. Lorand-Metze, Characteristics of nasal T/NK-cell lymphoma among Brazilians. *Neoplasma* 2002, 49, 55–60.
72. Sandlund, J.T., T. Fonseca, T. Leimig, L. Verissimo, R. Ribeiro, V. Lira, C.W. Berard, J. Sixbey, W.M. Crist, L. Mao, et al., Predominance and characteristics of Burkitt lymphoma among children with non-Hodgkin lymphoma in northeastern Brazil. *Leukemia* 1997, 11, 743–746.
73. Razzouk, B.I., Y.J. Gan, C. Mendonca, J.J. Jenkins, Q. Liu, M. Hudson, J.W. Sixbey, and R.C. Ribeiro, Epstein-Barr virus in pediatric Hodgkin disease: Age and histiotype are more predictive than geographic region. *Med. Pediatr. Oncol.* 1997, 28, 248–254.
74. Araujo, I., H.D. Foss, A. Bittencourt, M. Hummel, G. Demel, N. Mendonca, H. Herbst, and H. Stein, Expression of Epstein-Barr virus-gene products in Burkitt's lymphoma in Northeast Brazil. *Blood* 1996, 87, 5279–5286.
75. Bacchi, M.M., C.E. Bacchi, M. Alvarenga, R. Miranda, Y.Y. Chen, and L.M. Weiss, Burkitt's lymphoma in Brazil: Strong association with Epstein-Barr virus. *Mod. Pathol.* 1996, 9, 63–67.
76. Armstrong, A., F. Alexander, R.P. Paes, N. Morad, A. Gallagher, A. Krajewski, D. Jones, B. Angus, J. Adams, and R. Cartwright, Association of Epstein-Barr virus with pediatric Hodgkin's disease. *Am. J. Pathol.* 1993, 142, 1683.

77. Quintanilla-Martinez, L., C. Ridaura, F. Nagl, M. Saez-de-Ocariz, C. Duran-McKinster, R. Ruiz-Maldonado, G. Alderete, P. Grube, C. Lome-Maldonado, I. Bonzheim, et al., Hydroa vacciniforme-like lymphoma: A chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. *Blood* 2013, 122, 3101–3110.
78. Palma, I., A.E. Sanchez, E. Jimenez-Hernandez, F. Alvarez-Rodriguez, M. Nava-Frias, P. Valencia-Mayoral, C. Salinas-Lara, N. Velazquez-Guadarrama, J. Portilla-Aguilar, R.Y. Pena, et al., Detection of Epstein-Barr virus and genotyping based on EBNA2 protein in Mexican patients with hodgkin lymphoma: A comparative study in children and adults. *Clin. Lymphoma Myeloma Leuk.* 2013, 13, 266–272.
79. Garcéa-Álvarez, K.G., R. Garibaldi-Covarrubias, M.R. Flores-Márquez, and C. Ortiz-Hidalgo, Plasma cell myeloma associated with Epstein-Barr virus infection in an 11-year-old girl. *Pediatr. Dev. Pathol.* 2012, 15, 339–342.
80. Aviles-Salas, A., R. Herrera-Goepfert, D. Aguilar-Leon, M. Candelaria-Hernandez, E. Martinez-Cordero, and M. Corti, Plasmablastic lymphoma of the gastrointestinal tract in AIDS patients. *Medicina* 2011, 71, 536–541.
81. Hofscheier, A., A. Ponciano, I. Bonzheim, P. Adam, C. Lome-Maldonado, T. Vela, E. Cortes, C. Ortiz-Hidalgo, F. Fend, and L. Quintanilla-Martinez, Geographic variation in the prevalence of Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly: a comparative analysis of a Mexican and a German population. *Mod. Pathol.* 2011, 24, 1046–1054.
82. Dirnhofer, S., A. Angeles-Angeles, C. Ortiz-Hidalgo, E. Reyes, E. Gredler, J. Krugmann, F. Fend, and L. Quintanilla-Martinez, High prevalence of a 30-base pair deletion in the Epstein-Barr virus (EBV) latent membrane protein 1 gene and of strain type B EBV in Mexican classical Hodgkin's disease and reactive lymphoid tissue. *Hum. Pathol.* 1999, 30, 781–787.
83. Elenitoba-Johnson, K.S., A. Zarate-Osorno, A. Meneses, L. Krenacs, D.W. Kingma, M. Raffeld, and E.S. Jaffe, Cytotoxic granular protein expression, Epstein-Barr virus strain type, and latent membrane protein-1 oncogene deletions in nasal T-lymphocyte/natural killer cell lymphomas from Mexico. *Mod. Pathol.* 1998, 11, 754–761.
84. Magana, M., P. Sanguenza, J. Gil-Beristain, S. Sanchez-Sosa, A. Salgado, G. Ramon, and O.P. Sanguenza, Angiocentric cutaneous T-cell lymphoma of childhood (hydroa-like lymphoma): A distinctive type of cutaneous T-cell lymphoma. *J. Am. Acad. Dermatol.* 1998, 38, 574–579.
85. Quintanilla-Martinez, L., C. Lome-Maldonado, F. Schwarzmann, E. Gredler, E. Reyes, A. Angeles-Angeles, and F. Fend, Post-transplantation lymphoproliferative disorders in Mexico: An aggressive clonal disease associated with Epstein-Barr virus type A. *Mod. Pathol* 1998, 11, 200–208.
86. Quintanilla-Martínez, L., C. Lome-Maldonado, G. Ott, A. Gschwendtner, E. Gredler, E. Reyes, A. Angeles-Angeles, and F. Fend, Primary non-Hodgkin's lymphoma of the intestine: high prevalence of Epstein-Barr virus in Mexican lymphomas as compared with European cases. *Blood, The Journal of the American Society of Hematology.* 1997, 89, 644–651.
87. Quintanilla-Martinez, L., A. Gamboa-Dominguez, I. Gamez-Ledesma, H. Orozco-Estevez, and A. Angeles-Angeles, High prevalence of the Epstein-Barr virus in a Mexican population with Hodgkin's disease. *Rev. Investig. Clin.* 1994, 46, 355–362.
88. Quintanilla-Martinez, L., A. Gamboa-Domnquez, I. Gamez-Ledesma, A. Angeles-Angeles, and A. Mohar, Association of Epstein-Barr virus latent membrane protein and Hodgkin's disease in Mexico. *Mod. Pathol.* 1995, 8, 675–679.
89. Zarate-Osorno, A., L.N. Roman, D.W. Kingma, A. Meneses-Garcia, and E.S. Jaffe, Hodgkin's disease in Mexico. Prevalence of Epstein-Barr virus sequences and correlations with histologic subtype. *Cancer* 1995, 75, 1360–1366.
90. Cordova Perez, F.J., C.I. Gonzalez-Keelan, and R. Velez, Epstein-Barr virus in biopsies from patients with Hodgkin and non-Hodgkin lymphoma at the University of Puerto Rico immunohistochemistry laboratory. *P. R. Health Sci. J.* 2003, 22, 125–129.
91. Aybar, A. and J.R. Krause, Coexpression of major histocompatibility complex class I and LMP1 in Epstein-Barr virus-positive Hodgkin's lymphoma in a pediatric age group. *Microsc. Res. Tech.* 2005, 68, 247–249.
92. Riverend, E., E. Rengifo, M. Longchong, R. Ruiz, B. Tormo, J. García, R. Portero, S. Quintero, M. Valdés, T. Rodríguez, et al., Burkitt's lymphoma in Cuba. I. Clinical and morphological features and EBV association. *Oncology* 1984, 41, 13–18.
93. Quijano, S., C. Saavedra, S. Fiorentino, O. Orozco, and M.M. Bravo, Epstein-Barr virus presence in Colombian Hodgkin lymphoma cases and its relation to treatment response. *Biomedica* 2004, 24, 163–173.
94. Quijano, S.M., C. Saavedra, M.M. Bravo, S. Fiorentino, and O. Orozco, Expression of heat shock proteins HSP72 and HSP73 in Colombian patients with Hodgkin lymphoma positive and negative for Epstein Barr virus. *Revista Medica de Chile* 2003, 131, 1375–1381.

95. Beltran, B.E., P. Quinones, D. Morales, J.M. Malaga, J.C. Chavez, E.M. Sotomayor, and J.J. Castillo, Response and survival benefit with chemoimmunotherapy in Epstein-Barr virus-positive diffuse large B-cell lymphoma. *Hematol. Oncol.* 2018, 36, 93–97.
96. Aguilar, C., B. Beltran, P. Quiñones, T. Carbajal, J. Vilcapaza, A. Yabar, P. Segura, L. Quintanilla-Martinez, R.N. Miranda, and J.J. Castillo, Large B-cell lymphoma arising in cardiac myxoma or intracardiac fibrinous mass: A localized lymphoma usually associated with Epstein-Barr virus? *Cardiovasc. Pathol.* 2015, 24, 60–64.
97. Beltran, B.E., I. Maza, C.B. Moises-Alfaro, L. Vasquez, P. Quinones, D. Morales, G. Sanchez, G. Paredes, M. Oscanoa, J. Geronimo, et al., Thalidomide for the treatment of hydroa vacciniforme-like lymphoma: Report of four pediatric cases from Peru. *Am. J. Hematol.* 2014, 89, 1160–1161.
98. Ernesto Beltran, B., P. Quinones Avila, D. Morales Luna, E. Cotrina Montenegro, A. Gallo Lopez, and M. Lopez Ilasaca, Gastrointestinal Epstein Barr virus positive diffuse large B cell lymphoma in elderly: Report of five cases and review of literature. *Revista de Gastroenterologia del Peru* 2011, 31, 285–288.
99. Rodriguez-Pinilla, S.M., C. Barrionuevo, J. Garcia, M. de los Angeles, R. Pajares, S. Casavilca, J. Montes, A. Martinez, S. Montes-Moreno, L. Sanchez, et al., Epstein-Barr virus-positive systemic NK/T-cell lymphomas in children: report of six cases. *Histopathology* 2011, 59, 1183–1193.
100. Beltran, B.E., J.J. Castillo, D. Morales, F.H. de Mendoza, P. Quinones, R.N. Miranda, A. Gallo, M. Lopez-Ilasaca, J.N. Butera, and E.M. Sotomayor, EBV-positive diffuse large B-cell lymphoma of the elderly: A case series from Peru. *Am. J. Hematol.* 2011, 86, 663–667.
101. Morales, D., B. Beltran, F.H. De Mendoza, L. Riva, A. Yabar, P. Quinones, J.N. Butera, and J. Castillo, Epstein-Barr virus as a prognostic factor in de novo nodal diffuse large B-cell lymphoma. *Leuk. Lymphoma* 2010, 51, 66–72.
102. Beltran, B., R. Salas, P. Quiñones, D. Morales, F. Hurtado, E. Cotrina, L. Riva, and J. Castillo, EBV-positive diffuse large B-cell lymphoma in a human T-lymphotropic virus type 1 carrier. *Infect. Agent. Cancer* 2009, 4, 1–4.
103. Rodriguez-Pinilla, S.M., C. Barrionuevo, J. Garcia, M.T. Martinez, R. Pajares, S. Montes-Moreno, S. Casavilca, J. Montes, F. Bravo, M. Zaharia, et al., EBV-associated cutaneous NK/T-cell lymphoma: Review of a series of 14 cases from peru in children and young adults. *Am. J. Surg. Pathol.* 2010, 34, 1773–1782.
104. Barrionuevo, C., M. Zaharia, M.T. Martinez, L. Taxa, O. Misad, A. Moscol, G. Sarria, I. Guerrero, L. Casanova, C. Flores, et al., Extranodal NK/T-cell lymphoma, nasal type: Study of clinicopathologic and prognosis factors in a series of 78 cases from Peru. *Appl. Immunohistochem. Mol. Morphol.* 2007, 15, 38–44.
105. Barrionuevo, C., V.M. Anderson, E. Zevallos-Giampietri, M. Zaharia, O. Misad, F. Bravo, H. Caceres, L. Taxa, M.T. Martinez, A. Wachtel, et al., Hydroa-like cutaneous T-cell lymphoma: A clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. *Appl. Immunohistochem. Mol. Morphol.* 2002, 10, 7–14.
106. Quintanilla-Martinez, L., J.L. Franklin, I. Guerrero, L. Krenacs, K.N. Naresh, C. Rama-Rao, K. Bhatia, M. Raffeld, and I.T. Magrath, Histological and immunophenotypic profile of nasal NK/T cell lymphomas from Peru: High prevalence of p53 overexpression. *Hum. Pathol.* 1999, 30, 849–855.
107. Arber, D.A., L.M. Weiss, P.F. Albújar, Y.Y. Chen, and E.S. Jaffe, Nasal lymphomas in Peru. High incidence of T-cell immunophenotype and Epstein-Barr virus infection. *Am. J. Surg. Pathol.* 1993, 17, 392–399.
108. Chang, K.L., P.F. Albuja, Y.Y. Chen, R.M. Johnson, and L.M. Weiss, High prevalence of Epstein-Barr virus in the Reed-Sternberg cells of Hodgkin's disease occurring in Peru. *Blood* 1993, 81, 496–501.
109. Montalvo, N. and L. Redroban, Hydroa Vacciniforme-Like EBV-Positive Cutaneous T-Cell Lymphoma, First Report of 2 Cases in Ecuador. *Am. J. Dermatopathol.* 2016, 38, e57–e59.
110. Sánchez-Giler, S., A. Herrera-Vásquez, C. Castillo-Zambrano, L. Solórzano-Alava, D. Zambrano-Castro, C. Kuon-Yeng, A. Silva-Orellana, J. Murillo-Zambrano, and G. Cucalón-González, Detección del Virus de Epstein-Barr en linfoma mediante qPCR//Detection of Epstein-Barr Virus (EBV) in lymphoma through qPCR. *Ciencia Unemi* 2018, 11, 126–133.
111. Zoroquiain, P., S. González, M. Molgó, A. Rodríguez, and J.R. Valbuena, Leukocytoclastic vasculitis as early manifestation of Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly. *Am. J. Dermatopathol.* 2012, 34, 330–334.
112. Martin, C., C. Carrasco, C. Sotomayor, and C. Otth, Prevalence of Epstein-Barr virus associated with nasal lymphoma in patients attending the regional hospital of Valdivia, Chile, between 1987 and 2005. *J. Med. Virol.* 2010, 82, 825–828.
113. Cabrera, M.E., Y. Eizuru, T. Itoh, C. Koriyama, Y. Tashiro, S. Ding, S. Rey, S. Akiba, and A. Corvalan, Nasal natural killer/T-cell lymphoma and its association with type “i”/XhoI loss strain Epstein-Barr virus in Chile. *J. Clin. Pathol.* 2007, 60, 656–660.

114. Gutierrez, M.I., K. Bhatia, F. Barriga, B. Diez, F.S. Muriel, M.L. de Andreas, S. Epelman, C. Risueno, and I.T. Magrath, Molecular epidemiology of Burkitt's lymphoma from South America: Differences in breakpoint location and Epstein-Barr virus association from tumors in other world regions. *Blood* 1992, 79, 3261–3266.
115. Ambinder, R.F., P.J. Browning, I. Lorenzana, B.G. Leventhal, H. Cosenza, R.B. Mann, E.M. MacMahon, R. Medina, V. Cardona, S. Grufferman, et al., Epstein-Barr virus and childhood Hodgkin's disease in Honduras and the United States. *Blood* 1993, 81, 462–467.
116. Monterroso, V., Y. Zhou, S. Koo, C. Glackin, W. Bujan, and L.J. Medeiros, Hodgkin's disease in Costa Rica: A report of 40 cases analyzed for Epstein-Barr virus. *Am. J. Clin. Pathol.* 1998, 109, 618–624.
117. Weinreb, M., P.J. Day, F. Niggli, J.E. Powell, F. Raafat, P.B. Hesseling, J.W. Schneider, P.S. Hartley, F. Tzortzatou-Stathopoulou, E.R. Khalek, et al., The role of Epstein-Barr virus in Hodgkin's disease from different geographical areas. *Arch. Dis. Child.* 1996, 74, 27–31.
118. Gulley, M.L., P.A. Eagan, L. Quintanilla-Martinez, A.L. Picado, B.N. Smir, C. Childs, C.D. Dunn, F.E. Craig, J.W. Williams, Jr., and P.M. Banks, Epstein-Barr virus DNA is abundant and monoclonal in the Reed-Sternberg cells of Hodgkin's disease: Association with mixed cellularity subtype and Hispanic American ethnicity. *Blood* 1994, 83, 1595–1602.
119. Takano, Y., R.P. Colanzi, and J. Siga, High incidence of Epstein-Barr virus associated non-Hodgkin's lymphomas in the Bolivian mountains. *Pathol. Int.* 1994, 44, 237–240.
120. Schwartz, E.J., H. Molina-Kirsch, S. Zhao, R.J. Marinelli, R.A. Warnke, and Y. Natkunam, Immunohistochemical characterization of nasal-type extranodal NK/T-cell lymphoma using a tissue microarray: An analysis of 84 cases. *Am. J. Clin. Pathol.* 2008, 130, 343–351.
121. Grufferman, S. and E. Delzell, Epidemiology of Hodgkin's disease. *Epidemiol. Rev.* 1984, 6, 76–106.
122. Howlader N, N.A., Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, and L.D. Mariotto A, Chen HS, Feuer EJ, Cronin KA, SEER Cancer Statistics Review, 1975–2016; National Cancer Institute: Bethesda, MD, USA, 2016.
123. Macfarlane, G.J., T. Evstifeeva, P. Boyle, and S. Grufferman, International patterns in the occurrence of Hodgkin's disease in children and young adult males. *Int. J. Cancer* 1995, 61, 165–169.
124. Kalisz, K., F. Alessandrino, R. Beck, D. Smith, E. Kikano, N.H. Ramaiya, and S.H. Tirumani, An update on Burkitt lymphoma: A review of pathogenesis and multimodality imaging assessment of disease presentation, treatment response, and recurrence. *Insights Imaging* 2019, 10, 56.
125. Crawford, D.H., Biology and disease associations of Epstein-Barr virus. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 2001, 356, 461–473.
126. Ferreira, J.M., C.E. Klumb, R. de Souza Reis, M. de Oliveira Santos, J.F. Oliveira, B. de Camargo, and M.S. Pombo-de-Oliveira, Lymphoma subtype incidence rates in children and adolescents: First report from Brazil. *Cancer Epidemiol.* 2012, 36, e221–e226.
127. Chabay, P.A. and M.V. Preciado, EBV primary infection in childhood and its relation to B-cell lymphoma development: A mini-review from a developing region. *Int. J. Cancer* 2013, 133, 1286–1292.
128. Pedraza, R.M., L.P.A. Arboleda, C. Sanchez-Romero, J.A.A. Quinones, C.J.M. Tovar, J.R. Henao, and O.P. de Almeida, Intraoral EBV-positive sporadic Burkitt lymphoma in an elderly patient with bilateral presentation. *Autops. Case Rep.* 2019, 9, e2019117.
129. Swerdlow, S.; Campo, E.; Harris, N.L.; Jaffe, E.S. et al., WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues; IARC Press: Lyon, France, 2008.
130. Shimoyama, Y., K. Yamamoto, N. Asano, T. Oyama, T. Kinoshita, and S. Nakamura, Age-related Epstein-Barr virus-associated B-cell lymphoproliferative disorders: Special references to lymphomas surrounding this newly recognized clinicopathologic disease. *Cancer Sci.* 2008, 99, 1085–1091.
131. Hoeller, S., A. Tzankov, S.A. Pileri, P. Went, and S. Dirnhofer, Epstein-Barr virus-positive diffuse large B-cell lymphoma in elderly patients is rare in Western populations. *Hum. Pathol.* 2010, 41, 352–357.
132. Beltran, B., D. Morales, P. Quiñones, R. Salas, and A.A. Carrasco-Yalan, Distribution and Pathology Characteristics of Non Hodgkin Lymphoma in Peru: A Study of 1014 Cases Using WHO Classification of Lymphoid Neoplasm. *Blood* 2007, 110, 4419.
133. Babcock, G.J., L.L. Decker, M. Volk, and D.A. Thorley-Lawson, EBV persistence in memory B cells in vivo. *Immunity* 1998, 9, 395–404.
134. Kim, W.Y., I.A. Montes-Mojarro, F. Fend, and L. Quintanilla-Martinez, Epstein-Barr Virus-Associated T and NK-Cell Lymphoproliferative Diseases. *Front. Pediatr.* 2019, 7, 71.

135. Coleman, C.B., J. Lang, L.A. Sweet, N.A. Smith, B.M. Freed, Z. Pan, B. Haverkos, R. Pelanda, and R. Rochford, Epstein-Barr Virus Type 2 Infects T Cells and Induces B Cell Lymphomagenesis in Humanized Mice. *J. Virol.* 2018, 92, doi:10.1128/JVI.00813-18.
 136. Coleman, C.B., E.M. Wohlford, N.A. Smith, C.A. King, J.A. Ritchie, P.C. Baresel, H. Kimura, and R. Rochford, Epstein-Barr virus type 2 latently infects T cells, inducing an atypical activation characterized by expression of lymphotactic cytokines. *J. Virol.* 2015, 89, 2301–2312
 137. Cohen, J.I., E.S. Jaffe, J.K. Dale, S. Pittaluga, H.E. Heslop, C.M. Rooney, S. Gottschalk, C.M. Bollard, V.K. Rao, A. Marques, et al., Characterization and treatment of chronic active Epstein-Barr virus disease: A 28-year experience in the United States. *Blood* 2011, 117, 5835–5849.
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