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High-grade B-cell lymphoma with 11q aberration in the HIV setting: a clinicopathological study of 10 cases and literature review

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Abstract

High-grade B-cell lymphoma with 11q aberration (HGBL-11q) is a distinct lymphoma entity according to the 5th edition of the WHO classification of hematolymphoid tumors. It lacks *MYC* translocation but carries proximal gains and/or telomeric losses of chromosome 11q. This rare type of B-cell lymphoma is less frequently reported in people living with HIV (PLWH), and its exact frequency remains unclear. Our goal was to retrospectively analyze its frequency in a cohort of aggressive B-cell lymphomas in PLWH, including Burkitt lymphoma (BL, $n=35$), diffuse large B-cell lymphoma (DLBCL, $n=48$), high-grade B-cell lymphoma, not otherwise specified (HGBL-NOS, $n=13$), which was diagnosed as AIDS-related lymphoma (ARL) at our institution. In total, 10/96 (10.4%) cases harbored the typical 11q aberration pattern, predominantly those that had been classified as BL (6/35, 17.1%), DLBCL (2/48, 4.2%), and HGBL, NOS (2/13, 15.4%). We also evaluated 7 cases of AIDS-related HGBL-11q (AR-HGBL-11q) reported in the literature. The median age of our cohort was 35 years, and all the patients were male. Most cases (70%) had a history of HIV infection for over 1 year, and all were involved in lymph nodes (100%), frequently involved extranodal sites (60%), and Ann Arbor stage III/IV. In histomorphology, the cases exhibited diverse cytological features, reminiscent of BL (6 cases), DLBCL (2 cases), and HGBL (2 cases). A comparison of the combined cohort of 17 AR-HGBL-11q cases with 11 ARL cases that lacked both *MYC* rearrangement and 11q aberration at our institution showed that HGBL-11q cases were characterized by strikingly coarse apoptotic debris ($P<0.001$), background rich in eosinophils ($P=0.002$), higher expression of the germinal centre marker LMO2 ($P=0.080$), lower expression of MUM1 ($P=0.004$), BCL2 ($P=0.007$), and LEF1 ($P=0.080$), and lower positivity for EBER in situ hybridisation ($P=0.027$). Notably, one case in our series was EBV-positive, a finding not previously reported in the literature. Furthermore, comparing the prognosis between these two groups, AR-HGBL-11q showed a relatively favorable prognosis ($P=0.15$), although the difference was not statistically significant. We analyzed this rare lymphoma entity in the HIV setting and highlighted the importance of integrating histomorphological and immunophenotypic features in its diagnosis and classification.

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Keywords High-grade B-cell lymphoma, 11q aberration, PLWH, ARL, Apoptotic debris, Fluorescence in situ hybridization

Introduction

In the revised 4th edition of the World Health Organization (WHO) classification of hematopoietic tumors, the provisional diagnostic category "Burkitt like lymphoma with 11q aberration" was introduced [1]. This rare type of B-cell lymphoma was renamed as "high-grade B-cell lymphoma with 11q aberration (HGBL-11q)" in the 5th edition [2], and tentatively defined as "large B-cell lymphoma with 11q aberration (LBCL-11q)" in the International Consensus Classification (ICC) [3]. This type of aggressive B-cell lymphoma lacks *MYC* translocation and carries 11q-arm aberrations characterised by proximal gains and/or telomeric losses [4]. Previous studies have suggested that transplantation may increase the incidence of HGBL-11q [5], but reports on people living with HIV (PLWH) are scarce. AIDS-related lymphoma (ARL) is a major risk factor for PLWH and has a high incidence and mortality [6]. In the era of combined antiretroviral therapy (cART), approximately 28% of AIDS patients die of tumor-related causes, with non-Hodgkin lymphoma being the most common cause [7]. To date, only 7 cases of HGBL-11q in PLWH have been reported in the literature [8–14]. Due to its rarity, the clinicopathological characteristics, treatment, and prognosis of HGBL-11q in this special population have not been well described.

To better understand the features of this lymphoma type, we used fluorescence in situ hybridization (FISH) to screen for HGBL-11q in AIDS-related aggressive B-cell lymphomas diagnosed at our center over the past 8 years, referred to as AIDS-related HGBL-11q (AR-HGBL-11q). We summarized the clinical information, histomorphology, immunohistochemistry, EBER in situ hybridization, and FISH characteristics of these samples. In addition, we analyzed 7 AR-HGBL-11q cases reported in the literature and summarized these findings to better understand the clinicopathological characteristics of HGBL-11q in the HIV setting.

Methods

Case cohort

We retrospectively analyzed the pathological data of ARL cases diagnosed at Beijing Youan Hospital, Capital Medical University, from January 2015 to December 2022. A total of 107 aggressive B-cell lymphoma samples were identified, of which 11 were excluded due to limited tissue, and 96 cases were finally included in the study. The cohort included 35 cases of Burkitt lymphoma (BL), 48 cases of diffuse large B-cell lymphoma (DLBCL), and 13 cases of high-grade B-cell lymphoma, not otherwise specified (HGBL, NOS). All samples were first tested for *MYC*-FISH, and based on the FISH results, samples negative for *MYC* were tested for 11q-FISH, ultimately screening 10 cases of HGBL-11q. All cases were analyzed using hematoxylin and eosin (HE) staining, immunohistochemical (IHC) staining, Epstein-Barr virus-encoded small RNA (EBER) in situ hybridization, and FISH. When necessary, additional IHC staining was performed to confirm the diagnosis. This study was conducted in accordance with the Declaration of Helsinki and approved by our Institutional Review Board (reference number: Jing You Ke Lun Zi<2020>107).

Literature review

We conducted an extensive literature search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) for previously reported cases of HGBL-11q in PLWH using various keyword combinations, including "HIV/AIDS", "lymphoma", and "11q aberration", without any limiting conditions. After reviewing and merging data from redundant cases, we extracted the necessary clinicopathological data from 7 cases that met our criteria and included them in this study [8–14].

Histomorphology, immunohistochemistry, and EBER in situ hybridization analysis

HE stained sections were used to evaluate histomorphological characteristics. Immunohistochemical staining was performed on formalin-fixed and paraffin-embedded (FFPE) tissues using antibodies for CD20, CD10, BCL6, Ki-67, MYC, BCL2, MUM1, LMO2, LEF1, and EBNA2. The cut-off values for CD10, BCL6, and MUM1 were 30%, 40% for MYC, and 50% for BCL2. Ki-67 was recorded in 10% increments and marked as "positive/high" when the staining rate was ≥90%. EBER was detected using the EBV probe in situ hybridization kit (ISH-6021, Zhongshan Golden Bridge Biotechnology Co., Ltd., Beijing, China) according to the manufacturer's instructions, with positive signals appearing brownish-yellow in the cell nucleus.

Fluorescence in situ hybridization

FISH testing was performed on 4 μm thick unstained sections from FFPE tissue blocks using a *MYC* break-apart probe and 11q23.3/11q24.3 gene deletion probes (Guangzhou Anbiping Medical Technology Co., Ltd.), according to the manufacturer's instructions. The *MYC* probe detected *MYC* gene separation with red-green signals in over 20% of tumor cells, indicating rearrangement. The 11q23.3/11q24.3 probes were used to detect copy number changes in the 11q23 and 11q24 regions,

with a change in the number of red and green signals in more than 20% of tumor cells, indicating an abnormality in the corresponding region of chromosome 11q. At least 200 cells were counted in each case. We used 11q23.3 / CEP11 dual-color and 11q24.3/CEP11 dual-color probes. 11q23.3 and 11q24.3 are red probes, and CEP11 is a green probe. The FISH constellation in a normal case is characterized by two signals per probe, while the pattern corresponding to the 11q gain/loss aberration would be two green, three to five red signals, and one red signal.

Statistical analysis

Statistical analyses were performed using the SPSS software (version 26.0). Comparisons of categorical variables between groups were conducted using either the chi-square test or Fisher's exact test, depending on the sample size. The Kaplan-Meier method was used for survival analysis, and the log-rank test was used to compare survival differences between groups. A two-sided P-value ≤ 0.05 was considered statistically significant.

Results

Clinical features

The clinical characteristics of the 10 AR-HGBL-11q patients were summarized in Table 1. The median age was 35 years (range: 26-66y), and all patients were male. Most patients (70%) had a history of HIV infection for more than 1 year. More than half of the patients (60%) had previously received cART, with a median CD4+T cell count of 157 cells/μL (range: 4-723 cells/μL) and a median HIV viral load of 15,600 copies/mL (range: <40−1,344,339copies/mL). All patients had lymph node involvement, with 60% also exhibiting extranodal involvement, including the gastrointestinal tract, liver, spleen and pancreas. According to the Ann Arbor staging system, 1 case (10%) was in stage II, 3 cases (30%) were in stage III, and 6 cases (60%) were in stage IV. B symptoms were present in 4 cases (40%), bulky disease in 5 cases (50%), and the Eastern Cooperative Oncology Group (ECOG) score ≥ 2 in 2 cases (20%). Elevated serum lactate dehydrogenase (LDH) levels were observed in 7 cases (70%). The lymphocyte-to-monocyte ratio (LMR) was < 3 in 4 cases (40%), and anemia (hemoglobin < 130 g/L) was present in 4 cases (40%). Most patients (80%) received rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) as first-line treatment, while 2 patients (20%) received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). One patient died shortly after the first cycle of chemotherapy, and the other patient died after 4 cycles of chemotherapy. At the time of the last follow-up, 8 patients were alive and 2 had died. The median follow-up time was 57 months (range: 1–102 m).

Table 1 Clinicopathological characteristics of 10 AR-HGBL-11q cases

Case#	1	2	3	4	5	6	7	8	9	10
Age (years)	32	34	38	27	36	66	26	57	45	35
Gender	M	M	M	M	M	M	M	M	M	M
Site of biopsy (LN)	Axillary LN	Cervical LN	Cervical LN	Retro-peritoneal tumor	Axillary LN	Colon tumor	Abdominal tumor	Axillary LN	Tonsil	Abdominal tumor
Bulky	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes
B symptoms	No	No	Yes	No	No	Yes	Yes	No	No	Yes
BM involvement	No	No	No	No	No	No	No	No	No	No
Ann Arbor Stage	III	IV	IV	IV	III	IV	IV	III	II	IV
ECOG ≥ 2	No	No	No	No	No	Yes	Yes	No	No	No
Serum LDH > ULN	Yes	No	Yes	Yes	Yes	Yes	Yes	NO	NA	Yes
LMR	3.43	3.16	3.36	2.00	3.53	1.64	1.78	6.67	6.68	2.00
HGB < 130 g/L	No	Yes	No	No	No	Yes	Yes	No	No	Yes
Previous AIDS	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Previous cART	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes
CD4 + T cell count (cells/μL)	377	4	190	157	123	535	87	552	723	132
HIV load	TND	90,000	52,378	TND	1,344,339	< 40	15,600	< 40	< 40	TND
EBV load	< 500	$7.9x10^3$	< 500	< 500	< 500	< 500	< 500	< 500	< 500	< 500
Treatment	R-EPOCHx6	R-CHOPx6	R-CHOPx6	R-EPOCHx8	R-EPOCHx6	R-EPOCHx1	R-EPOCHx4	R-EPOCHx8	R-EPOCHx6	R-EPOCHx6
Follow-up (m)	102	97	94	84	72	1	15	42	38	11
Outcome	Alive, CR	Alive, CR	Alive, CR	Alive, CR	Alive, CR	DOD	DOD	Alive, CR	Alive, CR	Alive, CR

Abbreviations: LN, lymph node; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal; NA, not available; LMR, lymphocyte-to-monocyte ratio; HGB, hemoglobin; AIDS, acquired immunodeficiency syndrome; cART, combined anti-retroviral therapy; TND, target not detected; EBV, Epstein-Barr virus; R-EPOCH, rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; DOD, died of disease

Table 2 Overview of the histomorphology, Immunophenotype, EBER-ISH and FISH profile of 10 AR-HGBL-11q cases

Case#	1	2	3	4	5	6	7	8	9	10
Histomorphology	BL	DLBCL	BL	BL	HGBL	HGBL	BL	BL	DLBCL	BL
Hans classifier	GCB	non-GCB	GCB	GCB	GCB	GCB	GCB	GCB	GCB	GCB
Immunophenotype, EBER-ISH										
CD20	+	+	+	+	+	+	+	+	+	+
CD10	+	-	+	+	-	+	+	+	-	+
BCL6	+	-	+	+	+	+	+	+	+	+
MUM1	-	+	-	-	-	+	-	+	-	-
LMO2	-	+	-	-	+	+	+	+	+	-
LEF1	-	-	-	-	+	-	-	+	-	-
BCL2	-	+	-	-	-	-	-	-	-	-
CD38	+	-	-	-	-	-	+	+	-	-
MYC	80%	20%	30%	30%	20%	20%	40%	40%	20%	30%
Ki-67 ≥ 90%	+	-	+	+	+	+	+	+	-	+
EBNA2	-	+	-	-	-	-	-	-	-	-
EBER	-	+	-	-	-	-	-	-	-	-
FISH										
MYC	-	-	-	-	-	-	-	-	-	-
11q23 gain	+	-	+	+	-	-	+	+	-	+
11q24 loss	+	+	+	+	+	+	+	+	+	+

Abbreviations: GCB, germinal center B-cell; EBNA2, Epstein-Barr virus nuclear antigen 2; EBER, Epstein-Barr virus-encoded small RNA; ISH, in situ hybridization; FISH, fluorescence in situ hybridization

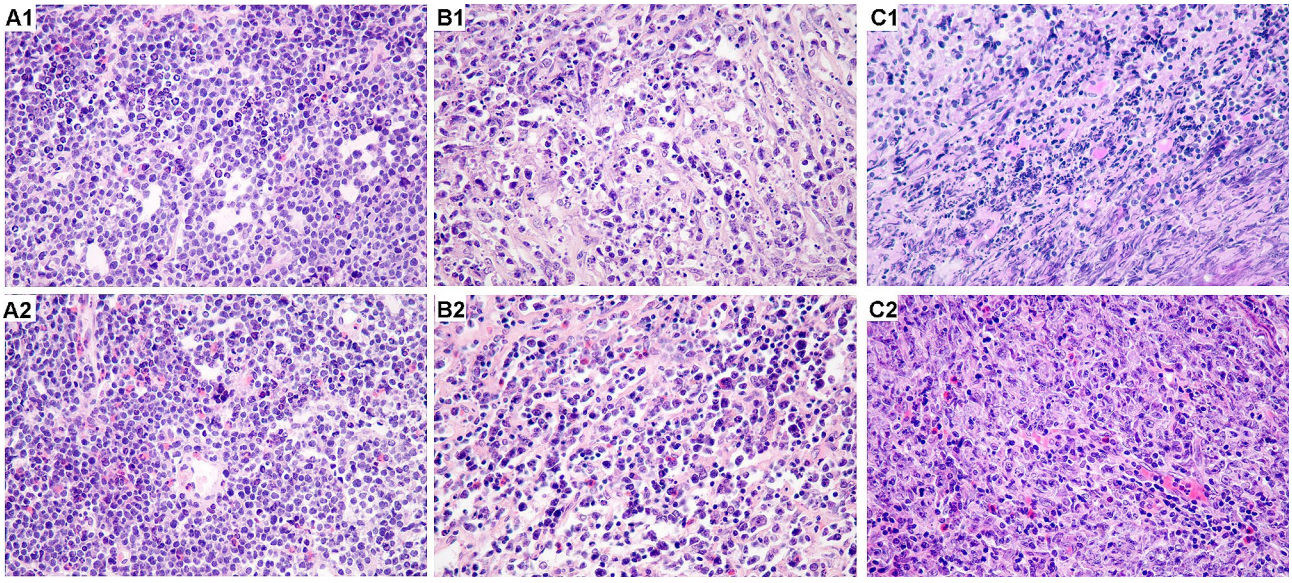

Fig. 1 Morphological features of AR-HGBL-11q, presenting Burkitt lymphoma (A1), high-grade B-cell lymphoma, NOS (B1) and diffuse large B-cell lymphoma (C1), illustrating a particular pattern of abundant apoptotic debris, and background rich in eosinophils (A2, B2 and C2, HE staining, ×400)

Histomorphology, immunophenotype, and EBER status

The histomorphological, immunohistochemical, and EBER characteristics of the 10 AR-HGBL-11q cases are summarized in Table 2. Six cases (60%) showed typical BL morphology, exhibiting monomorphic medium-sized cells and a high nuclear-to-cytoplasmic ratio (Fig. 1A1), and two cases with a "starry sky" appearance. Two cases (20%) showed morphological features between BL and DLBCL, characterized by irregular nuclei and variations in size, and were classified as HGBL, NOS (Fig. 1B1). Two cases (20%) were morphologically similar to DLBCL, with a large cell size, oval or round vesicular nuclei, and a big nucleolus (Fig. 1C1). These were identified as the immunoblastic type of DLBCL, and one case showed spindle cell morphology, related to its site of occurrence in the tonsil. In all cases, distinct and coarse apoptotic nuclear debris was easily observed (Fig. 1A1, B1 and C1), and the background contained varying numbers of eosinophils (Fig. 1A2, B2, C2). Based on the Hans classifier, 9

samples (90%) were of germinal center B-cell (GCB) type, and 1 case (10%) had a non-GCB phenotype.

Immunohistochemical analysis (Fig. 2) showed that the tumor cells were positive for CD20 in all cases (100%), CD10 in 7 cases (70%), BCL6 in 9 cases (90%), MYC diffuse positive in 1 case (10%), BCL2 in 1 case (10%), MUM1 in 3 cases (30%), LMO2 in 6 cases (60%), and LEF1 in 2 cases (20%). The Ki-67 index was ≥90% in 8 cases (80%). One case (10%) was EBER-positive by in situ hybridization, and this case also expressed EBNA2 (Fig. 2).

Fluorescence in situ hybridization

To identify HGBL-11q cases, we reevaluated the presence of *MYC* translocation in 96 cases diagnosed as AIDS-related aggressive B-cell lymphoma, including BL (35 cases), DLBCL (48 cases), and HGBL, NOS (13 cases). A total of 21 cases were negative for *MYC* rearrangement by FISH analysis, including BL (11 cases), DLBCL (8 cases), and HGBL (2 cases). Subsequently, 10/96 (10.4%) cases harbored the typical 11q aberration pattern, predominantly those that had been classified as BL (6/35, 17.1%), DLBCL (2/48, 4.2%), and HGBL, NOS (2/13, 15.4%). In particular, 6 instances exhibiting typical BL morphology showed gain in the 11q23 region and loss in the 11q24 region, while 4 cases presented with morphological features of DLBCL and HGBL which exhibited 11q24 loss (Fig. 2). The other 11 cases lacked both *MYC* rearrangement and 11q aberration.

Comparison of clinical and pathological characteristics between AR-HGBL-11q cases and MYC/11q negative ARL cases

Through a literature review, we identified 7 cases of AR-HGBL-11q [8–14], which were combined with the 10 cases in our study to form a joint cohort of 17 patients. All patients were male, with a median age of 37 years (range: 23-66y). Among them, 88% (14/16) of the cases were in advanced clinical stages (III/IV). All patients received chemotherapy, including 8 cases of R-EPOCH, 4 cases of R-CHOP, 3 cases of DA-EPOCH-R, and 1 case of R-CTOEP; the remaining 1 case started high-dose methotrexate, cytarabine, thiotepa, and rituximab therapy due to central nervous system involvement [9], and all chemotherapy regimens were concomitantly administered with ART. Survival data for all patients were available, with a median follow-up time of 40 months (range: 1–112 m). Most patients achieved complete remission, with 3 patients dying 1–40 months (average 10 m) after diagnosis and 2 from our cohort, both succumbing to septic shock after 1 and 4 cycles of R-EPOCH therapy, respectively. Both patients presented with large abdominal masses (≥10 cm), B symptoms, elevated LDH levels (852U/L and 941U/L), low hemoglobin levels (84 g/L and 103 g/L), and a lymphocyte-to-monocyte ratio of less than 2 (1.636 and 1.776). Another patient reported in the literature [9] had lymphoma involving the central nervous system and died of septic shock after 2 cycles of high-dose chemotherapy. The 2-year overall survival rate

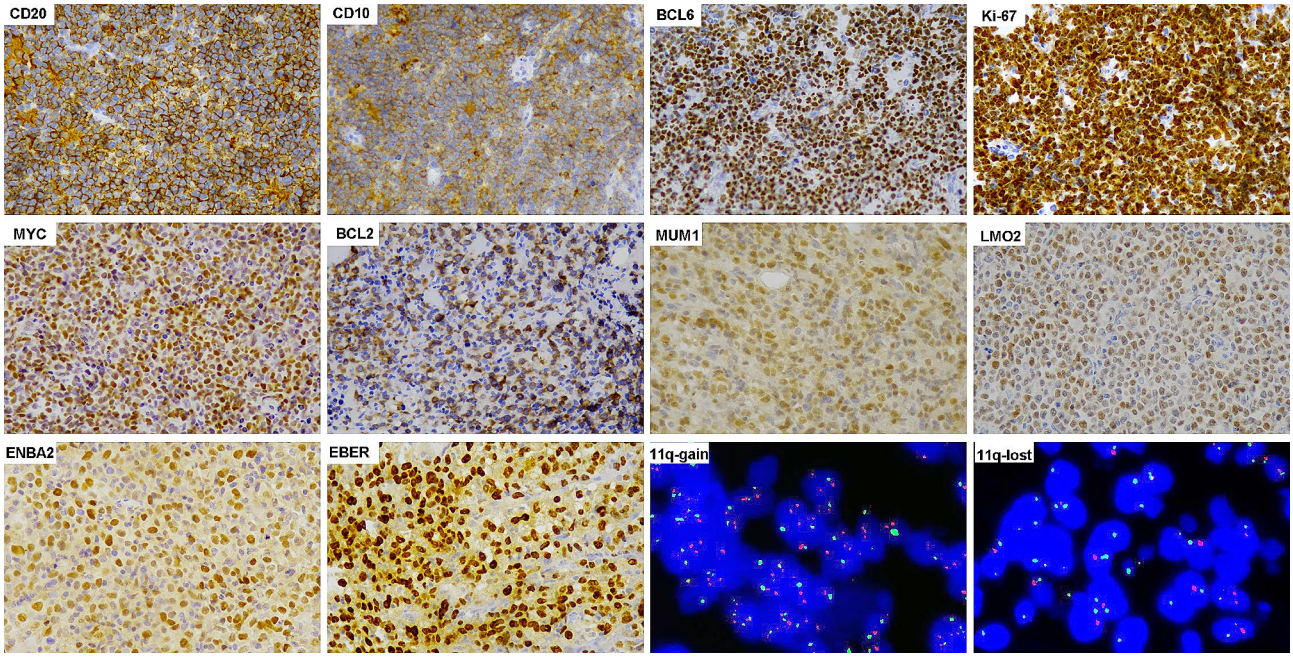

Fig. 2 Immunophenotype, EBER-ISH, and FISH features of AR-HGBL-11q. The tumor cells were positive for CD20 (100%), CD10 (70%), BCL6 (90%), MYC (10%), BCL2 (10%), MUM1 (30%), LMO2 (60%), and the Ki-67 proliferation index was high (≥ 90%). One case showed EBNA2 expression, and positive for EBER in situ hybridization. FISH analysis using 11q23.3/11q24.3 probes revealed gain of 11q23 and loss of 11q24 (IHC, ×400; EBER-ISH, ×400; FISH, ×1000)

Table 3 Comparison of clinicopathology features between 17 AR-HGBL-11q cases and 11 *MYC*/11q negative ARL cases

	MYC-,11q-	MYC-,11q+			*P*-value
	Our cohort (*N* = 11)	Our cohort(*N* = 10)	Literature(*N* = 7)	Total (*N* = 17)	
Age, median (range: y)	42 (29–64)	35 (26–66)	41 (23–56)	37 (23–66)	0.813
Male/female	11/0	10/0	7/0	17/0	-
BM involvement, n/N (%)	0/11(0)	0/10 (0)	1/6 (17)	1/16 (6)	1.000
Ann Arbor stage (I/II vs. III/IV)	0/11	1/9	1/5	2/14	0.499
Front-line therapy regimen (%)					
R-EPOCH	6 (55)	8 (80)	-	8 (47)	-
R-CHOP	3 (27)	2 (20)	2 (29)	4 (23)	-
DA-EPOCH-R	-	-	3 (43)	3 (18)	-
R-CTOEP	-	-	1 (14)	1 (6)	-
MATRix			1 (14)	1 (6)	
Median follow-up (range: m)	33 (1–69)	57 (1-102)	29 (2-112)	40 (1-112)	-
Outcome (died/alive)	5/6	2/8	1/6	3/14	0.150
Two years OS (%)	55%	79%	86%	81%	-
Morphology, n/N (%)					
Coarse apoptotic debris	3/11 (27)	10/10 (100)	6/6 (100)	16/16 (100)	**< 0.001**
Eosinophils background	2/11 (18)	9/10 (90)	NA	9/10 (90)	**0.002**
IHC, n/N (%)					
CD20	11/11 (100)	10/10 (100)	5/5 (100)	15/15 (100)	-
CD10	5/11 (45)	7/10 (70)	6/6 (100)	13/16 (81)	0.097
BCL6	7/11 (64)	9/10 (90)	6/6 (100)	15/16 (94)	0.125
MUM1	9/11 (82)	3/10 (30)	0/5 (0)	3/15 (20)	**0.004**
BCL2	6/11 (55)	1/10 (10)	0/7 (0)	1/17 (6)	**0.007**
LMO2	2/11 (18)	6/10 (60)	1/1 (100)	7/11 (64)	0.080
LEF1	7/11 (64)	2/10 (20)	NA	2/10 (20)	0.080
Ki-67 ≥ 90%	8/11 (73)	8/10 (80)	6/6 (100)	14/16 (88)	0.370
EBER	5/11 (45)	1/10 (10)	0/6 (0)	1/16 (6)	**0.027**

Abbreviations: DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide doxorubicin, and rituximab; R-CTOEP, rituximab, cyclophosphamide, pirarubicin, vincristine, and prednisone; MATRix, high-dose methotrexate, cytarabine, thiotepa, and rituximab; P-values were calculated comparing AR-HGBL-11q and *MYC*/11q-HGBL groups and statistically significant *P*-values are highlight

for this combined cohort was 81% (Table 3). For comparison, we selected 11 cases of AIDS-related aggressive B-cell lymphoma negative for both *MYC* and 11q from our institution as the control group and conducted a comparative analysis of clinical and pathological characteristics. The control group consisted entirely of males, with a median age of 42 years (range 29-64y), mostly in advanced stage (III/IV) without bone marrow involvement. There were no statistically significant differences between the two groups in basic clinical characteristics (Table 3). However, in terms of histomorphology and immunophenotype, the AR-HGBL-11q group exhibited some unique features. Microscopically, AR-HGBL-11q showed more apoptotic nuclear debris ($P<0.001$) and eosinophils in tumor background ($P=0.002$) (Table 3). About immunophenotype, the expression rate of the germinal center marker LMO2 ($P=0.080$) was higher in AR-HGBL-11q, while the expression rates of LEF1 ($P=0.080$), BCL2 ($P=0.007$), and MUM1 ($P=0.004$) and EBER positivity ($P=0.027$) in situ hybridization were lower (Table 3). In this comparative cohort, 6 cases received R-EPOCH therapy, 3 cases received R-CHOP therapy, and the remaining 2 cases died before starting chemotherapy. All patients had follow-up data, with a median follow-up age of 33 months (range: 1–69 m), and 5 patients died of lymphoma-related diseases during follow-up, resulting in a 2-year survival rate of 55% (Table 3). Finally, we compared the survival periods of the combined 17 cases with those of 11 ARL cases negative for *MYC* and 11q (Fig. 3) and found that the former group presented a better prognosis, although the difference was not statistically significant ($P=0.15$).

Discussion

In a previous study, despite the effective use of cART, the standardized incidence ratio of NHL in PLWH compared to the general population was 11.5, making lymphoma one of the leading causes of death among PLWH [15]. The mechanisms underlying the high incidence of lymphomas in individuals with HIV infection include HIV-induced immune suppression, genetic abnormalities, cytokine dysregulation, chronic antigen stimulation, and concurrent infections with γ-herpesviruses (EBV and KSHV), alongside dysregulated immune responses

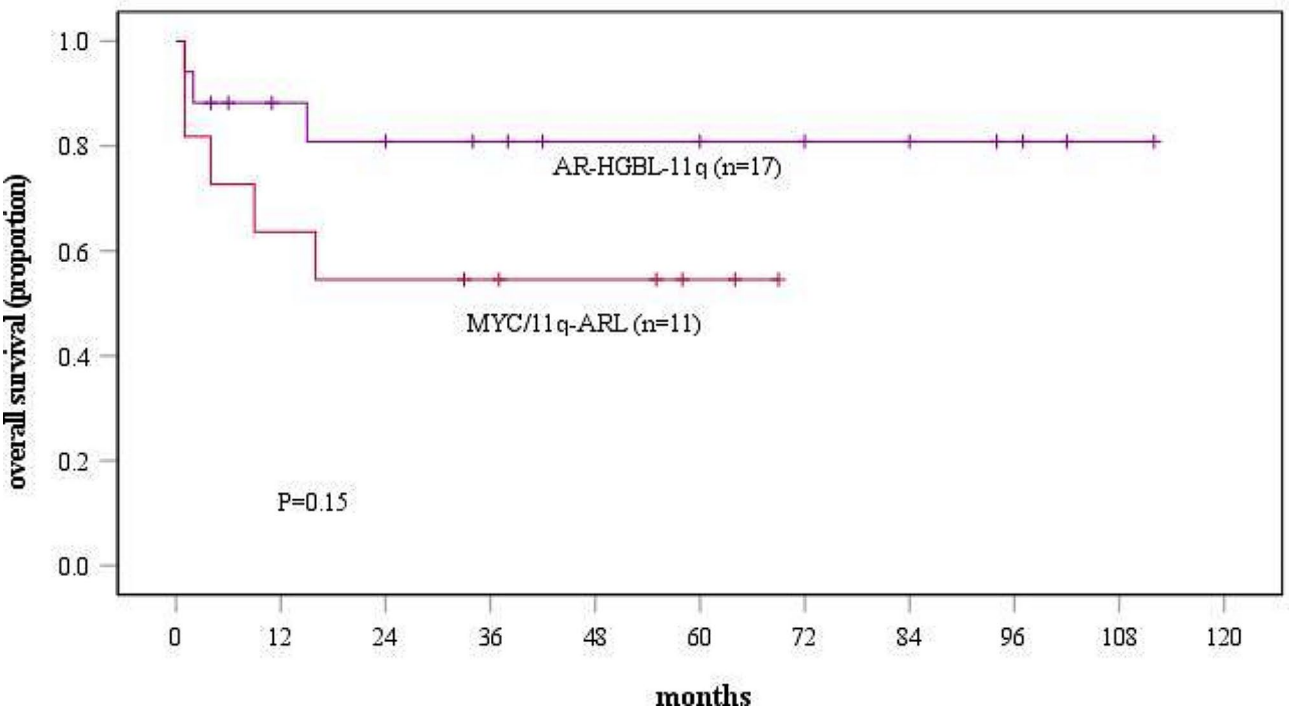

Fig. 3 Survival analysis of AR-HGBL-11q and MYC/11q-ARL. Kaplan-Meier curves comparing the overall survival of patients with AR-HGBL-11q and MYC/11q-ARL ($P=0.15$, log-rank test)

controlling these viruses [16]. Particularly noteworthy is the observation that ARL exhibit a higher frequency of genetic mutations compared to non-HIV-infected individuals [17]. HGBL-11q is a recently described high-grade mature B-cell neoplasm characterized by gain in the 11q23.2-11q23.3 region and loss in the 11q24.1-qter region, but lack of *MYC* translocation and the presence of 11q aberration. Due to its rarity, reports on HGBL-11q in PLWH are limited. Literature reports indicated that 43% of post-transplant Burkitt lymphoma cases and 60% of post-transplant EBV-negative Burkitt lymphoma cases had 11q abnormalities, suggesting a possible association of such tumors with transplantation and immune deficiency [5]. Because lymphoma is one of the main risk factors for PLWH, we evaluated the incidence and clinicopathological characteristics of HGBL-11q in PLWH. In this study, we retrospectively analyzed the clinicopathological features of 10 AR-HGBL-11q cases at our institution and compared them with 7 previously reported cases to better understand this distinct lymphoma entity in PLWH. The incidence of AR-HGBL-11q in our AIDS-related aggressive B-cell lymphoma cohort was 10.4% (10/96), which was slightly higher than the prevalence of 7.96% (9/113) in the HIV-negative population [18]. Most of our patients had a long history of HIV infection, with a median duration of 38 months, which was consistent with previous reports [8–14]. AR-HGBL-11q primarily affects young to middle-aged men, with a median age of 35 years in our series, younger than the median age of 49.5 years reported for the general population [19]. All our patients were male, and a similar male predominance was observed in the literature [18].

AR-HGBL-11q tends to be present at an advanced stage with frequent extranodal involvement. In our cohort, 60% of patients were diagnosed with stage IV disease with extranodal involvement, most commonly affecting the gastrointestinal tract, followed by the liver and spleen. In contrast, the majority of HIV-negative HGBL-11q patients are in stage I/II [20]. B symptoms and bulky disease were observed in 40% and 50% of the patients. Elevated serum LDH levels were common (70%). However, none of our patients had central nervous system or bone marrow involvement at presentation. Morphologically, AR-HGBL-11q exhibits features reminiscent of BL, DLBCL, and HGBL, NOS. In our series, 60% of cases showed classical BL morphology, 20% resembled DLBCL, and 20% were classified as HGBL, NOS. Notably, all cases featured a peculiar pattern of prominent apoptotic bodies or coarse apoptotic debris, which is uncommon in other aggressive B-cell lymphomas, consistent with the characteristics of HIV-negative HGBL-11q [19]. Additionally, eosinophils can be present in B-cell lymphomas, and their quantity contributes to lymphoma classification [21]. However, analysis of eosinophil count in tissues from HGBL-11q cases has not been reported. In our observation of the histomorphology of AR-HGBL-11q,

we found that 90% (9/10) of cases exhibited an increase in eosinophils in tumor background under the microscope. These distinct morphological features may provide clues to the diagnosis of HGBL-11q. In clinical practice, for the final diagnosis of the last AR-HGBL-11q case, we relied on the summarized histological features of the previous 9 cases-prominent apoptotic debris, along with eosinophils in tumor background, and thereby considered the case as AR-HGBL-11q. Subsequently, FISH testing was conducted to confirm the diagnosis, which validated the importance of the particular morphology in the diagnosis of this rare type of B-cell lymphoma.

The immunophenotype of AR-HGBL-11q was characterized by a high frequency of the GCB phenotype (90% in our cohort) according to the Hans algorithm, which is consistent with previous reports [12]. CD10 and BCL6 were expressed in 70% and 90% of cases, respectively. Interestingly, the expression of LMO2, a germinal center marker, was observed in 60% of our cases, higher than the reported rate of 38% in HIV-negative HGBL-11q [22]. Another interesting finding is the significant decrease in the expression of lymphocyte-enhancing factor-binding factor 1 (LEF1), as revealed by proteomic and transcriptomic of HGBL-11q [23]. Immunohistochemical detection of LEF1 has not previously been performed in HGBL-11q. To address this research gap, we conducted immunohistochemical analysis of LEF1 in AR-HGBL-11q screened cases. The results showed that LEF1 was weakly positive in only 20% of the cases. Furthermore, the expression of MUM1 has a negative impact on the prognosis of HIV-related BL [11]. Grzegorz et al.'s study showed that MUM1 is generally negative in HGBL-11q of HIV-negative individuals [24]. However, in our cohort, 30% (3/10) of cases were positive for MUM1, which may support the view that AR-HGBL-11q has a worse prognosis than non-HIV-infected individuals. These findings suggest that AR-HGBL-11q may have a unique immunophenotypic profile compared with its HIV-negative counterpart.

EBV infection is rare in HGBL-11q, with no positive cases reported in the literature [25]. In our series, one case (10%) was EBER-positive and expressed EBNA2, indicating a EBV-latency infection type III, which suggested low immunity. The patient's CD4+T cell count was very low (only 4 cells/μL), the lowest of the 10 cases in our study, and his EBV serum was positive. This finding expands the spectrum of EBV-associated HGBL-11q and highlights the need for routine EBER testing for this type of lymphoma, especially in the HIV setting. FISH analysis confirmed the absence of *MYC* rearrangement and presence of 11q aberrations in all AR-HGBL-11q cases. The characteristic 11q aberration pattern, featuring proximal gains and telomeric losses, was observed in 60% and 100% of our cases, respectively. This complex aberration pattern is considered a defining feature of HGBL-11q and is crucial for its diagnosis [26].

To further characterize AR-HGBL-11q, we conducted a comparative analysis of 11 cases of ARL from our institution, which lacked both *MYC* rearrangement and 11q aberration and were referred to as *MYC*/11q-ARL. Our investigation revealed distinct clinicopathological features that distinguished AR-HGBL-11q from *MYC*/11q-ARL. Notably, AR-HGBL-11q exhibited a significantly higher frequency of coarse apoptotic debris ($P<0.001$) and eosinophils ($P=0.002$), higher expression of LMO2 ($P=0.080$), and lower frequencies of LEF1 ($P=0.080$), BCL2 ($P=0.007$), MUM1 ($P=0.004$), and EBER positivity ($P=0.027$) compared to *MYC*/11q-ARL. These distinct features suggest that AR-HGBL-11q represents a unique subgroup of ARL with characteristic morphological, immunophenotypic, and molecular profiles.

Regarding treatment and prognosis, 80% of our patients received EPOCH as the first-line regimen, and all but 2 achieved complete remission. Anti-CD20 antibody therapy has been proven effective in treating ARL and is typically used in combination with chemotherapy to enhance treatment efficacy, which was also widely used among our patients [27]. However, other targeted inhibitors, such as BTK and PI3K inhibitors, have been less reported in the treatment of ARL and are still in the research phase. The use of immune checkpoint inhibitors such as PD-1 and PD-L1 inhibitors may increase the risk of immune-related adverse events, necessitating careful evaluation for their application in PLWH [28]. Currently, there are no reports on the use of targeted therapies and immune therapies, such as BTK inhibitors or PI3K inhibitors, specifically for AR-HGBL-11q patients. Future studies are expected to explore whether these treatment modalities can further improve patient survival and quality of life, particularly in patients who have become resistant to conventional treatments or have relapsed. Nevertheless, treatment decisions for ARL should comprehensively consider the immune status and the impact of ART to ensure treatment safety and efficacy. The estimated 2-year overall survival rate was 79%, less favorable compared to the over 90% survival rate reported for HIV-negative HGBL-11q [12, 29]. Compared with *MYC*/11q-ARL, AR-HGBL-11q showed a trend towards better survival, however, the difference was not statistically significant ($P=0.15$), possibly due to the limited sample size.

Our study had several limitations. First, although our AR-HGBL-11q cohort study is relatively large compared to previous studies, the number of cases remains relatively small, limiting the statistical power and generalizability of our findings. Future studies will require a larger sample size to validate our results. Second, to summarize the clinical and pathological characteristics of this rare entity, we analyzed cases collected from

different institutions' literature and further compared global *MYC*/11q-ARL cases. Thus, there may be bias in this information. Third, due to the retrospective nature of case identification and the majority of samples from live tissue examinations, despite the fact that FISH analysis is a common molecular technique, next-generation sequencing can provide more comprehensive genetic features and insights into potential therapeutic targets, which is necessary for further research.

Conclusion

In conclusion, AR-HGBL-11q is a distinct subtype of ARL characterized by frequent extranodal involvement, advanced stage at presentation, morphological diversity with abundant apoptotic debris and common eosinophils, high frequency of the GCB phenotype, rare EBV association, and complex 11q aberrations. In particular, the finding of coarse apoptotic debris and eosinophil background is a diagnostic approach for the identification of AR-HGBL-11q in histomorphology. Our findings contribute to a better understanding of this rare lymphoma entity in the HIV setting and highlight the importance of integrating histomorphological as well as immunophenotypic features in its diagnosis and classification. Larger studies are needed to further characterize the biological and clinical behavior of AR-HGBL-11q and optimize its therapeutic strategies.

Abbreviations

AIDS	acquired immunodeficiency syndrome
AR-HGBL-11q	AIDS-related high-grade B-cell lymphoma with 11q aberration
BL	Burkitt lymphoma
cART	combined antiretroviral therapy
DLBCL	diffuse large B-cell lymphoma
EBER	Epstein-Barr virus-encoded small RNA
EBNA	Epstein-Barr virus nuclear antigen
FISH	fluorescence in situ hybridization
GCB	germinal center B-cell
HGBL	high-grade B-cell lymphoma
ISH	in situ hybridization
MYC/11q-ARL	*MYC*/11q negative AIDS-related lymphoma
PLWH	people living with HIV
CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
R-EPOCH	rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

Author contributions

Jing Chang contributed to the manuscript drafting. Yin Liang, Yuxue Gao and Menghua Wu contributed to the collection of documents. Mulan Jin revised the editable manuscript. Fudong Lv, Hui Liu, Lin Sun, Zhujun Yue, Lingjia Meng contributed to the study concept and design. All authors read and approved the final manuscript. Mulan Jin was the corresponding author.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Youan Hospital and performed in accordance with the 1975 Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

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