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Human herpes virus 8-driven neoplasia across multiple cellular lineages: clonally related human herpes virus 8+/Epstein-Barr-virus+ germinotropic and plasmablastic lymphoproliferations with concurrent nodal Kaposi sarcoma

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To date, the WHO recognizes only two lymphoproliferative disorders characterized by dual Epstein–Barr virus (EBV) and human herpesvirus 8 (HHV8) co-infection: germinotropic lymphoproliferative disorder (GLPD) and primary effusion lymphoma (PEL)^{1 2}. Here, we report an HIV-negative patient with an HHV8+/EBV+ lymphoproliferative disorder (LPD) initially displaying features of GLPD and a clonally related aggressive plasmablastic LPD identified in a second lymph node (LN). The case was additionally remarkable for concurrent HHV8+ Kaposi sarcoma (KS) and in situ follicular B-cell neoplasm (ISFN) within the same LN - an exceptionally rare constellation that expands the spectrum of HHV8/EBV-driven proliferative disorders and offers potential insights into their shared pathogenesis.

A 44-year-old previously healthy man presented with a one-year history of progressive cervical LN (cLN) enlargement. When followed by fatigue, and recurrent low-grade fevers the patient requested further investigations.

Histology of the cLN showed preserved architecture with reactive follicles and several GCs partially or completely replaced by HHV8+/EBV+ plasmablasts (Fig. 1A). The remaining follicles showed no regressed GCs, mantle-zone expansion or onion-skinning, and there was no prominent interfollicular plasmacytosis or mantle-zone accumulation of HHV8+ plasmablasts suggestive for HHV8-associated MCD. The lesional cells were weakly CD20+/CD79a+, CD19–, CD30+, MUM1+, CD38+, EMA+, CD138– and lambda light-chain restricted. Their predominantly GC-restricted distribution with preserved follicular dendritic cell networks was firstly consistent with GLPD (Fig. 1B).

The same LN contained perihilar HHV8+ KS (Fig. 1C) and an incidental ISFN involving a single GC, without evidence of HHV8 or EBV association (Fig. 1D).

Clinical work-up revealed mild lymphopenia with slightly reduced CD4+ T cells and NK cells, preserved polyclonal B cells, polyclonal hypergammaglobulinemia, markedly elevated IgE, and increased free light chains with a preserved ratio. An IgM/lambda paraprotein was detected. Complement studies showed elevated C1q (60.3 mg/dl) with mildly decreased C3 (81.7 mg/dl), implying alternative/MBL pathway activation in the context of elevated acute phase reactants (CRP, procalcitonin). The subsequent clinical course deteriorated and was complicated by fever, cytopenias, hyperferritinemia and Klebsiella sepsis, and subsequent suspicion of secondary hemophagocytic syndrome; bone marrow biopsy showed neither hemophagocytosis nor involvement by lymphoma.

Staging revealed multiple pathologically enlarged LNs in the cervical, axillary, and supra- and infradiaphragmatic regions as well as splenomegaly. Given the atypically widespread distribution for a usually localized entity, an excisional inguinal LN (iLN) biopsy was performed ten days later during rapid clinical deterioration for further characterization. The iLN showed a substantially more extensive HHV8+/EBV+ plasmablastic proliferation forming confluent

interfollicular and sinusoidal sheets (Fig. 2A-C). The plasmablasts exhibited an identical immunophenotype as the GLPD-like LPD of the cLN, with expression of HHV8, EBER, CD38, MUM1, CD30 and EMA, with again weak CD20 expression, absence of CD19 and CD138, and monotypic IgM lambda. The phenotype, however, showed substantial overlap with extracavitary (EC)-PEL, and the exact diagnostic classification of the aggressive component in context with the clear-cut germinotropic features in the same lymph node was challenging. HHV8+ KS was again present.

NGS-based clonality analysis performed in both LN demonstrated identical clonal IG heavy- and light-chain rearrangements. Three identical light-chain clonotypes were identified, one acquiring a subclonal CDR3 point mutation in the iLN, consistent with intraclonal evolution. Two shared heavy-chain rearrangements were also detected, and the dominant clone increased 4.6-fold in the iLN (Fig. 2D).

Targeted NGS (TSO500) of the iLN revealed a low tumor mutational burden, microsatellite stability, and a single potentially clinically relevant ZNF217 p.(E914_P915delinsDS) alteration (evidence level IID), although its significance in HHV8-associated lymphoproliferative disorders remains uncertain.

Because of the critical clinical condition, weekly rituximab with one dose of liposomal doxorubicin, ganciclovir and intravenous immunoglobulin was initiated, followed by R-CHOP after stabilization. Recurrent lymphadenopathy and anemia after cycle 1 prompted addition of brentuximab vedotin from cycle 2. Serum IL-6 subsequently normalized (22.0 to 6.59 pg/mL; reference ≤ 7 pg/mL), while ferritin decreased (5549.2 to 2866.0 $\mu\text{g/L}$); however, concomitant inflammatory complications preclude attribution specifically to HHV8-driven cytokine dysregulation. After three cycles (1 R-CHOP, 2 R-BrV-CHP), the patient remained clinically stable; PET-CT response assessment is pending.

According to institutional regulations, formal Ethics Committee approval was not required for this report. Informed written consent for publication was obtained from the patient.

This case represents a clonal HHV8+/EBV+ LPD displaying a predominantly germinotropic pattern with features of a GLPD-like disorder in the cLN and an aggressive plasmablastic proliferation in the subsequently excised iLN. Concurrent nodal HHV8+ KS and incidental ISFN further illustrate the unusual clinicopathologic setting and raise questions regarding the boundaries among currently recognized HHV8-associated LPDs.

GLPD is characterized by germinal-center colonization by HHV8+/EBV+ plasmablasts and generally follows an indolent clinical course.³⁻⁷ In our patient, cervical lymphadenopathy had

evolved slowly for approximately one year before the onset of constitutional symptoms, generalized lymphadenopathy, cytopenias, and rapid clinical deterioration. Histologically, the cLN showed a predominantly germinotropic proliferation largely confined to selected germinal centers, whereas the iLN, excised ten days later during the systemic phase of the disease, contained extensive interfollicular and sinusoidal sheets of plasmablastic cells. Although the short interval between biopsies precludes definitive demonstration of temporal progression and both lesions could represent different morphologic manifestations of an already disseminated disease, the preceding one-year indolent clinical course followed by rapid deterioration supports evolution toward a more aggressive phenotype. Progression of localized or indolent HHV8+/EBV+ germinotropic proliferations to aggressive lymphoproliferative disease has previously only rarely been reported^{4,8,9}.

The molecular findings provide strong evidence that both morphologic patterns represent the same clonal disease. NGS-based clonality analysis demonstrated identical IG heavy- and light-chain rearrangements in both LNs, accompanied by increased representation of the dominant clone and intraclonal sequence evolution in the iLN. These findings argue against independent HHV8/EBV-driven proliferations and support clonal evolution within a single lymphoproliferative process. However, the monoclonal B-cell population already present in the cLN differs from the polyclonal or oligoclonal pattern typically demonstrated in classical GLPD^{1,2,7}. We therefore consider the initial lesion more appropriately classified as an HHV8+/EBV+ germinotropic LPD with features of GLPD rather than the classical GLPD acknowledged in the current lymphoma classifications^{1,2}.

The classification of the aggressive plasmablastic component also warrants consideration. Its phenotype, including HHV8/EBV co-infection, plasmablastic morphology, expression of CD30, MUM1, CD38 and EMA, loss of CD19, and monotypic IgM lambda expression, shows substantial overlap with EC-PEL^{3,4,10,11}. Conversely, weak residual CD20 expression and absence of CD138 are less typical of conventional PEL. Most importantly, the aggressive proliferation was clonally related to the preceding germinotropic HHV8+/EBV+ proliferation. We therefore favor an aggressive plasmablastic manifestation¹² arising within this clonal HHV8+/EBV+ LPD, while acknowledging substantial phenotypic overlap with EC-PEL. Thus, rigid assignment to either PBL or EC-PEL may not fully reflect the biology of the present lesion.

HHV8-associated MCD represents another important differential diagnosis^{3-5,13}. The overall cLN architecture was preserved, and the uninvolved follicles lacked the typical morphologic features of MCD. Moreover, HHV8+ plasmablasts predominantly colonized GC rather than showing the characteristic mantle-zone distribution of HHV8-associated MCD. These findings argue against MCD and support the germinotropic nature of the initial proliferation.

The concomitant nodal KS and extensive HHV8+/EBV+ LPD in an HIV-negative patient raised suspicion of impaired antiviral immune surveillance. The immune phenotype, characterized by decreased CD4+ T-cell and NK-cell numbers, preserved polyclonal B-cell counts, mild plasmablast expansion without light-chain restriction, and polyclonal hypergammaglobulinemia, argues against a primary humoral immunodeficiency and instead suggests reactive or dysregulated B-cell and plasma-cell activation in the context of impaired T-cell- and NK-cell-mediated immune surveillance^{14,15}. This may have provided a permissive immunologic background for the development of multiple HHV8-associated proliferations, although an underlying immune defect has not been established. Serum IL-6 was transiently elevated during the clinically progressive phase with clinically HLH, but normalized shortly thereafter. With respect to the concomitant inflammatory complications, this elevation cannot be specifically attributed to HHV8-associated cytokine dysregulation with certainty, and viral IL-6 has unfortunately not been assessed.

The coexistence of KS and an HHV8-associated lymphoproliferative disorder is recognized in patients predisposed to HHV8-associated diseases and is therefore not unique to this case¹³. However, the occurrence of both processes in an HIV-negative patient, together with the abnormalities of cellular immunity described above, is consistent with impaired control of HHV8 infection. The incidental ISFN involving a single germinal center appeared morphologically and virologically unrelated to the HHV8+/EBV+ proliferation and most likely represents an independent precursor B-cell lesion^{1,2}. Its biological relationship, if any, to the altered immune background remains uncertain.

In summary, this case provides compelling morphological and molecular evidence that clonally related germinotropic and aggressive plasmablastic manifestations represent different stages of a single HHV8+/EBV+ LPD across anatomically distinct LNs. Although the short interval between biopsies does not establish temporal progression, the preceding indolent clinical course, subsequent rapid systemic deterioration, distinct morphologic patterns, increased representation of the dominant clone, and intraclonal sequence evolution support evolution toward an aggressive plasmablastic phenotype. The substantial overlap with GLPD-like proliferations, HHV8+/EBV+ plasmablastic LPD and EC-PEL illustrates the limitations of rigid diagnostic boundaries within the spectrum of HHV8-associated lymphoproliferative disorders. Concurrent KS in the setting of suspected impaired T-cell/NK-cell immune surveillance further supports an unusual immunologic background permissive for multiple HHV8-associated neoplasia.

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Table 1. Differential diagnoses according to Alaggio et al. 2022¹ and Zanelli et al. 2020⁷.

	GLPD	Case	EC-PEL	PBL
Clinical features	(isolated) lymphadenopathy	initial isolated then generalized lymphadenopathy, systemic symptoms	nodal or extranodal tumors	mostly extranodal, exclusively nodal possible
Immunodeficiency	absent	suspicious of, not proven	mostly present	mostly present
HIV	- (rarely +)	-	mostly +	often +
Histology	PB/IB aggregates in GC, polytypic plasmocytosis	PB in aggregates in GC, followed by sinusoidal and diffuse infiltration	PB/IB/AB sinusoidal, diffuse	destructive infiltrates of PB/IB
Immunohistochemistry				
BC markers	CD20-, CD19-, CD79a-, PAX5-	CD20+/-, CD19-, CD79a-/+, PAX5-, Oct-2+, BOB.1+	CD20-/+, CD19-, CD79a-/+, PAX5-/+, Oct-2-, BOB.1-	CD20-/~, CD79a+/-, PAX5-/~
GC markers	CD10-, BCL6-	CD10-, BCL6-	CD10-, BCL6-	CD10-/+, BCL6-
Post-GC markers	MUM1+, CD30+/-, CD38+/-, CD138-/~, EMA-/+	MUM1+, CD30+, CD38+/-, CD138-, EMA+	MUM1+, CD30+, CD38+, CD138+, EMA+/-	MUM1+, CD30+/-, CD38+, CD138+, EMA+
Cytoplasmatic Ig	2/3+ (kappa or lambda)	+ (IgM, lambda)	usually absent	+ (often IgG, kappa or lambda)
HHV8	+	+	+	usually -
EBV (EBER)	+	+	+	+
Clonality	polyclonal or oligoclonal	monoclonal	monoclonal	monoclonal
Outcome	mostly favorable	to be followed	poor	poor

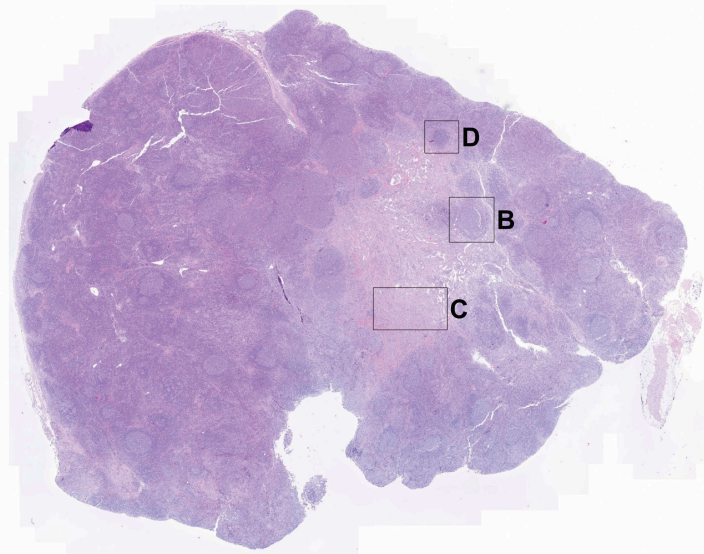
EC-PEL = extracavitary primary effusion lymphoma, GC = germinal center, GLPD = germinotropic lymphoproliferative disorder, IB = immunoblasts, Ig = Immunoglobulin, PBL = plasmablastic lymphoma, PB = plasmablasts

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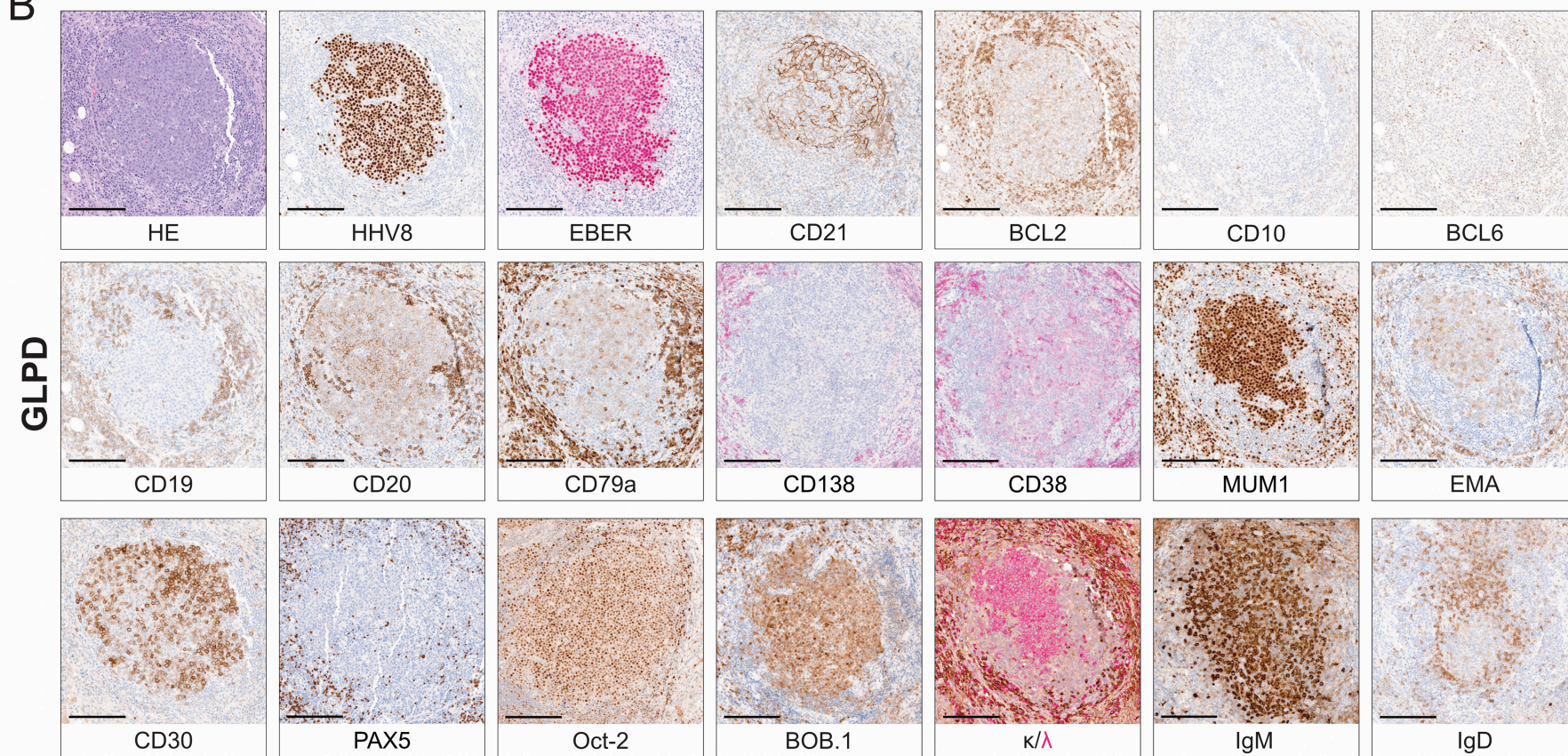
Fig. 1 Three pathologies within one cervical lymph node (cLN). (A) Overview of the cervical lymph node. (B) Germinotropic lymphoproliferative disorder (GLPD)-like proliferation composed of plasmablasts (PBs) populating a germinal center (GC) and co-expressing HHV8 and EBV (EBER); embedded in preserved networks of CD21+ follicular dendritic cells, PBs are negative with BCL2 and lack the GC markers CD10 and BCL6. PBs display an attenuated B-cell profile with loss of CD19 and partial/weak positivity for CD20 and CD79a. They are negative for CD138 and otherwise exhibit a post-GC phenotype with expression of CD38, MUM1, EMA and CD30. Although PAX5 expression is downregulated, Oct-2 and BOB.1 are still expressed. PBCs exhibit cytoplasmic monotypic immunoglobulin (lambda, IgM); IgD marks the preserved mantle-zone. (C) Vascular proliferations composed of HHV8-expressing spindle cells with slit-like spaces containing numerous erythrocytes, consistent with Kaposi sarcoma (KS). (D) In-situ follicular neoplasm (ISFN) composed of centrocytes with aberrant BCL2 expression, positive for the germinal center markers CD10 and BCL6. Scale bars 200 μ m. GLPD = germinotropic lymphoproliferative disorder, ISFN = in-situ follicular neoplasia, KS = Kaposi sarcoma.

Fig. 2 Morphological and clonal evolution of HHV8+/EBV+ germinotropic and plasmablastic lymphoproliferation across distinct lymph nodes. (A) Cervical lymph node (cLN): full section stained for HHV8 and EBV (EBER), demonstrating plasmablastic proliferation largely confined to the germinal centers (GCs). (B) Inguinal lymph node (iLN): half-section stained for HHV8 and EBV (EBER), showing a markedly more extensive infiltration by HHV8+/EBV+ plasmablasts (PBs). (C) PBs (close-up) forming confluent sheets beyond the GCs (upper image) and extending into LN sinuses (lower image), (D) showing a consistent immunophenotype: CD19-, CD20+/-, CD79a-/+, CD138-, CD38+, MUM1+, CD30+, PAX5-, Oct-2+, BOB.1+, lambda+, IgM+; the IgD+ mantle zone is clearly disrupted and PBs infiltrate beyond networks of CD21+ follicular dendritic cells. (E) NGS-based clonality analysis (Oncomine BCR Pan-Clonality Assay (IgH/kappa/lambda; Thermo Fisher Scientific, Ion Torrent platform) identified three shared immunoglobulin light chain clonotypes across cLN and iLN (upper table). A subclone exclusive to the iLN harbored CDR3 somatic point mutations, indicating intraclonal evolution via ongoing somatic hypermutation (SHM). Two heavy chain clonotypes shared identical CDR3 sequences despite divergent IGHV segments (lower table), consistent with V-segment replacement during germinal center transit. Clonal expansion was evidenced by a 4.6-fold increase in frequency of the dominant heavy chain clonotype (IGHV1-46/IGHD2-2/IGHJ5). Scale bar: 2 mm (overviews, HHV8 and EBER), 100 μ m (close-ups, HE). AA = amino acids, cLN = cervical lymph node, Freq. = frequency, iLN = inguinal lymph node, NT = nucleotides, SHM = somatic hypermutation.

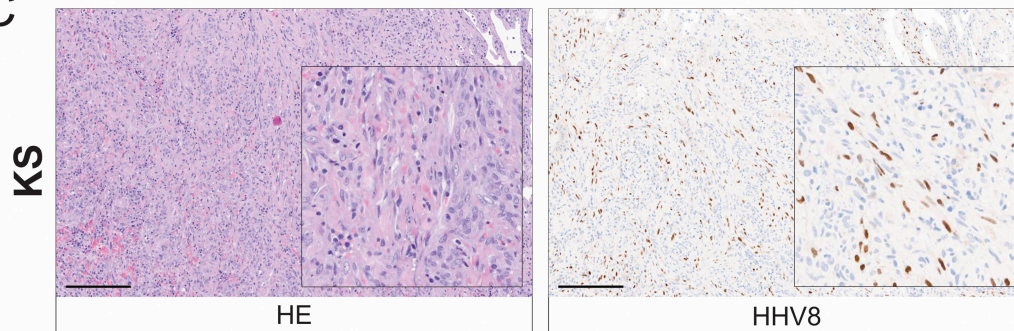
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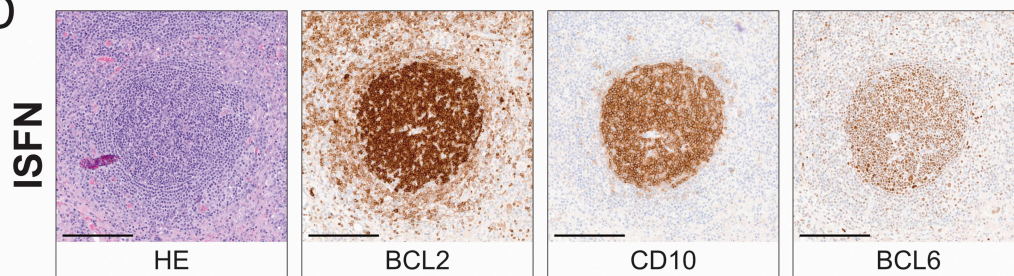
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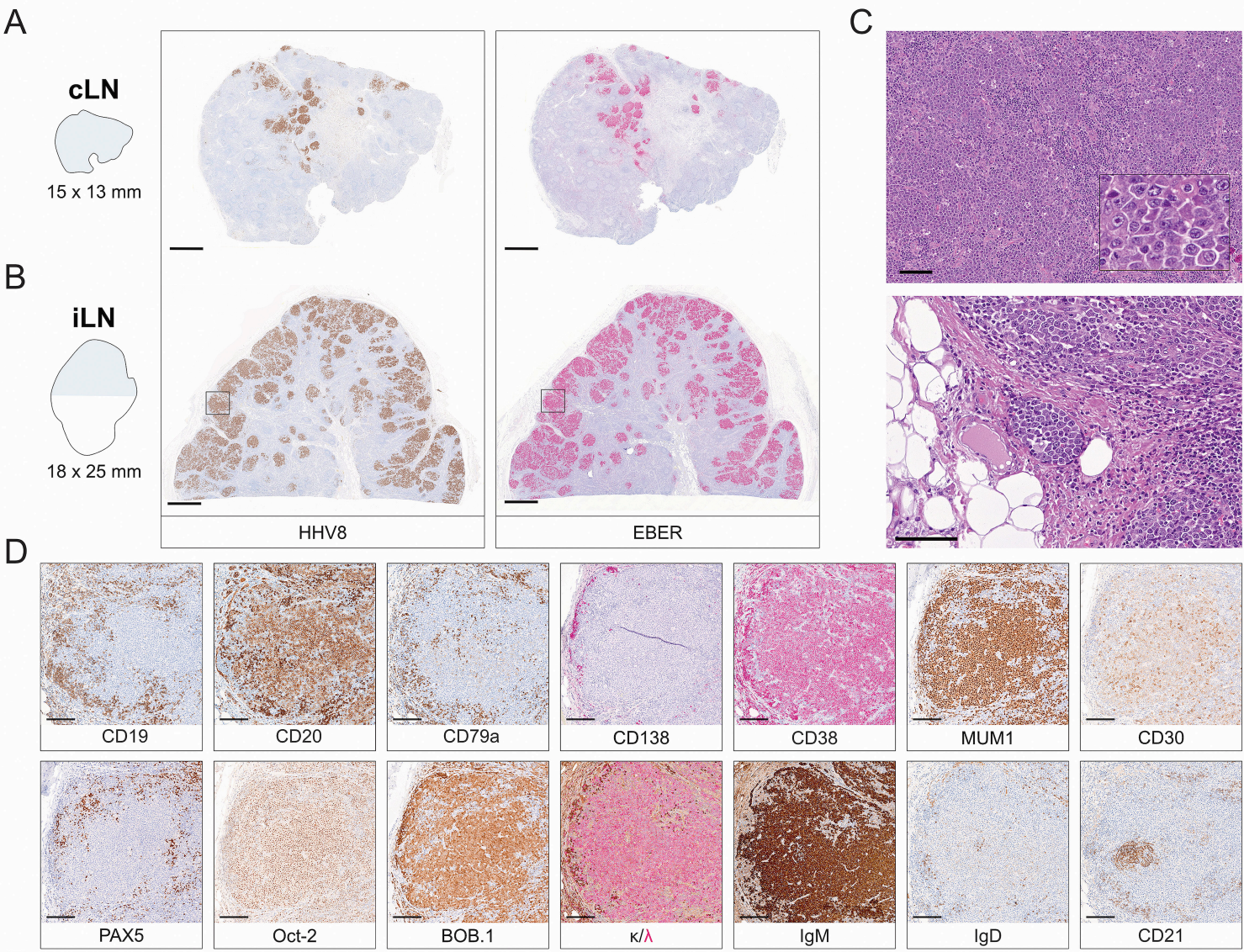


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D





E

Rank	Sample	Freq. (%)	SHM rate	Variable	Diversity	Joining	CDR3 (NT)	CDR3 length (NT)	CDR3 (AA)	Clonal match
1	cLN	6,5	0	IGKV2-28	IGKdel		ACTCCGAGCCCTAGTGGCAGCC	22	— (unproductive)	✓
1	iLN	22,6	0	IGKV2-28	IGKdel		ACTCCGAGCCCTAGTGGCAGCC	22	— (unproductive)	
2	cLN	3,7	0	IGLV3-19	IGLJ3		AACTCCCGGGACAGCAGTGGTAACC TCTGGGTG	33	NSRDSSGNLWV	✓
2	iLN	14,5	0	IGLV3-19	IGLJ3		AACTCCCGGGACAGCAGTGGTAACC TCTGGGTG	33	NSRDSSGNLWV	
3	cLN	2,0	0	IGKV2-40	IGKJ4		ATGCAACGTATAGAGTTTCCCCCCT CACT	30	MQRIEFPPLT	✓
3	iLN	6,0	0	IGKV2-40	IGKJ4		ATGCAACGTATAGAGTTTCCCCCCT CACT	30	MQRIEFPPLT	
4	iLN	1,5	0.028	IGKV2-40	IGKJ4		ATGCAACGTATACGAGTTTCCCCCCT CACT	30	MQRIRVSPLT	SHM-variant

Rank	Sample	Freq. (%)	SHM rate	Variable	Diversity	Joining	CDR3 (NT)	CDR3 length (NT)	CDR3 (AA)	Clonal match
1	cLN	5,1	0	IGHV1-46	IGHD2-2	IGHJ5	GCGAGAGAGGAGAGATATTGTAG TAGTACCAGCTGCCGATTCTTCTG GTTTCGACCCC	57	AREERYCSSTSCRFFWFDP	✓
1	iLN	23,3	0	IGHV1-46	IGHD2-2	IGHJ5	GCGAGAGAGGAGAGATATTGTAG TAGTACCAGCTGCCGATTCTTCTG GTTTCGACCCC	57	AREERYCSSTSCRFFWFDP	
2	cLN	2,3	0	IGHV1-69	IGHD2-2	IGHJ5	GCGAGAGAGGAGAGATATTGTAG TAGTACCAGCTGCCGATTCTTCTG GTTTCGACCCC	57	AREERYCSSTSCRFFWFDP	✓
2	iLN	7,3	0	IGHV1-69	IGHD2-2	IGHJ5	GCGAGAGAGGAGAGATATTGTAG TAGTACCAGCTGCCGATTCTTCTG GTTTCGACCCC	57	AREERYCSSTSCRFFWFDP	