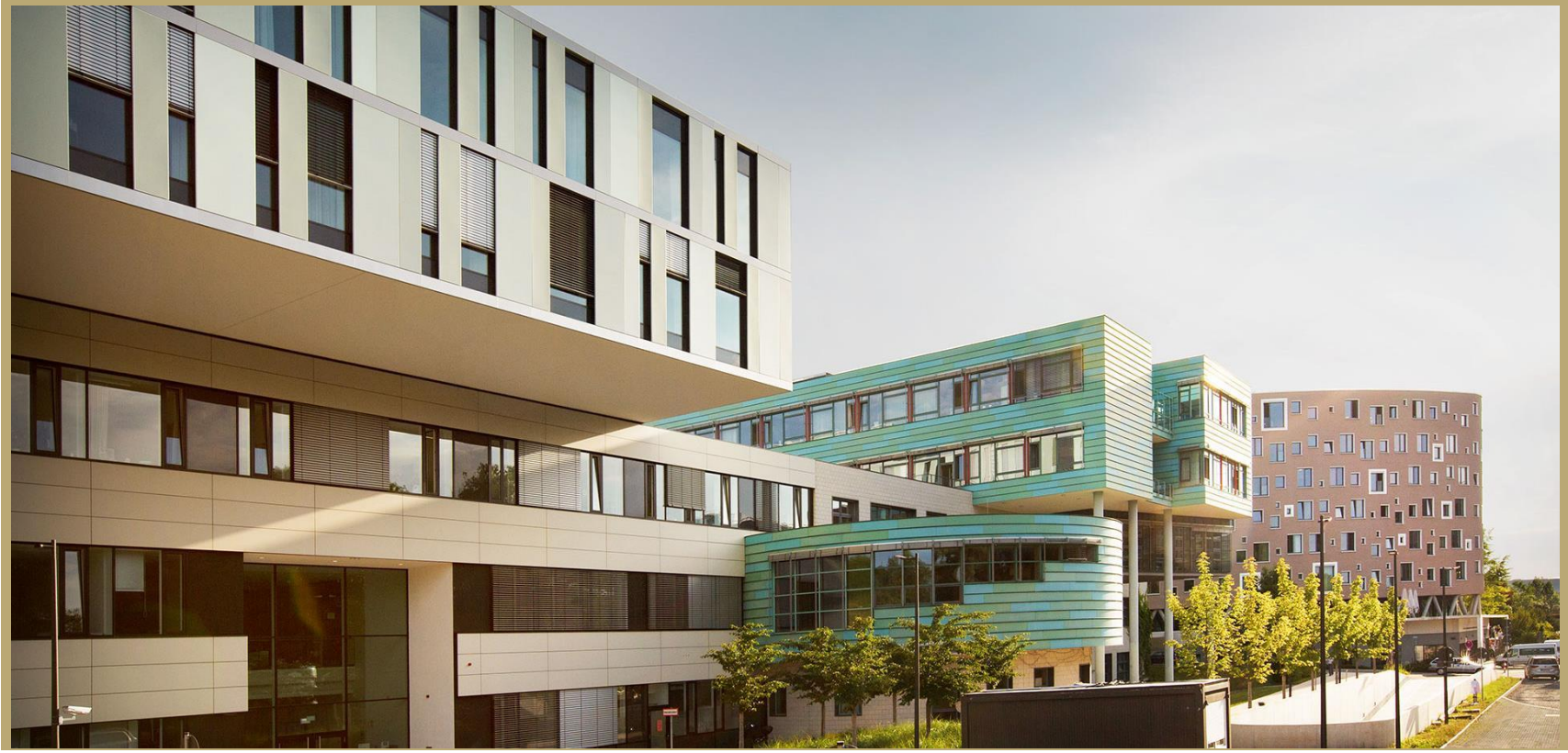
HHV8+ Lymphoproliferative disorders



Leticia Quintanilla-Fend
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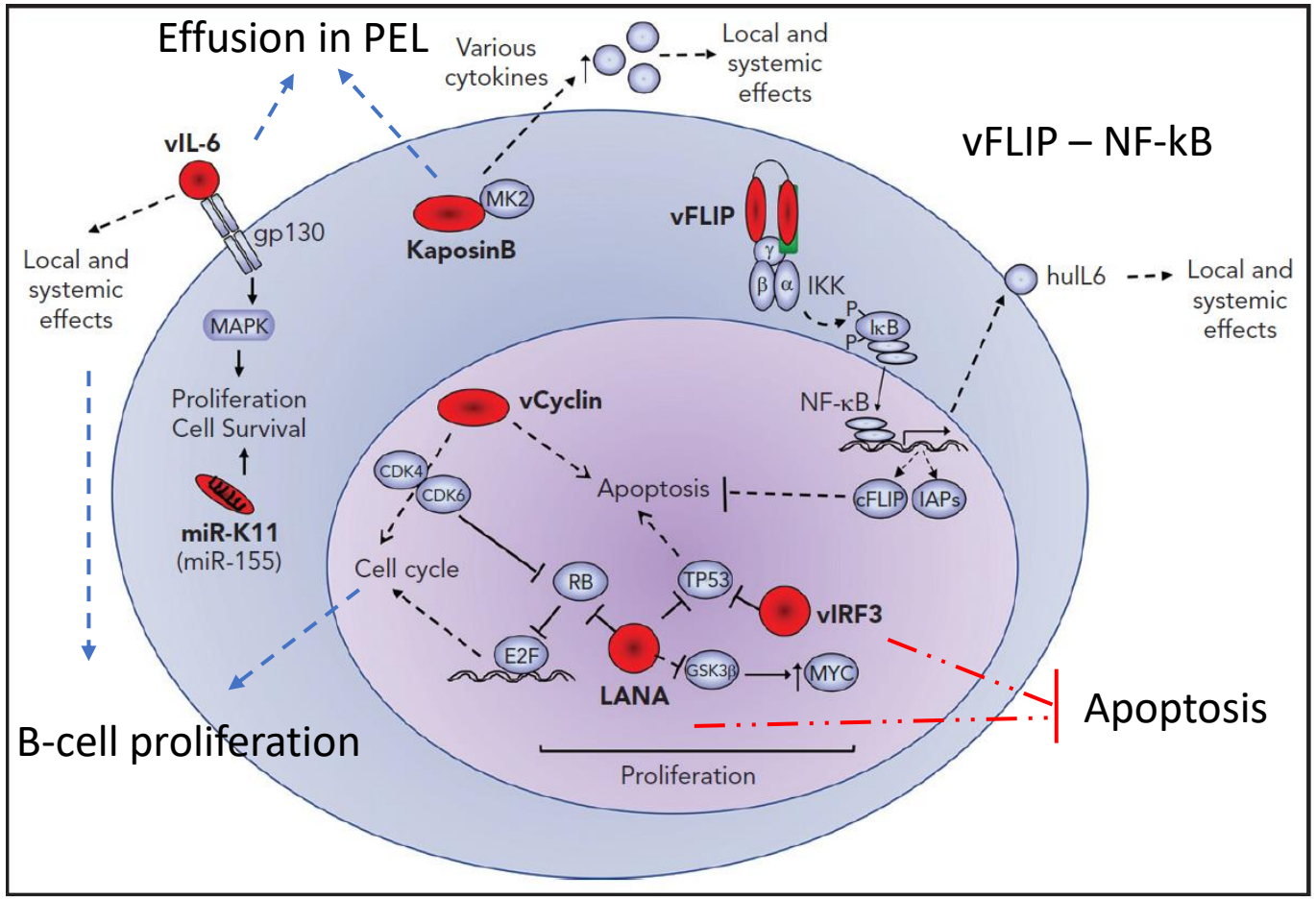
Tübingen

HSVH/HHV8-associated LPDs

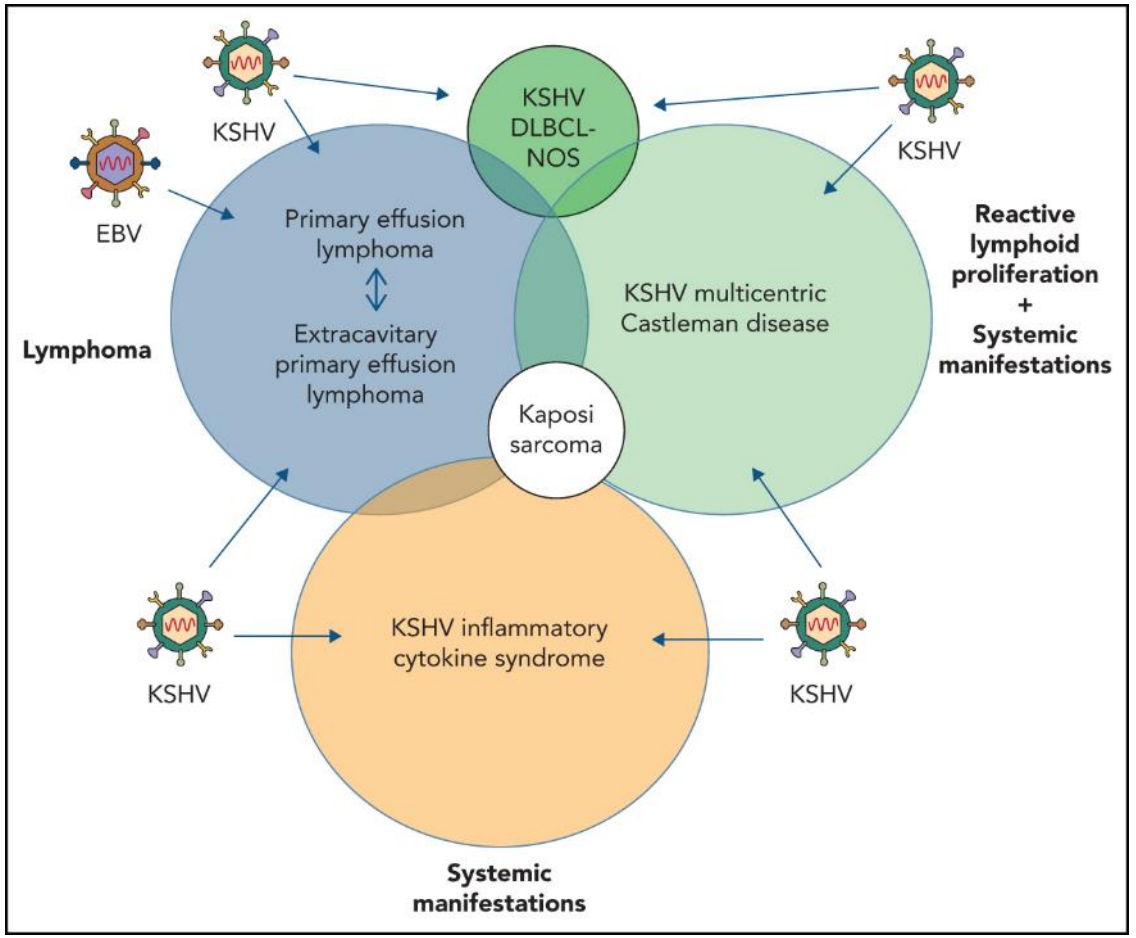
- Oncogenic effects of viral oncoproteins
- Latent viral proteins (LANA, vCyc, vFLIP, IRF3 and Kaposin B) and miR-K11
- This latent viral proteins interact with different cellular proteins either through induction or inhibition
- The pathogenic effects includes cellular proliferation, inhibition of apoptosis and enhance cell survival and production of human cytokines (IL-10) that might have local and systemic effects



Cesarman E, et al. Blood 2022

HSVH/HHV8-associated LPDs

- Multicentric Castleman disease
- HHV8+ germinotropic LPD
- HHV8+ diffuse large B-cell lymphoma, NOS
- Primary effusion lymphoma (PEL)
  - Extracavitary PEL
- *HHV8 and EBV-negative primary effusion-based lymphoma* (ICC)
- Fluid-overload lymphoma (WHO)



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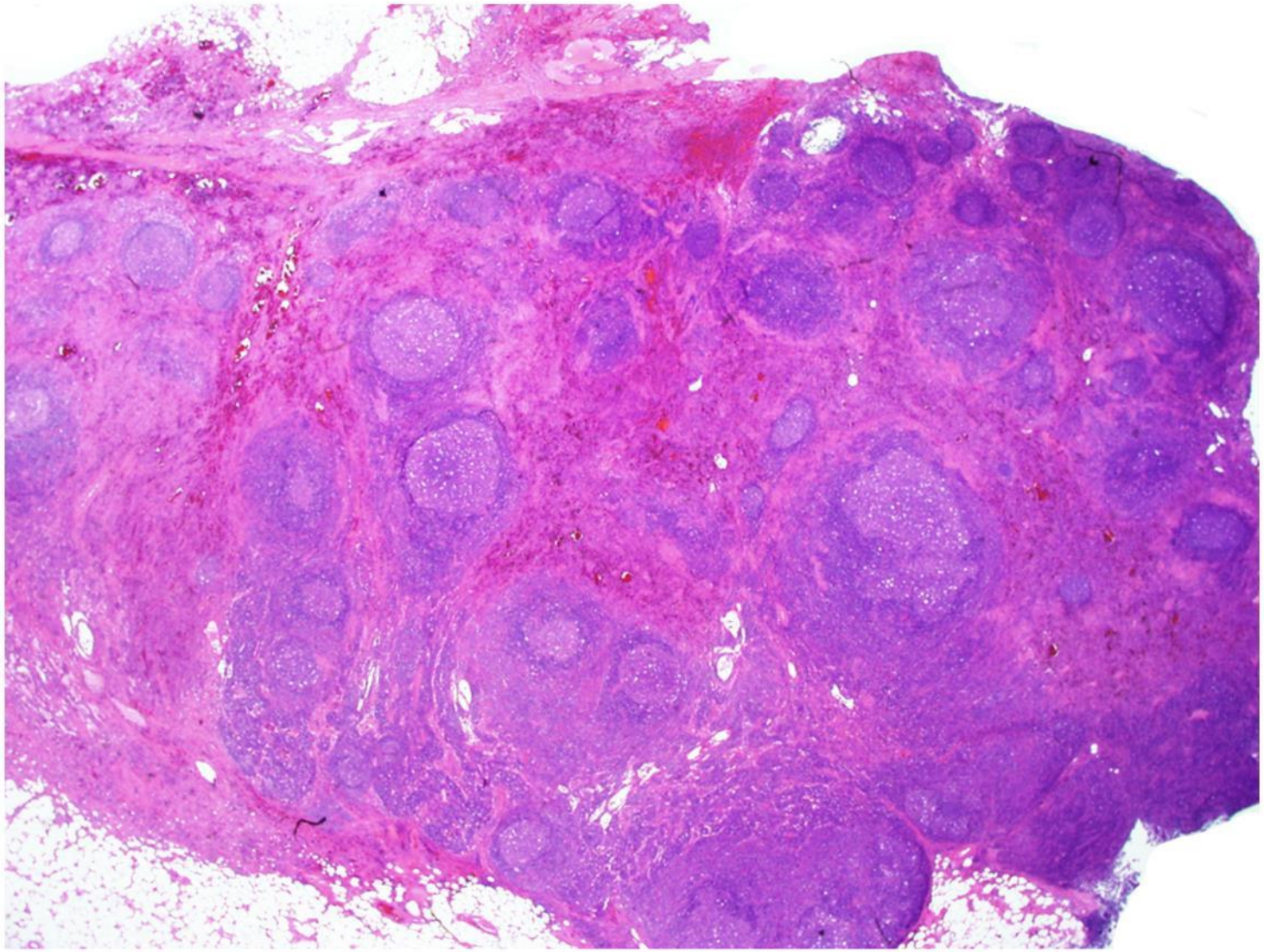
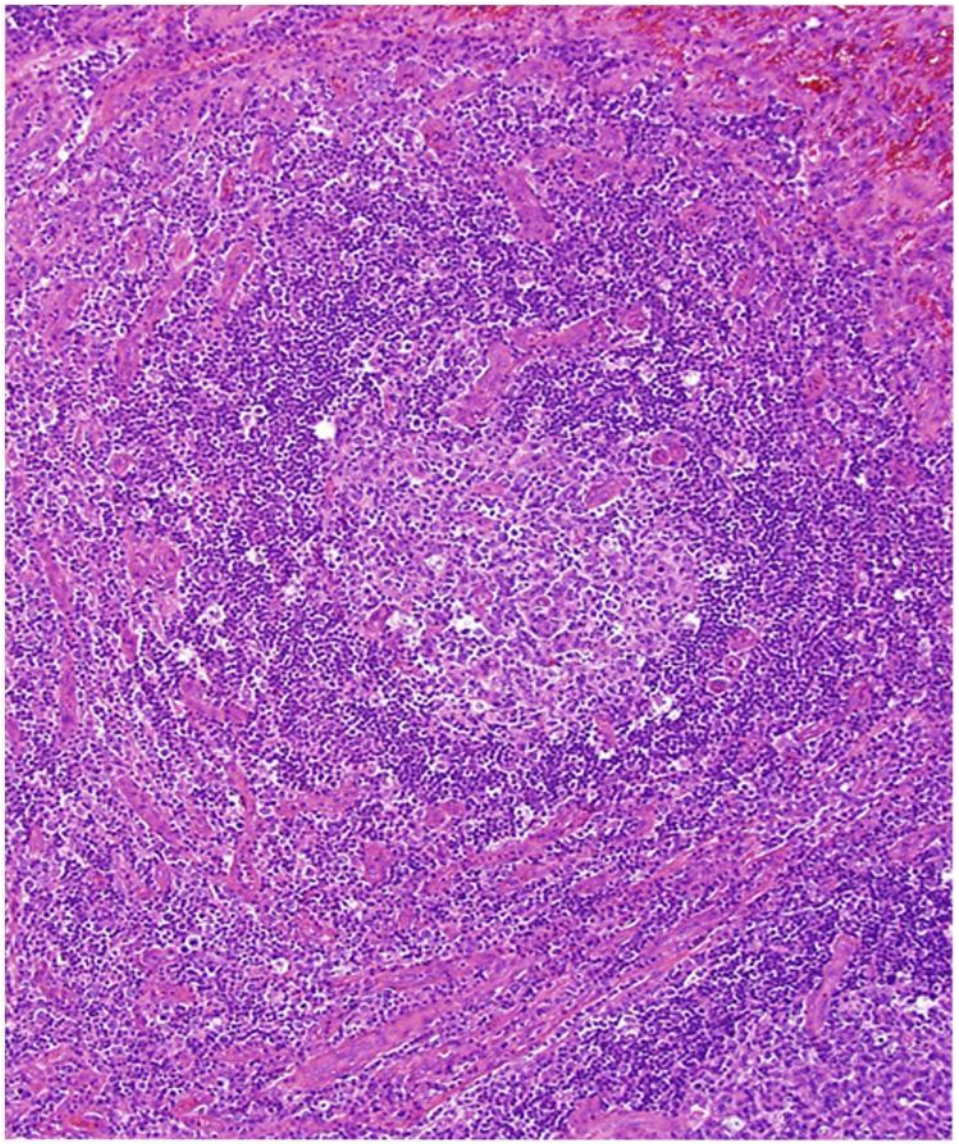
Case presentation

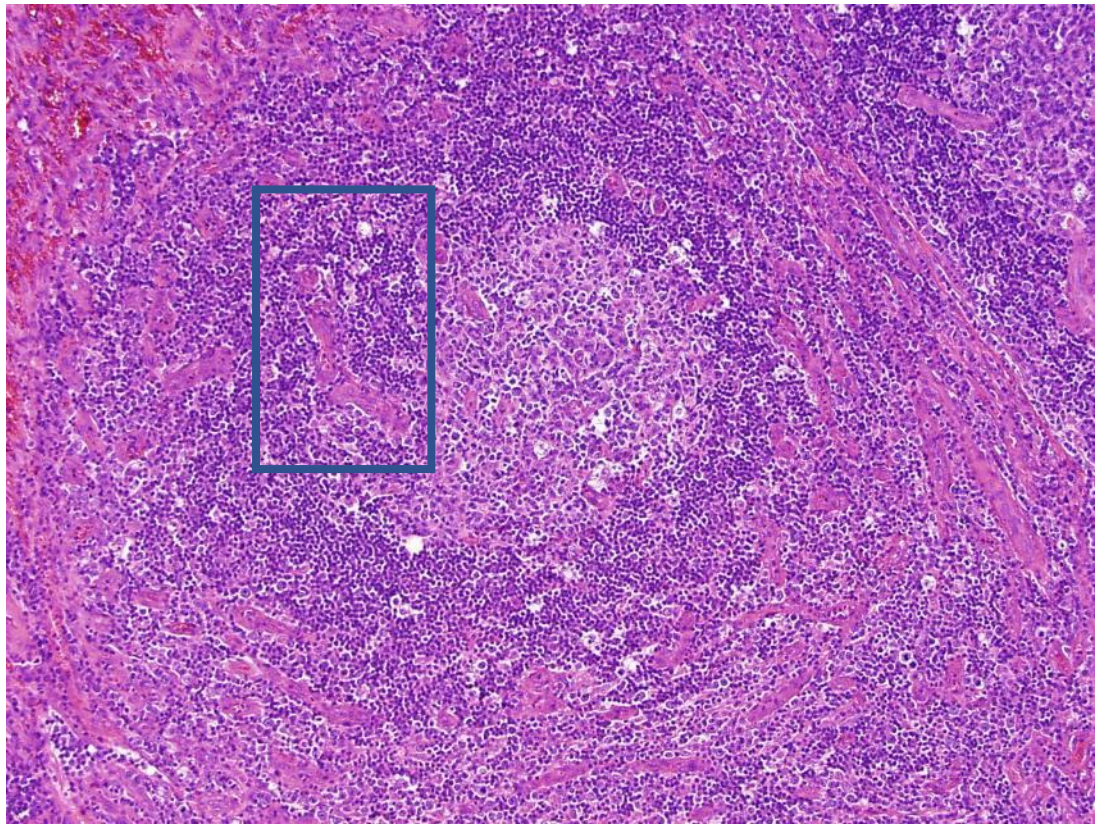
- Clinical history:
- 37 year old male
- Intravenous druge use
- Presented to the hospital because of skin lesions and generalized lymphadenopathy
- Inguinal lymph node excision

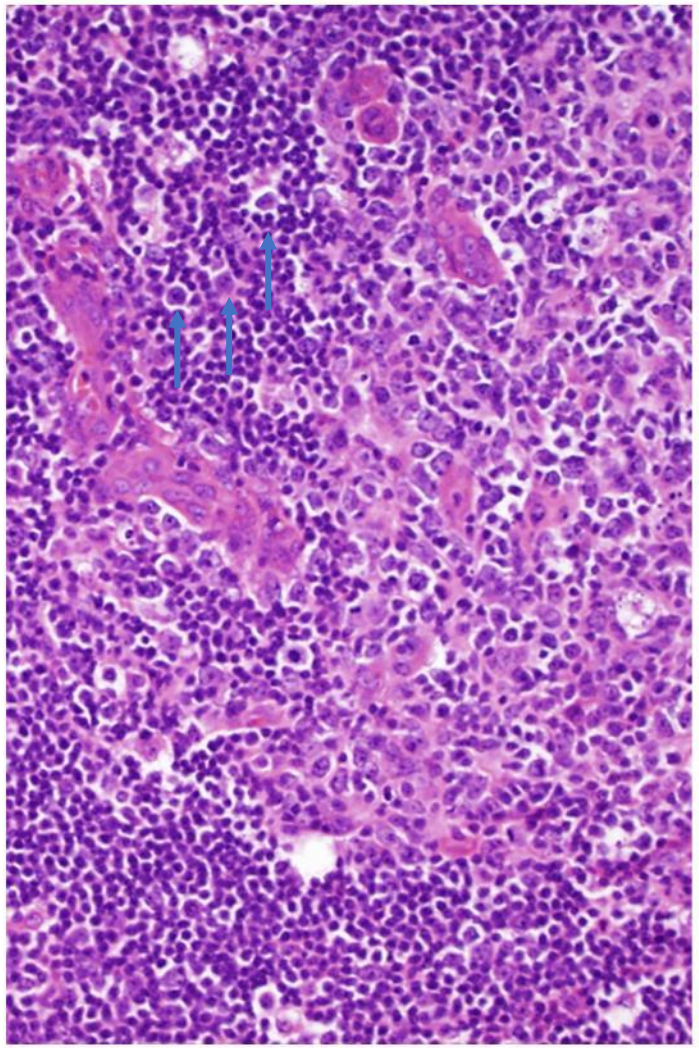
Morphology

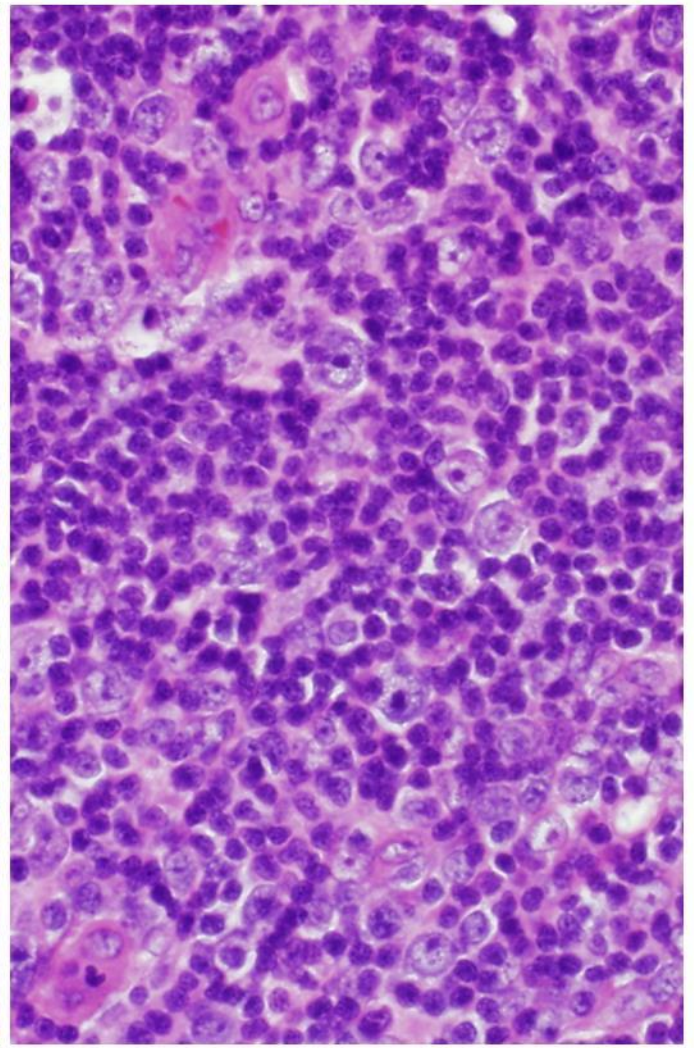


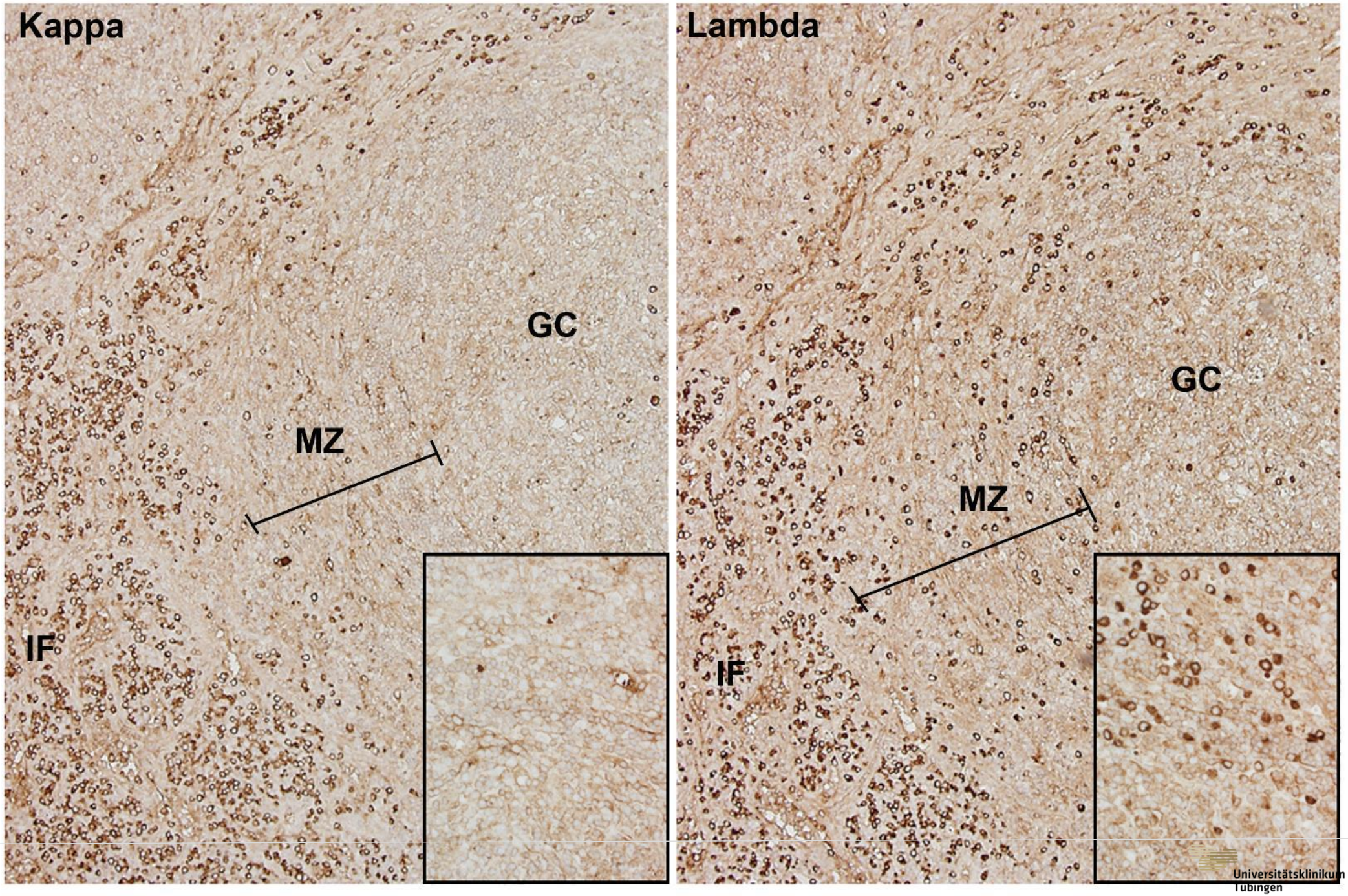


Morphology

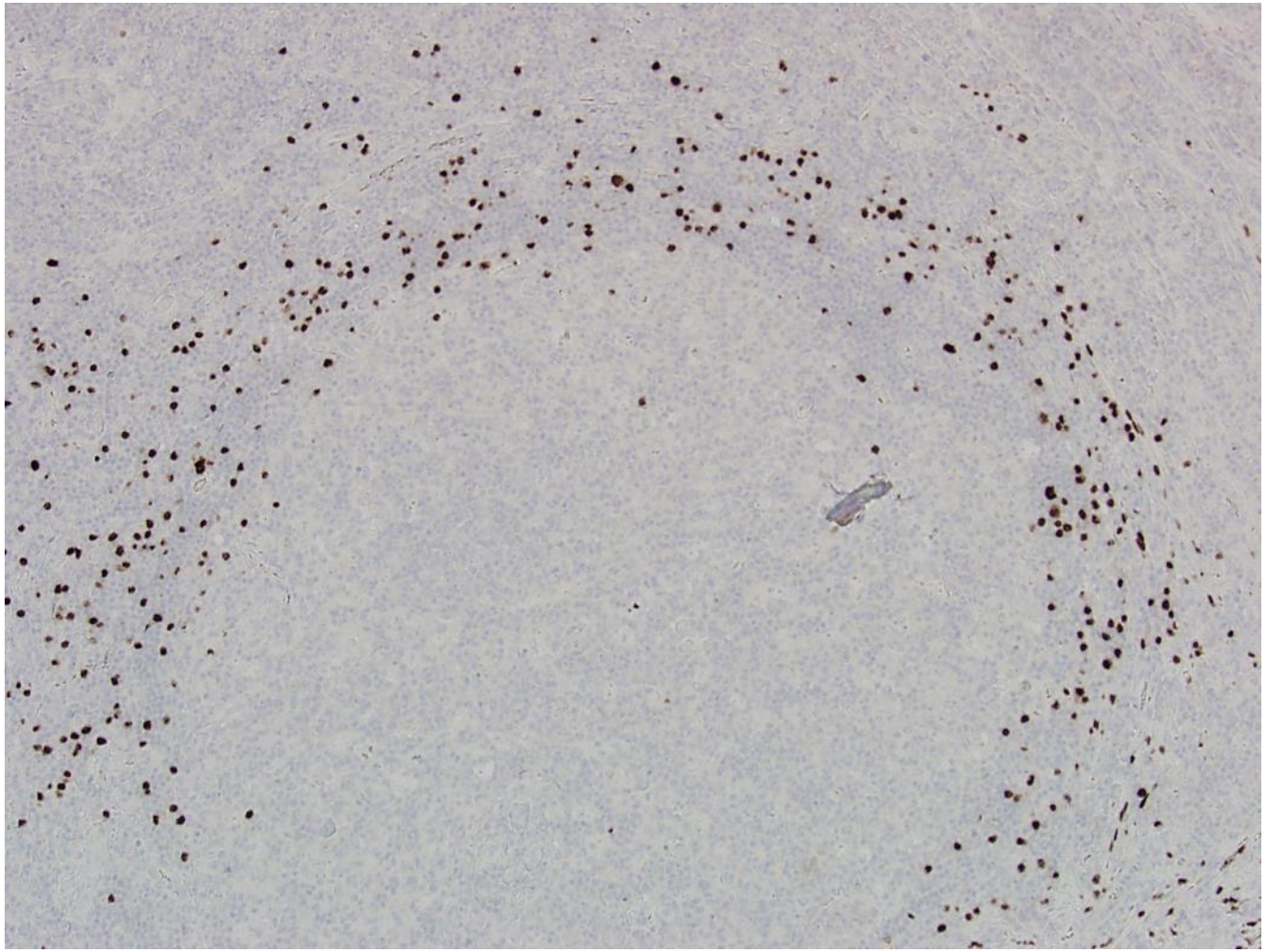


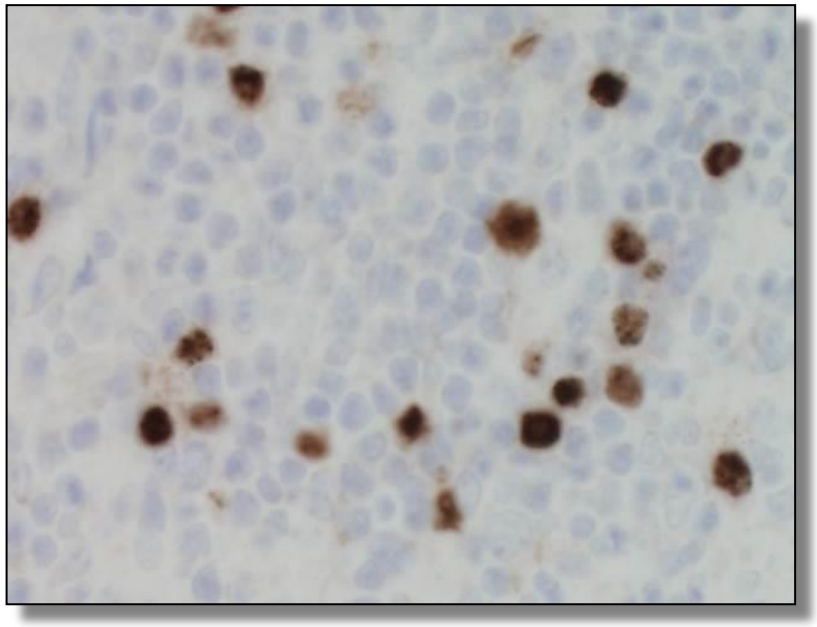




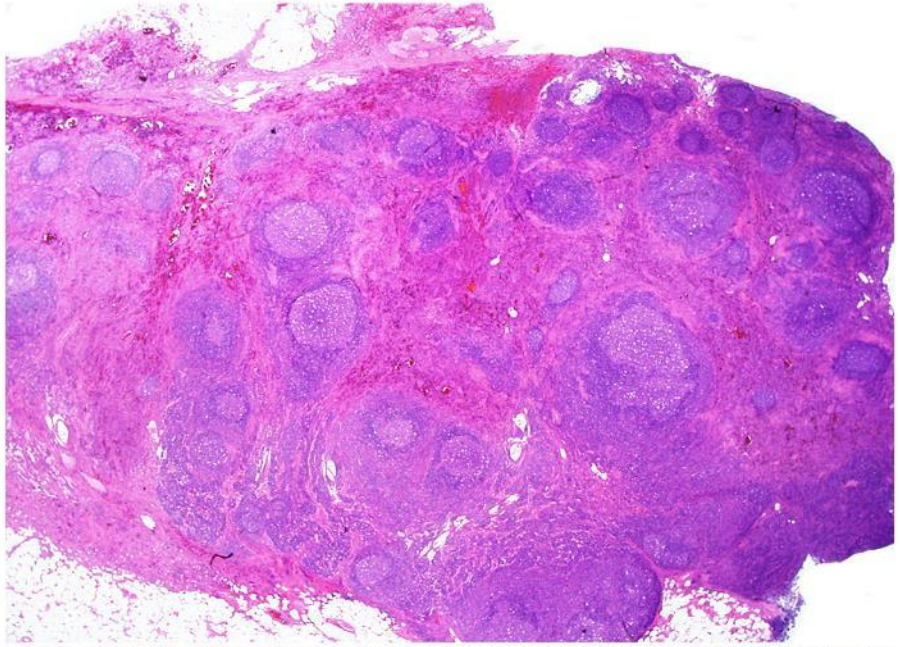

Kappa
GC
MZ
IF
Lambda
GC
MZ
IF

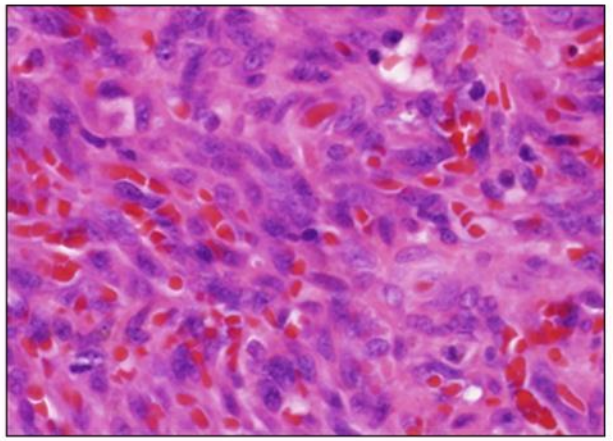
Immunohistochemistry



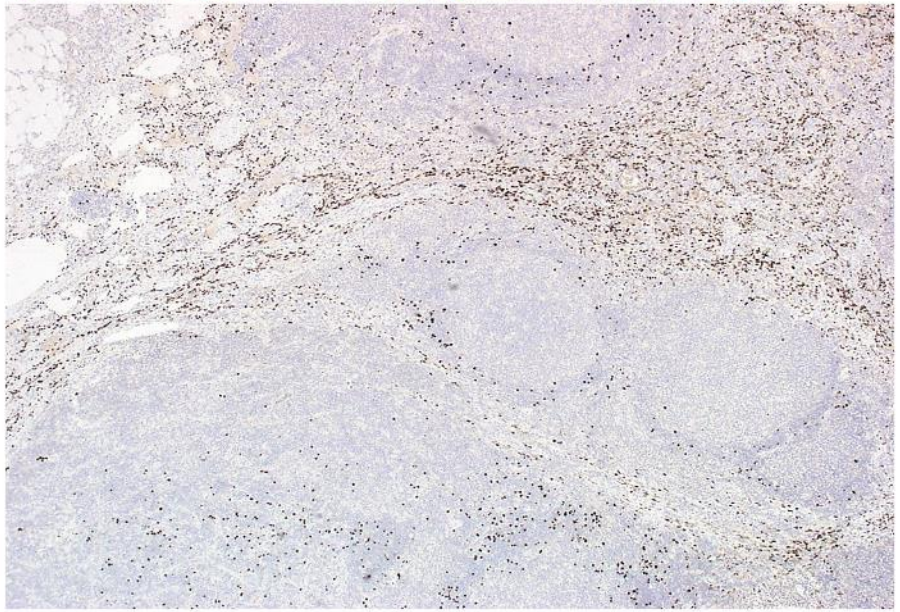


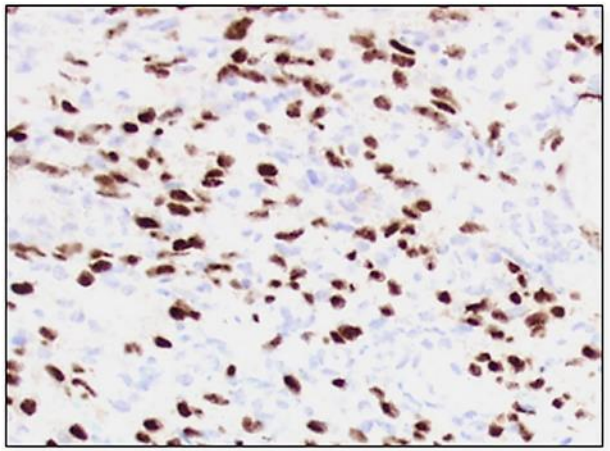
HHV8/LANA





Diagnosis:
Multicentric Castleman disease
HHV8 positive, HIV-associated
Kaposi Sarcoma



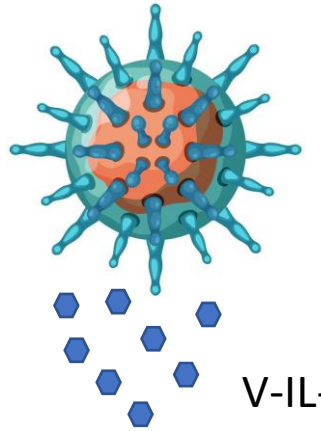


HHV8/LANA

Multicentric Castleman disease

- Definition:
- MCD is a systemic polyclonal lymphoproliferative disorder in which there is proliferation of morphologically bening lymphocytes, plasma cells and vessels due to excessive production of IL-6
- Morphologically:
- It is similar to the hyalinized form but with increased interfollicular plasma cells and in the mantle zone atypical „plasmablasts“ infected with HHV8, which are LANA positive (50-70% also have KS)
  - might express B-cell markers (CD20, CD79a)
  - MUM1+, BLIMP1+, OCT2+, CD38+
  - Monotypic IGM lambda (but PCR polyclonal)
  - CD138 negative, EBV negative
- Clinically:
- Patients present with fever, other systemic symtpoms lympadenopathy and cytopenias

Pathogenesis of MCD



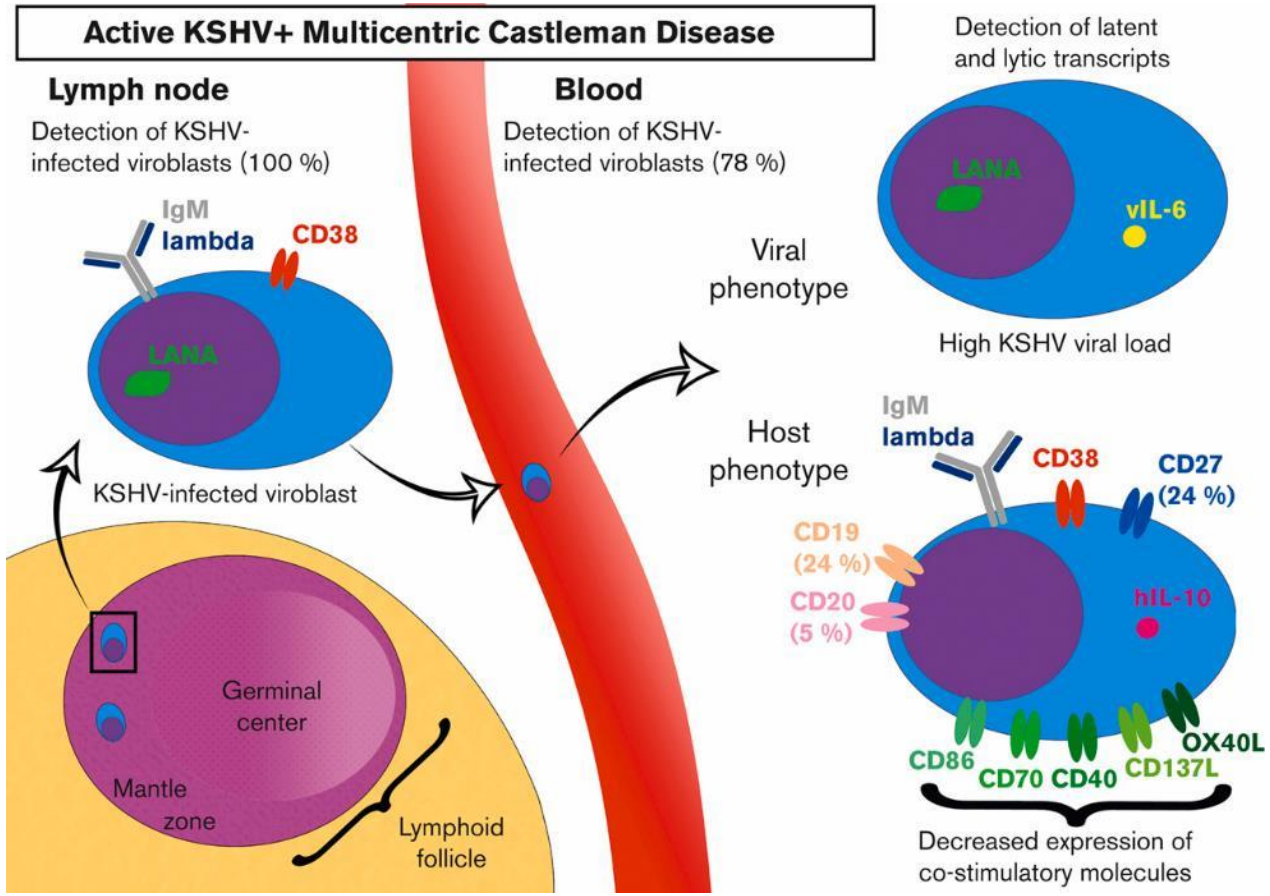
B-cell proliferations
MCD, PEL, etc

Multicentric Castleman disease

Table 3. Summary of the surface phenotype of KIV and conventional plasmablasts

	KIVs	Conventional plasmablasts
CD19	Heterogeneous (~25% positivity)	Uniformly low
CD20	Heterogeneous (~5% positivity)	Negative
CD38	100% high positivity	100% high positivity
IgM	100% high positivity	Heterogeneous (~20% positivity)
κ/λ	Monotypic λ (100% high positivity)	Balanced κ/λ ratio (60/40%)
CD27	Heterogeneous (~25% positivity)	100% high positivity
CD40	Low/negative	Heterogeneous
CD70	Heterogeneous (6% positivity)	Negative
CD86	Heterogeneous (10% positivity)	Mostly positive
CD137L	Negative	Negative
OX40-L	Negative	Negative
ICOS-L	Negative	Negative
BAFF-R	Negative	Negative
PD-L1	Negative	Negative

Cell of origin: Naive B-cell



Chadburn A et al, Arch Pathol Lab Med 2013

Cesarman E et al, Blood 2022

MARTIN de FRÉMONT et al 9 MAY 2023 • VOLUME 7, NUMBER 9

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Helping hematologists conquer blood diseases worldwide

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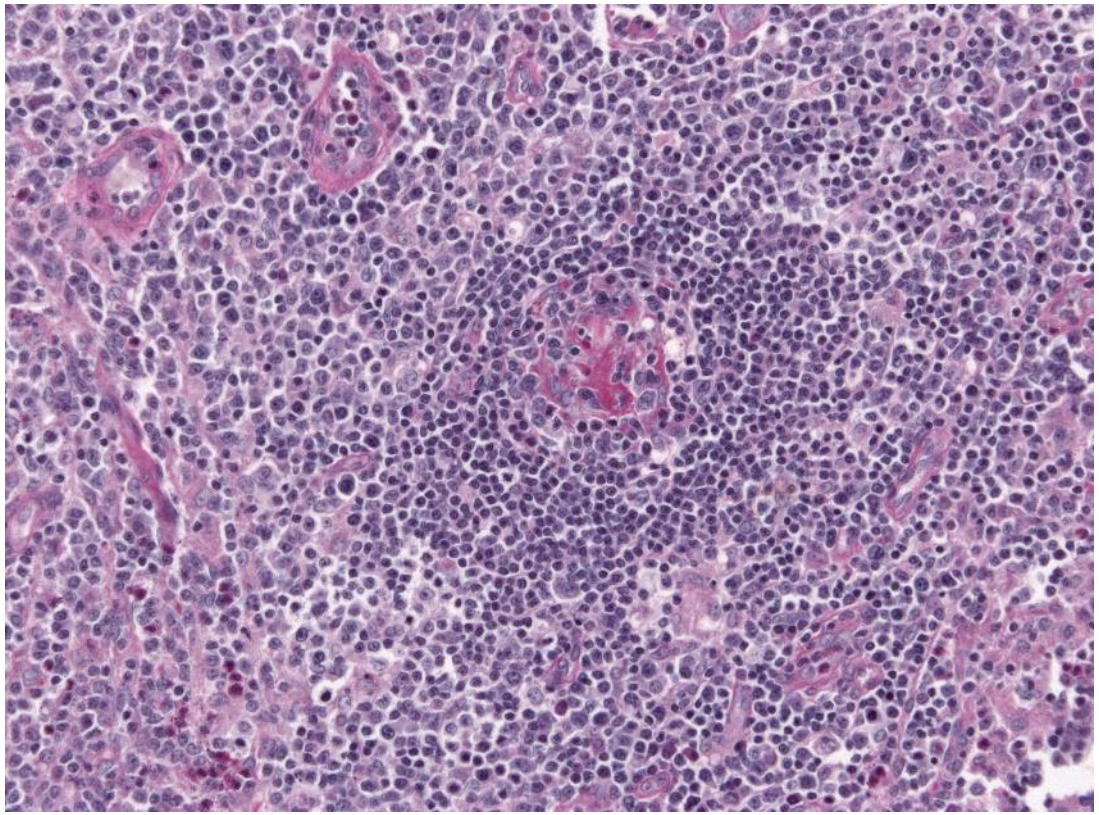
Multicentric Castleman disease

- Differential diagnosis:
- Non-specific lymphadenitis with polytypic plasmacytosis
- Autoimmune lymphadenitis
- Reactive follicular and paracortical hyperplasia
- TFH lymphoma, angioimmunoblastic type
- Castleman´s disease, hyaline vascular variant
- Castleman´s disease, plasma cell variant, idiopathic

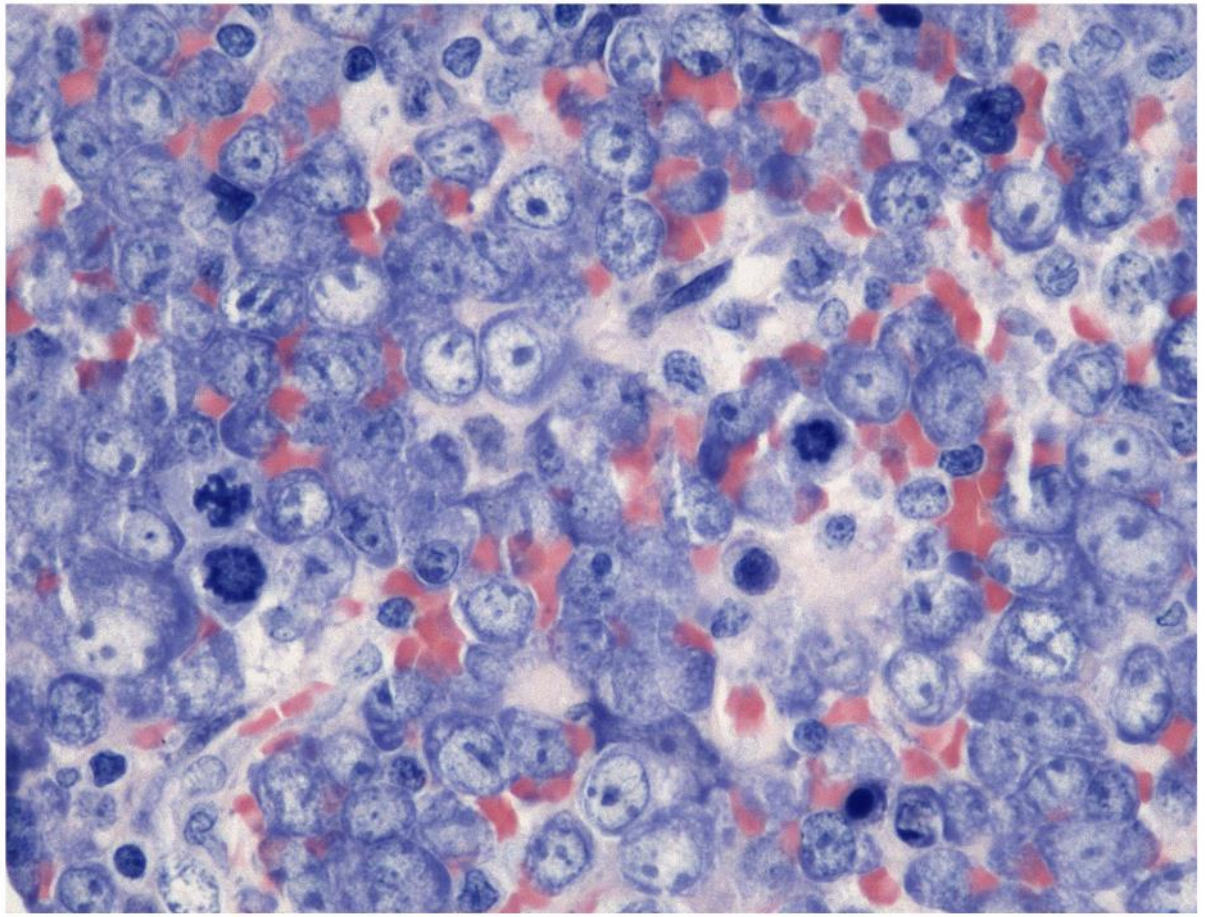
Angioimmunoblastic T-cell lymphoma



HHV8-positive diffuse large B-cell lymphoma, NOS

- Definition:

- HHV8-associated DLBCL usually arises in association with MCD; however, cases without MCD do exist.
- The lymphoma is characterized by a monoclonal proliferation of HHV8 infected cells resembling plasmablasts and expressing IGM-lambda
- It is usually associated with HIV infection.
- The cell of origin is a naive IGM producing B-cell without IG somatic hypermutations
- EBV is negative
- Extremely aggressive lymphoma



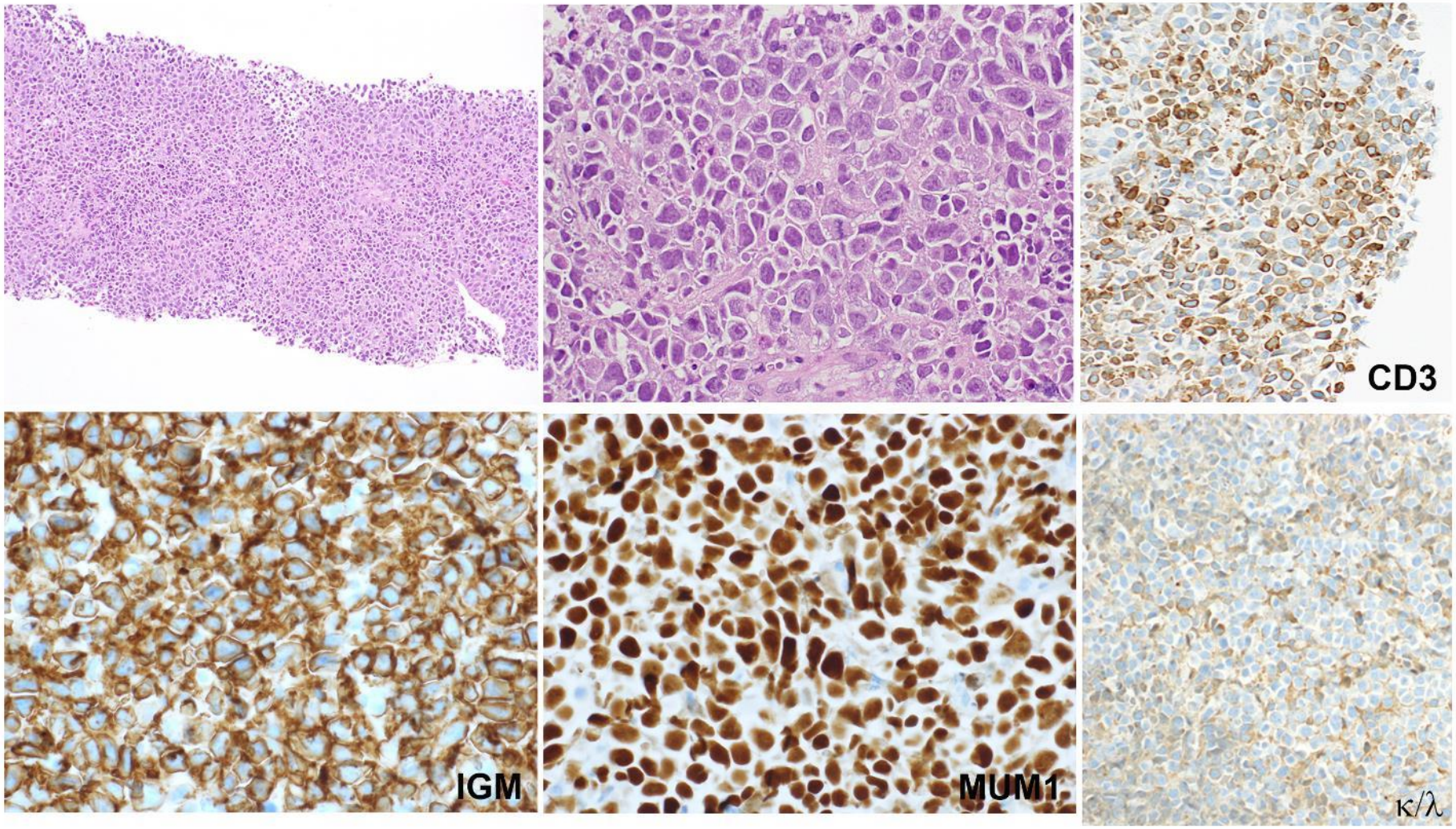
HHV8-positive diffuse large B-cell lymphoma, NOS

Immunophenotype:

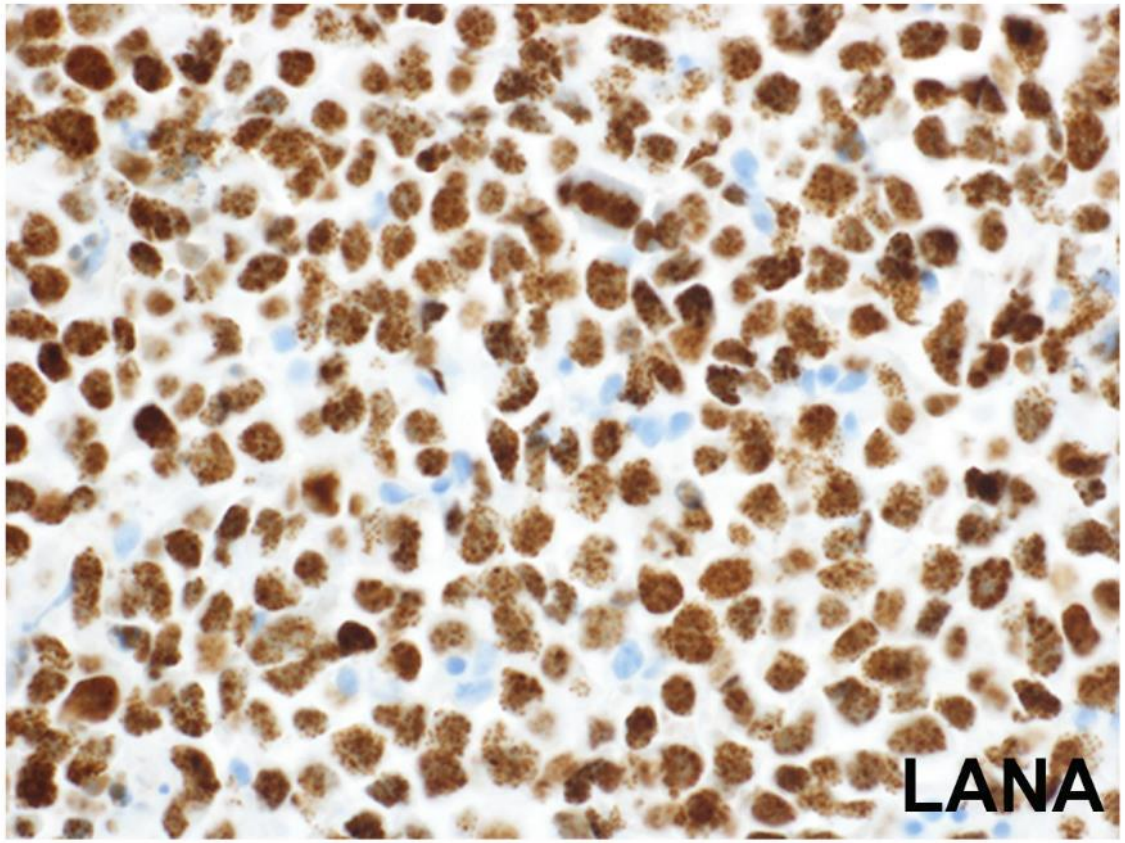
- CD20+/-, CD79a-
- CD138-, CD38-/+
- CD27-
- MUM1+
- LANA+
- EBER-

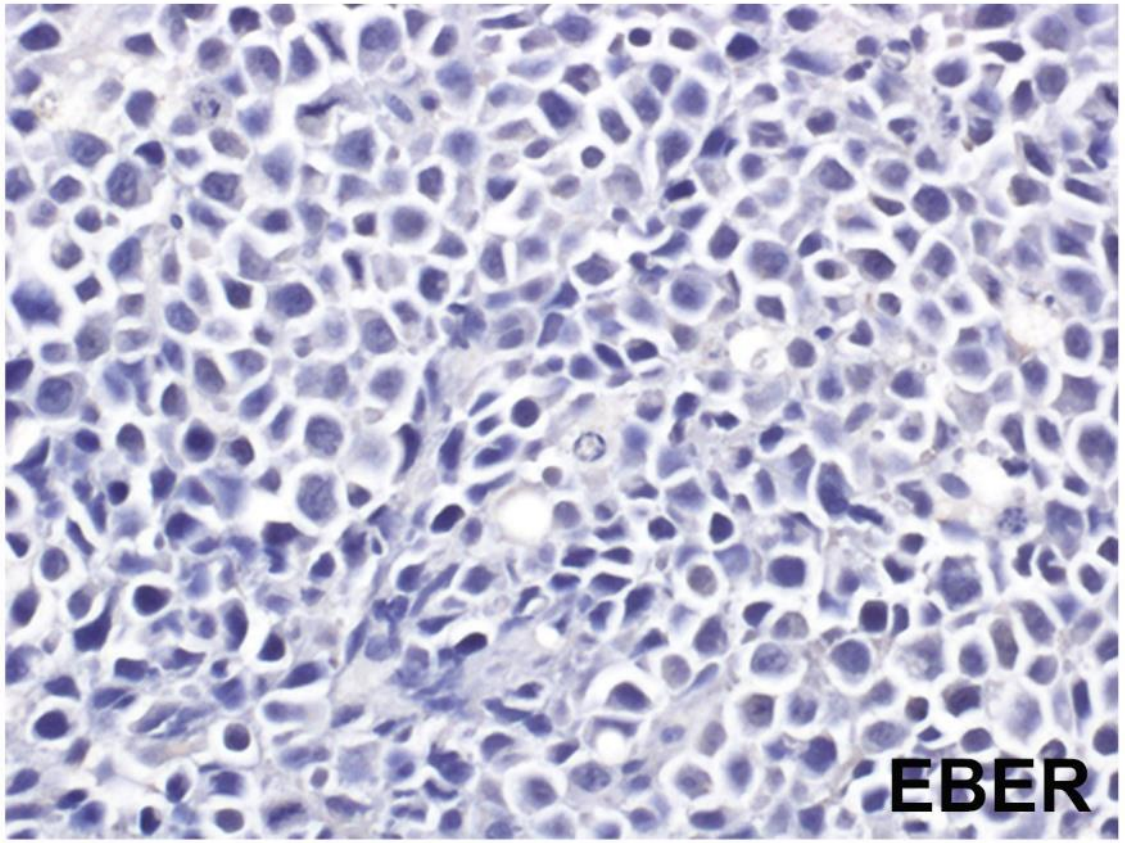
Molecular:

- IG monoclonal and unmutated



HHV8-positive diffuse large B-cell lymphoma, NOS





Revised 4th Edition WHO Classification

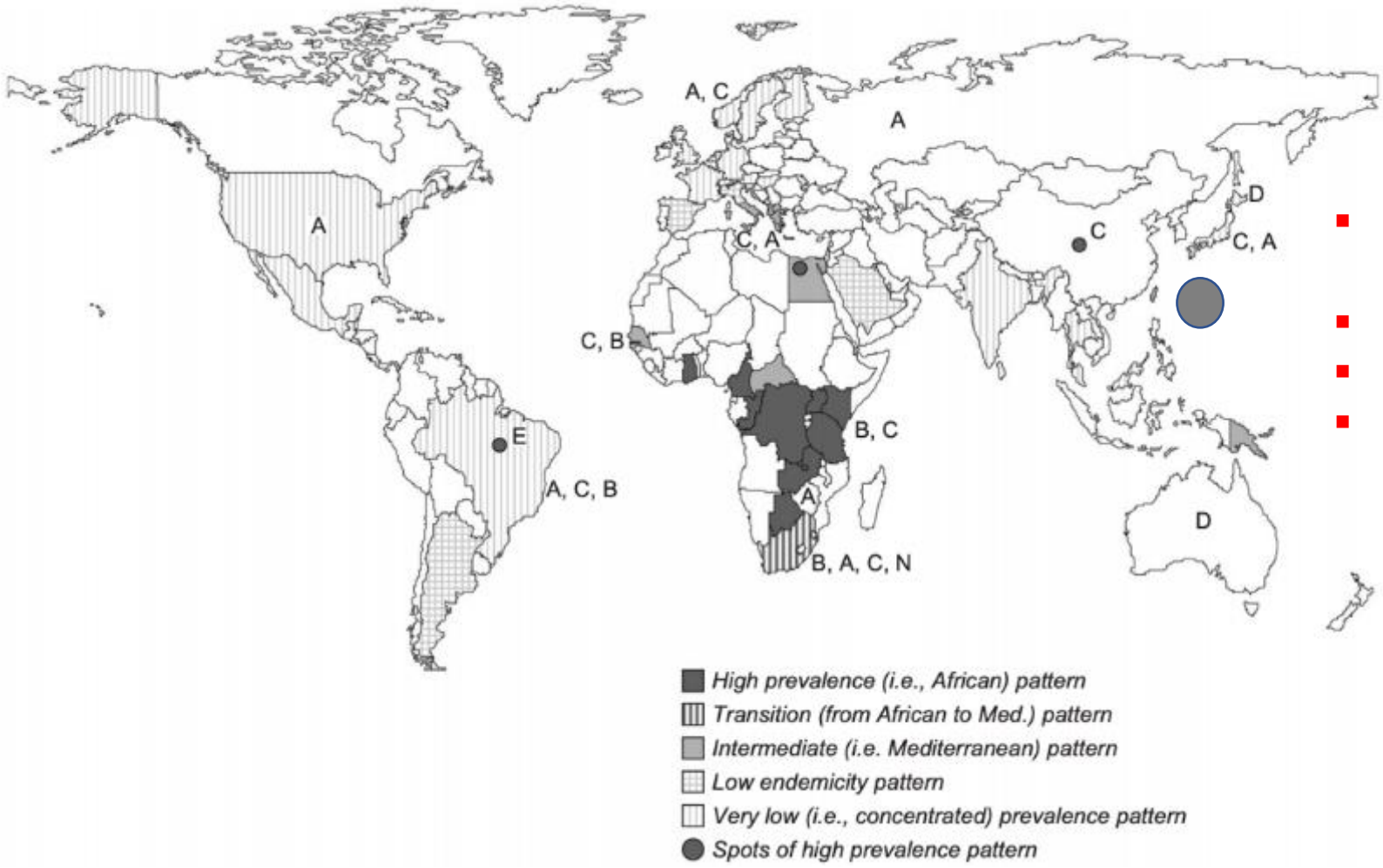
Campo E, Blood 2022

Feature	HHV8-positive MCD	HHV8-positive DLBCL, NOS
Clinical presentation	Generalized lymphadenopathy General symptoms, splenomegaly	Large lymph node, splenic mass Extranodal sites, peripheral blood
Morphology	Castleman disease morphology with „plasmablasts“ in the mantle zone Interfolicular plasma cell hyperplasia	Sheets of large „plasmablastic cells“
Immunophenotype	B-cell antigens +/- IGM lambda+ MUM1+ CD138 -	B-cell antigens +/- IGM lambda+ MUM1+ CD138 -
Clonality	IG polyclonal	IG monoclonal
HHV8	positive	positive
EBER	negative	negative
HIV status	+/-	+/-
Prognosis	Poor but has improved with new therapies	Poor

Campo E, Blood 2022

Revised 4th Edition WHO Classification

Prevalence of HHV-8 in the world



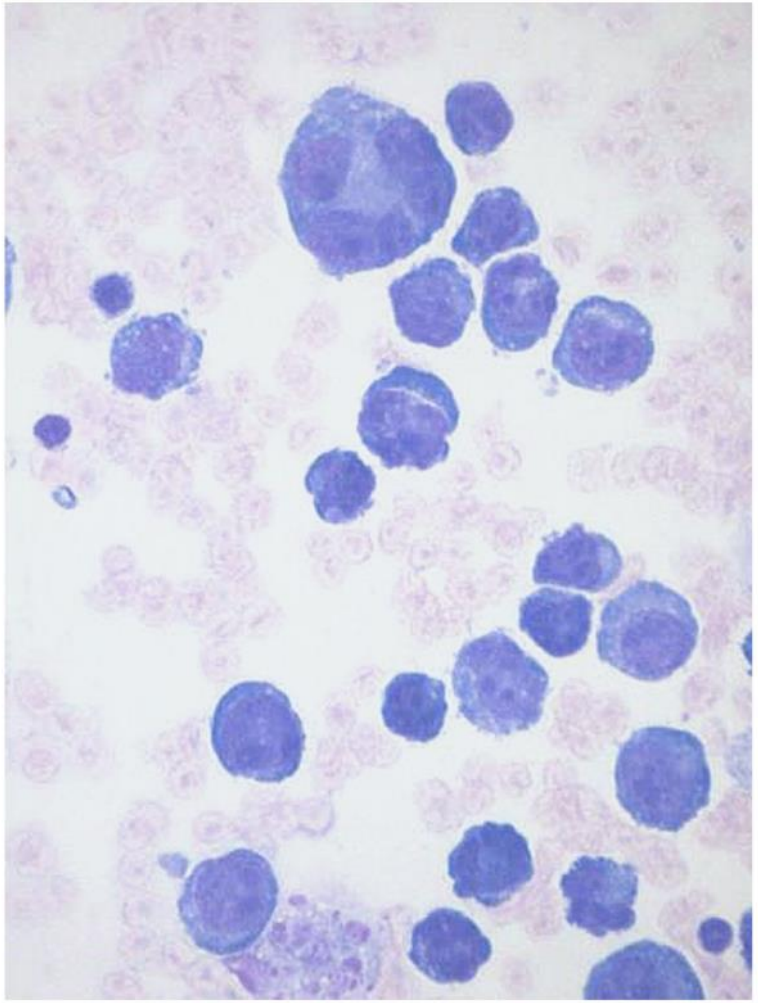
- 80% of people in Sub-Saharan Africa are HHV8 serological positive
- Mediterranean region (intermediate)
- 20% Shinjang Uyghur in China
- 20% Okinawa in Japan
  - Increase risk of developing KS (>50 years)
  - Environmental factors: high altitude

Whitby *JNCI* 1998, Dukers *AIDS* 2003, Awazawa *J Infect Dis* 2017

Primary effusion lymphoma

- Definition:
- Large B-cell lymphoma usually presenting as serous effusions without detectable tumor masses
- Universally associated with HHV8
- Usually coinfected with EBV
- Occurs in the setting of immunodeficiency, usually HIV
- Some patients might develop solid tumors in adjacent structures such as the pleura

➢Cases indistinguishable from PEL might present as solid tumor masses known as „extracavitary“ PEL

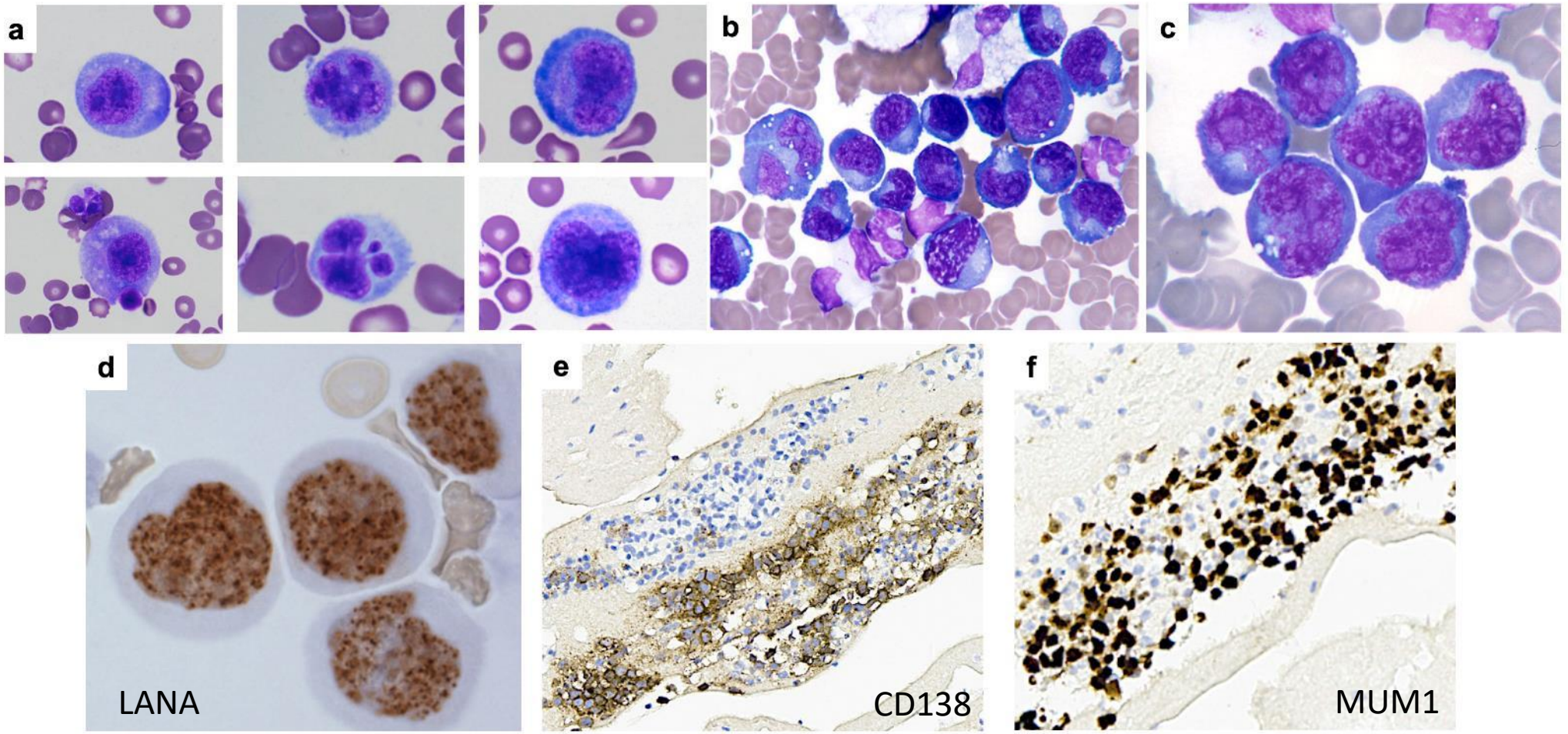


Cesarman E et al, Blood 2022 *Chadburn A, et al, AJCP 2017* *Campo E, Blood 2022* *Revised 4th Edition WHO Classification*

Primary effusion lymphoma

LYWS-1050 A. Shestakov

LYWS-1194 P Barone



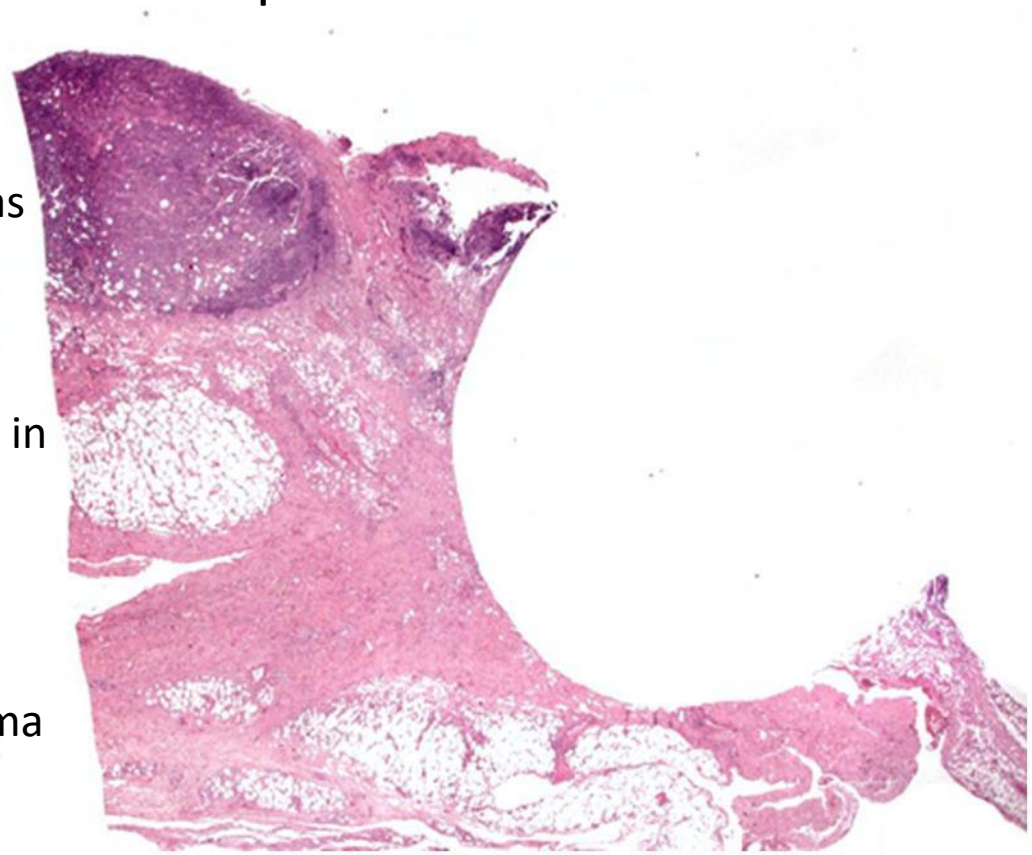
Di Napoli A, Soma L, et al, submitted to Virchows Archiv

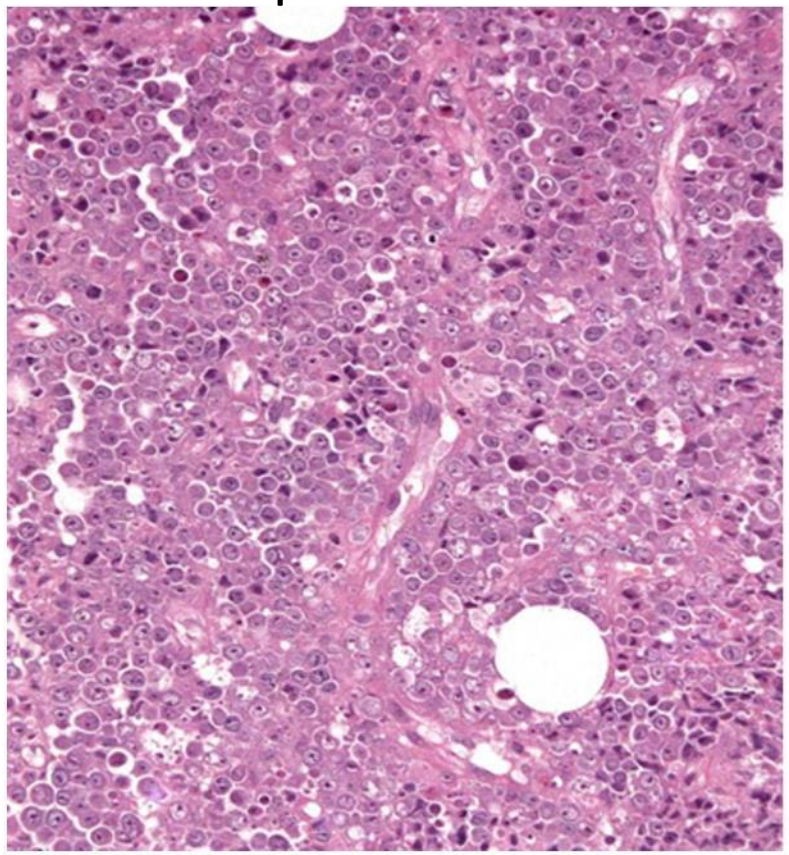
Primary effusion lymphoma

Clinical presentation:

- Median age at presentation in HIV patients is 42 years
- 2-4% of HIV+ lymphomas
- Occurs in HIV-negative elderly individuals from endemic areas (median 73 years) and solid organ transplant reciepients
  - Usually EBV-negative
- Patients present with effusion in the absence of lymphadenopathy or organomegaly
- CD4 counts are very low
- 30-75% develop Kaposi sarcoma
- 33% MCD

42 year old man with HIV infection that presented with pleural effusion and a tumor mass in the pleura





Cesarman E et al, Blood 2022

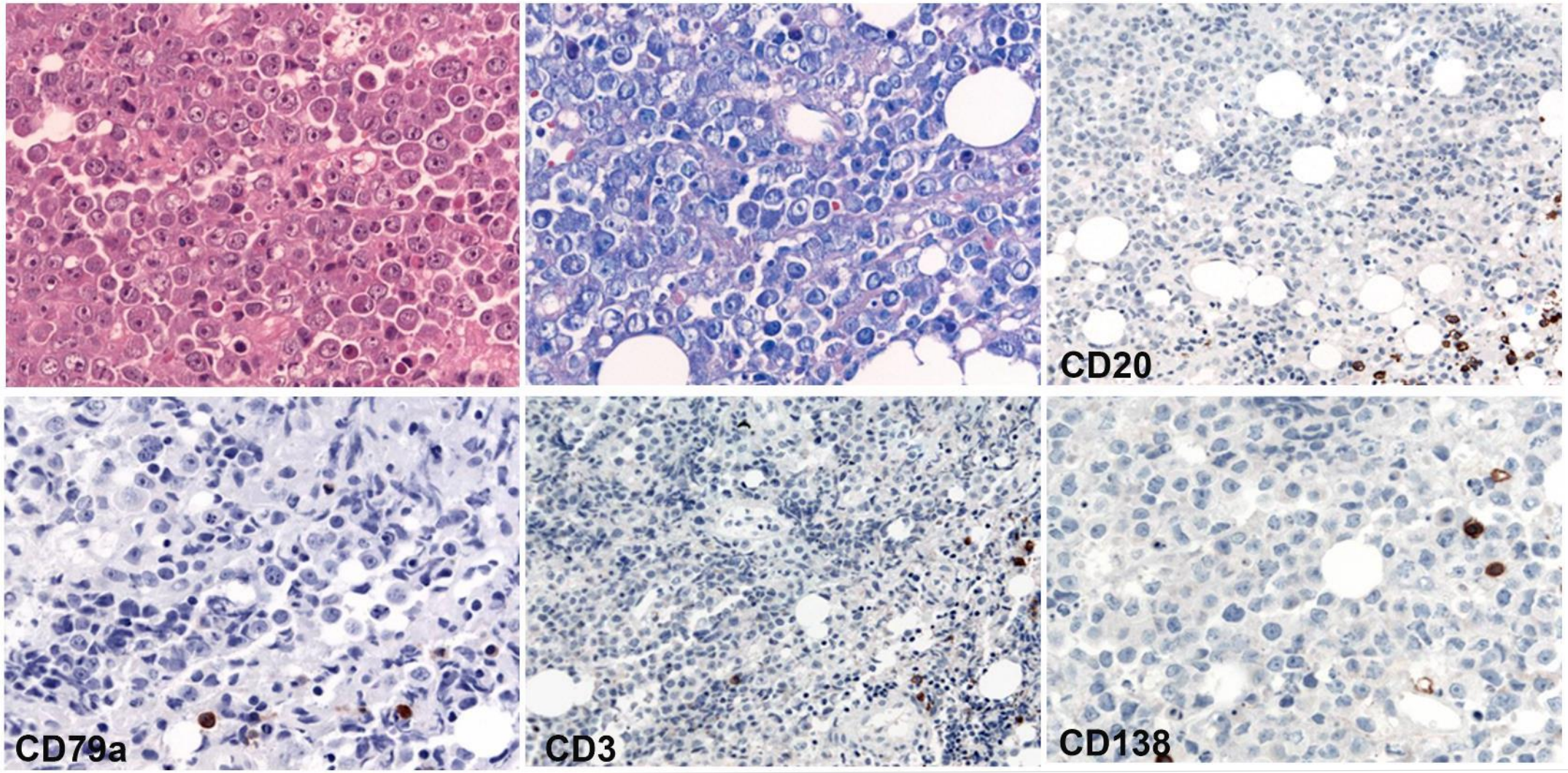
Chadburn A, et al, AJCP 2017

Campo E, Blood 2022

Revised 4th Edition WHO Classification

Primary effusion lymphoma

- ✓ Immunoblastic
- ✓ Plasmablastic
- ✓ anaplastic

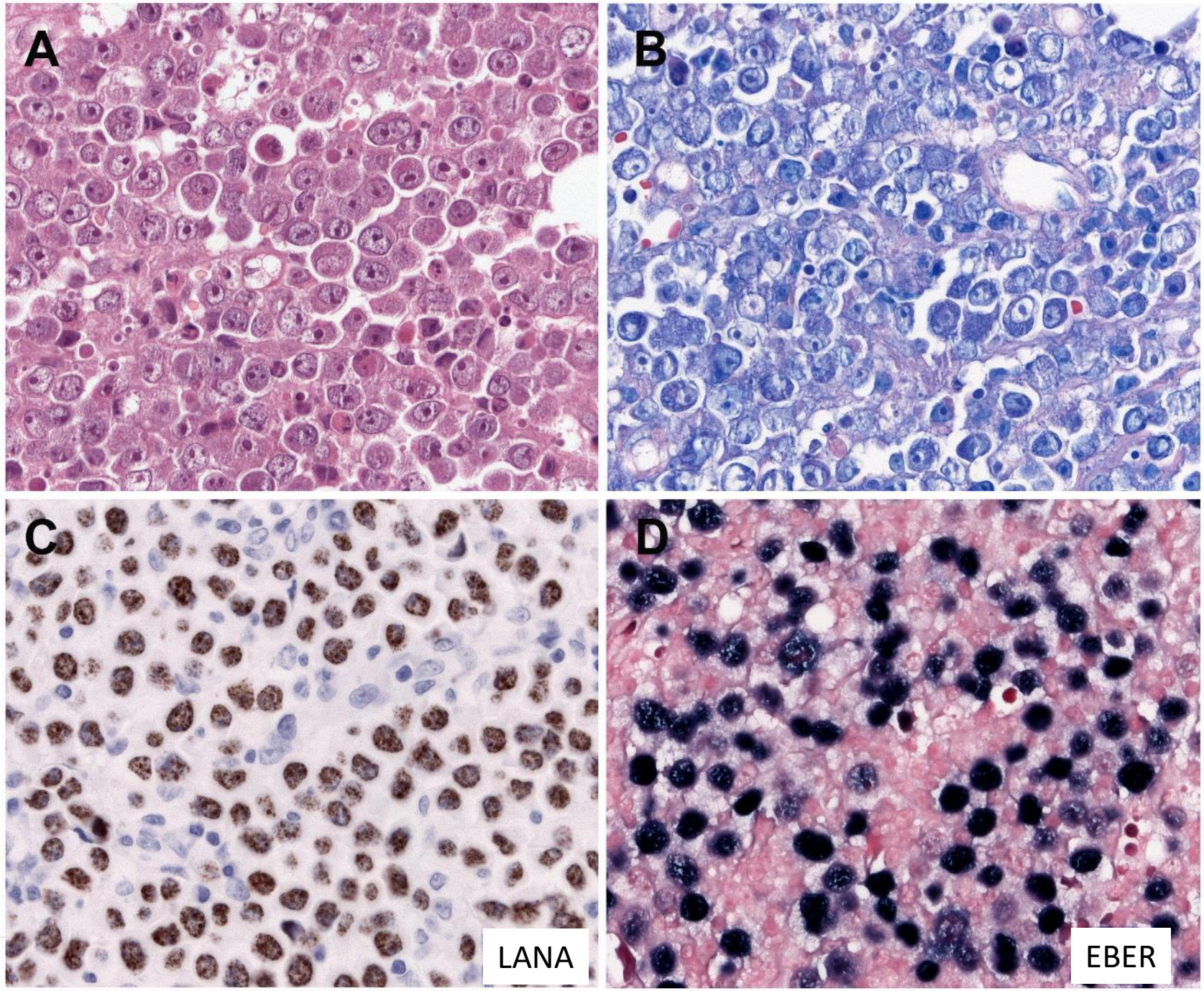


PEL

Immunophenotype:

- Lack pan-B-cell markers such as CD19, CD20 or CD79a
- Surface and cytoplasmic IG is absent
- Positive for CD30, CD38, CD138, EMA, HLA-DR, MUM1, BLIMP1
- Aberrant expression of T-cell antigens migh occur, more often in EC PEL
- LANA positive
- EBER positve (Latency 1)
- Post-germinal center B-cell with plasmablastic differentiation

➢ EBV negative PEL occur in elderly HIV negative individuals from HHV8 endemic areas like the Mediterranean

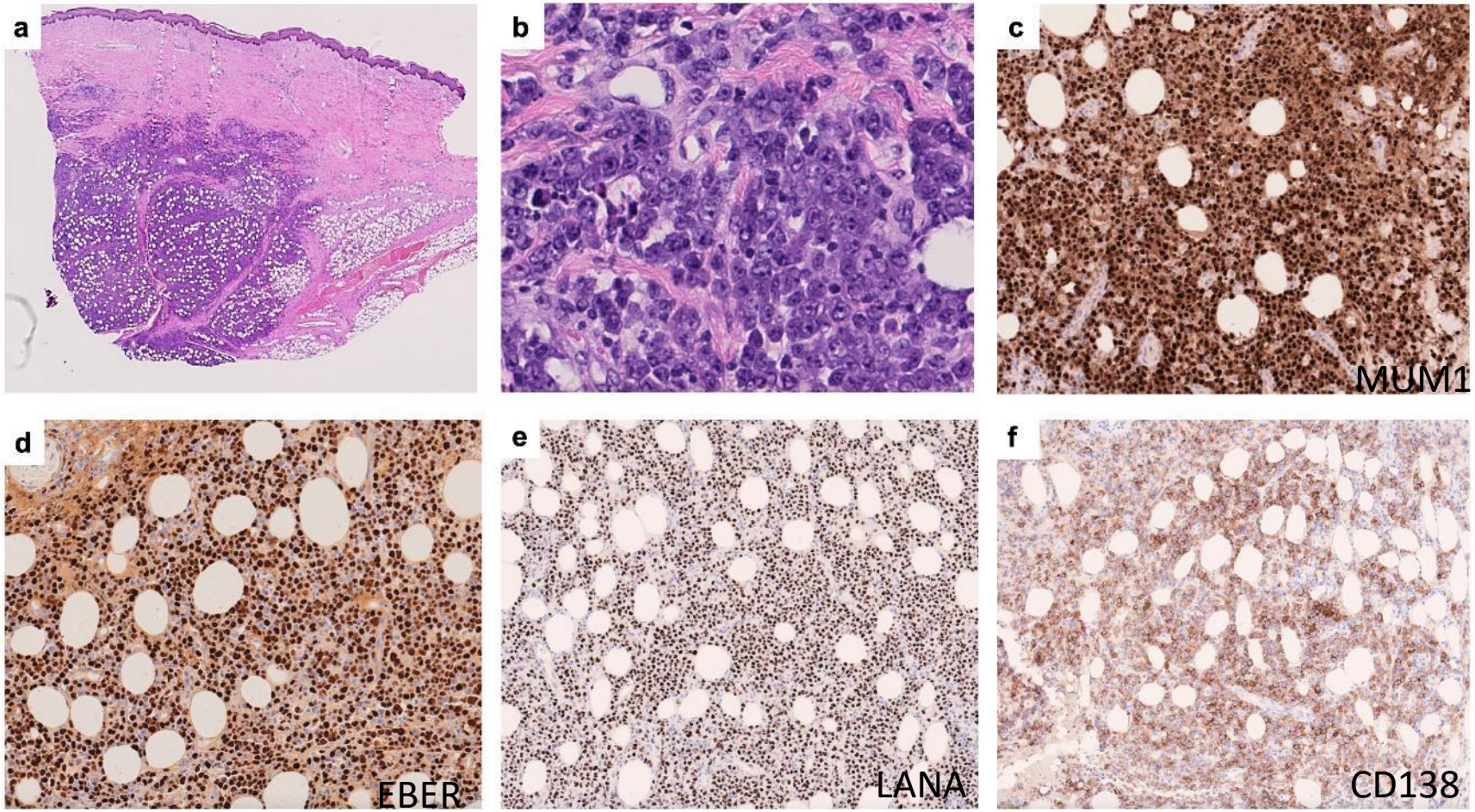


Extracavitary Primary effusion lymphoma

- EC PEL occurs in lymph nodes, gastrointestinal tract and and skin
- There are otherwise indistinguishable from PEL

54 year-old-male, HIV positive

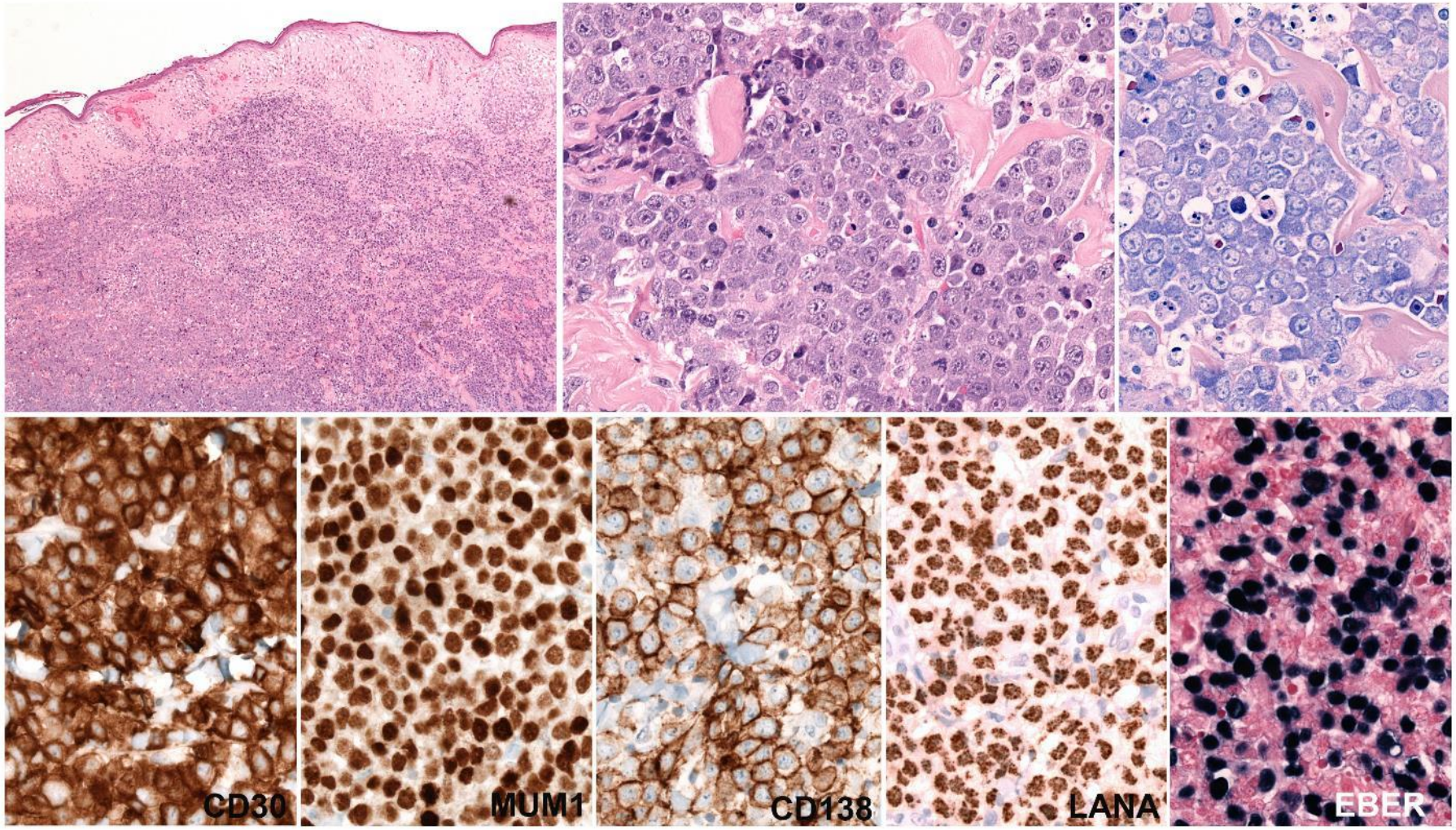
LYWS-1192 A Dashora



Di Napoli A, Soma L, et al, submitted to Virchows Archiv

Extracavitary Primary effusion lymphoma

A 37 year-old man, HIV+
2017 HHV8+ MCD
2018 PEL
2019 skin lesion in the right axila



Comparison of PEL and EC PEL submitted to the 21 EA4HP workshop

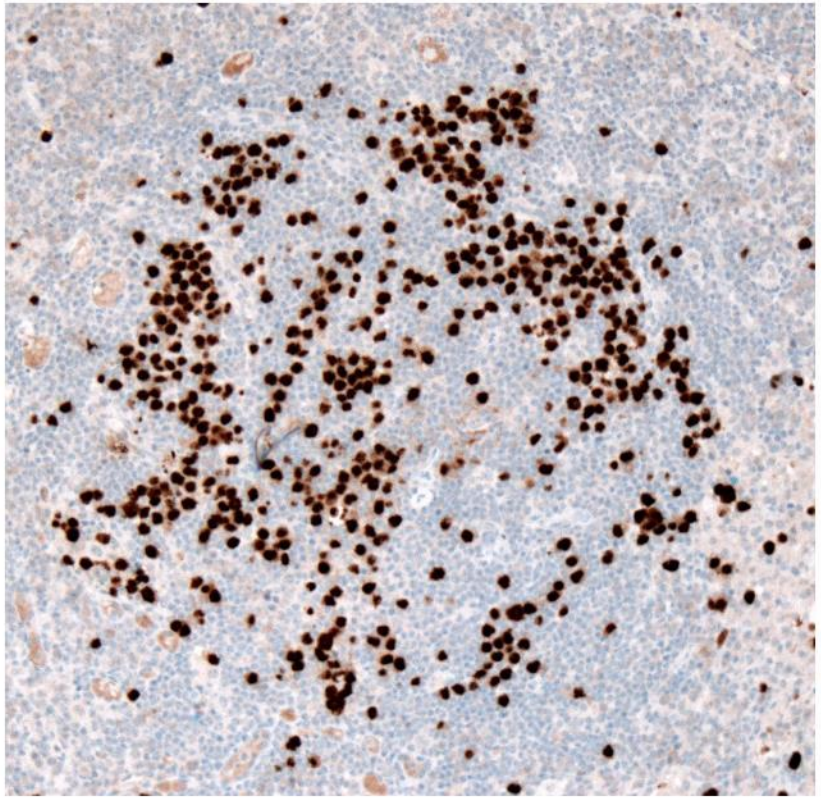
	Primary effusion lymphoma EBV+ (5 cases)	Primary effusion lymphoma EBV- (8 cases)	Extracavitary primary effusion lymphoma (5 cases)
Sex	100% male	100% male	100% male
Median age	HIV+ 35 years HIV – 89 years	HIV+ 43.5 years HIV- 79 years	HIV+ 54 years
HIV +	4/5 (80%)	2/8 (25%)	4/4 100%
Extracavitary disease	2/5 (40%)	2/8 (25%)	100%
Posttransplant	0/4 (0%)	3/8 (38%)	0/5 (0%)
CD138 +	1/4 (25%)	7/7 (100%)	3/5 (60%)
CD20+	none	none	none
IGM+	1 case	NA	2/3 (67%)
Light chains*	1 kappa, 1 lambda	All negative	2 kappa
MYC alterations	none	none	none

* Surface and cytoplasma IG negative, according to definition; however, recent studies show light chain expression (Chadburn et al and Hu et al)

Di Napoli A, Soma L, et al, submitted to Virchows Archiv

HHV8+ germinotropic lymphoproliferative disorder

- Definition:
- GLPD is a monotypic HHV-8 positive LPD that usually occurs in HIV-negative individuals
- HHV8+ plasmablasts partially or completely replace germinal centers,
- kappa or lambda are restricted
- Polyclonal or oligoclonal
- EBV is positive
- Clinically:
- Affects mainly men between 50-60 years
- Nodal disease, asymptomatic
- Lymphadenopathy is slow growing (3-10 years before diagnosis)

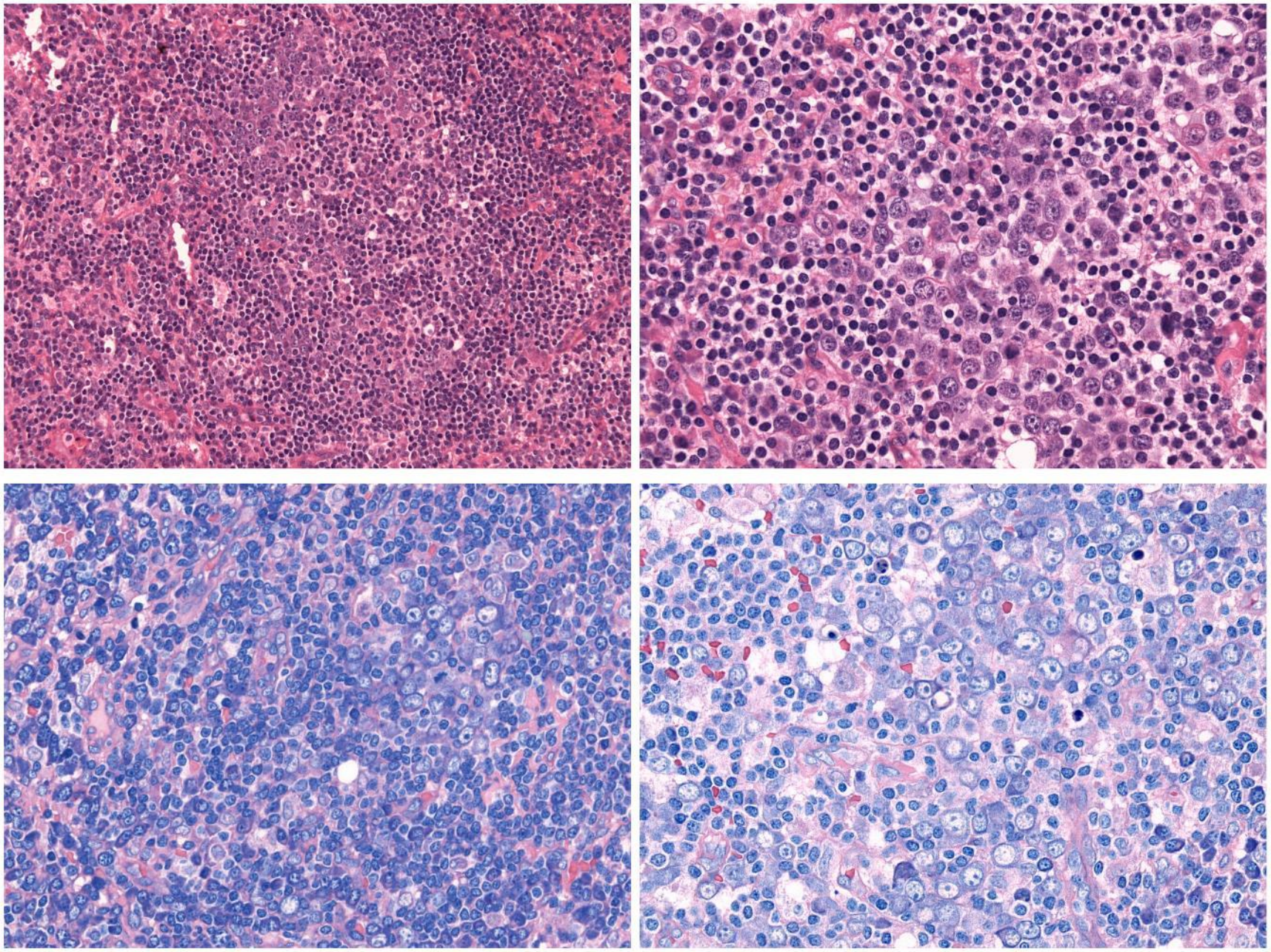


HHV8/LANA

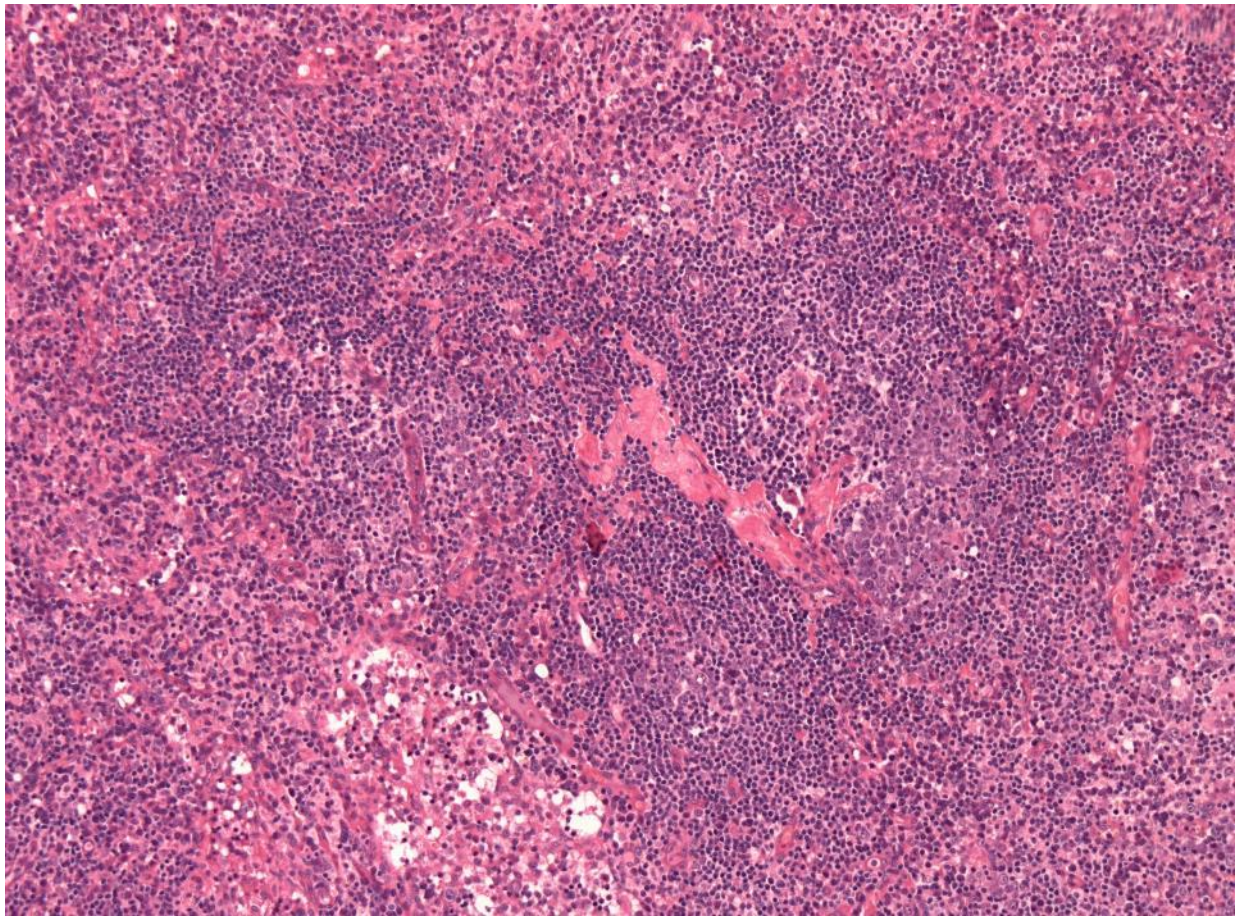
Zanelli M, et al. Ann Hematol 2020; 99:2243

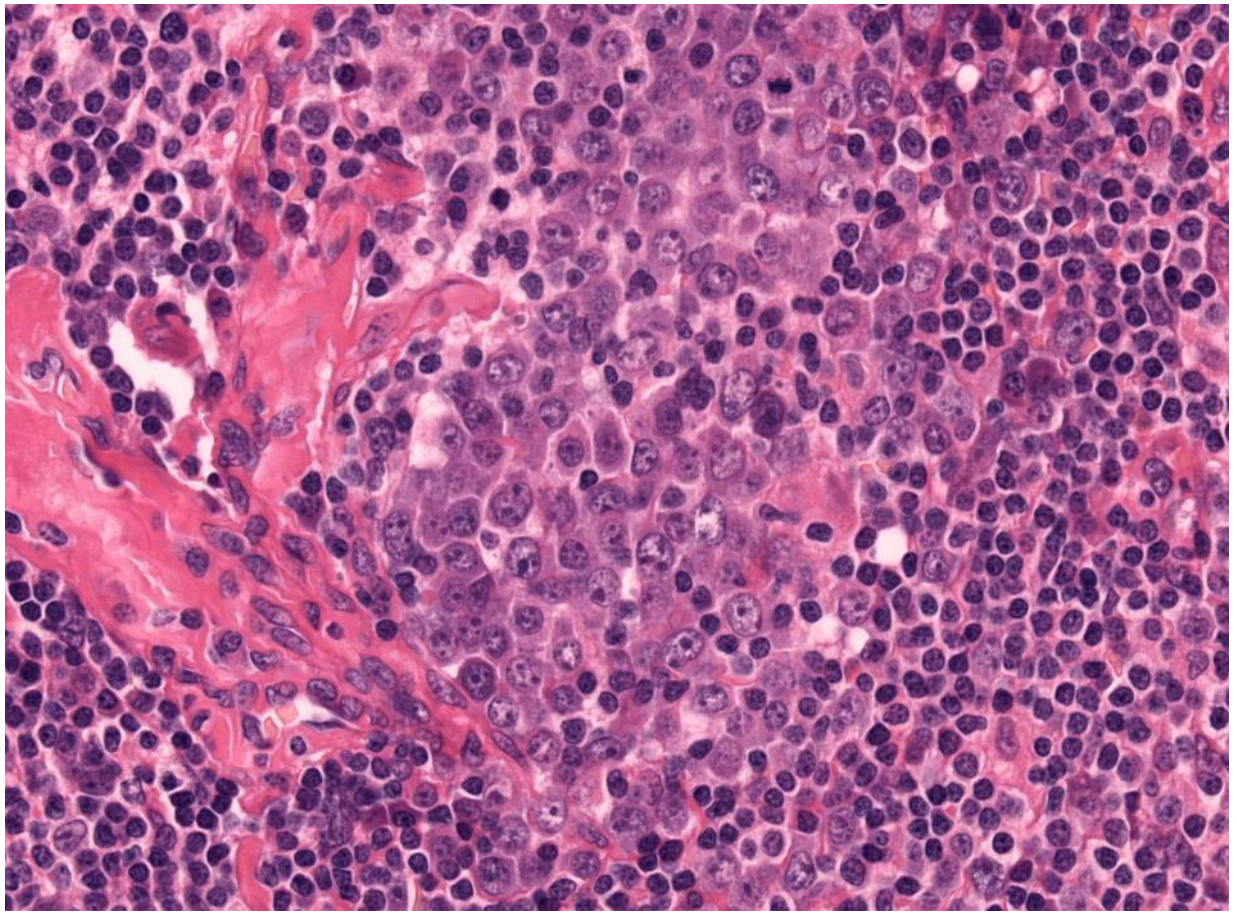
GLPD

- Morphology:
- Retention of nodal architecture
- Lymphoid proliferation characterized by large cells resembling plasmablasts that involve and replace GC
- Atrophic follicles resembling those of Castleman disease



HHV8+ germinotropic lymphoproliferative disorder

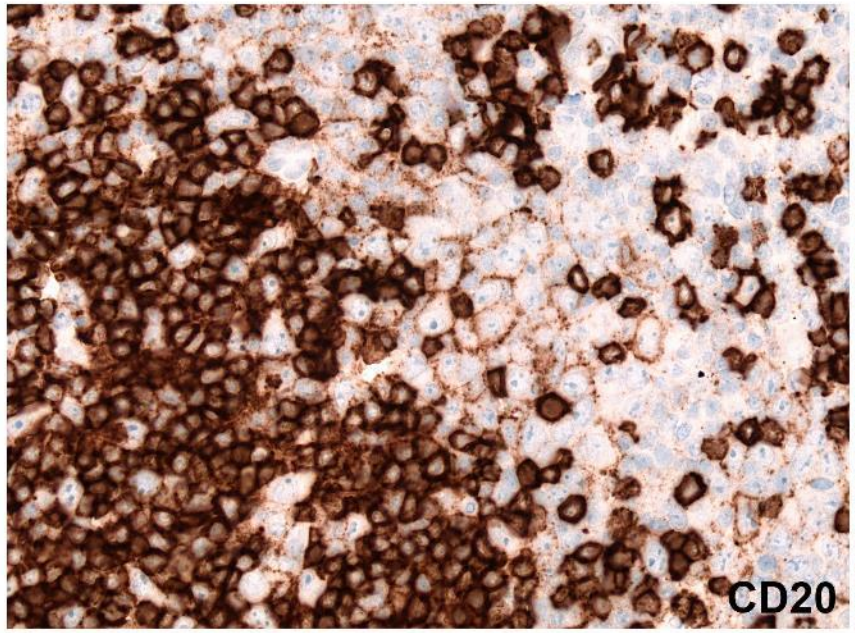


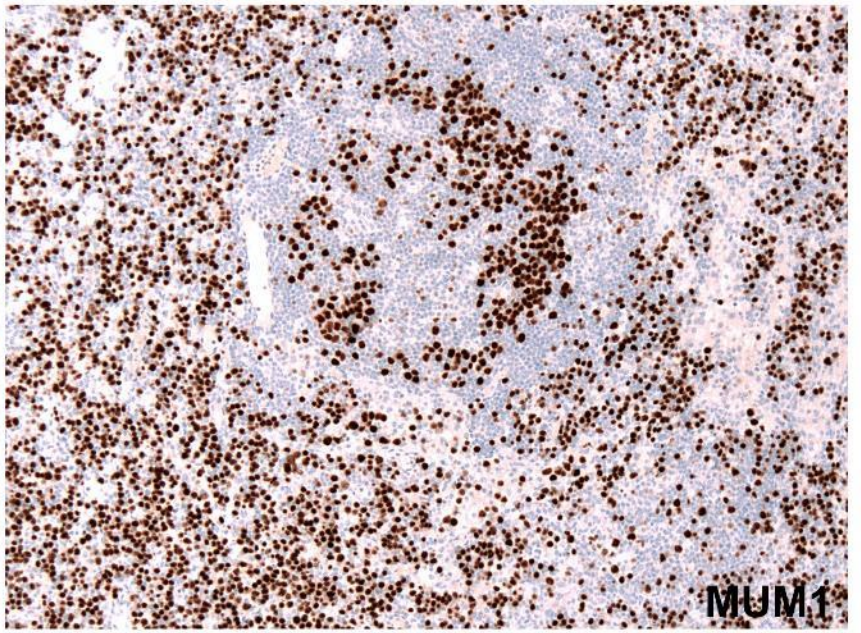


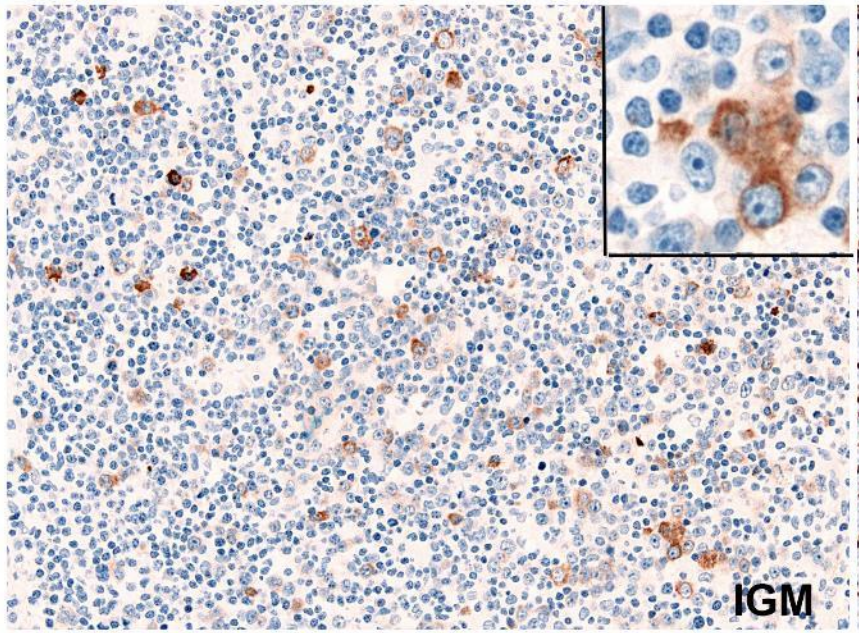
Atrophic follicles resembling those of Castleman disease, hyaline variant

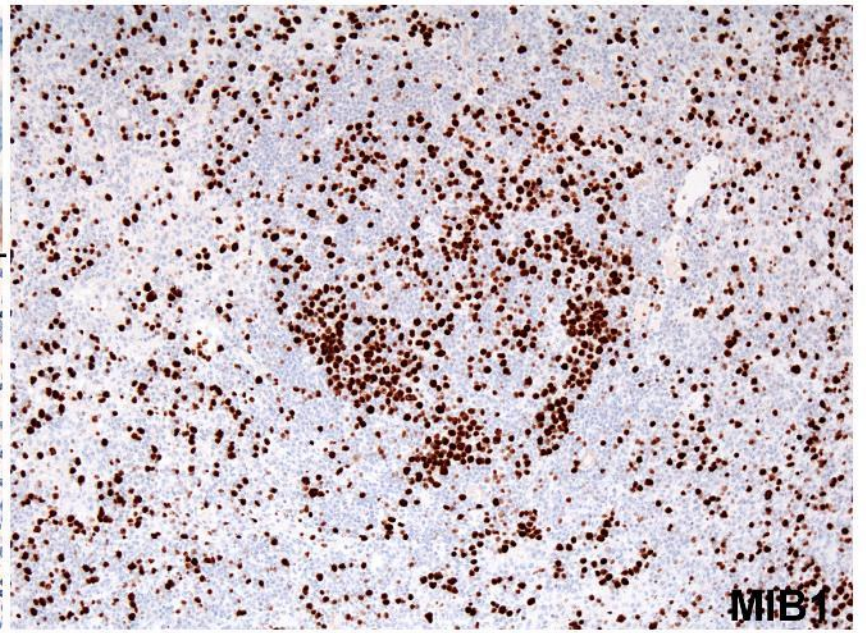
GLPD

- Immunophenotype:
- Usually negative for B-cell markers
- CD138, BCL6 and CD10 negative
- May coexpress CD3
- MUM1+
- May show monotypic κ/λ
- In some cases no Ig expression
- PCR polyclonal



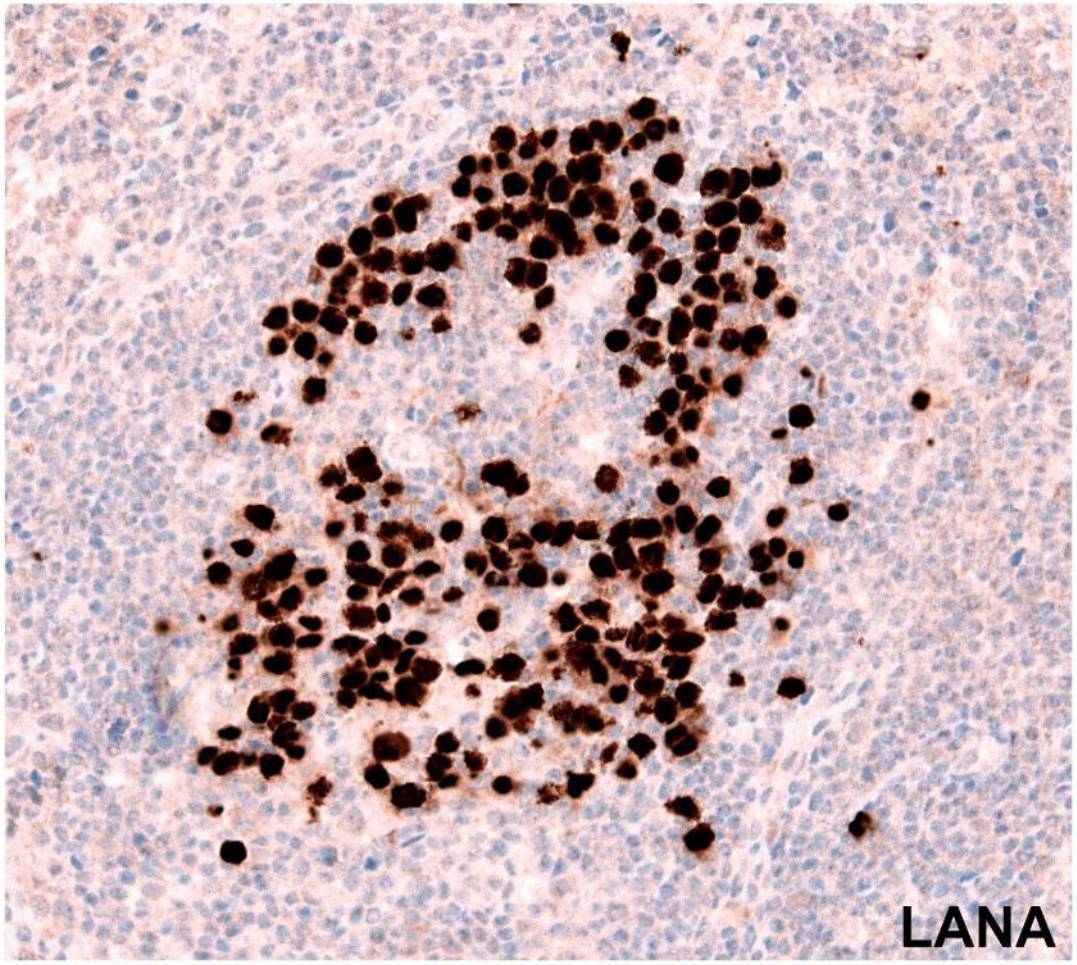


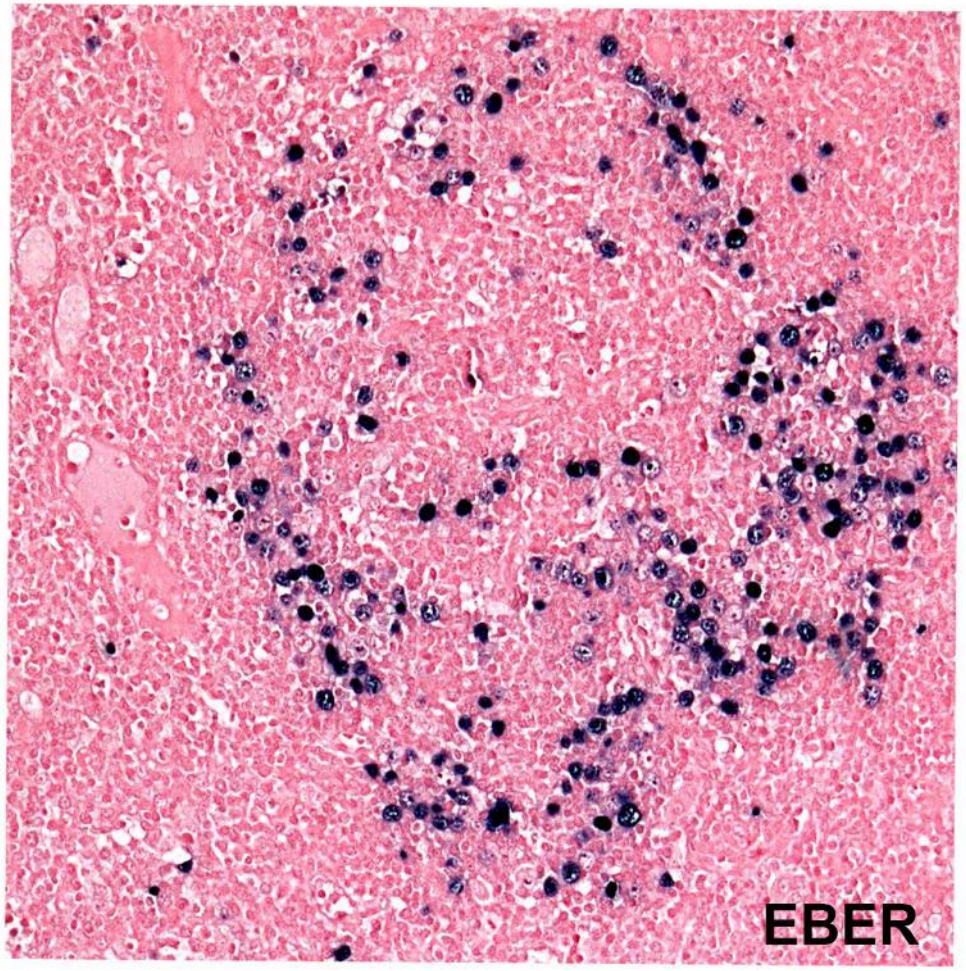




HHV8+ germinotropic lymphoproliferative disorder

GLPD are positive for HHV8 and EBER. LMP1, EBNA2 and BZLF1 are negative indicating EBV latency 1



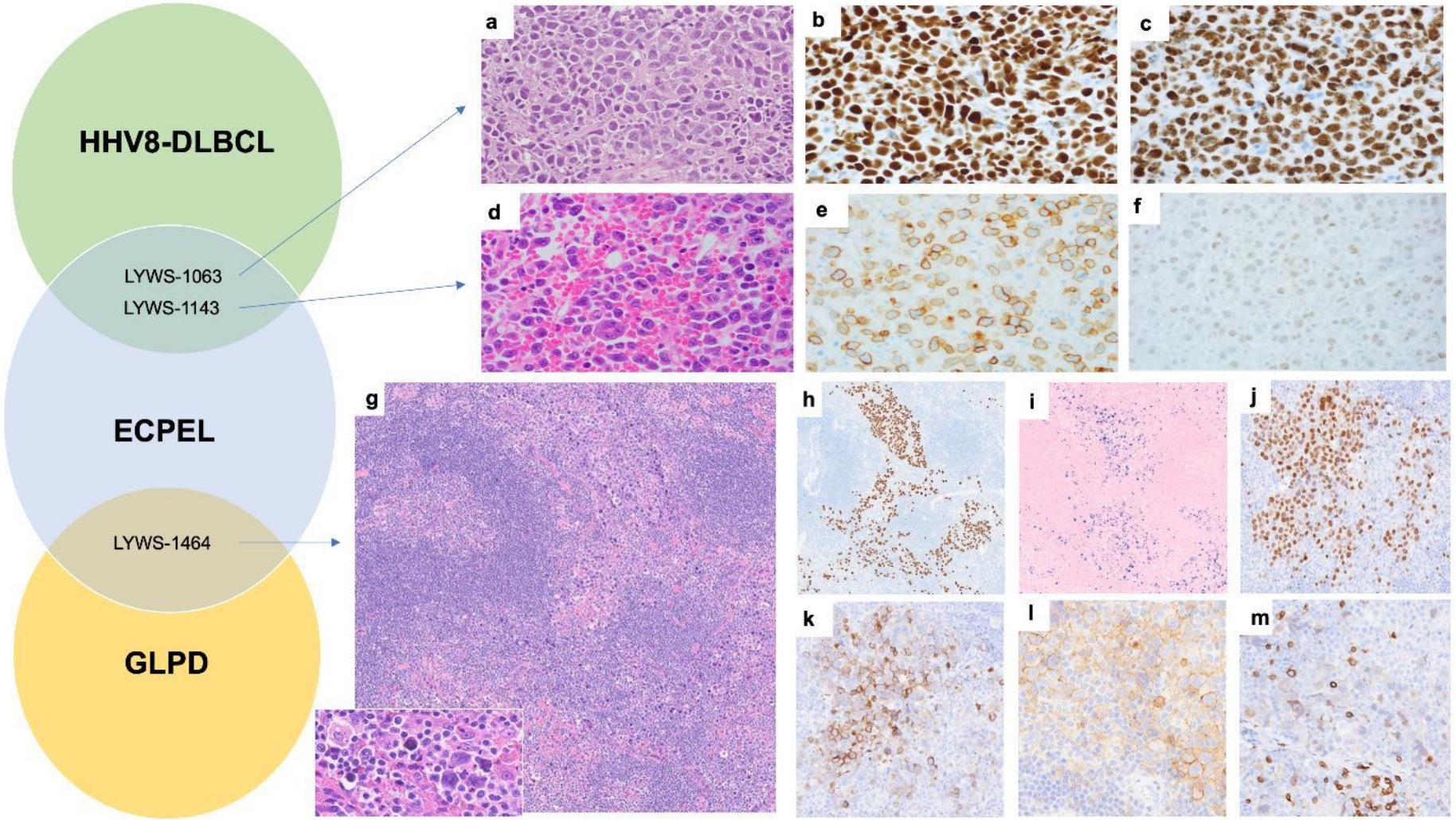


Comparison of HHV8 positive lymphomas/lymphoproliferative disorders

	PEL	EC PEL	HHV8+ DLBCL	GLPD
Site/B symptoms	Body cavity effusion (can disseminate) B Symptoms	Lymph nodes, skin and GI tract B symptoms	Lymph nodes, splenomegaly, extranodal sites and blood B symptoms	Localized lymph node (multifocal lymphadenopathy uncommon but may occur) B symptoms uncommon
Morphology	Plasmablastic, immunoblastic, anaplastic	Similar to PEL	Effacement of tissue architecture by diffuse sheets of plasmablasts	Retention of nodal architecture. Replacement of GC by plasmablasts. (Limited involvement of MZ, interfollicular region or sinus accepted)
B-cell stage	Terminal (SHM+)	Terminal (SHM+)	Naive, IGM-lambda+ SHM negative	Terminal (SHM+)
EBV	Mostly positive Latency 1	Mostly positive Latency 1	Negative*	Positive Latency 1
Immunophenotype	CD20-, CD138+, MUM1+, κ/λ -/+	CD20-, CD138+, MUM1+, κ/λ -/+ Often aberrant T-cell expression	CD20+/-, CD138-, MUM1+, IGM+, Lambda+	CD20-, CD138-, MUM1+, κ/λ +
IG clonality	Monoclonal	Monoclonal	Monoclonal	Polyclonal or oligoclonal
HIV association	Mostly EBV+ cases	Mostly	Mostly	Usually no . Rare cases reported
MCD	Uncommon	Uncommon	Typical	Not reported

*Some reports include EBER+ cases. This is acknowledge in the 5th edition of the WHO

Overlapping features between HHV8-associated LPDS



- Cases EBV negative, which do not express IGM/λ and are not associated to MCD
- Cases EBV positive with IGM/λ

- Interfollicular infiltration
- IG polyclonal
- HIV negative

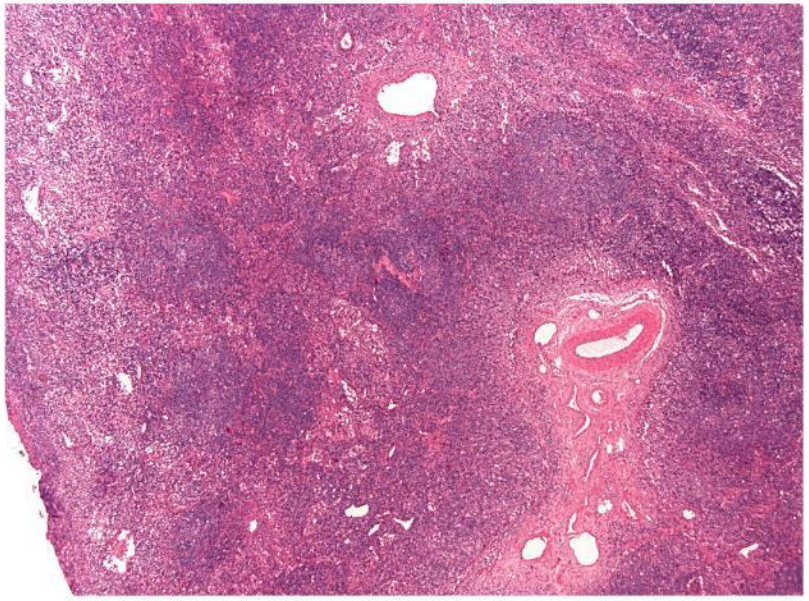
Bhavsar T, AJSP 2017; Zanelli M, Annals Hematol 2020; Wang W, Histopathology 2018

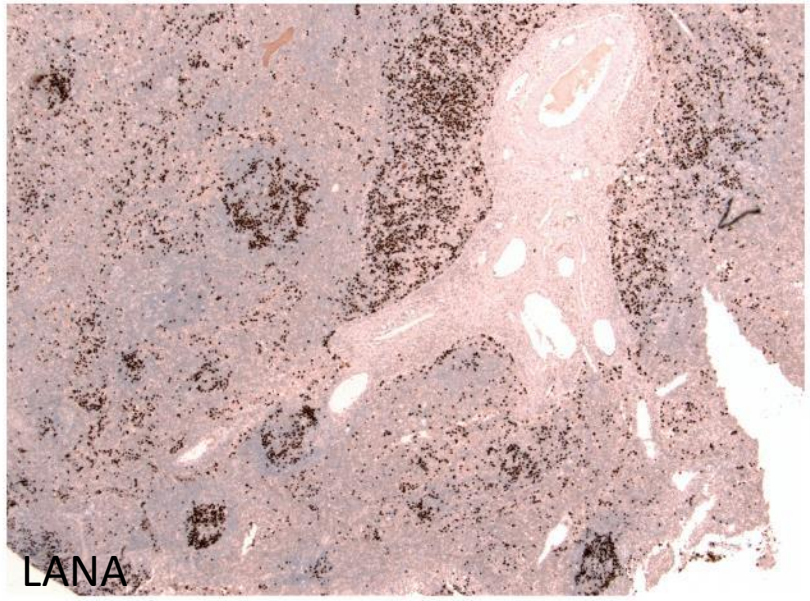
Di Napoli A, Soma L, et al, submitted to Virchows Archiv

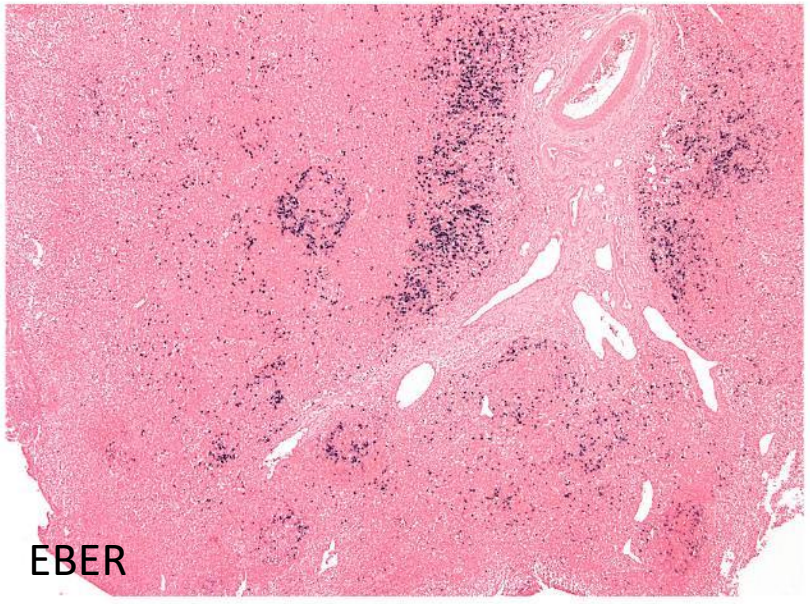
Overlapping features between HHV8-associated LPDS

- A 52-year-old male with HIV who stop his therapy one year ago
- The patient presented with one enlarged cervical lymph node
- HHV8+ and EBV+ proliferation within and outside GC

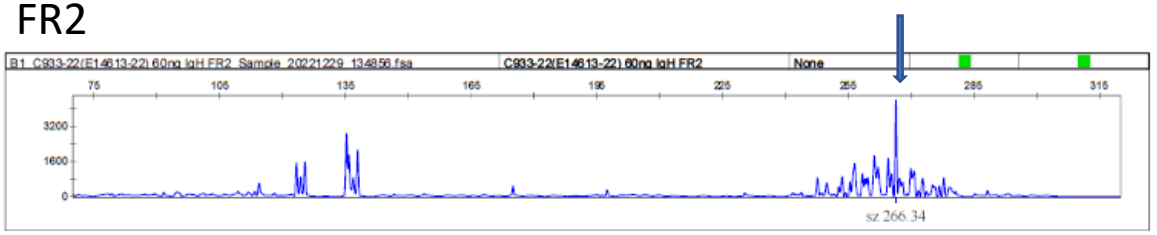
Early LN infiltration by Extracavitary PEL



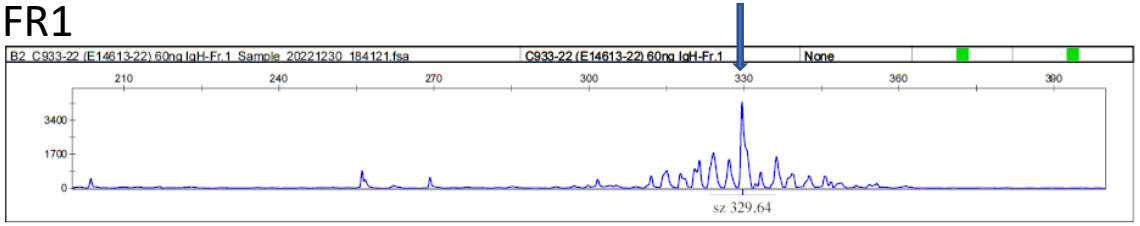




FR2



FR1



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Conclusions HHV8 lymphoproliferative disorders

- PEL/EC-PEL
  - EBV+ predominantly HIV/AIDS
  - EBV- predominantly elderly
  - Pitfall: expression of t cell antigens and even + for T cell clone
- Overlap of HHCV8+DLBCL/ECPEL/GLPD
  - HHV8+LBCL: naive B cell, IGM and lambda positive
    - EBV negative
    - Some cases overlap with EC-PEL
  - EC-PEL: sometimes limited or early LN involvement
  - Incidental, DD with GLPD

EAHP SH 2022

Thank you for your attention

The workshop cases submitters

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Di Napoli A, Soma L, et al, submitted to Virchows Archiv