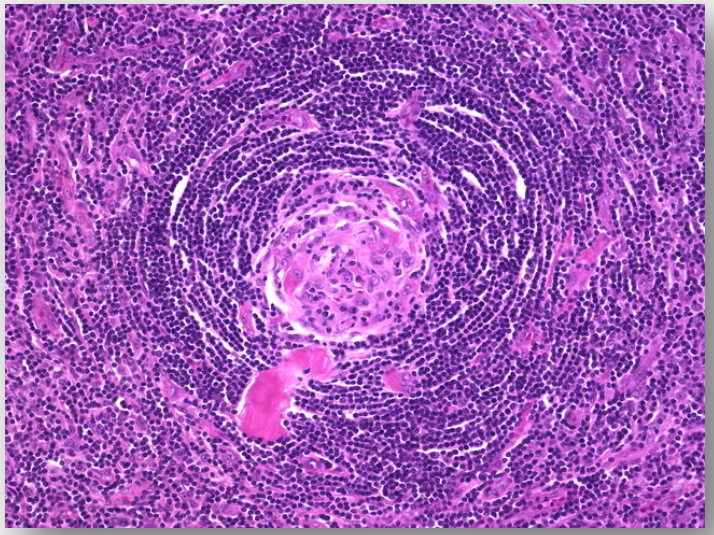
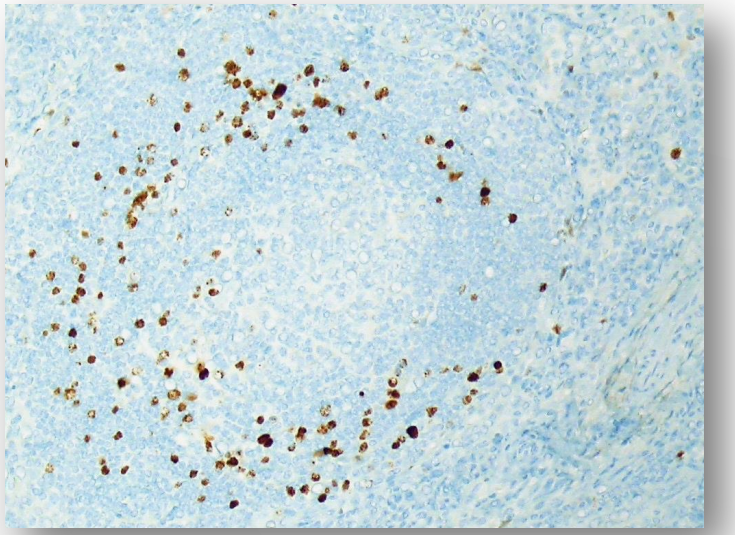
The spectrum of Castleman disease including insights from the EAHP-Workshop 2024





Stefan Dirnhofer
Head SAKK Swiss Lymphoma Reference Center
Deputy Director Institute of Medical Genetics and Pathology

University Hospital Basel

Lymphoma Forum of Ireland
Enfield, Co. Meath
November 8, 2025

Outline

- Introduction
- Classification
- UCD
  - HV - CD
- Oligo CD
- MCD
  - HHV8 - associated MCD
  - iMCD-NOS
  - iMCD-TAFRO
  - iMCD-IPL
  - (POEMS)
- Summary

Historical perspective

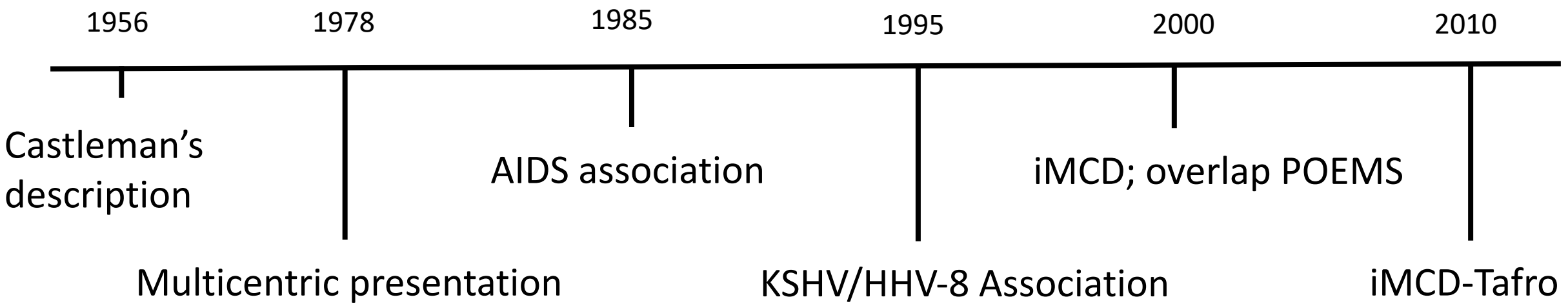
LOCALIZED MEDIASTINAL LYMPH-NODE HYPERPLASIA RESEMBLING THYMOMA

BENJAMIN CASTLEMAN, M.D., LALLA IVERSON, M.D., AND V. PARDO MENENDEZ, M.D.

«A series of thirteen cases of mediastinal masses resembling thymoma grossly and microscipically are shown to be a peculiar form of lymph node hyperplasia characterized by marked capillary proliferation»

Castleman B, N Engl J Med. 1954

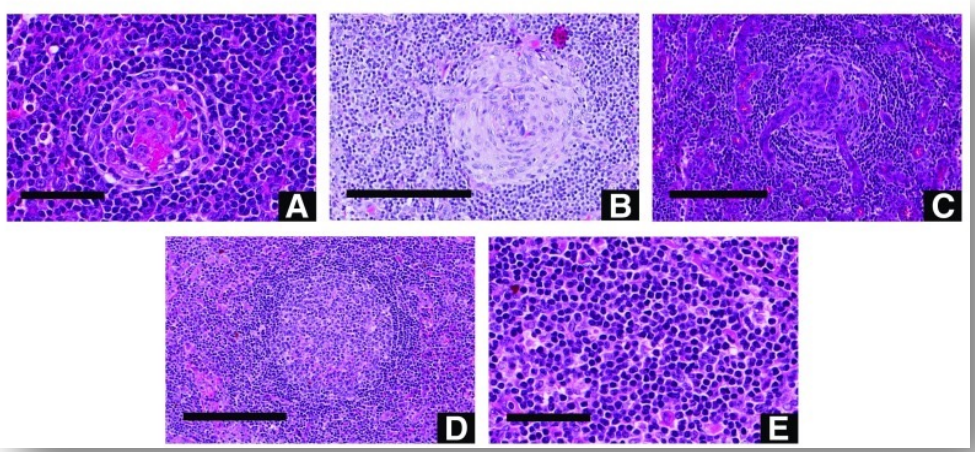
Historical perspective

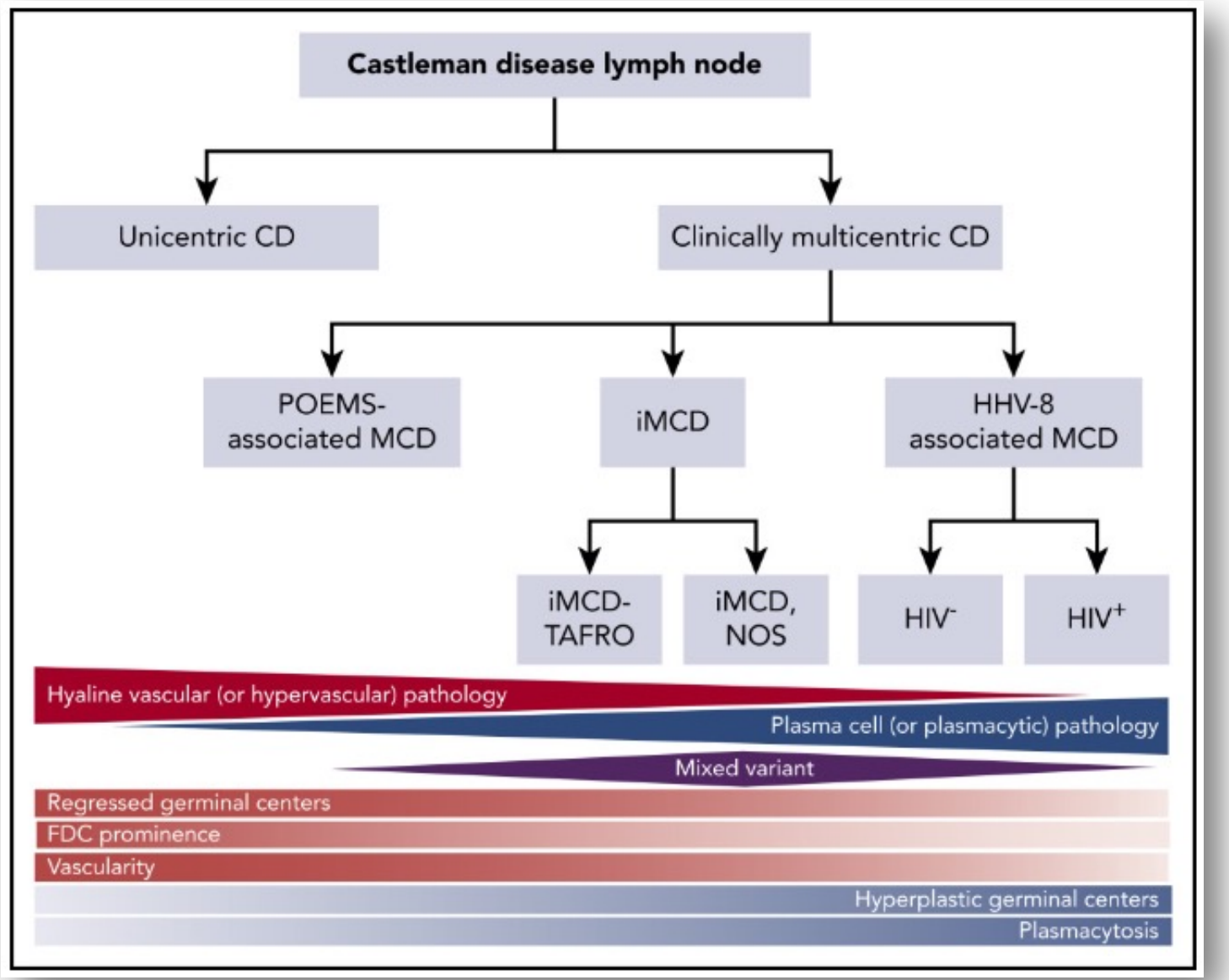


Castleman B, N Engl J Med. 1954; **Frizzera G**, Am J Surg Pathol. 1983; **Weisenburger DD**, Hum Pathol. 1985; **Lachant NA**, Am J Clin Pathol. 1985; **Soulier J**, Blood 1995; **Takai K**, Rinsho Ketsueki. 2010, **Fajgenbaum DC**, Blood 2017; **Dispenzieri A**, *Blood*. 2020; **Nishimura MF**, J Clin Exp Hematop. 2022

CD: a complex and heterogenous entity

- **Multiple rare disorders** with different etiologies, presentations and outcomes
- A **spectrum** of histopathological features
- **Incidence**: 5-16 cases /1 mln/y.





Fajgenbaum DC, Blood 2017
Dispenzieri A, *Blood*. 2020

WHO-5

Tumour like lesions with B - cell predominance

- Unicentric Castleman disease (UCD)
- Idiopathic multicentric Castleman disease (iMCD)
- KSHV/HHV8-associated multicentric Castleman disease (HHV8 – MCD)

ICC

Reactive lesions not included

Classification

CLINICAL

Unicentric vs Multicentric

- **UNICENTRIC VARIANT:**
  - Single enlarged lymph node/multiple lymph nodes in one ln station
  - Asymptomatic (rarely constitutional symptoms)

- **MULTICENTRIC VARIANT:**
  - Enlarged lymph nodes in at least two lymph node stations
  - Frequently associated with (episodic) systemic symptoms

Oligocentric Variant

- **UNICENTRIC VARIANT:**
  - Single enlarged lymph node/multiple lymph nodes in one ln station

- **OLIGOCENTRIC VARIANT:**
  - Enlarged lymph nodes in 2-3 adjacent stations
  - Most HV histology
  - Symptoms between UCD & MCD
  - Localized therapy often adequate
  - Similar survival as UCD

- **MULTICENTRIC VARIANT:**
  - Enlarged lymph nodes in at least two lymph node stations

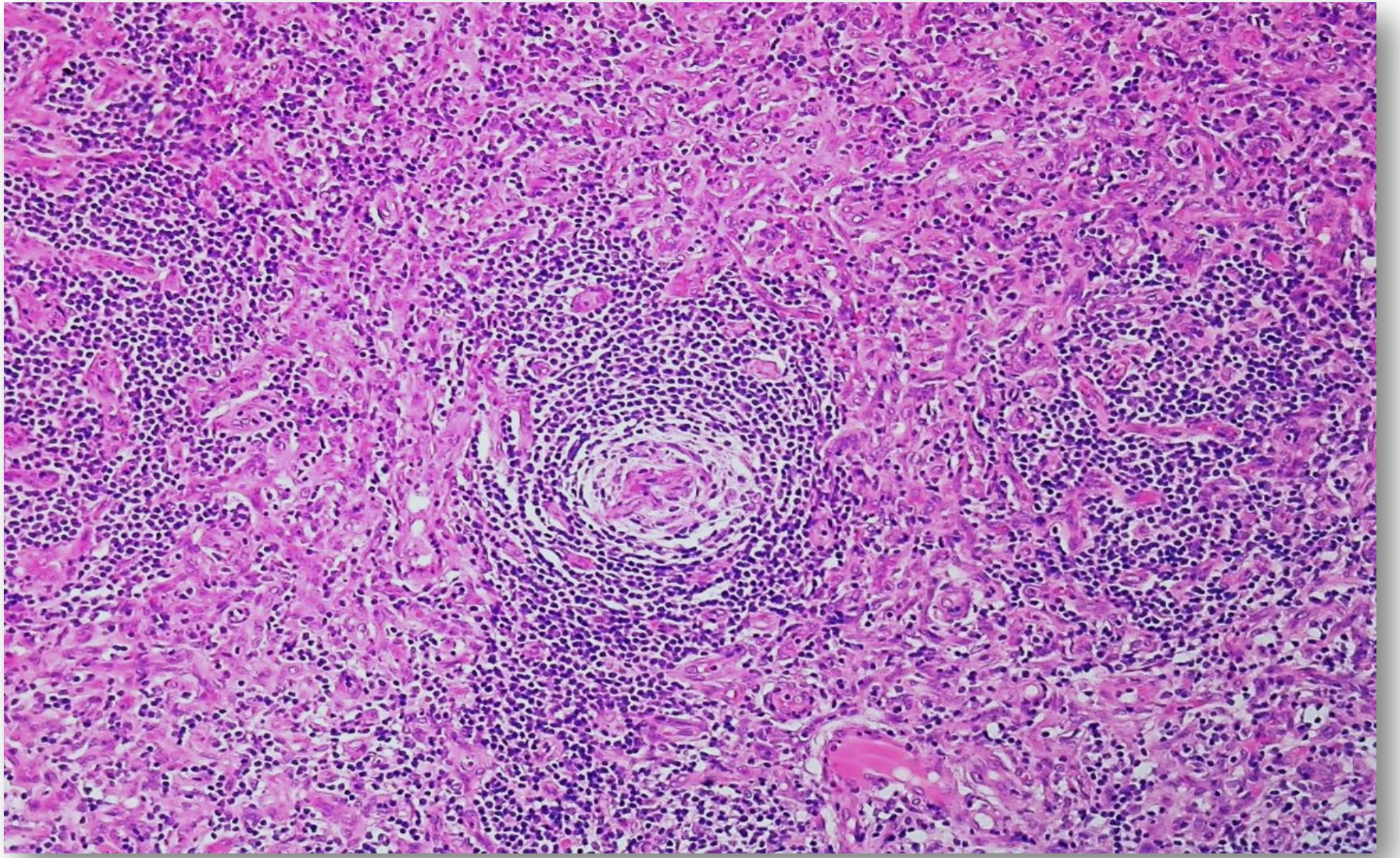
Pierson S, Blood Adv 2025

Classification

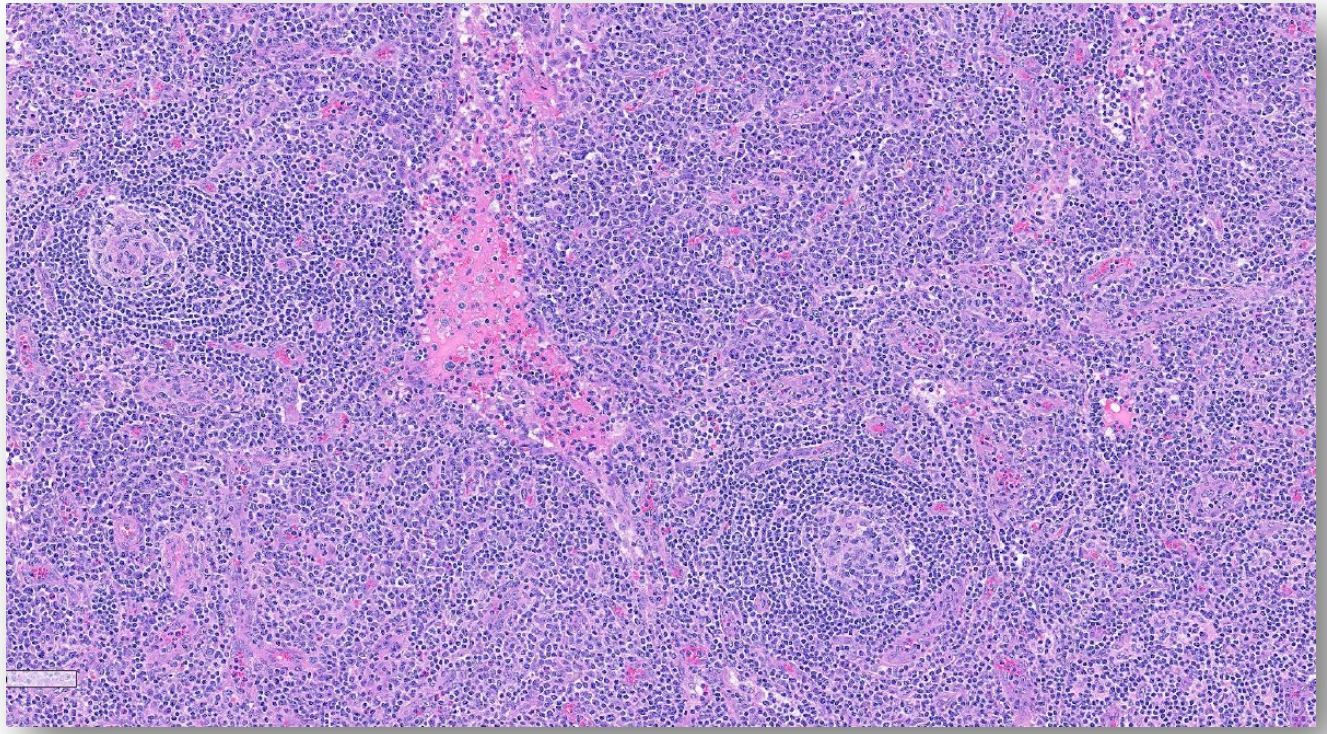
CLINICAL

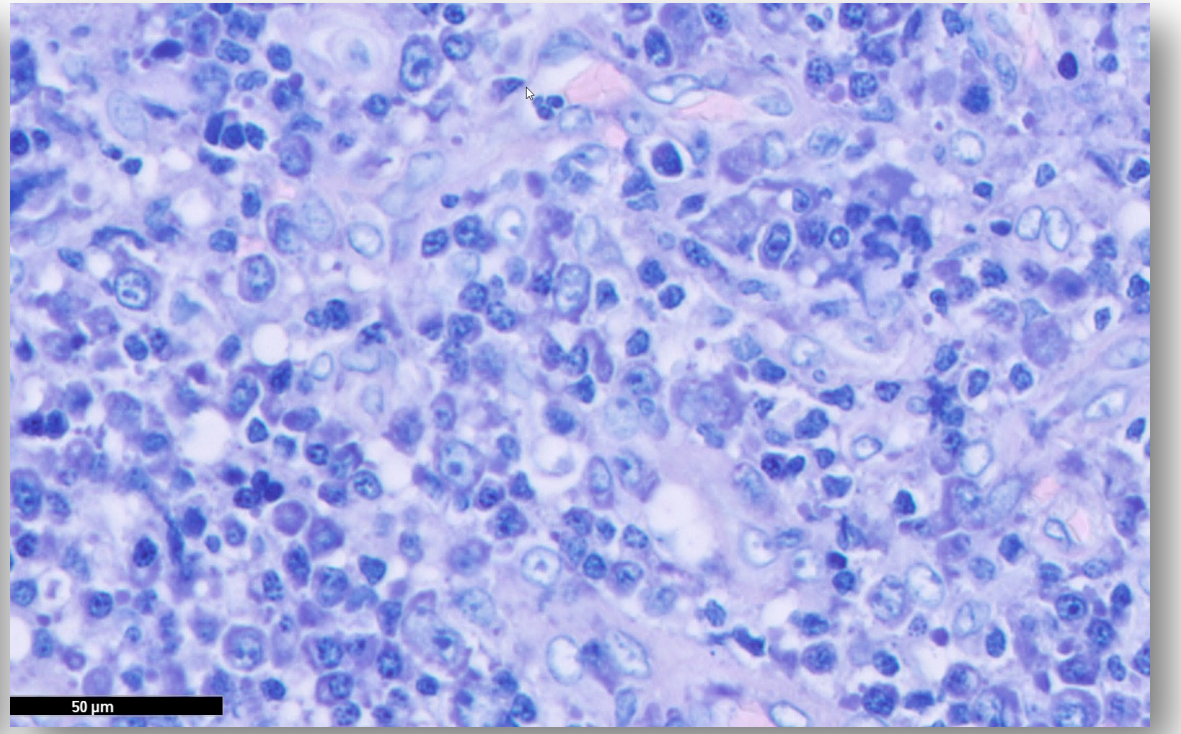
HISTOLOGICAL

Hyaline vascular pathology



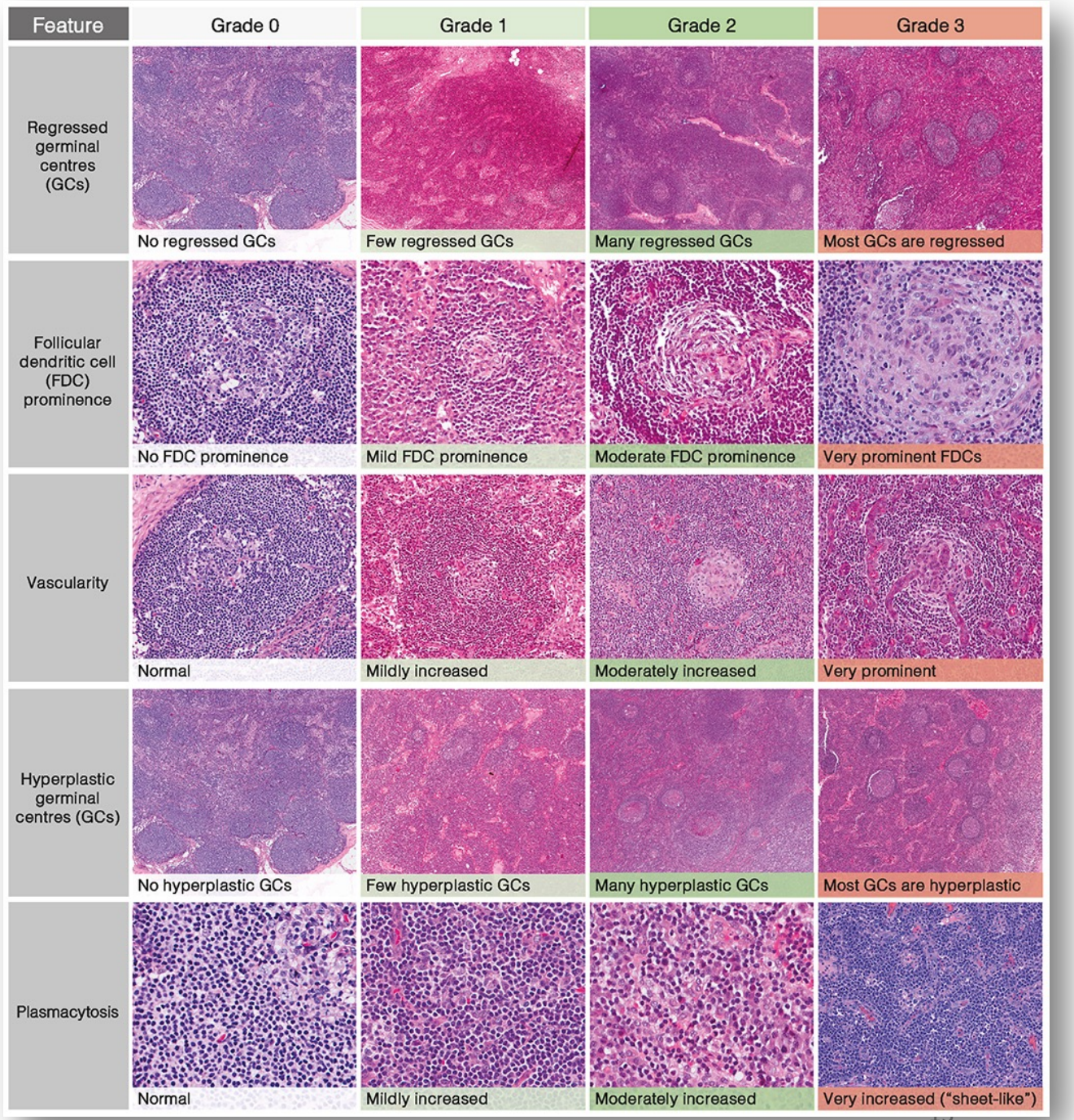
Plasma cell pathology





Castleman disease: pathology

- The diagnosis requires lymph node <u>excision</u>
- **Hyaline vascular** (75% UCD, <10% MCD):
  - capsular and parenchymal fibrosis
  - increased number of lymphoid follicles with regressed GC
  - >1 GC within the same mantle zone (twinning)
  - GC penetrating vessels (lollipop appearance)
  - concentrically arranged mantle-zone (onion-skin-like appearance)
  - prominent and occasionally atypical FDC
- **Plasmacytic** (25% UCD, >90% MCD):
  - follicular hyperplasia
  - interfollicular sheets of mature polytypic PC
  - no prominent vascular proliferation or hyaline deposits
- **Mixed**: extensive regressed germinal centers associated with sheet-like plasmacytosis



Fajgenbaum DC Blood 2017; **Wu D** Hematol Oncol Clin North Am. 2018; **Dispenzieri A**. *Blood*. 2020

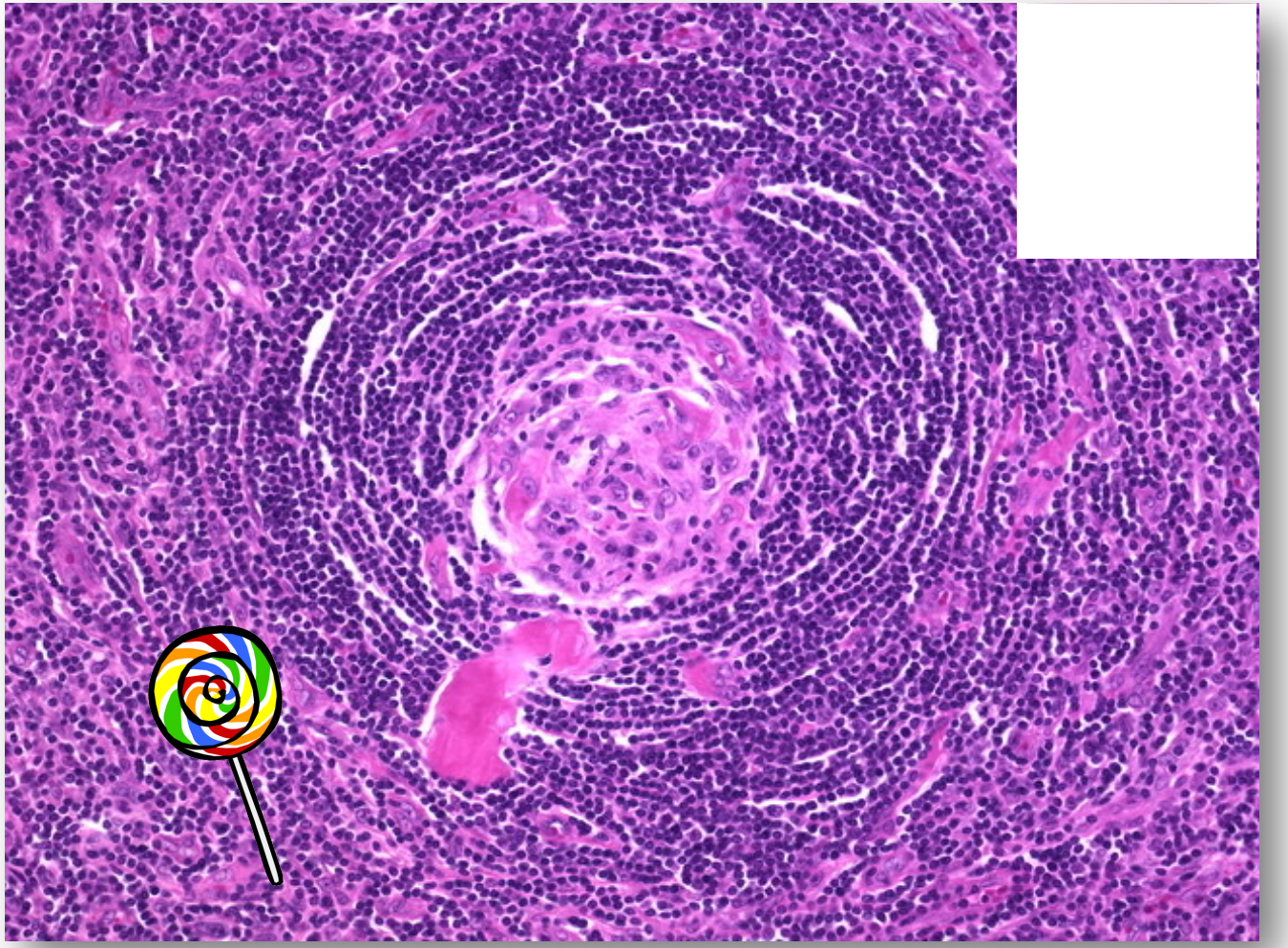
Unicentric Castleman disease (UCD): Clinical Aspects

- Young adults
- Localized mass
- Mediastinal, abdominal & cervical lymph nodes
- Asymptomatic
- Diagnosed on excision (cave CNB!)
- Diagnosis of exclusion
- HV (75-80%) vs PLV (20-25%)
- Surgical resection
- No systemic therapy

Griffin GK, Mod Pathol. 2016; **Andersen EF**, Mod Pathol. 2017; **Li Z**, Leukemia. 2019; **Massoth LR**, Oncologist. 2021; **Lorenzi L**, Haematologica. 2024.

Hyaline vascular variant (HVCD)

- Atrophic (regressed) germinal centers
- Expanded mantle zone
- «Twinning» of germinal centers
- Hypervascular interfollicular zone
- Hyalinized vessels
- «Onion skin» and «lollipop» sign
- «Sclerosis («Spleen-like»)
- Spectrum (from “follicular” to “stroma-rich”)



UCD – HV: Pathogenesis

- Pathogenesis (COO) enigmatic

  Reactive lesion, but rare cases with clonal marker (HUMARA, Cytogentics)

- No association with HHV8

- Is it a low-grade mesenchymal neoplasm ?

  Stroma-rich variant, heterologous differentiation

  Dysplastic stromal cells/FDCs can be seen in HV-CD: a possible precursor of FDCS?

  FDCS associated with HV-CD/UCD (up to 20%)

  Recurrent PDGFRB mutations in 10-20%

- Association with indolent T lymphoblastic proliferation (iT-LBP)

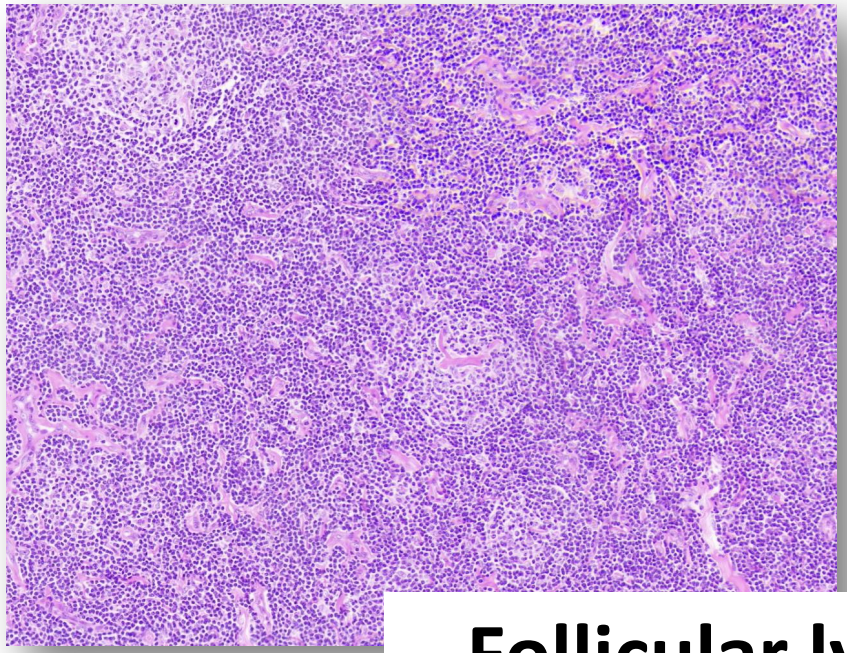
Singh et al., Front Oncol. 2022
Facchetti et al., VIAR 2017
Facchetti et al., Pathologica 2021
Sun et al., Hum Pathol 2003
Chang et al., Modern Pathology 2014
Li et al., Leukemia 2019
Pauwels et al., Am J Surg Pathol 2000

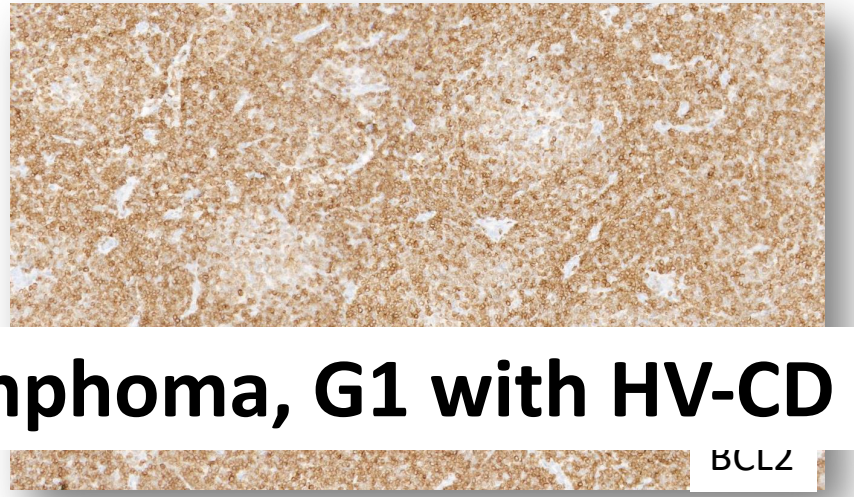
UCD - HVCD – Differential Diagnosis

- Lymphoma:
  - FL, MCL, MZL
  - T-FH lymphoma
  - T-LBL
  - cHL
- FDC - sarcoma, Vascular (mesenchymal) neoplasms
- Ig4-RD (iMCD)
- Non-specific, reactive lymphadenopathy

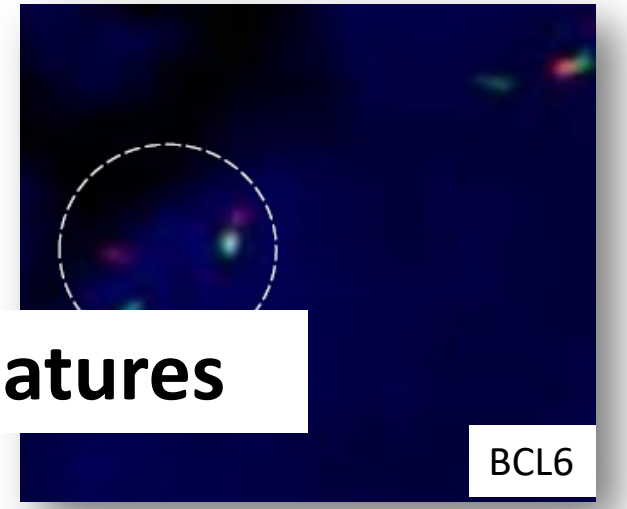
EAHP 2024
LYWS 62 Dr. Neira, Spain

- Male, 70 yr
- weight loss, anorexia and abdominal pain
- Palpable adenopathy (2 cm) inguinal right



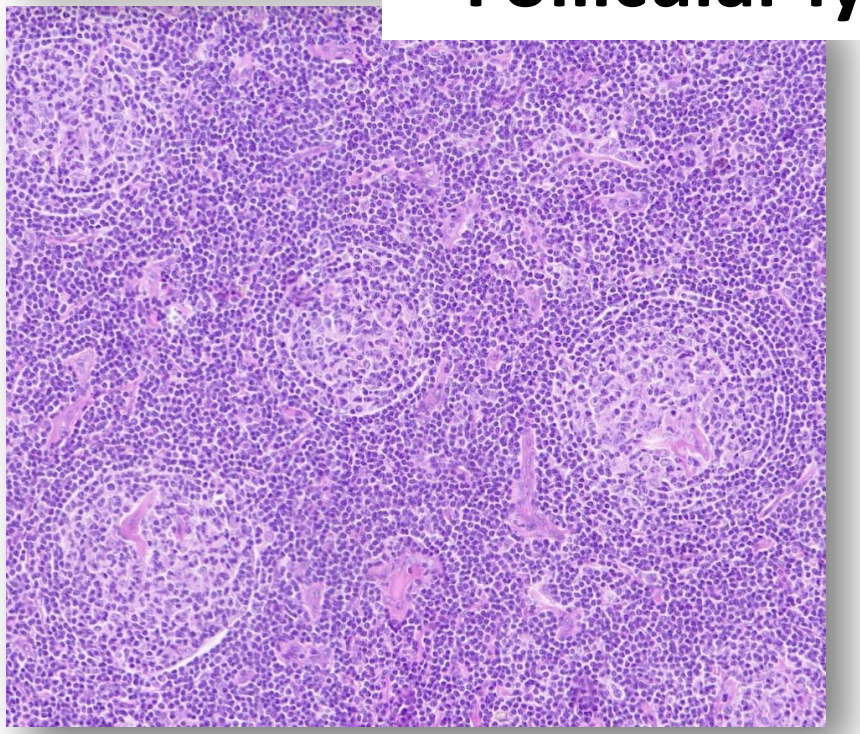


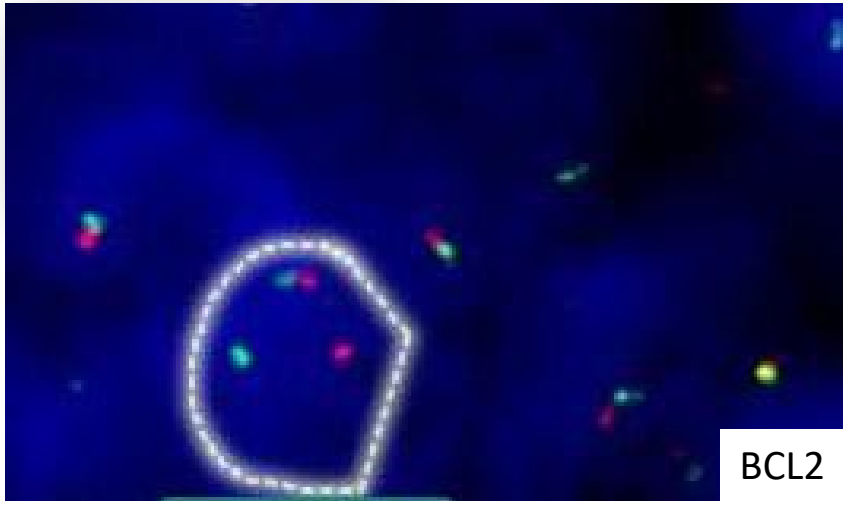
BCL2



BCL6

Follicular lymphoma, G1 with HV-CD features



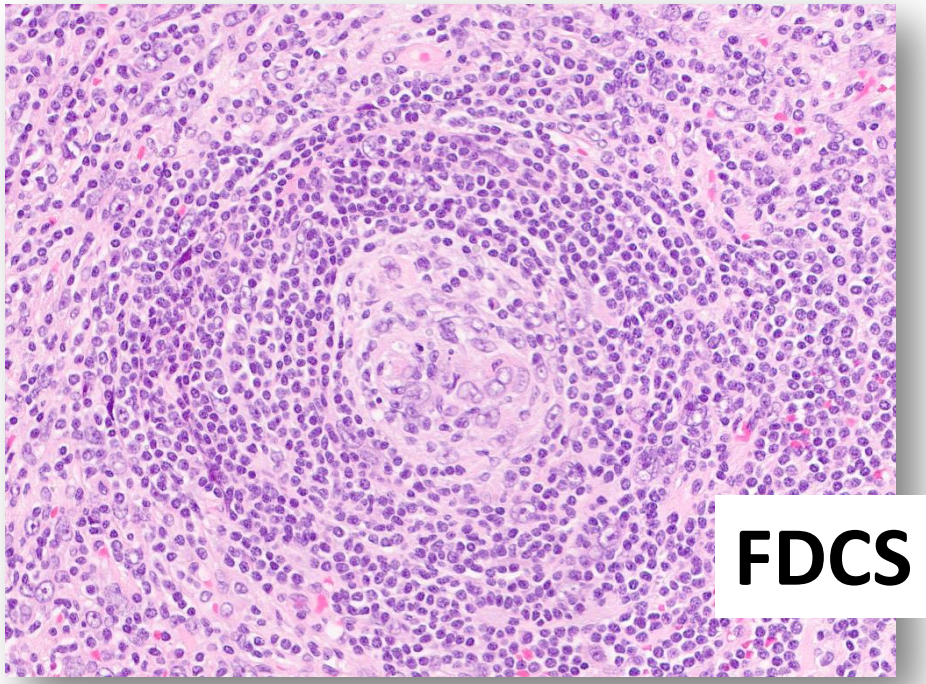


BCL2

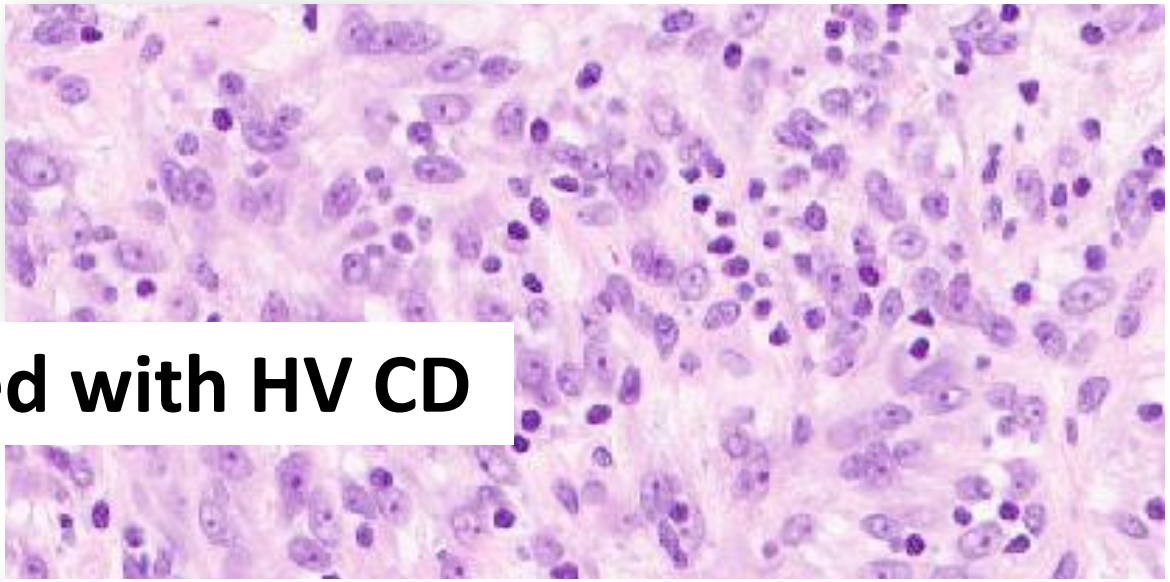
- IgH: clonal rearrangement
- NGS: KMT2D, BCL2, CARD11, CXCR4

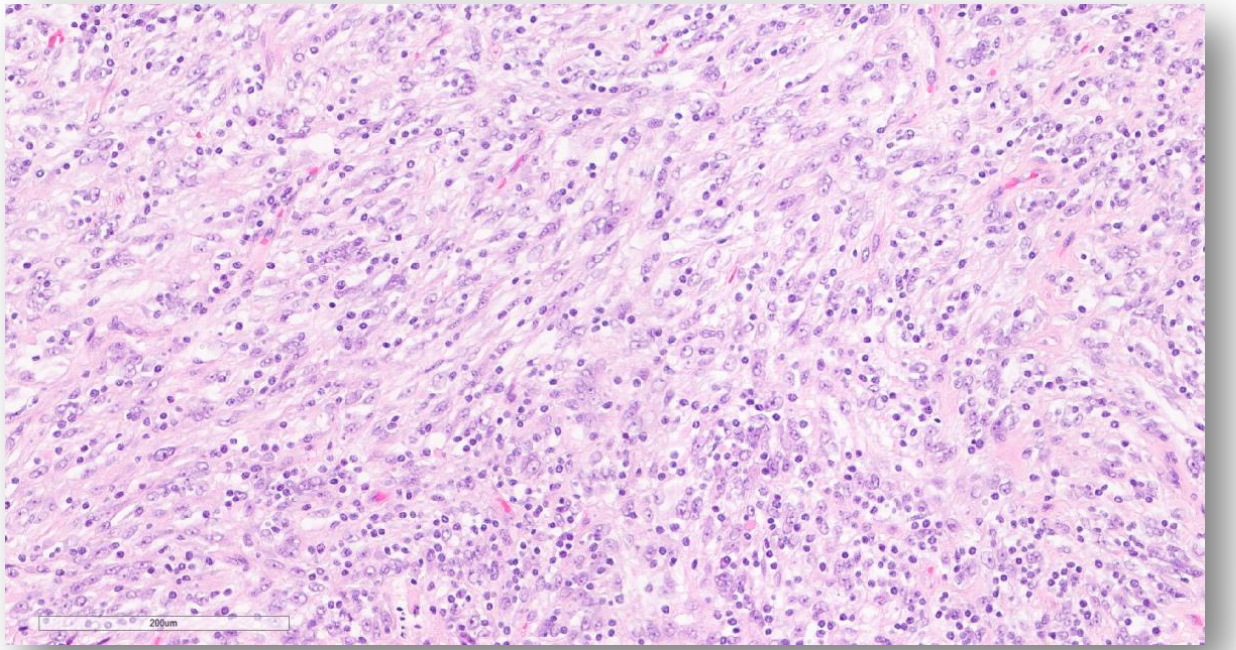
EAHP 2024
LYWS 260 Dr. Eren, N.Y.

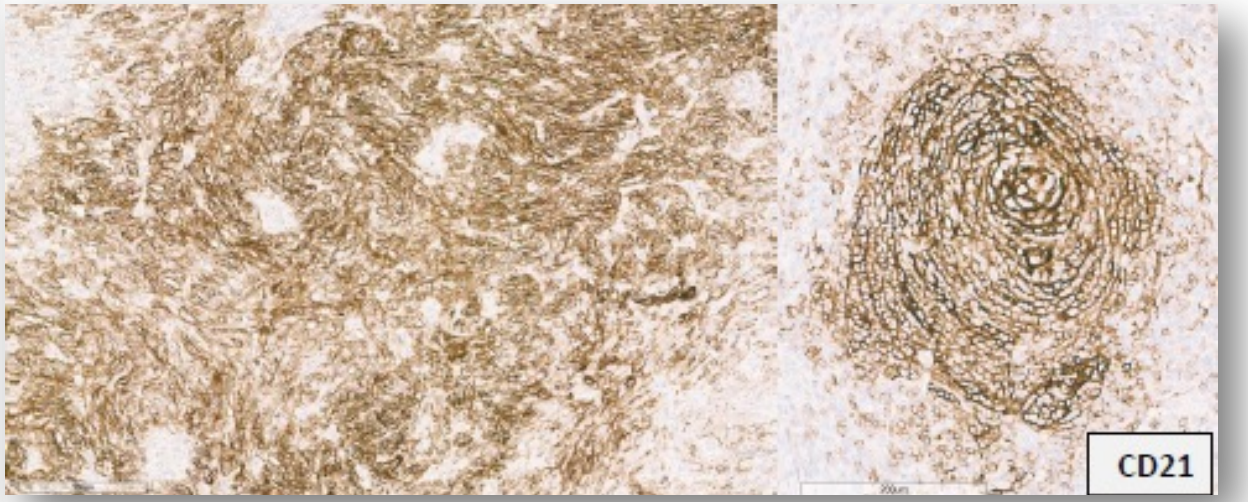
- Female, 60 yr
- CT: right paratracheal mass (5.2 cm)
- Endometrial cancer (T1bN0)



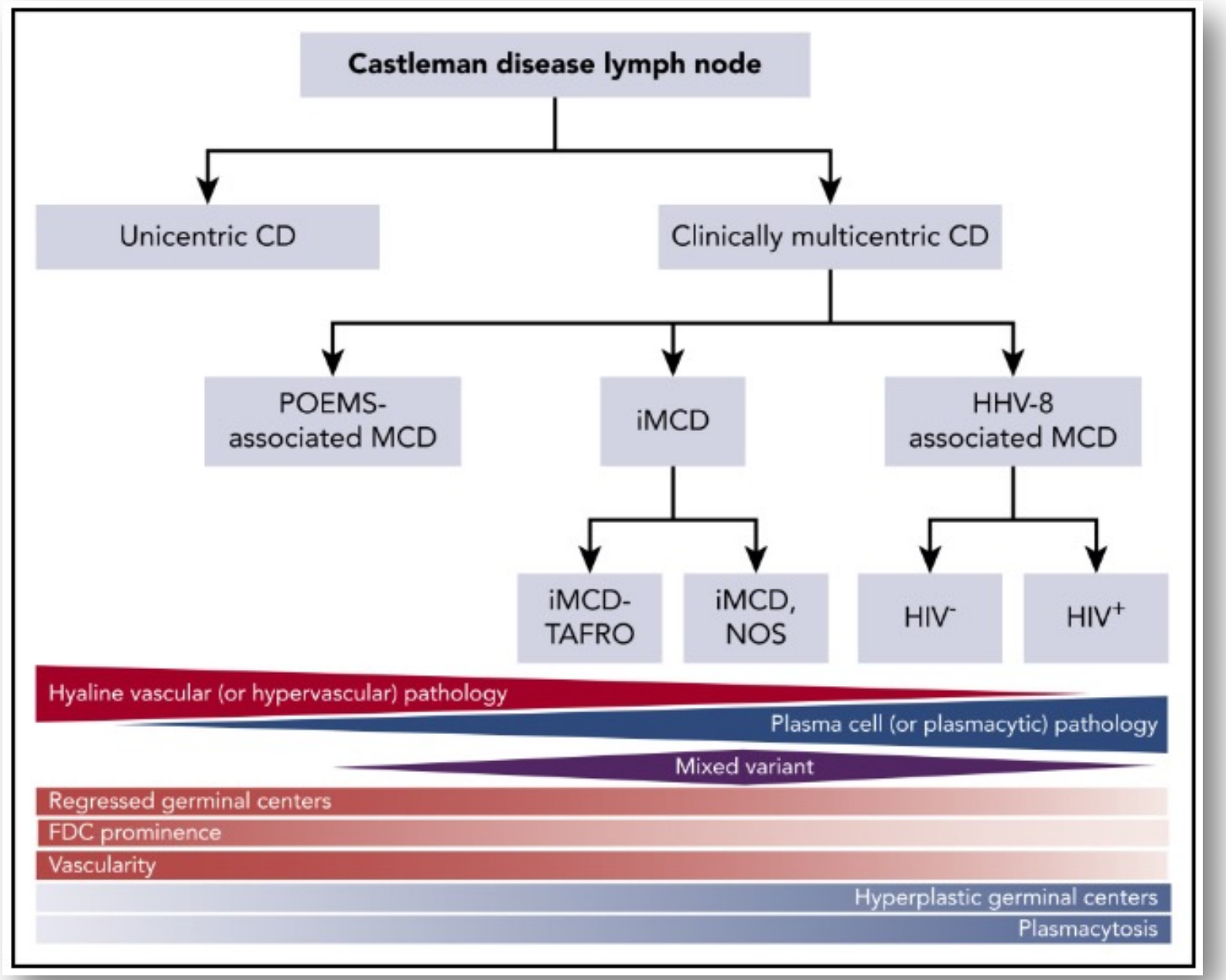
FDCS associated with HV CD





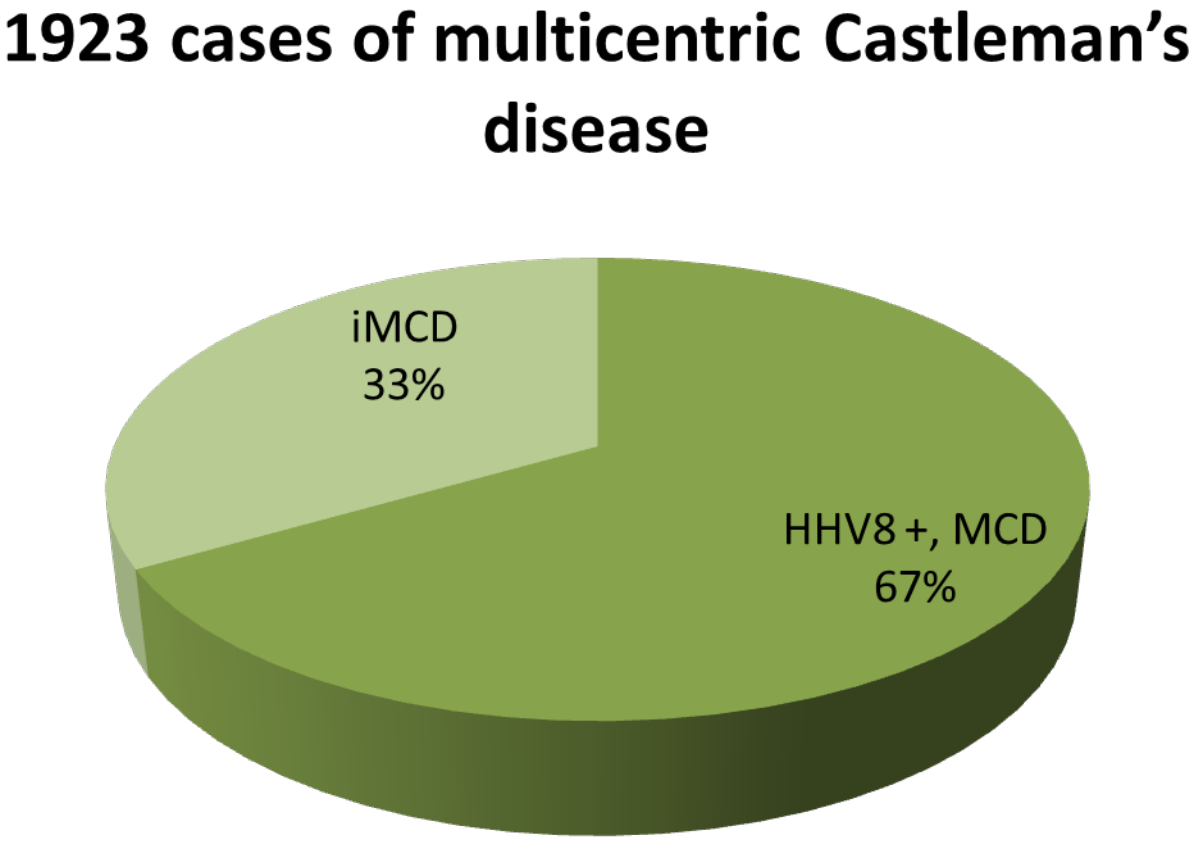


Positive: CD35, Fascin, CXCL13 (subset), Clusterin



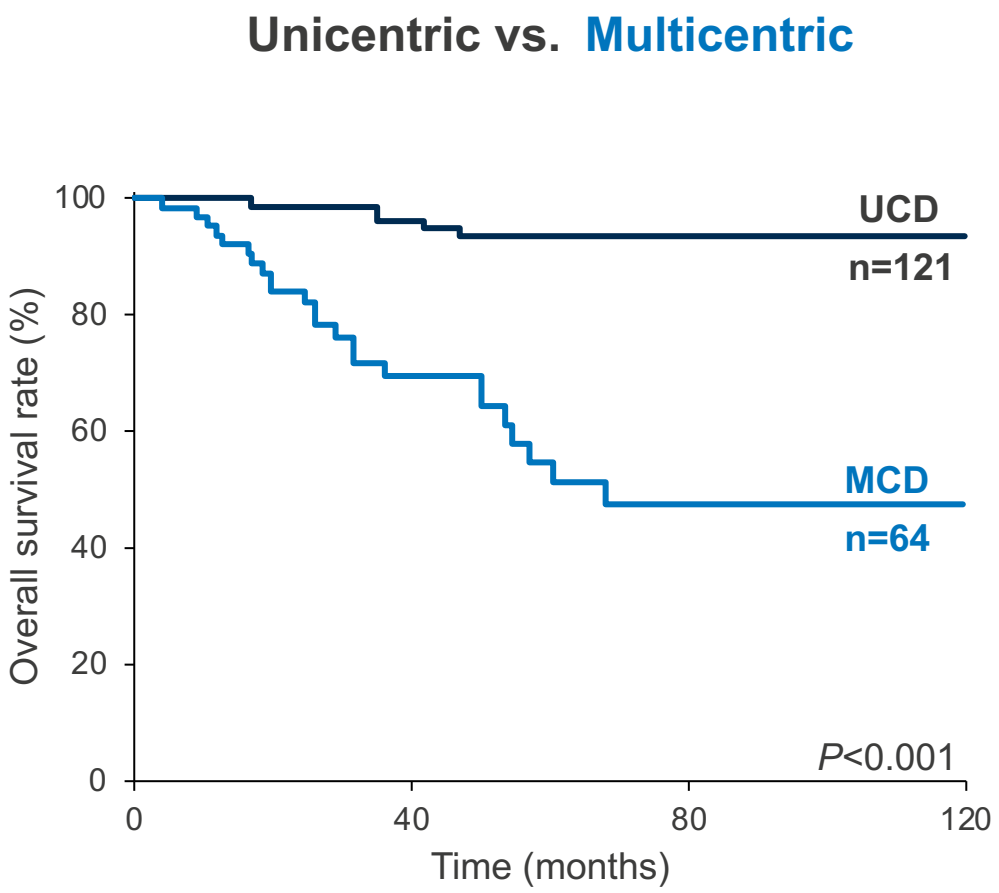
Dispenzieri A, *Blood* 2020

Epidemiology, MCD



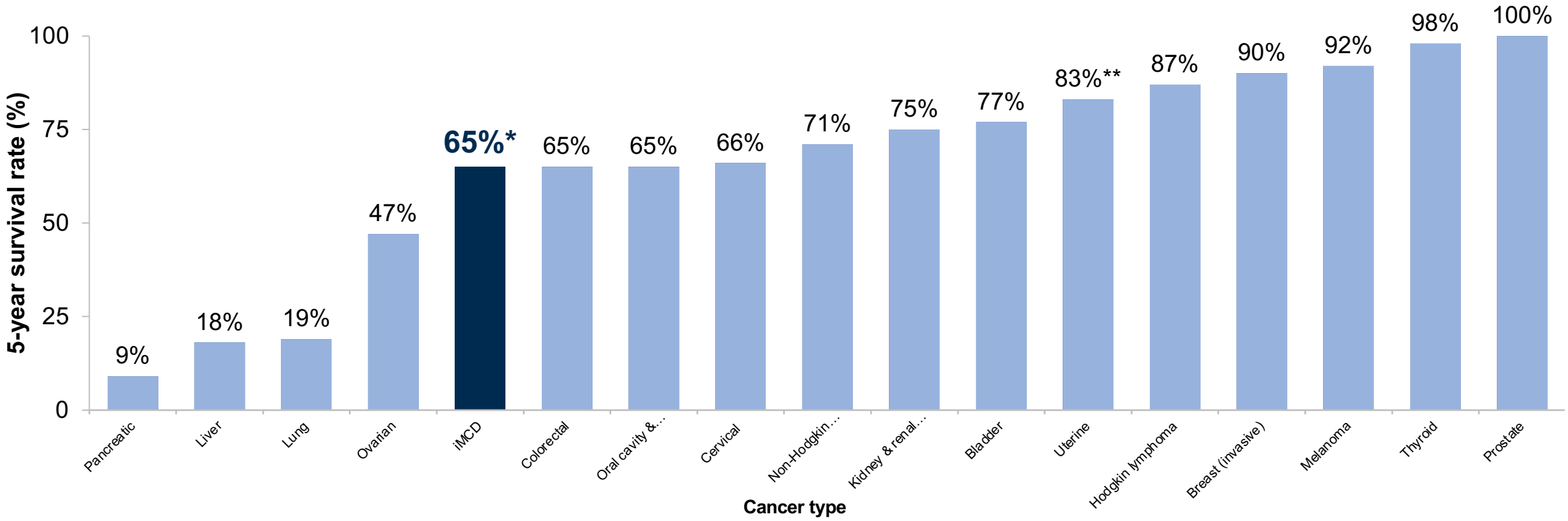
Idiopathic multicentric Castleman's disease: a systematic literature review, Fajgenbaum DC. Lancet Haematol. 2016

Castleman disease – the clinical perspective



Zhang X, et al. *Cancer Sci*. 2018;109(1):199-206.

5 yr OS – the clinical dimension of Castleman Disease (MCD)



Dispenzieri, A., et al. Am J Hematol. 2012
American Cancer Society (2019) https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2019.html

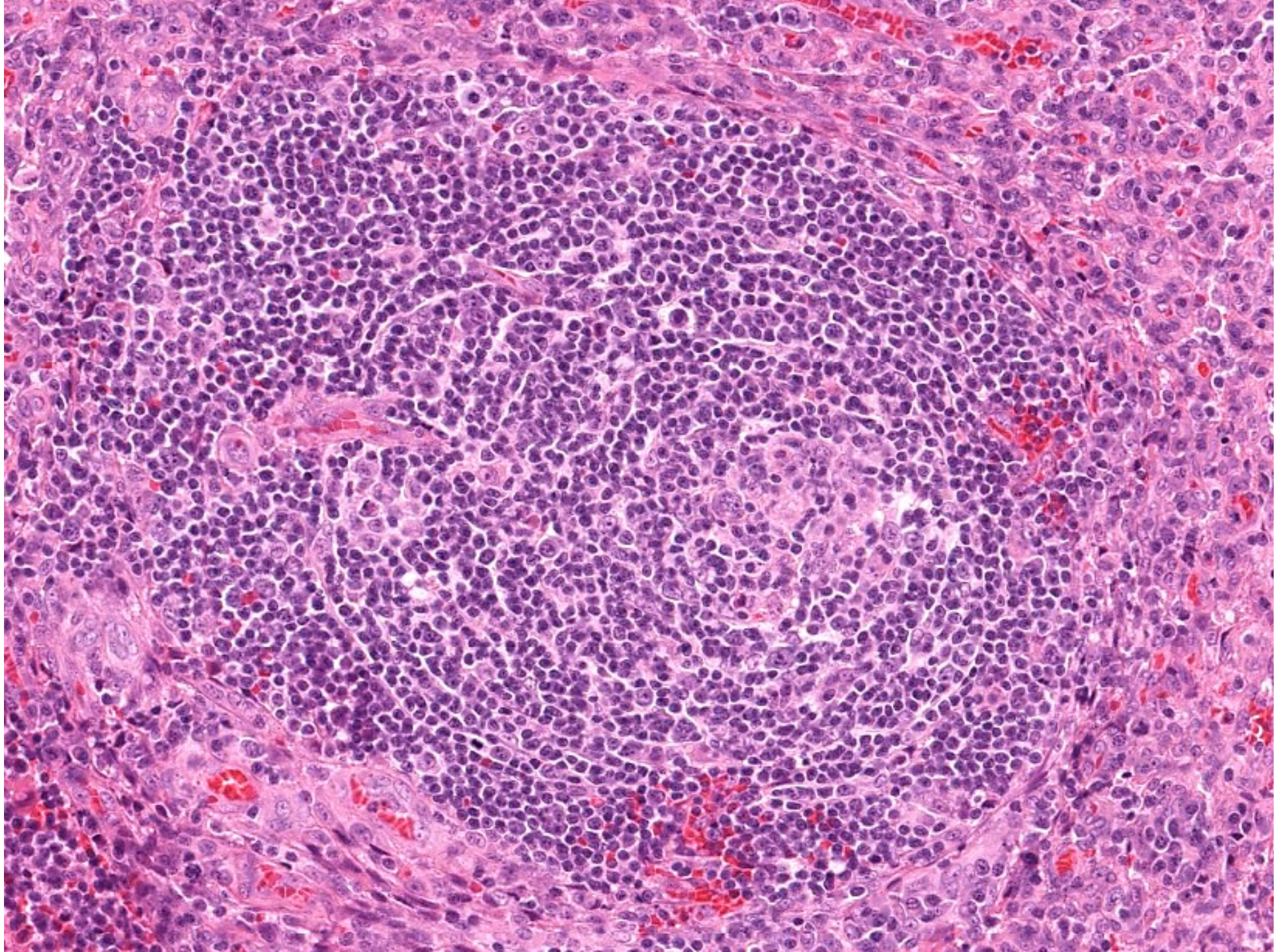
KSHV/HHV8-ASSOCIATED MCD

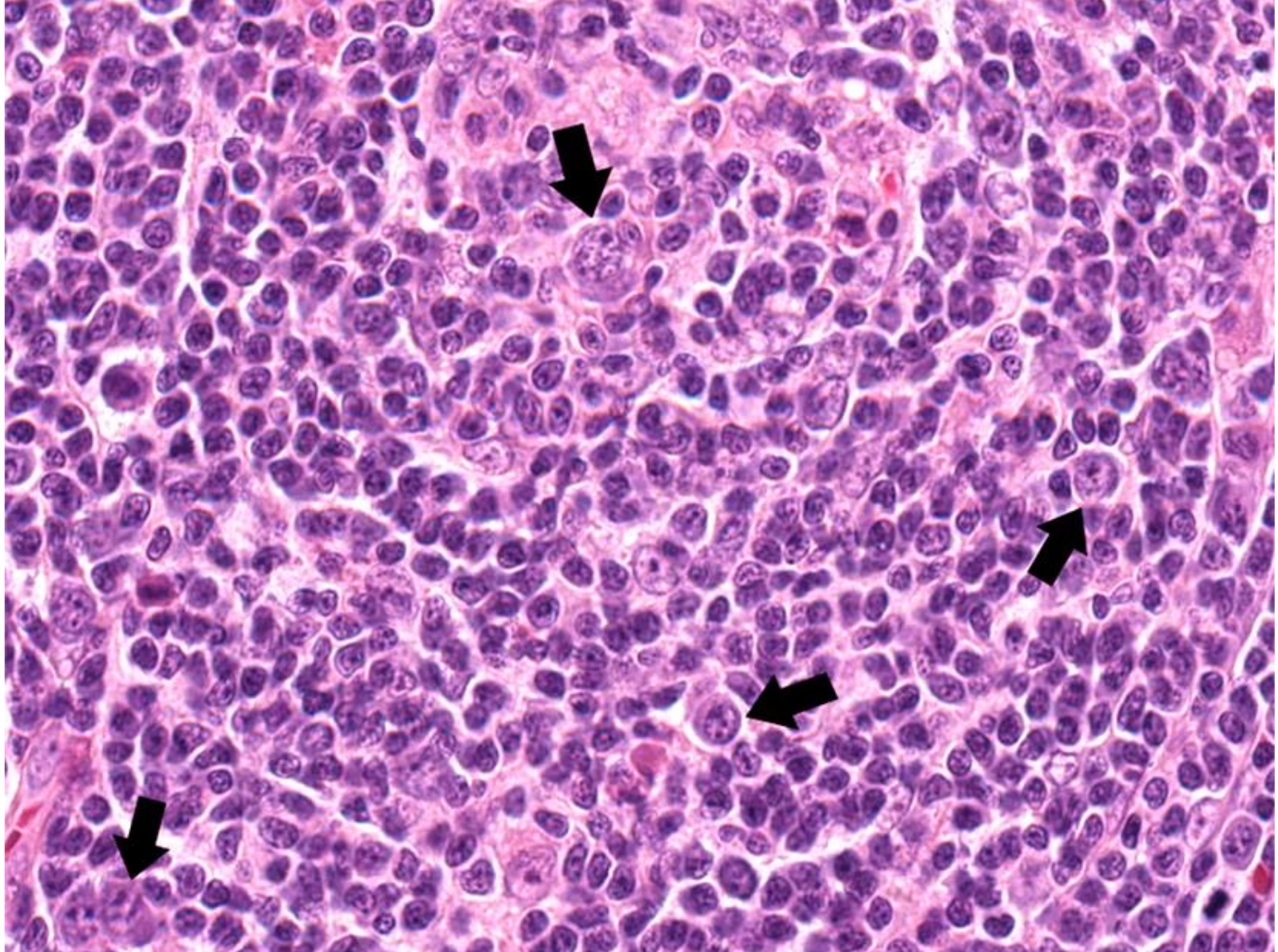
- Systemic inflammatory symptoms (fever, fatigue, weight loss etc.)
- Generalized lymphadenopathy
- Hepatosplenomegaly, effusions
- High serum levels of IL-6
- HIV – positive: 75 – 80%
- 10 – 20% (concurrent or subsequent) lymphoma, most HHV8-associated
- Frequently associated with Kaposi sarcoma (capsule, trabeculae or LN hilum)
- Poor prognosis (OS 3 – 4 yrs)

Münz, Nat Rev Microbiol 2019
Di Napoli, Virchows Arch 2023
Chadburn, Am J Clin Pathol 2017

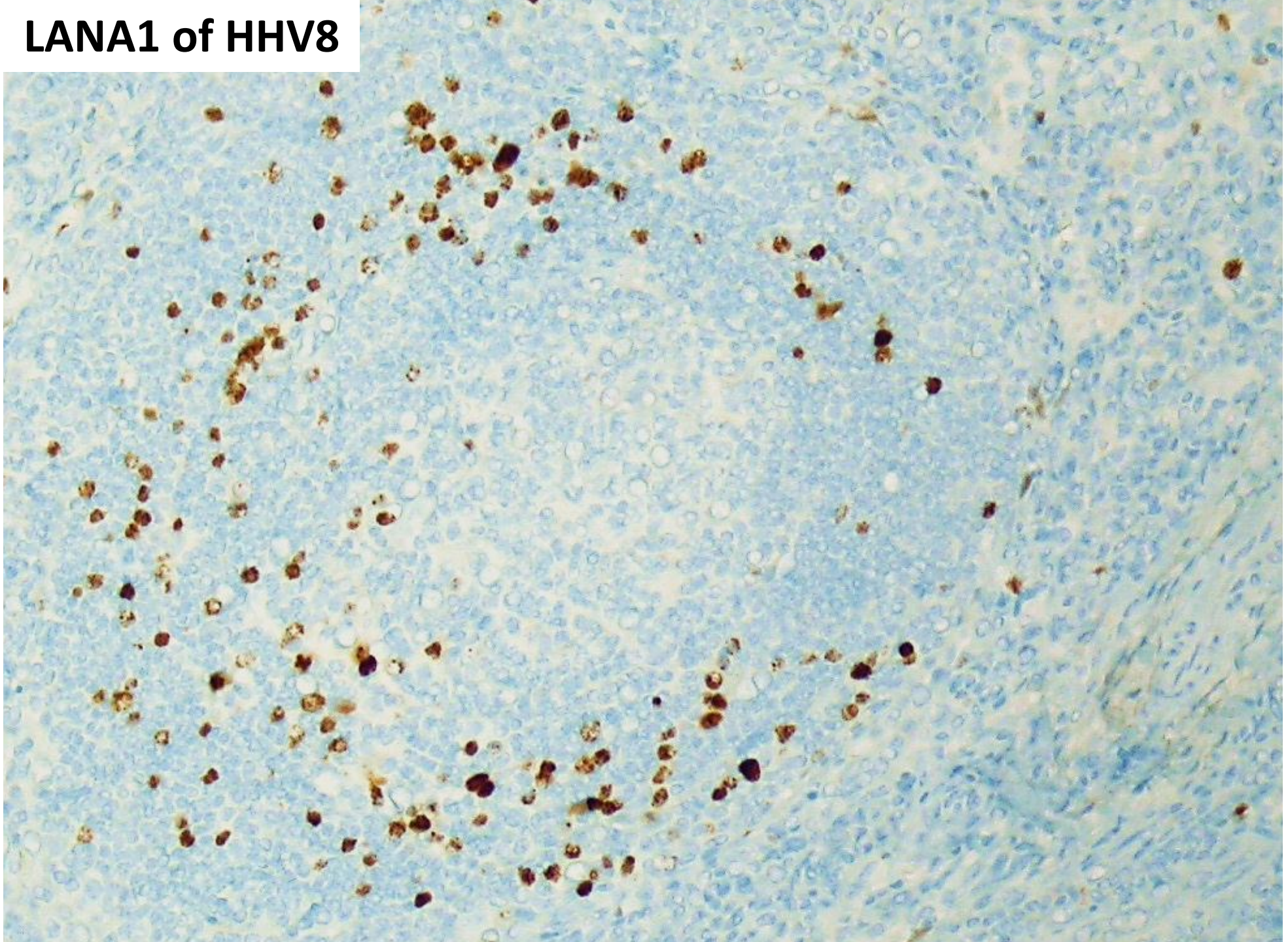
KSHV/HHV8-ASSOCIATED MCD: Histopathology

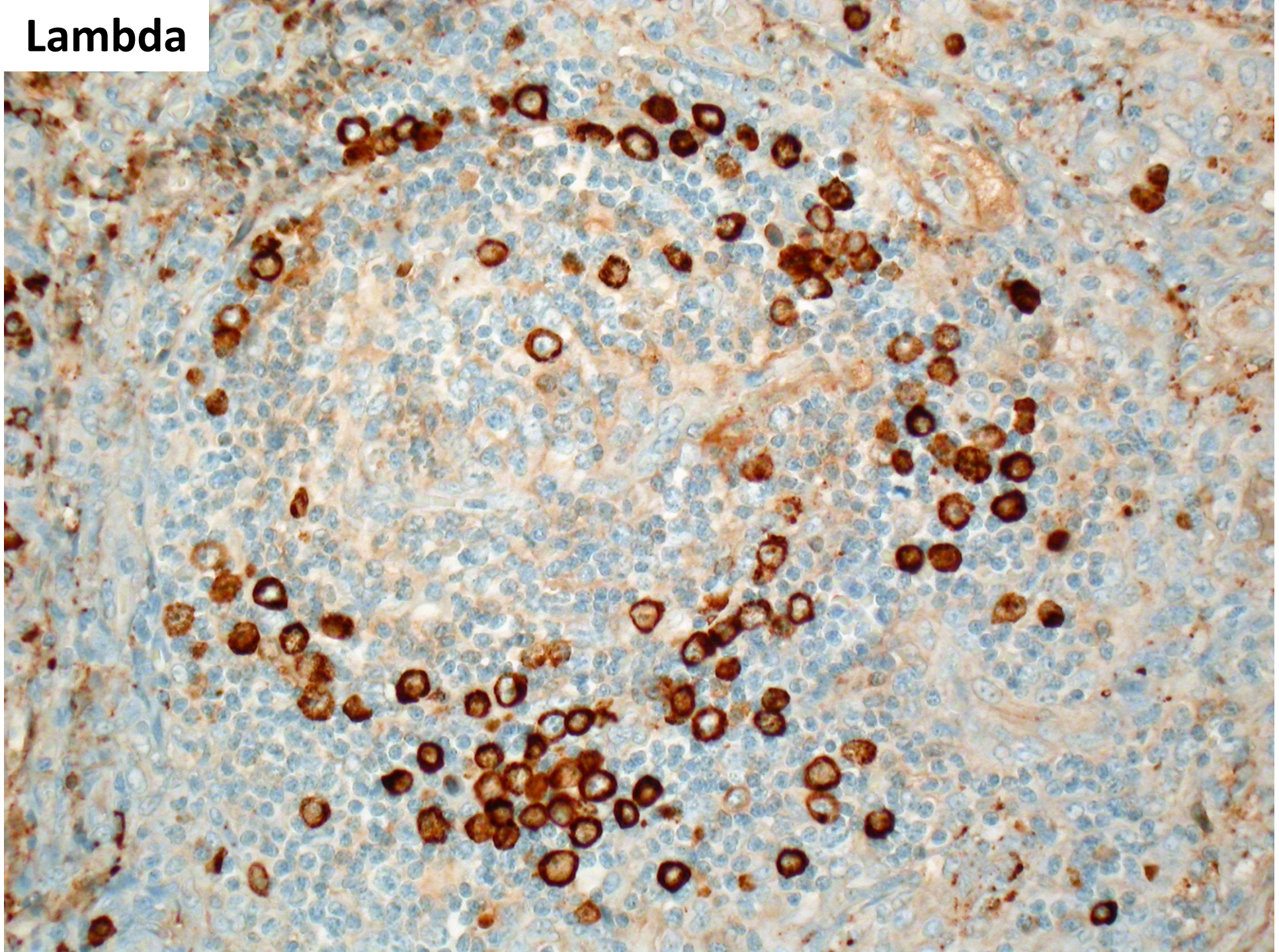
- iMCD-like morphology
- KSHV/HHV8+ plasmablasts in mantle zone
- PC variant > mixed pattern
- Plasmablasts may form small clusters or larger aggregates (formerly called “microlymphomas”)
- Plasmablasts:
  - LANA1 –positive; monotypic IgM lambda
  - Negative for CD20, CD79A, CD138, T-cell antigens, and EBV
- Grey-zone exist between KHSV/HHV8-associated MCD, HHV8-positive DLBCL, GLPD and ePEL

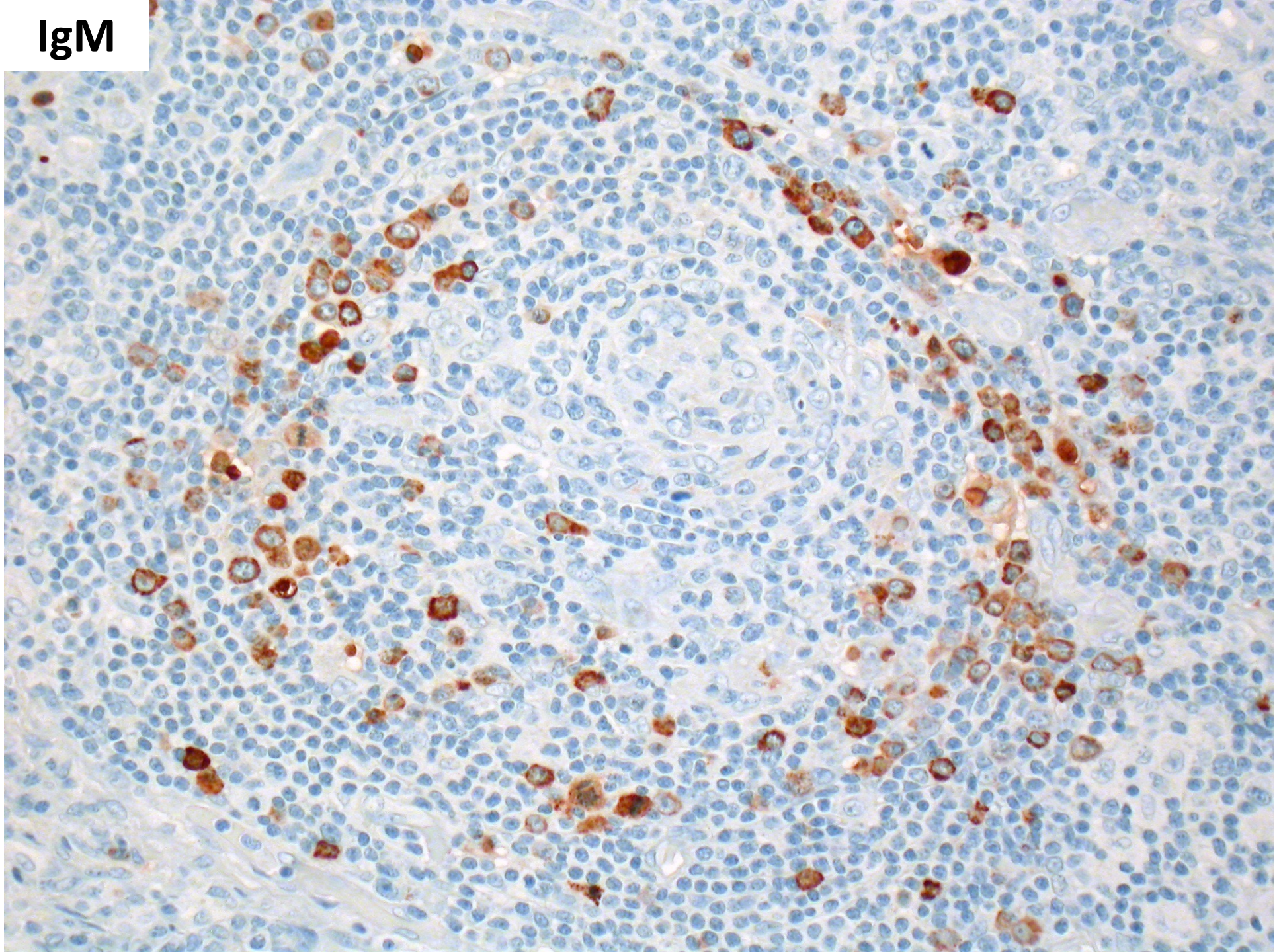




LANA1 of HHV8

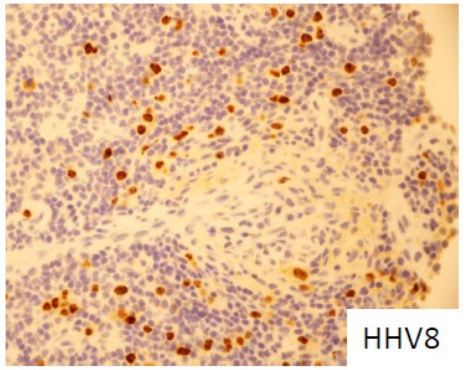



Lambda

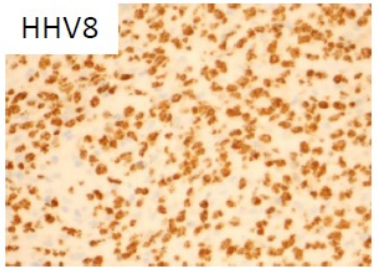

IgM

KSHV/HHV8-LPD in 2022 WHO and ICC

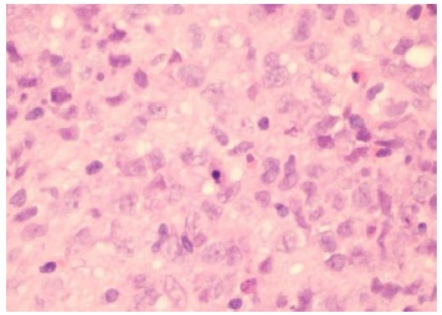
KSHV/HHV8+ MCD



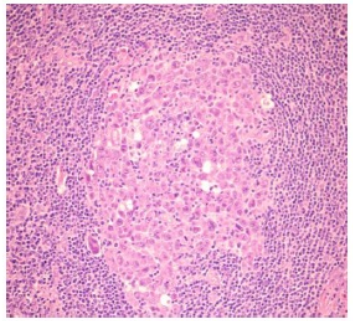
HHV8



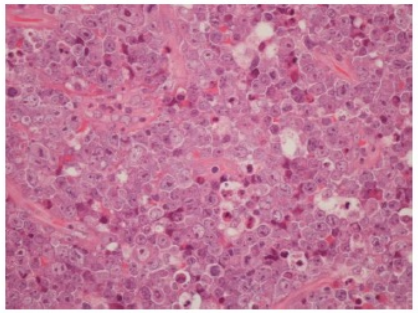
KSHV/HHV8+ DLBCL



The spectrum of HHV8-associated lymphoproliferative disorders



Germinotrophic Lymphoproliferative Disorder

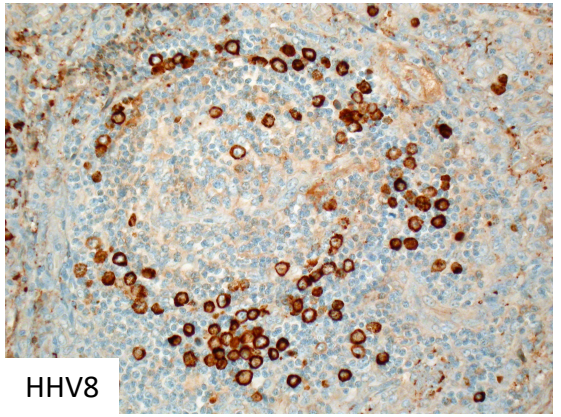


Primary Effusion Lymphoma / Extracavitary PEL

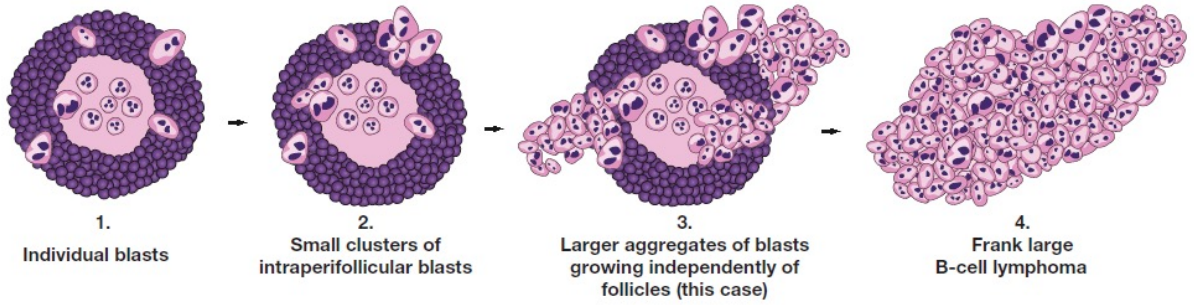
KSHV/HHV8-associated MCD with plasmablastic aggregates

- HHV8+ “plasmablasts” (IgM lambda) in the mantle zones of KHSV/HHV8+ MCD
- B-cell antigens negative, CD138 negative
- May form non-disruptive aggregates in a variety of locations:

  within the mantle zone, involving the germinal centre, interfollicular
- Previously termed “microlymphoma”
- Not diagnostic of lymphoma “on thero own”
- Possible progression of KSHV/HHV8+ MCD to KSHV/HHV8+ MCD with plasmablastic aggregates to KSHV/HHV8+ DLBCL
- Risk of NHL (including KSHV/HHV8+ DLBCL) in HIV+ persons is 15x higher in those with MCD vs those without MCD.



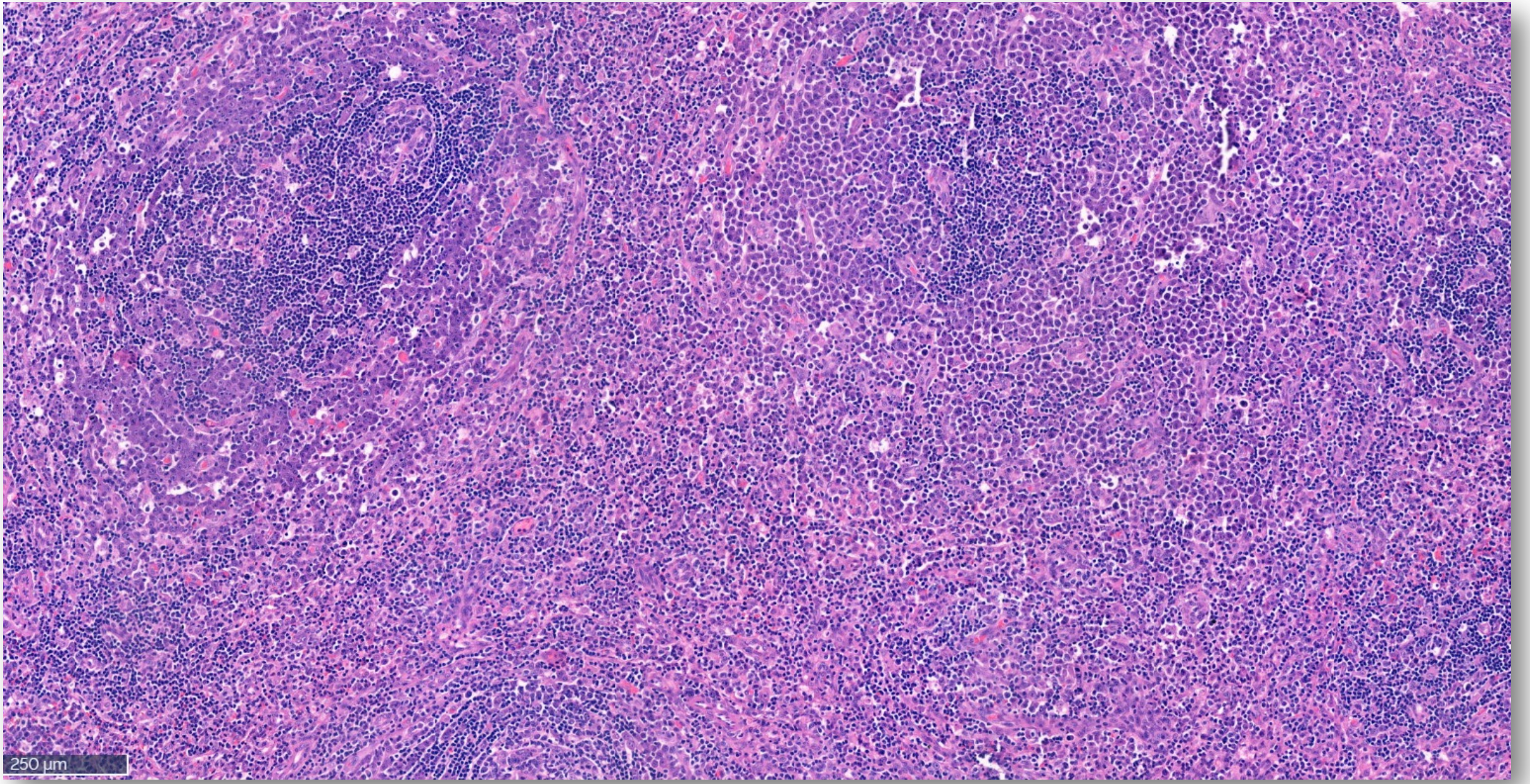
HHV8

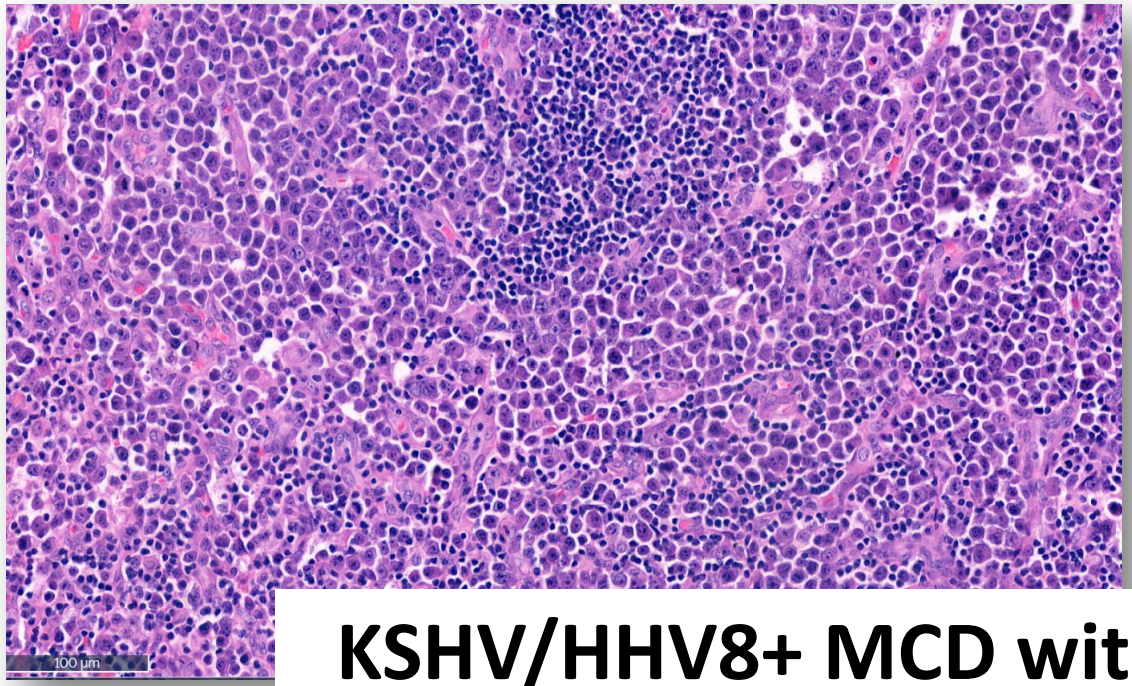


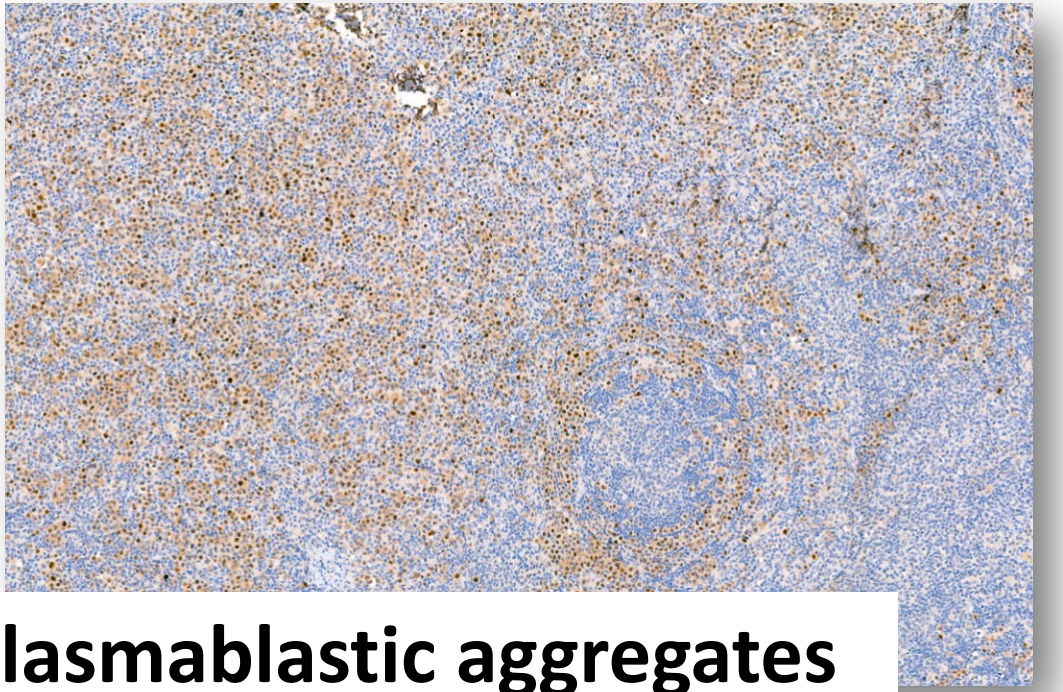
Chadburn A et al. Am J Clin Pathol . 2017
Oksenhendler E et al. Blood. 2002

Case of Dr. C. Bacchi, Brazil

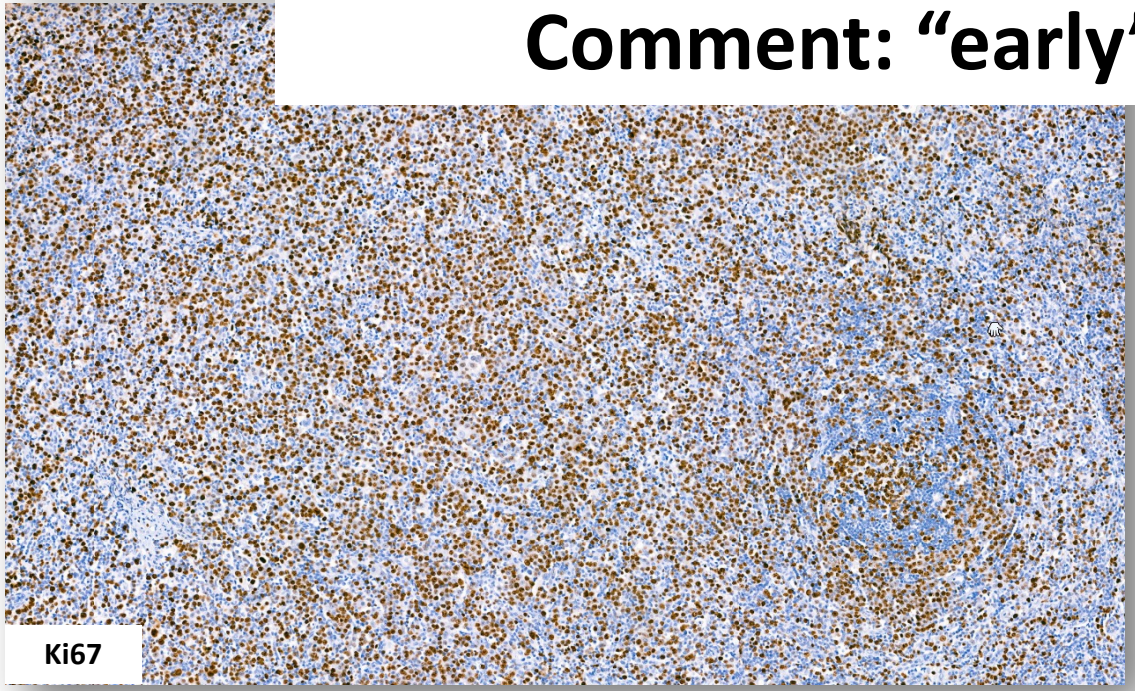
- Male, HIV-positive
- Lymphadenopathy

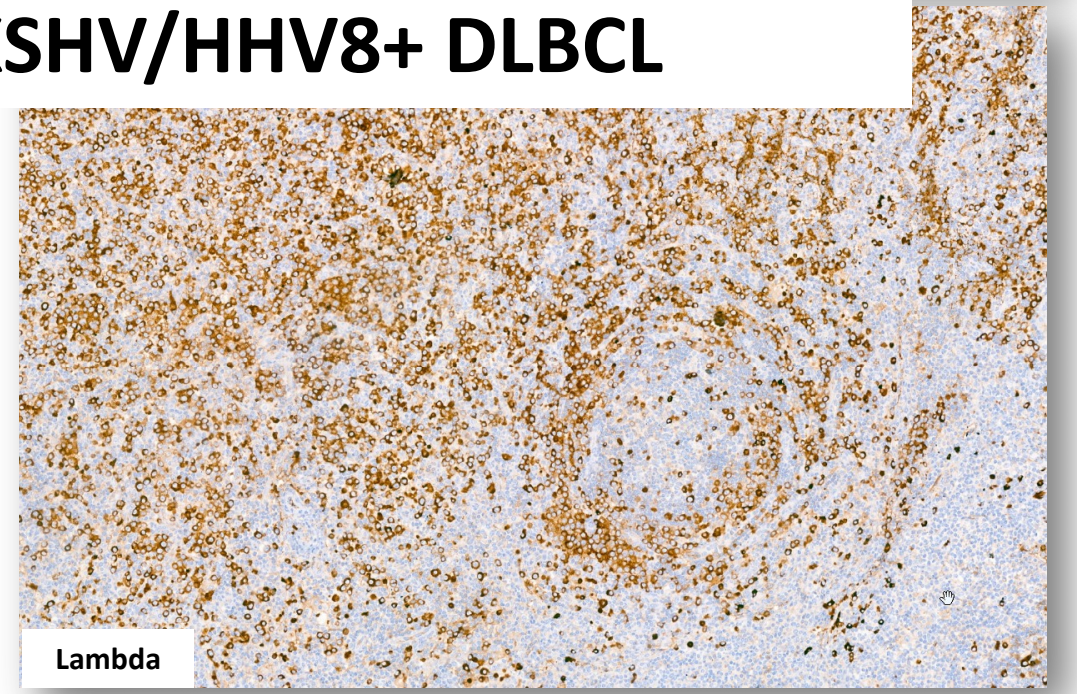






KSHV/HHV8+ MCD with plasmablastic aggregates
Comment: “early” KSHV/HHV8+ DLBCL





KSHV/HHV8+ LPD: challenges

- Rare entities
- Overlapping clinical, morphological and immunophenotypical features
  - W*hen do large plasmablastic aggregates in HHV8+ MCD become HHV8+ DLBCL?*
  - *When does GLPD become ePEL?*
  - *When is EBV- PEL actually HHV8+ DLBCL?*
  - *When are EBV+ plasmablastic aggregates in HHV8+ MCD actually GLPD (and vice versa)*
- KSHV/HHV8+ diseases frequently co-occur
  - KSHV/HHV8+ MCD: 10-20% have concurrent or subsequent lymphoma (& Kaposi sarcoma)
- **Differentiating these diagnoses requires a holistic approach, including clinico-radiological, morphological, immunophenotypicaland molecular details**

Slide (modified): Dr. Anna Green, London, UK

iMCD

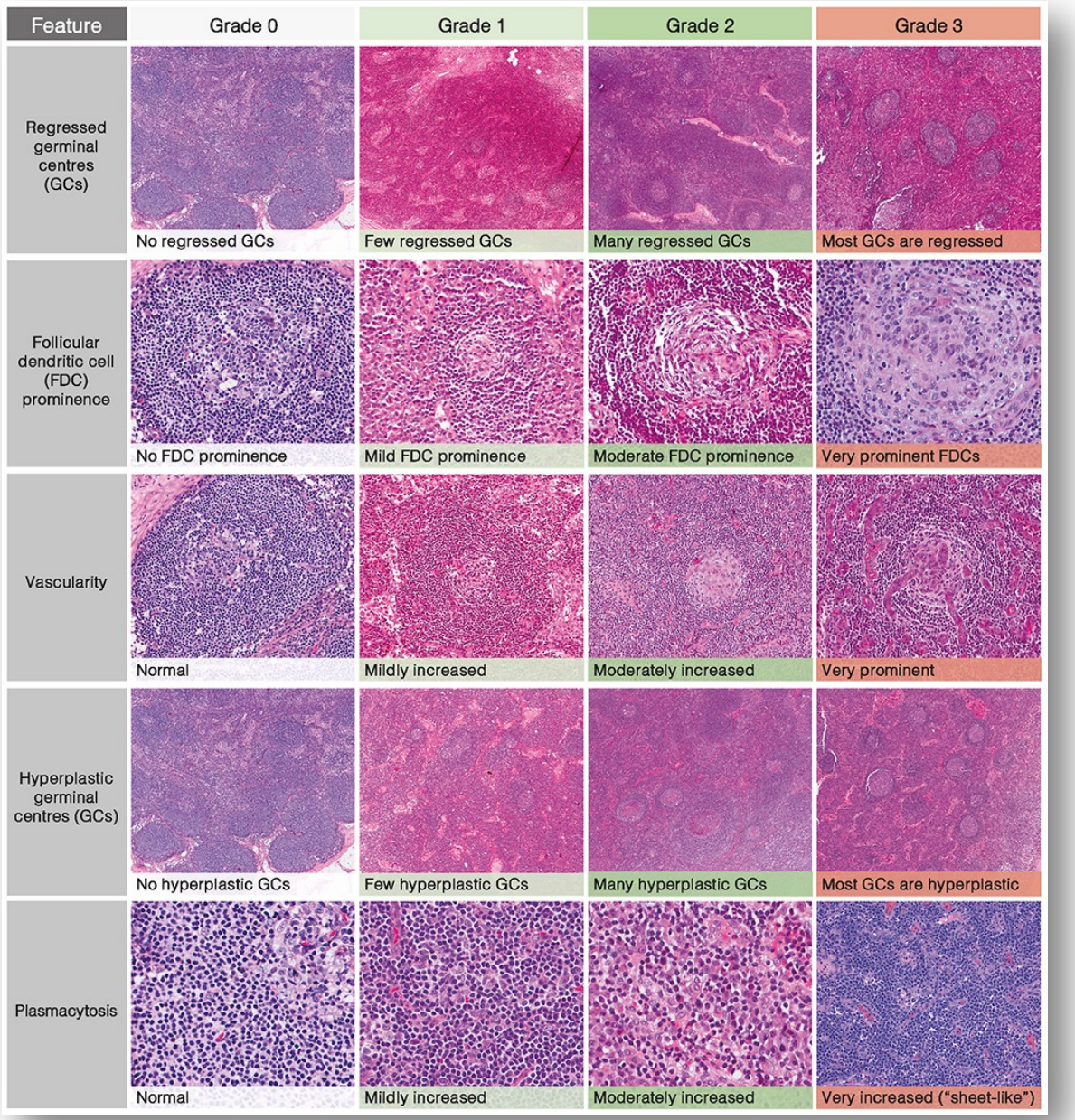
- Systemic inflammatory symptoms (fever, fatigue, renal dysfunction etc.)
- Generalized lymphadenopathy (two ore more)
- Hypercytokinaemia (IL-6, IL-2R, VEGF) and polyclonal hypergammaglobulinaemia
- HHV8 - negative
- Diagnosis requires morphological, clinical and laboratory criteria
- …. and exclusion of infections, malignancies & autoimmine/inflammatory disorders
- Subtypes:
  - iMCD, NOS
  - iMCD, TAFRO

Fajgenbaum DC, Blood. 2017
Carbone A, Nat Rev Dis Primers. 2021
Chadburn A, WHO-5 2024

iMCD: Histopathology

- Regressed germinal centres*
- Follicular dendritic cell prominence
- Vascularity
- Hyperplastic follicles
- Plasmacytosis*

- Grade 0-3
- Grade 2-3 required for dx*



Fajgenbaum DC, Blood. 2017
Chadburn A, WHO-5 2024

iMCD: Major diagnostic criteria

all 3 are required

- Enlarged (>1 cm) lymph nodes (2 or more)
- iMCD morphology with Grade 2-3 for regressed germinal centres or plasmacytosis
- HHV8 – negative (LANA1 IHC)

Fajgenbaum DC, Blood. 2017
Chadburn A, WHO-5 2024

iMCD: Minor diagnostic criteria

at least two, with at least one laboratory

Laboratory

- Anaemia
- Thrombocytopenia or thrombocytosis
- CRP elevation
- Renal dysfunction or proteinuria
- Polyclonal hypergammaglobulinaemia

Clinical

- Constitutional symptoms
- Large spleen and/or liver
- Fluid accumulation (oedema, effusions, anasarca)
- Eruptive cherry haemangiomatosis or violaceous papules
- Lymphocytic interstitial pneumonitis

Fajgenbaum DC, Blood. 2017
Chadburn A, WHO-5 2024

iMCD: Exclusion criteria

Infections

- EBV, COVID-19, HIV, KSHV/HHV8, tuberculosis, etc

Malignancies

- lymphoma, myeloma, metastatic cancer, POEMS syndrome

Autoimmine/inflammatory disorders

- SLE, RAs, adult-onset Still disease, juvenile idiopathic arthritis, Sjögren syndrome, ALPS, HLH, IgG4-related disease

iMCD-TAFRO and iMCD-NOS

iMCD-TAFRO

- Thrombocytopenia
- Anasarca
- Fever
- Reticulin myelofibrosis, renal dysfunction
- Organomegaly

iMCD-NOS

- Not all 5 TAFRO criteria
- Thrombocytosis frequent

	iMCD-NOS	iMCD-TAFRO
Age	Fifth to sixth decade	Fifth decade
Systemic symptoms*	++ And occasional PN	+++ And anasarca
Lymphadenopathy	Peripheral plus central; often small volume	Peripheral plus central; often small volume
Organomegaly	++	+++
Abnormal inflammatory markers†	+++	+++ Also increased procalcitonin
Anemia, thrombocytopenia, abnormal LFTs	++ Sometimes thrombocytosis	+++
Hypergammaglobulinemia	+++	±
Renal dysfunction	+	++ Intravascular coagulation and fibrinolysis
Autoimmune phenomena	++ AIHA, PNP, ITP, interstitial lung disease	±
Pathologic features	Usually PC variant	Usually mixed or hypervascular type
Therapy	IL-6–targeted therapy; rituximab; systemic therapies	Same as iMCD, but also calcineurin inhibitors
Clinical course	Variable	Very aggressive
Risk for lymphoma	+	±

Fajgenbaum DC, Blood. 2017
Chadburn A, WHO-5 2024

iMCD-IPL

Idiopathic Plasmacytic Lymphadenopathy – «the new kid on the block»

Definition

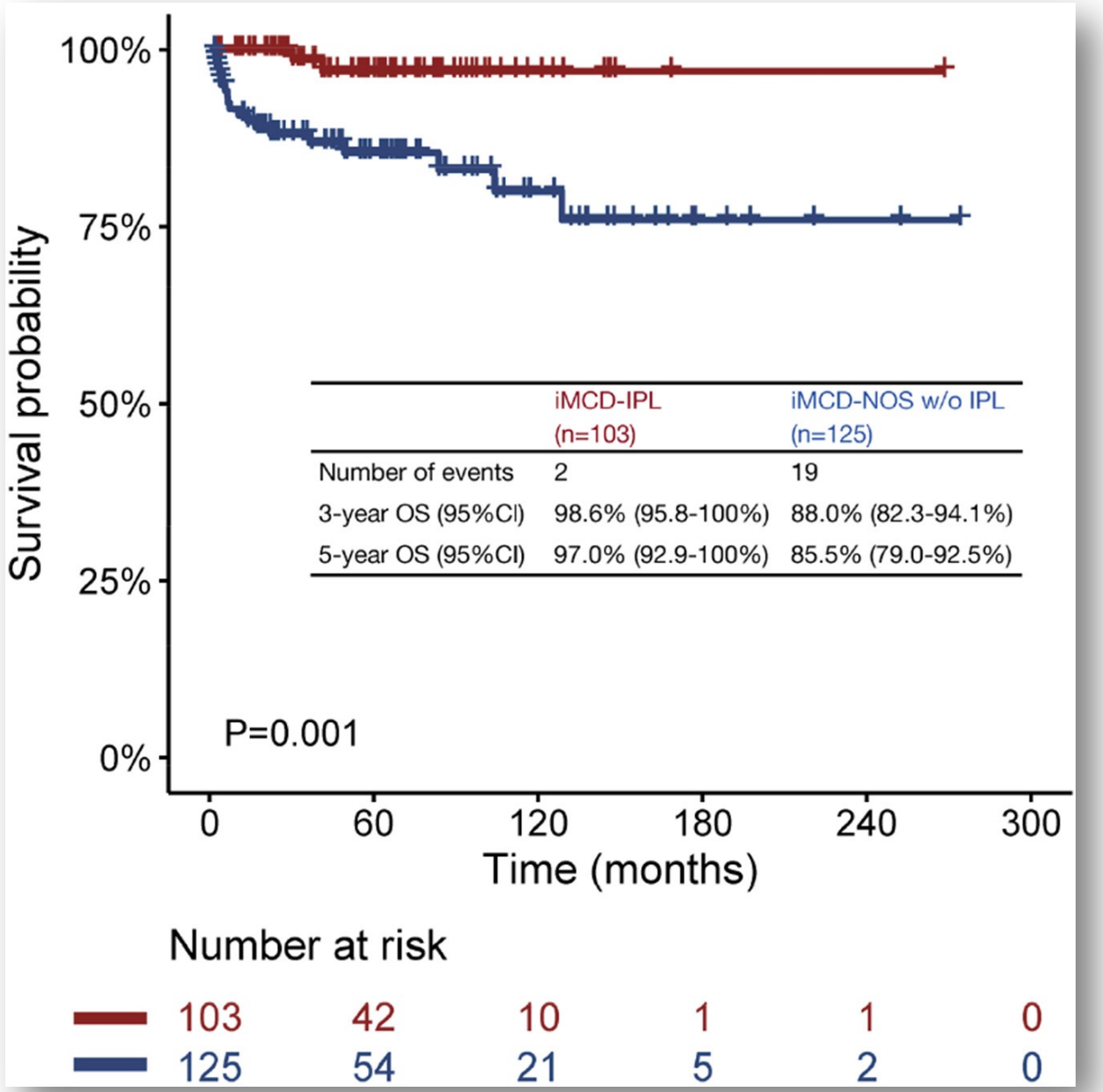
- Not TAFRO
- Plasmacytic histopathology
- Polyclonal hypergammaglobulinemia
- Thrombocytosis

Other characteristics

- Lower Hb and albumin
- Higher IL-6 levels
- Higher inflammatory state
- Better response to myeloma – like & IL6-blocking treatments

Gao YH, Br J Haematol. 2024
Nishikori A, Int J Mol Sci. 2022

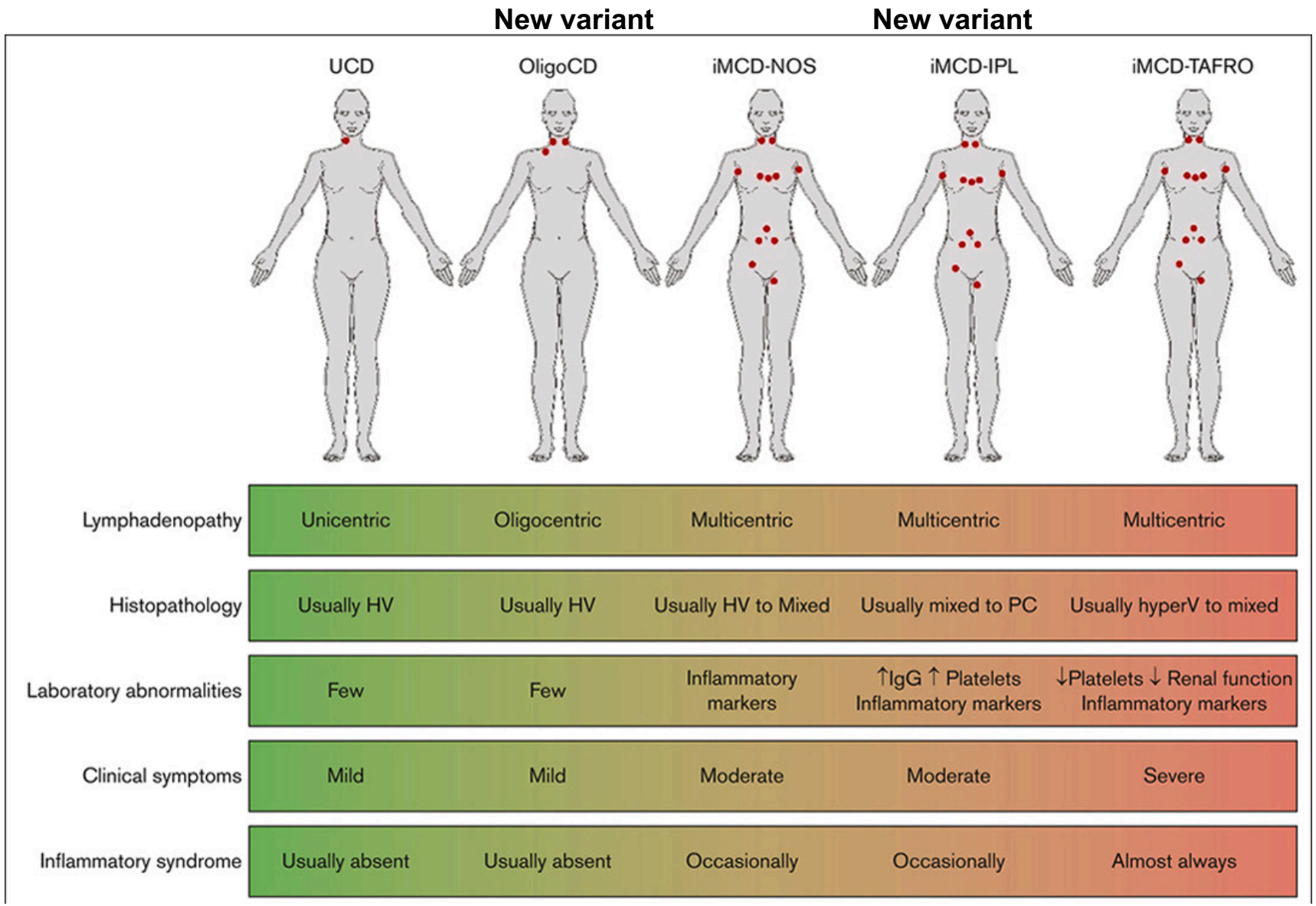
OS of iMCD



	iMCD-IPL (n=103)	iMCD-NOS w/o IPL (n=125)
Number of events	2	19
3-year OS (95%CI)	98.6% (95.8-100%)	88.0% (82.3-94.1%)
5-year OS (95%CI)	97.0% (92.9-100%)	85.5% (79.0-92.5%)

Gao YH, Br J Haematol. 2024

The spectrum of CD



Pierson S, Blood Adv 2025

Castleman disease: Summary

- CD is not a single disorder
- Several different, etiologically unrelated diseases
- HV, PLV, mixed
- Grading of histological features (WHO-5)
- UCD vs MCD
- Oligocentric CD potential new variant
- HHV8+ MCD; iMCD-NOS, iMCD-TAFRO, iMCD-IPL (provisional), POEMS-MCD
- Diagnosis requires morphological, clinical & laboratory criteria
- Exclude mimickers of CD

The Power of Diagnostics

Pathology Basel

stefan.dirnhofer@usb.ch

POEMS-associated MCD

- **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**-protein, **S**kin changes
- Paraneoplastic syndrome in λ-restricted plasma cell neoplasms
- Pathology:
  - 60% plasmacytic CD features in LN
  - 50-90% megakaryocyte hyperplasia and clustering in BM (MPN!)
  - 2/3 λ-restricted plasma cells in BM (median < 5%)
  - 50% BM with lymphoid aggregates rimmed by PC

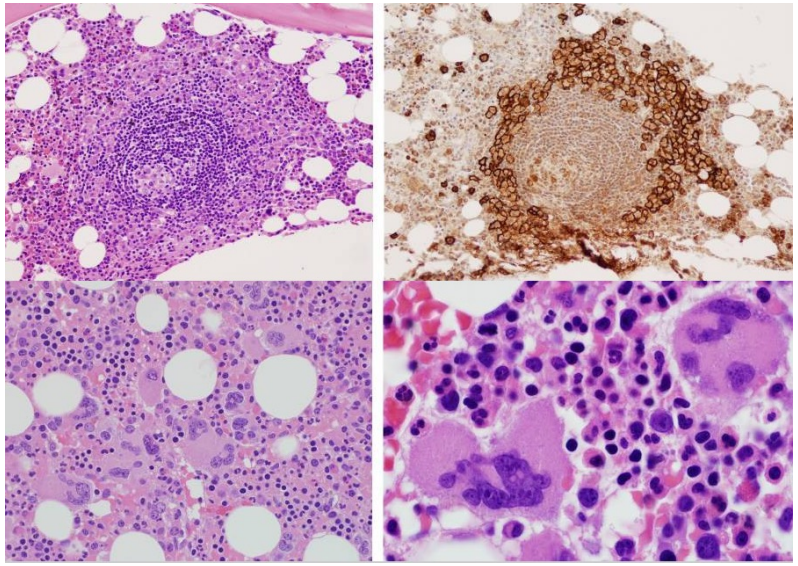


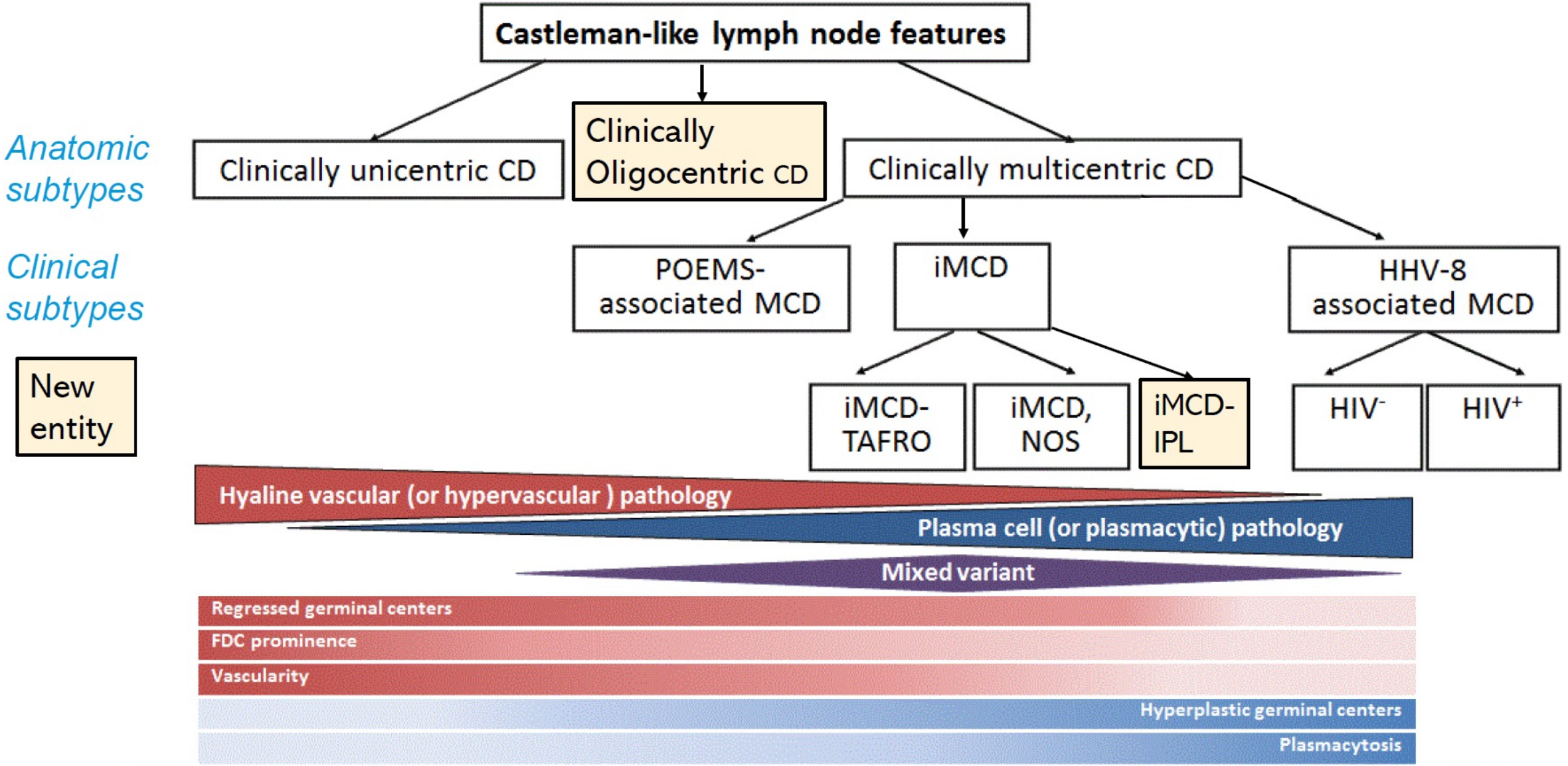
TABLE 1 Criteria for the diagnosis of POEMS syndrome[a]

Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3. Castleman disease[a]
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,[b] pituitary, gonadal, parathyroid, pancreatic[b])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis / polycythemia[c]

Dao LN, *Blood*. 2011; **Wang C**, *Leuk Res*. 2016; **Nagao Y**, Leukemia. 2019; **Dispenzieri A,** *Am J Hematol*. 2021

	HHV8-associated MCD with plasmablastic aggregate	KSHV/HHV8+ DLBCL	ePEL	Germinotropic Lymphoproliferative Disorder
HIV / Immunodeficiency	+/- (HIV- tend to be older)	+	+	-
Distribution	Multiple lymph nodes *+/- spleen*	Lymph node &/or spleen	Lymph node or extra-nodal	Lymph nodes
Morphology / Location of Plasmablasts	Retained architecture. Plasmablasts: - Involving the germinal centre - Within the mantle zone - In the interfollicular area Background features of HHV8+ MCD	Effacement of architecture. Sheets; plasmablastic/immunoblastic morphology	Effacement of architecture (may be focal involvement) Sheets; plasmablastic/immunoblastic/anaplastic morphology	Retained LN architecture. Cells with plasmablastic/immunoblastic/anaplastic morphology partially or completely replacing a proportion of germinal centres. +/- involvement of mantle zones, interfollicular areas, sinuses Atrophic or hyperplastic follicles. Interfollicular, polytypic plasmacytosis.
B-cell Antigens	Usually negative, may be dim. CD138 -	CD20 variable. Other B-cell antigens negative. CD138 -	Few or absent. CD138 +/-	Negative CD138 -/+
HHV8	+	+	+	+
EBV	- (rare reports of EBV+)	- (rare reports of EBV+)	+ (>80%) LMP1-	EBER+ LMP1-
Immunoglobulin	IgM Lambda	IgM Lambda (>>Kappa)	Negative.	+/- Kappa or Lambda
Ig Gene Rearrangement	Polyclonal Lacks somatic hypermutations	Monoclonal Lacks somatic hypermutations.	Monoclonal Somatic hypermutations.	Polyclonal or oligoclonal. With somatic hypermutations.
Clinical Course	Relapsing and remitting. Increased risk of lymphoma	Aggressive.	Aggressive, but more favourable than PEL	Good prognosis. Rare cases of progression to KSHV/HHV8+ DLBCL or EBV+ DLBCL

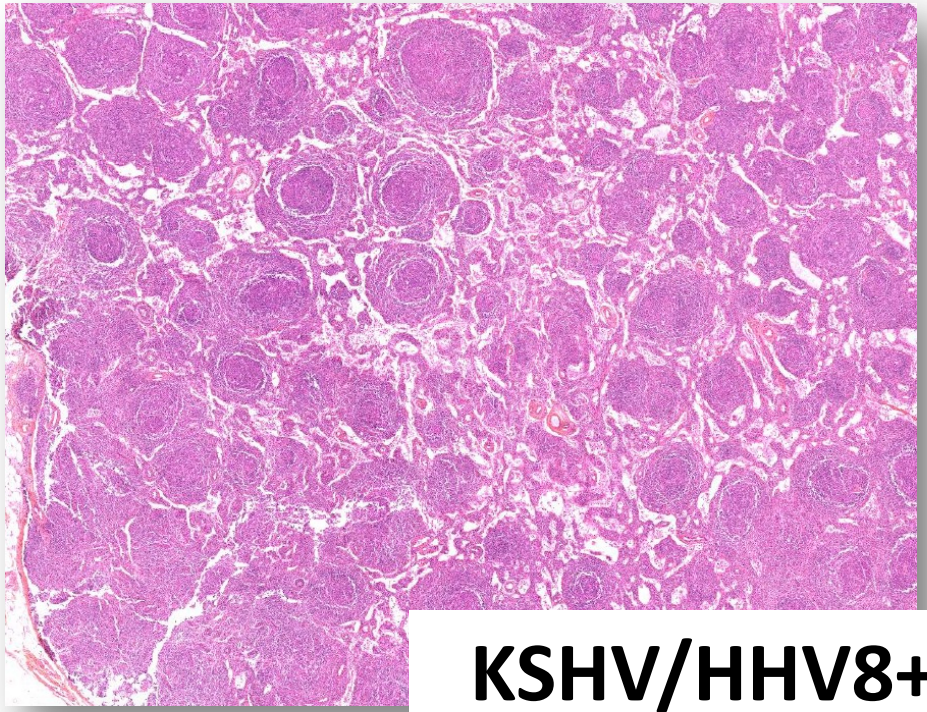
Modified from WHO 5th Ed.



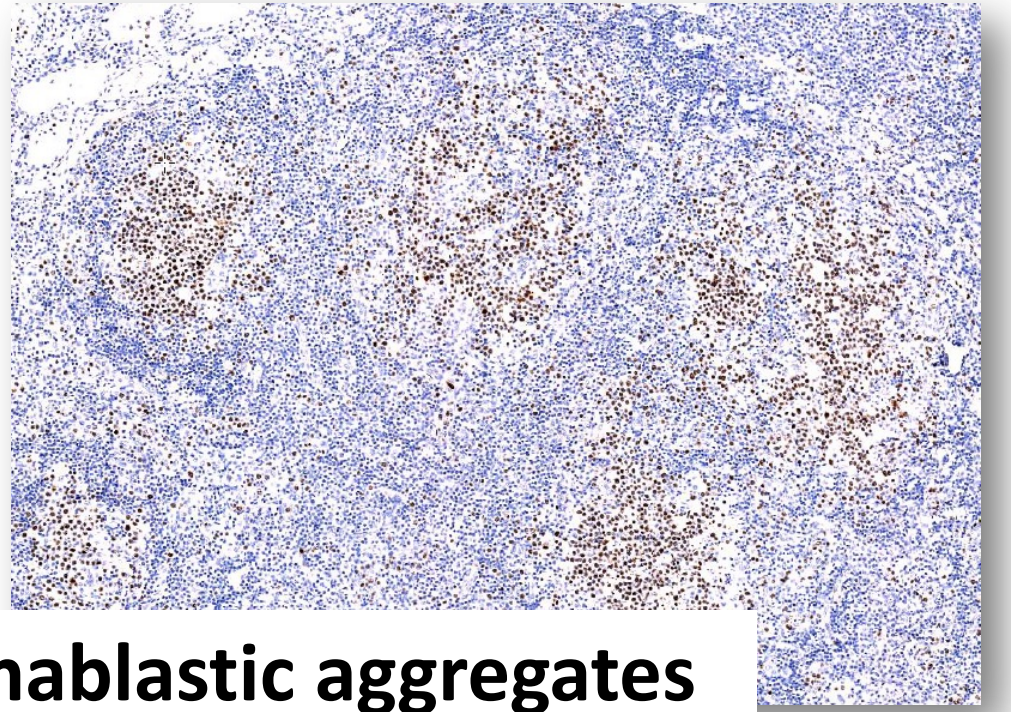
Modified from: Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood. 2020;135(16):1353-64.

Slide courtesy of: A. Dispenzieri

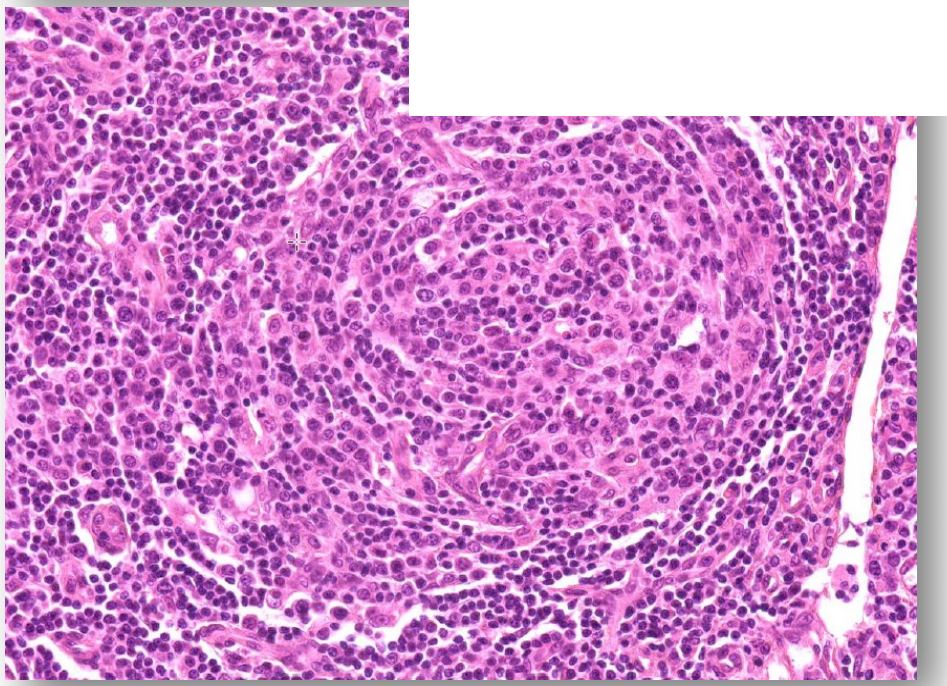
EAHP 2024
LYWS 28 Dr. Xerri, France

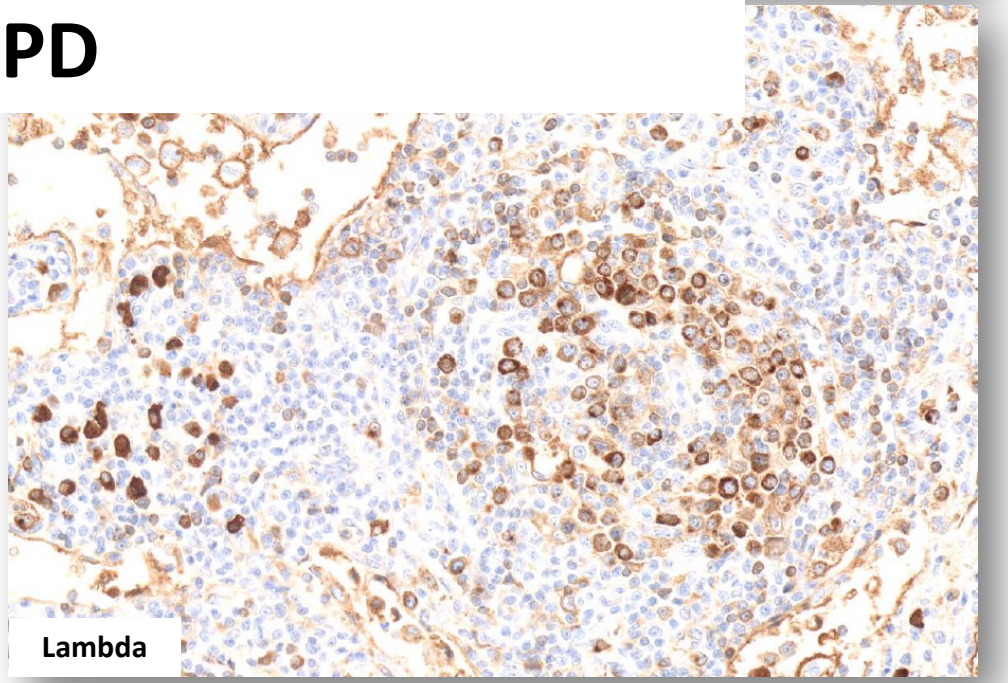


- Male, 50 yr
- Inflammatory syndrome
- CT: Generalized adenopathy
- HIV-negative

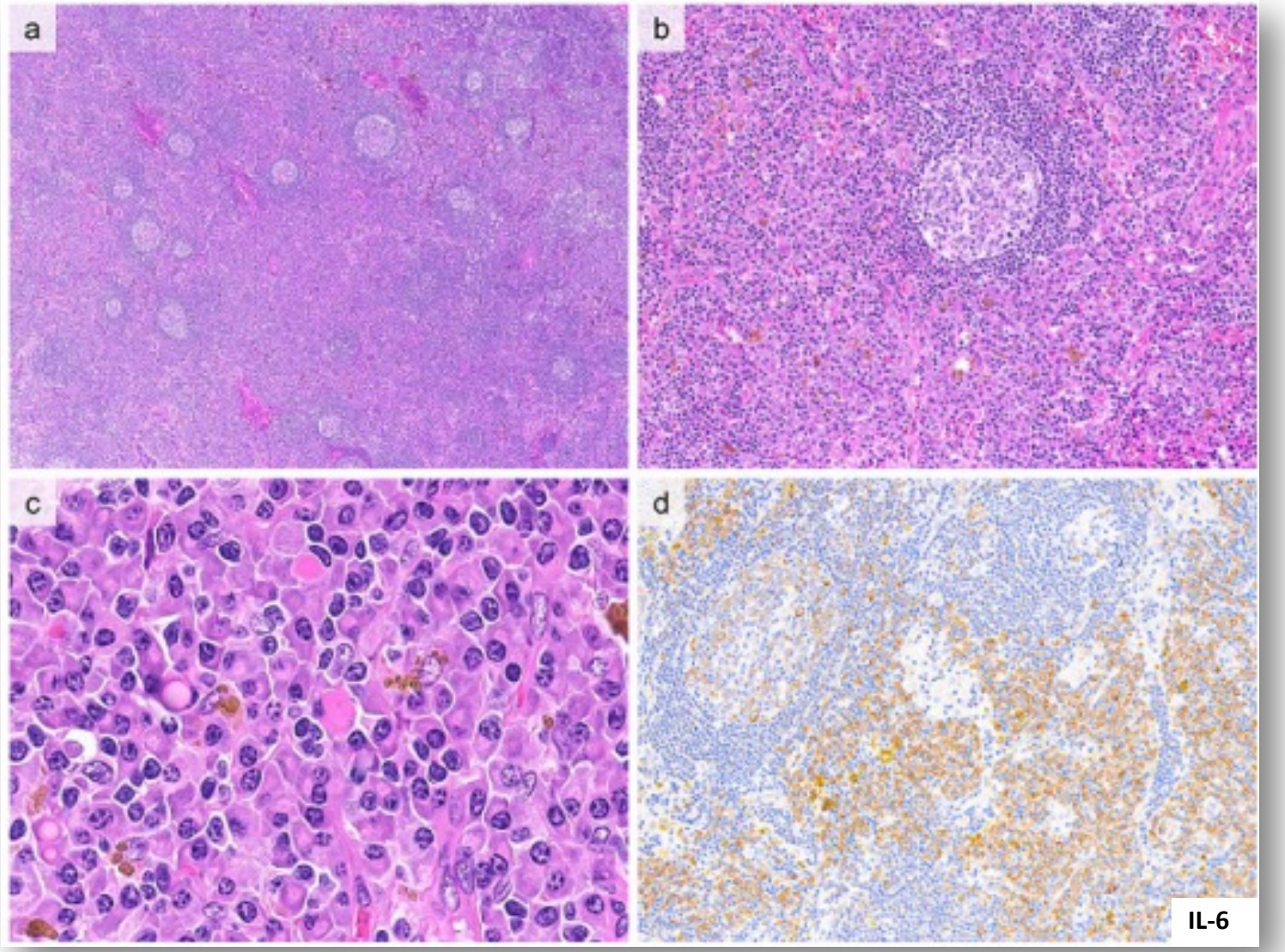


KSHV/HHV8+ MCD with plasmablastic aggregates mimicking GLPD

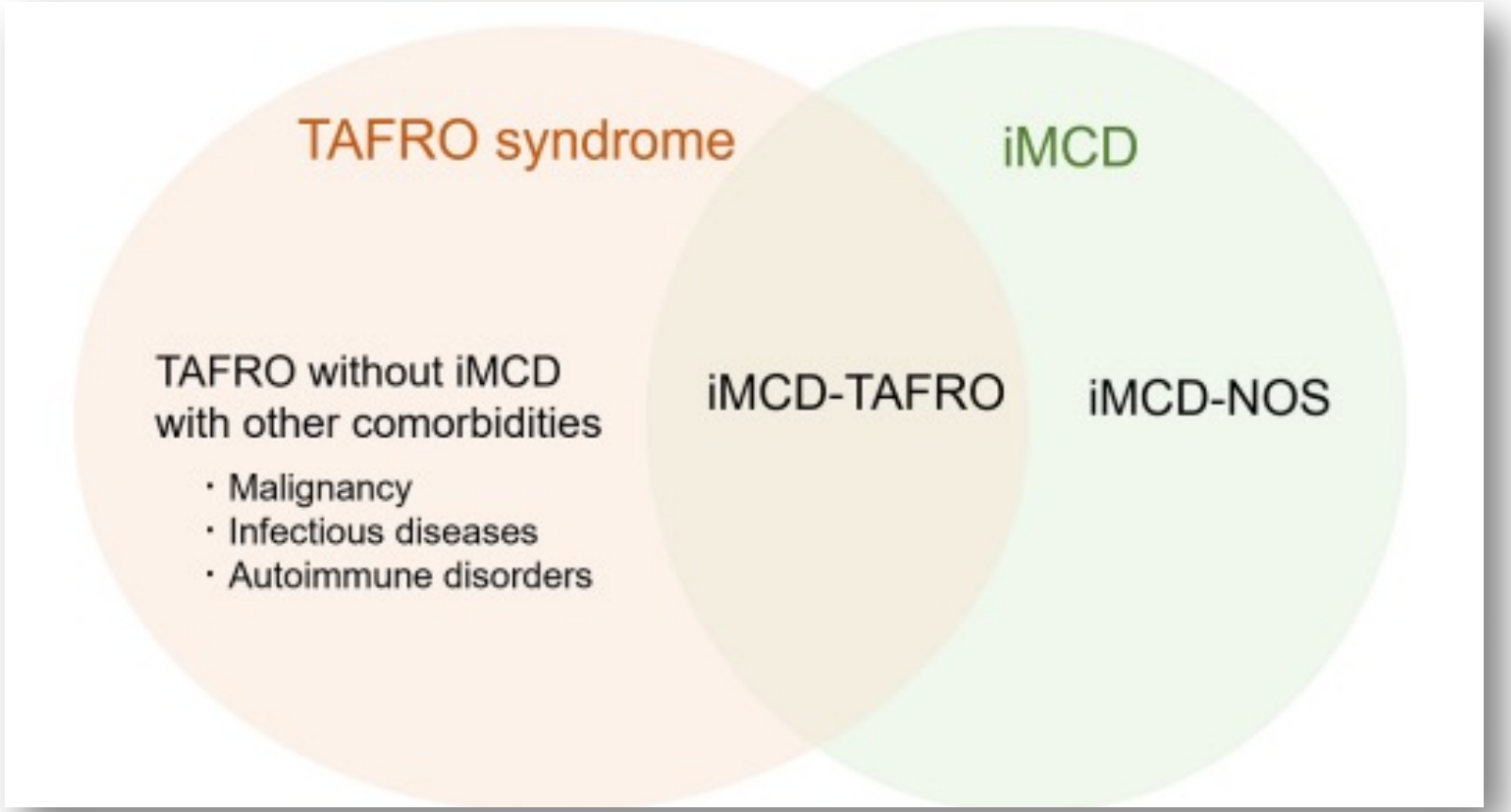




iMCD-NOS



Nishimura MF, J Clin Exp Hematop. 2022



Nishimura MF, J Clin Exp Hematop. 2022

CD mimickers

- CD histopathological features may be observed in a number of reactive and neoplastic conditions.
  - CD grading may help (no formal diagnostic criteria for DD)
  - multidisciplinarity is mandatory

- CD features in lymphomas **(#LYWS 325, Dr. G. Terinte-Balcan**)
  - Observed in different hystotypes (e.g. FL, MZL, CHL)
  - Often focal

- Infection may give rise to CD-like features in LN
  - HV-CD: HIV, KSHV/HHV8, CMV, EBV etc.
  - mixed/PLV: HIV, KSHV/HHV8, COVID-19, syphilis

- Autoimmune/autoinflammatory diseases and CD-like LN
  - SLE, RA, SjS

Byasa alcinous (Papilionidae)

Epicopeia hainesii (Arctiidae)

Pina-Oviedo S, Pathology. 2017; **Larroche C**, *Am J Hematol*. 2002

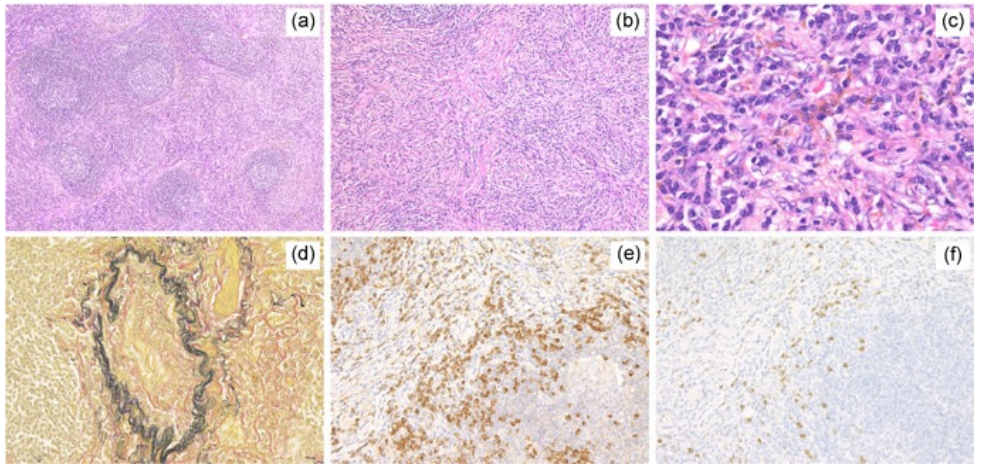
CD mimickers- IgG4 related disease

- A systemic autoinflammatory disease of unknown etiology characterized by:
  - mass lesions of storiform fibrosis
  - obliterative phlebitis
  - lymphoplasmacytic infiltrate with (>400/1mm^2 IgG4+ plasma cells (LN) and/or >40 % IgG4+/IgG+ ratio (extraLN).

- Differential diagnosis between CD and IgG4-RD with iMCD-like patter must be based on multidisciplinary integration **(#LYWS 020, Dr. K. Karube**).

- Histopathology
  - iMCD-NOS have:
    - hyperplastic GCs with interfollicular sheets of IgA+ or IgM+ plasma cells;
    - hemosiderin deposition.
  - IgG4-RD shows a mixed proliferation of eosinophils, small lymphocytes, immunoblasts, and plasma cells, .

	IgG4-RD	iMCD
Clinical features		
• Atopic history (atopic dermatitis, allergic rhinitis, asthma)	Often	Rare
• Exocrine gland involvement (lacrimal glands, salivary glands or pancreas)	Often	Rare
• Lymph node involvement	Sometimes	Major criteria for diagnosis
Biomarkers		
• CRP	Normal	High
• Haemoglobin	Normal	Low
• Platelet	Normal	High/low
• Albumin	Normal	Low
• IgG4: IgG ratio	High	Normal
• IgA	Normal	High
• IgM	Normal	High
• IL-6	Normal	High
Histology		
• Germinal centres expansion	Often	Sometimes
• Mature plasma cells with sheet-like proliferation	Rare	Often
• Haemosiderin deposition	Rare	Often
• IgA+ cells	Rare	Abundant



Sasaki T, *RMD Open*. 2017; **Deshpande V**, *Mod Pathol*. 2012; **González García A**, Rheumatology (Oxford) 2023; **Nishikori A**, Pathol Int. 2022

MCD, a agressive disease….

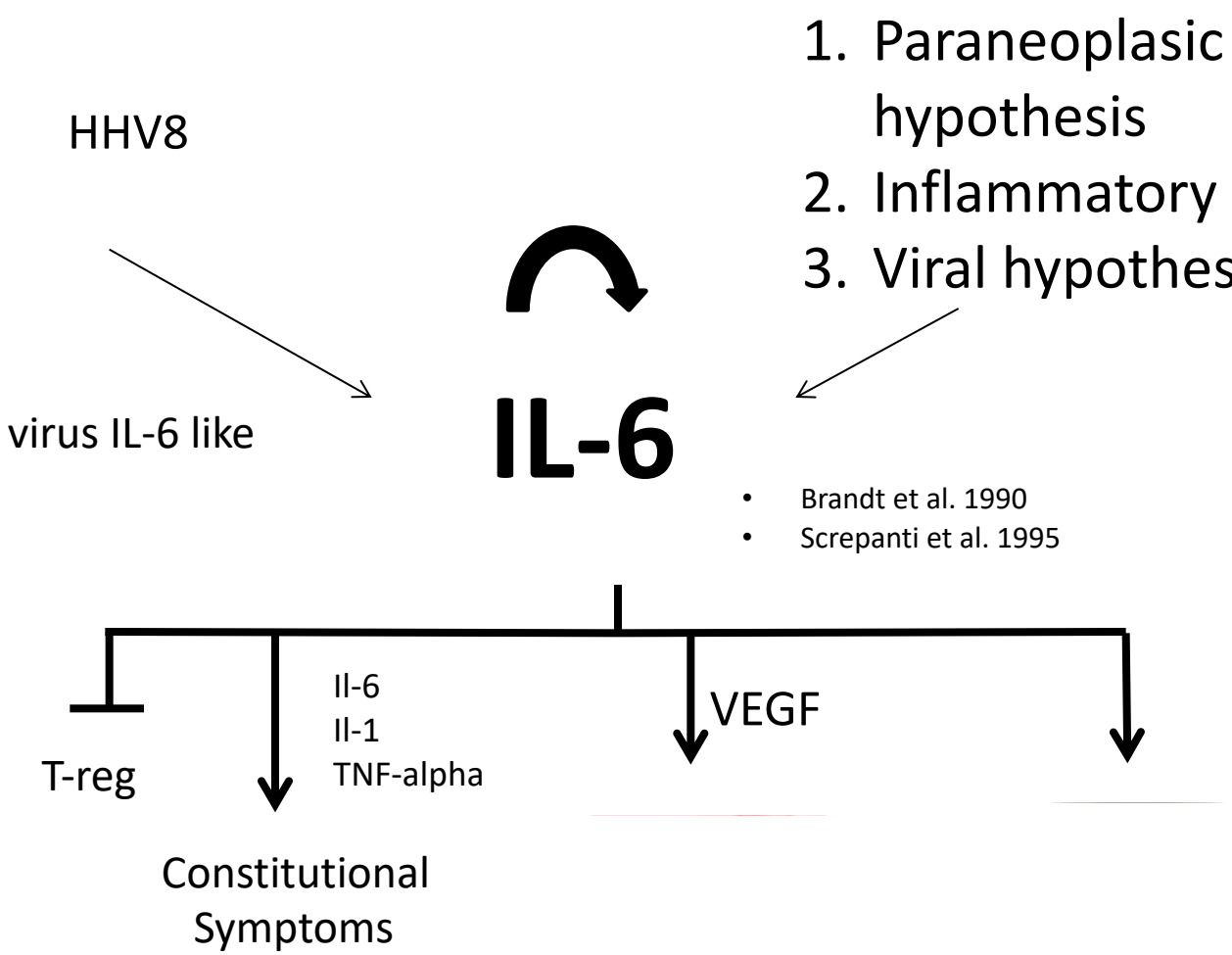
5 years mortality rates !!!!

http://www.cdcn.org/

Difficulties…

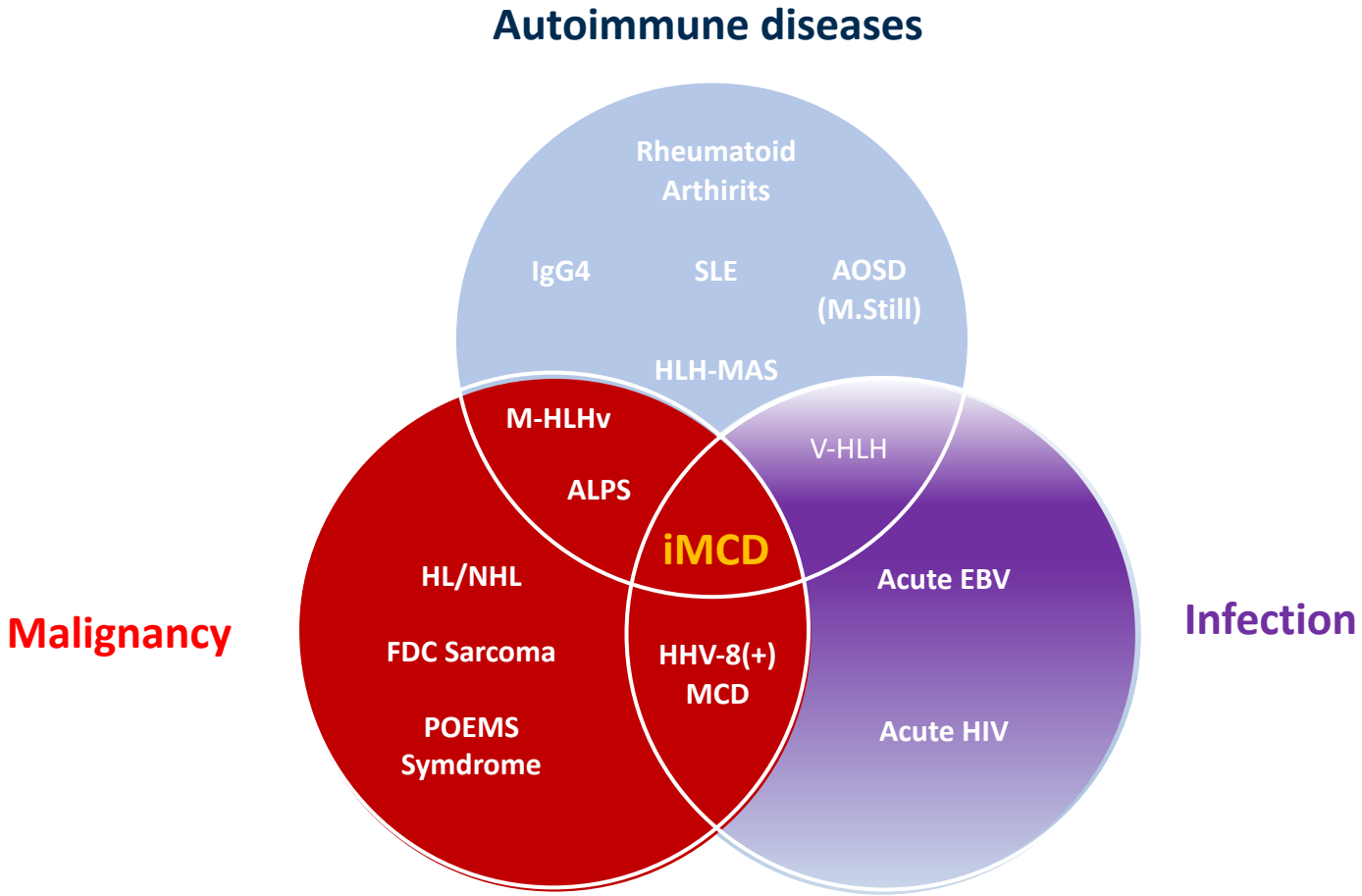
- Castleman-like changes can be seen in other disease
- Castleman disease = group of 3 disease with common morphological features
- In fact the term Castleman disease should be avoided !!!!

Pathogenesis, MCD



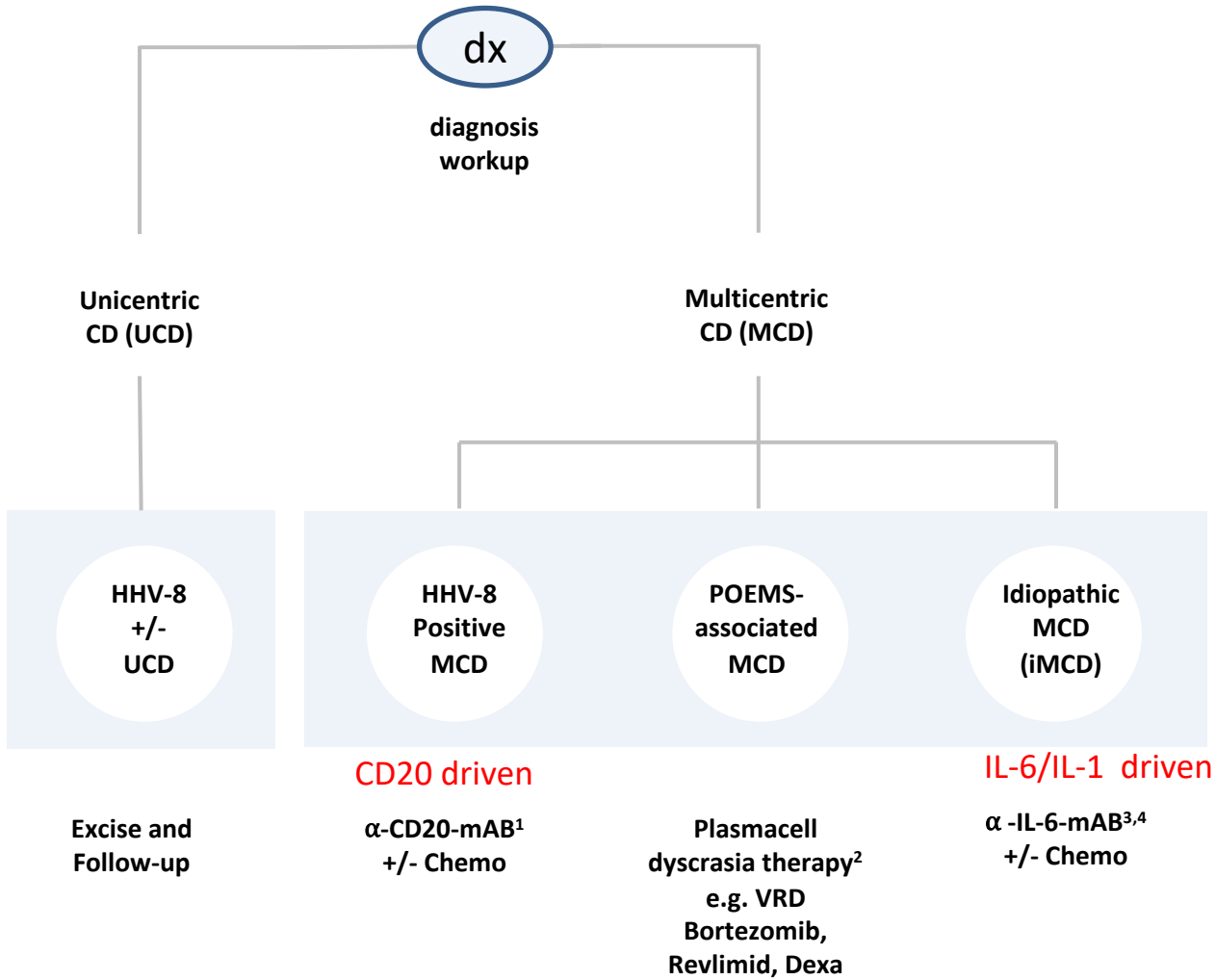
Fajgenbaum DC, van Rhee F, Nabel CS. Blood. 2014 Review.

Diseases overlapping with iMCD



ALPS=autoimmune lymphoproliferative syndrome; AOSD=adult-onset Still disease; EBV=Epstein-Barr virus; FDC=follicular dendritic cell; HHV-8=human herpes virus-8; HIV=human immunodeficiency virus; HL=Hodgkin lymphoma; HLH-MAS=hemophagocytic lymphohistiocytosis-macrophage activation syndrome; IgG4=IgG4-related disease; iMCD=idiopathic multicentric Castleman disease; JIA=juvenile idiopathic arthritis; M-HLH=malignancyassociated hemophagocytic lymphohistiocytosis; NHL=non-Hodgkin lymphoma; POEMS=polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes; RA=rheumatoid arthritis; SLE=systemic lupus erythematosus; V-HLH=viral hemophagocytic lymphohistiocytosis. Fajgenbaum DC, et al. Blood. 2017;129(12):1646-1657.

A proposed algorithm for UCD/ MCD



[1]Hoffmann, C. et al.In Improved Outcome in Patients with HIV-associated Multicentric Castleman's Disease during Recent Years: An Effect of Rituximab?, 18th Conference on Retroviruses and Opportunistic Infections, Boston, 2011; p. 86
[2]Sobas MA, Alonso Vence N, Diaz Arias J, et al. Efficacy of bortezomib in refractory form of multicentric Castleman disease associated to poems syndrome (MCD-POEMS variant) Ann Hematol. 2010;89:217–9
[3]Galeotti C, Tran TA, Franchi-Abella S, et al. IL-1RA Agonist (Anakinra) in the Treatment of Multifocal Castleman Disease. J Pediatr Hematol Oncol. 2008;30:920–4.
[4] El-Osta H, Janku F, Kurzrock R. Successful treatment of Castleman's disease with interleukin-1 receptor antagonist (Anakinra) Mol Cancer Ther. 2010;9:1485–8

Histopathology 2001, 38, 510–518

Development of follicular dendritic cell sarcoma in hyaline-vascular Castleman's disease of the nasopharynx: tracing its evolution by sequential biopsies

A C L Chan, K W Chan,[1] J K C Chan, W Y Au,[2] W K Ho[3] & W M Ng[3]
Department of Pathology, Queen Elizabeth Hospital, [1]Department of Pathology, Canossa Hospital, and Departments of [2]Medicine and [3]Surgery, Queen Mary Hospital, Hong Kong

Date of submission 19 September 2000
Accepted for publication 30 November 2000

Chan A C L, Chan K W, Chan J K C, Au W Y, Ho W K & Ng W M
(2001) *Histopathology* 38, 510–518

Development of follicular dendritic cell sarcoma in hyaline-vascular Castleman's disease of the nasopharynx: tracing its evolution by sequential biopsies

Aims: Hyaline-vascular Castleman's disease (HVCD) and follicular dendritic cell (FDC) sarcoma occurring in the nasopharynx are both extremely rare. We report the first case of transformation of the former into the latter as documented by sequential biopsies. The steps involved in the transformation were described in detail and the possible role of p53 studied.

Methods and results: The patient presented at the age of 23 years with nasopharyngeal HVCD. Hyaline-vascular Castleman's disease with FDC overgrowth was diagnosed in a recurrence 8 years later, and a CNA.42 and in-situ hybridization for Epstein–Barr virus-encoded RNAs was negative. Over-expression of p53 protein was observed in the FDC sarcoma and an increased number of weakly p53-positive spindly cells could also be demonstrated in the HVCD specimen. This finding suggested a possible role of p53 in the evolution from HVCD to FDC sarcoma. Critical analysis of the literature shows that, among the 13 reported cases of FDC sarcoma associated with Castleman's disease, possible progression from the latter to the former is documented in only two cases.

Summary

- Castleman Disease (CD) is a group of rare lymphoproliferative disorders of unknown aetiologies sharing common and overlapping lymph node morphologic features with each other and other diseases[1-3]
- Diagnosis of CD requires **morphologic findings** that fit within the CD spectrum in patients with clinical findings and symptoms also within the CD spectrum, but also fulfilling the exclusion criteria[1]
- A **multidisciplinary approach** to diagnosis is important to ensure patients receive the treatment they need – this is often instigated by pathologists

But in practice what does this look like and how to we disentangle CD from the other long list of potential diagnoses?

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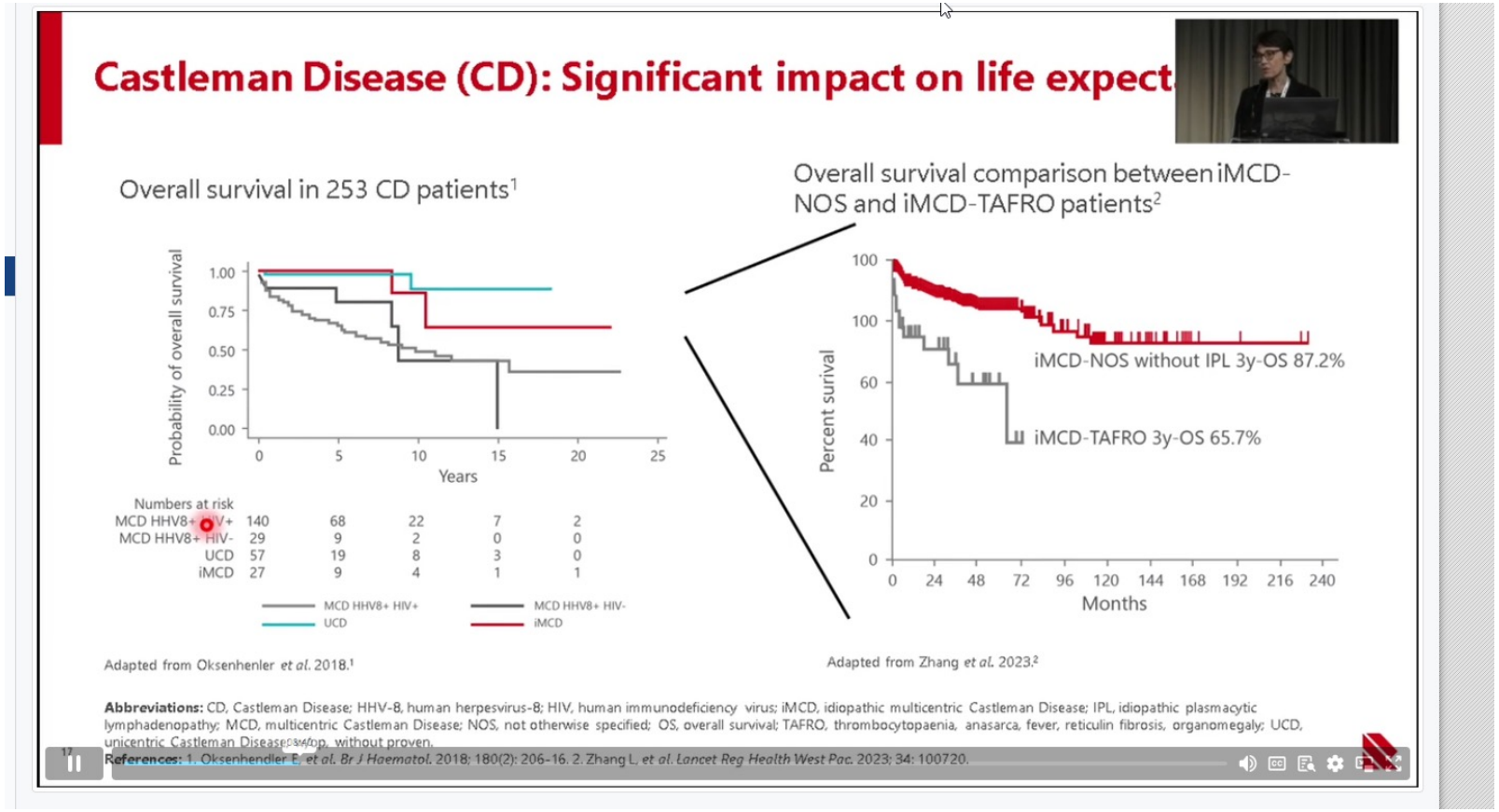

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Idiopathic multicentric Castleman Disease (iMCD)[1-3]

iMCD

TAFRO

Clinical

1. **T**hrombocytopaenia (<100K/uL)
2. **A**nasarca (effusion or subcutaneous oedema)
3. **F**ever or hyperinflammatory status (elevated CRP)
4. **O**rganomegaly (≥2 LN regions, HM or SM)

Pathologic

- LN morphology common with iMCD

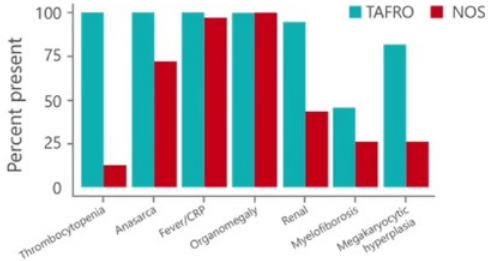
Additional (1 required)

1. **R**enal insufficiency
2. **R**eticulin fibrosis or MK hyperplasia w/o altered diagnosis

NOS

- Does not exhibit all 5 TAFRO criteria
- More often have thrombocytosis
- Usually larger lymph nodes

Performance of the present definition to distinguish iMCD-TAFRO from iMCD-NOS in ACCELERATE natural history registry cohort[3]



Abbreviations: CRP, C-reactive protein; HM, hepatomegaly; iMCD, idiopathic multicentric Castleman Disease; LN, lymph node; MK, megakaryocytic; NOS, not otherwise specified; SM, splenomegaly; TAFRO, thrombocytopaenia, anasarca, fever, reticulin fibrosis, organomegaly; w/o, without.

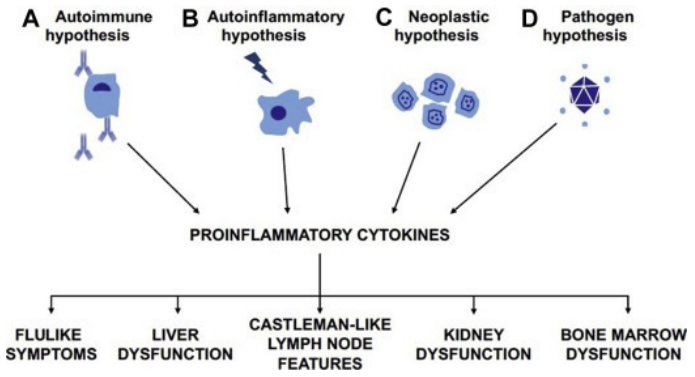
References: 1. World Health Organisation Classification of Tumours, 5th Edition, Volume 11. Available at: https://tumourclassification.iarc.who.int/chaptercontent/63/358. Accessed: September 2024. 2. Belyaeva E, *et al. Hematol Oncol.* 2022; 40(2): 191-201. 3. Nishimura Y, *et al. Am J Hematol.* 2021; 96(10): 1241-52. 3.

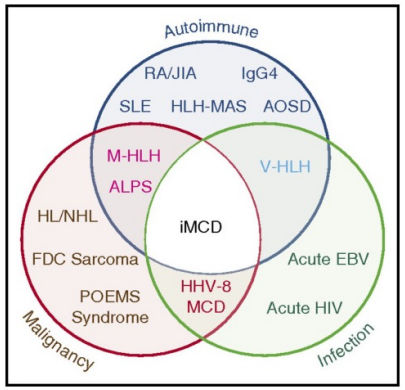
EA4HP-SH 2024 Media Library

iMCD, NOS and TAFRO (1)

- iMCD, NOS: hypercytokinemia, polyclonal hypergammaglobulinemia, B-symptoms, anasarca, organomegaly
  - multiple possible etiology,
  - large overlap with other conditions **(#LYWS 273, Dr Z. Hu)**

- iMCD TAFRO: thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly
  - a separate entity or a subtype of iMCD? **(#LYWS 153, M. M. Nichols)**



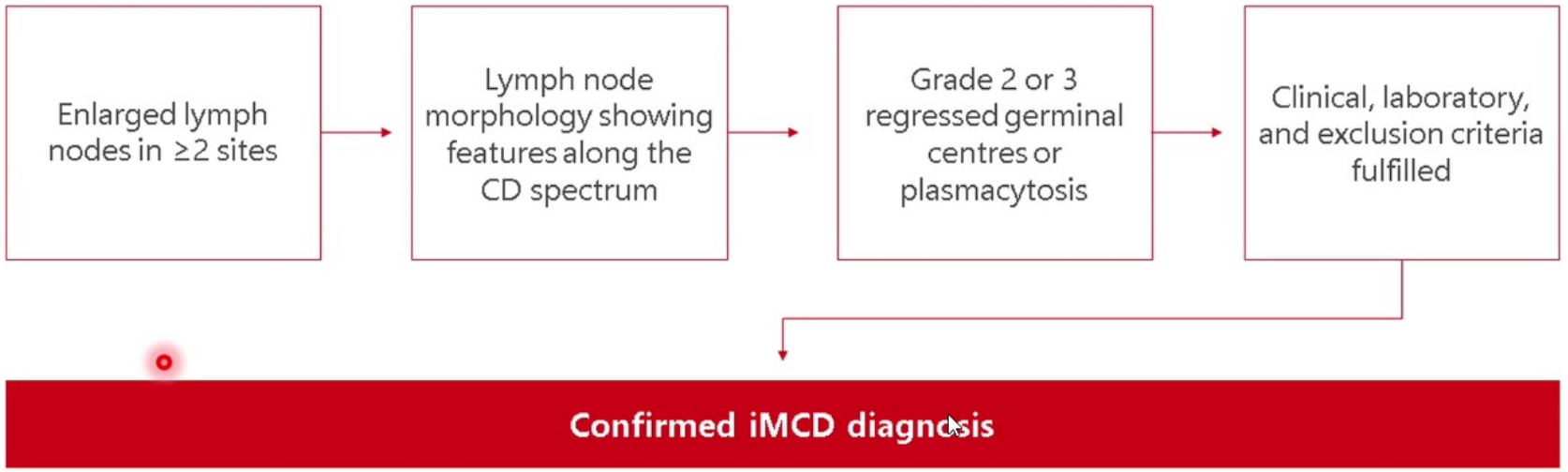


	iMCD-NOS	iMCD-TAFRO
Age	Fifth to sixth decade	Fifth decade
Systemic symptoms*	++ And occasional PN	+++ And anasarca
Lymphadenopathy	Peripheral plus central; often small volume	Peripheral plus central; often small volume
Organomegaly	++	+++
Abnormal inflammatory markers†	+++	+++ Also increased procalcitonin
Anemia, thrombocytopenia, abnormal LFTs	++ Sometimes thrombocytosis	+++
Hypergammaglobulinemia	+++	±
Renal dysfunction	+	++ Intravascular coagulation and fibrinolysis
Autoimmune phenomena	++ AIHA, PNP, ITP, interstitial lung disease	±
Pathologic features	Usually PC variant	Usually mixed or hypervascular type
Therapy	IL-6–targeted therapy; rituximab; systemic therapies	Same as iMCD, but also calcineurin inhibitors
Clinical course	Variable	Very aggressive
Risk for lymphoma	+	±

Fajgenbaum DC, Blood. 2017; **Yoshizaki K**, *Hematol Oncol Clin North Am*. 2018; **Fajgenbaum DC**, Hematol Oncol Clin North Am. 2018; **Carbone A**, Nat Rev Dis Primers. 2021.

Idiopathic multicentric Castleman Disease (iMCD)*1

WHO 5 Criteria



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iMCD NOS, MCD TAFRO, POEMS syndrome CONCLUSIONS

- iMCD NOS, POEMS and TAFRO can show substantial clinical overlap
- Comprehensive integration of clinical, laboratory, histologic and imaging data is crucial
- To rule out other diseases with MCD-like symptoms and/or histology

Dispenzieri Am. J Hematology. 2023
Nishimura Am. J. Hematopath 2021
Miura K et al: Biomedicines 2024
Masaki Y et al: Int J Hematol 2020

- iMCD NOS: rare association with sarcoidosis and secondary amyloidosis (AA type)
- HL or NHL: can arise after it (PLV/mix→cHL; HV→NHL)
- precise relationship between CD, HL and NHLs is still unclear; Risk: low

Yoshizaki K et al: Hem/oncol Clin 2018
Rincon M: Int. J. Biol. Sci. 2012
de Asúa et al: Clin Epidemiol 2014
Abdulgaffar R et al: Ann Diagn Pathol
Laroche C et al: Am J Hematol 2002
Lyapichev KA et al: Virchows Arch 2020
Zarate-Osorno A et al: Arch Pathol Lab Med 1994

- SARS-CoV-2 infection or mRNA SARS-CoV-2 vaccination:
  - iMCD NOS and TAFRO sy occurrence/worsening
  - chronic inflammatory demyelinating polyneuropathy (CIDP)
- ↑VEGF in SARS-CoV-2 infection; serum levels correlate with severity of disease

Hoffman C et al: Vaccines (Basel) 2022
Yamada M et al: J Infect Chemother 2022
Tane M et al: Biomedicines 2024
Liu Y et al: Ther Adv Hematol 2024
Mehta P et al: Lancet 2020
Iosuttis B et al: J Intensive Care Med 2023
Tallotta R: Microorganisms 2022

CD : Differental diagnosis & Mimickers

- Lymphoma
  - FL, MCL, MZL, LPL
  - T-FH
  - cHL
- Non-specific, reactive lymphoproliferations (FH, EBV-assoc. LPD, HIV, SARS-CoV2, other infections)
- Autoimmune disorders (SLA, rheumatoid arthritis, ALPS, etc.)
- IgG4-related disease (IgG4-RD):
  - overlap with iMCD with increased IgG4 - positive plasma cells
  - no constitutional symptoms; extranodal mass lesion (pancreas, orbita, salivary glands)
  - storiform fibrosis and obliterative phlebitis
  - IgG4 >400/mm2, IgG4/IgG ratio >40%, HHV8-negative
  - Eosinophils, polymorphic, lack of hemosiderin deposits
  - Elevated serum IgG4, normal IL-6 & CRP, steroid responsive
  - Dx: clinical, laboratory, radiological and histological features

Chapman et al. Am J Surg Pathol 2020
Desphande et al., Modern Pathol 2012
Cheuk et al., Seminars in Diagn Pathol 2012
Lyiapichev et al., VIAR 2020
Satou et al., Pathol Int. 2020
Nishikori A et al: J Clin Pathol 2024
WHO 5th ed. 2024