



# CASTLEMAN DISEASE – HOW MANY?

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Research support from Menarini/Stemline

Speaker honoraria from Stemline, Astra Zeneca and EUSAPharma

# LOCALIZED MEDIASTINAL LYMPH-NODE HYPERPLASIA RESEMBLING THYMOMA

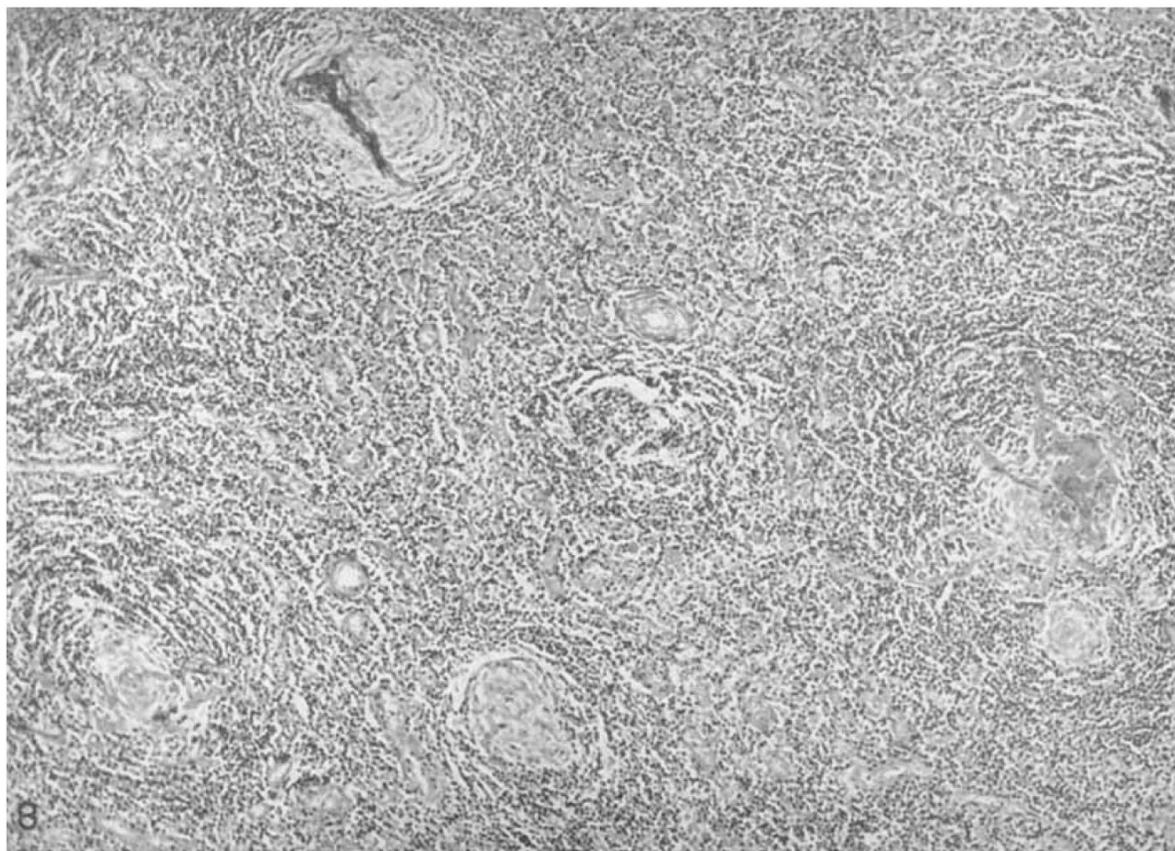
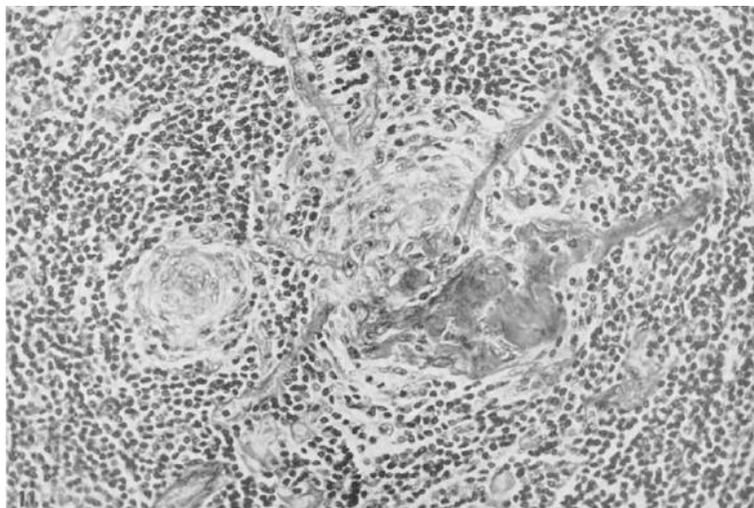
*Cancer* 1956;  
9 (4): 822–30.

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

Description of 13 patients (aged 19-54) with  
mediastinal masses

Initially interpreted as thymoma, recognized  
as form of benign lymph node hyperplasia

(6 pages of pictures, no abstract, 5  
references)



<http://www.iapcentral.org>

# HYALINE-VASCULAR AND PLASMA-CELL TYPES OF GIANT LYMPH NODE HYPERPLASIA OF THE MEDIASTINUM AND OTHER LOCATIONS

Cancer 1972  
29(3):670-83.

ALBERT R. KELLER, MD,\* LISELOTTE HOCHHOLZER, MD,† AND  
BENJAMIN CASTLEMAN, MD‡

## Detailed study of 81 cases

- Designation of hyaline vascular and plasma cell type (7 cases) previously recognized by other authors (JA Flendrig 1969)
- Description of seminal features of the 2 subtypes
- How did the concept evolve in the last 50 years?

HV CD	PC CD
Single mass	Multiple lymph nodes
Sometimes satellite lymph nodes involved	Remnant lymph node architecture
Typical regressed GC	Regressed GC rare (2/7)
„Onion skin“ appearance	Hyperplastic follicles
No/few plasma cells	Massive plasma cell sheets
Local symptoms (3% systemic sy.)	Systemic symptoms common (50%)
Good prognosis	Fever, anemia, elevated ESR, hypergamma-globulinemia, leukocytosis

# DIAGNOSIS OF CD – A CASE-BASED APPROACH

## CASE 1

20-year-old male

Increasing cervical lymphadenopathy over the last two years, otherwise healthy

Status post *Borrelia* infection

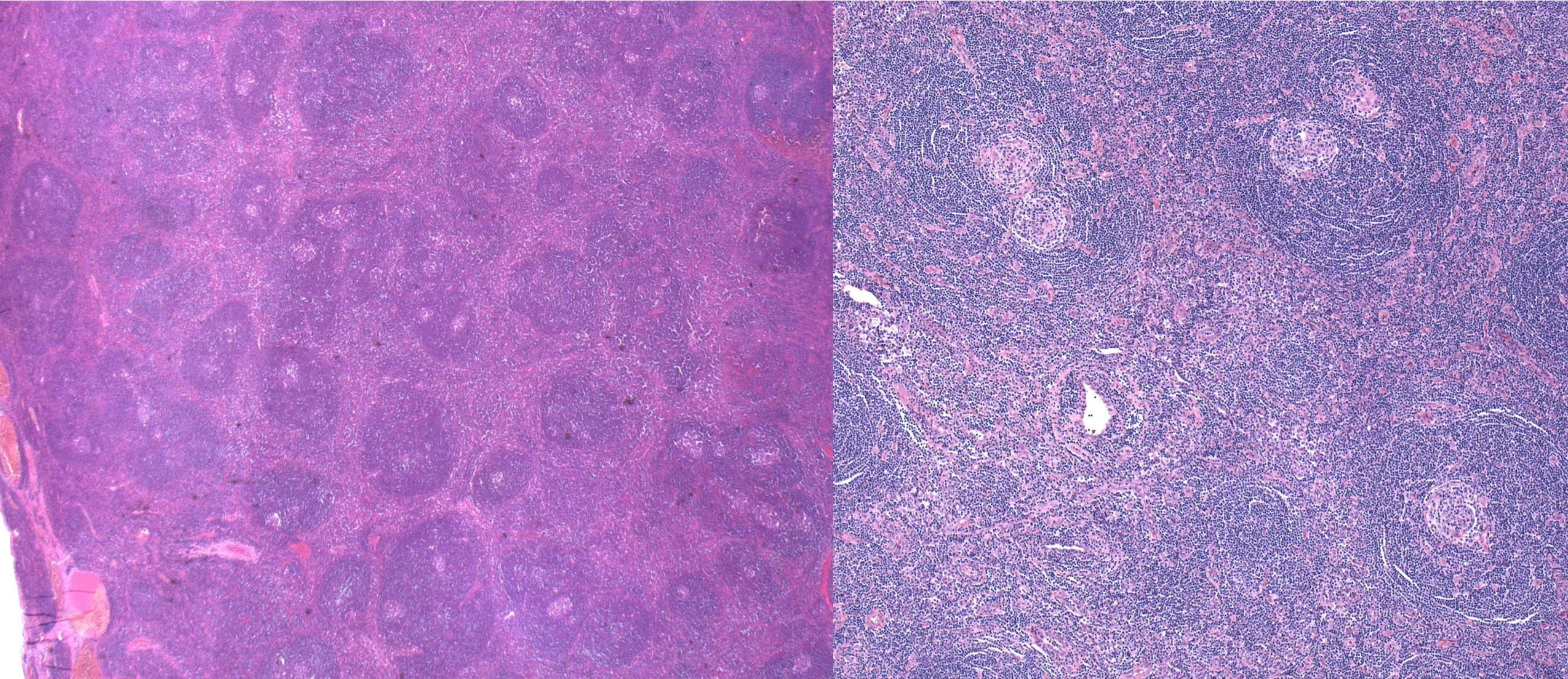
Whole body CAT scan: localized right-sided cervical lymphadenopathy, otherwise normal

BM biopsy not performed

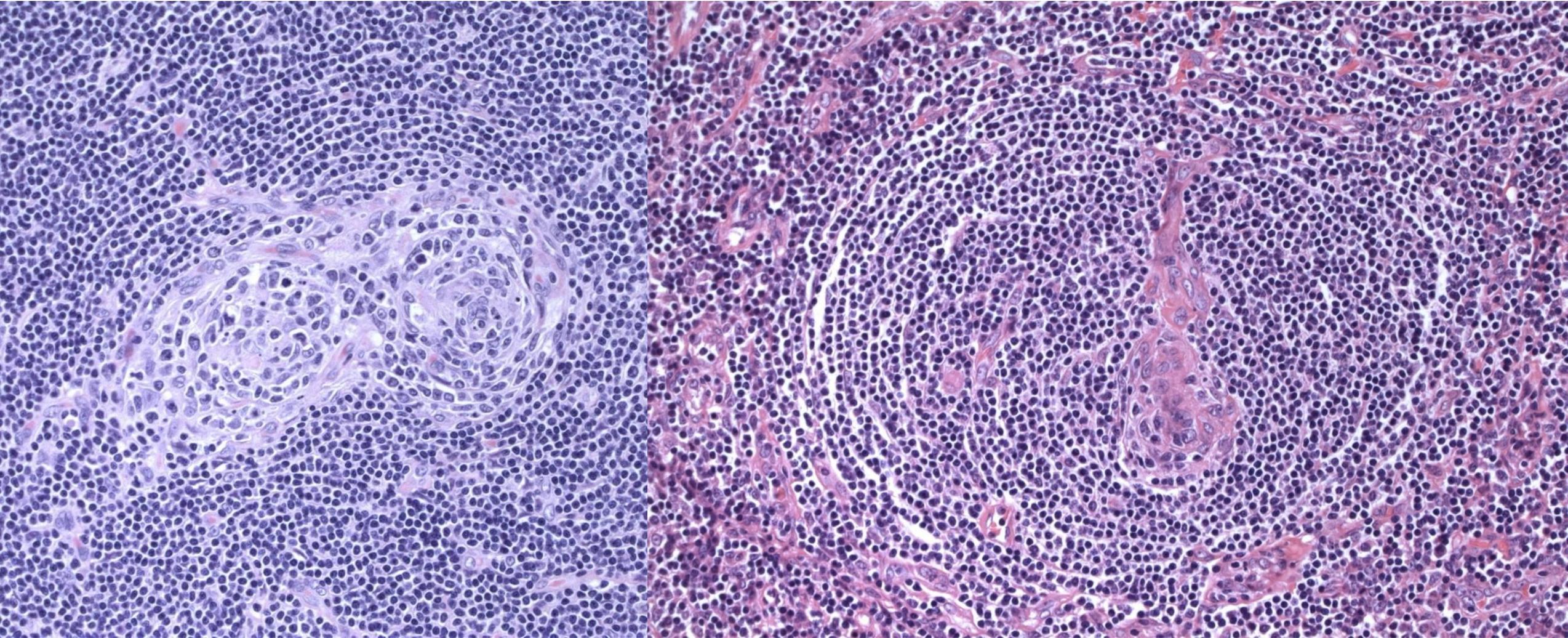
Lab findings: normal PB counts and differential, CRP, liver enzymes, LDH,  $\beta$ 2-MG, total protein, electrolytes, etc. in normal range

Excision of a cervical node 3.5x2.5 cm

# CASE 1



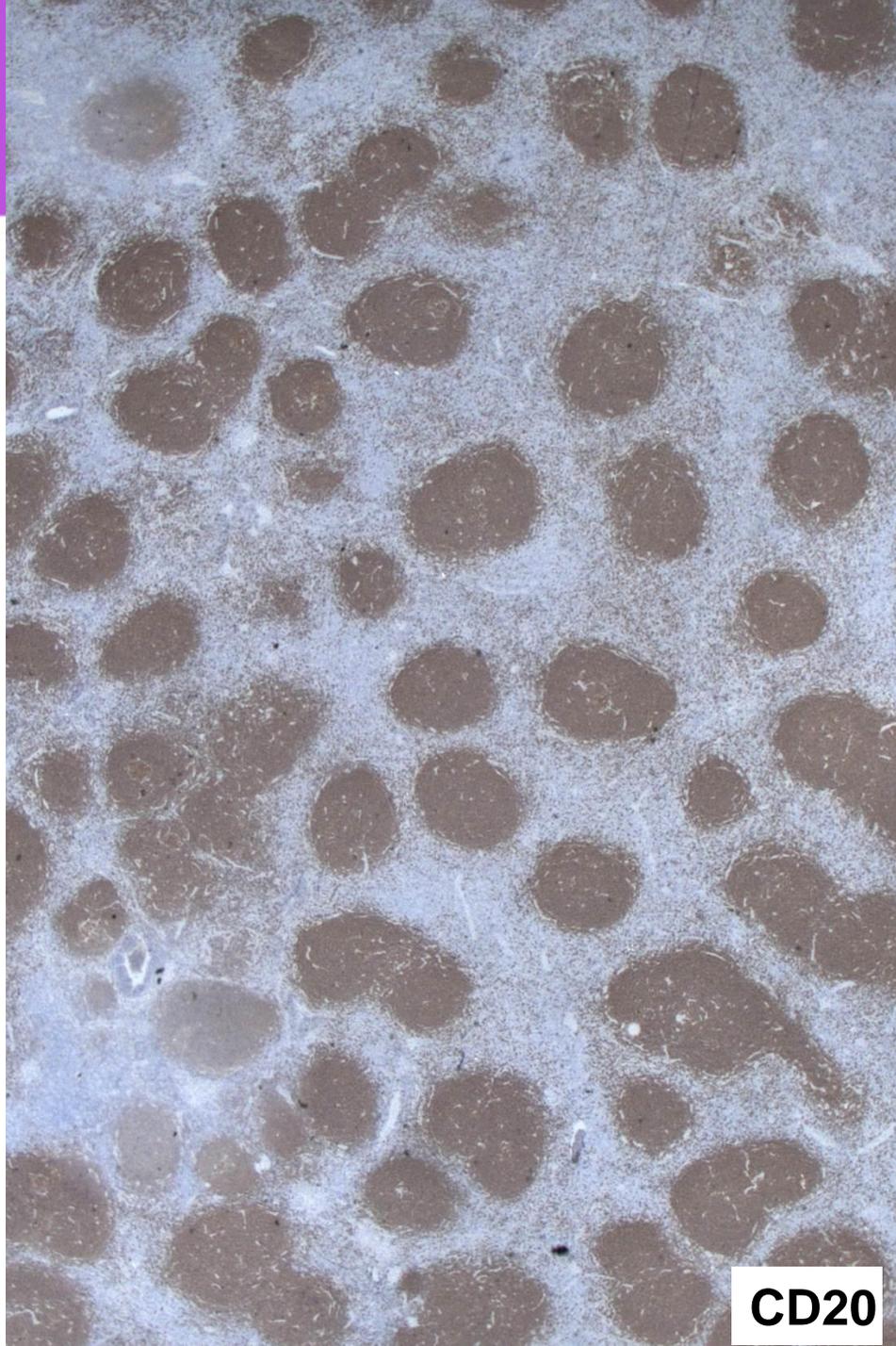
# CASE 1



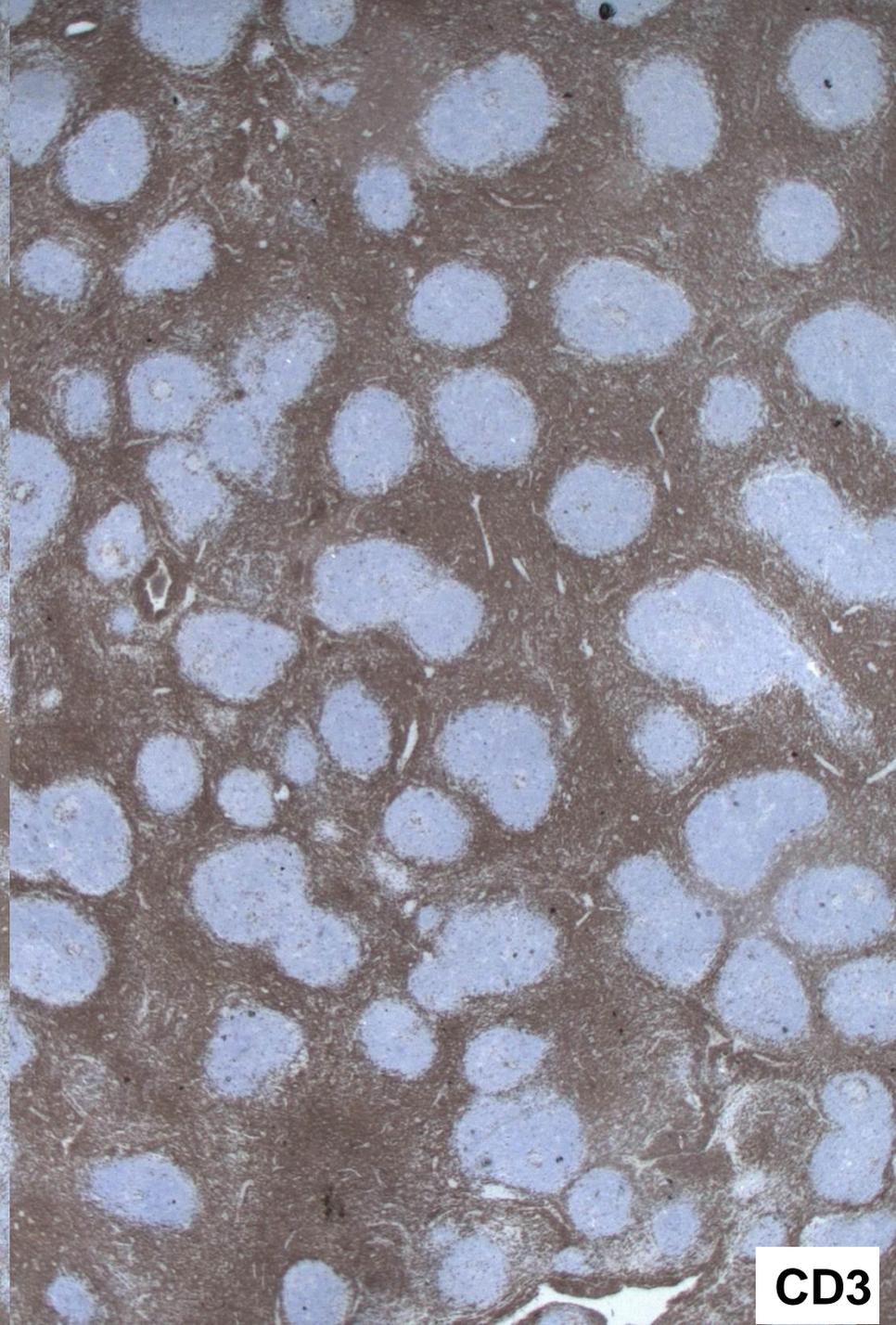
# CASE 1

Anatomical separation  
into (abnormal) B cell  
follicles and  
interfollicular T-cell  
area

No lymph node sinuses



**CD20**



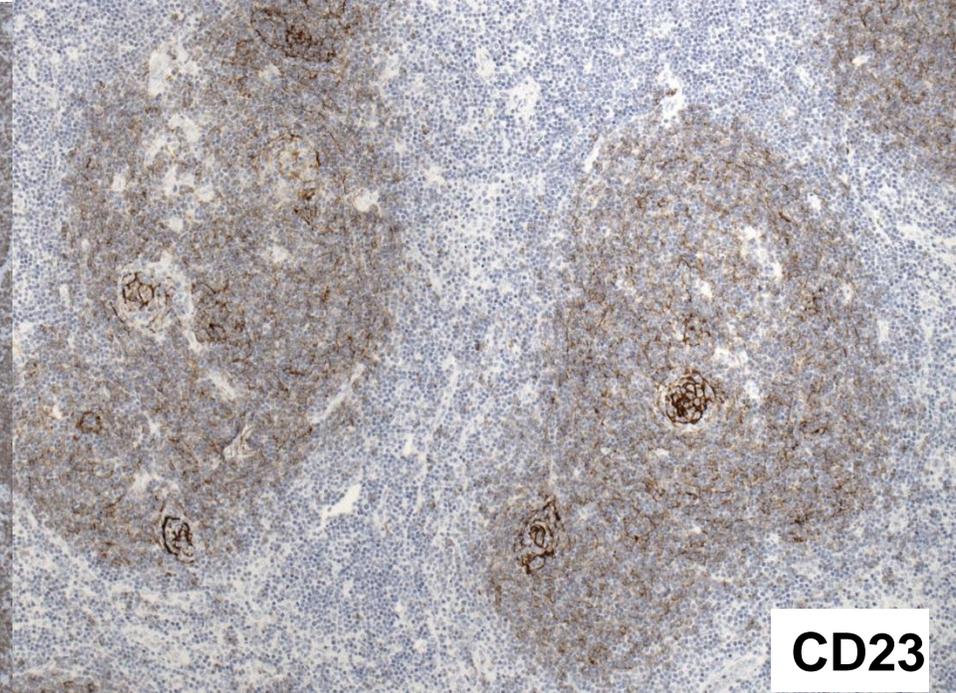
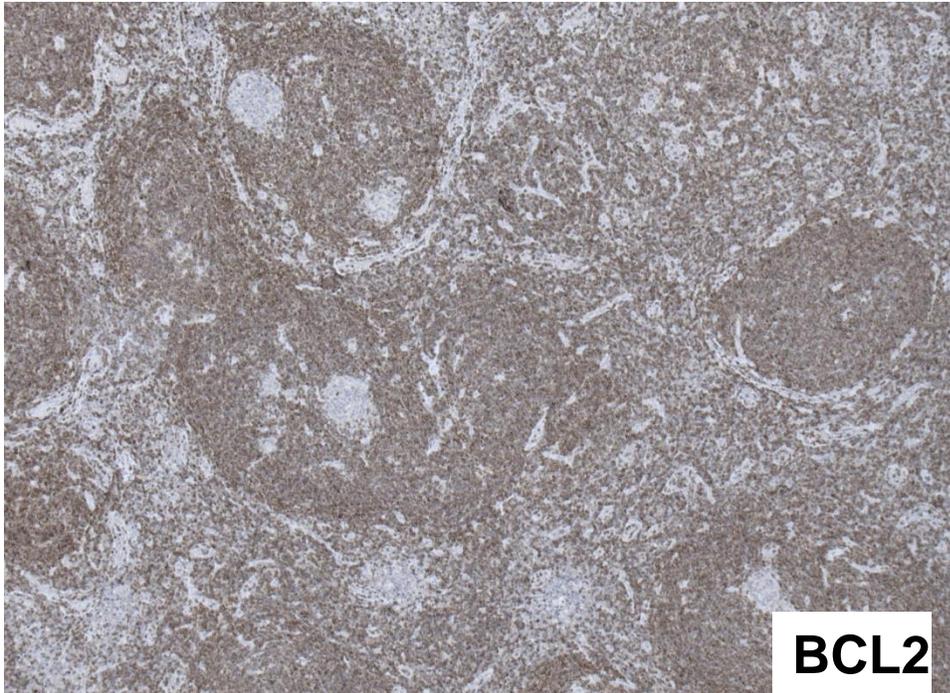
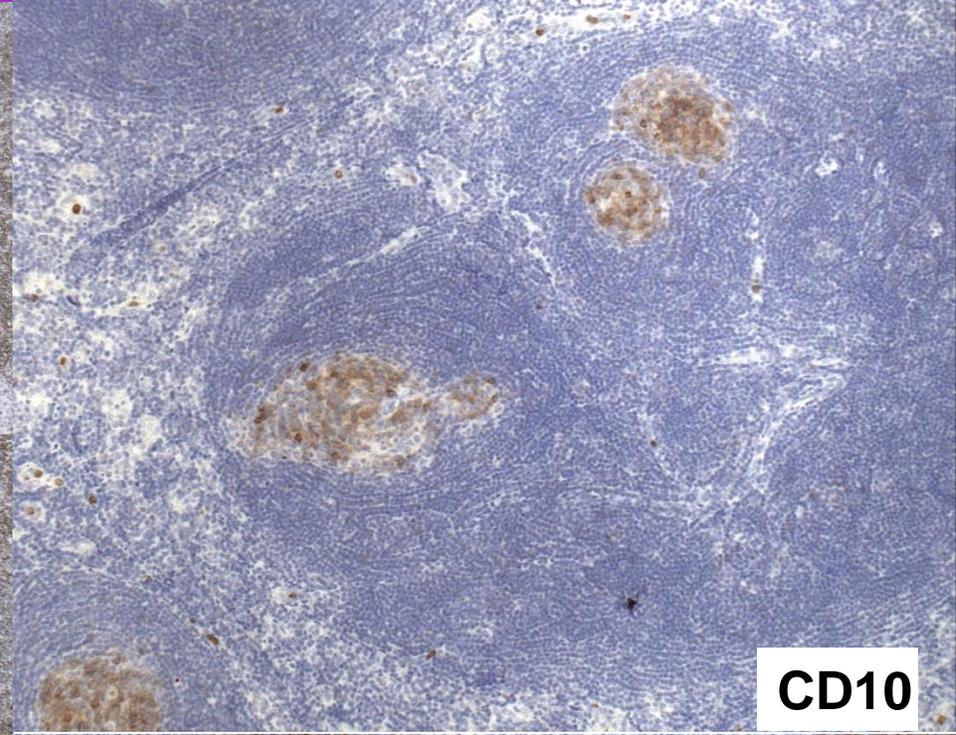
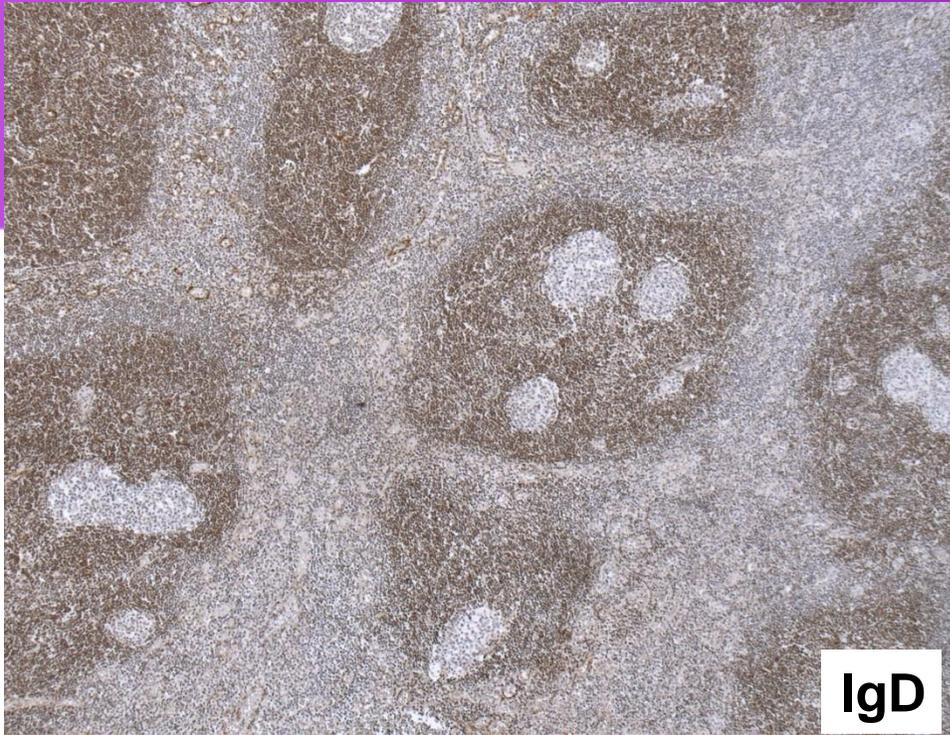
**CD3**

# CASE 1

Expanded CD23/IgD+  
follicle mantles

Sometimes multiple  
regressed GC per follicle

Condensed FDC networks  
and reduction in GC B cells



# DIAGNOSIS: UNICENTRIC CD, HYALINE-VASCULAR TYPE

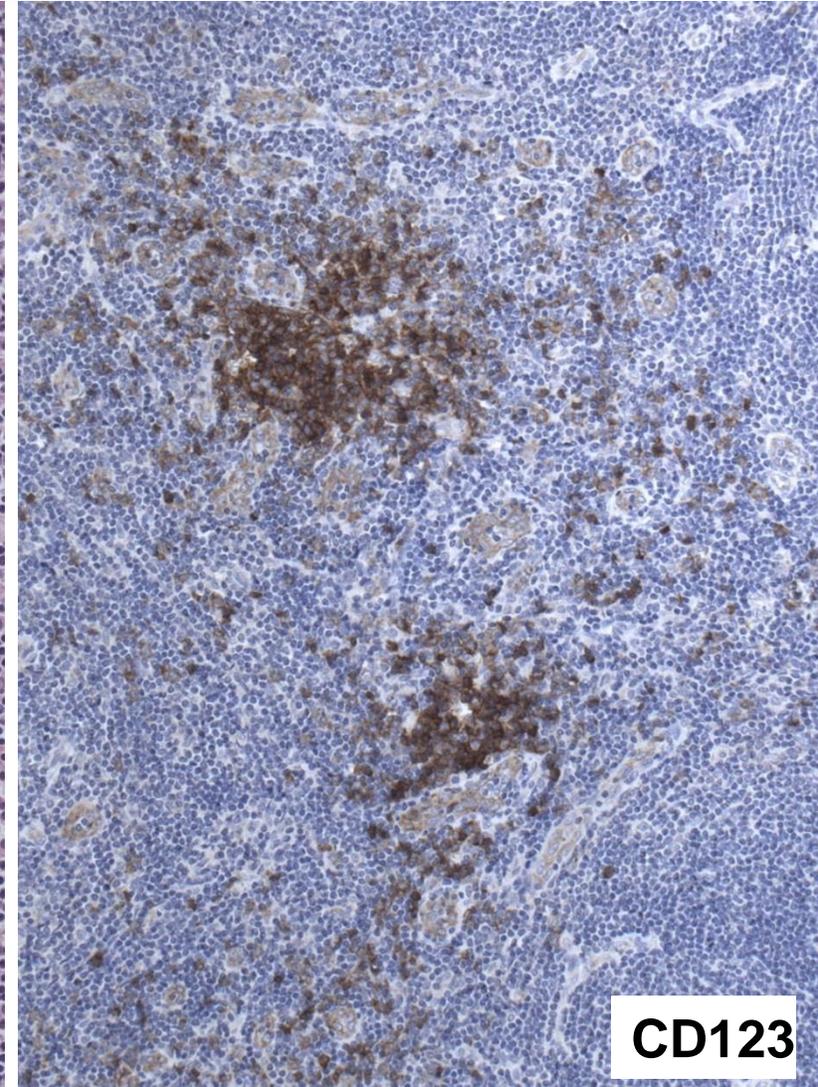
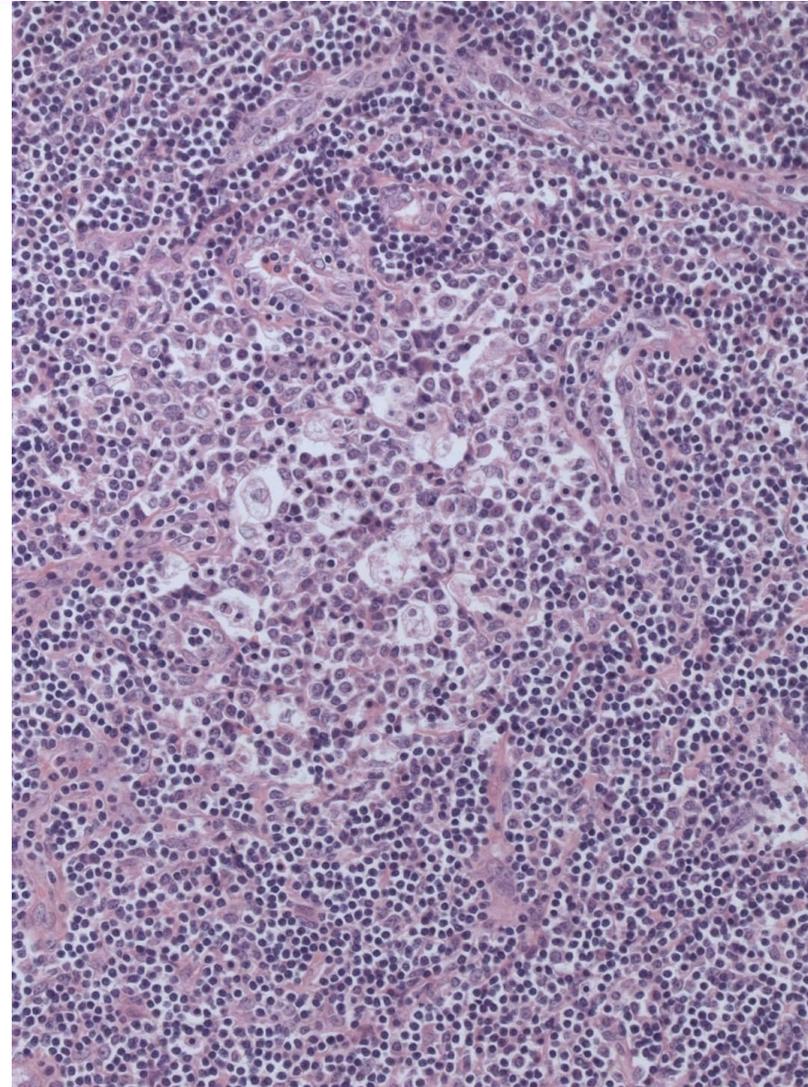
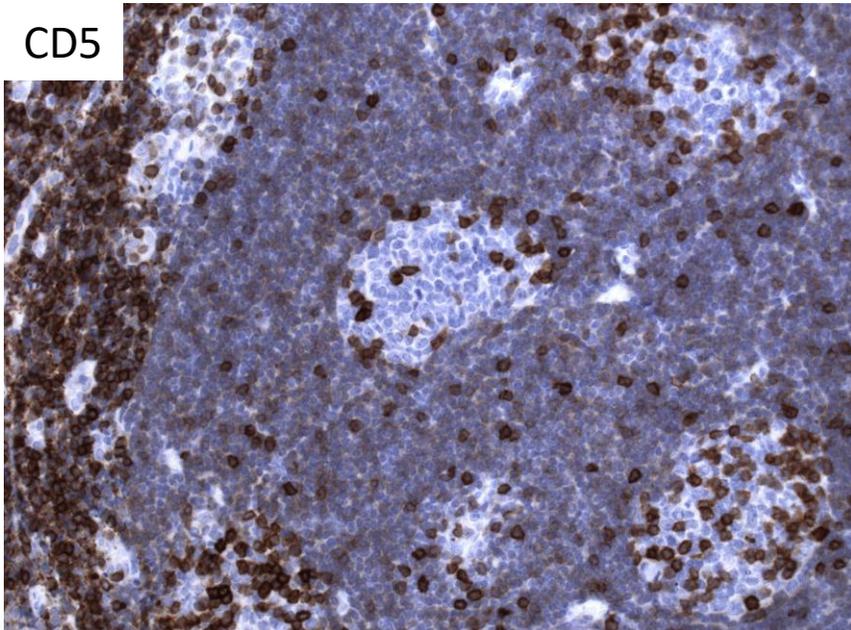
## Additional features

Clusters of plasmacytoid dendritic cells  
(CD123+, TCL1+)

Aberrant expression of CD5  
(Liu Q et al, Histopathol 2013)

Presence of TdT+ T-precursor cells  
(Ohgami et al, AJSP 2012)

CD5



CD123

# UNICENTRIC CD

Most common form of CD (70-90%), usually of hyaline-vascular type (70-90%)

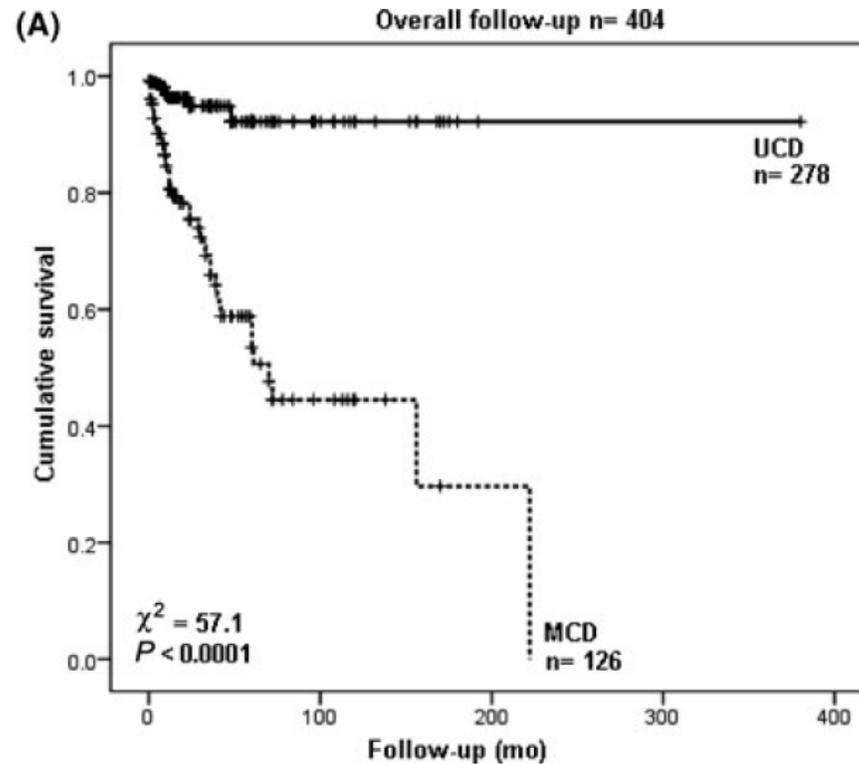
May affect several neighboring LNs

Children and (young) adults

Mediastinum most common localization (70%)

Systemic symptoms rare (paraneoplastic pemphigus, bronchiolitis obliterans), usually remit after surgical excision

DFS 91% after 10 years



## DIFFERENTIAL DIAGNOSIS

- Reactive lymph node with regressed germinal centers
- Multicentric Castleman disease, HHV8-associated
- Idiopathic multicentric Castleman disease
- Marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma with mantle zone growth pattern

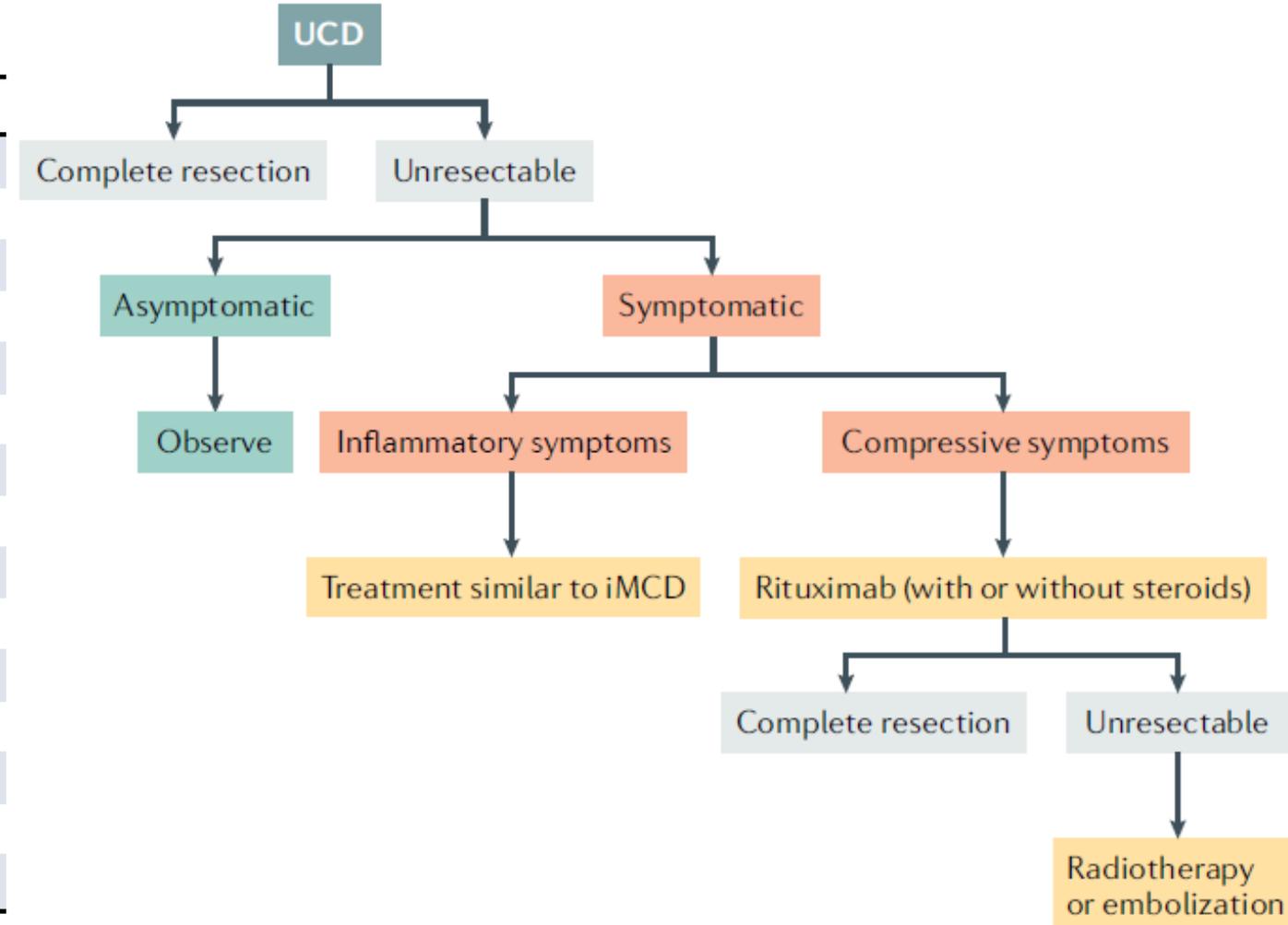
(Ann Surg 2012;255:677–684)

# International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease

**Table 2. Conditions that can overlap with UCD**

Condition
<b>Infectious diseases</b>
HIV-related adenopathy
Syphilis
EBV infection
Inflammatory pseudotumor
<b>Neoplasia</b>
Hodgkin lymphoma
NHL (follicular, marginal zone, mantle cell, lymphoplasmacytic)
FDCS
Plasmacytoma
<b>Autoimmunity/other</b>
Systemic lupus erythematosus, rheumatoid arthritis, Felty's syndrome
Follicular hyperplasia
Autoimmune lymphoproliferative syndrome
HHV-8-associated MCD or iMCD

EBV, Epstein-Barr virus; NHL, non-Hodgkin lymphoma.



Absence of abnormal lymphocyte populations, no B-/T-cell clonality, no viruses

Disorder of follicular dendritic cells with dysplasia (?), clonal cytogenetic abnormalities

Clonality by HUMARA assay detected in 22/28 HVCD, but no B- or T-cell clonality\*

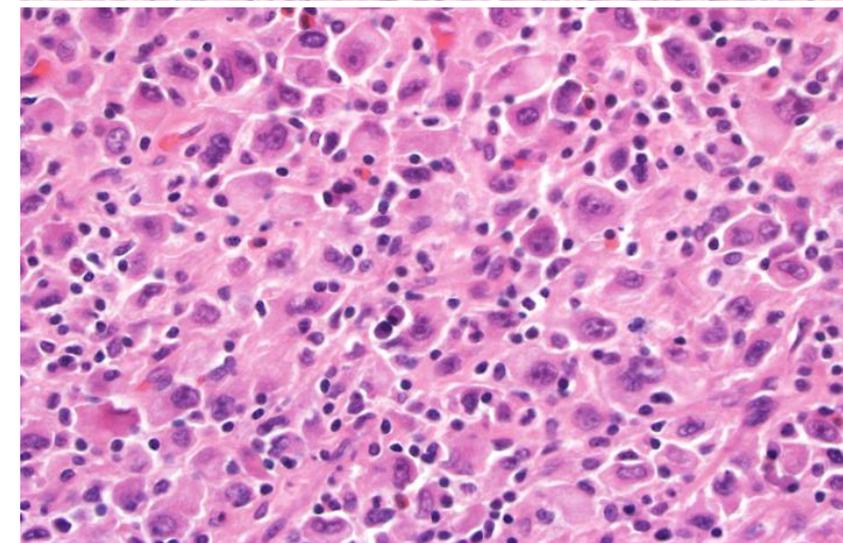
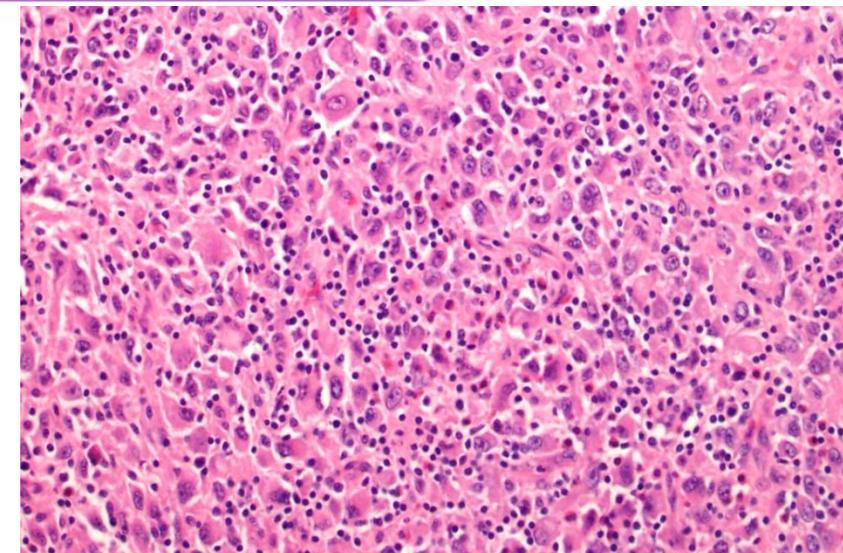
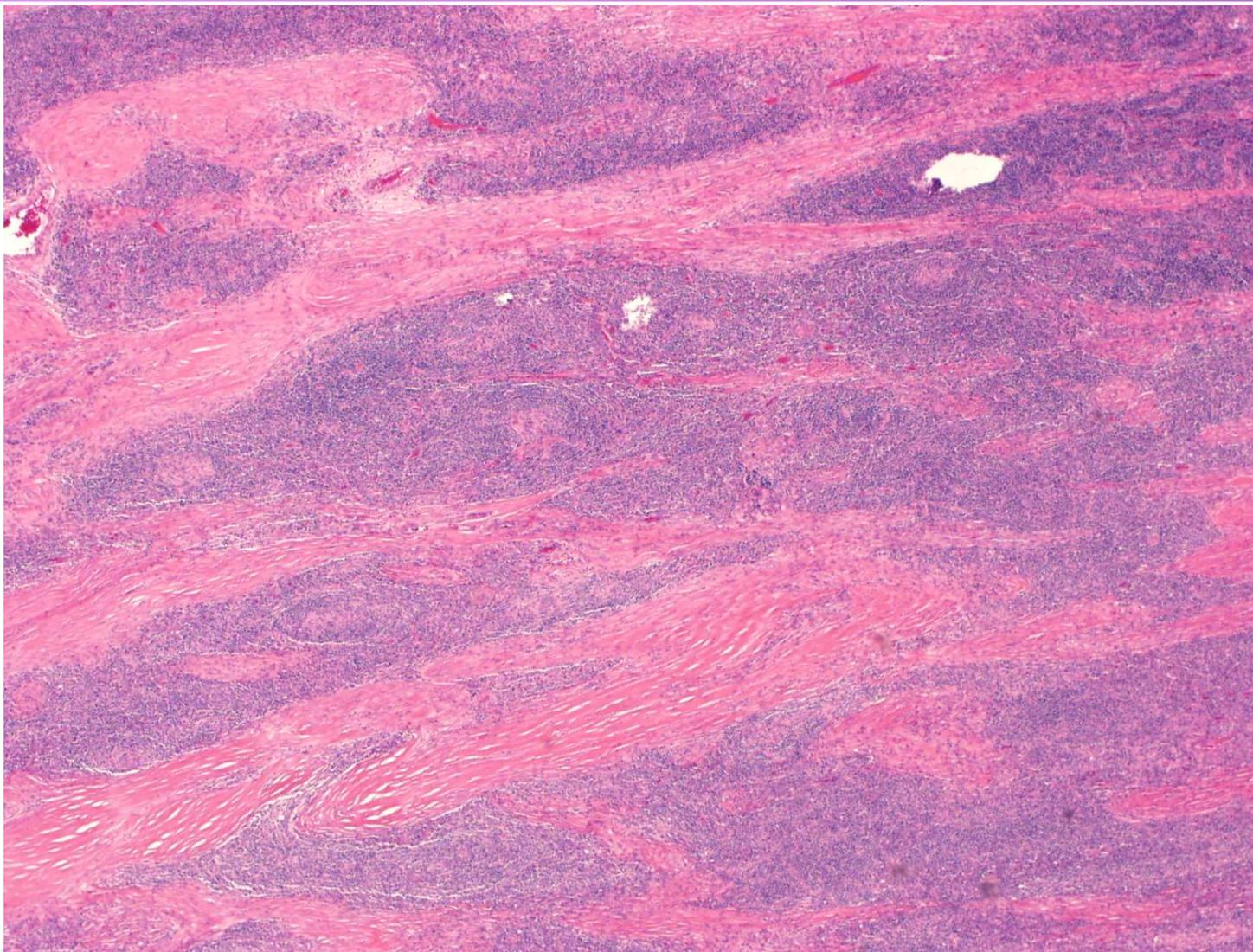
Increased production of VEGF and expression of EGFR by follicular dendritic cells

*PDGFRB* mutations detected in 17%# of UCD

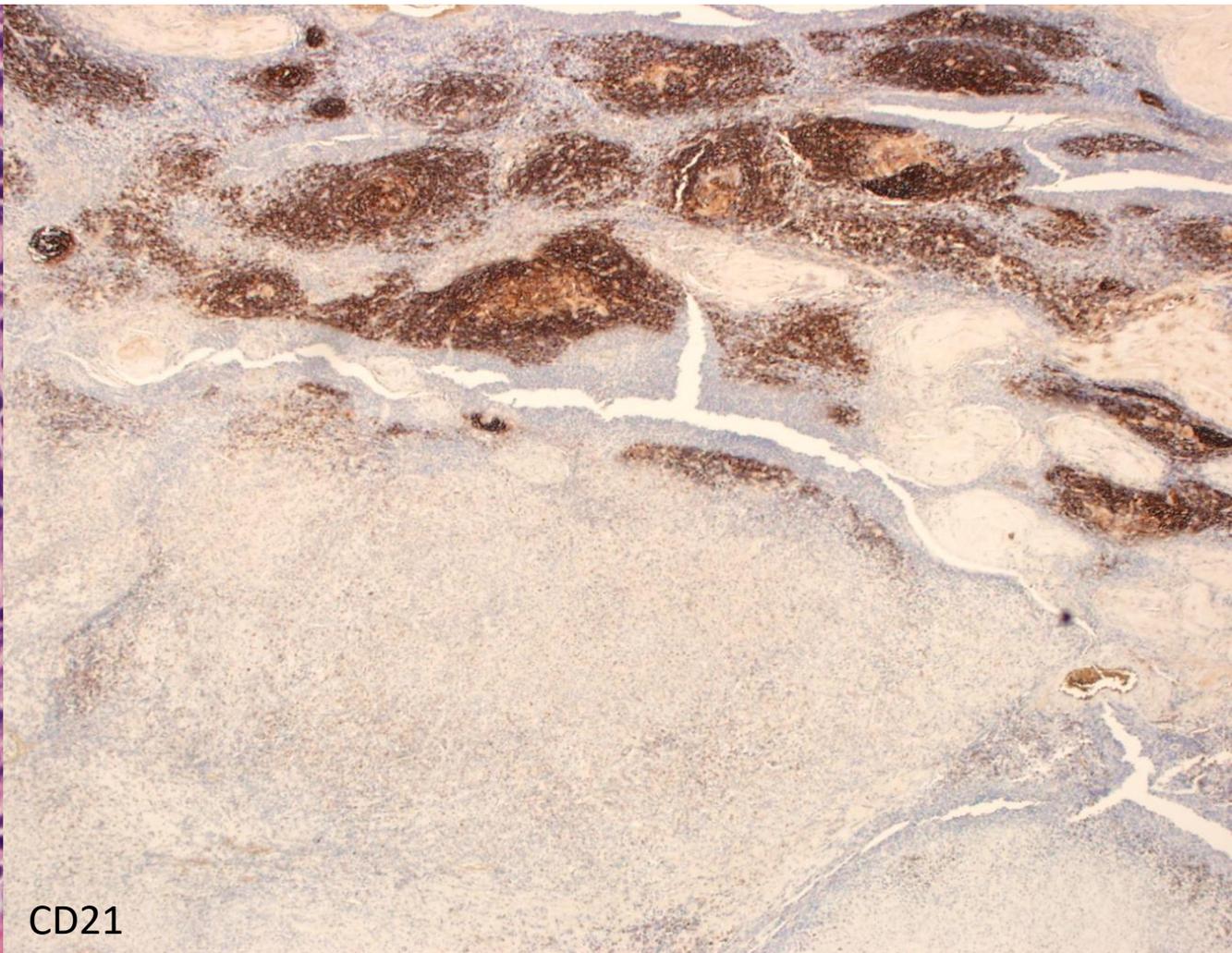
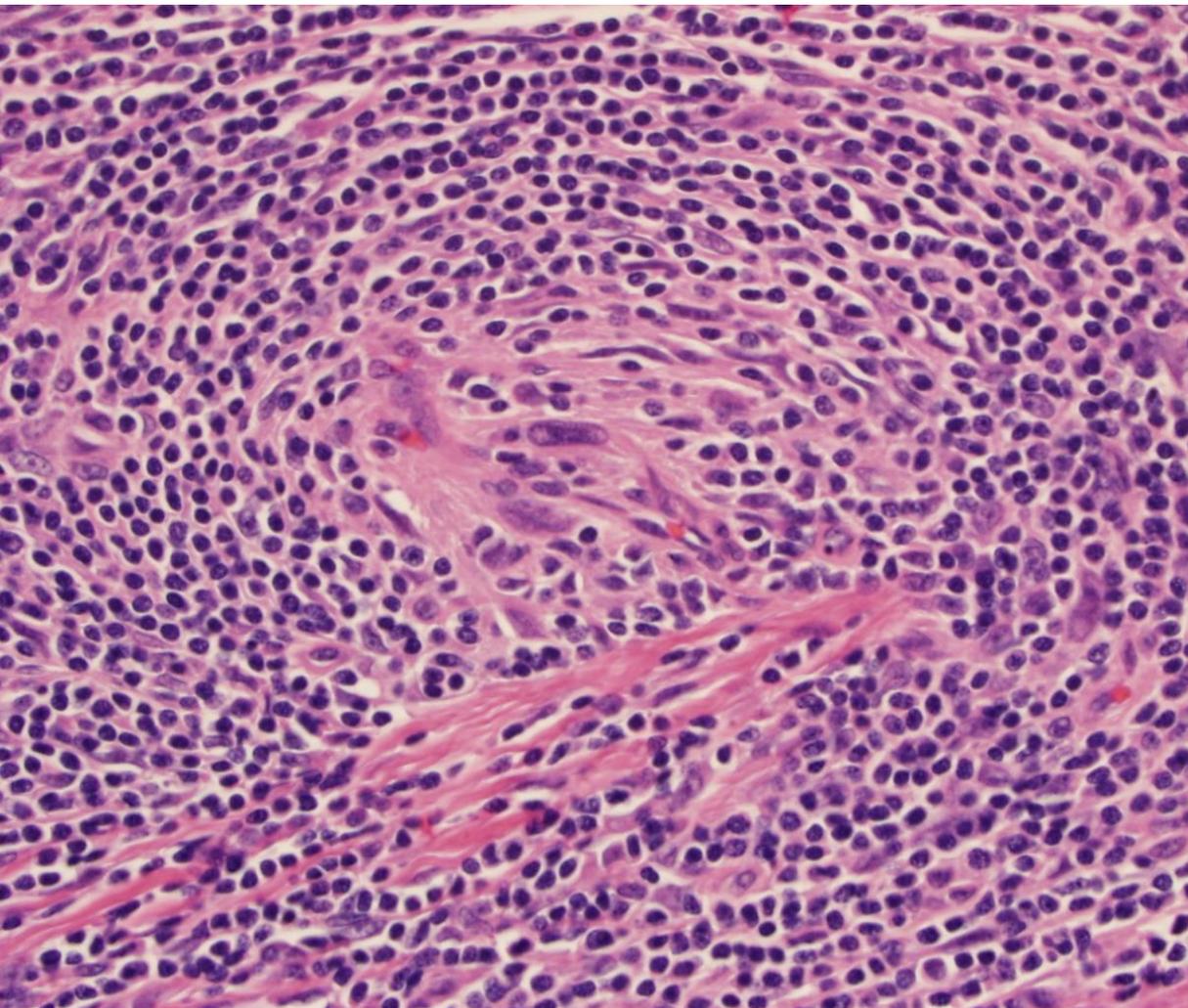
Recent study\*\* failed to detect mutations in 15 UCD cases with 405 gene panel, CNV involving *PTPN6*, *ETS1* and *TGFBR2* in 2 cases (1 UCD and 1 iMCD)

\*Chang KC et al, Mod Pathol 2014; \*\*Nagy A et al, Blood Adv 2018; #Li Z et al, Leukemia 2019

# CASE 2: 54-YEAR OLD MALE, ABDOMINAL DISCOMFORT 6 CM MASS IN MESENTERY



# CASE 2



CD21

# IMMUNOPHENOTYPE

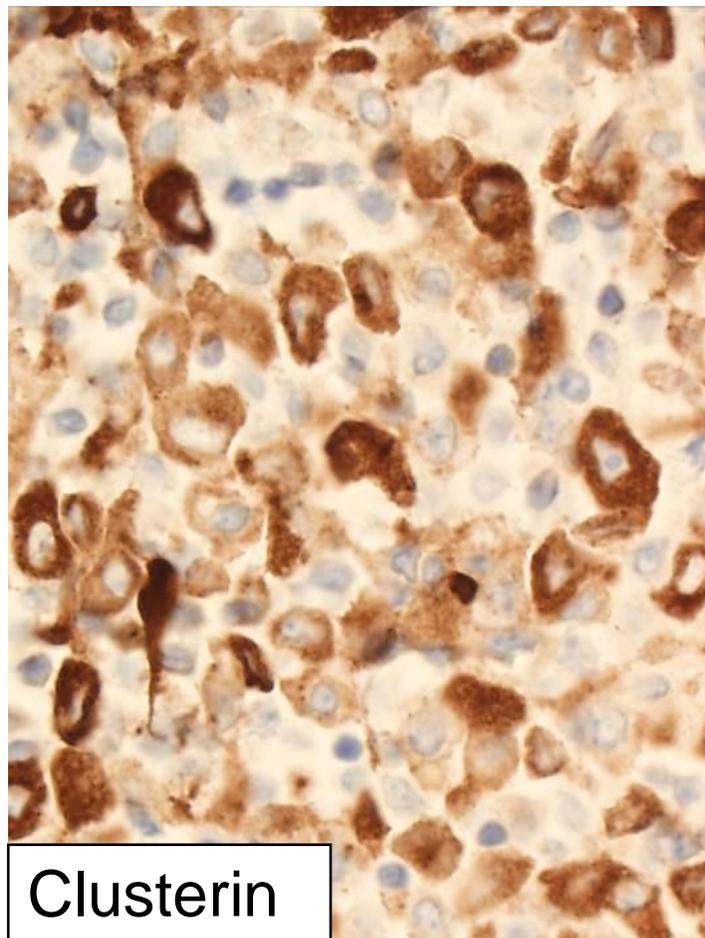
## Positive:

Clusterin, fascin, podoplanin,  
CD23-/+ , CXCXL13

## Negative:

CD21, S100, CD35, SMA, Desmin,  
CD117, ALK

EBV, HHV8



Podoplanin

CXCL13

# DIAGNOSIS: FOLLICULAR DENDRITIC CELL SARCOMA ARISING IN UCD

Mostly low grade sarcoma with localized disease and rare metastasis

- Variable expression of FDC markers (CD21, CD23, fascin, CD35)
- Variable admixture of benign lymphocytes
- Mutation profile little known

## Differential diagnosis

- GIST
- Inflammatory pseudotumor/inflammatory myofibroblastic tumor
- High grade sarcoma, NOS
- Non-specific chronic inflammation with fibrosis
- Retroperitoneal fibrosis

# CASE 3

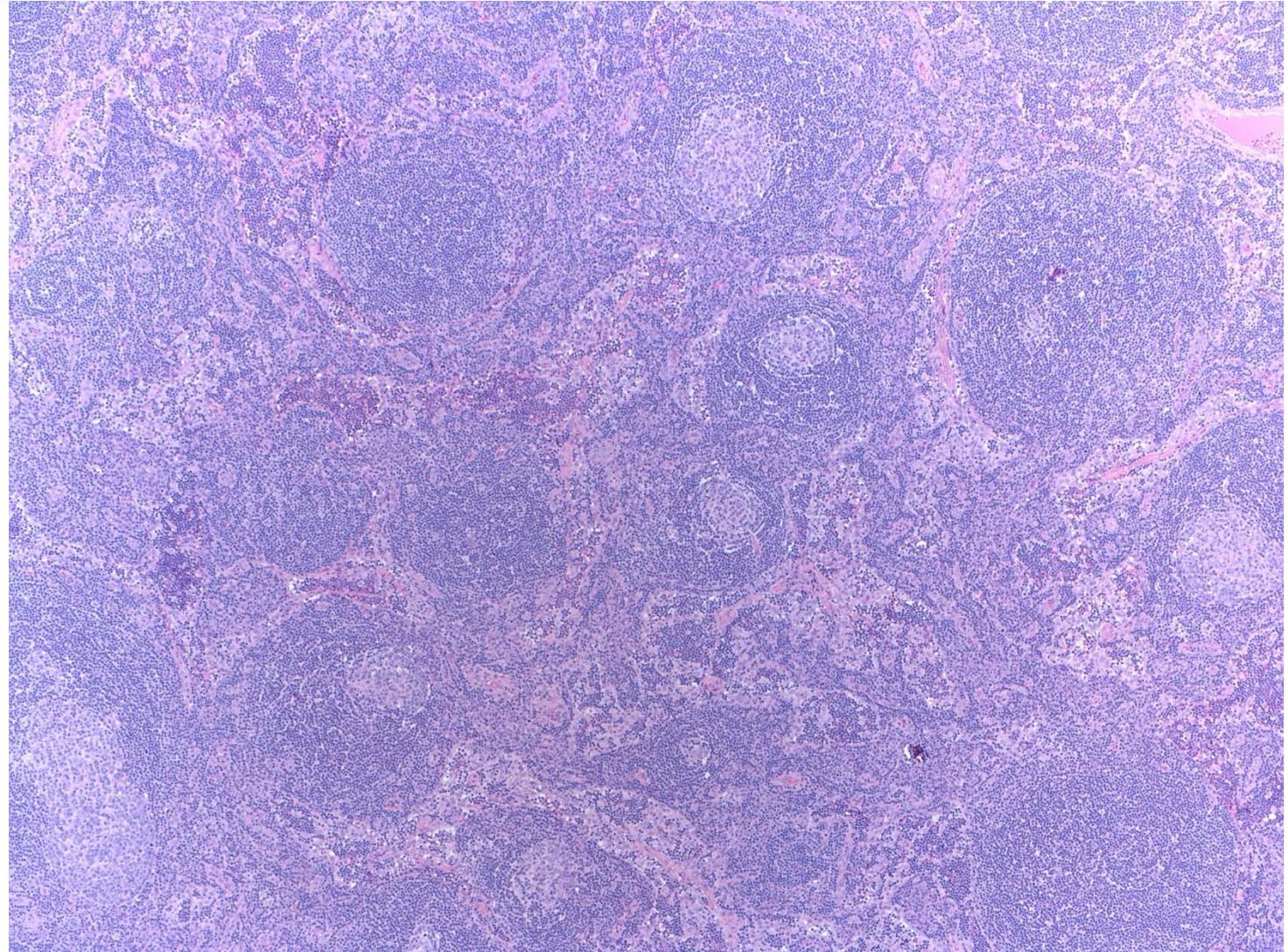
58 year-old male

2001: proteinuria, night sweats

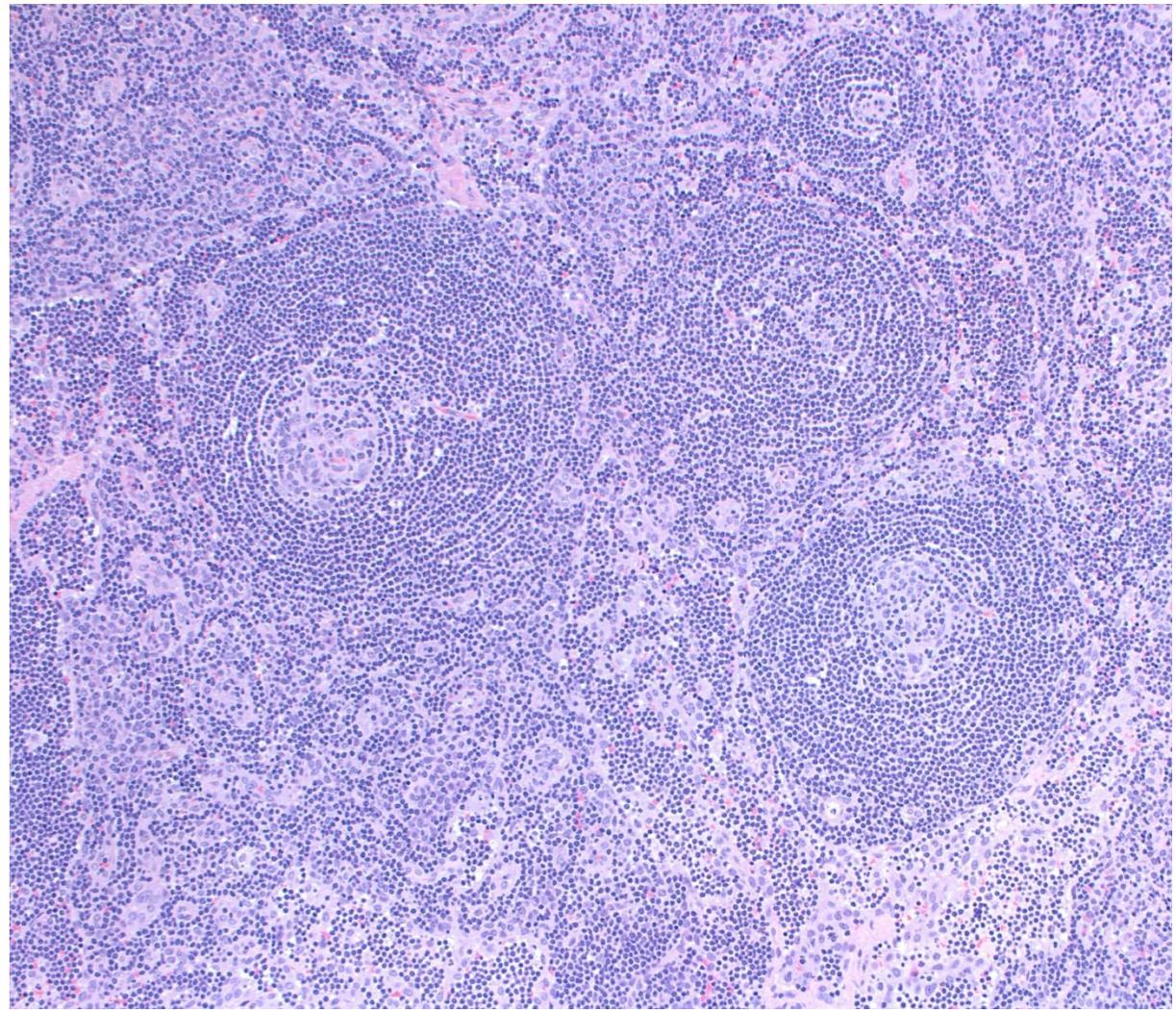
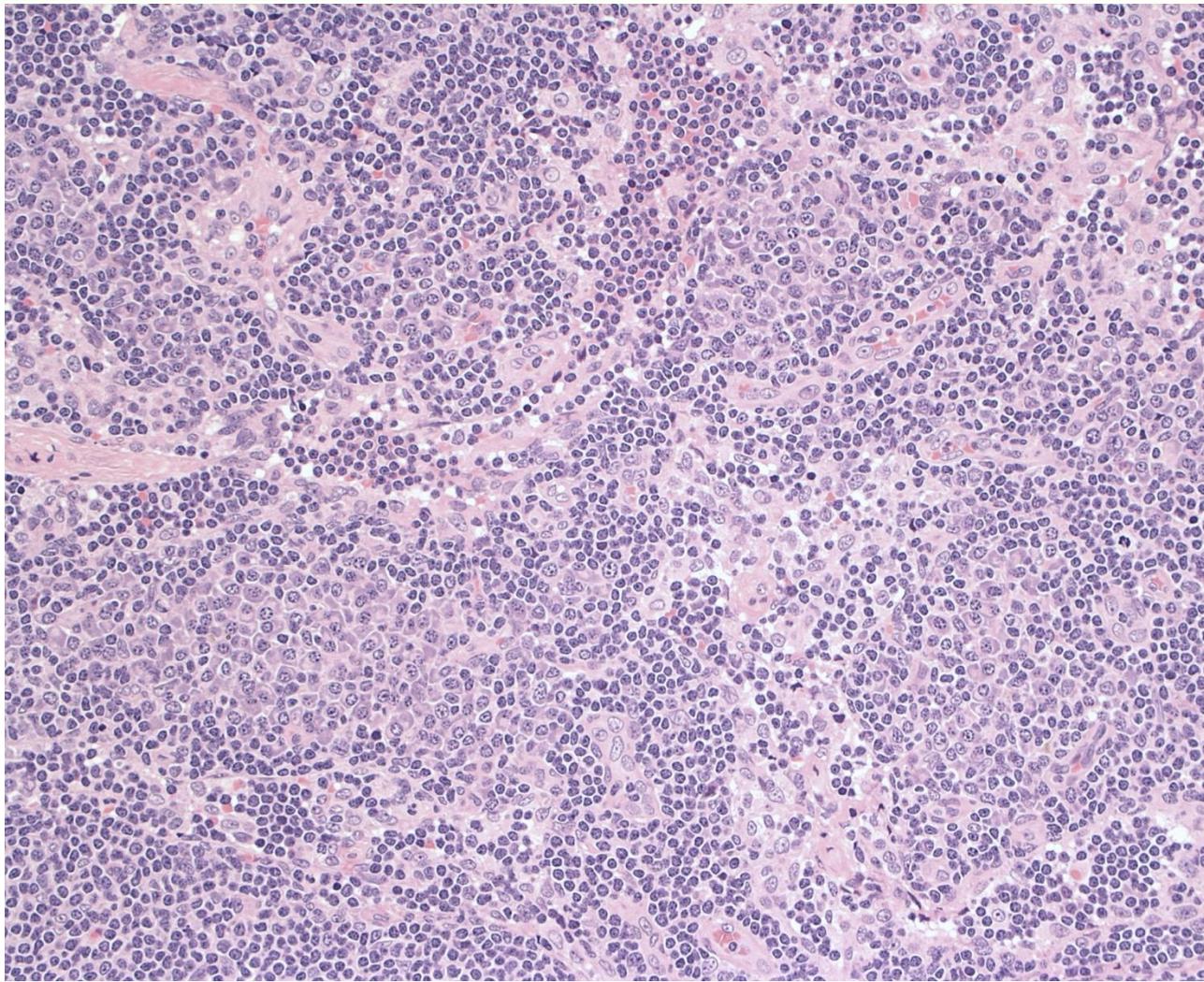
CT scans: hepatosplenomegaly,  
abdominal lymphadenopathy

Serology: IgG 17g/L (elevated), IgA:  
7.86 g/L (elevated), IgM 1.61 g/L  
(normal)

A lymph node biopsy was performed.



# CASE 3



# DIFFERENTIAL DIAGNOSIS

Nodal marginal zone lymphoma  
Lymphoplasmacytic lymphoma  
Multicentric CD, plasma cell variant

# IDIOPATHIC MULTICENTRIC CD

Generalized LAP with preserved architecture and regressed GC

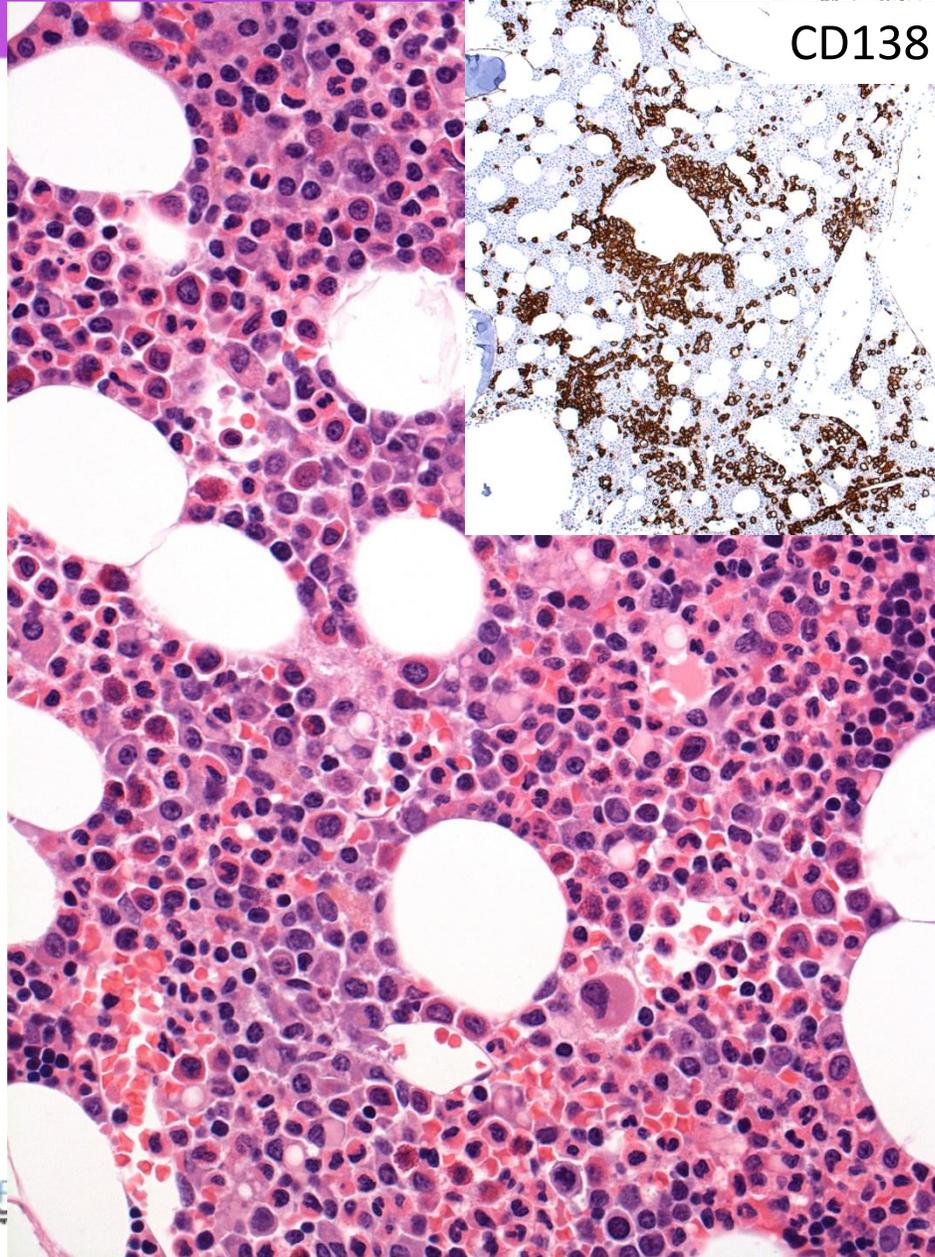
Interfollicular increase in polytypic PC

Polytypic plasmacytosis in BM

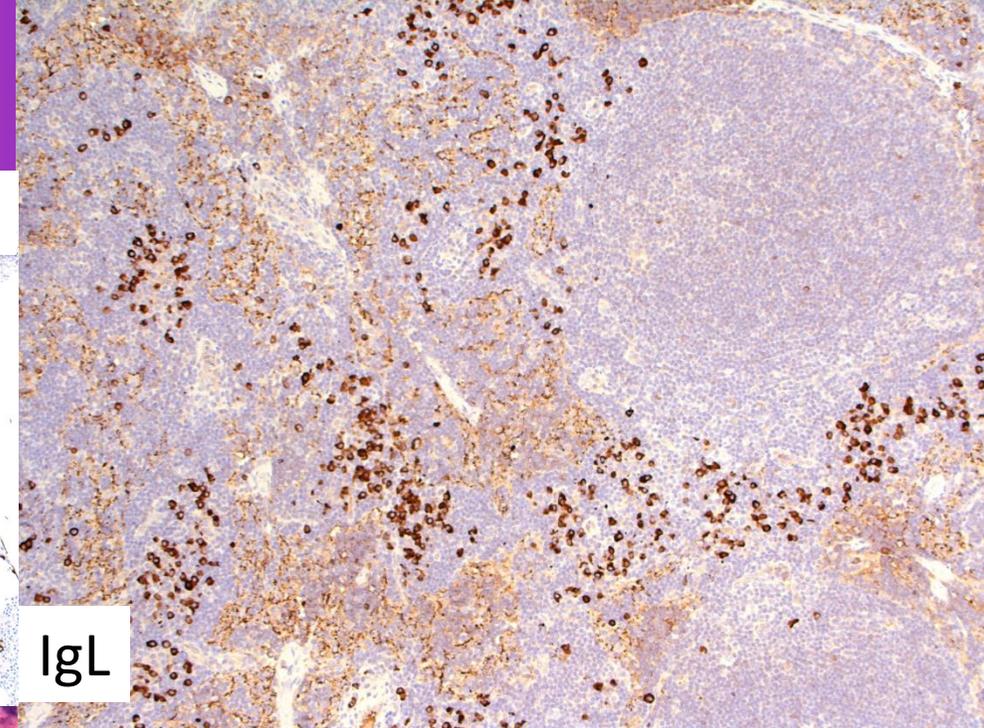
EBV and HHV8 negative

iMCD may show any histological subtype

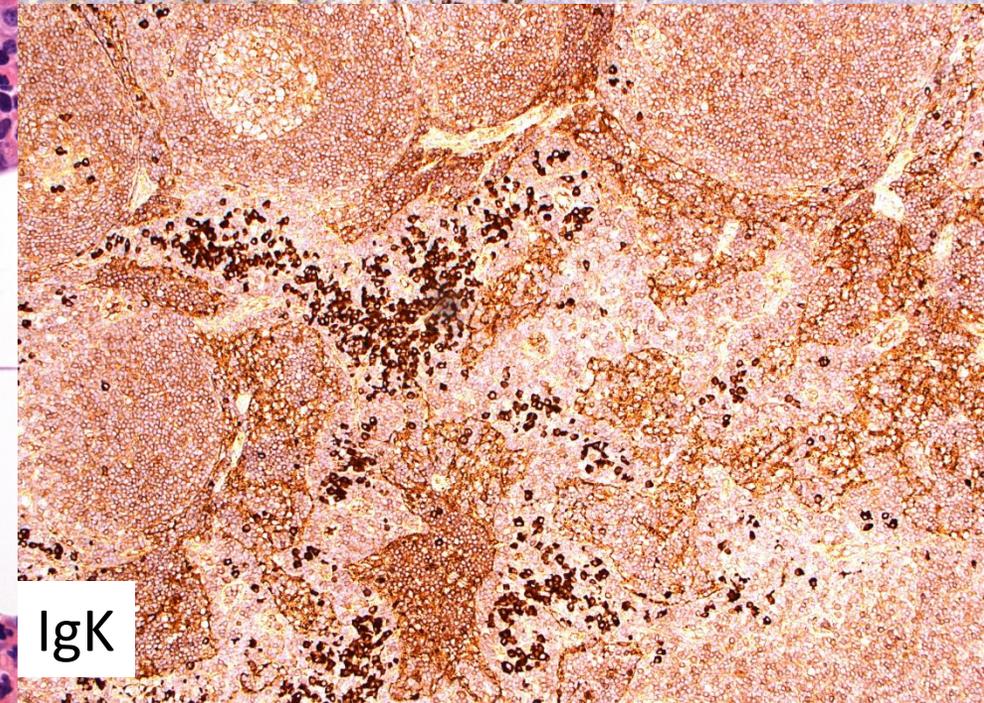
- 17-49% (!) hyaline vascular type
- 46-77% plasma cell type
- 4-20% mixed type



CD138



IgL



IgK

# CASE 4

23 year-old female

2005, 2006, 2007: recurrent Bell's palsy (periods of two months each time with spontaneous resolution)

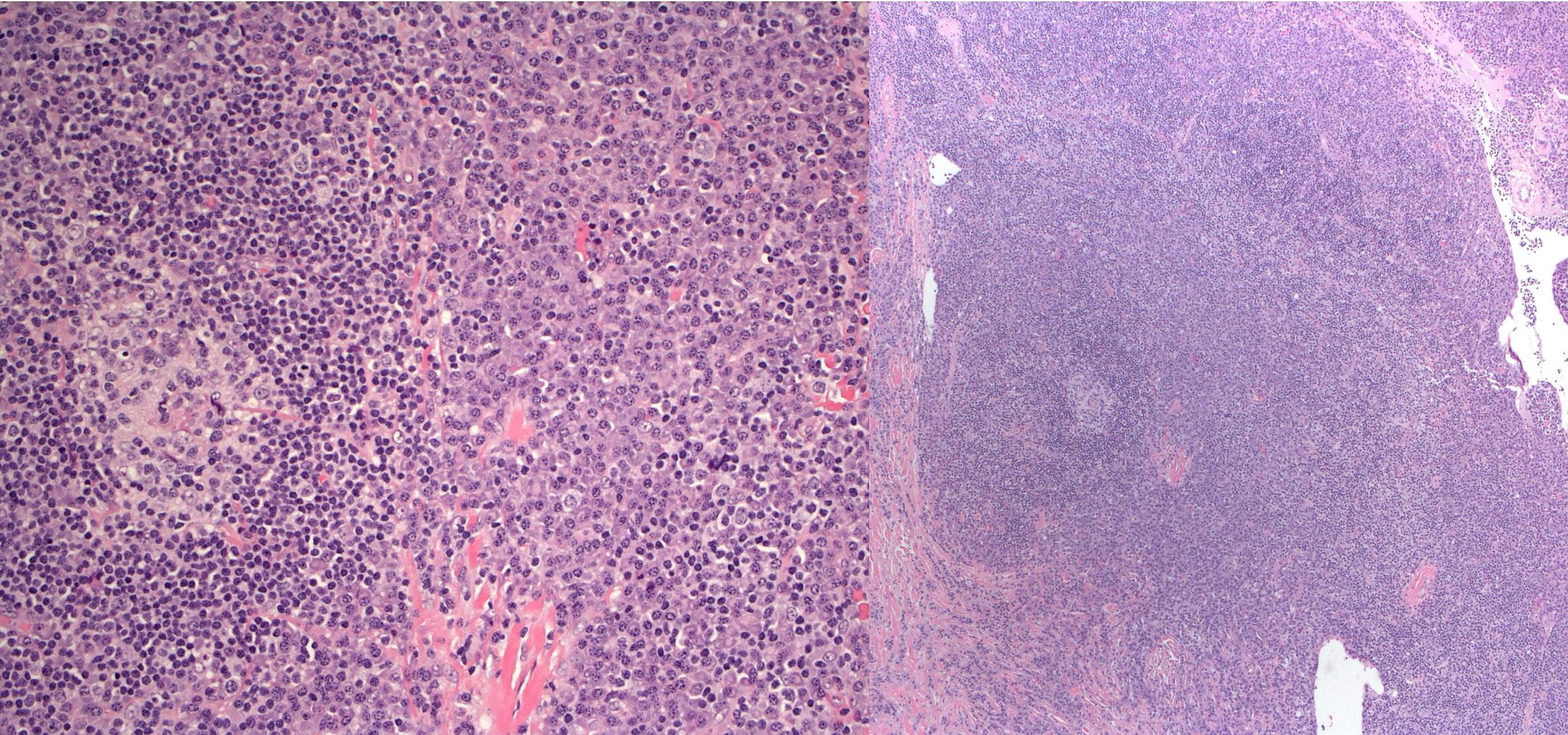
2013: chest pain, increasing in intensity over weeks.

Severe microcytic **anemia** (Hb 63 g/L), **ESR**:128, **CRP**:111 mg/L, **IgG**:40,1 g/L (elevated), **IgA**:5,35 g/L (elevated), **IgM**:1,48 g/L, **IgG4**:1,77 g/L (elevated)

**Imaging:** large mass at the anterior aortic root causing aortic compression and pulmonary artery compression. Invasion in the pulmonary artery was also present. There is also some mediastinal lymphadenopathy

Mini-thoracotomy with biopsy of the mass

# CASE 4 HISTOLOGY

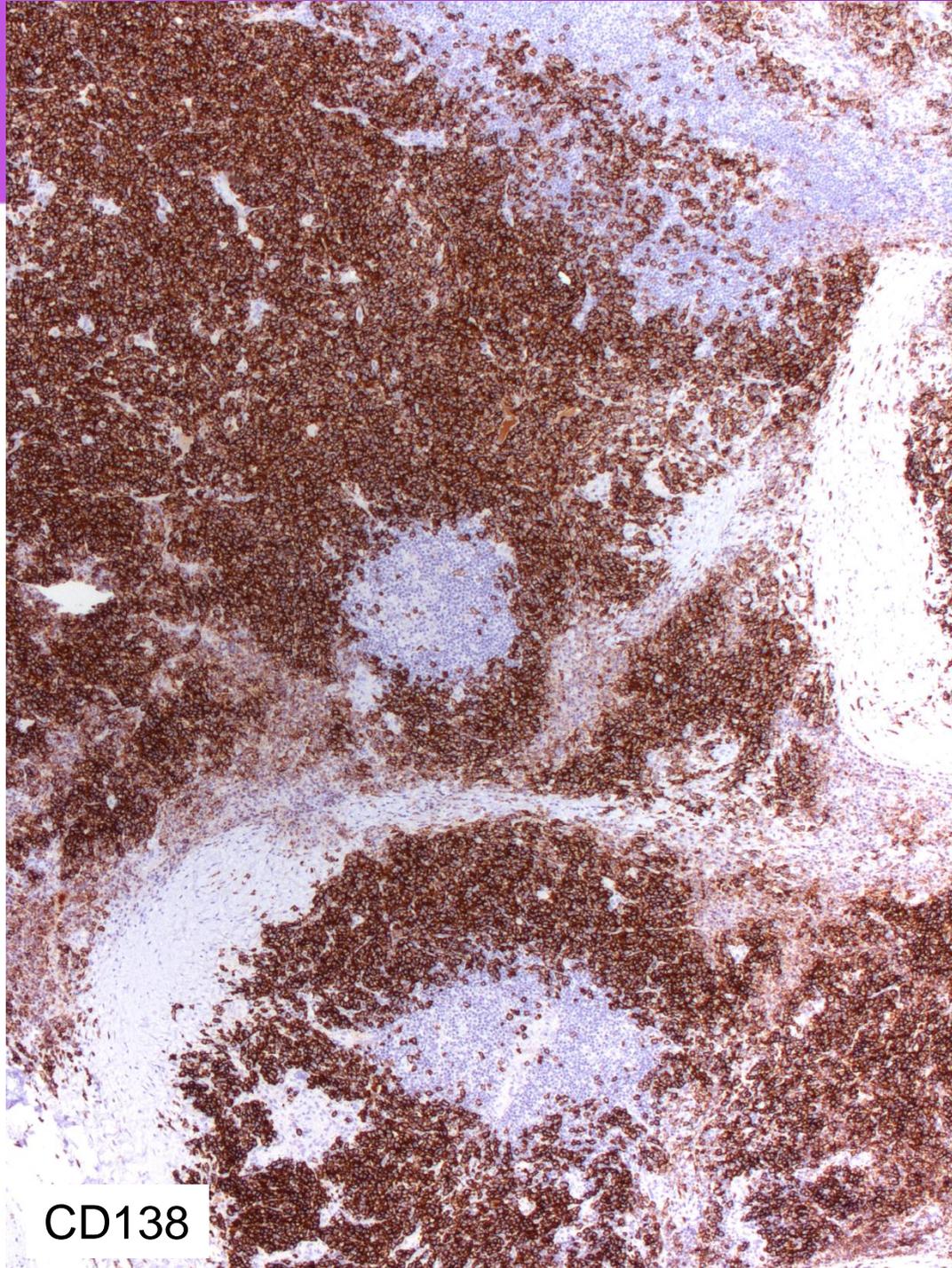


CD20+ B-cells  
confined to the  
follicles with  
interspersed CD3+  
T-cells

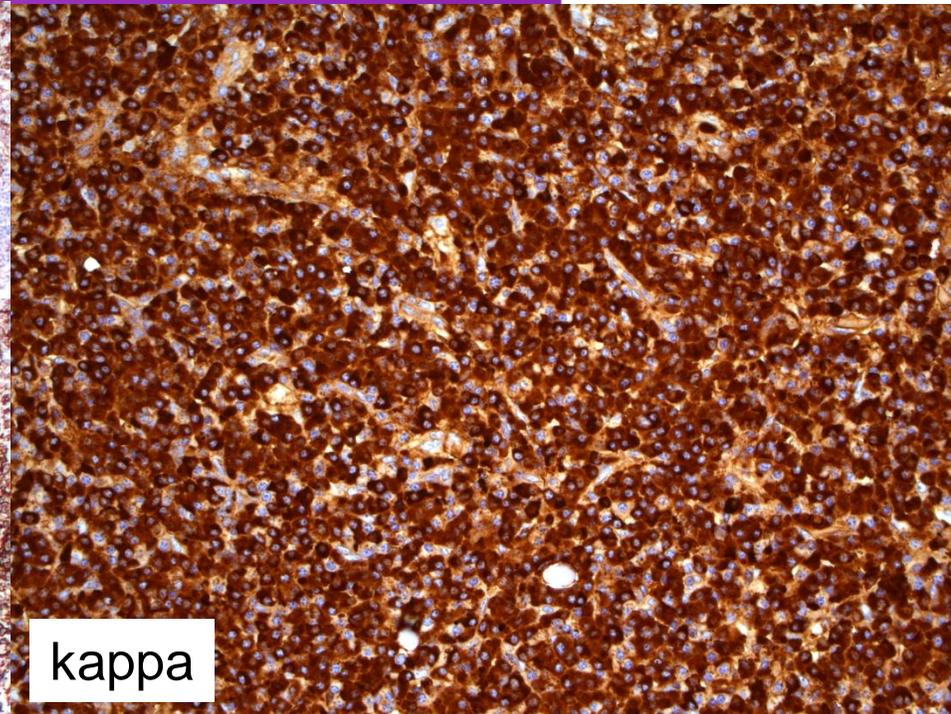
Plasma cell  
immunophenotype  
: CD138+,  
IgK/IgL:5/1, IgG+,  
IgG4+(5-10%), IgA-,  
IgM-

HHV8-, EBV- no B-  
cell clone detected

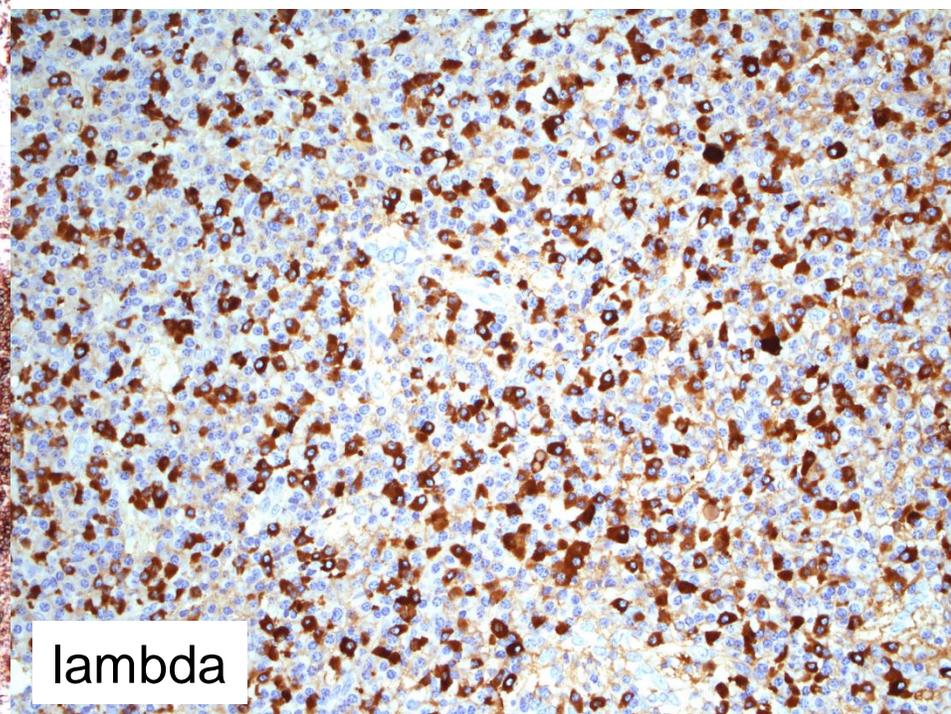
Diagnosis: likely  
MCD, PC variant



CD138



kappa



lambda

# IDIOPATHIC MULTICENTRIC CD

Multisystem, frequently life-threatening disease with hyperinflammatory syndrome

- Fever
- Weight loss
- Anasarca
- Generalized small-volume LAP
- Anemia, hypoalbuminemia
- Renal impairment

Rare (2.5-25/million person years), male preponderance, ratio to HHV8/KSHV-associated MCD depends on endemicity

**Excisional lymph node biopsy AND correlation with clinical features required for diagnosis**

## Differential Diagnosis

- Lymphadenopathy with reactive plasmacytosis
- IGG4-related lymphadenopathy

## Exclusion criteria

### *Infection-related disorders*

- Kaposi sarcoma herpesvirus infection
- Epstein–Barr virus-associated lymphoproliferative disease
- Inflammation and adenopathy by other infection

### *Autoimmune or inflammatory diseases*

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Adult-onset Still disease
- Juvenile idiopathic arthritis
- Autoimmune lymphoproliferative syndrome

### *Malignant lymphoproliferative diseases*

- Lymphoma
- Multiple myeloma
- Primary lymph node plasmacytoma
- Follicular dendritic cell sarcoma
- POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) syndrome

# TAFRO SYNDROME AND IMCD

**TAFRO** (thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly)\*

considered to be an **aggressive variant of IMCD**, despite significant clinical differences

- Very aggressive clinical course
- Thrombopenia
- No/rare hypergammaglobulinemia
- Renal dysfunction with intravascular coagulation and fibrinolysis
- Hyaline-vascular or mixed morphology

\*Masaki Y et al, J Clin Exp Hematop 2013, Takai et al, Rinsho Ketsueki 2010

**Table 3. Diagnostic criteria for iMCD-TAFRO**

Criteria
<b>Histopathological criteria: need all</b> Typical LN pathology (atrophic GCs with enlarged nuclei of ECs, proliferation of endothelial venules, small numbers of mature PCs) Negative LANA-1 for HHV8
<b>Major criteria: need 3 of 5</b> Thrombocytopenia (<100 000/ $\mu$ L) Anasarca (pleural effusions and ascites on CT) Fever (>38°C) Reticulin fibrosis Organomegaly
<b>Minor criteria: at least 1</b> Hyper/normoplasia of megakaryocytes High alkaline phosphatase without markedly elevated transaminases

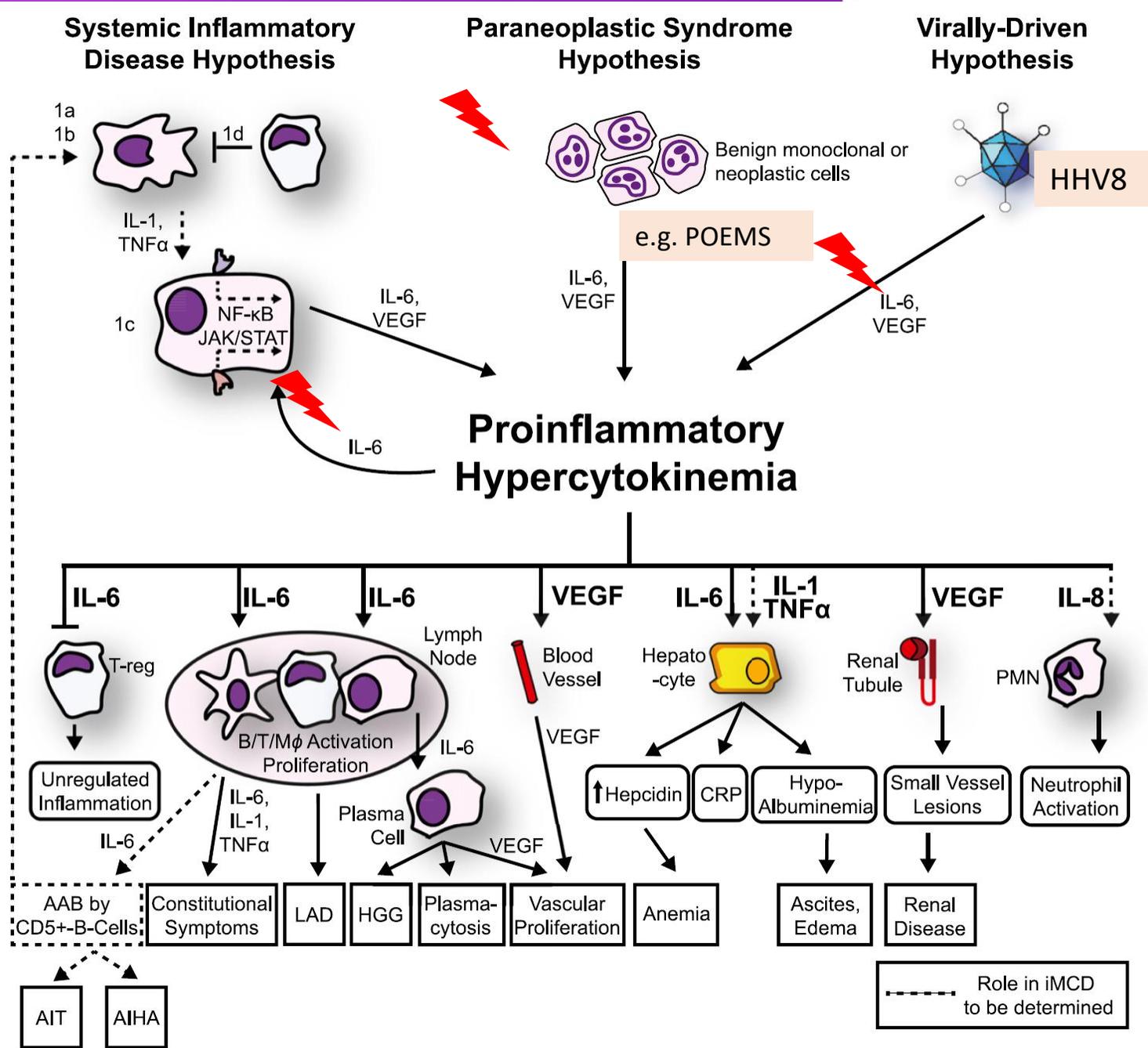
# PATHOGENESIS OF IMCD

Cytokine storm with overproduction of IL-6 and VEGF

T-cell activation?

mTOR, JAK-STAT and type I interferon signaling ?

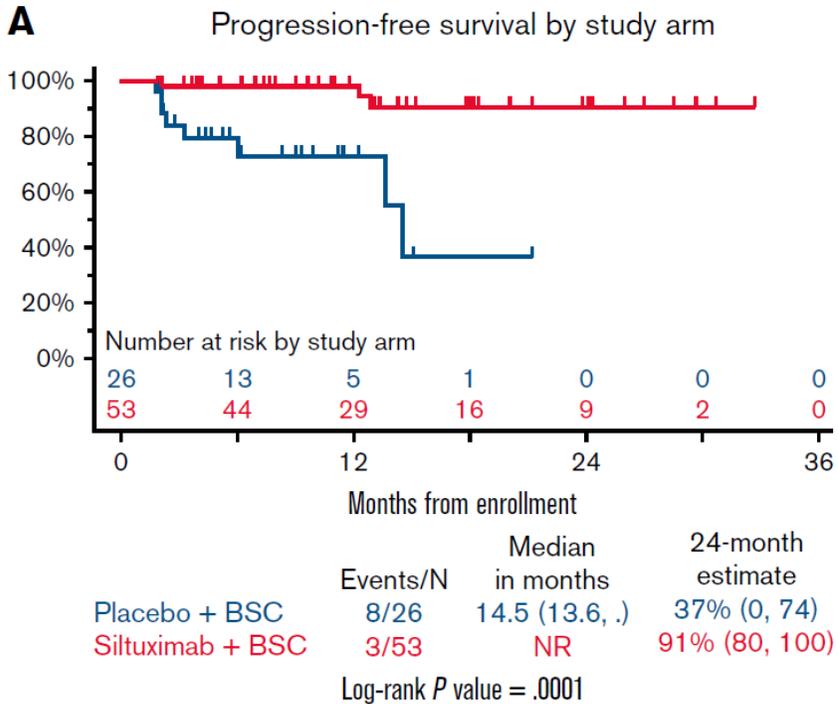
SNP in genes associated with autoinflammation



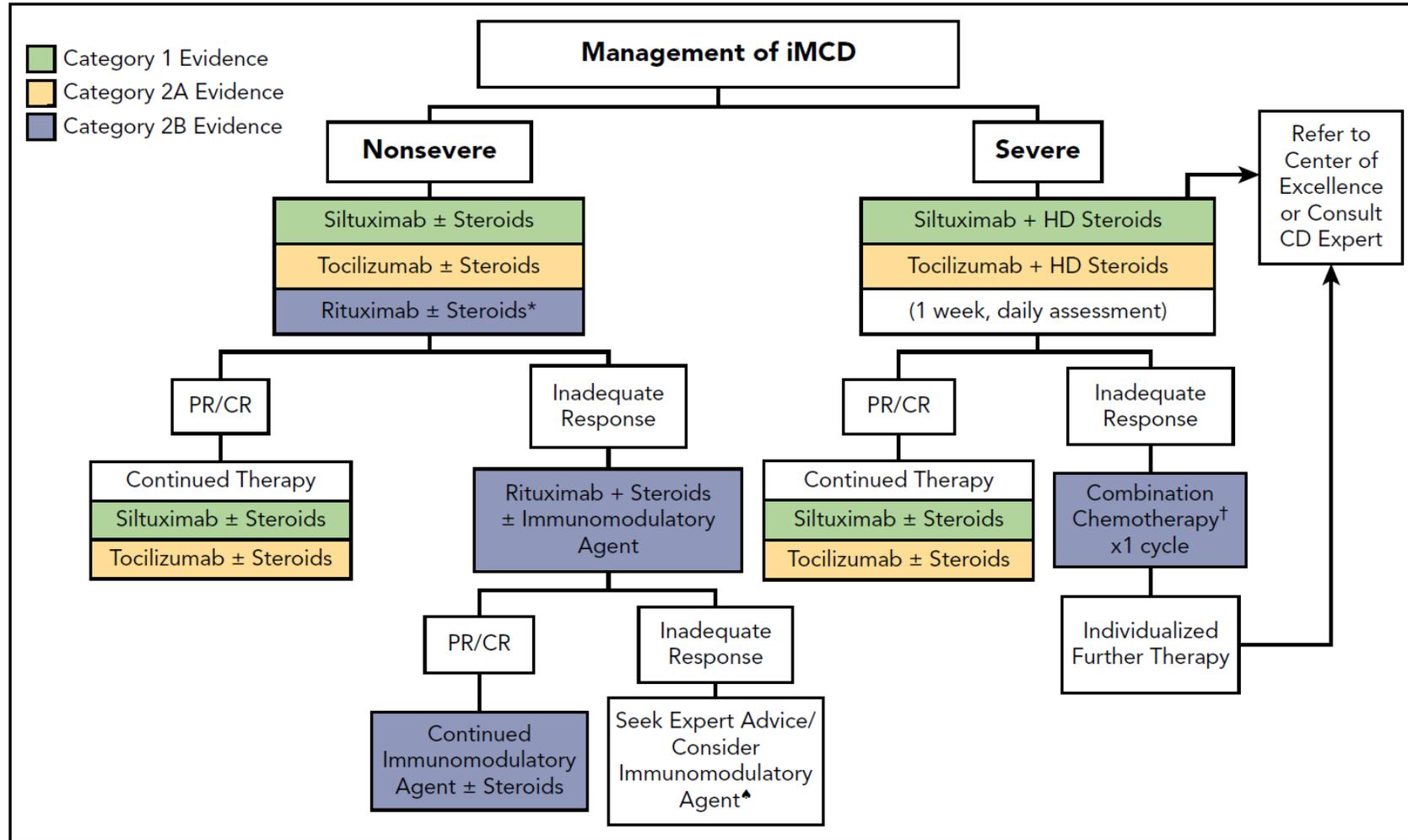
# IMCD TREATMENT

IL-6 hypercytokinemia is central pathogenetic feature

IL-6-based therapy as first line +/- steroids



Van Rhee F et al, Blood Adv 2022



Van Rhee F et al, Blood 2018

# CASE 5

48 year-old male

2004: peripheral edema, progressive shortness of breath, peripheral neuropathy

CT scans: splenomegaly and enlarged lymph nodes in peri-aortic, mesenteric, bilateral axillary and inguinal regions.

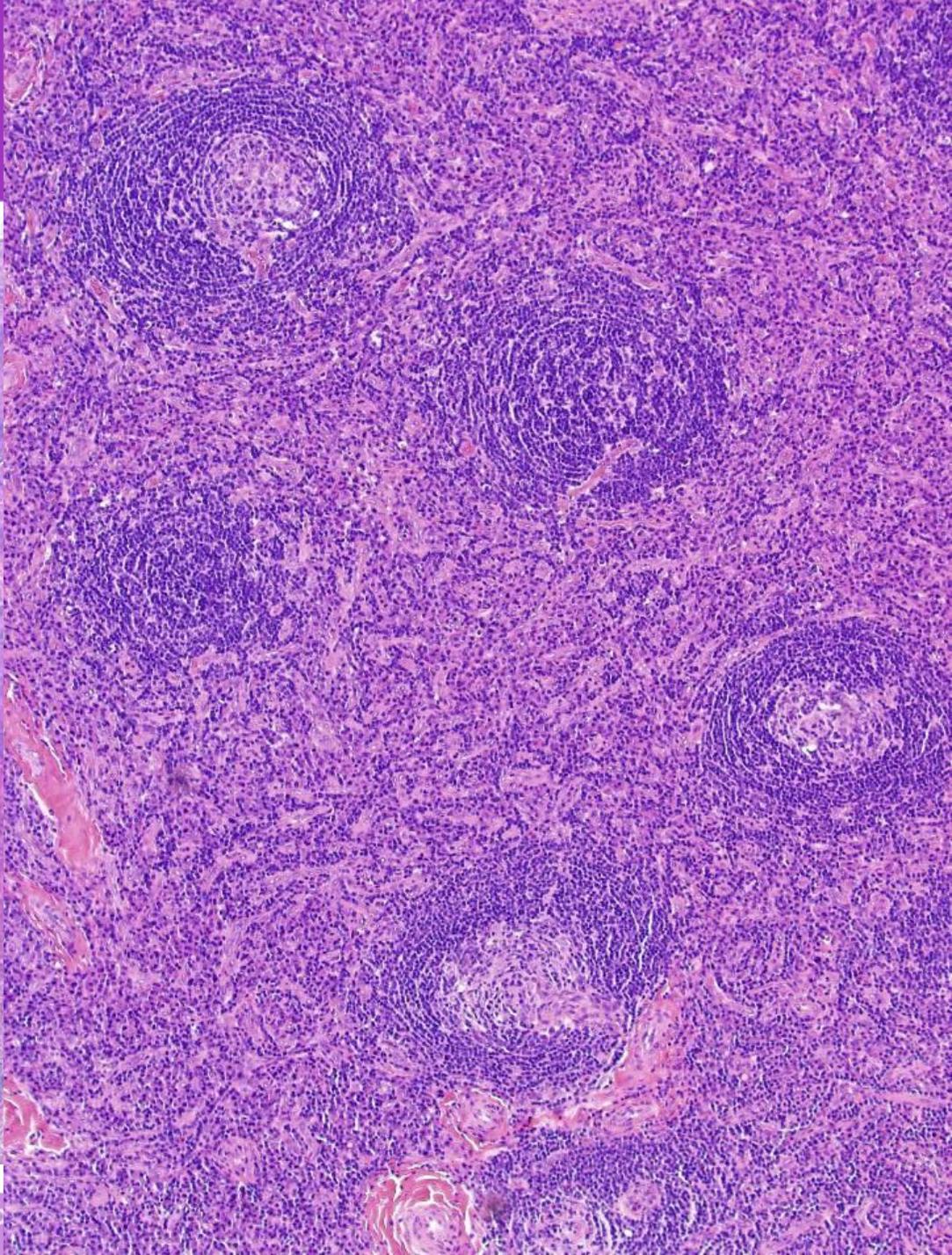
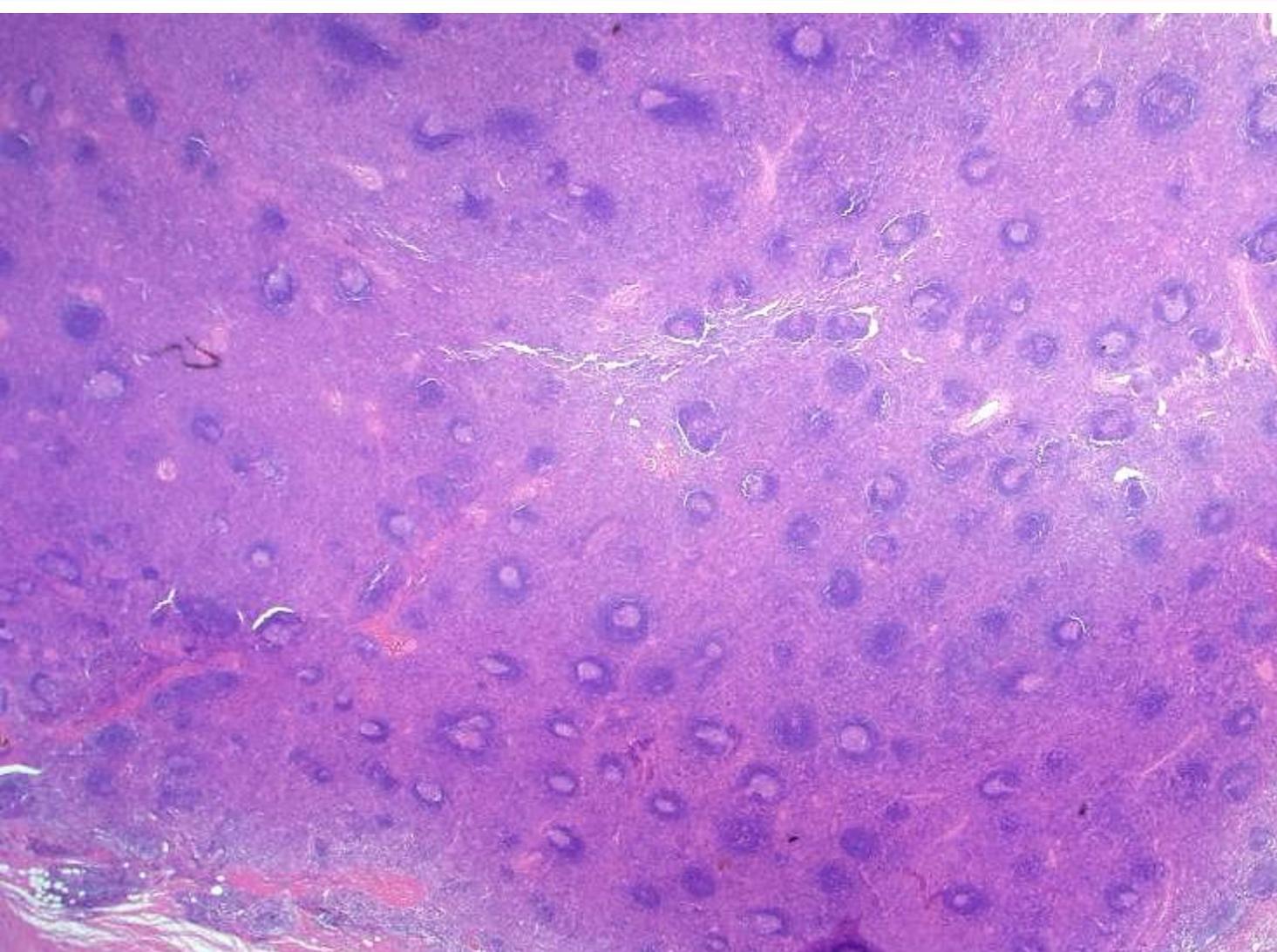
An axillary lymph node biopsy was performed.

Serology: **IgA/Lambda paraprotein**

Imaging: **Lytic/sclerotic lesions** in the vertebra, sacrum and iliac bones

Bone marrow: A small population of IgA/lambda plasma cells

# CASE 5



# MULTICENTRIC CD, PLASMA CELL VARIANT ASSOCIATED WITH POEMS SYNDROME

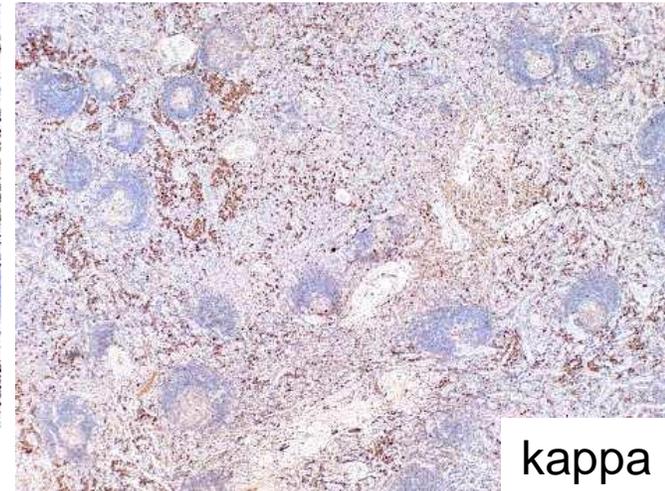
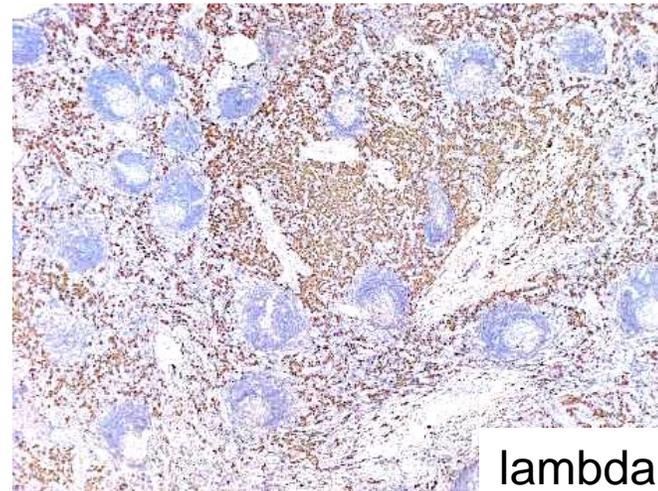
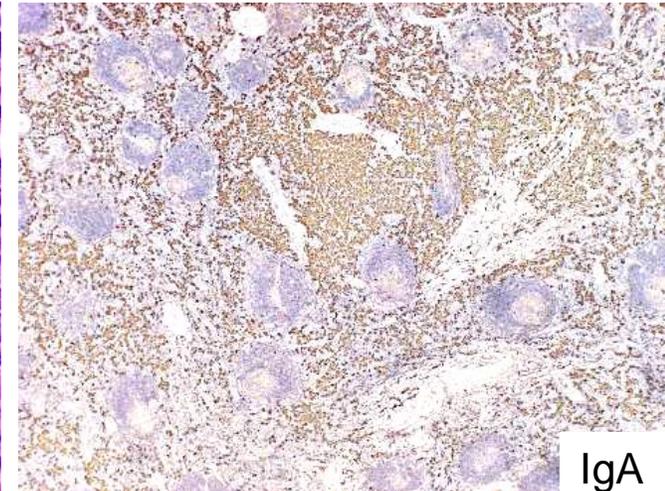
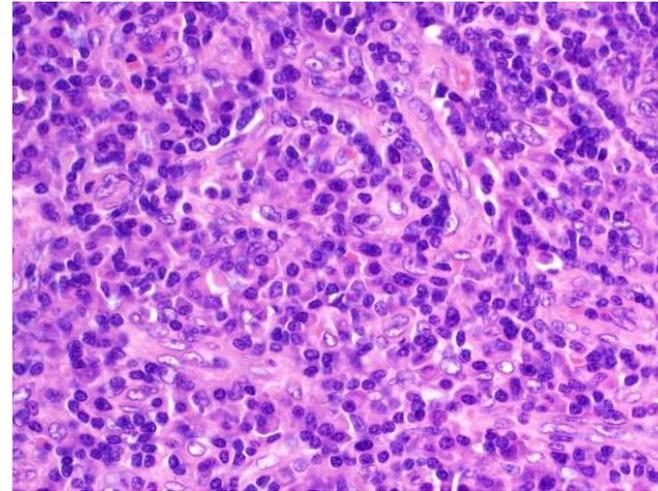
Clonal plasma cell disorder (sclerotic PC myeloma, mostly lambda) with range of paraneoplastic symptoms, associated with increased VEGF production

**P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal PC disorder, **S**kin changes

Further symptoms include:

- **CD, Plasma cell variant (15-60%)**
- **Sclerotic bone lesions**
- **Extravascular volume overload**
- Thrombocytosis/Erythrocytosis
- Papilledema
- **Abnormal pulmonary function tests**

Response to anti-neoplastic therapy



# POEMS SYNDROME DIAGNOSTIC CRITERIA

**Table 1. Criteria for the diagnosis of POEMS syndrome**

	Criteria/other symptoms and signs	Affected, %*
Mandatory major criteria (both required)	1. Polyradiculoneuropathy (typically demyelinating)	Dispenzieri A, Blood 2012 100
	2. Monoclonal plasma cell disorder (almost always λ)	100†
Other major criteria (1 required)	3. Castleman disease‡	11-25
	4. Sclerotic bone lesions	27-97
	5. VEGF elevation§	
Minor criteria (1 required)	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)	45-85
	7. Extravascular volume overload (edema, pleural effusion, or ascites)	29-87
	8. Endocrinopathy (adrenal, thyroid,   pituitary, gonadal, parathyroid, pancreatic  )	67-84
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, white nails)	68-89
	10. Papilledema	29-64
	11. Thrombocytosis/polycythemia¶	54-88
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B <sub>12</sub> values	

The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, 1 of the 3 other major criteria, and 1 of the 6 minor criteria are present.

\*Summary of frequencies of POEMS syndrome features based on largest retrospective series.<sup>2,7-11</sup>

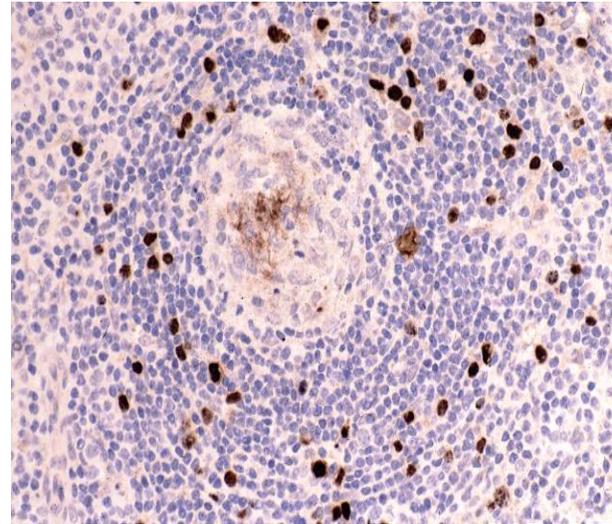
# HHV8-ASSOCIATED MCD

Proliferation of IgM-lambda  
restricted, polytypic, HHV8-infected  
plasmablasts in the mantle zone of  
follicles

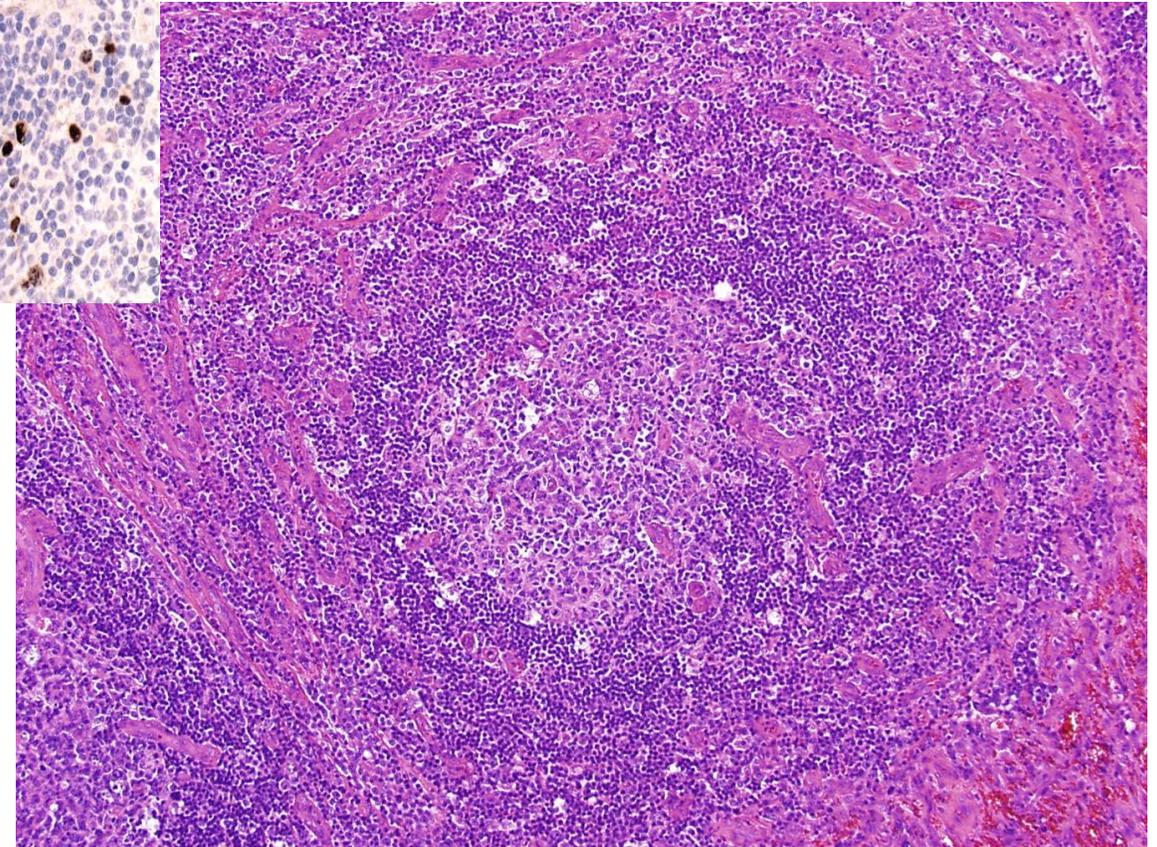
Common co-occurrence of Kaposi  
sarcoma

Increased risk for other HHV8-  
associated lymphoproliferative  
disorders

- Primary effusion lymphoma
- HHV8+ DLBCL
- HHV8+ germinotropic  
lymphoproliferative disorder



HHV8



# HHV8+ MCD: PATHOGENESIS AND CLINICAL FEATURES

Expression of both latent (LANA-1) and lytic (vIL-6, vIRF1) viral proteins in MCD

MCD IgM $\lambda$  plasmablasts show downregulation of co-stimulatory molecules (CD40) and IL-10 expression and are detectable in PB

**Hypercytokinemia** (vIL-6, hIL-6, IL-1, IL-10, TNF) results in systemic symptoms (anemia, fever, hypoalbuminemia)

KSHV inflammatory cytokine syndrome (KCIS) without diagnosis of MCD

**Prognosis** improved with appropriate therapy, worse in HIV infection and with Kaposi sarcoma (>90% 5y OS with Rituximab +/- chemotherapy)

High risk of HHV8-associated **lymphoma**

**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)
$\kappa/\lambda$	Monotypic $\lambda$ (100% high positivity)	Balanced $\kappa/\lambda$ 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

# CASTLEMAN DISEASE

CD is a morphological pattern, but not a clinico-pathological entity

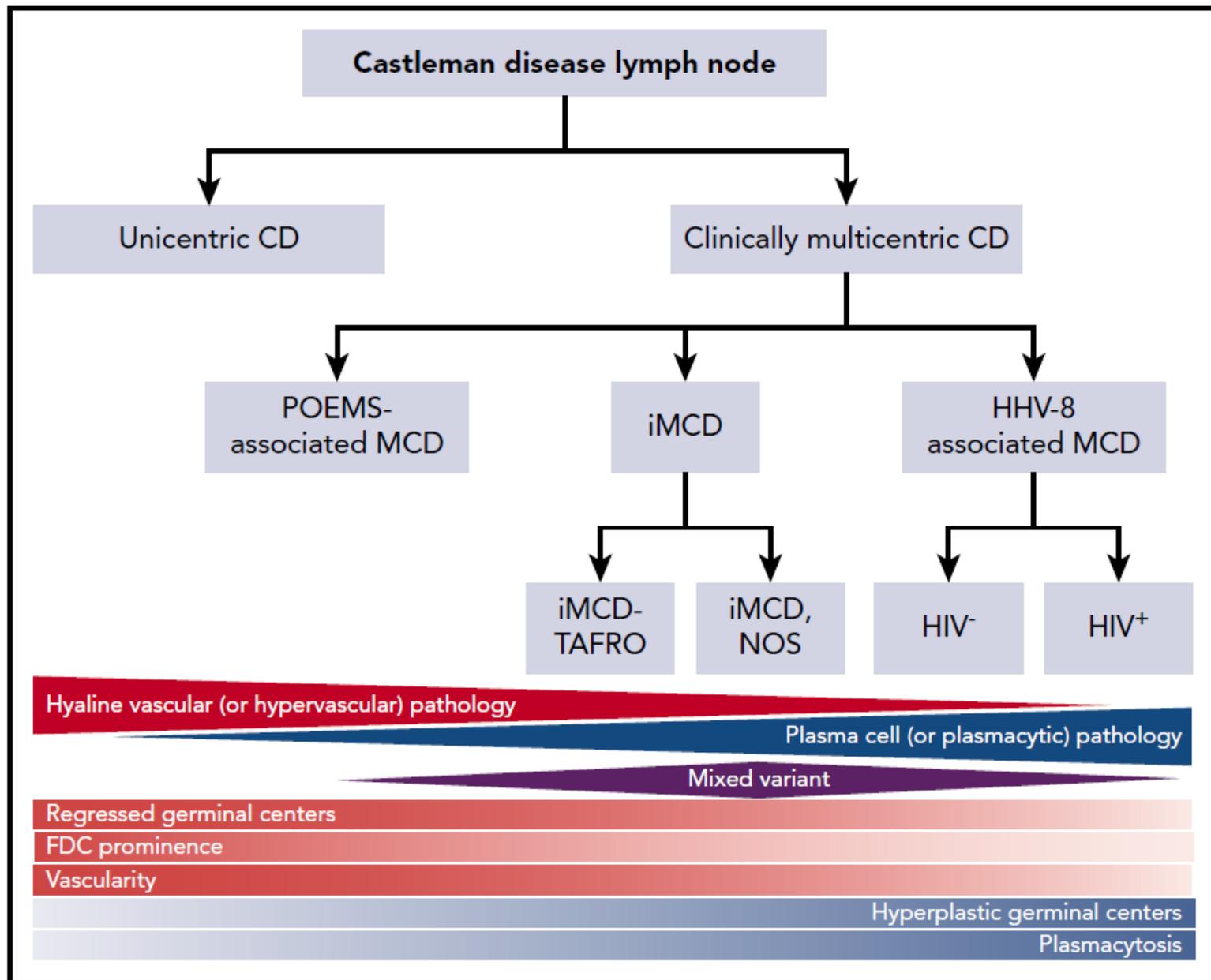
## Unicentric CD

- Hyaline vascular type (>90% of cases)
- Rare plasma cell type

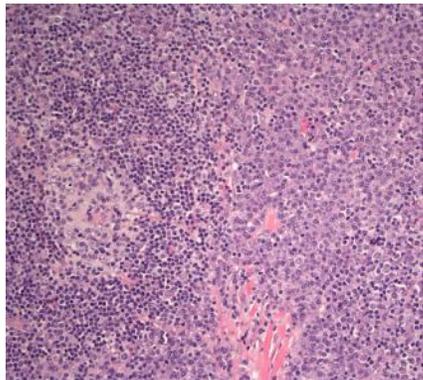
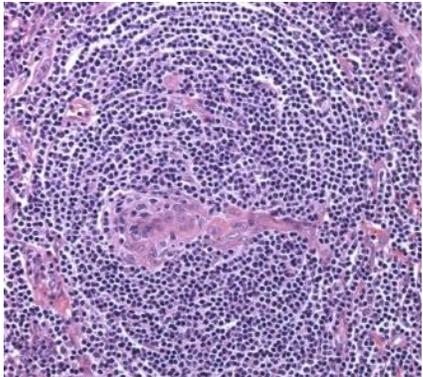
## Multicentric CD

- HHV8+ MCD, plasma cell (plasmablastic) type
- MCD associated with POEMS or plasma cell neoplasia (osteosclerotic myeloma)
- Idiopathic MCD
  - TAFRO subtype of iMCD

Histopathological subtyping is difficult to reproduce and not predictive of response to Siltuximab (Fajgenbaum et al, AJH 2020)



Diagnosis of MCD requires a high level of suspicion, appropriate workup and clinical information



## Clinical features

- Multi/-unicentric?
- Hyperinflammatory symptoms?
- Autoimmune disorder?
- Plasma cell dyscrasia?
- Lymphoma?
- HIV?
- EBV or other infections?

## Diagnostic tests in (M)CD

- Appropriate immunostaining to rule out lymphoma (AITL, FL, MZL)
- IG heavy and light chains
- B-cell clonality
- IgG/IgG4 ratio
- HHV8 (LANA)
- EBV (EBERs)

UCD: mostly typical HV morphology, no systemic sy.

iMCD: usually PC type, polyclonal plasma cells, HHV8-, systemic symptoms

MCD-POEMS/osteosclerotic MM: clonal PC (lambda restricted) in LN and BM

MCD HHV8+: LANA+ +/- Kaposi sarcoma, mostly in setting of immunosuppression

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