36th ANNUAL PARK CITY ANATOMIC PATHOLOGY UPDATE
The Lodges at Deer Valley
February 5-9, 2023

Friend or Foe: Are "benign lymphadenopathies" still benign?

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Agenda

- Discuss the WHO-HAEM5 updates on “tumor-like lesions” of lymphoid tissue
- Review the most current diagnostic and therapeutic considerations for Castleman disease and IgG4-related disease
- Propose a practical approach to the diagnosis of key tumor-like lesions

Disclosures

- None

- The new WHO classification will be mentioned only once; ICC – not at all
- No “hardcore” flow or molecular

WHO, 5th Edition

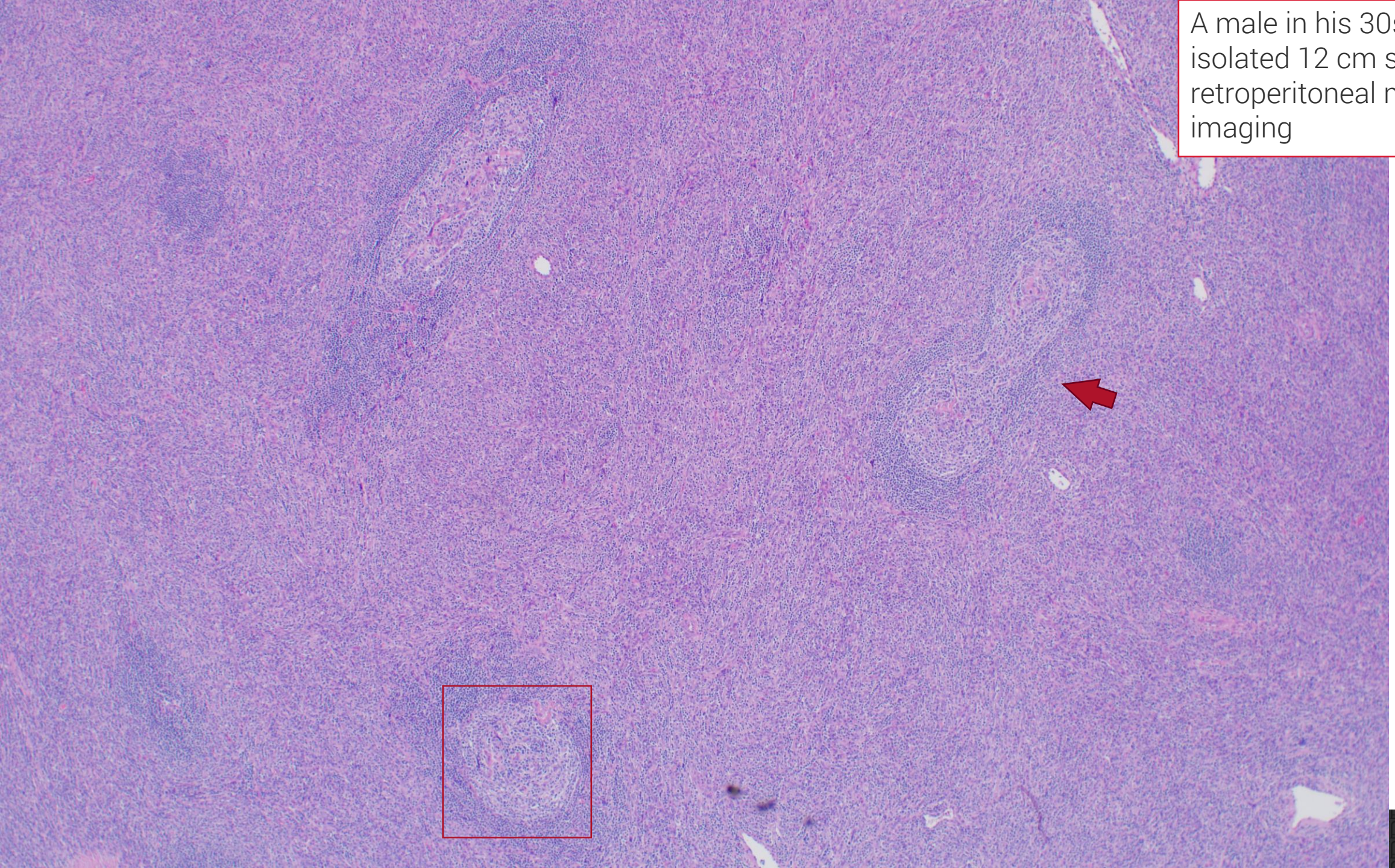
Tumor-like lesions with B-cell predominance

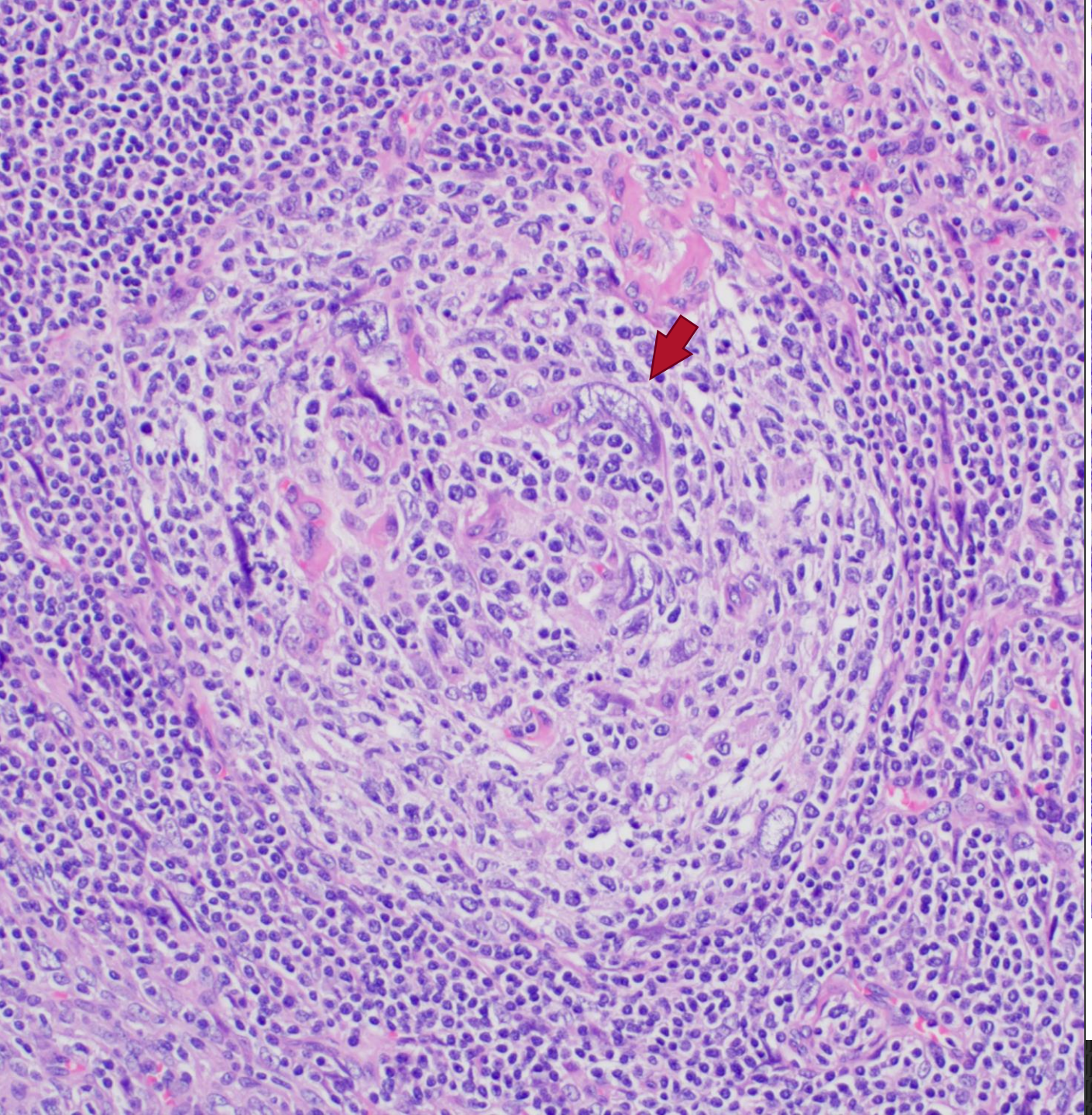
- Reactive B-cell-rich LPs that can mimic lymphoma
- IgG4-related disease
- Castleman disease (CD)
  - » Unicentric CD
  - » Idiopathic multicentric CD
  - » KSHV/HHV8-associated multicentric CD

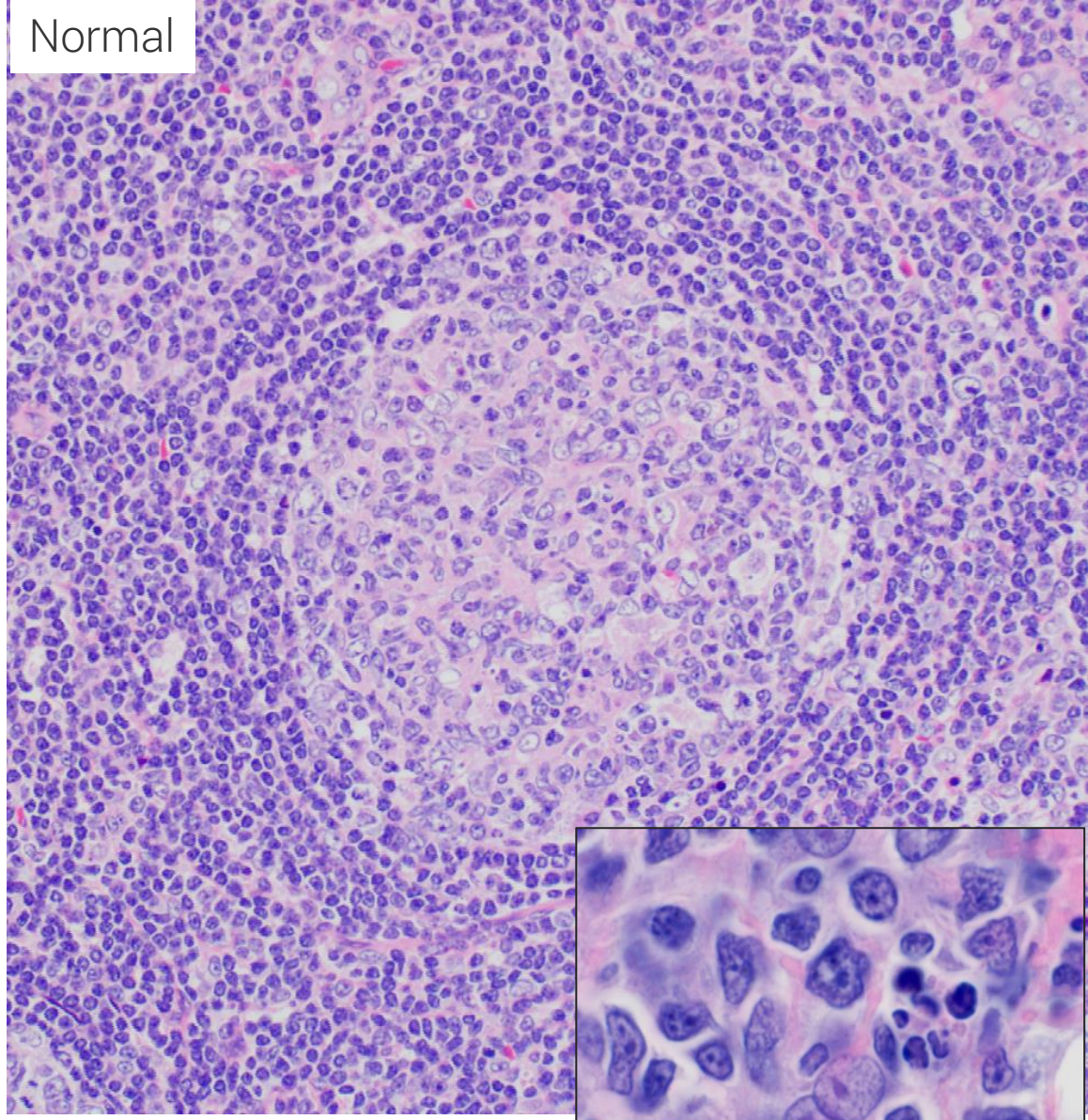
Tumor-like lesions with T-cell predominance

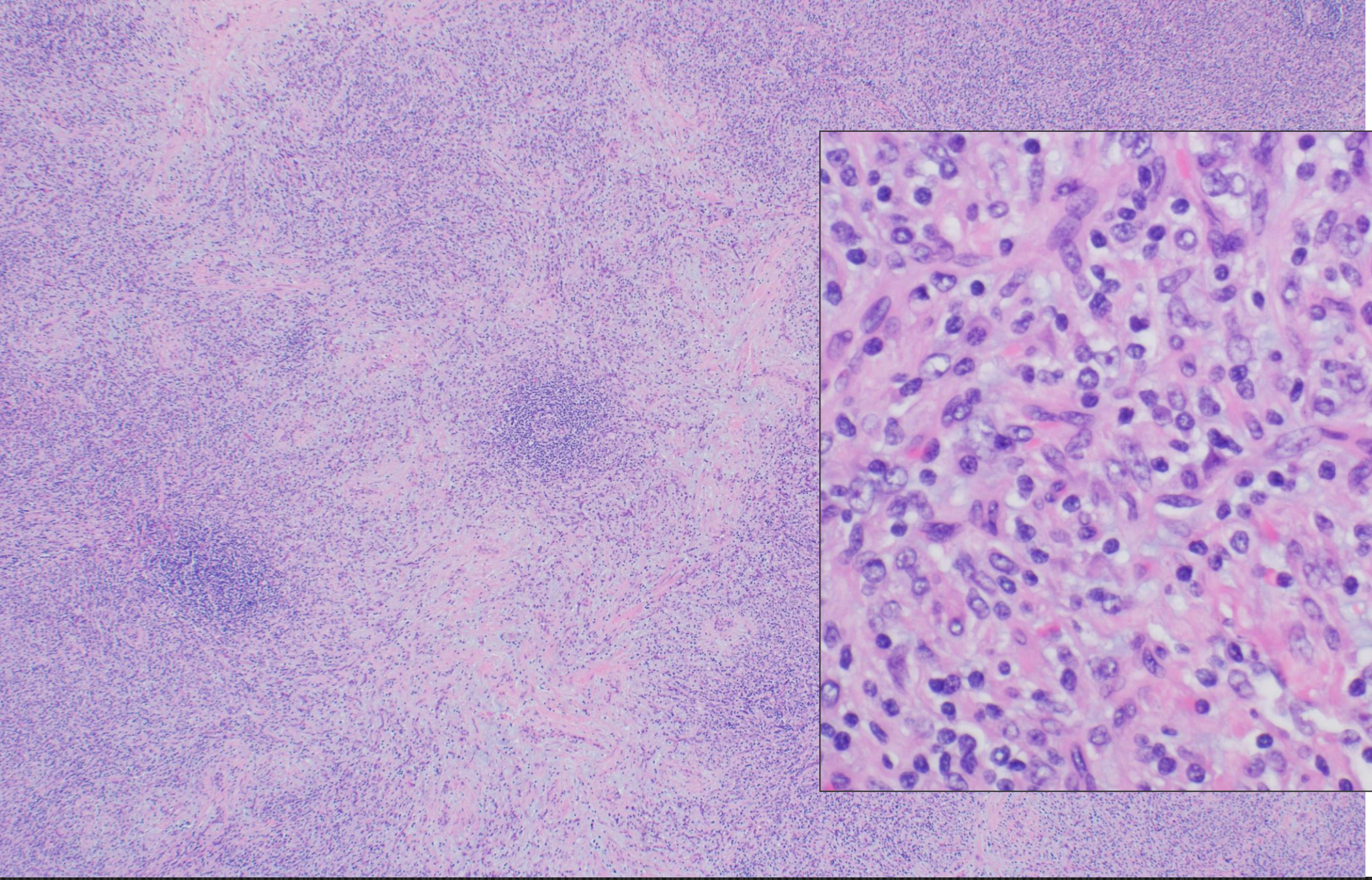
- Kikuchi-Fujimoto disease
- Autoimmune lymphoproliferative syndrome
- Indolent T-lymphoblastic proliferations

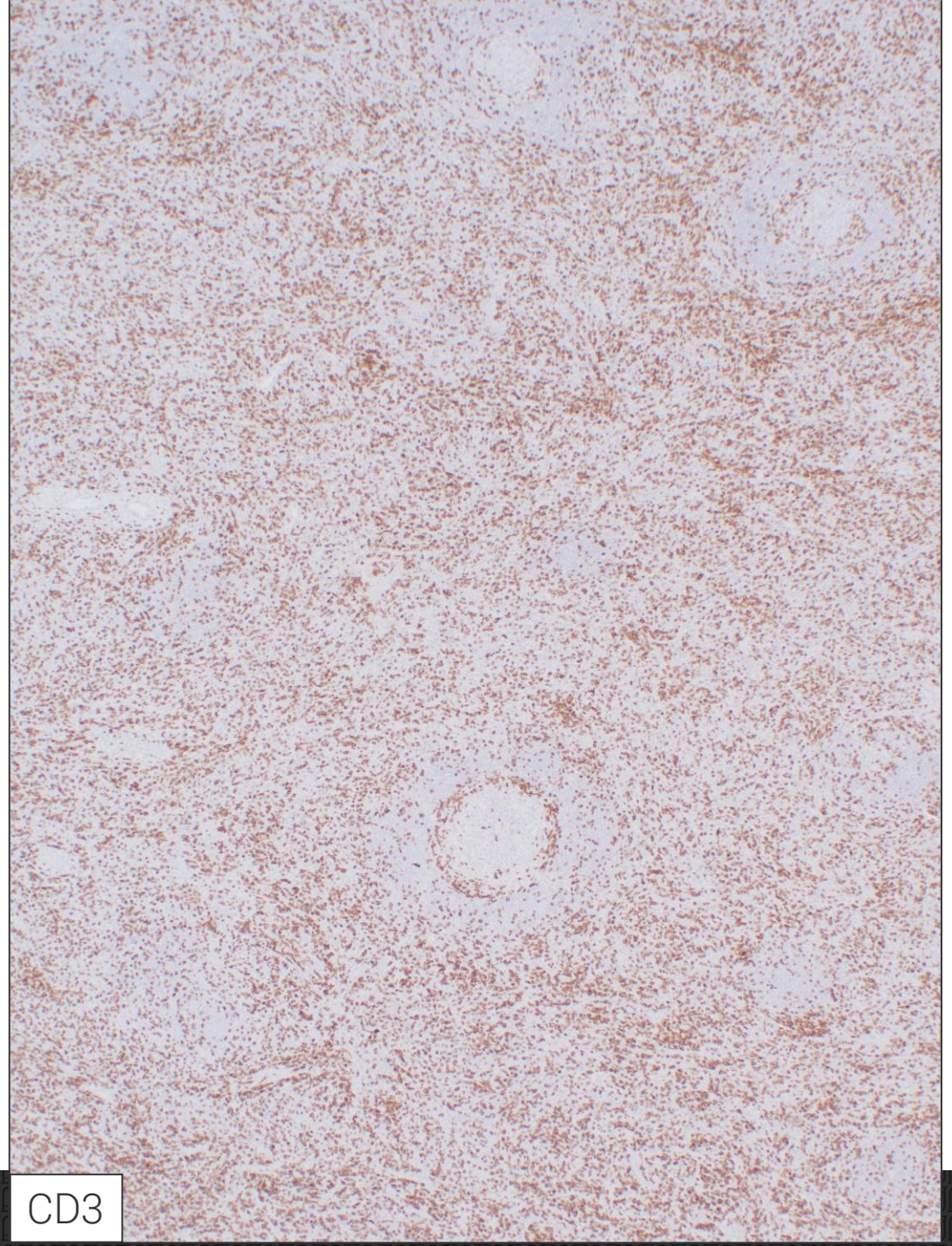
A male in his 30s with an isolated 12 cm suprarenal retroperitoneal mass on imaging



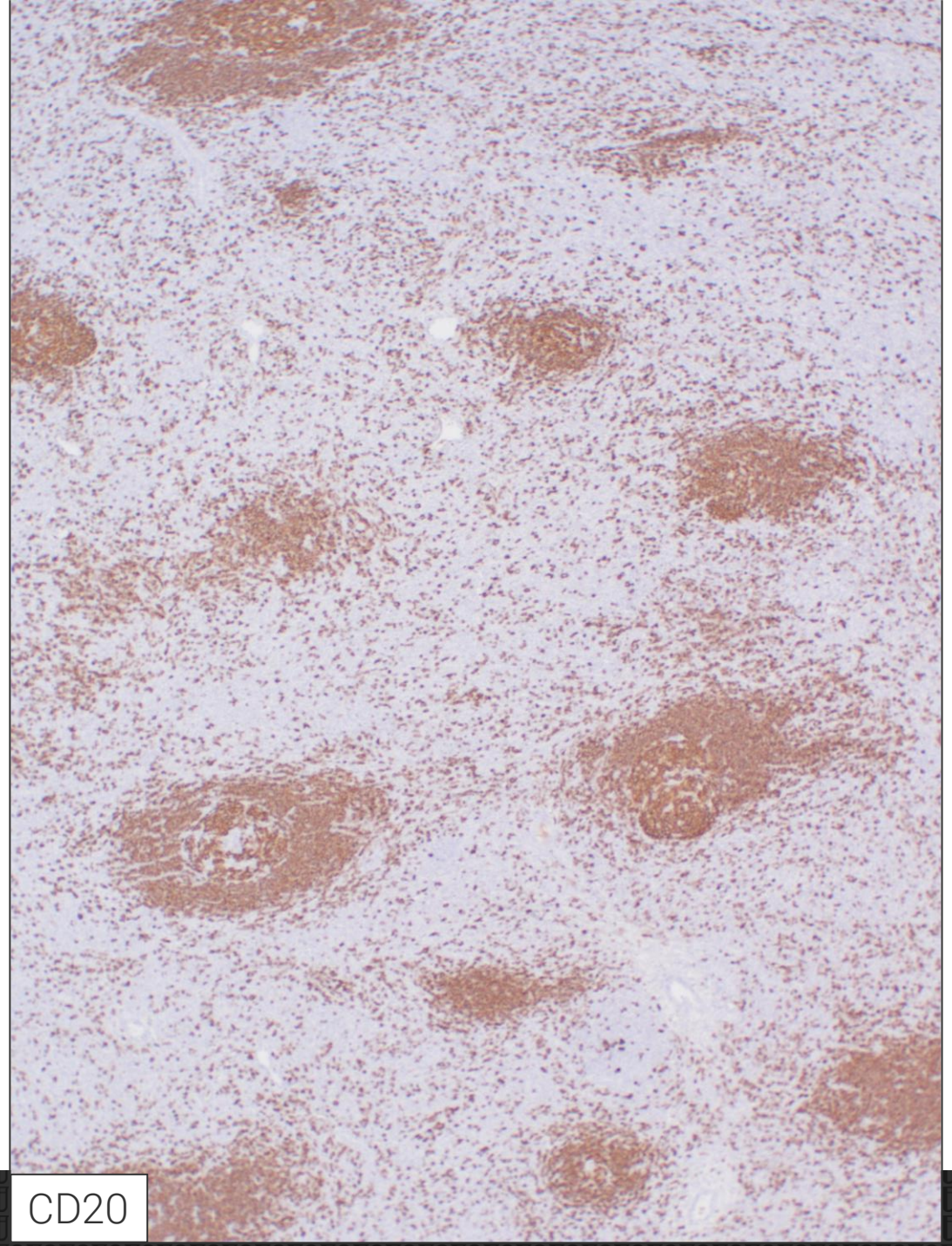



Normal





CD3

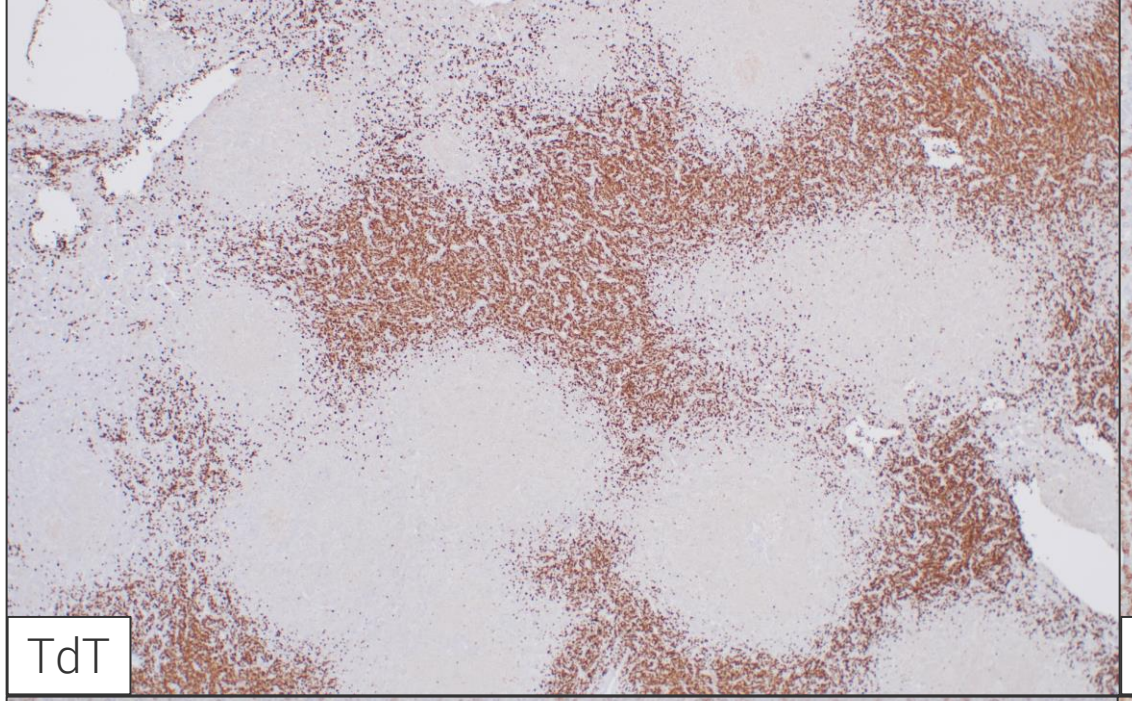


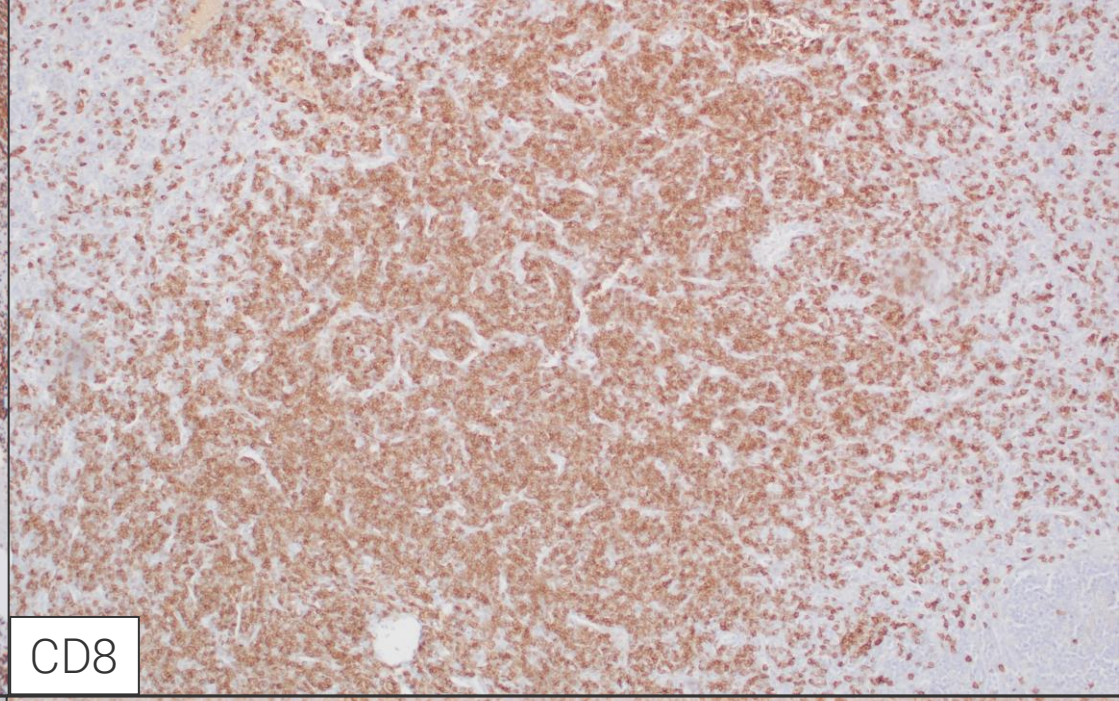
CD20

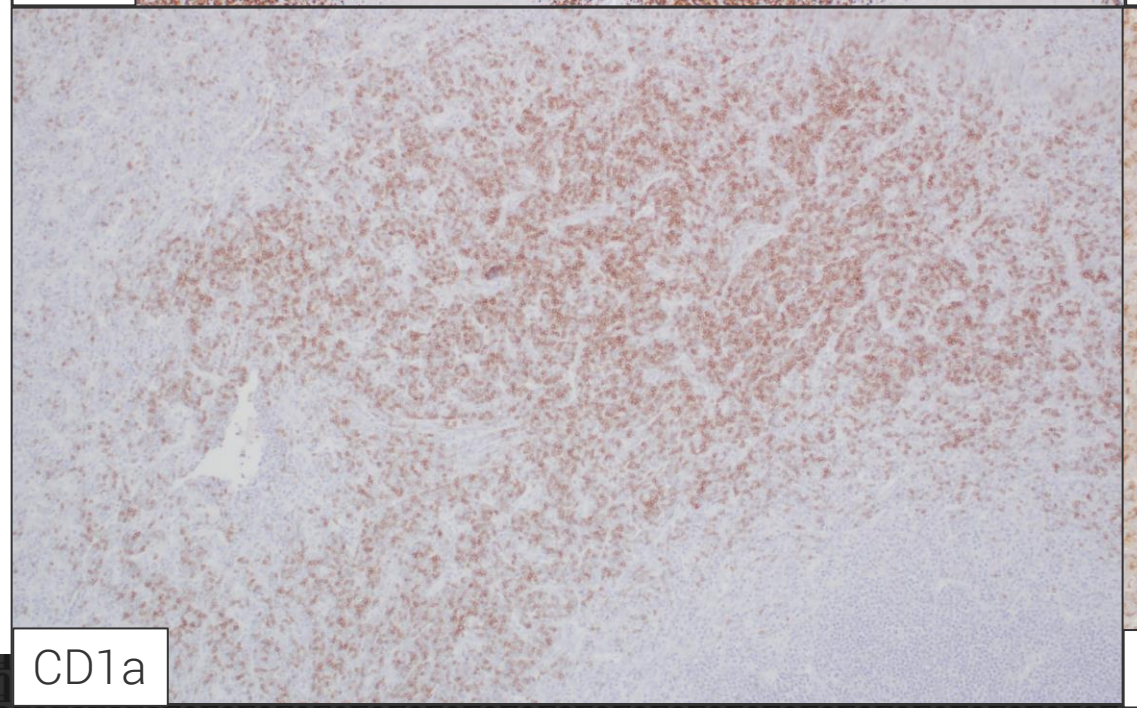
Flow cytometry:

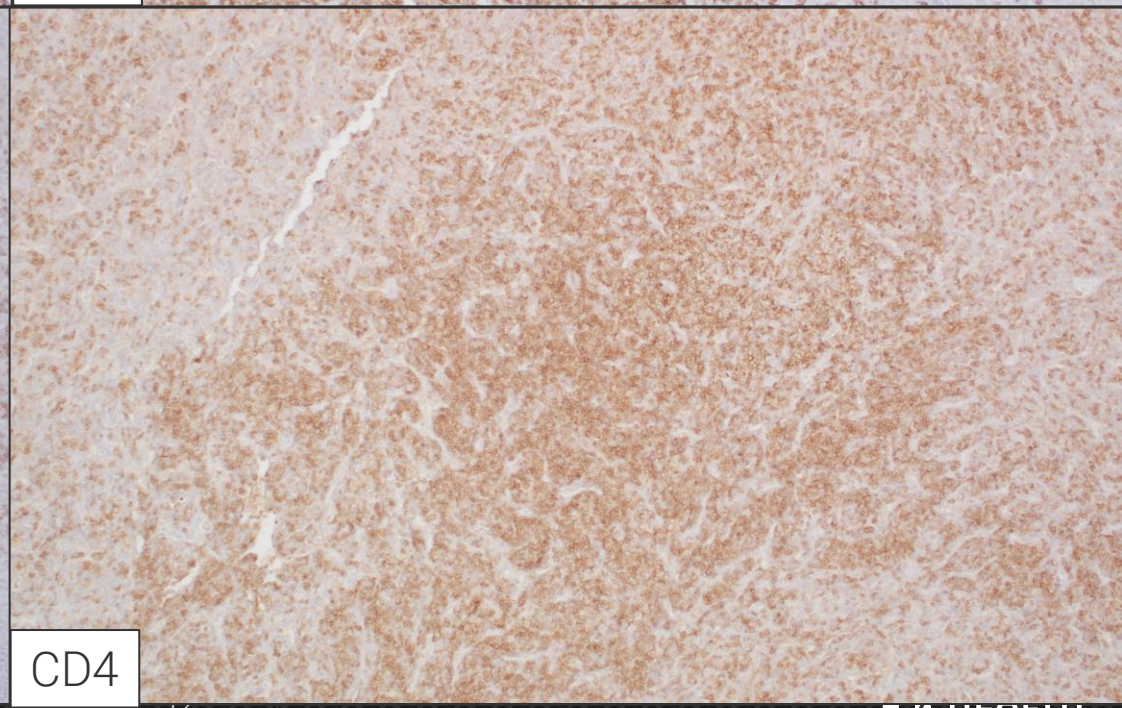
T-cell precursors, 25% of leukocytes

Positive for CD3, CD4, CD8, CD1a, TdT


TdT


CD8


CD1a


CD4

Differential Diagnosis

Overall appearance

- Castleman disease
- Infection
- Lymphoma
- Castleman-like changes, nonspecific

Immature T-cells

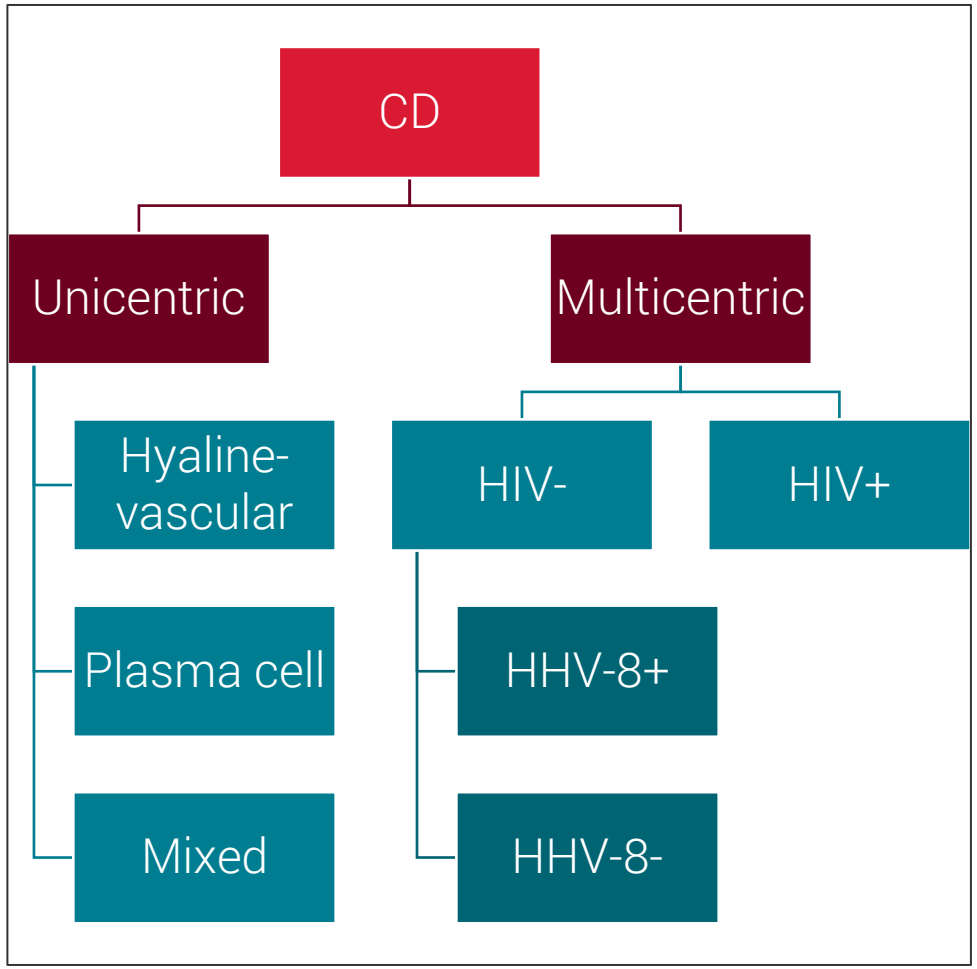
- T-ALL?
- T-lymphoblastic something else

Castleman Disease

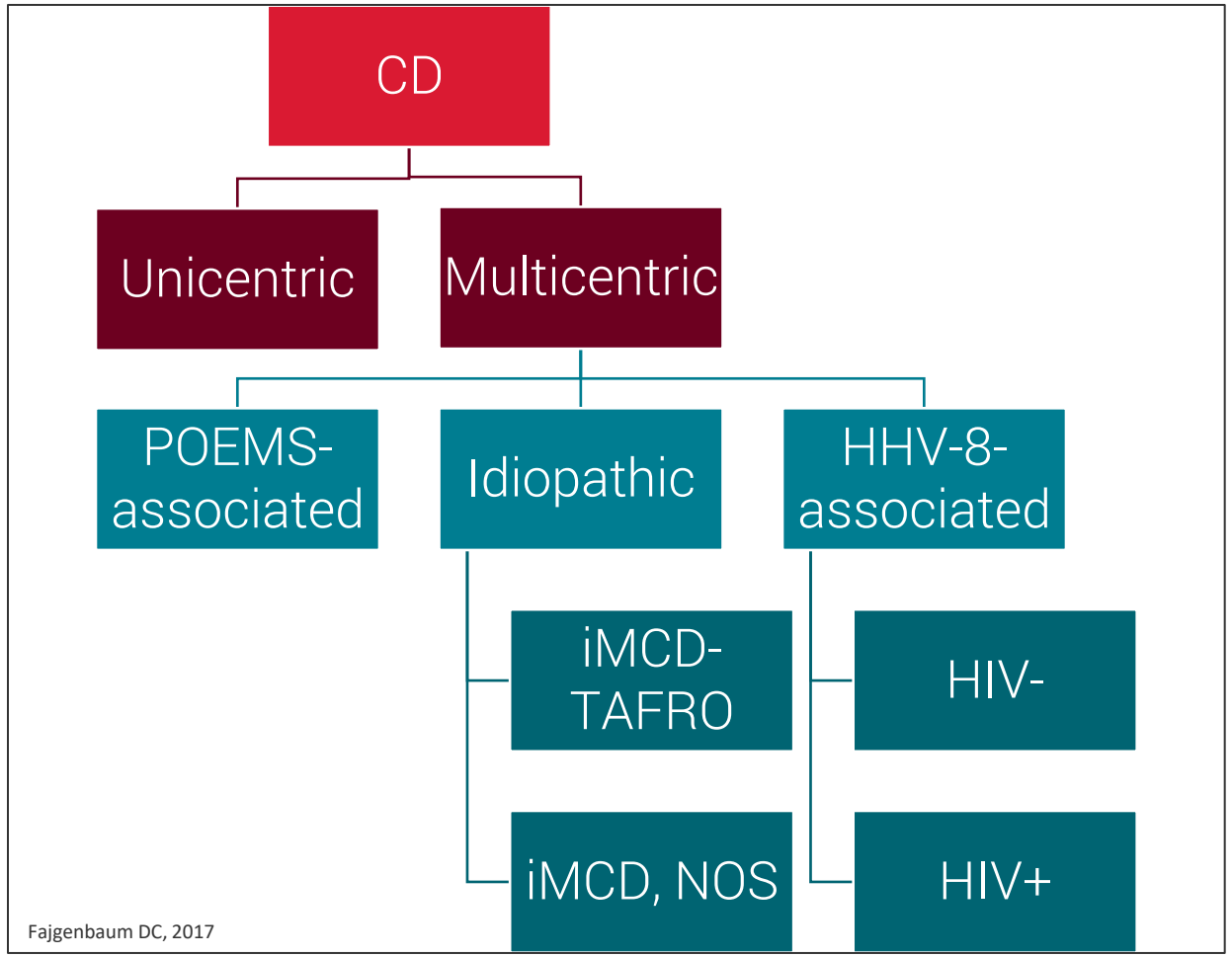
- Several (at least 4) different clinicopathologic entities
  - » Share spectrum of characteristic histopathologic features
  - » Wide range of etiologies, presentations, treatments, and outcomes
- 1950s – initial description by Benjamin Castleman in 1950s
- 1960s – Flendrig subcategorized “plasma cell”, “hyalinized”, and “intermediate” forms
- 1980s – unicentric CD and multicentric CD
- 1980s-1990s – association with HIV, POEMS, and HHV8

Classification

Former



Current



Fajgenbaum DC, 2017

Epidemiology

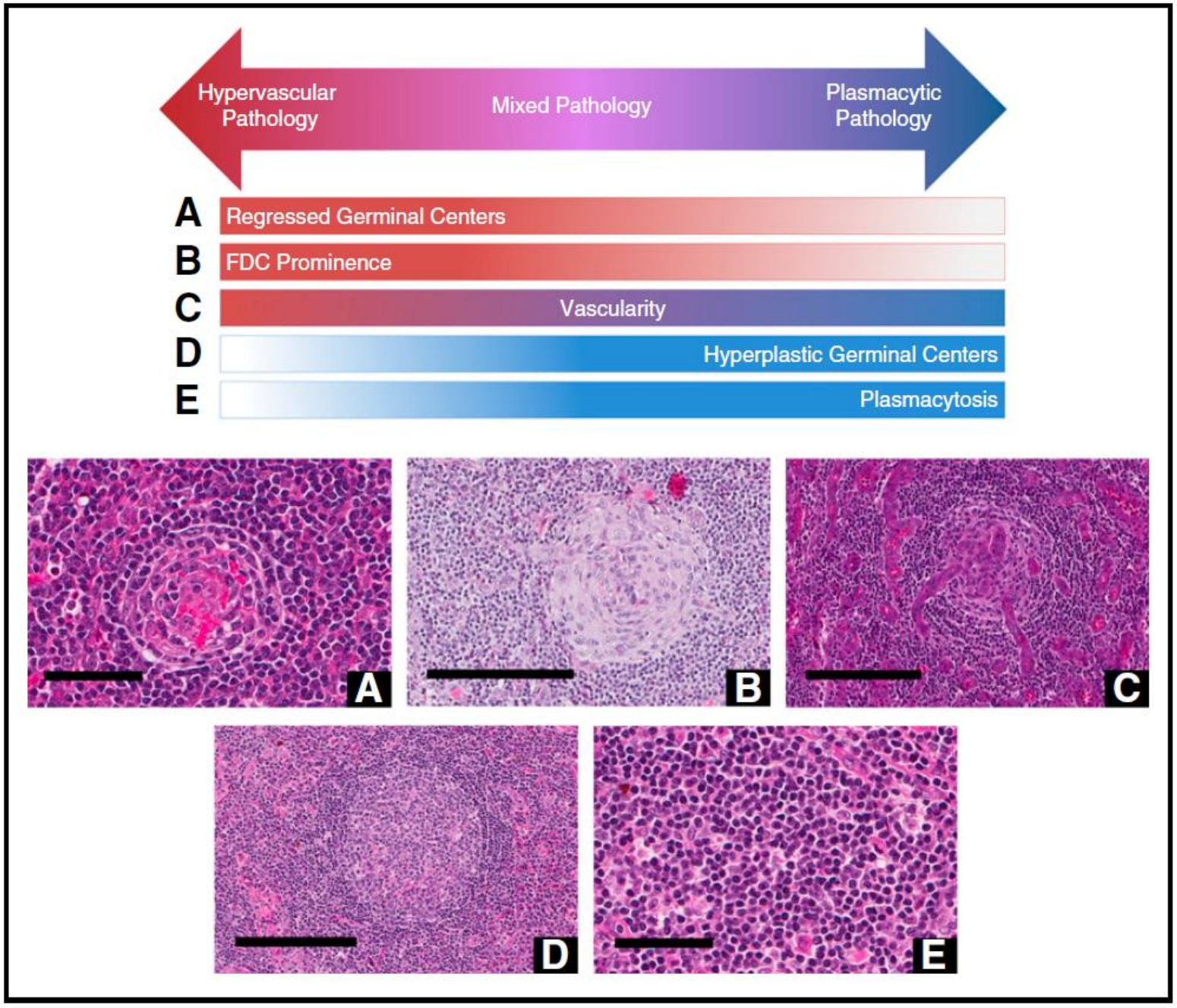
	UCD	MCD
M:F	No predilection	M slightly > F
Age	Any, usually younger (40s)	Any, usually older (60s)
Risk factors	No known	Immunosuppression (for HIV and HHV-8)
Annual incidence in USA	4,300	5,200

Morphology

Hypervascular/hyaline-vascular – regressed GCs and FDC prominence

Plasmacytic – hyperplastic GC and profound plasmacytosis

Mixed – combination



Important points

- Involves single LN region
- Demonstrates characteristic “Castleman” histopathologic changes
- Systemic manifestations are usually mild

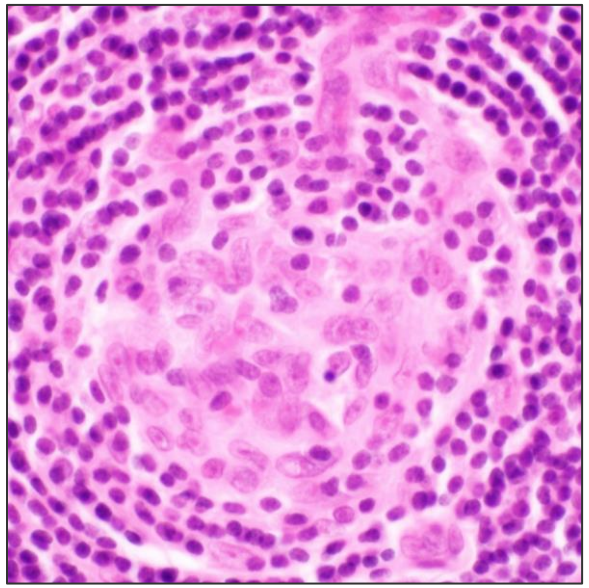
Pathogenesis

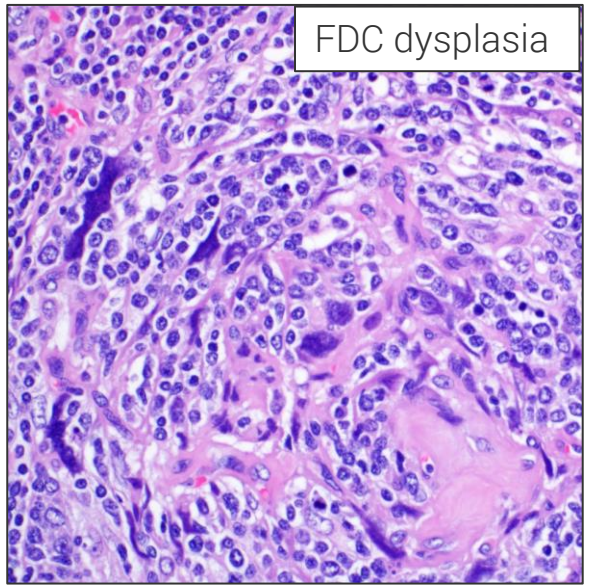
Clonal/neoplastic transformation of follicular dendritic cells (FDC)

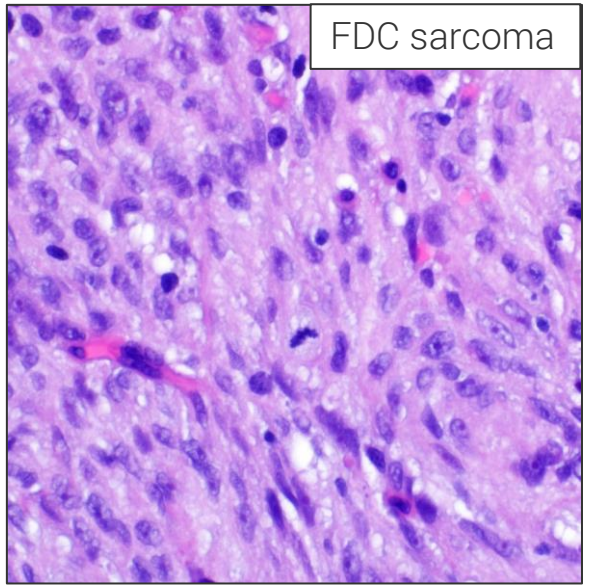
20% cases have mutated *PDGFRB* - gain of function mutation

FDC dysplasia

Association with FDC sarcoma







Morphology

LN enlargement

Distorted architecture, but no effacement

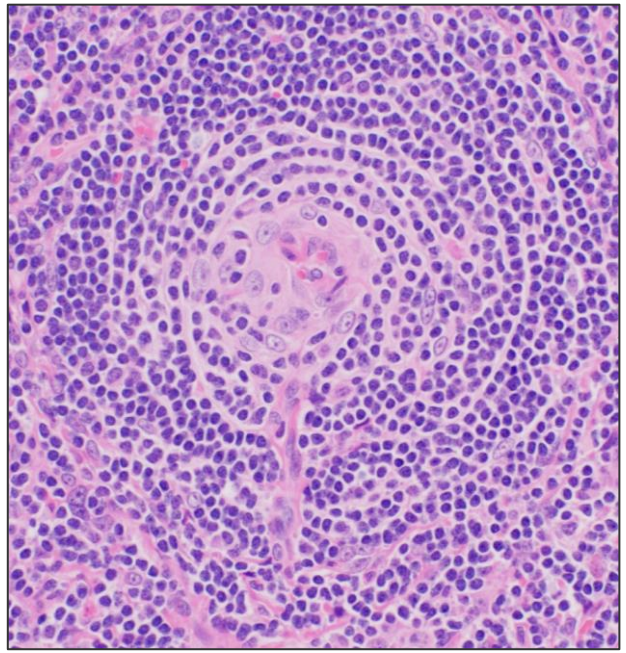
Depleted and hyalinized GCs

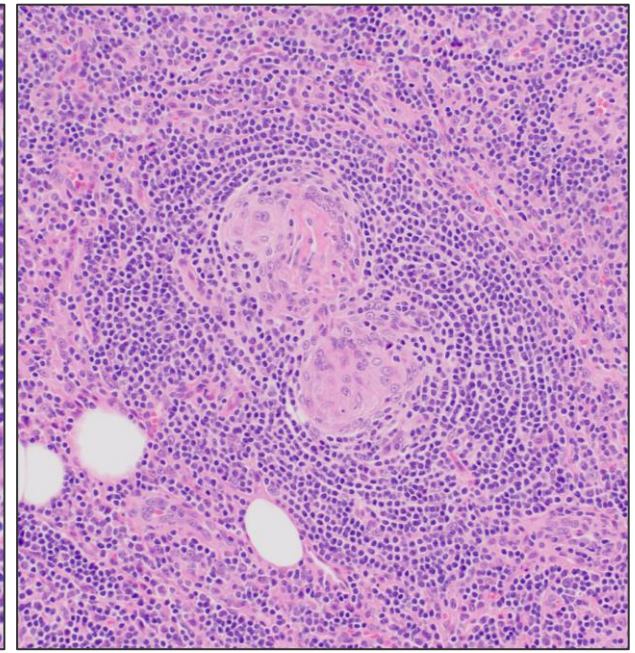
Penetrating vessels – “lollipop”

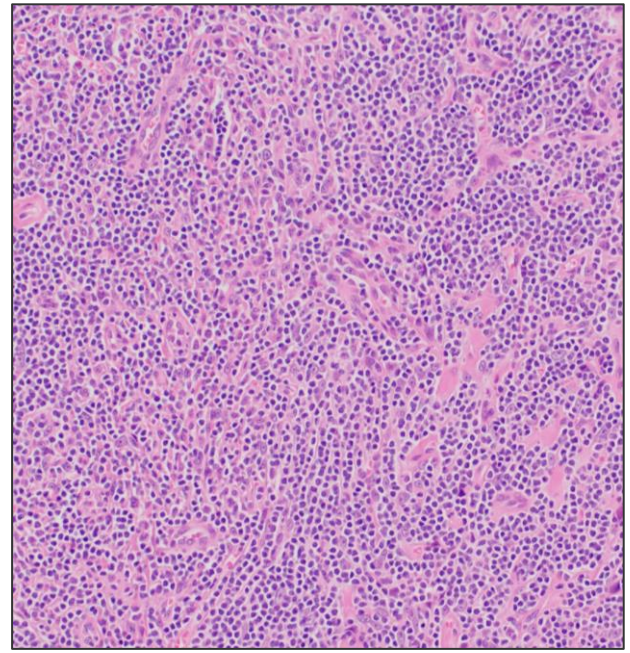
Concentric mantle zones – “onion skin”

Interfollicular vascular proliferation

Usually, rare plasma cells







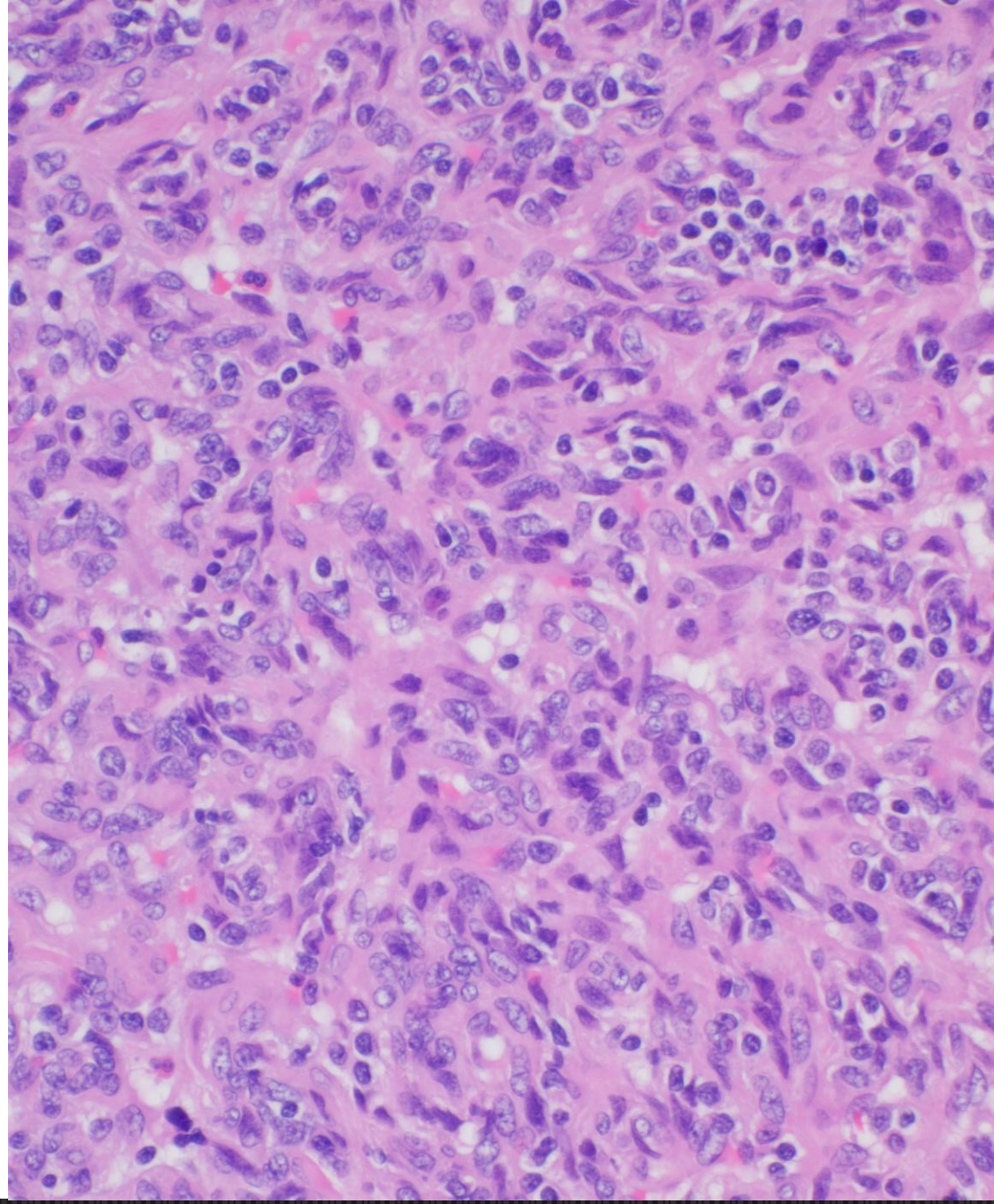
Stroma-rich variant

Relatively newly identified variant of UCD

Vague nodularity and prominent expansion of interfollicular areas by various stromal cells

- Positive for desmin
- Negative for CD34, F VIII, S100, CD21, and CD68

No prognostic differences

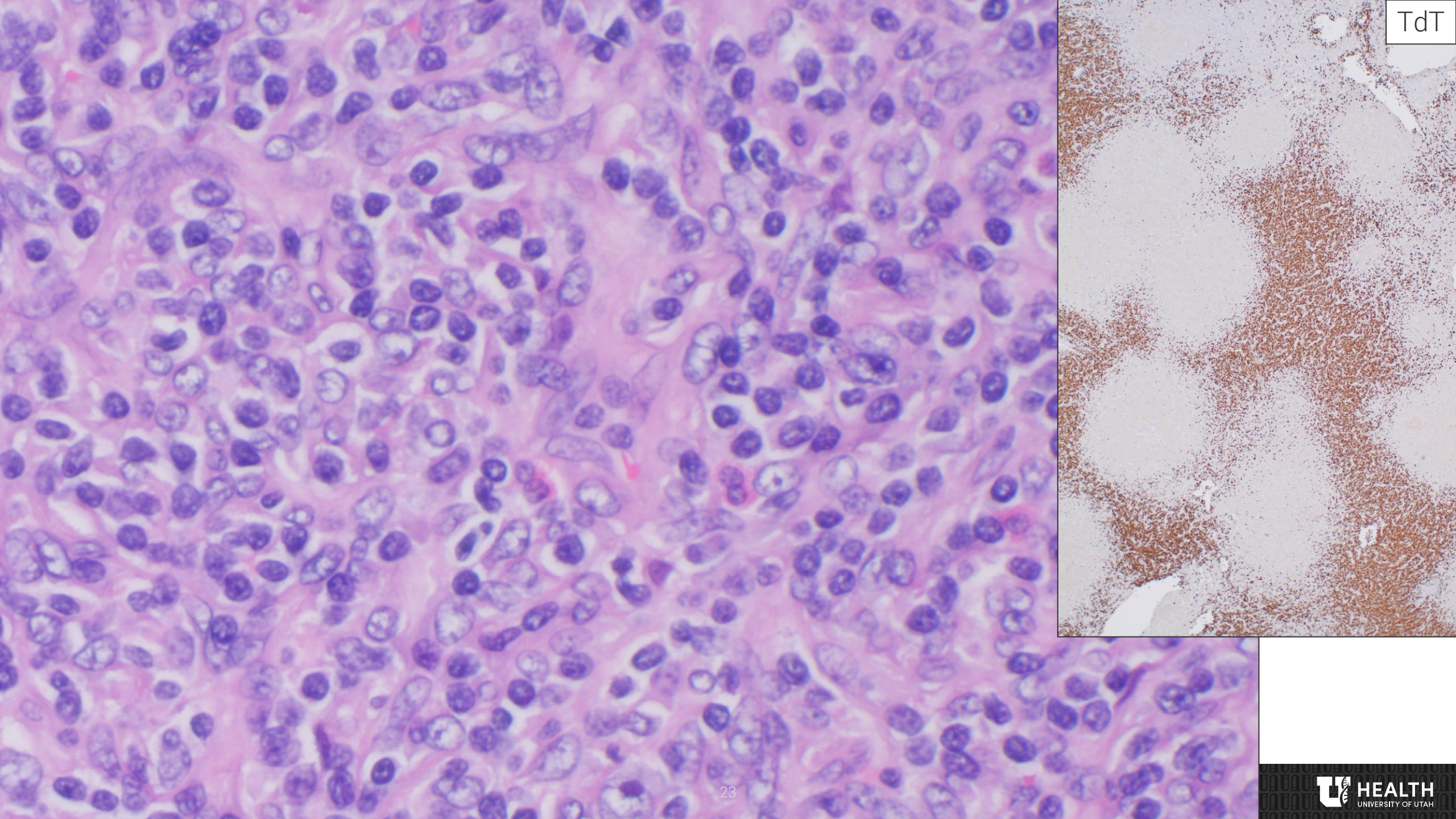


Izumi M et al.. Angiomyoid proliferative lesion: an unusual stroma-rich variant of Castleman's disease of hyaline-vascular type. Virchows Arch. 2002 Oct;441(4):400-5.

T-lymphoblastic proliferations

- Rare but a well described finding
- Non-clonal
- Involve lymph nodes but not bone marrow or blood
- Interfollicular localization without architectural effacement
- Frequent mitoses, high proliferative rate by MIB1
- Associations: thymoma, myasthenia gravis, hepatocellular carcinoma, acinic cell carcinoma, CD

Woo CG, Huh J. TdT+ T-Lymphoblastic Proliferation in Castleman Disease. J Pathol Transl Med. 2015 Jan;49(1):1-4.

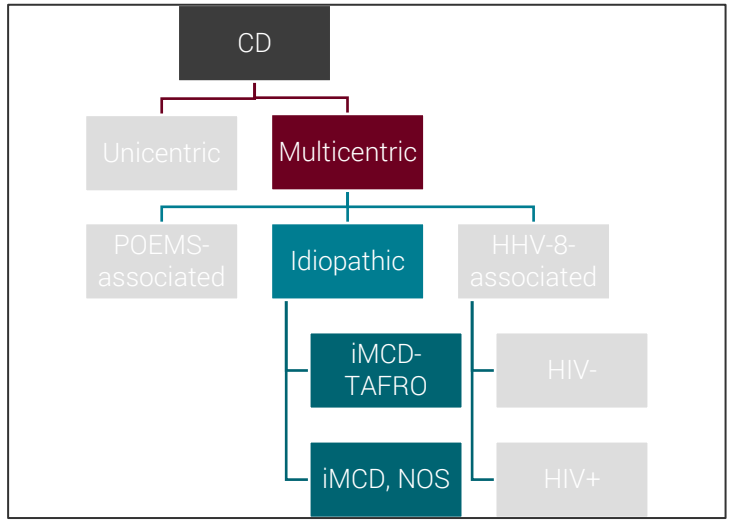


Our diagnosis

Unicentric Castleman disease

- hyaline-vascular/hypervascular pattern
- stroma-rich variant
- indolent T-lymphoblastic proliferation

Idiopathic Multicentric CD

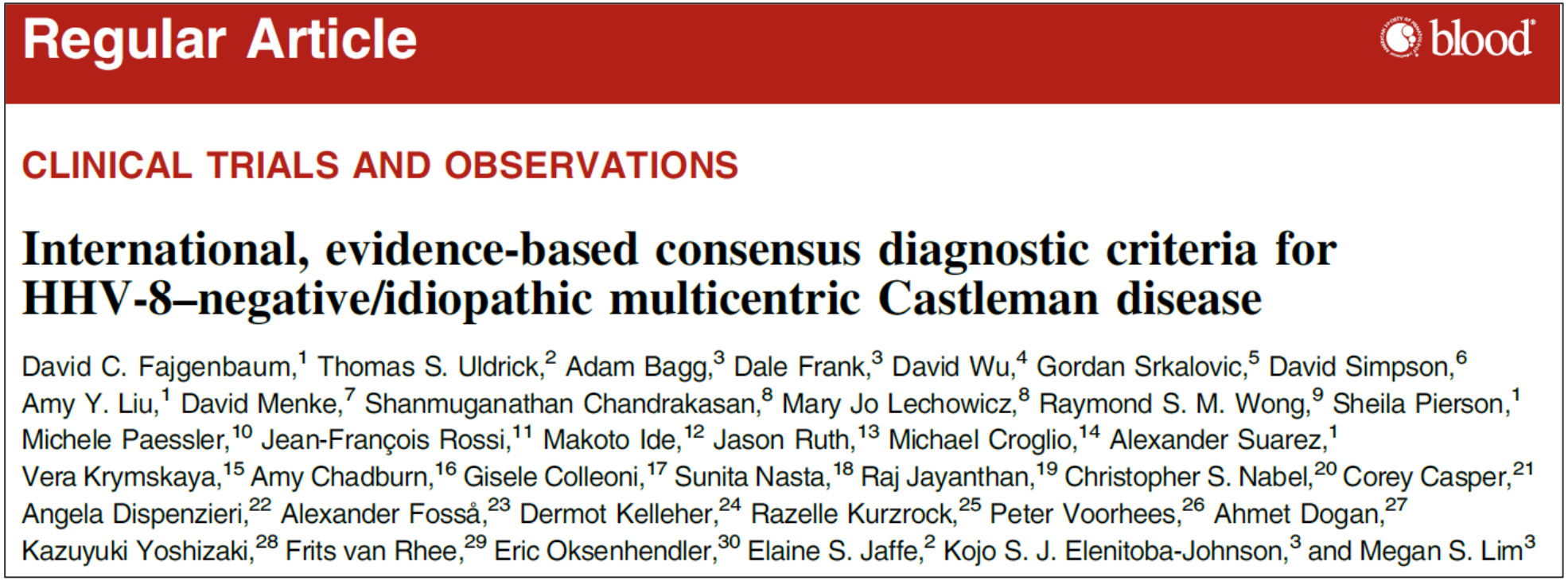


- Involves many LN regions
- Poorly understood entity with no nonspecific biomarkers
- Unknown etiology
- Systemic symptoms, polyclonal lymphoid proliferation, and wide spectrum of symptoms, e.g., night sweats, LAD, hepatosplenomegaly, hypoalbuminemia, anemia, etc.
- Poor prognosis: 35% die within 5 years, 60% die within 10 years; increased prevalence of malignancy

Pathogenesis

- IL-6 is a critical driver
  - many patients respond to anti-IL-6 or anti-IL-6R treatment
- Some iMCD cases are associated with other cytokines, e.g., mTOR pathway activators
- Autoantibodies are seen in 1/3 iMCD patients
- Paraneoplastic (?) – higher association with CHL and myelofibrosis

IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE



Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease

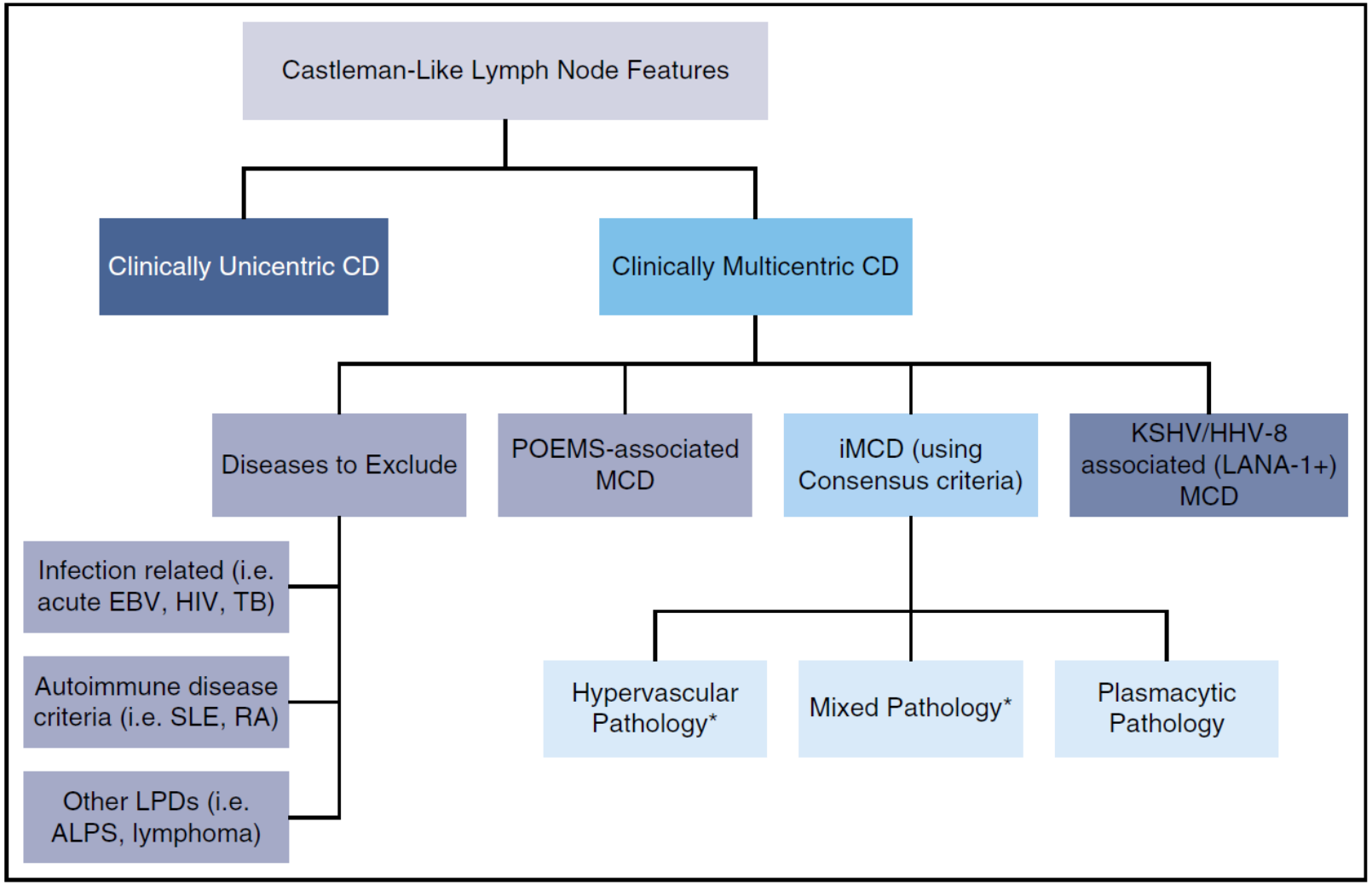
David C. Fajgenbaum,[1] Thomas S. Uldrick,[2] Adam Bagg,[3] Dale Frank,[3] David Wu,[4] Gordan Srkalovic,[5] David Simpson,[6] Amy Y. Liu,[1] David Menke,[7] Shanmuganathan Chandrakasan,[8] Mary Jo Lechowicz,[8] Raymond S. M. Wong,[9] Sheila Pierson,[1] Michele Paessler,[10] Jean-François Rossi,[11] Makoto Ide,[12] Jason Ruth,[13] Michael Croglio,[14] Alexander Suarez,[1] Vera Krymskaya,[15] Amy Chadburn,[16] Gisele Colleoni,[17] Sunita Nasta,[18] Raj Jayanthan,[19] Christopher S. Nabel,[20] Corey Casper,[21] Angela Dispenzieri,[22] Alexander Fosså,[23] Dermot Kelleher,[24] Razelle Kurzrock,[25] Peter Voorhees,[26] Ahmet Dogan,[27] Kazuyuki Yoshizaki,[28] Frits van Rhee,[29] Eric Oksenhendler,[30] Elaine S. Jaffe,[2] Kojo S. J. Elenitoba-Johnson,[3] and Megan S. Lim[3]

CD Collaborative Network Scientific Advisory Board: 34 physicians from 8 countries on 5 continents

- Data derived from 244 iMCD patients
- 88 LN biopsies
- Literature reviews

van Rhee F, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018 Nov 15;132(20):2115-2124.

Proposed diagnostic algorithm



Steps:

1. Evaluation for sites of involvement: one vs. multiple
2. If MCD, exclude other diseases
3. Evaluate for HHV-8
4. Consider iMCD – use proposed criteria

van Rhee F, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018 Nov 15;132(20):2115-2124.

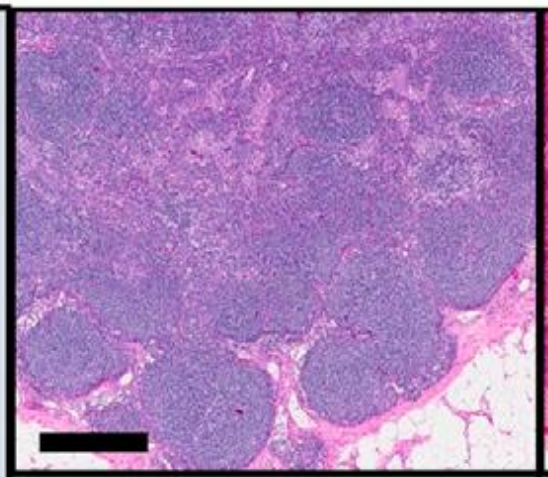
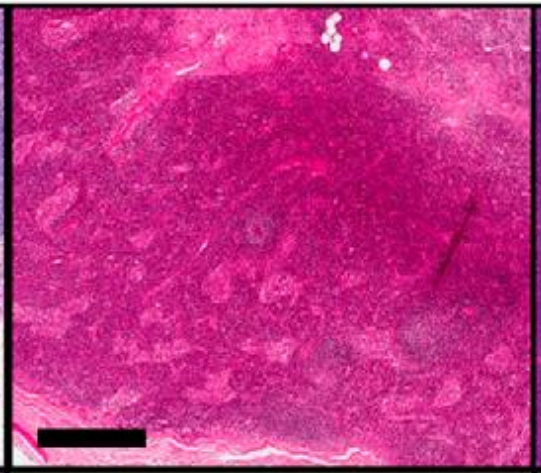
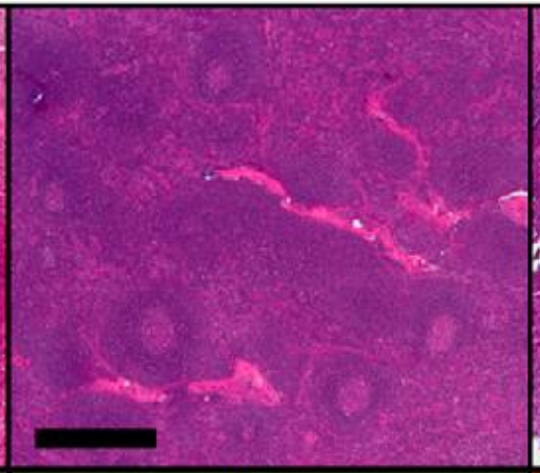
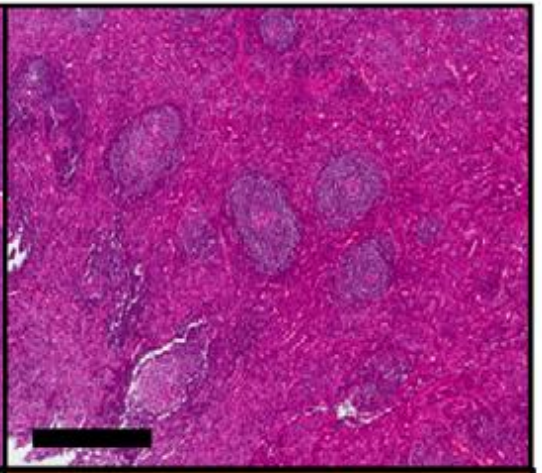
Consensus Diagnostic Criteria

Inclusion criteria	Exclusion criteria
I. Major criteria (need both) 1. Histopathologic lymph node 2. Enlarged lymph nodes in ≥2 lymph node stations **II. Minor criteria (need ≥2 of 11 with ≥1 laboratory criterion)** Laboratory 1. Elevated ESR or CRP 2. Anemia 3. Thrombocytopenia/tosis 4. Renal dysfunction or proteinuria 5. Polyclonal hypergammaglobulinemia 6. Hypoalbuminemia Clinical 1. Constitutional symptoms 2. Large spleen and/or liver 3. Fluid accumulation 4. Eruptive cherry angiomata or violaceous papules 5. Lymphocytic interstitial pneumonitis	**Infection-related disorders** 1. HHV8 2. EBV LPD 3. Inflammation and adenopathy by other infection **Autoimmune/inflammatory disease** 1. SLE 2. Rheumatoid arthritis 3. Adult-onset Still disease 4. Juvenile idiopathic arthritis 5. Autoimmune LPS **Malignant LPD** 1. Lymphoma 2. Multiple myeloma 3. Primary lymph node plasmacytoma 4. FDC sarcoma 5. POEMS syndrome

Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood. 2020 Apr 16;135(16):1353-1364.

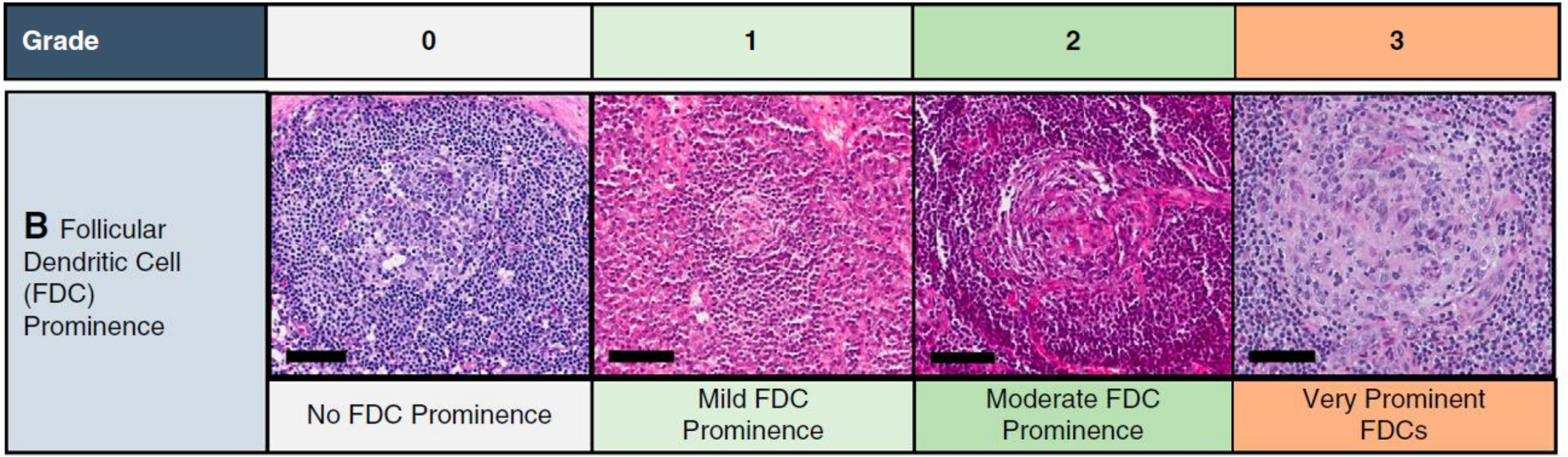
Pathologic features

At least

Grade	0	1	2	3
A Regressed Germinal Centers (GCs)				
	No Regressed GCs	Few Regressed GCs	Many Regressed GCs	Most GCs Regressed

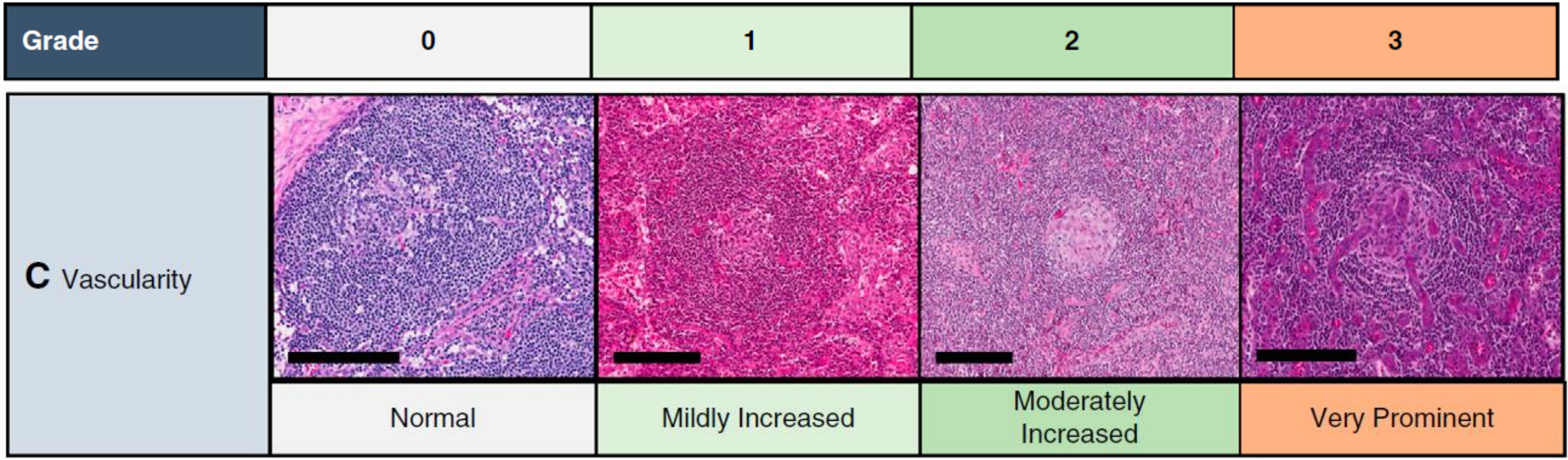
van Rhee F, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018 Nov 15;132(20):2115-2124.

Pathologic features



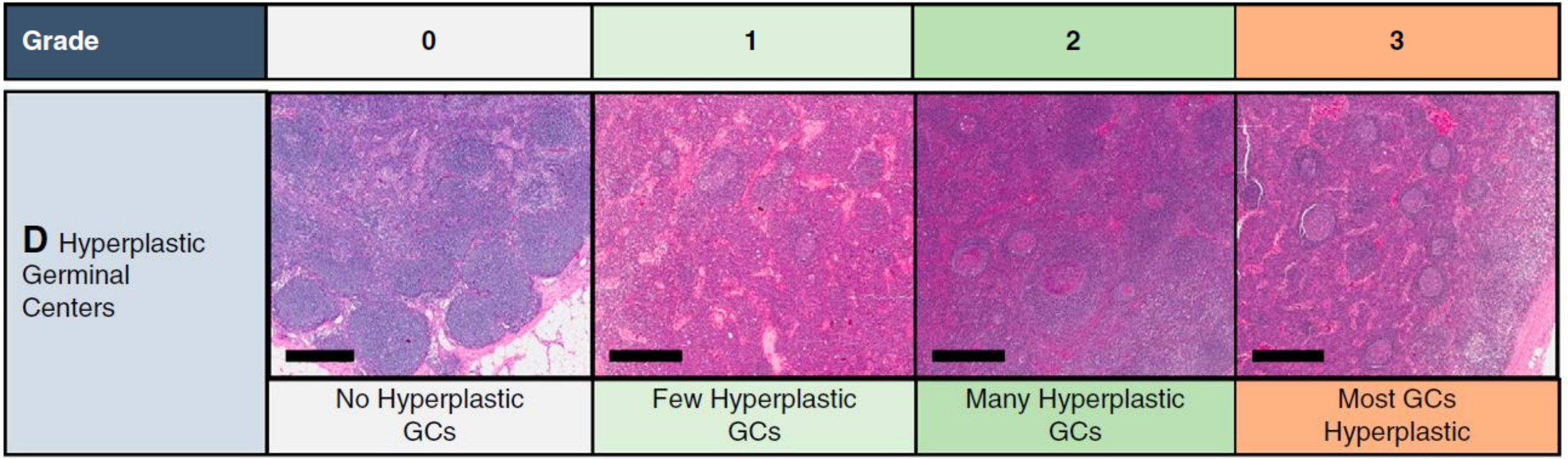
van Rhee F, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018 Nov 15;132(20):2115-2124.

Pathologic features



van Rhee F, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018 Nov 15;132(20):2115-2124.

Pathologic features



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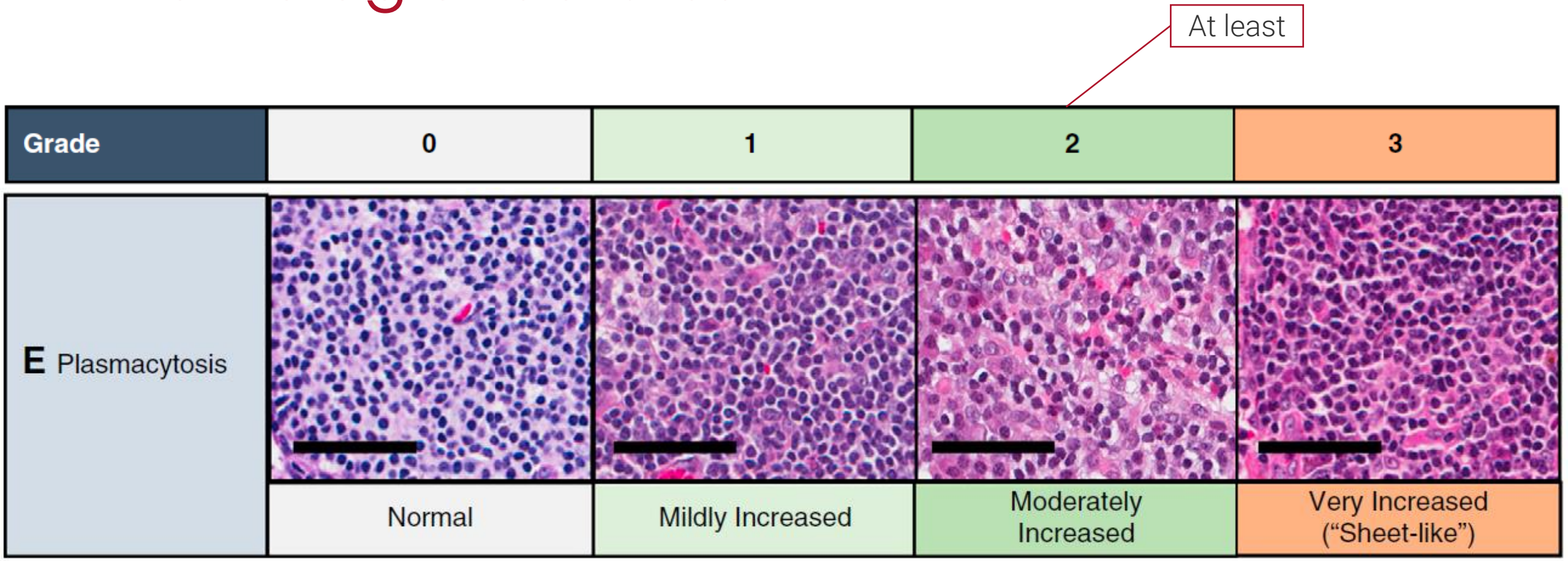
Pathologic features



van Rhee F, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018 Nov 15;132(20):2115-2124.

TAFRO-iMCD

Clinical findings

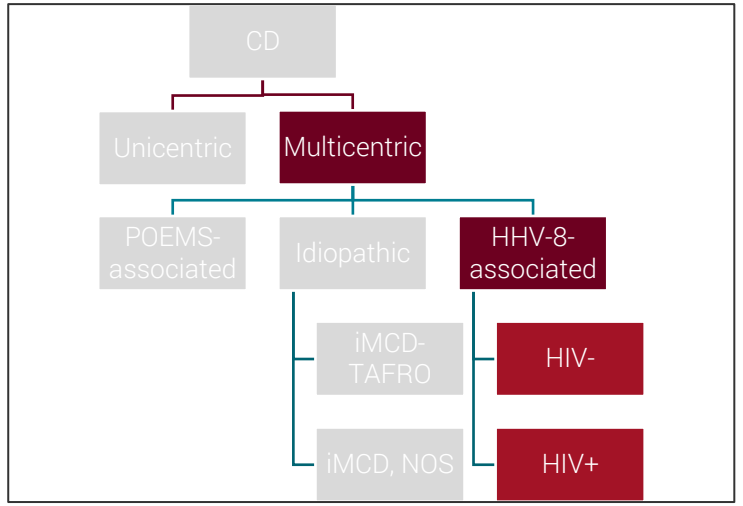
- Thrombocytopenia
- Anasarca/ascites
- Fever
- Organomegaly (LAD, splenomegaly, hepatomegaly)

+ Additional findings (at least 1)

- Bone marrow reticulin fibrosis
- Renal insufficiency

+ Histopathology consistent with iMCD

Important points



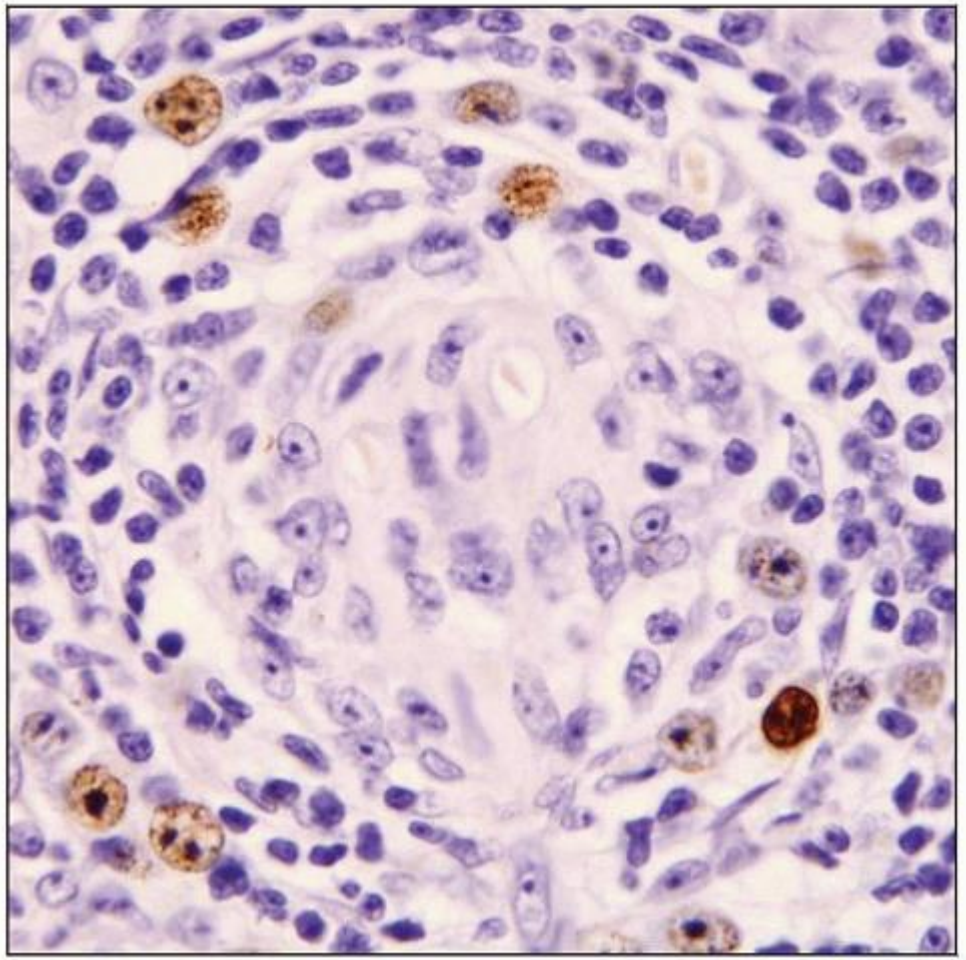
- Occurs in patients with and without HIV infection
- Populations with high risk of HHV-8 infection, e.g., men having sex with men
- Inflammatory flares, fever, LAD, hepatosplenomegaly, cytopenia, etc.
- If not treated, rapid evolution to organ failure and hemophagocytic syndrome

Pathogenesis

- HHV-8 infects naïve κ and λ B-cells
- It reinduces Rag-mediated V(D)J recombination in both but preferentially IgM-λ B-cells
- Infected cells undergo “immunoblastic” transformation and proliferation
- Infected cells acquire marginal zone-like phenotype
- Replication is associated with transcription of viral analog of IL-6

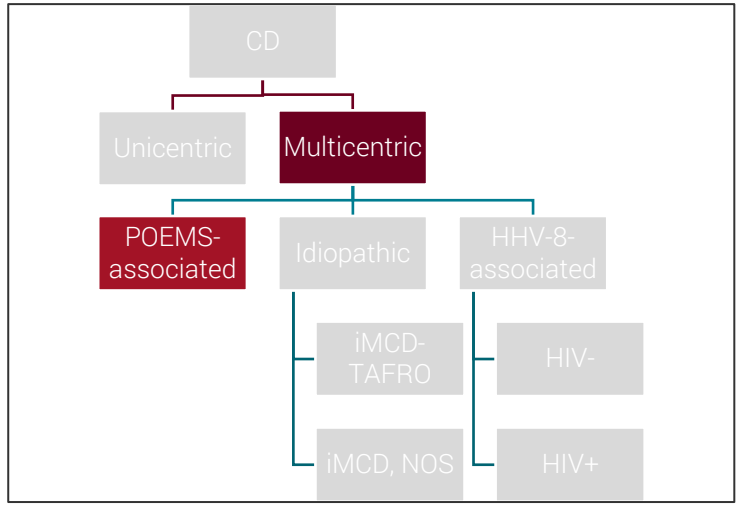
HHV-8 detection

- HHV-8 PCR
- HHV-8 LANA-1 (latent nuclear antigen)
  - Infected cells are in the mantle zones
  - EBV coinfection is possible, although rare
  - Infected cells have plasmablastic appearance
    - IgM-λ restricted, but no clonal
    - CD38+, MUM1/IRF4+, CD20-, PAX5-, CD30-, CD138-



HHV-8 LANA-1
https://basicmedicalkey.com/multicentric-castleman-disease/

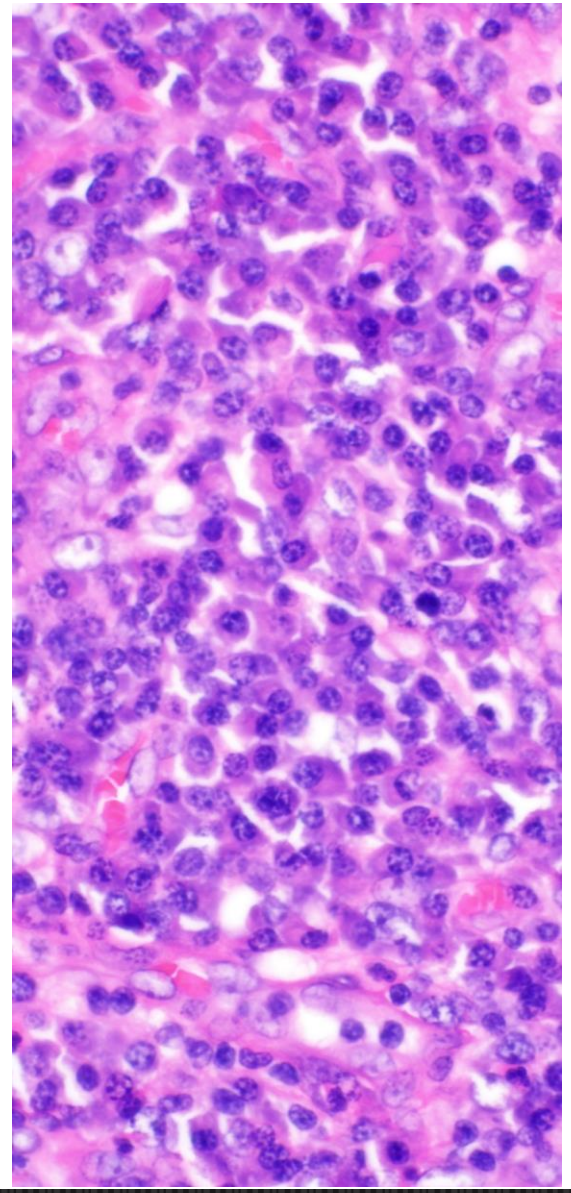
POEMS-associated MCD



Paraneoplastic syndrome associated with a plasma cell neoplasm

- Polyneuropathy
- Organomegaly
- Endocrinopathy
- Monoclonal gammopathy
- Skin changes

VEGF is elevated (diagnostic criterion)



Morphology

LN with distorted architecture

Obliterated sinuses

Prominent interfollicular plasma cells, λ-restricted

“Castleman” follicles

Negative for EBV and HHV-8

Diagnostic criteria (WHO, 2022)

Mandatory major criteria (both are required)

- Polyneuropathy
- Monoclonal plasma cells (almost always λ-restricted)

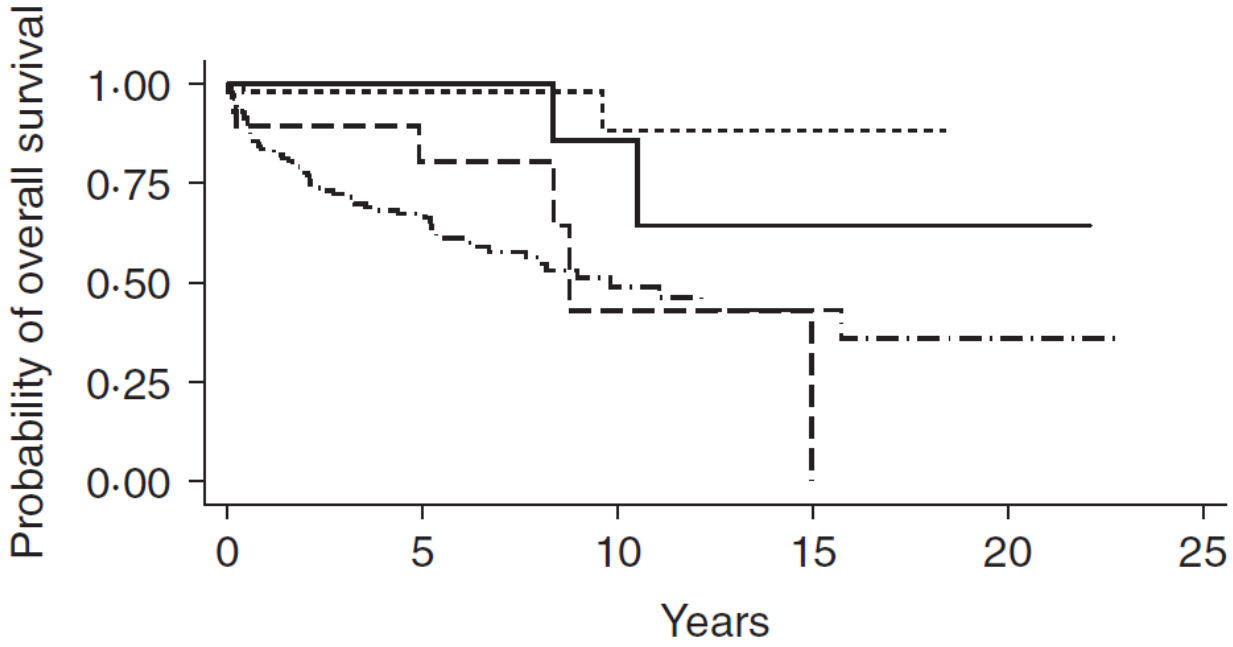
Major criteria (CD + one more)

- **Castleman disease**
- Sclerotic bone lesions
- VEGF elevation

Minor criteria (at least one)

- Organomegaly
- Extravascular volume overload
- Endocrinopathy
- Skin changes
- Papilledema
- Thrombocytosis/polycythemia

Prognosis



Oksenhendler E, et al. The full spectrum of Castleman disease: 273 patients studied over 20 years. Br J Haematol. 2018 Jan;180(2):206-216

Secondary malignancy

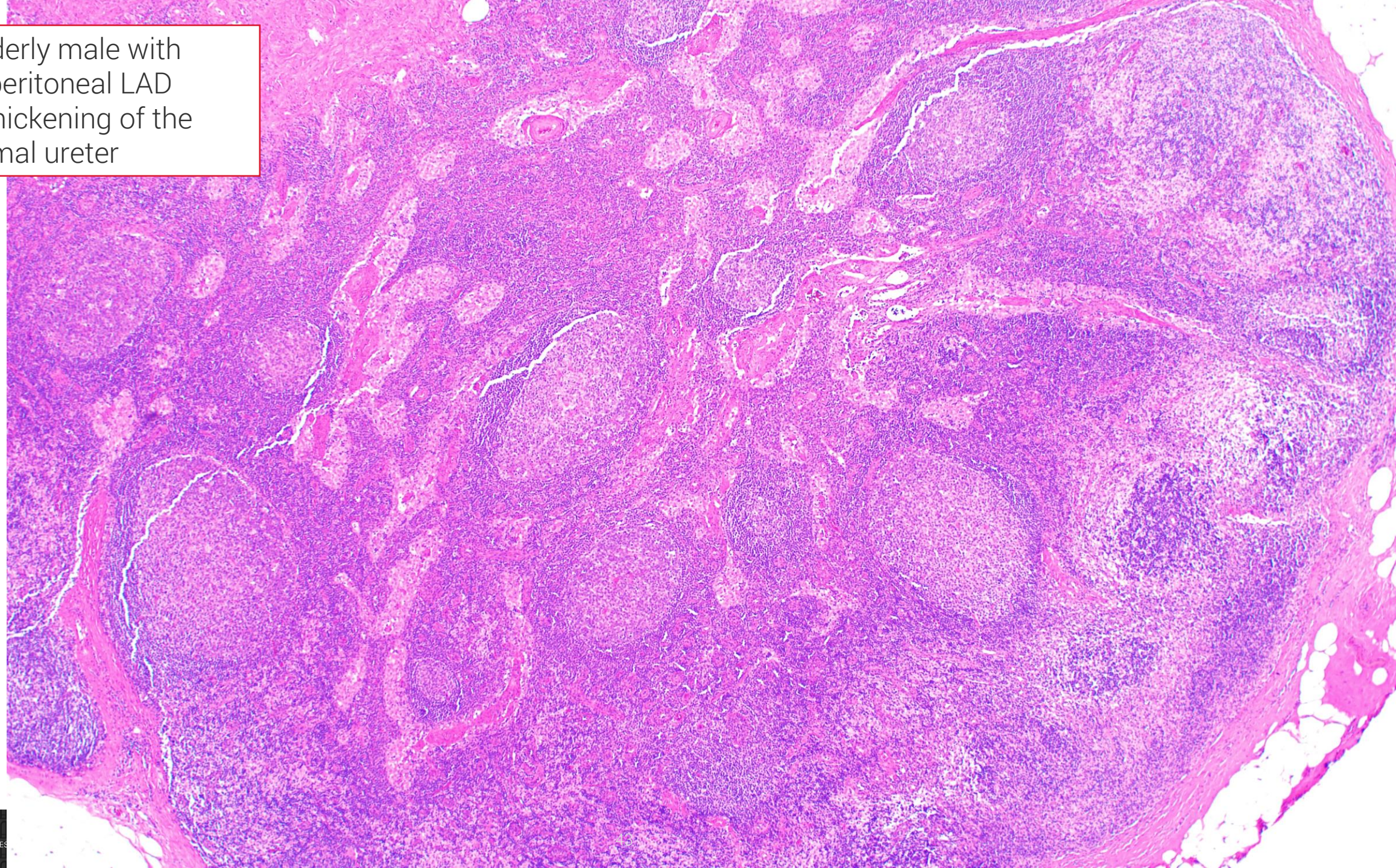
UCD, uncommon but higher risk for
- FDC sarcoma
- Hodgkin and non-Hodgkin lymphoma

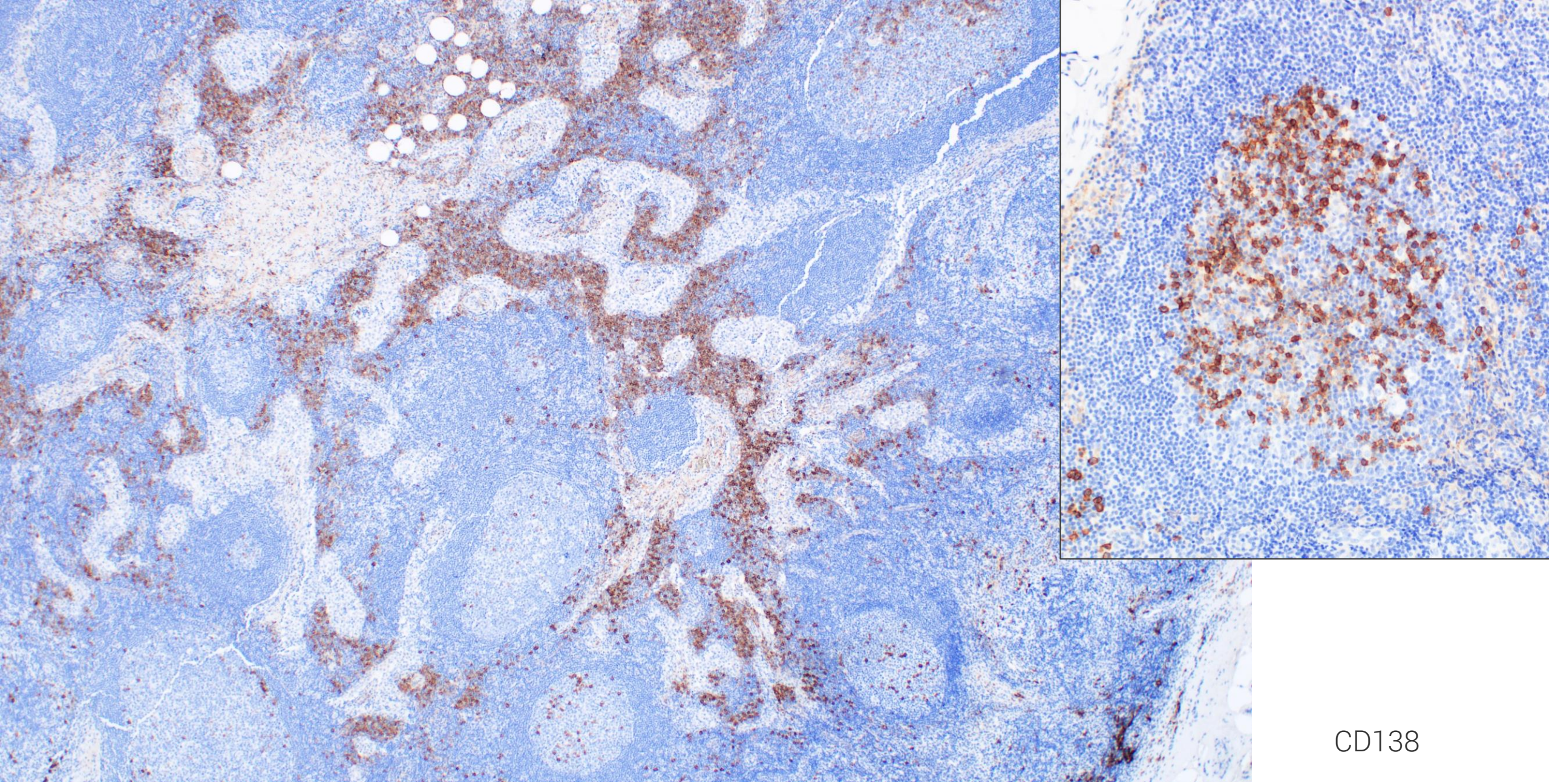
iMCD
- Lymphoma (3 times more likely)

HHV-8+/HIV-
- Lymphoma (15%)
- Kaposi sarcoma (50%)

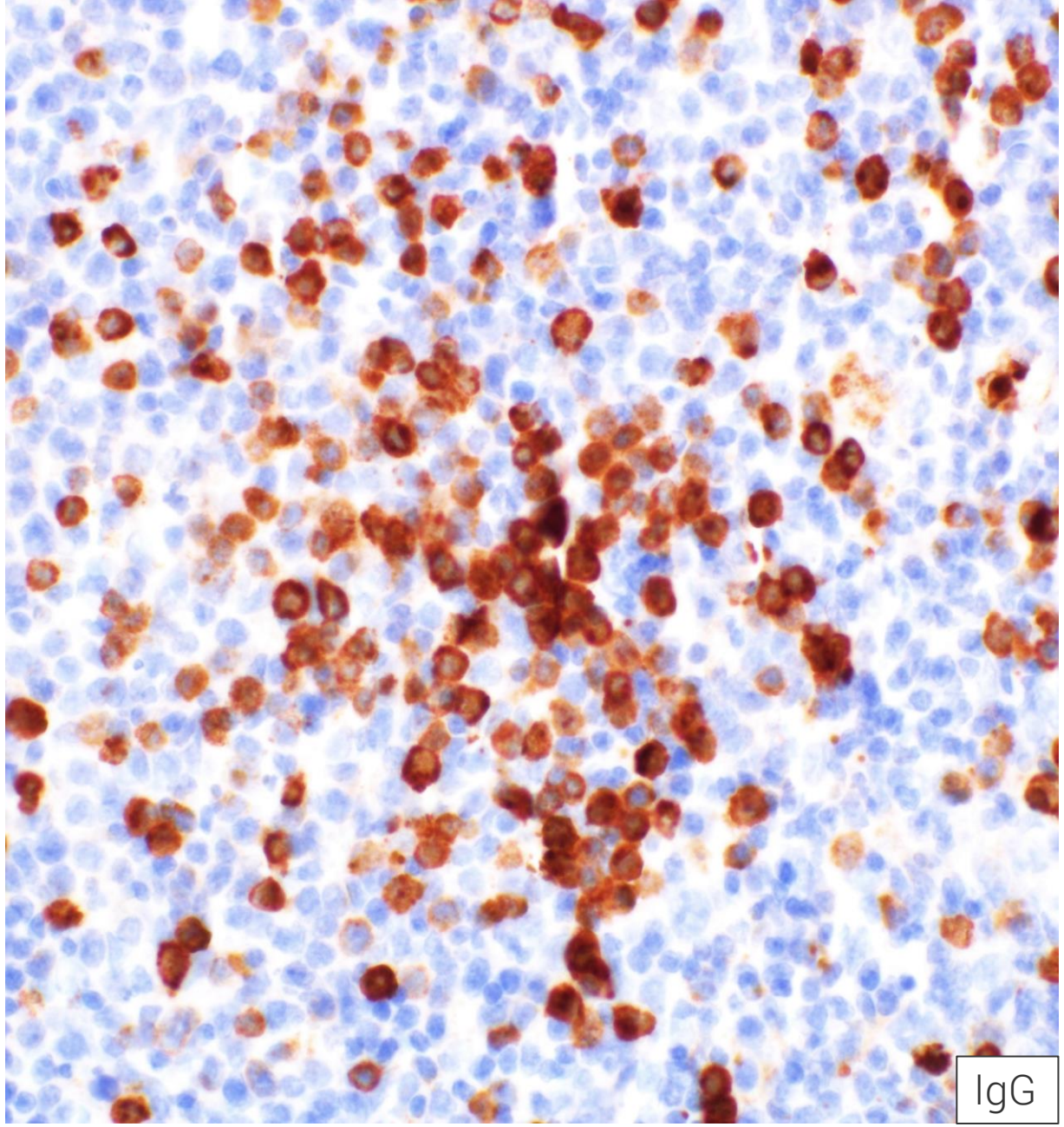
HHV-8+/HIV+
- Lymphoma (15 times more likely compared to HIV+ and no CD)

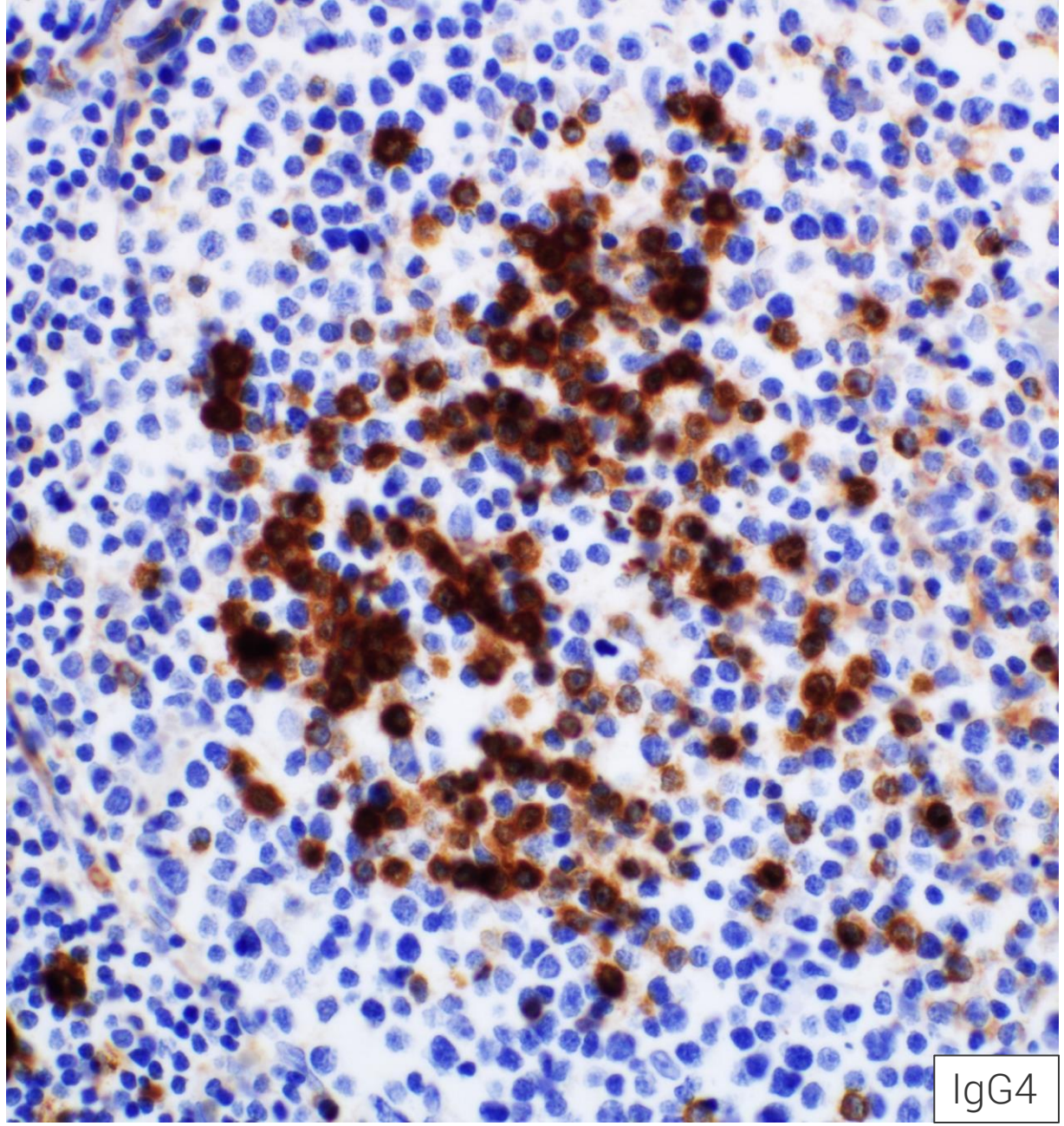
An elderly male with retroperitoneal LAD and thickening of the proximal ureter





CD138





Important points

- Multisystem fibroinflammatory disorder
  - » Mass-forming lesion
  - » Characteristic clinicopathologic features
  - » Sensitivity to treatment with steroids
- Pancreas, salivary glands, hepatobiliary system, lung, kidney, retroperitoneum
- Lymph node involvement is common and may be the only manifestation or may precede other sites
- Early diagnosis is beneficial to prevent end-stage damage

Clinical Features

- Usually, <2 cm but can be up to 5 cm
- Painless
- Common locations: cervical, supraclavicular, mediastinal, pulmonary/hilar, abdominal, axillary, inguinal
- Systemic symptoms are uncommon
- LDH is not significantly elevated

General morphologic features

Characteristic morphologic appearance

1. Dense lymphoplasmacytic infiltrate
2. *Fibrosis with at least focal storiform pattern**
3. *Obliterative phlebitis**

Other common findings:

- phlebitis without obliteration of the lumen
- tissue eosinophilia

* commonly absent in LNs

Elevated number of IgG4+ PCs

Variability of absolute IgG4+ PCs numbers depends on the organ

IgG4+/IgG+ ratio >40% is a comprehensive number of any organ

Three 40X fields are recommended

V Deshpande et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol, 2012

Key Findings

Common findings

- Tissue eosinophilia
- Elevated IgG4 > 135 mg/dL
  - » helpful but not essential
  - » may be useful to assess disease extent and activity
  - » Not specific: also elevated in atopic dermatitis, parasitic infections, etc.

Elevated number of IgG4+ PCs

IgG4+ PCs >100 per HPF

IgG4+/IgG+ ratio >40%

- Essential but not sufficient for Dx
- Distribution can be patchy and uneven
- Count in “hot spots”

Histologic Patterns

Type	I. Multicentric Castleman disease-like	II. Reactive follicular hyperplasia-like	III. Interfollicular expansion and immunoblastosis	IV. Progressive transformation of GCs-like	V. Inflammatory pseudotumor-like
Key morphology	Retained architecture Hyperplastic and/or regressed GCs Increased PCs Vascular proliferation EOS	Preserved architecture Reactive GCs with discrete mantle zones Paracortex with rare transformed cells and scattered EOS	Distorted architecture with paracortical expansion Spectrum of cells in paracortex Numerous immunoblasts Scattered EOS	Preserved architecture Transformed follicles IgG4+ PCs localized in preserved but not in progressive GCs Granulomas forming rings around GCs (rare)	Fibrosis with hyalinization Scattered PCs and EOS Hyperplastic GCs in residual nodal tissue
Differential Dx	MCD Nonspecific LAD with Castleman-like features	Nonspecific FH RA-associated LAD	Viral LAD Dilantin-associated LAD AITCL	Nonspecific PTGC NLPHL	Inflammatory pseudotumor Syphilis

Histologic Patterns

Other patterns described in patients with known IgG4-RD

1. Rosai-Dorfman-like changes

2. Infectious mononucleosis-like features

3. Crescent-shaped or wreath-like perifollicular granulomas

Approach to testing and diagnosis

YES	NO
1. LAD in patient with documented IgG4-RD	1. Limited to a single LN/region, AND no clinical suspicion for IgG4-RD
2. Persistent and/or systemic LAD without a known underlying cause (lymphoma, autoimmune, medication, infection)	2. Patients with known infection, autoimmune disorders, medication
3. LAD with increased PCs in CGs and/or interfollicular areas	3. LAD associated with a malignancy or surgical procedure in vicinity
4. LAD with PTGC and excluded NLPHL	4. Small inactive LN
	5. Reactive LAD with known etiology

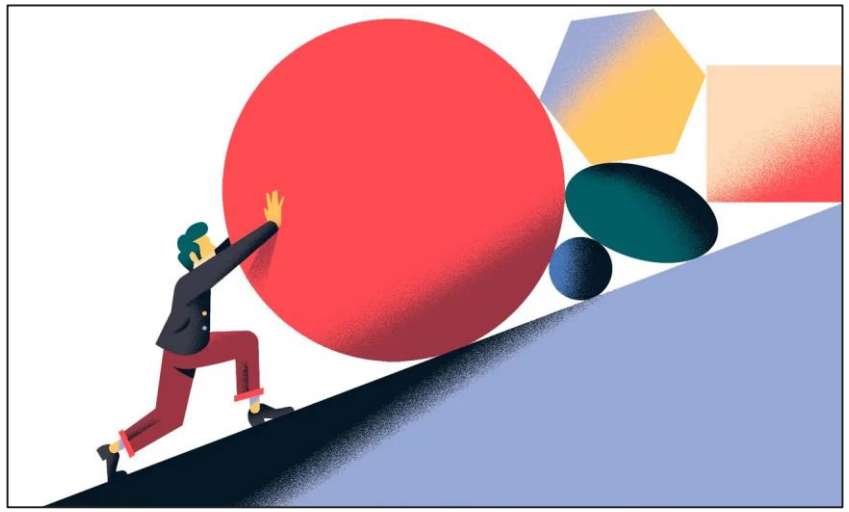
Exclude specific entities that may have increased IgG4 PCs: multicentric Castleman, RA, RDD, etc.

If systemic and persistent LAD or Hx of IgG4-disease "*reactive lymphoid hyperplasia with increased IgG4 PCs; suggestive of IgG4-related LAD in an appropriate clinical and laboratory setting*"

Otherwise *"reactive lymphoid hyperplasia with increased IgG4 PCs, uncertain clinical significance"*

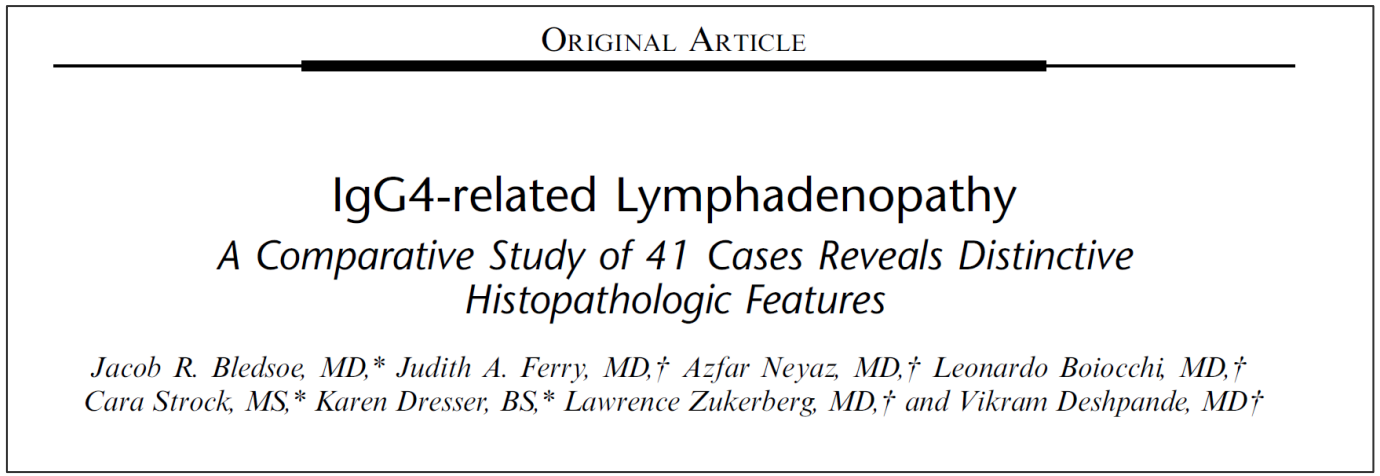
More problems

- Increasing recognition of IgG4-RD
  - » Samples from more locations are evaluated for IgG4-RD
  - » Broadly available IHCs



- Morphologic criteria are relatively non-specific
- Uncertain significance of elevated IgG4 PCs in LN
  - » MCD, Rosai-Dorfman disease, RA, CHL, etc.
- A small proportion of IgG4-RD patients do not have increased IgG4 PCs

IGG4-RELATED DISEASE



ORIGINAL ARTICLE

IgG4-related Lymphadenopathy

A Comparative Study of 41 Cases Reveals Distinctive Histopathologic Features

Jacob R. Bledsoe, MD, Judith A. Ferry, MD,† Azfar Neyaz, MD,† Leonardo Boiocchi, MD,† Cara Strock, MS,* Karen Dresser, BS,* Lawrence Zukerberg, MD,† and Vikram Deshpande, MD†*

Study design

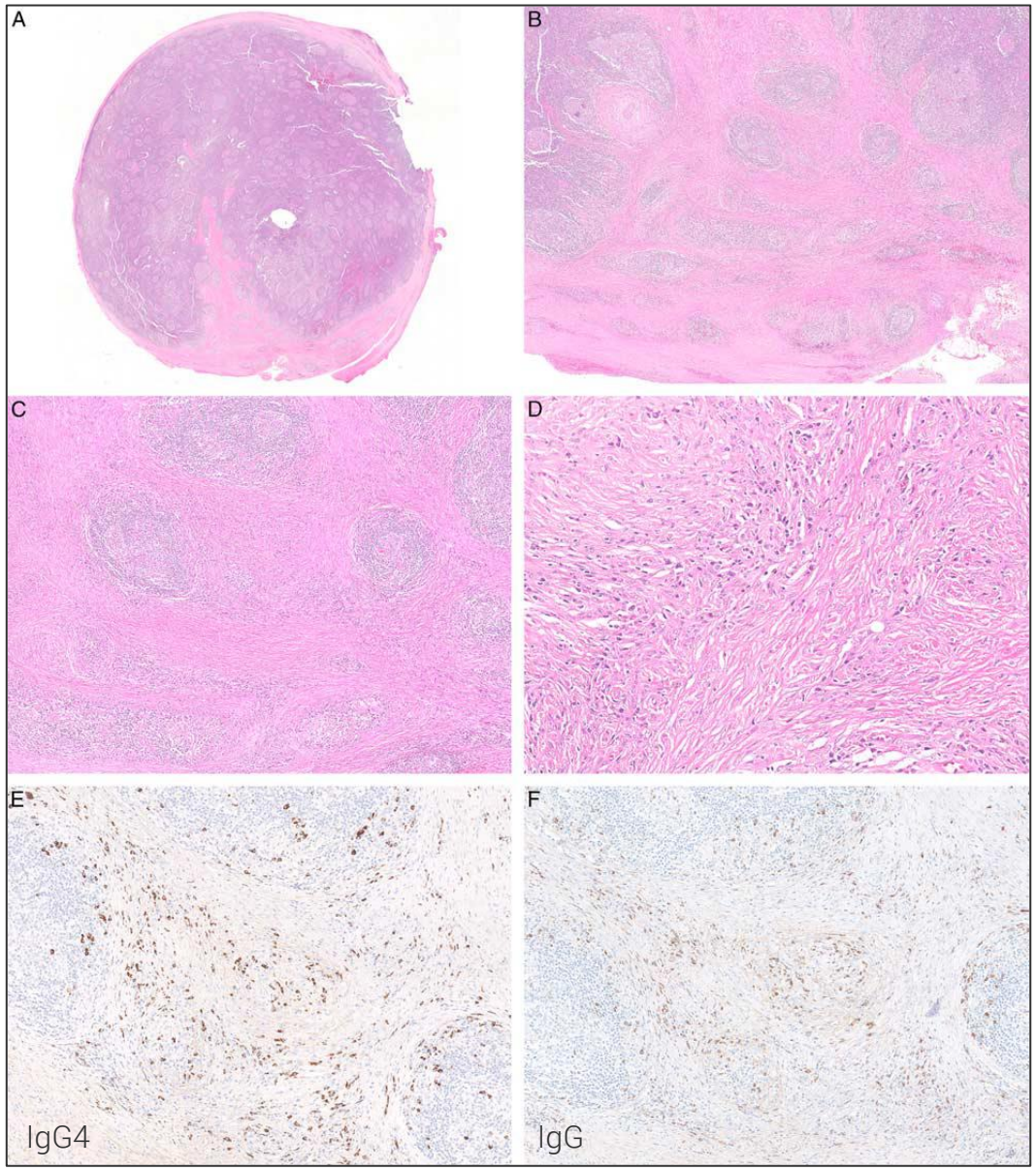
- 41 patients with established IgG4-RD
- Control: 60 patients with unexplained LAD and not IgG4-LAD

- Is the work-up for IgG4-RD justified?
- Any specific morphologic features?
- Develop diagnostic approach for pathologists

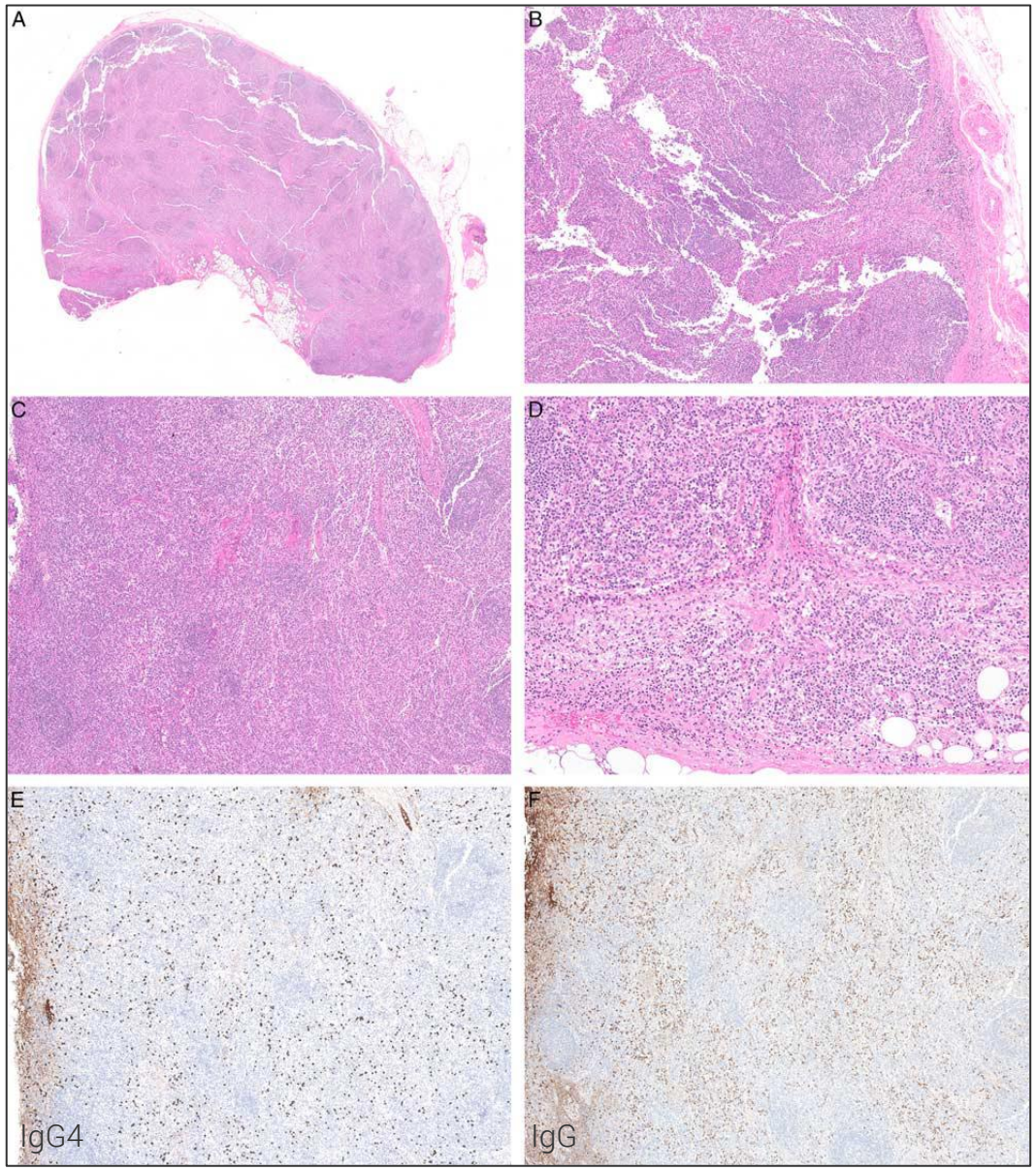
Specific Morphologic Findings

- Increased in EXTRAfollicular IgG4-positive plasma cells and IgG4/IgG ratio
- Two major morphologic patterns:
  1. Nodal fibrosis with increased IgG4+ PCs specifically within the areas of fibrosis
  2. Marked interfollicular expansion associated with increased interfollicular IgG4+ PCs
- Of the 5 “classic” patterns, “Inflammatory pseudotumor-like” and “Interfollicular expansion”

IgG4-RD, capsular and IPT-like fibrosis



IgG4-RD, paracortical expansion



Bledsoe JR, et al. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. APMIS. 2018 Jun;126(6):459-476.

Non-specific Morphologic Findings

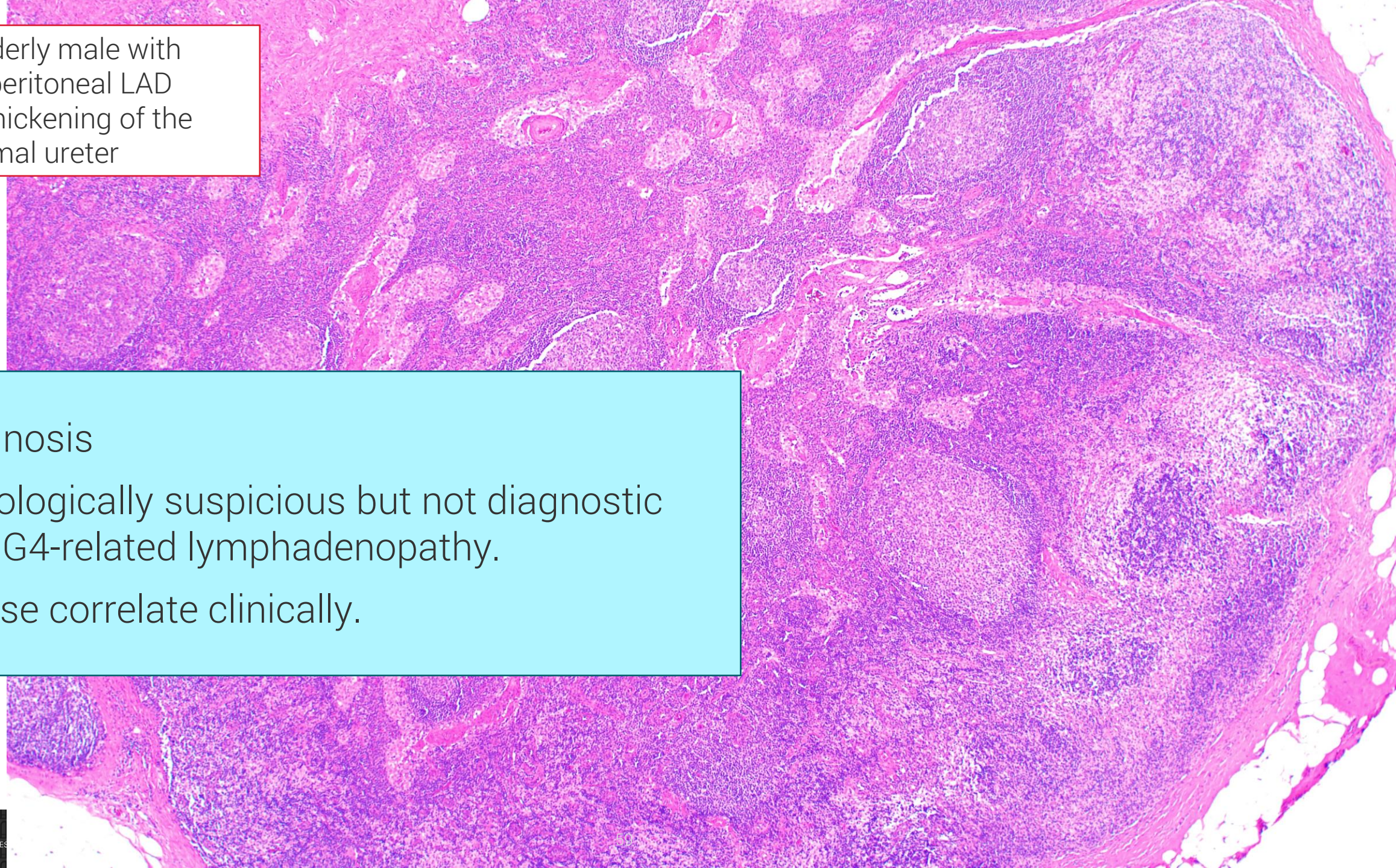
- Three “classic” patterns, other than IPT-like and interfollicular expansion
- Increased IgG4+ PCs and increased IgG4/IgG within the reactive follicles
- But increased both inter- and intra-follicular IgG4+ PCs is more suggestive of IgG4-RD

Reporting

Recommended reporting	Pattern	IgG4 and IgG4/IgG
Highly suspicious for IgG4-related LAD	- Capsular/parenchymal fibrosis and admixed eosinophils	IgG4>100 HPF and IgG4/IgG>40%
	- Interfollicular expansion	INTERfollicular IgG4>100 HPF and IgG4/IgG>40%
Suspicions but not diagnostic	Absence of marked interfollicular expansion	IgG4>100 HPF and IgG4/IgG>40% within extrafollicular regions but not within fibrosis
Atypical but unclear significance	Submandibular/neck LAD with PTGC	INTRAfollicular IgG4>100 HPF and IgG4/IgG>40%
	Perifollicular granulomas	No increased IgG4/IgG
Nonspecific	Other patterns	INTRAfollicular IgG4>100 HPF and IgG4/IgG>40%
	Any pattern	Either but not both increased IgG4 or IgG4/IgG

Adopted from Bledsoe JR, et al. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. APMIS. 2018 Jun;126(6):459-476.

An elderly male with retroperitoneal LAD and thickening of the proximal ureter

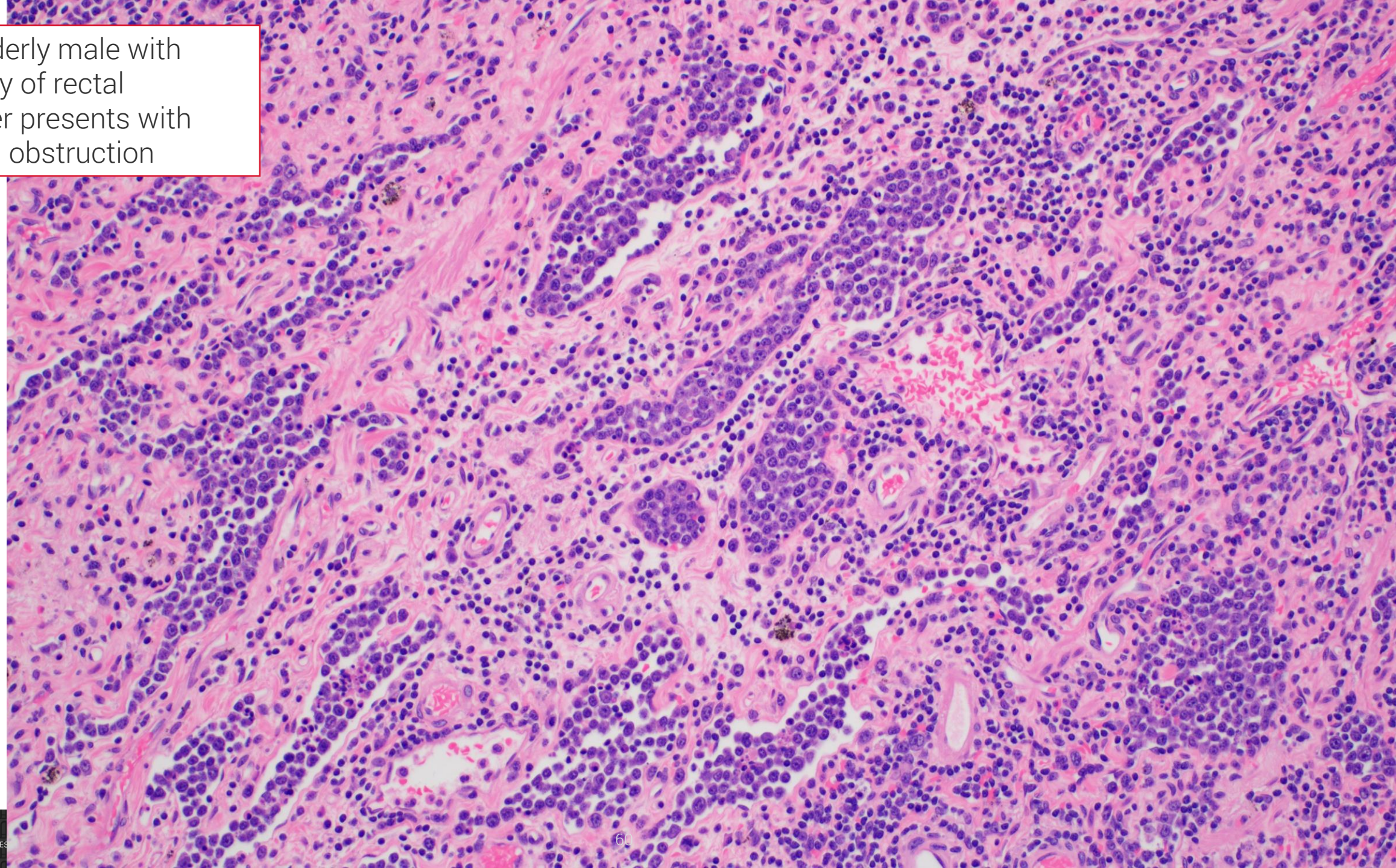


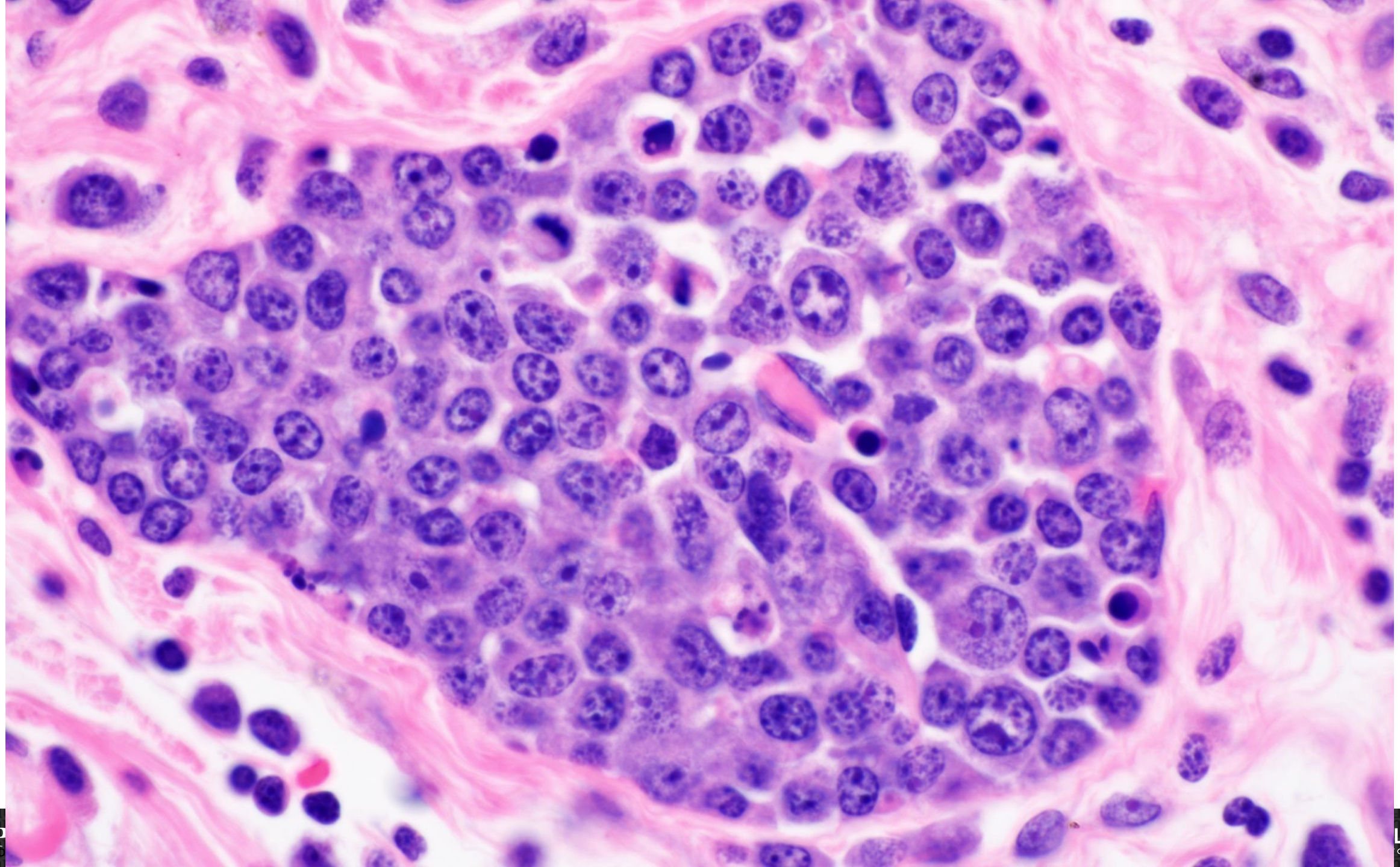
Diagnosis

Histologically suspicious but not diagnostic of IgG4-related lymphadenopathy.

Please correlate clinically.

An elderly male with history of rectal cancer presents with bowel obstruction

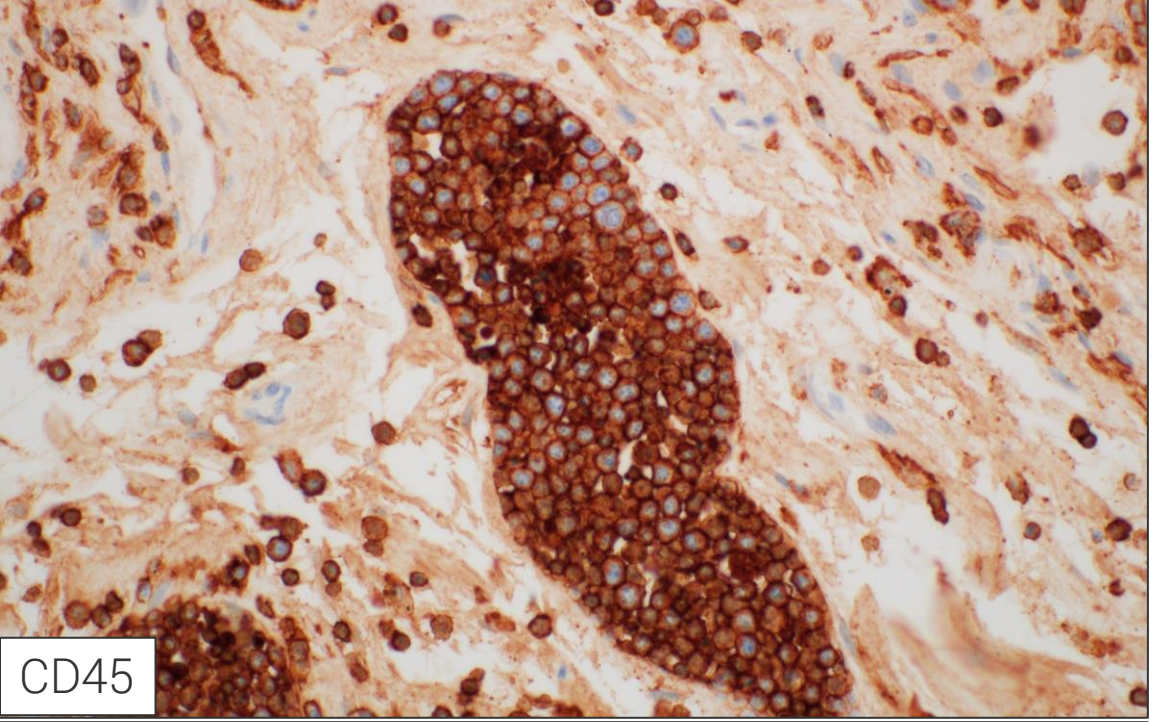


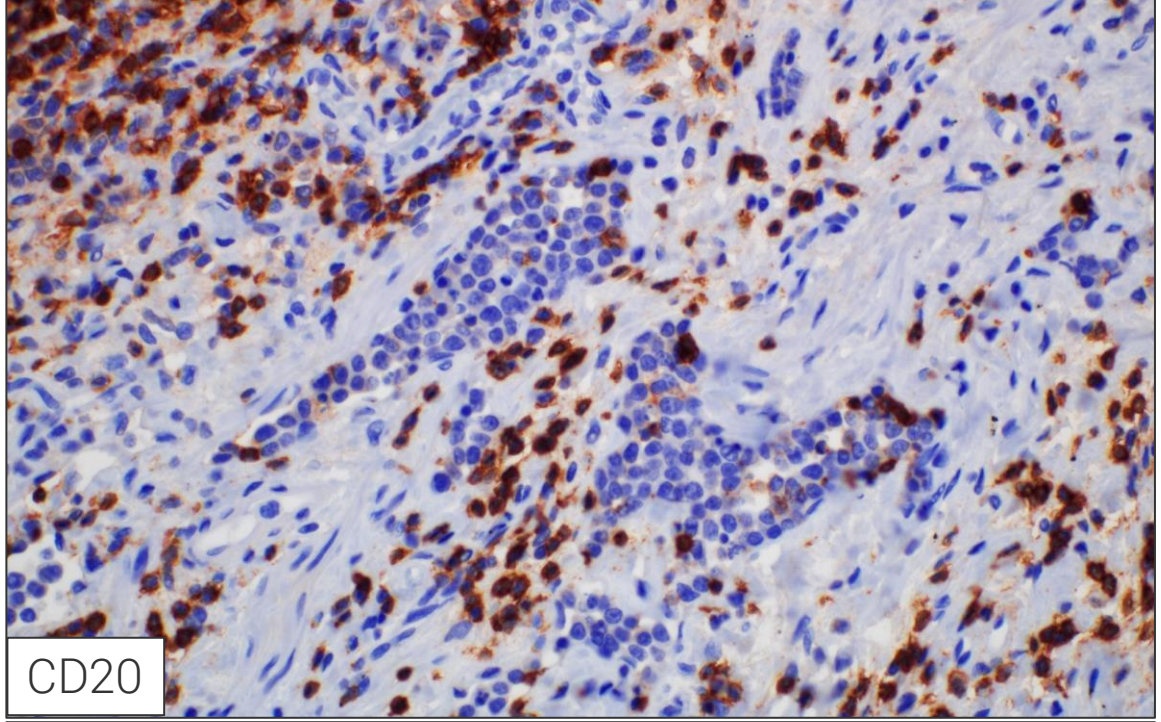


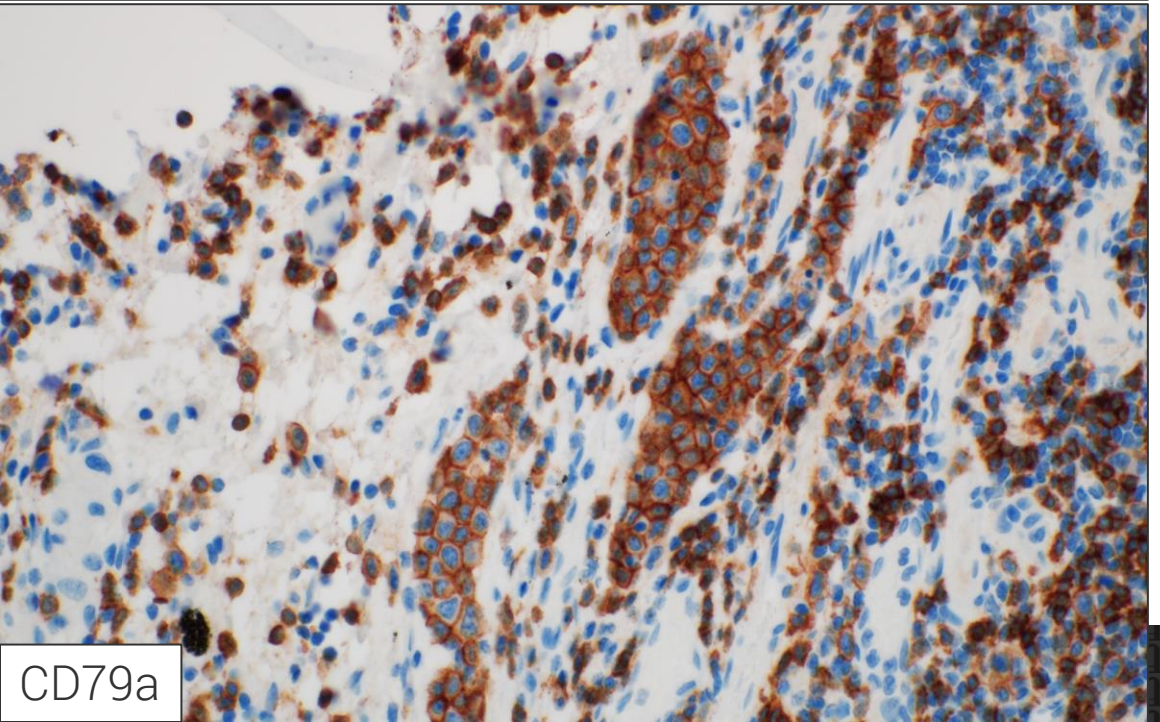
Differential Diagnosis

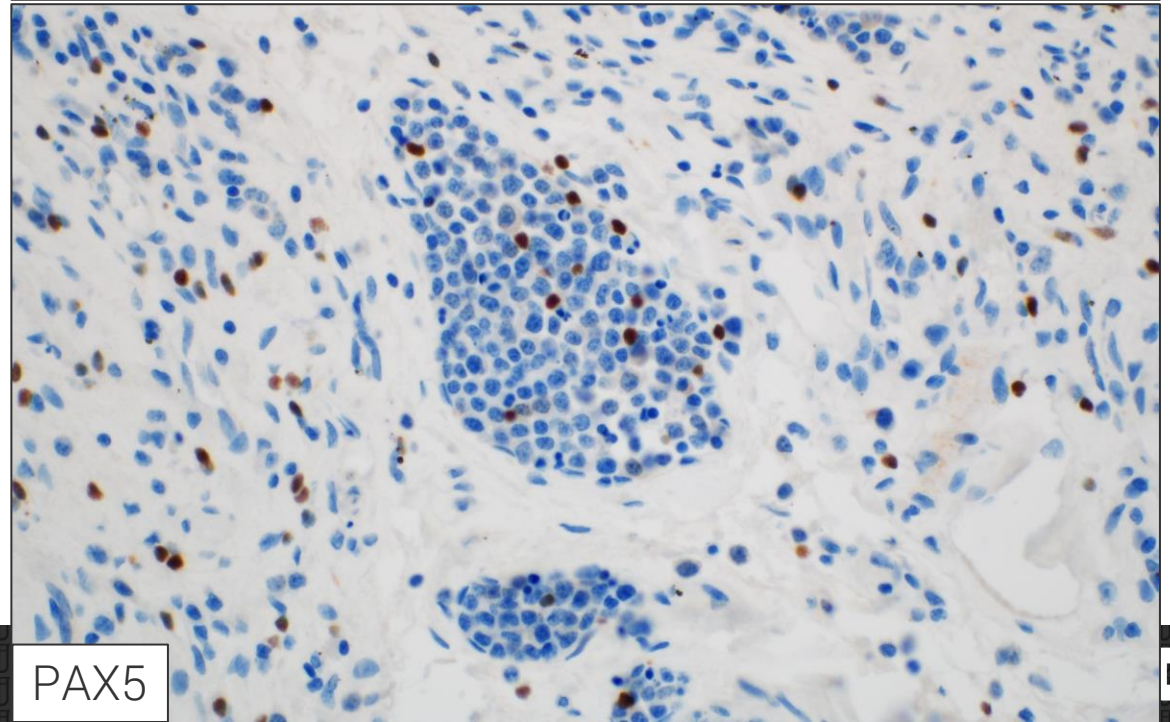
- Intravascular large B-cell lymphoma
- T-cell lymphoma
- NK-cell lymphoma
- Anaplastic large cell lymphoma

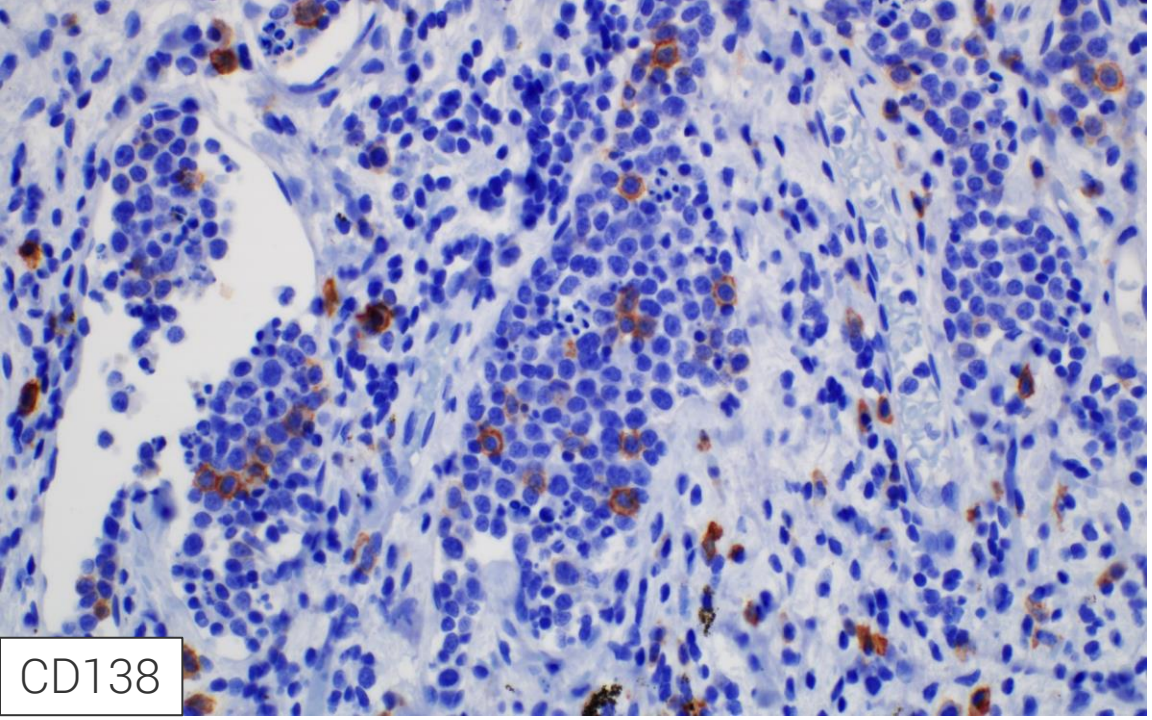
- Benign lesions, e.g., intravascular lymphocytosis
  - » Common finding in appendectomy specimens
  - » Resembles CLL/SLL
  - » Mixture of T- and B-cell with normal immunophenotype

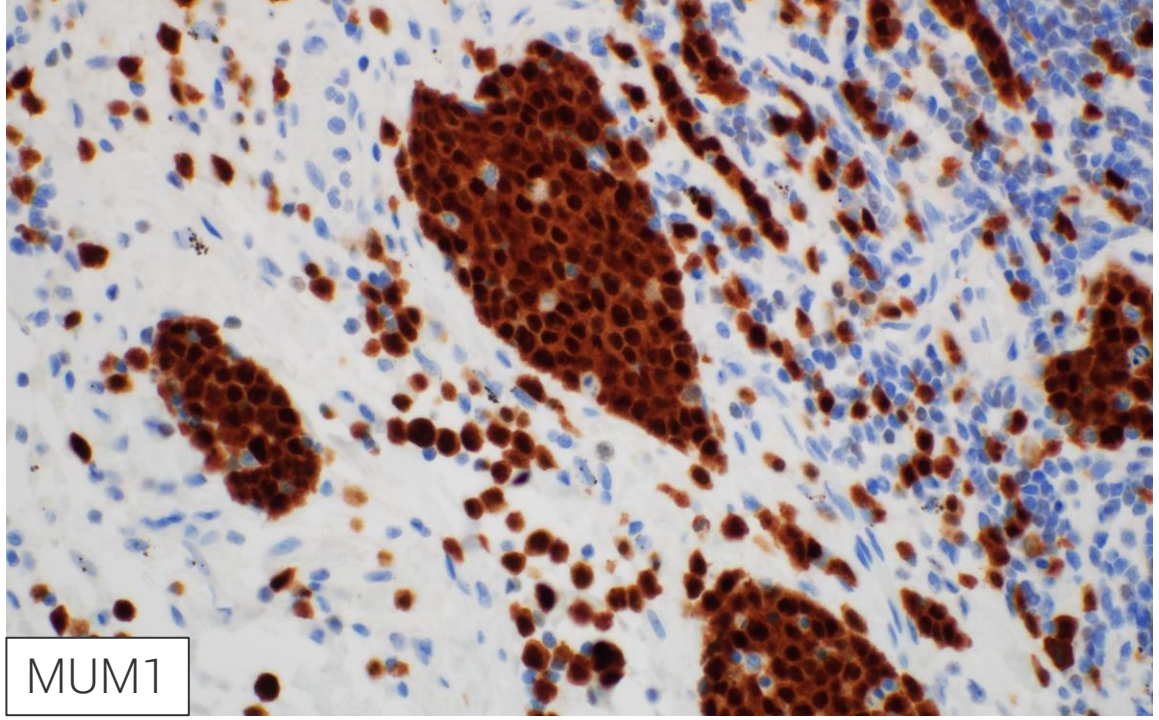


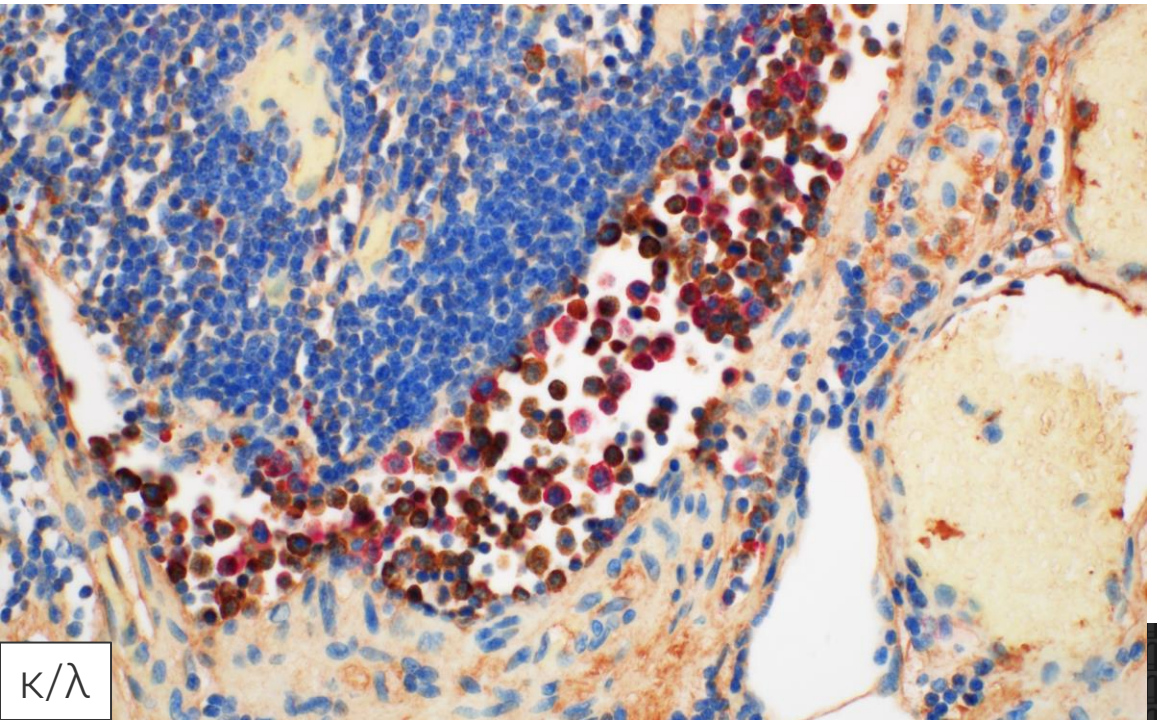


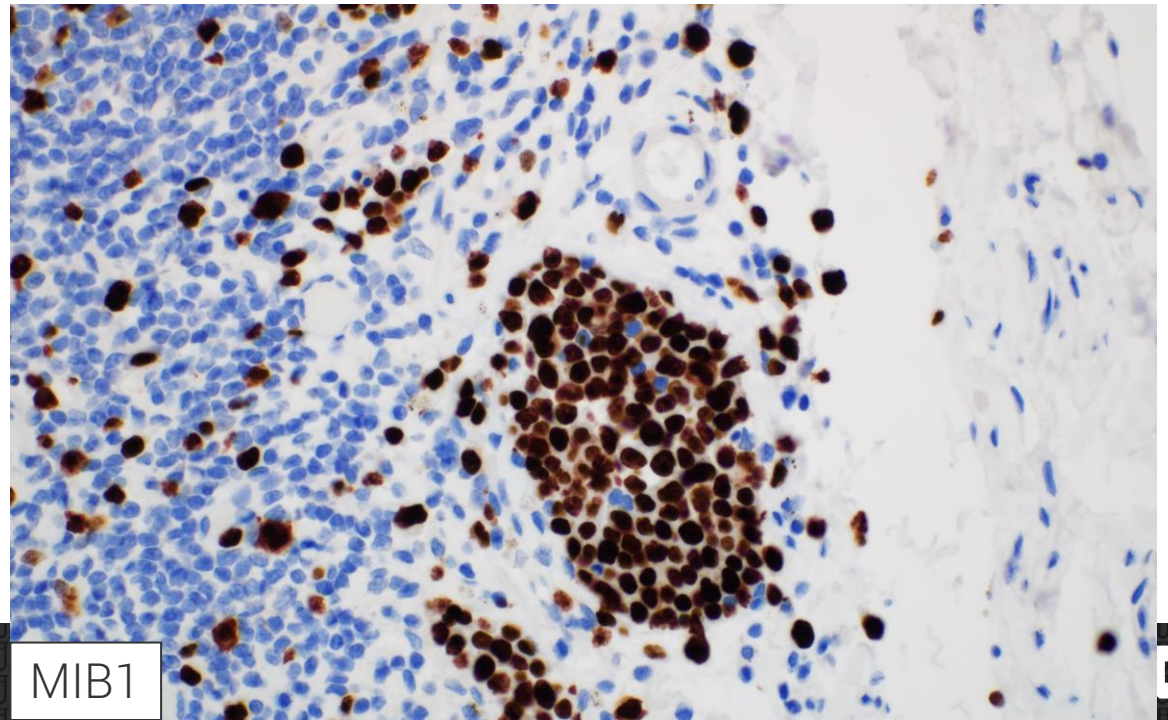












Reactive intralymphovascular immunoblastic proliferation

- Rare finding seen mostly in GI surgical specimens
- Likely reactive response to infection/inflammation
- Large lymphoid cells within lymphovascular lumens
- Potential pathogenesis is decreased expression of surface adhesion molecules allowing the cells to bypass the LNs

Reactive intralymphovascular immunoblastic proliferation

B-cells of post-GC immunophenotype

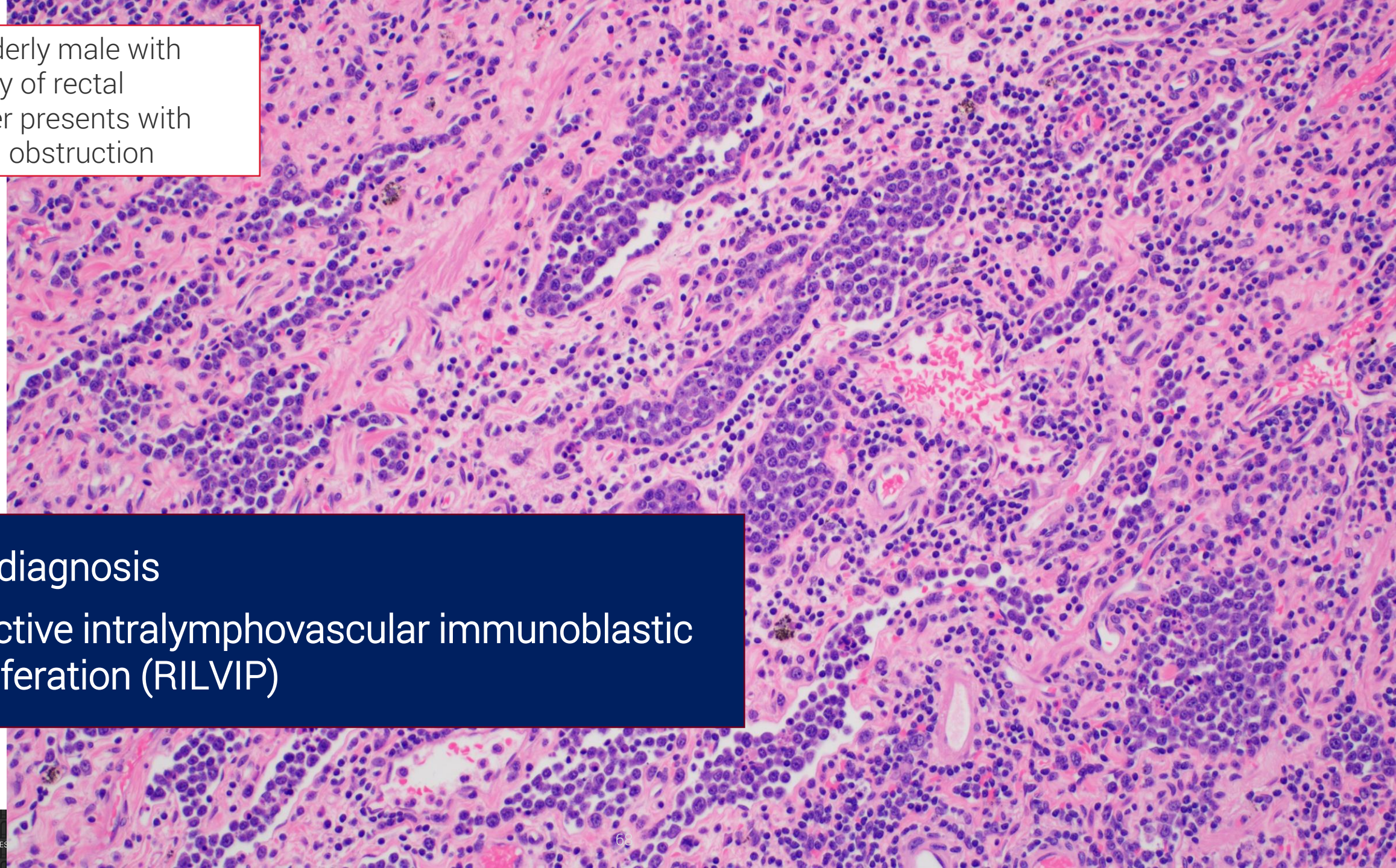
- positive: CD38, CD79a, MUM1/IFR4
- negative: Bcl-2, Bcl-6, CD138
- also, positive for CD30 and/or PAX5
- high proliferation index
- polytypic
- negative for *BCR* rearrangement

RILVIP vs IV-LBCL

	RILVIP	IV-LBCL
Presentation	Incidental finding	Disseminated disease with common skin, liver, spleen involvement
Morphology	Large cells often intermixed with small lymphocytes	Uniformly large cells, exclusively intravascular
Key immunophenotype	CD20-/CD30+/CD10-/ Bcl2-	CD20+/CD30-/CD10+/Bcl2+
Involved vessels	Lymphatics	Small/intermediate-sized arteries and veins
Clonality	Absent	Present

Adopted from Fang H et al. Reactive Intralymphovascular Immunoblastic Proliferations Mimicking Aggressive Lymphomas. Am J Surg Pathol. 2022 Mar 1;46(3):326-335.

An elderly male with history of rectal cancer presents with bowel obstruction



Our diagnosis

Reactive intralymphovascular immunoblastic proliferation (RILVIP)

Take home points

- "Benign" LADs may not be clinically benign
  - » Idiopathic multicentric Castleman disease
- Some "benign" LADs may be associated with a clonal process
  - » FDC clonality in unicentric Castleman disease
- Molecular and flow cytometric studies are useful but can be misleading
  - » Light chain restriction may not mean clonality
  - » Clonality may not mean malignancy
- Morphology and clinical context are key to accurate diagnosis


Lake Blanche, Big Cottonwood Canyon

QUESTIONS?

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ARUP is a nonprofit enterprise of the University of Utah and its Department of Pathology.