EHA&EuroBloodNet Spotlight on Castleman Disease
Session 1: Overview on Castleman Disease

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the Health Programme
of the European Union

EUROPEAN HEMATOLOGY ASSOCIATION

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for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars on Castleman disease: Overview

25th of January 2022

No 1: Overview on CD

Kai Hübel & Elena Sabatini

- Introduction, History
- Classification
- Pathology
- Diagnosis

1st of February 2022

No 2: Unicentric CD

Eric Oksenhendler

- Imaging (cases)
- Diagnosis, initial Assessment
- Pathophysiology
- Treatment

15th of February 2022

No 3: Idiopathic multicentric CD

Simone Ferrero

- Clinical Phenotypes
- Differential diagnosis
- Relationship with TAFRO, IgG4RD, POEMS
- Pathophysiology
- Treatment

8th of March 2022

No 4: KSHV/HHV8 associated multicentric CD

Mark Bower & David Boutboul

- Diagnosis
- Complications
- Pathophysiology
- Treatment

Practical issues before starting

- ✓ **30-35min presentation + 15 min Q&A session**
- ✓ **Microphones will be muted by host to avoid back noise**
- ✓ **Please, stop your video to improve internet connexion**
- ✓ **Send your questions during the presentation through the chat, they will be gathered and answered after the presentations.**

Learning objectives of the today webinar

1. To raise awareness of Casteleman disease
2. To emphasise the morbidity and mortality risk of undetected Castleman disease
3. To provide an overview on general aspects of pathology and diagnostics

Conflicts of interest Kai Hübel

- Advisory board: Roche, Celgene/BMS, Incyte, EUSA Pharma, and Gilead
- Honoraria: Roche, Celgene/BMS, Servier, EUSA Pharma, Novartis, and Hexal
- Research funding: Roche, Celgene/BMS, Servier, and Janssen

Conflicts of interest Elena Sabattini

- Advisory board: EUSA Pharma
- Honoraria: EUSA Pharma, Novartis

1954: First describtion of Castleman disease

The NEW ENGLAND JOURNAL of MEDICINE

Case records of the Massachusetts General Hospital: Case No. 40231
B CASTLEMAN, V W TOWNE

„peculiar form of lymph-node hyperplasia resembling thymoma“

Bildquelle: Massachusetts General Hospital

1954	Localized mediastinal lymph node enlargement characterized by increased numbers of lymphoid follicles with germinal center involution and marked capillary proliferation
1969	Description of the plasma cell, the hyalinized and the mixed histopathological variants
1983	Division into unicentric CD and multicentric CD
1985	Description of the association between HIV and CD, followed by the description of the co-occurrence with and overlap between POEMS syndrome and MCD
1990s	Identification of HHV8 as the etiological driver of all HIV+ and some HIV- MCD cases
2010	First description of the „TAFRO“ syndrome

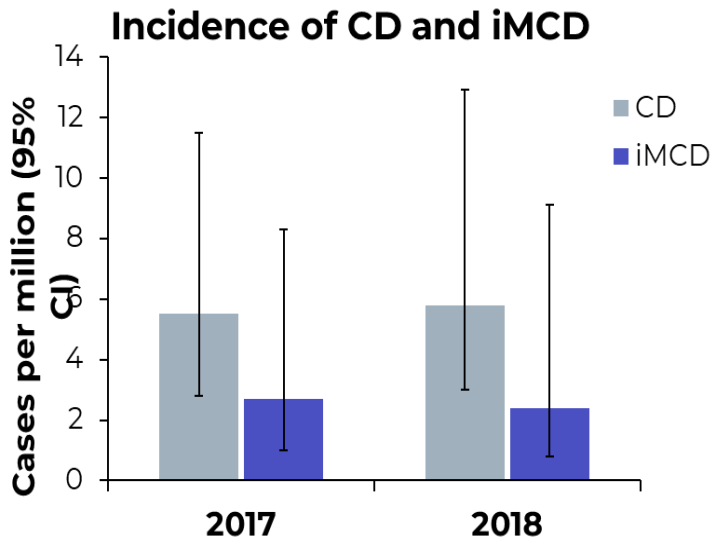
What is Castleman disease?

- Castleman disease represents a cluster of disorders, encompassing the fields of hematology, immunology, oncology, rheumatology, and virology.
- This heterogeneous group of disorders is characterized by shared histological features.
- There are different clinical subtypes dependent on the localisation of the CD and the underlying aetiology:

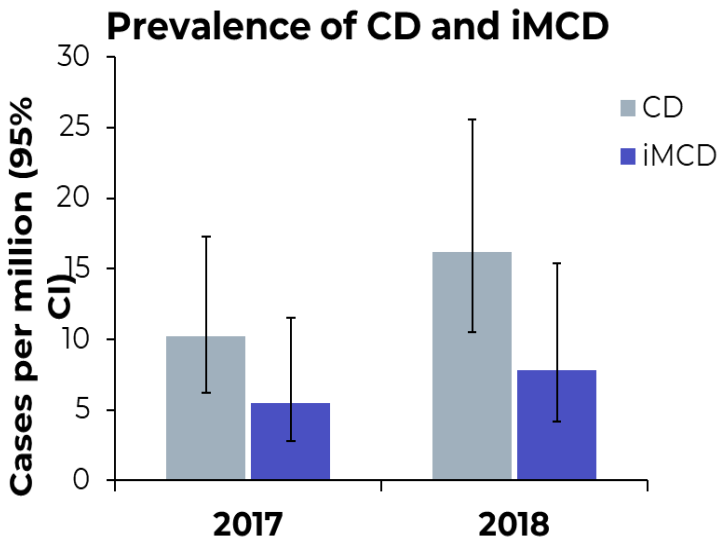
Unicentric CD

Multicentric CD

Incidence and prevalence of Castleman disease



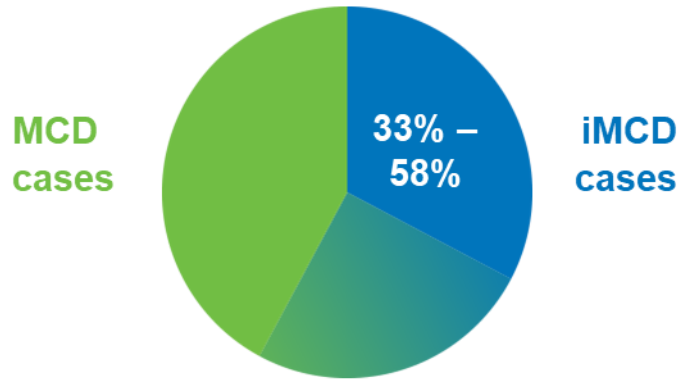
Cases per million	5.5	2.7	5.8	2.4



Cases per million	10.2	5.5	16.2	7.8

Mukherjee S *et al.* Oral presentation at the virtual 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; December 5–8, 2020.

Proportion of iMCD Cases



iMCD accounts for **33% – 58%** of all MCD cases

van Rhee F, et al. Blood. 2018;132(20):2115-2124.

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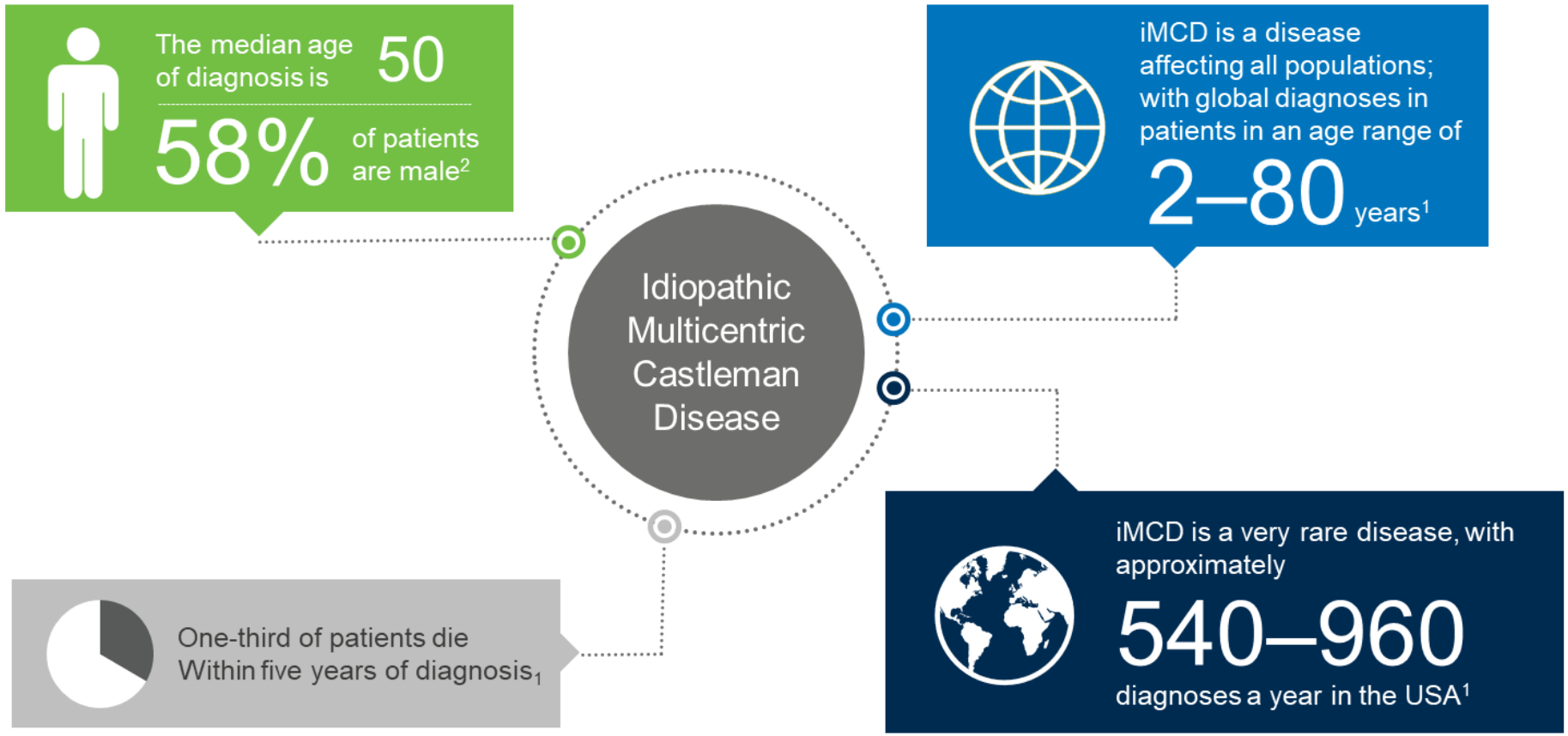
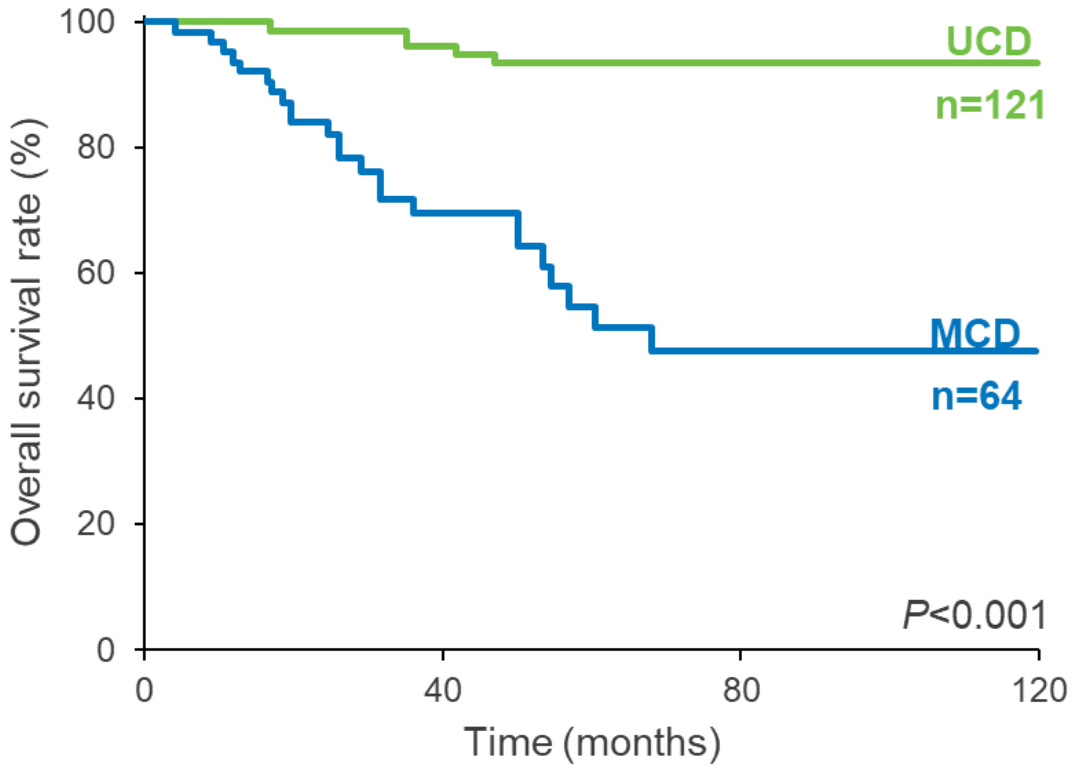
Epidemiology



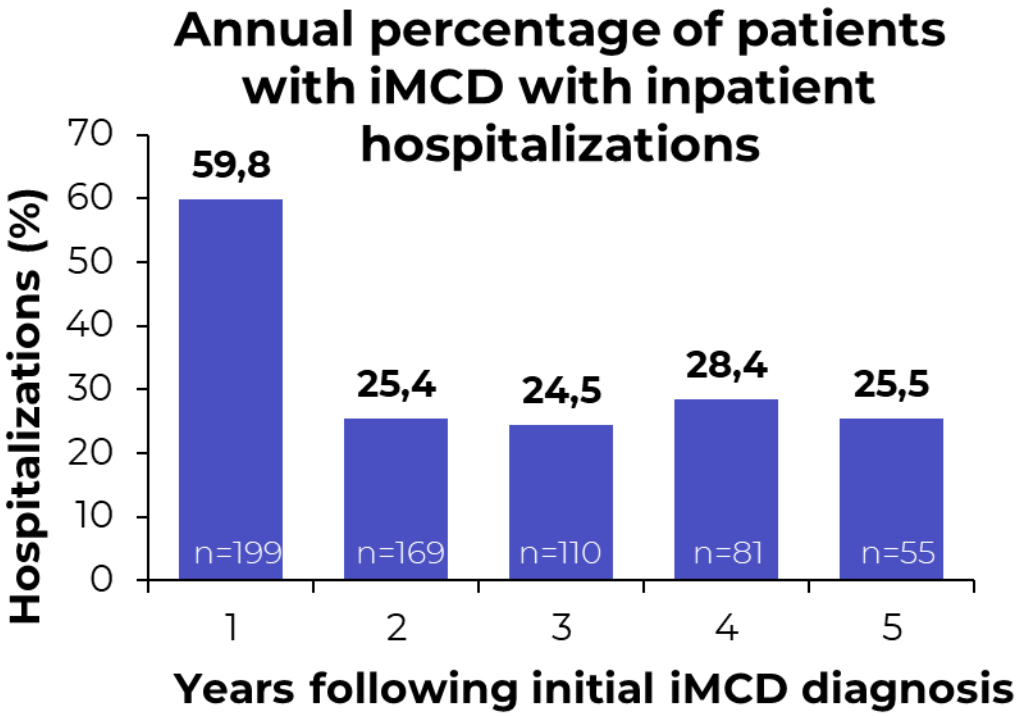
1. Fajgenbaum DC, et al. Blood 2017; 129(12): 1646–1657, 2. Liu et al. Lancet Haematol 2016; 3(4): e163–75

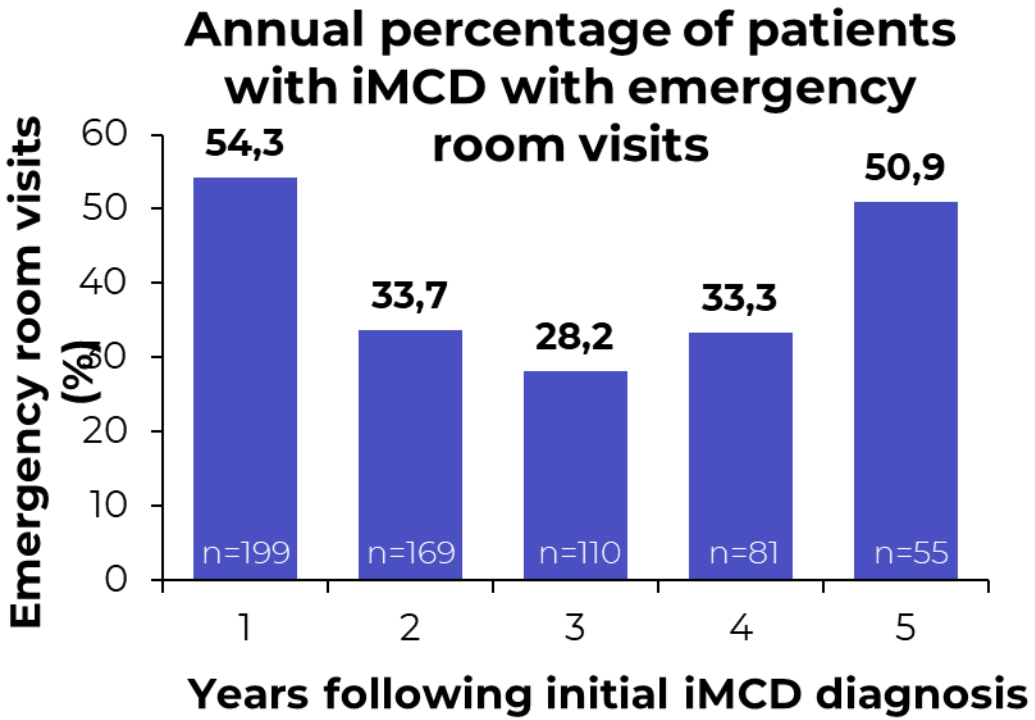
Overall survival in patients with Castleman disease



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

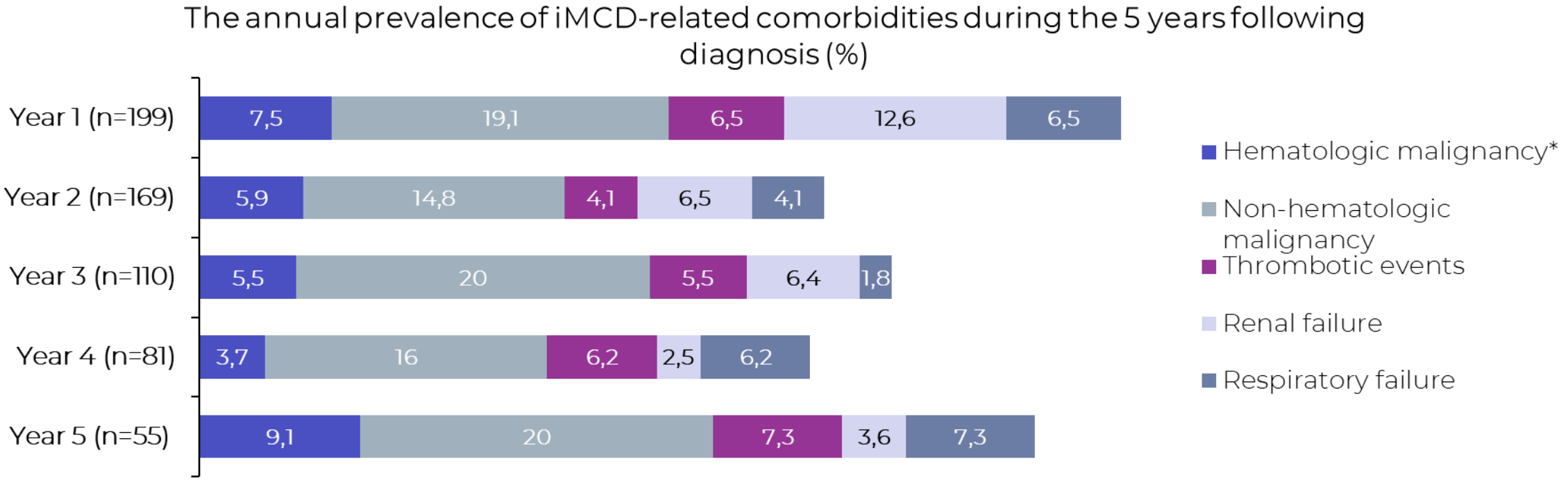
Hospitalization and emergency room visits of patients with iMCD





Mukherjee S *et al.* Oral presentation at the virtual 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; December 5–8, 2020.

iMCD-related comorbidities



*Excludes lymphomas and myelomas.

Mukherjee S *et al.* Oral presentation at the virtual 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; December 5–8, 2020.

Possible reasons for Castleman-related malignancies

- Malignant cells might be secreting IL-6 and other proinflammatory cytokines that cause the histopathological and clinical features of CD.
- Multicentric CD might be a premalignant state that can eventually transform.
- A common genetic mutation might make a patient susceptible to both CD and malignant diseases.
- Excessive cytokine release might promote malignant transformation.
- Treatment of CD – eg, cytotoxic chemotherapy – might amplify susceptibility to malignant disease.
- An unidentified virus might cause both CD and malignant disease.

Early and precise diagnosis of CD is essential to reduce morbidity and mortality!

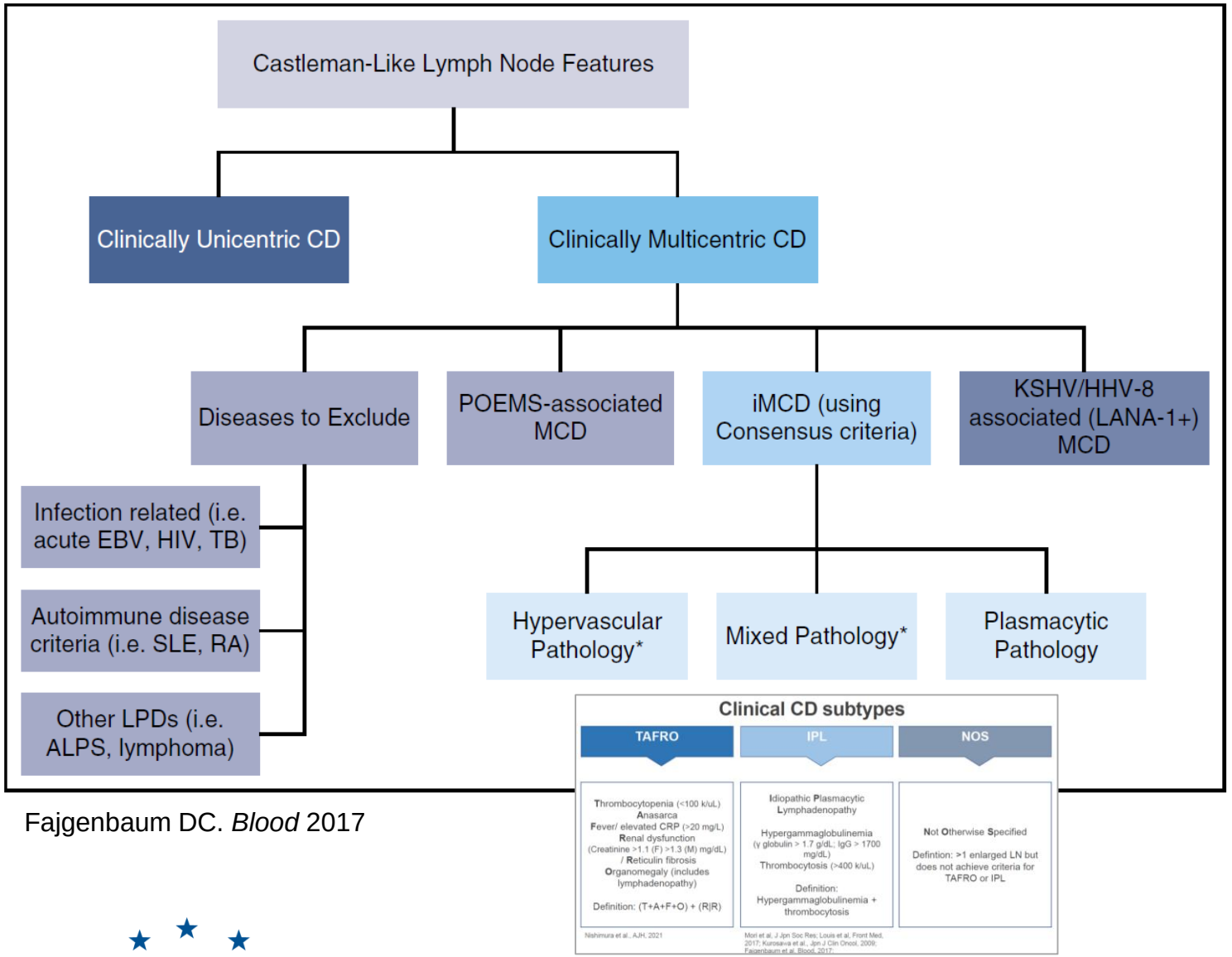
Liu AY et al, Lancet Oncol 2016, 3:e163ff

PATHOLOGY SUBSESSION

1. Defining histopathologic features of CD

2. Histopathologic subtyping of CD

3. Possible mimics of CD



Fajgenbaum DC. *Blood* 2017

- Lymph node based disease (though extranodal involvement can be observed)
- Similar histologic features in different clinical variants/settings

From Pierson S – Accelerate – Rome -16-17 Sept 2021

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1. Defining histopathologic features of CD

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

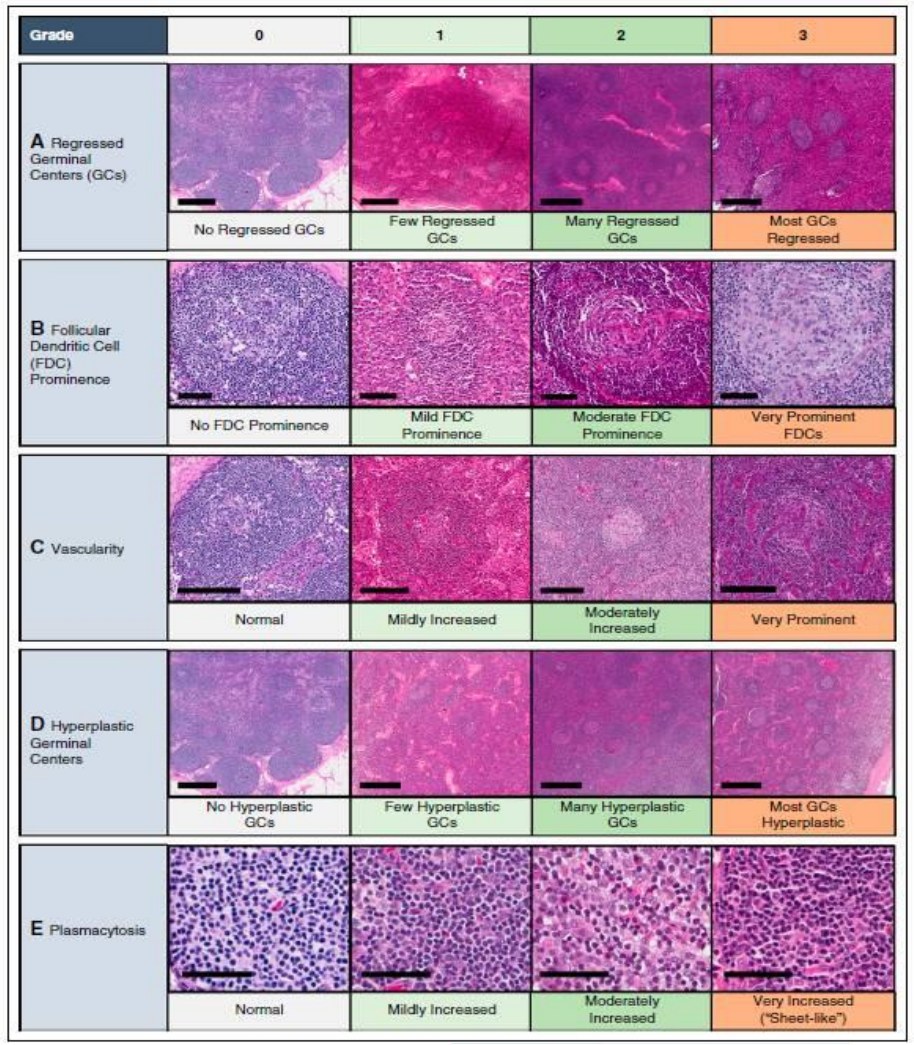
David C. Fajgenbaum,[1] Thomas S. Uldrick,[2] Adam Bagg,[3] Dale Frank,[3] David Wu,[4] Gordan Srkalovic,[5] David Simpson,[6] Amy Y. Liu,[1] David Menke,[7] Shanmuganathan Chandrakasan,[8] Mary Jo Lechowicz,[8] Raymond S. M. Wong,[9] Sheila Pierson,[1] Michele Paessler,[10] Jean-François Rossi,[11] 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 Cas 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

Major criteria (need both)

1) Histopathologic lymph node features consistent with the iMCD spectrum
   - defined 5 primary lesions: 3 refer to features of GCs of the lymphoid follicle, 2 refer to features of the paracortical/interfollicular area
   - all cases show a preserved node architecture

2) Enlarged lymph nodes (≥ 1 cm in short-axis diameter) in ≥ 2 lymph node stations spectrum

These are referred to idiopathic multicentric CD (all clinical subtypes), but with few mild differences they can apply to other clinical subtypes of mCD (HHV8, POEMS) and to uCD



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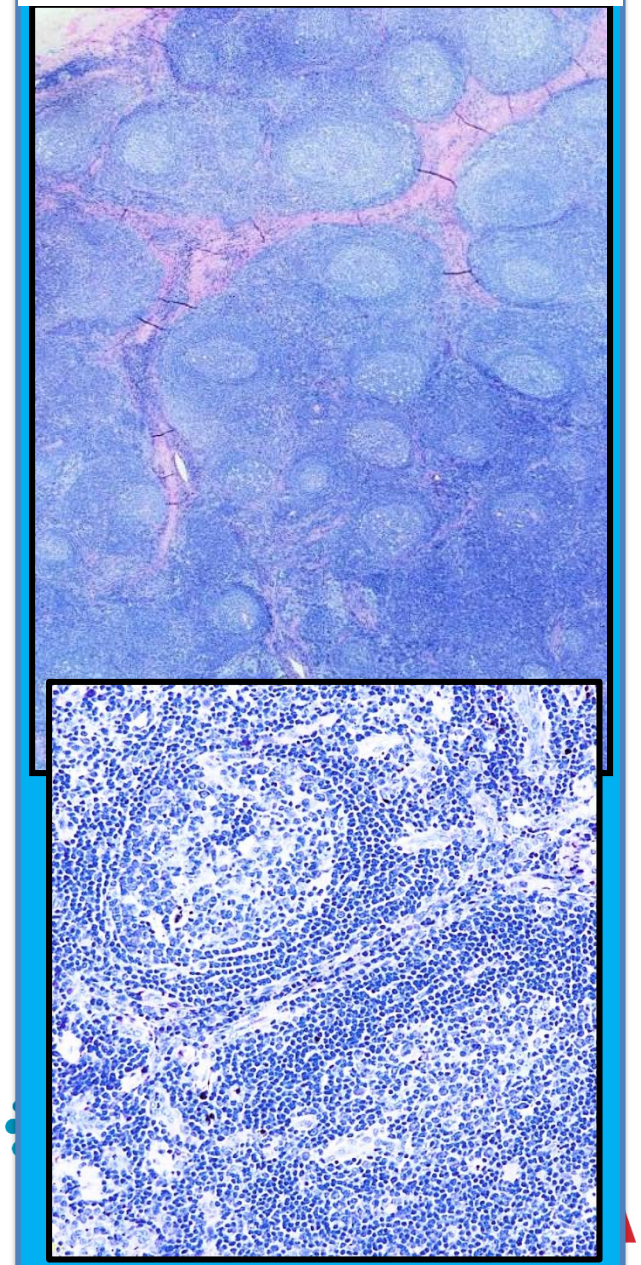
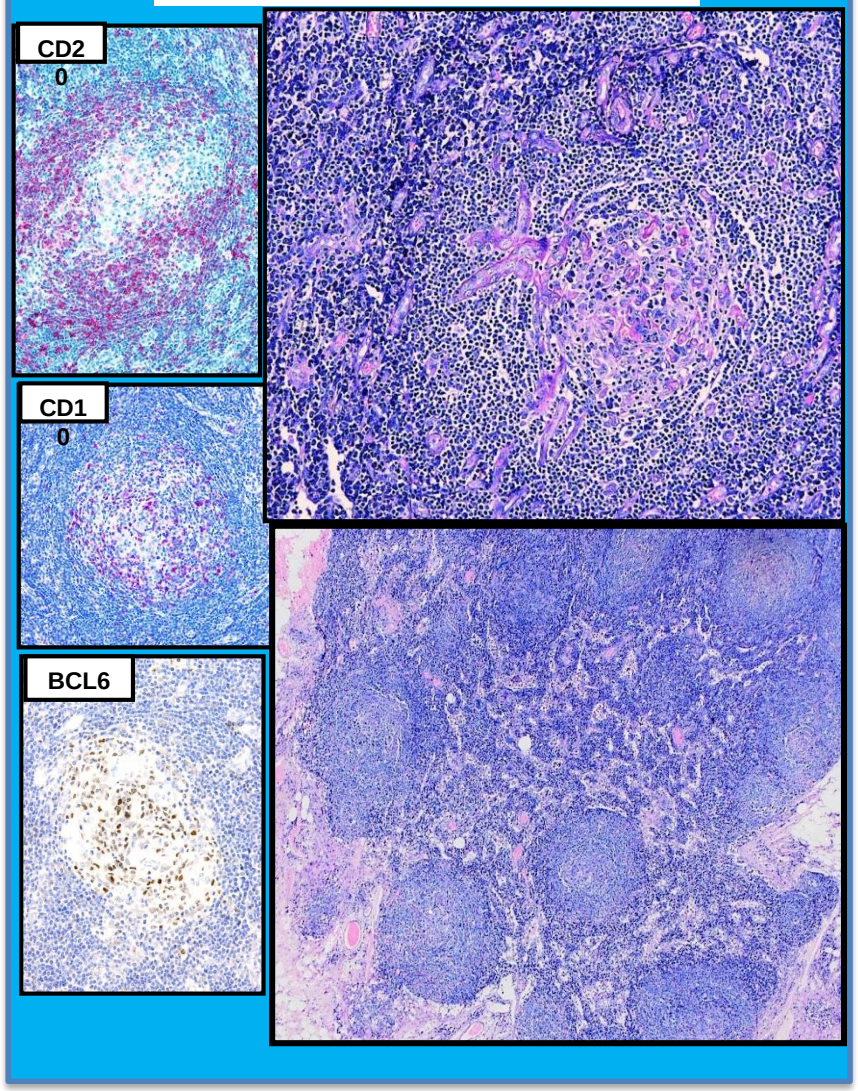
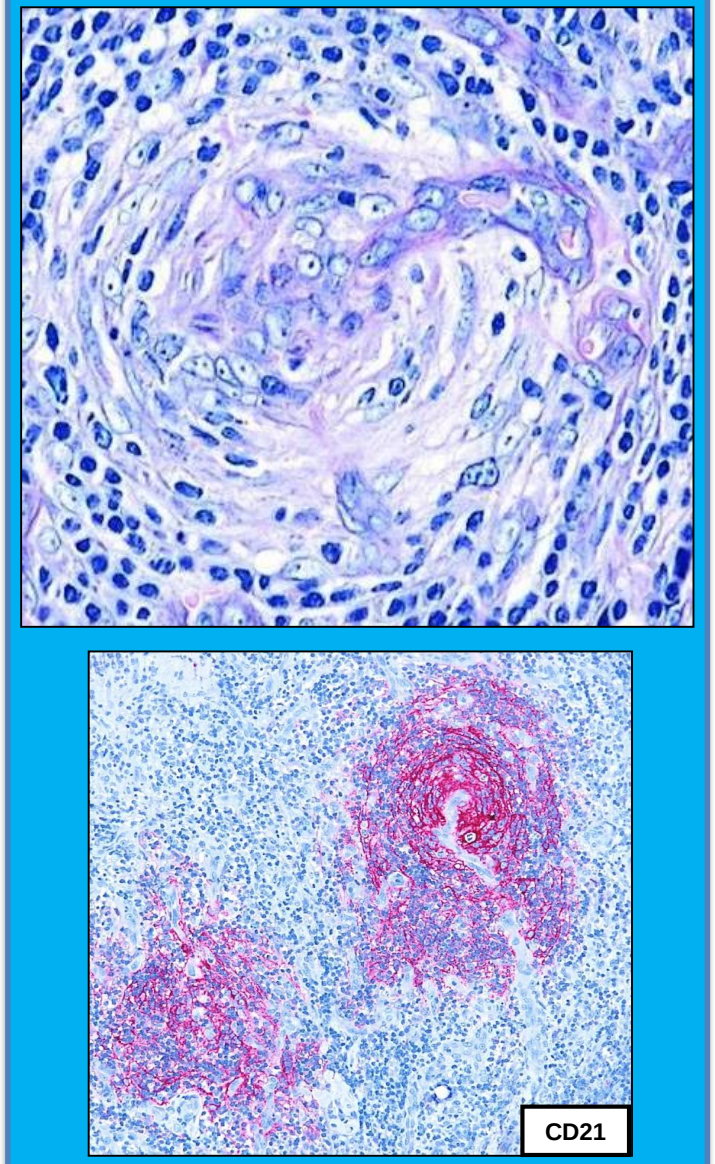
Hyperplastic GC



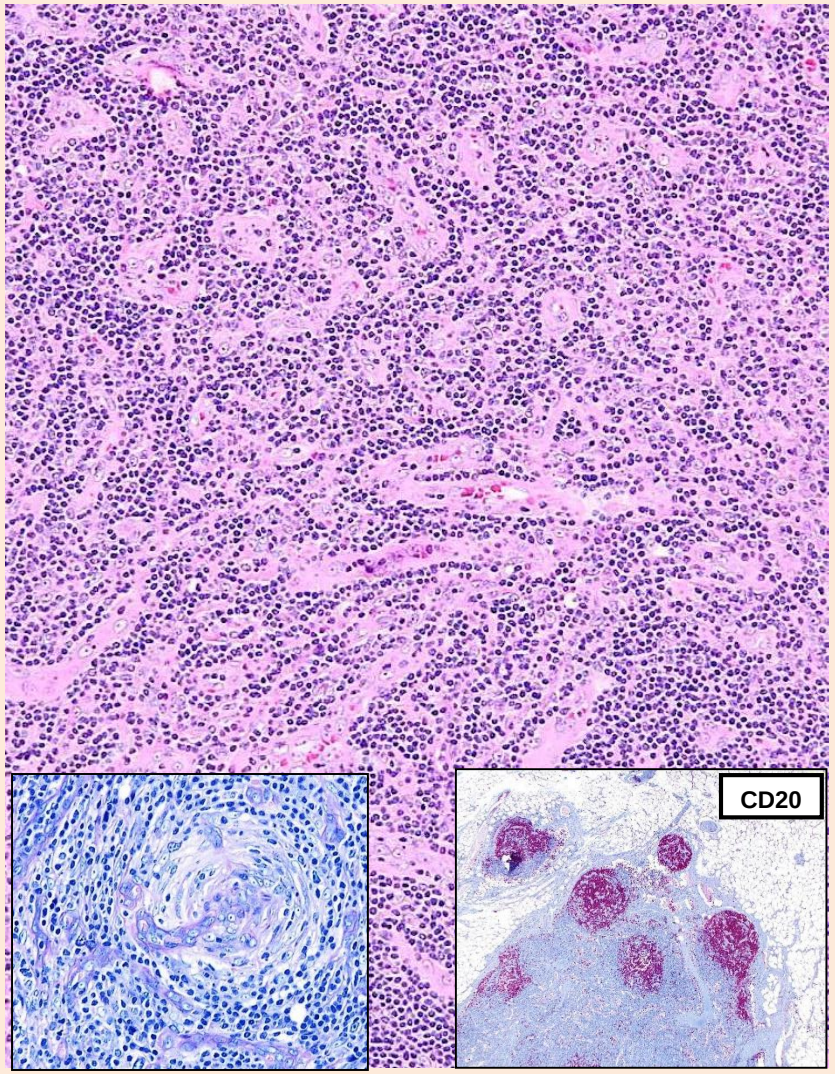
Regressed GC



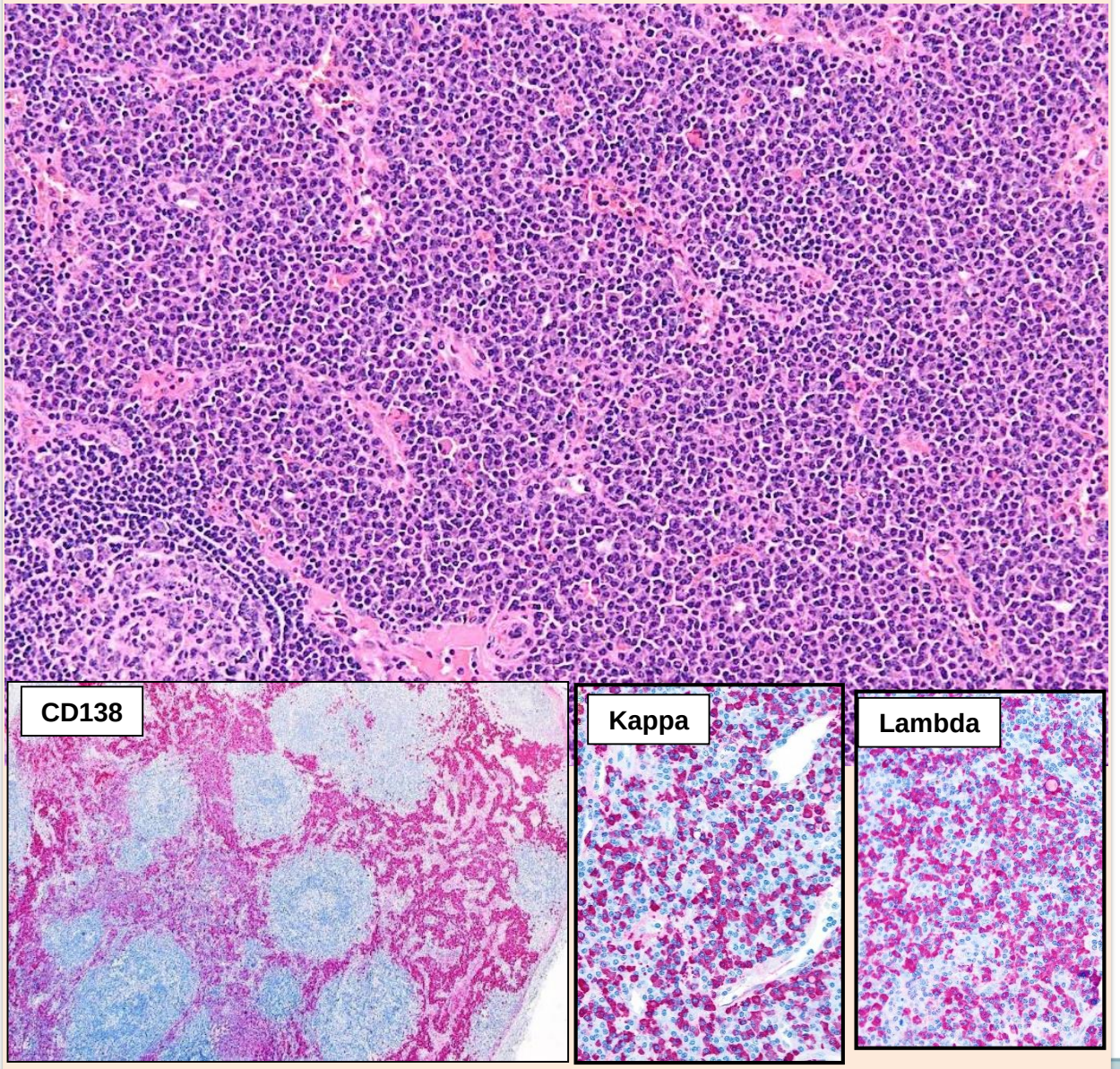
Follicular dendritic cell prominence



Increased Vascularity



Interfollicular Plasmacytosis



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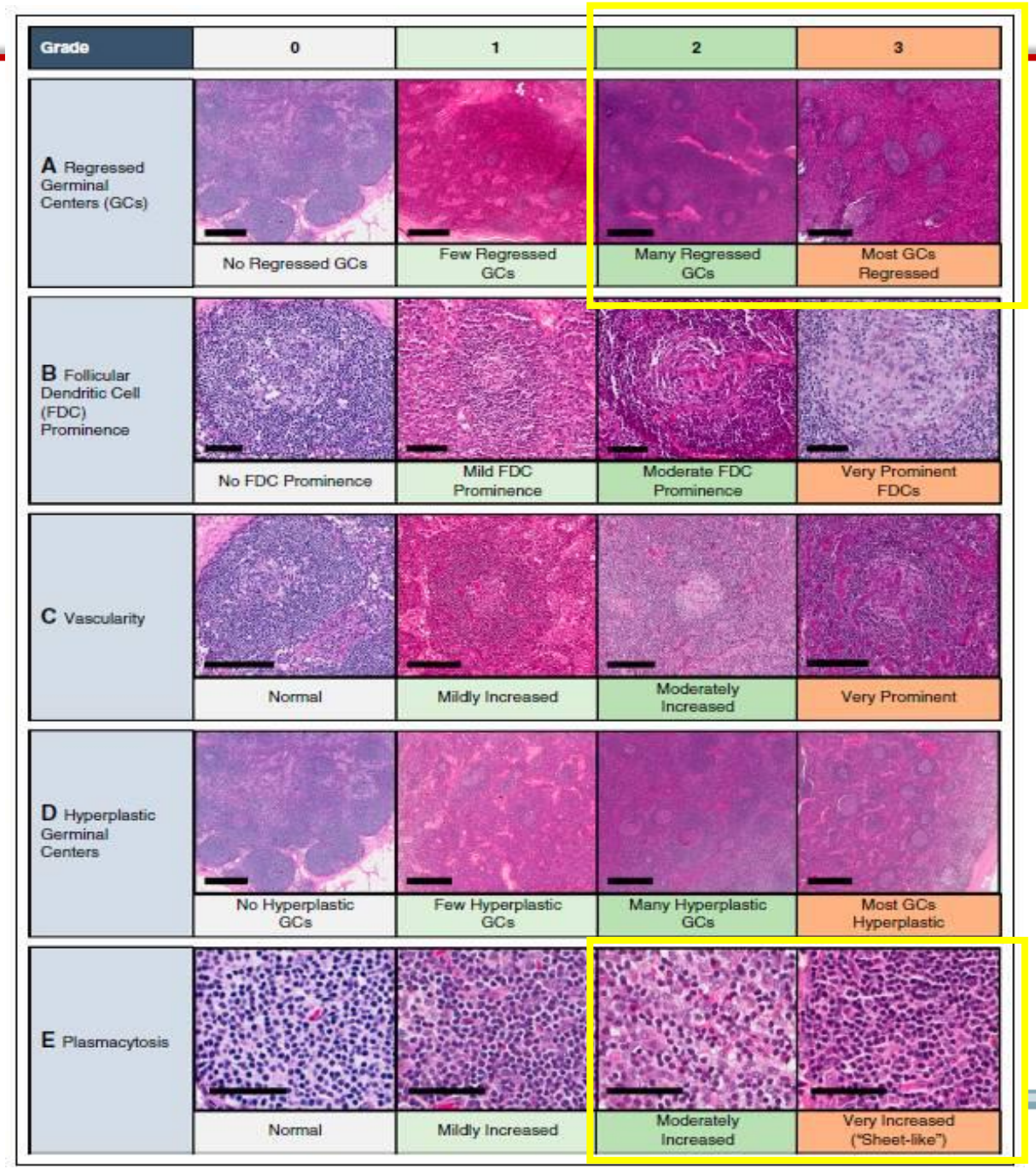
- These “primary” lesions are not specific in isolation
- Need of grading
  RGC: grade 2-3: most GC should be involved
  PC: grade 2-3: should be prominent and involve the whole lymph node



Fajgenbaum DC et al. *Blood* 2017;129:1646–1657.

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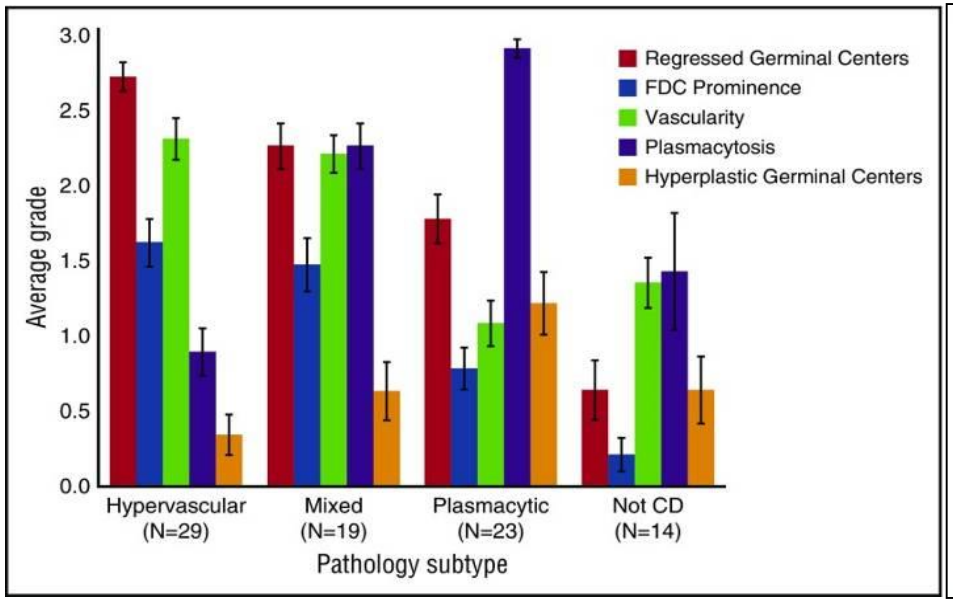
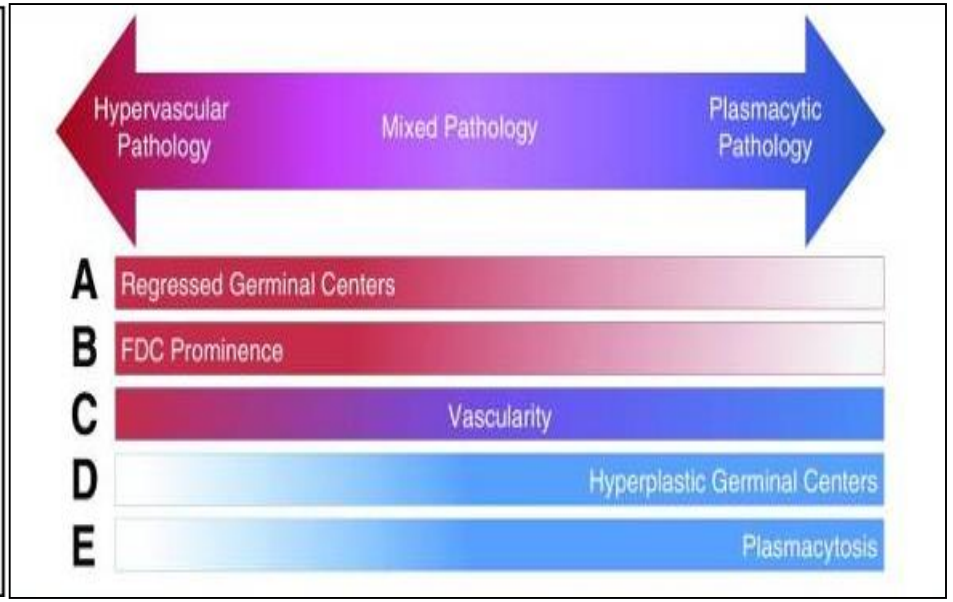
2. Histopathologic subtyping of CD





- Cases easily classified as HyperV/HV or PC; others show a wider spectrum of combination of histologic features that do not allow clear attribution to either HyperV/HV or PC: Mixed
- Mixed concept: variably applied; some include the mixed variant within the spectrum of PC-CD
- These histologic subtypes can coexist, in serial concurrent or sequential biopsies from the same patient

Fajgenbaum DC et al. *Blood* 2017;129:1646–1657; 2. Yu L et al. *Blood* 2017;129:1658–1668.; Wang W and Medeiros J. *Surg Pathol.* 2019; 12(3): 849-863. 3. Weisenburger DD. *Am J Surg Pathol.* 1988; 12(3): 176-81

Match of clinical and histopathologic variants

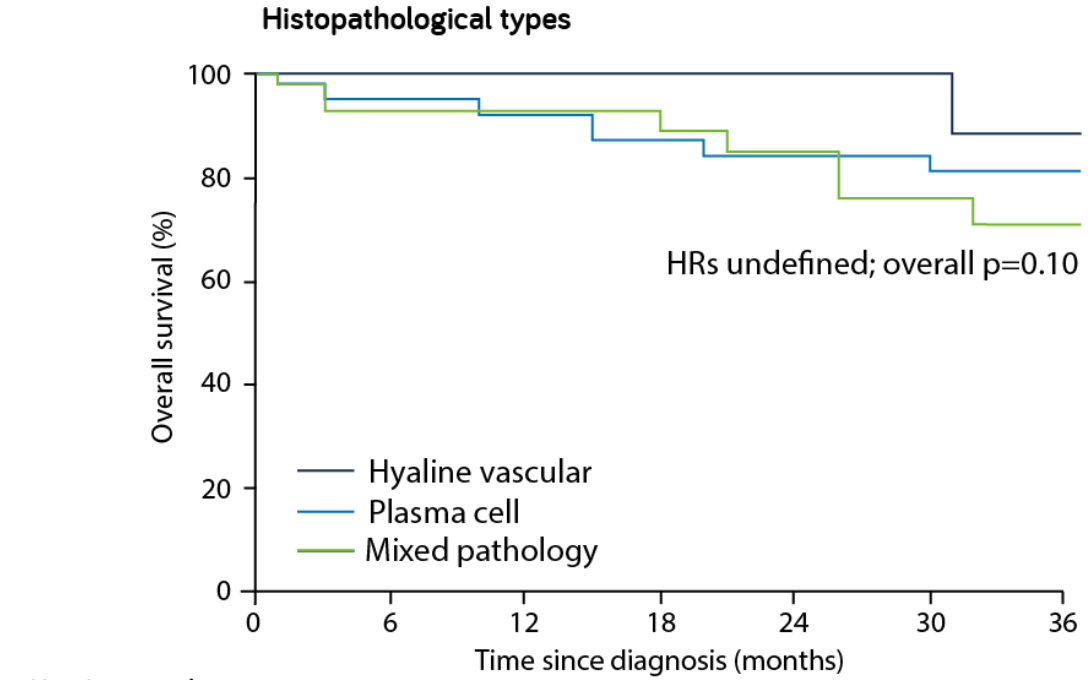
- **UCD**: 90% HV or mixed, 10% PC
- **MCD**
  - **HHV8+ MCD:** Commonly PC (possibly with plasmablastic features)
  - **POEMS-MCD**: Commonly PC
  -

iMCD*	NOS N=17	IPL N=9	TAFRO N=28
Plasmacytic	0	5	0
Mixed	5	2	9
Hypervascular	8	1	19
Hyaline Vascular	4	0	0

*From Pierson S – Rome – 16-17 Sept 2; Wu D, *et al. Hematol Oncol Clin North Am.* 2018; Wang W and Medeiros *J. Surg Pathol.* 2019; Dispenzieri A and Fajgenbaum DC. *Blood*. 2020;

histological type and survival

- 2-year survival seemed to be worse in patients with the PC histopathological subtype (84% [95% CI, 72–99]) and mixed pathology (84% [95% CI, 73–97])[1]
  - Compared to those with hyaline vascular features (100% [100–100])



Number at risk							
Hyaline vascular	19	19	18	13	10	10	8
Plasma cell	38	33	26	25	20	18	15
Mixed pathology	41	38	36	31	29	27	24

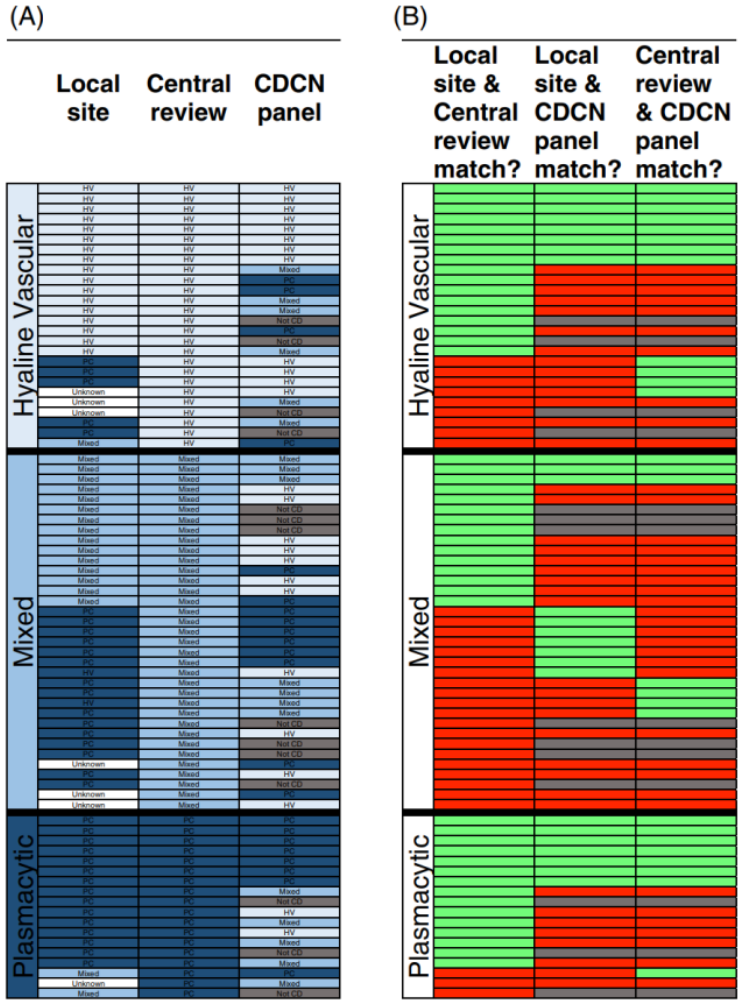
Liu A, *et al. Lancet Haematology.* 2016; Dispenzieri A, *et al. Am J Hematol*. 2012

Is histopathological sutyping the key for patients' treatment?

- *Only 23%(18/79) patients had the same iMCD histopathologic subtype selected by all three groups of evaluators (Local site/Central pathology review/CDCN expert panel/Expanded panel*

- Histopathology for diagnosing iMCD
- Histopathologic subtyping for clinical association, potential impact on survival, future relationship with biology
- *currently insufficient evidence to use histopathologic subtype to guide treatment of iMCD*
- Better subcategorize patients by clinicopathologic categories[1]

- Data from *Accelerate, real life, Fajgenbaum 2020 AJH :* no clear cut impact of histopathology subtyping on anti-IL6 response



white (unknown), grey (not CD), light blue (HV), blue (mixed), dark blue (PC).
red (no match), green (match), grey (not CD).

Fajgenbaum DC, *et al. Am J Hematol.* 2020; 95: 1553–1561.

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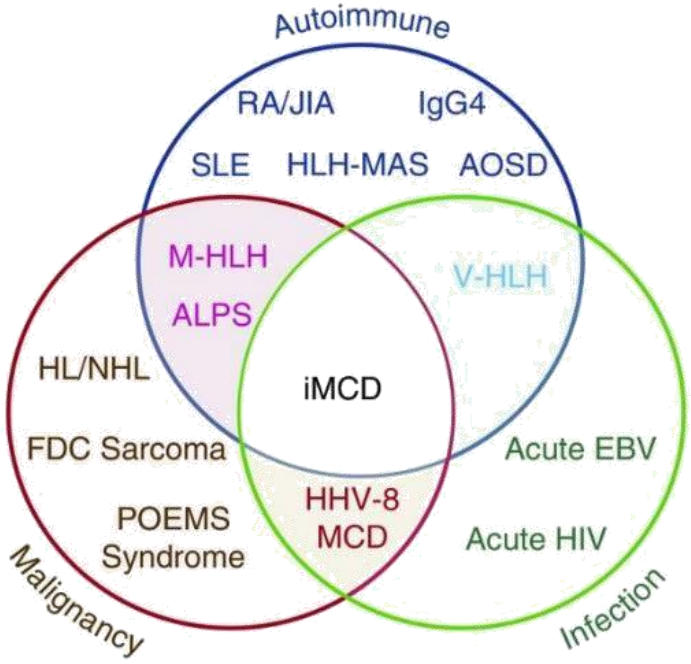
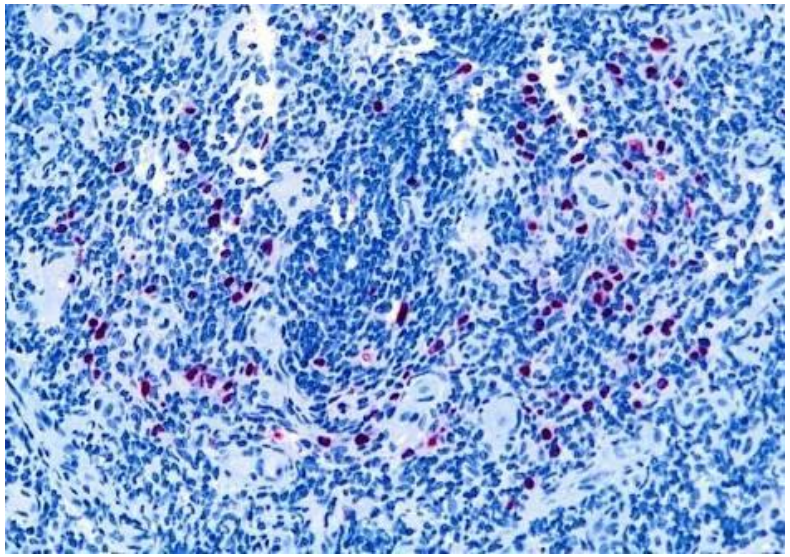
3. Possible mimics of CD

- Look for/exclude features suggestive of AI/AI diseases or pseudoneoplastic proliferations

- Exclude neoplasms
  >lymphomas, PCN
  FDC sarcoma (mostly for UCD)



- Exclude HHV8-related CD (with IHC for LANA-1 marker)
- Exclude EBV infection (with ISH with EBER1/2 probe)



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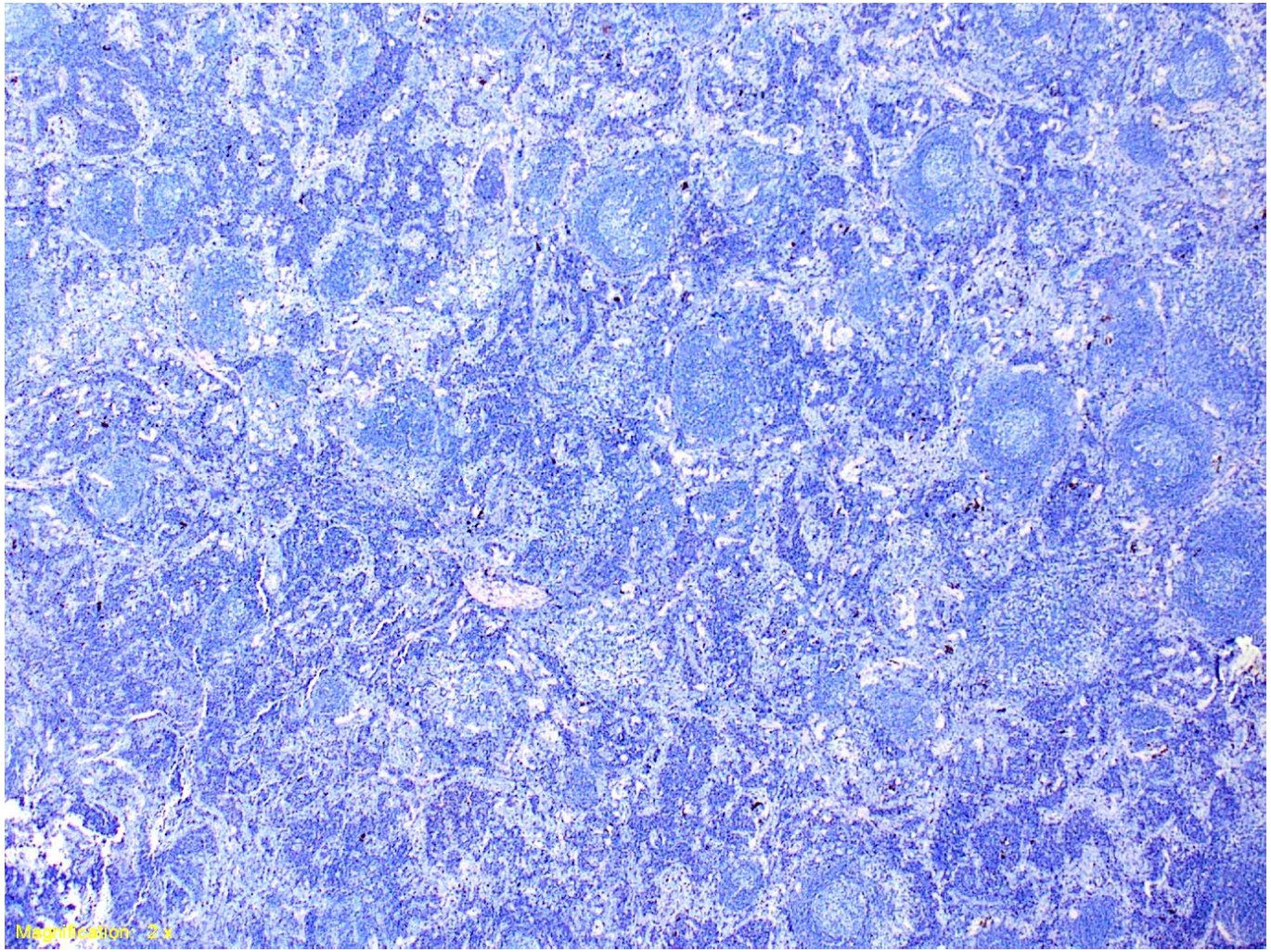
Fajgenbaum DC et al. Blood 2017; Liu et al. Blood 2017

IgG4-Related disease, PC predominant CD-like



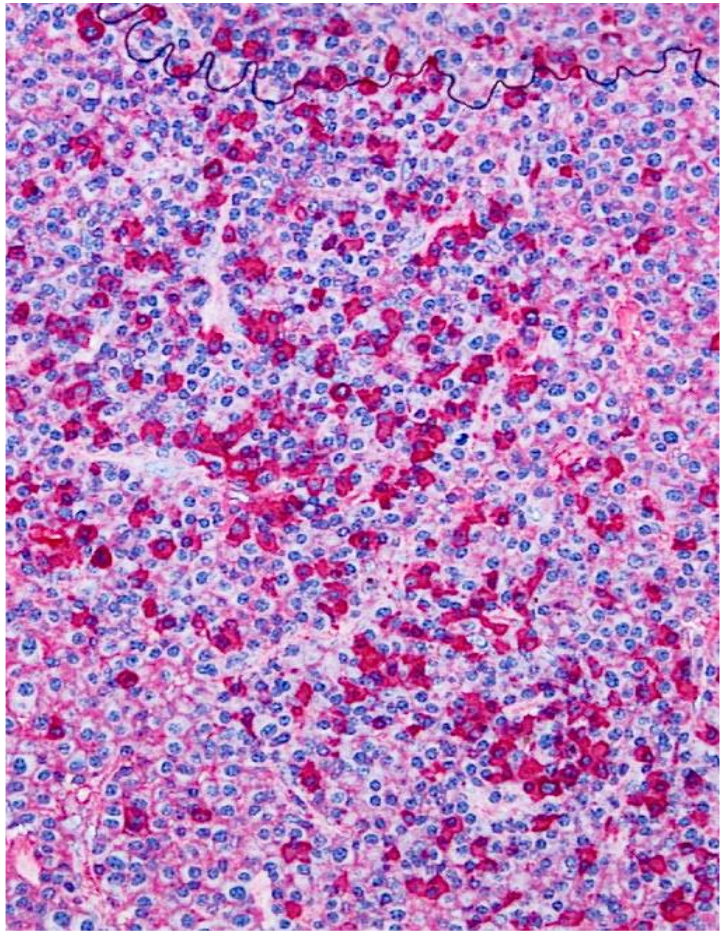
Five histological patterns are recognized: (1) multicentric Castleman's disease-like, (2) follicular hyperplasia, (3) interfollicular expansion, (4) progressive transformation of germinal center, and (5) nodal inflammatory pseudotumor-like. The specificity of these histologic changes in the absence of other evidence of IgG4-RD remains controversial

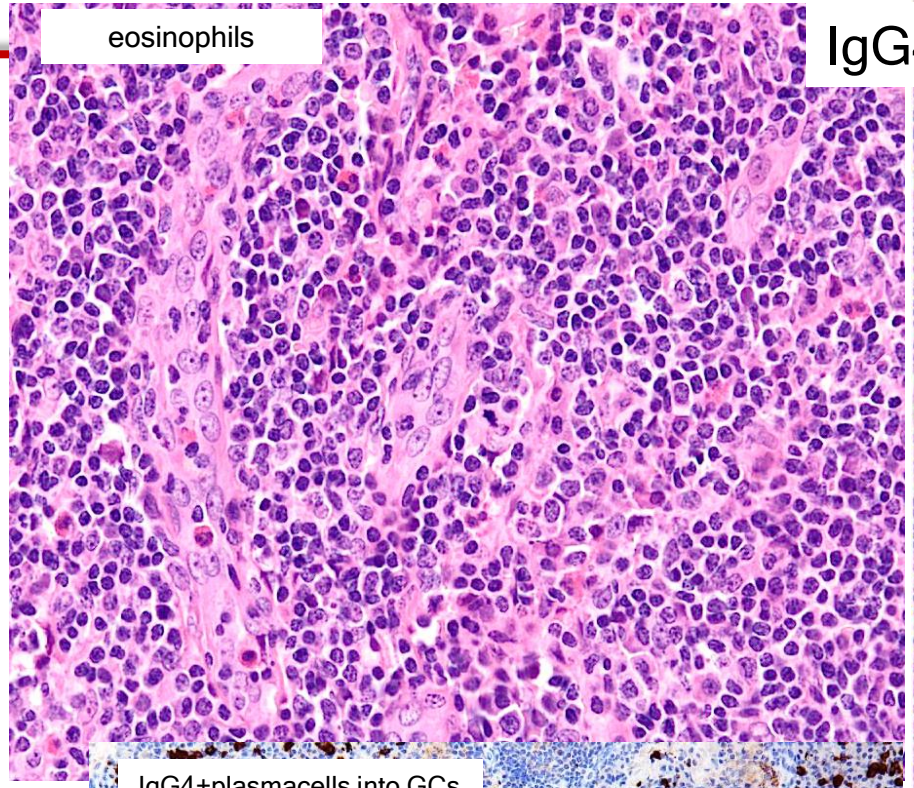
Obliterative arteritis is often seen in pulmonary manifestations, particularly solid lesions

iMCD patients
50% with elevated IgG4;
PC-iMCD
25% have IgG4/IgG+ ratio >40%;
72.7% meet diagnostic criteria of IgG4-RD

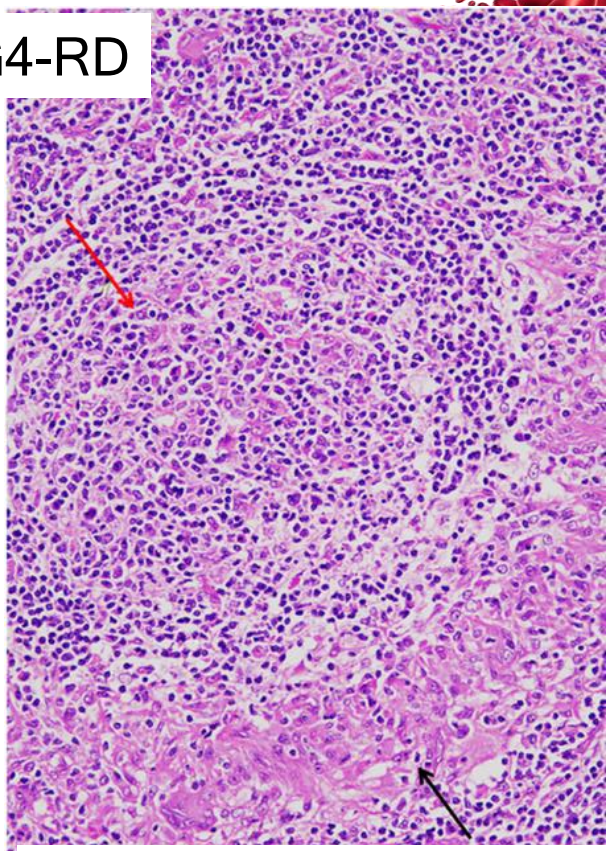
Deshpande V. Semin Diagn Pathol. 2012

iMCD: Tissue IgA plasma cells more densely distributed

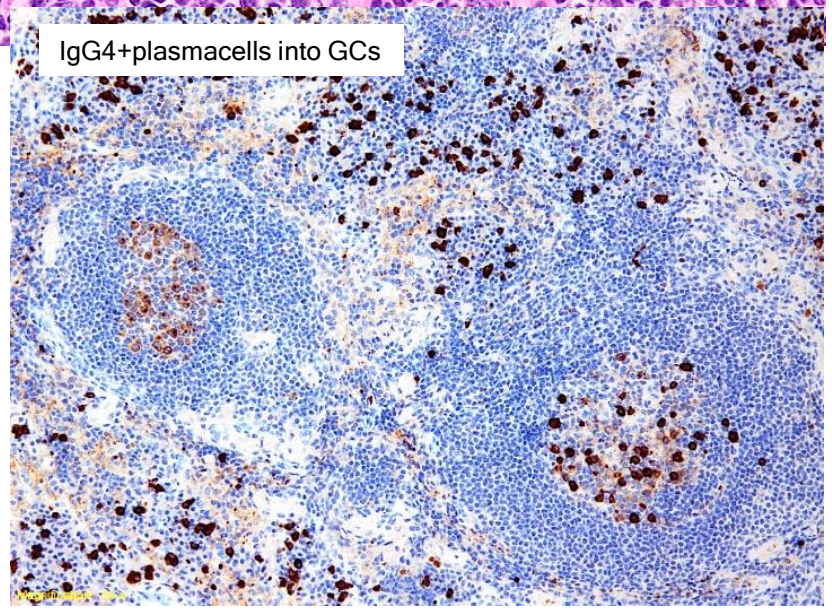




IgG4-RD



Horse-shoe epithelioid granuloma around follicles



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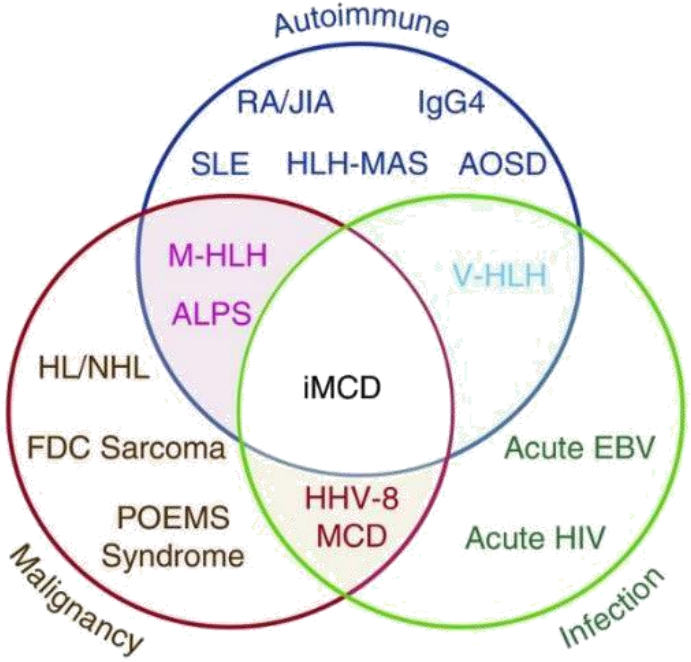
Sato et al. Mod Pathol 2009; Sun C et al. Clin Lab 2018; Manabe A et al Med Mol Morpohol

CD features and haematologic neoplasm (HN)

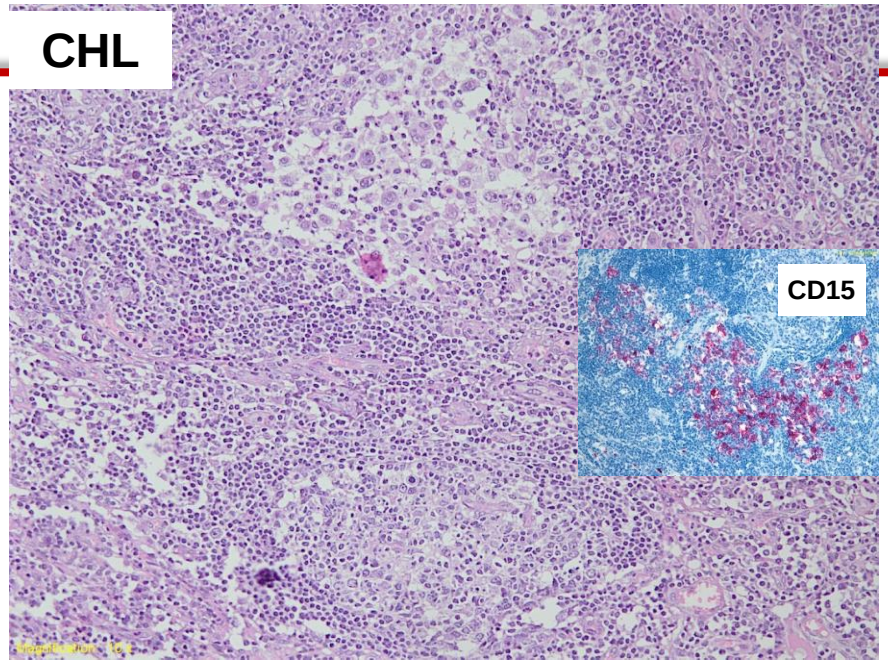
- HN and CD : one can co-occur, preceed or follow the other
- CD-like features can be induced by HN
- HN can itself mimic CD
- HN diagnosed **before/concurrently/shortly after** iMCD may have been responsible for the cytokine storm that caused MCD-like histopathology (and clinical) features --- malignancies have to be excluded before diagnosing iMCD

  HN diagnosed **more than one year after** iMCD diagnosis (with no evidence of the malignancy on the original diagnostic lymph node or imaging) should not overturn the initial iMCD diagnosis



Faigenbaum et al. Blood 2017

CHL



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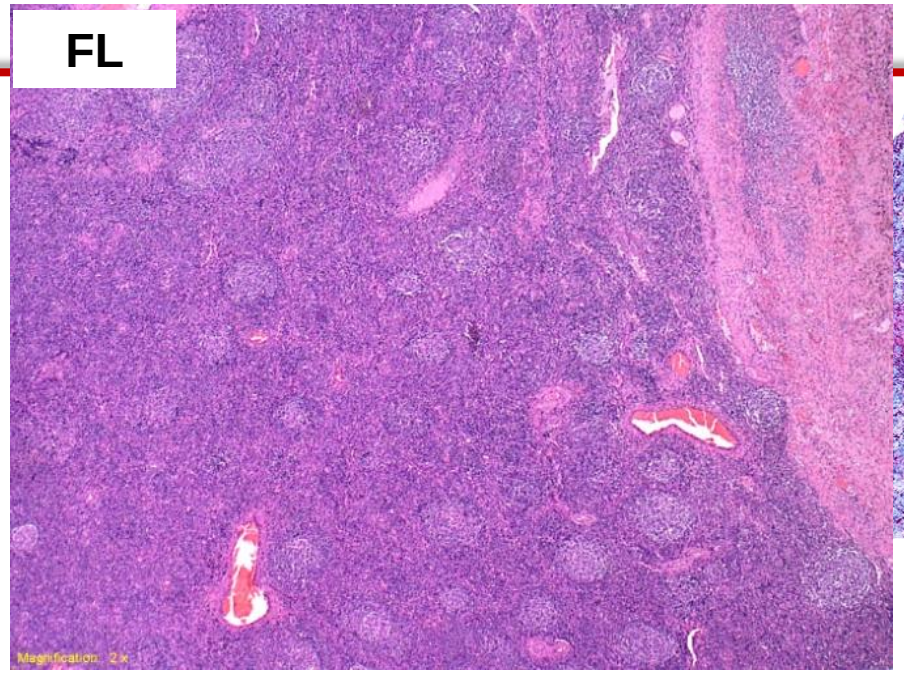

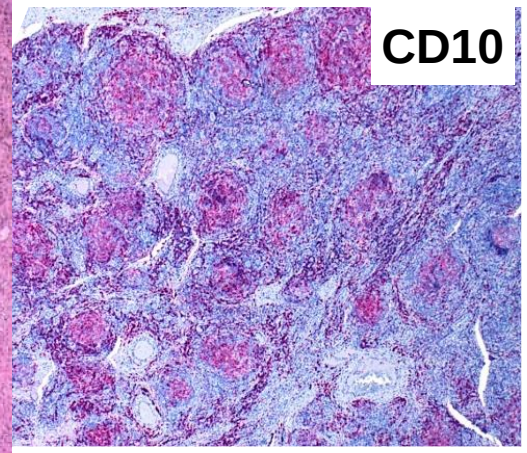

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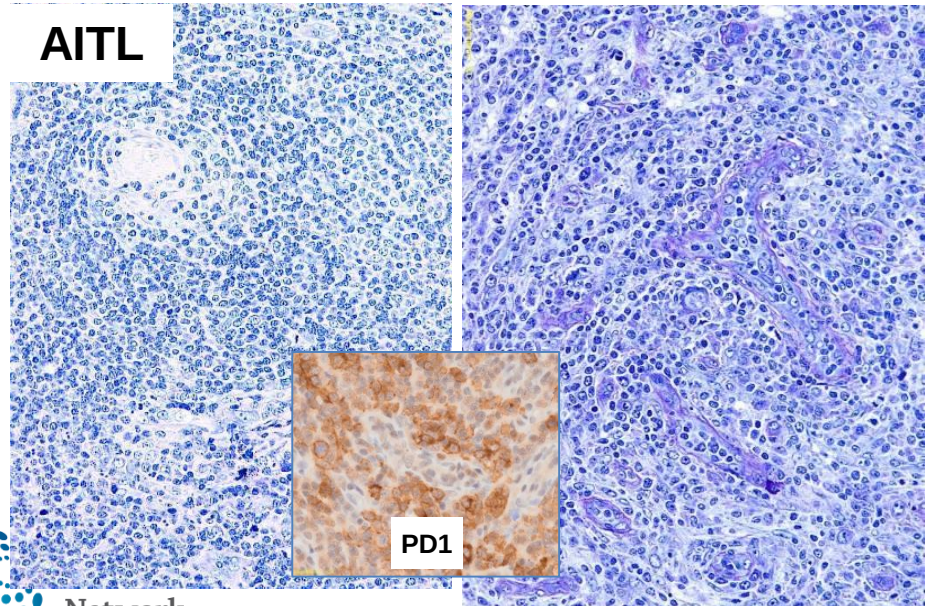

MZL

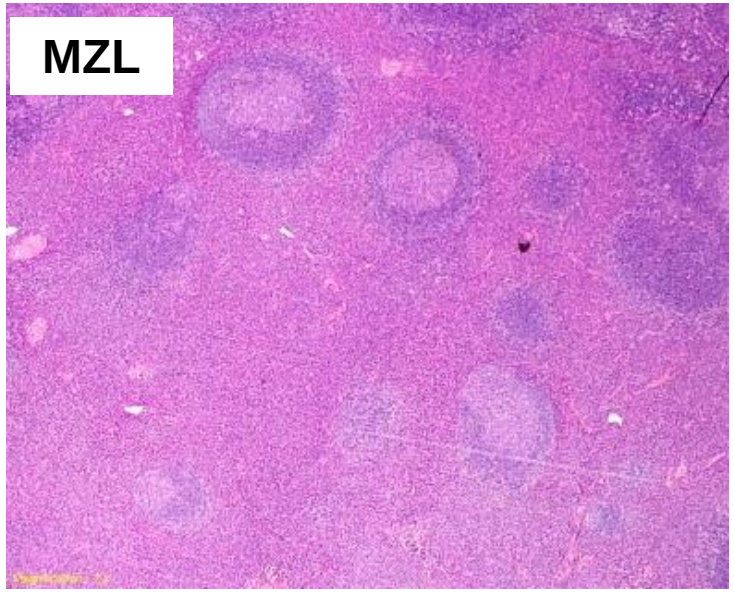

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Table 3. Immunohistochemical findings in plasma cells of the interfollicular areas

Patient no.	IgG	IgA	IgM	kappa	lambda
1	+++	+	–	+++	++
2	++	–	–	++	+
4	+	+++	–	+	+++
5	++	+	–	++	++
7	+++	+++	–	++	+++
8	+++	–	–	++	++
10	+++	–	–	+++	++
11	+++	+	–	+++	++
12	+++	+	–	++	++
13*	++	++	+	++	++
14	++	+	–	+	++
15	+++	–	–	–	+++
16	+++	–	–	–	+++
17	+++	–	–	–	+++
18	+++	–	–	–	+++
19	–	+++	–	–	+++
20	+++	–	–	–	+++
21	–	+++	–	–	+++

*Patient with Takatsuki syndrome.
– = no positive cells; + = some positive plasma cells; ++ = many positive plasma cells; +++ = coalescent sheets of cells.

Radaszkiewicz T, Histopathology 1989

MCD picture with monotypic plasmacells w/o monoclonal IgH

McAloon EJ. N Engl J Med. 1985, Maheswaran PR et al. Histopathology. 1991; Hsu SM et al. Am J Pathol. 1992; Saletti P et al. Ann Hematol. 1999; Molinie et al. Annales de Patologie 1994; Molinié V et al. Ann Pathol. 1995. Zarate-Osorno A, Arch Pathol Lab Med. 1994; Pina-Oviedo S et al Hum Pathol. 2017; Chapman J et al. Am J Surg Pathol. 2020; Siddiqi et al AJCP 2011; Xerri L et al. Virchows Arch. 2016; *Al-Maghrabi J et al. Histopathology. 2006; Wu D et al. Hematol Oncol N Am 2018; Hsi E et al. American Journal of Clinical Pathology; Dispenzieri A. Blood Rev. 2007; Menke et al. AJCP 2001; Lin BT et al. Hum Pathol 1997; Radaszkiewicz T et al. Histopathology 1989*

Diagnosis of Castleman disease

General aspects

Symptoms of patients with multicentric Castelman disease

Organomegaly:
Enlarged liver or spleen

Generalized Lymphadenopathy:
Enlargement seen across multiple groups of lymph nodes

Flu-Like Symptoms:
Fevers, night sweats, fatigue, and weight loss

Fluid Accumulation:
Edema, ascites, and/or other symptoms of fluid overload

Laboratory abnormalities:
Anemia, Hypoalbuminemia, elevated CRP levels

Fajgenbaum DC et al., Blood 2017; 129: 1646ff; Casper C, Br J Haematol 2005; 129: 3ff.

Diagnostic work-up

Imaging

- A whole-body CT should be performed to distinguish unicentric from multicentric CD and to assess the number of enlarged lymph nodes
- An FDG-PET scan may help with identifying FDG-avid nodes for biopsy and with distinguishing CD from lymphoma

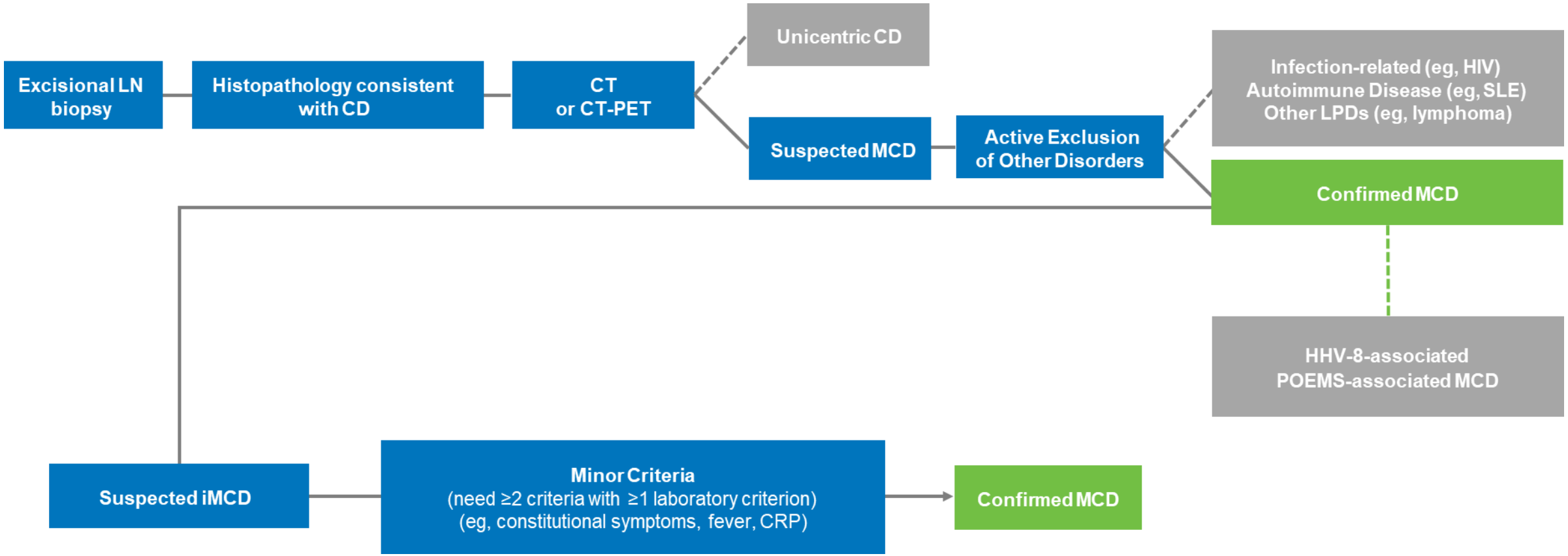
Excision biopsy

- Histopathologic lymph nodes features must be consistent with CD spectrum
- It is suggested that the biopsy is reviewed by a pathologist who has CD expertise

Laborytory testing

- Check hemoglobin, platelets, CRP, ESR, immunoglobulin, and albumin levels
- Asses renal function
- Check cytokine levels, including IL-6 and VEGF (if possible)

Diagnosing Castelman disease



Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. van Rhee F, et al. *Blood*. 2018:132(20):2115-2124.

CDCN Diagnostic criteria for idiopathic multicentric Castelman disease

I. Major Criteria (need both)

1. Histopathologic lymph node features consistent with the iMCD spectrum.

2. Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations

II. Minor Criteria (need ≥2 of 11 criteria with ≥1 laboratory criterion)

Laboratory

1. Elevated CRP
2. Anemia
3. Thrombocytopenia
4. Hypoalbuminemia
5. Renal dysfunction or proteinuria
6. Polyclonal hypergammaglobulinemia

Clinical

1. Constitutional symptoms: night sweats, fever, weight loss, or fatigue
2. Large spleen and/or liver
3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion
4. Eruptive cherry hemangiomatosis or violaceous papules
5. Lymphocytic interstitial pneumonitis

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Fajgenbaum D *et al.* Blood 2017; 129(12):1646–1657.

Webinars EuroBloodNet

Challanges with Castleman disease

Diagnosis is often delayed because of various factors:

- Biopsies are non-specific („no signs of malignancies“, „reactive“)
- Some biopsies are non-diagnostic
- Symtoms can be episodic, or they appear to resolve
- Clinical experience is highly variable among hematologists
- Local experience is often limited
- There is a limited amount of guidelines

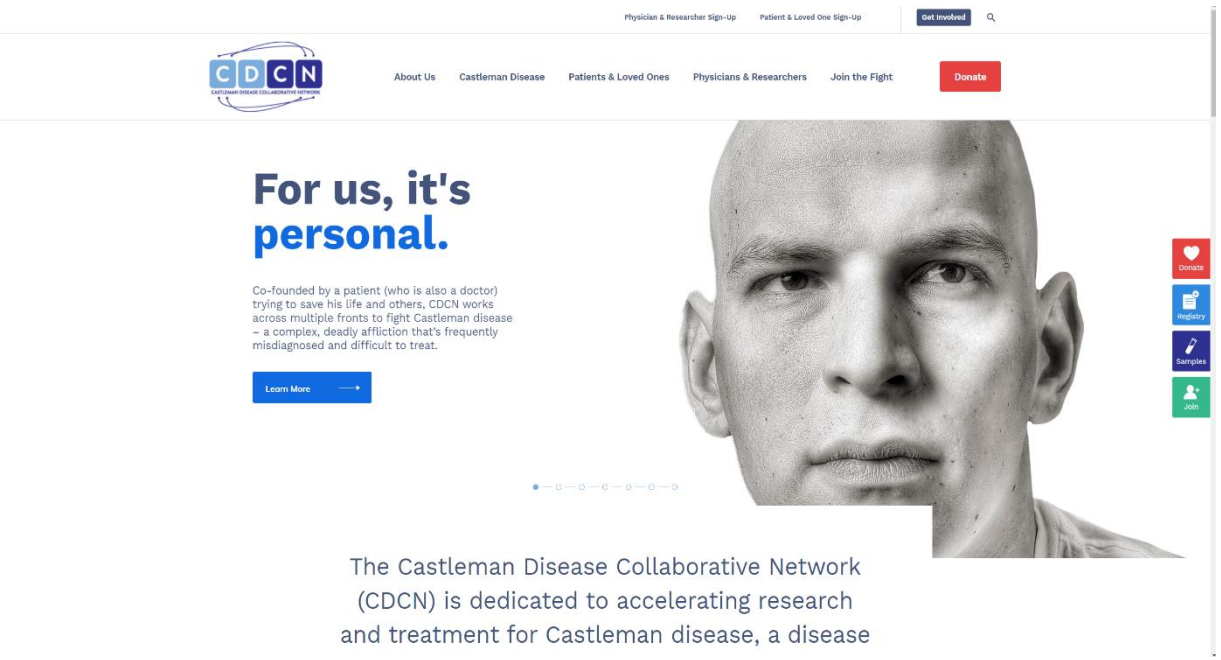
Multicentric CD is a rare but life-threatening disease!

- If diagnosis is not made by a pathologist who is experienced in hematology diagnosis, ask for a second reading from an expert.

- Take the time to discuss the case with a regional or national expert network; this will be helpful for diagnosis purposes, making treatment choices, and conducting clinical research.

- In case of any doubt, call the pathologist and discuss the case in depth together.

Castleman Disease Collaborative Network (CDCN)



CDCN researchers have massively contributed to the disease area which have led to

- a unique ICD-10 code for CD to allow physicians to easily treat CD and navigate insurance;
- the first set of international diagnostic and treatment guidelines for unicentric and multicentric CD;
- the first novel targeted treatment for iMCD in 25 years;
- the first clinical trial recruiting patients with treatment-refractory iMCD.

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EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars
EuroBloodNet

Take home messages

1. Castleman disease consists of a group of lymphoproliferative disorders that share a spectrum of histological features.
2. Avoiding time delay in diagnostic is essential, especially multicentric CD is not an indolent disease.
3. Diagnosis requires a close cooperation between clinician and pathologist.

Thank you!