Castleman Disease: Recognizing a Rare and Often Missed Diagnosis

Focus: diagnostic complexity, IL-6 pathway and current management, distinguishing from other conditions

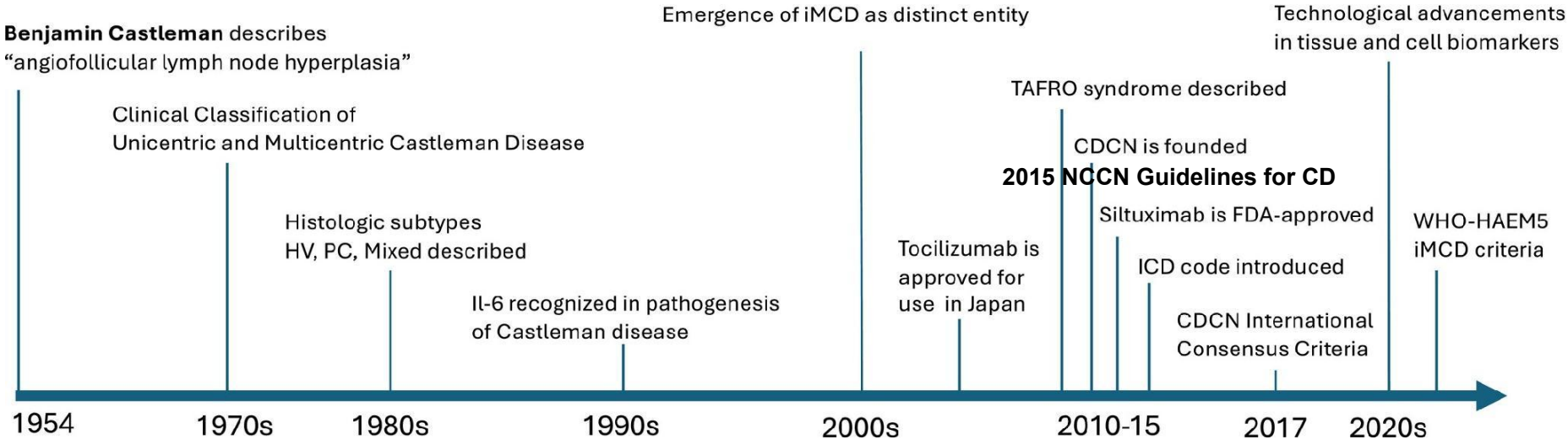
FLASCO Clinical Oncology Series: Rare Disease
August 22, 2026

Lubomir Sokol, MD, PhD

Benjamin Castleman, MD 1906-1982

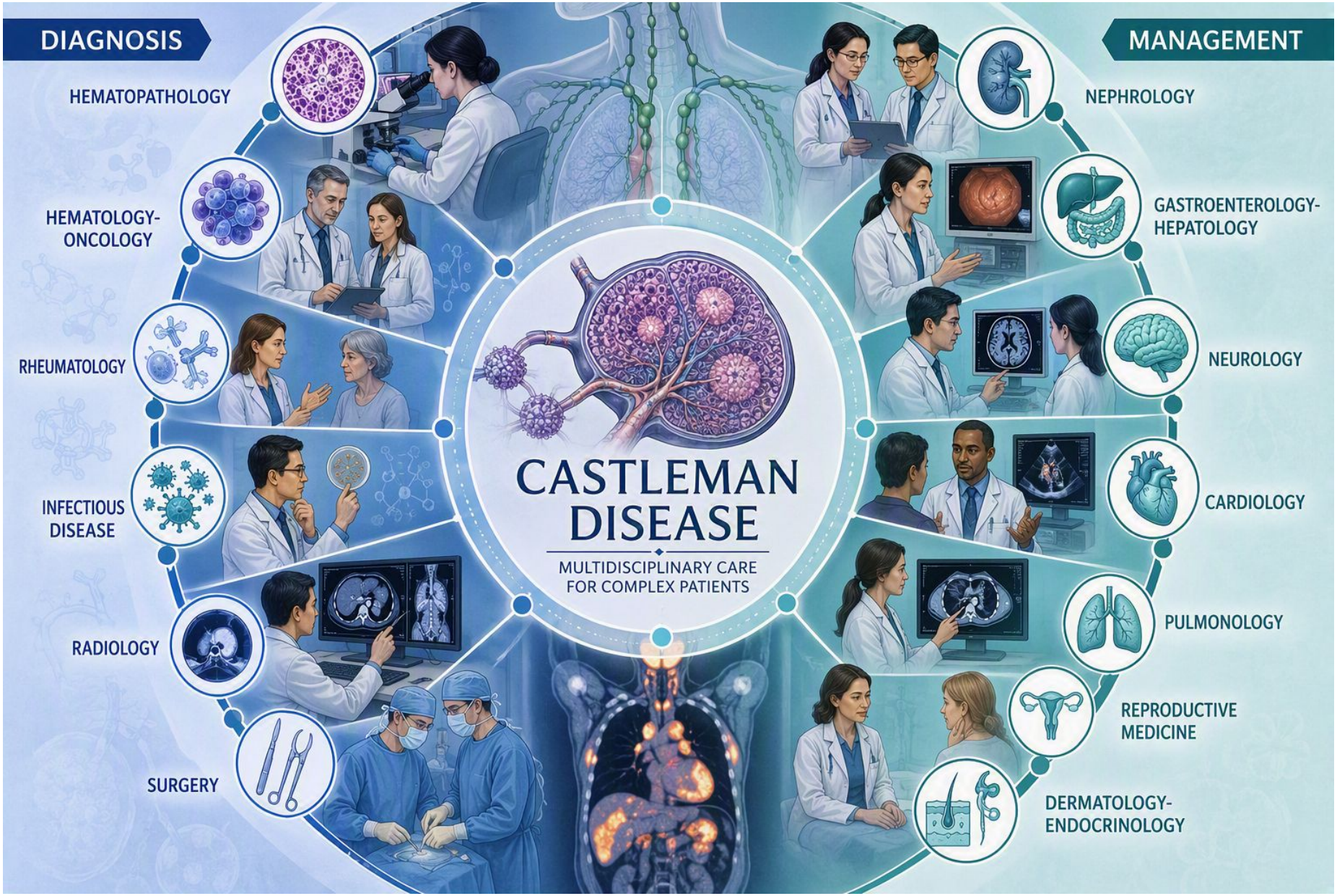
"Hyperplasia of the mediastinal node" - MGH Case Records, 1954.

"Localized mediastinal lymph node hyperplasia resembling thymoma**"-** Cancer, 1956.



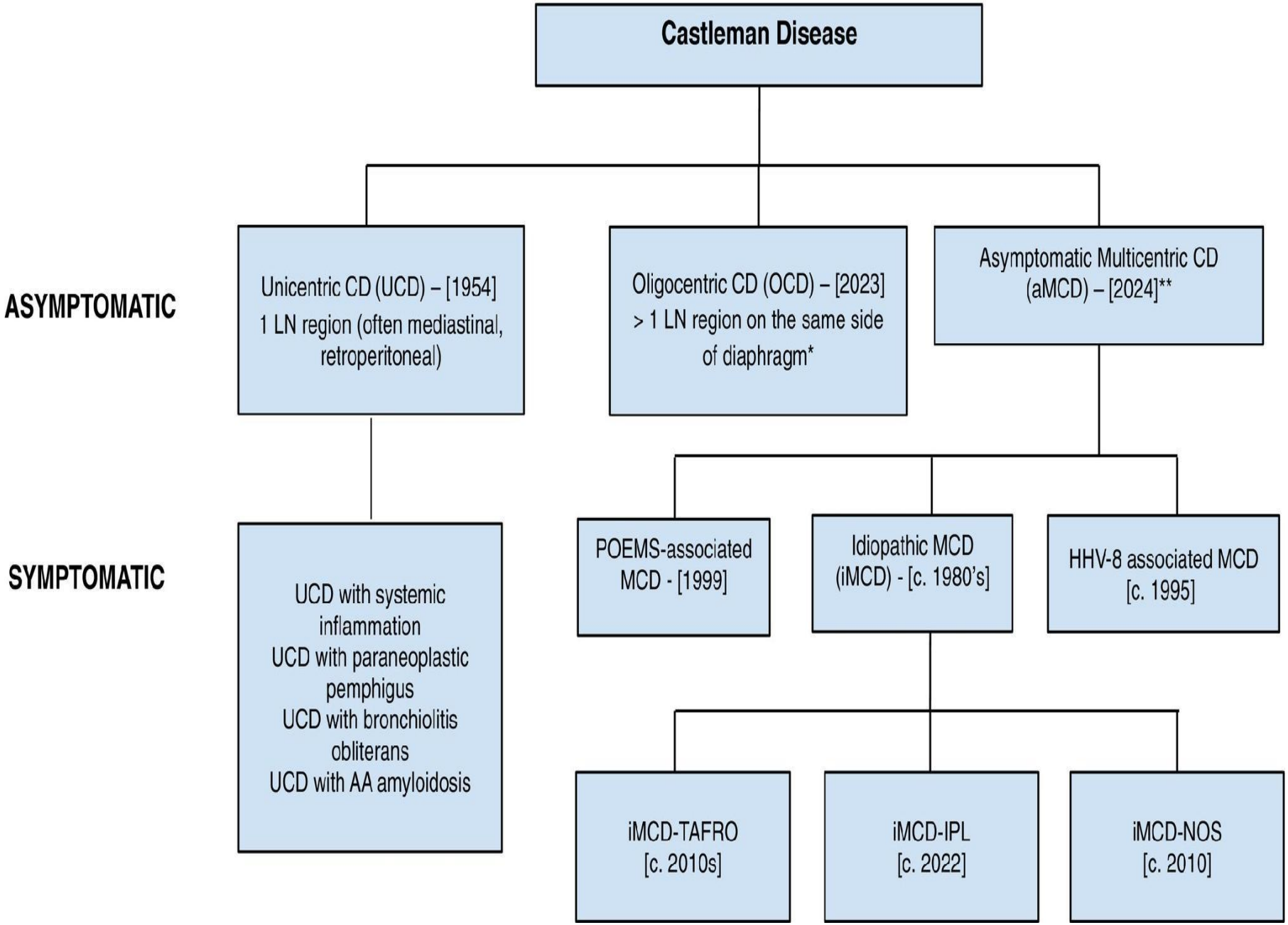
Modified from Alnoor F et al. AJH 2025

Castleman Disease: Multidisciplinary Diagnosis and Management



Clinician-pathologist collaboration is central to accurate classification and coordinated specialty care.

Sokol L, unpublished, AI-assisted figure, 2026.



Chen LYC et al. Arthritis & Rheumatology, 2025.

Contemporary Classification and Definition of Castleman Disease Subtypes

1. UCD: **Clonal/oligoclonal localized stromal-cell neoplasm** (BRC/FDC lineage) with secondary polyclonal lymphoproliferation and VEGF/CXCL13/PGF-driven microenvironmental remodeling

2. iMCD-NOS: **Polyclonal systemic inflammatory syndrome** with normal/elevated platelets; emerging evidence implicates **T peripheral helper cell–derived CXCL13 as a key pathogenic driver.** Residual iMCD subtype characterized by a less intense.

3. iMCD-TAFRO: **VEGF/IL-6–vascular endothelial cell–driven systemic inflammatory disorder** with thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly; possible clonal contribution (MEK2/RUNX1 mutations) in a subset; nosologic relationship to iMCD debated

4. iMCD-IPL: **Polyclonal plasma-cell/IL-6–driven lymphoproliferative disorder** with XBP1/ER-stress–associated plasma cell IL-6 production, thrombocytosis, hyperplastic germinal centers, and frequent IgG4 positivity requiring distinction from IgG4-RD

5. HHV-8+ MCD: **Virus-driven polyclonal plasmablastic lymphoproliferation** (characteristically IgM-λ restricted plasmablasts) with vIL-6/hIL-6–mediated cytokine storm

6. POEMS-Associated MCD: **Paraneoplastic manifestation of a clonal λ-restricted plasma cell disorder** with VEGF-driven systemic syndrome; classified separately from iMCD

Sokol L, unpublished, 2026.

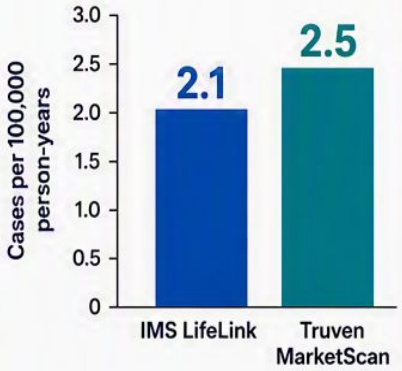
EPIDEMIOLOGY OF CASTLEMAN DISEASE

ANNUAL INCIDENCE IN THE UNITED STATES

2.1–2.5

cases per 100,000 person-years

Equivalent to approximately 21–25 cases per million person-years.



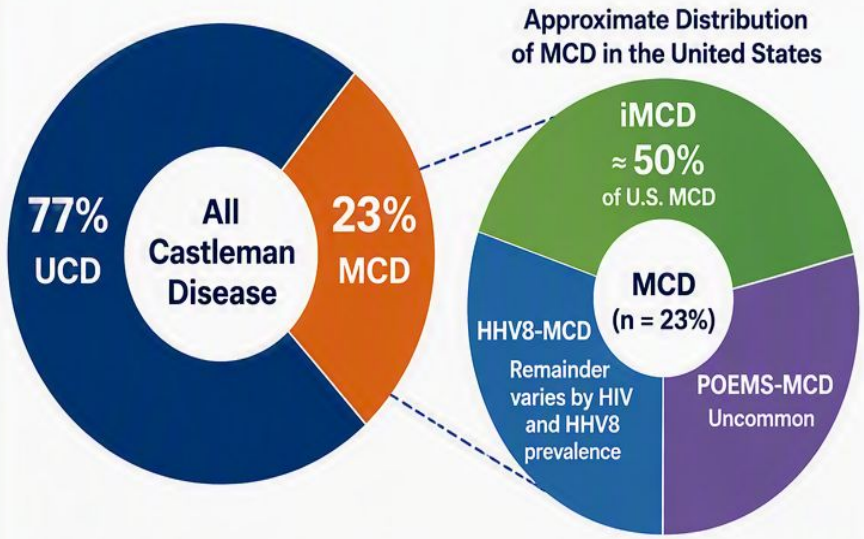
ESTIMATED ANNUAL U.S. DIAGNOSES*

~7,000–8,500 new cases/year

UCD	MCD	iMCD
~5,500–6,500 cases/year	~1,600–2,000 cases/year	~1,000–1,700 cases/year

**Population-scaled extrapolation from published incidence estimates; true incidence may differ because Castleman disease was historically underrecognized and lacked a dedicated ICD code prior to 2016.*

CASTLEMAN DISEASE CLASSIFICATION



Relative proportions vary according to HIV prevalence, HHV-8 seroprevalence, referral population, and geographic region.

DEMOGRAPHIC FEATURES

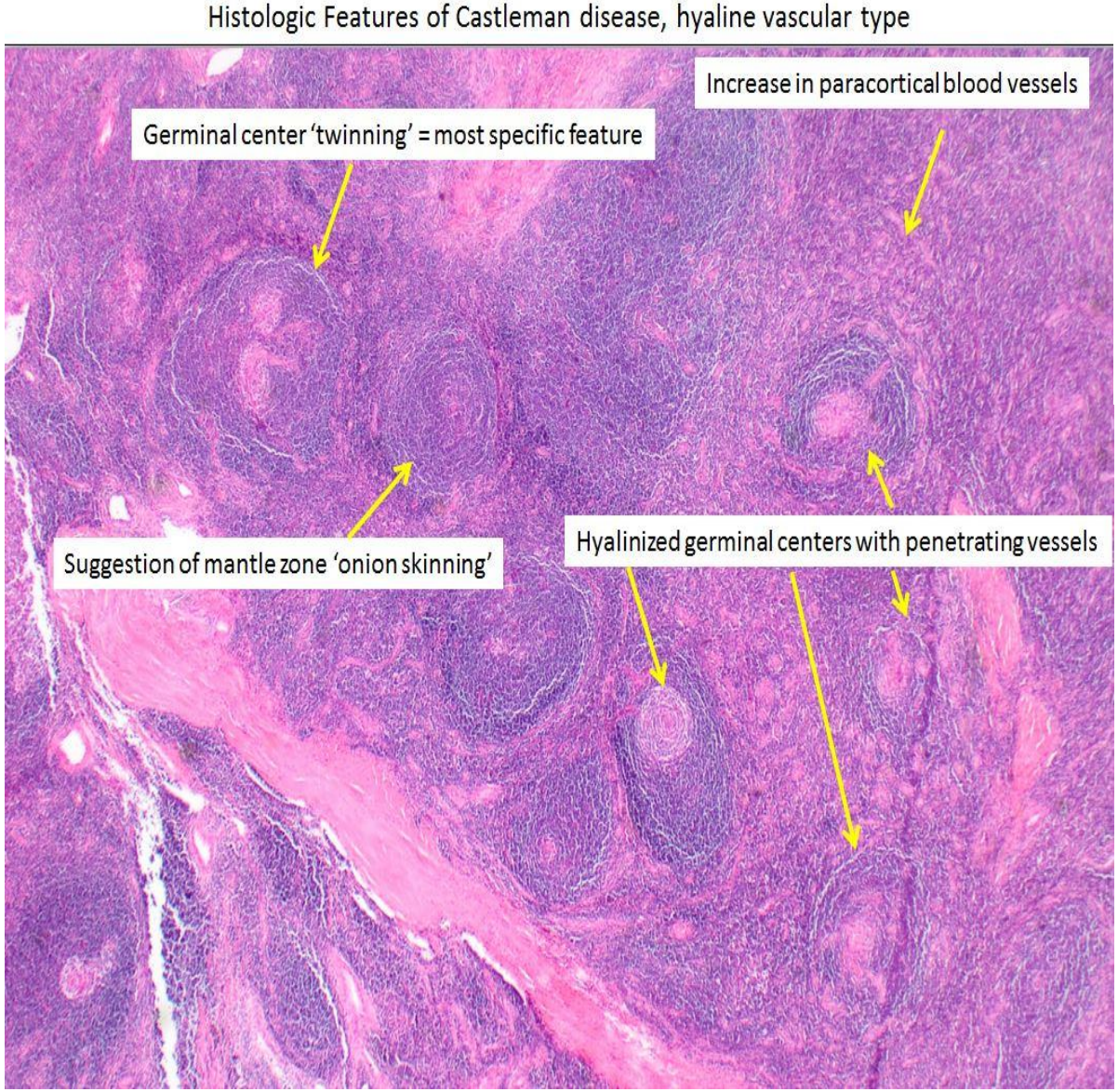
FEATURE	UCD	MCD (ALL SUBTYPES)
Median age at diagnosis	35–40 years	45–55 years
Sex distribution	Slight female predominance	Approximately equal M:F

REFERENCES

1. Munshi N, Mehra M, van de Velde H, et al. Use of a Claims Database to Characterize and Estimate the Incidence Rate for Castleman Disease. *Leuk Lymphoma.* 2015.
2. Simpson D. Epidemiology of Castleman Disease. *Hematol Oncol Clin North Am.* 2018.
3. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, Evidence-Based Consensus Diagnostic Criteria for HHV-8-negative/ idiopathic MCD. *Blood.* 2017.
4. Mukherjee S, Shupo F, Wayi-Wayi G, et al. Symptom Burden in Patients With iMCD and Its Impact on Daily Life: An International Patient and Caregiver Survey. *EClinicalMedicine.* 2023.

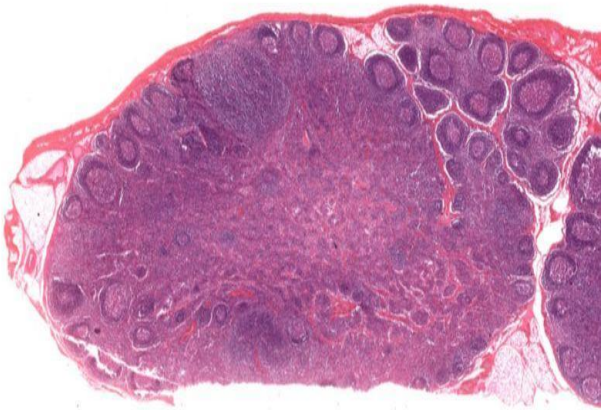
Sokol L, unpublished, AI-assisted figure, 2026.

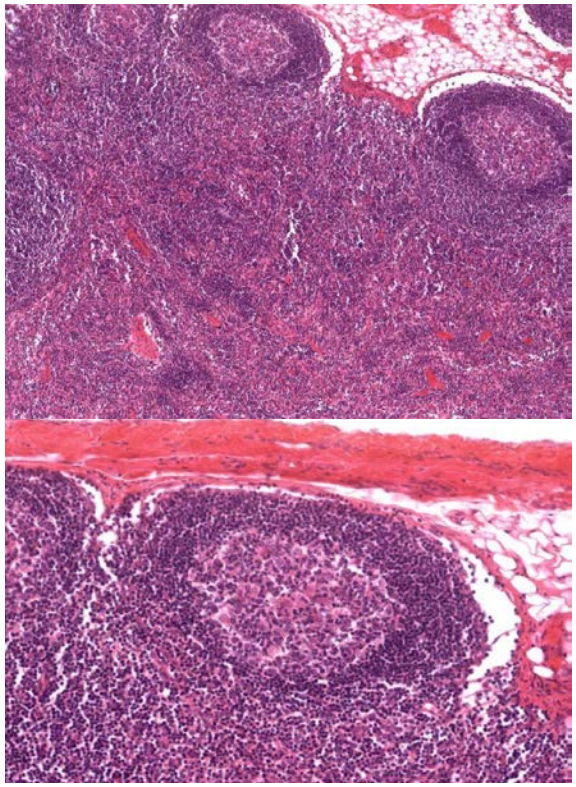
Castleman Disease and Normal Lymph Node Architecture



Michael Cascio, M.D.@mjcascio Pathology – Castleman disease.

Mediastinal mass in a younger woman [grepmed.com]

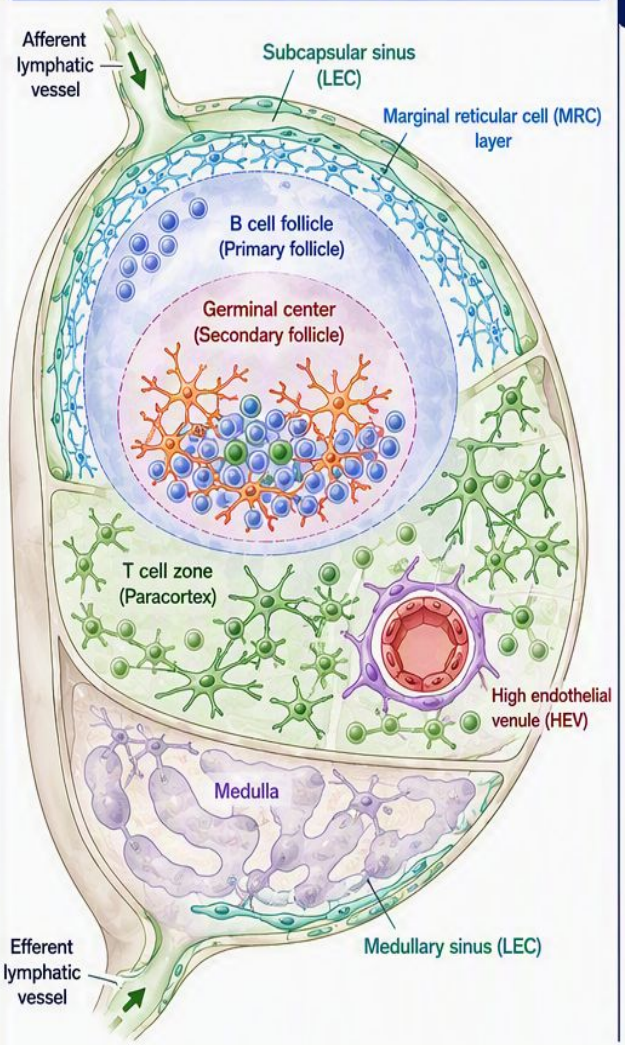




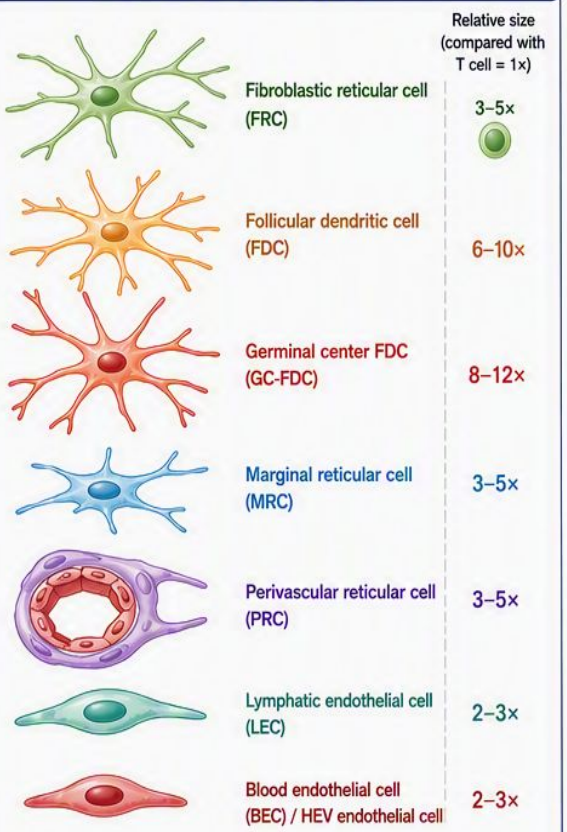
T. Clark Brelje and Robert L. Sorenson. MH 076-077-078 Lymph Node Chapter 10-Lymphoid Tissue 2005-2026

Lymph Node Stromal Cell Network and Cellular Crosstalk

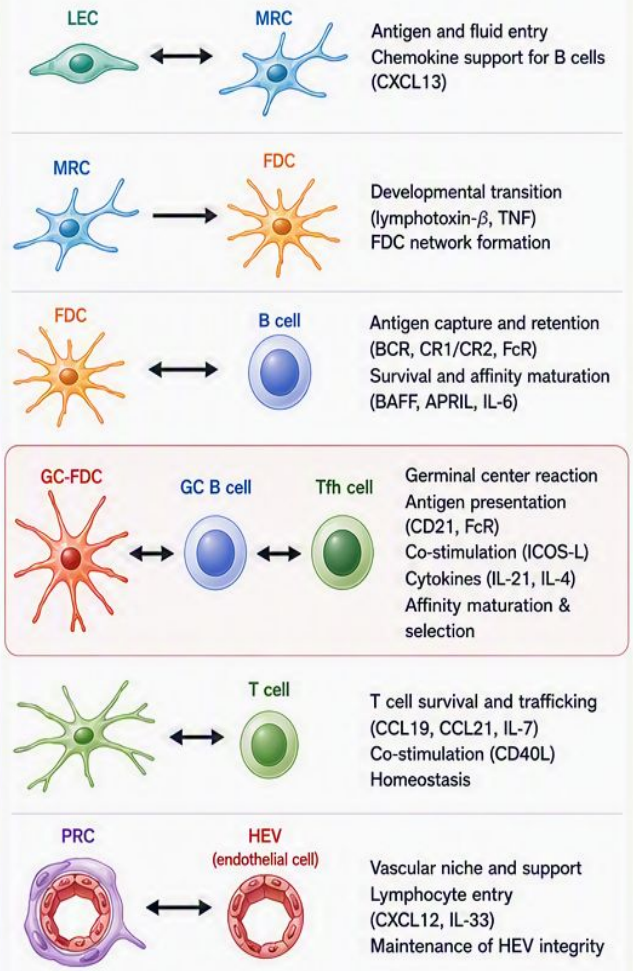
1. ANATOMIC COMPARTMENTS



2. STROMAL CELL POPULATIONS (relative to lymphocytes)



3. KEY CELL–CELL INTERACTIONS



FRC: Fibroblastic reticular cell
FDC: Follicular dendritic cell
GC-FDC: Germinal center FDC
MRC: Marginal reticular cell
PRC: Perivascular reticular cell
LEC: Lymphatic endothelial cell
BEC: Blood endothelial cell
HEV: High endothelial venule

B cell
T cell
T follicular helper (Tfh) cell

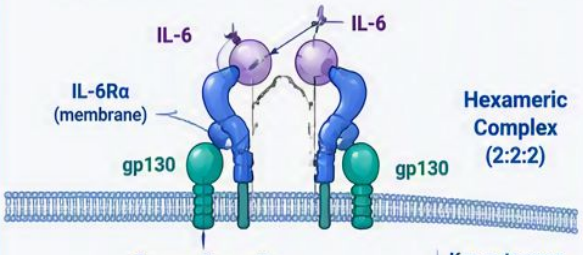
Arrows indicate major functional interactions. Multiple additional molecular interactions exist.

Sokol L, unpublished, AI-assisted figure, 2026.

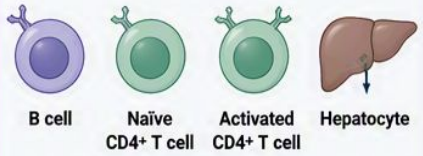
IL-6 Signaling Networks: Extracellular Mechanisms and Intracellular Pathways

A. CLASSIC SIGNALING

IL-6 binds membrane IL-6Rα on the same responding cell



Responding cells

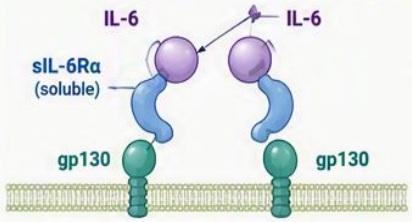


Key outcomes

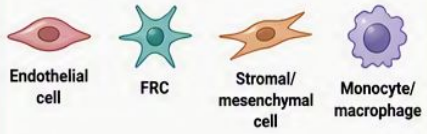
- Plasma-cell differentiation
- Immunoglobulin production
- Acute-phase response
- Tfh differentiation

B. TRANS-SIGNALING

IL-6 first complexes with soluble IL-6Rα and then binds gp130 on target cells



Responding cells (gp130+, IL-6Rα- or low)

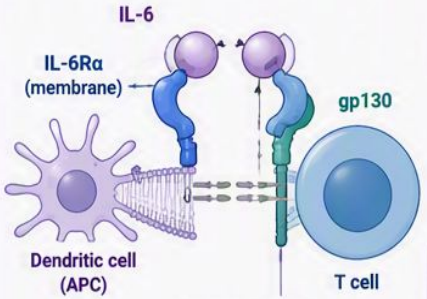


Key outcomes

- Endothelial activation
- Vascular leak
- Angiogenesis
- Cytokine amplification
- Stromal activation

C. TRANS-PRESENTATION

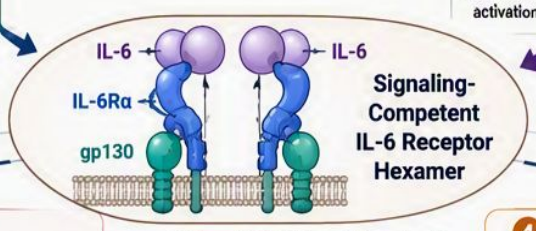
IL-6 bound to membrane IL-6Rα on APC is presented to gp130 on adjacent T cell



Responding cells

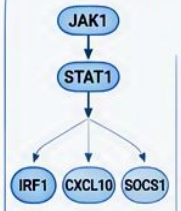
Key outcomes

- Tfh expansion
- IL-21 production
- CXCL13 production
- Germinal-Center activation



gp130-mediated intracellular signaling

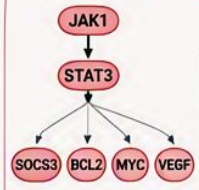
1 JAK1 → STAT1



Key functions

- Antiviral responses
- Antigen presentation
- Inflammation

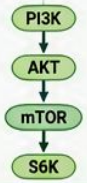
2 JAK1 → STAT3



Key functions

- Cell survival (anti-apoptosis)
- Proliferation
- Angiogenesis
- Inflammation

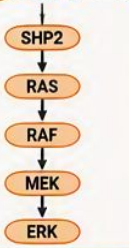
3 PI3K → AKT → mTOR



Key functions

- Cell survival
- Metabolism
- Protein synthesis

4 SHP2 → RAS → MAPK



Key functions

- Proliferation
- Cell growth
- Differentiation

5 YES1 → YAP/TAZ

Key functions

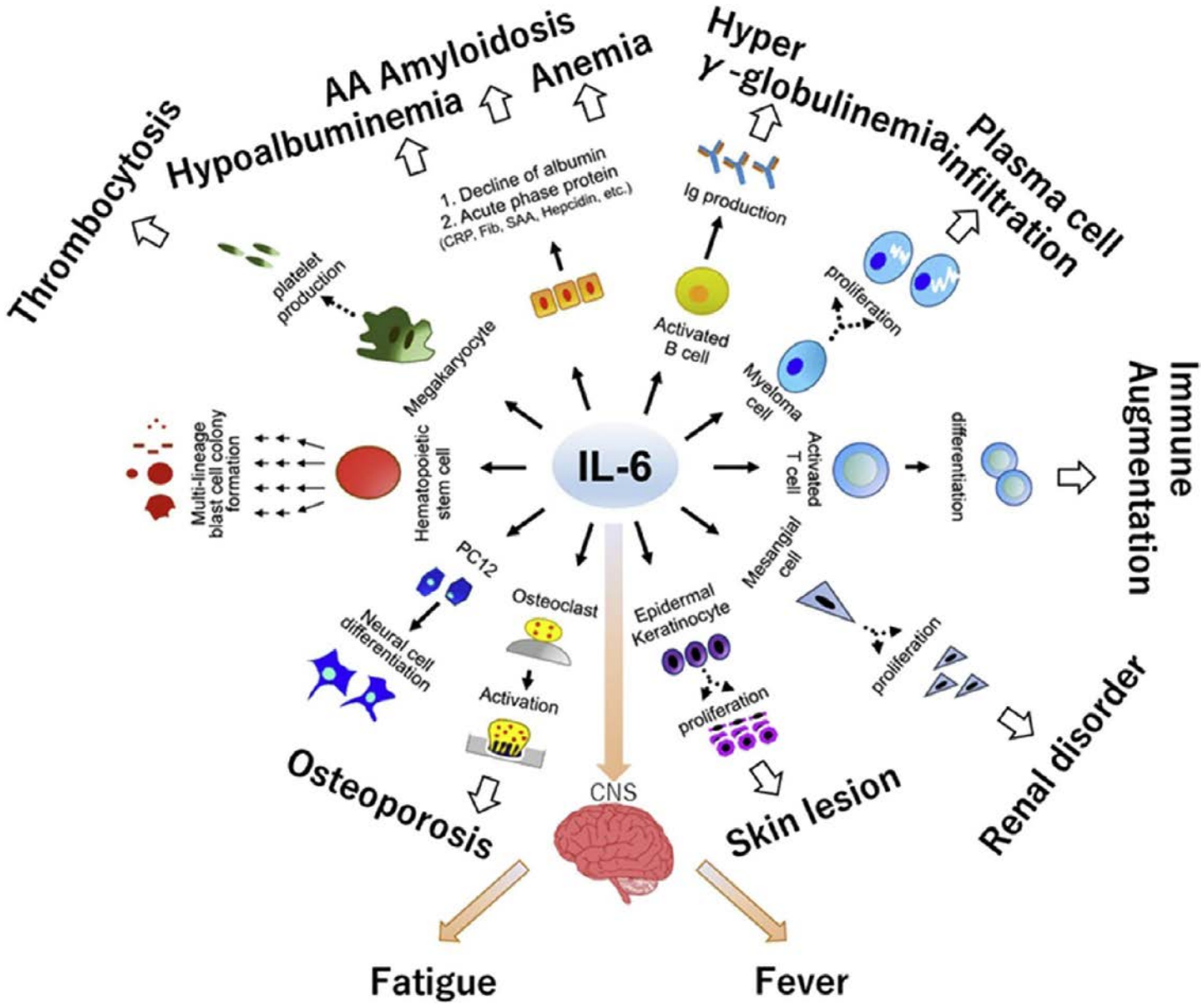
- Fibrosis
- Tissue remodeling
- Angiogenesis

Integrated Biological Outcomes

Key Concept: Three distinct extracellular IL-6 signaling mechanisms converge on a common hexameric receptor complex that activates multiple intracellular pathways driving diverse biological effects in health and disease.

Sokol L, unpublished, AI-assisted figure, 2026.

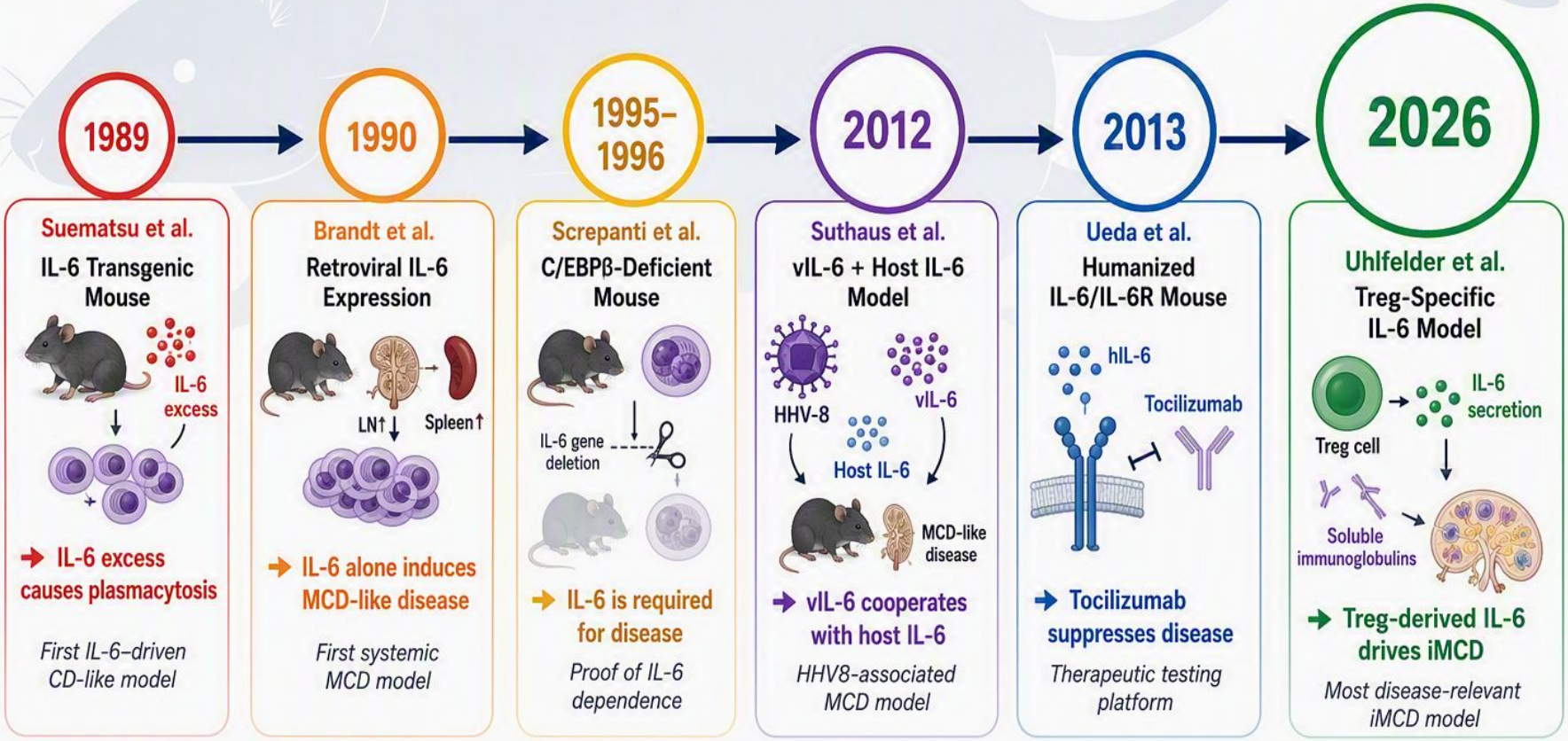
CENTRAL ROLE OF IL-6 IN CASTLEMAN DISEASE



Yoshizaki K et al. Hematology/Oncology Clinics of North America, 2018

From IL-6 Excess to iMCD: Evolution of Castleman Disease Biology in Mice

Experimental models recapitulating key features of Castleman disease, 1989–2026



IL-6 Excess → Systemic MCD → IL-6 Dependence → HHV8-MCD → Therapeutic Modeling → iMCD Biology

★ **Animal models evolved from demonstrating the consequences of IL-6 excess to reproducing subtype-specific Castleman disease biology and therapeutic responses.**

References: Suematsu 1989 | Brandt 1990 | Screpanti 1995/1996 | Suthaus 2012 | Ueda 2013 | Uhlfelder 2026

Sokol L, unpublished, AI-assisted figure, 2026.

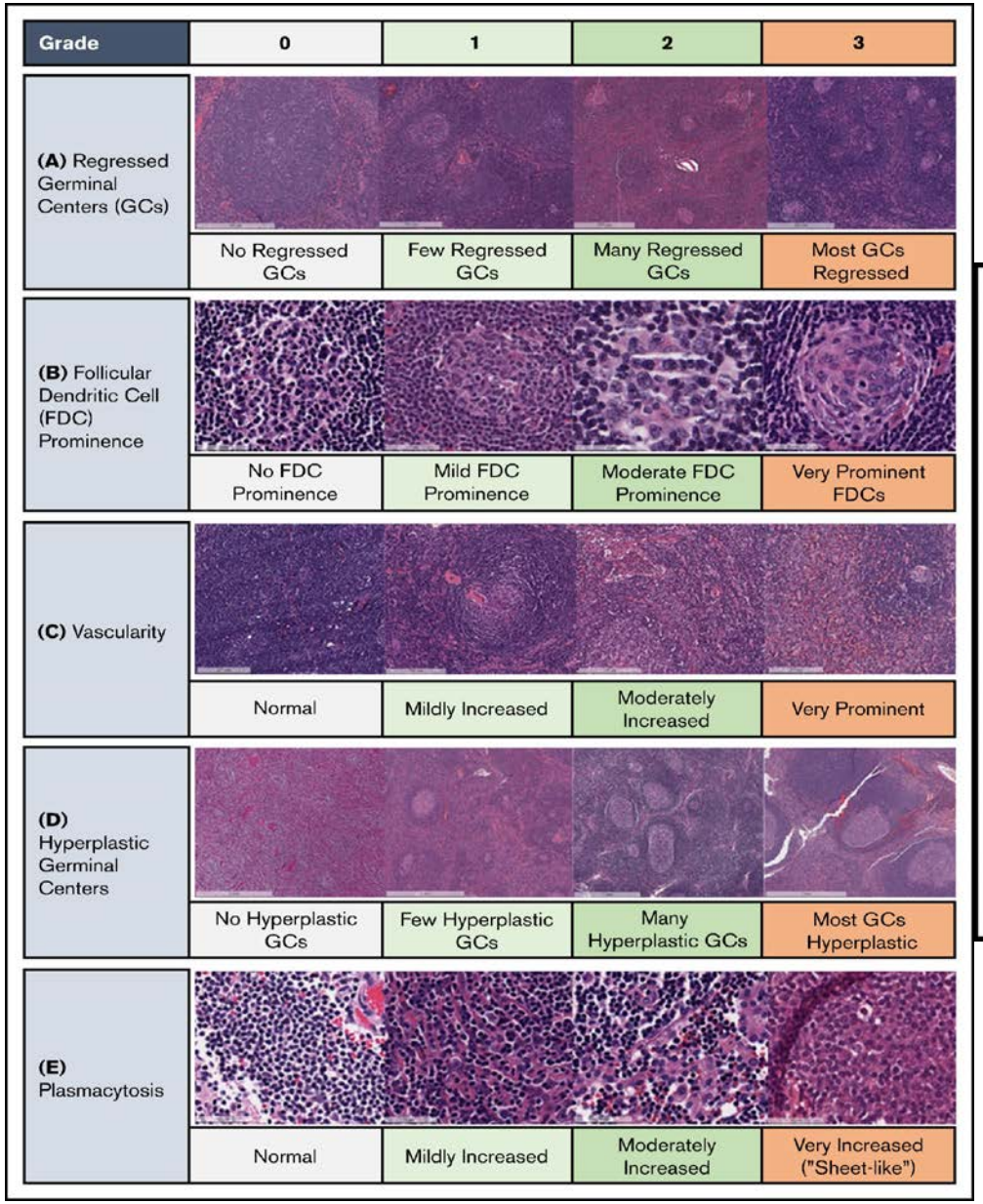
UNICENTRIC CASTLEMAN DISEASE

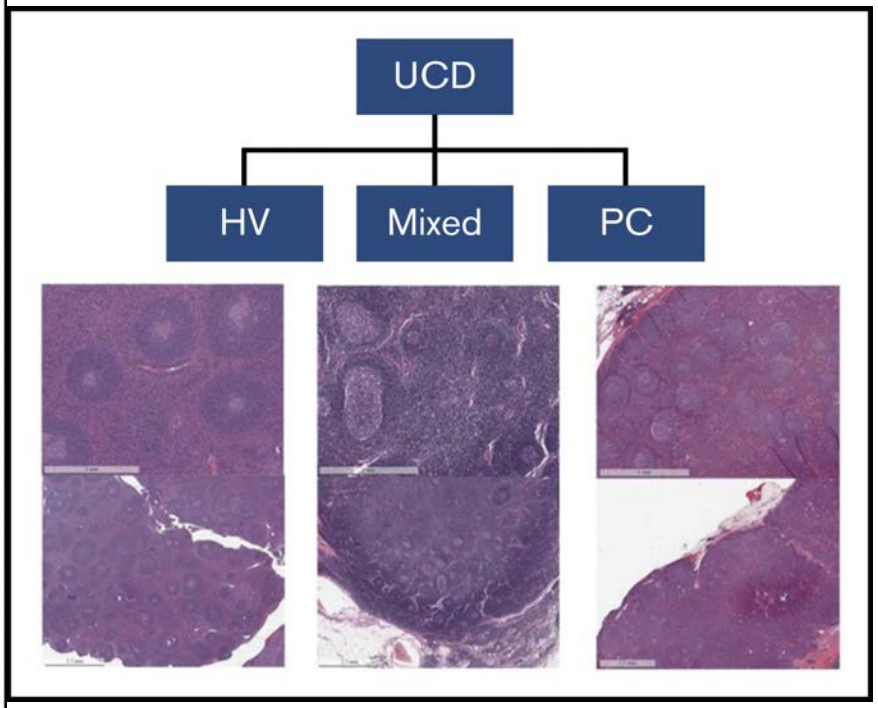
WHO-HAEM5 2024

Tumour-like lesions with B-cell predominance

Localized lymphoid/stromal proliferation

International Evidence-Based Consensus Diagnostic and Treatment Guidelines for Unicentric Castleman Disease





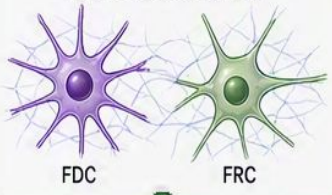
Frits van Rhee, Blood Adv, 2020.

Genetic and Molecular Landscape of Castleman Disease

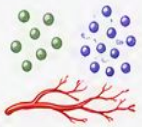
Distinct genetic, cellular, and cytokine features define unicentric and idiopathic multicentric Castleman disease subtypes

1. UCD
(Unicentric Castleman Disease)

PRINCIPAL DRIVER CELL
FDC/FRC stromal cell



DOMINANT CYTOKINES / CHEMOKINES
- IL-6
- CXCL13
- VEGF

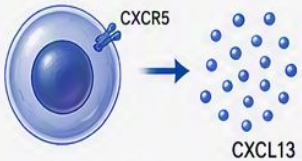


MAJOR GENETIC DRIVERS
- *PDGFRB* N666S (9–17%) *
- *KRAS*
- *MAP2K1*
- *BRAF*

DOMINANT SIGNALING PATHWAYS
- PDGFRB–MAPK
- PI3K–AKT–mTOR
- VEGF / Angiogenesis
- JAK–STAT3

2. iMCD-NOS
(Idiopathic MCD-NOS)

PRINCIPAL DRIVER CELL
T peripheral helper (TPH) cell



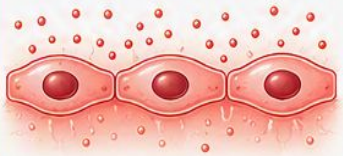
DOMINANT CYTOKINES / CHEMOKINES
- CXCL13
- IL-6
- IL-10

REPORTED SOMATIC VARIANTS
- *NCOA4*
- *DNMT3A*
- *TET2*
- *KMT2D*

DOMINANT SIGNALING PATHWAYS
- JAK–STAT3
- B-cell activation
- Cytokine storm network
- PI3K–AKT–mTOR

3. iMCD-TAFRO
(Idiopathic MCD-TAFRO)

PRINCIPAL DRIVER CELL
Activated vascular endothelial cell



DOMINANT CYTOKINES / CHEMOKINES
- VEGF
- CXCL10
- IL-6

REPORTED SOMATIC VARIANTS
- *MEK2*
- *RUNX1*
- *DNMT3A*
- *TET2*

DOMINANT SIGNALING PATHWAYS
- Type I IFN signaling
- VEGF / Endothelial activation
- JAK–STAT3
- PI3K–AKT–mTOR

4. iMCD-IPL
(Idiopathic MCD-IPL)

PRINCIPAL DRIVER CELL
Plasma cell / plasmablast

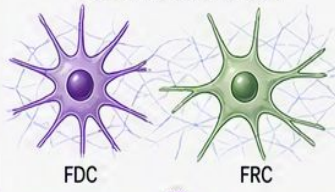
DOMINANT CYTOKINES / CHEMOKINES
- IL-6
- IL-10

REPORTED SOMATIC VARIANTS
- *NCOA4*
- *TET2*
- *KMT2D*
- *ARID1A*

DOMINANT SIGNALING PATHWAYS
- IL6–JAK–STAT3
- Plasma-cell differentiation
- B-cell activation
- Immunoglobulin synthesis

5. UCD-PNP
(Unicentric Castleman Disease–Paraneoplastic Pemphigus)

PRINCIPAL DRIVER CELL
FDC/FRC stromal cell



DOMINANT CYTOKINES / CHEMOKINES
- IL-6
- CXCL13

MAJOR GENETIC DRIVERS

• *IL6ST* (gp130) mutation	32%
• *PDGFRB* mutation	32%

OTHER RECURRENT SOMATIC ALTERATIONS

• *DPP6* mutation	18%
• *MUC4* mutation	18%

DOMINANT SIGNALING PATHWAYS
- IL6ST (gp130)–JAK–STAT3
- PDGFRB–MAPK
- PDGFRB–PI3K–AKT
- Autoimmunity / B-cell activation

Reported somatic variants have been identified in sequencing studies but are not yet established as subtype-defining pathogenic drivers.

Frequencies are shown only for genomic alterations with reproducible prevalence estimates in published Castleman disease cohorts.

* *PDGFRB* N666S reported in 9–17% of UCD cases.

ABBREVIATIONS:

UCD, unicentric Castleman disease; iMCD, idiopathic multicentric Castleman disease; NOS, not otherwise specified; IPL, idiopathic plasmacytic lymphadenopathy; PNP, paraneoplastic pemphigus; FDC, follicular dendritic cell; FRC, fibroblastic reticular cell.

KEY REFERENCES:

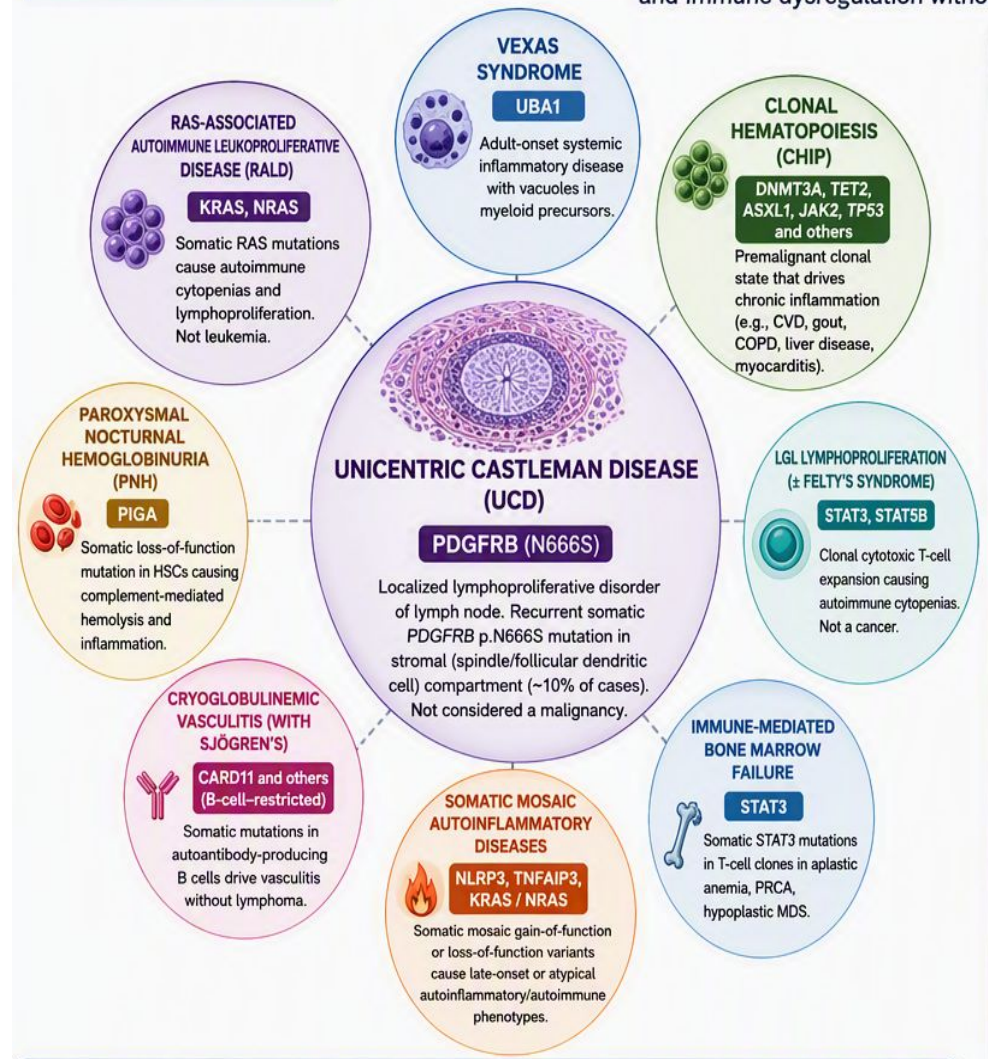
1. Li Z, et al. Recurrent *PDGFRB* mutations in unicentric Castleman disease. *Am J Med Genet A.* 2017;173(5):1251–1256.
2. Oksenhendler E, et al. Unicentric Castleman disease: clinical and molecular features. *Br J Haematol.* 2026;202:29–41.
3. Wang S, et al. Whole-exome sequencing reveals the genomic profile and IL6ST variants as a prognostic biomarker of PNP-associated UCD. *J Invest Dermatol.* 2024;144:585–592.e1.

- Cytokines / Chemokines
- Genetic alterations
- Signaling pathways

Sokol L, unpublished, AI-assisted figure, 2026

Non-Malignant Inflammatory Disorders Driven by Somatic Mutations

Acquired (postzygotic) somatic mutations in hematopoietic or stromal cells can directly drive chronic inflammation and immune dysregulation without meeting criteria for cancer.



Key Entities at a Glance

Entity	Somatic Mutation(s)	Concise Characterization (Non-Malignant)
VEXAS Syndrome	*UBA1*	Myeloid-restricted *UBA1* mutations cause systemic inflammation (relapsing polychondritis, PAN, Sweet's syndrome, GCA). Frequently coexists with MDS but is not a malignancy.
Clonal Hematopoiesis (CHIP)	*DNMT3A, TET2, ASXL1, JAK2, TP53* and others	Age-related clonal hematopoiesis that promotes chronic inflammation and systemic diseases (e.g., atherosclerotic CVD, heart failure, gout, COPD, liver disease, myocarditis, pericarditis).
LGL Lymphoproliferation (± Felty's Syndrome)	*STAT3, STAT5B*	Expanded cytotoxic T-cell clones with STAT3/5B mutations target hematopoietic progenitors, causing autoimmune cytopenias. Not a cancer.
Immune-Mediated Bone Marrow Failure	*STAT3*	Somatic *STAT3* mutations in T-cell clones in aplastic anemia, pure red cell aplasia, and hypoplastic MDS.
Somatic Mosaic Autoinflammatory Diseases	*NLRP3, TNFAIP3, KRAS / NRAS*	Somatic mosaic mutations drive autoinflammatory/autoimmune syndromes (e.g., CAPS due to *NLRP3*, A20 haploinsufficiency due to *TNFAIP3*, *RAS*-associated autoimmune disease).
Cryoglobulinemic Vasculitis (with Sjögren's)	*CARD11* and others (B-cell–restricted)	Somatic mutations in autoantibody-producing memory B cells drive cryoglobulinemic vasculitis without constituting lymphoma.
Unicentric Castleman Disease (UCD)	*PDGFRB* (N666S)	Localized lymph node disease with recurrent somatic *PDGFRB* p.N666S mutation in stromal (spindle/FDC) cells (~10% of cases). Activated stromal cells produce IL-6, VEGF and other inflammatory mediators. Not a malignancy.
Paroxysmal Nocturnal Hemoglobinuria (PNH)	*PIGA*	Somatic loss-of-function mutation in *PIGA* in HSCs leads to complement-mediated hemolysis and inflammation. A benign clonal disorder.

These disorders illustrate that somatic mutations can create clonal immune or stromal populations that drive inflammation without meeting criteria for cancer.

Shared principles: Somatic (acquired) mutations occur after conception → present in a subset of cells (mosaicism or clones). Variant allele fraction (VAF) can rise during flares and fall during remission → important diagnostic and therapeutic implications. Many of these genes are also implicated in inherited autoinflammatory syndromes and in cancers; phenotype depends on cell lineage, clonal dynamics, and VAF.

Abbreviations: CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; FDC, follicular dendritic cell; GCA, giant cell arteritis; HSC, hematopoietic stem cell; IL-6, interleukin-6; MAPK, mitogen-activated protein kinase; MDS, myelodysplastic syndrome; PAN, polyarteritis nodosa; PRCA, pure red cell aplasia; VEGF, vascular endothelial growth factor.

Selected References:

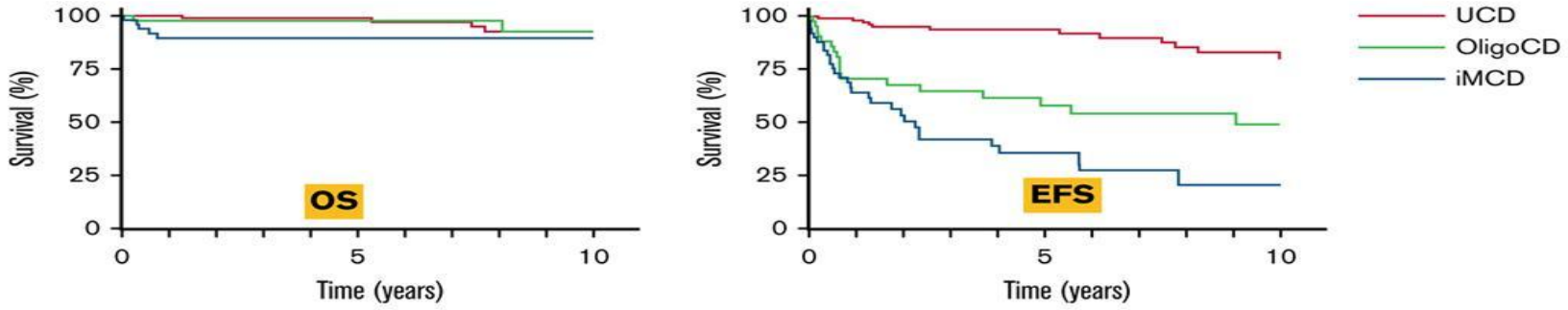
1. Beck DB, et al. *N Engl J Med.* 2020;383:2628–2638.
2. Butzmann A, et al. *Biology (Basel).* 2021;10:251.
3. Roujohn G, et al. *Blood.* 2023;141:2425–2438.
4. Cocco M, et al. *Leukemia.* 2020;34:243–252.
5. Loughran TP Jr. *Blood.* 2021;137:1082–1093.
6. Ombrello AK, et al. *J Exp Med.* 2017;214:1411–1423.
7. Lamy T, et al. *Nat Rev Rheumatol.* 2021;17:391–404.
8. Jaiswal S, et al. *N Engl J Med.* 2014;371:2488–2498.
9. Genovese G, et al. *Nat Rev Rheumatol.* 2017;13:10–24.
10. Fuster JJ, et al. *N Engl J Med.* 2017;377:377:111–121.

Sokol L, unpublished, AI-assisted figure, 2026.

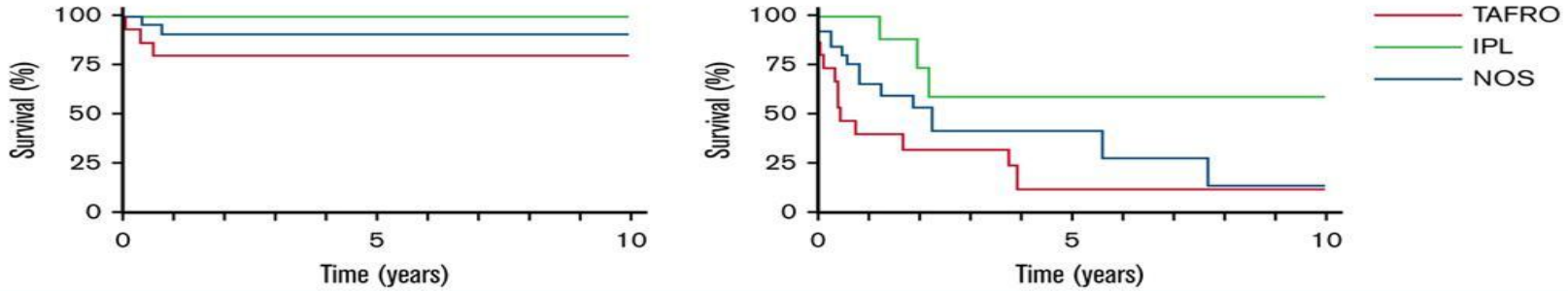
Comprehensive analysis of subtype-specific outcomes and management in Castleman disease: a 20-year cohort study

Subtype-Specific Outcomes and Management in Castleman Disease

OligoCD: Intermediate EFS between UCD and iMCD



iMCD-IPL: Higher OS and EFS than iMCD-TAFRO & NOS



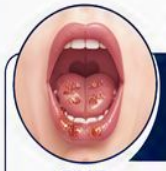
Conclusions: **The survival outcome in OligoCD was intermediate between UCD and iMCD. iMCD-IPL had a favorable survival outcome similar to non-Western countries.**

*Nishimura et al. DOI: 10.1182/**bloodadvances**.2025018324*

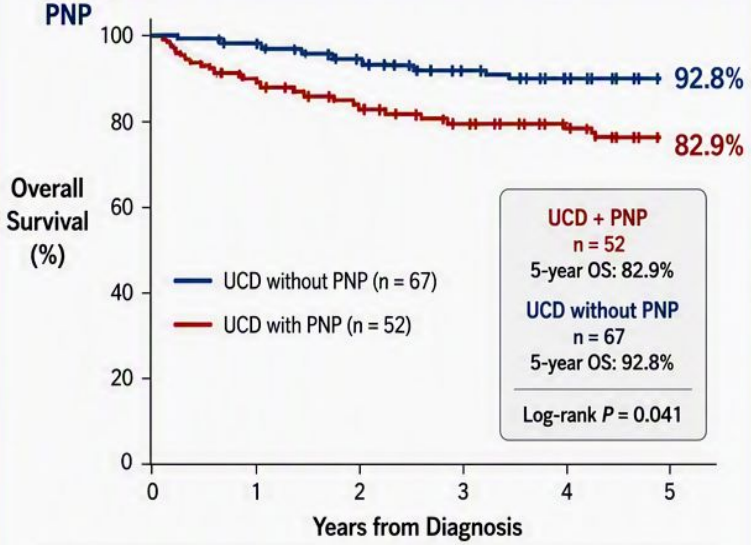
blood advances Visual Abstract

Paraneoplastic Pemphigus and Bronchiolitis Obliterans Define High-Risk UCD Phenotypes

Complete surgical resection is usually curative, but autoimmune complications are associated with inferior survival



A. Paraneoplastic Pemphigus (PNP) Adversely Impacts Survival



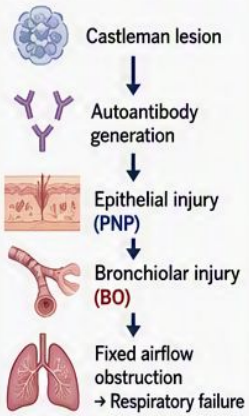
PNP identifies a biologically distinct UCD subset associated with significantly inferior overall survival despite localized disease.

Source: *Retrospective cohort evaluation of non-HIV Castleman disease from a single academic center in Beijing, China. Blood Adv. 2023.* Total UCD = 119; UCD with PNP = 52; without PNP = 67

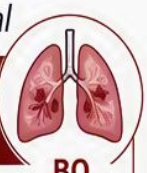
KEY FINDING

Autoimmune complications, rather than the Castleman lesion itself, account for most excess mortality in UCD.

PROPOSED PATHOBIOLOGY



B. Bronchiolitis Obliterans (BO) Represents the Highest-Risk UCD Phenotype



UCD + BO

18 of 281 patients (6.4%)

PNP present in 83.3%

Severe BO in 83.3%

Overall survival significantly inferior compared with UCD without BO

Severe BO (without transplant)

5-year OS: **62.5%**

(95% CI, 20.8–100%)

LUNG TRANSPLANTATION

- 4 of 4 patients survived (100%)
- No BO recurrence
- No UCD recurrence

Source: *Liu YT, et al. Br J Haematol. 2025;206:1129–1135.* Total UCD = 281; UCD with BO = 18; without BO = 263

CLINICAL CONTINUUM IN UCD

Typical UCD
Localized lymphoproliferative disorder
Excellent long-term survival

→

UCD + PNP
Autoimmune mucocutaneous disease
Inferior overall survival

→

UCD + PNP/BO
Autoimmune bronchiolar injury
Progressive airflow obstruction
High risk of respiratory failure

→

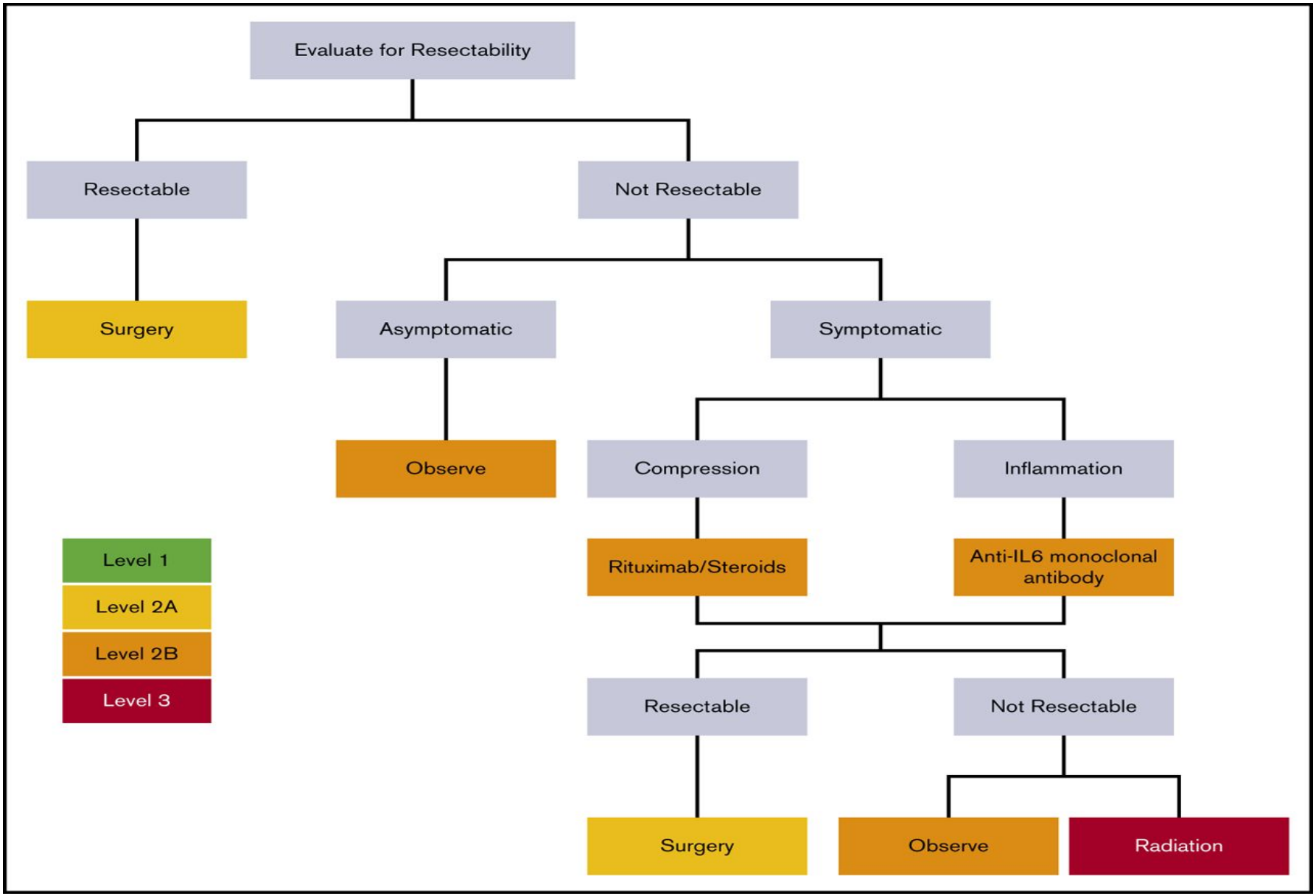
Respiratory Failure
Major cause of UCD-related mortality

UCD is typically curable with complete surgical excision. However, development of PNP and particularly BO identifies a rare but clinically distinct subgroup characterized by persistent autoimmune injury, respiratory failure risk, and significantly worse survival.

UCD, unicentric Castleman disease; PNP, paraneoplastic pemphigus; BO, bronchiolitis obliterans; OS, overall survival; CI, confidence interval.

Sokol L, unpublished, AI-assisted figure, 2026,

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



Frits van Rhee, Blood Adv, 2020

IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE

WHO-HAEM5 2024

Tumor-like lesions with B cell predominance

Systemic inflammatory lymphoproliferative disorder

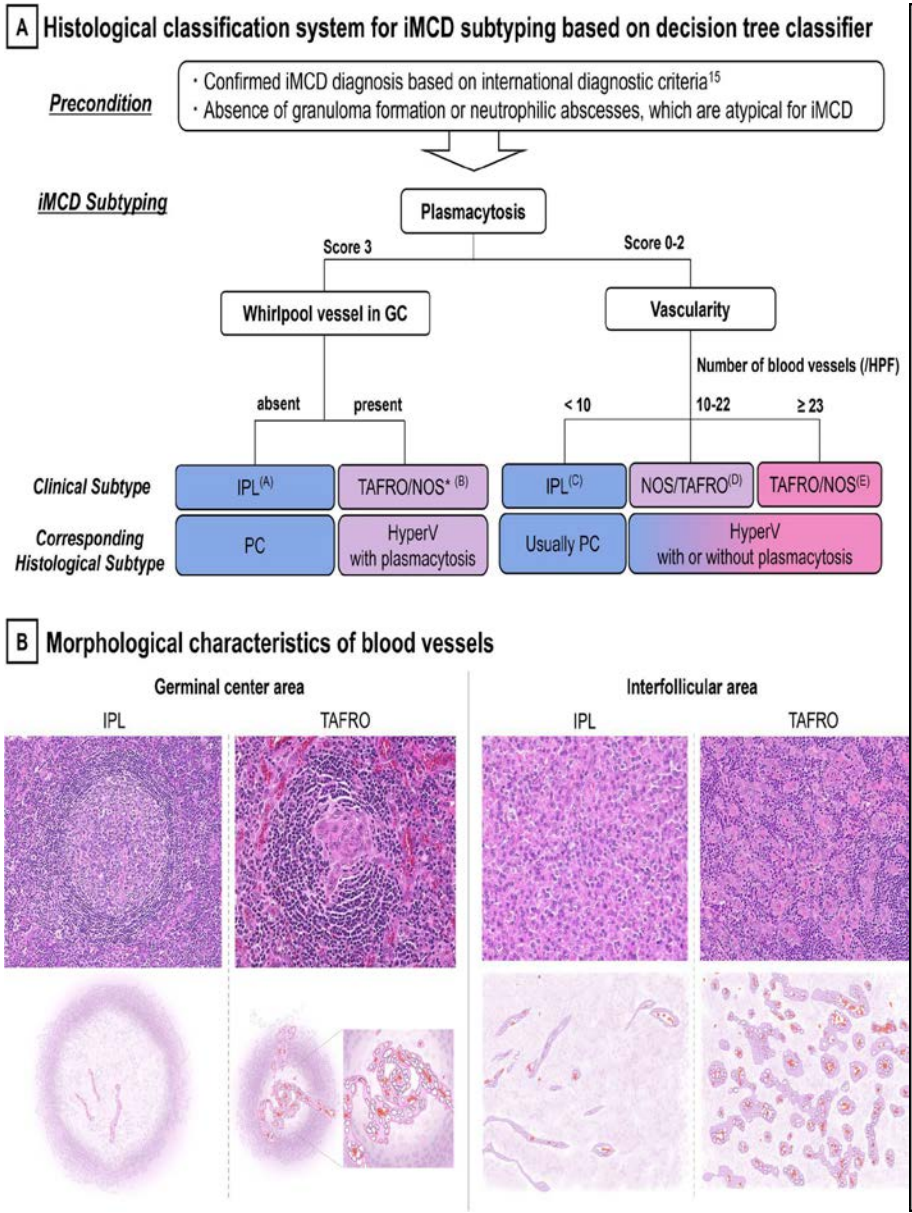
Consensus Diagnostic Criteria for Idiopathic MCD[a]		
I. Major Criteria (need both):	1. Histopathologic lymph node features consistent with the iMCD spectrum. Features along the iMCD spectrum include (need grade 2–3 for either regressive GCs or plasmacytosis at minimum): - Regressed/atrophic/atretic germinal centers, often with expanded mantle zones composed of concentric rings of lymphocytes in an "onion skinning" appearance - FDC prominence - Vascularity, often with prominent endothelium in the interfollicular space and vessels penetrating into the GCs with a "lollipop" appearance - Sheetlike, polytypic plasmacytosis in the interfollicular space - Hyperplastic GCs 2. Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations	
II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)	Laboratory* 1. Elevated CRP (>10 mg/L) or ESR (>15 mm/h)† 2. Anemia (hemoglobin <12.5 g/dL for males, hemoglobin <11.5 g/dL for females) 3. Thrombocytopenia (platelet count <150 μ/mL) or thrombocytosis (platelet count >400 μ/mL) 4. Hypoalbuminemia (albumin <3.5 g/dL) 5. Renal dysfunction (eGFR <60 mL/min/1.73m^2) or proteinuria (total protein 150 mg/24 h or 10 mg/100 mL) 6. Polyclonal hypergammaglobulinemia (total γ globulin or immunoglobulin G >1700 mg/dL)	Clinical 1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (≥2 CTCAE lymphoma score for B-symptoms) 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
III. Exclusion Criteria (must rule out each of these diseases that can mimic iMCD)	Infection-related disorders 1. HHV-8 (infection can be documented by blood PCR; diagnosis of HHV-8–associated MCD requires positive LANA-1 staining by IHC, which excludes iMCD) 2. Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (detectable EBV viral load not necessarily exclusionary) 3. Inflammation and adenopathy caused by other uncontrolled infections (eg, acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis)	Autoimmune/autoinflammatory diseases (requires full clinical criteria; detection of autoimmune antibodies alone is not exclusionary) 1. Systemic lupus erythematosus 2. Rheumatoid arthritis 3. Adult-onset Still disease 4. Juvenile idiopathic arthritis 5. Autoimmune lymphoproliferative syndrome Malignant/lymphoproliferative disorders (these disorders must be diagnosed before or at the same time as iMCD to be exclusionary): 1. Lymphoma (Hodgkin and non-Hodgkin) 2. Multiple myeloma 3. Primary lymph node plasmacytoma 4. FDC sarcoma 5. POEMS syndrome‡

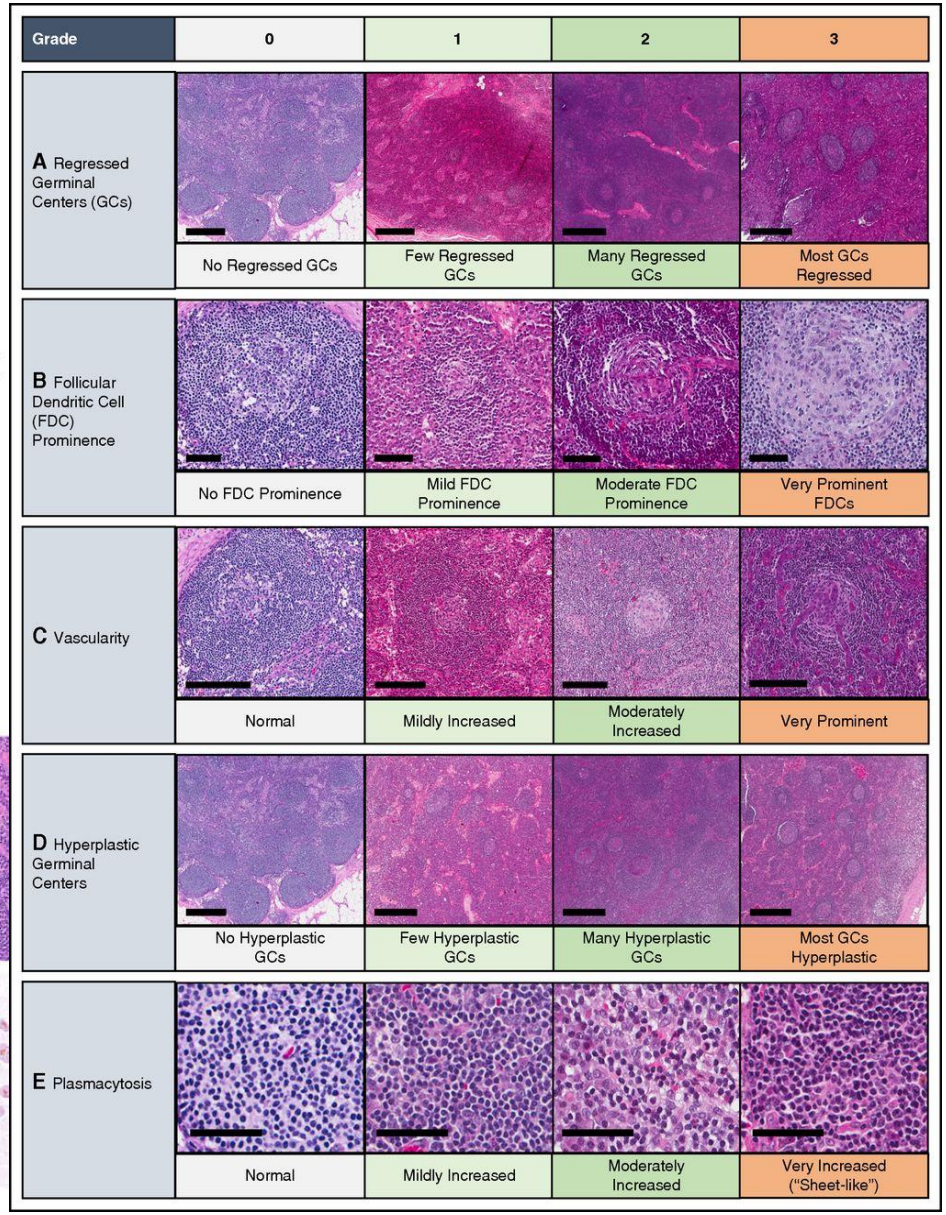
[a] Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129:1646-1657.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

International Consensus Histopathological Criteria for Subtyping Idiopathic Multicentric Castleman Disease Based on Machine Learning Analysis





Nishimura et al. AJH 2025

Fajgenbaum et al. Blood 2017

Principal Cellular Drivers and Cytokines in Subtypes of iMCD

	iMCD-NOS (Not Otherwise Specified)	iMCD-TAFRO	iMCD-IPL
PRINCIPAL CELLULAR DRIVER(S)	**T peripheral helper (Tph) cells** CXCL13-producing Tfh-like cells in germinal centers *Polyclonal*	**Vascular endothelial cells** VEGF/IL-6–driven endothelial activation *Polyclonal; possible clonal contribution (MEK2/RUNX1 mutations) in a subset*	**Plasma cells** XBP1/ER-stress–associated plasma cell IL-6 production *Polyclonal*
KEY CYTOKINES / CHEMOKINES	**CXCL13** (key pathogenic driver) IL-6, IL-10, IL-1β	**IL-6** (central) **VEGF** (key driver) IL-1β, IL-8, TNF-α	**IL-6** (central) IL-10, BAFF (± IgG4–related cytokines)
KEY CLINICAL FEATURES	• Polyclonal systemic inflammatory syndrome • Fever, constitutional symptoms, lymphadenopathy • Normal or ↑ platelets	• Thrombocytopenia • Anasarca (edema, effusions), ascites • Fever, organomegaly • Reticulin fibrosis (bone marrow) • Renal dysfunction	• Thrombocytosis • Hyperplastic germinal centers • Hypergammaglobulinemia, frequent IgG4 positivity • Lymphadenopathy
NOTES	Emerging evidence implicates Tph cell–derived CXCL13 as a key pathogenic driver.	Distinctive clinical syndrome driven by VEGF/IL-6–mediated endothelial activation. Nosologic relationship to iMCD debated.	Polyclonal plasma cell–driven disorder associated with ER stress (XBP1). Important to distinguish from IgG4-RD.

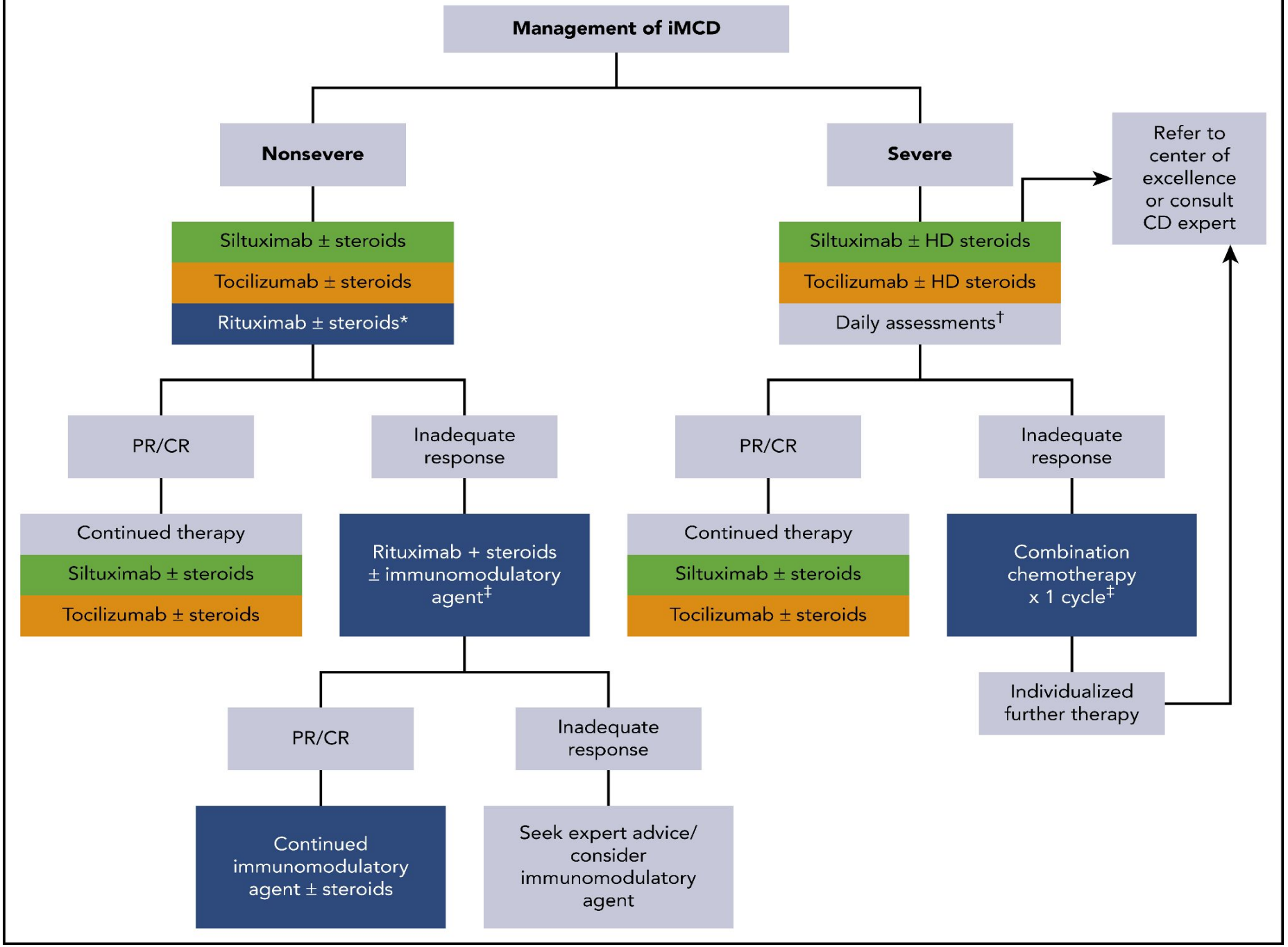
Sources: Harada T et al. *Nat Commun.* 2023;14:7417. Goubran M. *Haematologica.* 2026;111:xxx–xxx (Editorial). **Abbreviations:** ER, endoplasmic reticulum; Tfh, T follicular helper; iMCD, idiopathic multicentric Castleman disease.

Sokol L, unpublished, AI-assisted figure, 2026,

Clinical Studies in Multicentric Castleman Disease

Feature	Siltuximab	Tocilizumab	Rituximab
Disease	iMCD (HIV-/HHV8-)	MCD (Japan)	HHV8+/KSHV-MCD
Target	IL-6	IL-6R	CD20
Key study	van Rhee 2014	Nishimoto studies	Bower 2007
Design	Randomized Phase II	Open-label	Open-label Phase II
Dosing/schedule	11 mg/kg IV q 3 weeks until treatment failure	8 mg/kg IV q 2 weeks continuous therapy	375 mg/m2 IV weekly x 4 4 doses only
N (pts)	79	35	21
Clinical response	34% durable response vs 0%	Major symptom/lab improvement	95% symptom remission
Radiologic response	38%	LN regression majority >50%	67%
PFS/EFS	PFS NR vs 14.5 mo placebo	NR	2-yr DFS 79%
OS	NR	NR	2-yr OS 95%
Long-term data	Sustained disease control	>5 yr benefit	5-yr OS 92%; RFS 82%

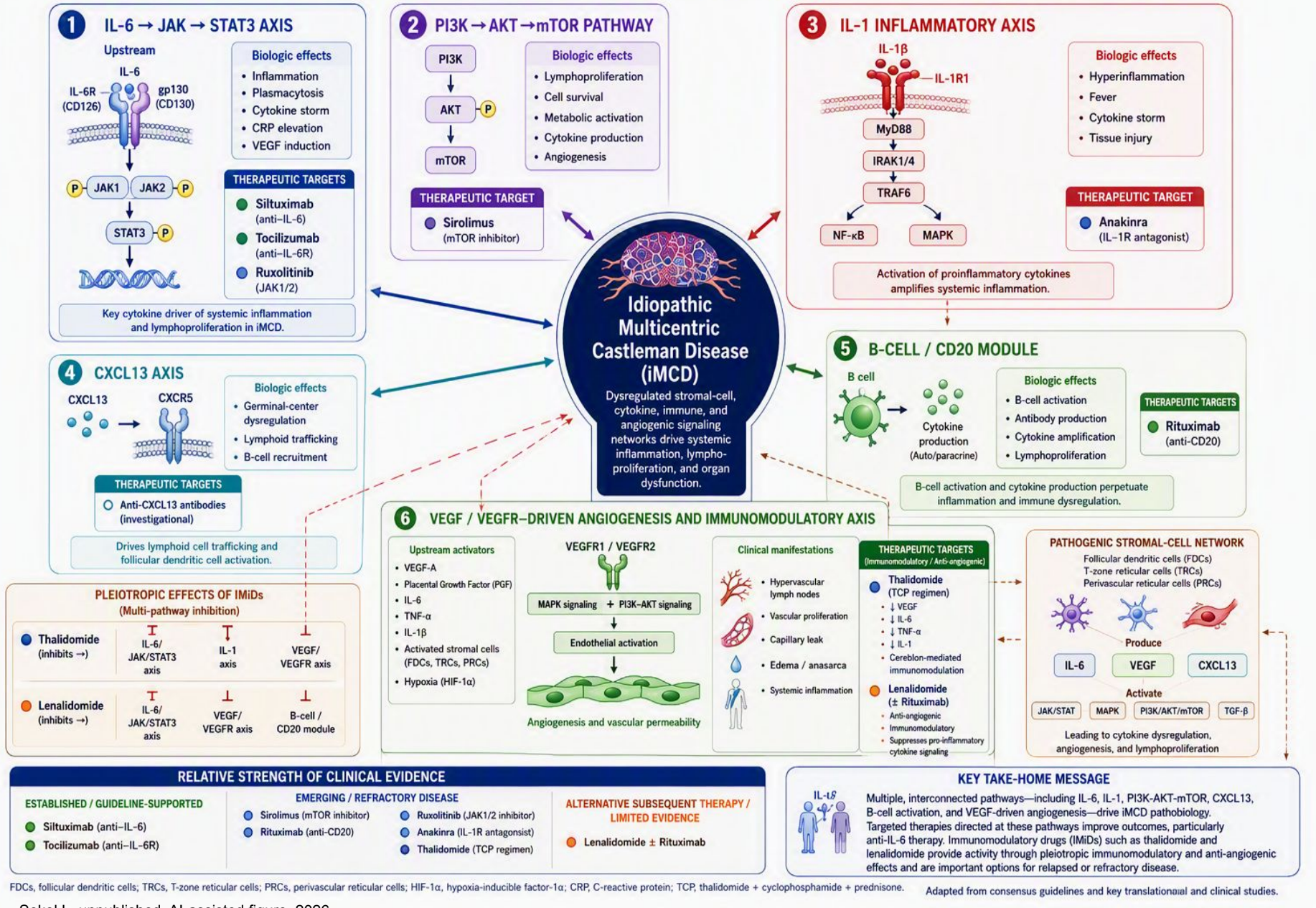
Sokol L, unpublished, 2026.



Dispenzieri A et al. Blood 2020.

Key Upregulated Pathways and Therapeutic Targets in Idiopathic Multicentric Castleman Disease (iMCD)

Integration of cytokine, stromal-cell, angiogenic, and immune signaling pathways with established and emerging therapeutic targets



Sokol L, unpublished, AI-assisted figure, 2026.

POEMS-ASSOCIATED MCD

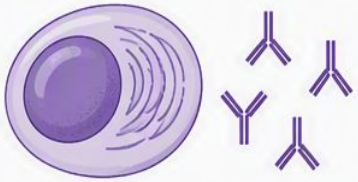
POEMS-ASSOCIATED MULTICENTRIC CASTLEMAN DISEASE

Pathobiology: Key Pathways and Cytokines

Paraneoplastic syndrome driven by an underlying λ-restricted plasma cell clone

1 CENTRAL PATHOGENIC AXIS

λ-RESTRICTED PLASMA CELL CLONE



Monoclonal plasma cell clone secretes cytokines and growth factors

OVERPRODUCTION OF PRO-INFLAMMATORY MEDIATORS
(Central driver)

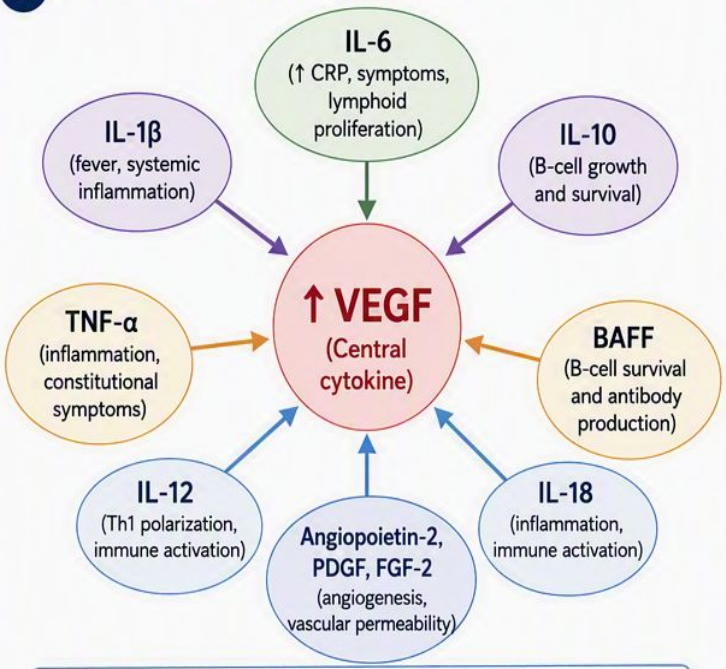
Key features supported by evidence

- Monoclonal plasma cell disorder
- Almost universally λ light-chain restricted
- Highly restricted immunoglobulin gene usage
  - IGLV1-40
  - IGLV1-44
  - IGLV1-36
  - IGLV1-47
- Somatic mutations within the variable region of Ig genes
- Distinct genomic landscape from multiple myeloma

POEMS-associated MCD manifestations

- Angiogenesis (e.g., MCD lymphadenopathy)
- Vascular leak and edema
- Immune activation and systemic inflammation
- End-organ dysfunction (neuropathy, endocrinopathy, etc.)

2 KEY CYTOKINES AND PATHWAYS



Major Pathways Activated

- VEGF/VEGFR signaling
- Angiogenesis
- Endothelial activation
- Microvascular permeability
- Cytokine amplification loops
- Plasma cell–immune cell cross-talk

KEY CONCEPT: A λ-restricted plasma cell clone drives excess production of VEGF and other cytokines, leading to angiogenesis, vascular permeability, and immune activation—resulting in Castleman lymphadenopathy and the clinical manifestations of POEMS.

References: Nagao S, et al. *Leukemia*. 2019;33:1833–1843. | Isshiki Y, et al. *JCI Insight*. 2022;7(20):e151482. | D'Sa S, et al. *Hemasphere*. 2022;6(11):e796.

MCD = multicentric Castleman disease; VEGF = vascular endothelial growth factor.

Sokol L, unpublished, AI-assisted figure, 2026.

Treatment Algorithm for POEMS Syndrome

1 TREATMENT-NAÏVE LOCALIZED DISEASE
(1–2 dominant bone lesions)

1–2 Dominant Bone Lesions
(sclerotic / plasmacytoma)

↓

Radiotherapy
(35–50 Gy)

↓

Response Assessment
(Symptoms, VEGF, M-protein)

↓

Observe
(or systemic therapy if progression)

2 TREATMENT-NAÏVE SYSTEMIC DISEASE
(Disseminated)

Systemic POEMS
(No dominant 1–2 bone lesions)

↓

Transplant Eligible?
(Age, performance status, organ function)

- **Yes** → **ASCT** (Preferred for transplant-eligible patients)
- **No** → **Lenalidomide + Dexamethasone ± Daratumumab**

↓

Response Assessment
(Symptoms, VEGF, M-protein)

3 RELAPSED / REFRACTORY POEMS SYNDROME

Relapsed / Refractory Disease

↓

Plasma Cell–Directed Therapy Options

- **Anti-CD38 Therapy** (Daratumumab-based)
- **IMiD-Based Therapy** (Lenalidomide or Pomalidomide ± Dexamethasone)
- **Proteasome Inhibitor–Based Therapy** (Bortezomib or Carfilzomib–based)

BCMA-Directed Therapy (Emerging / Promising)

- **Teclistamab** (BCMA × CD3 Bispecific Antibody)
- **BCMA CAR-T** (e.g., cilta-cel or other BCMA CAR-T)

Clinical Trial / Other Options

POEMS DIAGNOSTIC CRITERIA (2026)

MANDATORY MAJOR CRITERIA (Both required)	ADDITIONAL MAJOR CRITERIA (≥1 required)	MINOR CRITERIA (≥1 required)
• Polyneuropathy • Monoclonal plasma cell disorder (usually λ)	• Elevated VEGF • Sclerotic bone lesion(s) • Castleman disease	• Organomegaly • Endocrinopathy • Skin changes • Extravascular volume overload • Papilledema • Thrombocytosis / Polycythemia

DIAGNOSTIC RULE
Diagnosis =
Polyneuropathy + Clonal Plasma Cell Disorder
PLUS
≥1 Additional Major Criterion
PLUS
≥1 Minor Criterion

Reference: Dispenzieri A. POEMS Syndrome: 2026 Update on Diagnosis, Risk-Stratification, and Management. American Journal of Hematology. 2026;101(6):E234–E246. doi:10.1002/ajh.27018.

Sokol L, unpublished, AI-assisted figure, 2026,

Outcomes of POEMS-Associated Multicentric Castleman Disease

Study	Outcomes	
Suichi et al. 2020 (N=102) POEMS-MCD: 14 POEMS: 56	89% vs 61%	10-year OS POEMS-MCD vs POEMS
Lau et al. 2026 (N=150) POEMS-MCD: 18 POEMS: 132	38% vs 74%	5-year PFS POEMS-MCD vs POEMS Median PFS: 49 vs 126 months HR 1.90 (95% CI 0.63–5.72); P = 0.25
Abdallah et al. 2022 (N=34) POEMS-MCD: 18 Non-POEMS MCD: 16	84% / 71%	5-year OS / 10-year OS Median TTNT: 11.5 yr vs 2.9 yr ASCT vs No ASCT
Dispenzieri et al. 2012 (N=113) MCD-POEMS: 62 MCD without POEMS: 51	90% vs 27%	5-year OS Osteosclerotic vs non-osteosclerotic POEMS-MCD UCD 91%; MCD without POEMS 65%

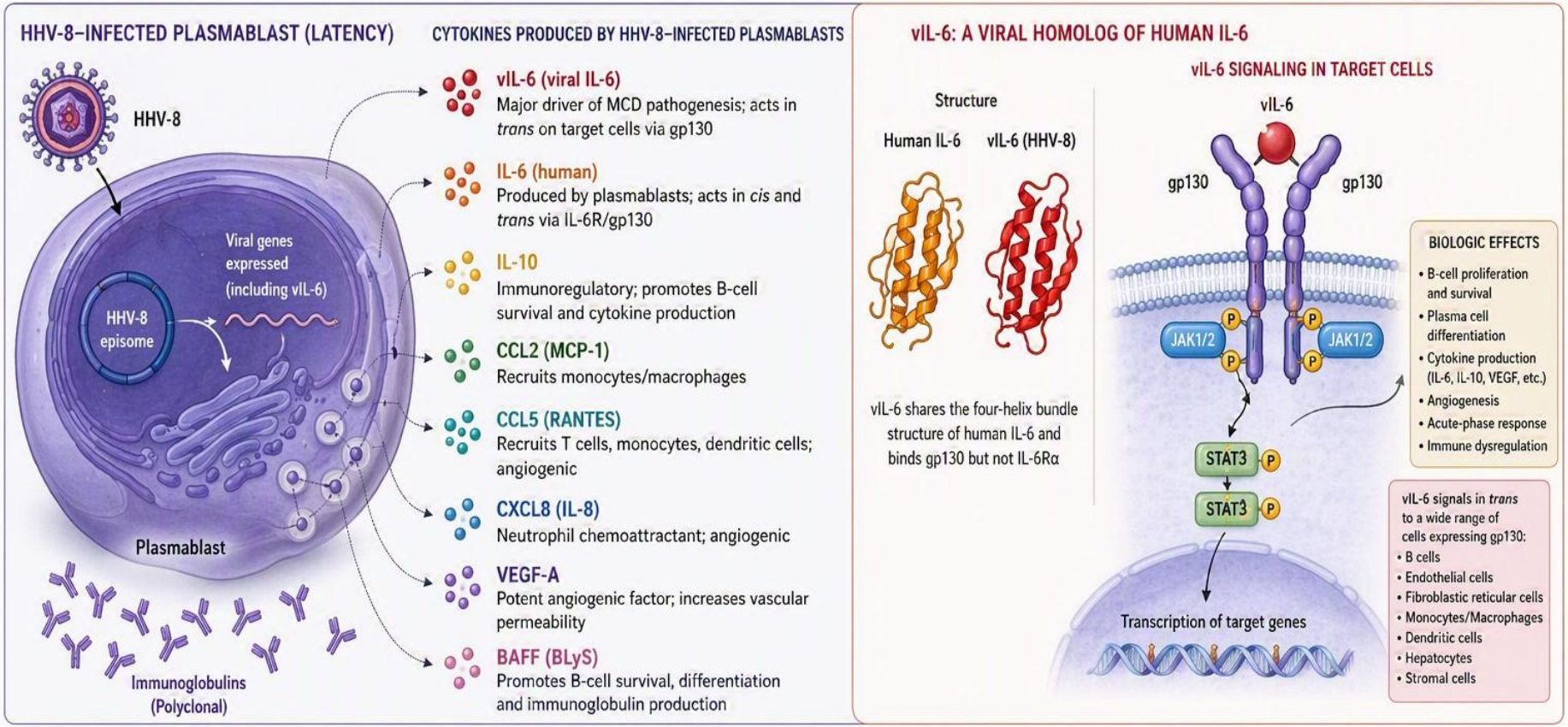
Published cohorts demonstrate heterogeneous outcomes in POEMS-associated MCD, influenced by osteosclerotic phenotype, treatment era, and study design.

References: **1.** Suichi et al. 2020, *J Neurol Sci.* 2020;417:116976. | **2.** Lau et al. 2026, *Blood Adv.* 2026;10(4):953-963. | **3.** Abdallah et al. 2022, *Am J Hematol.* 2022;97(12):E539-E543. **4.** Dispenzieri et al. 2012, *Am J Hematol.* 2012;87(9):829-832.

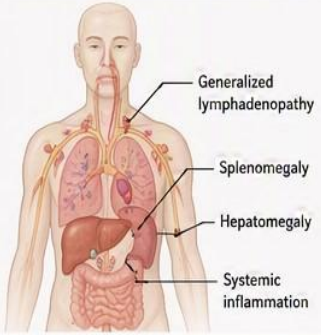
Sokol L, unpublished, AI-assisted figure, 2026,

HHV-8-ASSOCIATED MCD

vIL-6 in HHV-8–Infected Plasmablasts and Its Role in HHV-8$^+$ Multicentric Castleman Disease (MCD)



CONSEQUENCES IN HHV-8$^+$ MULTICENTRIC CASTLEMAN DISEASE (MCD)



PATHOGENIC CASCADE

HHV-8 infects naïve B cell → plasmablast

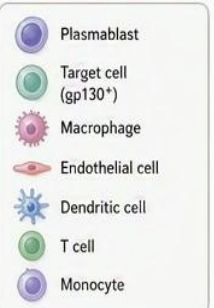
Secretion of vIL-6 and other cytokines (IL-6, IL-10, CCL2, CCL5, CXCL8, VEGF-A, BAFF)

Activation of target cells via gp130 (vIL-6) and other cytokine pathways

Lymphoid hyperplasia, angiogenesis, and systemic inflammation

CLINICAL MANIFESTATIONS

- Fever, night sweats, fatigue
- Generalized lymphadenopathy
- Hepatosplenomegaly
- Anemia, thrombocytopenia
- Hypergammaglobulinemia
- Elevated CRP/ESR, IL-6
- Effusions, edema
- Organ dysfunction

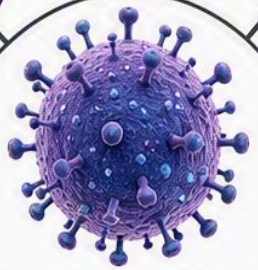


Key Takeaway: HHV-8–infected plasmablasts secrete vIL-6 and a spectrum of cytokines that act on gp130-expressing cells to drive the lymphoproliferation, angiogenesis, and systemic inflammation characteristic of HHV-8$^+$ multicentric Castleman disease.

Sokol L, unpublished, AI-assisted figure, 2026.

HHV-8–Associated Disorders

Clinical Spectrum of Human Herpesvirus 8 (KSHV) Infection



HHV-8 (KSHV)

Oncogenic γ-herpesvirus

One virus • Multiple inflammatory and neoplastic disorders

1 Kaposi Sarcoma (KS) ~50%

Kaposi Sarcoma (KS)

- Most common HHV-8–associated neoplasm
- Endothelial tumor driven predominantly by latent infection

2 HHV-8–Associated MCD ~20%

HHV-8–Associated MCD

- Polyclonal IgM λ plasmablast–driven disease
- Viral IL-6–mediated systemic inflammation

3 KICS ~10%

KSHV Inflammatory Cytokine Syndrome (KICS)

- Cytokine storm–like syndrome
- MCD-like inflammatory presentation without pathologic MCD

4 Primary Effusion Lymphoma (PEL) ~8%

Primary Effusion Lymphoma (PEL)

- Aggressive HHV-8+ B-cell lymphoma
- High lytic viral activity

5 HHV-8+ DLBCL, NOS ~7%

HHV-8+ DLBCL, NOS

- Monoclonal plasmablastic lymphoma
- Frequently associated with HHV-8 MCD

6 Germinotropic LPD (GLPD) ~3%

Germinotropic Lymphoproliferative Disorder (GLPD)

- Indolent lymphoproliferative disorder
- Frequently EBV coinfected

7 HHV-8–Associated HLH ~2%

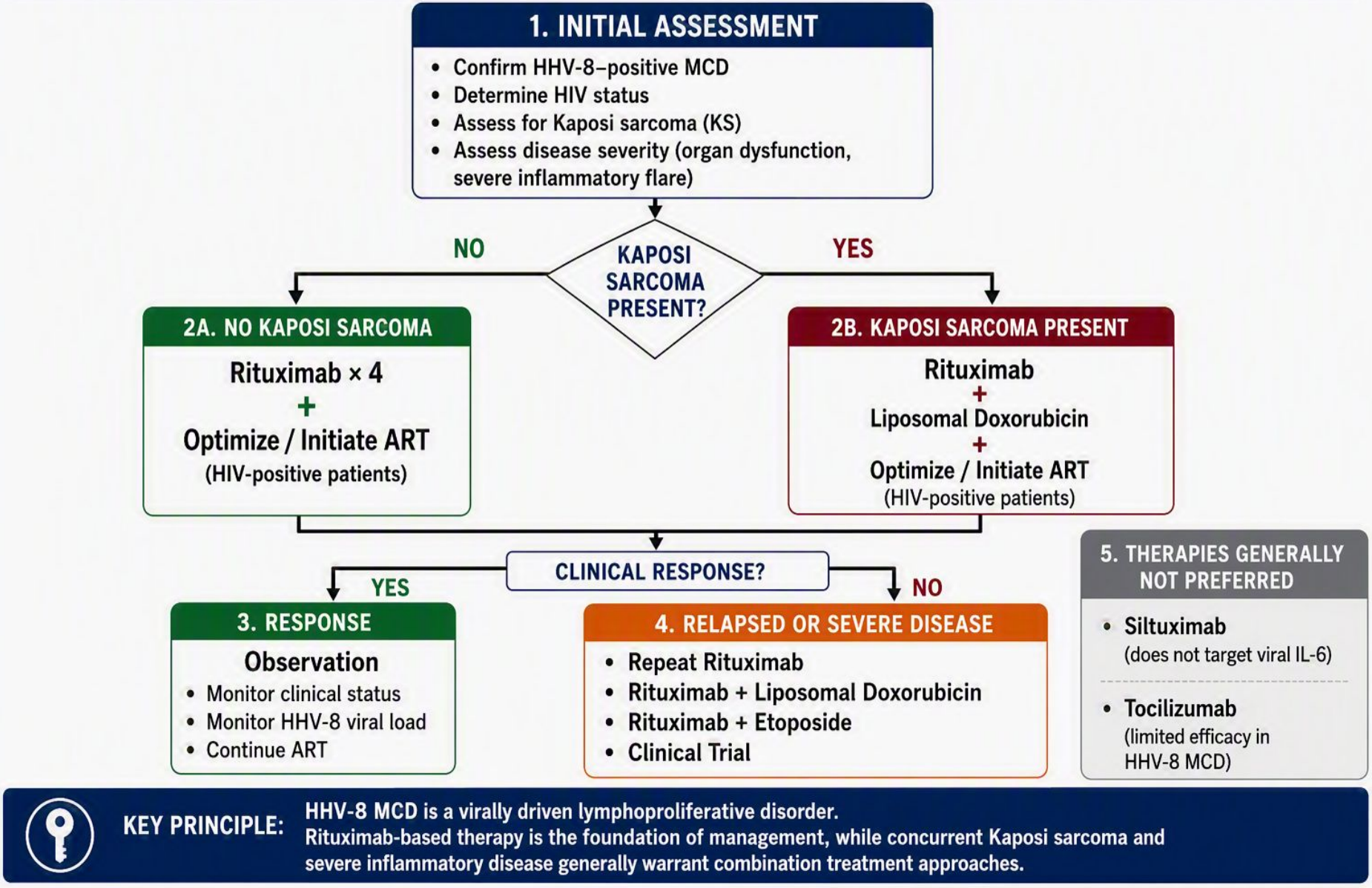
HHV-8–Associated HLH

- Hyperinflammatory syndrome
- Immune activation–driven disease

KEY PRINCIPLE: HHV-8 infection gives rise to a spectrum of disorders ranging from cytokine-mediated inflammatory syndromes (HHV-8 MCD, KICS, HLH) to lymphoid and endothelial neoplasms (PEL, HHV-8+ DLBCL, and Kaposi sarcoma).

Sokol L, unpublished, AI-assisted figure, 2026.

HHV-8–Associated Multicentric Castleman Disease: Treatment Algorithm

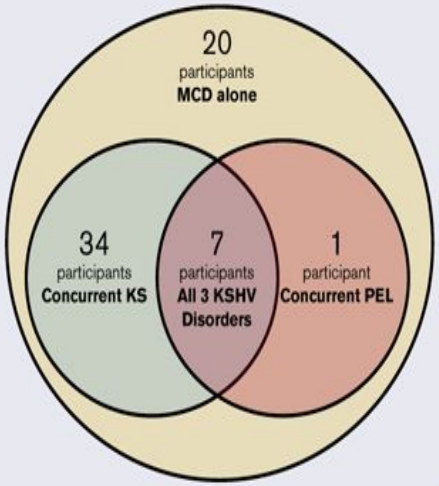


Sokol L, unpublished, AI-assisted figure, 2026.

Characteristics and outcomes of KSHV-associated multicentric Castleman disease with or without other KSHV diseases

Characteristics and Outcomes of Kaposi sarcoma Herpesvirus (KSHV)-Associated Multicentric Castleman Disease (MCD)

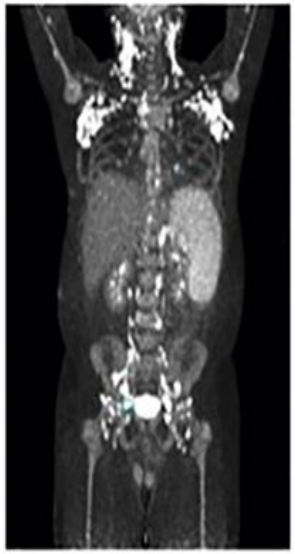
62 participants with HIV and KSHV-MCD



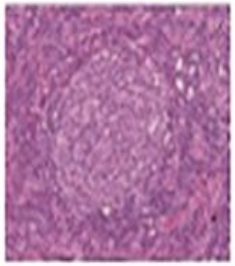
Cytokines elevated during flares

↑ IFN-γ, IL-10, IL-1β, IL-4, IL-6, IL-8, and TNF-α

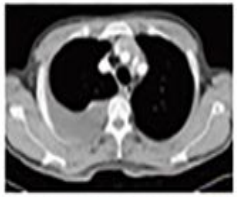
Concurrent KSHV disorders did not affect the cytokine profiles of MCD flares

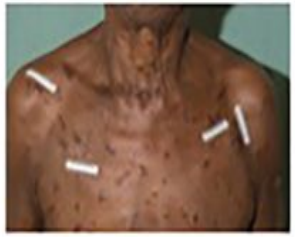


FDG-PET in MCD

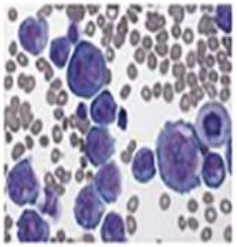


Lymph node biopsy showing MCD

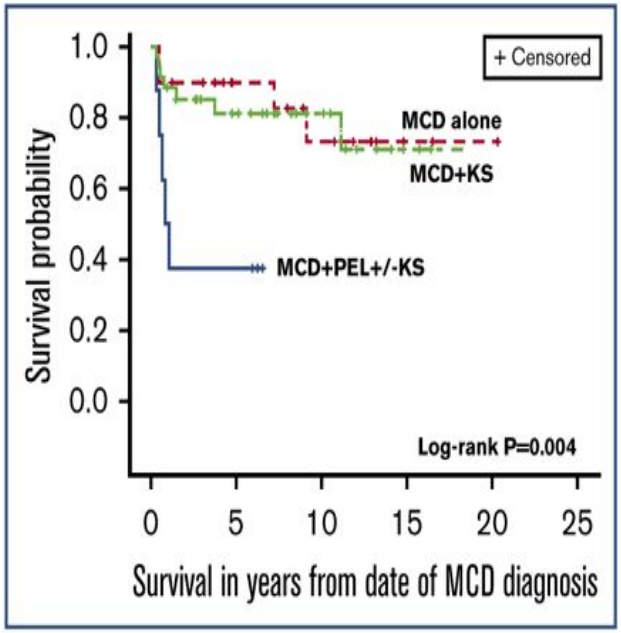




Cutaneous Kaposi sarcoma (KS)



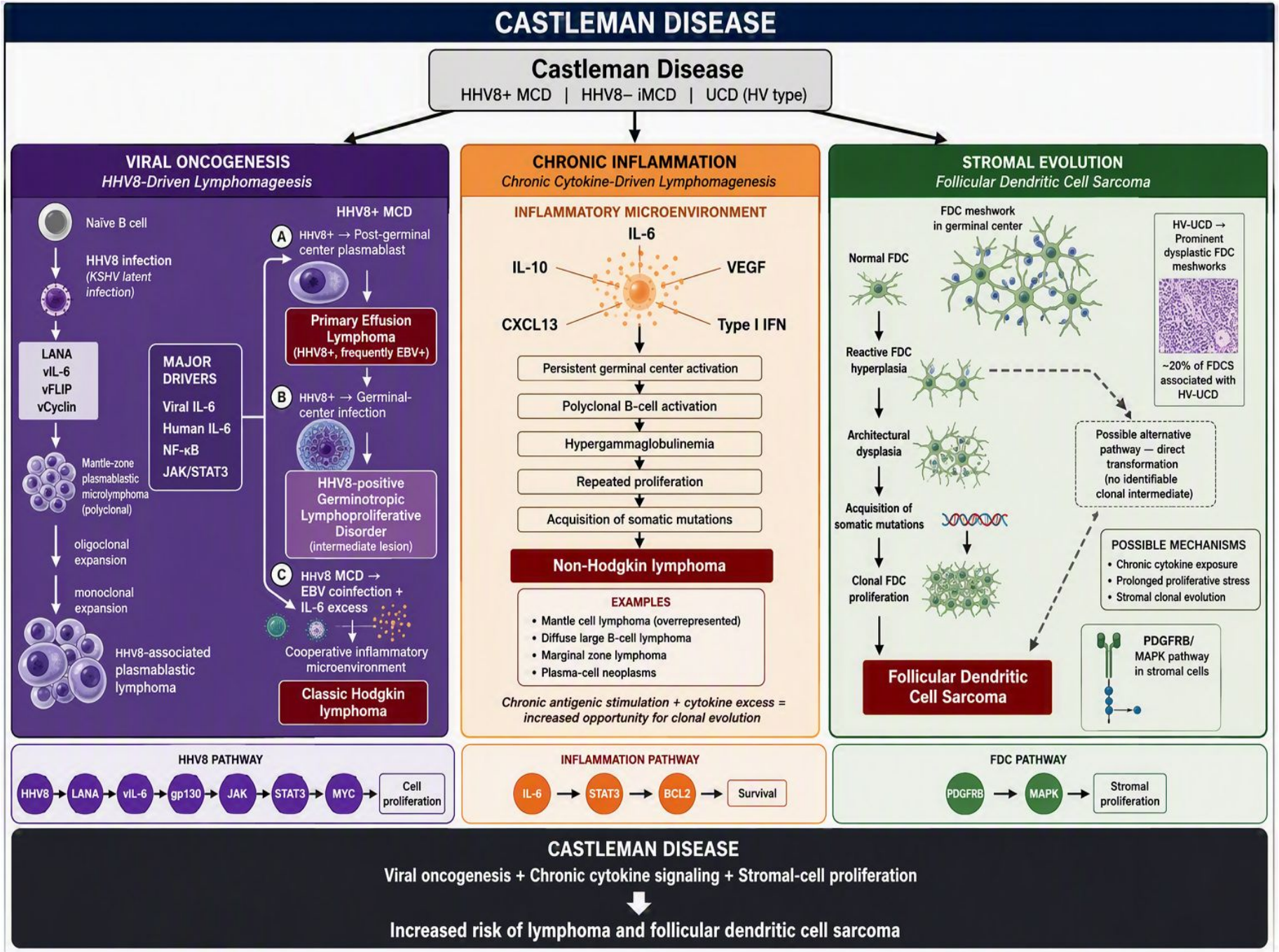
Chest CT and pleural fluid cytology showing primary effusion lymphoma (PEL)



10-year survival was 71% (95% CI: 56-82%) for all participants

Patients with concurrent PEL had worse survival MCD survival HR: 5.4 (95% CI: 1.8, 16.8)

Ramaswami R et al. Blood Adv, 2021



Sokol L, unpublished, AI-assisted figure, 2026.

Conclusions

iMCD has three subtypes — TAFRO, NOS, and IPL

Diagnosis remains clinicopathologic and exclusionary

iMCD is a stromal/immune cell-driven hyper-cytokinemia extending beyond IL-6 to mTOR, TNF, CXCL13, VEGF, IFN-γ and JAK-STAT.

UCD-clonal/oligoclonal PRC/FRC/FDC-driven process

Siltuximab is first-line for all iMCD subtypes; rituximab-based therapy for HHV8 -MCD; surgery for resectable UCD; POEMS directed therapy for POEMS-MCD

Refractory iMCD is the principal unmet need — sirolimus is the best-supported non–anti-IL-6 option, with JAK/STATi, CXCL13 blockade (Mab 5261) in early development

THANK YOU!