Focus on a Rare Disease: Idiopathic Multicentric Castleman Disease

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What are Rare or Orphan Diseases?

Definition

- In the United States, a “rare” or orphan disease affects fewer than 200,000 people (per the 1983 Orphan Drug Act)

Prevalence

- Over 7,000 distinct rare diseases have been identified, together affecting >30 million Americans (~1 in 10 people)

Global Impact

- Worldwide, rare diseases are estimated to affect around 300 million people equivalent to the population of the world’s third-largest country

Severity

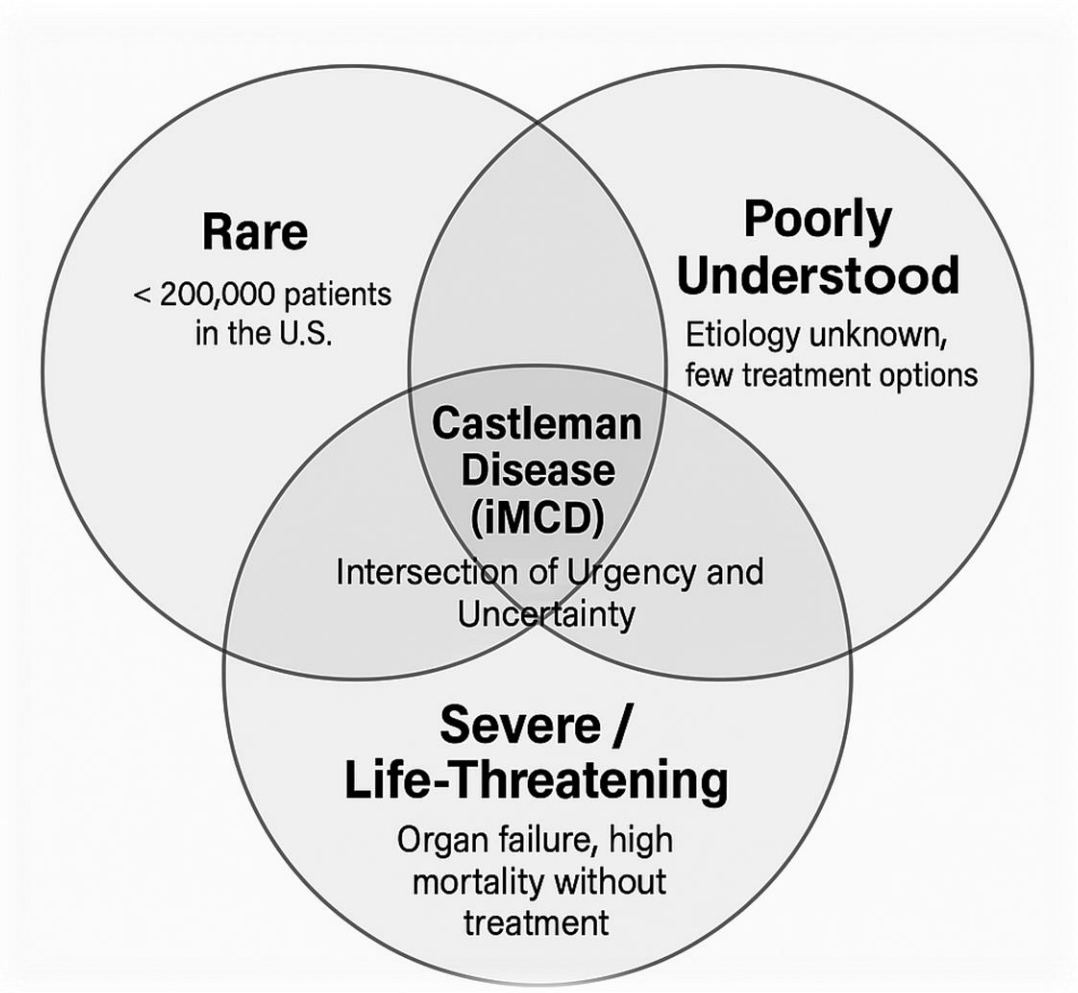
- ~80% have a genetic origin many are serious conditions. many with chronic, progressive illness and significant morbidity and early mortality.

Unmet Needs

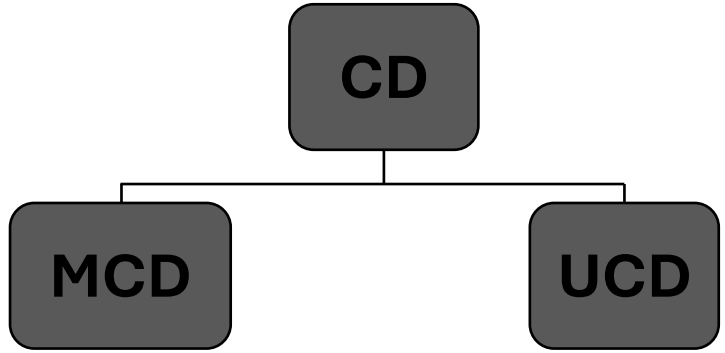
- >90% of rare diseases have no FDA-approved treatment

Zooming in on rare diseases: Castleman Disease

- Among the thousands of rare diseases, many are diagnostically and therapeutically challenging
- Castleman disease, particularly idiopathic multicentric Castleman disease (iMCD) is one such case
- Studying iMCD allows us to understand the real-world urgency, complexity, and opportunity in rare disease research



Overview of Castleman Disease (CD)



What is Castleman Disease?

- A heterogeneous group of rare lymphoproliferative disorders with characteristic lymph node changes

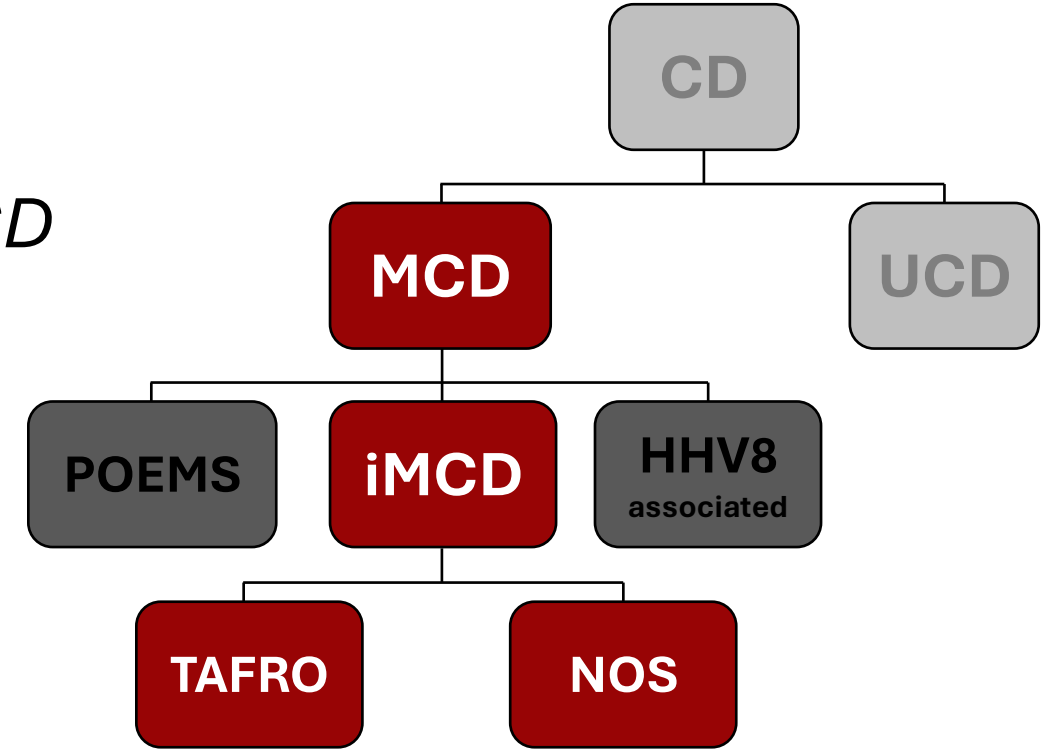
Two Clinical Forms

- Unicentric CD (UCD) localized single-region disease
- Multicentric CD (MCD) generalized lymphadenopathy with systemic inflammation

Overview of Castleman Disease (CD)

MCD Subtypes by Etiology

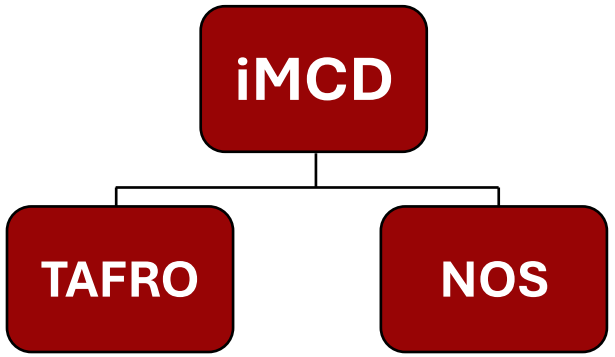
- *Human herpesvirus 8 (HHV-8) associated MCD* (often in HIV+ patients)
- *POEMS-associated MCD:* Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes
- *Idiopathic MCD (iMCD),* all other MCD cases with no identified cause (HHV-8 negative, no POEMS)



What is idiopathic Multicentric Castleman Disease (iMCD)?

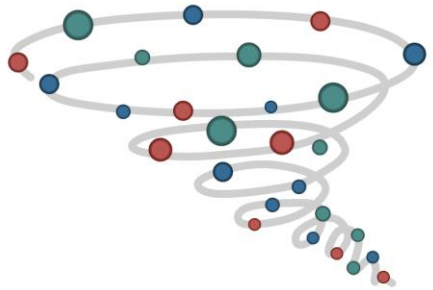
Definition

- Multicentric Castleman disease with no identifiable etiology
- By definition HHV-8 negative and not associated with POEMS syndrome
- The cause is *unknown:* “idiopathic”



Immune Cytokine Dysregulation

- Characterized uncontrolled cytokine storm with systemic inflammation
- iMCD patients have high levels of IL-6 and often other inflammatory markers


Cytokine storm

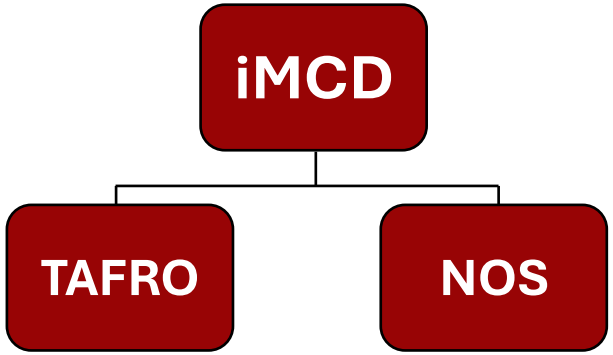
Clinical Presentation

- Generalized lymph node enlargement plus systemic symptoms: fever, night sweats, weight loss, fatigue, enlarged spleen and liver, fluid accumulation
- Some patients develop multiorgan failure in severe cases

What is idiopathic Multicentric Castleman Disease (iMCD)?

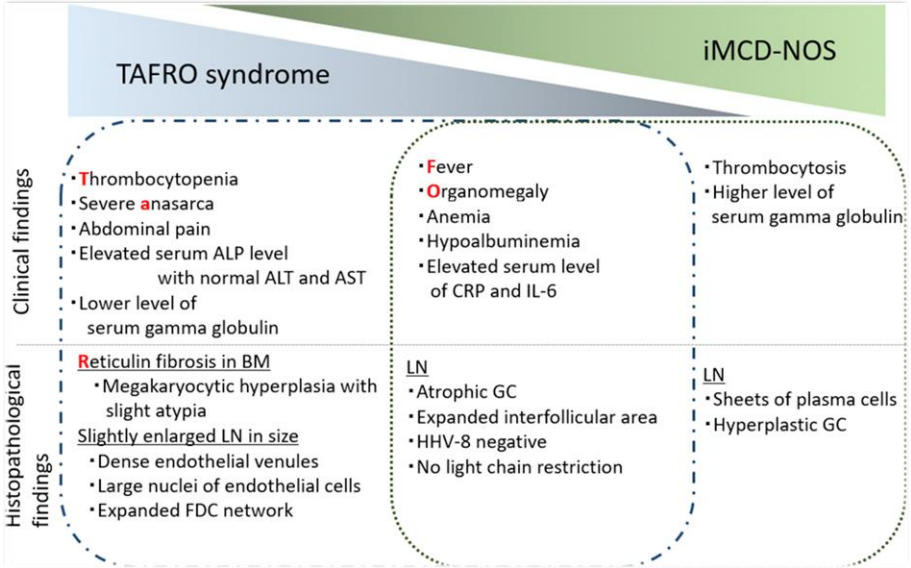
Subtypes of iMCD

- *iMCD-TAFRO:* a severe variant defined by **T**hrombocytopenia, **A**nasarca (massive edema/pleural effusions), **F**ever and high CRP, **R**eticulin fibrosis of marrow (with renal dysfunction), and **O**rganomegaly
- *iMCD-NOS:* "Not Otherwise Specified," a more heterogenous group with milder or more chronic course



Significance

- Although rare (annual incidence ~3.1-3.4 per million; prevalence ~7-10 per million in the US
- iMCD outcomes are poor if untreated, ~35-40% of patients may die within 5 years without proper therapy



TAFRO Syndrome Igawa, Takuro et al. Hematology/Oncology Clinics, Volume 32, Issue 1, 107 - 118

What Drives iMCD?

Cytokine Storm

- MCD is driven by dysregulated immune signaling
- IL-6 is key and drives B-cell proliferation, acute phase reactions (fever, CRP), and angiogenesis

Unknown Trigger

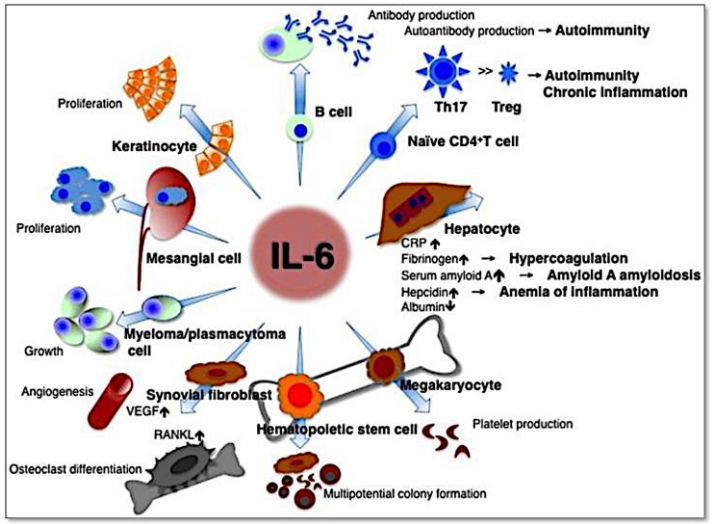
- The root cause of the IL-6 storm remains unclear
- Hypotheses include: infection, a germline genetic or autoimmune abnormality, or a somatic mutation in immune system cells

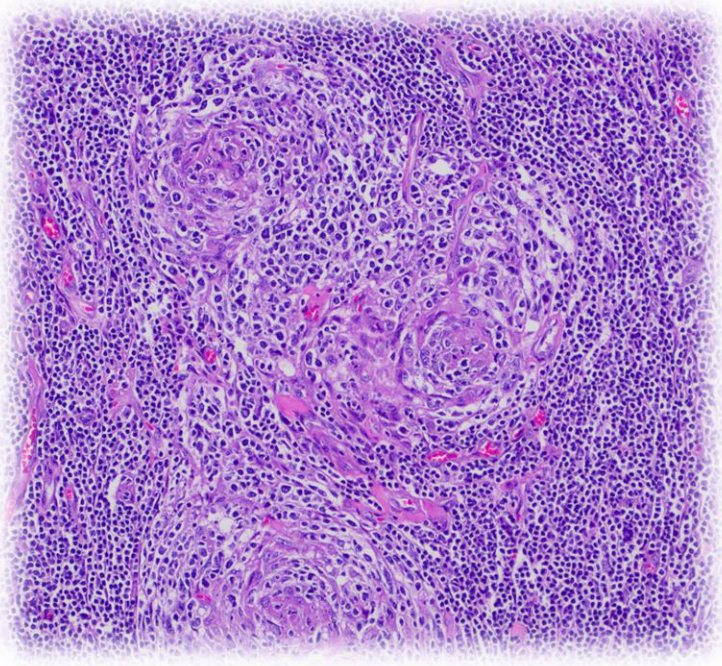
Other Immune Pathways

- iMCD lymph nodes often have elevated VEGF, IL-10, and CXCL13, and Th2-skewed immune activation
- The mTOR and JAK-STAT signaling pathways have been implicated in sustaining the cytokine storm

New Discoveries (2024–2025)

- Machine learning analyses of iMCD patient data found TNF pathway upregulation, which is druggable



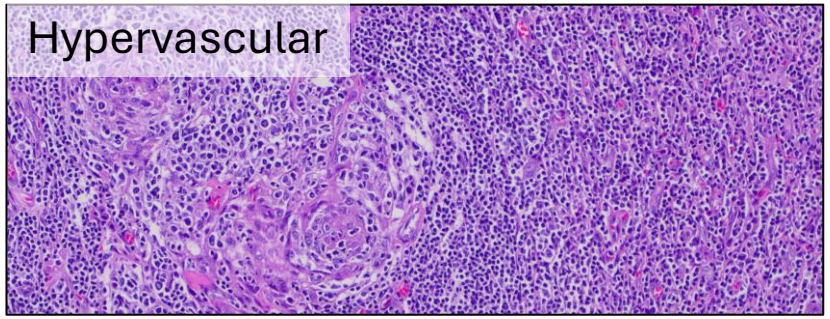


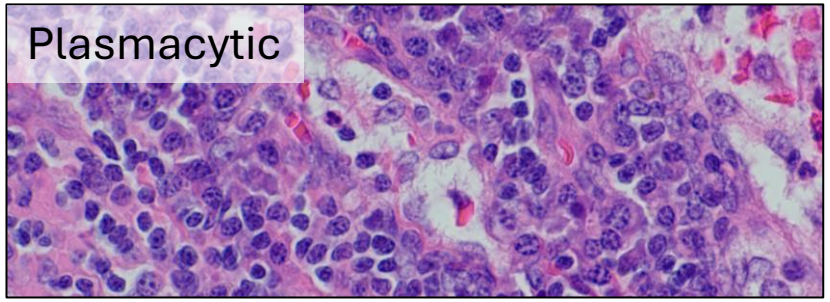
Tanaka T, Kishimoto T. Targeting Interleukin-6: All the Way to Treat Autoimmune and Inflammatory Diseases. Int J Biol Sci 2012; 8(9):1227-1236. doi:10.7150/ijbs.4666.

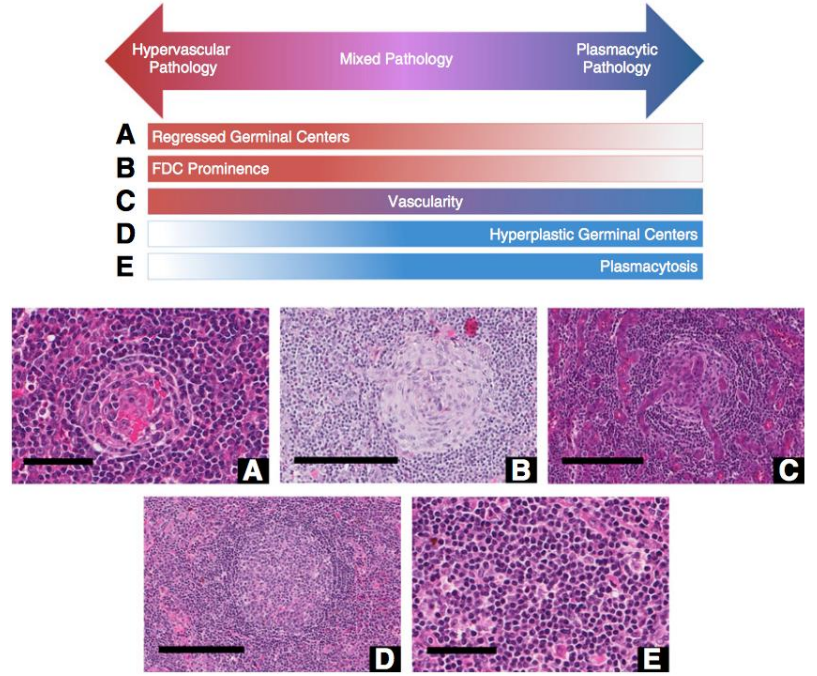
Pathologic features of iMCD

Lymph Node Pathology

- **Hypervascular:** regressed (atrophic) germinal centers with concentric layers of mantle cells (“onion-skinning”) and proliferating blood vessels penetrating follicles (“lollipop” lesions), associated with excess VEGF and FDC (follicular dendritic cell) activation
- **Plasmacytic:** sheets of polyclonal plasma cells in interfollicular areas (driven by IL-6), lymph nodes can resemble plasma cell tumors but polytypic
- **Mixed:** Many cases show a mixture of both patterns







Fajgenbaum DC, et al., Blood. 2017 Mar 23;129(12):1646-1657.

Diagnosing iMCD: Updates and Criteria

	Category	iMCD-NOS	iMCD-TAFRO
Major	**Major Criteria - Lymph Nodes**	≥2 lymph node stations enlarged	≥2 lymph node stations enlarged
	Major Criteria - Morphology	Grade 2–3 regressed follicles or plasmacytosis	Grade 2–3 regressed follicles or plasmacytosis
	Major Criteria - KSHV/HHV8 LANA IHC	Negative	Negative
minor	**minor Criteria - Lab**	≥2 (≥1 lab): anemia, thrombocytosis/-penia, CRP >1, renal dysfunction, polyclonal hypergammaglobulinemia	≥2 (≥1 lab): anemia, thrombocytosis/-penia, CRP >1, renal dysfunction, polyclonal hypergammaglobulinemia
	minor Criteria - Clinical	Constitutional, hepatosplenomegaly, anasarca, skin lesions, LIP	Constitutional, hepatosplenomegaly, anasarca, skin lesions, LIP
exclude	**exclusion - Infection**	Exclude EBV, HIV, COVID-19, TB, HHV8, etc.	Exclude EBV, HIV, COVID-19, TB, HHV8, etc.
	exclusion - Autoimmune/Inflammatory	Exclude SLE, RA, Still, JIA, Sjögren, ALPS, HLH, IgG4, etc.	Exclude SLE, RA, Still, JIA, Sjögren, ALPS, HLH, IgG4, etc.
	exclusion - Malignancy	Exclude NHL, myeloma, POEMS, etc.	Exclude NHL, Hodgkin, myeloma, FDC sarcoma, POEMS, etc.
	subclassifying iMCD-TAFRO - anasarca	Not required	Required
	subclassifying iMCD-TAFRO - thrombocytopenia	Not required	Required
	subclassifying iMCD-TAFRO - systemic inflammation	Not required	Fever >37.5°C or CRP ≥2
	subclassifying iMCD-TAFRO - organomegaly	Not required	Small-volume LAD + hepatomegaly/splenomegaly
	subclassifying iMCD-TAFRO - additional features	Not required	BM fibrosis or renal dysfunction/failure
	histopathological features	Grade 2–3 vascularity, small LN (<10 mm), plasmacytic/mixed	Grade 2–3 vascularity, small LN (<10 mm), plasmacytic/mixed
	other supportive features	Elevated IL-6, sIL-2R, VEGF, B2M, ALP	Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, B2M

https://www.captodayonline.com/idiopathic-multicentric-castleman-disease/

Diagnostic traps, where mistakes happen

Differential diagnostic overlap and complexity

- Infections: Chronic viral infections (EBV, CMV), tuberculosis, or even sepsis, or HLH can mimic
- Autoimmune diseases: Often misdiagnosed as lupus, adult Still's disease, rheumatoid arthritis, or IgG4-related disease
- Malignancies: Can be confused with cancers like lymphoma or multiple myeloma

"Rarity" Bias

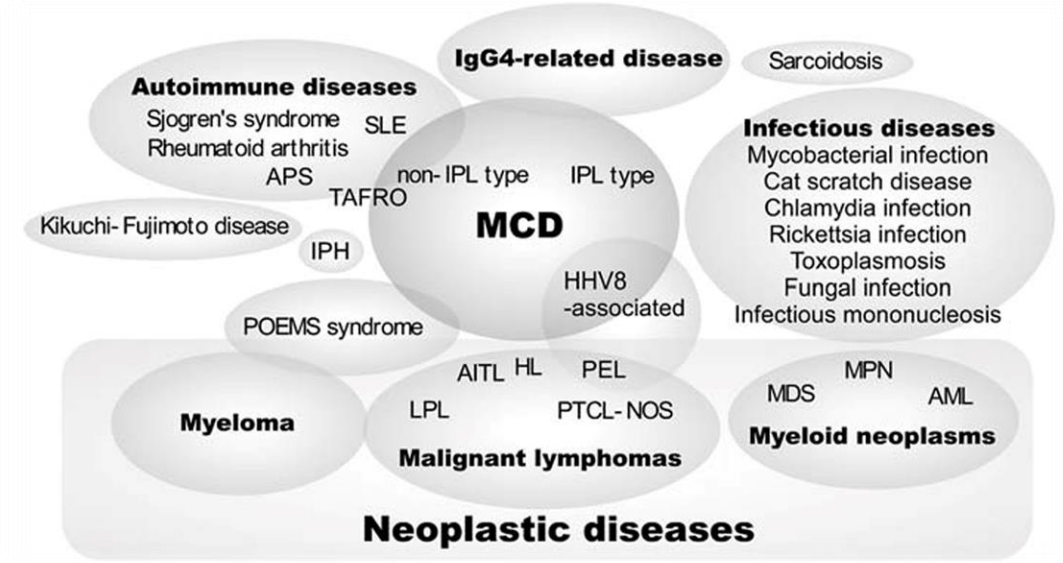
- Because it's rare, many physicians don't have iMCD on their radar
- Patients often see multiple specialists over months to years. This delay can lead to empiric treatments for other diseases (steroids, IVIG, antibiotics) that cloud the picture

Inadequate Biopsy Sample

A common pitfall is relying on a needle biopsy

Communication Gaps:

- A trap can occur if the pathologist sees Castleman-like features but the clinical team isn't considering iMCD
- Close clinician-pathologist collaboration is vital



Kawabata, Hiroshi et al. "Clinical features and treatment of multicentric castleman's disease : a retrospective study of 21 Japanese patients at a single institute." *Journal of clinical and experimental hematopathology : JCEH* vol. 53,1 (2013): 69-77.

Clinical Consequences of Missing the Diagnosis

Delay Can Be Dangerous

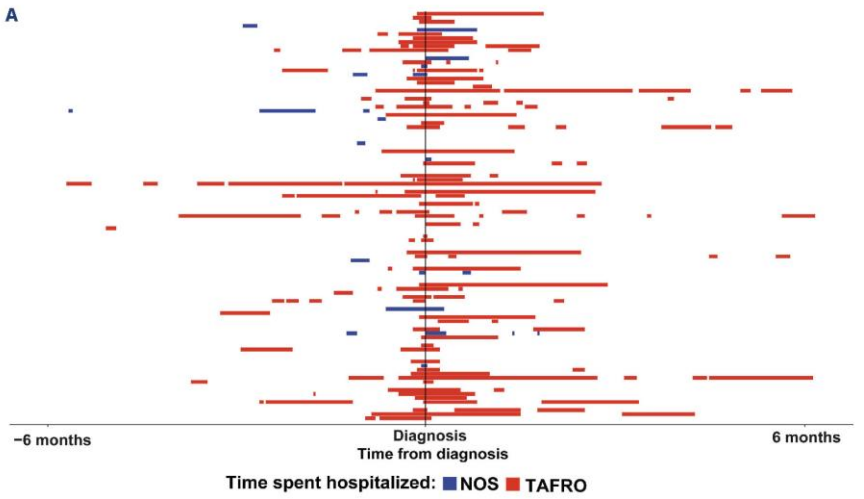
- Untreated or unrecognized iMCD can rapidly progress

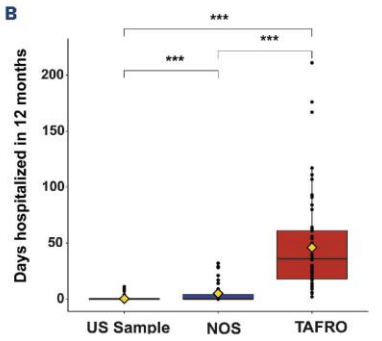
Organ Failure and ICU-level Illness

- In severe iMCD (especially TAFRO), patients can develop life-threatening organ dysfunction.
- In a large registry, 17% of iMCD patients required mechanical ventilation and 27% needed dialysis during their disease course.
- ~35-45% 5-year mortality in iMCD patients without effective therapy

Healthcare Utilization and Morbidity

- Undiagnosed iMCD patients endure frequent hospitalizations and interventions
- Patients with TAFRO spent a median of ~36 days in the hospital, versus 0-4 days for non-TAFRO (milder) cases





Bustamante, Mateo Sarmiento et al. "Longitudinal, natural history study reveals the disease burden of idiopathic multicentric Castleman disease." *Haematologica* vol. 109,7 2196-2206. 1 Jul. 2024

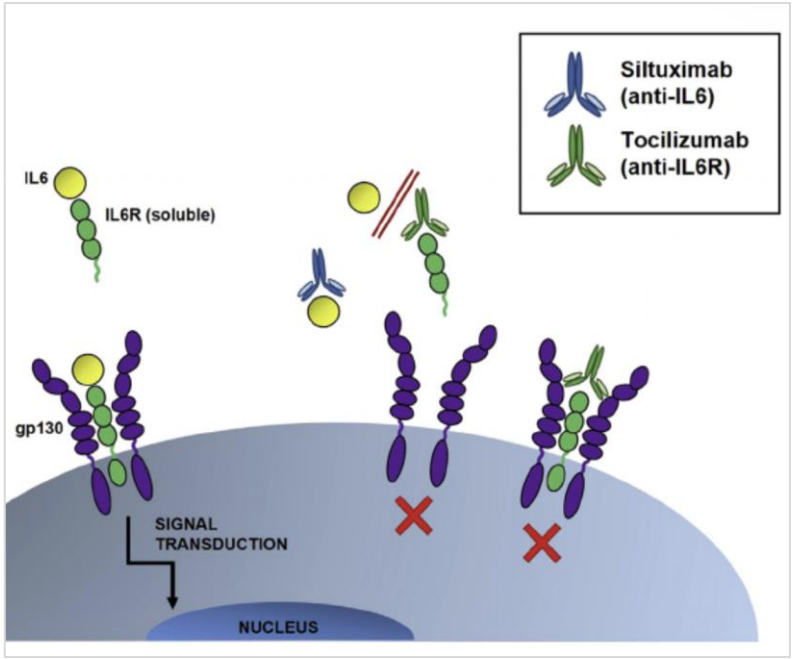
Treatment Approaches: Current and Emerging

First-Line Therapy is IL-6 Blockade

- The cornerstone of iMCD treatment is targeting Interleukin-6
- Siltuximab (Sylvant), a monoclonal antibody against IL-6, is FDA-approved. Approved in 2014 after a trial showed ~34% durable tumor and symptom response rate
- Tocilizumab, an IL-6 receptor blocker, is also used (approved for MCD in Japan and used off-label elsewhere)
- High-dose corticosteroids (e.g. prednisone) are sometimes given initially to tamp down the cytokine storm

Chemotherapy and Immunosuppressants

- Before targeted therapies, iMCD was treated with chemotherapy (e.g. CHOP) or immunomodulatory (rituximab), or immunosuppressants (cyclophosphamide, cyclosporine)



Treatment of Idiopathic Castleman Disease van Rhee, Frits et al. Hematology/Oncology Clinics, Volume 32, Issue 1, 89 - 106

Treatment Approaches: Current and Emerging

Refractory iMCD: Second-Line Options

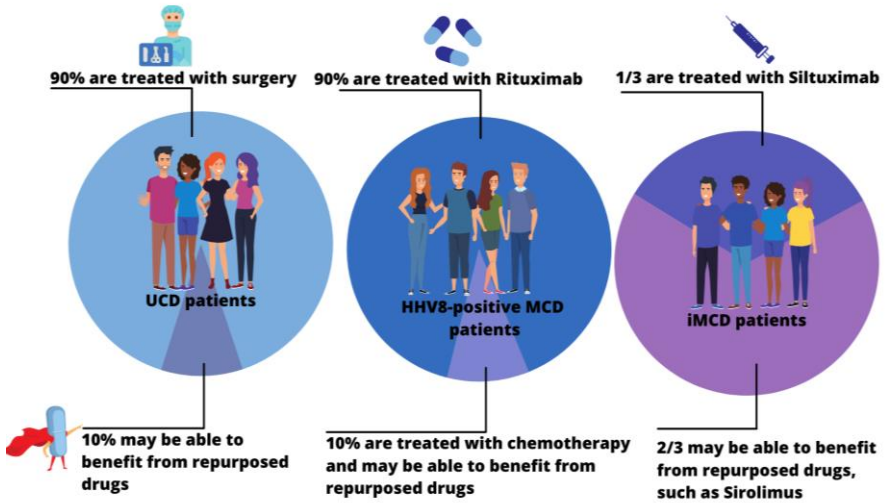
- Sirolimus, JAK inhibitors (Ruxolitinib targeting JAK1/2) are sometimes considered if other options fail

Emerging Therapies

- Anti-TNF therapy: A refractory patient achieved remission with adalimumab
- BTK ihibitors: Some ibrutinib (to target B-cell signaling) in iMCD has been reported
- Anti-IL-1 therapy: Anakinra (IL-1Ra) has been tried

Supportive Care

- Manage organ complications, prevent infections, and rehabilitate nutrition and strength
- Multidisciplinary care (hematology, rheumatology, critical care, etc.) is often needed with regular clinical and laboratory assessments



https://cdcn.org/repurposecd/

Case Example: A Diagnostic Odyssey

Case: 42-year-old male with subacute constitutional symptoms, later hospitalized with multiorgan dysfunction

Initial Presentation:

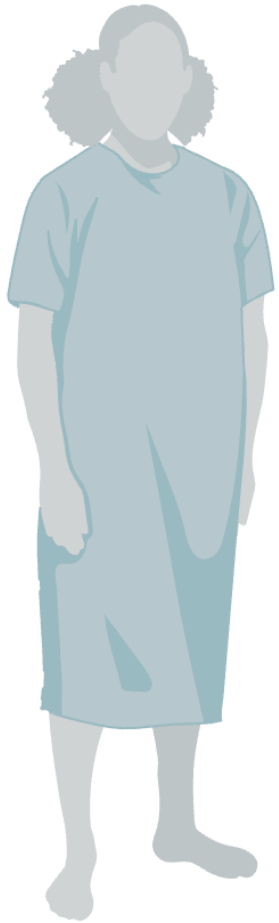
- Presented with two weeks of worsening fatigue, low-grade fever, and edema. Hypotensive (BP 86/52), tachycardic (HR 115), and appeared confused. Labs showed thrombocytopenia (22k), acute kidney injury (creatinine 3.8), and transaminitis

Prior History

- Three months prior: fatigue, weight loss (~15 lbs), and vague abdominal pain. Autoimmune hepatitis was suspected based on ANA positivity and elevated IgG.

ICU Work-up

- Repeat labs showed pancytopenia (Hb 7.8, WBC 2.3, platelets 20k), worsening renal failure, markedly elevated ferritin (>15,000), high CRP and IL-6, low fibrinogen, and low haptoglobin. Bone marrow biopsy showed reactive plasmacytosis and mild reticulin fibrosis; no evidence of lymphoma. Imaging revealed splenomegaly and diffuse lymphadenopathy. Work-up for infectious causes was negative.
- The constellation of findings (fever, thrombocytopenia, renal dysfunction, organomegaly, and hyperinflammation) raised concern for TAFRO subtype of iMCD.



Case Example: A Diagnostic Odyssey

Lymph Node Biopsy

- An excisional biopsy was performed. Histology revealed regressed germinal centers, prominent endothelial venules, and interfollicular plasmacytosis. No clonal B-cell population, no HHV8, normal IgG4.

Diagnostic Challenge

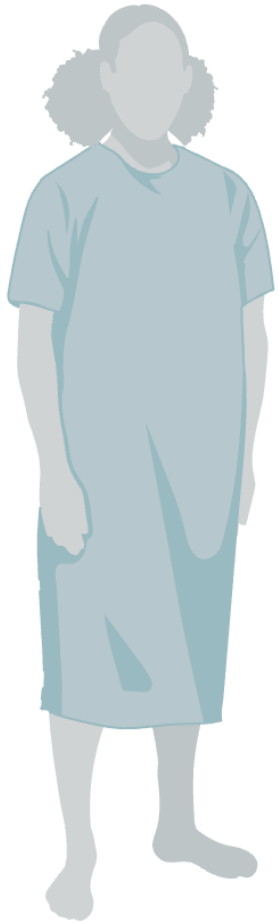
- The pathologist initially interpreted the lymph node as “reactive with features suggestive of chronic inflammation.”

Re-evaluation

- The treating team reached out to the pathologist noting: “We’re not convinced this is autoimmune, she’s not responding to high-dose steroids.” The pathologist re-reviewed the case, and an amended report read: “Consistent with Castleman disease, in the appropriate clinical context.”

Final Diagnosis

- Idiopathic Multicentric Castleman Disease, TAFRO subtype with the pathology/histology, the clinical picture, and lab values.



Case Example: A Diagnostic Odyssey

Treatment and Outcome

- Anti-IL-6 therapy (siltuximab) was initiated. Fevers, cytopenias, renal dysfunction, and inflammatory markers improved rapidly. She was weaned off vasopressors, discharged 10 days later and she remained on siltuximab with steroid taper and showed sustained remission

Lessons

- iMCD (TAFRO subtype) can mimic severe autoimmune or inflammatory conditions
- Early lymph node biopsy is key
- Collaboration between clinical and pathology teams is critical
- Early anti-IL-6 treatment can be life-saving and dramatically improve outcomes

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Summary

Diagnostic Diligence

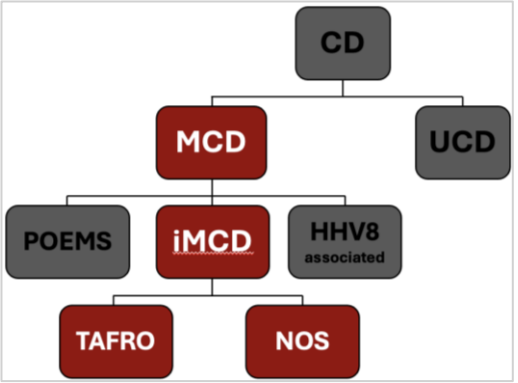
- Keep iMCD in the differential for patients with unexplained systemic inflammation and multicentric lymphadenopathy
- Diagnosing iMCD requires a careful, *multidisciplinary* approach
- Adhere to the consensus criteria: confirm the three major criteria (multicentric nodes, Castleman-type histopathology, no HHV8) and make sure the patient meets minor criteria and doesn't have an alternative diagnosis

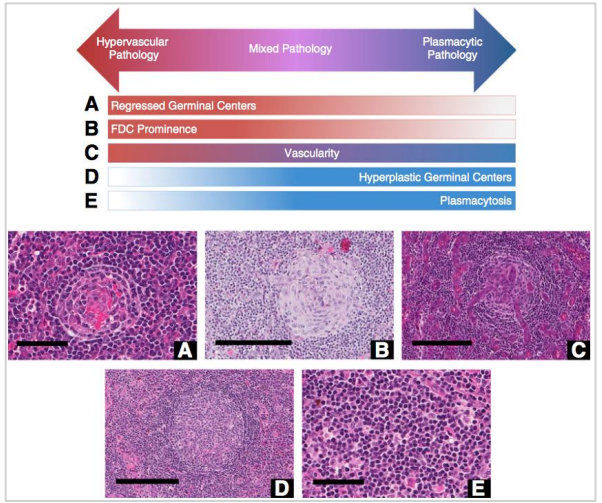
Avoiding Traps and Consequences of Missing iMCD

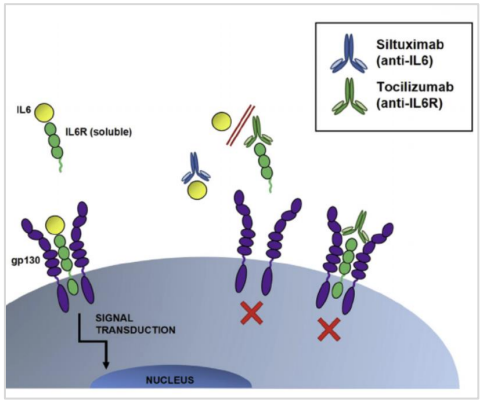
- iMCD can mimic many conditions (infection, autoimmune, cancer), leading to misdiagnosis
- An excisional biopsy and comprehensive workup are needed to avoid false diagnoses
- The "cost" of missing iMCD is measured in organ damage, quality of life, and survival

Therapeutic Advances & Future Directions

- iMCD is treatable though some patients don't respond fully to first-line therapy
- Ongoing research is unraveling new pathways (i.e. mTOR, JAK-STAT, and most recently TNF signaling and testing novel treatments (like sirolimus, TNF blockers)







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