Castleman Disease Overview

This presentation was developed by RRD Medical and is intended to be used by health care providers for medical, scientific, and educational purposes.

RECORDATI RARE DISEASES

Overview

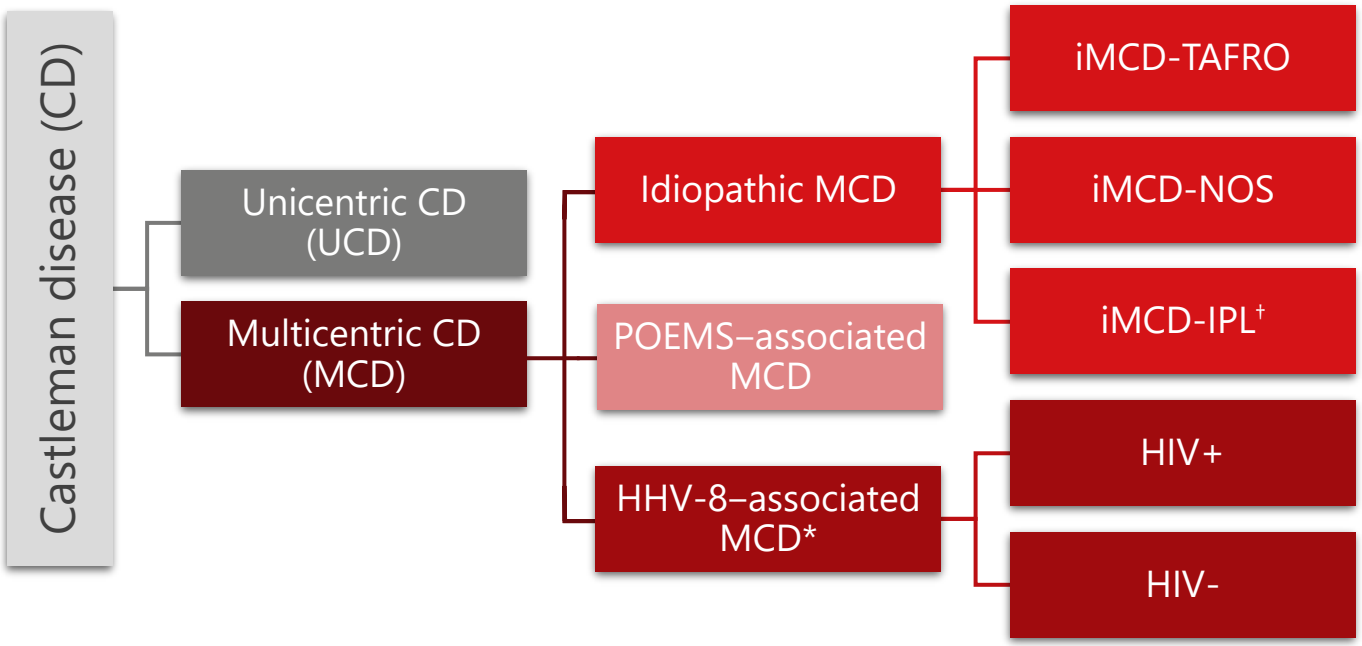
Learning Objectives: This medical slide deck is intended to provide a disease overview of Castleman disease, including its subtypes, and a summary of diagnosis and treatments

Table of Contents:

Background and Classification of Castleman Disease

Castleman disease (CD), first described in the 1950s by Benjamin Castleman, is a collection of rare cytokine-driven disorders with a wide range of etiologies, clinical presentations, treatments, and outcomes.[1]

- CD is classified into distinct clinical subtypes based on the number of enlarged lymph node regions, histopathological features, and clinical presentation.[2]
- All types of CD may be symptomatic, progressive, and require treatment.[1,3]



Unicentric CD (UCD)

UCD is CD that is localized to a single lymph or lymph node group, most often in the neck or abdomen.[2,3]

Multicentric CD (MCD)

MCD is CD that affects multiple lymph node groups, most often in the neck, abdomen, mediastinum, and axillary.[2,3]
MCD is further divided by etiology[1]:

- Idiopathic MCD
- POEMS-associated MCD
- HHV-8-associated MCD

*Also known as Kaposi sarcoma-associated with herpesvirus (KSHV).[1,4] †iMCD-IPL has been identified as a potential subtype of iMCD, although it is not well understood and is still being researched.[4,5]

Abbreviations: CD, Castleman disease; HHV-8, human herpes virus-8; HIV, human immunodeficiency virus; iMCD, idiopathic multicentric CD; iMCD-IPL, iMCD-idiopathic plasmacytic lymphadenopathy; iMCD-NOS, iMCD-not otherwise specified; iMCD-TAFRO, iMCD-thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly; MCD, multicentric CD; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; UCD, unicentric CD.
References: 1. Dispenzieri A, Fajgenbaum DC. *Blood*. 2020;135(16):1353-1364. 2. Fajgenbaum D. *Blood*. 2018;132(22):2323-2330 3. Yu L, et al. *Blood*. 2017;129(12):1658-1668. 4. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. 5. Gao YH, et al. *Br J Haematol*. 2024;204(5):1830-1837.

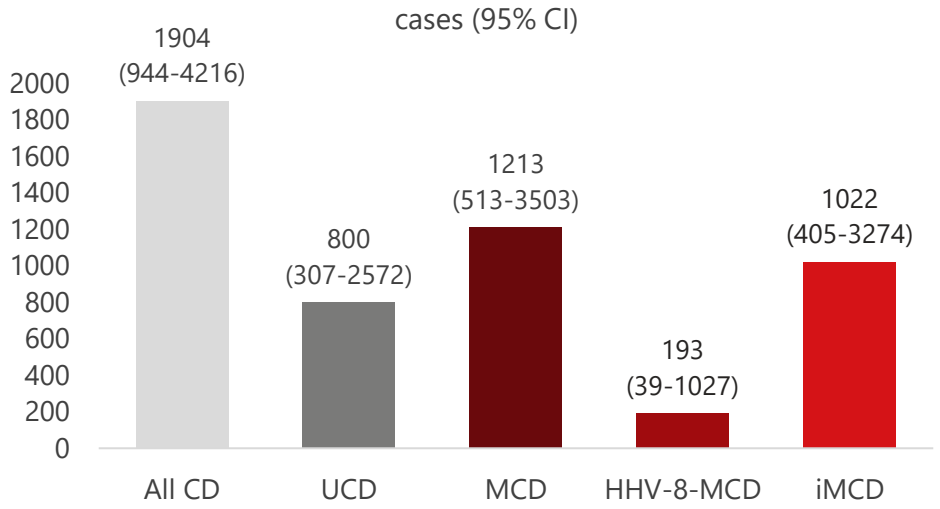
Epidemiology of Castleman Disease

Incidence and prevalence can vary across subtypes of Castleman disease (CD).[1]

A specific ICD-10 diagnosis code for CD (D47.Z2) was introduced in 2016, and diagnostic criteria for iMCD and UCD were published in 2017 and 2020, respectively.[2-4] More accurate estimations of epidemiology are expected.

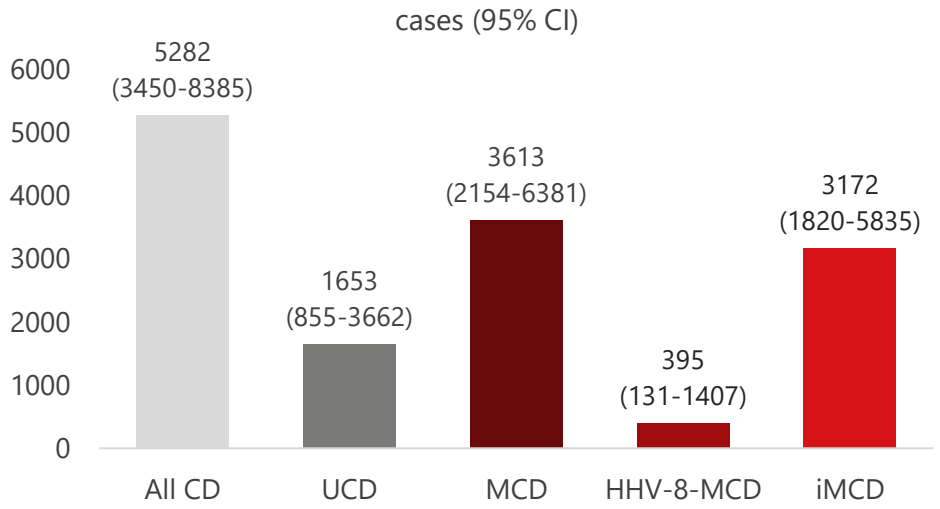
Incidence

Estimated New Annual Cases in the US in 2018[1]



Prevalence

Estimated Total Cases in the US in 2018[1]



*__Study Methodology:__ A retrospective claims-based analysis evaluated the burden of illness using Truven MarketScan® data in the US from 2006 to 2020. Out of 30.7 million eligible patients, 254 were identified as having iMCD based on diagnosis code and ≥2 minor diagnostic and lab criteria.[1] The incidence of iMCD likely reflects individuals with a new diagnosis, and the prevalence of iMCD likely reflects individuals with a diagnosis currently listed in their medical records. Patients with claims associated with the ICD-9 code before 2017 were not included in incidence calculations. __Limitations:__ The data from this analysis is retrospective and has less evidentiary value than prospective studies. The study uses health claims datasets, which lack histopathology confirmation and detailed clinical documentation, are subject to coding and data entry errors, and thus results cannot be generalized to the full U.S. patient population. This research was sponsored by EUSA Pharma, now owned by Recordati Rare Diseases Inc. One of its employees participated in the analysis and interpretation of data.

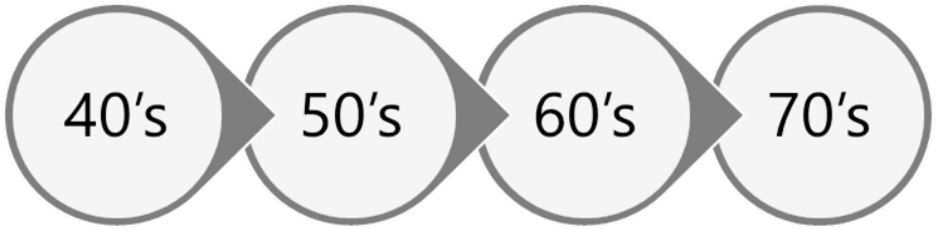
Abbreviations: CD, Castleman disease; CI, confidence interval; HHV-8, human herpes virus-8; iMCD, idiopathic multicentric CD; MCD, multicentric CD; UCD, unicentric CD.

References: 1. Mukherjee S, et al. *Blood Advances*. 2022; 6(2):359-367. 2. Hoffmann C, et al. *Oncol Res Treat*. 2022;45(11):693-704. 3. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. 4. van Rhee F, et al. *Blood Adv*. 2020;4(23):6039-6050.

Epidemiology of Castleman Disease

Age: patients of all ages, including young children, can be diagnosed with any form of Castleman disease (CD)[1-3]

Average age at diagnosis[1]:



- UCD
- **iMCD**
- POEMS-MCD
- HHV-8–MCD*
- **iMCD**
- HHV-8–MCD†

*HIV-positive. †HIV-negative.

Gender:

- **UCD:** no gender associations[3‡]
- **POEMS syndrome:** males slightly more affected[4§]
- **HHV-8–MCD:** majority male[3‡]
- **iMCD:** no gender associations[3‡]

‡A retrospective claims-based analysis evaluated the burden of illness using Truven MarketScan® data in the US from 2006 to 2020. Out of 30.7 million eligible patients, 254 were identified as having iMCD based on diagnosis code and ≥2 minor diagnostic and lab criteria.[3]
§POEMS–MCD unknown. Data from a literature-based analysis of 600 studies, which included 1,946 cases of POEMS syndrome in Chinese patients.[4]

Race: no ethnicity associations[5]

- In a US study using the National Inpatient Sample (NIS), 791 hospitalizations of patients with CD were identified.[6‖] Of these patients, the majority of total hospitalizations were White (50.1%), Black (28.1%), and Hispanic (12.8%) patients.

‖A retrospective analysis evaluated hospital stays using the NIS database from 2016 to 2019. Out of 24 million hospital stays, 791 adult patients (18 years old) with a clinical diagnosis of CD (ICD-10 code, D47.Z2) were identified.[6]

Abbreviation: CD, Castleman disease; HHV-8, human herpes virus-8; iMCD, idiopathic multicentric CD; MCD, multicentric CD; ICD, International Classification of Diseases; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; UCD, unicentric CD; US, United States.

References: 1. Dispenzieri A, Fajgenbaum DC. *Blood*. 2020;135(16):1353-1364. 2. Borocco C, et al. *Orphanet J Rare Dis*. 2020;15(1):95. 3. Mukherjee S, et al. *Blood Advances*. 2022;6(2):359-367 4. Wang Y, et al. *Front Immunol*. 2019;10:1428 5. Carbone A, et al. *Nat Rev Dis Primers*. 2021;7:84. 6. Patel R, et al. *Ann Hematol*. 2024;103(4):1255-1260.

Epidemiology of Castleman Disease

Survival

Overall Survival (OS) Rates	
UCD[1]*	95% 5-year OS
HHV-8–MCD[2†]	92% 5-year OS
POEMS syndrome[3‡]	79% 5-year OS
iMCD[1,4*§]	**74-84% 5-year OS**

*A 15-year retrospective study of patients with CD at 12 major health centers in the US and China (1994 to 2018; N=428).[1]
†A prospective cohort analysis of 84 patients with HIV–positive HHV-8–MCD treated with risk-stratified rituximab-based therapy over a median follow-up period of 6.9 years.[2]
‡POEMS–MCD survival is unknown. This data is from a study that included 291 patients with POEMS syndrome diagnosed at the Mayo Clinic between 1974 and 2014.[3]
§An analysis using a machine learning model that identified 267 patients with iMCD from the Flatiron Health database, which included over 3.5 million patients from ~280 US cancer clinics and ~800 sites of care in the US.[4]

Prognosis

Associated risk factors for worse OS in patients with iMCD[1]:

- Age >60 years
- B symptoms
- Serous effusion
- Enlarged liver and/or spleen
- Leukopenia
- Low hemoglobin
- Low albumin

Risk Factors

- There are no known risk factors for UCD, POEMS–MCD, or iMCD[5]
- The primary risk factor for HHV-8–MCD is being immunocompromised[5]

The mortality rate of iMCD was historically reported as 35% within 5 years of diagnosis.[6] The improvement in survival rates can be attributed to several factors, including the establishment of formal diagnostic criteria, the approval of targeted therapies, and the development of comprehensive treatment guidelines.[6,7] This emphasizes the importance of a rapid, definitive diagnosis and subsequent recommended therapy.

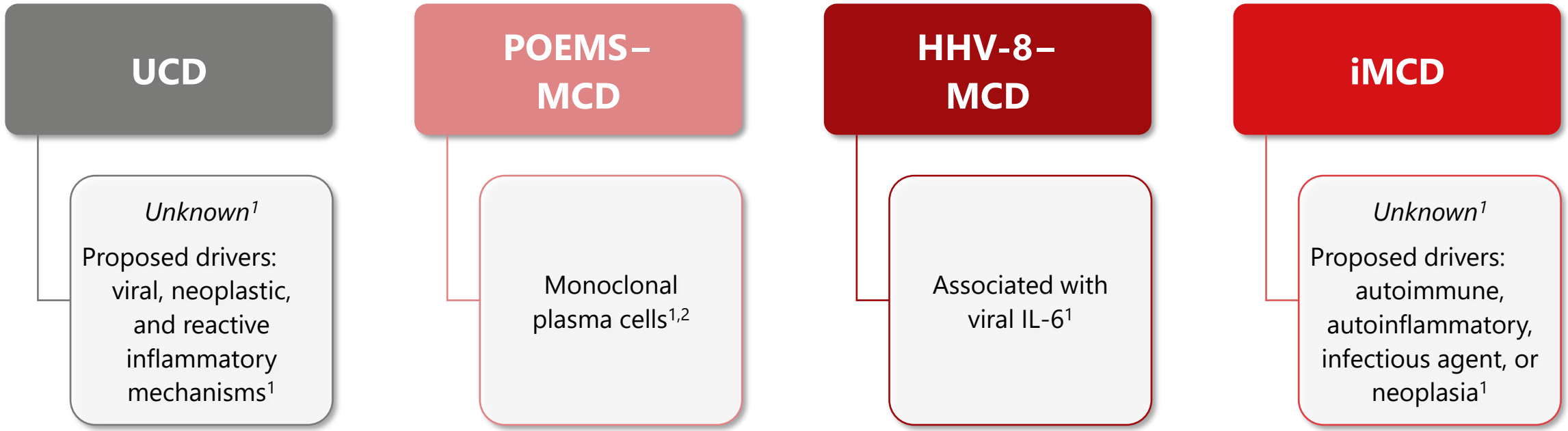
Unmet needs persist in patients with iMCD[4]

Abbreviations: CD, Castleman disease; iMCD, idiopathic multicentric CD; HHV-8, human herpes virus-8; MCD, multicentric CD; OS, overall survival; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin change; UCD, unicentric CD; US, United States.

References: 1. Liu W, et al. *Am J Cancer Res*. 2022;12(9):4227-4240. 2. Pria et al. *Blood*. 2017;129:2143–2147. 3. Kourelis TV, et al. *Am J Hematol*. 2016;91(6):585-589. 4. Cohen A, et al. *Blood*. 2023;142(suppl 1): 907. 5. Dispenzieri A, Fajgenbaum DC. *Blood*. 2020;135(16):1353-1364. 6. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. 7. van Rhee F, et al. *Blood*. 2018;132(20):2115-2124.

Etiology of Castleman Disease Subtypes

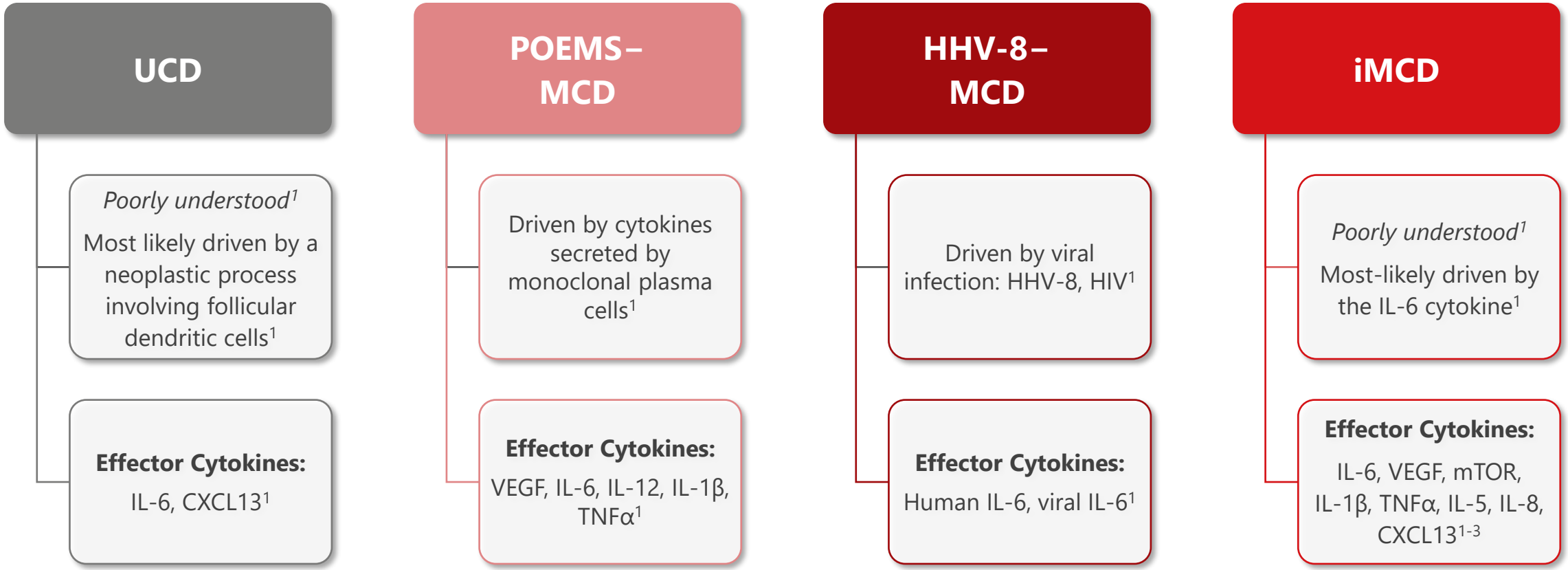
The etiology varies across the different subtypes of Castleman disease (CD).[1,2]



Abbreviations: CD, Castleman disease; HHV-8, human herpes virus-8; iMCD, idiopathic multicentric CD; IL-6, interleukin-6; MCD, multicentric CD; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin change; UCD, unicentric CD.

References: 1. Fajgenbaum DC, Shilling D. *Hematol Oncol Clin N Am.* 2018;32:11-21. 2. Dispenzieri A, Fajgenbaum DC. *Blood.* 2020;135(16):1353-1364.

Pathogenesis of Castleman Disease Subtypes



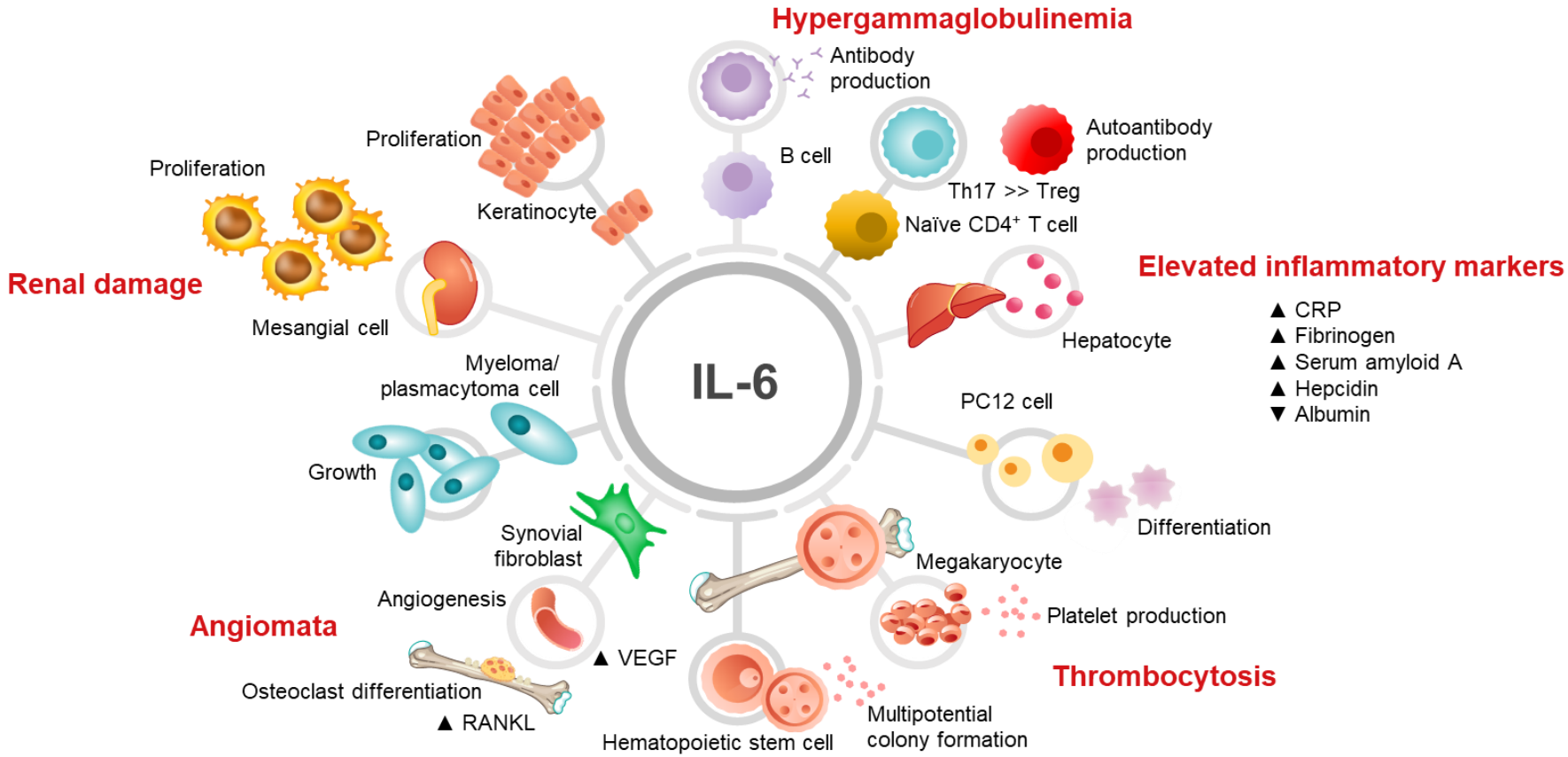
Abbreviations: CD, Castleman disease; CXCL13, cysteine-X-cysteine motif chemokine ligand 13; HHV-8, human herpes virus-8; HIV, human immunodeficiency virus; iMCD, idiopathic multicentric CD; IL, interleukin; MCD, multicentric CD; mTOR, mammalian target of rapamycin; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin change; TNFα, tumor necrosis factor α, UCD, unicentric CD; VEGF, vascular endothelial growth factor.

References: 1. Fajgenbaum DC, Shilling D. *Hematol Oncol Clin N Am.* 2018;32:11-21. 2. Hoffmann C, et al. *Oncol Res Treat*. 2022;45(11):693-704. 3. Fajgenbaum DC. *Blood*. 2018;132(22):2323-2330.

Overproduction of IL-6

IL-6 is a cytokine that produces an inflammatory storm across many tissues and organs.[1,2]

Most signs and symptoms of iMCD have been linked to overproduction of IL-6.[1] However, the cause of increased IL-6 in iMCD is unknown.[2]



Adapted from Tanaka T, et al. *Cancer Immunol Res*. 2014;2(4):288-294.

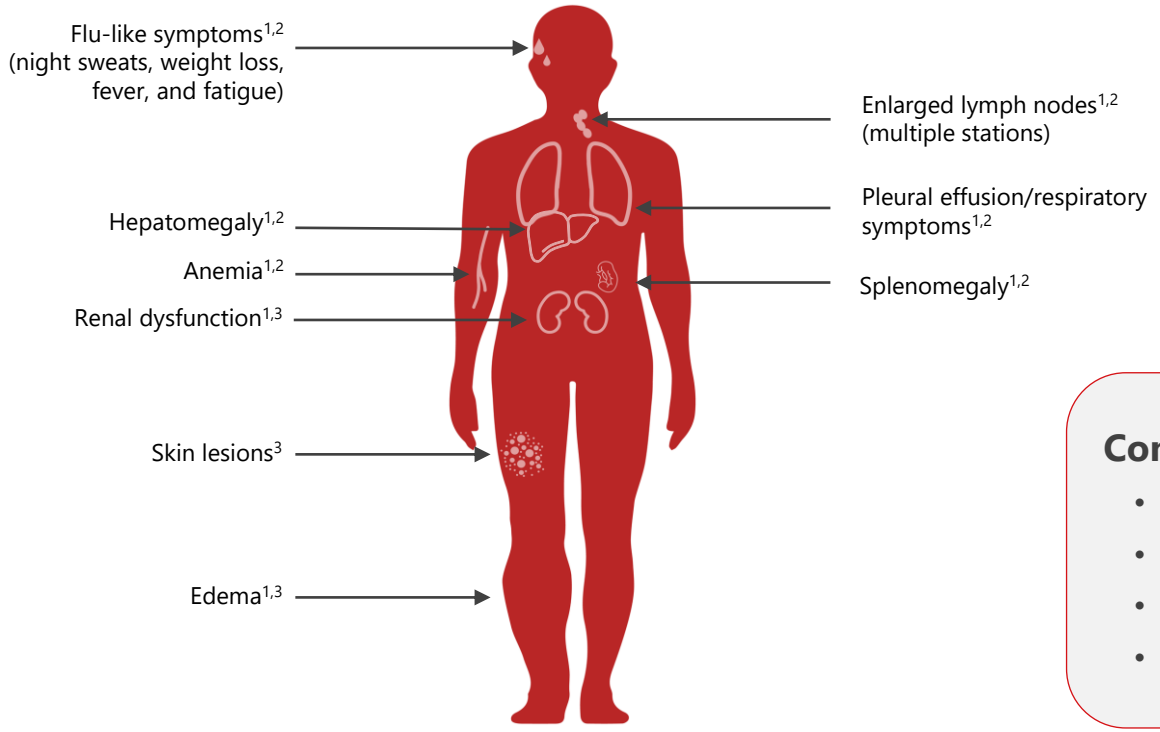
Abbreviations: CRP, C-reactive protein; iMCD, idiopathic multicentric Castleman disease; IL-6, interleukin-6; PC12, pheochromocytoma cell line; RANKL, receptor activator of nuclear factor-κβ ligand; Th17 cell, T-helper cell 17; VEGF, vascular endothelial growth factor.

References: 1. Yoshizaki K, et al. *Hematol Oncol Clin N Am*. 2018;32(1):23-36. 2. Tanaka T, et al. *Cancer Immunol Res*. 2014;2(4):288-294.

Clinical Features of iMCD

iMCD can be challenging to diagnose due to its heterogeneous clinical presentation and overlap with other conditions.[1]

Clinical features of iMCD may include:



Common laboratory findings:[1-3]

- Elevated ESR, IL-6, VEGF, and CRP
- Hypoalbuminemia
- Hypergammaglobulinemia
- Thrombocytopenia, thrombocytosis

The clinical spectrum of iMCD ranges from mild constitutional symptoms to multiorgan failure.[1,3]

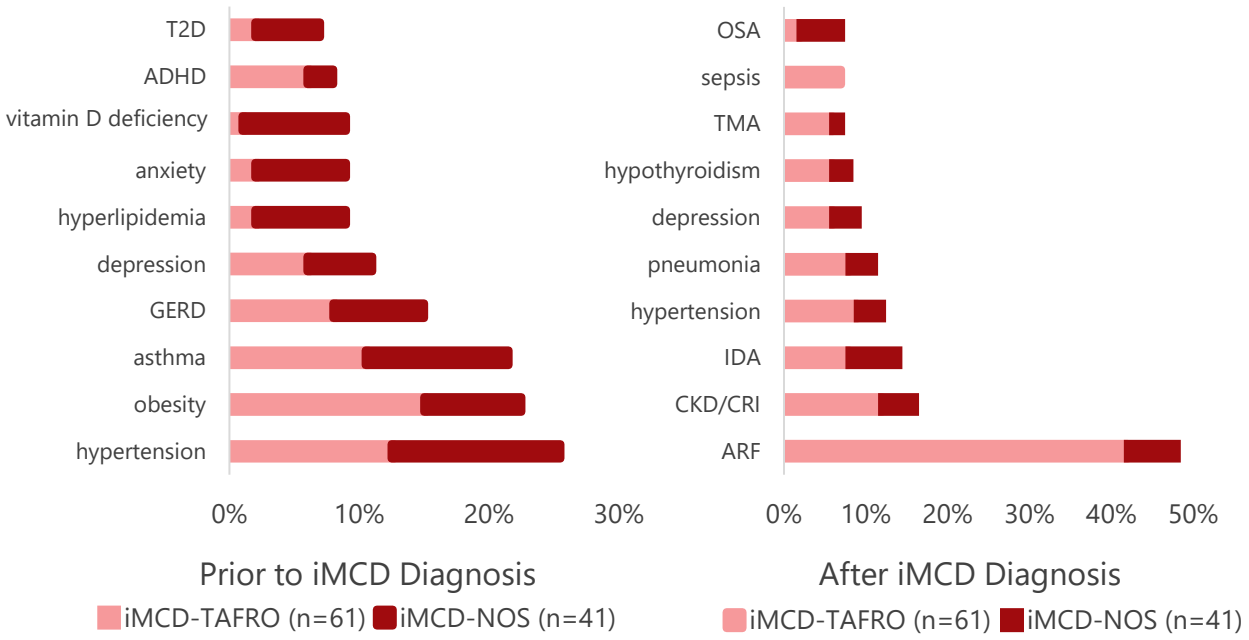
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; iMCD, idiopathic Multicentric Castleman Disease; VEGF, vascular endothelial growth factor.

References: 1. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. 2. Liu AY *et al. Lancet Haematol.* 2016;3(4):e163–e175. 3. Oksenhendler E *et al. Br J Haematol.* 2018;180(2):206–216.

Clinical Features of iMCD

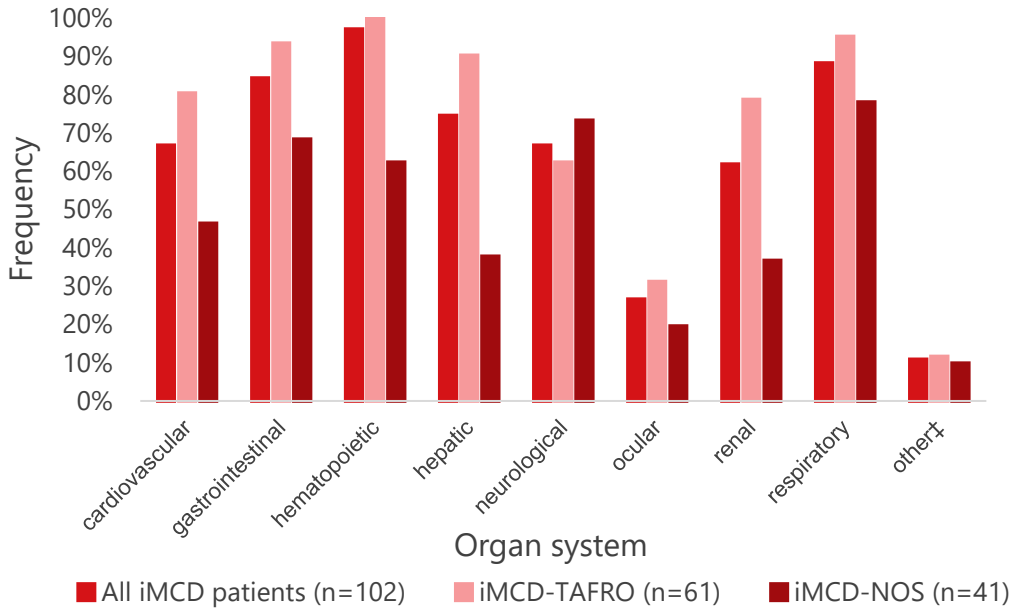
Patients with iMCD often have serious comorbidities and multiple organ dysfunction.[1-3]

Top 10 Comorbidities Among Patients with iMCD Before and After Diagnosis[1]*



*A natural history study evaluating the burden of illness using the ACCELERATE Natural History registry (NCT02817997) in 102 patients with iMCD (iMCD-NOS, n=41; iMCD-TAFRO, n=61).[1]

Organ System Involvement Among Patients with iMCD[1,2†]



†A natural history study evaluating the burden of illness using the ACCELERATE Natural History registry (NCT02817997) in 102 patients with iMCD.[1]
‡Other is comprised of penile/scrotal pain, back pain, mouth sores/ulcers, ear bleeding, and sclerotic lesions.[2]

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ARF, acute renal failure; CKD/CRI, chronic kidney disease/chronic renal insufficiency; GERD, gastroesophageal reflux disease; IDA, iron deficiency anemia; iMCD, idiopathic multicentric Castleman disease; NOS, not otherwise specified; OSA, obstructive sleep apnea; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly; TMA, thrombotic microangiopathy; T2D, type 2 diabetes.

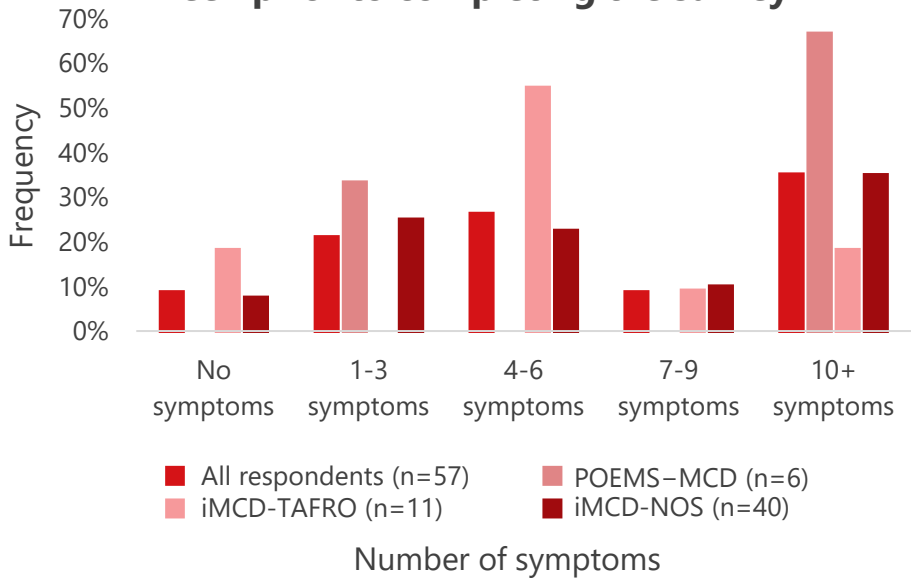
References: 1. Bustamante MS, et al. *Haematologica*. 2024;109(7):2196-2206. 2. Bustamante MS, et al. *Haematologica*. Supplementary appendix. 2024;109(7):2196-2206. 3. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657.

Burden of Symptoms

In a survey of patients with iMCD and informal caregivers, patients experienced an average of 7 symptoms in the week before they completed the survey.[1,2]

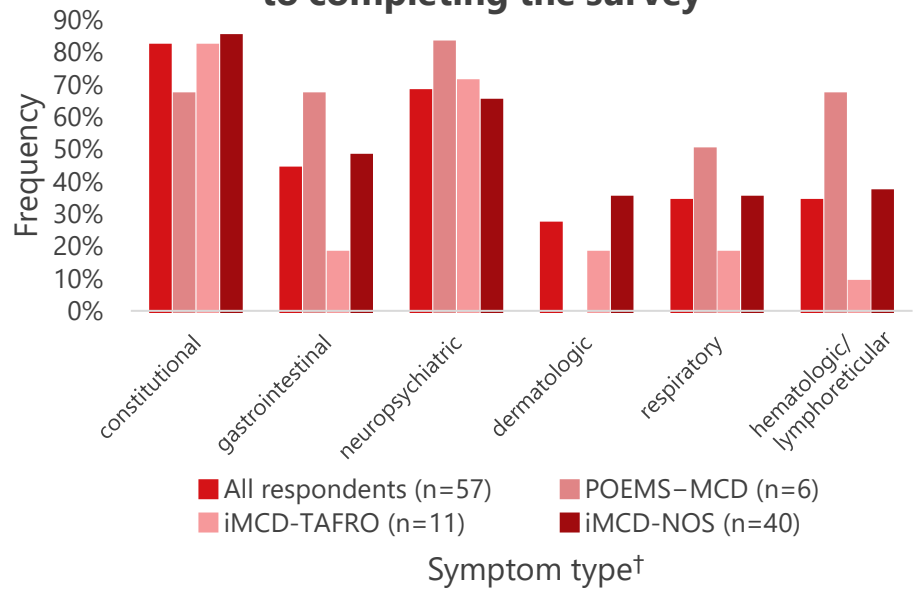
The number of symptoms varied, ranging between 0 and 22.[2]

Number of symptoms experienced a week prior to completing the survey[1,2*]



Constitutional symptoms were most commonly reported.[2]

Type of symptoms experienced a week prior to completing the survey[1,2*]



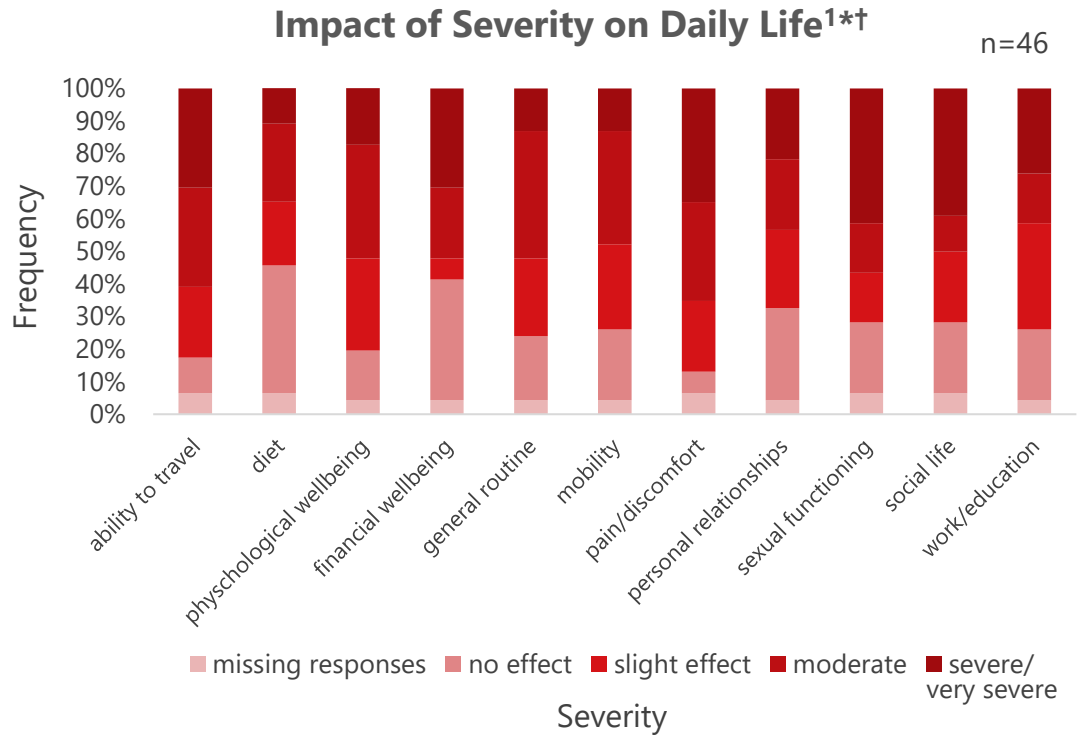
*An international patient-based survey from April 2021 to November 2021 to assess the burden of disease-related symptoms and the effects of symptoms on daily life.[1,2] The survey included 57 patients with a physician-confirmed diagnosis of iMCD-NOS, iMCD-TAFRO, or POEMS-MCD.[1] †Type of symptoms were grouped as follows – Constitutional symptoms: tiredness, weakness (physical), fever, night sweats, weight loss, weight gain, flu-like symptoms, sweating/hot flashes, dry mouth, sluggishness, and stupor/feeling lethargic; Gastrointestinal symptoms: loss of appetite, abdominal pain, bloating, nausea/vomiting; Neuropsychiatric: numbness/tingling, dizziness, impaired cognitive function, depression, anxiety, forgetfulness, headaches; Dermatologic: sores/rashes, persistent itching; Respiratory: cough and shortness of breath; Hematologic/Lymphoreticular: swollen lymph nodes.[1]

Abbreviations: iMCD, idiopathic multicentric Castleman disease; MCD, multicentric Castleman disease; NOS, not otherwise specified; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly.

References: 1. Shupo F, et al. Poster presented at: CDCN 11th Annual "Accelerating Research & Treatments for Castleman disease"; December 10, 2022; New Orleans, LA. 2. Mukherjee S, et al. *EClinicalMedicine*. 2023;64:102192.

Burden of Illness on Daily Life

In a survey of patients with iMCD and informal caregivers, more than half of patients who experienced any iMCD symptom reported moderate to very severe impact on daily life.[1]



Average of 6.7 (range: 0 to 22) symptoms per patient[1]

Age, gender, and employment status played a role in how symptoms impact daily life[1]

Caregivers face challenges that affect their social lives, emotional well-being, and more[1]

*An international patient-based survey from April 2021 to November 2021 to assess the burden of disease-related symptoms and the effects of symptoms on daily life.[1] The survey included 51 patients with a physician-confirmed diagnosis of iMCD-NOS or iMCD-TAFRO. The burden of Illness (BOI) was quantitatively measured using a 5-point frequency Likert scale (from 0, 'Does not affect my daily life' to 4, 'Very severely affects my daily life'), and mean impact scores (MIS) were calculated. †Sample size of n=46 accounts for only those patients who reported experiencing symptoms, with 5 patients having reported not experiencing any iMCD symptoms.[1]

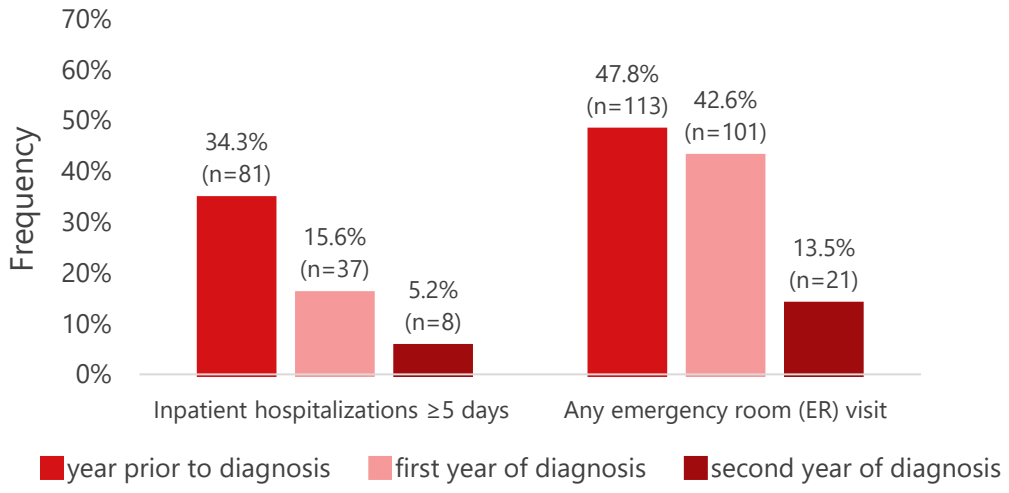
Abbreviations: iMCD, idiopathic multicentric Castleman disease; NOS, not otherwise specified; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly.

References: 1. Mukherjee S, et al. *EClinicalMedicine*. 2023;64:102192.

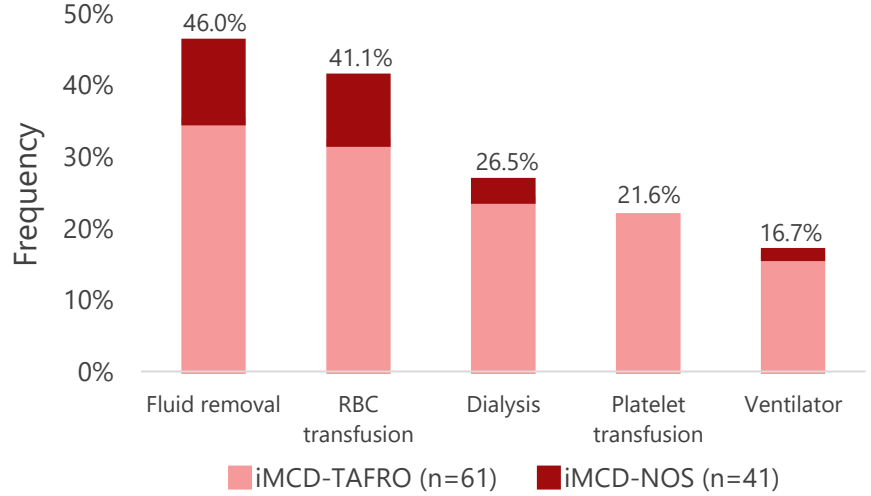
Need for Healthcare Resources

iMCD is associated with disease-related morbidity and the need for healthcare resources.[1]

A High Proportion of Patients With iMCD Require ER Visits and Hospitalizations[1]



A High Proportion of Patients With iMCD Require Supportive Care[2]



***Study Methodology:** A retrospective claims-based analysis evaluated the burden of illness using Truven MarketScan® data in the US from 2006 to 2020.[1] Out of 30.7 million eligible patients, 271 were identified as having iMCD based on diagnosis code and ≥2 minor diagnostic and lab criteria. Key morbidities and healthcare metrics were analyzed using iMCD patients matched with non-iMCD controls. **Limitations:** The data from this analysis is retrospective and has less evidentiary value than prospective studies. The study uses health claims datasets, which lack histopathology confirmation and detailed clinical documentation, are subject to coding and data entry errors, and thus results cannot be generalized to the full U.S. patient population.

†A natural history study evaluating the burden of illness using the ACCELERATE Natural History registry (NCT02817997) in 102 patients with iMCD (iMCD-NOS, n=41; iMCD-TAFRO, n=61).[2]

Abbreviations: ER, emergency room; iMCD, idiopathic multicentric Castleman disease; NOS, not otherwise specified; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly.

References: 1. Mukherjee S, et al. *Leukemia*. 2022;36(10):2539-2543. 2. Bustamante MS, et al. *Haematologica*. 2024;109(7):2196-2206.

Delayed Diagnosis of Castleman Disease

Diagnostic Delay in Patients with CD[1*]

- A retrospective analysis of 1634 patients with CD from 40 institutions in China showed a maximum time to diagnosis of **353 months** in patients with MCD and **362 months** in patients with UCD.

Time to Diagnosis[1]		
CD subtype	**≥12 months after initial onset of symptoms, n (%)**	**Maximum time to diagnosis, months**
UCD (n=668)	177 (26.5)	362
MCD (n=572)	215 (37.6)	353

*A national, multicenter, retrospective study of CD in China implementing CDCN criteria in CD patients (CD, N=1634; UCD, n=903; MCD, n=731) at 40 Chinese institutions from 2000 to 2021.[1]

Diagnosing iMCD is challenging[2,3]

- Lack of unique biomarkers[2,3]
- Overlapping symptoms with infectious, immune, and malignant diseases[2]
  - Clinical hallmarks: lymphadenopathy, fever, night sweats, hypoalbuminemia, anemia, ascites, hepatosplenomegaly, elevated C-reactive protein (CRP)[2]

Diagnostic delays among patients with CD contribute to an overall increase in the **burden of disease** and an increase in **morbidity** and **mortality** for these patients.[2,3]

A major cause of **delayed diagnosis** in iMCD is **clinical presentation** (i.e., nonspecific symptoms and unknown etiologies).[1-3]

Abbreviations: CD, Castleman disease; CDCN, Castleman Disease Collaboration Network; iMCD, idiopathic multicentric CD; MCD, multicentric CD; UCD, unicentric CD.

References: 1. Zhang L, et al. *Lancet Reg Health West Pac*. 2023;34:100720. 2. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. 3. Zinzani PL, et al. *Hemasphere*. 2023;7(6):e891.

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Diagnostic Criteria for iMCD

Major criteria (both needed)[1]	
1. Histopathologic lymph node features consistent with iMCD (**using an excisional lymph node biopsy**; see the following slide) 2. Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations (**using CT/PET scans**; see the following slide)	
Minor criteria (≥2 of 11 including ≥1 laboratory criterion)	
Laboratory	**Clinical**
1. Elevated ESR or CRP* 2. Anemia 3. Thrombocytopenia or thrombocytosis 4. Renal dysfunction or proteinuria 5. Polyclonal hypergammaglobulinemia 6. Hypoalbuminemia	1. Constitutional symptoms 2. Large spleen and/or liver 3. Fluid accumulation 4. Eruptive cherry angiomata or violaceous papules 5. Lymphocytic interstitial pneumonitis
Exclusion criteria	
Must rule out mimickers of disease (see the following slide)	

Adapted from Fajgenbaum DC, et al. *Blood.* 2017;129(12):1646-1657.

*Evaluation of CRP is mandatory, and tracking is highly recommended, but ESR is acceptable where CRP is not available.

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ESR, Erythrocyte sedimentation rate; iMCD, idiopathic multicentric Castleman disease; PET, positron emission tomography.
Reference: 1. Fajgenbaum DC, et al. *Blood.* 2017;129(12):1646-1657.

Diagnostic Criteria for iMCD

Exclusion criteria (must rule out each of these diseases that can mimic iMCD)[1]

1. Infection-related disorders

- HHV-8 (infection documented with PCR; positive LANA-1 staining by IHC excludes iMCD)
- Clinical EBV-lymphoproliferative disorders (eg, infectious mononucleosis, chronic active EBV)
- Inflammation and adenopathy caused by other uncontrolled infections (eg, CMV, HIV, active TB)

2. Autoimmune/autoinflammatory diseases*

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

3. Malignant/lymphoproliferative disorders†

- Lymphoma (Hodgkin and non-Hodgkin)
- Multiple myeloma
- Primary lymph node plasmacytoma
- FDC sarcoma
- POEMS syndrome (considered a disease "associated" with CD)

4. Select Additional Features‡

- Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M
- Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
- Diagnosis of disorders that have been associated with HHV-8-negative MCD: paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (without diagnosing POEMS), glomerular nephropathy, myofibroblastic tumor

Adapted from Fajgenbaum DC, et al. *Blood.* 2017;129(12):1646-1657.

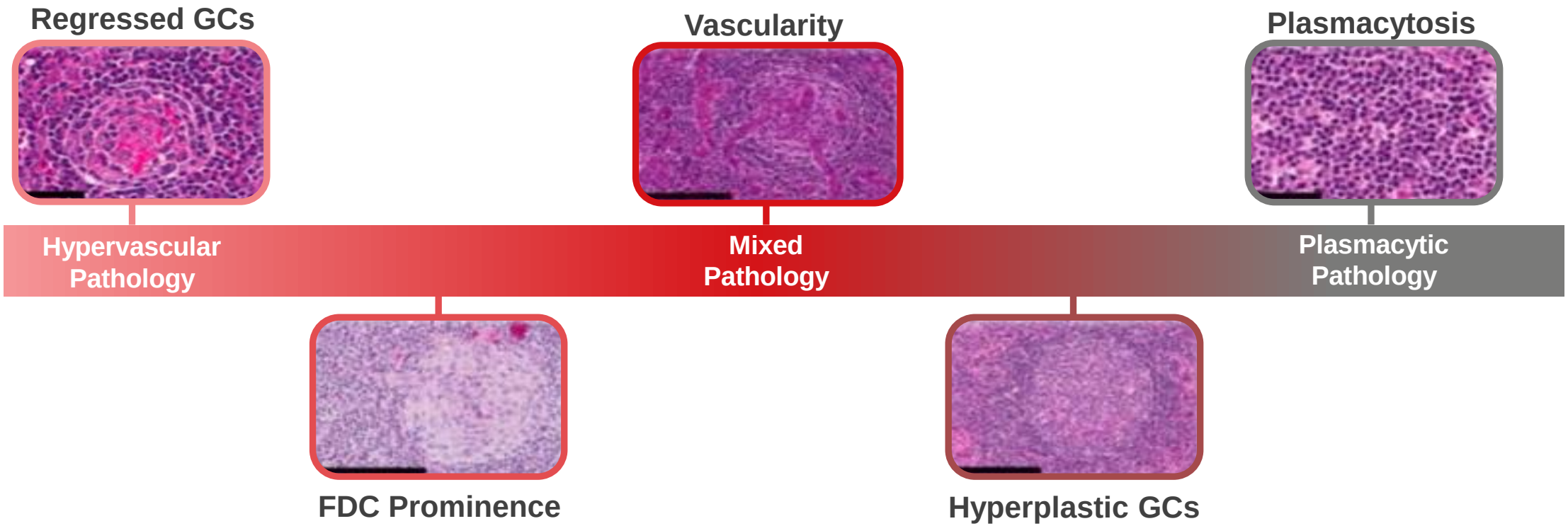
*Requires full clinical criteria; detection of autoimmune antibodies alone is not exclusionary. †Must be diagnosed before or at the same time as iMCD to be exclusionary. ‡Supportive, but not required for diagnosis.

Abbreviations: B2M, beta-2 macroglobulin; CD, Castleman disease; CMV, Cytomegalovirus; EBV, Epstein–Barr virus; FDC, follicular dendritic cell; HHV-8, human herpes virus-8; HIV, human immunodeficiency virus; IHC, immunohistochemical; IL-6, interleukin-6; iMCD, idiopathic multicentric CD; KSHV, Kaposi's sarcoma-associated herpesvirus; LANA, latency-associated nuclear antigen; LDH, lactate dehydrogenase; MCD, multicentric CD; PCR, polymerase chain reaction; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; sIL, serum interleukin; TB, tuberculosis; VEGF, vascular endothelial growth factor.

Reference: 1. Fajgenbaum DC, et al. *Blood.* 2017;129(12):1646-1657.

Role of Histopathology and Immunohistochemistry in iMCD

Patients need a Grade 2 or 3 for regressed germinal centers (GC) or plasmacytosis, as well as other features consistent with the iMCD histologic spectrum.[1]



Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. Copyright © 2017 American Society of Hematology.

The diagnosis of Castleman disease is dependent upon the expertise of both the treating clinician and the pathologist.[1]

Abbreviations: FDC, follicular dendritic cell; iMCD, idiopathic multicentric Castleman disease.

References: 1. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657.

Role of Imaging and Immunohistochemistry in Castleman Disease

Imaging and immunohistochemistry (IHC) are important steps in the definitive diagnosis of Castleman disease (CD).[1]

Imaging tests show how many lymph nodes are affected, thus distinguishing between UCD or MCD subtypes.[1]

- Imaging with combined fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) demonstrate the involvement of multiple sites.[2]
- CT of the neck, chest, abdomen, and pelvis may be chosen as an alternative, depending on the availability of imaging tests.[2,3]
- If a PET/CT scan is performed, a lymph node biopsy with the highest standardized uptake value (SUV) is recommended.[3]

IHC is part of both the major and exclusion criteria for the diagnosis of CD, specifically for iMCD.[1]

- As mentioned previously, IHC can determine lymph node features consistent with the iMCD histopathologic spectrum, such as hypervascularity, plasmacytosis, or mixed.[1]
- Diagnosis of HHV-8–associated MCD requires positive LANA-1 staining by IHC, thus excluding iMCD.[1]

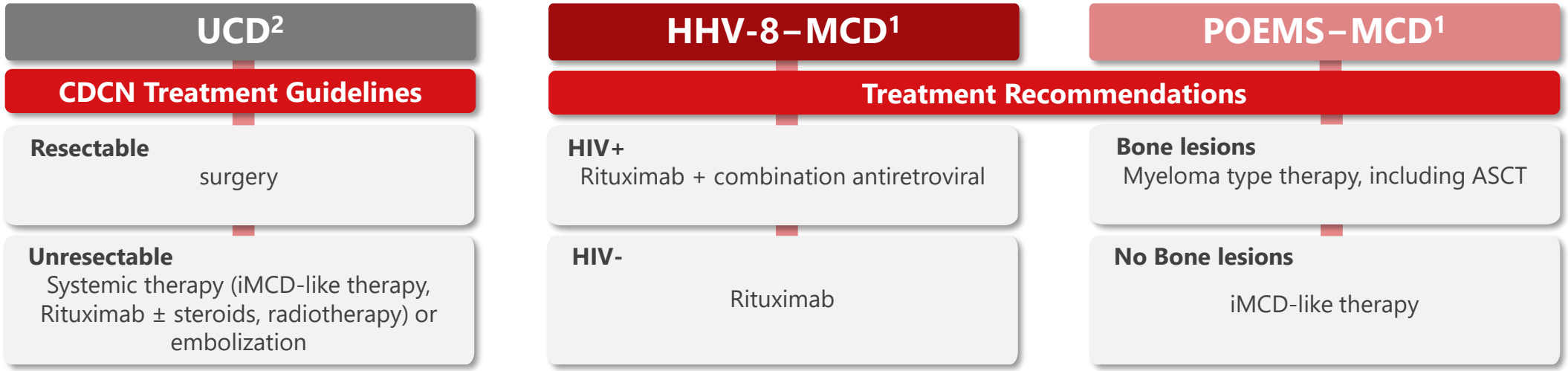
A definitive diagnosis of CD requires an **excisional lymph node biopsy**, as fine needle aspiration (FNA) and core needle biopsy (CNB) are insufficient procedures.[3]

Abbreviations: CD, Castleman disease; HHV-8, human herpes virus-8; iMCD, idiopathic multicentric CD; IHC, immunohistochemistry; LANA, latency-associated nuclear antigen; MCD, multicentric CD; UCD, unicentric CD.

References: 1. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. 2. van Rhee F, et al. *Blood*. 2018; 132: 2115-2124.. 3. Montes-Moreno S, et al. *Rev Esp Patol*. 2023;56(3):158-167.

Treatment Approaches for Castleman Disease Subtypes

The various types of Castleman disease (CD) have varying clinical outcomes and require different treatments.[1]



UCD is typically treated with surgical excision[3]

- Approximately 10% of cases may recur after excision, and 13% may be unresectable[4,5]
- Both should be treated like MCD

Improper treatment of MCD is common and can lead to progression and relapse[5]

See the following slide for treatment guidelines for iMCD

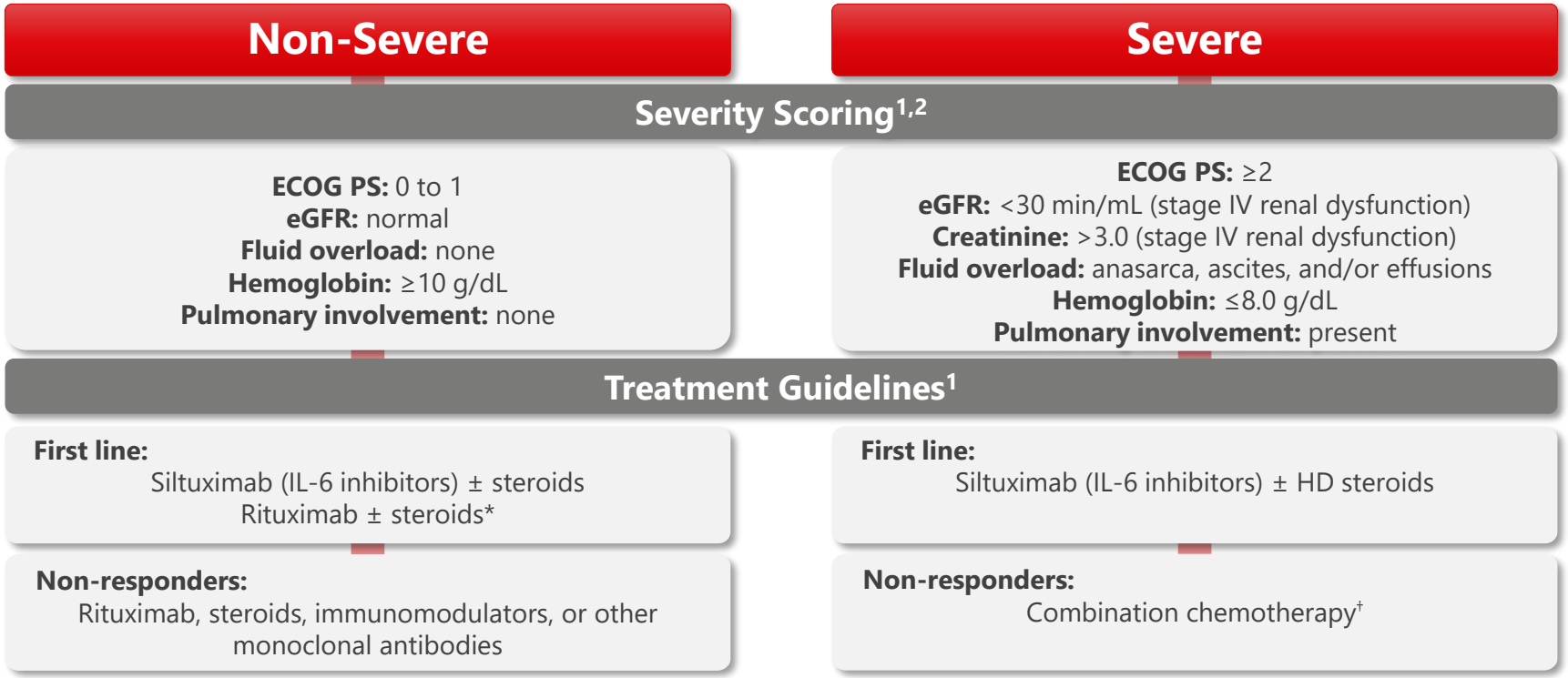
Abbreviations: ASCT, autologous stem-cell transplant; CD, Castleman disease; CDCN, Castleman Disease Collaborative Network; HHV-8, human herpes virus-8; HIV, human immunodeficiency virus; iMCD, idiopathic multicentric CD; MCD, multicentric CD; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; UCD, unicentric CD.

References: 1. Dispenzieri A, Fajgenbaum DC. *Blood*. 2020;135(16):1353-1364. 2. van Rhee, F. et al. *Blood Adv*. 2020;4:6039–6050. 3. Kaur H, et al. *Fed Pract*. 2015;32(suppl 7):41S-46S. 4. Mohan M, et al. *Blood*. 2018;132(suppl 1):2415. 5. Yu L, et al. *Blood*. 2017;129(12):1658-1668.

CDCN Treatment Guidelines for iMCD

iMCD is categorized into non-severe or severe disease[1]:

- Patients with non-severe iMCD typically have a good ECOG performance status without evidence of abnormal organ function[1,2]
- Patients with severe iMCD usually have evidence of organ failure, are likely to require critical care, and often present as the iMCD-TAFRO subtype[1]



*For patients with mild symptomatology, a limited course of rituximab is an alternative option.[2] †Examples of chemotherapy include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), R-VDT-PACE (rituximab, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide), or etoposide/ cyclophosphamide/rituximab.[2]

Abbreviations: CDCN, Castleman Disease Collaborative Network; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; HD, high-dose; IL-6, interleukin-6; iMCD, idiopathic multicentric Castleman disease; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly.

References: 1. van Rhee F, et al. *Blood*. 2018;132(20):2115-2124. 2. Dispenzieri A, Fajgenbaum DC. *Blood*. 2020;135(16):1353-1364.

Monitoring Treatment Response in Patients with iMCD

The CDCN response evaluation criteria take into account all aspects of iMCD, including clinical (symptoms), radiologic (lymph node), and laboratory (biochemical) responses.[1]

Overall Response	Biochemical	Lymph Node	Symptoms
CR	Normal CRP, Hemoglobin, Albumin, GFR	CR	Normalization to baseline
PR	>50% improvement in all of CRP, Hemoglobin, Albumin, GFR	PR	Improvement in all 4 symptom categories, but not to baseline
SD	<50% improvement (or <25% worsening) in all of CRP, Hemoglobin, Albumin, GFR	No PR or CR	Improvement in≥1 (but not all) symptoms
PD	>25% worsening in any of CRP, Hemoglobin, Albumin, GFR	>25% increase	Any symptoms worse on ≥2 assessments

Symptom	Improvement Criteria
Fatigue	Decrease of ≥1 CTC grade point relative to baseline
Anorexia	Decrease of ≥1 CTC grade point relative to baseline
Fever	Decrease of ≥1°C relative to baseline
Weight	Increase of ≥5% relative to baseline

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

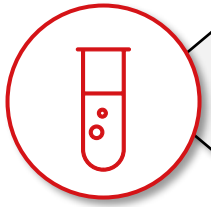
A complete response requires normalization of biochemical markers, lymph node response by CT scan, and improvements in clinical symptoms to baseline.[1]

Abbreviations: CDCN, Castleman Disease Collaborative Network; CR, complete response; CRP, C-reactive protein; CT, computed tomography; CTC, common toxicity criteria; GFR, glomerular filtration rate; IL-6, interleukin-6; iMCD, idiopathic multicentric Castleman disease; PD, progressive disease; PR, partial response; SD, stable disease.

Reference: 1. van Rhee F, et al. *Blood*. 2018;132(20):2115-2124.

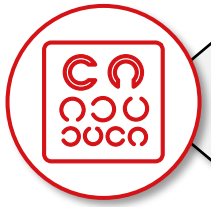
Follow-up for Patients with iMCD

The following outlines patient follow-up as part of the CDCN response evaluation criteria[1]:



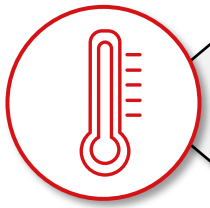
Laboratory: Objective biochemical markers of inflammatory response and organ function (hemoglobin, CRP, albumin, eGFR)

Response Evaluation: Monthly



Radiologic: Lymph node size

Response Evaluation: First recommended at 6 weeks and at 3-month intervals thereafter until maximum regression



Clinical: symptoms such as fatigue, anorexia, fever, and weight change, as assessed by the clinician

Response Evaluation: Monthly

Abbreviations: CDCN, Castleman Disease Collaborative Network; CRP, C-reactive protein; CT, computed tomography; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; iMCD, idiopathic multicentric Castleman disease.

Reference: 1. van Rhee F, et al. *Blood*. 2018;132(20):2115-2124.

Key Takeaways

Background & Classification

- CD refers to a heterogeneous group of rare cytokine-driven disorders.[1]
- Subtypes vary by the number of enlarged lymph node groups, histopathological features, and clinical presentation.[1]

Epidemiology, Etiology & Pathogenesis

- Incidence and prevalence vary across subtypes.[2]
- Over 1000 iMCD new cases are diagnosed yearly.[2]
- Patients of any age or gender can be diagnosed with any form of CD.[2,3]
- Overproduction of IL-6 is a key proposed driver in the pathogenesis of iMCD.[4]

Clinical Features

- The clinical spectrum of iMCD ranges from mild constitutional symptoms to multiorgan failure.[1]
- Patients often have serious comorbidities and multiple organ dysfunction.[1]

Diagnosis & Evaluation

- Diagnosis requires major, minor, and exclusion criteria.[1]
- A lymph node biopsy is required for diagnosis.[1]
- Excisional lymph node biopsy recommended.[1,5]

Treatment & Management

- Treatment varies by subtype and severity.[3,6]
- IL-6 inhibitors recommended for iMCD subtype.[6]
- Requires regular evaluation of biochemical markers, lymph node size, and clinical symptoms.[6]

Abbreviations: CD, Castleman disease; IL-6, interleukin-6; iMCD, idiopathic multicentric Castleman disease.

References: 1. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. 2. Mukherjee S, et al. *Blood Advances*. 2022; 6(2):359-367. 3. Dispenzieri A, Fajgenbaum DC. *Blood*. 2020;135(16):1353-1364. 4. Fajgenbaum DC, Shilling D. *Hematol Oncol Clin N Am*. 2018;32:11-21. 5. Montes-Moreno S, et al. *Rev Esp Patol*. 2023;56(3):158-167. 6. van Rhee F, et al. *Blood*. 2018;132(20):2115-2124.

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