Recognizing Idiopathic Multicentric Castleman Disease

HIV- and HHV-8–negative, idiopathic multicentric Castleman disease (iMCD) is a rare and serious disorder involving systemic inflammatory symptoms, lymphadenopathy, cytopenias, and multiple organ system dysfunction that can be caused by a cytokine storm often including interleukin-6.[1]

Epidemiology [2,3]

- Men and women are affected equally
- No clear associations with ethnicity established
- **Can occur at any age, median age 50 years**

In the U.S. [3]

>1,000

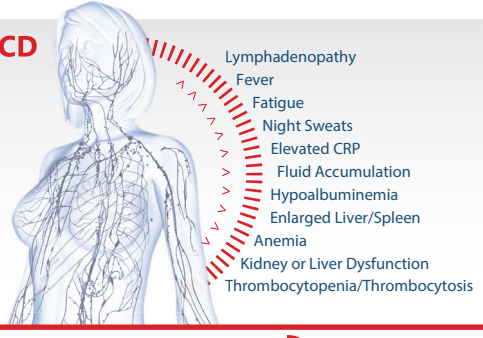
new cases annually

iMCD is associated with a 5-year overall survival of

84% [4]

Signs and Symptoms of iMCD can be driven by: [1,2,5]

IL-6



The clinical spectrum of iMCD ranges from mild constitutional symptoms to multiorgan failure [2]

UNDER-RECOGNIZED iMCD SYMPTOMS may lead to delay in diagnosis [5]

iMCD is associated with disease-related morbidity and the need for healthcare resources[2]

- Renal Failure [2]
- Increased Hospitalizations [2]
- Respiratory Failure [2]
- Hematologic Malignancies [2]
- Thromboses [2]
- Non-hematologic Malignancies [2]

HHV-8, Human Herpes Virus-8; HIV, Human Immunodeficiency Virus; IL-6, Interleukin-6; iMCD, idiopathic Multicentric Castleman Disease

1. Fajgenbaum DC et al. *Blood*. 2017;129:1646-1657. **2.** Hoffman C, et. al. *Oncol Res Treat* 2022;45:693–704. **3.** Mukherjee S et. al. *Blood Advances*. 2022;6(2):359-367. **4.** Cohen AB et al. *Blood*. 2023;142:907. https://doi.org/10.1182/blood-2023-174924. **5.** Carbone, A, et al. *Nat Rev Dis Primers* 2021;7:84

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Study Methodology [3]

- A retrospective claims-based analysis evaluated the burden of illness using Truven MarketScan data in the US from 2006-2020. Out of 30.7 million eligible patients, 254 were identified as having iMCD based on diagnosis code and ≥2 minor diagnostic and lab criteria.
- 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 record. Patients with claims associated with the ICD-9 code before 2017 were not included in incidence calculations.

Limitations [3]

- 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.

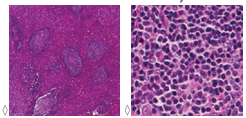
- This research was sponsored by EUSA Pharma now owned by Recordati Rare Diseases Inc. Some of its employees participated in the analysis and interpretation of data.

Diagnostic Criteria for iMCD [1]

Major Criteria
(Need both)

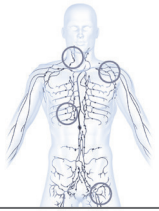
1

Histopathologic lymph node features consistent with the iMCD spectrum (need grade 2-3 for either regressive germinal centers or plasmacytosis at minimum)



2

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



Minor Criteria
(Need ≥2, with ≥1 laboratory criterion)

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

Laboratory*

1. Elevated CRP *(>10 mg/L) or ESR (>15 mm/h)*†
2. Anemia *(Hb <12.5 g/dL males, Hb <11.5 g/dL females)*
3. Thrombocytopenia *(platelet count <150 k/μL)* or thrombocytosis *(platelet count >400 k/μL)*
4. Hypoalbuminemia *(albumin <3.5 g/dL)*
5. Renal dysfunction *(eGFR <60 mL/min/1.73m²)* or proteinuria *(total 150 mg/24 h or 10 mg/100 mL)*
6. Polyclonal hypergammaglobulinemia *(total γ globulin or immunoglobulin G >1700 mg/dL)*

Exclusion Criteria
(Must rule out each of these diseases that can mimic iMCD)

Infection-related Disorders

- HHV-8 infection
- Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV
- Inflammation and adenopathy caused by other uncontrolled infections

Autoimmune/autoinflammatory diseases

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

Malignant/lymphoproliferative diseases

- Lymphoma (Hodgkin and non-Hodgkin)
- Multiple myeloma
- Primary lymph node plasmacytoma
- FDC sarcoma
- POEMS syndrome

Select additional features supportive of, but not required for diagnosis:

- Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or β_2M
- Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
- Diagnosis of disorders that have been associated with iMCD: paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (without diagnosing POEMS‡), glomerular nephropathy, inflammatory myofibroblastic tumor

* Laboratory cutoff thresholds are provided as guidance; however some laboratories have slightly different ranges. Use upper and lower ranges from your particular laboratory to determine if a patient meets a particular laboratory Minor Criterion.

† Evaluation of CRP is mandatory and tracking CRP levels is highly recommended, but ESR will be accepted if CRP is not available.

‡ POEMS is considered to be a disease "associated" with CD. Because the monoclonal plasma cells are believed to drive the cytokine storm, it is not considered iMCD, but rather "POEMS-associated MCD."

◊ Reprinted from Blood, 129/12, Fajgenbaum DC et al, International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease, Pages 1646-1657, © 2017, with permission from Elsevier.

CRP, C-Reactive Protein; CTCAE, Common Terminology Criteria for Adverse Events; EBV, Epstein-Barr virus; eGFR, estimated Glomerular Filtration Rate; ESR, Erythrocyte Sedimentation Rate; FDC, Follicular Dendritic Cells; Hb, Hemoglobin; HHV-8, Human Herpesvirus-8; IgA, Immunoglobulin A; IgE, Immunoglobulin E; LDH, Lactate dehydrogenase; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin changes; TAFRO, Thrombocytopenia, Anasarca/Ascites, Reticulin Fibrosis, Renal dysfunction, and Organomegaly; VEGF, Vascular Endothelial Growth Factor. **1.** Fajgenbaum DC et al. Blood. 2017;129:1646–1657.

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