

Consensus diagnostic criteria for idiopathic multicentric Castleman disease (iMCD)¹

CDCN Major Criteria

Upon examination, the lymph node must have histopathologic features consistent with CD. The patient is then sent for imaging if multiple lymph node groups are involved and MCD is suspected.

(Need both)

Histopathologic lymph node features consistent with the iMCD spectrum

Features along the spectrum include:
(need grade 2 to 3 for either regressive GCs or plasmacytosis at minimum)

Regressed/atrophic/atretic GCs, 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

Enlarged lymph nodes

≥1 cm in short-axis diameter in ≥2 lymph node stations

CDCN Minor Criteria

If the patient meets at least 2 minor criteria requirements (with at least 1 being a laboratory abnormality) for diagnosis of iMCD, disease is confirmed.

(Need ≥2 of 11 criteria with ≥1 laboratory criterion)

Laboratory^a

Elevated CRP (>10 mg/L) or ESR (>15 mm/h)^b

Anemia (hemoglobin <12.5 g/dL for males, hemoglobin <11.5 g/dL for females)

Thrombocytopenia (platelet count <150 k/μL) or thrombocytosis (platelet count >400 k/μL)

Hypoalbuminemia (albumin <3.5 g/dL)

Renal dysfunction (eGFR <60 mL/min/1.73 m²) or proteinuria (total protein 150 mg/24 h or 10 mg/100 mL)

Polyclonal hypergammaglobulinemia (total γ globulin or immunoglobulin G >1700 mg/dL)

Select additional features supportive of but not required for diagnosis

Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (≥2 CTCAE lymphoma score for B symptoms)

Enlarged spleen and/or liver

Fluid accumulation: edema, anasarca, ascites, or pleural effusion

Eruptive cherry hemangiomas or violaceous papules

Lymphocytic interstitial pneumonitis

Abbreviations: CD, Castleman disease; CRP, C-reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FDC, follicular dendritic cell; GCs, germinal centers; MCD, multicentric Castleman disease; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

^aLaboratory cutoff thresholds are provided as guidance, but it is recognized that some laboratories have slightly different ranges. It is suggested that you use the upper and lower ranges from your particular laboratory to determine if a patient meets a particular laboratory minor criterion.

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

^cPOEMS is considered to be a disease “associated” with CD. Because the monoclonal plasma cells are believed to drive the cytokine storm, the CDCN guidelines do not consider it iMCD, but rather “POEMS-associated MCD.”

Methodology

The CDCN convened an international working group comprising 34 pediatric and adult hematopathology, hematology/oncology, rheumatology, immunology, and infectious diseases experts in iMCD and related disorders, including 2 physicians that are also iMCD patients, to establish evidence-based, patient-guided, expert consensus diagnostic criteria for the treatment of iMCD. The working group reviewed clinical data from 244 iMCD cases using clinical and published data, as well as 79 cases from a randomized controlled study of siltuximab in subjects with symptomatic iMCD (NCT01024036).¹

CDCN Exclusion Criteria¹

After excluding other diseases that can mimic iMCD, one must exclude POEMS-associated MCD and HHV-8. If those subtypes of MCD are excluded, one must suspect iMCD.

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

Infection-related disorders

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)

Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (detectable EBV viral load not necessarily exclusionary)

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)

Systemic lupus erythematosus

Rheumatoid arthritis

Adult-onset Still disease

Juvenile idiopathic arthritis

Autoimmune lymphoproliferative syndrome

Malignant/lymphoproliferative disorders

(Must be diagnosed before or at the same time as iMCD to be exclusionary)

Lymphoma (Hodgkin and non-Hodgkin)

Multiple myeloma

Primary lymph node plasmacytoma

FDC sarcoma

POEMS syndrome^c

Select additional features supportive of but not required for diagnosis

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 iMCD: paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (without diagnosing POEMS^c), glomerular nephropathy, or inflammatory myofibroblastic tumor

Recent WHO international guidelines recognize the complexity of iMCD diagnosis^{2,3}

Contributors to the 5th edition of the WHO Classification of Haematolymphoid Tumors, composed of expert members in haematopathology, haematology, oncology, genetics, epidemiology, radiation oncology, immunology, and molecular biology, convened in 2021 to provide guidelines for the diagnosis and treatment of haematolymphoid tumours, including iMCD.³

Requirements for iMCD Diagnosis²

Fulfillment of morphologic, clinical, and laboratory criteria^a

Exclusion of other diseases, including HIV-infection, Kaposi sarcoma herpesvirus/human herpesvirus-8 (KSHV/HHV8) infection and other forms of Castleman disease

Histopathology²

The histopathologic findings in iMCD are variable and non-specific, with morphologic findings showing overlap with other forms of Castleman disease.^b

Essential Diagnostic Criteria²

Enlarged lymph nodes in ≥ 2 sites

Lymph node morphology showing Grade 2 or 3 regressed germinal centers or plasmacytosis

Clinical, laboratory, and exclusion criteria fulfilled

^aWHO laboratory criteria do not include hypoalbuminemia, a minor criteria listed in CDCN diagnostic guidelines.^{1,2}

^bOverlapping histopathological findings may include unicentric CD, MCD-POEMS (plasma cell neoplasm with associated paraneoplastic syndrome), and KSHV/HHV8-associated MCD.²

References: 1. 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(12):1646-1657. 2. WHO Classification of Tumours Editorial Board. *Haematolymphoid tumours* [Internet; beta version ahead of print]. WHO classification of tumours series, 5th ed.; vol. 11. Lyon (France): International Agency for Research on Cancer; 2022. Accessed May 31, 2023. <https://tumourclassification.iarc.who.int/chapters/63>. 3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748.