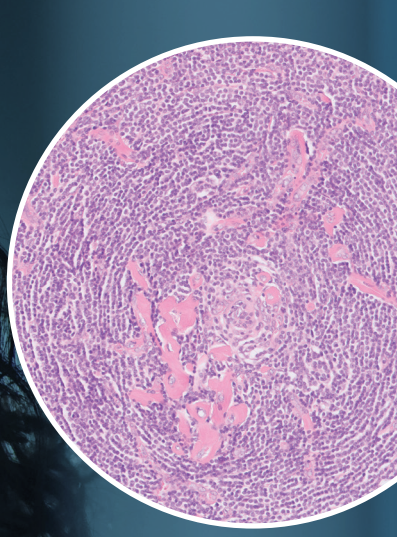


THINK iMCD

A guide to recognizing and diagnosing idiopathic multicentric Castleman disease (iMCD)

iMCD is a rare, cytokine storm–driven disease characterized by lymphadenopathy at multiple lymph node sites[1]

Expert guidelines from the CDCN and WHO can help identify and diagnose iMCD[1-3]

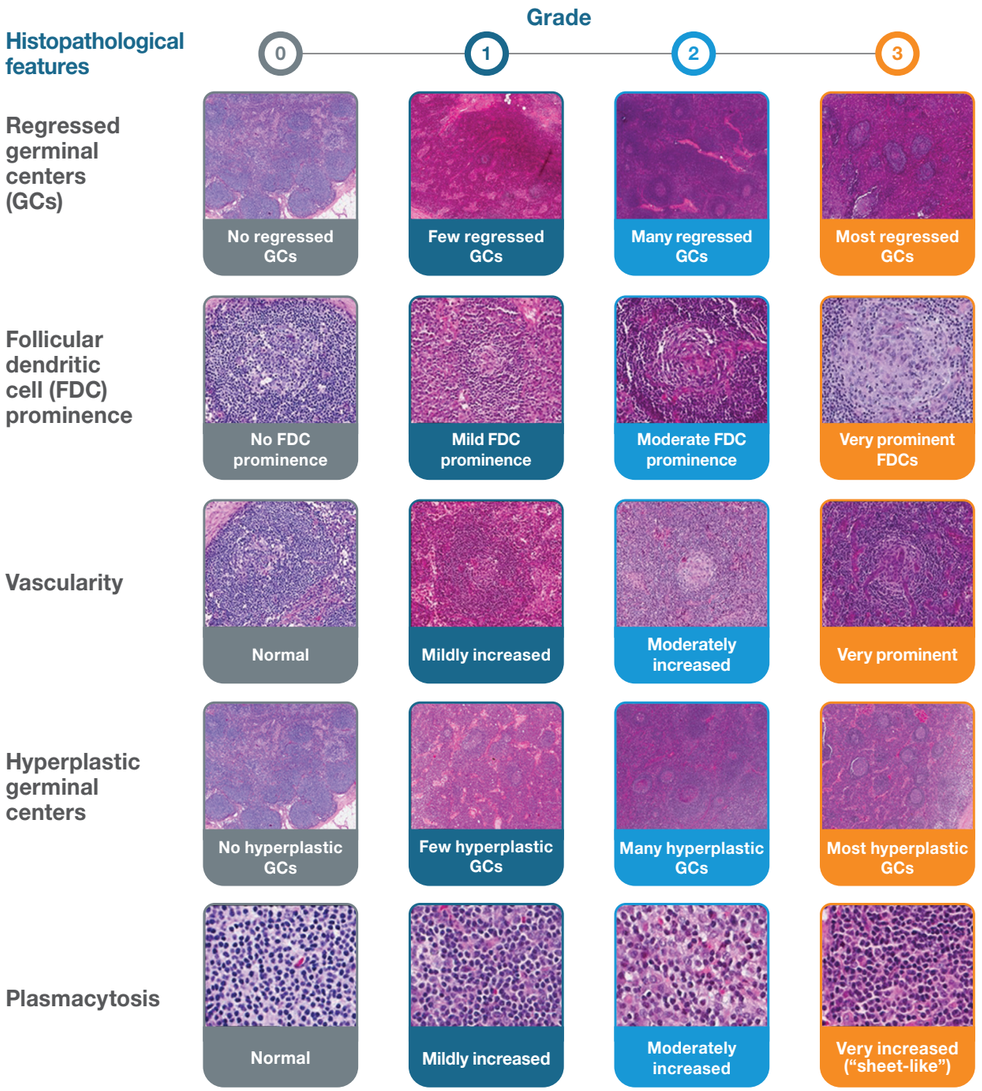
CDCN, Castleman Disease Collaborative Network; WHO, World Health Organization.

Expert guidance on the assessment of excisional biopsies for iMCD

Experts recommend following a 3-step process when assessing excisional lymph node biopsies[1]

Step 1 Grading

- There are 5 histopathological features that should be graded when assessing excisional biopsies for iMCD[1]
- Patients need a Grade 2 or 3 for regressed germinal centers or plasmacytosis, as well as other features consistent with the HHV-8–negative histologic spectrum[1]



Expert guidance on applying exclusion criteria and histopathological subtyping

Step 2 Exclusionary requirements

- Once the presence of histopathological features has been confirmed, a diagnosis of iMCD requires the exclusion of diseases that can have similar presentations[1]
- Some diseases can be excluded by pathology, and others must be excluded by the treating physician[1]

Step 3 Histopathological subtyping

- The final step in the process is to assess which histopathological subtype applies
- There are three established histopathological subtypes of iMCD[1]:
  - Hypervascular (hyaline-vascular)
  - Mixed
  - Plasmacytic pathology
- The clinical relevance of these subtypes remains somewhat unknown, but in certain scenarios, the confirmation of subtype may help drive treatment decisions[1]

Clinical collaboration with the treating physician facilitates appropriate diagnosis and management[1]

- Communicate and reinforce the need for an excisional biopsy or full architecture
- Determine definite diagnosis and create a dialogue with treating physician based on active communication and interactions, such as asking for full patient picture (i.e., lab values, definitive diagnosis) and proactively sharing full scope of analysis

Guidelines from the CDCN help identify and diagnose iMCD[1]

Major criteria (both needed)

1 Histopathologic lymph node features consistent with iMCD

2 Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations (e.g., neck and armpit)

Minor criteria (≥2 of 11 including ≥1 laboratory criterion)

Laboratory

1 Elevated CRP or ESR

2 Anemia

3 Thrombocytopenia/thrombocytosis

4 Renal dysfunction or proteinuria

5 Polyclonal hypergammaglobulinemia

6 Hypoalbuminemia

Clinical

1 Constitutional symptoms

2 Enlarged spleen and/or liver

3 Fluid accumulation

4 Eruptive cherry hemangiomatosis or violaceous papules

5 Lymphocytic interstitial pneumonitis

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 (e.g., 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

(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]

Select additional features supportive of but not required for diagnosis

1 Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M

2 Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)

3 Diagnosis of disorders that have been associated with iMCD: paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (without diagnosing POEMS[a]), glomerular nephropathy, or inflammatory myofibroblastic tumor

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

B2M, beta-2 microglobulin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; FDC, follicular dendritic cell; HHV-8, human herpesvirus-8; HIV, human immunodeficiency virus; IgA, immunoglobulin A; IgE, immunoglobulin E; IHC, immunohistochemistry; IL-6, interleukin-6; iMCD, idiopathic multicentric Castleman disease; LANA-1, latency-associated nuclear antigen 1; LDH, lactate dehydrogenase; MCD, multicentric Castleman disease; PCR, polymerase chain reaction; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; sIL-2R, soluble interleukin-2 receptor; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly; VEGF, vascular endothelial growth factor.

WHO international guidelines also recognize the complexity of iMCD diagnosis[2,3]

Requirements for iMCD diagnosis[2]

1 Fulfillment of morphologic, clinical, and laboratory criteria[a]

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

Histopathology[2]

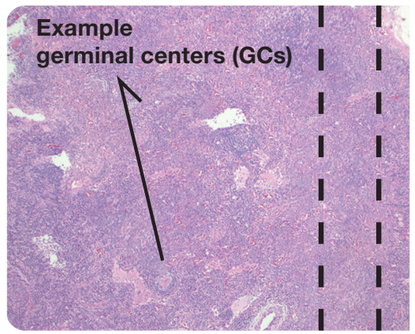
The histopathologic findings in iMCD are variable and non-specific, with morphologic findings showing overlap with other forms of Castleman disease[b]

Essential diagnostic criteria[2]

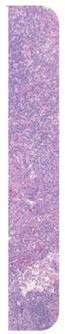
1 Enlarged lymph nodes in ≥2 sites

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

3 Clinical, laboratory, and exclusion criteria fulfilled



Excisional biopsy



Core biopsy

Image courtesy of Adam Bagg, MD. Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania.

Excisional biopsies are recommended by the CDCN as the most effective way to diagnose iMCD[1,4]

- Fine needle or core biopsies are unlikely to capture affected tissue and may be inadequate for accurate diagnosis[4,5]
- An excisional biopsy provides a more complete picture of the histopathological changes in an affected lymph node[4,5]

WHO Classification of iMCD: Contributors to the 5th edition of the WHO Classification of Haematolymphoid Tumors, composed of expert members in hematopathology, hematology, oncology, genetics, epidemiology, radiation oncology, immunology, and molecular biology, convened in 2021 to provide guidelines for the diagnosis and treatment of hematolymphoid tumors, including iMCD.[3]

[a]WHO laboratory criteria do not include hypoalbuminemia, a minor criterion listed in CDCN diagnostic guidelines.[1,2]

[b]Overlapping histopathological findings may include unicentric CD, MCD-POEMS (plasma cell neoplasm with associated paraneoplastic syndrome), and KSHV/HHV-8–associated MCD.[2]

THINK iMCD

Diagnosing iMCD relies on the confirmation of histopathological features[1]

Collaboration with the treating physician facilitates appropriate diagnosis and management[1]

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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. **4.** Carbone A, Borok M, Damania B, et al. Castleman disease. *Nat Rev Dis Primers.* 2021;7(1):84. **5.** Puram SV, Hasserjian RP, Faquin WC, Lin HW, Rocco JW. Castleman disease presenting in the neck: report of a case and review of the literature. *Am J Otolaryngol.* 2013;34(3):239-244.

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