Consensus diagnostic criteria for iMCD[1]

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

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 m^2) or proteinuria (total protein 150 mg/24 h or 10 mg/100 mL)
- ☐ Polyclonal hypergammaglobulinemia (total γ globulin or immunoglobulin G >1700 mg/dL)

Clinical

- ☐ 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 hemangiomatosis 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; iMCD, idiopathic multicentric Castleman disease; MCD, multicentric Castleman disease; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

[a] Laboratory 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.
[b] Evaluation of CRP is mandatory and tracking CRP levels is highly recommended, but ESR will be accepted if CRP is not available.
[c] POEMS is considered to be a disease "associated" with CD. Because the monoclonal plasma cells are believed to drive the cytokine storm, they do not consider it iMCD, but rather "POEMS-associated MCD."

METHODOLOGY

The Castleman Disease Collaborative Network (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).

Exclusion Criteria

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

Abbreviations: 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.

Reference: 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.

US-NPS-2100051 12/21

EUSA Pharma™ | Know iMCD