



Diagnostic criteria¹

ESTABLISH

Major criteria

- 1. Multiple enlarged lymph nodes**
 - Measuring ≥ 1 cm in short-axis diameter in multiple lymph node stations
- 2. Histopathologic lymph node features consistent with the iMCD spectrum**
 - Requires lymph node biopsy (excisional biopsy preferred)

ADD

Minor criteria

Need at least 2 of 11 minor criteria, with at least 1 laboratory parameter:

Clinical symptoms

- Constitutional symptoms: night sweats, fever ($>38^{\circ}\text{C}$), weight loss or fatigue (≥ 2 CTCAE lymphoma score for B-symptoms)
- Fluid accumulation: edema, anasarca, ascites or pleural effusion
- Large spleen and/or liver
- Eruptive cherry hemangiomas or violaceous papules
- Lymphocytic interstitial pneumonitis

Laboratory parameters

- Elevated CRP (>10 mg/L) or ESR (>15 mm/h)*
- Anemia (hemoglobin <12.5 g/dL for males, <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/ 1.73m^2) or proteinuria (total protein; 150 mg/24h or 10 mg/100ml)
- Polyclonal hypergammaglobulinemia (total γ globulin or immunoglobulin G >1700 mg/dL)

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

Abbreviations: **CD**, Castleman Disease; **CMV**, cytomegalovirus; **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 cell; **HHV-8**, human herpesvirus-8; **HIV**, human immunodeficiency virus; **IHC**, immunohistochemical staining; **iMCD**, idiopathic Multicentric Castleman Disease; **LANA-1**, latency-associated nuclear antigen; **PCR**, polymerase chain reaction; **POEMS**, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes.

Reference: 1. Fajgenbaum DC, et al. *Blood*. 2017; 129: 1646–57.

EXCLUDE

Exclusion criteria

Infection-related

- 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 (e.g., acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis)

Autoimmune/autoinflammatory

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

Requires full clinical criteria, detection of autoimmune antibodies alone is not exclusionary

Malignant/lymphoproliferative

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

These disorders must be assessed at the same time as iMCD to be exclusionary