International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease


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Article Title: International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease

Short Title: Diagnostic criteria for iMCD

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Key Points:
An international panel established the first ever diagnostic criteria for iMCD based on review of 244 clinical cases and 88 tissue samples.

The criteria require multicentric lymphadenopathy with defined histopathology, 2 or more clinical/lab changes, and exclusion of iMCD mimics.
Abstract:

Human Herpesvirus-8 (HHV-8)-negative, idiopathic multicentric Castleman disease (iMCD) is a rare and life-threatening disorder involving systemic inflammatory symptoms, polyclonal lymphoproliferation, cytopenias, and multiple organ system dysfunction due to a cytokine storm often including interleukin-6. iMCD accounts for one-third to one-half of all cases of MCD and can occur in individuals of any age. Accurate diagnosis is challenging, as no standard diagnostic criteria or diagnostic biomarkers currently exist, and there is significant overlap with malignant, autoimmune, and infectious disorders. An international working group comprising 34 pediatric and adult pathology and clinical experts in iMCD and related disorders from eight countries, including two physicians that are also iMCD patients, was convened to establish iMCD diagnostic criteria. The working group reviewed data from 244 cases, met twice, and refined criteria over 15 months (June 2015 - September 2016). The proposed consensus criteria require both Major Criteria (characteristic lymph node histopathology and multicentric lymphadenopathy), at least 2 of 11 Minor Criteria with at least 1 laboratory abnormality, and exclusion of infectious, malignant, and autoimmune disorders that can mimic iMCD.

Characteristic histopathologic features may include a constellation of regressed or hyperplastic germinal centers, follicular dendritic cell prominence, hypervascularization, and polytypic plasmacytosis. Laboratory and clinical Minor Criteria include elevated C-reactive protein or erythrocyte sedimentation rate; anemia; thrombocytopenia or thrombocytosis; hypoalbuminemia; renal dysfunction or proteinuria; polyclonal hypergammaglobulinemia; constitutional symptoms; hepatosplenomegaly; effusions or edema; eruptive cherry hemangiomatosis or violaceous papules; and lymphocytic interstitial pneumonitis. iMCD consensus diagnostic criteria will facilitate consistent diagnosis, appropriate treatment, and collaborative research.
Introduction:

Castleman disease (CD) encompasses several clinicopathologic disorders at the intersection of hematology, oncology, rheumatology, and virology with overlap in histopathological and clinical features. Historically, CD has been classified as unicentric or multicentric. A subset of multicentric CD (MCD) is caused by human herpesvirus-8 (HHV-8; also known as Kaposi’s sarcoma-associated herpesvirus) (HHV-8-associated MCD), while HHV-8-negative MCD cases remain idiopathic (iMCD). Unicentric CD (UCD) involves a single lymph node region showing characteristic “Castleman-like” histopathological changes. Inflammatory manifestations are generally mild in UCD and usually disappear after surgical excision of the lymph node. In contrast, both iMCD and HHV-8-associated MCD are characterized by multifocal lymphadenopathy with a range of histopathology and episodic systemic inflammatory symptoms. HHV-8-associated MCD is most commonly diagnosed in HIV-infected or otherwise immunocompromised individuals. Virally-encoded interleukin (IL)-6 and human IL-6 are implicated in disease pathogenesis.

HHV-8-negative/iMCD is less well understood and has no specific biomarkers. Currently, iMCD is diagnosed when a constellation of non-specific but characteristic lymph node histopathological features commonly described as “hyaline vascular,” “plasmacytic,” or “mixed” are observed in patients with appropriate clinical features. HHV-8-associated MCD and a range of malignant, autoimmune, and infectious disorders known to mimic these features (Figure 1) should be excluded. The etiology of iMCD is unknown, although it is hypothesized to involve one or more of the following mechanisms: autoimmunity/autoinflammation (i.e. pathologic auto-antibodies or germline genomic alterations in inflammatory pathways); paraneoplastic (i.e.
somatic mutations in clonal cells), or infection with a virus other than HHV-8. It is possible that multiple pathways culminate in a cytokine storm that results in similar clinical presentations.

iMCD patients experience systemic inflammation, polyclonal lymphoproliferation, and a wide spectrum of symptoms due to a cytokine storm often including IL-6 and vascular endothelial growth factor (VEGF). Clinical hallmarks include fever, night sweats, lymphadenopathy, ascites, hepatosplenomegaly, elevated C-reactive protein (CRP), hypoalbuminemia, and anemia. Some patients experience mild flu-like symptoms while others experience severe sepsis-like multiple organ system failure, anasarca, and death.

The recently described “TAFRO syndrome” identifies a subset of iMCD patients with shared manifestations, including thrombocytopenia, anasarca/ascites, reticulin fibrosis in bone marrow, renal dysfunction, organomegaly (TAFRO), and typically normal immunoglobulin levels. Although first described in Japan in 2010, iMCD patients with TAFRO features have been observed around the world for decades. iMCD patients without TAFRO syndrome typically have thrombocytosis, hypergammaglobulinemia, and less severe fluid accumulation. This non-TAFRO group has been called idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia or IPL-type.

There are an estimated 6,500–7,700 new CD cases diagnosed/year in the USA with about 1,650 cases of MCD. iMCD accounts for 33-58% of published MCD cases. iMCD can occur in individuals of any age with a range of 2-80 years (median: 50). Historically, 35% die within 5 years of diagnosis, 60% die within 10 years, and patients have a three-fold increased
prevalence of malignancy. Corticosteroids, rituximab, cytotoxic chemotherapy, immunosuppressants, immunomodulators, and anti-IL-6 therapies have all been reported for the treatment of iMCD. Antibodies targeting IL-6 (siltuximab) or the IL-6 co-receptor, gp80 (tocilizumab) can reverse symptoms in many patients and may improve long-term outcomes. Siltuximab was recently approved for iMCD based on results from an international randomized controlled trial, where 34% of patients attained a complete or partial response compared to 0% on placebo. However, the lack of defined diagnostic criteria or disease-specific biomarkers can impede timely administration of treatment before organ dysfunction and death may occur. Clinicopathologic diagnostic criteria are urgently needed to facilitate timely recognition, diagnostic work up, and research into pathogenesis and treatment. In this study, we present a multi-disciplinary, evidence-based consensus diagnostic criteria for iMCD.

Methods:
In 2013, the Castleman Disease Collaborative Network (CDCN) Scientific Advisory Board prioritized the establishment of an evidence-based, patient-guided, expert consensus diagnostic criteria. An international working group comprising 34 pediatric and adult hematopathology, hematology/oncology, rheumatology, immunology, and infectious diseases experts in iMCD and related disorders representing eight countries on five continents, including two physicians that are also iMCD patients, was assembled (Figure 2). The CDCN assembled clinical data for 244 iMCD patients as well as 88 lymph node tissue biopsies for histopathological review. One-hundred twenty eight cases came from a systematic literature review of pathology-based iMCD where HHV-8 was excluded and individual clinical data were available. 37 cases were submitted by working group members, and 79 were from a randomized controlled study of
siltuximab in subjects with symptomatic iMCD (NCT01024036). Cases with less than 80k/µL platelets, elevated transaminases, and/or kidney dysfunction were excluded from NCT01024036, and (46/79) 58% of included cases received treatment prior to enrollment.

An international symposium sponsored by the CDCN and University of Pennsylvania Orphan Disease Center was held on November 20-21, 2015 in Philadelphia, Pennsylvania with 21 expert participants, and a follow-up meeting was held on December 6, 2015 in Orlando, Florida with 19 participants. All votes were anonymous and >75% agreement was needed to pass an individual decision. The final criteria vote required 100% consensus.

Literature reviews and expert interviews were performed to select a hybrid Delphi method and Nominal Group Technique (NGT) approach to guide criteria development. Clinical and laboratory parameters were chosen for consideration from literature review and expert nomination via the Delphi method in advance of the meetings (Table 1). NGT was used during the meetings to select parameters through group discussion and secret ballots and to achieve consensus. A team of expert hematopathologists (AB, DF, MSL, KEJ) examined hematoxylin-eosin stained lymph node slides from 88 cases with a presumptive diagnosis of iMCD and graded the following histopathological features using a scale of 0-3: regressed germinal centers (GC), follicular dendritic cell (FDC) prominence, vascular proliferation, plasmacytosis, and hyperplastic GCs (Figure 3). The team expanded during the working group meeting to include additional hematopathologists (EJ, DM, MP, DW). The group reviewed each case simultaneously at a multi-head microscope until a majority of reviewers voted on a grade for each feature. The average grade for each histopathological feature assigned during review was
calculated and compared between subtypes by 2-way analysis of variance (ANOVA) using a
generalized linear model. Three out of the 88 submitted pathology cases had insufficient tissue to
be fully assessed.

At the conclusion of the meetings, the newly established diagnostic criteria were applied
separately to cases that met both Major Criteria from the literature review, submitted cases, and
NCT01024036 to evaluate the number of reported Minor Criteria required for the case definition.
We also calculated response to siltuximab in NCT01024036 based on the number of Minor
Criteria. We calculated summary statistics by tabulation and percentages. Fisher’s exact test was
used to assess significant differences in treatment response rate. P-value less than 0.05 was
considered significant. Statistical tests were performed using SAS 9.4.

Proposed Diagnostic Criteria:
Members of the working group first discussed the scope of an iMCD diagnosis and voted
unanimously in favor of using the iMCD definition depicted in Figure 4. The framework
highlights that “Castleman-like” features can be observed in multiple regions of enlarged lymph
nodes in four settings: diseases other than MCD (i.e. diseases to exclude), HHV-8-negative MCD
associated with POEMS syndrome, iMCD (HHV-8-negative MCD without POEMS), and HHV-
8-associated MCD. There was agreement to distinguish MCD patients with POEMS
(polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)
syndrome from iMCD, because POEMS is associated with a monoclonal plasma cell disorder
and has a different natural history and therapeutic approach from iMCD.
The 3-part criteria in Table 2 were unanimously accepted by the working group. To diagnose iMCD, a patient must meet both Major Criteria, have at least 2 of 11 Minor Criteria including at least 1 laboratory abnormality, and have diseases listed in the Exclusion Criteria ruled out.

**Major Criteria:**

Major Criterion 1 requires histopathological features consistent with iMCD on an excisional lymph node biopsy. Following extensive histological review and discussion, the group voted in favor of defining the two ends of the histological spectrum as well as cases with “mixed” characteristics in between these two ends that would be compatible with a diagnosis of iMCD and meet Major Criterion 1 (Figure 5). To satisfy Major Criterion 1, patients need a Grade 2 or 3 for regressed GCs or plasmacytosis as well as other features consistent with the iMCD histological spectrum. Using the established criteria based on consensus discussions, 71/85 cases with sufficient tissue exemplified the newly-accepted histopathologic criteria, which included 63/76 patients from NCT01024036. Following the meeting, these cases were re-reviewed to classify them into one of three subtypes defined during the meeting and the scoring of particular features were assessed for each group (Figure 6).

One group of cases (n=29) showed regressed GCs, FDC prominence, hypervascularization with proliferation of high endothelial venules, and patent sinuses. Mantle zones were also expanded in some cases with “onion skinning,” displayed by concentric rings of small lymphocytes around atrophic GCs. We occasionally observed the “lollipop sign” of prominent blood vessels radially penetrating GCs and “budding” or “twinning” of follicles, which involves two or more GCs located within a single follicle. Historically, many features of this group would be described as
consistent with the “Hyaline Vascular” (HV) histopathological subtype of MCD. However, many hematopathologists consider HV to only occur in UCD based on the classic descriptions by Benjamin Castleman, and a few HV-UCD features, such as FDC dysplasia and sclerotic vessels, are not often observed in MCD. Recently, many HV features have been described in iMCD patients with TAFRO syndrome. To avoid confusion, we voted to consider iMCD patients with this constellation of HV-like histopathological features, including regressed GCs and hypervascularization without plasmacytosis, as having the “hypervascular” (HyperV) histopathological subtype. Of note, most iMCD cases with TAFRO clinical features from our study and the literature demonstrated HyperV or mixed histopathology, but some cases did not. Also, we observed iMCD patients with HyperV or mixed histopathology that did not have the TAFRO clinical syndrome.

On the other end of the spectrum were patients (n=23) with sheet-like plasmacytosis and increased numbers of follicles with large hyperplastic GCs. These cases, which represent the “plasmacytic” (PC) subtype of iMCD, also have occasional regressed GCs and mild vascularity. A subset of cases (n=19) demonstrated histologic features that were intermediate between the HyperV and PC subtypes with regressed lymphoid follicles and plasmacytosis, which were considered “mixed.”

The reliability and clinical utility of subtyping into HyperV, PC, and mixed is currently unclear, as there are reports of transitions between variants on subsequent biopsies and simultaneous presence of both subtypes at separate sites within the same patient. Nevertheless, histopathologic subtype has been associated with non-response to anti-IL-6 therapy.
efforts to validate these histopathologic features in a separate cohort and elucidate the utility of these histopathologic subtypes are needed.

To meet Major Criterion 2, there must be enlarged lymph nodes (≥1cm in short-axis diameter) in two or more lymph node stations. There was inadequate data to support counting splenomegaly towards the minimum of two stations. Imaging, such as whole-body computerized tomography, should be performed to assess the number of enlarged lymph node stations. If available, $^{18}$[F] fludeoxyglucose positron emission tomography (FDG-PET) may help with identifying FDG-avid nodes for biopsy and distinguishing iMCD from lymphoma. iMCD$^{34}$ and HHV-8-associated MCD$^{35}$ may show diffuse lymph node hypermetabolic abnormalities with lower uptake than high-grade lymphomas.$^{36}$

**Minor Criteria:**

Minor Criteria were selected by the working group from the existing evidence base and subdivided into clinical features and laboratory abnormalities, although additional features may be observed. Clinical Minor Criteria include: constitutional symptoms, hepatosplenomegaly, edema or effusions, eruptive cherry hemangiomatosis or violaceous papules, and lymphocytic interstitial pneumonitis (LIP).$^{23,37}$ Laboratory Minor Criteria include elevated CRP, anemia, thrombocytopenia or thrombocytosis, hypoalbuminemia, renal dysfunction, and polyclonal hypergammaglobulinemia. CRP should be tracked longitudinally for all patients with iMCD, but erythrocyte sedimentation rate may suffice if CRP is not available. Anemia in iMCD is often microcytic and consistent with anemia of chronic inflammation. Patients often have abnormal platelet counts with some having thrombocytosis and others having thrombocytopenia.
Particularly in TAFRO patients, platelet count tends to reflect iMCD activity, with a drop indicating a flare. Experts agreed that there must be at least one laboratory abnormality to diagnose iMCD.

At the conclusion of the meetings, the working group voted to evaluate the minimum number of required Minor Criteria by assessing the number of Minor Criteria at baseline among the 63 patients from NCT01024036 that met the Major Criteria, 128 cases from the literature review, and 25 cases submitted by working group members with patient-level data. The NCT01024036 patients had an average of 3.11 Minor Criteria at time of enrollment out of the 9 criteria assessed. Data on the presence of LIP and Castleman-specific skin lesions were not systematically captured. Twenty-five cases (40%) met ≥4 Minor Criteria with ≥1 laboratory abnormality, 37 cases (59%) met ≥3 Minor Criteria with ≥1 laboratory abnormality, and 45 cases (71%) met ≥2 Minor Criteria with ≥1 laboratory abnormality at enrollment. The 128 literature review cases had an average of 3.79 Minor Criteria out of an average of 5.11 criteria reported. Sixty cases (47%) met ≥4 Minor Criteria with ≥1 laboratory abnormality, 91 cases (71%) met ≥3 Minor Criteria with ≥1 laboratory abnormality, and 115 cases (90%) met ≥2 Minor Criteria with ≥1 laboratory abnormality. The 10% of cases that did not meet the minimum Minor Criteria had an average of 0.54 reported Minor Criteria. The average number of Minor Criteria was 6.0 out of an average of 10.72 criteria assessed for the 25 cases submitted by working group members with patient-level clinical data. Twenty-two cases (88%) met ≥4 Minor Criteria with ≥1 laboratory abnormality, 24 cases (96%) met ≥3 Minor Criteria with ≥1 laboratory abnormality, and 24 cases (96%) met ≥2 Minor Criteria with ≥1 laboratory abnormality.
Then, we evaluated response to therapy according to the NCT01024036 study’s primary endpoint (decrease in lymph node size as per modified Cheson criteria\textsuperscript{38} in the absence of symptom progression) for the 54/79 patients randomized to the siltuximab arm (Figure 7). Siltuximab-treated patients meeting proposed Major Criteria and \textgreater{}2 Minor Criteria with \textgreater{}1 laboratory abnormality (n=35) had a slightly lower overall response rate (43\%) than patients with \textgreater{}3 Minor Criteria (46\%; n=28) and \textgreater{}4 Minor Criteria (55\%; n=22). However, overall response rate dropped significantly (p=0.0003) to 0\% for the 16 siltuximab-treated patients who did not satisfy our Major Criteria or Minor Criteria threshold. Together, these data supported the minimum threshold of at least two Minor Criteria with at least one laboratory abnormality for the diagnosis of iMCD.

\textit{Exclusion Criteria:}

The characteristic “Castleman-like” histopathological changes and clinical abnormalities in iMCD may be present in several malignant, infectious, and autoimmune conditions. For instance, nearly all enlarged lymph nodes from patients with rheumatoid arthritis (RA) and 15-30\% of systemic lupus erythematosus (SLE) display MCD-like histopathology.\textsuperscript{39-42} Therefore, disorders that can mimic iMCD should be excluded before a diagnosis of iMCD is accepted. The diagnostic evaluation required to exclude other diseases should be based on the clinical presentation, and may require additional biopsies, serologic or microbiology studies as indicated, in addition to careful clinical correlation.

HHV-8-associated MCD can be excluded by negative latency-associated nuclear antigen-1 (LANA-1) staining in a diagnostic lymph node.\textsuperscript{5} Other virally-associated lymphoproliferations or
uncontrolled infections that should be considered include EBV-associated lymphoproliferative disorders, such as infectious mononucleosis or chronic active EBV infection, but low levels of EBV are not necessarily exclusionary.

In addition to SLE and RA, adult-onset Still disease, autoimmune lymphoproliferative syndrome, and juvenile idiopathic arthritis should also be excluded. However, the presence of auto-antibodies without a definitive autoimmune diagnosis should not exclude iMCD, as auto-antibodies, including anti-nuclear (ANA), anti-platelet, and anti-Sjögren-syndrome-related antigen A (SS-A), or autoimmune hemolytic anemia were found in approximately 30% of iMCD patients in the largest series to date. A discussion about the overlap between IgG4-related disease (IgG4-RD) and iMCD led to consensus that iMCD should supersede a diagnosis of IgG4-RD, even with very high IgG4 levels, which is in agreement with recommendations from two IgG4-RD expert panels. Dense immunostaining of IgA in the lymph node and low serum IgG4/IgG also supports a diagnosis of iMCD over IgG4-RD. Hemophagocytic lymphohistiocytosis (HLH) shares significant overlap with iMCD, but our group decided that more data is needed to determine if HLH should be excluded or considered an associated disease.

The relationship between iMCD and malignancy is poorly understood. iMCD patients have a three-fold increased prevalence of malignancy than age-matched controls. However, some of those malignancies diagnosed before, concurrently with, and shortly after their iMCD diagnosis may have been responsible for the cytokine storm that caused the iMCD-like lymph node histopathology and clinical features. Therefore, we recommend that lymphoma, multiple myeloma, primary lymph node plasmacytoma, and FDC sarcoma should be excluded before
diagnosing iMCD. Hematologic malignancies diagnosed more than one year after iMCD with no evidence of the malignancy upon re-review of the diagnostic lymph node or previous imaging should not overturn the initial iMCD diagnosis.

We recommend considering bone marrow biopsy on all patients with suspected iMCD to evaluate for malignancy, POEMS-associated MCD, and findings that can be seen in iMCD.\textsuperscript{46} POEMS-associated MCD is defined by the presence of either bone lesions (sclerotic or lytic) or a lambda-restricted plasma cell disorder as demonstrated by immunofixation, bone marrow aspirate/biopsy, or biopsy of a bone lesion.\textsuperscript{22} Megakaryocyte hyperplasia and lymphoid aggregates rimmed by plasma cells can be seen in POEMS-associated MCD and iMCD.\textsuperscript{47} Also, patients meeting the diagnostic criteria for iMCD, who exhibit POEMS-like complications, but do not meet the criteria for POEMS, should be considered to have iMCD. More data are needed to better understand the relationship of iMCD to malignancy.

\textit{Additional Features:}

Though not included in the Minor Criteria because they lacked sufficient data, additional features that support an iMCD diagnosis include elevated blood levels of IL-6, soluble IL-2 receptor (sIL2R), VEGF, IgA, IgE, lactate dehydrogenase, beta-2-microglobulin, characteristic bone marrow pathology (e.g. reticulin fibrosis and polyclonal plasmacytosis), and several associated diseases.\textsuperscript{20,50-55}

\textbf{Discussion:}
We present the first formal criteria for the diagnosis of iMCD, which require both Major Criteria and at least two Minor Criteria including at least one laboratory abnormality in the absence of diseases listed in Exclusion Criteria. Taken together, the Major Criteria requirement of characteristic histopathology, clinical and laboratory Minor Criteria, and Exclusion Criteria appear relatively sensitive and specific among causes of multicentric lymphadenopathy. The data regarding response to anti-IL-6 therapy support our threshold of requisite Minor Criteria as all patients who benefited from siltuximab in the clinical trial would have met the threshold.

The role of IL-6 as a mediator of iMCD symptomatology, histopathology, and pathogenesis has been consistently demonstrated. Symptoms typically wax and wane with serum IL-6 levels, which are often elevated in iMCD, and many patients respond to IL-6 blockade. While IL-6 was elevated in 57/63 patients with iMCD in a recent literature review, IL-6 levels are non-specific and can be elevated in many inflammatory and malignant disorders. Measured IL-6 levels rise following administration of anti-IL-6 therapy, which complicates the interpretation of such data and can falsely suggest that a patient has active iMCD. There are also iMCD patients with normal or moderately elevated IL-6 levels and others who do not respond adequately to anti-IL-6 therapy, suggesting that other cytokines may contribute to pathogenesis in these patients. Elevated sIL2R, a marker of T-cell activation, has been found to be frequently elevated in iMCD and may parallel disease activity. VEGF, a potent angiogenic factor, has also been found to be elevated during flares and to rise before other markers of flare, and may be responsible for features such as hypervascularity, cherry hemangiomas, and vascular leak syndrome.
More research is needed to determine if patients, who meet Major Criteria and Exclusion Criteria but who do not meet the Minor Criteria, which we consider “probable iMCD,” should be managed in the same way as patients with a definitive diagnosis. From a clinical perspective, physicians are advised to monitor patients closely and/or pursue alternative diagnoses that may explain the multicentric lymphadenopathy in cases with inadequate clinical features. We have also observed patients on the borderline between UCD and iMCD, who have multiple enlarged nodes in one region or in adjacent regions (e.g. bilateral cervical or cervical and axillary on one side) and mild clinical symptoms, which we have temporarily referred to as “oligocentric” CD or “regional” CD. More research is needed to determine if these patients should be treated more like UCD or iMCD. There is also a lack of data regarding optimal management of patients with unresectable UCD. More research is also needed into the differences between iMCD patients with TAFRO syndrome and non-TAFRO/IPL patients, which are both included within these diagnostic criteria.

There are several limitations to our criteria. Though the evidence base was composed of the largest collection of clinical and histological iMCD data that has ever been analyzed, case reports with short follow-up times make up a portion of cases. We included a broad range of patient data from multiple sources to overcome this limitation, but the actual number of Minor Criteria evaluated from each of the cohorts varied. There was no diagnostic definition for iMCD, so our expert working group had to choose minimum requirements to select cases for the study (“Castleman-like” histopathology, multicentric lymphadenopathy, and negative HHV-8 testing). Additionally, 46 cases from NCT01024036 were previously treated symptomatic patients who did not have clinical data at time of initial presentation, and the most severe cases were excluded.
from NCT01024036 and therefore underrepresented. However, NCT01024036 is the only iMCD randomized controlled trial, and the other 165 cases, which included data at presentation and did not exclude severe cases, had comparable numbers of Minor Criteria. The analysis of response to siltuximab could suggest that this is a predictive response criterion and biased against recognizing cases that will not respond to siltuximab. However, we evaluated response after the criteria were already developed by the working group in order to evaluate the specificity of the minimum number of Minor Criteria. Also, overlapping diseases were not systematically evaluated in our dataset to identify features specific for iMCD. We believe the Exclusion Criteria should help to overcome this limitation until further studies are done to directly compare iMCD against related diseases. These criteria were selected to be applicable to patients worldwide, but violaceous papules and LIP are more commonly described among Asian individuals and these specific findings were not systematically assessed in NCT01024036. The expert working group included representation from eight countries in order to incorporate patient data from around the world and overcome ascertainment limitations. A portion of the data that informed the working group’s selection of the parameters was later used to evaluate the threshold of required features. Due to the rarity of iMCD and our efforts to collect all available data to assist the expert working group with selecting the parameters, there were no additional datasets to perform separate validation.

Conclusion:

The clinical heterogeneity, overlap with other disorders, and lack of specific biomarkers pose challenges for the diagnosis and management of patients with iMCD. Patients are often misdiagnosed with other illnesses and/or forced to endure months without appropriate treatment
despite the availability of effective treatments. We believe that these proposed consensus criteria will contribute to streamlining the diagnostic evaluation of patients, standardize nomenclature, and diminish the time from presentation to administration of treatments, which may improve clinical outcomes and survival. The outlined criteria will require collaboration between laboratory physicians and the clinical team. Patients experiencing lymphadenopathy and symptoms listed in the Minor Criteria with no alternative diagnosis should be evaluated for iMCD with an excisional lymph node biopsy.

This international effort represents the first attempt to develop consensus criteria for this rare disease. We recognize the challenges of utilizing retrospective data to define diagnostic criteria, and prospective use of the criteria is necessary for further refinement. We plan to analyze and validate these criteria through the international ACCELERATE Natural History Registry (www.CDCN.org/ACCELERATE), which the CDCN and University of Pennsylvania launched in 2016. All individuals with “Castleman disease” mentioned on a pathology report, including those diagnosed with another disease, can enroll prospectively and central review of clinical data and histopathology is performed. The use of these criteria will facilitate discoveries pertaining to etiology and pathogenesis, assessment of biomarkers, and sub-stratification, which should enable further iterations of these criteria and a precision approach to iMCD.

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**Author Contributions:**

David C. Fajgenbaum and Amy Y. Liu analyzed and interpreted data, participated in the working group, performed statistical analyses, and wrote the manuscript. Sheila Pierson analyzed and interpreted data, performed statistical analyses, and reviewed and approved the final manuscript. Thomas S. Uldrick, Adam Bagg, Dale Frank, David Wu, Gordan Srkalovic, David Simpson, David Menke, Shanmuganathan Chandrakasan, Mary Jo Lechowicz, Raymond S. M. Wong, Michele Paessler, JF Rossi, Makoto Ide, Jason Ruth, Michael Croglio, Alexander Suarez, Vera Krymskaya, Amy Chadburn, Gisele Colleoni, Sunita Nasta, Raj Jayanthan, Christopher S. Nabel, Corey Casper, Angela Dispenzieri, Alexander Fossa, Dermot Kelleher, Razelle Kurzrock, Peter Voorhees, Ahmet Dogan, Kazuyuki Yoshizaki, Frits van Rhee, Eric Oksenhendler, Elaine S. Jaffe, Kojo S. J. Elenitoba-Johnson, and Megan S. Lim participated in the working group, contributed to the manuscript, and reviewed and approved the final manuscript.

**Conflict of Interest Disclosures:**

DCF and CC have received research funding from Janssen Pharmaceuticals and served on advisory boards for Janssen Pharmaceuticals.
TSU has a patent for an immunomodulatory compound for KSHV malignancies (Inst).

PV has served on advisory boards for Janssen Pharmaceuticals.

DS has received research funding from Amgen and honoraria from Celgene, Roche, and Janssen Pharmaceuticals.

RSMW has performed consultancy for Novartis, Bayer, Boehringer-Ingelheim, and GlaxoSmithKline and received research funding from Alexion, Baxalta, Bayer, Biogen-Idec, Boehringer-Ingelheim, GlaxoSmithKline, Janssen, MSD, Novartis, Omeros, Pfizer, and Sanofi.

RK has received research funding from Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, and Guardant, as well as consultant/advisory board fees from Actuate Therapeutics and Xbiotech, and an ownership interest in Novena, Inc. and Curematch, Inc.

FVR has performed consultancy for Takeda and Amgen.

AF has received honoraria from Janssen Pharmaceuticals.

AD has served on an advisory board for Cancer Genetics and been a speaker for the Peer Review Institute.

ESJ, MC, JR, DM, GS, AS, AD, SN, GC, JFR, EO, AYL, AB, MI, VK, DK, MJL, DW, SP, SC, KY, MP, RJ, CSN, ML, DF, KSJEJ, and AC have nothing to disclose.
References:

16. Inoue M, Ankou M, Hua J, Iwaki Y, Hagiwara M, Ota Y. Complete resolution of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) after
FAJGENBAUM et al

DIAGNOSTIC CRITERIA FOR iMCD


Table 1. Subset of clinical and laboratory features considered in determining diagnostic criteria

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Systematic literature review cases (N=128)</th>
<th>Siltuximab trial cases (N=79)</th>
<th>Submitted cases (N = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reported positive finding</td>
<td>Reported positive or negative finding</td>
<td>% of patients, minimum&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>128</td>
<td>128</td>
<td>100</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Night sweats</td>
<td>21</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Weight loss</td>
<td>33</td>
<td>64</td>
<td>26</td>
</tr>
<tr>
<td>Fever</td>
<td>52</td>
<td>67</td>
<td>41</td>
</tr>
<tr>
<td>Enlarged liver +/- spleen (per CT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpable liver</td>
<td>10</td>
<td>79</td>
<td>13</td>
</tr>
<tr>
<td>Palpable spleen or splenomegaly</td>
<td>9</td>
<td>79</td>
<td>11</td>
</tr>
<tr>
<td>Edema, ascites, +/- anasarca&lt;sup&gt;c&lt;/sup&gt;</td>
<td>29</td>
<td>37</td>
<td>23</td>
</tr>
<tr>
<td>Laboratory Features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low haemoglobin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>79</td>
<td>91</td>
<td>62</td>
</tr>
<tr>
<td>Thrombocytopenia&lt;sup&gt;e&lt;/sup&gt;</td>
<td>28</td>
<td>63</td>
<td>22</td>
</tr>
<tr>
<td>Thrombocytosis&lt;sup&gt;f&lt;/sup&gt;</td>
<td>16</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Elevated ESR&lt;sup&gt;g&lt;/sup&gt;</td>
<td>44</td>
<td>48</td>
<td>34</td>
</tr>
<tr>
<td>Elevated CRP&lt;sup&gt;h&lt;/sup&gt;</td>
<td>65</td>
<td>79</td>
<td>51</td>
</tr>
<tr>
<td>Elevated sIL-2R&lt;sup&gt;i&lt;/sup&gt;</td>
<td>20</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Elevated VEGF&lt;sup&gt;j&lt;/sup&gt;</td>
<td>16</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Elevated IL-6&lt;sup&gt;k&lt;/sup&gt;</td>
<td>57</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Elevated IgG levels&lt;sup&gt;l&lt;/sup&gt;</td>
<td>63</td>
<td>82</td>
<td>49</td>
</tr>
<tr>
<td>Elevated IgA levels&lt;sup&gt;m&lt;/sup&gt;</td>
<td>32</td>
<td>79</td>
<td>41</td>
</tr>
<tr>
<td>Hypoalbuminemia&lt;sup&gt;n&lt;/sup&gt;</td>
<td>57</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Renal dysfunction&lt;sup&gt;p&lt;/sup&gt;</td>
<td>12</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Positive cases divided by the number of total cases.

<sup>b</sup> Positive cases divided by reported positive and negative findings.
For Siltuximab trial patients, definition of "fluid retention" was used.

For systematic review patients: hemoglobin less than 115 g/L or stated “anemic;” for Siltuximab trial patients, hemoglobin less than stated reference range; and for submitted cases patients, hemoglobin less than 125 g/L.

For systematic review patients, platelet count less than 150x10^9/L or stated “thrombocytopenia;” for Siltuximab trial patients, platelet count less than stated reference range; and for submitted cases patients, platelet count less than 150x10^9/L.

For systematic review patients, platelet count greater than 500x10^9/L or stated "thrombocytosis;" for Siltuximab trial patients, platelet count greater than stated reference range; and for submitted cases patients, platelet count greater than 500x10^9/L.

For systematic review patients, ESR greater than 30 mm/h or stated "elevated ESR;" and for Siltuximab trial patients, ESR greater than stated reference range.

For systematic review patients, CRP greater than 10mg/L or CRP greater than 95.24 nmol/L; for Siltuximab trial patients, CRP greater than stated reference range; and for submitted cases patients, CRP greater than 10mg/L.

For systematic review patients, sIL-2R greater than stated reference range; and for submitted cases patients, sIL-2R greater than stated reference range.

For systematic review patients, VEGF greater than 100 pg/mL or VEGF greater than stated reference range; and for Submitted cases patients, VEGF greater than stated reference range.

For systematic review patients, IL-6 greater than 6pg/mL or IL-6 greater than stated reference range; for Siltuximab trial patients, IL-6 greater than stated reference range; and for submitted cases patients, IL-6 greater than stated reference range.

For systematic review patients, IgG greater than 17000 g/L or IgG greater than 1700 mg/dL or stated “hypergammaglobulinemia;” for Siltuximab trial patients, IgG greater than stated reference range; and for submitted cases patients, IgG greater than 17000 g/L.

For Siltuximab trial patients, IgA greater than stated reference range.

For systematic review patients, albumin less than 35 g/L or albumin less than 3.5 g/dL; for Siltuximab trial patients, albumin less than stated reference range; and for submitted cases patients, albumin less than 35 g/L.

For systematic review patients, creatinine greater than 106μmol/L or BUN greater than 7.14 mmol/L; for Siltuximab trial patients, creatinine greater than stated reference range; and for submitted cases patients, creatinine greater than 106μmol/L or BUN greater than 7.14 mmol/L or creatinine greater than stated reference range.

CT indicates computed tomography, ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; sIL-2R, soluble interleukin-2 receptor; VEGF, vascular endothelial growth factor; IL-6, Interleukin-6; IgG, immunoglobulin G; IgA, immunoglobulin A; BUN, blood urea nitrogen.
Table 2. Consensus diagnostic criteria for iMCD

<table>
<thead>
<tr>
<th>Major Criteria (need both):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Histopathological lymph node features consistent with the iMCD spectrum (Figure 5). Features along the iMCD spectrum include (need Grade 2-3 for either regressive germinal centers or plasmacytosis at minimum):</td>
</tr>
<tr>
<td>- Regressive/atrophic/attretic germinal centers, often with expanded mantle zones composed of concentric rings of lymphocytes in an ‘onion skinning’ appearance</td>
</tr>
<tr>
<td>- Follicular dendritic cell prominence</td>
</tr>
<tr>
<td>- Vascularity, often with prominent endothelium in the interfollicular space and vessels penetrating into the germinal centers with a ‘lollipop appearance’</td>
</tr>
<tr>
<td>- Sheet-like, polytypic plasmacytosis in the interfollicular space</td>
</tr>
<tr>
<td>- Hyperplastic germinal centers</td>
</tr>
<tr>
<td>2. Enlarged lymph nodes (&gt;1cm in short-axis diameter) in two or more lymph node stations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria (need at least 2 out of 11 criteria with at least 1 laboratory criterion):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
</tr>
<tr>
<td>1. Elevated CRP (greater than 10mg/L) or ESR (greater than 15mm/hr)†</td>
</tr>
<tr>
<td>2. Anemia (hemoglobin less than 12.5g/dL for males, hemoglobin less than 11.5g/dL for females)</td>
</tr>
<tr>
<td>3. Thrombocytopenia (platelet count less than 150k/µL) or thrombocytosis (platelet count greater than 400k/µL)</td>
</tr>
<tr>
<td>4. Hypoalbuminemia (albumin less than 3.5g/dL)</td>
</tr>
<tr>
<td>5. Renal dysfunction (eGFR &lt;60 mL/min/1.73m²) or proteinuria (total protein &gt;150mg/100ml)</td>
</tr>
<tr>
<td>6. Polyclonal hypergammaglobulinemia (total gamma globulin or immunoglobulin G &gt;1700mg/dL)</td>
</tr>
</tbody>
</table>

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 |

<table>
<thead>
<tr>
<th>Exclusion Criteria (must rule out each of these diseases that can mimic iMCD):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection Related Disorders:</td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td>2. Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (Detectable EBV viral load not necessarily exclusionary)</td>
</tr>
<tr>
<td>3. Inflammation and adenopathy due to other uncontrolled infections, e.g. acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis</td>
</tr>
</tbody>
</table>

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 (ALPS)

**Malignant/lymphoproliferative disorders (these 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. Follicular dendritic cell sarcoma
5. POEMS syndrome‡

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‡), glomerular nephropathy, inflammatory myofibroblastic tumor

Additional notes:
*: We have provided laboratory cut-off thresholds as guidance, but we recognize that some laboratories have slightly different ranges. We suggest that you use the upper and lower ranges from your particular lab 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. Since the monoclonal plasma cells are believed to drive the cytokine storm, we do not consider it iMCD, but rather “POEMS-associated MCD.”

CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate; CTCAE, common terminology for adverse events; LANA-1, latency-associated nuclear antigen; IHC, Immunohistochemistry; EBV, Epstein-Barr virus; CMV, cytomegalovirus; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes; IL-6, interleukin-6; sIL-2R, soluble interleukin-2 receptor; VEGF, vascular endothelial growth factor; IgA, immunoglobulin A; IgE, immunoglobulin E; LDH, lactate dehydrogenase; B2M, beta-2-microglobulin.
Figure Legend

Figure 1. Significant clinical, histologic and immunologic overlap between iMCD, malignancy, autoimmune, and infectious disorders. The exact location for iMCD on the spectrum from autoimmune, malignant, and infectious diseases is currently unknown and may vary from patient to patient. ALPS, Autoimmune lymphoproliferative syndrome; AOSD, Adult Onset Still Disease; EBV, Epstein-Barr Virus; FDC, Follicular Dendritic Cell; HHV-8, Human Herpesvirus-8; HIV, Human Immunodeficiency Virus; HL, Hodgkin Lymphoma; HLH-MAS, Hemophagocytic Lymphohistiocytosis- Macrophage Activation Syndrome; IgG4, IgG4-Related Disease; iMCD, idiopathic Multicentric Castleman Disease; JIA, Juvenile Idiopathic Arthritis; M-HLH, Malignancy-associated Hemophagocytic Lymphohistiocytosis; NHL, Non-Hodgkin Lymphoma; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammapathy, and Skin Changes; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; V-HLH, Viral Hemophagocytic Lymphohistiocytosis.

Figure 2. Process of criteria development. An international working group with 34 leading physicians, pathologists, and clinicians was created to develop the diagnostic criteria for iMCD. A modified Delphi Method & Nominal Group Technique was selected to guide the criteria development process. A total of 244 patients’ clinical data were gathered along with lymph node slides from 88 cases. Two working group meetings were held to establish an agreed upon diagnostic criteria. Post-meeting analyses were performed to reapply the agreed upon diagnostic criteria to 79 cases from NCT01024036 and to use the newly-defined histopathological spectrum to subtype cases. The consensus criteria and results from analyses were compiled into a manuscript that was reviewed by the full expert working group.

Figure 3. Grading of pathologic features seen in iMCD. The following images are examples of the respective grades for each histopathologic feature. De-identified lymph node slides were obtained pre-stained with hematoxylin and eosin from Janssen Pharmaceuticals and scanned using Aperio CS scanner (Leica Biosystems, Wetzlar, Germany) at 20x/0.75NA Plan Apochromat. Images were captured using Aperio Imagescope and enhanced to 300dpi using Photoshop. Bars represent 500 μm (A, D), 80 μm (B), 200 μm (C), 60um (E). (A) Atrophic germinal centers. (B) Follicular dendritic cell prominence. (C) Vascularity. (D) Hyperplastic germinal centers. (E) Plasmacytosis.

Figure 4. Algorithmic approach for assessment of lymph node with features of CD. Patients with lymph nodes with histologic features suggestive of CD should be evaluated for sites of involvement. If lymph node involvement is restricted to one site, the lesion most likely represents Clinically Unicentric CD. If multiple sites are involved, patients would be considered Clinically Multicentric CD and should be evaluated for HHV-8, POEMS, and other infectious, malignant, and autoimmune disorders listed in Table 2 Exclusion Criteria. If these conditions are excluded, a diagnosis of iMCD should be considered. There are three major histopathologic subtypes of iMCD: Hypervascular (formerly Hyaline-Vascular), Mixed, and Plasmacytic pathology. *iMCD patients with TAFRO syndrome frequently demonstrate Hypervascular or Mixed Pathology.
Figure 5. Histopathological Features of CD. Hypervascular subtype is characterized by the presence of atrophic germinal centers and FDC prominence, whereas the Plasmacytic subtype exhibits hyperplastic germinal centers and profuse plasmacytosis. Mixed subtype exhibits a combination of hypervascular and plasmacytic features. Vascularity is frequently observed in iMCD, but can be seen with either subtype. De-identified lymph node slides were obtained pre-stained with hematoxylin and eosin from Janssen Pharmaceuticals and scanned using Aperio CS scanner (Leica Biosystems, Wetzlar, Germany) at 20x/0.75NA Plan Apochromat. Images were captured using Aperio Imagescope and enhanced to 300dpi using Photoshop. Bars represent 60µm (A, E), 200µm (B-D). (A) Atrophic germinal center. (B) FDC prominence in germinal center. (C) Blood vessels penetrating germinal center demonstrate prominent vascularity. (D) Hyperplastic germinal center. (E) Sheet-like plasmacytosis. FDC, follicular dendritic cells.

Figure 6. Average grade for histopathologic features for each subtype of iMCD. Average grades for regressed germinal centers, FDC prominence, vascularity, plasmacytosis, and hyperplastic germinal centers in Hypervascular, Plasmacytic, and Mixed subtypes of iMCD as well as cases determined to not be CD (not CD) as assessed by hematopathological review. See Figure 3 for the grading scale for each feature. The bars depict average grades for histopathological features for a given subtype with mean ± 95% CI. FDC, follicular dendritic cells.

Figure 7. Percentage of patients meeting proposed Major Criteria who responded to therapy in the siltuximab study, based on number of proposed Minor Criteria. n represents total number of patients treated with at least that number of Minor Criteria and one or more laboratory abnormalities. Using Fisher’s exact test, those who met 2 or more minor criteria were significantly more likely to respond to siltuximab than those who did not meet 2 minor criteria (p=0.0003).
**Assembled Expert Working Group:** 34 members

**Selected Modified Delphi Method & Nominal Group Technique as Method to Establish Criteria:**
- >75% agreement required for each individual decisions
- 100% consensus required for final criteria decision

**Gathered Data:**
- 244 Patients’ clinical data
- 88 Lymph node slides

**Held Expert Meetings with Email Follow-Up**

**Three Major Decisions:**
- Chose iMCD framework (Figure 4)
- Selected specific parameters to include in major/minor criteria
- Voted on complete criteria (Table 2)

**Diagnostic Criteria Agreed Upon**

1. Reapplied diagnostic criteria to reviewed cases
2. Reapplied newly-defined histopathological spectrum to assign subtypes to the histopathologic cases reviewed

**Manuscript written and reviewed by full expert working group**
<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Regressed Germinal Centers (GCs)</strong></td>
<td>No Regressed GCs</td>
<td>Few Regressed GCs</td>
<td>Many Regressed GCs</td>
<td>Most GCs Regressed</td>
</tr>
<tr>
<td><strong>(B) Follicular Dendritic Cell (FDC) Prominence</strong></td>
<td>No FDC Prominence</td>
<td>Mild FDC Prominence</td>
<td>Moderate FDC Prominence</td>
<td>Very Prominent FDCs</td>
</tr>
<tr>
<td><strong>(C) Vascularity</strong></td>
<td>Normal</td>
<td>Mildly Increased</td>
<td>Moderately Increased</td>
<td>Very Prominent</td>
</tr>
<tr>
<td><strong>(D) Hyperplastic Germinal Centers</strong></td>
<td>No Hyperplastic GCs</td>
<td>Few Hyperplastic GCs</td>
<td>Many Hyperplastic GCs</td>
<td>Most GCs Hyperplastic</td>
</tr>
<tr>
<td><strong>(E) Plasmacytosis</strong></td>
<td>Normal</td>
<td>Mildly Increased</td>
<td>Moderately Increased</td>
<td>Very Increased (“Sheet-like”)</td>
</tr>
</tbody>
</table>

Figure 3
Figure 4

Castleman-Like Lymph Node Features

Clinically Unicentric CD

Diseases to Exclude
- Infection related (i.e. acute EBV, HIV, TB)
- Autoimmune disease criteria (i.e. SLE, RA)
- Other LPDs (i.e. ALPS, lymphoma)

Clinically Multicentric CD

POEMS-associated MCD

iMCD (using Consensus criteria)

KSHV/HHV-8 associated (LANA-1+) MCD

Hypervascular Pathology*

Mixed Pathology*

Plasmacytic Pathology
Figure 5

- Hypervascular Pathology
- Mixed Pathology
- Plasmacytic Pathology

A. Atrophic Germinal Centers
B. FDC Prominence
C. Vascularity
D. Hyperplastic Germinal Centers
E. Plasmacytosis

Images:
- A: Atrophic Germinal Centers
- B: FDC Prominence
- C: Vascularity
- D: Hyperplastic Germinal Centers
- E: Plasmacytosis
Figure 6

The bar chart illustrates the average grades for different pathology subtypes, including Hypervascular (N=29), Mixed (N=19), Plasmacytic (N=23), and Not CD (N=14). The chart compares various features such as Regressed Germinal Centers, FDC Prominence, Vascularity, Plasmacytosis, and Hyperplastic Germinal Centers. The y-axis represents the average grade, while the x-axis shows the pathology subtypes.
Did not meet (n=16)

At least 2 (n=35)

At least 3 (n=28)

At least 4 (n=22)

Figure 7