HHV-8-negative/idiopathic multicentric Castleman disease

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INTRODUCTION

Castleman disease (CD, angiofollicular lymph node hyperplasia) describes a heterogeneous group of lymphoproliferative disorders that share common histopathologic features.

CD is classified into at least three distinct disorders based on the number of regions of enlarged lymph nodes with characteristic histopathologic features and the presence/absence of human herpesvirus 8 (HHV-8, also called Kaposi sarcoma associated herpesvirus [KSHV]) infection:

- Unicentric CD (UCD) involves one or more enlarged lymph node(s) in a single region of the body that demonstrates CD histopathologic features that lie along a spectrum with hyaline vascular histopathologic subtype on one end and plasma cell histopathologic subtype on the other. A subset of patients have systemic symptoms.

- Multicentric CD (MCD) involves multiple regions of lymphadenopathy that demonstrate CD histopathologic features that lie along a spectrum with hypervascular histopathologic subtype on one end and plasma cell histopathologic subtype on the other. These patients also have systemic inflammatory symptoms with generalized lymphadenopathy, hepatosplenomegaly, cytopenias, and organ dysfunction due to excessive pro-inflammatory hypercytokinemia, often including interleukin (IL)-6. MCD is further subclassified according to the presence of HHV-8:

- HHV-8-associated MCD: Approximately half of MCD cases are caused by HHV-8 infection in human immunodeficiency virus (HIV)-positive or otherwise immunocompromised individuals, and these cases are referred to as HHV-8-associated MCD.

- HHV-8-negative/idiopathic MCD (iMCD): Approximately half of patients with MCD are HHV-8 negative. These cases have nearly identical clinical and histopathologic features as HHV-8-associated MCD, but the etiology is unknown. These cases are referred to as HHV-8-negative MCD, idiopathic MCD, or iMCD.

It is essential that all cases of CD are subdivided into UCD, HHV-8-associated MCD, or HHV-8-negative MCD at the time of diagnosis as all three subtypes have varying clinical features, treatments, and outcomes. CD is also associated with a number of malignancies, including non-Hodgkin lymphoma, Hodgkin lymphoma, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).

This topic review will discuss the epidemiology, pathogenesis, clinical features, pathologic features, diagnosis, and treatment of HHV-8-negative/idiopathic MCD. The diagnosis and treatment of UCD and HHV-8-associated MCD are presented separately.

- (See "HHV-8-associated multicentric Castleman disease".)

- (See "Unicentric Castleman disease".)

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of HHV-8-associated MCD are well understood, while the etiology and pathogenesis of UCD and HHV-8-negative/idiopathic MCD (iMCD) are poorly understood. All three subtypes of Castleman disease have had individual cases reported with elevated levels of human interleukin (IL)-6 or viral IL-6 (a homolog of IL-6 that is encoded in the HHV-8 genome), but IL-6 is not elevated or the pathologic driver in all cases.

The pathogenesis of HHV-8-negative/idiopathic MCD is presented here. The pathogenesis of UCD and HHV-8-associated MCD are discussed in more detail separately. (See "Unicentric Castleman disease", section on 'Pathogenesis' and "HHV-8-associated multicentric Castleman disease",

section on 'Etiology and pathogenesis'.)

Potential etiologic drivers — The etiology of iMCD is unknown. The clinical and pathologic abnormalities are heterogeneous and overlap with a wide range of other immunologic disorders, suggesting that multiple processes may give rise to iMCD each involving immune dysregulation and a common pathway of increased cytokines [1]. Four candidate etiologic drivers of iMCD pathogenesis have been proposed:

- Autoimmune mechanisms: iMCD may be due to self-reactive antibodies, which drive the release of cytokines. Autoimmune diseases can demonstrate clinical and histopathologic features that are identical to iMCD [2,3], and approximately 30 percent of iMCD case reports have autoantibodies and autoimmunity [4].

- Autoinflammatory mechanisms: iMCD may be due to germline mutations in genes regulating inflammation. Two patients with iMCD have been found to have mutations in genes known to cause monogenic disease, but these associations require confirmation and functional analysis [5,6].

- Neoplastic mechanisms: iMCD may be due to acquired oncogenic mutations. iMCD has clinical and histopathologic overlap with lymphoma, patients have increased rates of malignancies compared to age-matched controls, and monoclonality has been detected in iMCD lymph nodes [4,7].

- Infectious mechanism: iMCD may be due to infection with a pathogen other than HHV-8. The overlap with HHV-8-associated MCD makes this a compelling hypothesis.

In-depth investigation into each of these hypothesized etiologies is underway.

There are at least three clinical subgroups of iMCD that may each arise from different drivers proposed above:

- POEMS-associated, iMCD: Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) is a paraneoplastic syndrome that often co-occurs with iMCD. Monoclonal plasma cells that have undergone genomic events, such as translocations or deletions, are thought to cause both the POEMS syndrome and the iMCD due to excess cytokine production. Nearly all POEMS cases are lambda light chain restricted.

The primary role of monoclonal plasma cells in POEMS-associated iMCD pathogenesis is highlighted by the fact that radiation to an isolated plasmacytoma is often curative [8].

- TAFRO syndrome, iMCD: Thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly (TAFRO) often occur in patients with iMCD. These cases often have mixed or hypervascular (formerly called hyaline vascular) histopathologic features and normal gamma globulin levels. The etiology and pathological cell types are completely unknown.

- Not otherwise specified, iMCD (iMCD-NOS): Patients with iMCD who do not have POEMS syndrome or the TAFRO subtype, are considered iMCD-NOS. These patients often have thrombocytosis, hypergammaglobulinemia, and mixed or plasmacytic histopathologic features. The etiology and pathological cell types are completely unknown.

Pathologic cell type — The pathologic cell types in iMCD are not known. Multiple cell types, including B cells, T cells, plasma cells, monocytes, endothelial cells, and follicular dendritic cells have been proposed to be cell types driving iMCD pathogenesis and/or producing IL-6 and/or other proinflammatory cytokines [9-13].

Some evidence for a pathogenic role of B cells and/or T cells exists in cases of iMCD. CD5+ mantle zone B cells in HIV-negative (HHV-8-unknown) MCD cases proliferate and secrete autoantibodies, and a subset of patients with iMCD improve with B cell depletion with rituximab. However, other cell types must be involved in the pathogenesis of most iMCD cases, because B cell depletion is not effective in most patients. Serum soluble IL-2 receptor, a marker of T cell activation, was elevated in 20 of 21 published cases of iMCD, suggesting a potential role of T cells in iMCD pathogenesis [4]. Further research is needed.

Role of IL-6 and other cytokines — Although the etiology and pathologic cell types in iMCD are unknown, it is clear from human and animal studies that IL-6 is necessary and sufficient to drive iMCD symptomatology, histopathology, and pathogenesis in a portion of patients.

IL-6 is a multi-functional cytokine involved in a wide range of activities, including plasmacytosis, hypergammaglobulinemia, thrombocytosis, acute-phase protein production by the liver, and activation of macrophages and T cells [14]. Elevated IL-6 was first found in one case of HHV-8-unknown MCD in 1989 before HHV-8 was discovered [9]. Clinical symptoms have since been found to wax and wane with IL-6 levels, which can be highly elevated in patients with iMCD during

disease flares [15]. However, the precise cells within the lymph node responsible for production of IL-6 have remained elusive [16]; candidate cells include germinal center B cells, follicular dendritic cells, or cells present in the interfollicular regions [9,10]. Mouse models of elevated IL-6 recapitulated many features of human iMCD including peripheral lymphadenopathy, extensive plasma cell infiltration of lymphoid tissues, splenomegaly, anemia, and hypergammaglobulinemia, and the administration of anti-IL-6R monoclonal antibody (mAb) is effective in treating such mice [17-19]. Moreover, the administration of IL-6 to humans can lead to an iMCD-like syndrome [20].

An important pathogenic role for human IL-6 (hIL-6) is consistent with the effects of neutralizing anti-hIL-6 antibodies. Interruption of IL-6 signaling with anti-IL-6 or anti-IL-6R mAb is effective at ameliorating symptoms and shrinking lymph nodes in some patients [4,21,22]. However, more than half of patients with iMCD in the randomized controlled study of anti-IL-6 mAb did not respond to siltuximab treatment, approximately half of which did not have elevated IL-6 levels [23]. Another study of 17 patients with iMCD revealed that more than half had undetectable IL-6 during flare [24]. It is, therefore, likely that other cytokines or soluble factors can also drive iMCD pathogenesis.

Considering the redundancy of functions played by proinflammatory cytokines, it is certainly plausible that excess secretion of cytokines similar to IL-6 could result in iMCD. A systematic review of iMCD case reports found that vascular endothelial growth factor (VEGF) was elevated in 16 of 20 cases [4]. Similar results were found in another cohort of 17 cases [24]. Elevated VEGF may be involved in the capillary leak syndrome and eruptive cherry hemangiomatosis observed in some patients with iMCD [25]. VEGF is the cytokine that best correlates with disease activity in POEMS-associated, iMCD [26], although other cytokines are also likely contributory because VEGF blockade has provided only mixed results clinically [27]. Examples of other potential drivers include:

- Mechanistic target of rapamycin (mTOR) – mTOR is a regulator of VEGF expression, T cell activation, and cellular proliferation. One patient with anti-IL-6 refractory iMCD-TAFRO, who experienced multiple relapses, had a prolonged remission on the mTOR inhibitor sirolimus [28].

- IL-1b – IL-1b inhibition has been effective in a few case reports, including two patients with iMCD refractory to anti-IL-6 therapy [29,30]. IL-1b is upstream of IL-6 and VEGF in the inflammatory cascade and leads to IL-6 production through NF-kB activation.

Regardless of cause, excessive activation of inflammatory pathways in immune cells leads to histopathologic changes in the lymph node and systemic symptoms observed in iMCD. It is essential to uncover mechanisms to target for the treatment of patients with iMCD who do not respond to anti-IL-6 therapy.

EPIDEMIOLOGY

It is estimated that approximately 6500 to 7700 new cases of Castleman disease (CD) are diagnosed each year in the United States, of which approximately 75 percent are estimated to be unicentric CD (UCD) and the remaining 25 percent are estimated to be HHV-8-associated MCD or HHV-8-negative/idiopathic MCD (iMCD) [31]. No epidemiologic studies have explored MCD incidence outside of the United States, but communication among the international community of CD physicians suggests no clear associations with particular ethnicities. Now that there is a unique ICD-10 code for CD (D47.Z2), more accurate estimations of epidemiology are expected.

Patients with iMCD can present at any age (youngest is one year old), but the median age at diagnosis is between 50 and 65 years [32-42]. Fifty to 65 percent are male.

No trends have been detected in incidence among iMCD cases.

CLINICAL FEATURES

Patients with MCD present with lymphadenopathy in multiple lymph node regions [32,33,35]. Nearly all patients present with fever and other nonspecific symptoms suggestive of an inflammatory illness, including night sweats, weight loss, weakness, and fatigue [11,43]. Other symptoms include hepatosplenomegaly, cytopenias, organ dysfunction, and skin findings such as rash, hemangiomata, and pemphigus [44,45]. The pace of disease development in MCD is variable, with some patients reporting a slow onset over a few years and others becoming acutely ill [35,46].

While there are some signs, symptoms, and laboratory findings in common, different subtypes of iMCD can demonstrate quite heterogeneous clinical features and laboratory features, as described in the following sections.

Common signs, symptoms, and laboratory features — A systematic review that included 127 patients with iMCD reported the following systemic symptoms [4]:

- Fever – 26 to 52 percent
- Night sweats – 62 percent
- Unintended weight loss – 16 to 72 percent
- Enlarged liver or spleen – 41 to 78 percent
- Edema (swelling), ascites (fluid accumulation in the abdomen), and/or other symptoms of fluid overload – 23 to 78 percent

Other symptoms included loss of appetite, nausea, and vomiting; severe abdominal pain; weakness and fatigue; peripheral neuropathy (numbness in the hands and feet); decreased urine output and systemic toxicity due to kidney failure; bruising, easy bleeding, and risk of infection due to bone marrow failure; and eruption of cherry hemangiomas (benign proliferations of blood vessels) on the skin. Neuropathy seen in patients with iMCD is variable and can range from a mild sensory neuropathy to the severe sensory and motor neuropathy of POEMS-associated, iMCD [47].

In the same study, the following abnormal laboratory values were noted [4]:

- Elevated erythrocyte sedimentation rate (ESR) – 34 to 92 percent
- Elevated C-reactive protein (CRP) – 51 to 82 percent
- Low hemoglobin (anemia) – 62 to 87 percent
- Low platelet count (thrombocytopenia) – 22 to 44 percent
- Elevated creatinine and/or blood urea nitrogen (BUN), proteinuria – 9 to 71 percent
- Low albumin – 45 to 90 percent
- Elevated IL-6 – 45 to 90 percent
- Elevated vascular endothelial growth factor (VEGF) – 13 to 80 percent
- Positive Coombs test – 9 to 71 percent
- Positive anti-nuclear antibody (ANA test) – 12 to 37 percent
- Hypergammaglobulinemia – 49 to 77 percent

Other notable laboratory features included elevated fibrinogen and the presence of autoimmune antibodies (eg, anti-erythrocyte autoantibodies and anti-platelet autoantibodies).

POEMS-associated, iMCD — iMCD can co-occur with POEMS, a paraneoplastic syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, a monoclonal immunoglobulin spike, and skin changes such as hypertrichosis, acrocyanosis and plethora, hemangioma/telangiectasia, thickening, or hyperpigmentation [8]. Castleman disease is a major criterion in the diagnosis of POEMS syndrome (table 1).

The diagnosis of POEMS syndrome in a patient with iMCD requires both polyneuropathy and monoclonal plasma cell proliferative disorder (positive M protein, almost always lambda) along with at least one of the following (see "POEMS syndrome"):

- Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
- Extravascular volume overload (edema, pleural effusion, or ascites)
- Endocrinopathy (adrenal, pituitary, gonadal, parathyroid, thyroid and pancreatic)
- Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails)
- Papilledema
- Thrombocytosis or polycythemia

Patients also experience sclerotic bone lesions, extravascular fluid accumulation (edema, pleural effusion, ascites), papilledema, clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, and diarrhea. Sclerotic bone lesions are also commonly observed.

In POEMS-associated, iMCD, typical laboratory abnormalities include a monoclonal M protein on serum protein electrophoresis, increased VEGF, thrombocytosis, polycythemia, low vitamin B12 levels, and abnormal endocrine laboratory tests (increased prolactin, hypothyroidism).

TAFRO syndrome, iMCD — iMCD cases with thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly (TAFRO) often have an acute, critical clinical course. The median time from symptom onset to lymph node biopsy is six weeks, which is shorter than other forms of iMCD [28].

Diagnosing TAFRO syndrome in a patient with iMCD requires all three of the following major criteria along with at least one minor criterion.

Major criteria include:

- Anasarca (pleural effusion, ascites and generalized edema)
- Thrombocytopenia (≤100,000/microL)
- Systemic inflammation (fever of unknown etiology above 37.5°C and/or serum CRP concentration ≥2 mg/dL)

Minor criteria include:

- Reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow
- Mild organomegaly (hepatomegaly, splenomegaly and lymphadenopathy)
- Progressive renal insufficiency

Patients with iMCD-TAFRO often have smaller lymph nodes than the other subtypes of iMCD. Occasionally these enlarged lymph nodes are painful [28,48]. Patients with iMCD-TAFRO often exhibit:

- Fever without obvious infection (61 to 84 percent)
- Severe anasarca with massive pleural effusions and/or ascites (96 to 100 percent)
- Organomegaly (89 to 100 percent)
- Abdominal pain at disease onset (32 percent)

Typical laboratory abnormalities include severe thrombocytopenia; normal to mildly elevated gamma globulin levels; elevated alkaline phosphatase levels typically without corresponding elevations in transaminase levels; anemia; hypoalbuminemia; and elevated levels of CRP, sIL2R, and creatinine, which can represent progressive acute kidney failure that requires transient hemodialysis. Serum lactate dehydrogenase (LDH) levels are not often elevated in iMCD-TAFRO [28,48].

Autoantibodies, such as anti-nuclear antibody (ANA), anti-RBC (Coombs), and anti-platelet antibodies are often present. iMCD-TAFRO may co-occur with autoimmune disorders including autoimmune hemolytic anemia, immune thrombocytopenia (ITP), and acquired factor VIII deficiency. Autoimmunity-related symptoms, including arthritis, renal dysfunction, and proteinuria, are more often observed in iMCD than HHV-8-associated MCD or unicentric Castleman disease (UCD).

Not otherwise specified, iMCD — Patients with iMCD who do not have POEMS syndrome or the TAFRO subtype are considered to have idiopathic MCD, not otherwise specified (iMCD-NOS). These patients often have constitutional symptoms, thrombocytosis, hypergammaglobulinemia, and mixed or plasmacytic histopathologic features [28].

Though hepatosplenomegaly and fluid accumulation can occur in iMCD-NOS, they are less intense than in iMCD-TAFRO. Lymphocytic interstitial pneumonitis and violaceous papules with lymphoplasmacytic infiltrate may be present in iMCD-NOS. An uncommon presentation of iMCD in young adults includes perioral pemphigus and idiopathic pulmonary fibrosis, and is associated with a poor outcome.

Typical laboratory abnormalities in iMCD-NOS include:

- Anemia
- Thrombocytosis
- Polyclonal hypergammaglobulinemia with negative immunofixation and no monoclonal spike
- Hypoalbuminemia
- Elevated total protein, LDH, IL-6, VEGF, CRP, ferritin, and fibrinogen

Platelet counts are normal to slightly elevated in the majority of patients and are >500,000/mm^3 in a limited number.

We are also aware of patients with iMCD with only two regions of enlarged lymph node stations in neighboring areas and mild symptoms. These cases typically can demonstrate features like UCD and iMCD and may warrant a new disease subtype of "oligocentric" or "regional" Castleman disease. Further research is needed to guide optimal treatment of these patients.

Imaging — Imaging findings are nonspecific, but may include the following:

- **Chest radiograph** – The chest radiograph may show bilateral reticular or ground glass opacities, mediastinal widening, and/or bilateral pleural effusions [49]. Less commonly, lung nodules or rounded areas of consolidation are seen.

- **Computed tomography (CT) of the chest** – On CT of the chest, most patients have multiple enlarged mediastinal and hilar lymph nodes (1 to 3 cm diameter) [49,50]. A spectrum of lung parenchymal findings may be seen, including subpleural nodules, interlobular septal

thickening, peribronchovascular thickening, ground glass opacities, and patchy, rounded areas of consolidation. Small to moderate bilateral pleural effusions may be present.

- **Positron emission tomography (PET)** – iMCD is ^{18}F-fluorodeoxyglucose (FDG) PET avid, usually with a relatively low standardized uptake value (SUV, 2.5 to 8). High SUV values (eg, >8) are uncommon and should raise the suspicion of alternative diagnoses (eg, lymphoma). SUV may also differ by subtype. As an example, uptake of FDG in the enlarged lymph nodes is only slightly elevated in iMCD-TAFRO [51].

PATHOLOGY

HHV-8-negative/idiopathic MCD (iMCD) is characterized by nodal expansions that usually leave the structure of the underlying lymph node at least partially intact. B cells and plasma cells are polyclonal, and T cells show no evidence of an aberrant immunophenotype.

The mantle zone lymphocytes in all histopathologic subtypes are polyclonal IgM- or IgD-expressing cells [46,52]. The plasma cells in the interfollicular areas are generally also polyclonal. Localized clonal expansions are sometimes seen [53-55], but do not appear to affect prognosis [53,56,57].

Three histopathologic subtypes are recognized for iMCD [11,43], though the clinical utility of distinguishing these histological subtypes is unknown:

- **The hypervascular histopathologic subtype of iMCD** (previously referred to as hyaline vascular, which is now reserved only to describe unicentric Castleman disease [UCD]) is characterized by the following features:
    - Small, regressed or atrophic germinal centers – There are increased numbers of follicles that vary in size from hyperplastic to regressed. Most germinal centers are regressed and depleted of lymphocytes.
    - "Onion-skin appearance" of the mantle zone around the germinal centers – The follicles are surrounded by prominent/widened mantle zones containing small lymphocytes arranged in a concentric fashion.
    - Prominent follicular dendritic cells (FDCs) – The regressed germinal centers are depleted

of lymphocytes and mainly consist of a prominent population of FDCs.

- "Lollipop appearance" – Blood vessels radially penetrate atrophic germinal centers.
- Increased vascularity, most notably of high endothelial venules in interfollicular zones – The interfollicular lymphoid tissue contains numerous small blood vessels known as high endothelial venules that are lined by plump, activated endothelial cells.
- Patent sinuses with no architectural disruption.

The hypervascular histopathologic subtype of iMCD and hyaline vascular histopathologic subtype of UCD have overlapping features (eg, "onion-skin" and "lollipop" appearances), but the hypervascular subtype does not typically demonstrate twinning, FDC dysplasia, hyalinized sclerotic vessels, obliterated sinuses/architectural disruption, or aggregates of plasmacytoid dendritic cells. Therefore, hypervascular was proposed to replace hyaline vascular when describing iMCD, and hyaline vascular is reserved only when there is a solitary, UCD lymph node. (See "Unicentric Castleman disease", section on 'Pathology'.)

- **The plasma cell histopathologic subtype of iMCD** is identical to the plasma cell histopathologic subtype of UCD and characterized by the following features:
  - Interfollicular plasmacytosis – The interfollicular region is hypervascular and contains sheets of plasma cells.
  - Hyperplastic germinal centers – The germinal centers are primarily hyperplastic (unlike the regressed germinal centers in hypervascular histopathologic subtype). They can also have typical reactive features, including polarization into light and dark zones, frequent mitotic figures, and numerous macrophages containing apoptotic debris (tingible body macrophages).
  - Follicle size variability – Abnormally enlarged or hyperplastic germinal centers are often present along with some regressed or "hypervascular"/"hyaline vascular"-like follicles in the same lymph node.
  - Increased vascularity, most notably of high endothelial venules in interfollicular zones – The interfollicular lymphoid tissue contains numerous small blood vessels known as high

endothelial venules that are lined by plump, activated endothelial cells.

- Patent sinuses with no architectural disruption.

- **Mixed variant histopathologic subtype of iMCD** is characterized by a mix of hypervascular (predominantly regressed germinal centers) and plasma cell (hyperplastic germinal centers and interfollicular plasmacytosis) features in the same lymph node.

The clinical utility of these histopathologic subtypes is not clear. Transitions between histopathologic subtypes on subsequent biopsies in the same patient have been reported in iMCD as well as simultaneous presence of different histopathologic subtypes at separate sites within the same patient.

DIAGNOSIS

Evaluation — The diagnosis of HHV-8-negative/idiopathic MCD (iMCD) should be suspected in patients presenting with peripheral lymphadenopathy, constitutional symptoms, and an elevated C-reactive protein. Whole body computed tomography (CT) with fluorodeoxyglucose (FDG) positron emission tomography (PET) should demonstrate multiple regions of enlarged lymph nodes, usually with a relatively low standardized uptake value (SUV, 2.5 to 8).

The diagnosis of iMCD requires pathologic review of an excisional biopsy of a lymph node. The most enlarged or FDG-avid node should be selected for biopsy. If no single node predominates, the choice should be made based on accessibility (peripheral more accessible than visceral). The pathologic review of the lymph node should evaluate for pathologic features described above. (See 'Pathology' above.)

Once Castleman-like histopathology is identified, immunohistochemical staining of the patient's lymph node for latency-associated nuclear antigen-1 (LANA-1) should be performed to determine whether the patient has HHV-8-associated MCD or iMCD. Repeat biopsies may be necessary to confirm the diagnosis if an initial biopsy fails to confirm the diagnosis and the clinical suspicion remains high.

The evaluation must exclude other disorders that can demonstrate iMCD-like histopathologic

lymph node features, such as Hodgkin lymphoma, rheumatoid arthritis, other connective tissue diseases, and HIV infection (table 2). This includes IgH gene rearrangement studies to evaluate for a clonal B cell disorder. This is discussed in more detail separately. (See "Unicentric Castleman disease", section on 'Differential diagnosis'.)

Diagnostic criteria — Diagnostic criteria for iMCD have been established by an international working group of pediatric and adult pathology and clinical experts and are shown in the table (table 2) [43]. The proposed consensus criteria require characteristic histopathologic findings on lymph node biopsy, enlargement of multiple lymph node regions, the presence of multiple clinical and laboratory abnormalities, and the exclusion of infectious, malignant, and autoimmune disorders that can mimic iMCD. (See 'Pathology' above.)

PRETREATMENT EVALUATION

Once the diagnosis of HHV-8-negative/idiopathic MCD (iMCD) has been established based on clinical features and pathologic evaluation of a lymph node, a pretreatment evaluation provides a baseline of disease activity and assessment of comorbidities that may impact treatment decisions. In addition to a history and physical examination, it is our practice to perform the following pretreatment studies in patients with MCD:

Laboratory studies include:

- Complete blood count with differential; liver and renal function chemistries, electrolytes, lactate dehydrogenase (LDH), and albumin.
- Viral testing for hepatitis B, HHV-8 (PCR of serum during acute symptoms), and HIV, with quantitative assays if positive.
- Serum protein electrophoresis with immunofixation, free light chains, and quantitative immunoglobulins.
- Testing for acute phase reactants, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and fibrinogen; and measurement of serum IL-6, soluble IL-2 receptor, and vascular endothelial growth factor (VEGF) along with a panel of other proinflammatory

cytokines, when available.

- Serologic investigations for autoimmune disorders, such as ANA, rheumatoid factor, SS-A, SS-B, and anti-dsDNA are performed if suspected clinically.

Imaging with a combined whole body 18-fluorodeoxyglucose positron emission tomography with contrast-enhanced computed tomography (FDG PET/CT) is performed to detect all areas of lymph node involvement and to document the standardized uptake value (SUV) of involved areas. CT of the neck, chest, abdomen, and pelvis may be used as an alternative if FDG PET/CT is not readily available. (See 'Imaging' above.)

We also routinely perform pretreatment echocardiography to evaluate for pericardial effusion and pulmonary function testing to evaluate for lung involvement.

TREATMENT

Choice of therapy — It is critical to distinguish patients with HHV-8-associated MCD from those with HHV-8-negative/idiopathic MCD (iMCD) at the time of diagnosis as their management differs. (See "HHV-8-associated multicentric Castleman disease".)

Our preferred treatment of iMCD depends on disease aggressiveness and whether there is concurrent POEMS syndrome (algorithm 1). (See 'POEMS-associated, iMCD' above.)

Data regarding the treatment of iMCD come from a single randomized controlled trial, systematic reviews of the literature, case series, and case reports. Clinical practice varies between centers and the approach described below reflects our practice and is generally consistent with guidelines from an international group of adult and pediatric iMCD experts [58]. We encourage patients to enroll themselves directly on the ACCELERATE Natural History Study, which is collecting data on clinical features, treatments, and treatment efficacy. There is a paucity of interventional clinical trials.

iMCD without POEMS — Where available, treatment that incorporates the anti-IL-6 monoclonal antibody siltuximab is preferred for most patients with iMCD (algorithm 1). Additional agents are added for patients with iMCD who develop life-threatening complications such as

respiratory failure, renal failure, liver failure, and/or pancytopenia.

This approach has resulted in two-year overall survival and relapse-free survival rates of 94 to 95 percent and 79 to 85 percent, respectively. Siltuximab is preferred based on its benefit in the only randomized trial and its approval in the United States and Europe for this purpose. If siltuximab is not available, tocilizumab, a monoclonal antibody targeted against the IL-6 receptor, can be used in its place. (See 'IL-6 inhibitors' below.)

Identify disease severity — A more aggressive treatment approach is used for patients with iMCD who present with poor performance status thought to be due to the iMCD or who develop life-threatening complications such as respiratory failure, renal failure, liver failure, and/or pancytopenia. We and others consider patients with any two of the following five features to have severe disease requiring close monitoring and more aggressive therapy [58]:

- ECOG performance status ≥2 (table 3)
- Estimated glomerular filtration rate <30 or creatinine >3
- Anasarca, ascites, pleural effusion, and/or pericardial effusion
- Hemoglobin ≤8 g/dL
- Pulmonary involvement or interstitial pneumonitis with dyspnea

Severe disease (with life-threatening organ failure) — Treatment of iMCD without POEMS syndrome and with life-threatening organ failure or poor performance status thought to be due to the iMCD is complicated and coordination with an expert in iMCD is advised. For such patients, we suggest (algorithm 1):

- Initial treatment with siltuximab plus high dose glucocorticoids. (See 'IL-6 inhibitors' below.)
    - The addition of glucocorticoids aims to decrease the time to symptom control. (See 'Glucocorticoids' below.)
    - Aggressive monitoring and treatment should be continued even in the setting of multi-organ failure and ventilator support, because critically ill patients with iMCD can have dramatic responses and durable remissions following IL-6 blockade and/or cytotoxic chemotherapy.
    - Accelerated dosing of siltuximab at weekly intervals is used while the patient is

experiencing severe disease [58].

- Response is assessed daily using clinical features and laboratory studies (complete blood count [CBC], lactate dehydrogenase [LDH], biochemical profile, albumin, liver function tests, and C-reactive protein [CRP]).

- This initial treatment is continued as long as the clinical status is stable or improving. If clinical and laboratory values normalize, glucocorticoids are tapered and single agent siltuximab is administered every three weeks in order to maintain the remission. Siltuximab is given until progression of disease or continued indefinitely if worsening/disease progression does not occur.

- If the patient's clinical status does not improve within one week or if there is worsening of organ (liver, kidney, pulmonary) dysfunction at any time, we add multi-agent systemic chemotherapy (eg, R-CHOP, R-CVP, CER, VDT-ACE-R). The choice of chemotherapy regimen is described in more detail below. (See 'Chemotherapy and immunomodulators/immunosuppressants' below.)

- Patients refractory to siltuximab and combination chemotherapy are managed individually with serial trials of various combinations of systemic chemotherapies and/or immunomodulators/immunosuppressants (eg, sirolimus, cyclosporine, anakinra, thalidomide, bortezomib, intravenous immune globulin [IVIg]). Patients who achieve a sufficient response following therapy that incorporates an immunomodulator/immunosuppressant proceed to maintenance with that agent. Siltuximab is not continued as a maintenance therapy in remission if it was not effective during active disease. (See 'Chemotherapy and immunomodulators/immunosuppressants' below.)

Non-severe disease (without life-threatening organ failure) — For patients with iMCD without POEMS syndrome and without evidence of life-threatening organ failure or poor performance status thought to be due to the iMCD, we suggest (algorithm 1):

- Initial treatment with single agent siltuximab with or without glucocorticoids. While glucocorticoids can decrease the time to symptom control, they also increase toxicity. (See 'IL-6 inhibitors' below and 'Glucocorticoids' below.)

While elevated pre-treatment IL-6 levels are associated with a trend toward increased likelihood of response to siltuximab, IL-6 levels should not be used to guide treatment decisions. In the phase II trial of siltuximab, there were iMCD patients with low/normal IL-6 levels who responded to siltuximab while others with high IL-6 levels did not [23].

- While a formal response assessment is performed after four cycles, disease progression involving organ failure at any time should lead to an escalation of treatment. (See 'Response evaluation' below.)

    - If clinical and laboratory values normalize after four cycles, siltuximab is typically continued indefinitely since symptoms can recur once therapy is discontinued.

    - If clinical and laboratory values remain abnormal after four cycles without a trend toward improvement and there is still no evidence of progressive organ dysfunction, we discontinue siltuximab and offer rituximab plus glucocorticoids with or without an immunomodulator/immunosuppressant (eg, sirolimus, cyclosporine, anakinra, thalidomide, bortezomib, IVIg) until a response is achieved. Our preference for this approach over cytotoxic chemotherapy places a high value on the avoidance of toxicities associated with cytotoxic chemotherapy in a patient without evidence of progressive organ dysfunction. (See 'Chemotherapy and immunomodulators/immunosuppressants' below.)

    - Patients who achieve a sufficient response following therapy that incorporates an immunomodulator/immunosuppressant proceed to maintenance with that immunomodulator/immunosuppressant. Whether that agent should be continued indefinitely, dosing extended, or discontinued at some point is not known.

    - Patients are followed with serial computed tomography (CT) scans every three months until maximum response has occurred after which the frequency of imaging can be reduced to six and later 12 months.

- If the patient's clinical status does not improve with first-line siltuximab or second-line rituximab plus glucocorticoids with or without an immunomodulator/immunosuppressant, but the patient does not progress to "severe" disease, then we offer serial administration of other immunomodulators/immunosuppressants (eg, sirolimus, cyclosporine, anakinra, thalidomide,

bortezomib, IVIg).

- If the patient experiences progression to "severe" disease (life-threatening organ failure) at any time, we treat the patient as a "severe" disease patient with serial trials of various combinations of systemic chemotherapy with or without an immunomodulator/immunosuppressant. Experience is greatest with rituximab, cyclophosphamide, and/or etoposide as an initial regimen. Once a sufficient clinical response is achieved with chemotherapy, an immunomodulator/immunosuppressant should be selected or continued for maintenance therapy. (See 'Chemotherapy and immunomodulators/immunosuppressants' below.)

iMCD with POEMS — Our management of patients with iMCD with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome is focused on treating the POEMS syndrome. The iMCD is considered to be a secondary finding in these cases and traditional iMCD-directed treatments are typically ineffective in these cases. As described in more detail separately, treatment depends on the number of bone lesions and whether clonal plasma cells are found on iliac crest biopsy. (See "POEMS syndrome".)

Classes of therapies

IL-6 inhibitors — Monoclonal antibodies targeted against interleukin (IL)-6 (siltuximab) or the IL-6 receptor (tocilizumab, also called atlizumab or MRA) can be used to control symptoms and decrease lymph node size in iMCD without POEMS syndrome [21,22,59-64]. There is no role for IL-6 inhibitors in POEMS-associated iMCD. Tocilizumab is approved for the treatment of iMCD in Japan, but not in Europe or the United States. Siltuximab is approved for the treatment of iMCD in many countries, including the United States and all of Europe [65]. Data about combining other modalities with anti-IL-6-directed treatment are limited. Where available, siltuximab is preferred over tocilizumab based on its benefit in the only randomized trial. If siltuximab is not available, tocilizumab can be used in its place.

Anti-IL-6-directed treatment is typically continued indefinitely since symptoms can recur once therapy is discontinued [1,66]. Whether siltuximab should be continued indefinitely (as indicated on the label), dosing extended, or discontinued at some point is not known.

As at least half of iMCD patients treated with anti-IL-6 therapy will not achieve a sufficient clinical

response; patients should be closely monitored for insufficient response and alternative treatments must be tried in nonresponders. (See 'Response evaluation' below.)

Toxicities and assay interference — The most common toxicities of anti-IL-6 treatment include pruritus, increased weight, rash, hyperuricemia, and upper respiratory tract infection [65]. Symptoms of infusion reaction (eg, back or chest pain, nausea/vomiting, flushing, erythema, palpitations) are seen in approximately 5 percent. Anti-IL-6 treatment should not be administered to patients with severe infection, and physicians should have a high index of suspicion for infection since these agents may mask common signs and symptoms of acute inflammation (eg, fever, acute phase reactants). Live vaccines should be avoided.

Of note, serum/plasma IL-6 measurements should not be performed or used to guide therapy for at least 18 to 24 months after the last dose of siltuximab or tocilizumab. These assays detect complexed IL-6+siltuximab or detect increased levels of IL-6 due to increased half-life in tocilizumab-treated patients, and are therefore uninterpretable. Values often rise above the upper limits of quantification almost immediately after these drugs are administered, changes which likely represent a false positive result.

Efficacy — The efficacy of siltuximab and tocilizumab in iMCD was illustrated in two small trials described below. Both trials demonstrated high response rates and improvement in symptoms and laboratory abnormalities. Further follow-up is needed to determine whether these high response rates translate into a survival advantage.

IL-6 levels should not be used to determine candidacy for anti-IL-6 therapy as IL-6 is not a strong predictive biomarker of response. There has been no defined minimal IL-6 level for the activity of these agents in iMCD. However, approximately half of the patients not responding to siltuximab in the randomized trial did not have elevated IL-6 levels at baseline [23]. Patients should be closely monitored by clinical and laboratory testing for insufficient response and alternative treatments must be tried in nonresponders.

- A multicenter, randomized, double-blind, phase II trial of siltuximab in 79 HIV-negative patients with symptomatic iMCD demonstrated significant benefit of siltuximab for all end points in a large portion of patients [67]. When compared with placebo, siltuximab (11 mg/kg intravenous infusion every three weeks) resulted in the following:

- Higher overall response rate (34 versus 0 percent) and longer median time to treatment failure (not reached versus 134 days).
- Improvements in anemia (hemoglobin ≥15 g/L at week 13, 61 versus 0 percent) and markers of inflammation (CRP, erythrocyte sedimentation rate [ESR], and fibrinogen).
- Durable symptomatic response (57 versus 19 percent).
- Frequencies of treatment-emergent adverse events were similar between siltuximab and placebo. Infusion reactions were infrequent (8 percent) and low grade, except for one anaphylactic reaction that led to treatment discontinuation.
- Severe (grade 3/4) adverse events included fatigue (9 percent); night sweats (8 percent); and hyperkalemia, hyperuricemia, localized edema, hyperhidrosis, neutropenia, thrombocytopenia, hypertension, and weight increased (4 percent each).

- A multicenter, open-label, single-arm trial evaluated the safety and efficacy of tocilizumab in 26 symptomatic patients with HIV-negative, iMCD of the plasma cell histopathologic subtype [68]. The patients were initially treated with tocilizumab at a dose of 8 mg/kg intravenously every two weeks for 16 weeks, with an extension phase permitting variable dosing after this time. Major results of this study include:
  - After 16 weeks of treatment, nutritional status and fatigue scores were significantly improved, as were lymphadenopathy and markers of inflammation, such as CRP and ESR.
  - Mean hemoglobin levels improved from 9.2 to 12.0 g/dL; no patient required transfusion during this period.
  - Of the 15 patients receiving treatment with corticosteroids at baseline, the average daily dose of prednisolone (16 mg/day) decreased by approximately one-half over the course of therapy.
  - During the extension period, all patients remained on treatment, and the efficacy observed during the first 16 weeks was sustained or improved over the course of one year, with some subjects receiving this agent for up to three years.

- Adverse reactions were common but mild, and included symptoms related to the common cold (eg, cough, rhinorrhea, pharyngitis). Infusion-related symptoms (eg, low grade fever) were also readily manageable.

Chemotherapy and immunomodulators/immunosuppressants — Cytotoxic chemotherapy nonspecifically targets rapidly dividing cells for destruction, which includes many immune cell populations. Immunomodulators/immunosuppressants also target immune cell populations. As such, these cytotoxic chemotherapy and immunomodulators/immunosuppressants can be used in iMCD to target the highly activated immune cells.

These agents have not been evaluated for the treatment of iMCD in a clinical trial and data on efficacy are limited to case reports and case series, many of which were included in a 2016 systematic review [4]. We offer immunomodulators/immunosuppressants to patients who do not achieve an adequate response to initial therapy with siltuximab and do not demonstrate evidence of organ failure (algorithm 1). We typically reserve chemotherapy for patients with evidence of organ failure or poor performance status thought to be related to the iMCD.

- **Single agent chemotherapy (not including rituximab)** – Cyclophosphamide, vinblastine, and etoposide have all been used as single agents to induce remissions [4]. However, symptoms generally recur after treatment discontinuation. Once a sufficient clinical response is achieved with chemotherapy, an immunomodulator/immunosuppressant should be selected or continued for maintenance therapy.

- Rituximab – While there is strong evidence for the use of rituximab in HHV-8-associated MCD [69-71], there is sparse evidence for its effectiveness in iMCD. In one series, five of eight patients receiving rituximab without cytotoxic chemotherapy attained a complete response with a median time to response of two months [4]. We offer rituximab with or without other chemotherapies to patients with iMCD who do not have life-threatening organ failure and do not achieve a sufficient clinical response to anti-IL-6 therapy. (See "HHV-8-associated multicentric Castleman disease", section on 'Rituximab-based therapy'.)

- **Multi-drug combinations** – Selected patients may benefit from more aggressive combination chemotherapy, including agents like cyclophosphamide, etoposide, doxorubicin, rituximab, and bortezomib as part of regimens such as [4,28,72]:

- R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab)
- R-CVP (cyclophosphamide, vincristine, prednisone, and rituximab)
- CER (cyclophosphamide, etoposide, rituximab)
- VDT-ACE-R (bortezomib, dexamethasone, thalidomide, doxorubicin, cyclophosphamide, etoposide, and rituximab)
- TCP (thalidomide, cyclophosphamide, prednisone)

Paradoxically, the most acutely ill iMCD patients may be the cases that may benefit from multi-agent chemotherapy the most. We continue aggressive multi-agent chemotherapy treatment even in the setting of multi-organ failure and ventilator support, because critically ill iMCD patients can have dramatic responses and durable remissions following IL-6 blockade and/or cytotoxic chemotherapy. In two studies, approximately 50 percent of patients with HHV-8-unknown MCD achieved durable complete responses after treatment with four-drug combinations such as CHOP or CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) [32,33]. A single-center, single-arm phase 2 study of TCP in iMCD reported durable tumor and symptomatic response in 48 percent of patients treated [72]. Case reports of CHOP in iMCD and HHV-8-unknown MCD have had mixed results with some patients achieving durable response [73,74].

- **Immunomodulators/immunosuppressants** – Case reports and small case series have described durable responses to other agents, including the combination of sirolimus and intravenous immune globulin [1]; single agent bortezomib [75-78]; and immunomodulatory agents (thalidomide, lenalidomide) [79,80]. We use these agents for patients with relapsed and refractory disease. In a single-center, single-arm phase 2 study of first-line TCP in iMCD reported durable tumor and symptomatic response in 48 percent of patients treated [72]. Further research is needed to understand the efficacy of TCP in other populations and the role for individual components of TCP in iMCD.

- **Hematopoietic cell transplantation (HCT)** – For POEMS-associated, iMCD, high dose chemotherapy with autologous HCT has been used for patients with widespread osteosclerotic lesions or evidence of bone marrow involvement [81]. In contrast, we do not recommend HCT for iMCD not associated with POEMS syndrome; in this population there is limited experience and mixed results with autologous HCT and only one reported case of allogeneic HCT. (See "POEMS syndrome", section on 'Hematopoietic cell transplantation

(HCT)'.)

Glucocorticoids — Glucocorticoids have been frequently used as a systemic therapy in patients with iMCD [4,28]. Glucocorticoid monotherapy can offer mild symptomatic improvement during acute exacerbations of iMCD, however most patients do not achieve a meaningful benefit and others relapse during steroid tapering. Thus, we typically use glucocorticoids along with other agents for patients with life-threatening organ failure or poor performance status thought to be due to the MCD.

Radiation — There is no role for radiation therapy in iMCD **without** POEMS syndrome.

The use of radiation therapy for the treatment of POEMS syndrome with or without concurrent iMCD is discussed separately. (See "POEMS syndrome", section on 'Radiation therapy'.)

Surgery — While surgical removal of lymph nodes is curative in unicentric Castleman disease, it does not have a role in the treatment of iMCD [41]. Splenectomy has been reported to result in transient symptomatic improvement in one patient with iMCD [35].

PATIENT FOLLOW-UP

After the initiation of therapy, patients should be evaluated to determine the disease response to treatment and should be followed longitudinally for progression and complications.

Response evaluation — Patients with organ dysfunction or poor performance status are assessed daily using clinical features and laboratory studies (complete blood count [CBC], lactate dehydrogenase [LDH], biochemical profile, C-reactive protein [CRP], albumin) to adjust treatment as needed. (See 'Severe disease (with life-threatening organ failure)' above.)

In contrast, for iMCD **without** organ dysfunction or poor performance status, we generally administer four doses of therapy (eg, siltuximab every three weeks for four doses) prior to reassessing disease status and a formal response to treatment. Concern for disease progression with organ failure at any time (to "severe") should lead to earlier evaluation and an escalation of treatment, if confirmed. (See 'Non-severe disease (without life-threatening organ failure)' above.)

Response evaluation includes a clinical assessment of physical findings and symptoms (fatigue,

anorexia, fever, weight), laboratory studies (CBC, creatinine, albumin, and CRP), and imaging (computed tomography of the neck, chest, abdomen, and pelvis or whole body PET/CT, if available) [58]. A clinical assessment and laboratory studies are performed every two weeks until lab values normalize. Imaging is performed six weeks after the initiation of therapy and then every three months until maximum response.

Uniform response criteria have been proposed by an international working group of pediatric and adult iMCD experts [58]:

- Complete response (CR) – Symptoms resolved to baseline, laboratory studies (CRP, hemoglobin, albumin, glomerular filtration rate) within normal range, and lymph nodes meet Lugano criteria for complete response (table 4).
- Partial response (PR) – An overall PR requires nothing less than a PR across all three categories, but not meeting criteria for CR. Improvement in all symptom categories, but not to baseline, at least 50 percent improvement in all laboratory studies, and lymph nodes meet Lugano criteria for partial response.
- Progressive disease (PD) – An overall PD occurs when any category has a PD. Worsening in any symptom on at least two assessments and/or >25 percent increase in lymph node size and/or >25 percent worsening in any laboratory study.
- Stable disease (SD) – Does not meet the criteria for CR, PR, or PD.

Regardless of the subtype or treatment approach, patients who achieve an at least partial response are seen at periodic intervals to monitor for treatment complications and assess for disease progression. The frequency and extent of these visits depends on the comfort of both the patient and physician. Our approach to patient surveillance is to schedule visits every two to three months. At these visits, we perform a history and physical examination and serum biomarkers, which include CBC, blood chemistries, VEGF, sIL2R, CRP (ESR, if CRP not available), fibrinogen, liver function tests with albumin, serum free light chain assay, and quantitative immunoglobulins.

Patients who attain a CR and remain in remission for a full year are followed every 6 to 12 months with CT or PET/CT and serum biomarkers. Annual imaging can be discontinued after five years if the patient remains disease free. Patients should continue to diligently monitor their disease

symptoms.

Of importance, after siltuximab or tocilizumab is administered, laboratory tests for IL-6 levels become uninterpretable; the assays detect complexed IL-6+siltuximab and tocilizumab increases the half-life of inactive/circulating IL-6. Therefore, IL-6 levels should not be used to guide or contribute to treatment decisions for at least 18 to 24 months after the last dose of siltuximab or tocilizumab is given.

Complications — Fatal cases of iMCD are associated with fulminant infection, multi-organ failure due to progressive disease [35,36,38], or related malignancies.

Malignancy — Patients with iMCD appear to have an increased risk of malignancies.

- **Solid tumors** – A systematic literature review found that 24 (19 percent) of 128 patients with iMCD were diagnosed with a separate malignant disease before (n = 4), concurrent with (n = 12), or after (n = 8) their diagnosis, which is higher than the expected age-adjusted prevalence of 6 percent [4]. Of these 24 patients, 11 had a hematologic malignancy and 13 had a solid tumor. The solid tumors included three cases of adenocarcinoma (two unknown primary site, one gastric), two cases of inflammatory myofibroblastic tumour, and one case each of basal cell carcinoma, dendritic cell sarcoma, metastatic gastric cancer, medullary thyroid cancer, neurinoma, spindle cell sarcoma, squamous cell carcinoma of lung, and tonsil cancer.

- **Hematologic malignancies** – The hematologic malignancies identified in the systematic literature review included six cases of non-Hodgkin lymphoma (two diffuse large B cell, one angioimmunoblastic T cell, one mantle cell, one orbital-mucosal associated lymphoid tissue, one not specified), three cases of Hodgkin lymphoma, one case of acute myeloid leukemia, and one case of multiple myeloma [4,82-84].

POEMS syndrome — iMCD can co-occur with another well-described constellation of symptoms, the POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes; also called osteosclerotic myeloma due to frequent associated bone changes). POEMS syndrome is described in more detail separately. (See "POEMS syndrome".)

As many as 15 percent of patients with POEMS syndrome have associated iMCD [85]. (See

'POEMS-associated, iMCD' above.)

In one study in which four of five patients with the POEMS syndrome also had iMCD, increased levels of IL-1 beta were noted in 13 of 13 serum samples, while IL-6 was increased in seven [86]. These similarities between POEMS syndrome and iMCD suggest a common underlying mechanism in at least some cases [87,88].

PROGNOSIS

The natural history of HHV-8-negative/idiopathic MCD (iMCD) is variable. Several different patterns of disease progression have been described [35,38,64]:

- An indolent form sometimes persists for months to a few years without worsening.
- An episodic relapsing form may be aggressive for a short period and then remit spontaneously or in response to treatment, only to recur at a later time.
- A rapidly progressive form that can lead to death within weeks. This form is most common in iMCD cases with TAFRO clinical features [89].

The prognosis of untreated MCD is poor. Few studies have investigated overall survival of iMCD cases alone. Four large series reported overall survival for HIV-negative, likely-HHV-8-negative MCD cases. Five-year overall survival ranges from 55 to 77 percent [45,90-92].

Progress in long-term outcomes of iMCD is anticipated with the advent of antibodies targeting the IL-6 signaling cascade. The ACCELERATE Natural History Registry is collecting data on effective treatments and their relation to long-term survival. Patients can e-consent and register themselves directly at www.CDCN.org/ACCELERATE.

ADDITIONAL RESOURCES

The Castleman Disease Collaborative Network (CDCN) connects an international community of physicians, researchers, patients, and loved ones to advance research and treatments for all subtypes of Castleman disease (CD).

Patients can visit the CDCN website to learn about and enroll themselves onto an international natural history registry of CD (www.CDCN.org/ACCELERATE). The CDCN also provides patient information and opportunities to engage others interested in CD through virtual communities and in-person meetings.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Castleman disease".)

SUMMARY AND RECOMMENDATIONS

- Multicentric Castleman disease (MCD) describes a heterogeneous group of lymphoproliferative disorders associated with systemic inflammatory symptoms.
- MCD is subclassified into human herpesvirus 8 (HHV-8)-associated MCD and HHV-8-negative/idiopathic MCD (iMCD) by staining lymph node tissue for LANA-1. HHV-8-associated MCD is caused by uncontrolled infection with HHV-8. The etiology of iMCD is unknown. (See 'Etiology and pathogenesis' above.)
- iMCD can present at any age with peripheral lymphadenopathy and systemic symptoms including fever, night sweats, weight loss, and fatigue, accompanied by nearly universal anemia, thrombocytosis or thrombocytopenia, hypoalbuminemia, polyclonal hypergammaglobulinemia, and an elevated C-reactive protein or erythrocyte sedimentation rate. (See 'Epidemiology' above.)

  Imaging with combined fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) demonstrates involvement of multiple sites, usually with a low standardized uptake value relative to aggressive lymphomas.
- The diagnosis of iMCD requires characteristic histopathologic findings on lymph node biopsy, multiple regions of enlarged lymph nodes, the presence of certain clinical and laboratory abnormalities, and the exclusion of infectious, malignant, and autoimmune disorders that can

mimic iMCD (table 2). (See 'Diagnostic criteria' above.)

- Our initial management of iMCD depends on whether the patient meets criteria for POEMS syndrome and disease severity (algorithm 1). (See 'Choice of therapy' above.)
  - Patients with POEMS syndrome and concurrent iMCD are managed similarly to those with POEMS syndrome alone. (See "POEMS syndrome", section on 'Therapy'.)
  - For patients with non-severe iMCD without POEMS syndrome, we suggest the use of siltuximab with or without glucocorticoids (**Grade 2B**). If effective, siltuximab is typically continued indefinitely since symptoms can recur once therapy is discontinued. (See 'Non-severe disease (without life-threatening organ failure)' above.)
  - For patients with severe iMCD without POEMS syndrome, we suggest combining accelerated weekly dosing of siltuximab with high dose glucocorticoids for all patients (**Grade 2C**). If clinical and laboratory values normalize, patients are transitioned to maintenance siltuximab every three weeks. If the patient's clinical status does not improve within one week or if progression occurs at any time, we add multi-agent systemic chemotherapy. (See 'Severe disease (with life-threatening organ failure)' above.)
- A significant proportion of patients with iMCD do not improve with IL-6 blockade. Patients should be evaluated to determine the disease response to treatment, and should be followed longitudinally for disease progression and complications. In cases with life-threatening organ dysfunction, we assess disease response daily. For more stable cases, we generally administer four doses of therapy prior to reassessing disease status. (See 'Response evaluation' above.)
- Patients are followed clinically and with biochemical and imaging exams. Importantly, interleukin (IL)-6 assays cannot be used to guide therapy for at least 18 to 24 months after the administration of siltuximab or tocilizumab because these assays detect complexed IL-6+drug and are therefore uninterpretable. (See 'Response evaluation' above.)

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Topic 117312 Version 5.0

GRAPHICS

Criteria for the diagnosis of POEMS syndrome

Mandatory major criteria (both required)
Polyneuropathy
Monoclonal plasma cell proliferative disorder (almost always lambda)
Other major criteria (one required)
Sclerotic bone lesions
Castleman disease
Elevated levels of vascular endothelial growth factor (VEGF)*
Minor criteria (one required)
Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
Extravascular volume overload (edema, pleural effusion, or ascites)
Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)¶
Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
Papilledema
Thrombocytosis/polycythemia

The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present.

* The source data do not define an optimal cut off value for considering elevated VEGF level as a major criterion. We suggest that VEGF measured in the serum or plasma should be at least three- to fourfold higher than the normal reference range for the laboratory that is doing the testing to be considered a major criterion.
¶ In order to consider endocrinopathy as a minor criterion, an endocrine disorder other than diabetes or hypothyroidism is required since these two disorders are common in the general population.

Original figure modified for this publication. Dispenzieri A. POEMS syndrome. Blood Rev 2007; 21:285. Illustration used with the permission of Elsevier Inc. All rights reserved.

Graphic 64782 Version 6.0

Consensus diagnostic criteria for idiopathic multicentric Castleman disease (iMCD)

I. Major criteria (need both)

1. Histopathologic lymph node features consistent with the iMCD spectrum. Features along the iMCD spectrum include (need grade 2-3 for either regressive GCs or plasmacytosis at minimum):
    - Regressed/atrophic/atretic germinal centers, 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
2. Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations

II. Minor criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)

Laboratory:*

1. Elevated CRP (>10 mg/L) or ESR (>15 mm/hour)¶
2. Anemia (hemoglobin <12.5 g/dL for males, hemoglobin <11.5 g/dL for females)
3. Thrombocytopenia (platelet count <150 k/microL) or thrombocytosis (platelet count >400 k/microL)
4. Hypoalbuminemia (albumin <3.5 g/dL)
5. Renal dysfunction (eGFR <60 mL/min/1.73 m^2) or proteinuria (total protein 150 mg/24 hours or 10 mg/100 mL)
6. Polyclonal hypergammaglobulinemia (total gamma-globulin or immunoglobulin G >1700 mg/dL)

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

III. 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 (eg, 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 (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. FDC sarcoma
5. POEMS syndrome$^{\Delta}$
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$^{\Delta}$), glomerular nephropathy, inflammatory myofibroblastic tumor

GC: germinal center; FDC: follicular dendritic cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; eGFR: estimated glomerular filtration rate; CTCAE: common terminology for adverse events; PCR: polymerase chain reaction; LANA-1: latency-associated nuclear antigen; IHC: immunohistochemistry; EBV: Epstein-Barr virus; CMV: cytomegalovirus; IL: interleukin; VEGF: vascular endothelial growth factor; Ig: immunoglobulin; LDH: lactate dehydrogenase; B2M: β-2-microglobulin.

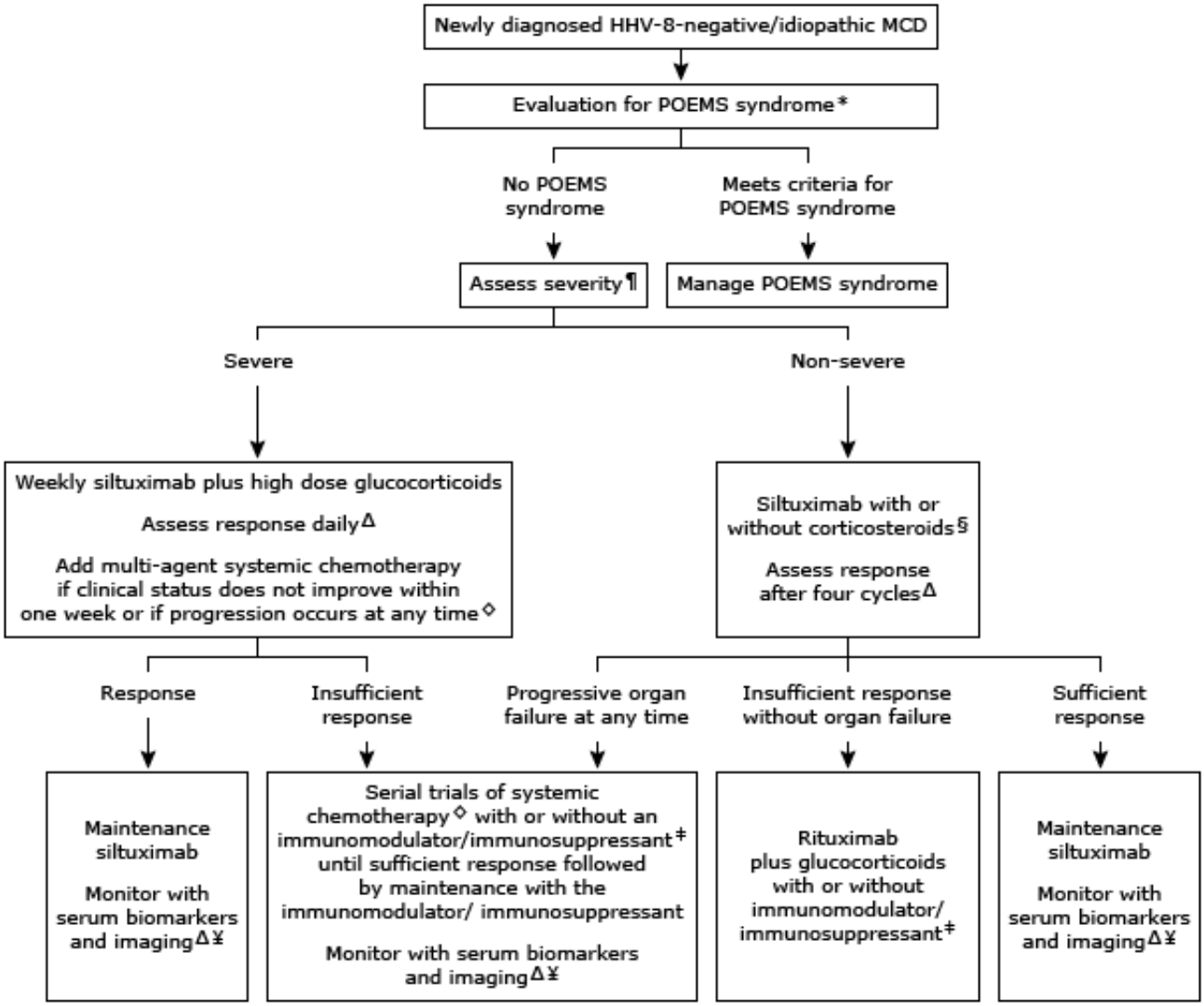
* We have provided laboratory cutoff thresholds as guidance, but we recognize that some laboratories have slightly different ranges. We suggest that you use the upper and lower ranges from your particular laboratory to determine if a patient meets a particular laboratory Minor criterion.

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

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

Graphic 112477 Version 4.0

Initial management of HHV-8-negative/idiopathic multicentric Castleman disease



HHV-8: human herpesvirus 8; MCD: multicentric Castleman disease; POEMS: syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; HCT: hematopoietic cell transplantation; ECOG: Eastern Cooperative Oncology Group; IL: interleukin; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP: rituximab, cyclophosphamide, vincristine, prednisone; VDT-ACE-R: bortezomib, dexamethasone, thalidomide, adriamycin, cyclophosphamide, etoposide, and rituximab; CER: cyclophosphamide, etoposide, rituximab; CT: computed tomography; PET/CT: combined positron emission tomography with computed tomography; CBC: complete blood count; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

* The diagnosis of POEMS syndrome in a patient with iMCD requires both polyneuropathy and monoclonal plasma cell proliferative disorder (positive M-protein, almost always lambda) along with at least one of the following: organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy); extravascular volume overload (edema, pleural effusion, or ascites); endocrinopathy (adrenal, pituitary, gonadal, parathyroid, thyroid, pancreatic); skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails); papilledema; thrombocytosis or polycythemia.

¶ A more aggressive treatment approach is used for patients who present with poor performance status thought to be due to the iMCD or life-threatening organ failure. We consider patients with any two of the following five

markers to have severe disease: ECOG performance status ≥2; estimated glomerular filtration rate <30 or creatinine >3; hemoglobin ≤8 g/dL; anasarca, ascites, pleural effusion, and/or pericardial effusion; pulmonary involvement, and/or interstitial pneumonitis with dyspnea.
Δ Patients with severe disease are followed daily with CBC, blood chemistries, LDH, CRP (ESR, if CRP not available), fibrinogen, and liver function tests with albumin to adjust treatment as necessary. For those with non-severe disease, a clinical assessment and laboratory studies (CBC, creatinine, albumin, CRP) are initially performed every two weeks until lab values normalize. The time between evaluations is then gradually extended. Of note, IL-6 assays cannot be used to guide therapy for at least 18 to 24 months after the administration of siltuximab or tocilizumab because these assays detect complexed IL-6+drug and are therefore uninterpretable.
◇ Chemotherapy options include cyclophosphamide, etoposide, doxorubicin, rituximab, bortezomib, or combinations such as R-CHOP, R-CVP, VDT-ACE-R, or CER.
§ Siltuximab (a monoclonal antibody targeted against IL-6) is approved in the US and Europe for the treatment of HHV-8-negative MCD and is preferred for this population. If siltuximab is not available, tocilizumab (a monoclonal antibody targeted against the IL-6 receptor) is an acceptable alternative. For patients with non-severe disease, these agents can be given with or without glucocorticoids. While glucocorticoids can decrease the time to symptom control, they also increase toxicity.
¥ CT or PET/CT of the chest, abdomen, and pelvis with contrast is performed six weeks after the initiation of therapy and then every three months until maximum response.
‡ Immunomodulator/immunosuppressant options include sirolimus, cyclosporine, anakinra, thalidomide, bortezomib, and IVIg. Immunomodulators/immunosuppressants are used for patients with organ failure not responding to siltuximab plus chemotherapy and for patients without organ failure who do not respond to siltuximab. Patients who achieve a sufficient response following therapy that incorporates one of these agents proceed to maintenance with that agent. Patients that do not experience a sufficient response should try alternative immunomodulators/immunosuppressants.

Graphic 117396 Version 4.0

Eastern Cooperative Oncology Group (ECOG, Zubrod, World Health Organization) performance scale

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

Graphic 72901 Version 10.0

Lugano criteria for response assessment in lymphoma

Response and site	PET/CT-based response	CT-based response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS[¶] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5[¶] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50 percent decrease in SPD of up to six target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50 percent in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in	Not applicable

	normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50 percent decrease from baseline in SPD of up to six dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50 percent from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50 percent of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be

		unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS: 5-point scale; CT: computed tomography; FDG: fluorodeoxyglucose; IHC: immunohistochemistry; LDi: longest transverse diameter of a lesion; MRI: magnetic resonance imaging; PET: positron emission tomography; PPD: cross product of the LDi and perpendicular diameter; SDi: shortest axis perpendicular to the LDi; SPD: sum of the product of the perpendicular diameters for multiple lesions.

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

¶ PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

From: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014; 32(27):3059-67. Reprinted with permission.

Graphic 97480 Version 6.0

Contributor Disclosures

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