HHV-8-associated 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/idiopathic 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-associated MCD. HHV-8-negative/idiopathic MCD, UCD, diseases associated with HHV-8 infection, and the virology of HHV-8 are presented separately.

- (See "Disease associations of human herpesvirus 8 infection".)

- (See "Virology, epidemiology, and transmission of human herpesvirus 8 infection".)

- (See "Unicentric Castleman disease".)

- (See "HHV-8-negative/idiopathic multicentric Castleman disease".)

ETIOLOGY AND PATHOGENESIS

Uncontrolled HHV-8 infection is the well-established etiology of HHV-8-associated MCD [1]. HHV-8 is a gamma herpesvirus similar to Epstein-Barr virus (EBV) that has been found in both endemic and HIV-associated Kaposi sarcoma (KS) [2,3]. (See "Disease associations of human herpesvirus 8 infection" and "AIDS-related Kaposi sarcoma: Clinical manifestations and diagnosis".)

DNA sequencing studies identified HHV-8 involvement in all cases of HIV-associated MCD and in

some cases of HIV-negative MCD [4,5]. The proportion of HHV-8-associated MCD cases who are HIV-negative may vary with the prevalence of HHV-8 in the population. In Japan, where the seroprevalence of HHV-8 is extremely low, HHV-8 was found only in HIV-infected patients with MCD [6,7].

HIV infection or another cause of immunodeficiency in HIV-negative cases enables HHV-8 to escape from host immune control, lytically replicate in lymph node plasmablasts, and signal for the release of cytokines that drive clinical and pathologic symptoms [6,8]. Symptomatic patients with HHV-8-associated MCD have HHV-8 viral loads that are 2 logs greater than asymptomatic patients with HHV-8-associated MCD; the increased viral load correlates with increased serum levels of interleukin (IL)-6 and IL-10 [9]. In contrast, this degree of increased serum HHV-8 viral load is not seen in patients with active KS [9,10].

HHV-8 infects B cells and plasmablasts, which can be detected by immunohistochemical staining of patients' lymph nodes for latency-associated nuclear antigen-1 (LANA-1). HHV-8 is present in approximately 10 to 30 percent of the mantle zone lymphoid cells of HHV-8-associated MCD [11-13]. These cells have immunoblastic morphology, are variably positive for CD20, and express the transcription factor MUM1/IRF4 [11-15]. Curiously, the HHV-8-infected cells always express high levels of cytoplasmic IgM lambda immunoglobulin, which is consistent with in vitro studies showing that HHV-8 preferentially establishes stable infection in tonsillar B cells expressing IgM lambda immunoglobulin [16]. Somatic hypermutation of the Ig genes is not observed, which may indicate an origin from a naïve B cell or, alternatively, from an IgM-expressing memory B cell; IgM memory cells have been identified in tonsils [16], the anatomic site where primary infection with HHV-8 is believed to occur. Immunoblasts with these features are not present in unicentric Castleman disease or HHV-8-negative/idiopathic MCD [15]. The interfollicular plasma cells, which are not infected with HHV-8 in HHV-8-associated MCD, express IgG or IgA immunoglobulins and are polytypic with respect to light chain expression [15]. Highlighting the critical role of B cells in HHV-8-associated MCD, their depletion with rituximab is a highly effective therapy [17]. Peripheral T cell levels, including polyfunctional effector memory CD8 T cells, have also been associated with HHV-8-associated MCD pathogenesis [18].

Other mechanisms that may be involved in the pathogenesis of HHV-8-assocated MCD include upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) by latently expressed viral-FLICE (viral Fas-associating protein with death domain-like interleukin-1-

converting enzyme) inhibitory protein or viral microRNA-K1 and upregulation of vascular endothelial growth factor (VEGF) and other factors by a viral G-protein couple receptor [19]. These secreted proteins induce B cell and plasma cell proliferation, angiogenesis, and an acute-phase reaction.

Human IL-6 and viral IL-6 (vIL-6, a homolog of IL-6 that is encoded in the HHV-8 genome) are both important drivers of the B cell proliferation and symptoms observed in HHV-8-associated MCD. Particularly during lytic (replicative) infection, but to a lesser degree during latent infection as well, HHV-8-positive B cells secrete vIL-6 that activates the human IL-6 receptor (gp130) and does not need its coreceptor, gp80, as human IL-6 does [19]. Thus, it is possible that a wider range of cells may be affected by vIL-6 than human IL-6. In addition to HHV-8-positive MCD, vIL-6 is also secreted from primary effusion lymphomas, but only rarely in KS [12,13,20,21]. Between 5 and 25 percent of the HHV-8-infected immunoblasts in the mantle zone of MCD lymph nodes express vIL-6 [12,13,20,21].

Human IL-6 (hIL-6) also plays an important role in HHV-8-associated MCD. Several sources of hIL-6 have been proposed in HHV-8-associated MCD. HHV-8 gene products, such as LANA-1 and vFLIP, induce the expression of hIL-6 in HHV-8-infected B cells through activation of the transcription factors NF-kB and AP-1 [22-26]. Alternatively, another model proposes that vIL-6 secreted by HHV-8-positive cells induces VEGF [27,28], and that VEGF in turn induces hIL-6 production by endothelial cells [14]. Increased VEGF expression in interfollicular areas of lymph nodes and elevated serum VEGF levels have been observed in patients with HHV-8-associated MCD, and are possibly responsible for the increased angiogenesis in lymph nodes in HHV-8-associated MCD cases.

In some cases, HHV-8-infected immunoblasts are highly proliferative [15] and may coalesce to form so-called "microlymphomas," or give rise to frank B cell plasmablastic lymphoma [14]. Despite their monotypic IgM lambda expression, the HHV-8-positive proliferation in MCD has polyclonal immunoglobulin gene rearrangements, even in most cases that have progressed to "microlymphomas" [14]. In addition, HHV-8 genomes within HHV-8-associated MCD lesions are also polyclonal [29].

Plasmablastic lymphomas arising out of HHV-8-associated MCD are monoclonal [14,15]. It is hypothesized that the hyperproliferative state induced by HHV-8 permits the accumulation of new

mutations in the genomes of the infected B immunoblasts. Positive selection for clones bearing mutations that enhance growth and survival then allows an initially reactive process to evolve over time into an overt lymphoma. This model is similar to that proposed for the continuum of lymphoproliferative disorders that are associated with EBV in immunosuppressed patients [14]. (See "Treatment and prevention of post-transplant lymphoproliferative disorders".)

Two other lymphoproliferative disorders are also associated with HHV-8: primary effusion lymphomas (PEL) [14,30-35] and germinotropic lymphoproliferative disorder [36]. HHV-8-associated MCD and plasmablastic lymphoma are not associated with EBV infection, whereas in PEL and germinotropic lymphoproliferative disorder, co-infection of the neoplastic B cells by HHV-8 and EBV is common. (See "AIDS-related lymphomas: Primary effusion lymphoma", section on 'Pathogenesis'.)

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 and the remaining 25 percent are estimated to be HHV-8-associated MCD or HHV-8-negative/idiopathic MCD (iMCD) [37]. 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 HHV-8-associated MCD can present at any age (youngest is one year old), but the median age at diagnosis is between 50 and 65 years [8,17,38-46]. Fifty to 65 percent are male.

Among HIV-infected individuals, the incidence of HHV-8-associated MCD has increased in the years since the introduction of antiretroviral therapy (ART) for the management of HIV.

The incidence of HHV-8-associated MCD among HIV-infected individuals was calculated from a prospective HIV database with 56,202 patient-years of follow-up and compared with that of Kaposi sarcoma (KS) during the same time period [47]. The incidence of HHV-8-associated MCD increased over the time periods designated as pre-ART (1983 to 1996), early-ART (1997 to 2001), and later ART (2002 to 2007) eras and was 0.6, 2.8, and 8.3 cases/10,000 patient-years,

respectively. In contrast, the incidence of KS decreased markedly during the same three time periods. The explanation for the apparent increase in HHV-8-associated MCD with the introduction of ART is uncertain. One possibility is that subtle forms of immune dysregulation are of greater importance in the etiology of HHV-8-associated MCD than immunosuppression per se. On multivariate analysis, risk factors for the development of HHV-8-associated MCD among HIV-infected individuals included the following [47]:

- Nadir CD4 count >200/microL
- Increased age (>33 years)
- No previous ART exposure
- Non-Caucasian ethnicity

CLINICAL FEATURES

Signs and symptoms — Patients with HHV-8-associated MCD present with lymphadenopathy in multiple lymph node regions [38,39,41]. Nearly all present with fever and nonspecific symptoms suggestive of an inflammatory illness, including night sweats, weight loss, weakness, and fatigue [48,49]. Other symptoms include hepatosplenomegaly, cytopenias, organ dysfunction, and skin findings such as rash, hemangiomata, and pemphigus [50,51]. The pace of disease development in HHV-8-associated MCD is variable, with some patients reporting a slow onset over a few years and others becoming acutely ill [41,52].

HIV-infected individuals with HHV-8-associated MCD tend to pursue an acute course, with a median duration of symptoms at the time of diagnosis of HHV-8-associated MCD of three months (range: 0.5 to 24 months) [17]. Only approximately 10 percent of HIV-negative cases with HHV-8-associated MCD have mediastinal or abdominal lymphadenopathy at presentation, but with disease progression or in HIV-infected patients at diagnosis, approximately 50 percent have lymph node involvement of these sites [41].

A systematic review that included 72 patients with HIV-positive, HHV-8-associated MCD reported the following symptoms at the time of presentation [53]:

- Fever – 100 percent
- Lymphadenopathy – 96 percent

- Splenomegaly – 86 percent
- Hepatomegaly – 63 percent
- Pulmonary signs or symptoms – 35 percent
- Edema – 29 percent
- Ascites – 6 percent

Kaposi sarcoma (KS) was also present in 52 patients (72 percent). Pulmonary symptoms in HIV-infected patients with HHV-8-associated MCD often include cough or dyspnea, sometimes associated with noninfectious pulmonary interstitial lymphocytic and plasma cell infiltrates in the absence of infection, with an overall picture that closely resembles lymphocytic interstitial pneumonia [17,43,54,55]. (See "Lymphoid interstitial pneumonia in adults".)

With increased screening measures for HIV, many patients are treated with antiretroviral therapy (ART) before the development of complications such as HHV-8-associated MCD. It is unknown how the clinical manifestations of HHV-8-associated MCD that develops in patients undergoing treatment with ART differ, if at all, from those of patients who are ART-naïve.

Laboratory abnormalities — Typical laboratory abnormalities include nearly universal anemia, thrombocytosis or thrombocytopenia, hypoalbuminemia, polyclonal hypergammaglobulinemia, and elevated C-reactive protein and erythrocyte sedimentation rate [56]. Several of these features are related to high interleukin (IL)-6 levels.

Anemia is usually mild to moderate, as hemoglobin levels <8 g/dL are uncommon. Platelet counts can be normal, low, or elevated.

Other findings include elevated serum levels of IL-6, vascular endothelial growth factor (VEGF), and lactate dehydrogenase (LDH). In one report, these laboratory abnormalities were associated with increased levels of a variety of cytokines, most notably IL-6 and IL-10, but also IL-5, IL-8, IL-12, and interferon gamma; however, these investigations are not routinely performed in patients with MCD [56].

Immunohistochemistry for HHV-8 LANA-1 in lymph node is the gold standard for HHV-8 detection in HHV-8-associated MCD. Measurement of HHV-8 viral load by polymerase chain reaction (PCR) of blood during active disease may also be helpful in determining HHV-8 status. Serologic titers for HHV-8 are of limited clinical utility and should not be performed. HIV testing is positive in a large

proportion of HHV-8-associated MCD 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 [57]. 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) [55,57]. 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)** – HHV-8-associated MCD is 18F-fluorodeoxyglucose (FDG) PET avid [58,59]. In one study of seven patients with HHV-8-associated MCD, lymph nodes demonstrated enhanced FDG uptake on PET scan with a median standardized uptake value (SUV) of 4.8 (range 2.6 to 9.3) [58].

PATHOLOGY

HHV-8-associated MCD 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 [52,60]. The plasma cells in the interfollicular areas are generally also polyclonal. Localized clonal expansions are sometimes seen [61-63], but do not appear to affect prognosis [61,64,65].

HHV-8-associated MCD cases all demonstrate plasmablastic histopathology, which is characterized by the following:

- HHV-8 positivity – HHV-8 can be demonstrated by immunohistochemistry using monoclonal antibodies specific for viral proteins, specifically latency-associated nuclear antigen-1 (LANA-1). These HHV-8-positive cells are predominantly plasmablasts in the mantle zone.

- Interfollicular plasmacytosis – The interfollicular region is hypervascular and contains sheets of plasma cells, similar to the plasma cell histopathologic subtype of HHV-8-negative MCD.

- Follicle size variability – There are increased numbers of follicles that vary in size from hyperplastic to regressed (picture 1).

- 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.

- Increased immunoblasts or plasmablasts – In contrast to the plasma cell histopathologic subtype of unicentric Castleman disease and HHV-8-negative/idiopathic MCD, plasmablastic histopathology in HHV-8-associated MCD demonstrates increased numbers of immunoblasts or plasmablasts in the outer mantle zones of the hyperplastic follicles and sometimes in the germinal centers as well [14,15].

  These cells may coalesce to form so-called "microlymphomas," a controversial term that has been used by some to describe the accumulation of plasmablasts that are monotypic with respect to immunoglobulin light chain expression, yet polyclonal when evaluated for immunoglobulin gene rearrangements [66], a highly unusual combination of findings. In most cases with these morphologic features, frank HHV-8-positive plasmablastic B cell lymphoma eventually develops [15].

- Coexistent Kaposi sarcoma (KS) – 40 percent of HIV-positive, HHV-8-associated MCD cases contain coexistent KS [43], often in the HHV-8-associated MCD lymph nodes [44,67-69].

- Nodal architecture – Nodal architecture is preserved.

DIAGNOSTIC EVALUATION

Evaluation — The diagnosis of HHV-8-associated MCD should be suspected in patients presenting with peripheral lymphadenopathy, constitutional symptoms, and an elevated C-reactive protein. Whole body computed tomography with fluorodeoxyglucose (FDG) positron emission tomography (FDG PET/CT) should demonstrate multiple regions of enlarged lymph nodes, usually

with a relatively low standardized uptake value (SUV, 2.5 to 8).

The diagnosis of HHV-8-associated MCD 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 LANA-1 should be performed to determine whether the patient has HHV-8-associated MCD or HHV-8-negative/idiopathic MCD. Repeat biopsies may be necessary to confirm the diagnosis if an initial biopsy fails to confirm the diagnosis and the clinical suspicion remains high. HIV testing should also be performed.

Most alternative diagnoses can be excluded based on the histologic evaluation, which should include 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'.)

Diagnosis — Formal criteria for diagnosing HHV-8-associated MCD have not been established. However, in patients presenting with typical clinical features (peripheral lymphadenopathy, constitutional symptoms, and an elevated C-reactive protein), the diagnosis generally requires:

- Plasmablastic histopathologic findings on lymph node biopsy (see 'Pathology' above)
- Detection of HHV-8 either by LANA-1 in the lymph node or by polymerase chain reaction (PCR) of the peripheral blood during active disease
- Enlargement of multiple lymph node regions
- Positive HIV testing is supportive of the diagnosis, but not required

PRETREATMENT EVALUATION

Once the diagnosis of HHV-8-associated MCD 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:

Laboratory studies include:

- Complete blood count (CBC) with differential; liver and renal function chemistries, electrolytes, lactate dehydrogenase (LDH), and albumin.
- Viral testing for hepatitis B, Epstein-Barr virus (IgG, IgM), HHV-8 (PCR of serum during acute symptoms), and HIV, with quantitative assays if positive.
- Serum protein electrophoresis with immunofixation and quantitative immunoglobulins.
- Testing for acute phase reactants, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and fibrinogen; and measurement of serum interleukin (IL)-6 and vascular endothelial growth factor (VEGF) along with a panel of other proinflammatory cytokines.
- Serologic investigations for autoimmune disorders are performed if suspected clinically (autoantibodies can be seen in both HHV-8-negative/idiopathic MCD and HHV-8-associated MCD).

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. (See 'Imaging' above.)

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. The treatment of iMCD is discussed separately. (See "HHV-8-negative/idiopathic multicentric Castleman disease".)

Our preferred treatment of HHV-8-associated MCD depends on the presence of concurrent Kaposi sarcoma (KS) and whether the patient has life-threatening organ failure or poor performance status thought to be related to HHV-8-associated MCD (algorithm 1). This is described in more detail in the following sections.

Data regarding the treatment of HHV-8-positive MCD come from systematic reviews of the literature, case series, and case reports. Clinical practice varies between centers and the approach described below reflects our practice. 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.

Without concurrent Kaposi sarcoma — The treatment of patients with HHV-8-associated MCD without concurrent KS depends on the clinical aggressiveness of the disease. More aggressive therapy is used for patients with HHV-8-associated MCD who develop life-threatening complications such as respiratory failure, renal failure, liver failure, and/or pancytopenia.

Without life-threatening organ failure — For patients with HHV-8-associated MCD without concurrent KS and without evidence of life-threatening organ failure or poor performance status thought to be due to the HHV-8-associated MCD, we suggest (algorithm 1):

- Initial treatment with weekly rituximab for four weeks. Multiple additional four-week cycles may be necessary to achieve a response. (See 'Rituximab-based therapy' below.)
- Antiretroviral therapy is started or continued for all patients with HIV infection. For patients with poorly controlled HIV infection (eg, low CD4 count and/or higher HIV load), we also include antiviral therapy aimed at the HHV-8 (eg, ganciclovir) with the above combination regimen and as maintenance therapy. (See 'Antiviral agents' below.)
- Once clinical and laboratory values normalize, rituximab is discontinued and the disease is followed clinically. Repeat treatment with rituximab is used upon relapse. (See 'Response evaluation' below.)
- If there is evidence of progressive organ dysfunction at any time, pegylated liposomal doxorubicin or etoposide is administered with rituximab until a response is achieved. Once clinical and laboratory values normalize, treatment is discontinued and the disease is followed

clinically. This same regimen is used for retreatment at the time of relapse.

With life-threatening organ failure — Patients with HHV-8-associated MCD may develop life-threatening complications such as respiratory failure, renal failure, liver failure, and/or pancytopenia. For patients with HHV-8-associated MCD without concurrent KS that have life-threatening organ failure or poor performance status thought to be due to HHV-8-associated MCD, we suggest (algorithm 1):

- Weekly rituximab for four weeks plus pegylated liposomal doxorubicin or etoposide. (See 'Rituximab-based therapy' below.)
- Antiretroviral therapy is started or continued for all patients with HIV infection. For patients with poorly controlled HIV infection (eg, low CD4 count and/or higher HIV load), antiviral therapy aimed at the HHV-8 (eg, ganciclovir) is included with the above combination regimen and as maintenance therapy. (See 'Antiviral agents' below.)
- Response is assessed daily using clinical features and laboratory studies (CBC, LDH, biochemical profile, CRP).
- Once clinical and laboratory values normalize, treatment is discontinued and the disease is followed clinically. Repeat treatment with rituximab plus pegylated liposomal doxorubicin or etoposide is used upon relapse. (See 'Response evaluation' below.)

With concurrent Kaposi sarcoma — For HHV-8-associated MCD with concurrent KS, we suggest:

- Weekly rituximab for four weeks plus pegylated liposomal doxorubicin. (See 'Rituximab-based therapy' below.)
- We generally administer four weeks of therapy prior to reassessing disease status. If responding, but with evidence of persistent disease activity, then a second round of therapy can be administered two to three months later. (See 'Response evaluation' below.)
- Antiretroviral therapy is started or continued for all patients with HIV infection. Antiviral therapy aimed at the HHV-8 (eg, ganciclovir) is included with the above combination regimen and as maintenance therapy. (See 'Antiviral agents' below.)

- Once clinical and laboratory values normalize, treatment is discontinued and the disease is followed clinically. Repeat treatment with rituximab plus pegylated liposomal doxorubicin is used upon relapse.

Importantly, in HIV-infected patients with HHV-8-associated MCD with concurrent KS, treatment with rituximab has been associated with exacerbation of the KS lesions in some patients [56,70,71], and remission of KS lesions in others [72]. We offer antiretroviral therapy aimed at the HHV-8 (eg, ganciclovir) to this patient population. (See 'Antiviral agents' below.)

The use of pegylated liposomal doxorubicin in KS is discussed separately. (See "AIDS-related Kaposi sarcoma: Staging and treatment", section on 'Liposomal anthracyclines'.)

Rituximab-based therapy — Rituximab-based therapy is the mainstay of treatment for patients with HHV-8-associated MCD. Rituximab, alone or in combination with chemotherapy, has significant activity in HHV-8-associated MCD [17,50,56,70,72-80], even when used in the setting of multiply relapsed disease [81].

Rituximab can be associated with exacerbations of cutaneous KS, infusion reactions, and infections related to immunosuppression. Rituximab carries a risk of hepatitis B virus reactivation among patients positive for HBsAg or anti-HBc. Rarely, JC virus infection can result in potentially fatal progressive multifocal leukoencephalopathy. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Some HIV-infected patients with HHV-8-associated MCD and concurrent KS have had exacerbation of their KS lesions after rituximab therapy [56,70,71], but others have undergone remission [72]. Accordingly, we offer antiviral therapy aimed at the HHV-8 to patients with poorly controlled HIV (eg, poorly controlled viral load, and/or CD4 counts <200 cells/mm^3) or active KS receiving rituximab. (See 'Antiviral agents' below.)

The use of rituximab in HIV-infected patients with HHV-8-associated MCD has only been evaluated in observational studies performed because frequent recurrences were observed following the cessation of single agent chemotherapy. Most patients had symptom resolution following treatment with rituximab (with or without systemic chemotherapy) and the majority had remissions lasting beyond five years [17,56,74,80].

Data regarding longer term outcomes come from retrospective analyses of treatment outcomes in HIV-infected patients with HHV-8-associated MCD:

- In a study in 52 HIV-infected patients with HHV-8-associated MCD, those who had received rituximab-based regimens had significantly higher complete remission rates (10 of 11, 91 percent) than those receiving chemotherapy with or without antiviral therapy (9 of 22, 41 percent) and also had significantly longer overall survival (not reached versus 5.1 years, respectively) [73].

- In a single-center prospective cohort of 113 HIV-infected patients with HHV-8-associated MCD followed for a median of 4.2 years, the incidence of non-Hodgkin lymphoma was 4.2 and 69.6 per 1000 person-years for those who did or did not receive rituximab-based treatment, respectively (hazard ratio 0.09; 95% CI 0.01-0.70) [71]. Flares of KS occurred in one-third of those treated with rituximab who had previously stable KS lesions. Two- and five-year overall survivals were 93 and 90 percent, respectively, for those receiving rituximab, and 68 and 47 percent, respectively, for those who did not receive rituximab.

- In a retrospective analysis of 84 HIV-infected, HHV-8-associated MCD patients treated with rituximab-based therapy and followed for a median of 6.9 years, the five-year overall and relapse-free survival rates were 92 and 82 percent, respectively [82]. The median time to first relapse was 30 months. Most patients were successfully retreated with rituximab-based therapy at the time of relapse.

Antiviral agents

Anti-HHV-8 — Clinical manifestations in HHV-8-associated MCD correlate with the serum viral load of HHV-8, which suggests that they may be directly related to replicating virus [9]. HHV-8 replication is sensitive in vitro to ganciclovir, foscarnet, and cidofovir at achievable plasma concentrations [83]. For most patients with HHV-8-associated MCD, ganciclovir can be added safely, but evidence suggests that it is not needed in most cases. We offer antiviral therapy directed at the HHV-8 to patients with poorly controlled HIV infection (eg, CD4 <200 cells/mm^3, higher HIV load; along with antiretroviral therapy) or active KS being treated with rituximab.

Although antiviral therapies have not proven effective against KS, which is characterized by latent HHV-8 infection, lytic HHV-8 infection is prevalent in HHV-8 associated MCD, providing a rationale

for such therapies [12,13]. Efficacy data are limited. In a pilot study, 14 HIV-infected patients with HHV-8-associated MCD were treated with high dose zidovudine (600 mg orally every six hours) and valganciclovir (900 mg orally every 12 hours) [84]. Major clinical and biochemical responses occurred in 12 and 7 patients, respectively. After a median follow-up of 43 months, overall survival at 12 months and beyond was 86 percent. Little clinical activity has been observed with foscarnet or cidofovir, however.

Data are also limited on the use of other antiviral drugs [12,13]:

- Ganciclovir resulted in both clinical and virologic responses in three HIV-infected patients with HHV-8-associated MCD [85].
- Interferon alfa induced a complete response in two of three patients with HHV-8-associated MCD that lasted for three to six months [43].
- Cidofovir produced little clinical benefit in seven treated HHV-8-associated MCD cases [72,86,87].

Antiretroviral therapy — Antiretroviral therapy (ART) is started or continued for all patients with HIV infection and HHV-8-associated MCD. For patients with HIV, the reduction in HIV viral load and improvement in immune function associated with ART is expected to result in better tolerance of chemotherapy, fewer opportunistic infections, and improvement in overall treatment outcome. With few exceptions, studies in HIV-associated lymphoma have shown that concomitant ART and antineoplastic chemotherapy have no clinically adverse effects on the metabolism of drugs in either the antiretroviral or conventional-dose antineoplastic regimens. There are few data to support one antiretroviral regimen over another. However, use of zidovudine is strongly discouraged due to the risk of overlapping myelotoxicity. (See "AIDS-related lymphomas: Treatment of systemic lymphoma", section on 'Incorporating ART'.)

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 life-threatening 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]) to adjust treatment as needed.

In contrast, for patients without organ dysfunction or poor performance status, we generally administer four doses of therapy prior to reassessing disease status and response to treatment.

The response to treatment should be documented by history and physical examination (clinical assessment), laboratory studies (CBC, LDH, biochemical profile, albumin, vascular endothelial growth factor [VEGF], IL-6, CRP, serum free light chain assay, and quantitative immunoglobulins), and imaging.

The post-treatment imaging study of choice is whole body 18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), which provides information on the size and activity of residual masses. Response to treatment is determined using information gathered from the clinical assessment, laboratory studies, and imaging.

No uniform response criteria have been established. In the absence of such criteria, we consider the following 11 abnormalities that might be found on laboratory and clinical parameters:

- Elevated CRP
- Anemia
- Thrombocytopenia
- Hypoalbuminemia
- Renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) or proteinuria
- Polyclonal hypergammaglobulinemia
- Constitutional symptoms (fever, night sweats, weight loss, fatigue)
- Splenomegaly or hepatomegaly
- Edema, anasarca, ascites, or pleural effusion
- Eruptive cherry hemangiomatosis or violaceous papules
- Lymphocytic interstitial pneumonitis

These are used to classify patients into the following response categories:

- Complete response (CR) – None of the 11 abnormalities described above remain (all normalize) and all lymph nodes are <1 cm in the short-axis.

- Partial response (PR) – When compared with baseline, the number of and/or degree of abnormal minor criteria has improved by at least 50 percent (but not 100 percent). When compared with baseline, the number of and/or size of enlarged lymph nodes has decreased by at least 50 percent (but not 100 percent).

- Progressive disease (PD) – When compared with baseline, the number of and/or degree of abnormal minor criteria has worsened by at least 50 percent. When compared with baseline, the number of and/or size of enlarged lymph nodes has increased by at least 50 percent.

- Stable disease (SD) is considered when a patient does not meet the criteria for CR, PR, or PD.

Follow-up — Regardless of the subtype or treatment approach, patients who achieve at least a 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, IL-6, CRP, serum free light chain assay, and quantitative immunoglobulins.

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

Complications — Fatal cases of HHV-8-associated MCD are associated with fulminant infection, multi-organ failure due to progressive disease [41,42,44], or related malignancies.

Many deaths are due to the well-described association of HHV-8-associated MCD with other malignancies, particularly Kaposi sarcoma (KS) and hematologic malignancies.

- **Kaposi sarcoma** – In older reports, KS was noted in approximately 13 percent of patients

with HHV-8-associated MCD; KS may be diagnosed beforehand, concomitantly, or afterward [52]. Among HIV-infected HHV-8-associated MCD patients, 70 percent of those with HHV-8-associated MCD have KS at some time during their course [15,43,88,89]. (See "AIDS-related Kaposi sarcoma: Staging and treatment" and "AIDS-related Kaposi sarcoma: Clinical manifestations and diagnosis".)

- **Non-Hodgkin and Hodgkin lymphoma** – Approximately 15 to 20 percent of HHV-8-associated MCD patients present with or develop non-Hodgkin lymphoma (NHL), most commonly some variant of diffuse large B cell lymphoma [39,41,42,44,90]. The incidence of NHL reported in retrospective series does not appear to vary with HIV status, but is limited by small numbers. The reported death rate is 85 percent for patients who develop NHL together with HHV-8-associated MCD, despite use of standard therapies [44,90].

  The pathogenesis of NHL in this setting is not entirely clear, but at least some cases appear to be related to uncontrolled HHV-8 infection. A prospective cohort study of 60 HIV-infected patients with HHV-8-associated MCD found that 14 developed NHL at up to 76 months after HHV-8-associated MCD diagnosis, for an actuarial two-year incidence of 24 percent, 15-fold greater than that expected for HIV-infected patients in general [89]. All of the NHLs were positive for HHV-8, with approximately half being primary effusion lymphomas and half being plasmablastic lymphomas.

  Of interest, in one study, the plasmablastic lymphomas have morphology similar to the HHV-8-positive immunoblasts (or "plasmablasts") found in the mantle zone of HHV-8-associated MCD lymph nodes [89]. Four of these plasmablastic lymphomas presented with a fulminant leukemic phase and were fatal within one week. The median survival from diagnosis of NHL in the HIV-positive HHV-8-associated MCD patients was one month.

  Although less common than NHL, there are multiple reports in the literature of Hodgkin lymphoma arising in association with HHV-8-associated MCD [67,90-97].

PROGNOSIS

The natural history of HHV-8-associated MCD is variable. Several different patterns of disease progression have been described [41,44,98]:

- 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.

The prognosis of untreated HHV-8-associated MCD is poor. The median survival of patients with HHV-8-associated MCD in the pre-HIV era was 26 to 30 months [41,44]. In the two largest series of HHV-8-associated MCD in HIV-infected patients (n = 28), the outcome was even poorer, with an overall mortality of 70 to 85 percent and a median survival of 8 to 14 months [15,43]. A retrospective study analyzed factors that predicted for the onset of active disease in 52 HIV-infected patients with HHV-8-associated MCD [99]. The strongest association on multivariate analysis was with rising plasma levels of HHV-8 DNA (hazard ratio 2.9; 95% CI 1.3-6.7).

It is unclear whether the historically poor outcomes are primarily due to HIV alone, to HHV-8 alone, or to an interaction between the two. The available literature suggests that HHV-8 infection is the more important factor. Of 10 patients identified as HIV negative and HHV-8 positive, seven have died, including several within a few months of diagnosis. Three of 10 developed lymphoma and 4 of 10 had Kaposi sarcoma [15,21,90].

Subsequent data suggest that successful treatment of HHV-8-associated MCD with rituximab-based approaches has dramatically improved survival and reduced the risk of associated lymphomas. In a prospective cohort of 84 patients treated with rituximab-based therapy, 92 percent were alive at five years [82]. Another large series found a two-year overall survival of 78 percent for HIV-positive, HHV-8-associated MCD [98].

Progress in long-term outcomes of HHV-8-associated MCD is anticipated to continue to improve with rituximab use. 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 by staining lymph node tissue for LANA-1. HHV-8-associated MCD is caused by uncontrolled infection with HHV-8. (See 'Pathology' above.)
- HHV-8-associated MCD 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 'Clinical features' 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.
- Though no diagnostic criteria exist for HHV-8-associated MCD, the diagnosis is made when

lymph node biopsy reveals classic histopathologic features for MCD and HHV-8 is detected in the lymph node. (See 'Diagnosis' above and 'Pathology' above.)

- The initial management of HHV-8-associated MCD depends on whether the patient has concomitant Kaposi sarcoma (KS) and if there is life-threatening organ failure (algorithm 1). (See 'Choice of therapy' above.)
  - Antiretroviral therapy is started or continued in all patients with HIV infection. In addition to the therapies below, we offer antiviral therapy directed at the HHV-8 to patients with poorly controlled HIV infection (eg, CD4 <200 cells/mm^3, higher HIV load; along with antiretroviral therapy) or active KS. (See 'Antiviral agents' above.)
  - For patients with HHV-8-associated MCD without evidence of life-threatening organ failure and without KS, we suggest rituximab, administered weekly, rather than combination chemotherapy (**Grade 2C**). (See 'Without life-threatening organ failure' above.)
  - For patients with HHV-8-associated MCD with life-threatening organ failure and without KS, we suggest weekly rituximab plus pegylated liposomal doxorubicin or etoposide rather than single agent rituximab (**Grade 2C**). (See 'With life-threatening organ failure' above.)
  - For patients with HHV-8-associated MCD with KS, we suggest weekly rituximab plus pegylated liposomal doxorubicin (**Grade 2C**). (See 'With concurrent Kaposi sarcoma' above.)
- 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 'Patient follow-up' above.)

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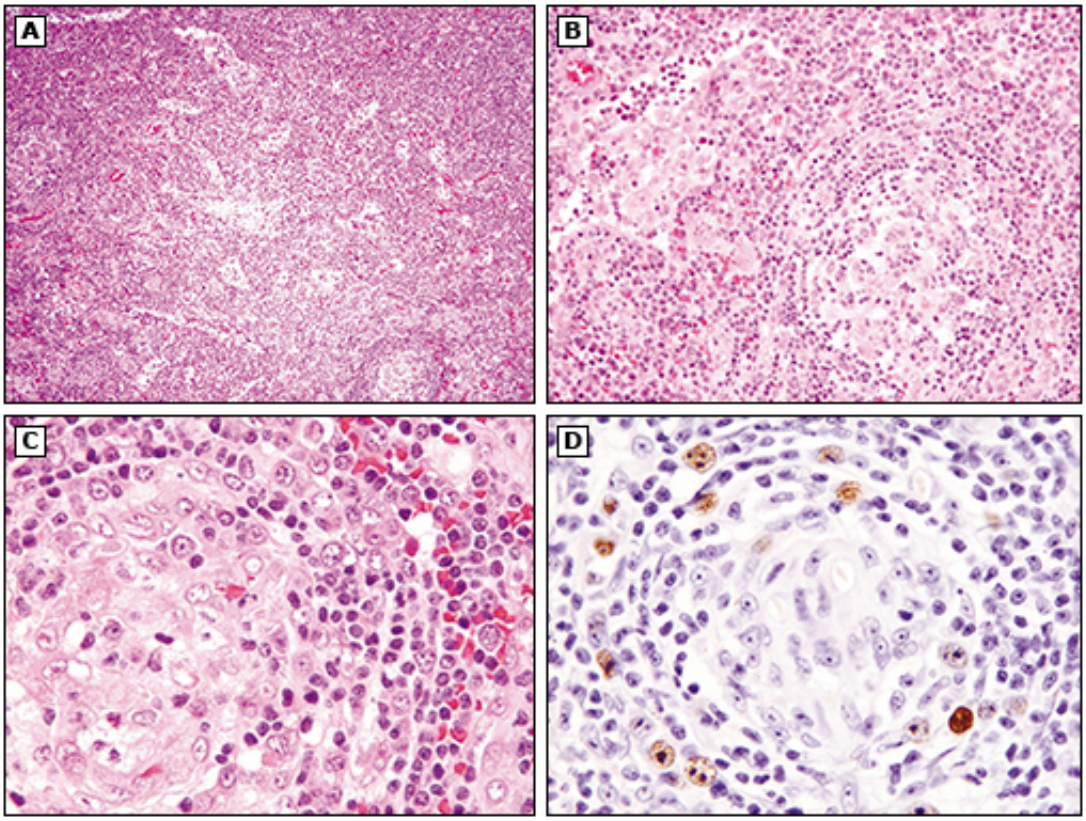
GRAPHICS

Pathologic features of HHV-8-associated multicentric Castleman disease, plasmablastic histopathology

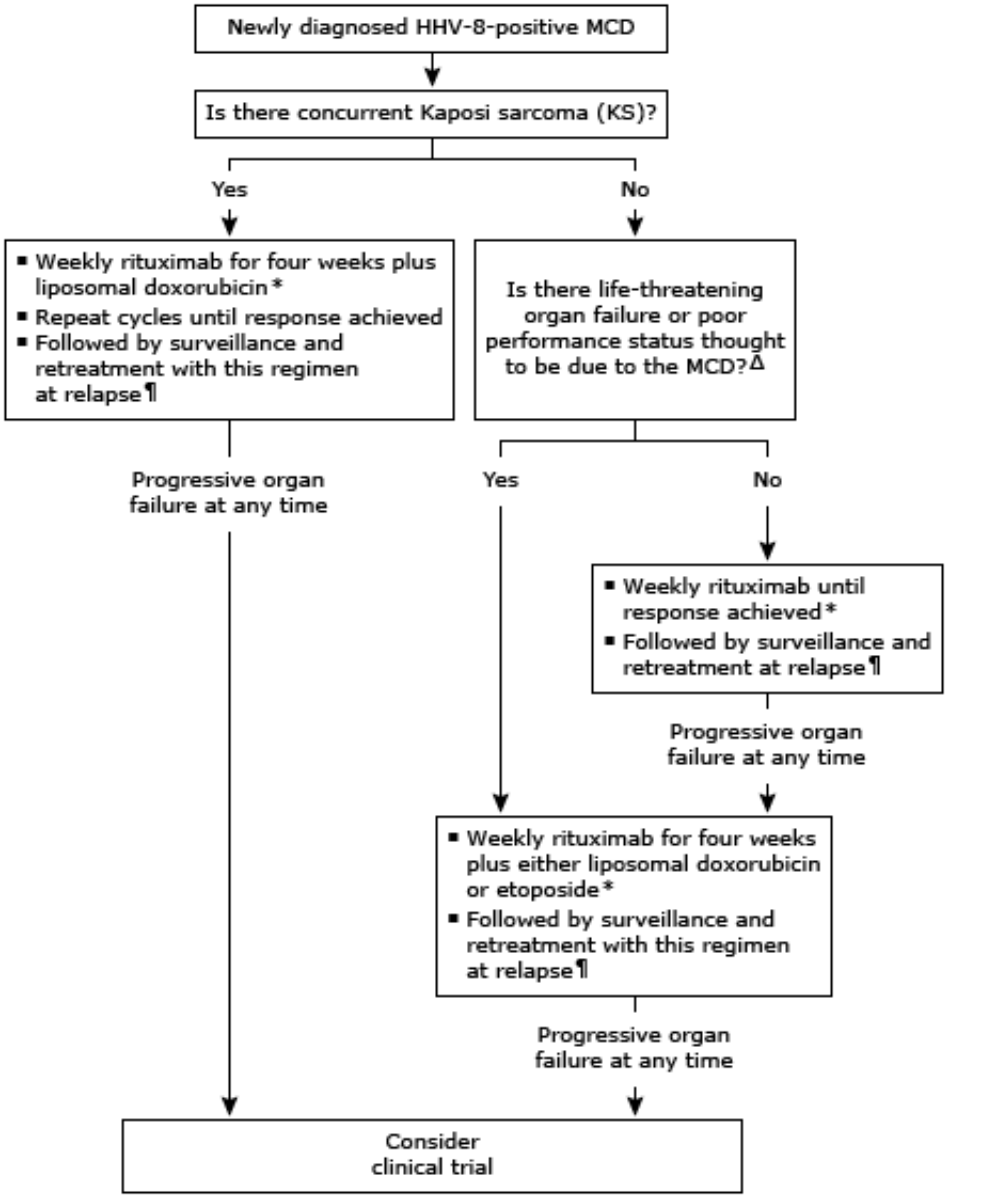


(A) In this field, the interfollicular regions are expanded by numerous plasma cells, and sinuses are patent. Small lymphoid follicles are also present. Hematoxylin and eosin stain.
(B) In this field, the boundary between the follicle mantle zone and the interfollicular region is indistinct. Hematoxylin and eosin stain.
(C) In the follicle mantle zones, large, atypical plasmablasts are present. Hematoxylin and eosin stain.
(D) HHV-8+ cells are preferentially identified in the mantle zones. Some of these cells are large, consistent with plasmablasts. Immunohistochemistry with antibody specific for HHV-8 latent nuclear antigen-1 with hematoxylin counterstain.

HHV-8: human herpesvirus-8.

Graphic 90403 Version 7.0

Initial management of HHV-8-positive multicentric Castleman disease



HHV-8: human herpesvirus 8; MCD: multicentric Castleman disease; HIV: human immunodeficiency virus; IL: interleukin; VEGF: vascular endothelial growth factor; FDG PET/CT: fluorodeoxyglucose positron emission tomography/computed tomography.

* Antiretroviral therapy is started or continued for all patients with HIV infection. In addition, antiviral therapy directed at HHV-8 with ganciclovir is offered to patients with concurrent KS and/or uncontrolled concomitant HIV infection (eg, CD4 count <200 cells/mm^3, high HIV viral load) since such patients are at risk for the development of or exacerbation of KS lesions when treated with rituximab.

¶ Surveillance includes clinical evaluation, serum biomarkers, and imaging. Serum biomarkers include complete blood count, blood chemistries, IL-6, VEGF, C-reactive protein, serum free light chain assay, and quantitative immunoglobulins. Imaging with

whole body FDG PET/CT is preferred.
Δ Examples of life-threatening organ failure that may be related to MCD include respiratory failure, renal failure, liver failure, and pancytopenia.

Graphic 117394 Version 1.0

Contributor Disclosures

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