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Treatment of Kaposi sarcoma herpesvirus-associated multicentric Castleman disease

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Synopsis

Kaposi sarcoma herpes virus (KSHV)-associated multicentric Castleman disease (MCD) is a rare, polyclonal lymphoproliferative disorder characterized by flares of inflammatory symptoms, edema, cytopenias, lymphadenopathy and splenomegaly. Diagnosis is established with a lymph node biopsy. Pathogenesis is related to dysregulated inflammatory cytokines, including human and viral interleukin (IL)-6. Rituximab alone or in combination with chemotherapy, such as liposomal doxorubicin, has led to long-term overall survival of over 90%. Monoclonal antibodies targeting human interleukin-6 activity remain experimental as they do not target viral interleukin-6. KSHV-MCD patients are at high risk for Kaposi sarcoma and non-Hodgkin lymphomas, which may be concurrent.

Keywords

Kaposi sarcoma herpesvirus; human herpesvirus-8; multicentric Castleman disease; human interleukin-6; viral interleukin-6; rituximab; liposomal doxorubicin

Introduction

Castleman disease is a term used to describe a variety of pathologic entities ranging from indolent localized angiofollicular hyperplasia (unicentric Castleman disease), as first described by Benjamin Castleman in the 1950s, to multicentric lymphoproliferations associated with inflammatory symptoms (multicentric Castleman disease, MCD). One epidemiologically distinct plasmablastic form of MCD described in patients with HIV and associated with high mortality¹ was found to be caused by a newly discovered virus, called

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Disclosures

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Kaposi sarcoma-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8). KSHV was first identified as the etiologic agent for Kaposi sarcoma (KS) and is now recognized as the cause of almost all MCD in HIV-positive patients and rare cases of MCD in HIV-negative patients.²

KSHV-MCD is clinically characterized by intermittent inflammatory symptoms, cytopenias, edema lymphadenopathy and splenomegaly which often wax and wane. The diagnosis is confirmed pathologically, generally through a lymph node biopsy. Disease manifestations are associated with elevated levels of cytokines, especially interleukin (IL)-6 and IL-10.³⁻⁵ Untreated, KSHV-MCD is generally lethal within 2 years.⁵ Its rarity, intermittent manifestations, association with HIV, and non-specific symptoms make diagnosing KSHV-MCD a challenge. However, the past decade has seen the development of several effective therapies and substantial improvement in overall survival; therefore increased recognition and timely diagnosis is important.

Epidemiology

KSHV-MCD incidence is unknown and the disease is almost certainly underdiagnosed. Powles *et al.* estimated the incidence of KSHV-MCD in HIV positive individuals to be 4.3 cases per 10,000 person-years and noted increasing incidence despite availability of effective antiretroviral therapy (ART) for HIV.⁶ KSHV-MCD often occurs in the setting of suppressed HIV, relatively preserved CD4⁺ T-cell counts and evidence of KSHV-specific CD8⁺ T-cell response.^{7,8} An improved understanding of the timing of KSHV-MCD diagnosis in relation to initiation of ART is required. It is possible that like KS and lymphoma, incidence is highest in the first year after ART initiation.⁹

KSHV-MCD is especially likely to be underdiagnosed in areas of sub-Saharan Africa with a high seroprevalence of both KSHV and HIV.¹⁰⁻¹² Unlike developed countries where KSHV prevalence in the general population is 2-5%, KSHV is endemic in large parts of sub-Saharan Africa, with 40 to >80% of adults seropositive in much of the region.^{10,11} The lack of reported KSHV-MCD cases almost certainly represents underdiagnosis, as KSHV-MCD has been described among African immigrants.^{13,14} Due to lack of pathology services in many parts of sub-Saharan Africa, KS is sometimes treated empirically, and without evaluation for concurrent KSHV-MCD in suspected cases. Additionally, fevers and lymphadenopathy, when present, are often empirically treated as tuberculosis.^{13,15} Increased diagnostic capacity for KSHV-associated diseases, including KSHV-MCD, is needed in this setting.

Pathogenesis

KSHV is a gammaherpesvirus, most closely related to Epstein Barr virus, with latent and lytic phases characteristic of all herpesviruses. In addition to KSHV-MCD, it is the etiologic agent of KS, primary effusion lymphoma (PEL), and KSHV-associated diffuse large B cell lymphoma. Also, it is the cause of a newly identified condition called KSHV inflammatory cytokine syndrome (KICS), in which patients have severe inflammatory symptoms that mimic KSHV-MCD but lack the requisite pathologic findings of KSHV-MCD.^{16,17}

KSHV encodes several proteins that allow for immune evasion via downregulation of surface proteins required for immune surveillance.^{18,19} The development of KSHV-MCD in HIV positive patients may be related to reduction or functional impairment of invariant natural killer T (iNKT) cells.²⁰ iNKT cells play a major role in innate immunity and control of EBV infected B-cells through activation of glycolipid antigens presented by the major histocompatibility complex class I-related molecule, CD1d, as well as stimulating the expansion and maturation of other immune cells.²¹ *In vitro* studies of human tonsillar B cells suggest KSHV-MCD pathogenesis begins with KSHV infection via oral transmission of tonsillar IgM λ -expressing B cells that proliferate into plasmablasts characteristic of KSHV-MCD.²²

Expression of latent and lytic genes varies among KSHV-associated disorders.²³ In KS and PEL, the majority of genes expressed are latent genes with lytic proteins expressed in only a minority of cells, although in PEL, a KSHV-encoded viral interleukin 6 (vIL-6) is sometimes expressed in the absence of other lytic genes. In KSHV-MCD, however, a substantial proportion of the KSHV-infected plasmablasts in affected lymph nodes express lytic proteins. In some cases the full lytic repertoire is expressed, and in other cases only vIL-6 is expressed.^{23–25} Excess human cytokines, namely IL-6 (hIL-6), IL-10, tumor necrosis factor- α (TNF α), and IL-1 are also important in the pathogenesis of KSHV-MCD.^{5,26,27} vIL-6 shares 25% homology with its human counterpart. Unlike hIL-6, it binds directly to and signals through glycoprotein (gp)130, allowing it to affect a broad range of cells.^{28–30} By contrast, hIL-6 signaling requires binding of both the classical IL-6 receptor, gp80, as well its coreceptor, gp130, which is ubiquitously expressed. Similar to hIL-6, serum vIL-6 levels correlate with the symptoms and laboratory abnormalities associated with active disease.^{26,31} Although vIL-6 is often considered a lytic gene, it may be specifically upregulated in KSHV-MCD by X-box binding protein 1 (XBP-1).³² There is also evidence that vIL-6 itself activates hIL-6, further driving KSHV-MCD pathogenesis.³³ Additional protein products of latently expressed genes also play a role in the pathogenesis of KSHV-MCD, particularly viral FLICE-inhibitory protein (vFLIP) which has been shown to induce significant disturbances in serum cytokines and expansion of suppressed myeloid cells allowing for host immune evasion, angiogenesis and tumor progression in mouse models.³⁴

Diagnosis

KSHV-MCD should be suspected in patients with an appropriate combination of risk factors and constellation of clinical and laboratory findings (Figure 1). Histopathologic confirmation of the diagnosis by lymph node biopsy is required. Populations at highest risk include men who have sex with men and sub-Saharan Africans. Diagnosis requires a high level of suspicion on the part of the clinician as the features of KSHV-MCD overlap significantly with those seen in uncontrolled infections and lymphoid malignancies. Clinical features of KSHV-MCD include fatigue, fevers, night sweats, weight loss, volume overload (including ascites and pulmonary effusions), rashes, and nonspecific neurologic, sinus, respiratory and gastrointestinal symptoms. The course may include relapsing and remitting symptoms. Many patients have concurrent KS and the clinician's suspicion for KSHV-MCD should be raised in patients with KS and the aforementioned symptoms and laboratory findings. Computerized tomography classically shows diffuse lymphadenopathy and

splenomegaly (Figure 2A).³⁵ KSHV-MCD patients with active disease essentially always have an elevated C-reactive protein (CRP) and KSHV viral load.

Plasma or peripheral blood mononuclear cell (PBMC) measurements of KSHV viral load should be performed and monitored throughout the disease course as this correlates with active disease and response to treatment.⁵ Patients may exhibit several other laboratory abnormalities during active disease including cytopenias, hypoalbuminemia, hyponatremia and elevated γ -globulin.^{1,5,7} Biopsy confirmation of KS should be pursued if indicated, as concurrent KS has implications for the choice of KSHV-MCD treatment. All patients with KSHV-MCD should be tested for HIV. While plasma levels of hIL-6 and IL-10 correlate with disease activity and response to treatment, these cytokines are not routinely followed outside of the scope of research activities.^{5,27,36} Patients may become critically ill due to sepsis-like manifestations in the absence of infection driven by cytokine excess or exhibit pathologic and laboratory findings consistent with hemophagocytic syndrome.³⁷

Histologically, KSHV-MCD-involved lymph nodes have expansion of KSHV-infected plasmablasts in the mantle zone of B cell follicles. They also have reactive KSHV-uninfected plasmablasts. KSHV-infected plasmablasts may form microscopic collections, sometimes referred to as microlymphomas, although these are generally polyclonal.³⁸ KSHV infected plasmablasts stain positive for KSHV-associated latent nuclear antigen-1 (LANA-1), and a proportion also express vIL-6. Unlike KSHV-associated germinotropic lymphoproliferative disorder and some cases of PEL, KSHV-MCD plasmablasts are negative for Epstein-Barr virus.^{39,40} KSHV-infected plasmablasts express cytoplasmic IgM that is λ light-chain restricted but with a polyclonal pattern of immunoglobulin gene rearrangement (Figure 3).⁴¹ KS may be noted in the same lymph node (Figure 4). A bone marrow biopsy is sometimes performed to evaluate cytopenias, but is not required for diagnosis. In general, plasmacytosis is the predominant feature in the bone marrow with lymphoid aggregates and scattered KSHV-infected mononuclear cells less frequently seen.⁴²

It is possible to diagnose KSHV-MCD from a lymph node core needle biopsy but an excisional lymph node biopsy is often required. In general, the most easily accessible enlarged lymph node should be chosen for pathologic evaluation. However, if an excisional lymph node biopsy does not show KSHV-MCD and the diagnosis is strongly suspected, 18-fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) scan should be performed. In KSHV-MCD, the most common findings are hypermetabolic symmetric ¹⁸FDG-avid adenopathy with increased uptake notable in the spleen and bone marrow (Figure 2B).³⁵ Suspicious lymph nodes, which are often the largest and/or most FDG avid, should be biopsied. Any effusions require cytopathologic examination. Effusions in KSHV-MCD may have elevated KSHV viral loads and show proliferation of polyclonal λ -restricted B cells; however, this finding has not been established as a method to definitively diagnose KSHV-MCD. More importantly, effusions should be examined to rule out PEL via cytopathology, flow cytometry and B-cell clonality. In addition to PEL, patients with KSHV-MCD are at high risk of developing other non-Hodgkin lymphomas.^{38,43,44}

Treatment

Although ART is generally insufficient for the treatment of KSHV-MCD, it is indicated for all patients with HIV. ART should be used concurrently along with KSHV-MCD-specific treatment in HIV-positive patients.^{6,45} Patients with HIV-associated KSHV-MCD may obtain long remissions on ART with appropriate KSHV-MCD therapy. Although the effect of ART in preventing relapses is not proven, ART decreases mortality related to HIV.^{46,47}

There is currently no Food and Drug Administration (FDA)-approved therapy for KSHV-MCD. Several cytotoxic chemotherapies with clinical activity in B-cell lymphomas have been used to treat KSHV-MCD, including etoposide, vincristine, vinblastine, cyclophosphamide and doxorubicin.¹ However, chemotherapy alone is relatively ineffective. In one analysis between 1985 and 2006, the reported survival with these chemotherapies either alone or in combination was poor, with a median overall survival of 12 months. However, major improvement in treatment responses and survival came with the development of rituximab, a humanized monoclonal antibody against CD20 antigen on B-cells.

Three prospective treatment studies and several cohort studies all show a substantial treatment effect of rituximab in KSHV-MCD. It is interesting that rituximab is effective despite the fact that proliferating KSHV-infected B cells in KSHV-MCD are usually CD20 negative. This may be due to the fact that KSHV uninfected CD20 positive B cells within the microenvironment secrete inflammatory cytokines and also serve as a major potential reservoir of KSHV infection and replication.⁴¹ Two prospective phase 2 studies published in 2007 established the efficacy of rituximab in KSHV-MCD.^{48,49} In the CastlemaB Trial, 24 patients with chemotherapy-dependent HIV-associated KSHV-MCD were administered 4 weekly infusions of rituximab (375 mg/m²) after the discontinuation of chemotherapy. Overall survival was 92% and 71% remained in remission at 1 year. A common problem was exacerbation of KS, noted in 8 out of 12 patients with a previous diagnosis of KS despite the use of ART.⁴⁹ Bower *et al.* reported similar results in 21 previously untreated patients with symptomatic HIV-associated KSHV-MCD treated with 4 weekly doses of rituximab 375 mg/m². At 2 years, overall survival was 95% and disease-free survival was 79%. However, more than one third of the patients had progression of KS.⁴⁸

To address the issue of KS exacerbation with the use of rituximab, a prospective trial evaluated the treatment of HIV-associated KSHV-MCD with a combination of rituximab 375 mg/m² and liposomal doxorubicin 20 mg/m², an FDA-approved KS therapy, every 3 weeks for a median of 4 cycles. Another potential advantage of concurrent use of liposomal doxorubicin is that it can potentially target KSHV-MCD plasmablasts. Twelve of the 17 patients treated had concurrent KS. Exacerbation of KS was seen in only 1 patient, and KS regressed in most patients. The 3-year overall survival with this combination regimen was 81% and the event-free survival was 69%.¹⁴ Rituximab also appears to be an effective therapy for KSHV-MCD in HIV-uninfected patients.⁵⁰ Infusion reactions that include rigors and fevers are common during the first administration of rituximab and may be due to a cytokine release syndrome. Premedication with steroids and benadryl, as well as slow infusion rates during the first cycle are warranted. When infusion reactions do occur, they

are generally short-lived and can be managed with meperidine. Infusions can be resumed at slower rates after resolution of symptoms. Although linked to exacerbation of KS, treatment with rituximab is associated with a substantially lower risk of non-Hodgkin's lymphoma in KSHV-MCD patients.⁴⁴

Anti-herpesvirus therapy has also been evaluated in KSHV-MCD. Remissions have been described with the use of ganciclovir in one small retrospective study.⁵¹ Two KSHV lytic genes, *ORF36* and *ORF21*, encode enzymes that can phosphorylate ganciclovir and AZT, respectively, leading to accumulation of triphosphate moieties which are toxic to KSHV-infected cells. Because of the role of viral enzymes in drug activation, non-KSHV-infected cells are spared.⁵² Based upon the principle of "virus activated cytotoxic therapy," a pilot study showed activity of high-dose zidovudine (AZT) (600 mg orally every 6 hours) and valganciclovir (900 mg orally every 12 hours) in HIV positive KSHV-MCD patients. Twelve of 14 patients achieved major clinical benefit with an 86% overall survival at 4 years. However, the median progression-free survival was only 6 months. While rituximab-based therapy is generally the treatment of choice, high-dose AZT and valganciclovir may be a useful alternative for patients with mild disease or who cannot tolerate rituximab.⁵³

We follow a risk-stratified approach to treatment of KSHV-MCD, which takes into account the presence of concurrent KS or severe symptoms (Figure 1 and Table 1). In patients with mild symptoms and laboratory abnormalities, 4 weekly doses of rituximab are generally sufficient to induce clinical remission in the vast majority of patients. Several case series have reported failure of rituximab in patients with aggressive disease, poor performance status, and organ failure.^{54,55} Therefore, in patients with severe symptoms or a concurrent diagnosis of KS, we usually treat patients with rituximab combined with liposomal doxorubicin every 3 weeks.¹⁴ More frequent initial rituximab dosing, i.e weekly during the first cycle, in combination with liposomal doxorubicin may also be appropriate. Excellent results of weekly rituximab combined with etoposide 100 mg/m² for KSHV-MCD patients with severe symptoms have also been described, although etoposide is a less effective drug for treating KS.⁵⁶ In the rituximab era, combination chemotherapy does not have a role in treating KSHV-MCD except in the setting of concurrent lymphoma.

Treatment of KSHV-MCD should be individualized. The initiation of KSHV-MCD therapy should not be based on abnormal radiographic findings alone, but instead upon symptoms and abnormal laboratory findings. Duration of therapy should also be symptom based. There are no consensus guidelines for treatment response in KSHV-MCD. The Castlemab Trial defined criteria for an MCD attack warranting treatment as the presence of fever, elevated CRP and presence of 3 clinical symptoms. The National Cancer Institute (NCI) Criteria for Treatment includes at least one clinical symptom; the presence of anemia, thrombocytopenia, or hypoalbuminemia; and an elevated CRP.⁵³ We generally treat until resolution of clinical symptoms and significant improvement in these marker laboratory abnormalities. Like KSHV-MCD treatment, there is no standardized approach for patient follow-up. We generally see patients in clinic and measure their KSHV viral load every 3 months for the first year after therapy and less frequently thereafter. Patients with a persistently elevated KSHV viral load, or residual adenopathy or splenomegaly are at higher risk of relapse, and may require more frequent monitoring, although we generally do not

treat patients with these findings in the absence of symptoms and laboratory abnormalities.⁵⁷ Although consolidation or maintenance therapy have been used in the past, there is no clear role for these approaches. A recent study of HIV-positive KSHV-MCD patients treated with rituximab-based therapy found that the 5-year relapse-free survival was 82% without maintenance rituximab or anti-herpes drugs. In addition, all patients with disease relapse were successfully retreated with rituximab-based therapy.⁵⁶ Therefore, there is little potential benefit to maintenance therapy as relapse rates are low and remission can be reinduced in the majority of patients. Importantly, KSHV-MCD patients should be monitored for the development of other KSHV-associated diseases.⁴³

While rituximab has revolutionized KSHV-MCD treatment, there remains a need for rituximab-sparing approaches, especially for patients with concurrent advanced KS, HIV patients with CD4⁺ counts <100 cells/uL, for patients allergic to rituximab, and in patients in resource-limited settings. Monoclonal antibodies targeting hIL-6 activity have been developed for KSHV-negative (idiopathic) MCD and several rheumatologic conditions and are promising for KSHV-MCD given the role hIL-6 plays in the pathogenesis of symptomatic disease. Siltuximab, a monoclonal antibody that binds directly to hIL-6, is FDA-approved for the treatment of idiopathic MCD but has not been evaluated in KSHV-MCD^{58,59}. Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor is FDA-approved for rheumatoid arthritis, and has shown activity in other forms of MCD and also 2 KSHV-associated cases.⁶⁰ Targeting hIL-6 is not expected to directly influence vIL-6 activity, which plays an essential role in pathogenesis of symptomatic KSHV-MCD. Therefore anti-IL6 agents may require combination with other approaches, such as virus-activated cytotoxic therapy.³³ We are currently studying tocilizumab in KSHV-MCD in a clinical trial at the NCI (NCT01441063). Pomalidomide has been shown to be effective against KS, and in the laboratory it can prevent the KSHV-induced downregulation of MHC-1.^{61,62} Based on these findings, our group is exploring the combination of pomalidomide and liposomal doxorubicin in patients with concurrent KS and KSHV-MCD (NCT02659930). We hypothesize that combination chemoimmunotherapy will debulk high KS tumor burden while decreasing KSHV driven immune evasion and counteracting paracrine growth signals within the microenvironment.⁶²

Conclusion

KSHV-MCD is a rare and potentially deadly B cell lymphoproliferative disorder with waxing and waning symptoms that make diagnosis a challenge. Physicians should have a high index of suspicion for KSHV-MCD, especially in high risk patients. Symptoms and laboratory abnormalities are associated with KSHV lytic activation and elevated inflammatory cytokines. Rituximab-based therapies have led to a drastic improvement with most recent studies reporting greater than 90% overall 5-year survival.⁵⁶ As KSHV-MCD patients continue to live longer with established and experimental treatment approaches, clinicians must remain vigilant for KSHV-MCD relapse and development of other KSHV-associated diseases.

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Key Points

- KSHV-MCD is a B-cell lymphoproliferative disorder caused by KSHV that is characterized by waxing and waning inflammatory symptoms, laboratory abnormalities, edema, adenopathy, and splenomegaly. It is most common in patients with HIV.
- Four weekly doses of rituximab 375 mg/m² leads to remission in the majority of mildly symptomatic patients but may lead to exacerbation of concurrent KS.
- Rituximab 375 mg/m² plus liposomal doxorubicin 20 mg/m² administered every 3 weeks effectively treats patients with aggressive disease or concurrent KS.
- Rituximab-based treatment has increased 5-year overall survival to over 90%.
- Current studies are evaluating targeted rituximab-sparing approaches that may decrease toxicity and/or be appropriate for patients with concurrent Kaposi sarcoma.

Figure 1.
Schema for the Diagnosis and Management of KSHV-associated Multicentric Castleman Disease.

Figure 2.

Computerized Tomography (CT) and ^{18}F Fluorodeoxyglucose positron emission tomography (^{18}F FDG PET) in KSHV-associated Multicentric Castleman Disease (KSHV-MCD). (A) Computerized tomography scans of an HIV-positive patient with KSHV-MCD prior to treatment showing hepatosplenomegaly and axillary and retroperitoneal adenopathy. (B) ^{18}F FDG PET of an HIV-positive patient with KSHV-MCD showing characteristic ^{18}F FDG-avid cervical and axillary adenopathy, as well as splenomegaly with diffuse increased ^{18}F FDG uptake.

Figure 3.

Lymph Node Findings in KSHV-associated Multicentric Castleman Disease. (A) Hematoxylin and eosin (H&E) stain showing typical features of KSHV-associated multicentric Castleman disease. The involved lymph nodes have a regressed germinal center surrounded by layered mantle cells, vascular proliferation and hyalinization, and plasmacytosis in the interfollicular regions. (B) LANA-1 immunohistochemistry highlighting KSHV-infected plasmablasts residing in the mantle cell layers. (C) vIL-6 immunohistochemistry showing vIL-6 in a proportion of KSHV-infected plasmablasts. (D-E) Kappa and lambda light chain immunohistochemistry showing restricted lambda expression in the KSHV-infected plasmablasts (black arrow), while the interfollicular plasma cells are polytypic (white arrow).

Figure 4. Concomitant Lymph Node Kaposi Sarcoma and KSHV-associated Multicentric Castleman Disease. (A) H&E stain demonstrating concomitant Kaposi sarcoma (left of the dotted line) and multicentric Castleman disease (MCD) (right of the dotted line). (B) LANA-1 immunohistochemistry highlighting the KSHV-infected cells. Note the different cytomorphology of Kaposi sarcoma cells (red arrow) and the plasmablasts in MCD (black arrow).

Table 1

Treatments for KSHV-MCD

Therapy	Dose	Mechanism of action	When to use
Rituximab	375 mg/m ² weekly x4 weeks	Depletes IL-6 secreting CD20+ B cells	Mild symptomatic disease
Rituximab + liposomal doxorubicin	Rituximab 375 mg/m ² + liposomal doxorubicin 20 mg/m ² every 3 weeks until response plateau	Addition of cytotoxic chemotherapy to treat CD20 negative MCD plasmablasts and KS spindle cells	Aggressive disease and/or concurrent KS
Rituximab + etoposide	Rituximab 375 mg/m ² + etoposide 100 mg/m ² IV weekly x4 weeks	Addition of cytotoxic chemotherapy to treat CD20 negative MCD plasmablasts	Aggressive disease
Zidovudine (AZT) + valganciclovir	Zidovudine 600 mg PO every 6 hours + valganciclovir 900 mg PO every 12 hours days 1–7 of 21-day cycle	Virus activated cytotoxic therapy	Mild disease with concurrent KS and/or patients allergic to rituximab