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Recent advances in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease

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Abstract

Purpose of review—The discovery of Kaposi sarcoma herpesvirus (KSHV) led to recognition of KSHV-associated multicentric Castleman disease (MCD) as a distinct lymphoproliferative disorder. The pathogenesis of KSHV-MCD is attributed to proliferation of KSHV-infected B cells, production of KSHV-encoded viral interleukin 6 by these cells, and dysregulation of human interleukin 6 and interleukin 10. This article reviews advances in the field of disease pathogenesis and targeted therapies.

Recent findings—Our understanding of the pathogenesis of KSHV-MCD has increased in recent years and improved therapies have been developed. Recent studies demonstrate that the anti-CD20 monoclonal antibody, rituximab, as well as virus-activated cytotoxic therapy using high-dose zidovudine and valganciclovir, can control symptoms and decrease adenopathy. With treatment, 1-year survival now exceeds 85%. Interestingly, even in the absence of pathologic findings of MCD, KSHV-infected patients may have inflammatory symptoms, excess cytokine production, and elevated KSHV viral load similar to KSHV-associated MCD. The term KSHV-associated inflammatory cytokine syndrome has been proposed to describe such patients.

Summary—Recent advances in targeted therapy have improved outcomes in KSHV-MCD, and decreased need for cytotoxic chemotherapy. Improved understanding of the pathogenesis of KSHV-MCD and KSHV-associated inflammatory cytokine syndrome is needed, and will likely lead to additional advances in therapy for these disorders.

Keywords

human herpesvirus-8; Kaposi sarcoma herpesvirus; KSHV-associated inflammatory cytokine syndrome; multi-centric Castleman disease; viral interleukin-6

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Conflicts of interest

The spouse of one of the authors (RY) is a co-inventor on a patent describing the measurement of KSHV vIL-6. This invention was made when the inventor was an employee of the US Government under 45 Code of Federal Regulations Part 7. All rights, title, and interest to this patent have been assigned to the US Department of Health and Human Services. The government conveys a portion of the royalties it received to its employee inventors under the Federal Technology Transfer Act of 1986 (P.L. 99–502). The authors have a Cooperative Research and Development Agreement with Celegene Corporation to develop pomalidomide for KS.

INTRODUCTION

Kaposi sarcoma herpesvirus (KSHV) associated multicentric Castleman disease (KSHV-MCD) is a lymphoproliferative disorder characterized by inflammatory symptoms, cytopenias, lymphadenopathy, splenomegaly and a waxing and waning course that is eventually lethal if untreated [1,2]. It is caused by KSHV, also called human herpesvirus 8 (HHV-8) [1], which is also the etiologic agent of Kaposi sarcoma [3], primary effusion lymphoma (PEL) [4,5] and a recently described interleukin 6 (IL-6) related disease called KSHV-inflammatory cytokine syndrome (KICS) [6,7■].

KSHV-MCD is one form of a cluster of diseases called Castleman disease. Benjamin Castleman first described angiofollicular lymph node hyperplasia in localized mediastinal masses in a disease now considered a hyaline vascular variant of Castleman disease (HV-CD) [8,9]. Variants with expansion of plasmacytic [10] or plasmablastic cells [11] were subsequently described and also called Castleman disease. Most plasmacytic or plasmablastic Castle-man disease cases are multicentric and remarkable for IL-6-associated inflammatory symptoms [2,12,13]. However, some cases of plasmacytic or plasmablastic Castleman disease are unicentric, and HV-CD may occasionally be multicentric [14,15]. After discovery of KSHV [3], it was appreciated that most plasmablastic MCD arising in HIV-infected individuals was KSHV-associated [1], and that this was a distinct form of MCD.

KSHV-negative Castleman disease may be associated with or difficult to distinguish from other malignancies including dendritic cell tumors [16–18] and lymphoma [19,20]. KSHV-negative MCD also has clinical overlap with other plasma cell disorders, including polyneuropathy, organomegaly, endocrinopathy, edema, M-protein and skin syndrome [21–24] and IgG4-related sclerosing disease [25]. The clinicopathologic spectrum of Castleman disease may be due to variable driving factors that lead to dysregulation of IL-6 and/or vascular endothelial growth factor (VEGF) [26,27], accounting for overlapping clinical and histopatho-logic findings. The remainder of this review focuses on KSHV-MCD.

CLINICAL FEATURES OF KAPOSI SARCOMA HERPESVIRUS-ASSOCIATED MULTICENTRIC CASTLEMAN DISEASE

KSHV-MCD most often presents in HIV-infected individuals; symptoms include progressive fatigue, fever, night sweats, weight loss and adenopathy. Many patients have concurrent Kaposi sarcoma. Nonspecific respiratory and gastrointestinal symptoms, rashes and neuropathy are also common; edema and effusions are observed less frequently. Patients can become critically ill, either due to sepsis-like manifestations or hemophagocytic syndrome [28,29]. Patients with symptomatic disease generally have elevated C-reactive protein (CRP) and KSHV viral load [30], usually with other laboratory abnormalities such as anemia, thrombocytopenia, hypoalbuminemia, hyponatremia and elevated g-globulin [2,31,32■■,33■, 34]. Computerized tomography typically shows diffuse adenopathy and splenomegaly (Fig. 1). Diagnosis requires pathologic confirmation, usually from a lymph node biopsy (Fig. 2). Patients with KSHV-MCD are at high risk of developing KSHV-associated lymphomas, including PEL and large cell-lymphoma arising in KSHV-MCD, the latter which may

represent clonal expansion of the KSHV-infected plasmablasts. Diffuse large B-cell lymphoma is also seen in this patient population [11,35,36▪,37]. In patients with effusions, PEL should be excluded through evaluation of cytopathology, Epstein–Barr virus and KSHV, flow cytometry and B-cell clonality [38,39].

EPIDEMIOLOGY OF KAPOSI SARCOMA HERPESVIRUS-MULTICENTRIC CASTLEMAN DISEASE

Although KSHV-MCD is considered to be extremely rare, its incidence and prevalence are uncertain. It is not tracked in cancer registries. Given its nonspecific symptoms and a waxing and waning course, KSHV-MCD is almost certainly underrecognized. Unlike Kaposi sarcoma, whose incidence decreased with broad availability of highly active antiretroviral therapy (HAART) [40▪], the incidence of KSHV-MCD appears to be increasing in the HAART era [41]. Biologically, this is plausible. Unlike Kaposi sarcoma that is associated with degree of immunosuppression [42] and lack of KSHV specific T-cell response[43], KSHV-MCD frequently occurs despite suppressed HIV, relatively preserved CD4 counts [32▪▪,33▪,36▪], evidence of KSHV-specific T-cell response [44] and elevated levels of antibodies directed against KSHV capsid protein K8.1 [45].

There are almost no reports of KSHV-MCD in sub-Saharan Africa, despite high prevalence of both HIV and KSHV [46,47,48▪▪]. This likely reflects underdiagnosis and underreporting of KSHV-MCD; indeed, of 32 cases of KSHV-MCD followed at the NIH Clinical Center in Bethesda, Maryland, USA, five were in recent African immigrants (Uldrick, Polizzotto, and Yarchoan, unpublished observation). Additional studies are needed to define the incidence and prevalence of KSHV-MCD in different populations.

PATHOGENESIS OF KAPOSI SARCOMA HERPESVIRUS-MULTICENTRIC CASTLEMAN DISEASE

Like other herpesviruses, KSHV has two principal phases of gene expression: a latent phase, and a lytic phase in which production of new virions occurs. Latency-associated nuclear antigen (LANA) and other latent genes, as well as 12 KSHV encoded microRNA (miRNA) are expressed in both phases, whereas lytic genes are generally expressed only during the lytic phase. Certain genes, such as KSHV-encoded viral IL-6 (vIL-6), are predominantly released during lytic replication but can also be produced in small amounts during latent infection [49]. In all MCD, the main pathological process is B-cell hyperproliferation, caused in part by auto-crine and paracrine signaling and symptoms and laboratory abnormalities are related to increased levels of IL-6 [2,6]. In KSHV-MCD, there is also production of KSHV-encoded vIL-6 with detectable levels in the serum, and this is believed to be an important cause of disease manifestations [6,50]. Unlike human IL-6, which first binds a coreceptor, gp80, and then to gp130, vIL-6 signals directly through gp130 [51–58], and thus potentially affects a wider range of cells than human IL-6. In addition, KSHV-MCD pathogenesis may involve upregulation of NF-kB by latently expressed viral-FLICE inhibitory protein (vFLIP) [59,60] or viral miRNA-K1 [61], and upregulation of VEGF and other factors by a viral G-protein coupled receptor [59–62]. Patients with KSHV-MCD also

frequently have elevated serum IL-10 and other cytokine abnormalities. The relative contribution of these various factors to KSHV-MCD (Table 1) [13,50,61,63,64,65■■,66–68,69■■] is poorly understood.

It is also unclear why only occasional KSHV-infected patients develop MCD. In asymptomatic KSHV-infected individuals, KSHV can often be detected in saliva [70–72,73■■,74], but relatively infrequently in peripheral blood mononuclear cells (PBMC) [47]. By contrast, patients with KSHV-MCD have a markedly increased KSHV viral load [6,33■, 75–81] and expansion of KSHV-infected plasmablasts in lymph nodes and spleen. Affected lymphoid tissues have regressed germinal centers, increased vascularization and mantle zone expansion notable for KSHV-infected plasmablastoid cells, usually IgM^+ [82], that are monotypic (λ-restricted) but polyclonal, and a larger population of KSHV-uninfected B cells [11,83]. All KSHV-infected cells express LANA, whereas a portion also express vIL-6 or other lytic genes [84–86].

KSHV has tropism for B cells, monocytes, dendritic cells, epitehelial, keratinocytes and endothelial cells [87–90]. Infection of target cells is complex [91]; xCT, integrin α3β1 [92–94] and DC-SIGN [95,96] can function as receptors for KSHV entry. B-cell infection by KSHV is enhanced by activation signals such as IL-4 and CD40-ligand [95–97]. Stable B-cell infection *in vitro* predominantly occurs in IgM^+, l-restricted B cells with a 'blasting' morphology that is promoted by IL-6, recapitulating lymph node findings [98■■]. There is evidence that vFLIP plays a role in the bias toward l-restriction [65■■]. Additional efforts to dissect interactions between specific KSHV genes and human genes associated with plasmablast differentiation [82,99,100] may provide insights into disease pathogenesis. KSHV-MCD patients also tend to have certain KSHV miRNA polymorphisms [101■■], and further assessment of these findings as well as assessment of polymorphisms in other KSHV genes or the host genome affecting IL-6 signaling is warranted.

More recently, we described a group of patients with MCD-like fever and inflammatory symptoms, elevated serum vIL-6, and elevated KSHV viral load, but without pathological findings of KSHV-MCD[6]; this syndrome has been tentatively named KSHV-associated inflammatory cytokine syndrome (KICS) [7■]. Studies to evaluate its natural history, pathogenesis and relation to KSHV-MCD are underway (NCT01419561).

THERAPY FOR KAPOSI SARCOMA HERPESVIRUS-MULTICENTRIC CASTLEMAN DISEASE

There is currently no established therapy for KSHVMCD. Until recently, most published literature consisted of case reports or small case series. Although HAART has not been formally studied, a strong case can be made for its use concurrent with specific therapy in HIV-infected patients with KSHV-MCD [30,102]. Additional specific treatment of KSHVMCD is generally reserved for patients with symptomatic disease. Such patients can become critically ill, and may require urgent treatment and supportive care, in an ICU if needed. Successful treatment has been reported with various chemotherapeutic agents, including etoposide, vincristine, vinblastine, cyclophosphamide or doxorubicin, either as singly or in combination. Likewise, temporary remission of symptoms after splenectomy has

been described, although splenectomy in HIV-infected patients carries a high risk of infectious complications [31,103,104■■]. Steroids may reduce inflammation in symptomatic patients; however, their utility is limited, and prolonged use commonly exacerbates Kaposi sarcoma [105]. Immunomodulation with interferon-α [31,106,107] and thalidomide [108] has also been noted to have activity. With most of these modalities, relapse is common, and until recently, overall survival has been poor; a pooled evaluation of 86 cases between 1985 and 2006 reported a median survival of about 12 months, although somewhat better in patients on HAART [102].

In the past several years, targeted approaches have been prospectively evaluated in KSHV-MCD. Results suggest improved outcomes over most modalities listed above. In clinical studies, several criteria have been employed for initiating therapy (Table 2), generally including elevated CRP and at least two to four clinical and laboratory abnormalities. Importantly, patients were not treated based on abnormal radiographic findings alone. Also, there are no commonly used response criteria. Investigators have primarily graded responses in relation to resolution of clinical symptoms and laboratory abnormalities. In an attempt to establish response criteria for KSHV-MCD, we prospectively evaluated KSHV-MCD response criteria that integrate clinical, common biochemical and radiographic findings [32■■]. Further efforts to harmonize response criteria among clinical trials are needed.

Radiographic responses and KSHV viral load dynamics have generally been evaluated as secondary outcomes [32■■,109,110]. Importantly, residual adenopathy, splenomegaly and detectable KSHV viral load have been noted even after resolution of symptoms. Such patients may represent a group with reservoirs of KSHV-infected B cells that are inadequately treated, and who may be at higher risk of recurrent KSHV-MCD symptoms [111■]. Nonetheless, optimal duration of therapy and approach to such patients remains an area of uncertainty.

Rituximab

The best-studied agent in KSHV-MCD is rituximab, a humanized monoclonal antibody against the B-cell antigen CD20. Rituximab has been evaluated in two prospective phase 2 studies. In the CastlemaB Study, 24 patients with HIV and KSHV-MCD received rituximab 375 mg/m^2 weekly for 4 weeks after completion of chemotherapy [109]. Ninety-two percent of patients met the primary outcome of sustained resolution of their MCD attack (Table 2) 60 days after completion of chemotherapy. In eight of 10 evaluated patients, splenomegaly resolved, and at 1 year, 71% were alive and disease-free [109]. In a separate study, 21 patients with symptomatic KSHVMCD were treated with rituximab 375 mg/m^2 weekly for 4 weeks without chemotherapy [110]. Ninety-five percent had resolution of symptoms and fever, with an estimated 79% of patients relapse-free at 2 years. In the latter study, none had a complete radiographic response by Response Evaluation Criteria in Solid Tumors criteria. However, KSHV viral load and CRP decreased significantly 1 month after completion of therapy [110].

Infusion reactions occur in most KSHV-MCD patients administered rituximab [109]. Additionally, rituximab is associated with worsening Kaposi sarcoma in 35–67% of patients [109,110]. The pathophysiology of Kaposi sarcoma relapses is unknown, but likely due to

adverse immunologic effects of B-cell depletion [45,112–115]. Risk of additional rare but serious infectious complications persist beyond dosing of rituximab [116,117]. Importantly, combination of rituximab with cytotoxic chemotherapy may be required for some patients with concurrent Kaposi sarcoma or severe manifestations of KSHV-MCD [118–120]. To address the issue of Kaposi sarcoma relapse, and to potentially also target Kaposi sarcoma spindle cells or monocytes that may be secreting vIL-6, we are currently evaluating rituximab in combination with liposomal doxorubicin in patients with concurrent KSHV-MCD and Kaposi sarcoma or severe KSHVMCD (NCT00099073).

Interestingly, the mechanism of action of rituximab in KSHV-MCD is unclear. KSHV-infected, vIL-6 expressing plasmablasts in KSHV-MCD [85,86] are generally CD20 negative and unlikely to be directly targeted by rituximab [82,121]. However, $CD20^+$ cells are noted in KSHV-uninfected lymphocytes within lymph node specimens [11] (Fig. 2), and rituximab activity likely results in part from diminished autocrine and paracrine signaling in the tumor microenvironment [122–127].

Ganciclovir and other inhibitors of Kaposi sarcoma herpesvirus replication

Ganciclovir is a 2′-deoxyguanosine nucleoside analogue phosphorylated by several herpesvirus thymidine kinases, including KSHV ORF36 [128–130] and ORF21 [128,129]. Ganciclovir triphosphate inhibits viral replication through incorporation into viral DNA and subsequent chain termination. Valganciclovir (VGC), an oral prodrug, decreases KSHV oral shedding [72]. In a case series of three patients with KSHV-MCD, ganciclovir administration led to at least short-term improvement in symptoms and decreased KSHV viral load, suggesting that control of KSHV replication may have a role in therapy [78]. However, cidofovir, a viral DNA polymerase inhibitor with greater in-vitro activity against KSHV replication [131] failed to demonstrate comparable activity in five patients with chemotherapy-dependent KSHV-MCD [132]. In a retrospective study of 52 patients with KSHV-MCD, 12 were treated with variable antiherpesvirus therapy with or without cytotoxic therapy (but no rituximab), and only 33% of these patients obtained a sustained clinical response [133▪]. Of eight patients who received valganciclovir, only three responded. This may be due to the fact that for B cells already infected with KSHV, ganciclovir blocks a late step in the KSHV lytic cycle and would not be expected to suppress vIL-6, an early lytic gene [134–136].

Virus activated cytotoxic therapy

Unlike most herpesvirus-induced tumors, many KSHV-infected plasmablasts in KSHV-MCD express lytic viral genes that can provide targets for selective cytotoxicity. In addition to ganciclovir, KSHV ORF21 phosphorylates zidovudine (AZT) [128,130]. Although antiviral activity of these drugs is through inhibition of viral DNA replication, their triphosphate moieties have cytotoxic effects at relatively high concentrations in PEL cells in which KSHV lytic genes are activated; these effects are at least additive [128]. This virus-induced cytotoxic activity is distinct from the antiviral activity of these drugs. On the basis of these findings, we performed a pilot study of high-dose AZT and VGC in 14 patients with symptomatic KSHVMCD. Patients received AZT 600 mg every 6 h combined with VGC 900 mg every 12 h. Eighty-six percent of the treated patients obtained a clinical partial

response (PR) or better, and 50% obtained a biochemical PR or better. Most patients had decreased adenopathy and splenomegaly, with 36% meeting criteria for PR or better. From baseline to time of best response, KSHV viral load, IL-6, IL-10 and CRP all decreased significantly. All five patients with detectable serum vIL-6 at baseline had decreases with therapy. These results support the activity of virus-activated cytotoxic therapy in KSHV-MCD. However, high-dose AZT combined with VGC has limitations. Toxicities are mainly hematologic, prohibiting continuous administration. Therapy was generally administered on days 1–7 of a 21-day cycle. Also, whereas long-term efficacy was observed in three of 14 patients (21%), additional therapies were required in the other patients because of persistent or recurrent KSHVMCD symptoms [32■■]. This regimen may be best utilized in patients with mild disease or in combination with other modalities. Future studies will be needed to define the best use of this approach.

Experimental approaches

Outcomes in therapeutic trials of rituximab and AZT and VCG have been considerably better than historical controls [31,102]. Nonetheless, KSHV-MCD remains a challenging disease. Relapses are common, current approaches have toxicities and have not been standardized, and new effective therapies are urgently needed. With improved understanding of KSHV biology and KSHV-MCD pathogenesis, several approaches merit exploration. One is targeting IL-6 using monoclonal antibodies. Tocilizumab is a humanized anti-IL-6 receptor (gp80) antibody [137–139], whereas siltuximab (formerly CNTO 328) [140] and sirukumab (CNTO 136) [141] are human monoclonal antibodies to IL-6. Tocilizumab and siltuximab have demonstrated activity in KSHV-negative MCD [140,142,143]. Although targeting human IL-6 does not directly affect vIL-6 signaling, it may still be sufficient in KSHV-MCD. Indeed, two patients with KSHV-MCD have been reported to respond to tocilizumab [143]. Tocilizumab is currently being evaluated alone and in combination with AZT and VGC (NCT01441063). Other agents worth considering for future studies include mTOR [144] inhibitors or newer immune modulators derivatives of thalidomide (IMiDs).

CONCLUSION

KSHV-MCD can be difficult to recognize and diagnose. Clinicians should be alert for this condition in HIV-infected patients with persistent, intermittent fever, especially if they have Kaposi sarcoma or are in a risk group for KSHV infection. Targeted therapy, combined with HAART, has led to substantial improvements in patient survival. Unlike early series in which median survival was about 12 months [31], overall survival with current targeted therapies exceeds 85% at 1 year and sustained responses are often seen [32■■,33■,109,133■]. Effective therapy for KSHV-MCD, especially rituximab, may also be associated with decreased risk of subsequent development of lymphoma [145], although this observation requires confirmation. Future studies evaluating novel therapies or rational combinations may further improve outcomes, limit toxicities and allow for personalized approaches in patients with KSHV-MCD, with concurrent KSHV-associated malignancies or with relapsed KSHV-MCD. Additional studies of biomarkers of KSHV viral reservoirs, such as KSHV viral load, or novel imaging modalities [146] may lead to improved risk stratification and allow for evaluation of consolidation therapy beyond resolution of symptoms. With

improved recognition of KSHV-MCD and ongoing therapeutic advances, KSHV-MCD should continue to move from being a highly fatal disorder to a manageable manifestation of chronic KSHV infection.

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KEY POINTS

- KSHV-MCD is a rare lymphoproliferative disorder diagnosed by biopsy, which shows characteristic findings of MCD with evidence of KSHV infection and KSHV-encoded viral IL-6.
- KSHV-MCD most often arises in patients with HIV, and can occur despite suppressed HIV and a relatively preserved CD4 count.
- KSHV-MCD presents with waxing and waning inflammatory symptoms that may include fevers, fatigue, nonspecific respiratory and gastrointestinal symptoms, adenopathy, splenomegaly, anemia, thrombocytopenia, low albumin and elevated inflammatory markers such as C-reactive protein.
- KSHV-MCD is likely underdiagnosed, especially in Africa, where HIV and KSHV coinfection is common.
- Targeted therapies for KSHV-MCD, including virus-activated cytotoxic therapy and rituximab, control symptoms and improve survival in patients with KSHV-MCD.

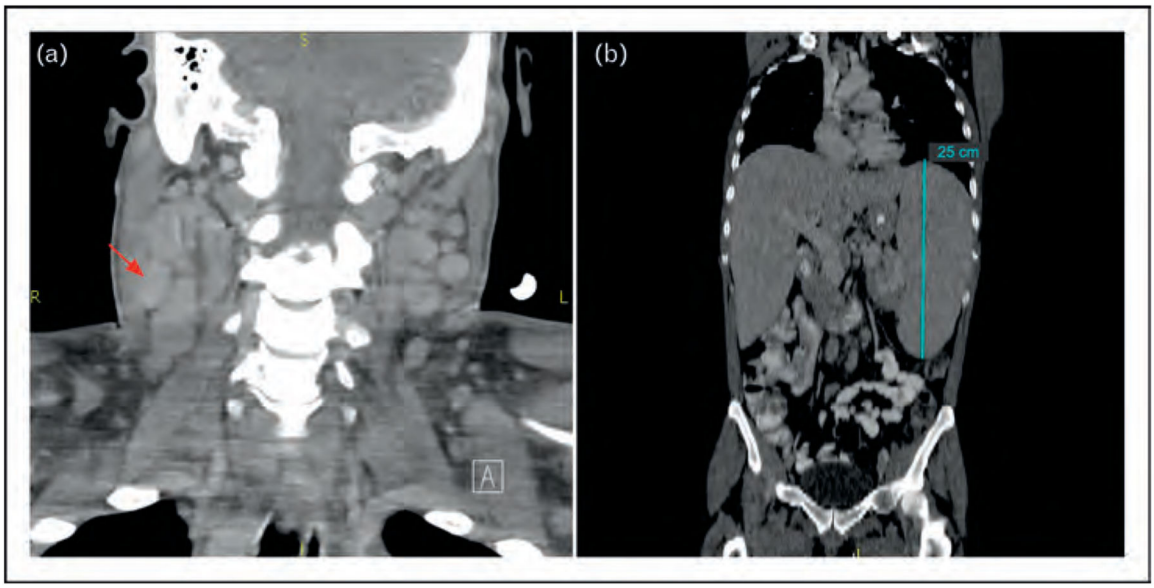

FIGURE 1.

Computerized tomography in Kaposi sarcoma herpesvirus-multicentric Castleman disease. (a) Coronal image of neck showing bilateral diffuse cervical adenopathy, red arrow points to example of enlarged lymph node on right. (b) Coronal image of torso, demonstrating dramatic splenomegaly, measuring 25 cm (upper limit of normal = 12 cm).

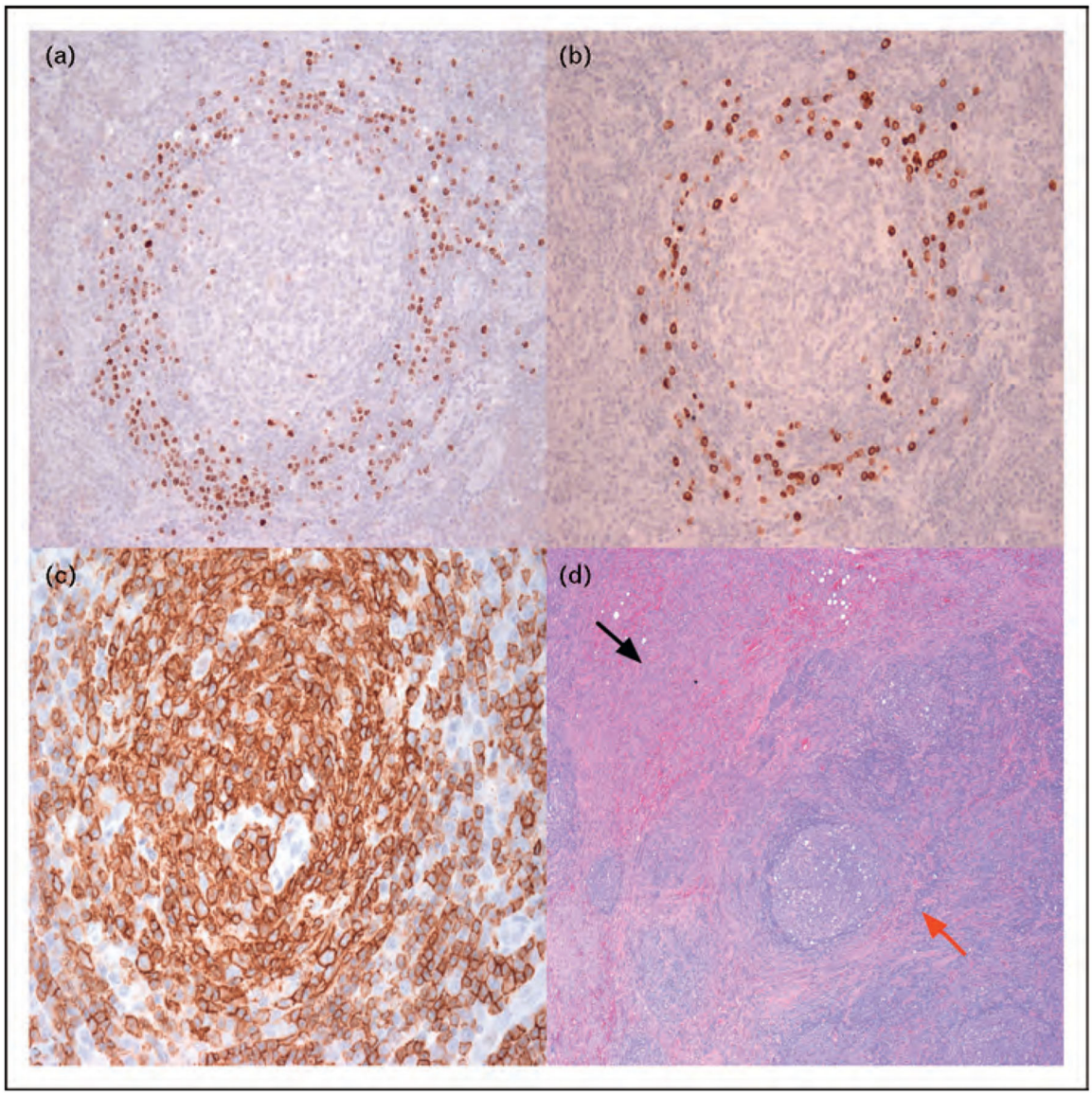

FIGURE 2.

Lymph node histopathology in Kaposi sarcoma herpesvirus-multicentric Castleman disease. (a) Regressed germinal center with expansion of plasmacytic cells in the mantle zone. Immunohistochemical staining for KSHV latency associated nuclear antigen (LANA) shows a proportion of the cells are KSHV infected. 20X magnification. (b) Immunohistochemical staining for viral interleukin-6 (vIL-6) shows a proportion of cells in the mantle zone express vIL-6. 20X magnification. (c) Immunohistochemistry demonstrating a high proportion of cells expressing CD20 (stained brown), with strongest expression in the germinal center, and a mixture of CD20 positive and negative cells in the mantle zone. 40X magnification. (d) Lymph node biopsy showing spindle cell expansion with leaky vascularity representing Kaposi sarcoma (black arrow), as well as typical finding of KSHV-MCD (red arrow) in the same lymph node. 10X magnification Images and pathology samples from patients on National Cancer Institute Institutional Review Board approved KSHV-MCD Natural History

Protocol (NCT00099073). All patients gave written informed consent in accordance with the Declaration of Helsinki.

Table 1.

Human and KSHV-encoded genes and KSHV-encoded microRNA implicated in KSHV-associated multicentric Castleman disease pathogenesis

Gene/miRNA	Model	Findings	Reference
Human Genes			
IL-6	Retroviral transfer of IL-6 gene into mouse hematopoietic stem cells, transplanted into congenitally anemic W/Wv mice	Anemia, leukocytosis, thrombocytopenia, polyclonal hypergammaglobinemia, massive splenomegaly, lymphadenopathy. Lesser infiltrates of kidney, lung and liver. Glomerular mesangial cell hyperplasia	Brandt, et al. [13]
IL-10	Placebo-controlled clinical study of recombinant human IL-10 in patients with Crohn's disease	Toxicity evaluation demonstrated dose-dependent anemia with markedly elevated ferritin, and thrombocytopenia	Fedorak, et al. [63] Tilg, et al. [64]
KSHV-encoded Genes/miRNA			
Viral IL-6	Murine fibroblasts transfected with vlL-6, inoculated into flank of nude mice	Leukocytosis, moderate splenomegaly, plasmacytosis in spleen and lymph nodes, polyclonal hypergammaglobinemia. Spindle cell tumors. Increased VEGF production in tumors, lymph nodes and spleen	Aoki, et al. [50]
vFLIP	Conditional knock-in transgenic mice that express vFLIP in all $CD19^+$ B cells or $lgG1^+$ germinal center B cells	Splenomegaly. Certain histologic features similar to those seen in KSHV-MCD: expansion of marginal zone B cells, lack of CD1 38 staining, impaired germinal center formation and increased λ-light chain production. Elevated IgE with immunization. Mice developed transgenic derived tumors with histologic features of histiocytic/dendritic cell sarcoma	Ballon, et al. [65■■]
miRNA-K1	Transfection of 293 T cells with mutated KSHV miRNA	Cells transfected with KSHV with mutated miRNA had decreased NF-κB activity due to downregulation of the NF-κB regulating protein IκBα by KSHV miRNA-K1, whereas miRNA-K1 transfection restored NF-κB activity	Lei, ef al. [61]
miRNA K12–3 and miRNA K12–7	Transfection of KSHV miRNA in murine macrophage and human myelomonocytic leukemia cell lines	Transfection lead to upregulation of human IL-6, IL-6 receptor, and IL-10. Mechanism of action is KSHV miRNA downregulation of C/EBP-β, a transcription factor that negatively regulates IL-6 [66,67]	Qin, et al. [68]
miRNAK12–11	Viral transfer of KSHV-encoded miRNA K12–1 1 in human hematopoietic progenitors and immune reconstitutions in NOD/LtSz-scid IL2Rγ(null) mice	Expansion of splenic $CD19^+$ cells. 3′ UTR of C/EBP-β contains a putative miRNA K1 2–11 binding site. Splenic B cells in miRNA Kl 2–11 transplanted animals had decreased C/EBP-β miRNA compared to controls	Boss, et al. [69■■]

vFLIP, viral-FLICE inhibitory protein; KSHV-MCD, Kaposi sarcoma herpesvirus-associated multicentric Castleman disease; miRNA, microRNA.

Table 2.

Criteria for patient selection for treatment of KSHV-associated multicentric Castleman disease utilized in two prospective studies

Revised NCI Criteria for Treatment[a]	MCD Attack Criteria (CastlemaB Trial) Criteria for Treatment[b]
At least one clinical symptom (commonest examples listed) and one laboratory abnormality probably or definitely attributed to KSHV-MCD and elevated serum CRP	Fever
Clinical symptoms	At least 3 of the following symptoms
Fatigue (CTCAE equivalent ≥ Grade 2)	Peripheral lymphadenopathy
Fever, night sweats	Enlarged spleen
Weight loss	Edema
Respiratory symptoms	Pleural effusion
Gastrointestinal symptoms	Ascites
Neurologic symptoms	Cough
Edema or effusions	Xerostomia
Rash	Rash
Laboratory abnormalities	Central neurologic symptom
Anemia	Jaundice
Thrombocytopenia	Autoimmune hemolytic anemia
Hypoalbuminemia	
Elevated serum CRP (>3 mg/l)	Elevated serum CRP (>20mg/l) in the absence of any other etiology
If HIV+, on effective combination antiretroviral therapy or willing to initiate therapy	If HIV+, on combination antiretroviral therapy for at least 3 months

CRP, C-reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; MCD, multicentric Castleman disease; NCI, National Cancer Institute; KSHVMCD, Kaposi sarcoma herpesvirus-associated multicentric Castleman disease.

[a] Original criteria proposed in 2004 [32■■] included additional liver function abnormalities, leukopenia, hyponatremia, and elevated creatinine as potential laboratory abnormalities. From clinical trial NCT00099073.

[b] Adapted with permission from [109].