Kaposi sarcoma herpesvirus-associated cancers and related diseases

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Purpose of review
This review discusses the pathogenesis and recent advances in the management of Kaposi sarcoma herpesvirus (KSHV)-associated diseases.

Recent findings
KSHV, a gammaherpesvirus, causes several tumors and related diseases, including Kaposi sarcoma, a form of multicentric Castleman disease (KSHV-MCD), and primary effusion lymphoma. These most often develop in patients infected with human immunodeficiency virus (HIV). KSHV inflammatory cytokine syndrome (KICS) is a newly described syndrome with high mortality that has inflammatory symptoms-like MCD but not the pathologic lymph node findings. KSHV-associated diseases are often associated with dysregulated human interleukin-6, and KSHV encodes a viral interleukin-6, both of which contribute to disease pathogenesis. Treatment of HIV is important in HIV-infected patients. Strategies to prevent KSHV infection may reduce the incidence of these tumors. Pomalidomide, an immunomodulatory agent, has activity in Kaposi sarcoma. Rituximab is active in KSHV-MCD but can cause Kaposi sarcoma exacerbation; rituximab plus liposomal doxorubicin is useful to treat KSHV-MCD patients with concurrent Kaposi sarcoma.

Summary
KSHV is the etiological agents of all forms of Kaposi sarcoma and several other diseases. Strategies employing immunomodulatory agents, cytokine inhibition, and targeting of KSHV-infected cells are areas of active research.

Keywords
human herpesvirus-8, Kaposi sarcoma, Kaposi sarcoma associated herpesvirus

INTRODUCTION

Kaposi sarcoma herpesvirus (KSHV), a gammaherpesvirus, was discovered in 1994 by Chang *et al.* [1▪▪], as the causative agent of AIDS-associated Kaposi sarcoma. It is also called human herpesvirus-8 (HHV-8). KSHV has been implicated as the etiologic agent of all forms of Kaposi sarcoma and several other diseases, including multicentric Castleman disease (MCD), primary effusion lymphoma (PEL) and a newly described syndrome, KSHV inflammatory cytokine syndrome (KICS) [2▪–4▪]. KSHV is a necessary but insufficient etiological agent for these diseases.

KAPOSI SARCOMA HERPESVIRUS LIFE CYCLE

KSHV is a double-stranded DNA gammaherpesvirus. After infection, the genome is maintained as an episome in the host cell nucleus. KSHV can infect a variety of cells including endothelial cells, B-cells, and monocytes. Figure 1 depicts the circularized KSHV genome. Upon infection of a cell, KSHV establishes latency, wherein only a few genes are expressed. Most reside in a cluster in the latency locus, and include ORFK12 (kaposins), ORF71 (vFLIP), ORF72 (vCyclin), ORF73 (latency-associated nuclear antigen, LANA), and various viral microRNAs (miRNAs). These help to maintain the viral episome, deter host immune responses, and promote survival and proliferation of infected cells [5,6,7▪,8▪▪].

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KEY POINTS

- KSHV-associated diseases include Kaposi sarcoma, KSHV-MCD, PEL, and KICS.
- KICS is a newly described high-mortality syndrome of KSHV-infected patients.
- There are few FDA-approved therapies to treat KSHV-associated diseases.
- KSHV-associated diseases are an important cause of morbidity and mortality in HIV patients.

Certain physiological signals cause the virus to enter the lytic phase, wherein all viral genes are expressed, progeny virions are produced and released, and the infected cell dies. The switch from latency to lytic replication is set in motion by ORF50 (replication and transcription activator protein, RTA). In addition to physiologic stressors such as hypoxia, various chemicals (sodium butyrate and valproic acid) can induce the lytic cycle [9]. Additional genes may be expressed in a more selective manner in otherwise latently infected cells and these are partially dependent on the specific cell type [10▪,11,12]. Latent infection is observed in the majority of tumor cells in Kaposi sarcoma lesions. However, around 1% of infected cells in Kaposi sarcoma express lytic genes, whereas a higher percentage express lytic genes in PEL and even more in MCD.

KAPOSI SARCOMA HERPESVIRUS TRANSMISSION

Kaposi sarcoma prevalence and new infections remain high in men who have sex with men (MSM) in the USA. KSHV is secreted in saliva, and there is evidence that common modes of transmission in MSM are through oral–anal contact, oral–penile contact, or use of saliva as a lubricant [13–17]; thus education regarding these practices may be useful in reducing its spread in this population. In Sub-Saharan Africa (SSA), transmission often occurs during childhood, and may be in part through food premastication [18▪▪].

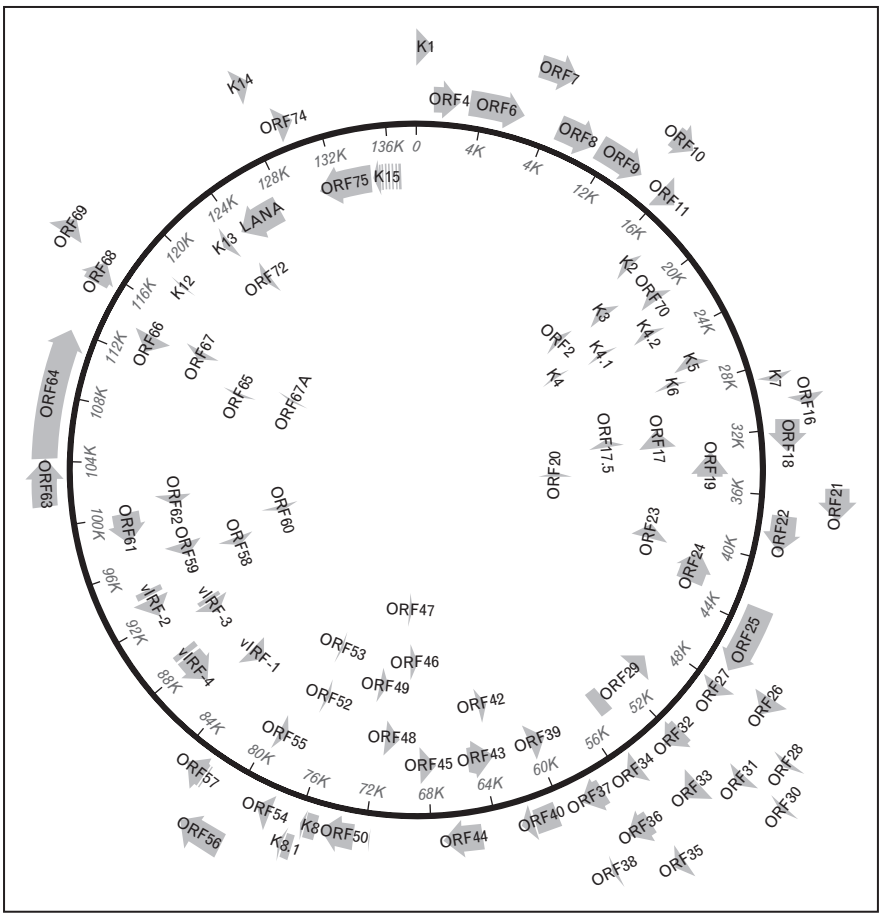

FIGURE 1. Kaposi sarcoma herpesvirus genome. The circular KSHV episome is shown with protein-encoding genes. Noncoding RNAs are not shown. KSHV, Kaposi sarcoma herpesvirus; ORF, open reading frame; LANA, latency-associated nuclear antigen; vIRF, viral interferon regulatory factor. Gene names starting with 'K' are unique to KSHV.

PATHOGENESIS OF KAPOSI SARCOMA HERPESVIRUS-ASSOCIATED MALIGNANCIES

KSHV has evolved strategies to evade innate and specific immunity, induce proliferation, and prevent apoptosis of infected cells. These strategies can promote oncogenesis. KSHV also has pleotropic effects on cell signaling that contribute to oncogenesis and angiogenesis, a hallmark of Kaposi sarcoma. For example, the KSHV protein vFLIP stimulates activation of NF-kB and is implicated in Kaposi sarcoma, KSHV-MCD, and PEL [19,20,21▪▪]. Various KSHV proteins promote activation of the AKT and mechanistic target of rapamycin (mTOR) pathways, which promote survival and growth and are upregulated in many cancers [12,22–24]. Importantly, sirolimus, an inhibitor of mTOR, can treat Kaposi sarcoma in transplant patients [25,26]. Expression of latent viral proteins is necessary for survival of PEL cell lines, and repression of specific KSHV latent genes can induce apoptosis [6,27]. Also, KSHV-encoded miRNAs can increase B-cell proliferation in an animal model and promote survival of infected cells [28–31]. p53 is wild-type in KSHV-infected cells; however, LANA can inhibit p53 activity [32]. Activation of p53 induces apoptosis in KSHV-infected cells, suggesting that repression of p53 is important for survival of these cells [33]. Human interleukin-6 (hIL-6) is up regulated upon KSHV infection; this is mediated by several KSHV genes, such as vFLIP, kaposin B, and a KSHV G-protein-coupled receptor [encoded by open reading frame 74 (ORF74)] [34]. Also, KSHV encodes a homolog of hIL-6, viral IL-6 (vIL-6). It is believed that increased IL-6 expression benefits KSHV infection in part by inducing proliferation of B lymphocytes [35,36]. Additionally, vIL-6 signaling can lead to increased vascular endothelial growth factor expression to stimulate angiogenesis [37]. In contrast to other oncogenic viruses, there is evidence that certain lytic KSHV genes are important in oncogenesis. In particular, several studies have shown that vGPCR (ORF74) is important in the pathogenesis of Kaposi sarcoma [38].

KAPOSI SARCOMA

Kaposi sarcoma is the most common KSHV-associated tumor. There are four major epidemiologic subtypes: classic; iatrogenic or transplant-associated; endemic or African; and AIDS-related or epidemic. Kaposi sarcoma was first described in elderly men in Mediterranean or Eastern European regions and this form is called 'classic' Kaposi sarcoma. Later on, a high incidence of Kaposi sarcoma in SSA was described [39]. In 1970s, association of Kaposi sarcoma with immunosuppressive therapies such as steroids and cyclosporin was reported, providing initial evidence that immunosuppression is an important cofactor [40]. In 1981, the development of Kaposi sarcoma in young gay men was one of the harbingers of the AIDS epidemic. MSM have a much higher incidence than other HIV-risk groups, suggesting that another etiologic agent was causal; in 1994, KSHV was identified as the etiologic agent. The prevalence of KSHV parallels the incidence of Kaposi sarcoma in various populations. In AIDS, a low $CD4^+$ count, lack of KSHV T-cell immunity, and HIV viremia are associated with the highest Kaposi sarcoma risk [41–43]. In the combination antiretroviral therapy (ART) era, Kaposi sarcoma incidence decreased by approximately 80%, but has since stabilized [44]. Kaposi sarcoma incidence in HIV patients remains substantially greater than the general population, even in those on ART with controlled HIV viremia and relatively preserved $CD4^+$ counts. The number of HIV-infected persons in the USA is increasing and ageing, and it is possible that this may lead to an increase in the incidence of AIDS Kaposi sarcoma. The incidence of Kaposi sarcoma is particularly high in SSA because of the high prevalence of both HIV and KSHV infection; in some SSA countries, Kaposi sarcoma is the most common tumor in men [45].

The most common presentation of Kaposi sarcoma is multifocal cutaneous macules or nodules commonly involving the lower extremities. Edema, ulceration, bleeding, pain, and secondary infection may cause significant morbidity, and patients often have psychological distress from visible stigmata of AIDS. Nodal, lung, gastrointestinal, bones, and other visceral Kaposi sarcoma may occur. Diagnosis is established with a biopsy showing KSHV-infected spindle cells. Staging requires evaluation of the skin and oral mucosa, whereas evaluation for visceral disease is generally limited to a chest X-ray and stool occult blood test, with additional evaluations prompted by symptoms or abnormal initial tests. Kaposi sarcoma patients were initially staged following the AIDS Clinical Trials Group (ACTG) Oncology Committee criteria, where T stands for tumor burden (T_0 or T_1), I for immune status (I_0 or I_1) and S for systemic illness (S_0 or S_1) [46]. Subscripts 0 and 1 denote good risk and poor risk, respectively. Criteria for poor-risk parameters are as follows: T_1 includes tumors with tumor-associated edema or ulceration, extensive oral or gastrointestinal Kaposi sarcoma, and Kaposi sarcoma in other nonnodal viscera; I_1 includes $CD4^+$ cell less than 150/μL; and S_1 includes history of opportunistic infections and/or thrush, B symptoms, Karnofsky performance status less than 70, or other HIV-related illnesses. In patients receiving ART, $CD4^+$ cell counts are less important

prognostically, and the ACTG classification has been modified, with T_1S_1 patients considered poor risk and all others (T_0S_0; T_1S_0, or T_0S_1) good risk [47]. Nonetheless, in patients with T_1 Kaposi sarcoma, advanced immunosuppression, as measured by CD4 count less than 100/μL, remains an important predictor of death in some regions [48].

The natural history of Kaposi sarcoma varies. Kaposi sarcoma may worsen or improve spontaneously, often in tandem with changes in underlying immune function. Some patients have an indolent pattern whereas others present with aggressive growth. Patients with rapidly progressive Kaposi sarcoma should be evaluated for concurrent KSHV-MCD, PEL, or KICS (see below). There is no evidence that Kaposi sarcoma can be 'cured', although long-term remissions without continued specific therapy are possible. Initial Kaposi sarcoma treatment should be aimed at correcting the underlying immunodeficiency when present. In HIV patients, this includes ART. In transplant-related Kaposi sarcoma, replacing cyclosporine with sirolimus may lead to disease remission [26]. If Kaposi sarcoma is indolent and not affecting quality of life, patients may be followed with a 'watch and wait' approach. Criteria for systemic treatment, that is, treatment over and above improving immune status, include Kaposi sarcoma-related symptoms, rapidly growing Kaposi sarcoma, or psychological distress from cosmetic disfigurement or stigmatization [47]. Localized treatment is generally avoided, because of its systemic nature and local toxicities. Table 1 summarizes the main systemic treatment options [49–56▪,57▪,58–60▪,61,62▪,63–65,66▪▪,67]. For patients requiring systemic treatment, most physicians now use Food and Drug Administration (FDA)-approved liposomal anthracyclines as initial therapy [49–53]. Paclitaxel is approved by the FDA for patients who fail or do not tolerate this initial approach [54,55]. Patients with Kaposi sarcoma often require treatment for many years, and current therapies are limited by toxicity or the risk of cumulative anthracycline cardiotoxicity. Effective and less toxic approaches are thus an unmet need. In addition, it will be important to develop effective oral agents for resource-limited settings. Pomalidomide has recently been shown to have promising activity in a Phase I/II trial [56▪].

MULTICENTRIC CASTLEMAN DISEASE

KSHV-associated MCD is a B-cell lymphoproliferative disorder most common arising in HIV-infected patients. It appears to be more common in the ART era [68]. It is rarely reported in SSA, but this is likely because of substantial under-diagnosis. KSHV-MCD presents with intermittent inflammatory symptoms such as fever, night sweats, weight loss, fatigue, and nonspecific respiratory and gastrointestinal symptoms, along with hepatosplenomegaly, lymphadenopathy and edema. KSHV viral load is elevated during symptomatic flares, and decreases with disease treatment and remission [69]. Laboratory abnormalities include elevated C-reactive protein, hypoalbuminemia, anemia, thrombocytopenia, hyponatremia, and elevated immunoglobulins [69,70]. There is no consensus definition of a KSHV-MCD flare; different groups use combinations of the symptoms and laboratory abnormalities [71,72]. KSHV-MCD-associated symptoms are believed to be caused by an excess of cytokines, especially vIL-6, hIL-6, and hIL-10 [69,73]. Patients with flares can have increased serum levels of vIL-6, hIL-6, or both [73]. There is evidence that vIL-6 can activate hIL-6, and may be the most important driving force [74].

KSHV-MCD diagnosis generally requires an excisional lymph node biopsy showing expansion of reactive plasma cells interspersed with KSHV-infected plasmablasts, as well as hyalinization of lymphoid follicles and increased capillary proliferation. A substantial subset express vIL-6, and a smaller subset also express other KSHV lytic antigens. Maturing B-cells have high levels of X-box binding protein 1 (XBP-1), and there is an evidence that this can contribute to KSHV-MCD pathogenesis by inducing KSHV lytic activation and directly inducing expression of vIL-6 [10▪].

KSHV-MCD can wax and wane, but untreated, is generally fatal within 2 years. There is no FDA-approved treatment. ART is indicated in HIV-associated KSHV-MCD but is generally insufficient. Control of HIV viremia, however, may reduce the likelihood of recurrence [75]. Treatment with rituximab or the combination of rituximab and liposomal doxorubicin often leads to clinical remission; prolonged remissions are observed, and this therapy can improve survival [71,76▪,77,78▪]. Patients may present with concurrent Kaposi sarcoma, and rituximab alone can cause Kaposi sarcoma exacerbation; rituximab plus liposomal doxorubicin can be particularly useful in such patients [76▪]. High-dose zidovudine in combination with valganciclovir targets KSHV-infected cells expressing lytic proteins, and has demonstrated activity in KSHV-MCD, although remissions appear more common with rituximab [79]. Table 2 summarizes the evidence for selected therapeutic options for KSHV-MCD.

PRIMARY EFFUSION LYMPHOMA

PEL is a KSHV-associated aggressive mature monoclonal B-cell lymphoma with a poor outcome [80].

Table 1. Select prospective studies of systemic therapies for the treatment of Kaposi sarcoma

Treatment	Dosage	Design	Response rate	Comments
Pegylated liposomal anthracycline (doxorubicin and daunorubicin)	20–40 mg/m^2 every 3 weeks	PLDa vs. DBV [49]^a; PLD vs. BV [50]^a; PLD vs. PLDa [51]; PLD vs. paclitaxel [52]; PLD vs. DBV [53]^a	25–59% (CR + PR)	Usually given as first line treatment because of similar RR to paclitaxel and better toxicity profile. Single agent-pegylated liposomal anthracyclines yield similar RR to drug combination with a less toxic profile. FDA-approved drug
Paclitaxel	100 mg/m^2 every 2 weeks and 135–175 mg/m^2 every 3 weeks	Phase II trials [54,^{a}55]	56–71% (CR + PR)	Needs to be given with steroids, which may exacerbate Kaposi sarcoma in HIV patients. FDA-approved drug
Pomalidomide	5 mg daily for 21 out of 28 days	Phase I/II [56▪,57▪]	73% (CR + PR)	Well tolerated, increases in CD4$^+$ and CD8$^+$ T cells. Effective in HIV infected and classic Kaposi sarcoma
Vinorelbine	30 mg/m^2 every 2 weeks	Phase II trial [58]^a	43% (CR + PR)	Antitubulin agent, usually reserved for patients that failed previous pegylated liposomal anthracycline (PLD) and/or paclitaxel therapy
Etoposide	50 mg once a day for 7 out of 21 days	Phase II trial [59]	36% (CR + PR)	Risk of secondary myelodysplastic syndrome and leukemia with long-term therapy
Nab-paclitaxel	Nab-paclitaxel 100 mg IV on days 1, 8, and 15 of each 4-week cycle	Phase II [60▪]	100% (CR + PR)	Well tolerated. Steroid sparing. Evaluated in a small number of HIV-negative patients
Bevacizumab	15 mg/kg every 3 weeks	Phase II trial [61]	31% (CR + PR)	Relatively low antitumor effect as monotherapy, but may improve tumor-associated edema
Imatinib	400–600 mg daily	Phase II trial [62▪]	33% (CR + PR)	Activating mutations in PDGF-R and c-kit did not correlated with responses
COL-3	MTD: 25 mg/m^2/day	Phase I trial [63]	44% (CR + PR)	MMPs are involved in tumor invasion and are overexpressed in Kaposi sarcoma. COL-3 is a MMP inhibitor
Interferon-alfa	Low-dose (1 million IU) or high-dose (8–10 million IU) once a day	Low-dose or high-dose with DDI [64]^a or AZT [65]^a	Low-dose group: DDI – 40% and AZT – 8% (CR + PR); high-dose group: DDI – 55% and AZT – 31% (CR + PR)	Unfavorable toxicity profile. FDA-approved drug
ART	Three-drug regimen following DHHS Guidelines	Description of a prospective stage-stratified approach. T_0 disease: ART alone. T_1 disease: ART + liposomal anthracycline [66▪▪]	No RR described. 5-year OS: T_0 – 95%; T_1 – 85%	Patients with T_1 Kaposi sarcoma treated with specific Kaposi sarcoma therapy in addition to ART still have a worse 5-year OS when compared with T_0 patients treated with ART alone
ART	Three-drug regimen	Summary of several studies of ART alone [67]	T_0 patients: 39/48 (81%) with (PR + CR). T_1 patients: only four patients identified in clinical trials that were treated with ART alone, of which three responded (PR + CR)	In review of entire literature up until 2004, only five documented cases were identified in which patients with T_1 Kaposi sarcoma responded to ART alone
ART	Three-drug regimen following DHHS Guidelines	Randomized controlled trial of patients with T_1 disease in SSA: ART vs. ART + CXT [48]	ART alone: 39% (CR + PR). ART + CXT: 66% (CR + PR)	CXT regimen in SSA trial reported in 2012: DBV or oral etoposide when DBV not available

ART, antiretroviral therapy; AZT, zidovudine; BV, bleomycin, vincristine; CR, complete response; CXT, chemotherapy; DBV, doxorubicin, bleomycin, vincristine; DDI, didanosine; DHHS, The US Department of Health and Human Services; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; MMP, matrix metalloproteinases; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PDGF-R, platelet-derived growth factor receptor; PLD, pegylated liposomal doxorubicin; PLDa, pegylated liposomal daunorubicin; PR, partial response; RR, response rate; SSA, sub-Saharan Africa.
^{a}Studies conducted in the pre-ART era.

Table 2. Select treatment strategies for KSHV-MCD

Therapy	Dosage	Rationale	Outcomes	Special considerations
Rituximab	375 mg/m^2 weekly × 4 weeks [71,76▪]	Rituximab eliminates CD20 + B-cells	92% sustained remission rate at day 60, 71% at 1 year. Patients should have been treated with chemotherapy for at least 3 months with clinical response and should have experienced at least one recurrence of MCD attack after attempt to discontinue chemotherapy prior to initiating rituximab [71]. 95% had remission of symptoms; 67% had a radiological response. 79% disease-free survival at 2 years [76▪]	Kaposi sarcoma progression may occur [National Comprehensive Cancer Network Guidelines version 1.2015 (NCCN Guidelines)]
Rituximab + liposomal doxorubicin	Rituximab 375 mg/m^2 + liposomal doxorubicin 20 mg/m^2 every 3 weeks [78▪]	Rituximab may lead to worsening of Kaposi sarcoma lesions. Rituximab alone may be inadequate as single agent to treat KSHV-MCD. LD can target CD20-KSHV-infected MCD plasmablasts and Kaposi sarcoma spindle cells	Clinical response: 94% major clinical response (PR or better); 88% CR. Biochemical response: 88% major response; 76% CR	Well tolerated, rapid clinical improvement. Listed as preferred line of treatment in patients with KSHV-MCD and concomitant Kaposi sarcoma (NCCN Guidelines)
High-dose AZT + valganciclovir	AZT 600 mg orally every 6 h + valganciclovir 900 mg orally every 12 h for 7 out of 21 days [79]	ORF21 (KSHV lytic gene) can phosphorylate AZT and ganciclovir to toxic moieties; ORF36 (KSHV lytic gene) can phosphorylate ganciclovir	Clinical responses: 86% major clinical response. Biochemical responses: 50% major response; 21% CR; 29% PR	Decrease in C-reactive protein and viral IL-6 noted from baseline to time of best clinical response (NCCN Guidelines)

AZT, zidovudine; IL-6: interleukin-6; CR, complete response; FDA, Food and Drug Administration; KSHV, Kaposi sarcoma herpesvirus; LD, liposomal doxorubicin; MCD, multicentric Castleman disease; NCCN, National Comprehensive Cancer Network; PR, partial response.

Most cases arise in HIV patients. Although relatively rare, PEL is likely to be under-diagnosed [81]. PEL presents with lymphomatous effusions, most commonly pleural, but also peritoneal, pericardial, and even joint [82]. Extra-cavitary forms can involve the skin, lymph nodes, gastrointestinal, and central nervous system (CNS) [83]. PEL should be considered in any HIV patient with effusions, especially if they have Kaposi sarcoma and/or inflammatory symptoms similar to MCD and laboratory criteria for KICS (described below). Even small effusions should be evaluated. PEL cells generally have immunoglobulin gene rearrangement, but often lack surface immunoglobulin or common B-cell surface markers such as CD19, CD20, or CD79a. A diagnosis of PEL requires the presence of KSHV in the malignant cells; about 80% are coinfected with EBV. The immunophenotypic profile may include CD45, CD30, CD38, CD138, and interferon regulatory factor 4 (IRF4) [83–85].

In addition to imaging of the chest, abdomen, and pelvis, staging should include brain MRI and lumbar puncture to look for CNS involvement. Serial evaluation of KSHV viral load may provide additional information. Currently, there is no standard therapy. Administration of ART is key component for HIV-infected patients, but is insufficient in itself. Dose-adjusted EPOCH (infusional cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with ART can yield 2-year survival rates of approximately 30–40% [80,86]. Preclinical studies of pomalidomide or lenalidomide show activity in PEL cells, due in part to a reduction of IRF4 [87▪▪,88▪]. Interestingly, both lenalidomide and pomalidomide have been shown to inhibit KSHV-induced downregulation of MHC class I expression in PEL cells [88▪]. A prospective trial using lenalidomide combined with rituximab and DA-EPOCH is being developed. Elevated cytokines such as IL-6 have been shown to correlate with poor prognosis in PEL patients and a substantial proportion meet criteria for KICS (described

Table 3. Working definition of the KSHV inflammatory cytokine syndrome (KICS)

(1) Clinical manifestations					
(a) Symptoms	Fever, fatigue, edema, cachexia, respiratory symptoms, gastrointestinal disturbance, arthralgia and myalgia, altered mental state, neuropathy	(b) Laboratory abnormalities	Anemia, thrombocytopenia, hypoalbuminemia, hyponatremia	(c) Radiographic abnormalities	Adenopathy, splenomegaly, hepatomegaly, body effusions
(2) Systemic Inflammation					
Elevated C-reactive protein					
(3) KSHV viral activity					
KSHV viral load in plasma ($\geq$1000 copies/mL) or PBMCs ($\geq$100 copies/10^6 cells)					
(4) No evidence of KSHV-MCD					
If adenopathy present, requires histopathologic assessment of nodes					

For a diagnosis of KICS to be made, must have at least two clinical manifestations from at least two categories (symptoms, laboratory abnormalities, and radiographic abnormalities), in addition to each of the criteria in 2–4. KSHV, Kaposi sarcoma herpesvirus; MCD, multicentric Castleman disease; PBMCs, peripheral mononuclear cells. Adapted with permission [89▪].

Table 4. Select on-going or recently completed therapeutic studies open to patients with KSHV-associated diseases

Therapy	Disease	Rationale	Clinical Trials.gov Identification (https://clinicatrials.gov)
Selumetinib	Kaposi sarcoma	MEK 1/2 inhibitor	NCT01752569
Nelfinavir	Gamma herpesvirus-related tumors including Kaposi sarcoma	Nelfinavir may activate lytic gene expression in gamma herpesvirus tumors	NCT02080416
Pembrolizumab	Patients with HIV and refractory/advanced malignancies, including Kaposi sarcoma and PEL	PD-1 inhibitor	NCT02595866
Nivolumab + ipilimumab	HIV-associated malignancies, including Kaposi sarcoma and PEL	PD-1 inhibition combined with CTLA4 inhibition	NCT02408861
Pomalidomide + liposomal doxorubicin	Kaposi sarcoma, MCD, KICS	Unmet need to treat patients with KSHV-MCD and Kaposi sarcoma as single agents alone are not usually sufficient	NCT02659930
DS-8895a	Advanced or metastatic EphA2 cancers	EphA2 is an entry receptor for KSHV	NCT02252211
Tocilizumab	HIV positive MCD	IL-6 overproduction plays a role in MCD. Tocilizumab is a humanized anti-IL6 receptor antibody. Blocking human IL-6 may be sufficient to treat MCD by blocking paracrine and autocrine stimulation	NCT01441063
Sirolimus	HIV positive MCD	Rapamycin is directly toxic to KSHV-infected cells [91]. Tumor responses in Kaposi sarcoma were associated with recovery of T cell memory responses against KSHV latent ORF73 and lytic K8.1 antigens [92]	NCT01441063
DA-EPOCH + lenalidomide	KSHV-associated lymphomas (including PEL)	Lenalidomide has in-vitro direct antitumor effect in KSHV-lymphomas as well as immunomodulatory and antiangiogenic effects	Anticipated opening in 2016
Lenalidomide	Kaposi sarcoma	Thalidomide has shown activity in Kaposi sarcoma. Lenalidomide is a more potent thalidomide derivative	NCT01057121

CTLA4, cytotoxic T-lymphocyte protein 4; DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; EphA2, ephrin receptor tyrosine kinase A2; HIV, human immunodeficiency virus; IL-6, interleukin-6; KICS, Kaposi sarcoma inflammatory cytokine syndrome; KSHV, Kaposi sarcoma herpesvirus; MCD, multicentric Castleman disease; MEK, mitogen-activated protein kinase; PD-1, programmed cell death protein 1; PEL, primary effusion lymphoma.

below) [86]. Even though PEL cells do not express CD20, rituximab should be used to treat PEL in patients with concurrent MCD, and may also be useful in other PEL patients by targeting cytokine production by KSHV-infected nontumor B-cells.

KAPOSI SARCOMA HERPESVIRUS INFLAMMATORY CYTOKINE SYNDROME

Our group observed that some KSHV-infected patients manifested inflammatory symptoms similar to those in KSHV-MCD but did not have KSHV-MCD pathology. We described six such patients in a retrospective analysis [4▪]. Serum vIL6, hIL-6, IL-10, and serum KSHV viral load were significantly higher than control patients with Kaposi sarcoma and no MCD-like symptoms. Based on this initial study, we have developed a working definition of KICS and have undertaken a prospective study of this condition [89▪,90]. Our current understanding is that as in KSHV-MCD, the symptoms in these patients are caused by cytokine excess directly or indirectly caused by KSHV infection and not attributable to uncontrolled HIV [89▪]. KICS patients have a high risk of death, and anemia and hypoalbuminemia were poor prognostic indicators [89▪]. Many have Kaposi sarcoma and/or PEL. Unrecognized KICS may be an important cause of death in certain patients with AIDS-associated Kaposi sarcoma. Our findings highlight the importance of recognizing KICS in critically ill patients with HIV/KSHV coinfection and stress the unmet need to develop treatment strategies for this patient population. Table 3 displays the working criteria for KICS. The National Cancer Institute is currently evaluating several strategies to treat KSHV-associated diseases, including KICS (Table 4).

CONCLUSION

KSHV-associated diseases represent a heterogeneous group of disorders. The principal manifestations are from tumor formation (Kaposi sarcoma and PEL) and from cytokine excess (MCD and KICS). A better understanding and recognition of this cluster of entities is essential for the development of improved prevention and treatment approaches. It will be useful to understand the factors leading to these different diseases in different KSHV-infected patients. Promising efforts to develop effective therapies include targeting specific viral genes, targeting dysregulated cellular pathways, inhibiting abnormal cytokine expression, and immunomodulatory approaches.

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Conflicts of interest

R.Y. reports a CRADA with Celgene Corp., nonfinancial support from Hoffman LaRoche and Bayer. In addition, R.Y. has a patent on the treatment of Kaposi sarcoma with IL-12, patents pending for a peptide vaccine against HIV, and a patent application for the use of pomalidomide and lenalidomide to treat KSHV-associated diseases and induce immunologic changes. The spouse of R.Y. is a coinventor on a patent describing the measurement of KSHV vIL-6. All these inventions were made when the scientists were employees of the United States government. All rights, title, and interest to these patents have been assigned to the US Department of Health and Human Services. The government conveys a portion of the royalties it receives to its employee inventors under the Federal Technology Transfer Act of 1986 (PL 99–502). T.S.U. reports a CRADA with Celgene Corporation, and nonfinancial support from Hoffman LaRoche and Bayer Corporation, outside the submitted work. In addition, T.S.U. is a coinventor on the patent application described above for pomalidomide and lenalidomide. All other authors report no potential conflicts.

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- ▪ of special interest
- ▪▪ of outstanding interest

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