Epidemiology, Pathophysiology, and Treatment of Kaposi Sarcoma–Associated Herpesvirus Disease: Kaposi Sarcoma, Primary Effusion Lymphoma, and Multicentric Castleman Disease

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Kaposi sarcoma–associated herpesvirus infection is associated with the development of 3 proliferative diseases: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. These conditions are also intimately associated with human immunodeficiency virus infection, and important synergistic interactions between these 2 viruses have been described. Despite differences in viral gene expression patterns in each condition, Kaposi sarcoma–associated herpesvirus encodes similar oncogenic proteins that promote the activation of sequential and parallel signaling pathways. Therapeutic strategies have been implemented to target these unique signaling pathways, and this sort of molecular targeting is the focus of many current research efforts. The scope of this review is to present contemporary knowledge about the epidemiology, virology, and immunology of Kaposi sarcoma–associated herpesvirus and to highlight several key oncogene products that may be targets for chemotherapy.

In 1994, a previously unrecognized γ-herpesvirus was discovered by Chang and Moore [1] with use of representational difference analysis to identify DNA fragments of this virus from Kaposi sarcoma (KS) tissue samples. Named Kaposi sarcoma–associated herpesvirus (KSHV), and also known as human herpesvirus-8, KSHV was subsequently identified in samples from patients with primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD) [2, 3]. This was more than a coincidental finding; KSHV infection is a requisite for the development of KS and PEL and is the pathogenic stimulant for many cases of MCD, including all HIV-associated MCD. In addition to these 3 "hallmark" diseases, other conditions, such as hemophagocytic lymphohistiocytosis [4], have been associated with KSHV.

Although infection with KSHV is necessary for the development of KSHV-associated disease, it is not sufficient. Both HIV coinfection and immunosuppression significantly increase the risk of KSHV-associated disease.

This review covers the basics of KSHV virology, epidemiology, immunology as it relates to the immunosuppressed host, and diagnosis. The key pathogenic mechanisms of KSHV that lead to tumorigenesis will be highlighted, with an emphasis on those mechanisms that use signaling pathways with known inhibitors. Additionally, the epidemiology, pathology, and clinical and diagnostic features of the 3 classic KSHV-associated diseases will be discussed. The rationale for antiviral therapy against KSHV in each of these diseases is addressed.

KSHV EPIDEMIOLOGY

Information about the epidemiology of KS comes from cancer registry data on the incidence of KS in various geographic and demographic groups; serologic and molecular epidemiologic studies have characterized the epidemiology of KSHV infection [5–7]. KS was initially described as an uncommon tumor among elderly Mediterranean men and was subsequently re-

ported in African children in the 1960s [8, 9]. The association with immunodeficiency was first reported in patients who were undergoing solid-organ transplantation, but in 1981, an epidemic of KS among young men who have sex with men in the United States served as the harbinger of a new immunodeficiency syndrome, subsequently identified as being caused by HIV [10, 11]. As the HIV epidemic progressed, KS was found almost exclusively among men who have sex with men [12]. Coupled with epidemiologic data, which found KS to be more common among persons who were at greater risk for sexually transmitted infections, an infectious etiology of KS was sought.

After the identification of KSHV as the etiologic agent of KS, the development of serologic assays allowed for seroepidemiologic studies that confirmed that KSHV prevalence varies widely, from 1%–3% of blood donors in North America to >70% of individuals in regions of Africa where KSHV is endemic [13]. The seroprevalence of KSHV has been found to roughly mirror the incidence of KS, although populations with gross disparities between seroprevalence and incidence highlight the importance of other potential cofactors in the progression from chronic KSHV infection to KS.

Definitive data on the mode of KSHV transmission are lacking. There is evidence for sexual, horizontal, and parenteral transmission in the medical literature. The virus is often shed from the oropharynx of both immunocompetent and immunocompromised men and women in areas where KSHV is endemic [14–16]. Behaviors associated with exposure to saliva are correlated with a higher risk of KSHV infection, implicating both sexual and horizontal transmission [17–19]. A relatively high KSHV seroprevalence has been described among injection drug users, and an increased incidence of KSHV infection has been noted among transfusion recipients in areas where KSHV is endemic, suggesting that parenteral transmission may be possible [20]. Finally, transmission of KSHV from donors of solid organs has been described [21–23]. Taken together, these disparate data make it difficult to counsel persons who are at risk for KSHV-associated disease regarding methods to reduce their risk of acquiring KSHV [24].

DIAGNOSIS AND VIROLOGY

An individual can receive a diagnosis of KSHV infection as a result of receiving a diagnosis of KS or PEL. Many indirect serologic tests for KSHV are available, although few commercial assays exist. Serologic assays for KSHV infection are limited in both sensitivity and specificity, and conflicting data have been produced with different methodologies. Additionally, with the limited availability of testing, there are few clinical indications for KSHV serologic testing apart from epidemiologic or research settings. Direct detection of KSHV DNA in clinical specimens with use of PCR may be reasonable in a restricted set of clinical conditions. Finally, in situ hybridization or immu-

nohistochemistry may reveal KSHV proteins expressed in human tissue, and these approaches are often used adjunctively in the diagnosis of KS, PEL, or MCD.

Like all herpesviruses, KSHV alternates between 2 phases of its life cycle. The lytic phase is hallmarked by active viral replication, and a wide range of KSHV gene products are expressed during this phase [25]. During the latent phase, however, gene expression is extremely limited. The virus is maintained as episomes attached to the host chromosome, is replicated with the host chromosomes, and is subsequently passed to daughter cells. KSHV-associated diseases vary in the degree of replication during the lytic phase. During the lytic phase, KS lesions are associated with limited viral replication, MCD is associated with a very high degree of viral replication, and PEL is associated with an intermediate level of viral replication.

PATHOGENESIS OF KSHV-ASSOCIATED TUMORIGENESIS

KSHV encodes for numerous specific proteins that are postulated to play a role in the pathogenesis of KS, PEL, and MCD. Many of these proteins have been pirated from the human host during the course of viral evolution. KSHV produces molecules that are critical in the transduction of signals that stimulate cell proliferation and inhibit apoptosis. The latency-associated nuclear antigen is one such protein that primarily functions to tether the viral genome to the infected host-cell's genome; however, it also promotes cell survival and contributes to the transformation of KSHV-infected cells by interacting with and altering the function of the tumor suppressor proteins p53 and retinoblastoma protein [26–28]. Another example is the viral G protein–coupled receptor, a lytic-phase gene product that shares significant homology with the high-affinity IL-8 receptor. Its dysregulated expression leads to oncogenesis through numerous cellular proliferation, transformation, proangiogenic, and antiapoptotic signaling pathways [29, 30]. The viral G protein–coupled receptor leads to proangiogenic signals by the upregulation of hypoxia-inducible factor 1-α and the subsequent expression of vascular endothelial growth factor (VEGF)–A and activation of VEGF-receptor-2, which in turn activates the phosphatidyl-inositol-3–kinase, Akt, and mammalian target of rapamycin (mTOR) pathway [29]. Additionally, blockade of the viral G protein–coupled receptor and inhibition of phosphatidyl-inositol-3–kinase leads to inactivation of the transcription factor and antiapoptotic protein nuclear factor–κB (NF-κB), thereby blocking transformation [29]. A third oncogenic protein is the viral FLICE inhibitory protein, which is associated with constitutively activated NF-κB and is purported to function as an oncogene through the manipulation of this pathway [31, 32]. Lastly, KSHV encodes for a human IL-6 homologue, viral IL-6, which stimulates the known human IL-6–induced signaling pathways via the shared cytokine signaling
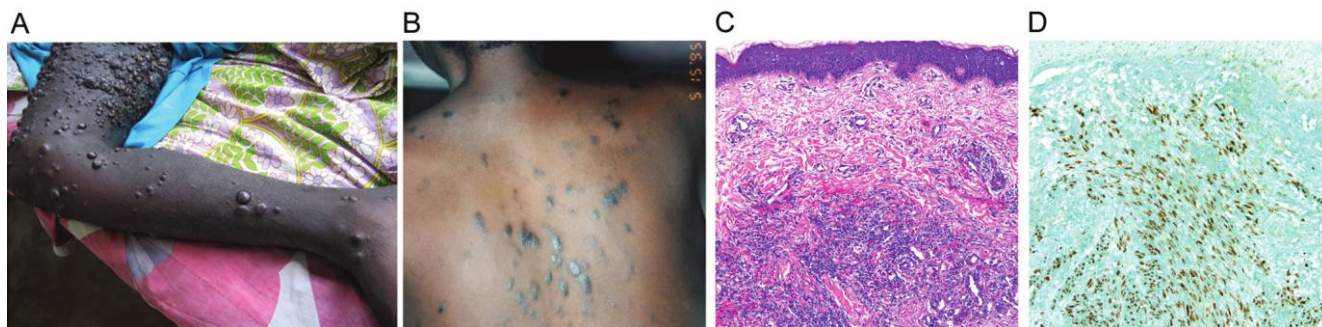
Figure 1. Extensive papular-nodular Kaposi sarcoma on the leg *(A)* and back *(B)* of a patient from Uganda. *C,* Cutaneous Kaposi sarcoma of plaque stage (hematoxylin-eosin stain; original magnification, ×200). *D,* Kaposi sarcoma cutaneous tumor in which the spindled tumor cells demonstrate Kaposi sarcoma–associated herpesvirus immunoreactivity (latency-associated nuclear antigen immunohistochemical stain; original magnification, ×200).

receptor gp130 coupled to the endogenous JAK-STAT pathway [33]. KSHV-infected cells induce and secrete viral IL-6 and can retain some portion of viral IL-6 intracellularly, which then binds to gp130 and activates STAT3 in an autocrine fashion [29].

Inhibitors to many of the mentioned pathways exist, are approved by the US Food and Drug Administration (FDA) for other indications, and may offer substantial therapeutic benefit in the treatment of KSHV-associated diseases. Anti-VEGF agents include bevacizumab, sunitinib, and sorafenib; inhibitors of mTOR include rapamycin, temsirolimus, and everlimus; and the proteosome inhibitor bortezomib blocks the effects of NF-κB. Inhibitors of the JAK and STAT pathways are being investigated for the treatment of various diseases, but none are FDA-approved for any indication at this time. Additionally, antibodies to IL-6 may be effective in treating some patients with MCD [34].

KSHV IN THE IMMUNOCOMPROMISED HOST

Clinical observations identify T cells as playing an important role in the control of KS, evidenced by the regression of KS with the reduction of immunosuppressive treatment after transplant and by clinical improvement and possible exacerbation (flare) of KS in subjects with immune reconstitution after receipt of HAART [35, 36]. Studies have found that HIV-infected KSHV-seropositive men do not have T cell proliferative responses to KSHV and that HIV-positive and HIV-negative persons with KS have low quantities of KSHV-specific T cells [37, 38]. In addition, increased cytotoxic lymphocyte responses to KSHV in HIV-infected persons who are receiving HAART have been shown, although the recent reporting of persistent KS despite effective HAART raises important questions about the mechanisms that control the progression of KSHV infection and KS [39, 40].

In experimental models, a relationship exists between KSHV and HIV in which the replication of each virus may be enhanced in the presence of the other. HIV Tat, for example, upregulates HIV gene expression and has been shown to play a crucial role in the development of KS via interaction with KSHV gene products. Tat promotes the migration and proliferation of cytokine-activated endothelial cells and stimulates KS cell growth in mouse models [41]. Accordingly, when injected subcutaneously into nude mice, Tat causes KS-like lesions [42]. Moreover, ~15% of male transgenic mice overexpressing the *tat* gene develop skin tumors resembling KS at 12–18 months of age [42].

Similarly, KSHV infection may enhance HIV replication [43]. The latency-associated nuclear antigen has been shown to activate long terminal repeats of HIV-1 through its association with Tat [44]. Interestingly, HIV infection leads to increased KSHV infectivity because of Tat [45]. It is believed that the actions of Tat may account for the rather aggressive course of KS in patients with AIDS, compared with the more indolent behavior of KS in HIV-negative persons.

KSHV-ASSOCIATED DISEASES: CLINICAL PRESENTATION AND MANAGEMENT

KS. KS occurs in several clinical-epidemiologic settings [46]. Classic KS is a nonaggressive disease that usually affects elderly Mediterranean men, is not associated with HIV infection, and presents with a limited number of cutaneous lesions on the lower extremities; disseminated disease is uncommon. Endemic KS affects persons from sub-Saharan Africa and is also not associated with HIV. Endemic KS is a more aggressive and morbid disease than classic KS (figure 1). Immunodeficiency clearly enables KS development, and patients who are taking immunomodulatory agents—most notably in the context of solid-organ transplantation—often develop transplant-associated KS. Lastly, AIDS-associated or "epidemic" KS is the most common cause of tumor development among HIV-infected patients. It is often characterized by widely disseminated cutaneous disease, with advanced cases involving the oral mucosa

and viscera (most frequently the lungs and gastrointestinal tract).

A wide range of treatments for KS are available. Independent of any other clinical factor, all patients with AIDS-associated KS should receive HAART [46]. Effective antiretroviral regimens are associated with a reduction in the incidence of AIDS-related KS, a regression in the size and number of existing lesions, and a histological regression of existing KS lesions. Few data exist on the comparative efficacy of various HAART regimens in the treatment of KS, although experimental models and anecdotal data may support the sole use of protease inhibitor–containing regimens [47]. Several antiviral agents, including ganciclovir, foscarnet, and cidofovir, have been shown to inhibit KSHV replication in vitro. Antiviral therapy (with cidofovir) aimed at KSHV has not been shown to be effective by itself for the treatment of KS, perhaps in part because of the small amount of lytic KSHV that is present in KS tumors [48, 49]. Antiviral treatments may be effective as an adjunct to more-conventional chemotherapy or in the treatment of diseases with a higher degree of lytic replication (i.e., MCD and PEL).

The clinical context of KS (i.e., HIV status, transplant status, and extent and site of disease) is crucial for the selection of appropriate treatment. Patients with limited local disease may benefit from a variety of therapies, including intralesional chemotherapy (vinblastine is most commonly used), topical ointments (alitretinoin gel), cryotherapy, laser therapy, photodynamic therapy, and infrequently, excisional surgery. Radiation therapy can effectively palliate symptomatic disease that is not extensive enough to warrant systemic therapy but is too extensive to be treated with intralesional chemotherapy. Patients with rapidly progressing, extensive cutaneous and/or visceral disease should receive systemic therapy. Systemic treatments have traditionally involved cytotoxic chemotherapy. Although numerous chemotherapeutic agents have been shown to be effective, only 3 have been approved by the FDA for this indication on the basis of clinical effectiveness and a reasonable adverse-effects profile. They include the 2 liposomal anthracyclines (pegylated liposomal doxorubicin and liposomal daunorubicin) and the taxane paclitaxel. Nontraditional therapies have been the focus of recent clinical investigation in the field. Some nontraditional therapies have shown promise in early clinical trials (thalidomide, imatinib, and COL3), and some are actively being investigated in clinical trials (rapamycin, bevacizumab, sunitinib, and sorafenib) [46].

Lastly, patients who develop KS while receiving immunomodulatory agents should, when feasible, receive an immunosuppressive regimen that includes rapamycin or one of its analogues. This recommendation is based on a series of solid-organ transplant recipients in whom KS regressed after treatment was switched to rapamycin [50].

PEL. PEL is an unusual lymphoproliferative disorder, accounting for ≤2% of HIV-associated lymphomas, and is even more rarely encountered in the HIV-negative population. PEL is divided into classic and solid variants. Classic PEL is characterized by lymphomatous involvement of the serosal surfaces, whereas solid PEL manifests initially with tissue-based tumors and no malignant effusions (figure 2) [51, 52]. Classic and solid PEL are similar with regard to morphology, immunophenotype, and molecular characteristics [53]. KSHV and high levels of interleukin (e.g., IL-6) may be found in PEL tumor cells, and this has frequently been demonstrated to aid in diagnosis. The ramifications of large and typically recurrent pleural, pericardial, and peritoneal effusions are grave and are responsible for the high morbidity and mortality associated with this condition [52].

PEL cells have a characteristic phenotype highlighted by CD45, CD30, CD38, CD138, and MUM1 coexpression [52]. Classic B cell markers (CD19 and CD20) and T cell markers (CD2, CD3, CD5, and CD7) are not typically seen. Gene expression profiling has shown that PEL expresses a gene profile distinct from other lymphomas but more akin to multiple myeloma cell lines.

There is no clear standard of care established in the treatment of PEL, and because of its low incidence, randomized clinical trials are not feasible. As with the other KSHV-associated diseases, if HIV coinfection is identified, antiretroviral therapy is critical, because spontaneous regression with the commencement of HAART has been described [52, 54]. Traditionally, the use of standard cytotoxic regimens used for the treatment of non-Hodgkin lymphomas are suboptimal, and median duration of survival in treated cohorts is poor [55]. Induction of apoptosis with the inhibition of NF-κB in PEL cell lines has led to the investigation of proteasome inhibitors that decrease the activation of NF-κB and its antiapoptotic effects [56]. Bortezomib, a proteosome inhibitor that has been approved by the FDA for use in multiple myeloma, has been shown to enhance the in vitro cytotoxic effects of doxorubicin and paclitaxel, and has been used successfully in combination with anthracycline-based cytotoxic chemotherapy regimens [57]. Inhibition of mTOR with rapamycin is effective at decreasing in vitro PEL growth and in vivo mouse xenograft model tumor growth, and its increasing use in the treatment of PEL can be foreseen [58]. Cases of prolonged survival for patients who were treated adjunctively with antiviral therapy (ganciclovir or cidofovir) have also prompted the adjunctive use of these drugs in PEL. When used to treat PEL, valproate induces lytic KSHV replication and leads to apoptosis in combination with antiviral agents [47].

MCD. MCD is an aggressive lymphoproliferative disorder that is characterized by constitutional symptoms, anemia, and generalized lymphadenopathy (figure 3). Small case-series have shown that most MCD cases are driven by KSHV, including
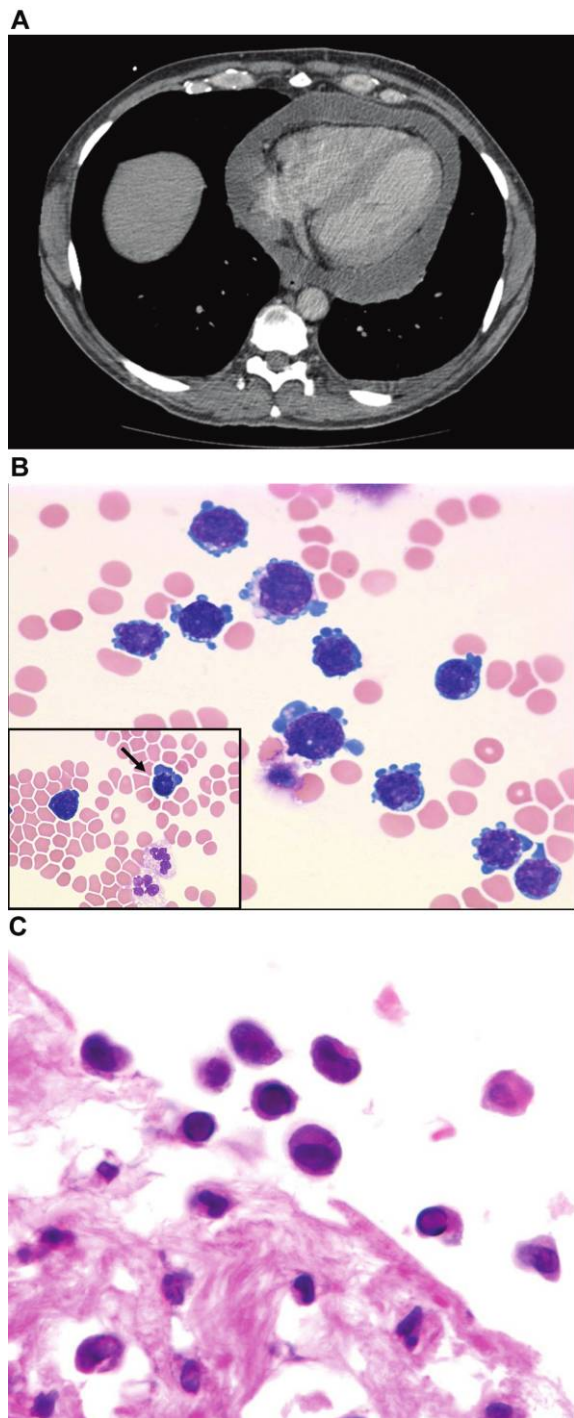
Figure 2. *A,* Pericardial primary effusion lymphoma (CT of the chest). *B,* Photomicrograph of pericardial fluid, cytospin preparation with atypical lymphoid cells with basophilic cytoplasm and vacuolization (Wright-Giemsa stain; original magnification, ×600); *inset,* prominent mitosis *(arrow)* in one of the lymphoma cells. *C,* HIV-associated primary effusion lymphoma showing lymphoma cells with Kaposi sarcoma–associated herpesvirus viral nuclear inclusions (cell block preparation; hematoxylin-eosin stain; original magnification, ×600). Images in figure 2*A* and 2*B* originally appeared in Braza et al. [51] and were reprinted with permission from CMPMedica.

100% of cases among HIV-positive patients and the majority of cases among HIV-negative patients [59]. Failure to identify KSHV in all MCD lesions may reflect technical limitations in KSHV detection, the ability of KSHV to induce MCD from a distance in the biopsied tissue, or an alternate etiology for a limited number of cases. On occasion, MCD may be associated with non-Hodgkin lymphoma, particularly the plasmablastic variant [33]. A key to making a diagnosis of MCD is to suspect MCD in high-risk individuals who present in the appropriate clinical context (i.e., an immunosuppressed individual with KSHV infection or other KSHV-associated disease). Definitive diagnosis can only be made by pathologic examination of an involved lymph node or extranodal mass. Detection of KSHV in biopsied tissue or in the peripheral blood can aid in the diagnosis. C-reactive protein, KSHV load, and serum IL-6 levels, if available, may be useful as markers of disease activity and response to therapy [33].

In patients with MCD and HIV infection, treatment with antiretroviral therapy is necessary, but caution should be taken, because life-threatening flares of MCD have been reported as a manifestation of immune reconstitution [60]. Systemic therapy is the mainstay of treatment for patients with MCD and includes aggressive remission-induction chemotherapy regimens (cyclophosphamide-doxorubicin-vincristine-prednisone or doxorubicin-bleomycin-vincristine), single-agent maintenance chemotherapy (oral etoposide, cyclophosphamide, or vinblastine), immunomodulatory agents (thalidomide or IFN-
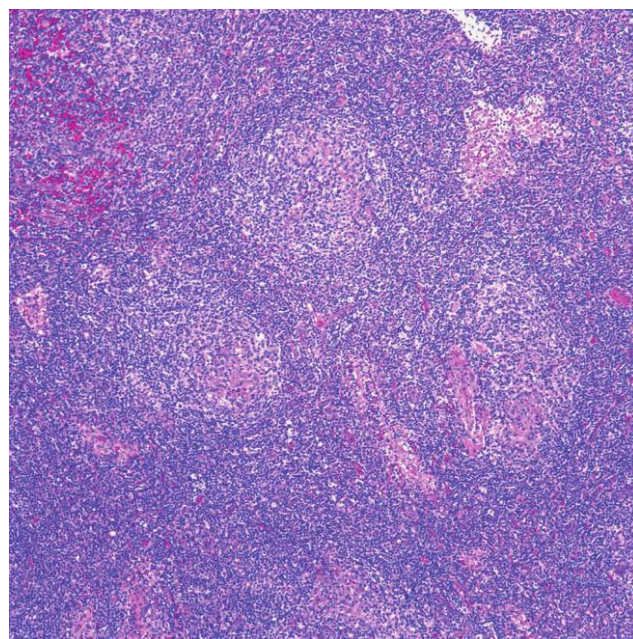

Figure 3. Lymph node with HIV-associated multicentric Castleman disease showing multiple regressing follicles surrounded by an expanded and vascular interfollicular zone (hematoxylin-eosin stain; original magnification, ×100).

α), and monoclonal antibodies against the IL-6 receptor (altizumab) and CD20 (rituximab) [33].

Among all of these treatments, rituximab has shown the most promise in inducing durable remission of MCD. In a prospective study of 24 individuals with chemotherapy-dependent HIV-associated MCD, rituximab was associated with sustained remission at day 60 after treatment (the primary end point) in 22 patients (92%) [61]. More recently, the efficacy and safety of 4 weekly infusions of rituximab in 21 consecutive patients with previously untreated plasmablastic HIV-associated MCD has been investigated [62]. All but 1 patient achieved clinical remission of symptoms, as well as hematological and serum chemistry normalization, and 70% of patients achieved a radiological response. In 3 patients who experienced relapse, retreatment with rituximab was successful [63]. The main adverse event seen in these patients was reactivation of KS, which is intriguing and may be attributable to a rapid B cell depletion that is observed during rituximab therapy or to an immune reconstitution inflammatory syndrome to hitherto latent antigens [64]. Rituximab therapy was shown to be associated with a decrease in KSHV levels both initially and at the successful treatment of a relapse [62].

Because of the lytic nature of KSHV in MCD, antiviral therapy is also a consideration. A recent randomized, controlled trial demonstrated the efficacy of valganciclovir in reducing KSHV replication in individuals with KSHV infection but without evidence of KS, PEL, or MCD [65]. In patients with MCD, ganciclovir and valganciclovir have been independently shown to induce remissions alone or in combination with other agents [66, 67].

CONCLUSIONS

Differential KSHV gene expression has the ability to promote the development of 3 distinct neoplastic conditions—KS, PEL, and MCD. Emerging knowledge about the various signal transduction pathways used by KSHV to mediate oncogenesis has helped to identify numerous drug targets. Promising therapeutic targets include mTOR and VEGF for KS; mTOR, NF-κB, and VEGF for PEL; and CD20$^+$ B cells and KSHV-lytic replication for MCD. Additionally, continued basic research focusing on KSHV gene products and their functions may uncover more telling details about the upregulation and utilization of molecular pathways that should provide additional and more-efficient therapeutic targets.

Acknowledgments

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