Curr Infect Dis Rep (2010) 12:147–154
DOI 10.1007/s11908-010-0092-5

Update on HHV-8-Associated Malignancies

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Published online: 26 March 2010

Abstract The human herpesvirus 8 (HHV-8) is the oncogenic virus associated with Kaposi's sarcoma (KS) and lymphoproliferative disorders, namely, primary effusion lymphoma and multicentric Castleman's disease. KS is among the most common malignancies seen in HIV-infected patients despite the decreased incidence of KS in the era of highly active antiretroviral therapy. Advances in molecular pathology reveal HHV-8 tumorigenesis is mediated through molecular mimicry wherein viral-encoded proteins can activate several cellular signaling cascades while evading immune surveillance. This knowledge has led to the evolution of multiple therapeutic strategies against specific molecular targets. Many such therapeutic modalities have shown activity, but none have proven to be curative. Identifying possible prognostic factors is another active area of research. This review summarizes the recent developments in the fields of virus transmission, molecular biology, and treatment of HHV-8-related neoplasms.

Keywords Human herpesvirus 8 · HHV-8 · KSHV · Kaposi's sarcoma · Primary effusion lymphoma · Multicentric Castleman's disease

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Introduction

Viruses have been linked to several human cancers since the latter half of the 20th century. This finding is especially so in immunosuppressed individuals. One of the harbingers of the HIV/AIDS epidemic in the 1980s was the sudden surge in the incidence of Kaposi sarcoma (KS) among male homosexuals [1]. Beral et al. [2] in 1990 proposed a sexually transmitted infectious agent could be the etiology of AIDS-related KS; however, it was not until 1994 that Chang et al. [3] identified the virus from KS tissues in a patient with AIDS and established its association with KS. This new γ herpesvirus was named KS-associated herpesvirus (KSHV)/human herpesvirus-8 (HHV-8). HHV-8 is one of several oncogenic viruses. In addition to KS, HHV-8 is associated with lymphoproliferative disorders including multicentric Castleman's disease (MCD), plasmablastic lymphoma, primary effusion lymphoma (PEL), and the solid variant of PEL [4–6]. A germinotropic lymphoproliferative disorder seen in HIV-seronegative patients is also linked to HHV-8 where the lesions are coinfected with Epstein-Barr virus (EBV) [7]. Deviations from these classic forms of HHV-8-associated malignancies have been reported, such as a case of large B-cell lymphoma coinfected with HHV-8 and EBV having histologic (although not immunophenotypic) similarities to classic Hodgkin's lymphoma in an immunocompetent person and another case of HHV-8-associated intravascular large B-cell lymphoma in an HIV-positive patient [8].

HHV-8 Transmission

The definite route of transmission of HHV-8 is still debated. Pica and Volpi [9•] reviewed the possible routes of HHV-8 transmission, including horizontal, sexual, vertical, blood

borne, and through organ transplantation. A large, population-based, cross-sectional study evaluating the epidemiology of HHV-8 in the general US adult population demonstrated that HHV-8 transmission may be related to sexual activity in men, especially in male homosexuals, whereas evidence was lacking for heterosexual transmission in women [10•]. HHV-8 infection was found to occur with increased prevalence among patients with recently acquired HIV infection in Sao Paulo, Brazil [11]. Both univariate and multivariate analysis found positive correlation between HHV-8 transmission during the first year of HIV infection and sexual practices: in men who have sex with men (MSM) and in persons with history of other sexually transmitted diseases.

In Africa, many have postulated the high seroprevalence observed in adults implied HHV-8 infection was acquired in childhood; however, recent data do not support this. Butler et al. [12] found a low seroprevalence of HHV-8 infection among children in South Africa, in contrast to Uganda, where an age-dependent pattern was observed (rates increased with age). This finding suggests the possibility of different patterns of transmission of HHV-8 in Africa, the continent with highest prevalence of HHV-8. A large prospective study conducted in Zambia in a cohort of children from birth to 48 months to estimate annual incidence of HHV-8 concluded that transmission in children is mainly horizontal, through maternal mastication of food. This study also found the presence of HIV-1 infection increases the risk for acquiring HHV-8 in areas highly endemic for both viruses [13].

Further HHV-8 transmission studies in the HIV-seronegative population demonstrate additional data in the transmission, development, and persistence of HHV-8-associated malignancy. Transmission of HHV8 has been documented in the setting of organ transplantation [14, 15]. Postallograft medical immunosuppression is associated with increased risk of KS, as well as other viral-associated malignancies (EBV lymphoproliferative disease). In this setting, reduction or withdrawal of immunosuppression can result in regression of KS, even in the absence of other specific therapy [15]. Similarly, immune reconstitution through use of highly active antiretroviral therapy (HAART) in persons with HIV can be associated with spontaneous regression of KS.

Oncopathogenesis

The past two decades have seen significant advances describing the molecular pathways involved in HHV-8-induced malignancies. There appears to be an intricate interplay between the host immune system and the virus, which results in tumorigenesis with evasion of immune surveillance. For a more comprehensive review of HHV-8-induced oncogenesis, the reader is referred to Liang et al. [16••] and Wen et al. [17••].

KSHV/HHV-8 displays a latent and a lytic phase. The latent phase, which is the default phase of HHV-8, helps with immune evasion and in establishing a persistent viral infection. The major latent viral proteins include latency-associated nuclear antigen (LANA1), viral cyclin (v-cyc), and the viral Fas-associated death domain interleukin-1B converting enzyme (FLICE) inhibitory protein (vFLIP). Kaposin, viral interferon regulatory factors 3 (vIRF3), and KSHV-encoded microRNA (miRNA) are among the other latent viral proteins [16••]. Viral G-protein coupled receptor (vGPCR) and viral interleukin-6 (vIL-6) are lytic-phase proteins, although vIL-6 is also often found in latently infected cells [16••, 18••].

Although KSHV is thought to involve infection of endothelial/spindle cells in KS, it infects lymphocytes in both PEL and MCD. KSHV latent gene products, including LANA and v-FLIP, appear to dominate the malignant states of KS and PEL; the virus is considered to be predominantly in a latent state within both tumors. By contrast, in the setting of MCD, high levels of KSHV lytic gene products—including ORF5, ORF59, ORF65, and K8—are typically found, particularly in the mantle zone region of the affected lymph nodes [19].

Functions and Oncogenicity of HHV-8 Viral Products

LANA1

This latent viral protein is essential to maintain latency and for cell proliferation. It may also have a role in immune evasion through inhibition of antigen presentation [20]. Transforming growth factor-β (TGF-β) signaling pathway is an important regulator of growth in several cell types and also has a role in immune surveillance. KSHV LANA has been shown to downregulate TGF-β type II receptor (TβRII) in KSHV-infected PEL cells through DNA methylation and deacetylation of proximal histones, blocking the TGF-β signaling pathway and thus contributing to the neoplastic process [21]. LANA1 also inhibits the tumor suppressors P53 and von Hippel-Lindau (VHL) through its E3 ubiquitin ligase activity, which targets these suppressors for proteasome degradation. The consequences of this process include impaired apoptosis and increased hypoxia-inducible factor-1α levels, which leads to activation of genes involved in angiogenesis, cell proliferation, and survival [22].

v-cyc

V-cyc is a homologue of cellular D-type cyclins; it activates the DNA damage checkpoint, especially in early premalignant

lesions, which would be expected to have protective effects against malignant transformation and persistence. However, the v-cyc may also lead to centrosomal abnormalities that could contribute to malignant transformation through genomic instability [23].

vFLIP

This latent viral protein has been associated with cell survival, morphologic change, and inflammatory activation. In addition, vFLIP appears to have a role in maintaining viral latency. Ye et al. [24] recently showed that vFLIP activation of the nuclear factor-κB (NF-κB) was associated with suppression of the activator protein-1 (AP-1) pathway, which in turn inhibited the reactivation transcriptional activator (RTA) expression involved in KSHV lytic replication. However, this inhibition of lytic replication by NF-κB activation can be bypassed partly or overcome during a full lytic infection, and NF-κB activation and lytic gene expression are not mutually exclusive in all circumstances [24, 25]. Adding to the functional repertoire of vFLIP is a role in maintaining host-pathogen equilibrium together with IRF-1 through regulation of antigen presentation, according to the model proposed by Lagos et al. [26].

vGPCR

A lytic gene, *vGPCR* is the only KSHV gene identified with transforming capacity. The *vGPCR* gene can drive autocrine and paracrine Akt activation in infected endothelial cells. Also, *vGPCR* unblocks a break on the mammalian target of rapamycin (mTOR) signaling pathway, which results in increased cell proliferation, cellular nutrient uptake, and angiogenesis [27].

MicroRNA

These are noncoding RNAs about 22 nucleotides in length; they function through interaction with messenger RNA, causing its degradation or preventing translation [28]. KSHV/HHV-8 encodes 12 microRNAs (miRNAs) coordinately expressed in the latency region. One of the viral miRNAs encoded by KSHV, miR-K12-11, appears to be homologous to cellular miR-155, and thus capable of using its binding sites [29, 30]. Also, miR-155 has a high expression in many human B-cell lymphomas, where it plays a significant role in differentiation, B-cell maturation, and regulation of the immune system, mediated via cytokine production [31]. Thus, viral miR-K12-11 and the oncogenic human miRNA, miR-155, potentially have the same target genes; this could possibly contribute to the pathogenesis of HHV-8-associated malignancies [29, 30]. Samols et al. [32] have revealed more cellular genes that are targeted by HHV-8 miRNAs, including thrombospondin 1 (THBS1), which is down regulated. THBS1 has a significant role in several cellular processes, including adhesion, migration, and angiogenesis [32].

LANA2

Another latent viral protein, LANA2 has a possible role in developing resistance to the drug paclitaxel by binding to the polymerized microtubules, decreasing their stability and interfering with the binding of the drug to the tubules [33].

ORF-K1

The variations found in the highly variable glycoprotein, an early lytic-cycle gene product encoded by the ORF-K1 gene, defined four major subtypes and 13 variants or clades of HHV-8 [34]. These subtypes are variably distributed in different geographic areas of the world [34]. Subtypes A and C were seen mostly in the United States and Europe, whereas subtype B was almost exclusive to Africa [34, 35]. In a recent study of Italian patients with classic KS, HHV-8 subtype A was shown to be associated with high blood levels of the virus, and these patients developed a rapidly progressive disease; thus, aggressive therapeutic strategies are required in persons infected with this subtype of HHV-8 [35].

Brown et al. [36] showed preliminary evidence linking host immunogenetic factors to control of HHV-8 infection. These investigators showed a high HHV-8 lytic antibody titer—a possible marker of lytic reactivation—was associated with genetic variations in cytokines in HIV-negative patients without KS.

HHV-8-Associated Malignancies

Clinical Features and Therapeutic Options

Kaposi Sarcoma

KS is an angioproliferative tumor and is among the most common malignancies seen in the HIV-infected population. The HIV/AIDS cancer match study by Engels et al. [37•] showed a greatly increased incidence of KS in the HIV-infected individuals compared with the general population (standardized incidence ratio 1300), and although incidence declined considerably in the HAART era, it still remains elevated in relation to the HIV-negative population. KS may involve the skin, lymph nodes, or viscera and is often multifocal. Compared with asymptomatic HHV-8 carriers, a significantly lower level of HHV-8-specific cytotoxic T cells has been noted in both AIDS-related and classic KS

[38]. The iatrogenic KS associated with organ transplantation often regresses with reversal of immunosuppression or dose reduction of immunosuppressive agents. Similarly, improvement in the immune system brought on by use of HAART helps to alleviate HIV-related KS. There has been a notable sixfold drop in the incidence rate of KS from the pre-HAART era to the HAART era, supporting the hypothesis that immune impairment is permissive of KS [39]. A study showed that low CD4 counts and lack of antiretroviral therapy (ART) were major risk factors in KS development in the HHV-8-seropositive male homosexuals with AIDS [40•]. These investigators also demonstrated that HAART had a significant protective role not only with respect to prevention of KS but also in lowering mortality of patients with KS.

In the HAART era, there are increasing reports of KS occurring in HIV-infected individuals with suppressed HIV viral loads and apparent immune reconstitution. Maurer et al. [41] reported on nine HIV-infected patients with persistent cutaneous KS despite being on HAART, with CD4 counts greater than 300 cells/mm^3 and viral load less than 300 copies/mL for nearly 2 years. Similar instances have been observed in the past, as noted by Krown et al. [42], which suggest the need to explore further the factors involved in development and progression of KS and to identify which patients respond to ART. A Swiss HIV cohort study followed 144 HIV-infected patients with KS from 1996 to 2004 with the aim of identifying adverse prognostic factors; T1 stage of tumor, CD4 count below 200 cells/μL, and a positive HHV-8 DNA in the plasma were associated with poorer outcomes [43]. In a retrospective cohort of 64 patients with KS who were treated with a combination of chemotherapy and HAART, the median time to initial response was as long as 9 months and the estimated time to complete resolution was 33 months [44]. The cumulative resolution probability at 3 years was 51%. Although both HAART and chemotherapy were independently associated with initial clinical improvement, the authors found only recent HAART use significantly correlated with complete resolution of the disease. However, they failed to find any impact of CD4 counts and tumor stage on either improvement or resolution of lesions, although a low HIV viral load was a predictor of response to therapy. Furthermore, the type of HAART regimen used did not impact response significantly. The association of HHV-8 viral load with development of new lesions or with disease progression was again demonstrated in two recent studies [45, 46]. Stebbing et al. [47] conducted a prospective cohort study to develop an easily quantifiable prognostic index for patients with AIDS-related KS. Four prognostic factors were identified: age, KS occurring at or after AIDS onset, presence of comorbidities, and CD4 cell count.

Treatment options for KS include surgical removal, radiation therapy, and chemotherapy. Several standard chemotherapeutic agents have activity alone and in combination against KS: anthracyclines—most notably liposomal preparations, microtubule inhibitors, and vinca alkaloids. Recent advances in understanding the molecular pathogenesis of KS has lead to novel strategies targeting HHV-8.

Rapamycin (sirolimus), an mTOR inhibitor, has been shown to improve the levels of HHV-8-specific cytotoxic T cells when used in HHV-8-seropositive organ transplant recipients [48–50]. Sirolimus has been recommended as an immunosuppressive agent for organ transplant recipients in light of its beneficial effects in causing regression of KS and other posttransplant tumors without adversely impacting the graft [51]. Matrix metalloproteinases (MMP), the zinc-dependent endopeptidases, are overexpressed in KS cells and are involved in tumor invasion and metastasis. The AIDS Malignancy Consortium recently conducted a phase 2 trial comparing two doses (50 mg and 100 mg) of an MMP inhibitor known as COL-3 (CollaGenex Pharmaceuticals, Newtown, PA), a modified tetracycline, in AIDS-related KS [52]. The overall response rate was 41% in the lower dose group and there were no serious adverse events, which raises the possibility of using this agent along with others for future therapy of AIDS-related KS. Another treatment approach is the induction of lytic viral proteins to render the virus more susceptible to the immune system and possibly enhance apoptosis or lysis of HHV-8-infected tumor cells. A recently published pilot trial using valproic acid was designed to determine the level of lytic expression of HHV-8 within the KS lesions [53]. The study results failed to show sufficiently high levels of lytic gene expression in a 30-day period on valproic acid. This therapeutic approach might still hold promise for the future, and additional studies using agents expected to be more potent inducers of lytic activation are underway.

Multicentric Castleman's Disease

HHV-8-associated MCD, an aggressive disease, is encountered mostly in immunosuppressed individuals, including HIV-infected patients. These patients are at risk of developing a plasmablastic lymphoma, a type of large B-cell lymphoma. For a comprehensive review of MCD in HIV-infected patients, the reader is referred to Stebbing et al. [54•]. In a histologic study of lymph nodes involved by HIV-associated MCD, as much as 63% of the lymph nodes tested positive for both MCD and KS, suggestive of coexistence of the two pathologic processes [55]. A rare instance of KSHV/HHV-8-associated hemophagocytic syndrome developing in an immunocompetent patient who also had coexistent MCD and KS was reported recently [56]. Wyplosz et al. [57] reported an instance of skin rash

secondary to reactivation of HHV-8 with subsequent development of MCD as a continuous process. The authors further hypothesized that infected plasmablasts in the blood may be implicated in transport of the virus to the various target tissues as well as in the development of other HHV-8-associated conditions such as KS. Seliem et al. [58] reported another unusual variant of MCD-associated plasmablastic lymphoproliferative disorder, which had overlapping histologic features of plasmablastic microlymphoma and germinotropic lymphoproliferative disorder in an HIV-positive patient with HHV-8 and EBV coinfection.

Treatment for MCD has traditionally involved aggressive chemotherapy, and lately monoclonal antibodies against CD20 (rituximab) and IL-6 (atlizumab) have been effective [18••]. A combination of rituximab with the immunomodulator thalidomide has been reported to cause regression of MCD in an HIV-infected patient [59]. A few recent trials have shown the beneficial effect of rituximab along with HAART in MCD with a prolonged resolution of symptoms. In the single-group, phase 2 trial by Bower et al. [60], the partial response was 67% and the 2-year overall survival (OS) was 95%. In another prospective, open-label trial by Gerard et al. [61••], sustained remission at 1 year was achieved in 71%, and OS at 1 year was 92%.

Primary Effusion Lymphoma

PEL is a rare form of lymphoproliferative disorder seen frequently in HIV-infected patients; it presents as a classic and solid variant and generally has a very poor prognosis [62]. Reports exist of PEL occasionally occurring in HIV-negative patients, especially in the setting of other forms of immunosuppression (eg, in organ transplant recipients and in patients with chronic hepatitis B) [62–65]. Morphologically, it shares features of large-cell immunoblastic and anaplastic large-cell lymphoma [62, 66]. PEL tumor cells have a null phenotype, but are believed to be of B-cell origin [62]. Occasionally, the tumor cells may express B-cell or T-cell markers, which make detection of HHV-8 an important confirmatory test [66]. The level of IL-6 in these tumor cells is quite high, which aids in the diagnosis of PEL and could be a potential target for therapy [18••]. De Filippi et al. [67], in their report of three HIV-negative patients with hepatitis C virus infection and PEL, showed elevated levels of free λ light chains in the serum; levels correlated with clinical response to treatment. This finding can possibly be used to monitor response to therapy.

The rarity of PEL precludes any large, prospective trials and optimal therapy is lacking. Apart from the traditional chemotherapy, various regimens that have been tried include the proteasome inhibitor, bortezomib, which inhibits the NF-κB pathway, antivirals including cidofovir and ganciclovir, and the mTOR inhibitor rapamycin [18••]. Rapamycin decreases production of vascular endothelial growth factor (VEGF) as well as VEGF-induced signaling, thereby inhibiting accumulation of body fluids; this has clinical relevance in PEL therapy, but at the same time resistance to rapamycin developed quickly, limiting its efficacy [68]. Despite beneficial effects of rapamycin use in the HHV-8 malignancies in organ transplant patients, PEL has been reported to develop in renal transplant recipients who were on rapamycin, which might possibly suggest that this drug may not be as effective in preventing PEL as it is with KS [63]. Reports are mixed regarding the activity of bortezomib in PEL [69]. There have been recent case reports of long-term remission with HAART alone as therapy for PEL, as well as remission seen with radiotherapy in a patient with PEL who was refractory to chemotherapy [70, 71].

Recently, a randomized, controlled trial showed efficacy of the antiviral drug valganciclovir in decreasing HHV-8 replication, which makes it useful as an adjunctive agent in HHV-8-associated disease processes, especially those with more lytic viral replication (eg, MCD) [72]. Another reported potential therapeutic approach included use of plant extracts, which were identified using a new fluorescence-based assay [73]. Last but not least, Bryant and Milliken [74] reported the successful treatment of PEL in an HIV-infected patient in second remission with allogeneic hemopoietic stem cell transplantation, who remained in complete remission at 31 months posttransplant only on HAART and with undetectable viral loads.

Conclusions

Our understanding of the pathophysiology and the molecular processes involved in the development of the various HHV-8-associated malignancies has increased dramatically over the past decade. Although many new targets have been identified at the molecular level for potential therapy of KS, MCD, and PEL, therapeutic outcomes for these malignancies remain far from satisfactory. Future research should aim to improve our understanding of the role of host and viral factors that influence tumorigenesis and prognosis in the various HHV-8-related disease states, identifying the most efficacious combination from among the different therapeutic options through controlled trials. Alternative modalities, including radiotherapy and stem cell transplantation, should be explored in aggressive HHV-8 malignancies. Studies for effective prevention strategies, including vaccines, could potentially add to our arsenal against HHV-8.

Disclosure No potential conflict of interest relevant to this article was reported.

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- • Of importance
- •• Of major importance

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