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Human Herpesvirus-8: Beyond Kaposi's

Doron Rimar MD, Yossi Rimar MD and Yoav Keynan MD

Department of Medicine, Carmel Medical Center, Haifa, Israel
Affiliated to Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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Abstract

Today, more than 10 years and 2000 articles since human herpesvirus 8 was first described by Chang et al., novel insights into the transmission and molecular biology of HHV-8 have unveiled a new spectrum of diseases attributed to the virus. The association of HHV-8 with proliferative disorders – including Kaposi's sarcoma, multicentric Castleman disease and primary effusion lymphoma – is well established. Other aspects of HHV-8 infection are currently the subject of accelerated research. Primary HHV-8 infection may manifest as a mononucleosis-like syndrome in the immunocompetent host, or in various forms in the immunocompromised host. The association of HHV-8 with primary pulmonary hypertension was observed by Cool et al. in 2003, but six clinical trials evaluating the role of HHV-8 in pulmonary hypertension have not been able to replicate this intriguing observation. It has been speculated that HHV-8 may secondarily infect proliferating endothelium in patients with pulmonary hypertension. HHV-8 epidemiology, modes of transmission, new spectrum of disease and treatment are presented and discussed.

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Human herpesvirus-8, also known as Kaposi's sarcoma-associated herpesvirus, is the most recent member of the gamma-herpesvirus family. It was described in 1994 by Chang et al. [1] after isolation from a patient with Kaposi's who had been infected with human immunodeficiency virus. The association was established by molecular analysis and further supported by epidemiologic studies. Therefore, it is now considered that the presence of HHV-8 is the initial step in the development of Kaposi's sarcoma. Further studies enabled researchers to link this virus with multicentric Castleman disease and primary effusion lymphoma, as well as several non-malignant diseases. In this article we review the epidemiology and expanding spectrum of diseases related to HHV-8 infection.

The virus

HHV-8 is a member of Rhadinovirus (related to the monkey rhadinoviruses) and possesses a typical herpesvirus morphology with a central icosahedral capsid surrounded by a lipid bilayer [2,3]. The capsid is composed of four structural proteins, three of which have significant homologies to alpha and beta-herpesviruses. Based on analysis of the open reading frame K1 and K15, six viral subtypes were identified (A,B,C,D,E and N) with marked clustering to geographic regions [4,5].

HHV-8 infects several cell types usually as a latent form. Lytic replication can take place in blood and tissues from Kaposi's sarcoma and multicentric Castleman disease. The virus can be latently maintained in B lymphocytes and monocytes which may serve as a reservoir [6].

Epidemiology

The exact modes of transmission of HHV-8 are not fully understood. The distribution of the virus parallels the pattern of Kaposi's; namely, low seroprevalence in central and northern Europe, North America and most of Asia, intermediate prevalence (> 20%) in the Middle East and Mediterranean, and high prevalence in central and southern Africa (up to 87% in the Congo Republic and Botswana) [4]. Several lines of evidence suggest that transmission modes differ between endemic regions and those in which infection is sporadic. In endemic countries HHV-8 prevalence is very low in the population under 2 years of age, after which it rises, and is consistent with transmission among close contacts and family members. This is further supported by the demonstration of viral DNA in saliva and buccal epithelial cells, along with lower viral loads in peripheral blood and genital secretions [7,8]. The situation is less clear in countries of low seroprevalence. The role of heterosexual transmission is probably minor, a fact explained by low viral loads in vaginal, seminal and prostatic secretions. Among HIV risk groups, injection drug users and hemophiliacs have the lowest frequencies of infection, while the prevalence is highest among homosexual men [5,8,9]. Kaposi's sarcoma is the most common cancer among HIV patients in this group. Although HHV-8 is uncommon in North America, 11–20% of HIV-seronegative homosexual males and 30–54% of HIV-seropositive homosexual males have detectable antibodies against HHV-8 [9]. Increasing numbers of sexual partners and history of sexually transmitted diseases are correlated with increased seroprevalence, supporting sexual transmission in this population [10].

New spectrum of HHV-8 infection

Primary HHV-8 infection in children

Primary HHV-8 in children may present with a mononucleosis-like illness. In a cohort from Alexandria, Egypt, 7% of 86 children

* The first two authors contributed equally

HHV-8 = human herpesvirus 8

HIV = human immunodeficiency virus

with a febrile syndrome of undetermined origin were found to have a positive polymerase chain reaction for HHV-8 in the saliva or plasma. Three of those children were proved later to seroconvert. The typical presentation involved a craniocaudal maculopapular exanthema with pharyngeal involvement, signs of upper respiratory tract infection, and no lymphadenopathy. All children recovered completely within 2 weeks [11].

A similar presentation in three children was recently reported by Chen and co-authors [12]. A transient disease characterized by fever, atypical lymphocytosis, a rash and elevated liver function tests was associated with a positive PCR for HHV-8, and later seroconversion in two of the children. A prolonged neutropenia that resolved only with granulocyte-stimulating factor treatment after 6 months was evident in another child who suffered from acampomelic campomelic dysplasia, with sex reversal and growth deficiency [12].

An association of HHV-8 with primary pulmonary hypertension has been suggested. Treatment is based on chemotherapy, antiviral agents, lytic phase inducers, augmentation of innate immune system, and immunologic strategies.

Primary HHV-8 infection in healthy adults

In healthy adults primary HHV-8 infection is probably only mildly symptomatic. Among 119 homosexual male patients negative for HIV, who were followed for 15 years, 5 seroconversions were noted. Symptoms observed around the presumed time of the primary HHV-8 infection included mild transient cervical and sub-mental lymphadenopathy, diarrhea, localized rash, fatigue, or no clinical signs at all. The overall incidence rate for HHV-8 infection was 3.7/1000 person-years [13].

Primary HHV-8 infection in immunocompromised hosts

The spectrum of primary HHV-8 in the immunocompromised host is wide and may include a febrile syndrome similar to infection in children (mononucleosis-like), bone marrow suppression, hemophagocytic syndrome and even disseminated fulminant infection.

Mononucleosis-like illness was described following autologous peripheral blood stem cell transplantation in a patient with non-Hodgkin's lymphoma. Reactivation of HHV-8 infection presented with fever, cutaneous rash, and mild hepatitis [14]. Oksenhendler and colleagues [15] reported a primary HHV-8 infection in a 43 year old HIV-positive homosexual man that manifested as sudden onset of fever, arthralgia, cervical lymphadenopathy and splenomegaly that spontaneously resolved within 8 weeks. Pathologic examination of the cervical nodes demonstrated angiolymphoid hyperplasia and foci of Kaposi's sarcoma. A retrospective study of stored serum documented recent seroconversion for HHV-8 [15]. Luppi and team [16] described two cases of bone marrow failure after transplantation due to an acquired HHV-8 infection from the donor transplant. The mode of acquisition was confirmed by identification of the highly variable *K1* gene sequence of the HHV-8 genome in both the donor's peripheral blood cells and the recipient's serum [16]. Hemophagocytic syndrome, a syndrome characterized by fever, pancytopenia, splenomegaly and hemophagocytosis in bone marrow was associated with HHV-8 infection in a renal transplant patient and resolved after treatment with foscarnet. Similar cases during reactivation of HHV-8 in HIV patients have been described [17,18]. Finally, a disseminated HHV-8 infection, including chronic active hepatitis, ulcerative colitis, esophagitis, and bronchopneumonia as evidenced by a positive HHV-8 PCR in these tissues, was reported in a 1 month old infant with DiGeorge anomaly who suffered graft-versus-host disease caused by engraftment of maternal lymphocytes [19].

HHV 8 and primary pulmonary hypertension

Primary pulmonary hypertension is a rare disease of unknown etiology, characterized histologically by proliferation of endothelium and smooth muscle in the pulmonary arterial walls (plexiform lesion) and leading to severe right heart failure [7]. Mutations in bone morphogenetic protein receptor 2 are associated with this disorder but cannot account for the majority of cases [20].

The association of primary pulmonary hypertension with HHV-8 latent infection was first suggested by Cool et al. in 2003 [20]. Several observations led these investigators to examine this association. First, an overlap of HHV-8, multicentric Castleman disease and pulmonary hypertension had been observed by the same group earlier that year. Second, HIV has been associated with HHV-8 and with pulmonary hypertension, which is indistinguishable clinically or pathologically from primary pulmonary hypertension, but the relation between these was not evaluated at that time. Third, vascular endothelial growth factor, which plays a major role in proliferation of endothelium within the plexiform lesions of primary pulmonary hypertension, is increased in multicentric Castleman disease and has been speculated to be induced by HHV-8 viral interleukin-6 homologue [20].

Cool and team found that 10 of 16 patients with primary pulmonary hypertension (62%) expressed HHV-8 latency-associated nuclear antigen 1 and viral cyclin gene within plexiform lesions by immunohistochemistry and PCR, respectively. No LANA-1 was expressed in lung tissue from 14 patients with secondary pulmonary hypertension. Additionally, the plexiform lesions of primary pulmonary hypertension were found to resemble lesions of Kaposi's sarcoma histologically, reflected by slit-like vascular spaces and sheets of spindle cells that express factor VIII-related antigen (an endothelial cell marker) and by an increased expression of bcl-2, VEGF and VEGF receptor 2.

PCR = polymerase chain reaction

LANA 1 = latency associated nuclear antigen 1
VEGF = vascular endothelial growth factor

Table I. Studies evaluating the association between HHV-8 and pulmonary hypertension

Reference	Methods	PPH	SPH	HRPH	Control
Cool et al. [20]	• LANA-1: immunohistochemically by antibodies to HHV-8 ORF 73 • HHV-8 viral cyclin: by PCR for sequence of ORF 72	62% (10/16)	0% (0/11)	33% (1/3)	
Katano et al. [21]	• LANA-1: immunohistochemically by antibodies to HHV-8 ORF 73 • *HHV-8 KS 330* gene: by PCR for sequence of ORF 26 • *HHV-8 K1* gene: nested PCR with K1 forward and reverse primers	0% 0/10	0% 0/12	–	
Daibata et al. [22]	• *HHV-8 KS 330* gene: by PCR for sequence of ORF 26 • HHV-8 viral cyclin: primary effusion lymphoma: by PCR for sequence of ORF 72	0% 0/9	–	–	
Henke-Gendo et al. [23]	• LANA-1: antibodies were detected by IFA • *K8.1 gene products*: by ELISA, cutoff value not delineated	2% (1/49)	12% (2/17)	–	2.7% (2/73)
Laney et al. [24]	• *HHV-8 ORF-65* and *K8.1* gene products: by ELISA with a cutoff of 0.04 optical density	0% (0/19)	4% (1/25)	50% (2/4)	0.7% (1/150)
Montani et al. [25]	• LANA-1: antibodies were detected by IFA on the primary effusion lymphoma BC-3 cell line • KSHV IgG IFA: used for confirmation of positive results	2% 1/47	17% 2/12	24% 8/34	–
Nicastri et al. [26]	• Anti-lytic test: immunofluorescent assay based on the BCBL-1 cell line	6% 1/16	0% 0/14	0% 0/3	Cystic fibrosis 17% (5/29) Interstitial lung disease 23% (3/13)

PPH = primary pulmonary hypertension, SPH = secondary pulmonary hypertension, HRPH = HIV-related pulmonary hypertension, LANA 1 = latency-associated nuclear antigen 1, ORF = open reading frame, PCR = polymerase chain reaction, ELISA = enzyme-linked immunosorbent assay, IFA = immunofluorescence assay, KSHV = Kaposi sarcoma-associated herpesvirus.

The intriguing association of HHV-8 and primary pulmonary hypertension suggested by Cool's group was evaluated in several follow-up studies on different populations but has not yet been confirmed [Table 1]. It was not correlated with HHV-8 infection in Japanese patients. [21,22]. Moreover, using different serologic assays, no association was found between HHV-8 and primary pulmonary hypertension in German, American, French and Italian patients, and no relation to HIV-related pulmonary hypertension was found among French patients [23-26]. Cool et al. argue that HHV-8 may be an organ-specific infection within the lung tissue of patients with primary pulmonary hypertension and therefore is not detected by serologic assays in the serum [23]. Indeed, only two studies evaluated HHV-8 infection in lung tissue similarly to Cool et al. Unfortunately, both these studies evaluated Japanese patients, in whom the prevalence of HHV-8 infection is known to be low (1.4%), and consequently no evidence of HHV-8 infection was found in these patients, neither in the primary pulmonary hypertension group nor in the controls. Thus, the lung sequestration theory has not been refuted, although a major argument against it claims that the demography of HHV-8 does not correlate with that of primary pulmonary hypertension. While the prevalence of HHV-8 increases with age, primary pulmonary hypertension is common in young women. HHV-8 is prevalent in Africa and the Mediterranean, but the rates of primary pulmonary hypertension are not higher than in other parts of the world [24].

Surprisingly, two serologic studies in which latent antigens of HHV-8 were evaluated revealed higher rates of HHV-8 infection in non-HIV-related secondary pulmonary hypertension [24,26]. Two other serologic studies in which seroprevalence of HHV-8 in secondary pulmonary hypertension was not found to be higher evaluated only antigens of the lytic phase [24,26]. The significance of these findings was not analyzed and needs further validation. If true, the association of HHV-8 with secondary pulmonary hypertension may reflect a secondary infection of the proliferating endothelium in the lung by HHV-8, due to an affinity to tissues expressing high levels of VEGF or pro-inflammatory cytokines, with no regard to the primary cause of proliferation. Indeed, HHV-8 was found to be frequent even in patients with idiopathic pulmonary fibrosis, interstitial lung disease and cystic fibrosis without pulmonary hypertension [26,27].

At this point no clear conclusion can be drawn regarding the relationship of HHV-8 with pulmonary hypertension. A large-scale, prospective, controlled, multicenter study evaluating serum and lung tissue for evidence of HHV-8 lytic and latent infection among primary, secondary, and HIV-related pulmonary hypertension patients of western origin may help resolve the controversy of HHV and pulmonary hypertension.

Treatment of HHV-8 infection

Primary HHV-8 infection in the immunocompetent host is generally self-limiting and usually does not require antiviral therapy [28]. Clinical experience with the treatment of primary HHV-8 infection in the immunocompromised host is sporadic and mostly based on the experience from treating Kaposi's sarcoma [29]. Traditionally, this involves cytotoxic chemotherapy with liposomal doxorubicin for which the response rate is high (42–79%), but there are many recurrences of resistant Kaposi's. Primary effusion lymphoma is much more resistant to therapy, with a response rate of less than 42% [30,31]. New strategies have recently been developed, targeting HHV-8 in these diseases.

Antiviral drugs and lytic phase induction

Sensitivity studies of HHV-8 to antiviral drugs have suggested resistance to acyclovir and pencilovir, but sensitivity to ganciclovir, adefovir and foscarnet. Clinical trials, however, have yielded disappointing results. Foscarnet is considered the most effective antiviral drug and significantly prolongs the time to progression in Kaposi's sarcoma, but remission is seldom achieved [30].

Antiviral agents are mostly active against viruses in the lytic phase. Kaposi's sarcoma and primary effusion lymphoma are characterized by a greater proportion of viruses in the latent phase, while many of the cells in multicentric Castleman disease are in the lytic phase [31].

The resistance of latent virus replication to antiviral drugs can be overcome by drugs that induce the virus to enter a lytic replication phase, rendering it more susceptible to antiviral therapy. Such agents include histone deacetylase inhibitors, phorbol esters, and nuclear factor κB inhibitors. This strategy, however, carries some risk if the production of infectious viruses is not fully contained by antiviral drugs, a state that can lead to dissemination of disease and even bone marrow aplasia [16,17].

The spectrum of primary human herpesvirus-8 infection includes a mononucleosis-like syndrome in the immunocompetent host and severe aplastic anemia or hemophagocytic syndrome in the immunocompromised host

Targeting latent viral replication and its gene production

During the latent phase HHV-8 is maintained as an episome in tumor cells and expresses products such as viral FLICE inhibitory protein (υ-FLIP) and LANA. These proteins block the function of tumor suppressor genes *p*53 and retinoblastoma gene, making the latently infected cell less likely to undergo apoptosis, thus enhancing the survival of virally infected cells. Glycyrrhizic acid, a component of licorice, decreases the expression of LANA *in vitro*, thereby killing cells latently infected by HHV-8 [32].

Hydroxyurea is another agent utilized against latently infected cells. Unfortunately, not all cells lose their episomes when incubated with hydroxyurea and resistance often develops [31].

Augmentation of innate antiviral defenses

Interferon-alpha and interferon-gamma augment cellular defenses to viral infection and trigger apoptosis in HHV-8-infected cells [30]. Cells that are in lytic replication are much more susceptible to pro-apoptotic effects. It has been suggested that interferon-alpha therapy prior to induction of the lytic phase is likely to result in a greater response, but this assumption has not been evaluated in clinical trials [33].

Immunologic strategies

The immune system plays a major role in tumor development in HHV-8-infected individuals. The improvement in immunologic function achieved by highly active antiretroviral therapy in HIV-infected patients often leads to regression of HHV-8 viral loads and regression of Kaposi lesions. Reduction or cessation of post-transplant immunosuppression also leads to regression of some Kaposi lesions [30].

Summary

HHV-8 is a virus relatively new to science and its role as a pathogen is still being characterized. A vast array of mechanisms used by HHV-8 for transmission replication and evasion of the immune system may explain its tumorogenicity and association with Kaposi's sarcoma, primary effusion lymphoma and multicentric Castleman disease. Recently, a new spectrum of non-malignant diseases associated with HHV-8 was observed. An association of HHV-8 with primary pulmonary hypertension was suggested, but it may reflect a secondary infection. Primary HHV-8 infection is clearly under-reported as it may go clinically unnoticed in adults or appear as a mononucleosis-like illness in children. The immunocompromised host may present with bone marrow failure, hemophagocytic syndrome and even disseminated invasive multi-organ failure. Antiviral drugs such as foscarnet and interferon are efficacious mostly against the viruses in the lytic replication phase and not for latent infection. Novel strategies may overcome this barrier by inducing HHV-8 to reenter the lytic phase, thus rendering it more susceptible. The immune system clearly modulates the response to primary infection, but further research is needed to delineate other factors influencing the presentation of primary HHV-8 infection.

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Correspondence: Dr. D. Rimar, Dept. of Medicine A, Carmel Medical Center, Haifa 34362, Israel.
Phone: (972-4) 825-0484
Fax: (972-4) 824-5581
email: doronrimar@gmail.com