H.K. Dermatol. Venereol. Bull. (2003) **11**, 68-72

Review Article

A review on human herpesvirus type 8 infection

人類疱疹病毒 8 型評論

PKS Chan 陳基湘, RCW Chan 陳志偉

Human herpesvirus type eight (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV) is the most recently identified human herpesvirus. Over the last decade, many studies have focused on the epidemiology and disease association of this novel virus. It is aetiologically associated with Kaposi's sarcoma and some rare malignancies that are mainly found in AIDS patients. A link between HHV-8 and several diseases such as basal cell carcinoma, multiple myeloma and pemphigus has been suspected. However, convincing evidence is still lacking. In contrast to all previous known human herpesviruses, the prevalence of HHV-8 varies substantially with geographical location. Current data suggest that the principal route of transmission is also different between populations. While Kaposi's sarcoma is rare in Hong Kong, the limited available data provide some hints that this infection might be more prevalent in this locality than one would have expected.

人類疱疹病毒 8 型(HHV-8) ，亦即多發性出血性肉瘤(卡波希肉瘤)關連性疱疹病毒(KSHV) ，是最近發現的人類疱疹病毒。在過往十年，有關此新病毒的流行病學及其相關疾病的研究為數不少。此病毒與卡波希肉瘤以及一些主要發生於愛滋病患者的罕見腫瘤有關。HHV-8亦可能與數種疾病有關，如基底細胞癌、多發性骨髓瘤及天疱瘡。然而，確實的證據仍然缺乏。與過往所有的人類疱疹病毒相反， HHV-8 的患病率具有相當程度的地域差異性。目前的研究顯示，在不同的人口中，其主要傳播途徑也有差異。雖然，卡波希肉瘤在香港較罕見，但現在有限的資料提示 HHV-8 的感染率可能較想像中高。

Keywords: Epidemiology, HHV-8, Hong Kong, KSHV, Kaposi's sarcoma

關鍵詞：流行病學，人類疱疹病毒 8 型，香港，卡波希肉瘤關連性疱疹病毒，卡波希肉瘤

Department of Microbiology, The Chinese University of Hong Kong, Hong Kong

PKS Chan, MRCP, MD
RCW Chan, MB ChB

Correspondence to: Dr. Paul KS Chan

Department of Microbiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

Introduction

The family *Herpesviridae* comprises about a hundred viruses, of which eight members are known to infect humans. Human herpesviruses are grouped into subfamilies according to their genomic organisation and biological characteristics. The alphaherpesviruses (herpes

simplex virus types 1 and 2, and varicella zoster virus) cause vesicular skin eruptions. The betaherpesviruses (human cytomegalovirus, human herpesvirus types 6 and 7) establish latency in peripheral blood mononuclear cells, whereas the gammaherpesvirus (Epstein-Barr virus) is well known for its association with malignancy. Human herpesvirus type 8 (HHV-8), the most recently identified human herpesvirus belonging to the subfamily *Gammaherpesviridae*, is the focus of this review.

Biology

HHV-8 is also known as Kaposi's sarcoma-associated herpesvirus (KSHV) because it was first detected by Chang et al in Kaposi's sarcoma (KS) tissues from a patient with AIDS.[1] HHV-8 exhibits typical herpesvirus morphology with the complex core of double stranded DNA enclosed by an icosahedral capsid, which is in turn covered by a lipid envelope giving rise to a whole viral particle of 120-150 nm in diameter. Based on phylogenetic analysis, HHV-8 is classified in the genus *Rhadinovirus* and is the only example of this genus known to infect humans.[2] HHV-8 is closely related to other rhadinoviruses, e.g. herpesvirus saimiri found in squirrel monkey, herpesvirus ateles found in spider monkeys. Recent studies also found related rhadinoviruses in other species of monkeys, chimpanzees and gorillas.[3,4] As for human herpesviruses, the closest relative of HHV-8 is Epstein-Barr virus.

Based on the genomic sequence variability of open reading frame (ORF)-K1 and ORF-15, HHV-8 variants can be divided into five groups. Different geno-groups seem to have a different geographic predilection. For instance, group B is predominant in Africa; groups D and E are confined to the Pacific region, whereas groups A and C are mainly found in Europe and North America.[5] This lineage-related distribution is likely to be a result of its co-evolution with the host. The biological and pathological implications of this geno-grouping system have yet to be elucidated.

The extent of tissue tropism and the possible sites of latency for HHV-8 are still an enigma. When a sensitive method such as PCR is being used, HHV-8 sequences can be detected from many types of disease tissues, including all forms of KS, primary effusion lymphoma (a distinct subset of AIDS-related lymphoma), and multicentric Castleman's disease.[6-9] HHV-8 sequences can also be found in a number of normal tissues, including lymph nodes, spleen, peripheral blood mononuclear cells, cervical secretion and seminal fluid.[10,11] Isolation of HHV-8 in vitro is difficult. At present, no cell line is readily permissive for HHV-8 infection. This property makes the diagnosis of HHV-8 infection difficult.

Epidemiology

As a general rule for herpesviruses, HHV-8 infection persists for the life of the host following primary infection. The most distinct epidemiological characteristic of HHV-8 is being non-ubiquitous. The prevalence of HHV-8 infection in the general population varies substantially by geographical location. In Europe and North America, the prevalence is relatively low, ranging from 0% to 15%.[12-14] In areas with higher incidence of KS such as Mediterranean and Eastern European countries, the prevalence of HHV-8 ranges from 4% to 24%.[15-17] In contrast, the prevalence is as high as 60% in certain African regions where KS is endemic.[18]

Another interesting epidemiological feature of HHV-8 is its mode of transmission. While HHV-8 can be transmitted by a few different routes, it seems that the principal route of transmission is different in different parts of the world. In North America and Europe, most studies indicate that sexual contact, in particular among men who have sex with men, is the primary route of

transmission.[19,20] These findings are in line with the well-established observation that the incidence of KS among AIDS patients is higher among men who have sex with men. In these geographical regions, HHV-8 is rare or non-exist in children indicating the absence of non-sexual horizontal transmission. However, in Brazil, Central Africa and Egypt, a prevalence of 40% to 50% has been reported among prepubescent children.[18] These data imply a non-sexual horizontal route of transmission occurs commonly in these regions. This horizontal route is likely to be saliva exchange as HHV-8 can be found in high titre from saliva.[21-23] In this regard, HHV-8 is similar to other herpesviruses such as herpes simplex virus type 1, Epstein-Barr virus, cytomegalovirus, human herpes virus types 6 and 7, for which saliva exchange is the major route of transmission and making them a common childhood infection.

There are also biological and epidemiological data to support that HHV-8 can be transmitted by the heterosexual route, blood transfusion, needle sharing, and vertically from mother to child.[24-26] However, the efficiency and overall importance of these routes in disseminating HHV-8 infection is not yet certain.

Clinical manifestations

Primary infection

Reported studies on the clinical manifestations of primary HHV-8 infection are still limited. Recently, a study based on immunocompetent Egyptian children (mean age of 36 months) showed that primary HHV-8 infection was associated with prolonged craniocaudal maculopapular rash for a mean duration of six days and persistent high fever for a mean duration of 10 days.[27] Isolated case reports on primary HHV-8 infection in immunosuppressed individuals have been described. Among these cases, fever, transient angiolymphoid hyperplasia, arthralgia, cervical lymphadenopathy, hepatitis, splenomegaly and marrow failure have been linked to the infection.[28,29] It is clear that more data are required to establish the full spectrum of clinical manifestations of primary HHV-8 infection.

Human cancers

It is now widely accepted that HHV-8 is a necessary cause of Kaposi's sarcoma.[30] The epidemiology of HHV-8 is very similar to that previously established for KS. HHV-8 DNA is detected in all clinical forms of KS and is specifically localised to KS lesions. In KS lesions, HHV-8 exists in a latent state in most spindle cells where the virus exerts cellular transformation. Lytic viral replication has been observed in a small proportion of spindle cells. Although lytic replication represents a terminal phase of the viral life cycle, several lytic viral products are known to carry oncogenic, angiogenic and antiapoptotic properties.[31] For the development of angioproliferative lesions such as KS, interactions between cytokines, extracellular matrix molecules and integrins are required. Further understanding on the role of HHV-8 in the oncogenic progression would lead to newer therapeutic options.

In addition to KS, HHV-8 has also been linked to the development of other malignant diseases. Primary effusion lymphoma, a rare disease previously known as body cavity-based B cell lymphoma, presents with collections of serous fluid within the pleural, pericardial or peritoneal cavities. The fluid contains malignant B-lymphocytes that are infected with HHV-8 and often, but not exclusively, co-infected with Epstein-Barr virus.[8,32] Another lymphoproliferative disorder linked to HHV-8 is the Castleman's disease, also known as multicentricangiofollicular lymphoid hyperplasia. Most of the patients are HIV-infected. The presenting syndrome includes fever, lymphadenopathy and splenomegaly. Affected tissues show polyclonal lymphoid hyper-proliferation with vascular hyperplasia.

Other diseases

There is still a growing list of diseases where the

association with HHV-8 is suspected but has yet to be proven. These include angiosarcoma, basal cell carcinoma, Bowen's disease, multiple myeloma, sarcoidosis, Kikuchi's disease, pemphigus vulgaris and foliaceus, pneumonitis in AIDS patients and haemophagocytic syndrome.

Local studies

Little is known about the epidemiology of HHV-8 infection in Hong Kong. From anecdotal experience, KS is rare in this locality and is uncommon among local AIDS patients. However, a few sources of data provide hints that HHV-8 infection in Hong Kong may be more prevalent than one would have expected.

We have conducted a study to examine the possible association between HHV-8 infection and the development of cervical neoplasia. In this study 404 Chinese women were examined for the presence of HHV-8 DNA in cervical scrape samples.[33] The results showed that 8.7% were positive for HHV-8 DNA by PCR. This positive rate was comparable to that of cytomegalovirus (9.2%). Although this study was not able to differentiate between active and latent infections, the results suggest that HHV-8 infection of the uterine cervix or its shedding in cervical fluid is not uncommon in our local population. It would be interesting to further investigate the role of sexual and vertical transmission of this virus in our population.

To assess the neurotropism of novel herpes viruses, we conducted a survey on normal brain tissues obtained from individuals who underwent post-mortem for clinical reasons.[34] Brain tissue samples were collected from both sides of cerebellum, frontal, temporal, parietal and occipital lobes of 30 post-mortem cases for HHV-8 DNA detection by PCR. Overall, 42/300 (14.0%) samples were positive with similar rates for each position. Nineteen patients (63.3%) were positive, and showed a significant increase in positivity with age ($P=0.007$). The results of this study indicate that HHV-8 has a neuro-invasive and neuropersistent potential. So far, HHV-8 has not been linked to neurological diseases. It is worthwhile to further pursue on this area. In addition, the outcome of this survey on brain tissues is in keeping with our study on cervical scrape samples that HHV-8 infection is not uncommon in Hong Kong.

References

1. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994;266:1865-9.
2. Moore PS, Gao SJ, Dominguez G, Cesarman E, Lungu O, Knowles DM, et al. Primary characterization of a herpesvirus agent associated with Kaposi's sarcomae. J Virol 1996;70:549-58.
3. Lacoste V, Mauclere P, Dubreuil G, Lewis J, Georges-Courbot MC, Gessain A. KSHV-like herpesviruses in chimps and gorillas. Nature 2000;407:151-2.
4. Lacoste V, Mauclere P, Dubreuil G, Lewis J, Georges-Courbot MC, Rigoulet J, et al. Simian homologues of human gamma-2 and betaherpesviruses in mandrill and drill monkeys. J Virol 2000;74:11993-9.
5. Schulz TF. KSHV (HHV8) infection. J Infect 2000;41: 125-9.
6. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 1995;332:1186-91.
7. Cesarman E, Nador RG, Aozasa K, Delsol G, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus in non-AIDS related lymphomas occurring in body cavities. Am J Pathol 1996;149:53-7.
8. Nador RG, Cesarman E, Chadburn A, Dawson DB, Ansari MQ, Sald J, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood 1996; 88:645-56.
9. Soulier J, Grollet L, Oksenhendler E, Miclea JM, Cacoub P, Baruchel A, et al. Molecular analysis of clonality in Castleman's disease. Blood 1995;86:1131-8.
10. Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. N Engl J Med 1995;332:1181-5.
11. Noel JC, Hermans P, Andre J, Fayt I, Simonart T, Verhest A, et al. Herpesvirus-like DNA sequences and Kaposi's sarcoma: relationship with epidemiology, clinical spectrum, and histologic features. Cancer 1996;77:2132-6.
12. Simpson GR, Schulz TF, Whitby D, Cook PM, Boshoff

C, Rainbow L, et al. Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet 1996;348:1133-8.
13. Baillargeon J, Deng JH, Hettler E, Harrison C, Grady JJ, Korte LG, et al. Seroprevalence of Kaposi's sarcoma-associated herpesvirus infection among blood donors from Texas. Ann Epidemiol 2001;11:512-8.
14. Blackbourn DJ, Ambroziak J, Lennette E, Adams M, Ramachandran B, Levy JA. Infectious human herpesvirus 8 in a healthy North American blood donor. Lancet 1997;349:609-11.
15. Gao SJ, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, Saah A, et al. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. N Engl J Med 1996;335:233-41.
16. Angeloni A, Heston L, Uccini S, Sirianni MC, Cottoni F, Masala MV, et al. High prevalence of antibodies to human herpesvirus 8 in relatives of patients with classic Kaposi's sarcoma from Sardinia. J Infect Dis 1998;177: 1715-8.
17. Calabro ML, Sheldon J, Favero A, Simpson GR, Fiore JR, Gomes E, et al. Seroprevalence of Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 in several regions of Italy. J Hum Virol 1998;1:207-13.
18 Gessain A, Mauclere P, van Beveren M, Plancoulaine S, Ayouba A, Essame-Oyono JL, et al. Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa. Int J Cancer 1999;81: 189-92.
19. Melbye M, Cook PM, Hjalgrim H, Begtrup K, Simpson GR, Biggar RJ, et al. Risk factors for Kaposi's-sarcoma-associated herpesvirus (KSHV/HHV-8) seropositivity in a cohort of homosexual men, 1981-1996. Int J Cancer 1998;77:543-8.
20. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med 1998;338:948-54.
21. Pauk J, Huang ML, Brodie SJ, Wald A, Koelle DM, Schacker T, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med 2000;343:1369-77.
22. Vieira J, Huang ML, Koelle DM, Corey L. Transmissible Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in saliva of men with a history of Kaposi's sarcoma. J Virol 1997;71:7083-7.
23. LaDuca JR, Love JL, Abbott LZ, Dube S, Freidman-Kien AE, Poiesz BJ. Detection of human herpesvirus 8 DNA sequences in tissues and bodily fluids. J Infect Dis 1998; 178:1610-5.
24. Cannon MJ, Dollard SC, Smith DK, Klein RS, Schuman P, Rich JD, et al. Blood-borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. N Engl J Med 2001;344:637-43.
25. Whitby D, Smith NA, Matthews S, O'Shea S, Sabin CA, Kulasegaram R, et al. Human herpesvirus 8: seroepidemiology among women and detection in the genital tract of seropositive women. J Infect Dis 1999; 179:234-6.
26. Bourboulia D, Whitby D, Boshoff C, Newton R, Beral V, Carrara H, et al. Serologic evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus infection. JAMA 1998;280:31-2.
27. Andreoni M, Sarmati L, Nicastri E, El Sawaf G, El Zalabani M, Uccella I, et al. Primary human herpesvirus 8 infection in immunocompetent children. JAMA 2002; 287:1295-300.
28 Oksenhendler E, Cazals-Hatem D, Schulz TF, Barateau V, Grollet L, Sheldon J, et al. Transient angiolymphoid hyperplasia and Kaposi's sarcoma after primary infection with human herpesvirus 8 in a patient with human immunodeficiency virus infection. N Engl J Med 1998;338:1585-90.
29. Luppi M, Barozzi P, Schulz TF, Setti G, Staskus K, Trovato R, et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med 2000;343:1378-85.
30. Ablashi DV, Chatlynne LG, Whitman JE Jr, Cesarman E. Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8, diseases. Clin Microbiol Rev 2002;15:439-64.
31. Boshoff C, Moore PS. Kaposi's sarcoma-associated herpesvirus: a newly recognized pathogen. AIDS Clin Rev 1997-98;323-47.
32. Dupin N, Fisher C, Kellam P, Ariad S, Tulliez M, Franck N, et al. Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. Proc Natl Acad Sci U S A 1999;96:4546-51.
33. Chan PK, Li WH, Chan MY, Cheng AF. Detection of human herpesvirus 8 in cervical cells of Chinese women with abnormal papanicolaou smears. Clin Infect Dis 1999;29:1584-5.
34. Chan PK, Ng HK, Cheung JL, Cheng AF. Survey for the presence and distribution of human herpesvirus 8 in healthy brain. J Clin Microbiol 2000;38:2772-3.